

# Canadian Guidelines for the Management of Plaque Psoriasis

1st Edition, June 2009



Endorsed by

Canadian Dermatology Association  
Association canadienne de dermatologie



Canadian Guidelines  
for the  
Management of **Plaque**  
**Psoriasis**

# TABLE OF CONTENTS

## *Canadian Guidelines for the Management of Plaque Psoriasis*

---

NOTES TO READERS .....	iii
GUIDELINES COMMITTEE, REVIEWERS, AND EDITORIAL SUPPORT .....	iii
ACKNOWLEDGMENTS .....	v
DISCLOSURES .....	v
LIST OF ABBREVIATIONS .....	viii
CHAPTER 1: INTRODUCTION .....	1
CHAPTER 2: METHODS .....	6
CHAPTER 3: DEFINITIONS.....	10
CHAPTER 4: DELIVERY OF CARE .....	16
CHAPTER 5: MANAGEMENT OF MILD PLAQUE PSORIASIS .....	19
CHAPTER 6: MANAGEMENT OF MODERATE TO SEVERE PLAQUE PSORIASIS.....	27
CHAPTER 7: SPECIAL POPULATIONS AND CIRCUMSTANCES.....	46
CHAPTER 8: EXACERBATION AND FLARE OF PSORIASIS .....	58
CHAPTER 9: MANAGEMENT OF FACIAL, FLEXURAL, AND GENITAL PSORIASIS .....	62
CHAPTER 10: MANAGEMENT OF NAIL PSORIASIS.....	65
CHAPTER 11: MANAGEMENT OF SCALP PSORIASIS.....	71
CHAPTER 12: MANAGEMENT OF PALMOPLANTAR PSORIASIS .....	75
CHAPTER 13: SOCIAL AND PSYCHOLOGICAL ASPECTS OF PSORIASIS .....	79
CHAPTER 14: COMORBIDITIES .....	84
CHAPTER 15: THE FUTURE OF PSORIASIS CARE .....	89
APPENDIX: TRADE NAME/GENERIC NAME TRANSLATOR .....	94

## NOTES TO READERS

**Disclaimer:** These Guidelines are intended to assist physicians in clinical decision making. As always, physicians should use their best clinical judgment when determining whether and how to apply treatment recommendations. Clinical decisions must take into account the patient's individual circumstances and any newer evidence that may come to light regarding treatments for plaque psoriasis. This document is not intended to substitute for or supersede the guidance found in the relevant Canadian product monographs or other official information available for the therapeutics discussed. Every reasonable effort has been made to ensure the accuracy of this document; any errors will be corrected in the next edition.

**Drug names:** Generic names have been used throughout this document. A trade name/generic name translator has been provided as an appendix.

**Website:** These Guidelines are also available online at <http://www.dermatology.ca/psoriasisguidelines>

**Citation:** Canadian Psoriasis Guidelines Committee. *Canadian Guidelines for the Management of Plaque Psoriasis*, June 2009. <http://www.dermatology.ca/psoriasisguidelines>

**Address academic correspondence to:** Kim Alexander Papp MD PhD FRCPC, Probity Medical Research, 135 Union Street East, Waterloo, Ontario, Canada N2J 1C4. Email: [kapapp@probitymedical.com](mailto:kapapp@probitymedical.com)

## COMMITTEE, REVIEWERS, AND EDITORIAL SUPPORT

### GUIDELINES COMMITTEE

#### STEERING COMMITTEE

**Kim Alexander Papp** MD PhD FRCPC (Chair)  
K. Papp Clinical Research, Waterloo, Ontario;  
Probity Medical Research, Waterloo, Ontario

**Wayne Gulliver** MD FRCPC  
Newlab Clinical Research Inc., St John's,  
Newfoundland; Memorial University,  
St John's, Newfoundland

**Charles W. Lynde** MD FRCPC  
Lynderm Research Inc., Markham, Ontario;  
University of Toronto, Toronto, Ontario

**Yves Poulin** MD FRCPC  
Centre Dermatologique du Québec  
Métropolitain, Québec, Québec;  
Université Laval, Québec, Québec

#### EXPERT PANEL

**Stewart P. Adams** MD FRCPC  
Adams Dermatology, Calgary, Alberta

**Lorne Albrecht** MD FRCPC  
Guildford Dermatology, Surrey, British Columbia

**Benjamin Barankin** MD FRCPC  
The Dermatology Centre, Toronto, Ontario

**Kirk Barber** MD FRCPC  
Kirk Barber Research, Calgary, Alberta

**Marc Bourcier** MD FRCPC  
Duronel C.P. Inc., Moncton, New Brunswick;  
affiliated with the Université de Sherbrooke,  
Sherbrooke, Québec

**Wayne Carey** MD FRCPC  
Siena Medical Research Corporation,  
Westmount, Québec

**Lyn C. Guenther** MD FRCPC  
The Guenther Dermatology Research Centre,  
London, Ontario; The University of Western  
Ontario, London, Ontario

**Vincent C. Ho** MD FRCPC  
University of British Columbia, Vancouver,  
British Columbia

**Neil H. Shear MD FRCPC**  
Sunnybrook Health Sciences Centre,  
Toronto, Ontario; University of Toronto,  
Toronto, Ontario

**John Toole MD FRCPC**  
Dermadvances Research, Winnipeg, Manitoba;  
University of Manitoba, Winnipeg, Manitoba

**Ronald Vender MD FRCPC**  
Dermatrics Research, Hamilton, Ontario;  
McMaster University, Hamilton, Ontario

**Norman Wasel MD FRCPC**  
Stratica Medical, Edmonton, Alberta;  
University of Alberta, Edmonton, Alberta

## EDITORIAL SUPPORT

**SCRIPT**, Toronto, Ontario:

**Helen Leask PhD**, Managing Editor, medical writer

**John Ashkenas PhD**, Senior Editor, medical writer

**Shereen Joseph BSc**, medical writer

**Meenakshi Kashyap PhD**, medical writer

**Oren Traub MD PhD**, medical writer

**Sarah von Riedemann MSc**, medical writer

## COMMUNITY REVIEWERS

*The Guidelines Committee would like to thank all Community Reviewers for their assistance. Community Reviewers may have reviewed all chapters or only those in which they felt they had expertise or an interest.*

**Bruce F. Bebo Jr PhD**  
National Psoriasis Foundation, Portland, Oregon, USA

**Vivian Bykerk MD FRCPC**  
University of Toronto, Toronto, Ontario, Canada

**Charles N. Ellis MD**  
University of Michigan Medical School, Ann Arbor,  
Michigan, USA

**Steven R. Feldman MD PhD**  
Wake Forest University School of Medicine,  
Winston-Salem, North Carolina, USA

**Nigel Flook MD CCFP FCFP**  
University of Alberta, Edmonton, Alberta, Canada

**Dafna D. Gladman MD FRCPC**  
University of Toronto, Toronto, Ontario, Canada

**Richard M. Haber MD FRCPC**  
University of Calgary, Calgary, Alberta, Canada

**Herag Hamboyan MD CCFP**  
Oakville, Ontario, Canada

**Dana W. Hanson MD**  
Canadian Medical Association, Ottawa, Ontario,  
Canada

**Gerald G. Krueger MD**  
University of Utah, Salt Lake City, Utah, USA

**Gilles Lauzon MD PhD**  
Canmore General Hospital, Canmore,  
Alberta, Canada

**Mark Lebwohl MD**  
Mount Sinai School of Medicine, New York,  
New York, USA

**Alan Menter MD**  
Baylor Research Institute, Dallas, Texas, USA

**Richard K. Scher MD**  
University of North Carolina, Chapel Hill,  
North Carolina, USA

**Peter C. M. van de Kerkhof MD**  
Radboud University Nijmegen Medical Centre,  
Nijmegen, the Netherlands

**Franklynne K. Vincent MD FRCPC**  
St. Joseph's Health Centre, Toronto, Ontario, Canada

**Richard A. Ward MD CCFP FCFP**  
University of Calgary, Calgary, Alberta, Canada

## ACKNOWLEDGMENTS

Financial assistance for the development of these Guidelines was generously provided by the following sponsors (in alphabetical order): Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Isotechnika Inc.; Janssen-Ortho Inc.; LEO Pharma Inc.; Schering-Plough Canada Inc.; and Wyeth.

Sponsors were permitted to submit unpublished manuscripts for consideration by the Guidelines Committee, with the proviso that the article had to be accepted for peer-reviewed publication by a designated cut-off date. Sponsors were not involved in any other aspect of the Guidelines' development, nor were they informed of the make-up of the Guidelines Committee.

## DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The following committee members report that, during the 5 years prior to the Guidelines' development, they had a financial interest in the following companies:

**Stewart P. Adams:** *Consultancy\**: Amgen Canada Inc.; LEO Pharma Inc.; Novartis Pharmaceuticals Canada Inc.; and Wyeth. *Contract research*: Abbott Laboratories, Limited; Astion Pharma; Biogen Idec Canada Inc.; Bristol-Myers Squibb Canada Co.; Centocor Ortho Biotech Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Janssen-Ortho Inc.; and Novartis Pharmaceuticals Canada Inc.

**Lorne Albrecht:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; EMD Serono Canada Inc.; Janssen-Ortho Inc.; LEO Pharma Inc.; and Schering-Plough Canada Inc. *Contract research*: Abbott Laboratories, Limited; Alza Pharmaceutical; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Biogen Idec Canada Inc.; Bristol-Meyers Squibb Canada Co.; Centocor Ortho Biotech Inc.; Celgene Corporation; Isotechnika Inc.; Pfizer Canada Inc.; and Schering-Plough Canada Inc.

**Benjamin Barankin:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Graceway Pharmaceuticals; Janssen-Ortho Inc.; LEO Pharma Inc.; Novartis Pharmaceuticals Canada Inc.; sanofi-aventis; Schering-Plough Canada Inc.; Stiefel Laboratories, Inc.; and Wyeth.

**Kirk Barber:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Galderma Canada Inc.; Johnson & Johnson Services, Inc.; LEO Pharma Inc.; Schering-Plough Canada Inc.; and Wyeth. *Contract research*: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Galderma Canada Inc.; LEO Pharma Inc.; Schering-Plough Canada Inc.; and Wyeth.

**Marc Bourcier:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Barrier Therapeutics, Inc.; EMD Serono Canada Inc.; Graceway Pharmaceuticals; Janssen-Ortho Inc.; LEO Pharma Inc.; Merck Frosst Canada Ltd.; Novartis Pharmaceuticals Canada Inc.; Pfizer Canada Inc.; Schering-Plough Canada Inc.; Stiefel Laboratories, Inc.; and Wyeth. *Contract research*: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Barrier Therapeutics, Inc.; EMD Serono Canada Inc.; LEO Pharma Inc.; Janssen-Ortho Inc.; Novartis Pharmaceuticals Canada Inc.; Pfizer Canada Inc.; Schering-Plough Canada Inc.; and Wyeth.

**Wayne Carey:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Centocor Ortho Biotech Inc.; Isotechnika Inc.; and Schering-Plough Canada Inc. *Contract research*: Abbott Laboratories, Limited; Amgen Canada Inc.; Centocor Ortho Biotech Inc.; Isotechnika Inc.; and Schering-Plough Canada Inc.

**Lyn C. Guenther:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Galderma Canada Inc.; LEO Pharma Inc.; Ortho Biotech; Schering-Plough Canada Inc.; and Wyeth. *Investigator-initiated studies*: Astellas Pharma Canada, Inc. *Contract research*: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Celgene Corporation; Centocor Ortho Biotech Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Isotechnika Inc.;

Janssen-Ortho Inc.; LEO Pharma Inc.; Novartis Pharmaceuticals Canada Inc.; Schering-Plough Canada Inc.; and Stiefel Laboratories, Inc.

**Wayne Gulliver:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Biogen Idec Canada Inc.; Centocor Ortho Biotech Inc.; Galderma Canada Inc.; Isotechnika Inc.; Janssen-Ortho Inc.; Merck Serono S.A.; Novartis Pharmaceuticals Canada Inc.; Redox Pharmaceutical Corporation; and Schering-Plough Canada Inc. *Contract research*: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Barrier Therapeutics, Inc.; Basilea Pharmaceutica Ltd.; Biogen Idec Canada Inc.; Centocor Ortho Biotech Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; GlaxoSmithKline Inc.; Impax Laboratories, Inc.; Isotechnika Inc.; Janssen-Ortho Inc.; Johnson & Johnson Services, Inc.; LEO Pharma Inc.; Merck Serono S.A.; Novartis Pharmaceuticals Canada Inc.; Pfizer Canada Inc.; Redox Pharmaceutical Corporation; Schering-Plough Canada Inc.; and Stiefel Laboratories, Inc.

**Vincent C. Ho:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Basilea Pharmaceutica Ltd.; Janssen-Ortho Inc.; Schering-Plough Canada Inc.; and Wyeth. *Contract research*: Abbott Laboratories, Limited; Isotechnika Inc.; Janssen-Ortho Inc.; Pfizer Canada Inc.; and Schering-Plough Canada Inc.

**Charles W. Lynde:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Celgene Corporation; Centocor Ortho Biotech Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Isotechnika Inc.; Johnson & Johnson Services, Inc.; LEO Pharma Inc.; Merck Serono S.A.; Ortho Biotech; Schering-Plough Canada Inc.; and Wyeth. *Investigator-initiated studies*: Astellas Pharma Canada, Inc.; Merck Serono S.A.; and Schering-Plough Canada Inc. *Contract research*: Abbott Laboratories, Limited; Astellas Pharma Canada, Inc.; Celgene Corporation; Centocor Ortho Biotech Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Isotechnika Inc.; LEO Pharma Inc.; Merck Serono S.A.; and Schering-Plough Canada Inc.

**Kim Alexander Papp:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Centocor Ortho Biotech Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Isotechnika Inc.; Janssen-Ortho Inc.; Johnson & Johnson Services, Inc.; LEO Pharma Inc.; Merck Serono S.A.; and Schering-Plough Canada Inc. *Investigator-initiated studies*: Merck Serono S.A. *Contract research*: Abbott Laboratories, Limited; Amgen Canada Inc.; Centocor Ortho Biotech Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Isotechnika Inc.; LEO Pharma Inc.; Merck Serono S.A.; and Schering-Plough Canada Inc. *Company stocks*: Isotechnika Inc.

**Yves Poulin:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Galderma Canada Inc.; Isotechnika Inc.; LEO Pharma Inc.; Merck Frosst Canada Ltd.; Schering-Plough Canada Inc.; and Wyeth. *Contract research*: Abbott Laboratories, Limited; Advitech Inc.; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Biogen Idec Canada Inc.; Boehringer Ingelheim (Canada) Ltd.; Bristol-Myers Squibb Canada Co.; Celgene Corporation; Centocor Ortho Biotech Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Isotechnika Inc.; La Roche-Posay Laboratoire Pharmaceutique; LEO Pharma Inc.; Novartis Pharmaceuticals Canada Inc.; Pfizer Canada Inc.; Pharmascience Inc.; Schering-Plough Canada Inc.; and Wyeth.

**Neil H. Shear:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Janssen-Ortho Inc.; LEO Pharma Inc.; Schering-Plough Canada Inc.; and Wyeth.

**John Toole:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; Biogen Idec Canada Inc.; EMD Serono Canada Inc.; LEO Pharma Inc.; and Schering-Plough Canada Inc. *Contract research*: Abbott Laboratories, Limited; Amgen Canada Inc.; and Astellas Pharma Canada, Inc.

**Ronald Vender:** *Consultancy\**: Abbott Laboratories, Limited; Amgen Canada Inc.; Astellas Pharma Canada, Inc.; EMD Serono Canada Inc.; Galderma Canada Inc.; Isotechnika Inc.; Janssen-Ortho Inc.; LEO Pharma Inc.; and Schering-Plough Canada Inc.

*Investigator-initiated studies:* Amgen Canada Inc.  
*Contract research:* Abbott Laboratories, Limited;  
Amgen Canada Inc.; Astellas Pharma Canada, Inc.;  
Barrier Therapeutics, Inc.; Biogen Idec Canada Inc.;  
Celgene Corporation; Centocor Ortho Biotech Inc.;  
EMD Serono Canada Inc.; Galderma Canada Inc.;  
Isotechnika Inc.; LEO Pharma Inc.; Janssen-Ortho Inc.;  
Novartis Pharmaceuticals Canada Inc.; and Pfizer  
Canada Inc.

**Norman Wasel:** *Consultancy\**: Abbott Laboratories,  
Limited; Amgen Canada Inc.; Astellas Pharma  
Canada, Inc.; Biogen Idec Canada Inc.; EMD  
Serono Canada Inc.; Isotechnika Inc.; Janssen-Ortho  
Inc.; Ortho Biotech; Schering-Plough Canada Inc.;  
and Wyeth. *Contract research:* Abbott Laboratories,  
Limited; Amgen Canada Inc.; Astellas Pharma  
Canada, Inc.; Biogen Idec Canada Inc.; Centocor  
Ortho Biotech Inc.; EMD Serono Canada Inc.;  
Isotechnika Inc.; and Wyeth.

\*Consultancy includes advisory boards, editorial  
advice, podium presentations, and travel grants.

During the 5 years prior to the Guidelines' development, the editorial team at SCRIPT had ongoing business relationships with the following companies (in alphabetical order): Amgen Canada Inc.; Astellas Pharma Canada, Inc.; EMD Serono Canada Inc.; and sanofi-aventis Canada Inc.



## LIST OF ABBREVIATIONS

### *Canadian Guidelines for the Management of Plaque Psoriasis*

AGREE = Appraisal of Guidelines for Research & Evaluation

AIDS = acquired immune deficiency syndrome

AZT = zidovudine

BIW = biweekly

BSA = body surface area

CDA = Canadian Dermatology Association

CVD = cardiovascular disease

DCs = dendritic cells

DISH = diffuse idiopathic skeletal hyperostosis

DLQI = Dermatology Life Quality Index

DQOLS = Dermatology Quality-of-Life Scales

FAEs = fumaric acid esters

FFG = facial, flexural, and genital

FDA = US Federal Drug Administration

GSS = Global Severity Score

HAART = highly active antiretroviral treatment

HADS = Hospital Anxiety and Depression Scale

HBV = hepatitis B virus

HCV = hepatitis C virus

HIV = human immunodeficiency virus

HRQL = Health-Related Quality of Life

IL = interleukin

LCs = Langerhans cells

LoE = level of evidence

MI = myocardial infarction

NAPSI = Nail Psoriasis Severity Index

NAS = Nail Area Severity

NB = narrowband

NSAIDs = nonsteroidal anti-inflammatory drugs

OLS = Overall Lesion Severity

PASI = Psoriasis Area and Severity Index

PDI = Psoriasis Disability Index

PGA = Physician's Global Assessment

PIIINP = procollagen III aminopeptide

PNSS = Psoriasis Nail Severity Score

PPP = palmoplantar pustulosis

PQLQ = Psoriasis Quality of Life Questionnaire

PsA = psoriatic arthritis

PSA Scale = Psoriatic Arthritis Scale

PSSI = Psoriasis Scalp Severity Index

PUVA = UVA with psoralen

QoL = quality of life

RA = rheumatoid arthritis

RAMBAs = retinoic acid metabolism-blocking agents

RCTs = randomized controlled trials

RePUVA = retinoid + PUVA

ReUVB = retinoid + UVB

SCC = squamous cell carcinoma

SF-36 = Short Form Health Survey

SIGN = Scottish Intercollegiate Guidelines Network

TB = tuberculosis

TcIs = topical calcineurin inhibitors

TNF = tumour necrosis factor

TSS = Total Severity Score

UV = ultraviolet

VAS = Visual Analogue Scale



# CHAPTER 1: INTRODUCTION

## Canadian Guidelines for the Management of Plaque Psoriasis

Plaque psoriasis is a chronic inflammatory skin disease that requires ongoing, lifelong care. Despite a widely held misconception that it is somehow less serious than other, non-dermatological illnesses, plaque psoriasis imposes a burden of disease that extends far beyond the physical dermatological symptoms; its impact on physical and mental function is similar to that of cancer, arthritis, hypertension, heart disease, diabetes, and depression.<sup>1</sup>

Plaques are often highly visible and may lead to stigmatization, high levels of stress, and poor self-esteem.<sup>2-7</sup> Psoriasis can therefore have a pervasive effect on social functioning, interpersonal relationships, and success at school or work.<sup>8,9</sup> Not surprisingly, people with plaque psoriasis have higher rates of depression<sup>10</sup> and suicidal ideation.<sup>11,12</sup>

Psoriasis patients are also at risk of a wide variety of serious comorbidities that add to their burden, complicate management, and increase the risk of early death. Cardiovascular disease (CVD) and metabolic syndrome are more common in psoriasis patients (see Chapter 14: Comorbidities). Psoriasis per se is a risk factor for CVD, conferring an approximately threefold increased relative risk of myocardial infarction (MI) in younger psoriasis patients.<sup>13</sup> Severe psoriasis is also associated with an increased risk of mortality, leading to a 3.5- and 4.4-year reduction in life expectancy for males and females, respectively, relative to individuals without psoriasis.<sup>14</sup>

Individuals with plaque psoriasis are also at increased risk of inflammatory diseases occurring at sites remote from the skin (see Chapter 14: Comorbidities). The most common and best known of these is a seronegative, erosive arthritis. Psoriatic arthritis, now considered a distinct syndrome, occurs in approximately one-third of psoriasis patients, with the onset of rheumatic symptoms commonly lagging behind skin symptoms by a decade or more. Autoimmune disorders of the gut,

manifesting as inflammatory bowel disease (Crohn's disease or ulcerative colitis),<sup>15</sup> are also associated with psoriasis.

Plaque psoriasis is frequently undertreated: recent studies in the US found that as many as 80% of patients had not received treatment in the previous year,<sup>16</sup> and 40% were receiving no treatment, even for the most severe disease.<sup>17</sup> The situation in Canada is unclear, since no similar data have yet been published; however, it is reasonable to assume that some degree of undertreatment is universal in this complex disease.

### KEY POINT

*However effective a therapy, it won't work if the patient doesn't use it. The central theme of these Guidelines is that physicians should not only choose therapies that work, but those that the patient will work with.*

Given the prevalence of plaque psoriasis, all physicians in Canada and elsewhere are likely to confront this burdensome chronic disease in the course of routine care. With new therapeutics introduced into the market at a rapid pace in recent years, dermatologists and other practitioners may be ill-equipped to choose among the various treatment options. The following chapters are therefore designed to offer solid, evidence-based recommendations, in the briefest possible form, to both specialist and non-specialist physicians.

### Presentation of psoriasis

The term 'psoriasis' encompasses a set of chronic inflammatory dermatoses, of which plaque psoriasis (psoriasis vulgaris) is the most common. Plaque psoriasis is distinguished by the presence of red, erythematous plaques, usually covered with silver, flaking scales. These plaques are frequently itchy or

painful; depending on their extent and location, they may also be physically debilitating or socially isolating.

Plaque psoriasis can be distinguished by its morphology from other forms, such as pustular, erythrodermic, and guttate psoriasis, although these different forms can sometimes be observed in the same individual. Thus, a history of guttate psoriasis, precipitated by streptococcal pharyngitis in a child or adolescent, is associated with increased risk of plaque psoriasis later in life.<sup>18</sup> Likewise, a person with chronic plaque psoriasis may experience an acute flare of pustular psoriasis. Pustular psoriasis affecting the palms and soles, which may be a genetically distinct condition,<sup>19,20</sup> can present either independently or comorbidly with plaque psoriasis (see Chapter 12: Management of palmoplantar psoriasis).<sup>21</sup>

### The central role of T cells in psoriasis pathophysiology

Histologically, psoriatic plaques are distinguished by three hallmark features: extravagant growth of poorly differentiated keratinocytes; the presence of prominent, dilated dermal blood vessels; and an inflammatory infiltrate, featuring T cells of several subtypes, along with neutrophils and macrophages.

T cell–driven inflammation is responsible for the keratinocyte growth and the angiogenesis seen in the psoriatic plaque, as has become clear in recent years. All of the newly introduced therapies for psoriasis were therefore devised to target T cells or their inflammatory mediators, including cytokines, receptors, and ligands. Indeed, with the exception of adjunctive moisturizers and exfoliants, most of the classic topical, systemic, and phototherapies also act at least in large part by quelling this same immune response.

T cells secreting the so-called type 1 cytokines (including tumour necrosis factor [TNF], as well as interferon- $\gamma$  and interleukin- [IL-] 2) are active in the dermis and epidermis of the psoriatic plaque. Memory type 1 T cells, including helper and cytolytic ( $T_h1$  and  $T_c1$ ) subtypes, are present even in the non-inflamed skin of individuals with established psoriasis. In the dermis underlying the psoriatic plaque, T cells aggregate with antigen-presenting cells such as dendritic cells, interactions that would ordinarily be expected to be restricted to peripheral lymph nodes.<sup>22</sup> It has been proposed that these

interactions contribute to the persistence of the psoriatic plaque.<sup>23,24</sup>

In addition to  $T_h1$  cells, a more recently identified T cell subset, the IL-17-secreting T helper cells ( $T_h17$ ), appears to play a central role in psoriasis. When stimulated by the cytokine IL-23, these  $T_h17$  cells express TNF and various other factors that can stimulate keratinocyte growth.<sup>25,26</sup> Rapidly proliferating keratinocytes in a plaque also release cytokines, thus recruiting additional immunocytes (T cells, neutrophils, and natural killer cells<sup>27</sup>) and setting up a vicious cycle that can sustain or extend local inflammation.<sup>26</sup>

The low activity of regulatory T cells ( $T_{reg}$ ) in the psoriatic plaque may be another key abnormality that permits the inflammatory state to occur.  $T_{reg}$  deficits are also seen in such disorders as type 1 diabetes and multiple sclerosis, conditions that are marked by chronic, organ-specific inflammation.<sup>28</sup> Langerhans cells (LCs), a class of ‘professional’ antigen-presenting cells found in the epidermis, are likewise proposed to help dampen cutaneous inflammation. Within the psoriatic plaque, the LC population is strikingly low relative to neighbouring symptom-free skin. Effective antipsoriatic therapy with a TNF inhibitor rapidly restores this population.<sup>29</sup> The proposed anti-inflammatory function of LCs is in contrast to the action of other antigen-presenting cell populations such as macrophages, myeloid dendritic cells (DCs), and plasmacytoid DCs. These cell types are thought to help drive psoriatic inflammation by producing IL-23 and thereby activating  $T_h17$  cells. Depletion of macrophages and DCs from the psoriatic plaque seems to be an early step in the successful clearance of a psoriatic plaque by TNF inhibitors.<sup>30</sup>

### Genetics

Plaque psoriasis, like other common conditions, is a disease with substantial heritability that fails to conform to a simple, single-gene Mendelian model. At least 20 genetic loci have been proposed to harbour psoriasis susceptibility (*PSORS*) genes, i.e., genes that may interact with environmental factors and with other features of a person’s genetic background to increase the likelihood of psoriasis development. Several of these loci, notably *PSORS1*, have been identified repeatedly in independent populations.<sup>31</sup>

After many years of effort, technological advances in gene mapping have now begun to yield the relevant genes, including the gene encoding the major histocompatibility protein HLA-C (mapping to the *PSORS1* locus), where one specific allele, HLA-Cw\*0602, has been tied to psoriasis risk in multiple studies in Asians and Caucasians.<sup>32,33</sup> Sequence variations affecting expression of the gene for TNF are implicated specifically in plaque psoriasis and psoriatic arthritis, with no apparent effect on the risk of pustular psoriasis.<sup>19,20</sup> Other recent developments include the identification of mutations in subunits of IL-23 and the IL-23 receptor, associated with psoriasis and Crohn's disease,<sup>34</sup> and the finding that *IL15* represents the psoriasis gene at the *PSORS9* locus.<sup>35</sup> Probable psoriasis genes at other *PSORS* loci have also been identified.<sup>31</sup>

Genetic analysis has helped clarify some of the variability that has long been noted in the natural history of psoriasis. For instance, individuals carrying the risk allele HLA-Cw\*0602 present with plaque psoriasis earlier than non-carriers, and homozygotes (carrying two copies of this allele) present at a still earlier age, although with no greater severity than is seen among HLA-Cw\*0602 heterozygotes.<sup>36</sup> Female carriers of this HLA-C allele typically experience substantial relief from symptoms during pregnancy, whereas pregnancy-associated remission is reported to be rare in non-carriers.<sup>37</sup> Conversely, nail dystrophy<sup>38</sup> and pustular forms of psoriasis<sup>39</sup> have been found preferentially among non-carriers.

Despite the recent successes and the promise of new targeted therapies based on the growing molecular understanding of the disease, genetic analysis has yet to alter the clinical landscape of psoriasis. Treatment decisions must still be made empirically, without regard to the patient's genotype.

### Psoriasis epidemiology and natural history

Reported prevalence estimates for psoriasis vary substantially, probably reflecting methodological differences as well as genuine genetic, demographic, and environmental differences between populations. Prevalence differs greatly across racial groups: West Africans are among those with a dramatically lower prevalence of psoriasis than Europeans, consistent with an approximately twofold difference between African and Caucasian Americans (1.3% versus

2.5%).<sup>40</sup> Prevalence among East Asians is under 1%.<sup>41</sup>

Large-scale population studies in the United Kingdom<sup>42</sup> and the United States<sup>2</sup> found that 1.5% and 2.6% of individuals, respectively, had been diagnosed with psoriasis. As shown in **Table 1**, application of age-specific psoriasis prevalence rates from the United Kingdom to the Canadian population suggests that more than 500 000 Canadians (approximately 1.7% of the population) have psoriasis. This affected population includes approximately 40 000 older individuals ( $\geq 70$  years) and 20 000 children ( $\leq 10$  years). Geriatric and pediatric psoriasis pose their own treatment challenges, discussed in Chapter 7 (Special populations and circumstances).

The events leading to initial presentation of psoriasis, or to a worsening of existing symptoms, are not well understood. Physical trauma to the skin, streptococcal infection,<sup>36,43</sup> exposure to various drugs (reviewed in Abel et al.<sup>44</sup>), and cigarette smoking<sup>45</sup> are among the commonly cited environmental factors that appear to aggravate the condition (see Chapter 8: Exacerbation and flare of psoriasis). Conversely, severity typically abates during summer months, consistent with long-standing evidence that natural or artificial ultraviolet (UV) exposure can be therapeutic.<sup>46</sup>

In general, spontaneous, durable remission is rare, and patients and physicians should expect psoriasis to persist throughout life, with unpredictable periods of improvement and exacerbation.

### Priorities for care in these Guidelines

The development of evidence-based recommendations for treating plaque psoriasis, as it presents in different forms and locations, presents a singular challenge. Standard treatments with long histories in dermatological practice are commonly supported by a relatively slender evidence base, compared to newer agents that have passed through phase 3 clinical trials. Head-to-head comparisons of therapies are rare in this field, making it difficult to judge the relative efficacy of different pharmacologic or phototherapeutic approaches. In preparing these Guidelines, we have therefore emphasized the broad range of therapeutic options that the physician should consider, deferring as much as possible to the patient's preferences and priorities.

### Therapies that work versus therapies the patient will work with

The pragmatic value of such a patient-centred approach is clear from the recent literature on treatment adherence. There is considerable evidence from clinical trials that dermatology patients commonly undertreat themselves, while inflating their reported use of the assigned treatment.<sup>47,48</sup> In general practice, non-adherence may be still more common, with direct deleterious effects on treatment efficacy.<sup>48</sup> This view is consistent with the finding that adherence spikes immediately prior to an office visit and the observation that the efficacy reported in phase 3 trials is frequently greater than that found in post-marketing studies (see Ali et al.<sup>49</sup> and references therein). Conversely, controlled treatment application in an inpatient setting, or changes in drug formulation that make patients more willing to use the treatment as instructed, can lead to a sudden dramatic increase in efficacy.

Physicians caring for patients with plaque psoriasis therefore face two tasks. First, they must identify therapies that are effective, safe, and suited to the symptoms that the patient presents. Second, and no less important, they must choose from among the appropriate options the one that the patient is most likely to use consistently, over the long term, to achieve and maintain control of his or her condition.

These Guidelines offer recommendations, based on a rigorous evaluation of the available evidence, to guide the physician in the first task. The second task — determining an optimal therapy in a given case — remains the province of the individual physician, taking into account the patient's habits and priorities and any practical considerations that may limit the availability of specific therapies.

**Table 1. Estimated prevalence of psoriasis in Canada**

Age group	Canadian population*	Estimated psoriasis prevalence by age group (per 10 000) <sup>†</sup>	Estimated number of Canadians with psoriasis by age group
0 to 9	3 499 915	55.02	19 257
10 to 19	4 220 415	137.37	57 976
20 to 29	4 065 965	151.04	61 412
30 to 39	4 228 500	178.01	75 272
40 to 49	5 231 055	203.43	106 415
50 to 59	4 441 920	222.78	98 957
60 to 69	2 824 445	225.95	63 818
70 to 79	1 933 360	161.39	31 202
80 to 89	989 390	88.44	8 750
Over 90	177 925	47.33	842
<b>Total</b>	<b>31 612 895</b>		<b>523 902</b>

\*Data from Canadian 2006 Census.<sup>50</sup>

<sup>†</sup>Based on published age-specific prevalence rates in the United Kingdom.<sup>42</sup>



## References

- Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 1999;41:401–7.
- Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. *Dermatol Clin* 1996;14:485–96.
- Krueger G, Koo J, Lebwohl M, et al. The impact of psoriasis on quality of life: Results of a 1998 National Psoriasis Foundation Patient-Membership Survey. *Arch Dermatol* 2001;137:280–4.
- Wahl AK, Gjengedal E, Hanestad BR. The bodily suffering of living with severe psoriasis: in-depth interviews with 22 hospitalized patients with psoriasis. *Qual Health Res* 2002;12:250–61.
- Ginsburg IH, Link BG. Feelings of stigmatization in patients with psoriasis. *J Am Acad Dermatol* 1989;20:53–63.
- Vardy D, Besser A, Amir M, et al. Experiences of stigmatization play a role in mediating the impact of disease severity on quality of life in psoriasis patients. *Br J Dermatol* 2002;147:736–42.
- Schmid-Ott G, Kuensebeck HW, Jaeger B, et al. Validity study for the stigmatization experience in atopic dermatitis and psoriatic patients. *Acta Derm Venereol* 1999;79:443–7.
- Eghlileb AM, Davies EEG, Finlay AY. Psoriasis has a major secondary impact on the lives of family members and partners. *Br J Dermatol* 2007;156:1245–50.
- Pearce DJ, Singh S, Balkrishnan R, et al. The negative impact of psoriasis on the workplace. *J Dermatolog Treat* 2006;17:24–8.
- Gupta MA, Gupta AK, Watteel GN. Perceived deprivation of social touch in psoriasis is associated with greater psychologic morbidity: an index of the stigma experience in dermatologic disorders. *Cutis* 1998;61:339–42.
- Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* 1998;139:846–50.
- Picardi A, Mazzotti E, Pasquini P. Prevalence and correlates of suicidal ideation among patients with skin disease. *J Am Acad Dermatol* 2006;54:420–6.
- Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006;296:1735–41.
- Gelfand JM, Troxel AB, Lewis JD, et al. The risk of mortality in patients with psoriasis: results from a population-based study. *Arch Dermatol* 2007;143:1493–9.
- Mrowietz U, Elder JT, Barker J. The importance of disease associations and concomitant therapy for the long-term management of psoriasis patients. *Arch Dermatol Research* 2006;298:309–19.
- Feldman SR, Fleischer AB, Jr, Cooper JZ. New topical treatments change the pattern of treatment of psoriasis: dermatologists remain the primary providers of this care. *Int J Dermatol* 2000;39:41–4.
- Horn EJ, Fox KM, Patel V, et al. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey. *J Am Acad Dermatol* 2007;57:957–62.
- Martin BA, Chalmers RJ, Telfer NR. How great is the risk of further psoriasis following a single episode of acute guttate psoriasis? *Arch Dermatol* 1996;132:717–8.
- Asumalahti K, Ameen M, Suomela S, et al. Genetic analysis of *PSORS1* distinguishes guttate psoriasis and palmoplantar pustulosis. *J Invest Dermatol* 2003;120:627–32.
- Mossner R, Kingo K, Kleensang A, et al. Association of TNF -238 and -308 promoter polymorphisms with psoriasis vulgaris and psoriatic arthritis but not with pustulosis palmoplantaris. *J Invest Dermatol* 2005;124:282–4.
- Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007;370:263–71.
- Gaspari AA. Innate and adaptive immunity and the pathophysiology of psoriasis. *J Am Acad Dermatol* 2006;54:S67–S80.
- Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. *Nature* 2007;445:866–73.
- Krueger JG. The immunologic basis for the treatment of psoriasis with new biologic agents. *J Am Acad Dermatol* 2002;46:1–23; quiz 23–26.
- Chan JR, Blumenschein W, Murphy E, et al. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *J Exp Med* 2006;203:2577–87.
- Nickoloff BJ. Cracking the cytokine code in psoriasis. *Nat Med* 2007;13:242–4.
- Ottaviani C, Nasorri F, Bedini C, et al. CD56brightCD16(-) NK cells accumulate in psoriatic skin in response to CXCL10 and CCL5 and exacerbate skin inflammation. *Eur J Immunol* 2006;36:118–28.
- Sugiyama H, Gyulai R, Toichi E, et al. Dysfunctional blood and target tissue CD4+CD25high regulatory T cells in psoriasis: mechanism underlying unrestrained pathogenic effector T cell proliferation. *J Immunol* 2005;174:164–73.
- Gordon KB, Bonish BK, Patel T, et al. The tumour necrosis factor-alpha inhibitor adalimumab rapidly reverses the decrease in epidermal Langerhans cell density in psoriatic plaques. *Br J Dermatol* 2005;153:945–53.
- Marble DJ, Gordon KB, Nickoloff BJ. Targeting TNFalpha rapidly reduces density of dendritic cells and macrophages in psoriatic plaques with restoration of epidermal keratinocyte differentiation. *J Dermatol Sci* 2007;48:87–101.
- Liu Y, Krueger JG, Bowcock AM. Psoriasis: Genetic associations and immune system changes. *Genes & Immunity* 2007;8:1–12.
- Elder JT. *PSORS1*: Linking genetics and immunology. *J Invest Dermatol* 2006;126:1205–6.
- Nair RP, Stuart PE, Nistor I, et al. Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. *Am J Hum Genet* 2006;78:827–51.
- Cargill M, Schrodi SJ, Chang M, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *Am J Hum Genet* 2007;80:273–90.
- Zhang XJ, Yan KL, Wang ZM, et al. Polymorphisms in interleukin-15 gene on chromosome 4q31.2 are associated with psoriasis vulgaris in Chinese population. *J Invest Dermatol* 2007;127:2544–51.
- Gudjonsson JE, Thorarinnsson AM, Sigurgeirsson B, et al. Streptococcal throat infections and exacerbation of chronic plaque psoriasis: a prospective study. *Br J Dermatol* 2003;149:530–4.
- Gudjonsson JE, Karason A, Runarsdottir EH, et al. Distinct clinical differences between HLA-Cw\*0602 positive and negative psoriasis patients — an analysis of 1019 HLA-C- and HLA-B-typed patients. *J Invest Dermatol* 2006;126:740–5.
- Gudjonsson JE, Karason A, Antonsson AA, et al. HLA-Cw6-positive and HLA-Cw6-negative patients with psoriasis vulgaris have distinct clinical features. *J Invest Dermatol* 2002;118:362–5.
- Fan X, Yang S, Sun LD, Wang ZM, et al. Comparison of clinical features of HLA-Cw\*0602-positive and -negative psoriasis patients in a Han Chinese population. *Acta Derm Venereol* 2007;87:335–40.
- Gelfand JM, Stern RS, Nijsten T, et al. The prevalence of psoriasis in African Americans: results from a population-based study. *J Am Acad Dermatol* 2005;52:23–6.
- Yip SY. The prevalence of psoriasis in the Mongoloid race. *J Am Acad Dermatol* 1984;10:965–8.
- Gelfand JM, Weinstein R, Porter SB, et al. Prevalence and treatment of psoriasis in the United Kingdom: A population-based study. *Arch Dermatol* 2005;141:1537–41.
- El-Rachkidy RG, Hales JM, Freestone PP, et al. Increased blood levels of IgG reactive with secreted *Streptococcus pyogenes* proteins in chronic plaque psoriasis. *J Invest Dermatol* 2007;127:1337–42.
- Abel EA, DiCicco LM, Orenberg EK, et al. Drugs in exacerbation of psoriasis. *J Am Acad Dermatol* 1986;15:1007–22.
- Fortes C, Mastroeni S, Leffondre K, et al. Relationship between smoking and the clinical severity of psoriasis. *Arch Dermatol* 2005;141:1580–4.
- Hancox JG, Sheridan SC, Feldman SR, Fleischer AB, Jr. Seasonal variation of dermatologic disease in the USA: a study of office visits from 1990 to 1998. *Int J Dermatol* 2004;43:6–11.
- Balkrishnan R, Carroll CL, Camacho FT, Feldman SR. Electronic monitoring of medication adherence in skin disease: results of a pilot study. *J Am Acad Dermatol* 2003;49:651–4.
- Carroll CL, Feldman SR, Camacho FT, Balkrishnan R. Better medication adherence results in greater improvement in severity of psoriasis. *Br J Dermatol* 2004;151:895–7.
- Ali SM, Brodell RT, Balkrishnan R, Feldman SR. Poor adherence to treatments: A fundamental principle of dermatology. *Arch Dermatol* 2007;143:912–5.
- Statistics Canada. Age (123) and Sex (3) for the Population of Canada, 2006 Census. Available: <http://www12.statcan.ca/english/census06/data/topics/RetrieveProductTable.cfm?Temporal=2006&APATH=3&PID=88989&THEME=66&PTYPE=88971&VID=0&GK=NA&GC=99&FL=0&RL=0&FREE=0&METH=0&S=1> (accessed January 2008).

## CHAPTER 2: METHODS

### *Canadian Guidelines for the Management of Plaque Psoriasis*

#### Overview of the process

These first *Canadian Guidelines for the Management of Plaque Psoriasis* were created by a Guidelines Committee of 16 Canadian dermatologists. Following review by the wider medical community and the Therapeutics Committee of the Canadian Dermatology Association (CDA), the Guidelines were formally endorsed by the CDA. The manuscript was developed by drawing on systematically graded evidence from an extensive literature review, as well as clinical judgment.

The Guidelines development process was designed to be as reproducible and as transparent as possible, in order to provide useful clinical guidance, based on the best available clinical evidence that could stand up to scrutiny. Therefore, the writing and revision process was guided by the following principles:

- Each recommendation should address a clinically important question concerning either the diagnosis or management of plaque psoriasis or its comorbidities
- Each recommendation had to be supported by the best evidence currently available, which would be identified by one or more citations next to the recommendation
- The strength of the evidence and the grade of recommendation should be stated, based on a pre-specified grading system
- Recommendations based on clinical judgment alone should be explicitly identified as such
- Industry partners would be allowed to contribute papers to the literature review but would have no role in appraisal of the evidence or development of the manuscript

As far as possible within timeline and budget constraints, the Guidelines process endeavoured to meet the standards of the international AGREE (*Appraisal of Guidelines for Research & Evaluation*) Instrument<sup>1</sup> and, when it became available, the Canadian Medical Association's newly published *Handbook on Clinical Practice Guidelines*.<sup>2</sup>

#### KEY POINT

*The Guideline development process was designed to be as reproducible and as transparent as possible, in order to provide useful clinical guidance, based on the best available clinical evidence that could stand up to scrutiny.*

#### Evidence-based guidelines in psoriasis

The intention of all evidence-based guidelines is to provide clinicians with the best available evidence to assist them in making clinical decisions. However, it is clearly impractical to insist on high-quality evidence as a basis for all decision making. Since physicians must often act despite the absence of data, an overly rigid approach to clinical guidance would not serve their interests or those of patients. This is especially true in the context of psoriasis. Not only is evidence lacking in many key areas of psoriasis management, but older therapies in extensive use lack the long-term trial data that have been required of newer therapies. Thus, psoriasis management has typically relied heavily on empirical trial and clinical judgment. The challenge for the developers of these Guidelines has been to capture this wealth of experience while at the same time drafting recommendations in a manner that is transparent and reproducible. The pragmatic solution is to employ a rating scale that separately evaluates the level of evidence and the grade of recommendation.

In the widely used Scottish Intercollegiate Guidelines Network (SIGN) system, applied here, the evidence behind a recommendation must be evaluated according to strict, pre-specified rules (**Table 1**). In contrast, when assigning grades to the recommendations, the developers retain the freedom to factor in their 'considered judgment' based on clinical experience, as well as the formal level of evidence. SIGN thus allows guideline developers to take into account the quantity, quality, and

consistency of the evidence, the generalizability of the study findings, and their potential clinical impact.<sup>2</sup>

In essence, a high grade in SIGN reflects a high degree of confidence that the recommendation will stand up to further scrutiny; a lower grade simply indicates that the recommendation is apt to change as the body of data evolves. Hence, as noted by other authors,<sup>3</sup> the grade of the recommendation does not reflect its clinical importance or how strongly the Committee members felt about it; it reflects the strength of the supporting evidence and the weight of clinical experience. Thus, even though formal evidence is lacking, a Grade D recommendation (evidence from case reports and expert opinion) may be very helpful for clinical management until further information comes to light.

### Structure of the Guidelines Committee

The Guidelines Committee was subdivided into four subcommittees: the Steering Committee, the Section Heads, the Evidence Committee, and the Recommendations Committee.

The Steering Committee set the parameters for the Guidelines and monitored the progress of the manuscript. The Section Heads worked with a team of professional medical writers to produce the first draft of the manuscript for consideration by the Steering and Evidence Committees. The Evidence Committee ratified the assigned level of evidence for each recommendation, while the Recommendations Committee did the same for the assigned grade of each recommendation. To ensure independent review, no member could serve on both the Evidence and Recommendations Committees, and Section Heads did not serve on either of these committees.

### The literature search

Each Section Head and his or her writing team developed a list of specific clinical questions for which recommendations would eventually be developed. The clinical questions allowed the generation of key terms that were used by a professional librarian to search PubMed and EMBASE for papers on psoriasis and antipsoriatic therapies published in 1980 or later. All peer-reviewed literature was considered. Papers were also identified by checking the reference lists of reviews and other guidelines, hand-searching personal libraries, forward-tracking citations, and

identifying further key literature (including newly published papers) as writing progressed.

In all, 5439 peer-reviewed research articles were identified and the citations subsequently maintained in an EndNote library. Meeting abstracts and posters, narrative reviews, and commentaries were excluded (except as a source of references) because they could not be critically appraised. Case reports were excluded from the initial literature search, although writers were permitted to cite them if necessary to address clinical questions that could not be answered by more systematic studies.

Sponsors were invited to submit peer-reviewed articles and unpublished manuscripts for consideration until a cut-off date of September 15, 2007. Unpublished data included in the initial draft Guidelines were required to be accepted for publication by February 15, 2008, to remain part of the final document.

### Drafting of the manuscript

Following the literature review, the Section Heads worked with the writers of each section, briefing them on key studies, reviewing outlines and draft recommendations, and editing successive drafts of the manuscript. As mentioned above, the first full draft of the manuscript underwent review by the Evidence and Recommendations Committees before being presented to the full Guidelines Committee.

In May 2008, the Guidelines Committee convened to review, debate, and finalize the Guidelines. For a recommendation to be adopted, support was required of no less than two-thirds of Committee members (i.e.,  $\geq 11$  people). Proxies were permitted.

Following adoption by the full Guidelines Committee, the Guidelines were circulated for comment to patient organizations, dermatologists, and primary care physicians, both nationally and internationally, and reviewed and subsequently endorsed by the Therapeutics Committee of the Canadian Dermatology Association. Industry sponsors saw the manuscript for the first time at final draft; no changes were permitted at that stage.

### Assignment of levels of evidence and grading the recommendations

A modified version of the SIGN system<sup>4</sup> was used to assign levels of evidence and grade the



recommendations (Table 1). SIGN assigns levels of evidence (1++, 1+, 1-, 2++, 2+, 2-, 3, 4) according to the type and quality of the study. A grade of recommendation (A, B, C, D) is then applied according to the level of evidence. As

noted earlier, ‘considered judgment’ allows some flexibility in converting the level of evidence into a recommendation grade, based on such subjective factors as the generalizability of the study findings to the relevant population.

**Table 1.** The modified SIGN scale<sup>4</sup> used by the Evidence and Recommendations Committees

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g., case reports, case series
4	Expert opinion

Grades of recommendation	
A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 1-, 2-, or 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

## References

1. The AGREE Collaboration. *Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument*. Available: [www.agreecollaboration.org](http://www.agreecollaboration.org) (accessed November 2006).
2. Canadian Medical Association. *Handbook on Clinical Practice Guidelines 2007*. Available: <http://www.cma.ca/multimedia/CMA/Content/Images/CMAInfobase/EN/handbook.pdf> (accessed June 2007).
3. Canadian Diabetes Association. 2003 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. *Can J Diabetes* 2003;27(Suppl 2):S1–152.
4. Scottish Intercollegiate Guidelines Network. *SIGN 50: A Guideline Developers' Handbook*. Available: [www.sign.ac.uk](http://www.sign.ac.uk) (accessed November 2006).

## CHAPTER 3: DEFINITIONS

### *Canadian Guidelines for the Management of Plaque Psoriasis*

---

#### **Types of psoriasis**

The term ‘psoriasis’ encompasses a number of morphologically distinct presentations that can occur in isolation, simultaneously, or sequentially. Until recently, classification and description of these different phenotypes was not well standardized. Recent advances in our understanding of the genetic<sup>1</sup> and pathogenic mechanisms leading to the different manifestations of psoriasis<sup>2</sup> have necessitated more precise phenotypic classification. A recent consensus meeting of the International Psoriasis Council created the following simplified, phenotype-based classification of psoriasis, intended for use in both clinical practice and research.<sup>3</sup>

#### ***Plaque psoriasis***

This most common form of the disease is present in roughly 90% of psoriasis patients; it is characterized by red, scaly, discoid lesions (plaques) at least 0.5 cm in diameter. Plaques may occur as single lesions at predisposed sites (e.g., knees, elbows) or as generalized disease across wider areas of the body. There is sharp demarcation between the plaque and surrounding normal skin. Expanding plaques may show clearance in the middle, leading to an annular pattern. Plaque psoriasis can be further classified according to specific anatomical sites and phenotypic variations.

#### ***Flexural psoriasis***

*(see Chapter 9: Management of facial, flexural, and genital psoriasis)*

Also called intertriginous or inverse psoriasis, this classification refers to thin, minimally scaly, well-defined plaques confined to skin folds such as those in the inframammary, groin, axillary, genital, and/or natal cleft regions. The shiny surface of the plaques may display secondary fissuring or maceration.

#### ***Nail psoriasis***

*(see Chapter 10: Management of nail psoriasis)*

Nail involvement is common in plaque psoriasis patients, and it occasionally presents as an isolated condition in the absence of skin plaques. Nail involvement can affect the nail bed and nail matrix and commonly leads to thickening, pitting, discolouration, and splintering of the nail plate, as well as separation of the nail plate from the nail bed.<sup>4</sup>

#### ***Scalp psoriasis***

*(see Chapter 11: Management of scalp psoriasis)*

The scalp is the body area most commonly affected by plaque psoriasis and is the initial site of presentation in many patients. Scalp involvement rarely extends more than 2 cm beyond the hairline.

#### ***Palmoplantar psoriasis (non-pustular)***

*(see Chapter 12: Management of palmoplantar psoriasis)*

Plaque psoriasis on the palms of the hands or the soles of the feet can have a wide range of manifestations, from confluent redness and scaling without discernable plaques to poorly defined scaly or fissured areas to large plaques covering the palm or sole and extending to the surrounding skin.

#### ***Sebopsoriasis***

The seborrheic form of plaque psoriasis is so named because of its similarity to seborrheic dermatitis, both in location (usually on the face, notably the nasolabial folds) and morphology (thin, red, well-demarcated lesions that may be ‘greasy’ in appearance). It may occur in isolation or be associated with plaque psoriasis elsewhere on the body; in the absence of other psoriasis, it may be difficult to distinguish from seborrheic dermatitis.

**Non-plaque forms of psoriasis**

Although these Guidelines focus on the treatment of plaque psoriasis, it is important to understand the presentation of non-plaque forms and their relationship to plaque psoriasis.

*Guttate psoriasis*

This form of psoriasis presents as an acute eruption of small papules on the trunk, limbs, or face. In about two-thirds of cases, the guttate flares are triggered by streptococcal infection.

*Pustular psoriasis*

Generalized pustular psoriasis is characterized by sheets of small, monomorphic pustules developing within erythrodermic skin or along the edges of expanding inflammatory plaques. It may arise from established plaque psoriasis or may present *de novo*. The most common variety is palmoplantar pustulosis (PPP; see Chapter 12: Management of palmoplantar psoriasis), which was traditionally viewed as a variant or manifestation of psoriasis. Indeed, PPP is associated with plaque psoriasis in about one-fifth of cases. However, it has been proposed that PPP constitutes a separate entity, due to its unique clinical, epidemiological, genetic,<sup>1</sup> and biological features.

Another variant, also presenting with localized eruptions, is acrodermatitis continua of Hallopeau. This pustular disease involves the nail beds and the periungual area, with characteristic nail dystrophy, paronychia redness, scaling, and chronic periungual swelling. The condition is often associated with palmoplantar pustulosis or plaque psoriasis on other body sites.

*Erythroderma*

In erythrodermic psoriasis, the patient experiences acute or subacute onset of diffusely red, inflammatory psoriatic patches, often covering 90% or more of the patient's total skin surface, and typified by sparse scaling. In contrast, widespread flares of chronic plaque psoriasis, which cause far less physiological stress, may have thicker plaques, as well as variable scaling. Although erythroderma can arise *de novo*, it is most commonly associated with long-standing, active disease.

**KEY POINT**

*Most of the commonly used definitions of disease severity, treatment success, and treatment failure have been developed for use in clinical trials. Such numerical cut-off values, involving easily quantified parameters like BSA affected, are poorly suited to routine clinical practice because they fail to reflect patients' actual burden of disease. In clinical practice, more patient-centred standards are needed to assess disease burden and treatment success.*

**Metrics used to determine plaque psoriasis severity**

In clinical practice, assessment of the severity of a patient's plaque psoriasis includes both an objective evaluation of the extent and symptoms of the disease and a subjective evaluation of the impact of psoriasis on the patient's life. Standardized disease severity measures therefore include symptom- and involvement-based metrics such as BSA and PASI, as well as quality-of-life (QoL) instruments such as the DLQI and the SF-36 (Table 1).<sup>5</sup> Metrics specifically developed for palmoplantar, nail, and scalp psoriasis are less widely used. These are described in the corresponding chapters (below).

**Table 1. Metrics used for defining disease severity**

Measure	Description
<b>Measures of symptoms and involvement</b>	
BSA (body surface area) <sup>6</sup>	Percentage of body surface affected by psoriasis. BSA estimation uses the palm (subject's flat hand and thumb together, fingers included) as representing around 1% of the total BSA
PASI (Psoriasis Area and Severity Index) <sup>7</sup>	<p>An index of the severity (thickness, redness, scaling) and extent of body surface coverage of psoriasis. Scores range from 0 to 72 (0 — no disease, 72 — maximal disease). The PASI combines assessment of four body areas: head and neck (H), upper limbs (U), trunk (T), and lower limbs (L). The proportion of skin affected by psoriasis in each area is given a numerical score (A) representing the proportion involved:</p> <ul style="list-style-type: none"> <li>• 1: 0–9%</li> <li>• 2: 10–29%</li> <li>• 3: 30–49%</li> <li>• 4: 50–69%</li> <li>• 5: 70–89%</li> <li>• 6: 90–100%</li> </ul> <p>Within each area the severity of each of three signs, erythema (E), thickness/induration (I), and desquamation/scaling (S), is assessed on a five-point scale:</p> <ul style="list-style-type: none"> <li>• 0: none</li> <li>• 1: mild</li> <li>• 2: moderate</li> <li>• 3: severe</li> <li>• 4: very severe</li> </ul> <p>For each of the four body areas, the three signs' scores are added and then multiplied by the area score. Each body region's score is then multiplied by the following proportions to reflect its contribution to total body area:</p> <ul style="list-style-type: none"> <li>• neck and head: 0.1</li> <li>• upper limbs: 0.2</li> <li>• trunk: 0.3</li> <li>• lower limbs: 0.4</li> </ul> <p>Finally, the scores for all four body areas are added to yield the overall PASI score</p>
PASI change <sup>8</sup>	Change in severity is indicated in terms of percentage change from baseline score. Thus, PASI-75 would indicate a 75% decrease (improvement) in severity as measured using the PASI scale. PASI-125 would indicate an increase (worsening) in severity of 25% greater than baseline
Physician's Global Assessment (static PGA) <sup>8</sup>	An assessment of disease severity (clear, almost clear, mild, moderate, severe, very severe) at a particular point in time
Dynamic PGA (PGA of change) <sup>8</sup>	An assessment of disease response to treatment (worse, unchanged, slight improvement, fair improvement, good improvement, excellent improvement, cleared). This approach to disease response is limited by recall or recording of disease severity previously observed

**Table 1. Metrics used for defining disease severity (cont.)**

Measure	Description
<b>QoL measures</b>	
DLQI (Dermatology Life Quality Index) <sup>9</sup>	A patient questionnaire to assess itch, pain, feelings of embarrassment/self-consciousness, problems with treatment and interference of skin disease with the patient's daily activities, relationships, and sexual activity. Score from 0 (no impairment) to 30 (maximal impairment)
Short Form (SF-36) Health Survey	A general (not dermatology-specific) QoL instrument with subscales for physical functioning, "role: physical", bodily pain, general health perceptions, vitality, social functioning, "role: emotional", and mental health

**Definitions of terms used in these Guidelines**

Most of the commonly used definitions of disease severity, treatment success, and treatment failure have been developed for use in clinical trials, where definite classifications and cut-offs are required to identify a population for inclusion and to ensure the interpretability of results. Even within this literature, there is no consensus as to how disease severity should be defined. For instance, to define severe psoriasis, some authors may apply the 'Rule of Tens', which defines a patient's disease as severe if any one of several criteria is met (PASI  $\geq$  10, DLQI  $\geq$  10 or

BSA  $\geq$  10%). Others may set a single criterion of BSA  $\geq$  20% (Table 2).

Regardless, such numerical cut-off values are poorly suited to routine clinical practice because they fail to reflect patients' actual burden of disease.<sup>10</sup> In clinical practice, patient-centred standards are needed to assess disease severity and treatment success,<sup>11</sup> such as the definitions for clinical practice outlined in Table 2. These definitions are used consistently throughout these Guidelines.

**Table 2. Terms used in evaluating psoriasis**

Term	Definitions used in clinical trials	Definition for clinical practice, as applied in these Guidelines
<b>Measures of disease severity</b>		
Mild plaque psoriasis	Not commonly defined; the US National Psoriasis Foundation suggests BSA = 5% as an upper limit for mild disease <sup>12</sup>	Disease with a minimal impact on the patient's QoL; patient can achieve an acceptable level of symptomatic control by routine skin care measures and/or topical therapy
Moderate plaque psoriasis	The lower limit of moderate to severe psoriasis may be set at PASI = 8 <sup>13,14</sup> or, in trials of biologics, typically higher  Several biologics trials have used criteria as stringent as PASI $\geq$ 12 and BSA $\geq$ 10% to define the lower limit of "moderate to severe" psoriasis, <sup>15,16</sup> although the same limits have also been used to define "severe" psoriasis <sup>17</sup>	Disease that cannot be, or would not be expected to be, controlled to an acceptable degree by routine skin care measures and/or disease that significantly affects the patient's QoL, either because of the extent of the disease, the physical discomfort it causes (pain or pruritus), or the location where the disease manifests (e.g., the face, hands, feet, or genitals)

**Table 2. Terms used in evaluating psoriasis (cont.)**

Term	Definitions used in clinical trials	Definition for clinical practice, as applied in these Guidelines
<b>Measures of disease severity (cont.)</b>		
Severe plaque psoriasis	The Rule of Tens requires PASI $\geq 10$ or DLQI $\geq 10$ or BSA $\geq 10\%$ <sup>18</sup>  In some phototherapy trials, BSA $\geq 20\%$ is the lower limit of severe disease <sup>19,20</sup>	Disease that cannot be, or would not be expected to be, satisfactorily controlled by topical therapy and that causes severe degradation of the patient's QoL
<b>Measures of treatment success</b>		
Clearance	Absence of disease signs	
Control	A satisfactory response to therapy, as defined by the patient and/or physician; does not necessarily involve complete clearance	
Remission	Disease control maintained over an extended period, which is sometimes defined operationally by the time between patient-scheduled treatments <sup>21</sup>	Suppression of signs and symptoms of psoriasis (not necessarily requiring complete clearance) persisting over a specified period, despite the absence of treatments beyond routine skin care measures
<b>Measures of treatment failure</b>		
Exacerbation	Any worsening of a patient's psoriasis symptoms	
Flare	An exacerbation occurring while the patient is on therapy, in which the worsening of disease differs from the foregoing disease, either in its morphology (e.g., an erythrodermic or pustular flare in a patient with plaque psoriasis) or in the extent or severity of individual lesions	
Rebound	An exacerbation (classically defined by a PASI-125-level or greater increase in severity or a change in the morphology of the psoriasis) associated with treatment discontinuation. For a rebound to be considered discontinuation-related, its onset should occur within 3 months of treatment cessation <sup>22</sup>	
Relapse	Loss of disease control in a patient previously achieving satisfactory control, classically defined as a 50% loss of the gain achieved by treatment. Therefore, a patient with baseline PASI-20 who achieved PASI-10 with therapy would be considered to relapse at PASI-15 <sup>22</sup>	



## References

1. Asumalahti K, Ameen M, Suomela S, et al. Genetic analysis of *PSORS1* distinguishes guttate psoriasis and palmoplantar pustulosis. *J Invest Dermatol* 2003;120:627–32.
2. Christophers E. Explaining phenotype heterogeneity in patients with psoriasis. *Br J Dermatol* 2008;158:437–41.
3. Griffiths CE, Christophers E, Barker JN, et al. A classification of psoriasis vulgaris according to phenotype. *Br J Dermatol* 2007;156:258–62.
4. Rich P, Scher RK. Nail Psoriasis Severity Index: A useful tool for evaluation of nail psoriasis. *J Am Acad Dermatol* 2003;49:206–12.
5. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. *J Invest Dermatol* 2007;127:2726–39.
6. Long CC, Finlay AY, Averill RW. The rule of hand: 4 hand areas=2 FTU=1 g. *Arch Dermatol* 1992;128:1129–30.
7. Fredriksson T, Pettersson U. Severe psoriasis — oral therapy with a new retinoid. *Dermatologica* 1978;157:238–44.
8. Weisman S, Pollack CR, Gottschalk RW. Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. *J Dermatolog Treat* 2003;14:158–65.
9. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) — a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19:210–6.
10. Feldman SR. A quantitative definition of severe psoriasis for use in clinical trials. *J Dermatolog Treat* 2004;15:27–9.
11. Krueger GG, Feldman SR, Camisa C, et al. Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? *J Am Acad Dermatol* 2000;43:281–5.
12. Pariser DM, Bagel J, Gelfand JM, et al. National Psoriasis Foundation clinical consensus on disease severity. *Arch Dermatol* 2007;143:239–42.
13. Heydendael VM, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med* 2003;349:658–65.
14. Yones SS, Palmer RA, Garibaldino TT, Hawk JLM. Randomized double-blind trial of the treatment of chronic plaque psoriasis: efficacy of psoralen-UV-A therapy vs narrowband UV-B therapy. *Arch Dermatol* 2006;142:836–42.
15. Menter A, Tying SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol* 2008;58:106–15.
16. Dubertret L, Sterry W, Bos JD, et al. Clinical experience acquired with the efalizumab (Raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial. *Br J Dermatol* 2006;155:170–81.
17. Feldman SR, Gordon KB, Bala M, et al. Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: a double-blind placebo-controlled trial. *Br J Dermatol* 2005;152:954–60.
18. Finlay AY. Current severe psoriasis and the rule of tens. *Br J Dermatol* 2005;152:861–7.
19. Tanew A, Guggenbichler A, Honigsmann H, et al. Photochemotherapy for severe psoriasis without or in combination with acitretin: A randomized, double-blind comparison study. *J Am Acad Dermatol* 1991;25:682–4.
20. Asawanonda P, Nateetongrungsak Y. Methotrexate plus narrowband UVB phototherapy versus narrowband UVB phototherapy alone in the treatment of plaque-type psoriasis: a randomized, placebo-controlled study. *J Am Acad Dermatol* 2006;54:1013–8.
21. Perlmutter A, Cather J, Franks B, et al. Alefacept revisited: Our 3-year clinical experience in 200 patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2008;58:116–24.
22. Gordon KB, Feldman SR, Koo JY, et al. Definitions of measures of effect duration for psoriasis treatments. *Arch Dermatol* 2005;141:82–4.

## CHAPTER 4: DELIVERY OF CARE

### *Canadian Guidelines for the Management of Plaque Psoriasis*

Little has been published regarding the state of psoriasis care or the patient experience in Canada specifically. More surveys and observational studies are needed to assess patterns of care in this country — how and where care is delivered, as well as levels of satisfaction, among patients and physicians, with standards of care and treatment options. However, if the state of psoriasis care in Canada is similar to that in other relatively prosperous countries where somewhat more information is available, levels of care and patient satisfaction can be assumed to be far from optimal.

Psoriasis is almost certainly undertreated in Canada. A recent observational study in the United States found that up to 80% of psoriasis patients did not receive care for their condition in a given calendar year,<sup>1</sup> while a survey conducted by the US National Psoriasis Foundation showed that almost 40% of respondents were receiving no treatment at all for their psoriasis at the time of the survey.<sup>2</sup> Worse, the proportion of patients receiving no current therapy did not change significantly with increasing disease severity.<sup>2</sup>

#### KEY POINT

*Psoriasis is almost certainly undertreated in Canada, as it is elsewhere; some severely affected patients may be receiving no therapy at all.*

#### The locus of psoriasis care

##### *Roles of generalist and specialist physicians*

Many psoriasis patients can be managed adequately through their regular primary care visits. Educational programs for primary care physicians increase the rate of appropriate referrals of psoriasis patients without significantly increasing the overall referral rate.<sup>3</sup> Such programs help ensure that patients who require specialized care will be adequately treated.

Referrals to a specialist should be considered when disease is extensive, distressing, or unresponsive, or where the patient requires in-depth counselling or education outside the scope of a primary care practice. It may also be appropriate to involve a specialist to confirm a diagnosis, to assess or help establish an appropriate therapeutic regimen, or to help manage more complex cases. Patients who become unresponsive to previously successful treatments or who experience other adverse reactions to topical medications should also be referred (see Chapter 5: Management of mild plaque psoriasis).<sup>3</sup> In addition, a patient's request for a referral to a dermatologist should be respected.

##### *Outpatient care for severe psoriasis*

In Canada and elsewhere, psoriasis care has shifted from an inpatient to an outpatient setting in recent years. Hospitalization for treatment with topical tars or steroids, anthralin, or UV light was the standard of care for severe psoriasis until the mid-1970s, when the introduction of new therapies such as UVA with psoralen (PUVA) made outpatient treatment of severe cases more feasible. These innovations coincided with budgetary restrictions and changes to reimbursement policies that have led to a significant drop in hospitalizations for chronic but non-life-threatening conditions across North America and Europe.<sup>4</sup> Although inpatient care for severe psoriasis has been associated with improved quality of life<sup>5,6</sup> and significantly faster disease clearance compared with outpatient care,<sup>7</sup> designated hospital beds for dermatological care are no longer available, a consequence of changes in the nature of psoriasis treatment and increasing financial pressures.

Psoriasis treatment is now almost exclusively delivered in the outpatient setting. Instead of aiming to achieve complete disease clearance through intensive inpatient care, now the primary goal is to improve the acute or severe manifestations of the

disease so that the patient can be managed on an outpatient basis.<sup>5</sup> Nevertheless, severe psoriasis may in some cases require hospitalization. The risk of death from psoriasis or related complications is not high, but it does exist: a recent US survey calculated an annual death rate attributable to psoriasis of one in 156 250 psoriasis patients.<sup>8</sup>

Patients experiencing acute unstable psoriasis, generalized erythrodermic psoriasis, or generalized pustular psoriasis may require admission for emergency inpatient care to address the underlying condition and to reduce the risk of severe infection, dehydration, and electrolyte imbalance, and potential cardiac and renal complications.<sup>3</sup>

### **Treatment adherence and physician engagement**

Successful care of psoriasis, like that of other chronic diseases, relies equally on the appropriate use of effective therapies and on adequate two-way communication between patients and their healthcare providers.<sup>2</sup> Treatment efficacy depends to a great extent on patients' ability to manage their own disease and to adhere to a prescribed course of treatment. It is incumbent on the physician to work with the patient to develop a management plan that the patient can adhere to.

Unfortunately, patient surveys have relatively low levels of agreement between physicians' assessments and patients' expectations of disease burden and treatment efficacy. When asked to report the severity of their disease and its impact on their daily lives, 74% of patients in a European survey self-assessed their psoriasis as "at least moderately severe".<sup>9</sup> In contrast, clinical assessment metrics generally identify approximately one-third of psoriasis patients as "moderate to severe".<sup>10</sup> Among respondents in the US-based survey, 78% of patients with psoriasis clinically classified as severe reported that their current treatment was not effective enough and did not make their disease more manageable. Respondents cited lack of physician support and communication as the most common (59%) reason for dissatisfaction with treatment.<sup>11</sup>

Patient surveys have found treatment non-adherence rates as high as 73% in the general psoriasis population<sup>9</sup>; even among populations where most patients classify their own disease and its impact on their lives as "severe", up to two in five patients will still fail to follow their prescribed treatment regimen.<sup>12</sup> Such non-adherence can create a vicious cycle leading to poor outcomes. The patient, disappointed or frustrated because the therapy is not working as well as expected, stops following it or does not use it appropriately, further lowering the chances of treatment success.<sup>13</sup>

Poor adherence is thus both a cause and consequence of inadequate treatment efficacy, as the patient perceives it.<sup>13</sup> Successful treatment will rely not only on clinical markers of therapeutic efficacy, but also on understanding and addressing any reasons why the patient might or might not adhere to the prescribed therapy. Clinical decision making in psoriasis must go beyond questions of efficacy — "Which therapy will work for my patient?" — to take into account patient satisfaction and the risk of non-adherence — "Which therapy will my patient work with?"

### **Patient-centred psoriasis therapy**

Measures that address these issues may improve treatment adherence and overall outcomes. The most commonly cited reasons for patient non-adherence with therapy include frustration with medication efficacy, inconvenience of administration, and fear of side effects.<sup>14</sup> It is important for physicians to discuss these issues with patients and determine which of the various treatment options is likely to fit most easily into the patient's normal routine. In addition, since patients generally increase their adherence to treatment around the time of visits to their healthcare providers, regular and frequent follow-up visits or between-visit telephone or e-mail communications from the physician's office may help some patients remain on therapy.<sup>15</sup> Patient education, through training programs<sup>16</sup> or involvement in advocacy groups,<sup>17</sup> can also help patients understand the importance of adhering to their prescribed treatment regimen.

## Recommendations

Recommendation & level of evidence	Grade of recommendation
<p>Physicians should recognize the ubiquity of treatment non-adherence and take steps to address it in their patients.<sup>13</sup> These could include any or all of the following:</p> <ul style="list-style-type: none"> <li>• Providing regular follow-up visits after medication prescription, in a patient-specific manner (Ref. 15, LoE 4)</li> <li>• Providing specialized education aimed at improving patients' sense of control over their disease and their knowledge about treatments (e.g., videos, handouts, Internet-based educational programs) (Ref. 16, LoE 4)</li> <li>• Encouraging patients to join support groups or foundations to improve their awareness of treatment options and satisfaction with treatment outcomes (Ref. 17, LoE 4)</li> <li>• Ensuring effective two-way communication between patient and caregivers regarding the impact of psoriasis on the patient's mental and physical health (Ref. 2, LoE 4)</li> </ul>	<p><b>Grade D</b></p> <p><b>Grade D</b></p> <p><b>Grade D</b></p> <p><b>Grade D</b></p>
<p>Urgent referral to a dermatologist and, where possible, hospital admission, should be considered for patients with acute unstable psoriasis, generalized erythrodermic psoriasis, or generalized pustular psoriasis (Ref. 3, LoE 4)</p>	<p><b>Grade D</b></p>

## References

1. Feldman SR, Fleischer AB, Jr., Cooper JZ. New topical treatments change the pattern of treatment of psoriasis: dermatologists remain the primary providers of this care. *Int J Dermatol* 2000;39:41–4.
2. Horn EJ, Fox KM, Patel V, et al. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey. *J Am Acad Dermatol* 2007;57:957–62.
3. British Association of Dermatologists. *Psoriasis Guidelines* 2006.
4. Stern RS, PUVA Follow-up Study. Inpatient hospital care for psoriasis: a vanishing practice in the United States. *J Am Acad Dermatol* 2003;49:445–50.
5. Ayyalaraju RS, Finlay AY, Dykes PJ, et al. Hospitalization for severe skin disease improves quality of life in the United Kingdom and the United States: a comparative study. *J Am Acad Dermatol* 2003;49:249–54.
6. Kurwa HA, Finlay AY. Dermatology in-patient management greatly improves life quality. *Br J Dermatol* 1995;133:575–8.
7. Cockayne SE, Cork MJ, Gawkrödger DJ. Treatment of psoriasis: Day care vs. inpatient therapy. *Br J Dermatol* 1999;140:375–6.
8. Pearce DJ, Lucas J, Wood B, et al. Death from psoriasis: representative US data. *J Dermatolog Treat* 2006;17:302–3.
9. Fouere S, Adjadj L, Pawin H. How patients experience psoriasis: results from a European survey. *J Eur Acad Dermatol Venereol* 2005;19 Suppl 3:2–6.
10. Gottlieb AB. Psoriasis: Emerging therapeutic strategies. *Nat Rev Drug Discov* 2005;4:19–34.
11. Krueger G, Koo J, Lebwohl M, et al. The impact of psoriasis on quality of life: Results of a 1998 National Psoriasis Foundation Patient-Membership Survey. *Arch Dermatol* 2001;137:280–4.
12. Richards HL, Fortune DG, O'Sullivan TM, et al. Patients with psoriasis and their compliance with medication. *J Am Acad Dermatol* 1999;41:581–3.
13. Ali SM, Brodell RT, Balkrishnan R, Feldman SR. Poor adherence to treatments: A fundamental principle of dermatology. *Arch Dermatol* 2007;143:912–5.
14. Brown KK, Rehms WE, Kimball AB. Determining the relative importance of patient motivations for nonadherence to topical corticosteroid therapy in psoriasis. *J Am Acad Dermatol* 2006;55:607–13.
15. Feldman SR, Camacho FT, Krejci-Manwaring J, et al. Adherence to topical therapy increases around the time of office visits. *J Am Acad Dermatol* 2007;57:81–3.
16. Skarpathiotakis M, Fairlie C, Ryan S. Specialized education for patients with psoriasis: a patient survey on its value and effectiveness. *Dermatol Nurs* 2006;18:358–61.
17. Nijsten T, Rolstad T, Feldman SR, Stern RS. Members of the national psoriasis foundation: more extensive disease and better informed about treatment options. *Arch Dermatol* 2005;141:19–26.

## CHAPTER 5: MANAGEMENT OF MILD PLAQUE PSORIASIS

### *Canadian Guidelines for the Management of Plaque Psoriasis*

Psoriasis is a common skin disorder characterized by erythematous papules and plaques with a silver scale, although other presentations occur. Most cases are classified as mild chronic plaque psoriasis, a condition that typically does not affect general medical health, although its impact on psychosocial health can still be profound.

Fortunately, there is a variety of therapies for mild chronic plaque psoriasis that allow effective treatment in the outpatient setting. Topical agents are the most widely used and can result in good control of mild psoriatic disease, with a low incidence of systemic side effects.<sup>1,2</sup> Regardless, there is no lasting cure for mild psoriatic disease, and chronic therapy is often necessary.

The following material reviews the evidence for the use of different topical therapies in patients with mild psoriasis, specifically with involvement of the trunk, limbs, and neck. Treatment of moderate to severe plaque psoriasis — which, by definition, cannot be adequately controlled by the approaches discussed here — will be considered in Chapter 6 (Management of moderate to severe plaque psoriasis). Mild as well as more severe psoriasis affecting the face, hands, genitals, and scalp will be discussed in subsequent chapters.

#### KEY POINT

*Individualized approaches are central to the management of mild psoriasis because there is such wide variation in patients' presentations, their psychosocial health, and their personal opinions as to what constitutes acceptable treatment. Thus, adequate psoriasis care should look beyond clinical parameters (e.g., body surface area or PASI scores) to maintain a focus on the patient's health-related quality of life.*

#### Corticosteroids

Corticosteroids are the most widely used agents for the topical treatment of psoriasis and have been the mainstay of therapy for over half a century. They are well tolerated and often efficacious, and they come in a variety of forms, including ointments, creams, gels, lotions, sprays, and solutions.

Considering their widespread use, corticosteroids have been studied in relatively few large-scale, randomized, placebo-controlled trials and even fewer head-to-head comparisons against other therapies. The most comprehensive analysis of topical psoriasis treatment to date was the study by Mason et al.,<sup>1</sup> in which all of the topical treatments considered outperformed placebo; the highest-potency steroids were found to be the most efficacious, followed by vitamin D3 analogues.

Despite the demonstrated efficacy of corticosteroids, their use is limited by their potential to produce side effects.<sup>3</sup> Long-term use of topical corticosteroids, particularly the most potent of these drugs, may be associated with local cutaneous changes (e.g., atrophy, contact dermatitis, hypertrichosis, folliculitis, hypopigmentation, perioral dermatitis, striae, telangiectases, traumatic purpura).<sup>3-6</sup> Hypothalamic-pituitary-adrenal axis suppression can also occur.<sup>7</sup>

Although the repeated use of topical corticosteroids can result in progressive decrease in their biological action (i.e., tachyphylaxis),<sup>8</sup> the clinical significance of this effect is difficult to verify.<sup>9</sup> Regardless, Katz et al. reported that 'pulse-dosing' of topical corticosteroid treatment may prevent tachyphylaxis and reduce the incidence of adverse effects associated with topical corticosteroid treatment.<sup>7</sup> This finding is supported by a report from Lebwohl et al., who found that using fluticasone propionate twice daily for 2 weeks and then once daily for 2 days of the week for 8 weeks did not cause atrophy in steroid-sensitive areas. This tapering regimen maintained control of facial and



intertriginous lesions (see Chapter 9: Management of facial, flexural, and genital psoriasis), although it was associated with gradual loss of control at other sites.<sup>10</sup>

### Vitamin D3 analogues

Topical calcipotriol exerts its therapeutic effect by modulating keratinocyte growth and differentiation and by inhibiting T lymphocyte activity.<sup>11</sup> Calcipotriol is currently the only topical vitamin D3 analogue available in Canada.

Various clinical trials have validated the safety and efficacy of calcipotriol<sup>12-35</sup> in patients with mild plaque psoriasis. For example, calcipotriol has been compared with Class 2 (potent) corticosteroid ointments and found to be comparable or slightly more effective than these agents.<sup>20,36</sup> One double-blind right-left comparison study found that calcipotriol offered a mean PASI reduction of 69% after 6 weeks of treatment, compared with a 61% reduction with 0.1% betamethasone 17-valerate ointment.<sup>36</sup> In other studies, vitamin D3 analogues were also more effective than fluocinonide<sup>18</sup> and betamethasone dipropionate plus salicylic acid.<sup>34</sup> A meta-analysis of randomized placebo-controlled trials involving topical psoriasis treatments<sup>1</sup> indicated that vitamin D3 analogues were as effective as all but the most potent corticosteroids. It was also reported that calcipotriol was superior to anthralin in terms of clinical efficacy.<sup>37</sup>

Although calcipotriol is not as effective as Class 1 topical corticosteroids, it may be better tolerated, with fewer adverse effects. A systematic review by Bruner et al.<sup>2</sup> reported that, in comparison with other topical therapies, vitamin D3 analogues were associated with a relatively low rate of adverse events. The most common adverse effect associated with vitamin D3 analogues is a mild irritant contact dermatitis.<sup>38</sup> Hypercalcemia has also been reported but is rare with the doses used in clinical settings,<sup>39</sup> which should be limited to 5 mg calcipotriol (100 g of calcipotriol cream or ointment) per week.

### Retinoids

The topical retinoid tazarotene is one of the more recently approved topical therapies for psoriasis. Like oral retinoids, tazarotene is thought to exert its therapeutic effect by modulating keratinocyte

proliferation and differentiation.<sup>40</sup> Retinoids also act to clear the inflammatory infiltrate in the psoriatic plaque,<sup>41</sup> although it has not been established whether their anti-inflammatory effects are an indirect consequence of their actions on keratinocytes.

When used as monotherapy, tazarotene can be effective at achieving remission of psoriatic plaques.<sup>42-48</sup> One placebo-controlled trial of daily 0.1% or 0.05% tazarotene gel found that this agent reduced plaque elevation, scaling, and erythema over a period of 1–12 weeks. The therapeutic effect of tazarotene, judged by severity at target lesions, was maintained for 12 weeks after cessation of treatment.<sup>49</sup> Similar results have been reported by other investigators.<sup>50</sup> Another study found that tazarotene had equal efficacy and induced a longer remission period when compared with a Class 2 corticosteroid, 0.05% fluocinonide.<sup>45</sup>

Tazarotene monotherapy is associated with a high incidence of irritation at the site of application. This dose-dependent effect, which can manifest as itching, burning, and erythema,<sup>49</sup> may restrict the use of tazarotene in some patients. In a systematic review of studies, tazarotene had a slightly higher incidence of adverse effects than corticosteroids or vitamin D3 analogues, but less than anthralin or coal tar.<sup>2</sup>

### Anthralin and tars

There are very few well-designed studies to determine the efficacy of either tar or anthralin. The study by Mason et al.<sup>1</sup> included data from five head-to-head trials of vitamin D3 analogues versus anthralin and reported that anthralin showed inferior efficacy. Several attempts have been made to minimize the stain and irritation associated with anthralin in order to promote treatment adherence and thereby increase efficacy through the use of different regimens, formulations, and adjuncts.<sup>51-53</sup> Indeed, a recent randomized controlled study<sup>54</sup> reported that once-daily short-contact anthralin was as effective as calcipotriol in an outpatient setting. Commercial formulations of anthralin are not currently available in Canada.

Coal tar is the main formulation of tar therapy employed for patients with mild plaque psoriasis. One recent study reported that coal tar was significantly less effective than betamethasone valerate (mean PASI reduction 38% versus 69%).<sup>55</sup>

Randomized controlled trials have reported that coal tar and calcipotriol showed comparable clinical efficacy and similar relapse rates. However, calcipotriol has a faster onset of action and is more acceptable to patients on cosmetic grounds.<sup>56,57</sup> Calcipotriol is also better tolerated than tar, which can cause acne, folliculitis, phototoxicity, and local irritation.<sup>2,56,57</sup> Coal tar, formulated in lotions and shampoos, is commonly used to treat scalp psoriasis (see Chapter 11: Management of scalp psoriasis); other preparations are used for plaque-type psoriasis of the hands and feet (see Chapter 12: Management of palmoplantar psoriasis).

Tars, like anthralin, are associated with significant adverse effects,<sup>2</sup> including staining and irritation, and their use has declined since the introduction of topical products that are typically more acceptable to patients. Regardless, these agents can still play a role in psoriasis treatment, provided the patient uses them as prescribed.

### Combination therapy

In general, combination therapy is more efficacious and can result in reduced incidence of adverse effects when compared with monotherapy alone. Several studies have examined the concomitant or sequential use of topical corticosteroids with vitamin D3 analogues for the treatment of patients and demonstrated this combination was safe,<sup>58</sup> effective, and reduced the irritation associated with either agent alone.<sup>26,28,35,59-65</sup> Thus, in one study, calcipotriol was applied in the morning and halobetasol ointment in the evening, resulting in a reduced overall severity of psoriasis versus monotherapy.<sup>66</sup> Another study used a similar regimen for 2 weeks and then switched patients to pulse therapy consisting of halobetasol ointment twice daily on weekends and calcipotriol ointment twice daily on weekdays.<sup>67</sup> This approach was superior to either of the two agents when pulsed with placebo.

Studies of a fixed-dose preparation of calcipotriol and betamethasone dipropionate have confirmed the efficacy of this vitamin D3 analogue/corticosteroid combination.<sup>26,61,64,65,68,69</sup> For instance, one randomized study examined the use of calcipotriol/betamethasone dipropionate for 4 weeks followed by maintenance with calcipotriol for 8 weeks, comparing this treatment with calcipotriol alone for 12 weeks. Clinical endpoints

were not significantly different when comparing the two groups at the 12-week time point, but the combination therapy group experienced a faster response to therapy, with superior clinical parameters at the 2-week and 4-week time points.<sup>70</sup> The calcipotriol and betamethasone dipropionate combination is available premixed.

Calcipotriol/betamethasone dipropionate is more effective than calcipotriol or betamethasone alone when used as first-line therapy for mild plaque psoriasis.<sup>71</sup> However, use of this combination strategy must also take into account the adverse effects associated with potent corticosteroids, particularly in patients with greater affected body surface area (e.g., > 3–5%), who would receive a higher effective dose of steroids.

Corticosteroid/topical retinoid combination regimens appear to confer enhanced therapeutic effect, with a reduction in the local irritation produced by the retinoids.<sup>43,45</sup> In one study, treatment with tazarotene gel combined with a mid- or high-potency corticosteroid caused a significant reduction in scaling, erythema, and overall lesion severity and a decrease in the incidence of adverse events versus tazarotene plus low-potency corticosteroid or plus placebo.<sup>45</sup> Part of the success of this particular combination may result from the rapid onset of action of corticosteroids compared with tazarotene and the fact that tazarotene-induced irritation is reduced by the anti-inflammatory effect of a steroid. Further, tazarotene increases epidermal thickness, and the use of tazarotene in conjunction with topical corticosteroids reduces the degree of corticosteroid-induced atrophy by as much as 37%.<sup>72</sup> Another trial comparing combination treatment for psoriasis with calcipotriol ointment and tazarotene gel versus clobetasol ointment found no difference in efficacy between the regimens.<sup>73</sup>

Finally, as a result of its ability to reduce scale and soften lesions, salicylic acid can enhance steroid efficacy by increasing penetration.<sup>74</sup> This agent promotes the desquamation of corneocytes from psoriatic plaques<sup>75</sup> and the absorption of corticosteroids in human skin explants.<sup>76</sup> Salicylic acid is available in combination with corticosteroids such as betamethasone dipropionate and diflucortolone valerate.



## Other approaches

### *Non-medicinal topical treatments*

Emollients, moisturizers, ointments, and similar, non-medicinal topical treatments are widely used, but their efficacy has not been thoroughly investigated, and there is little direct evidence that they are beneficial, either in mild or in more severe psoriasis. However, one study<sup>77</sup> established that the use of a water-in-oil cream or lotion in combination with betamethasone dipropionate cream can increase the efficacy of steroid treatment and allow patients to achieve control with lower corticosteroid doses. The steroid-sparing effects of such emollients, as well as their still-unproved benefits as monotherapy, have been attributed to their ability to restore normal hydration and water barrier function to the epidermal layer of the psoriatic plaque.<sup>78</sup>

Regardless of their efficacy or their mechanism of action, moisturizers and related topicals are unquestionably central to the routine skin care that dermatologists prescribe and that individuals with psoriasis commonly use, even when not under a physician's care.

The presumed benefit of these agents raises a common methodological issue in the literature on mild psoriasis, since the more rigorous studies typically employ the vehicle, or some other bland emollient, as the comparator (placebo) treatment. In some cases, both the experimental arm and the placebo arm of the trial show significant improvement relative to the patients' condition at baseline, although there is no significant difference between treatment arms. In such cases, it remains possible that the experimental treatment (e.g., plant products such as *Aloe vera* gel<sup>79</sup> or kukui nut oil<sup>80</sup>) is indeed superior to leaving the disease untreated, although the emollient properties of the treatment may fully explain any such benefit.

For certain other topical treatments that have been explored for use in mild psoriasis, a relatively slender evidence base supports the claim of benefits over and above those of a simple emollient. This is the case for fish oil-based topicals

and other preparations containing omega-3 fatty acids. These fatty acids are proposed to be anti-inflammatory, due to their effects on eicosanoid lipid metabolism. However, the benefits of topical or dietary fatty acid supplementation on psoriasis severity are equivocal, and a clear dose-dependent effect has not been established for any such treatment (reviewed in Mayser et al.<sup>81</sup>). Fatty acid infusion has been explored as a potential treatment for chronic moderate to severe plaque psoriasis.<sup>82</sup>

### *Intralesional corticosteroid injection*

Although the practice of injecting psoriatic plaques with triamcinolone or similar corticosteroids appears to be maintained in the dermatologist's toolkit (particularly for use in treating a small number of isolated plaques that fail to respond to topical therapy), there is little published information on this approach.<sup>83,84</sup> This treatment carries a risk of atrophy and depigmentation.<sup>85</sup>

## Measures of success

Various assessment tools have been developed to quantify the response to treatment and compare the efficacy of topical regimens. These scales can include\* physician-assessed response (PASI, OLS, PGA, and target lesion assessment), patient-assessed response (DLQI, DQOLS, SF-36, VAS, PSA Scale), or composite tools.<sup>86-97</sup> However, there are no large-scale randomized controlled studies to evaluate the comparative utility of these different scales during routine clinical visits or the optimal frequency of assessment.

The physical manifestations of psoriasis can have a profound impact on psychosocial health (see Chapter 13: Social and psychological aspects of psoriasis). Fortunately, many topical treatments, including steroids, vitamin D3 analogues, retinoids, anthralin, and tar, are superior to placebo and can help mitigate these clinical endpoints of psoriasis.<sup>1</sup> However, each treatment is also associated with a distinct profile of factors (e.g., convenience, tolerability, adverse effects) that can have a negative effect on health-related quality of life, interfering with treatment adherence and thereby limiting real-world efficacy.<sup>2,98-100</sup>

\*PASI = Psoriasis Area and Severity Index; OLS Scale = Overall Lesion Severity Scale; PGA = Physician's General Assessment; DLQI = Dermatological Life Quality Index; DQOLS = Dermatology Quality-of-Life Scales; SF-36 = Short-Form 36 Health Survey; VAS = Visual Analogue Scale; PSA Scale = Psoriatic Arthritis Scale.

Because there is wide variation in patients' psoriatic presentations, personal values, psychosocial health, and expectations regarding the acceptable implications of therapy, individualized approaches are indicated in choosing specific treatments. As has been argued elsewhere,<sup>101</sup> adequate psoriasis care should look beyond clinical parameters (e.g., body surface area or PASI score) to maintain a focus on the patient's health-related quality of life. A good physician–patient relationship, in which the patient's expectations and the advantages and disadvantages of each therapy are reviewed and the patient participates in the choice of therapy, is critical to achieve treatment success and overall patient satisfaction (see Chapter 13: Social and psychological aspects of psoriasis).

### Recommendations

Care for individuals with chronic mild plaque psoriasis affecting the trunk, limbs, and neck should follow the recommendations shown below. More severe psoriasis is considered in the following chapter (Chapter 6: Management of moderate to severe plaque psoriasis); acute flares are discussed in Chapter 8 (Exacerbation and flare of psoriasis). For recommendations on treating psoriasis affecting the palms or soles; the nails; scalp; or facial, flexural, or genital regions, the physician is referred to the appropriate chapters of these Guidelines.

Recommendations	
Recommendation & level of evidence	Grade of recommendation
Topical corticosteroids may be used as first-line therapies for patients with mild plaque psoriasis (Refs. 1, 2, LoE 1++)	Grade A
Other appropriate first-line options include topical calcipotriol (Refs. 1, 2, 16, LoE 1++) and calcipotriol/betamethasone dipropionate in combination (Ref. 69, LoE 1++)	Grade A
For appropriate patients, tazarotene may be used, either alone or in combination with topical corticosteroids (Refs. 42, 49, LoE 1+)	Grade B
Non-medicinal emollients, including creams, ointments, and lotions, should be used in combination with the above agents to potentiate their effects (Ref. 77) and to help restore the barrier function of the skin (LoE 4)	Grade D
Because many standard topical therapies for the treatment of mild chronic plaque psoriasis are superior to placebo, including corticosteroids, calcipotriol, tazarotene, anthralin, tars, and various combination products, individualized approaches are indicated in choosing specific treatments and may supersede the above recommendations (LoE 4)	Grade D
Physicians should consider the vehicle used in topical agents and select formulations that will be acceptable to the patient (LoE 4)	Grade D
Clinical endpoints of treatment success should rely on patient satisfaction and health-related quality of life in addition to traditional objective indicators of disease response (LoE 4)	Grade D

Recommendations (cont.)	
Recommendation & level of evidence	Grade of recommendation
<p>Patients with mild, uncomplicated plaque psoriasis who respond to first- or second-line therapy can be safely managed by their primary care providers.</p> <p>Dermatologic referral may be indicated:</p> <ul style="list-style-type: none"> <li>• For those with more severe disease, as judged by the extent of the disease or the distress it causes the patient</li> <li>• For patients requiring in-depth counselling or education outside the scope of primary care practice</li> <li>• To assess an uncertain diagnosis</li> <li>• To assess or help establish an appropriate therapeutic regimen</li> <li>• Upon request by a patient</li> <li>• For patients failing to respond to therapy or becoming unresponsive to a previously successful treatment</li> <li>• For patients with involvement of the face, scalp, hands/feet, or intertriginous areas</li> <li>• For patients with complicated psoriasis (pustular, guttate, erythrodermic) or concomitant psoriatic arthritis (LoE 4 for all)</li> </ul>	<p><b>Grade D</b></p>
<p>For patients with uncontrolled mild plaque psoriasis, physicians should follow up regularly to address issues of adherence, monitor for clinical response, and consider adjustments in therapy. Those undergoing stable maintenance therapy should be followed up each 3–6 months (LoE 4)</p>	<p><b>Grade D</b></p>

## References

- Mason J, Mason AR, Cork MJ. Topical preparations for the treatment of psoriasis: a systematic review. *Br J Dermatol* 2002;146:351–64.
- Bruner CR, Feldman SR, Ventrapragada M, Fleischer AB, Jr. A systematic review of adverse effects associated with topical treatments for psoriasis. *Dermatol Online J* 2003;9:2.
- Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol* 2006;54:1–18.
- Morman MR. Possible side effects of topical steroids. *Am Fam Physician* 1981;23:171–4.
- Prawer SE, Katz HI. Guidelines for using superpotent topical steroids. *Am Fam Physician* 1990;41:1531–8.
- Roeder A, Schaller M, Schafer-Korting M, Korting HC. Safety and efficacy of fluticasone propionate in the topical treatment of skin diseases. *Skin Pharmacol Physiol* 2005;18:3–11.
- Katz HI, Prawer SE, Medansky RS, et al. Intermittent corticosteroid maintenance treatment of psoriasis: A double-blind multicenter trial of augmented betamethasone dipropionate ointment in a pulse dose treatment regimen. *Dermatologica* 1991;183:269–74.
- du Vivier A, Stoughton RB. Tachyphylaxis to the action of topically applied corticosteroids. *Arch Dermatol* 1975;111:581–3.
- Miller JJ, Roling D, Margolis D, Guzzo C. Failure to demonstrate therapeutic tachyphylaxis to topically applied steroids in patients with psoriasis. *J Am Acad Dermatol* 1999;41:546–9.
- Lebwohl MG, Tan MH, Meador SL, Singer G. Limited application of fluticasone propionate ointment, 0.005% in patients with psoriasis of the face and intertriginous areas. *J Am Acad Dermatol* 2001;44:77–82.
- Gerritsen MJ, Rulo HF, van Vlijmen-Willems I, et al. Topical treatment of psoriatic plaques with 1,25-dihydroxyvitamin D<sub>3</sub>: a cell biological study. *Br J Dermatol* 1993;128:666–73.
- Adisen E, Gulekon A, Gurer MA. The clinical efficacy of topical calcipotriol and methylprednisolone aceponate in chronic plaque psoriasis. *Gazi Tip Dergisi* 2003;14:175–9.
- Kragballe K, Austad J, Barnes L, et al. A 52-week randomized safety study of a calcipotriol/betamethasone dipropionate two-compound product (Dovobet/Daivobet/Taclonex) in the treatment of psoriasis vulgaris. *Br J Dermatol* 2006;154:1155–60.
- Safety and tolerability of calcipotriol in psoriasis. *Br J Clin Pract Suppl* 1996;83:26–8.
- Ashcroft DM, Li Wan Po A, Williams HC, Griffiths CE. Cost-effectiveness analysis of topical calcipotriol versus short-contact dithranol in the treatment of mild to moderate plaque psoriasis. *Pharmacoeconomics* 2000;18:469–76.
- Ashcroft DM, Li Wan Po A, Williams HC, Griffiths CEM. Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis. *BMJ* 2000;320:963–7.
- Berth-Jones J, Chu AC, Dodd WAH, et al. A multicentre, parallel-group comparison of calcipotriol ointment and short-contact dithranol therapy in chronic plaque psoriasis. *Br J Dermatol* 1992;127:266–71.
- Bruce S, Epinette WW, Funicella T, et al. Comparative study of calcipotriene (MC 903) ointment and fluocinonide ointment in the treatment of psoriasis. *J Am Acad Dermatol* 1994;31:755–9.
- Crosti C, Finzi AF, Mian E, Scarpa C. Calcipotriol in psoriasis vulgaris: a controlled trial comparing betamethasone dipropionate + salicylic acid. *Int J Dermatol* 1997;36:537–9.
- Cunliffe WJ, Berth-Jones J, Claudy A, et al. Comparative study of calcipotriol (MC 903) ointment and betamethasone 17-valerate ointment in patients with psoriasis vulgaris. *J Am Acad Dermatol* 1992;26:736–43.
- Green C, Ganpule M, Harris D, et al. Comparative effects of calcipotriol (MC903) solution and placebo (vehicle of MC903) in the treatment of psoriasis of the scalp. *Br J Dermatol* 1994;130:483–7.
- Harrington CI, Goldin D, Lovell CR, et al. Comparative effects of two different calcipotriol (MC 903) cream formulations versus placebo in psoriasis vulgaris. A randomised, double-blind, placebo-controlled, parallel group multi-centre study. *J Eur Acad Dermatol Venereol* 1996;6:152–8.
- Highton A, Quell J, Breneman D, et al. Calcipotriene ointment 0.005% for psoriasis: A safety and efficacy study. *J Am Acad Dermatol* 1995;32:67–72.
- Kose O. Calcipotriol ointment vs clobetasol solution in scalp psoriasis. *J Dermatolog Treat* 1997;8:287.
- Kragballe K. Treatment of psoriasis by the topical application of the novel cholecalciferol analogue calcipotriol (MC 903). *Arch Dermatol* 1989;125:1647–52.
- Kragballe K, Barnes L, Hamberg KJ, et al. Calcipotriol cream with or without concurrent topical corticosteroid in psoriasis: Tolerability and efficacy. *Br J Dermatol* 1998;139:649–54.
- Kragballe K, Fogh K, Sogaard H. Long-term efficacy and tolerability of topical calcipotriol in psoriasis. Results of an open study. *Acta Derm Venereol* 1991;71:475–8.
- Molin L, Cutler TP, Helander I, et al. Comparative efficacy of calcipotriol (MC903) cream and betamethasone 17-valerate cream in the treatment of chronic plaque psoriasis. A randomized, double-blind, parallel group multicentre study. *Br J Dermatol* 1997;136:89–93.
- Moazzanica N, Cattaneo A, Schmitt E, et al. Topical calcipotriol (MC 903) for psoriasis: a clinical study. *Acta Derm Venereol Suppl (Stockh)* 1994;186:169–70.
- Oh PI, Gupta AK, Einarson TR, et al. Calcipotriol in the treatment of psoriasis of limited severity: Pharmacoeconomic evaluation. *J Cutan Med Surg* 1997;2:7–15.
- Ortonne JP, Humbert P, Nicolas JF, et al. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3 microg g(-1) ointment and calcipotriol 50 microg g(-1) ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. *Br J Dermatol* 2003;148:326–33.
- Pinheiro N. Comparative effects of calcipotriol ointment (50µg/g) and 5% coal tar/2% allantoin/0.5% hydrocortisone cream in treating plaque psoriasis. *Br J Clin Pract* 1997;51:16–9.
- Ruzicka T, Lorenz B. Comparison of calcipotriol monotherapy and a combination of calcipotriol and betamethasone valerate after 2 weeks' treatment with calcipotriol in the topical therapy of psoriasis vulgaris: a multicentre, double-blind, randomized study. *Br J Dermatol* 1998;138:254–8.
- Scarpa C. Calcipotriol: clinical trial versus betamethasone dipropionate + salicylic acid. *Acta Derm Venereol Suppl (Stockh)* 1994;186:47.
- Cassano N, Miracapillo A, Coviello C, et al. Treatment of psoriasis vulgaris with the two-compound product calcipotriol/betamethasone dipropionate followed by different formulations of calcipotriol. *Clin Drug Invest* 2006;26:227–33.
- Kragballe K, Gjertsen BT, De Hoop D, et al. Double-blind, right/left comparison of calcipotriol and betamethasone valerate in treatment of psoriasis vulgaris. *Lancet* 1991;337:193–6.
- Wall ARJ, Poyner TF, Menday AP. A comparison of treatment with dithranol and calcipotriol on the clinical severity and quality of life in patients with psoriasis. *Br J Dermatol* 1998;139:1005–11.
- Lebwohl M, Ali S. Treatment of psoriasis. Part 1. Topical therapy and phototherapy. *J Am Acad Dermatol* 2001;45:487–98; quiz 99–502.
- Mortensen L, Kragballe K, Wegmann E, et al. Treatment of psoriasis vulgaris with topical calcipotriol has no short-term effect on calcium or bone metabolism. A randomized, double-blind, placebo-controlled study. *Acta Derm Venereol* 1993;73:300–4.
- Duvic M, Nagpal S, Asano AT, Chandraratna RA. Molecular mechanisms of tazarotene action in psoriasis. *J Am Acad Dermatol* 1997;37:S18–24.
- Gottlieb S, Hayes E, Gilleaudeau P, et al. Cellular actions of etretinate in psoriasis: enhanced epidermal differentiation and reduced cell-mediated inflammation are unexpected outcomes. *J Cutan Pathol* 1996;23:404–18.
- Green L, Sadoff W. A clinical evaluation of tazarotene 0.1% gel, with and without a high- or mid-high-potency corticosteroid, in patients with stable plaque psoriasis. *J Cutan Med Surg* 2002;6:95–102.
- Guenther LC, Poulin YP, Pariser DM. A comparison of tazarotene 0.1% gel once daily plus mometasone furoate 0.1% cream once daily versus calcipotriene 0.005% ointment twice daily in the treatment of plaque psoriasis. *Clin Ther* 2000;22:1225–38.
- Lebwohl M, Ast E, Callen JP, et al. Once-daily tazarotene gel versus twice-daily fluocinonide cream in the treatment of plaque psoriasis. *J Am Acad Dermatol* 1998;38:705–11.
- Lebwohl MG, Breneman DL, Goffe BS, et al. Tazarotene 0.1% gel plus corticosteroid cream in the treatment of plaque psoriasis. *J Am Acad Dermatol* 1998;39:590–6.
- Poulin YP. Tazarotene 0.1% gel in combination with mometasone furoate cream in plaque psoriasis: a photographic tracking study. *Cutis* 1999;63:41–8.
- Scher RK, Stillier M, Zhu YI. Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. *Cutis* 2001;68:355–8.
- Tzung T-Y, Wu J-C, Hsu N-J, et al. Comparison of tazarotene 0.1% gel plus petrolatum once daily versus calcipotriol 0.005% ointment twice daily in the treatment of plaque psoriasis. *Acta Derm Venereol* 2005;85:236–9.
- Weinstein GD, Krueger GG, Lowe NJ, et al. Tazarotene gel, a new retinoid, for topical therapy of psoriasis: Vehicle-controlled study of safety, efficacy, and duration of therapeutic effect. *J Am Acad Dermatol* 1997;37:85–92.
- Weinstein GD, Koo JY, Krueger GG, et al. Tazarotene cream in the treatment of psoriasis: Two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. *J Am Acad Dermatol* 2003;48:760–7.
- Ramsay B, Lawrence CM, Bruce JM, Shuster S. The effect of triethanolamine application on anthralin-induced inflammation and therapeutic effect in psoriasis. *J Am Acad Dermatol* 1990;23:73–6.
- Volden G, Bjornberg A, Tegner E, et al. Short-contact treatment at home with Micanol. *Acta Derm Venereol Suppl (Stockh)* 1992;172:20–2.
- Runne U, Kunze J. Short-duration ("minutes") therapy with dithranol for psoriasis: a new out-patient regimen. *Br J Dermatol* 1982;106:135–9.
- de Korte J, van der Valk PG, Sprangers MA, et al. A comparison of twice-daily calcipotriol ointment with once-daily short-contact dithranol cream therapy: quality-of-life outcomes of a randomized controlled trial of supervised treatment of psoriasis in a day-care setting. *Br J Dermatol* 2008;158:375–81.

55. Thawornchaisit P, Harncharoen K. A comparative study of tar and betamethasone valerate in chronic plaque psoriasis: a study in Thailand. *J Med Assoc Thai* 2007;90:1997–2002.
56. Sharma V, Kaur I, Kumar B. Calcipotriol versus coal tar: a prospective randomized study in stable plaque psoriasis. *Int J Dermatol* 2003;42:834–8.
57. Tzaneva S, Honigsmann H, Tanew A. Observer-blind, randomized, intrapatient comparison of a novel 1% coal tar preparation (Exorex) and calcipotriol cream in the treatment of plaque type psoriasis. *Br J Dermatol* 2003;149:350–3.
58. Kragballe K, Austad J, Barnes L, et al. Efficacy results of a 52-week, randomised, double-blind, safety study of a calcipotriol/betamethasone dipropionate two-compound product (Daivobet/Dovobet/Taclonex) in the treatment of psoriasis vulgaris. *Dermatology* 2006;213:319–26.
59. Lahfa M, Mrowietz U, Koenig M, Simon JC. Calcitriol ointment and clobetasol propionate cream: a new regimen for the treatment of plaque psoriasis. *Eur J Dermatol* 2003;13:261–5.
60. Kaufmann R, Bibby AJ, Bissonnette R, et al. A new calcipotriol/betamethasone dipropionate formulation (Daivobet) is an effective once-daily treatment for psoriasis vulgaris. *Dermatology* 2002;205:389–93.
61. Guenther L, Cambazard F, van de Kerkhof PCM, et al. Efficacy and safety of a new combination of calcipotriol and betamethasone dipropionate (once or twice daily) compared to calcipotriol (twice daily) in the treatment of psoriasis vulgaris: A randomized, double-blind, vehicle-controlled clinical trial. *Br J Dermatol* 2002;147:316–23.
62. Singh S, Reddy DC, Pandey SS. Topical therapy for psoriasis with the use of augmented betamethasone and calcipotriene on alternate weeks. *J Am Acad Dermatol* 2000;43:61–5.
63. Ortonne JP, Kaufmann R, Lecha M, Goodfield M. Efficacy of treatment with calcipotriol/betamethasone dipropionate followed by calcipotriol alone compared with tacalcitol for the treatment of psoriasis vulgaris: a randomised, double-blind trial. *Dermatology* 2004;209:308–13.
64. van de Kerkhof PC. The impact of a two-compound product containing calcipotriol and betamethasone dipropionate (Daivobet/ Dovobet) on the quality of life in patients with psoriasis vulgaris: a randomized controlled trial. *Br J Dermatol* 2004;151:663–8.
65. van Rossum MM, van Erp PEJ, van de Kerkhof PCM. Treatment of psoriasis with a new combination of calcipotriol and betamethasone dipropionate: A flow cytometric study. *Dermatology* 2001;203:148–52.
66. Lebwohl M, Siskin SB, Epinetto W, et al. A multicenter trial of calcipotriene ointment and halobetasol ointment compared with either agent alone for the treatment of psoriasis. *J Am Acad Dermatol* 1996;35:268–9.
67. Lebwohl M, Yoles A, Lombardi K, Lou W. Calcipotriene ointment and halobetasol ointment in the long-term treatment of psoriasis: effects on the duration of improvement. *J Am Acad Dermatol* 1998;39:447–50.
68. Gollnick H, Altmeyer P, Kaufmann R, et al. Topical calcipotriol plus oral fumaric acid is more effective and faster acting than oral fumaric acid monotherapy in the treatment of severe chronic plaque psoriasis vulgaris. *Dermatology* 2002;205:46–53.
69. Papp KA, Guenther L, Boyden B, et al. Early onset of action and efficacy of a combination of calcipotriene and betamethasone dipropionate in the treatment of psoriasis. *J Am Acad Dermatol* 2003;48:48–54.
70. Saraceno R, Andreassi L, Ayala F, et al. Efficacy, safety and quality of life of calcipotriol/betamethasone dipropionate (Dovobet) versus calcipotriol (Daivonex) in the treatment of psoriasis vulgaris: a randomized, multicentre, clinical trial. *J Dermatolog Treat* 2007;18:361–5.
71. Kragballe K, van de Kerkhof PC. Consistency of data in six phase III clinical studies of a two-compound product containing calcipotriol and betamethasone dipropionate ointment for the treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2006;20:39–44.
72. Kaidbey K, Kopper SC, Sefton J, Gibson JR. A pilot study to determine the effect of tazarotene gel 0.1% on steroid-induced epidermal atrophy. *Int J Dermatol* 2001;40:468–71.
73. Bowman PH, Maloney JE, Koo JYM. Combination of calcipotriene (Dovonex) ointment and tazarotene (Tazorac) gel versus clobetasol ointment in the treatment of plaque psoriasis: a pilot study. *J Am Acad Dermatol* 2002;46:907–13.
74. Koo J, Cuffie CA, Tanner DJ, et al. Mometasone furoate 0.1%-salicylic acid 5% ointment versus mometasone furoate 0.1% ointment in the treatment of moderate-to-severe psoriasis: a multicenter study. *Clin Ther* 1998;20:283–91.
75. Davies M, Marks R. Studies on the effect of salicylic acid on normal skin. *Br J Dermatol* 1976;95:187–92.
76. Krochmal L, Wang JC, Patel B, Rodgers J. Topical corticosteroid compounding: effects on physicochemical stability and skin penetration rate. *J Am Acad Dermatol* 1989;21:979–84.
77. Watsky KL, Freije L, Leneveu MC, et al. Water-in-oil emollients as steroid-sparing adjunctive therapy in the treatment of psoriasis. *Cutis* 1992;50:383–6.
78. Rim JH, Jo SJ, Park JY, et al. Electrical measurement of moisturizing effect on skin hydration and barrier function in psoriasis patients. *Clin Exp Dermatol* 2005;30:409–13.
79. Paulsen E, Korsholm L, Brandrup F. A double-blind, placebo-controlled study of a commercial Aloe vera gel in the treatment of slight to moderate psoriasis vulgaris. *J Eur Acad Dermatol Venereol* 2005;19:326–31.
80. Brown AC, Koett J, Johnson DW, et al. Effectiveness of kukui nut oil as a topical treatment for psoriasis. *Int J Dermatol* 2005;44:684–7.
81. Maysner P, Grimm H, Grimminger F. N-3 fatty acids in psoriasis. *Br J Nutr* 2002;87 Suppl 1:S77–82.
82. Maysner P, Mrowietz U, Arenberger P, et al. Omega-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, multicenter trial. *J Am Acad Dermatol* 1998;38:539–47.
83. Weidman AI. Treatment of psoriasis and other dermatoses with intraleisional injections of triamcinolone acetonide. *Curr Ther Res Clin Exp* 1963;5:7–11.
84. Hasegawa J, Livingston W. The intraleisional use of triamcinolone acetonide in psoriasis. A double blind study. *Arch Dermatol* 1962;85:258–60.
85. Gupta AK, Rasmussen JE. Perilesional linear atrophic streaks associated with intraleisional corticosteroid injections in a psoriatic plaque. *Pediatr Dermatol* 1987;4:259–60.
86. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. *Br J Dermatol* 1999;141:185–91.
87. Berth-Jones J, Grotzinger K, Rainville C, et al. A study examining inter- and intrarater reliability of three scales for measuring severity of psoriasis: Psoriasis Area and Severity Index, Physician's Global Assessment and Lattice System Physician's Global Assessment. *Br J Dermatol* 2006;155:707–13.
88. Cassell SE, Bieber JD, Rich P, et al. The modified Nail Psoriasis Severity Index: Validation of an instrument to assess psoriatic nail involvement in patients with psoriatic arthritis. *J Rheumatol* 2007;34:123–9.
89. Fortune DG, Main CJ, O'Sullivan TM, Griffiths CEM. Assessing illness-related stress in psoriasis: The psychometric properties of the psoriasis life stress inventory. *J Psychosom Res* 1997;42:467–75.
90. Gupta MA, Gupta AK. The psoriasis life stress inventory: A preliminary index of psoriasis-related stress. *Acta Derm Venereol* 1995;75:240–3.
91. Husted JA, Gladman DD, Farewell VT, et al. Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. *J Rheumatol* 1997;24:511–7.
92. Jacobson CC, Kimball AB. Rethinking the Psoriasis Area and Severity Index: the impact of area should be increased. *Br J Dermatol* 2004;151:381–7.
93. Kirby B, Fortune DG, Bhushan M, et al. The Salford Psoriasis Index: An holistic measure of psoriasis severity. *Br J Dermatol* 2000;142:728–32.
94. Kirby B, Richards HL, Woo P, et al. Physical and psychological measures are necessary to assess overall psoriasis severity. *J Am Acad Dermatol* 2001;45:72–6.
95. Nichol MB, Margolies JE, Lippa E, et al. The application of multiple quality-of-life instruments in individuals with mild-to-moderate psoriasis. *Pharmacoeconomics* 1996;10:644–53.
96. Rich P, Scher RK. Nail Psoriasis Severity Index: A useful tool for evaluation of nail psoriasis. *J Am Acad Dermatol* 2003;49:206–12.
97. Shiklar R, Willian MK, Okun MM, et al. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. *Health Qual Life Outcomes* 2006;4:71.
98. Brown KK, Rehmus WE, Kimball AB. Determining the relative importance of patient motivations for nonadherence to topical corticosteroid therapy in psoriasis. *J Am Acad Dermatol* 2006;55:607–13.
99. Zaghoul SS, Goodfield MJ. Objective assessment of compliance with psoriasis treatment. *Arch Dermatol* 2004;140:408–14.
100. Carroll CL, Feldman SR, Camacho FT, Balkrishnan R. Better medication adherence results in greater improvement in severity of psoriasis. *Br J Dermatol* 2004;151:895–7.
101. Krueger GG, Feldman SR, Camisa C, et al. Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? *J Am Acad Dermatol* 2000;43:281–5.



## CHAPTER 6: MANAGEMENT OF MODERATE TO SEVERE PLAQUE PSORIASIS

### *Canadian Guidelines for the Management of Plaque Psoriasis*

Definitions of moderate to severe psoriasis in the clinical literature are varied and contradictory. Commonly, moderate psoriasis is distinguished from milder forms of the disease on the basis of scores on one or more clinical metrics, such as the Psoriasis Area and Severity Index (PASI), the percent of body surface area (BSA) affected, or the Dermatological Life Quality Index (DLQI). While numerical cut-offs are necessary in clinical trial design, they have little value in daily practice, as discussed in Chapter 3 (Definitions). For the purposes of these Guidelines, therefore, patients are considered to have moderate to severe psoriasis if they cannot achieve, or would not be expected to achieve, adequate control using topical agents, with adequacy defined by the patient's own perception of the disease and its burdens.

#### **Clinical goals**

Appropriate clinical goals for managing plaque psoriasis are also a matter of dispute. Some years ago, it was prominently argued that disease clearance represents an unrealistic standard for success in treating this lifelong, chronic condition. Amelioration, i.e., short-term improvement and limited long-term disease control, was suggested as a more appropriate goal in the real world of a dermatology clinic, where patient histories are more heterogeneous than in clinical trials and where treatment adherence is far from optimal.<sup>1</sup>

For some patients with moderate to severe psoriasis, amelioration may be an adequate treatment goal, and indeed, many therapeutic tools are available that can be used, even as monotherapy, to achieve some degree of control. There is abundant evidence that each of the therapies listed in **Table 1** can be used to this end, as documented by at least a 50–75% reduction in PASI score in a significant proportion of treated patients.

However, the literature also shows that clearance can be achieved using phototherapy and that this goal has become all the more realistic with the introduction of biologic agents in recent years. Indeed, some patients on biologics experience periods essentially

free of psoriatic symptoms.<sup>2</sup> With these newer tools in hand, it has been possible to document the quality-of-life benefits associated with dramatic disease suppression (e.g., achieving a score of < 3 on the 72-point PASI scale), as well as the further, significant benefits of achieving a PASI score of 0.<sup>3,4</sup> Hence, full clearance represents an achievable and appropriate goal in treating many patients.

Although many antipsoriatic therapies are ameliorative, fewer of them can be used to achieve complete or nearly complete clearance of symptoms. This more ambitious clinical goal is also more difficult to document, since only rarely (and only in the most recent publications) is a 100% reduction in PASI score included as a clinical endpoint. However, some papers do cite final PASI scores and present the number of patients achieving a specific, low PASI score (e.g., 0–4). Others report a 90% reduction in PASI, which, for the great majority of patients, will necessarily correspond to a final PASI score in this same low range. Still other reports cite rates of “complete clearance”, “complete remission”, or “minimal residual activity”. For instance, in phototherapy studies, it is common to provide as many UV sessions as the patient requires to reach a pre-specified treatment target, such as clearance. In such studies, the phototherapy treatments are evaluated not only for their ability to meet such a target, but also to meet it rapidly, with minimal UV exposure.

#### **KEY POINT**

*For some patients with moderate to severe psoriasis, amelioration may be an adequate treatment goal, and many therapeutic tools are available that can be used, even as monotherapy, to achieve some degree of control (see **Table 1**). However, the literature also shows that clearance is feasible, particularly with the introduction of biologic agents in recent years. Hence, full clearance represents an appropriate goal in treating many patients (see **Table 2**).*

### Safety, efficacy, and tolerability of the various therapeutic options

The discussion below centres on the issues that could limit use of each of the therapeutic options described in **Table 1**, as well as on the efficacy of these options when used as monotherapy. Although all of these approaches ameliorate plaque psoriasis in patients with moderate to severe disease, their efficacy in the real world may be compromised by poor adherence.<sup>5</sup> It is therefore necessary to select those options that are likely to be both safe for and acceptable to the individual patient.

While not all of the ameliorative therapies shown in **Table 1** induce full clearance of psoriatic symptoms, some may be better suited to this purpose when used in combination regimens. **Table 2** presents monotherapies and combination regimens that have been used successfully to achieve complete or nearly complete clearance in a significant proportion of patients.

Note that this chapter specifically addresses chronic plaque psoriasis affecting the trunk and extremities; the reader should consult other chapters of these Guidelines for recommendations on managing psoriasis of the palms and soles; the scalp; nails; and facial, flexural, and genital areas. However, patients whose disease affects both the trunk and some of these other areas may benefit from the systemic and phototherapeutic regimens considered here.

#### Topical treatment

For patients with moderate to severe psoriasis, the topical agents used in mild psoriasis (see Chapter 5: Management of mild plaque psoriasis) remain useful adjuncts. Because it is assumed that the patient's condition is intractable with strictly topical therapy, these agents are not discussed below unless they are to be used in combination regimens with systemic or phototherapies.

One exception is a two-compound calcipotriol and betamethasone ointment, which has been examined in randomized controlled trials in patients with relatively severe disease, including those with baseline PASI score averaging 22.6. More than half of those treated experienced a 75% reduction in PASI score within 4 weeks.<sup>6</sup>

This combination ointment is well tolerated but should not be used on facial, flexural, and genital

areas (see Chapter 9: Management of facial, flexural, and genital psoriasis). If this ointment is used in quantities exceeding the recommended limit of 5 mg calcipotriol (100 g ointment) per week, the patient's serum calcium level should be monitored regularly. Overdose carries potential risk of systemic toxicity, including hypothalamic-pituitary-adrenal axis suppression, associated with betamethasone, and hypercalcemia, associated with calcipotriol.

#### Systemic therapy with traditional and biologic agents

Traditional systemic agents remain mainstays of treatment for plaque psoriasis. As discussed below, methotrexate and cyclosporine can offer effective control in many cases, but their use is limited by toxicity; acitretin carries less risk of specific end-organ toxicity, but it is teratogenic and therefore inappropriate for many female patients of childbearing age. All three of these agents also have the potential for interactions with other drugs (**Table 3**), which may limit their use in certain patients.

The biologic agents currently available for psoriasis represent significant recent additions to the dermatologist's toolkit. Although their record of use in psoriasis remains shorter than that of other treatments, their safety records all extend for multiple years of pre- and post-marketing use. In the case of the TNF- $\alpha$  antagonists, the safety record for psoriasis is supported by a longer history of use in other indications, such as rheumatoid or psoriatic arthritis. As described below, the various biologics have been linked to specific adverse events, but none is associated with common safety concerns, such as the end-organ toxicity observed in cyclosporine and methotrexate or the risk of squamous cell carcinoma (SCC) associated with PUVA.

There is no clinical reason, therefore, to reserve the biologics for second-line use.<sup>7</sup> In many cases, the safety of these agents, as well their relatively good tolerability and acceptability to patients, represent deciding factors for their use.



### Systemic agents

#### *Acitretin*

Acitretin is the only antipsoriatic retinoid drug available for systemic use in Canada. Retinoids as a class are teratogenic, placing severe constraints on the use of acitretin in women of childbearing age and potential (see **Table 1**). Common side effects include mucocutaneous dryness (often obvious as chapped lips) and elevation of triglycerides.<sup>8</sup> Rarer events, including skeletal abnormalities such as diffuse idiopathic skeletal hyperostosis (DISH) syndrome, remain a concern, but their incidence appears to be low in individuals receiving the standard doses.<sup>9</sup> Low-dose acitretin (25 mg/day) is safer and better tolerated than higher-dose (50 mg/day) treatment.

There is little evidence for the benefit of acitretin monotherapy in plaque psoriasis,<sup>10,11</sup> but the combination of acitretin with topical calcipotriol has been reported to increase rates of clearance,<sup>12</sup> and the combination of acitretin with biologic therapy has also been explored.<sup>13</sup> Use of acitretin in combination with phototherapies is discussed below.

#### *Cyclosporine*

Cyclosporine is a calcineurin inhibitor used as an immunomodulator in a variety of indications, including chronic plaque psoriasis. Although it can be effective in long-term, continuous use,<sup>14</sup> cyclosporine is associated with cumulative renal toxicity,<sup>15</sup> causing loss of renal function that may be reversible following discontinuation.<sup>16,17</sup> In addition to its adverse effects on the kidney, this drug can cause hypertension and hypertriglyceridemia, particularly in patients with prior elevation of diastolic blood pressure or triglycerides.<sup>18</sup> The risk of SCC and other forms of non-melanoma skin cancer also rises with increasing time on cyclosporine.<sup>19</sup>

It has been proposed that continuous cyclosporine, for periods up to 2 years, is appropriate for a subset of patients. Annual monitoring of glomerular filtration rate is recommended when cyclosporine is provided in this manner, in addition to routine, monthly assessments of blood pressure and creatinine

clearance, with more frequent measurements during the initial 6 weeks of treatment.<sup>20-22</sup> However, cyclosporine should normally be reserved for intermittent use in periods up to 12 weeks,<sup>23,24</sup> and kidney function, blood pressure, and triglyceride levels should be carefully monitored before, during, and after treatment. When used in this intermittent fashion, a course of cyclosporine treatment can induce an average decrease of > 75% in psoriasis severity, an effect that is consistent over at least three treatment cycles.<sup>21</sup>

In isolated cases, sudden discontinuation of cyclosporine has led to a dramatic rebound of psoriasis.<sup>22</sup>

#### *Methotrexate*

Methotrexate is an inhibitor of folate biosynthesis and therefore impairs DNA replication. It was originally used in psoriasis for its cytostatic properties, but it is now recognized to be directly anti-inflammatory because of its effects on T cell gene expression patterns.<sup>25</sup> Some but not all of these effects are related to folate depletion, consistent with clinical evidence that folate supplementation can diminish the efficacy of methotrexate treatment in psoriasis.<sup>26</sup> Folate supplementation is commonly justified on the basis of a reduced risk of toxic effects of methotrexate. A recent study in rheumatoid arthritis (RA) raised some doubt about the efficacy of folate treatment for preventing pancytopenia, a rare but potentially fatal side effect of low-dose methotrexate. However, this study confirmed that folate supplementation significantly reduced the incidence of liver toxicity and thereby prevented treatment discontinuation.<sup>27</sup>

Although the use of folate remains controversial in dermatological practice,<sup>28</sup> there appears to be little doubt that it improves the tolerability of methotrexate treatment and may therefore increase treatment adherence.<sup>29</sup> Hence, this practice may be justified by greater real-world efficacy and a wider therapeutic window, even if folate partially inhibits the therapeutic action of methotrexate.<sup>26,30</sup>

Compared with cyclosporine, methotrexate has a more modest and inconsistent effect on

psoriasis severity over a 12-week period,<sup>31</sup> but it is valuable because it can be used continuously over a period of years or decades, with durable benefits.<sup>32</sup> The predominant safety issue with methotrexate is cumulative liver toxicity, which was shown in a Canadian study to be severe in nearly one-fourth of patients receiving the drug over the course of 1–11 years.<sup>33</sup> Patients with comorbid diabetes were at particularly high risk of severe liver fibrosis and cirrhosis.

Guidelines have traditionally recommended routine pre-treatment liver biopsies and subsequent biopsies at intervals based on cumulative methotrexate consumption, e.g., every time a cumulative dose of 1.5 g of the drug is taken. However, pre-treatment biopsies may not be practical or appropriate in all cases.<sup>34,35</sup>

In addition to its effects on the liver, methotrexate can lead to pancytopenia and pulmonary toxicity,<sup>36,37</sup> and it has also been associated with a small but significant increase in lymphoma<sup>38</sup> and acute myelosuppression,<sup>39</sup> a potentially fatal outcome. In isolated cases, methotrexate treatment has led to Epstein-Barr virus-associated lymphoproliferative disease<sup>40</sup> or to an osteoporotic condition that remits upon withdrawal of methotrexate.<sup>41</sup> Methotrexate frequently causes nausea that can be severe enough to lead to treatment discontinuation. It is also an abortifacient and teratogen and is therefore strictly contraindicated during pregnancy; men as well as women should be counselled to use effective contraception while being treated with methotrexate. Men should continue to use contraception for 3 months, and women should do so for at least one ovulatory cycle after discontinuing methotrexate (see Chapter 7: Special populations and circumstances).

#### *Other systemic agents*

Several agents are occasionally used for recalcitrant moderate to severe plaque psoriasis, although they are not approved in Canada for this indication. These include mycophenolate mofetil<sup>42</sup> and hydroxyurea.<sup>43</sup> Several small studies and case reports indicate that these agents can be effective over a course of 12 weeks, but comparative studies<sup>44,45</sup> provide little evidence that they offer superior efficacy,

relative to standard systemic treatments such as methotrexate and cyclosporine. Mycophenolate mofetil is an immunosuppressive agent commonly used in transplant patients. In these patients, the drug can cause neutropenia and a possible increased risk of lymphoma and opportunistic infections. Hydroxyurea, an antineoplastic agent, can lead to bone marrow suppression as well as mucocutaneous effects, such as reversible hyperpigmentation, localized tenderness, and erythema.<sup>46</sup>

#### Biologic agents targeting TNF- $\alpha$

The biologic agents adalimumab, etanercept, and infliximab share a common mechanism of action and offer the prospect of more rapid disease control than is commonly seen with the other biologics. They also share a number of overlapping safety concerns, including serious infections (notably sepsis, new-onset or reactivated tuberculosis [TB], and certain viral infections), autoimmune conditions (lupus and demyelinating disorders), and malignancies such as lymphoma.

Despite the difficulty of establishing causality, these rare events may represent class effects for the TNF- $\alpha$  antagonists. However, it should not be assumed that the three TNF inhibitors are identical in their safety profiles. The risk of granulomatous infections, such as TB, is well established to vary among the three agents, with the lowest risk seen in patients treated with etanercept and higher risk in infliximab-treated patients.<sup>47</sup> The risk of reactivated or new-onset TB associated with adalimumab appears to be intermediate between those of etanercept and infliximab, although the data on this point remain equivocal.<sup>47,48</sup>

#### *Adalimumab*

Adalimumab offers effective control of plaque psoriasis, with complete or nearly complete clearance in some cases. For some patients, significant improvement is evident within 1 week of initiating treatment.<sup>49</sup> In one trial, approximately one-fifth of patients achieved a 100% reduction of PASI score within 16 weeks. Clinical benefits, at the PASI-75 level or better, were maintained for at least 1 year with continuous therapy, although approximately

10% of initially responsive patients were judged to have lost their adequate response in the course of further therapy.<sup>50</sup>

In a direct comparison with methotrexate and placebo, adalimumab proved to have higher rates of 75%, 90%, and 100% PASI improvement and a lower rate of adverse events and treatment discontinuation than methotrexate,<sup>2</sup> as well as a significantly greater beneficial effect on patient quality of life.<sup>4</sup>

The safety record of adalimumab, based largely on use in rheumatoid and psoriatic arthritis, has revealed few alarming adverse events, although this may reflect its shorter history of use compared to the other TNF- $\alpha$  antagonists. There is little evidence to date that adalimumab increases the risk of lymphoma, demyelinating disorders, or opportunistic infections beyond the background rate seen in the psoriatic population. However, adalimumab is associated with reactivation of latent TB, and risk of TB can be minimized but not eliminated altogether by screening and prophylaxis.<sup>51</sup> As with the other biologics of this class, adalimumab may also activate pre-existing malignant melanoma.<sup>52</sup>

In addition, like the other TNF- $\alpha$  antagonists (etanercept and infliximab, discussed below), adalimumab can lead in isolated cases to flares of pustular psoriasis.<sup>53</sup> This reaction has typically been seen in individuals undergoing treatment for non-dermatological conditions such as rheumatoid arthritis, but it is sometimes seen in patients with a personal history of pustular psoriasis<sup>54</sup> (see Chapter 8: Exacerbation and flare of psoriasis).

Adalimumab is administered subcutaneously, usually at a dose of 40 mg every other week, following a loading dose of 80 mg,<sup>2,50</sup> although more frequent dosing has been explored.<sup>49</sup>

#### *Etanercept*

Etanercept, a fusion protein targeting TNF- $\alpha$  signalling, is indicated for rheumatoid and psoriatic arthritis, as well as for moderate to severe psoriasis.

Etanercept is generally initiated at a dose of 50 mg BIW, which is stepped down to 25 mg BIW

after the first 12 weeks of treatment.<sup>55</sup> This dosing is sufficient to achieve a 75% reduction in PASI score after 24 weeks of therapy in more than half of patients and a  $\geq 90\%$  reduction in one-fifth of patients.<sup>56</sup> However, the best evidence for clearance or near clearance of symptoms comes from patients receiving a constant dose of 50 mg BIW.<sup>57</sup> This dosing has not been associated with any additional safety concerns, and it allows for approximately one-third of patients to achieve a 90% reduction in PASI score by 36 weeks of treatment.<sup>57</sup>

Weaker responders ( $\leq 50\%$  PASI reduction after 24 weeks) need not discontinue, as they may experience continued improvement from maintaining etanercept for  $> 1$  year.<sup>58</sup> For patients with an inadequate response at 24 weeks, the physician should consider maintaining constant 50 mg BIW dosing, rather than stepping the dose down.<sup>57</sup>

Some patients appear to experience a partial loss of control between 36 and 96 weeks of treatment, even when maintained on the higher dose of etanercept.<sup>57</sup>

Serious safety concerns shared with the other TNF- $\alpha$  antagonists include the risk of serious infections and of reactivating latent TB,<sup>59</sup> malignant melanomas,<sup>52</sup> or squamous cell carcinomas.<sup>60</sup>

In isolated cases, etanercept treatment has induced guttate flares in patients being treated for plaque psoriasis.<sup>61</sup> This may be a class effect for the TNF inhibitors, since a similar response has also been reported in patients receiving adalimumab or infliximab for non-dermatological conditions.<sup>61</sup> With these exceptions, etanercept is generally well tolerated.

#### *Infliximab*

The TNF- $\alpha$  antagonist infliximab offers rapid and thorough suppression of psoriatic symptoms. Infliximab is approved for use in chronic moderate to severe psoriasis; it has been available longer than adalimumab and has been used more extensively to treat acute flares. When used in patients with particularly severe psoriasis (baseline PASI score up to 48), this agent was generally well tolerated for periods up to 2 years.<sup>62</sup>

Infliximab is administered by intravenous infusion; standard treatment requires three infusions (5 mg/kg) over a 6-week induction period, followed by regular infusions every 8 weeks. Nearly half of infliximab-treated patients experience a  $\geq 90\%$  decline in PASI score within 10 weeks of the initial treatment,<sup>63</sup> which can be associated with dramatic improvements in quality of life as assessed by a score of 0 on the Dermatological Life Quality Index.<sup>64</sup> However, at least half of responsive patients experience a decline in efficacy during the second year of continuous treatment.<sup>63,65,66</sup> It has been suggested that concomitant therapy with methotrexate plus folate is useful for patients developing resistance to infliximab<sup>67</sup>; this combination regimen has been explored for patients with psoriatic arthritis<sup>68</sup> and, more systematically, for patients with rheumatoid arthritis.<sup>69</sup>

Infliximab is associated with a risk of infusion reactions, as well as other adverse events that have been reported for the other TNF inhibitors, such as serious infections and reactivated TB,<sup>59</sup> lupus, demyelinating disorders, thrombocytopenia, and malignancies.<sup>63,66,70</sup> In rare instances, infliximab has been associated with cholecystitis and autoimmune hepatitis, which may be a class effect for TNF inhibitors.<sup>71,72</sup> The potential for hepatitis B reactivation with infliximab and other TNF inhibitors is discussed in Chapter 7 (Special populations and circumstances).

The incidence of serious adverse events leading to discontinuation was reported to be approximately 25% in one small study of patients receiving regular infliximab infusions for up to 21 months.<sup>66</sup> By contrast, infliximab discontinuation due to adverse events occurred in only 9% of patients in a 50-week phase 3 trial.<sup>73</sup>

#### Biologic agents targeting T cells

Alefacept is currently the only biologic agent available in Canada that interacts directly with T cell surface proteins.

Alefacept acts in part by triggering the death of pathogenic T lymphocytes. It was the first biologic to be approved for moderate to severe psoriasis and has accumulated an extensive and reassuring safety record. There is no evidence in

humans that alefacept increases the incidence of infections, cancers, or any other serious adverse outcome beyond background levels.<sup>74</sup> The sole exception is a laboratory finding, depletion of CD4 T lymphocytes; the patient's CD4 cell counts must therefore be monitored and treatment withheld when this cell population declines below 250/ $\mu\text{L}$ . In case of persistent decline in CD4 count, alefacept should be discontinued.

Alefacept is unique among the biologics in that it is intended for intermittent rather than long-term continuous use. A 12-week course of alefacept allows for a 50–75% reduction in PASI score in approximately one-fourth of patients, and this improvement may be maintained in some patients for periods beyond 1 year. Courses may be repeated when the loss of control becomes unacceptable, up to twice per year. While some patients benefit from repeated courses of alefacept,<sup>75</sup> the number of such responders is difficult to estimate.<sup>76</sup>

Although alefacept is described as a remittive therapy, remission with this treatment is relative, not absolute; there is little evidence that alefacept monotherapy can be used to achieve full clearance of symptoms,<sup>77</sup> and indeed, it appears that this biologic is often used in combination regimens.<sup>78</sup> However, in combination with narrowband (NB) UVB treatment, alefacept permits a reduction in PASI score to 3 or lower in 43% of patients within 12 weeks. This combination significantly reduces the number of UVB treatments that would otherwise be necessary to achieve clearance.<sup>77</sup>

#### ***Phototherapy and photochemotherapy***

Use of UV phototherapy was an outgrowth of traditional climate and balneotherapy, in which psoriasis patients were advised to vacation in sunny environments such as saltwater spas. The effects of UV therapies on cutaneous inflammatory cell populations are well established. Both narrowband UVB and PUVA cause a rapid depletion of cell populations that are implicated in psoriasis pathogenesis, including dermal and epidermal lymphocytes, macrophages, and dendritic cells.<sup>79</sup>



In both of these common forms of phototherapy, the dose of UV light must be carefully titrated, based initially on the patient's complexion and likeliness to burn or to tan. Treatment is offered on a regular schedule until patients achieve the desired degree of symptomatic improvement. The requirement to appear one to four times per week at a phototherapy clinic can be burdensome for some patients and may limit the efficacy of this approach if clearance cannot be achieved quickly.

Acute safety issues with phototherapy are rare but can include treatment-related effects such as erythema or blistering.<sup>80</sup> However, because PUVA and perhaps also UVB therapy pose a risk of carcinogenesis, it is important to limit patients' cumulative exposure to therapeutic UV light.<sup>81-83</sup>

#### *PUVA monotherapy*

PUVA refers to a variety of therapeutic techniques that use 5- or 8-methoxypsoralen to sensitize cells to the effects of longer-wavelength UV light (320–400 nm). Common variations allow for psoralen to be administered topically, either by bathing in a psoralen solution, by painting the compound on affected skin, or orally. Oral psoralens can cause nausea but are generally well tolerated. PUVA is generally highly effective, commonly leading to clearance within 4–6 weeks at four treatment sessions per week<sup>84</sup> or over a longer period with less frequent sessions.<sup>85</sup>

PUVA leads to skin aging and freckling and has been associated with non-melanoma skin cancers, including SCC and, less frequently, basal cell carcinomas.<sup>86</sup> This heightened risk appears to correlate with the patient's total cumulative dose, increasing dramatically in individuals who have undergone more than 200 treatments,<sup>87</sup> and it persists for up to 15 years after PUVA treatment is discontinued.<sup>88</sup>

One large prospective study in the US has identified an additional risk of melanoma with increasing cumulative UVA doses.<sup>86</sup> In a Scandinavian cohort, however, no such effect on melanoma risk could be detected, although the study confirmed the excess of non-melanoma skin cancers, relative to background incidence.<sup>89</sup> The basis for this difference in outcome is not

known. Regardless, to minimize the risk of cancer, lifetime exposure should be capped if possible at 200 PUVA sessions.<sup>88</sup> Patients with a history of PUVA use may be inappropriate for subsequent treatment with immunomodulatory agents, such as cyclosporine, which could allow the emergence of SCC and other non-melanoma skin cancers.<sup>19</sup>

#### *UVB monotherapy*

When used without concomitant therapy, NB-UVB treatment can also lead to full clearance of psoriatic symptoms, although efficacy within 3 months depends in part on the frequency of treatment. For instance, it has been reported that thrice-weekly NB-UVB treatment is as effective as twice-weekly PUVA,<sup>90</sup> whereas twice-weekly NB-UVB treatment is less likely to lead to clearance.<sup>91</sup>

Despite the extensive history of this treatment, the long-term safety of UVB therapy remains a matter of speculation. Unlike PUVA, it has not been established whether UVB is carcinogenic in humans,<sup>92,93</sup> although preclinical data suggest that NB-UVB could be somewhat more carcinogenic, on a dose-by-dose basis, than natural exposure to the sun.<sup>81</sup> There are no immediate prospects of UVB trials with sufficient power to quantify this risk<sup>81</sup>; in the absence of such evidence, it is prudent to use appropriate combination therapies when possible to reduce exposure to NB-UVB radiation.

#### *UV combination regimens*

A wide variety of photochemotherapeutic regimens have been studied, and many offer clear advantages over the corresponding phototherapy. The best studied is the addition of retinoids, typically acitretin, to PUVA or UVB therapy (RePUVA or ReUVB).<sup>94</sup> RePUVA can be used to achieve clearance with up to a twofold reduction in total UV exposure, compared with PUVA alone.<sup>95</sup> Relative to phototherapy alone, combined treatment with acitretin can significantly reduce exposure to UVB.<sup>96,97</sup>

Whereas acitretin is inappropriate for many female patients because of its teratogenicity and long elimination half-time (see **Table 1**), topical agents such as calcipotriol and

tazarotene can be combined more freely with UV treatment. Both of these topical agents, used daily<sup>98,99</sup> in combination with NB-UVB, can significantly reduce the UV dose needed to achieve clearance. In a study of calcipotriol used daily in combination with twice-weekly broadband UVB, this combination allowed for 60% of patients to achieve clearance within 12 weeks. This result was similar to that seen in a comparator group who received thrice-weekly UVB plus placebo, but control was achieved with significantly lower ultraviolet exposure.<sup>100</sup>

One older photochemotherapeutic regimen that appears no longer to be used widely in Canada is the so-called Goeckerman protocol. This procedure requires multiple, day-long treatment sessions with crude coal tar and UVB irradiation. Because of the inconvenience and time involved, the procedure is appropriate only for strongly motivated patients, and it requires a specialized treatment centre that can accommodate them. Goeckerman therapy is commonly combined with other approaches ('modified Goeckerman treatment'), making it difficult to assess the relative contribution of

the different components.<sup>101</sup> However, recent findings confirm that even those patients treated with NB-UVB plus tar alone can achieve complete or nearly complete clearance, with durable benefits over a period of months.

Numerous other therapeutics, including methotrexate<sup>102</sup> and biologics such as alefacept,<sup>77</sup> can be used in conjunction with UVB or PUVA to achieve a high degree of symptomatic control while limiting the patient's exposure to UV radiation.

### Achieving clearance

**Table 2** describes monotherapies and combination regimens that may be used to achieve complete or nearly complete clearance of psoriatic symptoms, along with the strength of evidence for each in this regard. The recommended regimens may be suitable for only a subset of patients, as a result of individual medical history, lifestyle, or other constraints. It is suggested that patients explore all appropriate choices to identify ones that can be used over the long term to achieve and maintain adequate control of their psoriasis.

## Recommendations

Recommendation & level of evidence	Grade of recommendation
For patients with moderate to severe plaque psoriasis affecting the trunk and extremities, the physician should aim to control the symptoms stably and to an extent that the patient judges adequate (LoE 4)	Grade D
In aiming to achieve complete control of moderate to severe plaque psoriasis, the physician should consider each of the regimens listed in <b>Table 2</b> and choose ones that are safe for and acceptable to the individual patient	Grade D
Cyclosporine should be reserved for intermittent control and ordinarily should not be used for periods greater than 12 weeks, unless clinically indicated (Ref. 103, LoE 1+; Refs. 23,104, LoE 2+)	Grade B
Phototherapy with PUVA should be restricted to a lifetime total of 200 treatment sessions unless clinically indicated, using UV-sparing combination regimens as appropriate (Ref. 88, LoE 2++)	Grade B
Phototherapy with UVB should be conducted to minimize cumulative lifetime exposure to UV light, using UV-sparing combination regimens as appropriate (Ref. 81, LoE 4)	Grade D



**Table 1.** Therapeutic options for ameliorating moderate to severe plaque psoriasis (alphabetical list, grouped by class)

	Considerations	Evidence for efficacy as monotherapy*	References
<b>Topical agent</b>			
Calcipotriol/ betamethasone dipropionate combination ointment	Effective in moderate to severe psoriasis (including baseline PASI > 17), as well as in milder disease; should not be used on facial, flexural, and genital areas	LoE 1++	Ref. 6
<b>Oral systemic agents</b>			
Acitretin	Retinoid drug; highly teratogenic and strictly contraindicated in pregnancy. Not to be used in women of childbearing age unless they are able and willing to use contraception for 3 years after discontinuing acitretin  Rarely used as monotherapy, but often combined with topical agents such as potent corticosteroids, or with other therapeutics to allow for more rapid/complete control, with reduced exposure to the other therapeutic	LoE 1-	Refs. 8, 10
Cyclosporine	Immunosuppressive drug; leads to cumulative renal toxicity; can exacerbate hypertension and hypertriglyceridemia  Can be highly effective in severe disease, but best employed intermittently, rather than for continuous long-term use <sup>23,103,104</sup>	LoE 1++	Ref. 21
Methotrexate	Immunomodulatory and anti-proliferative drug, often chosen for long-term management  Use is limited by risk of liver toxicity and the requirement for ongoing monitoring of liver function. <sup>33,105</sup> Sometimes administered with folate supplement to reduce systemic toxicity <sup>26</sup>	LoE 1+	Refs. 32, 106

**Table 1.** Therapeutic options for ameliorating moderate to severe plaque psoriasis (alphabetical list, grouped by class) (*cont.*)

	Considerations	Evidence for efficacy as monotherapy*	References
<b>Biologic agents</b>			
Adalimumab	<p>Targets TNF-<math>\alpha</math>. Safety profile, primarily based on record of use in rheumatoid and psoriatic arthritis, suggests some overlap in adverse events with other TNF-<math>\alpha</math> antagonists<sup>51</sup></p> <p>Approved for use in psoriatic arthritis as well as psoriasis. Appears to be appropriate for long-term continuous use</p>	LoE 1++	Refs. 2,50
Etanercept	<p>Targets TNF-<math>\alpha</math>; may be associated with risk of infections, demyelinating disorders,<sup>107</sup> and reactivation of latent TB or melanoma<sup>52</sup></p> <p>Approved for use in psoriatic arthritis as well as psoriasis. Appropriate for long-term continuous use</p>	LoE 1++	Ref. 108
Infliximab	<p>Targets TNF-<math>\alpha</math>. Highly effective on initial exposure, even in severe, acute flares. Variable efficacy following reinitiation or beyond the first year of continuous treatment<sup>63,66</sup></p> <p>Associated with infusion reactions and risk of infections, demyelinating disorders,<sup>107</sup> and reactivation of latent TB or tumours<sup>66</sup></p> <p>Approved for use in psoriatic arthritis as well as psoriasis</p>	LoE 1++	Ref. 73
Alefacept	<p>Targets pathogenic T cells. Generally benign safety record, but monitoring is required to avoid depletion of CD4 T lymphocytes<sup>74</sup></p> <p>Relative to the other biologics, alefacept monotherapy provides limited control of psoriasis, but with long periods of complete or incomplete remission in some cases. Can be combined with other therapies for fuller and more durable control<sup>77</sup></p>	LoE 1++	Refs. 109,110

**Table 1.** Therapeutic options for ameliorating moderate to severe plaque psoriasis (alphabetical list, grouped by class) (cont.)

	Considerations	Evidence for efficacy as monotherapy*	References
<b>Photo(chemo)therapeutic methods</b>			
UVA with psoralen (PUVA)	<p>Psoralen may be administered orally or by immersion of affected areas in a psoralen solution, prior to irradiation with UVA (oral versus bath PUVA). Associated with cumulative risk of non-melanoma skin cancer, primarily squamous cell carcinoma<sup>88</sup></p> <p>May be combined with other agents in suitable patients to reduce UV exposure<sup>84,95,111</sup></p>	LoE <sup>†</sup> 2++	Refs. 85,90,112
UVB	<p>Broadband UVB has been used for decades; now often applied using narrowband irradiation at 311 nm, a more effective option. Less durable remission than with PUVA,<sup>85,91</sup> but believed to have a more benign safety profile</p> <p>May be combined with topical, systemic, or biologic agents for more rapid and more complete control, potentially reducing exposure to both UV light and other therapeutic agents</p>	LoE <sup>†</sup> 2++	Refs. 85,90,112

\*Efficacy reflects at least a 75% improvement in PASI score, as determined by a statistically significant difference from placebo in studies of moderate to severe plaque psoriasis.

†Therapy not well suited to placebo control.

**Table 2.** Therapeutic regimens to be considered for potential clearance of moderate to severe plaque psoriasis (alphabetical listing)

Regimen	Evidence for disease clearance/near clearance within approximately 3 months of therapy	Evidence for disease clearance/near clearance at approximately 6 months of therapy	Evidence for disease clearance/near clearance beyond 1 year of therapy	Notes
Adalimumab	Some patients may achieve 100% PASI reduction within 16 weeks of treatment (LoE 1++ <sup>50</sup> )	Some additional patients achieve/maintain 100% PASI reduction by 24 weeks of treatment (LoE 2+++ <sup>50</sup> )		Intended for ongoing, continuous treatment
Etanercept (50 mg BIW, stepped down to 25 mg)	With the standard dosing regimen, some patients may achieve ≥ 90% PASI reduction within the initial 12 weeks of treatment, prior to step-down (LoE 1++ <sup>108</sup> )	Some patients achieve/maintain ≥ 90% PASI reduction by 24 weeks of treatment (LoE 2+++ <sup>55,56</sup> )		Intended for ongoing, continuous treatment
Etanercept (50 mg BIW)	Some patients achieve ≥ 90% PASI reduction within the initial 12 weeks of treatment (LoE 1++ <sup>108</sup> )	Some additional patients achieve/maintain ≥ 90% PASI reduction by 24 weeks of treatment (LoE 2+++ <sup>57</sup> )	Some patients maintain ≥ 90% PASI reduction through at least 96 weeks of treatment (LoE 2+++ <sup>57</sup> )	
Infliximab	Patients may achieve a ≥ 90% PASI reduction within the initial 6–10 weeks of treatment (LoE 1+ <sup>73</sup> )	Patients may maintain ≥ 90% PASI reduction through the initial 24 weeks of treatment (LoE 1+ <sup>73</sup> )	Patients may achieve/maintain ≥ 90% PASI reduction through at least 50 weeks of treatment (LoE 2+++ <sup>65,73</sup> )	Some patients who maintain control or clearance through 1 year of treatment may subsequently develop resistance to infliximab treatment <sup>65,66</sup>

**Table 2.** Therapeutic regimens to be considered for potential clearance of moderate to severe plaque psoriasis (alphabetical listing) (cont.)

Regimen	Evidence for disease clearance/near clearance within approximately 3 months of therapy	Evidence for disease clearance/near clearance at approximately 6 months of therapy	Evidence for disease clearance/near clearance beyond 1 year of therapy	Notes
PUVA or narrowband UVB administered twice weekly	Patients may achieve clearance within 4–15 weeks (LoE 1+ <sup>85,90,91</sup> )	Remission following treatment cessation may be maintained for 6 months in some patients (LoE 2++ <sup>85,91</sup> )		Treatment to be discontinued upon clearance of symptoms and may be reinitiated when needed
Narrowband UVB administered thrice weekly	Patients may achieve clearance within 4–15 weeks (LoE 1+ <sup>90</sup> )	Remission following treatment cessation may be maintained for 6 months in some patients (LoE 2+++ <sup>90</sup> )	Remission following treatment cessation may be maintained for at least 12 months in some patients (LoE 2+++ <sup>90</sup> )	Treatment to be discontinued upon clearance of symptoms and may be reinitiated when needed
RePUVA administered thrice weekly with daily oral acitretin	Patients may achieve a ≥ 90% PASI reduction within 6–12 weeks (LoE 1+ <sup>113</sup> )			Both systemic and phototherapy may be discontinued upon clearance of symptoms Addition of acitretin significantly decreases the UVA dose required for clearance <sup>95,113</sup> See <b>Table 1</b> for restrictions on acitretin use

**Table 2.** Therapeutic regimens to be considered for potential clearance of moderate to severe plaque psoriasis (alphabetical listing) (cont.)

Regimen	Evidence for disease clearance/near clearance within approximately 3 months of therapy	Evidence for disease clearance/near clearance at approximately 6 months of therapy	Evidence for disease clearance/near clearance beyond 1 year of therapy	Notes
Broadband ReUVB with daily oral acitretin	Patients may achieve 96–100% clearance of lesions within 30 phototherapy sessions (LoE 2+ <sup>111</sup> )			Both systemic and phototherapy may be discontinued upon clearance of symptoms See <b>Table 1</b> for restrictions on acitretin use
Narrowband ReUVB administered four times weekly with daily topical tazarotene	Clearance (PASI score = 0 or 1) may occur within 7 weeks (LoE 2+ <sup>98</sup> )			Phototherapy may be discontinued upon clearance of symptoms and reinitiated when topical treatment offers insufficient control See <b>Table 1</b> for restrictions on acitretin use
Narrowband UVB administered thrice weekly plus weekly alefacept	Clearance (PASI score ≤ 3) may occur within 12 weeks (LoE 2– <sup>77</sup> )			Systemic and phototherapy may be discontinued upon clearance of symptoms



**Table 2.** Therapeutic regimens to be considered for potential clearance of moderate to severe plaque psoriasis (alphabetical listing) (cont.)

Regimen	Evidence for disease clearance/near clearance within approximately 3 months of therapy	Evidence for disease clearance/near clearance at approximately 6 months of therapy	Evidence for disease clearance/near clearance beyond 1 year of therapy	Notes
Broadband UVB administered twice weekly with daily topical calcipotriol	Patients may achieve clearance within 12 weeks (LoE 2++ <sup>100</sup> )			Phototherapy may be discontinued upon clearance of symptoms and reinitiated when topical treatment offers insufficient control  Addition of calcipotriol significantly decreases the UVB dose required for clearance
UVB plus crude coal tar (Goeckerman and related procedures)	Clearance (PASI score $\leq 3$ ) may occur within 3–7 weeks of initiating UVB treatment (LoE 3 <sup>101</sup> )			Basic treatment is commonly supplemented with other phototherapeutic or systemic treatments (e.g., acitretin or cyclosporine)  All treatments are discontinued upon clearance of symptoms

**Table 3. Drug interactions with traditional systemic agents\***

Agent	Drug interactions	
Acitretin <sup>114</sup>	<ul style="list-style-type: none"> <li>• Other systemic retinoids, including vitamin A supplements</li> <li>• Methotrexate</li> <li>• Phenytoin</li> <li>• Progesterone preparations<sup>†</sup></li> <li>• Tetracyclines</li> </ul>	
Cyclosporine <sup>115</sup>	<ul style="list-style-type: none"> <li>• Etoposide</li> <li>• Lercanidipine</li> <li>• Potassium-sparing diuretics and other antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists)</li> <li>• Repaglinide</li> </ul> <p>For drugs that may alter cyclosporine exposure, consult the product monographs</p>	<p>Drugs and drug classes that may potentiate renal dysfunction when used with cyclosporine:</p> <ul style="list-style-type: none"> <li>• Aminoglycosides</li> <li>• Amphotericin B</li> <li>• Ciprofloxacin</li> <li>• Colchicine</li> <li>• Cotrimoxazole/trimethoprim</li> <li>• Digoxin</li> <li>• Fibrates, including bezafibrate and fenofibrate</li> <li>• Histamine H2 receptor antagonists</li> <li>• NSAIDs</li> <li>• Melphalan</li> <li>• Methotrexate</li> <li>• Statins</li> <li>• Tacrolimus</li> <li>• Vancomycin</li> </ul>
Methotrexate <sup>116</sup>	<p>Potentially hepatotoxic or nephrotoxic drugs:</p> <ul style="list-style-type: none"> <li>• Azathioprine</li> <li>• Aminoglycosides</li> <li>• Amphotericin B</li> <li>• Cyclosporine</li> <li>• Leflunomide</li> <li>• Mercaptopurine</li> <li>• Probenecid</li> <li>• Retinoids</li> <li>• Sulfasalazine</li> <li>• Sulfonyleureas</li> <li>• Theophylline</li> </ul>	<p>Drugs and drug classes that may alter methotrexate exposure:</p> <ul style="list-style-type: none"> <li>• Antibiotics</li> <li>• Salicylates</li> <li>• NSAIDs</li> <li>• Phenylbutazone</li> <li>• Phenytoin</li> <li>• Probenecid</li> <li>• Sulfonamides</li> </ul>

\* These potential adverse drug interactions are those noted in the Canadian product monographs for the three traditional systemic agents discussed in this chapter. The physician should consult the product monographs for information on the safe use of these agents, including fuller discussion of possible drug interactions.

<sup>†</sup>Acitretin is teratogenic and is absolutely contraindicated in women of childbearing age, unless they can be relied on to use effective contraception during treatment and for 3 years after. However, microdosed progesterone preparations (minipills) may be an inadequate method of contraception for women undergoing acitretin therapy.

Note added in proof: In December 2008, Health Canada approved an additional biologic agent, ustekinumab, on the strength of two reports (Refs. 117, 118). Ustekinumab is indicated for use in moderate to severe plaque psoriasis.

## References

- Al-Suwaidan SN, Feldman SR. Clearance is not a realistic expectation of psoriasis treatment. *J Am Acad Dermatol* 2000;42:796–802.
- Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008;158:558–66.
- Reich K, Nestle FO, Papp K, et al. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. *Br J Dermatol* 2006;154:1161–8.
- Revicki D, Willian MK, Saurat JH, et al. Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *Br J Dermatol* 2008;158:549–57.
- Ali SM, Brodell RT, Balkrishnan R, Feldman SR. Poor adherence to treatments: A fundamental principle of dermatology. *Arch Dermatol* 2007;143:912–5.
- Anstey AV, Kragballe K. Retrospective assessment of PASI 50 and PASI 75 attainment with a calcipotriol/betamethasone dipropionate ointment. *Int J Dermatol* 2006;45:970–5.
- Guenther L, Langley RG, Shear NH, et al. Integrating biologic agents into management of moderate-to-severe psoriasis: a consensus of the Canadian Psoriasis Expert Panel. February 27, 2004. *J Cutan Med Surg* 2004;8:321–37.
- van de Kerkhof PCM. Update on retinoid therapy of psoriasis in: An update on the use of retinoids in dermatology. *Dermatol Ther* 2006;19:252–63.
- Halverstam CP, Zeichner J, Lebowitz M. Lack of significant skeletal changes after long-term, low-dose retinoid therapy: case report and review of the literature. *J Cutan Med Surg* 2006;10:291–9.
- Olsen EA, Weed WW, Meyer CJ, Cobo LM. A double-blind, placebo-controlled trial of acitretin for the treatment of psoriasis. *J Am Acad Dermatol* 1989;21:681–6.
- Ling MR. Acitretin: optimal dosing strategies. *J Am Acad Dermatol* 1999;41:S13–7.
- Rim JH, Park JY, Choe YB, Youn JI. The efficacy of calcipotriol + acitretin combination therapy for psoriasis: comparison with acitretin monotherapy. *Am J Clin Dermatol* 2003;4:507–10.
- Conley J, Nanton J, Dhawan S, et al. Novel combination regimens: Biologics and acitretin for the treatment of psoriasis – A case series. *J Dermatolog Treat* 2006;17:86–9.
- Laburte C, Grossman R, Abi-Rached J, et al. Efficacy and safety of oral cyclosporin A (CyA; Sandimmun™) for long-term treatment of chronic severe plaque psoriasis. *Br J Dermatol* 1994;130:366–75.
- Zachariae H, Kragballe K, Hansen HE, et al. Renal biopsy findings in long-term cyclosporin treatment of psoriasis. *Br J Dermatol* 1997;136:531–5.
- Korstanje MJ, Bilo HJ, Stoof TJ. Sustained renal function loss in psoriasis patients after withdrawal of low-dose cyclosporin therapy. *Br J Dermatol* 1992;127:501–4.
- Powles AV, Baker BS, Fry L. Reversibility of impaired renal function after long-term cyclosporin for psoriasis. *Br J Dermatol* 1994;131:141–2.
- Grossman RM, Delaney RJ, Brinton EA, et al. Hypertriglyceridemia in patients with psoriasis treated with cyclosporine. *J Am Acad Dermatol* 1991;25:648–51.
- Paul CF, Ho VC, McGeown C, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: A 5 y cohort study. *J Invest Dermatol* 2003;120:211–6.
- Chaidemenos GC, Mourellou O, Avgoustinaki N, et al. Intermittent vs. continuous 1-year cyclosporin use in chronic plaque psoriasis. *J Eur Acad Dermatol Venereol* 2007;21:1203–8.
- Faerber L, Braeutigam M, Weidinger G, et al. Cyclosporine in severe psoriasis: Results of a meta-analysis in 579 patients. *Am J Clin Dermatol* 2001;2:41–7.
- Hong SB, Kim NI. Generalized pustular psoriasis following withdrawal of short-term cyclosporin therapy for psoriatic arthritis. *J Eur Acad Dermatol Venereol* 2005;19:522–3.
- Grossman RM, Chevret S, Abi-Rached J, et al. Long-term safety of cyclosporine in the treatment of psoriasis. *Arch Dermatol* 1996;132:623–9.
- Ho VC. The use of cyclosporin in psoriasis: a clinical review. *Br J Dermatol* 2004;150 Suppl 67:1–10.
- Sigmundsdottir H, Johnston A, Gudjonsson JE, et al. Methotrexate markedly reduces the expression of vascular E-selectin, cutaneous lymphocyte-associated antigen and the numbers of mononuclear leucocytes in psoriatic skin. *Exp Dermatol* 2004;13:426–34.
- Salim A, Tan E, Ilchyshtyn A, Berth-Jones J. Folic acid supplementation during treatment of psoriasis with methotrexate: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 2006;154:1169–74.
- van Ede AE, Laan RF, Rood MJ, et al. Effect of folic or folinic acid supplementation on the toxicity and efficacy of methotrexate in rheumatoid arthritis: a forty-eight week, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2001;44:1515–24.
- Kirby B, Lyon CC, Griffiths CE, Chalmers RJ. The use of folic acid supplementation in psoriasis patients receiving methotrexate: a survey in the United Kingdom. *Clin Exp Dermatol* 2000;25:265–8.
- Strober BE, Menon K. Folate supplementation during methotrexate therapy for patients with psoriasis. *J Am Acad Dermatol* 2005;53:652–9.
- Brownell I, Strober BE. Folate with methotrexate: Big benefit, questionable cost. *Br J Dermatol* 2007;157:213.
- Flytstrom I, Stenberg B, Svensson A, Bergbrant IM. Methotrexate vs. ciclosporin in psoriasis: effectiveness, quality of life and safety. A randomized controlled trial. *Br J Dermatol* 2008;158:116–21.
- van Dooren-Greebe RJ, Kuijpers ALA, Mulder J, et al. Methotrexate revisited: Effects of long-term treatment in psoriasis. *Br J Dermatol* 1994;130:204–10.
- Malatjalain DA, Ross JB, Williams CN, et al. Methotrexate hepatotoxicity in psoriasis: Report of 104 patients from Nova Scotia, with analysis of risks from obesity, diabetes and alcohol consumption during long term follow-up. *Can J Gastroenterol* 1996;10:369–75.
- Roenigk HH, Jr., Auerbach R, Maibach H, et al. Methotrexate in psoriasis: consensus conference. *J Am Acad Dermatol* 1998;38:478–85.
- Saporito FC, Menter MA. Methotrexate and psoriasis in the era of new biologic agents. *J Am Acad Dermatol* 2004;50:301–9.
- Kuitunen T, Malmstrom J, Palva E, Pettersson T. Pancytopenia induced by low-dose methotrexate. A study of the cases reported to the Finnish Adverse Drug Reaction Register from 1991 to 1999. *Scand J Rheumatol* 2005;34:238–41.
- Salaffi F, Manganello P, Carotti M, et al. Methotrexate-induced pneumonitis in patients with rheumatoid arthritis and psoriatic arthritis: report of five cases and review of the literature. *Clin Rheumatol* 1997;16:296–304.
- Stern RS. Lymphoma risk in psoriasis: results of the PUVA follow-up study. *Arch Dermatol* 2006;142:1132–5.
- Kuijpers AL, van de Kerkhof PC. Risk-benefit assessment of methotrexate in the treatment of severe psoriasis. *Am J Clin Dermatol* 2000;1:27–39.
- Paul C, Le Tourneau A, Cayuela JM, et al. Epstein-Barr virus-associated lymphoproliferative disease during methotrexate therapy for psoriasis. *Arch Dermatol* 1997;133:867–71.
- Zonneveld IM, Bakker WK, Dijkstra PF, et al. Methotrexate osteopathy in long-term, low-dose methotrexate treatment for psoriasis and rheumatoid arthritis. *Arch Dermatol* 1996;132:184–7.
- Zhou Y, Rosenthal D, Dutz J, Ho V. Mycophenolate mofetil (CellCept) for psoriasis: A two-center, prospective, open-label clinical trial. *J Cutan Med Surg* 2003;7:193–7.
- Kumar B, Saraswat A, Kaur I. Rediscovering hydroxyurea: its role in recalcitrant psoriasis. *Int J Dermatol* 2001;40:530–4.
- Pedraz J, Dauden E, Delgado-Jimenez Y, et al. Sequential study on the treatment of moderate-to-severe chronic plaque psoriasis with mycophenolate mofetil and cyclosporin. *J Eur Acad Dermatol Venereol* 2006;20:702–6.
- Ranjana N, Sharma NL, Shanker V, et al. Methotrexate versus hydroxycarbamide (hydroxyurea) as a weekly dose to treat moderate-to-severe chronic plaque psoriasis: a comparative study. *J Dermatolog Treat* 2007;18:295–300.
- Kumar B, Saraswat A, Kaur I. Mucocutaneous adverse effects of hydroxyurea: a prospective study of 30 psoriasis patients. *Clin Exp Dermatol* 2002;27:8–13.
- Wallis RS. Tumour necrosis factor antagonists: structure, function, and tuberculosis risks. *Lancet Infect Dis* 2008;8:601–11.
- Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor-alpha blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. *Rheumatology (Oxford)* 2007;46:327–34.
- Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006;55:598–606.
- Menter A, Tying SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol* 2008;58:106–15.

51. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. *Ann Rheum Dis* 2006;65:889–94.
52. Fulchiero Jr GJ, Salvaggio H, Drabick JJ, et al. Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies. *J Am Acad Dermatol* 2007;56:S65–7.
53. Pirard D, Arco D, Debrouckere V, Heenen M. Anti-tumor necrosis factor alpha-induced psoriasiform eruptions: Three further cases and current overview. *Dermatology* 2006;213:182–6.
54. Grinblat B, Scheinberg M. The enigmatic development of psoriasis and psoriasiform lesions during anti-TNF therapy: A review. *Semin Arthritis Rheum* 2008;37:251–5.
55. Papp KA, Tying S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol* 2005;152:1304–12.
56. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med* 2003;349:2014–22.
57. Tying S, Gordon KB, Poulin Y, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol* 2007;143:719–26.
58. Krueger GG, Elewski B, Papp K, et al. Patients with psoriasis respond to continuous open-label etanercept treatment after initial incomplete response in a randomized, placebo-controlled trial. *J Am Acad Dermatol* 2006;54:S112–9.
59. Orenstein R, Matteson EL. TNF inhibitors and infections. *Infections in Medicine* 2006;23:99–114.
60. Ly L, Czarnecki D. The rapid onset of multiple squamous cell carcinomas during etanercept treatment for psoriasis. *Br J Dermatol* 2007;157:1076–8.
61. Goiriz R, Dauden E, Perez-Gala S, et al. Flare and change of psoriasis morphology during the course of treatment with tumour necrosis factor blockers. *Clin Exp Dermatol* 2007;32:176–9.
62. Bianchi L, Giunta A, Papoutsaki M, et al. Efficacy and safety of long-term infliximab therapy in moderate to severe psoriasis and psoriatic arthritis. *Giornale Italiano di Dermatologia e Venereologia* 2006;141:73–8.
63. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2007;56:31 e1–15.
64. Feldman SR, Gordon KB, Bala M, et al. Infliximab treatment results in significant improvement in the quality of life of patients with severe psoriasis: a double-blind placebo-controlled trial. *Br J Dermatol* 2005;152:954–60.
65. Krathen RA, Berthelot CN, Hsu S. Sustained efficacy and safety of infliximab in psoriasis: a retrospective study of 73 patients. *J Drugs Dermatol* 2006;5:251–4.
66. Smith CH, Jackson K, Bashir SJ, et al. Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. *Br J Dermatol* 2006;155:160–9.
67. Ahmad K, Rogers S. Three years' experience with infliximab in recalcitrant psoriasis. *Clin Exp Dermatol* 2006;31:630–3.
68. Ogilvie AL, Antoni C, Dechant C, et al. Treatment of psoriatic arthritis with antitumor necrosis factor-alpha antibody clears skin lesions of psoriasis resistant to treatment with methotrexate. *Br J Dermatol* 2001;144:587–9.
69. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;354:1932–9.
70. Tektonidou MG. Neurological complications of infliximab. *J Rheumatol* 2007;34:237.
71. Saleem G, Li SC, MacPherson BR, Cooper SM. Hepatitis with interface inflammation and IgG, IgM, and IgA anti-double-stranded DNA antibodies following infliximab therapy: comment on the article by Charles et al. *Arthritis Rheum* 2001;44:1966–8.
72. Foeldvari I, Kruger E, Schneider T. Acute, non-obstructive, sterile cholecystitis associated with etanercept and infliximab for the treatment of juvenile polyarticular rheumatoid arthritis. *Ann Rheum Dis* 2003;62:908–9.
73. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005;366:1367–74.
74. Goffe B, Papp K, Gratton D, et al. An integrated analysis of thirteen trials summarizing the long-term safety of alefacept in psoriasis patients who have received up to nine courses of therapy. *Clin Ther* 2005;27:1912–21.
75. Menter A, Cather JC, Baker D, et al. The efficacy of multiple courses of alefacept in patients with moderate to severe chronic plaque psoriasis. *J Am Acad Dermatol* 2006;54:61–3.
76. Leonardi CL, Strober BE. On multiple courses of alefacept. *J Am Acad Dermatol* 2006;55:916–7.
77. Legat FJ, Hofer A, Wackernagel A, et al. Narrowband UV-B phototherapy, alefacept, and clearance of psoriasis. *Arch Dermatol* 2007;143:1016–22.
78. Perlmutter A, Cather J, Franks B, et al. Alefacept revisited: Our 3-year clinical experience in 200 patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2008;58:116–24.
79. Erkin G, Uur Y, Gurer CK, et al. Effect of PUVA, narrow-band UVB and cyclosporin on inflammatory cells of the psoriatic plaque. *J Cutan Pathol* 2007;34:213–9.
80. Martin JA, Laube S, Edwards C, et al. Rate of acute adverse events for narrow-band UVB and Psoralen-UVA phototherapy. *Photodermatol Photoimmunol Photomed* 2007;23:68–72.
81. Diffey BL. Factors affecting the choice of a ceiling on the number of exposures with TL01 ultraviolet B phototherapy. *Br J Dermatol* 2003;149:428–30.
82. Halpern SM, Anstey AV, Dawe RS, et al. Guidelines for topical PUVA: a report of a workshop of the British photodermatology group. *Br J Dermatol* 2000;142:22–31.
83. Ibbotson SH, Bilisland D, Cox NH, et al. An update and guidance on narrowband ultraviolet B phototherapy: a British Photodermatology Group Workshop Report. *Br J Dermatol* 2004;151:283–97.
84. Tzaneva S, Honigsmann H, Tanew A, Seeber A. A comparison of psoralen plus ultraviolet A (PUVA) monotherapy, tacalcitol plus PUVA and tazarotene plus PUVA in patients with chronic plaque-type psoriasis. *Br J Dermatol* 2002;147:748–53.
85. Yones SS, Palmer RA, Garibaldino TT, Hawk JLM. Randomized double-blind trial of the treatment of chronic plaque psoriasis: efficacy of psoralen-UV-A therapy vs narrowband UV-B therapy. *Arch Dermatol* 2006;142:836–42.
86. Stern RS, PUVA Follow-up Study. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001;44:755–61.
87. McKenna KE, Patterson CC, Handley J, et al. Cutaneous neoplasia following PUVA therapy for psoriasis. *Br J Dermatol* 1996;134:639–42.
88. Nijsten TEC, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen + ultraviolet A: A cohort study. *J Invest Dermatol* 2003;121:252–8.
89. Lindelof B. Risk of melanoma with psoralen/ultraviolet A therapy for psoriasis. Do the known risks now outweigh the benefits? *Drug Saf* 1999;20:289–97.
90. Markham T, Rogers S, Collins P. Narrowband UV-B (TL-01) phototherapy vs oral 8-methoxypsoralen psoralen — UV-A for the treatment of chronic plaque psoriasis. *Arch Dermatol* 2003;139:325–8.
91. Gordon PM, Diffey BL, Matthews JN, Farr PM. A randomized comparison of narrow-band TL-01 phototherapy and PUVA photochemotherapy for psoriasis. *J Am Acad Dermatol* 1999;41:728–32.
92. Berneburg M, Rocken M, Benedix F. Phototherapy with narrowband vs broadband UVB. *Acta Derm Venereol* 2005;85:98–108.
93. Weischer M, Blum A, Eberhard F, et al. No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: A first retrospective study. *Acta Derm Venereol* 2004;84:370–4.
94. Leibold M. Acitretin in combination with UVB or PUVA. *J Am Acad Dermatol* 1999;41:S22–4.
95. Tanew A, Guggenbichler A, Honigsmann H, et al. Photochemotherapy for severe psoriasis without or in combination with acitretin: A randomized, double-blind comparison study. *J Am Acad Dermatol* 1991;25:682–4.
96. Spuls PI, Rozenblit M, Leibold M. Retrospective study of the efficacy of narrowband UVB and acitretin. *J Dermatolog Treat* 2003;14 Suppl 2:17–20.
97. Kampitak T, Asawanonda P. The efficacy of combination treatment with narrowband UVB (TL-01) and acitretin vs narrowband UVB alone in plaque-type psoriasis: a retrospective study. *J Med Assoc Thai* 2006;89 Suppl 3:S20–4.
98. Schiener R, Behrens-Williams SC, Pillekamp H, et al. Calcipotriol vs. tazarotene as combination therapy with narrowband ultraviolet B (311 nm): efficacy in patients with severe psoriasis. *Br J Dermatol* 2000;143:1275–8.
99. Woo WK, McKenna KE. Combination TL01 ultraviolet B phototherapy and topical calcipotriol for psoriasis: a prospective randomized placebo-controlled clinical trial. *Br J Dermatol* 2003;149:146–50.
100. Ramsay CA, Schwartz BE, Lowson D, et al. Calcipotriol cream combined with twice weekly broad-band UVB phototherapy: A safe, effective and UVB-sparing antipsoriatic combination treatment. *Dermatology* 2000;200:17–24.
101. Lee E, Koo J. Modern modified 'ultra' Goeckerman therapy: a PASI assessment of a very effective therapy for psoriasis resistant to both prebiologic and biologic therapies. *J Dermatolog Treat* 2005;16:102–7.
102. Asawanonda P, Nateetongrungsak Y. Methotrexate plus narrowband UVB phototherapy versus narrowband UVB phototherapy alone in the treatment of plaque-type psoriasis: a randomized, placebo-controlled study. *J Am Acad Dermatol* 2006;54:1013–8.
103. Ho VC, Griffiths CE, Albrecht G, et al. Intermittent short courses of cyclosporin (Neoral(R)) for psoriasis unresponsive to topical therapy: a 1-year multicentre, randomized study. The PISCES Study Group. *Br J Dermatol* 1999;141:283–91.
104. Ho VCY, Griffiths CEM, Berth-Jones J, et al. Intermittent short courses of cyclosporine microemulsion for the long-term management of psoriasis: A 2-year cohort study. *J Am Acad Dermatol* 2001;44:643–51.
105. Zachariae H, Kragballe K, Sogaard H. Methotrexate induced liver cirrhosis. Studies including serial liver biopsies during continued treatment. *Br J Dermatol* 1980;102:407–12.
106. Heydendael VMR, Spuls PI, Opmeer BC, et al. Methotrexate versus cyclosporine in moderate-to-severe chronic plaque psoriasis. *N Engl J Med* 2003;349:658–65.

107. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum* 2001;44:2862–9.
108. Gordon K, Korman N, Frankel E, et al. Efficacy of etanercept in an integrated multistudy database of patients with psoriasis. *J Am Acad Dermatol* 2006;54:S101–11.
109. Gordon KB, Langley RG. Remittive effects of intramuscular alefacept in psoriasis. *J Drugs Dermatol* 2003;2:624–8.
110. Lebwohl M, Christophers E, Langley R, et al. An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. *Arch Dermatol* 2003;139:719–27.
111. Iest J, Boer J. Combined treatment of psoriasis with acitretin and UVB phototherapy compared with acitretin alone and UVB alone. *Br J Dermatol* 1989;120:665–70.
112. Schiener R, Brockow T, Franke A, et al. Bath PUVA and saltwater baths followed by UV-B phototherapy as treatments for psoriasis: A randomized controlled trial. *Arch Dermatol* 2007;143:586–96.
113. Saurat JH, Geiger JM, Amblard P, et al. Randomized double-blind multicenter study comparing acitretin-PUVA, etretinate-PUVA and placebo-PUVA in the treatment of severe psoriasis. *Dermatologica* 1988;177:218–24.
114. Actavis Group PTC EHF. Soriatane. Canadian Product Monograph. Date of preparation: May 16, 2008.
115. Novartis Pharmaceuticals Canada, Inc. Neoral. Canadian Product Monograph. Date of revision: October 3, 2008.
116. Wyeth Canada. Methotrexate. Canadian Product Monograph. Date of revision: March 28, 2006.
117. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008;371:1665–74.
118. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008;371:1675–84.

## CHAPTER 7: SPECIAL POPULATIONS AND CIRCUMSTANCES

### Canadian Guidelines for the Management of Plaque Psoriasis

#### KEY POINT

*Large, controlled clinical studies are almost unknown in special populations with psoriasis, so physicians must rely largely on the case literature and clinical judgment when treating these patients. Guidance is provided here, but no firm recommendations can be offered.*

#### Psoriasis in children

Although there is limited epidemiologic data available about psoriasis in children, it is evident that the therapeutic challenges differ from those in adult disease. Compared with those in adults, children's lesions are often smaller, thinner, and less scaly, which can make diagnosis more difficult.<sup>1</sup> Facial and flexural involvement are more common in children than in adults; this includes the special clinical variant known as psoriatic diaper rash, which can occur up to the age of 2 years and involves sharply demarcated, brightly red plaques, often on the inguinal folds.<sup>1</sup> Erythroderma and psoriatic arthritis are relatively rare in the pediatric population. Pediatric psoriasis also differs from adult disease in that it is more often attributable to direct precipitating factors, which may include trauma, infections, drugs, or stress.<sup>1</sup>

Ensuring treatment adherence in pediatric patients poses a special challenge. Both the patient and the caregivers may require appropriately tailored education to convey the chronic nature of the disease and the likelihood of lifelong follow-up and treatment.<sup>2</sup>

#### Topicals

In many pediatric patients, topicals are sufficient to control disease when combined with conscientious skin care.<sup>1</sup> It is recommended that, unless the disease is widespread and associated with significant quality-of-life issues, treatment of psoriasis in children should start with a topical

agent. These include various emollients, as well as topical corticosteroids, retinoids, calcipotriol, and tar- or salicylic acid-containing products, as discussed in Chapter 5 (Management of mild plaque psoriasis).

Corticosteroids are often the first therapeutic choice in children with psoriasis; they are effective, but care needs to be taken to limit long-term effects. It has been suggested that the therapeutic regimen should use the least potent steroid that is effective, and taper the strength and/or dose as lesions improve.<sup>3</sup> Parents of children with psoriasis may be fearful about the effects of long-term steroid therapy on their child's health; it is important to address these fears and provide education about the risks, benefits, and appropriate use of topical steroids.<sup>2</sup>

Calcipotriol is clinically effective in children and almost completely free of local or systemic side effects.<sup>4-6</sup> Due to the risk of hypercalcemia, it may be appropriate to monitor ionized calcium in children treated long-term with calcipotriol.<sup>3,5</sup>

Anthralin is another potentially useful option in mild to moderate pediatric psoriasis. Since therapeutic outcome and adverse events often depend on correct application, it is important to ensure that patients and parents are appropriately informed about application procedures.<sup>1</sup> However, commercial formulations of anthralin are not currently available in Canada.

#### Systemics

There are limited clinical data available about the use of systemic therapies in pediatric patients. Therefore, these agents should be reserved for children with severe and otherwise treatment-refractory disease.



*Cyclosporine*

Cyclosporine appears to be well tolerated in children, with no unanticipated side effects.<sup>7,8</sup> However, due to its potential for renal effects and hypertension, it should be reserved for the most severe and therapy-resistant cases in childhood and adolescence.

*Methotrexate*

Good clinical responses to methotrexate have been obtained in several studies; regular monitoring is required to prevent hepatotoxicity and hematotoxicity.<sup>9</sup> There is evidence that methotrexate can be used safely to control severe episodes in young patients, then withdrawn as disease subsides.<sup>9</sup>

*Retinoids*

Acitretin and related compounds have been used safely and successfully in children.<sup>10,11</sup> Long-term exposure to acitretin may lead to premature epiphyseal closure and impaired bone growth; therefore, regular and vigilant follow-up is required.<sup>1</sup> In addition, acitretin is teratogenic and is absolutely contraindicated in women in their reproductive years, unless they reliably commit to using contraception during the course of treatment and for 3 years thereafter. Similar considerations apply to adolescent girls and those nearing puberty.

*Biologics*

Of the biologic agents, the best studied for pediatric psoriasis is etanercept. One large randomized controlled trial showed that etanercept can be effective in children from age 4 to 17 years. Dosing was once weekly with 0.8 mg etanercept per kg body weight, up to a maximum of 50 mg. Significant improvements in PASI scores were evident within 4 weeks, with 90% improvements in PASI scores seen in approximately one-fourth of patients by 12 weeks of treatment; 75% improvement occurred in approximately half of patients receiving etanercept. These benefits were maintained up to at least 36 weeks of treatment.<sup>12</sup> There is also preliminary evidence that in pediatric psoriasis, etanercept therapy may allow tapering of other treatments.<sup>13</sup>

The safety of etanercept has been most extensively studied in children with polyarticular juvenile rheumatoid arthritis; no new safety concerns have emerged in these studies.<sup>14-16</sup> In the pediatric psoriasis trial for etanercept, there were isolated cases of severe infection associated with treatment.<sup>12</sup>

Preliminary reports suggest future therapeutic prospects for pediatric use of infliximab as well.<sup>1</sup>

*Phototherapy*

In severe, extensive, or treatment-resistant disease, particularly in older children and adolescents, UVB is an effective option that should be tried before moving to more toxic therapies such as methotrexate, retinoids, or cyclosporine.<sup>17,18</sup> It is best to minimize the cumulative UVB dose and thereby limit the long-term carcinogenic risk (see Chapter 6: Management of moderate to severe plaque psoriasis).

UVB should be used with caution in younger children, with due consideration of the treatment's risks and benefits.<sup>2</sup>

PUVA should likewise be used with caution in younger patients as it is carcinogenic and may accelerate skin aging.<sup>19</sup>

**Pregnancy**

The treatment of psoriasis in pregnant patients requires special care due to the potential teratogenic effects of several commonly used agents. Fortunately, many women may require minimal treatment while pregnant, as hormonal changes during pregnancy result in symptomatic improvement for more than half of patients surveyed.<sup>20,21</sup> The potential for pregnancy-associated remission appears to be linked to the presence of the HLA-Cw\*0602 allele of HLA-C.<sup>22</sup>

*Psoriasis treatment prior to or during pregnancy*

Some physicians may wish to withhold standard treatments to pregnant patients, due to concerns for the fetus's safety. However, for pregnant patients who require psoriasis treatment, there are effective options that are relatively safe. The fetal risks of any pharmaceutical treatment can be classified according to the US Food and Drug Administration's (FDA's) scale (see **Table 1**),

which takes into account the body of human and animal evidence regarding the drug's teratogenic potential. This classification system is currently under revision and should be considered as a general summary of overall evidence, rather than

as a tool for estimating the risk of developmental toxicity in individual patients.

Data concerning the use of major psoriasis therapies in pregnant patients are summarized in **Table 2**.

**Table 1. FDA classifications for fetal risk<sup>23</sup>**

Designation	Definition
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities
B	Either: <ul style="list-style-type: none"> <li>• Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women</li> </ul> or <ul style="list-style-type: none"> <li>• Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus</li> </ul>
C	Either: <ul style="list-style-type: none"> <li>• Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women</li> </ul> or <ul style="list-style-type: none"> <li>• No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women</li> </ul>
D	Studies (adequate and well-controlled, or observational) in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk
X	Studies (adequate and well-controlled, or observational) in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant

**Table 2. Treatment options and risk classifications in pregnant psoriasis patients**

Therapy	FDA classification*	Rationale	Comments
<b>Topicals</b>			
Anthralin and tars	C: Anthralin, tar-based bath products Uncharacterized: Other topical tar products	<ul style="list-style-type: none"> <li>• Measurable levels of systemic absorption but no adverse fetal effects have been reported<sup>24</sup></li> <li>• No difference between pregnancy outcomes in patients treated with tar and untreated patients<sup>24</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Tar products are likely safe when used in the second and third trimesters</li> </ul>
Calcipotriol	C	<ul style="list-style-type: none"> <li>• Limited data available in pregnancy<sup>24</sup></li> <li>• Systemic absorption is 6% — unlikely to have significant effects<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>• A reasonable option for use in pregnant patients requiring control of mild plaque psoriasis; the calcipotriol/ betamethasone combination product may also be used on appropriate areas</li> </ul>
Corticosteroids	C	<ul style="list-style-type: none"> <li>• Systemic effects are minimal because roughly 3% is absorbed<sup>25</sup></li> <li>• Safety varies with the strength of the agent, the vehicle, and the body surface involved<sup>26</sup></li> <li>• Two population-based studies found no increased risk of fetal abnormalities<sup>27</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Risks of high-potency agents on large areas may approach those of systemic steroids<sup>26</sup></li> <li>• Often used for mild, localized disease in pregnant patients<sup>24</sup></li> </ul>
Tazarotene	X	<ul style="list-style-type: none"> <li>• Highly teratogenic with systemic administration, but there is no evidence of significant systemic absorption with topical application.<sup>28</sup> Since a teratogenic risk cannot be ruled out, pregnant women should discontinue use of this topical retinoid<sup>29</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Although the X classification implies that a definite risk has been seen in controlled studies, teratogenicity has only been observed in studies of systemic administration<sup>28</sup></li> </ul>

**Table 2. Treatment options and risk classifications in pregnant psoriasis patients (cont.)**

Therapy	FDA classification*	Rationale	Comments
<b>Systemics</b>			
Biologics <ul style="list-style-type: none"> <li>• Adalimumab</li> <li>• Alefacept</li> <li>• Etanercept</li> <li>• Infliximab</li> </ul>	B	<ul style="list-style-type: none"> <li>• No malformations seen with etanercept or infliximab.<sup>25</sup> However, women on infliximab are advised to use contraception during treatment and for at least 6 months after discontinuation</li> <li>• Few animal studies available<sup>2-4</sup></li> </ul>	<ul style="list-style-type: none"> <li>• No specific contraception guidelines are available on the need for contraception in patients taking biologics<sup>2,4</sup></li> <li>• Biologics are generally considered safe but should ordinarily be discontinued during pregnancy, although they may be maintained if clearly needed</li> </ul>
Cyclosporine	C	<ul style="list-style-type: none"> <li>• Has been used in pregnant transplant patients with no clear evidence of adverse effects on outcomes, but studies on long-term effects are lacking<sup>25,26</sup></li> </ul>	<ul style="list-style-type: none"> <li>• A reasonable option for appropriate patients requiring systemic treatment during pregnancy; to be discontinued in individuals with compromised renal function, hypertension, or elevated triglycerides<sup>25</sup></li> </ul>
Methotrexate	X	<ul style="list-style-type: none"> <li>• Known abortifacient; teratogenic in surviving fetuses<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Female patients should be screened for pregnancy before starting methotrexate<sup>24</sup></li> <li>• Male and female patients should be counselled to use contraception during therapy.<sup>29</sup> Men should continue using contraception for at least 3 months following discontinuation of methotrexate. Women should do so for at least one ovulatory cycle after discontinuing methotrexate</li> </ul>

**Table 2. Treatment options and risk classifications in pregnant psoriasis patients (cont.)**

Therapy	FDA classification*	Rationale	Comments
<b>Systemics (cont.)</b>			
Acitretin	X	<ul style="list-style-type: none"> <li>Powerful teratogen<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>Female patients should avoid becoming pregnant during treatment and for 3 years after discontinuing acitretin</li> </ul>
<b>Phototherapy</b>			
PUVA	C: Psoralens	<ul style="list-style-type: none"> <li>No evidence of teratogenicity but known to be mutagenic<sup>2-5</sup></li> <li>No increase seen in infant or child mortality or congenital malformations<sup>30</sup></li> </ul>	<ul style="list-style-type: none"> <li>Should be given only in cases where clearly needed, due to mutagenic potential of systemic psoralens<sup>2-4</sup></li> <li>When PUVA is necessary during pregnancy, consider bath PUVA to minimize systemic effects and fetal exposure<sup>24</sup></li> </ul>
UVB	Not applicable	<ul style="list-style-type: none"> <li>Considered the safest treatment for extensive psoriasis during pregnancy; can be initiated or maintained in patients with widespread disease not controllable by topical agents<sup>25</sup></li> </ul>	<ul style="list-style-type: none"> <li>Potential for re-activation/eruption of herpes simplex — may require measures to avoid transmission to the infant at delivery.<sup>24</sup> Otherwise, there is no known fetal risk for either broadband or narrowband UVB treatment<sup>25</sup></li> </ul>

\*See Table 1.

Therefore, when psoriasis treatment is required in pregnant patients, topical corticosteroids, topical calcipotriol (either alone or in combination with corticosteroids), or anthralin may be used to control mild disease, whereas UVB is an appropriate option in more severe disease, and cyclosporine, bath PUVA, and biologics may be considered when the benefits clearly outweigh the risks of treatment.<sup>24</sup>

#### *Nursing mothers*

Female patients who have experienced a remission in psoriatic symptoms during pregnancy may flare following parturition.<sup>20</sup> In nursing mothers, systemic methotrexate is contraindicated, as it is secreted in the milk in quantities that may cause harm to the infant.<sup>26</sup> Psoralens are not absolutely contraindicated in nursing mothers but should be avoided if possible.

Although some investigators caution against using cyclosporine in nursing mothers,<sup>26</sup> there are cases where it has been used successfully and safely; breast-milk levels were variable but infant plasma levels, when detectable, were low. If cyclosporine must be continued, drug levels in the milk and the infant should be monitored.<sup>31</sup> Topical calcipotriol and corticosteroids appear to be reasonable options for nursing mothers, as is UVB in the case of more severe disease.

#### *Pregnancy in partners of male patients receiving psoriasis treatment*

Although little is known about the fetal effects of paternal psoriasis treatment, certain precautions are recommended for male patients who could potentially father children. Methotrexate has been linked to oligospermia, although there is no evidence to date of the sperm damage resulting in fetal malformations.<sup>24</sup> Although there is little hard evidence, some investigators suggest a conservative approach whereby male patients are advised to use contraception during methotrexate treatment<sup>29</sup> and delay conception attempts for at least 3 months after the end of therapy.<sup>24</sup> It is not currently known whether the teratogenic risk of systemic retinoids extends to the children of male patients treated with acitretin.<sup>29</sup> There is also no evidence of fetal harm with paternal PUVA therapy.<sup>32</sup>

#### **The elderly**

Elderly patients with psoriasis are more likely to experience adverse drug reactions than younger adults, mainly due to age-related changes to pharmacokinetics; existing comorbidities such as hypertension, type 2 diabetes, and hyperlipidemia, which may limit the use of some therapeutic options; and polypharmacy. In treating geriatric patients, physicians must be aware of the range of interactions that can occur between antipsoriatic agents and other drugs.

Dermatological drugs that are predominantly eliminated by the kidney (e.g., methotrexate) may be eliminated more slowly in the elderly, and, therefore, a dose reduction should be considered. Methotrexate is also hepatotoxic and, like other such drugs, should be used with caution in the elderly.<sup>33</sup>

Topical psoriasis treatments are often prescribed for elderly patients as first-line therapy due to the potential risk of adverse reactions and drug interactions caused by polypharmacy or altered pharmacokinetics with systemic therapy.<sup>34</sup> Calcipotriol/betamethasone dipropionate ointment given once daily is effective and well tolerated in the treatment of psoriasis regardless of the age group.<sup>34</sup>

Of the available biologic drugs, the only ones with published findings in the elderly population are alefacept and etanercept. Alefacept is well tolerated and effective in elderly patients.<sup>35</sup> Etanercept appears to be safe for this population as well. When used with standard dosing (25 mg subcutaneously, twice weekly, with or without an initial dose of 50 mg twice weekly for 12 weeks), incidence of adverse events in the elderly was similar to that with placebo.<sup>33,36</sup>

Phototherapy is also a potentially valuable although poorly studied option for elderly patients. Treatment with broadband UVB two to three times per week for 8–12 weeks is effective in postmenopausal women with moderate plaque psoriasis (baseline PASI 6–12).<sup>37</sup>

#### **Patients with hepatitis B or C**

Patients with psoriasis or other conditions that cause skin lesions may be at increased risk of contracting hepatitis B or C through skin contact with infected bodily fluids. Attaining effective control of psoriasis



can therefore play an important role in avoiding parenteral exposure to these viruses.<sup>38</sup>

Treatment of hepatitis B or C infection with interferons has been linked to the development of *de novo* psoriasis or the exacerbation of existing psoriasis in many patients.<sup>39-41</sup>

In patients with hepatitis, the benefits of using any immunosuppressive therapy must be weighed against the potential for viral reactivation or exacerbation of the infection. Due to their low potential for systemic absorption, topical therapies can generally be considered safe for control of psoriasis in patients with hepatitis. For more severe disease, there is accumulating evidence that certain systemic therapies, notably cyclosporine and the TNF- $\alpha$  antagonists, may be safe with appropriate screening and monitoring, as outlined below. Conversely, methotrexate is contraindicated in patients with any form of chronic liver disease, including alcoholic liver disease and hepatitis B or C.

#### **Hepatitis B**

Methotrexate should not be prescribed to patients with hepatitis B due to its potential hepatotoxicity. A case report describes a patient with severe psoriasis who developed fatal hepatorenal failure after treatment with methotrexate; she had no known history of liver disease but serology performed during her illness showed evidence of a long-standing HBV infection. Although the organ failure and fatal outcome cannot be definitively linked to the use of methotrexate, it is prudent to avoid this agent in patients with hepatitis B.<sup>42</sup>

Isolated instances of hepatitis B reactivation have been observed in patients undergoing treatment with TNF- $\alpha$  antagonists. Additionally, three cases of hepatic complications have been described in hepatitis B virus- (HBV-) positive patients treated with infliximab, with or without methotrexate, for Still's disease, ankylosing spondylitis, or RA; however, there was no evidence of HBV reactivation or exacerbation of hepatitis symptoms in any of these cases.<sup>43</sup> The fact that most of these patients were concomitantly treated with immunosuppressive agents complicates the

interpretation of these observations, and several case reports indicate that TNF- $\alpha$  antagonists can be safely used in patients with hepatitis B.

It is recommended that all psoriasis patients who are candidates for therapy with a TNF- $\alpha$  antagonist should be screened for HBV before initiating treatment. In HBV-positive patients with inactive disease, a course of antiviral therapy is recommended, starting 2–4 weeks before the TNF- $\alpha$  antagonist. All HBV-positive patients receiving anti-TNF therapy should undergo close follow-up to monitor liver function and viral load.<sup>43</sup>

#### **Hepatitis C**

There is a lack of available data concerning psoriasis treatment in patients with the hepatitis C virus (HCV), but the limited findings to date suggest that with appropriate monitoring, TNF- $\alpha$  antagonists may be safe in this population. Etanercept may act as an adjuvant to standard antiviral therapies for hepatitis C virus (HCV),<sup>44</sup> although at least one case study has identified an exacerbation of hepatitis C symptoms with etanercept therapy for RA.<sup>45</sup> However, a larger study of 24 HCV-positive patients receiving etanercept or infliximab for RA showed no significant adverse events or increases in liver enzymes or viral load.<sup>43</sup> A similar lack of HCV exacerbation was seen in a separate study of two patients whose psoriasis was treated with alefacept.<sup>46</sup> For HCV-positive patients treated with these biologic agents, serum aminotransferases and HCV RNA levels should be regularly monitored; if long-term use of the immunosuppressive therapy is anticipated, strong consideration should be given to a baseline liver biopsy.<sup>43</sup>

Cyclosporine may also be a useful treatment option in patients with comorbid psoriasis and hepatitis C, as there is *in vitro* evidence that cyclosporine can suppress replication of the hepatitis C virus. This finding is supported by a case study in which a single patient exhibited a dramatic improvement in his psoriasis with cyclosporine treatment but did not experience any exacerbation of hepatitis C symptoms.<sup>47</sup>

**HIV-positive patients**

Prior to the introduction of highly active antiretroviral treatment (HAART), skin disease was common in patients seropositive for the human immunodeficiency virus (HIV).<sup>48</sup> Psoriasis is not necessarily more common in HIV-positive individuals than in the general population, but the HIV-associated variant of psoriasis is more likely to be associated with arthritis, more resistant to treatment,<sup>49</sup> and often more severe<sup>50</sup> than other forms of the disease.

A significant proportion of patients with HIV-associated psoriasis will have pustular, acral involvement, sometimes accompanied by severe, destructive nail lesions.<sup>51</sup> Involvement of the inguinal creases and genitalia is also more common in people with HIV-associated psoriasis than in the general psoriasis population.<sup>52</sup> Treatment of HIV-associated genital psoriasis should follow the recommendations outlined in Chapter 9 (Management of facial, flexural, and genital psoriasis).

HIV-associated psoriasis has an apparently paradoxical pathology. HIV is a disease of decreasing T cell counts, but psoriasis is thought to be a T cell-mediated disease. Nevertheless, psoriasis therapies that target T cells are effective in HIV-associated disease, a counterintuitive finding that may be explained by HIV's preferential killing of CD4+ T cell subpopulations, sparing other, potentially pathogenic T cell populations.<sup>53</sup>

Since HIV/AIDS is a disease of immunosuppression, there has been understandable concern in the medical community about the use of immunosuppressive agents in this patient population. Many of the concerns may be exaggerated in the current era, when HAART is widely used in HIV-positive patients, reducing overall viral loads and improving immune status. However, it is still important to be vigilant when prescribing an immunosuppressive agent to an HIV-positive individual, regardless of the patient's antiviral therapy.<sup>43</sup>

**Antivirals**

Primary treatment of HIV with the antiviral drug zidovudine (AZT) can have secondary beneficial effects on skin lesions, including nearly complete or complete clearance of symptoms in up to 90% of patients with HIV-associated psoriasis.<sup>54</sup> The

same treatment was also beneficial, although less dramatically so, in approximately one-third of HIV-negative psoriasis patients.<sup>55</sup>

**Topicals**

Since HIV-associated psoriasis often has a more aggressive, extensive, and therapy-resistant presentation than other forms of the disease, topical agents in HIV-positive patients have limited success rates, although topical calcipotriol may be of benefit in some patients. As in other patient populations, psoriasis patients with HIV should not exceed the standard exposure limit of 100 g ointment/week; therefore, calcipotriol may be most appropriate for patients with limited body surface involvement.<sup>48</sup>

**Systemics***Cyclosporine*

Since HIV selectively attacks CD4+ T cells, cyclosporine, which also suppresses CD4 cells, would not be expected to be a viable therapeutic option. Therefore, cyclosporine has generally been avoided in HIV-positive patients, and its use has not been extensively studied.<sup>56</sup>

However, there have been isolated case reports of patients who achieved almost complete control of psoriasis using cyclosporine, without any signs of immune deterioration.<sup>56</sup>

*Methotrexate*

Methotrexate is considered to be inappropriate for HIV-positive patients, due to several reports of rapid progression of immunosuppression, some with fatal outcomes. In most cases, methotrexate was used in combination with sulfamethoxazole and/or trimethoprim; therefore, it is unclear whether the immunosuppressive effects were due to the methotrexate alone, to one of the other drugs, or to the combination.<sup>48</sup>

Although further studies in severe psoriatic arthritis failed to show any significant immunosuppressive risks in HIV-positive patients,<sup>57</sup> methotrexate should not be used in this population unless absolutely necessary.

**Retinoids**

Given the concerns about immunosuppression associated with most other systemic therapies in HIV-positive patients, systemic retinoids have been particularly useful for generalized disease.<sup>51</sup>

Acitretin appears to be safe and effective in HIV-associated psoriasis. In a pilot study of acitretin monotherapy in 11 patients, 54% had “good to excellent” responses, with 36% achieving complete clearance. There was no evidence of a link between baseline levels of immunosuppression and treatment success.<sup>49</sup>

**Biologics**

TNF- $\alpha$  may be intimately involved in HIV pathogenesis; it has been implicated in viral propagation and lymphocyte depletion, and may also mediate some of the clinical manifestations of AIDS. In vitro, HIV infection has been shown to induce TNF- $\alpha$  expression in cultured cells. Conversely, exogenous TNF- $\alpha$  enhances HIV replication.<sup>43</sup>

Inhibition of TNF- $\alpha$  in HIV-associated psoriasis is therefore a theoretically appealing strategy that could not only ameliorate the symptoms of psoriasis but potentially also have antiviral effects. However, there have been concerns that inhibiting TNF- $\alpha$  in patients who are already immunocompromised may leave them even more vulnerable to opportunistic infections.<sup>43</sup>

Several trials have examined the potential role of TNF- $\alpha$  inhibition in HIV-associated psoriasis. In three randomized trials of infliximab or etanercept in HIV-positive patients, no serious adverse events were associated with either agent. One of these studies also found that adding etanercept appeared to enhance the efficacy of standard antituberculous therapy in HIV-positive patients with TB.<sup>43</sup>

Despite these encouraging safety findings, the role of TNF- $\alpha$  in HIV-associated psoriasis is a matter of active debate. Although HIV-associated psoriasis is responsive to alefacept, which acts generally on T cells,<sup>53</sup> the efficacy of the TNF antagonists (adalimumab, etanercept, infliximab) in this patient population has not been established.

**Phototherapy**

The use of ultraviolet light in HIV-positive patients may at first seem counterintuitive, as both UVA and UVB activate HIV replication in vitro. However, the addition of psoralens to UVA has the opposite effect in cultured cells, leading to viral inactivation.<sup>58</sup>

In vivo, UVB therapy does not generally lead to opportunistic infections or malignancies,<sup>48</sup> nor is there evidence that PUVA causes viral activation.<sup>51,58</sup>

**PUVA**

PUVA may be particularly useful for treatment of thick plaques and/or palmoplantar lesions, which are claimed to be relatively common in HIV-associated psoriasis.<sup>51</sup> However, this therapeutic option should be used with caution, due to the gastrointestinal effects of psoralens and the potential for carcinogenesis in this immunocompromised patient population.<sup>51</sup>

**UVB**

UVB is an effective treatment for psoriasis in HIV-positive patients and is the most widely used phototherapy in this population.<sup>51</sup> The response to UVB in HIV-positive individuals is identical to that of matched seronegative controls, and no deterioration of immune status or other significant adverse events has been observed.<sup>59,60</sup>

**Patients with a history of solid tumours**

Since several of the systemic therapies used in psoriasis treatment have been linked to increased risk of reactivated<sup>61</sup> or *de novo* malignancies,<sup>62,63</sup> caution is required in choosing a therapeutic option for patients with a history of solid tumours.

In patients with a history of malignancy or existing malignancies, the T cell modulator alefacept is contraindicated, and the TNF- $\alpha$  antagonists should only be used with caution. Use of a biologic should be re-evaluated in the event that the patient develops a new malignancy while on therapy.

For patients with malignant or pre-malignant skin alterations, cyclosporine should only be used if no other option for successful therapy exists and only after the skin alterations have been treated.

### TNF- $\alpha$ antagonists and elective surgery

Because of a potential increased risk of post-surgical infection, authorities in RA recommend that TNF- $\alpha$  antagonists (etanercept, infliximab, and adalimumab) be withheld for a period of at least 1 week prior to and 1 week after surgery.<sup>64</sup> Several European studies have examined complication rates for patients with rheumatoid arthritis undergoing elective foot and ankle surgery<sup>65</sup> or other elective surgery.<sup>66</sup>

From this work, it does not appear that the use or pre-operative discontinuation of TNF- $\alpha$  antagonists influences the rates of surgical complications, including incidence of infections.<sup>65,66</sup> However, because no such analysis has been published outside of the setting of RA, the conservative choice of suspending TNF- $\alpha$  antagonist treatment should still be considered for psoriasis patients undergoing elective surgery. The optimal period of suspension is not known; following recommendations for RA patients cited in Ref. 66, the TNF- $\alpha$  antagonists should be discontinued for a period of four half-lives prior to surgery, thus: 12 days for etanercept, 39 days for infliximab, and 56 days for adalimumab.

### Systemic treatments and vaccination

Since most of the traditional and biologic systemic agents currently used in the treatment of psoriasis

act by modifying the immune response, the use of systemic treatments has the potential to alter the efficacy and safety of vaccinations. With the sole exception of acitretin, Canadian product monographs for each of the systemic or biologic agents discussed in Chapter 6 (Management of moderate to severe plaque psoriasis) note the possibility that the psoriasis treatment will affect the outcome of vaccination. Before vaccinating a patient with psoriasis or initiating treatment with one of these agents, the physician should consult the appropriate monograph.

For patients receiving a biologic agent, inactivated or subunit-based vaccines are generally thought to be safe and effective and can be administered when clinically indicated. These vaccines can also be used in patients undergoing methotrexate or cyclosporine treatment; however, it should be noted that the efficacy of the vaccination may be compromised.

Although there are no data showing a direct link between vaccination and infection in patients receiving systemic therapies, the use of live or live-attenuated vaccines in these patients is not recommended due to the theoretical risk that a live immunization agent could produce an infection when introduced into an altered immune environment.

### References

- Benoit S, Hamm H. Childhood psoriasis. *Clin Dermatol* 2007;25:555–62.
- Fischer G. Psoriasis in children. *Medicine Today* 2006;7:46.
- Coffey J, Landells I. Topical treatment of psoriasis in children. *Skin Therapy Lett* 2002;7:4–7.
- Darley CR, Cunliffe WJ, Green CM, et al. Safety and efficacy of calcipotriol ointment (Dovonex) in treating children with psoriasis vulgaris. *Br J Dermatol* 1996;135:390–3.
- Park SB, Suh DH, Youn JI. A pilot study to assess the safety and efficacy of topical calcipotriol treatment in childhood psoriasis. *Pediatr Dermatol* 1999;16:321–5.
- Saggese G, Federico G, Battini R. Topical application of 1,25-dihydroxyvitamin D3 (calcitriol) is an effective and reliable therapy to cure skin lesions in psoriatic children. *Eur J Pediatr* 1993;152:389–92.
- Pereira TM, Vieira AP, Fernandes JC, Sousa-Basto A. Cyclosporin A treatment in severe childhood psoriasis. *J Eur Acad Dermatol Venereol* 2006;20:651–6.
- Perrett CM, Ilchyshyn A, Berth-Jones J. Cyclosporin in childhood psoriasis. *J Dermatolog Treat* 2003;14:113–8.
- Kumar B, Dhar S, Handa S, Kaur I. Methotrexate in childhood psoriasis. *Pediatr Dermatol* 1994;11:271–3.
- Brecher AR, Orlow SJ. Oral retinoid therapy for dermatologic conditions in children and adolescents. *J Am Acad Dermatol* 2003;49:171–82; quiz 83–6.
- Lacour M, Mehta-Nikhar B, Atherton DJ, Harper JL. An appraisal of acitretin therapy in children with inherited disorders of keratinization. *Br J Dermatol* 1996;134:1023–9.
- Paller AS, Siegfried EC, Langley RG, et al. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med* 2008;358:241–51.
- Kress DW. Etanercept therapy improves symptoms and allows tapering of other medications in children and adolescents with moderate to severe psoriasis. *J Am Acad Dermatol* 2006;54:S126–8.
- Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;342:763–9.
- Lovell DJ, Giannini EH, Reiff A, et al. Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. *Arthritis Rheum* 2003;48:218–26.
- Lovell DJ, Reiff A, Jones OY, et al. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. *Arthritis Rheum* 2006;54:1987–94.
- Jain VK, Aggarwal K, Jain K, Bansal A. Narrow-band UV-B phototherapy in childhood psoriasis. *Int J Dermatol* 2007;46:320–2.
- Anonymous. New drugs for peripheral joint psoriatic arthritis. *Drug Ther Bull* 2006;44:1–5.
- Nyfors A. Psoriasis in children. Characteristics, prognosis and therapy. A review. *Acta Derm Venereol* 1981;61:47–53.
- Murase JE, Chan KK, Garite TJ, et al. Hormonal effect on psoriasis in pregnancy and post partum. *Arch Dermatol* 2005;141:601–6.
- Raychaudhuri SP, Navare T, Gross J, Raychaudhuri SK. Clinical course of psoriasis during pregnancy. *Int J Dermatol* 2003;42:518–20.
- Gudjonsson JE, Karason A, Runarsdottir EH, et al. Distinct clinical differences between HLA-Cw\*0602 positive and negative psoriasis patients — an analysis of 1019 HLA-C- and HLA-B-typed patients. *J Invest Dermatol* 2006;126:740–5.
- FDA. Current categories for drug use in pregnancy. 2001.



24. Tauscher AE, Fleischer AB, Jr., Phelps KC, Feldman SR. Psoriasis and pregnancy. *J Cutan Med Surg* 2002;6:561–70.
25. Al Hammadi A, Al-Haddab M, Sasseville D. Dermatologic treatment during pregnancy: practical overview. *J Cutan Med Surg* 2006;10:183–92.
26. Hale EK, Pomeranz MK. Dermatologic agents during pregnancy and lactation: an update and clinical review. *Int J Dermatol* 2002;41:197–203.
27. Oren D, Nulman I, Makhija M, et al. Using corticosteroids during pregnancy. Are topical, inhaled, or systemic agents associated with risk? *Can Fam Physician* 2004;50:1083–5.
28. Lam J, Polifka JE, Dohil MA. Safety of dermatologic drugs used in pregnant patients with psoriasis and other inflammatory skin diseases. *J Am Acad Dermatol* 2008;59:295–315.
29. Anonymous. Retinoid drugs have a place in the treatment of psoriasis but pregnancy is an absolute contraindication to their use. *Drugs & Therapy Perspectives* 2002;18:11–5.
30. Gunnarskog JG, Kallen AJB, Lindelof BG, Sigurgeirsson B. Psoralen photochemotherapy (PUVA) and pregnancy. *Arch Dermatol* 1993;129:320–3.
31. Moretti ME, Lee A, Ito S. Which drugs are contraindicated during breastfeeding? Practice Guidelines. *Can Fam Physician* 2000;46:1753–7.
32. Stern RS, Lange R. Outcomes of pregnancies among women and partners of men with a history of exposure to methoxsalen photochemotherapy (PUVA) for the treatment of psoriasis. *Arch Dermatol* 1991;127:347–50.
33. Anonymous. As there are no simple rules for dermatological drug dosing in the elderly, titrate to suit individual response. *Drugs & Therapy Perspectives* 2006;22:23–6.
34. Parslew R, Traulsen J. Efficacy and local safety of a calcipotriol/ betamethasone dipropionate ointment in elderly patients with psoriasis vulgaris. *Eur J Dermatol* 2005;15:37–9.
35. Gottlieb AB, Boehncke W-H, Darif M. Safety and efficacy of alefacept in elderly patients and other special populations. *J Drugs Dermatol* 2005;4:718–24.
36. Militello G, Xia A, Stevens SR, van Voorhees AS. Etanercept for the treatment of psoriasis in the elderly. *J Am Acad Dermatol* 2006;55:517–9.
37. Osmancevic A, Landin-Wilhelmsen K, Larko O, et al. UVB therapy increases 25(OH) vitamin D syntheses in postmenopausal women with psoriasis. *Photodermatol Photoimmunol Photomed* 2007;23:172–8.
38. Guadagnino V, Ayala F, Chirianni A, et al. Risk of hepatitis B virus infection in patients with eczema or psoriasis of the hand. *BMJ* 1982;284:84.
39. Ketikoglou I, Karatapanis S, Elefsiniotis I, et al. Extensive psoriasis induced by pegylated interferon alpha-2b treatment for chronic hepatitis B. *Eur J Dermatol* 2005;15:107–9.
40. Kartal ED, Colak H, Ozgunes I, Usluer G. Exacerbation of psoriasis due to peginterferon alpha-2b plus ribavirin treatment of chronic active hepatitis C. *Chemotherapy* 2005;51:167–9.
41. Bell TM, Bansal AS, Shorthouse C, et al. Low-titre auto-antibodies predict autoimmune disease during interferon-alpha treatment of chronic hepatitis C. *J Gastroenterol Hepatol* 1999;14:419–22.
42. Bottomley WW, Walton S, Keczes K, Piercy DM. Does prior hepatitis B infection potentiate the hepatotoxic hazard of methotrexate and azathioprine? *J Dermatol Treat* 1990;1:263–4.
43. Calabrese LH, Zein N, Vassilopoulos D. Safety of antitumor necrosis factor (anti-TNF) therapy in patients with chronic viral infections: hepatitis C, hepatitis B, and HIV infection. *Ann Rheum Dis* 2004;63 Suppl 2:ii18–ii24.
44. Zein NN. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. *J Hepatol* 2005;42:315–22.
45. Khanna M, Shirodkar MA, Gottlieb AB. Etanercept therapy in patients with autoimmunity and hepatitis C. *J Dermatol Treat* 2003;14:229–32.
46. Thaci D, Patzold S, Kaufmann R, Boehncke WH. Treatment of psoriasis with alefacept in patients with hepatitis C infection: a report of two cases. *Br J Dermatol* 2005;152:1048–50.
47. Imafuku S, Tashiro A, Furue M. Cyclosporin treatment of psoriasis in a patient with chronic hepatitis C. *Br J Dermatol* 2007;156:1367–9. Buchness MR. Treatment of skin diseases in HIV-infected patients. *Dermatol Clin* 1995;13:231–8.
49. Buccheri L, Katchen BR, Karter AJ, Cohen SR. Acitretin therapy is effective for psoriasis associated with human immunodeficiency virus infection. *Arch Dermatol* 1997;133:711–5.
50. Mamkin I, Mamkin A, Ramanan SV. HIV-associated psoriasis. *Lancet Infect Dis* 2007;7:496.
51. Gelfand JM, Rudikoff D. Evaluation and treatment of itching in HIV-infected patients. *Mt Sinai J Med* 2001;68:298–308.
52. Helton JL. Genital dermatology in the HIV-infected patient. *AIDS Patient Care & Stds* 1997;11:237–43.
53. Fife DJ, Waller JM, Jeffes EW, Koo JYM. Unraveling the paradoxes of HIV-associated psoriasis: A review of T-cell subsets and cytokine profiles. *Dermatol Online J* 2007;13:4.
54. Duvic M, Crane MM, Conant M, et al. Zidovudine improves psoriasis in human immunodeficiency virus-positive males. *Arch Dermatol* 1994;130:447–51.
55. Townsend BL, Cohen PR, Duvic M. Zidovudine for the treatment of HIV-negative patients with psoriasis: a pilot study. *J Am Acad Dermatol* 1995;32:994–9.
56. Allen BR. Use of cyclosporin for psoriasis in HIV-positive patient. *Lancet* 1992;339:686.
57. Maurer TA, Zackheim HS, Tuffanelli L, Berger TG. The use of methotrexate for treatment of psoriasis in patients with HIV infection. *J Am Acad Dermatol* 1994;31:372–5.
58. Pechere M, Yerly S, Lemonnier E, et al. Impact of PUVA therapy on HIV viremia: a pilot study. *Dermatology* 1997;195:84–5.
59. Fotiades J, Lim HW, Jiang SB, et al. Efficacy of ultraviolet B phototherapy for psoriasis in patients infected with human immunodeficiency virus. *Photodermatol Photoimmunol Photomed* 1995;11:107–11.
60. Meola T, Soter NA, Ostreicher R, et al. The safety of UVB phototherapy in patients with HIV infection. *J Am Acad Dermatol* 1993;29:216–20.
61. Fulchiero Jr GJ, Salvaggio H, Drabick JJ, et al. Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies. *J Am Acad Dermatol* 2007;56:S65–S7.
62. Paul CF, Ho VC, McGeown C, et al. Risk of malignancies in psoriasis patients treated with cyclosporine: A 5 y cohort study. *J Invest Dermatol* 2003;120:211–6.
63. Ly L, Czarnecki D. The rapid onset of multiple squamous cell carcinomas during etanercept treatment for psoriasis. *Br J Dermatol* 2007;157:1076–8.
64. Saag KG, Teng GG, Patkar NM, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. *Arthritis Rheum* 2008;59:762–84.
65. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. *Foot Ankle Int* 2004;25:331–5.
66. den Broeder AA, Creemers MC, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. *J Rheumatol* 2007;34:689–95.

## CHAPTER 8: EXACERBATION AND FLARE OF PSORIASIS

### Canadian Guidelines for the Management of Plaque Psoriasis

Psoriasis is a chronic condition whose onset and subsequent course cannot be predicted with any certainty. However, psoriatic exacerbations have been associated with various exogenous factors. Among other environmental factors, specific drugs and drug classes are known to trigger psoriatic exacerbations in individuals with pre-existing psoriasis. Some of these treatments can also induce psoriasis in individuals with no history of this disease.

Instances of drug-associated exacerbations, including idiosyncratic reactions to antipsoriatic drugs, have been widely reported. It is often difficult to establish the direct causal link between a therapeutic and a psoriatic exacerbation, especially when the episode occurs in a patient with a history of unstable psoriasis. In some cases, it may be possible to test the association by withdrawing the putative trigger therapy and then re-challenging the patient with it after the episode has resolved. However, such experiments should be undertaken only after a thorough analysis of potential benefits and risks.

#### KEY POINT

*Psoriasis is a chronic condition that often waxes and wanes in severity, so long-term management is a challenge for the treating physician. Understanding the factors that may cause psoriatic exacerbations, flares, and rebounds, such as environmental factors, emotional stress, and medications, will facilitate timely clinical intervention and reduce the risk of life-threatening flares.*

Unfortunately, much of the published evidence on drug-related flares and exacerbations is of low level, relying on isolated case reports; some potential triggers, such as chloroquine and other antimalarials, are therefore controversial.<sup>1-3</sup> However, exacerbations

have been documented in patients receiving biologic agents (TNF inhibitors) and non-biologic treatments (e.g., corticosteroids and cyclosporine).

#### New-onset psoriasis

##### *Infection*

In children and young adults, new-onset guttate psoriasis may be triggered by streptococcal infections, typically streptococcal pharyngitis, but sometimes also perianal streptococcal cellulitis.<sup>4</sup> Some individuals with guttate psoriasis may progress to plaque psoriasis, and parents of children with guttate psoriasis should be counselled accordingly. Pure guttate psoriasis is amenable to treatment with phototherapy and, in individuals with clinically diagnosed streptococcal infections, concomitant antibiotics.<sup>5</sup> Tonsillectomy has been suggested for patients with repeated streptococcal infections and guttate flares as a possible means to prevent recurrence of these episodes or progression to plaque psoriasis.<sup>6</sup> However, any benefits of such an approach remain speculative.

##### *TNF inhibitors*

When used to treat rheumatoid arthritis and other non-cutaneous inflammatory disorders, the TNF inhibitors (infliximab, adalimumab, and etanercept) have each been shown to induce psoriasis in individuals with neither a personal nor a family history of the disease. This new-onset psoriasis may exhibit either a plaque or a pustular morphology.<sup>7-15</sup> Curiously, in some plaque psoriasis patients treated with etanercept or infliximab, the exacerbations observed have been guttate in morphology, presenting as early as 15 days and as late as 18 months after starting therapy.<sup>10,14</sup>

In patients with new-onset psoriasis receiving TNF inhibitors for non-cutaneous disorders, treatment discontinuation should be approached cautiously, since a flare of the underlying disease could prove



more deleterious than the dermatological reaction. In some cases, the psoriatic flare has been managed successfully by adding a concomitant therapy. Transitioning the patient to another therapeutic of the same class (i.e., another TNF inhibitor), although helpful in some instances, has also been reported to provoke further flaring.<sup>9,12</sup>

### Exacerbation of existing psoriasis

Exacerbation is defined as any worsening of a patient's psoriasis. Patients with plaque psoriasis have been reported to experience worsening of their disease when subjected to a wide variety of putative triggers, including physical trauma to the skin, cold weather, emotional stress, streptococcal throat infection, smoking, alcohol intake, and postpartum hormonal changes (see Chapter 7: Special populations and circumstances), as well as certain drugs (see below and Chapter 14: Comorbidities).<sup>10,16-25</sup> Patients should therefore be encouraged to make lifestyle changes such as smoking cessation and avoid suspected triggering factors when possible. In the case of drug-induced exacerbation, it may be beneficial to discontinue the suspected drug if possible and replace it with an alternative agent, preferably one of a different therapeutic class.

### Flares

A psoriatic flare is an exacerbation occurring while the patient is on therapy. A flare differs from the foregoing psoriatic disease, either in its morphology or in the extent or severity of individual lesions.

Pustular psoriasis flares can be triggered by infection or ultraviolet light in patients with stable plaque psoriasis.<sup>26</sup> Approximately 6% of patients with acute generalized pustular (also called von Zumbusch) psoriasis have a history of plaque psoriasis. Patients with acute generalized pustular psoriasis are at greatest risk of developing serious medical complications.<sup>26</sup>

In patients with previously stable plaque psoriasis, allergic contact dermatitis has also been reported to induce pustular lesions. The allergens implicated include zinc pyrithione-containing shampoos and calcipotriol cream.<sup>27-29</sup> Such pustular flares, resulting from contact allergic dermatitis, have been successfully managed by narrowband UVB, short-term cyclosporine, or methotrexate treatment.<sup>27-29</sup>

Erythrodermic psoriasis is a form of inflammatory psoriasis characterized by intense, generalized erythema and with minimal scaling. Symptoms include fever, chills, pruritus, malaise, and fatigue. Patients may suffer from lower-extremity edema, hypothermia due to excessive heat dissipation from dilated capillary beds, and hypoalbuminemia.<sup>26</sup>

Erythrodermic flares may occur following use of drugs such as lithium (see Chapter 14: Comorbidities), and they have been associated, with varying degrees of evidence, with other environmental factors such as staphylococcal infection, emotional stress, physical trauma to the skin, and alcohol consumption.<sup>5</sup> In individuals receiving antipsoriatic treatments, such flares have also been ascribed to the use of topical anthralin or corticosteroids; systemic corticosteroids, cyclosporine, and etretinate; and UV burns associated with PUVA treatment.<sup>26,30-32</sup>

Erythrodermic psoriasis can be potentially life-threatening if not adequately managed. Infliximab has been used successfully to control severe erythrodermic flares.<sup>33,34</sup> Either adalimumab or infliximab may be considered for control of generalized pustular flares.<sup>35,36</sup>

### Rebound

By definition, rebound must occur within 3 months of discontinuing antipsoriatic therapy. Rebound is said to occur either when PASI scores reach 125% of baseline or when the patient experiences new generalized pustular, erythrodermic, or more inflammatory psoriasis. Rebound, sometimes with morphology different from the prior disease, may present *de novo* upon withdrawal of systemic treatments.<sup>37</sup> For instance, rebound manifesting as either generalized pustular or erythrodermal flares has also been reported in patients whose cyclosporine treatment was stopped abruptly.<sup>38</sup> The biologics etanercept and alefacept have been proposed as transitional therapies in patients who need to be weaned off cyclosporine.<sup>39,40</sup>

For generalized pustular rebound associated with cyclosporine withdrawal, etanercept<sup>38</sup> or, for appropriate patients, methotrexate plus systemic acitretin<sup>41</sup> should be considered. Methotrexate plus infliximab has been used successfully for erythroderma associated with cyclosporine withdrawal.<sup>42,43</sup>

### Conclusion

Since psoriasis is a chronic condition that often waxes and wanes in severity, long-term management of the disease can be difficult. Understanding factors that can induce psoriatic exacerbations, flares, and rebounds can facilitate timely clinical intervention and reduce the risk of life-threatening flares from occurring in psoriatic patients. The choice of therapy for treating exacerbations, flares, and rebounds should be based on the medical history of the patient, the severity of the disease, and the recommendations outlined below.

Recommendations	
Recommendation & level of evidence	Grade of recommendation
In patients who develop new-onset plaque, pustular, or guttate psoriasis while receiving TNF inhibitors for non-dermatological conditions, the psoriasis should, if possible, be controlled with topical agents (calcipotriol, corticosteroids, or both) while maintaining TNF therapy (Refs. 10, 14, LoE 3)	Grade D
Those who do not improve sufficiently with topical therapy may be switched to another biologic (Ref. 10, LoE 3), cyclosporine (Ref. 14, LoE 3), or another systemic or phototherapy (LoE 4)	Grade D

### References

- Sorbara S, Cozzani E, Rebora A, Parodi A. Hydroxychloroquine in psoriasis: Is it really harmful? *Acta Derm Venereol* 2006;86:450-1.
- Kuflik EG. Effect of antimalarial drugs on psoriasis. *Cutis* 1980;26:153-5.
- Gladman DD, Blake R, Brubacher B, Farewell VT. Chloroquine therapy in psoriatic arthritis. *J Rheumatol* 1992;19:1724-6.
- Ulger Z, Gelenava T, Kosay Y, Darcan S. Acute guttate psoriasis associated with streptococcal perianal dermatitis. *Clin Pediatr (Phila)* 2007;46:70-2.
- Weinstein GD, Gottlieb AB. *Therapy of moderate-to-severe psoriasis*, 2nd ed., (M. Dekker, New York, 2003).
- Hone SW, Donnelly MJ, Powell F, Blayney AW. Clearance of recalcitrant psoriasis after tonsillectomy. *Clin Otolaryngol Allied Sci* 1996;21:546-7.
- Grinblat B, Scheinberg M, Beuthien W, et al. Unexpected onset of psoriasis during infliximab treatment: Comment on the article by Beuthien et al. *Arthritis Rheum* 2005;52:1333-4.
- Grinblat B, Scheinberg M. The enigmatic development of psoriasis and psoriasiform lesions during anti-TNF therapy: A Review. *Semin Arthritis Rheum* 2008;37:251-5.
- Kary S, Worm M, Audring H, et al. New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving tumour necrosis factor alpha antagonists. *Ann Rheum Dis* 2006;65:405-7.
- de Gannes GC, Ghoreishi M, Pope J, et al. Psoriasis and pustular dermatitis triggered by TNF-[alpha] inhibitors in patients with rheumatologic conditions. *Arch Dermatol* 2007;143:223-31.
- Peek R, Scott-Jupp R, Strike H, et al. Psoriasis after treatment of juvenile idiopathic arthritis with etanercept. *Ann Rheum Dis* 2006;65:1259.
- Cohen JD, Bourmerias I, Buffard V, et al. Psoriasis induced by tumor necrosis factor-alpha antagonist therapy: a case series. *J Rheumatol* 2007;34:380-5.
- Sari I, Akar S, Birlık M, et al. Anti-tumor necrosis factor-alpha-induced psoriasis. *J Rheumatol* 2006;33:1411-4.
- Goiz R, Dauden E, Perez-Gala S, et al. Flare and change of psoriasis morphology during the course of treatment with tumour necrosis factor blockers. *Clin Exp Dermatol* 2007;32:176-9.
- Ubriani R, van Voorhees AS. Onset of psoriasis during treatment with TNF-[alpha] antagonists: a report of 3 cases. *Arch Dermatol* 2007;143:270-2.
- Gupta MA, Gupta AK, Kirkby S, et al. A psychocutaneous profile of psoriasis patients who are stress reactors. A study of 127 patients. *Gen Hosp Psychiatry* 1989;11:166-73.
- Zachariae R, Zachariae H, Blomqvist K, et al. Self-reported stress reactivity and psoriasis-related stress of Nordic psoriasis sufferers. *J Eur Acad Dermatol Venereol* 2004;18:27-36.
- Harvima RJ, Viinamaki H, Harvima IT, et al. Association of psychic stress with clinical severity and symptoms of psoriatic patients. *Acta Derm Venereol* 1996;76:467-71.
- Paljan D, Kansky A, Cividini-Stranic E. Psychosomatic factors influencing the course of psoriasis. *Acta Derm Venereol* 1984;64:121-2.
- Corn BM, Lemont H, Witkowski JA. Lesion pattern of psoriasis of the feet. Its relationship to the normal weight-bearing force curve. *Int J Dermatol* 1987;26:115-6.
- Allan SJR, Kavanagh GM, Herd RM, Savin JA. The effect of inositol supplements on the psoriasis of patients taking lithium: a randomized, placebo-controlled trial. *Br J Dermatol* 2004;150:966-9.
- Poikolainen K, Reunala T, Karvonen J. Smoking, alcohol and life events related to psoriasis among women. *Br J Dermatol* 1994;130:473-7.
- Boyd AS, Morris LF, Phillips CM, Menter MA. Psoriasis and pregnancy: hormone and immune system interaction. *Int J Dermatol* 1996;35:169-72.
- Gudjonsson JE, Thorarinsson AM, Sigurgeirsson B, et al. Streptococcal throat infections and exacerbation of chronic plaque psoriasis: a prospective study. *Br J Dermatol* 2003;149:530-4.
- Melski JW, Bernhard JD, Stern RS. The Koebner (isomorphic) response in psoriasis. Associations with early age at onset and multiple previous therapies. *Arch Dermatol* 1983;119:655-9.
- Arndt KA. *Cutaneous medicine and surgery: an integrated program in dermatology*. (Saunders, Philadelphia, 1996).
- Jo JH, Jang HS, Ko HC, et al. Pustular psoriasis and the Kobner phenomenon caused by allergic contact dermatitis from zinc pyrithione-containing shampoo. *Dermatitis* 2005;52:142-4.
- Nielsen NH, Menne T. Allergic contact dermatitis caused by zinc pyrithione associated with pustular psoriasis. *Am J Contact Derm* 1997;8:170-1.
- Georgala S, Rigopoulos D, Aroni K, Stratigos JT. Generalized pustular psoriasis precipitated by topical calcipotriol cream. *Int J Dermatol* 1994;33:515-6.
- Condon C, Lyons JF. Extensive unstable psoriasis — morbidity and medical management. *Irish J Med Sci* 1994;163:381-3.
- Boyd AS, Menter A. Erythrodermic psoriasis. Precipitating factors, course, and prognosis in 50 patients. *J Am Acad Dermatol* 1989;21:985-91.
- Maccarelli FJ, Shenenberger DW. Koebner's phenomenon: Skin trauma may trigger psoriatic flares. *Postgrad Med* 2005;118:45-6.

33. Lewis TG, Tuchinda C, Lim HW, Wong HK. Life-threatening pustular and erythrodermic psoriasis responding to infliximab. *J Drugs Dermatol* 2006;5:546–8.
34. Rongioletti F, Borenstein M, Kirsner R, Kerdel F. Erythrodermic, recalcitrant psoriasis: clinical resolution with infliximab. *J Dermatolog Treat* 2003;14:222–5.
35. Callen JP, Jackson JH. Adalimumab effectively controlled recalcitrant generalized pustular psoriasis in an adolescent. *J Dermatolog Treat* 2005;16:350–2.
36. Schmick K, Grabbe J. Recalcitrant, generalized pustular psoriasis: rapid and lasting therapeutic response to antitumour necrosis factor-alpha antibody (infliximab). *Br J Dermatol* 2004;150:367.
37. Carey W, Glazer S, Gottlieb AB, et al. Relapse, rebound, and psoriasis adverse events: an advisory group report. *J Am Acad Dermatol* 2006;54:S171–81.
38. Kamarashev J, Lor P, Forster A, et al. Generalised pustular psoriasis induced by cyclosporin A withdrawal responding to the tumour necrosis factor alpha inhibitor etanercept. *Dermatology* 2002;205:213–6.
39. Yamauchi PS, Lowe NJ. Cessation of cyclosporine therapy by treatment with etanercept in patients with severe psoriasis. *J Am Acad Dermatol* 2006;54:S135–8.
40. Magliocco MA, Lozano AM, van Saders C, et al. An open-label study to evaluate the transition of patients with chronic plaque psoriasis from cyclosporine to alefacept. *J Drugs Dermatol* 2007;6:424–7.
41. Hong SB, Kim NI. Generalized pustular psoriasis following withdrawal of short-term cyclosporin therapy for psoriatic arthritis. *J Eur Acad Dermatol Venereol* 2005;19:522–3.
42. Cacoub P, Artru L, Canesi M, et al. Life-threatening psoriasis relapse on withdrawal of cyclosporin. *Lancet* 1988;332:219–20.
43. Lisby S, Gniadecki R. Infliximab (Remicade) for acute, severe pustular and erythrodermic psoriasis. *Acta Derm Venereol* 2004;84:247–8.

## CHAPTER 9: MANAGEMENT OF FACIAL, FLEXURAL, AND GENITAL PSORIASIS

### Canadian Guidelines for the Management of Plaque Psoriasis

#### Introduction

Plaque psoriasis affecting the facial, flexural, and genital (FFG) areas, although pathophysiologically similar to other involved skin, presents a distinct clinical challenge because these areas are at heightened risk of adverse reactions to topical treatment.

Facial psoriasis has been viewed as a rare occurrence and has received little attention clinically as a result. Contrary to this long-held belief, however, facial involvement may affect up to two-thirds of patients with psoriasis.<sup>1</sup>

There are three subtypes of facial psoriasis: hairline psoriasis, sebopsoriasis, and true facial psoriasis, of which the last is characterized by a classical overall morphology of chronic plaque psoriasis, with sharply demarcated erythematous-squamous plaques. Hairline psoriasis can be grouped with scalp psoriasis (see Chapter 11: Management of scalp psoriasis), while sebopsoriasis is localized in the seborrheic areas (eyebrows and nasolabial fold). Sebopsoriasis has only mild scaling and is less indurated compared with chronic plaque psoriasis.<sup>2</sup> Patients with facial psoriasis tend to exhibit nail involvement and higher PASI scores on the whole body and the scalp.<sup>1</sup>

Flexural involvement may occur without signs of chronic plaque psoriasis at other sites or as part of chronic plaque psoriasis. Skin irritation from rubbing and sweat accumulation is a common problem for these patients. Flexural psoriasis, also called inverse or intertriginous psoriasis, affects the groin, axillae, inframammary region, abdominal body folds, gluteal cleft, perianal region, and retroarticular fold areas. Genital psoriasis, affecting the penis, scrotum, or vulva, is similar in presentation to flexural psoriasis. In all of these areas, the affected skin appears smooth and inflamed, with less scaling than would be seen in typical plaques on the trunk or limbs.<sup>2-4</sup>

Specific metrics for documenting the severity of FFG

psoriasis are lacking. In clinical trials, severity has been assessed using the Target Area Score<sup>5</sup> or the Disease Signs and Symptoms Score, a composite score of the signs and symptoms of erythema, induration, desquamation, and itching in these areas (expressed as a range from 0 to 3).<sup>6</sup>

Facial psoriasis is common in patients with long disease duration or early onset of disease.<sup>1</sup> In addition, patients with facial involvement may have more frequent pruritus, positive family history, and history of Koebner response. Early recognition of facial psoriasis may serve as a marker of severe disease or acute or subacute exacerbations, thus signalling a requirement for more intensive treatment.<sup>1</sup>

#### KEY POINT

*A patient-centred treatment approach is particularly important in facial or genital psoriasis, where the total body surface area affected is small but the effects of social isolation and other quality-of-life issues are profound.*

#### Management

Plaque psoriasis generally responds well to treatment with topical corticosteroids. However, skin tends to be thinner in the FFG regions, posing a treatment challenge as these areas are more sensitive to the local side effects of these agents, such as atrophy, telangiectasia, striae formation, bruising, and purpura, as well as to adrenocortical suppression.<sup>6,7</sup> Furthermore, although calcipotriol has been shown to be efficacious when used for facial and flexural psoriasis<sup>8</sup> (see below), this vitamin D3 analogue poses a risk of local skin irritation. Calcipotriol may not be tolerated in the FFG regions, particularly those flexural areas that naturally create some degree of occlusion.<sup>9</sup> For these reasons, topical calcineurin inhibitors (TCIs) may be an appropriate choice

for FFG psoriasis and may be supplemented as needed with short-term treatment with moderate-potency topical steroids. The TCIs pimecrolimus and tacrolimus are effective and well tolerated in flexural psoriasis,<sup>5,6,10-12</sup> although these agents are not approved for this indication or, indeed, for any form of psoriasis.

Moderately potent corticosteroids may also be used for the acute management of FFG psoriasis, particularly in areas with thicker plaques,<sup>7</sup> but long-term use should be avoided when possible. In patients with FFG psoriasis, 0.1% tacrolimus, 1% pimecrolimus, and 0.005% calcipotriol<sup>8,13</sup> have all been used for maintenance. These agents may be supplemented for short periods with moderate potency corticosteroids such as 0.1% betamethasone.<sup>7</sup>

Because it can cause irritation and erythema, calcipotriol is not approved for use on the face or intertriginous areas. Nevertheless, vitamin D3 analogues have been used successfully for facial and flexural psoriasis.<sup>8</sup> Likewise, TCIs are not currently indicated for psoriasis, although there is strong evidence that they are effective in FFG psoriasis and avoid the risk of atrophy associated with potent corticosteroids.<sup>5,6,11,12</sup> TCIs are widely prescribed by dermatologists for treating psoriasis in the FFG regions.

Because of the risk of social isolation and other profound quality-of-life issues for patients with facial or genital psoriasis, there is a good argument for

the use of systemic or biologic therapies if topical treatments fail. However, no comparative studies are available to substantiate the efficacy of methotrexate, cyclosporine, acitretin, or biologics in FFG psoriasis. Little has been published regarding the efficacy of PUVA treatment, although it is claimed to be effective in this context.<sup>3</sup> In some instances, however, long-term PUVA treatment has been linked to the appearance of recalcitrant psoriasis of the face and hands,<sup>14</sup> a consideration that may apply to any of the FFG areas. Concerns remain regarding the carcinogenicity of PUVA applied to these relatively sensitive areas of the skin.<sup>15</sup>

Other promising treatments for flexural psoriasis include NB-UVB. Although NB-UVB can be highly effective for flexural psoriasis, use of this therapy is limited by the difficulty of positioning the patient to ensure that skin lesions are exposed during whole-body irradiation.<sup>4</sup>

In the past, low-dose anthralin treatment and coal tar were used routinely for facial and flexural psoriasis. The side effects of staining, stinging, and irritation seen with this treatment make these options outdated.<sup>3</sup>

Management of FFG psoriasis poses a unique treatment challenge for physicians. Treatment strategies for patients with this indication should be tailored individually to suit each patient and should take into consideration the recommendations listed here.

### Recommendations

Recommendation & level of evidence	Grade of recommendation
In moderate flexural psoriasis, topical corticosteroids such as 0.1% betamethasone may be used on an occasional or intermittent basis (Ref. 7, LoE 1+)	Grade B
Topical calcineurin inhibitors (0.1% tacrolimus ointment or 1% pimecrolimus cream) may be used for facial, flexural, or genital areas (Ref. 5, LoE 1+; Ref. 6, LoE 1+; Refs. 11, 12 LoE 2+)	Grade B
Mild or moderate potency corticosteroids may also be used on an occasional or intermittent basis to treat facial and genital psoriasis (LoE 4)	Grade D
In moderate to severe facial, flexural, and genital disease, stronger corticosteroids may be applied to address non-responsive psoriasis or acute flares in these areas (Refs. 16, 17, LoE 2-)	Grade C
Accessible flexural areas may be treated with whole-body NB-UVB (Ref. 4, LoE 3)	Grade D

## References

1. Park JY, Rim JH, Choe YB, Youn JI. Facial psoriasis: Comparison of patients with and without facial involvement. *J Am Acad Dermatol* 2004;50:582–4.
2. van de Kerkhof PCM. *Textbook of psoriasis*. (Blackwell Science, Oxford; Malden, MA, 1999).
3. van de Kerkhof PC, Murphy GM, Austad J, et al. Psoriasis of the face and flexures. *J Dermatolog Treat* 2007;18:351–60.
4. Wang G, Li C, Gao T, Liu Y. Clinical analysis of 48 cases of inverse psoriasis: a hospital-based study. *Eur J Dermatol* 2005;15:176–8.
5. Gribetz C, Ling M, Lebwohl M, et al. Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. *J Am Acad Dermatol* 2004;51:731–8.
6. Lebwohl M, Freeman AK, Chapman MS, et al. Tacrolimus ointment is effective for facial and intertriginous psoriasis. *J Am Acad Dermatol* 2004;51:723–30.
7. Kreuter A, Sommer A, Hyun J, et al. 1% pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone in the treatment of intertriginous psoriasis: a double-blind, randomized controlled study. *Arch Dermatol* 2006;142:1138–43.
8. Ortonne JP, Humbert P, Nicolas JF, et al. Intra-individual comparison of the cutaneous safety and efficacy of calcitriol 3 microg g(-1) ointment and calcipotriol 50 microg g(-1) ointment on chronic plaque psoriasis localized in facial, hairline, retroauricular or flexural areas. *Br J Dermatol* 2003;148:326–33.
9. Murdoch D, Clissold SP. Calcipotriol. A review of its pharmacological properties and therapeutic use in psoriasis vulgaris. *Drugs* 1992;43:415–29.
10. Martin Ezquerro G, Sanchez Regana M, Herrera Acosta E, Umberto Millet P. Topical tacrolimus for the treatment of psoriasis on the face, genitalia, intertriginous areas and corporal plaques. *J Drugs Dermatol* 2006;5:334–6.
11. Freeman AK, Linowski GJ, Brady C, et al. Tacrolimus ointment for the treatment of psoriasis on the face and intertriginous areas. *J Am Acad Dermatol* 2003;48:564–8.
12. Yamamoto T, Nishioka K. Topical tacrolimus: An effective therapy for facial psoriasis. *Eur J Dermatol* 2003;13:471–3.
13. Duweb GA, Eldebani S, Alhaddar J. Calcipotriol cream in the treatment of flexural psoriasis. *Int J Tissue React* 2003;25:127–30.
14. Verhagen AR, van der Wiel AG, Wuite GG. Atypical psoriasis of the face and hands after PUVA treatment. *Br J Dermatol* 1984;111:615–8.
15. Stern RS, Bagheri S, Nichols K. The persistent risk of genital tumors among men treated with psoralen plus ultraviolet A (PUVA) for psoriasis. *J Am Acad Dermatol* 2002;47:33–9.
16. Lebwohl M, Peets E, Chen V. Limited application of mometasone furoate on the face and intertriginous areas: analysis of safety and efficacy. *Int J Dermatol* 1993;32:830–1.
17. Lebwohl MG, Tan MH, Meador SL, Singer G. Limited application of fluticasone propionate ointment, 0.005% in patients with psoriasis of the face and intertriginous areas. *J Am Acad Dermatol* 2001;44:77–82.



## CHAPTER 10: MANAGEMENT OF NAIL PSORIASIS

### Canadian Guidelines for the Management of Plaque Psoriasis

Nail psoriasis is among the most challenging manifestations of psoriasis, in part due to the challenge of drug delivery around and beneath the nail plate. Because of the paucity of good clinical data, evidence-based guidance is particularly difficult to develop for this manifestation of psoriasis. Nail psoriasis is nevertheless worthy of a clinician's treatment efforts because, quite apart from the psychosocial sequelae of disfigured nails, it causes significant pain and disability. A survey from the Netherlands reported that 93% of 1728 patients considered nail psoriasis to be a "major problem", with 52% describing pain as a symptom and 58% saying that it interfered with daily activities.<sup>1</sup> Nail involvement is more common in patients with psoriatic arthritis.<sup>2</sup> In patients with no diagnosis of psoriatic arthritis, 39–46% of adults<sup>2,3</sup> and 38% of children<sup>4</sup> are reported to have nail

involvement, as compared with 83–100% of psoriatic arthritis patients.<sup>2,3,5</sup>

#### Presentation and evaluation of nail psoriasis

The nail unit comprises the nail plate and four epithelial structures: the proximal nail fold (a continuation of the digital skin that folds underneath itself to protect the matrix), the matrix (from which the nail plate arises), the nail bed (the epithelium under the nail plate), and the hyponychium (the epithelium underneath the free edge of the nail plate). Each of these epithelial structures can be affected by psoriasis over differing time scales, which accounts for the variability of the clinical presentation of nail psoriasis. Clinical studies tend to focus on nail matrix psoriasis and nail bed psoriasis, each of which has four main characteristics, as shown in **Table 1**.

**Table 1. Manifestations of nail psoriasis**

Nail tissue involved	Clinical feature
Nail matrix	Pitting (small depressions in the uppermost layers of the nail plate)
	Leukonychia (smooth-surfaced lesions giving the nail a whitish appearance)
	Red spots in the lunula
	Nail plate crumbling
Nail bed	Subungual hyperkeratosis ('nail thickening', with hyperproliferation of keratinocytes underneath the nail plate)
	Onycholysis (separation of the nail plate and nail bed)
	Oil-drop or salmon-spot discolouration (serum-filled lesions within the nail bed)
	Splinter hemorrhages (minute lesions along the junction of the dermis and epidermis)

Until recently, there was no standardized method for assessing the severity of nail psoriasis, which prevented any straightforward comparison of therapies. Clinical trials have used a variety of metrics, from qualitative descriptors to objective numerical scales such as the Psoriasis Nail Severity Score (PNSS), the Nail Area Severity (NAS) index, or the Nail Psoriasis Severity Index (NAPSI).<sup>6</sup> The NAPSI requires physicians to score each nail based on the nail matrix and nail bed parameters described in **Table 1**.

### KEY POINT

*Nail psoriasis represents a disproportionately large challenge for patients and physicians, in view of the small body surface area involved. Although nail psoriasis can profoundly disrupt patients' lives, the evidence supporting most treatments is low-level. Adherence is also an issue since nail treatment is long-term, frequently ineffective, and sometimes painful. Patient preferences and quality-of-life considerations are thus central to the management of nail psoriasis.*

### Management of nail psoriasis

Although there are many effective treatment options for skin psoriasis, the choices are more limited for nail psoriasis (**Table 2**). The historically popular modalities are often tedious or painful to administer and of limited efficacy, with short-lived remissions.

Nail psoriasis is sometimes confused with onychomycosis; indeed, the two conditions may occur concomitantly, and it has been suggested that individuals with psoriasis,<sup>7</sup> and specifically with nail involvement,<sup>8</sup> are at elevated risk of toenail onychomycosis. Laboratory analysis of nail scrapings for fungal cells and/or nail biopsy can be helpful to clarify the diagnosis of nail abnormalities.<sup>9</sup>

Because of the clinical variability of nail psoriasis and differences among patients' life circumstances, it is crucial to tailor the treatment plan as much as possible to relieve any emotional or physical distress, or actual physical disability, that the patient experiences.

#### *Topical therapies*

The available data on topical therapies largely

focuses on improvements in subungual hyperkeratosis and onycholysis; the benefit of these therapies for other manifestations of nail psoriasis is still unclear, although the available data are presented below.

Topical steroids are only marginally effective in monotherapy for nail psoriasis, and there is significant regression once therapy is discontinued.<sup>10,11</sup> Steroid combinations give moderate relief after several months of treatment. Topical application of salicylic acid plus betamethasone dipropionate (see Chapter 5: Management of mild plaque psoriasis) reduced hyperkeratosis by approximately 50% over 5 months in responders in a randomized controlled trial; similar results were seen for calcipotriol (see below).<sup>12</sup>

Topical 5-fluorouracil was no more effective than a penetration-enhancer vehicle (urea and propylene glycol) in a double-blind study over 8 weeks, with only marginal benefit at 12 and 16 weeks on pitting and onycholysis.<sup>13</sup>

Topical tazarotene was ineffective for hyperkeratosis and conferred only modest improvements in pitting and onycholysis over 6 months in a randomized, placebo-controlled trial.<sup>14</sup> Better results were seen for hyperkeratosis with tazarotene in a small, open, prospective trial; onycholysis, pitting, and oil spots/salmon patches also improved.<sup>15</sup> Tazarotene was slightly more effective for hyperkeratosis than clobetasol cream 0.05% in a small, randomized, double-blind trial. Significant loss of control occurred once the treatments were discontinued.<sup>11</sup>

Topical calcipotriol had moderate success for hyperkeratosis and onycholysis over 3–6 months in several case series<sup>16,17</sup> and reduced hyperkeratosis by 49% and 41% (fingers and toes) in a small, randomized, controlled trial over 5 months.<sup>12</sup> In this trial, and as discussed above, topical calcipotriol was as effective as betamethasone dipropionate plus salicylic acid cream.<sup>12</sup>

The use of occlusive dressings is surprisingly rare in studies of nail psoriasis,<sup>11,14</sup> especially as it appears to greatly enhance the effectiveness of therapy. Scher et al. (2001) found that tazarotene was only effective for pitting when occlusion was used

and that onycholysis under occlusion responded within 4 weeks instead of the 24 weeks seen in non-occluded nails.<sup>14</sup>

Safety and tolerability are major considerations with topicals, in view of the length of treatment required, the need for daily application, and the modest results. The potential side effects of long-term therapy with potent steroids are well documented, including irreversible local effects such as skin atrophy, acroatrophy ('disappearing digit'),<sup>18,19</sup> striae formation, and telangiectasia.<sup>20</sup> However, in the study on salicylic acid plus betamethasone dipropionate described above, the only adverse events reported were three cases of erythema.<sup>12</sup>

The administration of potent corticosteroids under occlusion raises concerns about potentiating the local adverse effects of these drugs. However, one study in plaque psoriasis patients, comparing week-long administration of clobetasol propionate under occlusion with twice-daily application of the same corticosteroid without occlusion, offers some support for the use of occlusive dressings. The authors found no evidence of clinical atrophy after up to 6 weeks of treatment in either treatment group, although the patients receiving treatment under occlusion experienced more rapid clearance.<sup>21</sup> No such safety or efficacy data are available concerning the use of corticosteroids under occlusive dressing in nail psoriasis.

As in other indications for which calcipotriol is used, the most common adverse reactions for this topical treatment in nail psoriasis are skin irritation and burning.<sup>12,22</sup> Likewise, tazarotene under occlusion was reported to cause peeling, irritation of distant skin, paronychia, and erythema.<sup>11,14</sup> No adverse events were reported in the single trial of topical cyclosporine solution.<sup>23</sup>

#### ***Intralesional therapies***

Although commonly viewed as the standard of care for psoriatic nails, intralesional therapy suffers from a lack of high-quality supporting data. It involves introducing small quantities of corticosteroid (triamcinolone acetonide) into the affected tissue, either by needle<sup>24,25</sup> or by high-pressure jet.<sup>26-28</sup> High-pressure devices appeared quite successful for nail matrix disease in observational studies

in the 1970s,<sup>26-28</sup> but they have largely fallen out of favour in the post-HIV era due to the risk of blood splashback. Open-label studies suggest that monthly<sup>25</sup> or ad hoc<sup>24</sup> injections of triamcinolone acetonide are moderately effective overall and can be particularly effective for nail bed manifestations such as hyperkeratosis.<sup>24,25</sup>

The main disadvantage of intralesional injections is that they are very painful; Grover et al. (2005) found that one-third of the 50 patients discontinued therapy due to pain.<sup>25</sup> Prior local ring-block anesthesia is unacceptable to many patients since it involves further needle pricks. Patients should therefore be counselled about the pain associated with the procedure, with and without anesthesia, and their preferences should be respected. Other adverse events included proximal nail fold atrophy,<sup>25</sup> subungual hematoma,<sup>24,25</sup> and short-term paresthesia.<sup>24</sup>

#### ***Radiation and phototherapy***

Several radiation treatments and phototherapies have been tested on psoriatic nails, but high-quality evidence remains lacking; the small, prospective trials available demonstrated variable efficacy and lengths of remission. Oral PUVA (two to three times a week followed by weekly maintenance treatment) was effective for nail bed disease (hyperkeratosis and onycholysis) but showed only modest effects for nail matrix disease.<sup>29</sup> Even at UVA doses predicted to be too low to penetrate the nail plate, PUVA-paint treatment directed at the nail fold can be effective in treating onycholysis.<sup>30</sup> PUVA is contraindicated in patients with a history of photodermatoses, photosensitive disease, cutaneous malignancies, or immunosuppression.

In addition to PUVA treatment, other radiation-based approaches such as electron beam therapy<sup>31</sup> and superficial radiotherapy<sup>32</sup> have been used successfully to treat nail psoriasis.

#### ***Systemic therapies***

Systemic therapies for nail psoriasis have usually been tested in the context of broader treatment of skin psoriasis. Neither oral cyclosporine nor the retinoid etretinate significantly improved nail disease from baseline in a large, randomized trial.<sup>33</sup> However, cyclosporine did significantly improve nail symptoms in the subset of patients whose

skin symptoms also responded to cyclosporine therapy.<sup>33</sup> A case-control study found that oral cyclosporine achieved nail improvements in 48% of patients over 3 months; combination oral cyclosporine and topical calcipotriol increased success to 79%.<sup>34</sup> Hyperkeratosis, onycholysis, and pitting showed the greatest improvement with the combination treatment.<sup>34</sup>

The effectiveness of the biologic therapies for nail psoriasis has recently started to emerge from subanalyses of pivotal trials in skin disease as well as smaller pilot studies.<sup>35-39</sup> It appears that patients on a biologic for their skin psoriasis may see nail

benefits as well. In a large, multicentre, placebo-controlled trial, infliximab achieved complete clearance of the worst-affected nail in over half of patients within a year, assessed by the NAPSI, with improvements seen by 10 weeks and superior scores for nail bed disease versus those for the nail matrix.<sup>38,39</sup> A small open-label study achieved remission (defined as  $\geq 75\%$  improvement in NAPSI score) in all patients with moderately to severely affected nails by 22 weeks.<sup>35</sup> Alefacept has been tested in two small open-label studies in patients with moderate to severe nail psoriasis: it reduced the NAPSI score in three out of eight patients in one study<sup>36</sup> and by 39% overall in the other study.<sup>37</sup>

**Table 2. Therapeutic options for managing nail psoriasis**

Type of therapy	Important contraindications and therapeutic considerations
Topical corticosteroids	Topical corticosteroids appear to be moderately effective for hyperkeratosis in combination with calcipotriol or salicylic acid, but there is little evidence to support their effectiveness for other nail manifestations or as monotherapy. <sup>10-12,22</sup> Long-term use may be associated with tachyphylaxis and increases the risk of side effects such as skin atrophy, acroatrophy ('disappearing digit'), striae formation, and telangiectasias <sup>18-20</sup>
Injected corticosteroids	Intralesional injections of triamcinolone acetonide can be moderately effective for all lesion types, but the procedure is painful, and thus adherence is an issue <sup>24,25</sup>
Calcipotriol	Topical calcipotriol appears to be as effective as a steroid plus salicylic acid combination for hyperkeratosis and onycholysis. <sup>12</sup> Adverse events include skin irritation and burning <sup>12,22</sup>
Phototherapy	Phototherapy for psoriatic nails still suffers from a lack of convincing evidence, although small studies suggest that some patients may benefit. <sup>29,31,32</sup> Patients may find the treatment schedule onerous for only modest return and short remission
Topical tazarotene	Although open-label studies have shown improvements in hyperkeratosis with topical tazarotene, <sup>11,15</sup> it had no impact on hyperkeratosis in a randomized controlled trial and only modest effects on pitting and onycholysis
Cyclosporine	Oral cyclosporine as monotherapy has shown only modest results in nail psoriasis. The addition of topical calcipotriol to oral cyclosporine appears to improve efficacy and delay relapse <sup>34</sup>
Biologic agents	The small but growing body of data on the biologics suggests that patients on these therapies for skin involvement may also achieve nail benefits. Infliximab achieved complete clearance in over half of all patients with moderate to severe nail involvement in a large trial. <sup>38,39</sup> In open-label studies, alefacept showed promising results in patients with moderate to severe nail involvement <sup>36</sup>

Recommendations	
Recommendation & level of evidence	Grade of recommendation
For moderate to severe nail psoriasis or mild nail psoriasis that affects patient quality of life, appropriate first-line treatments include either topical calcipotriol or topical betamethasone dipropionate plus salicylic acid (Ref. 12, LoE 1–; Ref. 17, LoE 3; Ref. 16, LoE 3)	<b>Grade C</b>
Other topical steroid monotherapy, or calcipotriol plus betamethasone, may also be used (LoE 4)	<b>Grade D</b>
As a second-line option, topical tazarotene may be used (Refs. 11, 14, LoE 1– ; Ref. 15, LoE 2–)	<b>Grade C</b>
For severe nail psoriasis with hyperkeratosis as the predominant feature, the physician may also consider intralesional injection of triamcinolone acetonide ( $\geq 2.5$ mg/mL) into the proximal nail fold, repeated once after 2 months if no response (Refs. 24, 25, LoE 2–)	<b>Grade C</b>
<p>Patients with isolated nail psoriasis should not ordinarily be considered for systemic or phototherapy (LoE 4). However, in appropriate patients with other psoriatic manifestations, the presence of severe or intractable nail involvement may be a contributing factor in the decision to use any of the following to treat plaque psoriasis affecting other areas of the skin:</p> <ul style="list-style-type: none"> <li>• Infliximab (Refs. 38, 39, LoE 1++; Ref. 35, LoE 2–)</li> <li>• Alefacept (Refs. 36, 37, LoE 3)</li> <li>• Oral cyclosporine plus topical calcipotriol (Ref. 34, LoE 2+)</li> <li>• Oral cyclosporine alone in patients with a history of vigorous response to this treatment for plaque psoriasis (Ref. 33, LoE 1+)</li> </ul>	<p><b>Grade D</b></p> <p><b>Grade A</b></p> <p><b>Grade D</b></p> <p><b>Grade C</b></p> <p><b>Grade B</b></p>

Nail psoriasis represents a disproportionately large challenge for patients and physicians, in view of the small body surface area involved. Although nail psoriasis can profoundly disrupt patients' lives, evidence-based management decisions currently rely on open-label studies with differing endpoints

and uncertain baseline diagnoses. Moreover, adherence is an issue since the available therapies are necessarily long-term, frequently ineffective and sometimes painful. Patient preferences and quality-of-life considerations are thus central to the management of nail psoriasis.

## References

- De Jong E, Seegers B, Gulinck MK, et al. Psoriasis of the nails associated with disability in a large number of patients: Results of a recent interview with 1728 patients. *Dermatology* 1996;193:300–3.
- Salomon J, Szepletowski JC, Proniewicz A. Psoriatic nails: a prospective clinical study. *J Cutan Med Surg* 2003;7:317–21.
- Gladman DD, Anhorn KA, Schachter RK, Mervart H. HLA antigens in psoriatic arthritis. *J Rheumatol* 1986;13:586–92.
- Al-Mutairi N, Manchanda Y, Nour-Eldin O. Nail changes in childhood psoriasis: A study from Kuwait. *Pediatr Dermatol* 2007;24:7–10.
- Williamson L, Dalbeth N, Dockerty JL, et al. Nail disease in psoriatic arthritis — clinically important, potentially treatable and often overlooked. *Rheumatology* 2004;43:790–4.
- Rich P, Scher RK. Nail Psoriasis Severity Index: a useful tool for evaluation of nail psoriasis. *J Am Acad Dermatol* 2003;49:206–12.
- Leibovici V, Hershko K, Ingber A, et al. Increased prevalence of onychomycosis among psoriatic patients in Israel. *Acta Derm Venereol* 2008;88:31–3.
- Sanchez-Regana ML, Videla S, Villoria J, et al. Prevalence of fungal involvement in a series of patients with nail psoriasis. *Clin Exp Dermatol* 2008;33:194–5.
- Grover C, Reddy BS, Chaturvedi KU. Onychomycosis and the diagnostic significance of nail biopsy. *J Dermatol* 2003;30:116–22.
- Piraccini BM, Tosti A, Iorizzo M, Misciali C. Pustular psoriasis of the nails: Treatment and long-term follow-up of 46 patients. *Br J Dermatol* 2001;144:1000–5.
- Rigopoulos D, Gregoriou S, Katsambas A. Treatment of psoriatic nails with tazarotene cream 0.1% vs. clobetasol propionate 0.05% cream: A double-blind study. *Acta Derm Venereol* 2007;87:167–8.
- Tosti A, Piraccini BM, Cameli N, et al. Calcipotriol ointment in nail psoriasis: A controlled double-blind comparison with betamethasone dipropionate and salicylic acid. *Br J Dermatol* 1998;139:655–9.
- de Jong EM, Menke HE, van Praag MC, van de Kerkhof PC. Dystrophic psoriatic fingernails treated with 1% 5-fluorouracil in a nail penetration-enhancing vehicle: a double-blind study. *Dermatology* 1999;199:313–8.
- Scher RK, Stiller M, Zhu YL. Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. *Cutis* 2001;68:355–8.
- Bianchi L, Soda R, Diluvio L, Chimenti S. Tazarotene 0.1% gel for psoriasis of the fingernails and toenails: an open, prospective study. *Br J Dermatol* 2003;149:207–9.
- Kokelj F, Lavaroni G, Piraccini BM, Tosti A. Nail psoriasis treated with calcipotriol (MC 903): An open study. *J Dermatolog Treat* 1994;5:149–50.
- Zakeri M, Valikhani M, Mortazavi H, Barzegari M. Topical calcipotriol therapy in nail psoriasis: A study of 24 cases. *Dermatol Online J* 2005;11:5
- Requena L, Zamora E, Martin L. Acroatrophy secondary to long-standing applications of topical steroids. *Arch Dermatol* 1990;126:1013–4.
- Wolf R, Tur E, Brenner S. Corticosteroid-induced 'disappearing digit'. *J Am Acad Dermatol* 1990;23:755–6.
- Jiaravuthisan MM, Sasseville D, Vender RB, et al. Psoriasis of the nail: anatomy, pathology, clinical presentation, and a review of the literature on therapy. *J Am Acad Dermatol* 2007;57:1–27.
- van der Vleuten CJ, van Vijmen-Willems IM, de Jong EM, van de Kerkhof PC. Clobetasol-17 propionate lotion under hydrocolloid dressing (Duoderm ET) once weekly versus unoccluded clobetasol-17-propionate ointment twice daily in psoriasis: an immunohistochemical study on remission and relapse. *Arch Dermatol Research* 1999;291:390–5.
- Rigopoulos D, Ioannides D, Prastitis N, Katsambas A. Nail psoriasis: a combined treatment using calcipotriol cream and clobetasol propionate cream. *Acta Derm Venereol* 2002;82:140.
- Cannavo SP, Guarneri F, Vaccaro M, et al. Treatment of psoriatic nails with topical cyclosporin: A prospective, randomized placebo-controlled study. *Dermatology* 2003;206:153–6.
- de Berker DA, Lawrence CM. A simplified protocol of steroid injection for psoriatic nail dystrophy. *Br J Dermatol* 1998;138:90–5.
- Grover C, Bansal S, Nanda S, Reddy BSN. Efficacy of triamcinolone acetonide in various acquired nail dystrophies. *J Dermatol* 2005;32:963–8.
- Abell E, Samman PD. Intradermal triamcinolone treatment of nail dystrophies. *Br J Dermatol* 1973;89:191–7.
- Bleeker JJ. Intralesional triamcinolone acetonide using the Port-O-Jet and needle injections in localized dermatoses. *Br J Dermatol* 1974;91:97–101.
- Peachey RD, Pye RJ, Harman RR. The treatment of psoriatic nail dystrophy with intradermal steroid injections. *Br J Dermatol* 1976;95:75–8.
- Marx JL, Scher RK. Response of psoriatic nails to oral photochemotherapy. *Arch Dermatol* 1980;116:1023–4.
- Handfield-Jones SE, Boyle J, Harman RR. Local PUVA treatment for nail psoriasis. *Br J Dermatol* 1987;116:280–1.
- Kwang TY, Nee TS, Seng KT. A therapeutic study of nail psoriasis using electron beams. *Acta Derm Venereol* 1995;75:90.
- Yu RCH, King CM. A double-blind study of superficial radiotherapy in psoriatic nail dystrophy. *Acta Derm Venereol* 1992;72:134–6.
- Mahrle G, Schulze HJ, Farber L, et al. Low-dose short-term cyclosporine versus etretinate in psoriasis: improvement of skin, nail, and joint involvement. *J Am Acad Dermatol* 1995;32:78–88.
- Feliciani C, Zampetti A, Forleo P, et al. Nail psoriasis: Combined therapy with systemic cyclosporin and topical calcipotriol. *J Cutan Med Surg* 2004;8:122–5.
- Bianchi L, Bergamin A, de Felice C, et al. Remission and time of resolution of nail psoriasis during infliximab therapy. *J Am Acad Dermatol* 2005;52:736–7.
- Korver JEM, Langewouters AMG, van de Kerkhof PCM, Pasch MC. Therapeutic effects of a 12-week course of alefacept on nail psoriasis. *J Eur Acad Dermatol Venereol* 2006;20:1252–5.
- Parrish CA, Sobera JO, Robbins CM, et al. Alefacept in the treatment of psoriatic nail disease: a proof of concept study. *J Drugs Dermatol* 2006;5:339–40.
- Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet* 2005;366:1367–74.
- Rich P, Griffiths CE, Reich K, et al. Baseline nail disease in patients with moderate to severe psoriasis and response to treatment with infliximab during 1 year. *J Am Acad Dermatol* 2008;58:224–31.



## CHAPTER 11: MANAGEMENT OF SCALP PSORIASIS

### *Canadian Guidelines for the Management of Plaque Psoriasis*

Symptoms such as itching and scaling in the scalp occur in up to 86% of individuals with plaque psoriasis, causing significant psychological and social distress.<sup>1,2</sup> Indeed, the psychosocial effects due to scalp psoriasis are greater than with psoriasis at other body sites.<sup>2</sup>

Clinically, psoriatic lesions of the scalp appear as sharply demarcated erythematous-squamous plaques with thick silver-white scaling. They may occur in the area above the ears or the occipital region. Involvement of the frontal scalp margin is also common, but lesions at this site are usually less scaly. Permanent hair loss is uncommon. Psoriasis of the scalp superficially resembles seborrheic dermatitis, and it is often difficult to differentiate between the two.

Scalp psoriasis is typically classified as mild, moderate, or severe. In clinical trials, scales such as the Psoriasis Area and Severity Index (PASI), the Psoriasis Scalp Severity Index (PSSI), the Global Severity Score (GSS), and the Total Severity Score (TSS) have been used for assessing the severity of scalp psoriasis. The PSSI is a composite score derived from the sum scores for erythema, induration, and desquamation multiplied by a score for the extent of scalp area involved (range 0–72).<sup>3</sup>

#### KEY POINT

*Scalp psoriasis can cause significant psychological and social distress. Although physicians have a choice of several relatively effective topical therapies, treatment success is limited by the presence of hair, as well as by patients' unwillingness to use therapies they find cosmetically unsatisfactory or inconvenient.*

Scalp psoriasis is commonly treated with topical agents. However, the scalp surface and presence of hair make application of many topical products to the scalp difficult. Traditionally, scalp psoriasis has been treated with topical coal tar therapy and anthralin; treatment adherence with these approaches may be limited by the products' unpleasant smell and ability to stain skin and clothes. Indeed, vehicle formulations of topical treatments are an important factor in patient adherence.<sup>4</sup> Topical corticosteroids, the mainstay of scalp psoriasis management, are therefore available as lotions, solutions, gels, sprays, and shampoos. Other useful adjunct treatments for scalp psoriasis include: gels and shampoos containing refined coal tar in solution; anthralin in an emulsifying oil base; and 5% glycolic and 5% lactic acid scalp lotion plus betamethasone scalp application.<sup>5-7</sup>

Topical application of calcipotriol and phototherapy with UVB can be effective in the treatment of scalp psoriasis, especially when used together.<sup>3</sup> Since hair is a barrier to effective UV phototherapy, it may be necessary to use a broadband UVB comb to deliver phototherapy to the scalp.<sup>8</sup> This comb may be suggested for home use by suitable patients with otherwise intractable scalp psoriasis.

In patients with extensive plaque psoriasis of the body or recalcitrant psoriasis, systemic treatments<sup>9</sup> with methotrexate, cyclosporine, acitretin, and biologics such as etanercept,<sup>10</sup> infliximab, and alefacept have all proved beneficial. These treatments are not commonly used for treating isolated scalp psoriasis but, when used for controlling plaque psoriasis elsewhere on the body, they may provide the added benefit of improving scalp psoriasis. Open-label studies in patients with scalp psoriasis suggest that systemic therapies such as cyclosporine might benefit patients who have failed intensive topical therapy.

Scalp psoriasis remains a therapeutic challenge. The choice of antipsoriatic agents should be based on individual patient preferences and characteristics, considering the factors outlined in **Table 1**.

**Table 1. Topical and phototherapeutic options for managing scalp psoriasis**

Type of therapy	Important contraindications and therapeutic considerations
Corticosteroids	Although topical corticosteroids are widely used, limited clinical data are available to support their efficacy and safety during long-term use. Corticosteroids are available as lotions and in other formulations designed for scalp application. Foam formulations, <sup>10-12</sup> not presently available in Canada, have been marketed elsewhere for scalp psoriasis
Vitamin D3 derivatives	An open-label study lasting 52 weeks by Barnes et al. <sup>13</sup> suggests that calcipotriol can be safely used in the long-term treatment for scalp psoriasis. This study found no significant changes in mean serum calcium, parathormone, or urinary calcium/creatinine ratio. Vitamin D3 derivatives are contraindicated in patients with abnormal calcium metabolism or with severe hepatic or renal disease
Coal tar	Coal tar has an unpleasant smell and is difficult to apply to the scalp, although shampoos, oils, and other acceptable formulations are available. Coal tar is contraindicated in women who are pregnant or nursing
Anthralin	Anthralin is a keratolytic agent used in the treatment of stable plaque psoriasis. <sup>1</sup> Anthralin may induce temporary discolouration of hair and considerable irritation in plaques and surrounding healthy skin. Commercial formulations of anthralin are not currently available in Canada
Keratolytics	5–10% salicylic acid has a pronounced keratolytic effect and is useful for removing thick psoriatic scales on the scalp. When combined with a topical corticosteroid, salicylic acid enhances skin penetration by the steroid. <sup>14</sup> Anthralin in a urea base is keratolytic as well and is useful for the rapid removal of thick scale <sup>15</sup>
UVB phototherapy	Since hair blocks UV light treatments from reaching the scalp, better results can be achieved with conventional UV units if hair is parted in many rows or the head is shaved. UV therapy is contraindicated in patients with a history of photodermatoses, photosensitive diseases, cutaneous malignancies, or immunosuppression
Retinoids	Tazarotene has been successfully used in the treatment of plaque-type psoriasis on the body. Currently there are no published clinical data on its efficacy in the treatment of plaque psoriasis of the scalp. Like other retinoids, tazarotene is teratogenic; while not strictly contraindicated for topical use in women of reproductive age, it is not recommended for use during pregnancy

## Recommendations

Recommendation & level of evidence	Grade of recommendation
<p>Moderately potent to very potent topical corticosteroids and calcipotriol are all appropriate topical treatments for mild to moderate scalp psoriasis. Suitable agents include:</p> <ul style="list-style-type: none"> <li>• Betamethasone dipropionate lotion, clobetasol propionate solution, betamethasone valerate solution, or calcipotriol solution (Refs. 16, 17, LoE 1++; Refs. 18, 19, LoE 1+)</li> <li>• Clobetasol propionate shampoo (Ref. 20, LoE 1++; Ref. 21, LoE 1+)</li> <li>• Amcinonide lotion or fluocinonide (Ref. 22, LoE 1++; Ref. 23, LoE 1+)</li> <li>• Calcipotriol solution (Refs. 24, 25, LoE 1+)</li> </ul>	<p><b>Grade A</b></p> <p><b>Grade A</b></p> <p><b>Grade A</b></p> <p><b>Grade B</b></p>
<p>In severe cases, systemic therapies may be considered.<sup>1</sup> These include:</p> <ul style="list-style-type: none"> <li>• Traditional agents (methotrexate, cyclosporine, or, for suitable patients, acitretin) (LoE 4)</li> <li>• The biologic agents etanercept (Ref. 10, LoE 1–) and alefacept (Ref. 26, LoE 2–)</li> <li>• Other biologic agents (LoE 4)</li> </ul>	<p><b>Grade D</b></p> <p><b>Grade C</b></p> <p><b>Grade D</b></p>

Note added in proof: In November 2008, Health Canada approved a new product containing calcipotriol and betamethasone dipropionate in a gel formulation. This combination product is indicated for topical treatment of moderate to severe scalp psoriasis.

## References

- Arndt KA. *Cutaneous medicine and surgery: an integrated program in dermatology*. (Saunders, Philadelphia, 1996).
- van de Kerkhof PC, de Hoop D, de Korte J, Kuipers MV. Scalp psoriasis, clinical presentations and therapeutic management. *Dermatology* 1998;197:326–34.
- Thaci D, Daiber W, Boehncke WH, Kaufmann R. Calcipotriol solution for the treatment of scalp psoriasis: Evaluation of efficacy, safety and acceptance in 3,396 patients. *Dermatology* 2001;203:153–6.
- Feldman SR, Housman TS. Patients' vehicle preference for corticosteroid treatments of scalp psoriasis. *Am J Clin Dermatol* 2003;4:221–4.
- Langner A, Wolska H, Hebborn P. Treatment of psoriasis of the scalp with coal tar gel and shampoo preparations. *Cutis* 1983;32:290–1,295–6.
- Kostarelou K, Teknetzis A, Lefaki I, et al. Double-blind clinical study reveals synergistic action between alpha-hydroxy acid and betamethasone lotions towards topical treatment of scalp psoriasis. *J Eur Acad Dermatol Venereol* 2000;14:5–9.
- Wulff-Woesten A, Ohlendorf D, Henz BM, Haas N. Dithranol in an emulsifying oil base (Bio-Wash-Oil) for the treatment of psoriasis of the scalp. *Skin Pharmacol Physiol* 2004;17:91–7.
- Taneja A, Racette A, Gourgoulis Z, Taylor CR. Broad-band UVB fiber-optic comb for the treatment of scalp psoriasis: A pilot study. *Int J Dermatol* 2004;43:462–7.
- van de Kerkhof PC, Franssen ME. Psoriasis of the scalp. Diagnosis and management. *Am J Clin Dermatol* 2001;2:159–65.
- Moore A, Gordon KB, Kang S, et al. A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. *J Am Acad Dermatol* 2007;56:598–603.
- Andreassi L, Giannetti A, Milani M. Efficacy of betamethasone valerate mousse in comparison with standard therapies on scalp psoriasis: An open, multicentre, randomized, controlled, cross-over study on 241 patients. *Br J Dermatol* 2003;148:134–8.
- Bergstrom KG, Arambula K, Kimball AB. Medication formulation affects quality of life: a randomized single-blind study of clobetasol propionate foam 0.05% compared with a combined program of clobetasol cream 0.05% and solution 0.05% for the treatment of psoriasis. *Cutis* 2003;72:407–11.
- Barnes L, Altmeyer P, Forstrom L, Stenstrom MH. Long-term treatment of psoriasis with calcipotriol scalp solution and cream. *Eur J Dermatol* 2000;10:199–204.
- Hillstrom L. Comparison of topical treatment with desoxymethasone solution of 0.25% with salicylic acid 1% and betamethasone valerate solution 0.1% in patients with psoriasis of the scalp. *J Int Med Res* 1984;12:170–3.
- Hindson C. Treatment of psoriasis of the scalp. An open assessment of 0.1% dithranol in a 17% urea base (Psoradrate). *Clin Trials J* 1980;17:131–6.
- Olsen EA, Cram DL, Ellis CN, et al. A double-blind, vehicle-controlled study of clobetasol propionate 0.05% (Temovate) scalp application in the treatment of moderate to severe scalp psoriasis. *J Am Acad Dermatol* 1991;24:443–7.

17. Klaber MR, Hutchinson PE, Pedvis-Leftick A, et al. Comparative effects of calcipotriol solution (50 mug/ml) and betamethasone 17-valerate solution (1 mg/ml) in the treatment of scalp psoriasis. *Br J Dermatol* 1994;131:678–83.
18. Katz HI, Lindholm JS, Weiss JS, et al. Efficacy and safety of twice-daily augmented betamethasone dipropionate lotion versus clobetasol propionate solution in patients with moderate-to-severe scalp psoriasis. *Clin Ther* 1995;17:390–401.
19. Jarratt M, Davis JG, Giltner MP, et al. Comparative studies of augmented betamethasone dipropionate lotion 0.05% and clobetasol propionate solution 0.05%: Correlation of the vasoconstriction assay and clinical activity in scalp psoriasis. *AdvTher* 1991;8:103–11.
20. Jarratt M, Breneman D, Gottlieb AB, et al. Clobetasol propionate shampoo 0.05%: a new option to treat patients with moderate to severe scalp psoriasis. *J Drugs Dermatol* 2004;3:367–73.
21. Griffiths CE, Finlay AY, Fleming CJ, et al. A randomized, investigator-masked clinical evaluation of the efficacy and safety of clobetasol propionate 0.05% shampoo and tar blend 1% shampoo in the treatment of moderate to severe scalp psoriasis. *J Dermatolog Treat* 2006;17:90–5.
22. Ellis CN, Horwitz SN, Menter A. Amcinonide lotion 0.1% in the treatment of patients with psoriasis of the scalp. *Curr Therapeut Res Clin Exp* 1988;44:315–24.
23. Ellis CN, Katz HI, Rex Jr IH, et al. A controlled clinical trial of a new formulation of betamethasone dipropionate cream in once-daily treatment of psoriasis. *Clin Ther* 1989;11:768–74.
24. Duweb GA, Abuzariba O, Rahim M, et al. Scalp psoriasis: Topical calcipotriol 50 mug/g/ml solution vs. betamethasone valerate 1% lotion. *Int J Clin Pharmacol Res* 2000;20:65–8.
25. Green C, Ganpule M, Harris D, et al. Comparative effects of calcipotriol (MC903) solution and placebo (vehicle of MC903) in the treatment of psoriasis of the scalp. *Br J Dermatol* 1994;130:483–7.
26. Krell J, Nelson C, Spencer L, Miller S. An open-label study evaluating the efficacy and tolerability of alefacept for the treatment of scalp psoriasis. *J Am Acad Dermatol* 2008;58:609–16.

## CHAPTER 12: MANAGEMENT OF PALMOPLANTAR PSORIASIS

### *Canadian Guidelines for the Management of Plaque Psoriasis*

Psoriasis manifests on the palms and soles in up to 17% of patients,<sup>1</sup> taking either of two forms, which are sometimes observed in the same individual. One type is localized plaque psoriasis, which is similar to psoriasis vulgaris present on the rest of the body. Lesions typically are sharply demarcated, erythematous, and have overlying, very thick scale.<sup>2</sup> Delayed-type hypersensitivity to contact allergens and response to physical trauma (the Koebner phenomenon) are postulated to be precipitating factors for plaque-type palmoplantar psoriasis.<sup>3</sup>

The other type of psoriasis that affects palms and soles is palmoplantar pustular psoriasis (PPP), a chronic, relapsing disease that is often refractory to therapy. It is characterized by erythematous plaques studded with sterile, intraepidermal pustules that are caused by massive migration of neutrophils. Lesions may be painful and may develop fissures.<sup>2</sup>

#### KEY POINT

*Palmoplantar psoriasis is significantly disabling, especially when severe, since patients lose the effective use of their hands and/or feet. There are two types of palmoplantar psoriasis: localized plaque psoriasis and palmoplantar pustular psoriasis. Separate treatment recommendations have been provided for each.*

Approximately 24% of individuals with PPP experience plaque psoriasis, and between 10% and 25% have a family history of psoriasis among first-degree relatives.<sup>4</sup> Although individuals with plaque psoriasis are more susceptible to pustular reactions of the palms and soles, PPP is suspected to be a genetically distinct condition that can occur either independently or comorbidly with plaque psoriasis.<sup>5</sup> The demographics of PPP are also markedly different from those of chronic plaque psoriasis. PPP primarily affects women, presents most commonly between the ages of 20 and 60 years, and has a very striking association with smoking and with lithium therapy. Treatment with TNF inhibitors such as infliximab and etanercept can induce pustular flares, even in individuals with no prior history of psoriasis<sup>4,6-8</sup> (see Chapter 8: Exacerbation and flare of psoriasis).

In clinical trials, severity of plaque-type palmoplantar psoriasis is typically evaluated using a modified PASI score (range, 0–60 points). The score reflects the proportion of palm and sole area involved and the severity of erythema.<sup>9</sup> For PPP, a severity index is determined by summing the scores for erythema, scaling, pustulation, and infiltration separately.<sup>10</sup>

Palmoplantar psoriasis is a therapeutic challenge and the choice of antipsoriatic agents should be based on the individual patient and on the factors outlined in **Table 1**, as well as the recommendations listed below.

**Table 1. Therapeutic options for the control of palmoplantar psoriasis**

Type of therapy	Important contraindications and therapeutic considerations
Corticosteroids	Although they are commonly used as first-line therapy, there is little clinical evidence supporting the efficacy of topical corticosteroids in the treatment of either plaque-type palmoplantar psoriasis or PPP. Triamcinolone acetonide and clobetasol propionate under hydrocolloid occlusion have been used with some success in the treatment of PPP <sup>11,12</sup>
Coal tar	Traditionally, coal tar has been used in the treatment of plaque psoriasis. Patient preference for coal tar is low because of its smell and the difficulty in application. Use of coal tar in an ointment base at night and covering hands and feet with gloves and socks after application of the ointment, however, can be an acceptable modality of treatment. <sup>13</sup> Coal tar is contraindicated in women who are pregnant or nursing. Coal tar is also a carcinogen and the benefits and risks of using it in children should be carefully evaluated. There is no evidence for its effectiveness in PPP
Vitamin D3 derivatives	Topical calcipotriol is effective either as a non-occlusive twice-daily application or as an occlusive twice-weekly application for plaque-type palmoplantar psoriasis. <sup>14</sup> There is no clinical evidence for its effectiveness in PPP, although it is possible that some individuals with PPP were among the responders to calcipotriol described in this same study <sup>14</sup>
Phototherapy and photochemotherapy	Soak, emulsion, gel, and cream PUVA <sup>9,10,15-17</sup> limit photosensitization to the affected skin areas and avoid the typical side effects of systematically administered psoralens. The efficacy and safety of narrowband ultraviolet B (NB-UVB) phototherapy for the treatment of palmoplantar psoriasis is under investigation
Retinoids	Oral retinoids have been used with a degree of success in the treatment of PPP, especially when combined with PUVA therapy (RePUVA). <sup>18-20</sup> RePUVA with acitretin (currently the only oral retinoid approved for use in psoriasis in Canada) has not been studied systematically for palmo-plantar psoriasis <sup>21</sup>  Oral retinoids are contraindicated in women of childbearing potential unless suitable contraception is used
Methotrexate	Methotrexate is an effective treatment for acute or localized pustular psoriasis or extensive psoriasis that is unresponsive to less toxic therapies. Methotrexate is contraindicated in patients with liver and kidney disease, as well as in pregnancy <sup>2</sup>
Cyclosporine	In patients with PPP, treatment with cyclosporine brings about significant reduction in pustule formation, as compared with placebo <sup>22</sup>
Alefacept	Alefacept is efficacious in the treatment of palmoplantar psoriasis. <sup>23</sup> This biologic agent is specifically approved for use in plaque-type, rather than pustular, psoriasis



Recommendations	
Recommendation & level of evidence	Grade of recommendation
<p>First-line options for treating patients with plaque-type palmoplantar psoriasis include:</p> <ul style="list-style-type: none"> <li>• Topical coal tar and salicylic acid under occlusion (Ref. 13, LoE 2+)</li> <li>• Topical PUVA, including paint (Ref. 16, LoE 2++) and soak PUVA (Ref. 15, LoE 2++; Ref. 24, LoE 2+)</li> <li>• Topical calcipotriol, with or without occlusion (Ref. 14, LoE 2–)</li> </ul>	<p><b>Grade B</b></p> <p><b>Grade B</b></p> <p><b>Grade C</b></p>
<p>Other options for which weaker evidence is available may also be considered, including moderate to ultrapotent corticosteroids (alone or in combination with calcipotriol), tazarotene, topical calcineurin inhibitors, NB-UVB, and intralesional triamcinolone acetonide injection (LoE 4)</p>	<b>Grade D</b>
<p>As second-line options, the physician may use systemic treatments, including:</p> <ul style="list-style-type: none"> <li>• Alefacept (Ref. 23, LoE 3)</li> <li>• Acitretin (LoE 4)</li> <li>• Methotrexate (LoE 4)</li> <li>• Cyclosporine (LoE 4)</li> </ul>	<b>Grade D</b>
<p>First-line treatment options for PPP include application of triamcinolone acetonide or clobetasol propionate under occlusion (Ref. 11, LoE 2+)</p>	<b>Grade C</b>
<p>As second-line options in suitable patients with PPP, the physician may use systemic agents such as cyclosporine (Ref. 25, LoE 2+) or alefacept (Ref. 26, LoE 2+)</p>	<b>Grade C</b>
<p>Intralesional triamcinolone acetonide injection and RePUVA with acitretin may also be considered for suitable patients (Refs. 21, 27, LoE 3)</p>	<b>Grade D</b>

## References

- Kumar B, Saraswat A, Kaur I. Palmoplantar lesions in psoriasis: A study of 3065 patients. *Acta Derm Venereol* 2002;82:192–5.
- Arndt KA. *Cutaneous medicine and surgery: an integrated program in dermatology*. (Saunders, Philadelphia, 1996).
- Caca-Biljanovska N, V'Lckova-Laskoska M, Balabanova-Stefanova M, Grivceva-Panovska V. Frequency of delayed-type hypersensitivity to contact allergens in palmoplantar psoriasis. *Prilozi* 2005;26:131–41.
- Enfors W, Molin L. Pustulosis palmaris et plantaris. A follow-up study of a ten-year material. *Acta Derm Venereol* 1971;51:289–94.
- Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007;370:263–71.
- Eriksson MO, Hagforsen E, Lundin IP, Michaelsson G. Palmoplantar pustulosis: A clinical and immunohistological study. *Br J Dermatol* 1998;138:390–8.
- White SW. Palmoplantar pustular psoriasis provoked by lithium therapy. *J Am Acad Dermatol* 1982;7:660–2.
- Michaelsson G, Kajermo U, Michaelsson A, Hagforsen E. Infliximab can precipitate as well as worsen palmoplantar pustulosis: possible linkage to the expression of tumour necrosis factor-alpha in the normal palmar eccrine sweat duct? *Br J Dermatol* 2005;153:1243–4.
- Neumann NJ, Mahnke N, Korpusik D, et al. Treatment of palmoplantar psoriasis with monochromatic excimer light (308-nm) versus cream PUVA. *Acta Derm Venereol* 2006;86:22–4.
- Hofer A, Fink-Puches R, Kerl H, et al. Paired comparison of bathwater versus oral delivery of 8-methoxypsoralen in psoriasis plus ultraviolet A therapy for chronic palmoplantar psoriasis. *Photodermatol Photoimmunol Photomed* 2006;22:1–5.
- Kragballe K, Larsen FG. A hydrocolloid occlusive dressing plus triamcinolone acetonide cream is superior to clobetasol cream in palmo-plantar pustulosis. *Acta Derm Venereol* 1991;71:540–2.
- Nielsen PG, Madsen SM. Occlusive treatment of palmoplantar pustular psoriasis with clobetasol propionate ointment succeeded by short-term PUVA. *J Dermatolog Treat* 1995;6:77–9.
- Kumar B, Kumar R, Kaur I. Coal tar therapy in palmoplantar psoriasis: Old wine in an old bottle? *Int J Dermatol* 1997;36:309–12.
- Duweb GA, Abuzariba O, Rahim M, et al. Occlusive versus nonocclusive calcipotriol ointment treatment for palmoplantar psoriasis. *Int J Tissue React* 2001;23:59–62.
- Calzavara-Pinton PG, Zane C, Carlino A, De Panfilis G. Bath-5-methoxypsoralen-UVA therapy for psoriasis. *J Am Acad Dermatol* 1997;36:945–9.

16. Sezer E, Erbil AH, Kurumlu Z, et al. Comparison of the efficacy of local narrowband ultraviolet B (NB-UVB) phototherapy versus psoralen plus ultraviolet A (PUVA) paint for palmoplantar psoriasis. *J Dermatol* 2007;34:435–40.
17. Schiener R, Gottlober P, Muller B, et al. PUVA-gel vs. PUVA-bath therapy for severe recalcitrant palmoplantar dermatoses. A randomized, single-blinded prospective study. *Photodermatol Photoimmunol Photomed* 2005;21:62–7.
18. Lawrence CM, Marks J, Parker S, Shuster S. A comparison of PUVA-etretinate and PUVA-placebo for palmoplantar pustular psoriasis. *Br J Dermatol* 1984;110:221–6.
19. Rosen K, Mobacken H, Swanbeck G. PUVA, etretinate, and PUVA-etretinate therapy for pustulosis palmoplantaris. A placebo-controlled comparative trial. *Arch Dermatol* 1987;123:885–9.
20. Matsunami E, Takashima A, Mizuno N, et al. Topical PUVA, etretinate, and combined PUVA and etretinate for palmoplantar pustulosis: Comparison of therapeutic efficacy and the influences of tonsillar and dental focal infections. *J Dermatol* 1990;17:92–6.
21. Ettler K, Richards B. Acitretin therapy for palmoplantar pustulosis combined with UVA and topical 8-MOP. *Int J Dermatol* 2001;40:541–2.
22. Reitamo S, Erkkö P, Remitz A, et al. Cyclosporine in the treatment of palmoplantar pustulosis: A randomized, double-blind, placebo-controlled study. *Arch Dermatol* 1993;129:1273–9.
23. Myers W, Christiansen L, Gottlieb AB. Treatment of palmoplantar psoriasis with intramuscular alefacept. *J Am Acad Dermatol* 2005;53:S127–S9.
24. Gomez MI, Pirez B, Harto A, et al. 8-MOP bath PUVA in the treatment of psoriasis: Clinical results in 42 patients. *J Dermatolog Treat* 1996;7:11–2.
25. Camacho FM, Moreno JC. Cyclosporin A in the treatment of severe atopic dermatitis and palmoplantar pustulosis. *J Dermatolog Treat* 1999;10:229–35.
26. Guenther LC. Alefacept is safe and efficacious in the treatment of palmar plantar pustulosis. *J Cutan Med Surg* 2007;11:202–5.
27. Goette DK, Morgan AM, Fox BJ, Horn RT. Treatment of palmoplantar pustulosis with intralesional triamcinolone injections. *Arch Dermatol* 1984;120:319–23.

## CHAPTER 13: SOCIAL AND PSYCHOLOGICAL ASPECTS OF PSORIASIS

### *Canadian Guidelines for the Management of Plaque Psoriasis*

Management of psoriasis has historically attributed more value to physical sequelae, and response to therapy and has tended to overlook the psychological aspects of the disease. This bias may have been inadvertently perpetuated by the medical and research community, as illustrated by the fact that, between 1977 and 2000, only one out of a total of 249 randomized controlled trials assessed health-related quality of life (HRQL) in patients with psoriasis.<sup>1</sup> However, growing clinical experience and published literature suggest that the disease burden of psoriasis extends far beyond the physical symptoms experienced by patients, to affect virtually all aspects of HRQL.

Multiple studies have demonstrated that patients with psoriasis perceive themselves to have poorer health and overall lower HRQL than the general population.<sup>2-7</sup> In one notable example, Rapp et al.<sup>8</sup> noted that patients with psoriasis reported a decrement in physical and mental function that was comparable to that reported by patients with cancer, arthritis, hypertension, heart disease, diabetes, and depression. In another study,<sup>9</sup> psoriasis patients with other chronic comorbidities, such as asthma, diabetes, or bronchitis, reported that they regarded these diseases as “the same or better”, relative to living with psoriasis. These data stand in sharp contrast to the misconception held by the general population and medical community that psoriasis is somehow less serious than other, non-dermatological illnesses.

As a result of these and other studies, Krueger et al.<sup>10</sup> suggested in a position paper that the main endpoint of psoriasis treatment should focus on HRQL, rather than specific clinical parameters of response to treatment, such as BSA or PASI scores.

#### KEY POINT

*Management of psoriasis has historically attributed more value to physical sequelae and response to therapy and has tended to overlook the psychological aspects of the disease. However, growing clinical experience and published literature suggest that the disease burden of psoriasis extends far beyond the physical symptoms experienced by patients, to affect virtually all aspects of HRQL.*

#### Effect of psoriasis on psychosocial health

Psoriasis and the therapies used to control it influence multiple aspects of psychosocial health. Various studies have documented that rates of depression are increased in the population of patients with psoriasis, even when disease remission is achieved.<sup>2,11-14</sup> People with psoriasis also suffer from body cathexis problems,<sup>12</sup> as well as higher rates of both passive and active suicidal ideation.<sup>13,15</sup>

Patients with psoriasis frequently report poor self-esteem and high levels of psychological stress. For example, patients often feel self-conscious, helpless, embarrassed, angry, and frustrated about their disease.<sup>6,16,17</sup> Those with more severe disease or with involvement of a more visible area (e.g., face, scalp) or highly utilized area of the body (e.g., hands) may suffer disproportionately from these problems.<sup>18</sup> These psychological sequelae have a pervasive effect on social functioning, affecting interpersonal relationships<sup>19</sup> and productivity at work or school.<sup>20</sup>

While impaired social functioning in patients with psoriasis may arise from internal factors (e.g., secondary psychological morbidities, poor self-esteem), external factors such as stigmatization and social rejection also play a role.<sup>21-24</sup> For example, in

a study of more than 1300 patients with moderate to severe psoriasis, 26% of subjects reported that during the previous month they experienced an episode in which a person made a conscious effort not to touch them, even on body areas unaffected by psoriasis.<sup>25</sup> Even more striking was the finding that 19% of patients with moderate to severe psoriasis had experienced instances of gross social rejection, including being asked to leave a location (e.g., gym, swimming pool) due to their disease.<sup>26</sup> As a result, psoriasis patients may attempt to avoid interpersonal situations or leisure activities where they might encounter rejection, further reducing their social and occupational opportunities. These feelings of social rejection, in turn, correlate with higher rates of psychologic morbidity, including depression.<sup>25</sup> While men and women are affected equally by the impact that the disease has on appearance and socialization, the effect may be more pronounced in adolescents and young adults, as the stigma of having psoriasis exerts its greatest influence when patients are establishing their body image, social networks, and careers.<sup>27</sup>

Psoriasis is associated with a decrease in sexual functioning in a significant proportion of patients.<sup>28,29</sup> In one case series, 41% of patients reported a decline in sexual activity since being diagnosed with psoriasis, with 60% of those attributing it to the physical manifestations of their psoriasis.<sup>28</sup> Physical symptoms of psoriasis (e.g., scaling and pruritus and, for those with psoriatic arthritis, joint pain), as well as associated depression also negatively affected sexual function.<sup>28</sup>

Finally, psoriasis can have significant financial impact. Apart from direct costs related to treatment of the disease itself, 59% of working patients reported that they lost or were unable to find work for certain periods within the preceding year, due to the effects of psoriasis or its treatment.<sup>9,30</sup>

### Effect of psychological health on psoriasis

Studies demonstrating that poor psychosocial health is an independent risk factor for increased manifestations or flares of psoriatic disease support the notion of a reciprocal relationship between psoriasis disease activity and psychosocial health.<sup>31,32</sup> For example, Gupta et al.<sup>32</sup> reported that the

presence of depression in psoriasis can modulate itch perception and exacerbate pruritus. Further, about 40% of psoriatic patients report that psychosocial stress significantly exacerbates their condition,<sup>31</sup> and patients who have high levels of psychologic stress during remission periods experience significantly more flares of psoriatic disease when compared with those with low levels of psychologic stress, a finding that has been supported by other investigators.<sup>33,34</sup> Consoli et al.<sup>34</sup> recently reported that low levels of emotional awareness predict a better response to dermatological treatment in patients with psoriasis, which suggests that patient awareness of the negative psychosocial implications of psoriasis can interfere with clinical response to treatment. Finally, interventions to address psychosocial health may result in improvements in clinical indicators of psoriatic disease and response to treatment.<sup>35</sup>

The mechanism by which psychosocial health may modulate psoriatic disease activity remains unclear; investigators have proposed both direct biologic mechanisms (e.g., effects on autoimmunity) and indirect mechanisms (e.g., adverse effect on treatment adherence).<sup>36,37</sup> For example, Schmid-Ott et al.<sup>38</sup> demonstrated a significant stress-induced increase of certain cytolytic T cells in the blood of psoriasis patients, but not in healthy controls. Other investigators have reported that psychic stress potentiates psoriatic disease activity via an increase in neuropeptide content and a decrease in neuropeptide-degrading enzyme activity in mast cells<sup>39</sup> or by modulating the neurohormonal axis.<sup>36</sup>

Alternatively, psychologic aspects can modify the course of psoriasis by interfering with treatment adherence,<sup>3,40,41</sup> a finding that has been widely validated in numerous other disease states. In particular, feeling stigmatized can lead to treatment non-adherence and worsening of psoriasis.<sup>21</sup>

### Psychosocial assessment of patients with psoriasis

Clinical severity of psoriasis based on affected body surface area or other scales does not always correlate with patient-reported degrees of impairment.<sup>7,42,43</sup> Further, physicians frequently underestimate the degree of psychological and social morbidity associated with the disease.<sup>6,44,45</sup>

Conflicts between the clinical severity rating and the actual disability experienced by the patient can be reconciled if the psychosocial impact of psoriasis is assessed during routine clinical evaluation.

Various methods have been used to quantify the psychosocial impact of psoriasis, including the Skindex-29,<sup>46</sup> Psoriasis Disability Index (PDI),<sup>47</sup> Dermatology Life Quality Index (DLQI),<sup>48</sup> Psoriasis Quality of Life Questionnaire (PQLQ),<sup>6</sup> Salford Psoriasis Index (SPI),<sup>49</sup> Hospital Anxiety and Depression Scale (HADS),<sup>50</sup> Illness Perception Questionnaire (ILQ),<sup>42,51</sup> and Short-Form-36 (SF-36) Health Survey.<sup>52-54</sup> Both et al.,<sup>55</sup> comparing the utility of these various scales for dermatological disease, recommend use of the Skindex-29 and SF-36, both of which have been widely applied in psoriasis studies. Regardless, there is general consensus that some form of psychosocial assessment should be pursued in the routine course of treatment and that these more formal assessments may be useful in situations in which patients have self-reported dissatisfaction in treatment response, despite improvement in clinical parameters of disease activity.<sup>2,5,43,53,56-58</sup>

As with the comprehensive treatment of any patient with a chronic medical condition, screening psoriasis patients for clinical depression is appropriate and can be achieved within the constraints of the typical clinical encounter.<sup>11,12,59</sup>

### Interventions

Interventions to address psychosocial factors (e.g., education, optimization of treatment protocols, and treatment of depression) may result in improvements in HRQL as well as in clinical endpoints of psoriatic disease.

While systematic studies to investigate the efficacy of psychologic interventions are relatively sparse,

several studies provide proof of principle. For example, Kabat-Zinn et al.<sup>35</sup> reported that use of concomitant meditation therapy reduced the duration required for a predetermined clinical response to either PUVA or UVB therapy by 30–35%. Other investigators have reported positive results in attenuating psoriatic disease activity in response to hypnosis<sup>60</sup> and psychotherapy.<sup>61</sup> Further, Fortune et al. advocated the use of a comprehensive cognitive behavioural program including a structured educational program.<sup>62</sup> Conversely, one study has suggested that treatment with the biologic agent etanercept can improve the psychological symptoms associated with psoriasis and psoriatic arthritis. Improvement correlated significantly between various measures of depression, quality of life, and fatigue; surprisingly, the effect on depression did not correlate significantly with control of skin symptoms, as measured on the PASI scale.<sup>63</sup>

Treatment of depression and other psychological morbidities associated with psoriasis may require psychotherapy, medical treatment, or referral to a psychiatrist for further management.<sup>11,12,59</sup>

Some of the current therapies, by virtue of the fact that their administration may be impractical or associated with toxic effects, can have a negative effect on HRQL.<sup>16</sup> Thus, choice of management strategies should take into consideration adverse effects, cost, and convenience, with the goal of enhancing HRQL and subsequent adherence to treatment.<sup>64</sup> Since there are often several different therapeutic options for patients with psoriasis, engaging the patient in the selection of a treatment modality may help to manage expectations and improve adherence. Finally, as reviewed by Richards et al.,<sup>41</sup> establishment of an effective doctor–patient relationship can help promote adherence to treatment and thereby improve outcomes.

## Recommendations

Recommendation & level of evidence	Grade of recommendation
Quality-of-life factors (e.g., ability to perform daily activities, employability, self-esteem, body image, perceived stigma, quality of interpersonal relationships, and satisfaction with treatment regimen) should be central to the long-term management of psoriasis (LoE 4)	<b>Grade D</b>
Metrics such as the PDI, DLQI, DQOLS, SF-36, or the PSA Scale should be employed when practical, particularly in patients with self-reported dissatisfaction in treatment response despite improvement in clinical parameters of disease activity (LoE 4)	<b>Grade D</b>
When clinically appropriate, patients with psoriasis should be asked about DSM-IV signs of depression (e.g., poor self-esteem, sexual dysfunction, anxiety, and suicidal ideation) (Refs. 11, 12, 65, 66, LoE 1–)	<b>Grade C</b>
Patients who request referral and those showing evidence of clinically significant anxiety or depression should be treated or referred for mental health consultation (Refs. 35, 60–62, LoE 1–)	<b>Grade C</b>
Physicians should identify patients at risk of, or with a clear history of, stress-induced exacerbations. Stress-management programs should be considered for such patients (LoE 4)	<b>Grade D</b>
Practitioners should put in place or strengthen non-pharmacological strategies to improve patients' quality of life, including establishing good physician–patient rapport and communication and providing appropriate patient and family education (LoE 4)	<b>Grade D</b>

## References

- Naldi L, Svensson A, Diepgen T, et al. Randomized clinical trials for psoriasis 1977–2000: the EDEN survey. *J Invest Dermatol* 2003;120:738–41.
- Kimball AB, Jacobson C, Weiss S, et al. The psychosocial burden of psoriasis. *Am J Clin Dermatol* 2005;6:383–92.
- Al-Mazeedi K, El-Shazly M, Al-Ajmi HS. Impact of psoriasis on quality of life in Kuwait. *Int J Dermatol* 2006;45:418–24.
- Badia X, Mascaro JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. The Cavide Research Group. *Br J Dermatol* 1999;141:698–702.
- Choi J, Koo JY. Quality of life issues in psoriasis. *J Am Acad Dermatol* 2003;49:S57–61.
- Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. *Dermatol Clin* 1996;14:485–96.
- Zachariae R, Zachariae H, Blomqvist K, et al. Quality of life in 6497 Nordic patients with psoriasis. *Br J Dermatol* 2002;146:1006–16.
- Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 1999;41:401–7.
- Finlay AY, Coles EC. The effect of severe psoriasis on the quality of life of 369 patients. *Br J Dermatol* 1995;132:236–44.
- Krueger GG, Feldman SR, Camisa C, et al. Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? *J Am Acad Dermatol* 2000;43:281–5.
- Akay A, Pekcanlar A, Bozdogan KE, et al. Assessment of depression in subjects with psoriasis vulgaris and lichen planus. *J Eur Acad Dermatol Venereol* 2002;16:347–52.
- Devrimci-Ozguven H, Kundakci N, Kumbasar H, Boyvat A. The depression, anxiety, life satisfaction and affective expression levels in psoriasis patients. *J Eur Acad Dermatol Venereol* 2000;14:267–71.
- Picardi A, Mazzotti E, Pasquini P. Prevalence and correlates of suicidal ideation among patients with skin disease. *J Am Acad Dermatol* 2006;54:420–6.
- Sampogna F, Gisondi P, Tabolli S, et al. Impairment of sexual life in patients with psoriasis. *Dermatology* 2007;214:144–50.
- Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol* 1998;139:846–50.
- Krueger G, Koo J, Lebwohl M, et al. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient membership survey. *Arch Dermatol* 2001;137:280–4.
- Wahl AK, Gjengedal E, Hanestad BR. The bodily suffering of living with severe psoriasis: in-depth interviews with 22 hospitalized patients with psoriasis. *Qual Health Res* 2002;12:250–61.
- Heydendael VM, de Borgie CA, Spuls PI, et al. The burden of psoriasis is not determined by disease severity only. *J Invest Dermatol Symp Proc* 2004;9:131–5.
- Eghlileb AM, Davies EEG, Finlay AY. Psoriasis has a major secondary impact on the lives of family members and partners. *Br J Dermatol* 2007;156:1245–50.



20. Pearce DJ, Singh S, Balkrishnan R, et al. The negative impact of psoriasis on the workplace. *J Dermatolog Treat* 2006;17:24–8.
21. Ginsburg IH, Link BG. Feelings of stigmatization in patients with psoriasis. *J Am Acad Dermatol* 1989;20:53–63.
22. Vardy D, Besser A, Amir M, et al. Experiences of stigmatization play a role in mediating the impact of disease severity on quality of life in psoriasis patients. *Br J Dermatol* 2002;147:736–42.
23. Schmid-Ott G, Jaeger B, Kuensebeck HW, et al. Dimensions of stigmatization in patients with psoriasis in a 'Questionnaire on Experience with Skin Complaints'. *Dermatology* 1996;193:304–10.
24. Schmid-Ott G, Kuensebeck HW, Jaeger B, et al. Validity study for the stigmatization experience in atopic dermatitis and psoriatic patients. *Acta Derm Venereol* 1999;79:443–7.
25. Gupta MA, Gupta AK, Watteel GN. Perceived deprivation of social touch in psoriasis is associated with greater psychologic morbidity: an index of the stigma experience in dermatologic disorders. *Cutis* 1998;61:339–42.
26. Ginsburg IH, Link BG. Psychosocial consequences of rejection and stigma feelings in psoriasis patients. *Int J Dermatol* 1993;32:587–91.
27. Gupta MA, Gupta AK. Age and gender differences in the impact of psoriasis on quality of life. *Int J Dermatol* 1995;34:700–3.
28. Gupta MA, Gupta AK. Psoriasis and sex: A study of moderately to severely affected patients. *Int J Dermatol* 1997;36:259–62.
29. Buckwalter KC. The influence of skin disorders on sexual expression. *Sexuality Disab* 1982;5:98–106.
30. Feldman SR, Fleischer AB, Jr., Reboussin DM, et al. The economic impact of psoriasis increases with psoriasis severity. *J Am Acad Dermatol* 1997;37:564–9.
31. Gupta MA, Gupta AK, Kirkby S, et al. A psychocutaneous profile of psoriasis patients who are stress reactors. A study of 127 patients. *Gen Hosp Psychiatry* 1989;11:166–73.
32. Gupta MA, Gupta. Depression modulates pruritus perception. A study of pruritus in psoriasis, atopic dermatitis and chronic idiopathic urticaria. *Ann N Y Acad Sci* 1999;885:394–5.
33. Harvima RJ, Viinamaki H, Harvima IT, et al. Association of psychic stress with clinical severity and symptoms of psoriatic patients. *Acta Derm Venereol* 1996;76:467–71.
34. Consoil SM, Rohion S, Martin C, et al. Low levels of emotional awareness predict a better response to dermatological treatment in patients with psoriasis. *Dermatology* 2006;212:128–36.
35. Kabat-Zinn J, Wheeler E, Light T, et al. Influence of a mindfulness meditation-based stress reduction intervention on rates of skin clearing in patients with moderate to severe psoriasis undergoing phototherapy (UVB) and photochemotherapy (PUVA). *Psychosom Med* 1998;60:625–32.
36. Richards HL, Ray DW, Kirby B, et al. Response of the hypothalamic-pituitary-adrenal axis to psychological stress in patients with psoriasis. *Br J Dermatol* 2005;153:1114–20.
37. Farber EM, Lanigan SW, Rein G. The role of psychoneuroimmunology in the pathogenesis of psoriasis. *Cutis* 1990;46:314–6.
38. Schmid-Ott G, Jacobs R, Jager B, et al. Stress-induced endocrine and immunological changes in psoriasis patients and healthy controls. A preliminary study. *Psychother Psychosom* 1998;67:37–42.
39. Harvima IT, Viinamaki H, Naukkarinen A, et al. Association of cutaneous mast cells and sensory nerves with psychic stress in psoriasis. *Psychother Psychosom* 1993;60:168–76.
40. Ali SM, Brodell RT, Balkrishnan R, Feldman SR. Poor adherence to treatments: a fundamental principle of dermatology. *Arch Dermatol* 2007;143:912–5.
41. Richards HL, Fortune DG, Griffiths CE. Adherence to treatment in patients with psoriasis. *J Eur Acad Dermatol Venereol* 2006;20:370–9.
42. Fortune DG, Richards HL, Main CJ, Griffiths CE. What patients with psoriasis believe about their condition. *J Am Acad Dermatol* 1998;39:196–201.
43. Kirby B, Richards HL, Woo P, et al. Physical and psychologic measures are necessary to assess overall psoriasis severity. *J Am Acad Dermatol* 2001;45:72–6.
44. Richards HL, Fortune DG, Weidmann A, et al. Detection of psychological distress in patients with psoriasis: low consensus between dermatologist and patient. *Br J Dermatol* 2004;151:1227–33.
45. Jobling RG. Psoriasis — a preliminary questionnaire study of sufferers' subjective experience. *Clin Exp Dermatol* 1976;1:233–6.
46. Chren MM, Lasek RJ, Quinn LM, et al. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. *J Invest Dermatol* 1996;107:707–13.
47. Finlay AY, Kelly SE. Psoriasis — an index of disability. *Clin Exp Dermatol* 1987;12:8–11.
48. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) — a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994;19:210–6.
49. Kirby B, Fortune DG, Bhushan M, et al. The Salford Psoriasis Index: An holistic measure of psoriasis severity. *Br J Dermatol* 2000;142:728–32.
50. Lewis G, Wessely S. Comparison of the General Health Questionnaire and the Hospital Anxiety and Depression Scale. *Br J Psychiatry* 1990;157:860–4.
51. Scharloo M, Kaptein AA, Weinman J, et al. Patients' illness perceptions and coping as predictors of functional status in psoriasis: a 1-year follow-up. *Br J Dermatol* 2000;142:899–907.
52. Husted JA, Gladman DD, Farewell VT, et al. Validating the SF-36 health survey questionnaire in patients with psoriatic arthritis. *J Rheumatol* 1997;24:511–7.
53. de Korte J, Mommers FM, Sprangers MA, Bos JD. The suitability of quality-of-life questionnaires for psoriasis research: a systematic literature review. *Arch Dermatol* 2002;138:1221–7; discussion 7.
54. Sampogna F, Tabolli S, Soderfeldt B, et al. Measuring quality of life of patients with different clinical types of psoriasis using the SF-36. *Br J Dermatol* 2006;154:844–9.
55. Both H, Essink-Bot ML, Busschbach J, Nijsten T. Critical review of generic and dermatology-specific health-related quality of life instruments. *J Invest Dermatol* 2007;127:2726–39.
56. Nichol MB, Margolies JE, Lippa E, et al. The application of multiple quality-of-life instruments in individuals with mild-to-moderate psoriasis. *Pharmacoeconomics* 1996;10:644–53.
57. Shikhar R, Willian MK, Okun MM, et al. The validity and responsiveness of three quality of life measures in the assessment of psoriasis patients: results of a phase II study. *Health Qual Life Outcomes* 2006;4:71.
58. Yang Y, Koh D, Khoo L, et al. The psoriasis disability index in Chinese patients: contribution of clinical and psychological variables. *Int J Dermatol* 2005;44:925–9.
59. Fortune DG, Richards HL, Griffiths CEM. Psychologic factors in psoriasis: consequences, mechanisms, and interventions. *Dermatol Clin* 2005;23:681–94.
60. Tausk F, Whitmore SE. A pilot study of hypnosis in the treatment of patients with psoriasis. *Psychother Psychosom* 1999;68:221–5.
61. Zachariae R, Oster H, Bjerring P, Kragballe K. Effects of psychologic intervention on psoriasis: a preliminary report. *J Am Acad Dermatol* 1996;34:1008–15.
62. Fortune DG, Richards HL, Kirby B, et al. A cognitive-behavioural symptom management programme as an adjunct in psoriasis therapy. *Br J Dermatol* 2002;146:458–65.
63. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet* 2006;367:29–35.
64. Carroll CL, Feldman SR, Camacho FT, Balkrishnan R. Better medication adherence results in greater improvement in severity of psoriasis. *Br J Dermatol* 2004;151:895–7.
65. Russo PAJ, Ilchef R, Cooper A. Psychiatric morbidity in psoriasis: a review. *Australas J Dermatol* 2004;45:155–60.
66. Schmitt JM, Ford DE. Role of depression in quality of life for patients with psoriasis. *Dermatology* 2007;215:17–27.

## CHAPTER 14: COMORBIDITIES

### Canadian Guidelines for the Management of Plaque Psoriasis

The comorbidities associated with psoriasis are multifactorial and are in many cases linked to inflammation. Immune-mediated inflammatory diseases that arise in conjunction with psoriasis include arthritis, inflammatory bowel disease, cardiovascular disease, and metabolic syndrome. These diseases are thought to arise from related pathogenic mechanisms linked to cytokine dysregulation.<sup>1</sup> In addition to these inflammatory comorbid disorders, psoriasis is associated with depression and other affective disorders.<sup>2</sup>

Both because of the skin disease itself and as a consequence of these various non-cutaneous comorbidities, psoriasis significantly diminishes quality of life and can increase morbidity and even mortality rates, as discussed below. Indeed, one analysis found that the reported reduction in physical and mental functioning associated with psoriasis was similar to that found in cancer, arthritis, hypertension, heart disease, and depression.<sup>3</sup>

Physicians treating psoriasis patients must be aware of the comorbidities and take steps to manage them, either directly or by means of an appropriate referral. Management may be complicated, because certain psoriasis treatments have been found to either mimic or exacerbate existing comorbidities (see **Table 1**). Conversely, certain drugs used to treat comorbid conditions (see below) may exacerbate the psoriasis of these patients. As discussed in Chapter 8 (Exacerbation and flare of psoriasis), it is usually difficult to establish a firm causal link between a drug treatment and a psoriatic flare. The appropriateness of treatments must therefore be determined on an individual basis. Regardless, physicians should be aware of the risk of iatrogenic complications and should follow up with their patients accordingly.

#### KEY POINT

*People with plaque psoriasis are at a substantially increased risk of inflammatory diseases occurring at sites remote from the skin, including psoriatic arthritis, cardiovascular disease, and inflammatory bowel disease, due to common pathophysiological mechanisms. Young patients have a threefold risk of MI, and severe psoriasis is associated with a 3.5- to 4.4-year reduction in life expectancy in males and females, respectively. Depression and other affective disorders are also more common in psoriasis patients than in the broader population.*

#### Affective disorders

Management of comorbid depression and anxiety is an essential component of psoriasis treatment. As discussed in Chapter 13 (Social and psychological aspects of psoriasis), patients should be referred to a mental health professional if they request such a referral or exhibit signs of clinically significant anxiety or depression.

The use of lithium as a mood stabilizer can be problematic in psoriasis patients because of the risk of causing their skin disease to flare (see Chapter 8: Exacerbation and flare of psoriasis).<sup>4-6</sup> Psoriasis secondary to lithium treatment in a psychiatric patient has been controlled satisfactorily with etanercept, without the need to discontinue lithium.<sup>7</sup>

#### Cardiovascular disease

Psoriasis patients are at elevated risk of cardiovascular disease<sup>8</sup> and coronary artery calcification,<sup>9</sup> as well as various components of the metabolic syndrome. The metabolic syndrome<sup>10</sup> is associated with an increased risk of MI and other adverse cardiovascular outcomes.<sup>11-14</sup>

Some of the associations between psoriasis and metabolic syndrome components are stronger in individuals with earlier age at onset or with more severe skin disease.<sup>15,16</sup> Thus, a large-scale epidemiological study in the UK<sup>17</sup> showed that, compared to the general population, the relative risk of obesity in individuals with psoriasis was 1.3–1.8, depending on the severity of the psoriasis. This confirms evidence from another study, indicating that prevalence of obesity was 34% in psoriasis patients, as compared to 18% in the general population.<sup>18</sup> For hypertension and dyslipidemia, relative risks were approximately 1.2 and 1.3, respectively; for diabetes, the relative risk was up to 1.9 for those with severe psoriasis.<sup>17</sup> A large cross-sectional study from Israel showed a similar association between psoriasis and each of several components of the metabolic syndrome, including hypertension, hyperlipidemia, and obesity, as well as ischemic heart disease.<sup>19</sup>

Given these cardiovascular risk factors, cigarette smoking may be particularly worrisome in the psoriatic population, and the rate of smoking is also elevated in this group. Patients who smoke more than 20 cigarettes a day have been reported to be at a > 2-fold increased risk of severe psoriasis, relative to non-smokers.<sup>18,20</sup> For all of these reasons, clinicians should advocate smoking cessation programs and any other steps to correct modifiable cardiovascular risk factors.

In addition, primary care physicians and others caring for patients with psoriasis should monitor cardiovascular risk on an ongoing basis. Taking a complete history and doing a full clinical examination that includes blood pressure measurement is a useful first step toward identifying risk factors. Laboratory investigations should also be considered, including a blood lipid profile and fasting glucose measurement. Psoriasis patients are reported to have higher rates of impaired glucose tolerance, insulin resistance, as well as diabetes,<sup>17</sup> relative to the general population.<sup>21</sup>

Patients taking cyclosporine may be at a still greater risk of hypertriglyceridemia and hypertension and should be monitored regularly for these and other cardiovascular risk factors (see **Table 1**).<sup>22-25</sup> Acitretin has likewise been associated with triglyceride elevation, a risk that is particularly common in obese patients and those with diabetes.<sup>26</sup>

Psoriasis has been identified as an independent risk for MI and adverse outcomes of MI, especially in patients with an early age of onset and more severe disease.<sup>15,27</sup> In one large study comparing the incidence of MI in a control population and in psoriasis patients with different levels of severity, psoriasis emerged as an independent risk factor for incidence of MIs. When expressed as a relative risk, this effect was most striking in younger individuals, since the background incidence of MI was low in this population. For instance, in patients 30 years of age, the presence of severe psoriasis was found to increase the risk of MI by a factor of 3.1 compared to age-matched controls. Psoriasis significantly predisposed to MI in other age groups as well.<sup>27</sup> This increased MI incidence is directly related to cardiovascular mortality, which has been reported to occur at an elevated rate in individuals with a history of severe psoriasis.<sup>15</sup>

Few studies have addressed the question of whether effective psoriasis therapy can improve cardiovascular risk factors<sup>28</sup> or outcomes, but there is some evidence that methotrexate can decrease the risk of vascular disease. This beneficial effect of methotrexate is attributed to its anti-inflammatory properties and may be enhanced when methotrexate is given in combination with folic acid.<sup>29</sup> However, methotrexate should be used with caution, as it can lead to liver fibrosis or cirrhosis, among other adverse responses, particularly in patients with comorbid diabetes<sup>30</sup> (see **Table 1**).

Of the common medications used to treat cardiovascular disease, beta blockers (including atenolol, metoprolol, propranolol, timolol, and oxprenolol) and calcium channel blockers (including nifedipine, amlodipine, and felodipine) have been reported to cause psoriatic flares.<sup>31,32</sup> In some cases, the response proved reproducible when the patient was re-challenged with the same drug.<sup>31-33</sup> However, there is no evidence that either beta blockers or calcium channel blockers are significantly associated with increased skin involvement in the psoriatic population overall. Furthermore, a population-based case-control analysis of British medical records found no support for an association between antihypertensive drug use and risk of new-onset psoriasis.<sup>34</sup>

### Psoriatic arthritis

Psoriatic arthritis (PsA) is an erosive arthritis occurring in up to 30% of psoriasis patients.<sup>35</sup> The risk of developing PsA is still greater in patients with more extensive skin psoriasis.<sup>36</sup> Joint involvement can significantly reduce QoL relative to uncomplicated psoriasis of comparable severity.<sup>37,38</sup> Patients with psoriasis should therefore be asked routinely about joint pain and stiffness and should be treated or considered for referral to a rheumatologist if any signs or symptoms of PsA are found.

The pro-inflammatory cytokine TNF- $\alpha$  plays an important role in the pathophysiology of both PsA and psoriasis.<sup>35</sup> It has been proposed that, where possible, a single therapeutic should be used to treat both the rheumatological and dermatological components of PsA to minimize the risk of toxicity that may be associated with polypharmacy.<sup>39</sup> Agents that are effective against both classes of symptoms include methotrexate, cyclosporine, and the TNF inhibitors. All of these biologic and non-biologic options are used in uncomplicated psoriasis and are associated with specific benefits and risks, as outlined in Chapter 6 (Management of moderate to severe plaque psoriasis). The TNF- $\alpha$  antagonists adalimumab, etanercept, and infliximab are generally safe and effective in PsA patients with moderate to severe psoriasis.<sup>40-45</sup> Methotrexate and cyclosporine can each be effective in this population,<sup>46-48</sup> and the combination of these two agents has been used for patients with recalcitrant PsA.<sup>49</sup>

Long-term use of cyclosporine is limited by the risk of nephrotoxicity and hypertension.<sup>50</sup> Caution should also be used when prescribing methotrexate, particularly in individuals with diabetes, who are at heightened risk of liver toxicity.<sup>30,51</sup>

### Inflammatory bowel disease

There is a well-established epidemiological link between psoriasis and the inflammatory bowel diseases (Crohn's disease and ulcerative colitis),<sup>52</sup> apparently reflecting the involvement of a similar cytokine-dependent inflammatory pathway in the gut and the skin (see Chapter 1: Introduction).

Psoriasis is up to seven times more common in individuals with Crohn's disease than in the general

population.<sup>53</sup> Conversely, studies from Canada and Sweden have shown a 1.5–2.9-fold increased risk for Crohn's disease in individuals with psoriasis.<sup>52,54</sup> Patients with active inflammatory bowel disease as well as psoriasis should be considered for treatments that target both conditions. Of the systemic antipsoriatic agents, infliximab is approved for treating both Crohn's disease and ulcerative colitis, and adalimumab is approved for treating Crohn's disease.

Physicians caring for patients with psoriasis should conduct a thorough medical history to uncover any evidence of inflammatory bowel disease. Patients with signs and symptoms of ulcerative colitis or Crohn's disease should be referred to a gastroenterologist. In isolated cases, individuals receiving TNF inhibitors have experienced new-onset psoriasis (see Chapter 8: Exacerbation and flare of psoriasis).

### Therapies associated with psoriasis and psoriatic comorbidities

Certain drugs used to treat common comorbidities may trigger or exacerbate psoriasis (see Chapter 8: Exacerbation and flare of psoriasis), notably the anxiolytic agent lithium. Physicians treating comorbid conditions should be aware of the risks of using such agents and, equally, should attempt to minimize the danger of exacerbating the comorbidity with their choice of antipsoriatic treatment (Table 1).

**Table 1.** Antipsoriatic agents that may exacerbate common comorbidities

Medication	Adverse reaction	References
Acitretin	Hypertriglyceridemia	Ref. 26
Cyclosporine	Hypertension	Refs. 22, 23, 25
	Hyperlipidemia	Ref. 24
Methotrexate	Liver toxicity, fibrosis, and cirrhosis, especially in patients with comorbid diabetes or obesity	Refs. 30, 51

<b>Recommendations</b>	
<b>Recommendation &amp; level of evidence</b>	<b>Grade of recommendation</b>
Patients should be urged to stop, or to avoid starting, smoking and should be referred to smoking cessation programs if appropriate (Ref. 20, LoE 4)	<b>Grade D</b>
Psoriasis patients should be assessed, monitored, and treated for cardiovascular risk factors associated with metabolic syndrome (obesity, hypertension, dyslipidemia, and hyperglycemia) (Refs. 11, 17, 27, LoE 2++) and for cardiovascular disease, depression, and autoimmune manifestations such as arthritis and inflammatory bowel disease (Refs. 36, 54, 55, LoE 2++)	<b>Grade B</b>
Patients with moderate to severe psoriasis and concomitant PsA requiring systemic treatment should be considered as candidates for treatment with TNF inhibitors (Refs. 40, 43, 45, LoE 1++)	<b>Grade A</b>
Psoriasis patients should be referred to a rheumatologist if they experience arthritis or arthralgia and over-the-counter analgesics are inappropriate or not fully efficacious, or in case of doubt about the diagnosis of their rheumatic symptoms (LoE 4)	<b>Grade D</b>
Psoriasis patients should be referred to a gastroenterologist if they exhibit signs or symptoms of Crohn's disease or ulcerative colitis (LoE 4)	<b>Grade D</b>
Patients who exhibit clinically significant signs of anxiety or depression, or who request a referral, should be referred to a mental health care professional (LoE 4)	<b>Grade D</b>



## References

- Mrowietz U, Elder JT, Barker J. The importance of disease associations and concomitant therapy for the long-term management of psoriasis patients. *Arch Dermatol Research* 2006;298:309–19.
- Christophers E. Comorbidities in psoriasis. *J Eur Acad Dermatol Venereol* 2006;20:52–5.
- Rapp SR, Feldman SR, Exum ML, et al. Psoriasis causes as much disability as other major medical diseases. *J Am Acad Dermatol* 1999;41:401–7.
- Yeung CK, Chan HHL. Cutaneous adverse effects of lithium: Epidemiology and management. *Am J Clin Dermatol* 2004;5:3–8.
- Russo PAJ, Ilchef R, Cooper A. Psychiatric morbidity in psoriasis: A review. *Australas J Dermatol* 2004;45:155–60.
- Chan HH, Wing Y, Su R, et al. A control study of the cutaneous side effects of chronic lithium therapy. *J Affect Disord* 2000;57:107–13.
- Wachter T, Murach WM, Brocker EB, Schon MP. Recalcitrant lithium-induced psoriasis in a suicidal patient alleviated by tumour necrosis factor-alpha inhibition. *Br J Dermatol* 2007;157:627–9.
- Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. *Dermatologica* 1986;172:298–304.
- Ludwig RJ, Herzog C, Rostock A, et al. Psoriasis: a possible risk factor for development of coronary artery calcification. *Br J Dermatol* 2007;156:271–6.
- Grundt SM, Brewer HB, Jr., Cleeman JJ, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004;109:433–8.
- Gisondi P, Tessari G, Conti A, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. *Br J Dermatol* 2007;157:68–73.
- Hamming EA, van der Lely AJ, Neumann HA, Thio HB. Chronic inflammation in psoriasis and obesity: implications for therapy. *Med Hypotheses* 2006;67:768–73.
- Shapiro J, Cohen AD, David M, et al. The association between psoriasis, diabetes mellitus, and atherosclerosis in Israel: a case-control study. *J Am Acad Dermatol* 2007;56:629–34.
- Sterry W, Strober BE, Menter A. Obesity in psoriasis: the metabolic, clinical and therapeutic implications. Report of an interdisciplinary conference and review. *Br J Dermatol* 2007;157:649–55.
- Mallbris L, Akre O, Granath F, et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. *Eur J Epidemiol* 2004;19:225–30.
- Rocha-Pereira P, Santos-Silva A, Rebelo I, et al. Dyslipidemia and oxidative stress in mild and in severe psoriasis as a risk for cardiovascular disease. *Clin Chim Acta* 2001;303:33–9.
- Neimann AL, Shin DB, Wang X, et al. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006;55:829–35.
- Herron MD, Hinckley M, Hoffman MS, et al. Impact of obesity and smoking on psoriasis presentation and management. *Arch Dermatol* 2005;141:1527–34.
- Cohen AD, Sherf M, Vidavsky L, et al. Association between psoriasis and the metabolic syndrome. A cross-sectional study. *Dermatology* 2008;216:152–5.
- Fortes C, Mastroeni S, Lefondre K, et al. Relationship between smoking and the clinical severity of psoriasis. *Arch Dermatol* 2005;141:1580–4.
- Ucak S, Ekmekci TR, Basat O, et al. Comparison of various insulin sensitivity indices in psoriatic patients and their relationship with type of psoriasis. *J Eur Acad Dermatol Venereol* 2006;20:517–22.
- Coroas ASPS, de Oliveira JGG, Magina S, et al. Cyclosporine enhances salt sensitivity of body water composition as assessed by impedance among psoriatic patients with normal renal function. *J Ren Nutr* 2004;14:226–32.
- Magina S, Santos J, Coroas A, et al. Salt sensitivity of blood pressure in patients with psoriasis on ciclosporin therapy. *Br J Dermatol* 2005;152:773–6.
- Grossman RM, Delaney RJ, Brinton EA, et al. Hypertriglyceridemia in patients with psoriasis treated with cyclosporine. *J Am Acad Dermatol* 1991;25:648–51.
- Grossman RM, Chevret S, Abi-Rached J, et al. Long-term safety of cyclosporine in the treatment of psoriasis. *Arch Dermatol* 1996;132:623–9.
- van de Kerkhof PCM. Update on retinoid therapy of psoriasis in: An update on the use of retinoids in dermatology. *Dermatol Ther* 2006;19:252–63.
- Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006;296:1735–41.
- Martinez-Abundis E, Reynoso-von Drateln C, Hernandez-Salazar E, Gonzalez-Ortiz M. Effect of etanercept on insulin secretion and insulin sensitivity in a randomized trial with psoriatic patients at risk for developing type 2 diabetes mellitus. *Arch Dermatol Res* 2007;299:461–5.
- Prodanovich S, Ma F, Taylor JR, et al. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol* 2005;52:262–7.
- Rosenberg P, Urwitz H, Johannesson A, et al. Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment. *J Hepatol* 2007;46:1111–8.
- van Joost T, Sillevius Smitt JH. Skin reactions to propranolol and cross sensitivity to beta-adrenoreceptor blocking agents. *Arch Dermatol* 1981;117:600–1.
- Kitamura K, Kanasashi M, Suga C, et al. Cutaneous reactions induced by calcium channel blocker: high frequency of psoriasiform eruptions. *J Dermatol* 1993;20:279–86.
- Hu CH, Miller AC, Peppercorn R, Farber EM. Generalized pustular psoriasis provoked by propranolol. *Arch Dermatol* 1985;121:1326–7.
- Brauchli YB, Jick SS, Curtin F, Meier CR. Association between beta-blockers, other antihypertensive drugs and psoriasis: population-based case-control study. *Br J Dermatol* 2008;158:1299–307.
- Mease P. Management of psoriatic arthritis: the therapeutic interface between rheumatology and dermatology. *Curr Rheumatol Rep* 2006;8:348–54.
- Gelfand JM, Gladman DD, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. *J Am Acad Dermatol* 2005;53:573.
- Lundberg L, Johannesson M, Silverdahl M, et al. Health-related quality of life in patients with psoriasis and atopic dermatitis measured with SF-36, DLQI and a subjective measure of disease activity. *Acta Derm Venereol* 2000;80:430–4.
- Zachariae H, Zachariae R, Blomqvist K, et al. Quality of life and prevalence of arthritis reported by 5,795 members of the Nordic Psoriasis Associations. Data from the Nordic Quality of Life Study. *Acta Derm Venereol* 2002;82:108–13.
- Gordon KB, Ruderman EM. The treatment of psoriasis and psoriatic arthritis: an interdisciplinary approach. *J Am Acad Dermatol* 2006;54:S85–91.
- Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004;50:2264–72.
- Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000;356:385–90.
- Salvarani C, Cantini F, Olivieri I, et al. Efficacy of infliximab in resistant psoriatic arthritis. *Arthritis Rheum* 2003;49:541–5.
- Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 2005;64:1150–7.
- Bianchi L, Giunta A, Papoutsaki M, et al. Efficacy and safety of long-term infliximab therapy in moderate to severe psoriasis and psoriatic arthritis. *Giornale Italiano di Dermatologia e Venereologia* 2006;141:73–8.
- Gladman DD, Mease PJ, Ritchlin CT, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum* 2007;56:476–88.
- Helliwell PS, Taylor WJ. Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs — comparison of drugs and adverse reactions. *J Rheumatol* 2008;35:472–6.
- Salvarani C, Macchioni P, Olivieri I, et al. A comparison of cyclosporine, sulfasalazine, and symptomatic therapy in the treatment of psoriatic arthritis. *J Rheumatol* 2001;28:2274–82.
- Sarzi-Puttini P, Cazzola M, Panni B, et al. Long-term safety and efficacy of low-dose cyclosporin A in severe psoriatic arthritis. *Rheumatol Int* 2002;21:234–8.
- Fraser AD, van Kujik AWR, Westhovens R, et al. A randomised, double blind, placebo controlled, multicentre trial of combination therapy with methotrexate plus ciclosporin in patients with active psoriatic arthritis. *Ann Rheum Dis* 2005;64:859–64.
- Mahrle G, Schulze HJ, Brautigam M, et al. Anti-inflammatory efficacy of low-dose cyclosporin A in psoriatic arthritis. A prospective multicentre study. *Br J Dermatol* 1996;135:752–7.
- Malatjalian DA, Ross JB, Williams CN, et al. Methotrexate hepatotoxicity in psoriatics: report of 104 patients from Nova Scotia, with analysis of risks from obesity, diabetes and alcohol consumption during long term follow-up. *Can J Gastroenterol* 1996;10:369–75.
- Bernstein CN, Wajda A, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. *Gastroenterology* 2005;129:827–36.
- Yates VM, Watkinson G, Kelman A. Further evidence for an association between psoriasis, Crohn's disease and ulcerative colitis. *Br J Dermatol* 1982;106:323–30.
- Persson PG, Leijonmarck CE, Bernell O, et al. Risk indicators for inflammatory bowel disease. *Int J Epidemiol* 1993;22:268–72.
- Schmitt JM, Ford DE. Role of depression in quality of life for patients with psoriasis. *Dermatology* 2007;215:17–27.



## CHAPTER 15: THE FUTURE OF PSORIASIS CARE

### *Canadian Guidelines for the Management of Plaque Psoriasis*

The clinical landscape of psoriasis care has shifted significantly in recent years with the introduction into the market of new agents engineered to target inflammatory cells and mediators that drive plaque formation. In the coming years, after these Guidelines are published, additional new agents and new approaches will likely be introduced at a similar, if not more rapid, pace. Although the recommendations in these Guidelines are expected to reflect good dermatological practice for the foreseeable future, it is possible to anticipate some of the changes that may cause future readers to reconsider some of the practices described here.

#### **Standards of care in psoriasis treatment**

With the increased recognition of quality-of-life issues for psoriasis patients has come a greater impetus for achieving more adequate control if this can be accomplished safely. The newest agents are generally well tolerated and offer the prospect of long-term, clinically significant improvement for patients who failed to control their disease using standard pharmacological and phototherapies.

#### **KEY POINT**

*Although the recommendations in these Guidelines are expected to reflect good dermatological practice for the foreseeable future, it is possible to anticipate some of the changes that may cause future readers to reconsider some of the practices described in these Guidelines.*

It is questionable whether standards of routine care have yet shifted toward more effective treatment, especially for patients receiving primary care for their psoriasis. However, trends in the clinical literature seem to promise more ambitious therapeutic goals. Thus, the clinical benchmarks used in treating psoriasis have shifted. Whereas PASI-75-level

improvement continues to be used to define treatment efficacy in clinical trials, randomized controlled trials (RCTs) and retrospective analyses increasingly report PASI-90, and even PASI-100, responses as secondary endpoints.<sup>1-3</sup>

Similarly, the operational distinction between mild and moderate psoriasis, never well defined, has been subject to ongoing revision.<sup>4</sup> If determined by body surface area affected, the cut-off for moderate disease is sometimes taken to be as low as 2%.<sup>4</sup> Behind the push for such a liberal definition is the desire to expand the field of patients recognized as requiring aggressive, ongoing therapy. In these Guidelines, we have adopted a more nuanced definition of severity that looks past the numerical ratings to consider the subjective impact of the disease and the patient's ability to control it to his or her own satisfaction.

#### **Canadian implementation of practices used elsewhere**

Canadian psoriasis care will undoubtedly be altered in the coming years by the introduction of therapeutic agents and approaches that are presently in use in other countries. For instance, the requirement for routine liver biopsies to monitor the toxic effects of long-term methotrexate could be significantly reduced if a non-invasive method were available, such as the procollagen III aminopeptide (PIIINP) test.<sup>5</sup> This test is currently in routine use in other countries, including the UK, where it has been reported to reduce the need for biopsies by approximately sevenfold. The PIIINP test is not currently available in Canada.

The introduction of drugs not currently available or approved for use in Canada could also have a great effect on routine practice. For instance, fumaric acid esters (FAEs<sup>6</sup>) are approved and commonly used only in Germany.<sup>7</sup> FAEs are oral systemic agents that were originally proposed to act by interfering directly with keratinocyte proliferation. However, it appears that

some FAEs can alter the cytokine secretion profile of circulating T cells, possibly by modulating patterns of gene expression in dendritic cells.<sup>8</sup> It is not clear which of the FAEs present in commercially available preparations have the greatest antipsoriatic activity and which ones are responsible for the dose-limiting gastrointestinal side effects and flushing that patients on FAEs report.<sup>9</sup> There are no immediate prospects of introducing FAEs onto the Canadian market; it is possible that this will occur only when second-generation, chemically homogeneous, products are available, with better defined mechanisms of action, as well as better efficacy or fewer adverse effects.

New formulations of existing products may have a more immediate impact on psoriasis care. For instance, foam preparations of corticosteroids, which are currently in use in the US, appear to be better accepted by patients, relative to other formulations that are similar or identical in their active components.<sup>10,11</sup> Based solely on their cosmetic features, these products may lead to improved adherence and thereby better disease control, particularly of scalp psoriasis.<sup>12</sup>

### Priorities for future research

#### *Prospects for more head-to-head studies*

Solid clinical data are badly needed to help refine clinical decision making and tailor therapies for individual patients. To date, active-comparator trials in psoriasis have largely been restricted to topical treatments and occasional studies of alternative phototherapies.<sup>13</sup> More trials such as a recent one comparing methotrexate and adalimumab<sup>14</sup> are urgently needed to allow physicians to directly evaluate the relative efficacy and safety of various systemic and biologic therapies.

A few active-comparator trials are ongoing ([www.clinicaltrials.gov](http://www.clinicaltrials.gov); accessed February 2008), including comparisons of methotrexate versus infliximab and of cyclosporine versus the calcineurin inhibitor voclosporin (formerly ISA247; see below). The first and only registered trial to compare two biologics (etanercept versus the novel agent ustekinumab) began enrolling patients in 2007. However, for the foreseeable future, physicians caring for psoriasis patients will continue to make most of their treatment decisions without the benefit of head-to-head clinical trial data.

#### *Optimized combination treatments*

In current dermatological practice, topical agents are commonly combined. Likewise, photochemotherapy approaches such as PUVA and various UVB combination therapies (e.g., with coal tar, retinoids, or vitamin D3 analogues) are well established and, in many cases, highly effective. In contrast, researchers are only beginning to explore combination regimens incorporating the more recent additions to the pharmacological toolkit.<sup>15</sup> Combining therapies with distinct targets or complementary mechanisms of action may prove helpful when monotherapies fail.

#### *Individually tailored therapies*

The recent dramatic advances in understanding the genetics of psoriasis have yet to affect routine dermatological practice. However, this transition can be expected in coming years, as psoriasis researchers continue to define clinically distinct subtypes of this genetically heterogeneous disorder.

Genetic variation will also help predict response to various therapies. Even today it may be possible to predict responsiveness to vitamin D3 analogues based on genotype at the vitamin D3 receptor locus,<sup>16</sup> although there has been little practical incentive to do this in preference to a casual trial of topical therapy. Recent papers are beginning to offer retrospective efficacy analysis based on molecular markers at baseline, such as expression levels of various cytokine genes.<sup>17,18</sup> Likewise, it may be possible to identify patients at elevated risk of methotrexate-induced hepatotoxicity on the basis of their genotype at loci related to folate or nucleotide biosynthesis.<sup>19</sup>

As clinical differences by genotype continue to be explored, e.g., between carriers and non-carriers of the HLA-Cw\*0602 allele, it is likely that treatment decisions will be based increasingly on genotype, especially for non-topical therapeutic approaches. An individual's pharmacogenetic profile and other factors affecting the natural history of the disease<sup>20</sup> may ultimately be used to select treatments that will be safe and effective for a given patient.

#### *New agents*

In the immediate future, only two novel antipsoriatic agents are likely to become available to Canadian

physicians: voclosporin and ustekinumab. The former is a newer-generation calcineurin inhibitor, structurally similar to cyclosporine, the latter a biologic agent with a new molecular target.

#### Voclosporin and related small-molecule drugs

Compared to cyclosporine, voclosporin binds its target more tightly, has a simpler pattern of metabolic product, and is more rapidly eliminated. Cyclosporine use is limited by renal toxicity and the need to monitor kidney function on a monthly or semi-monthly basis, but kidney damage may be less of a consideration for voclosporin.

A 24-week phase 3 trial examining a range of voclosporin doses showed significant improvement in psoriasis symptoms as measured by PASI scores.<sup>21</sup> Both efficacy and safety issues were dose-dependent; at the highest dose, there was laboratory evidence of reduced kidney function in 6% of subjects. Incidence of glomerular filtration deficits was less common in patients receiving the lower doses, which offered lower response rates as well (PASI-75 response after 12 weeks in 44% of patients at the highest dose versus 25% at a lower dose). The optimal dosage and therapeutic window for this drug are therefore still undefined.

The use of other calcineurin inhibitors, including both topical<sup>22</sup> and systemic formulations,<sup>3</sup> has also been explored for psoriasis.

#### Biologics with novel targets

Ustekinumab, a novel biologic agent, is the first drug designed specifically to suppress inflammation by targeting signalling by the interleukin-12 (IL-12) family of cytokines. Earlier biologics act either on TNF signalling (etanercept, infliximab, and adalimumab) or on T cells (alefacept).

IL-12 and the closely related cytokine IL-23 are both dimeric proteins sharing a common subunit, termed p40. Although initially developed as a specific inhibitor of IL-12 signal transduction, ustekinumab binds to p40 and thereby suppresses both IL-12 and IL-23 signalling. IL-23 is produced by several cell types in the psoriatic plaque,<sup>23</sup> including dendritic cells and keratinocytes,<sup>24</sup> and it activates the production of T cells that secrete IL-17 (T<sub>H</sub>-17 cells).

Recent genetic<sup>25</sup> and cellular analyses suggest that suppression of the IL-23 signalling may be the key therapeutic mechanism of ustekinumab.<sup>26</sup> However, it cannot be excluded that suppression of IL-12 contributes as well, since this cytokine promotes the secretion of inflammatory factors such as the classic T<sub>H</sub>1 cytokine interferon- $\gamma$ , and ustekinumab blocks this response.<sup>27</sup>

Ustekinumab is expected to offer relatively stable remission from psoriasis, based on two phase 3 trials testing several doses against placebo treatment.<sup>28,29</sup> In these trials, patients with moderate to severe psoriasis received two initial subcutaneous doses at a 4-week interval, with ongoing injections every 12 weeks thereafter. Disease severity and quality of life were monitored for 52<sup>29</sup> or 76<sup>28</sup> weeks. The two trials were consistent in showing PASI-75-level improvement within 12 weeks in the majority of patients, at either of two doses tested (45 or 90 mg). With higher-dose ustekinumab, 100% PASI improvement occurred within 28 weeks in approximately 30% of patients, and this dramatic clinical improvement was reflected in significant betterment in patient quality of life.<sup>28,29</sup> In some cases, patients who were only partially responsive to higher-dose ustekinumab, i.e., those who experienced PASI-50- but not PASI-75-level improvement, achieved more complete control when the frequency of dosing was increased from once in 12 weeks to once in 8 weeks.<sup>29</sup> No drug-related safety issues were evident from these studies.

In addition to ustekinumab and a similar agent that is also in development (ABT-874<sup>30</sup>), other potentially therapeutic monoclonal antibodies have been generated to target other components of the IL-23/IL-17 axis, such as the p19 subunit of IL-23.<sup>31,32</sup>

#### Other therapeutic strategies

Vitamin D analogues, particularly calcipotriol, have emerged as a mainstay of topical therapy for psoriasis. However, this class of agents can cause discomfort on application (local burning) and may, at high doses, confer some risk of dysregulating the patient's calcium metabolism. Becocalcidiol is an alternative drug in development that appears to be free of both these risks.<sup>33</sup>

Treatment with retinoids is another classic approach to psoriasis. Retinoids appear to act directly on the keratinocyte cells to suppress their abnormal proliferation and differentiation in the psoriatic plaque. They can be effective, but their use in women is limited by their potent teratogenic action. For instance, acitretin is strictly contraindicated in women of childbearing age unless the patient can be relied on to use effective contraception for at least 3 years after treatment.

Because retinoic acid is naturally present in the skin, drugs that inhibit its catabolism (retinoic acid metabolism-blocking agents; RAMBAs) can have a therapeutic effect mimicking that of retinoids. The RAMBA liarozole has been shown to offer significant control of psoriasis over a 12-week period.<sup>34</sup> A second generation agent in this class, talarozole, likewise restores normal skin histology to plaques within 8 weeks.<sup>35</sup> The safety of this approach in the psoriasis population has not been established. Based on theoretical considerations and preclinical data,<sup>36</sup> it is reasonable to assume that RAMBAs are teratogenic and will not be suitable for women considering becoming pregnant, although they may not require an extended washout period like that used for acitretin.

An alternative approach to preventing plaque formation is to block the migration of inflammatory cells, as with alefacept treatment. Other large- and small-molecule drugs that interfere with this process could be chosen to target either chemokines (signalling molecules that induce leukocyte movement) and chemokine receptors or adhesive molecules such as selectins,<sup>37</sup> which allow circulating cells to adhere to and move across the endothelial lining and enter inflamed tissues.

Similarly, it is possible to target the intracellular signalling pathways by which immunocytes in the psoriatic plaque become activated. Molecular targets include mediators of signalling through cytokine receptors (notably Jak3 and its downstream Stat proteins), Toll-like receptors (NF- $\kappa$ B and molecules that affect its localization

or stability), and G-protein-coupled receptors (components of the MAP kinase pathway). In many cases, therapeutic agents specific for these signalling molecules have been developed for other indications (reviewed in O'Neill<sup>38</sup>). It is therefore likely that some of these agents will be tested off-label for their efficacy in psoriasis.

Finally, monochromatic excimer laser therapy has been explored as an alternative to standard phototherapies for treating psoriasis at various areas, including the scalp,<sup>39-41</sup> the palms and soles,<sup>42-44</sup> and flexures.<sup>45</sup>

### Primary prevention

Streptococcal throat infections have long been suspected to induce guttate psoriasis in children and young adults and to aggravate adult plaque psoriasis. It has been suggested that the M protein from certain strains of *Streptococcus pyogenes* includes antigenic peptides that activate pathogenic T cells in HLA-Cw\*0602-positive individuals.<sup>46</sup> These T cells are proposed to be activated within the infected tonsils and to acquire the CTA<sup>+</sup> phenotype, which allows them to home to the skin. The interaction between these CTA<sup>+</sup> T cells (presumably of the T<sub>h</sub>1 or T<sub>h</sub>-17 subtype) and the antigen-presenting cells in the skin is not yet fully defined. However, the mechanism offers the hope of interfering with the earliest stages of pathogenesis, potentially by vaccinating an appropriate, genetically defined subpopulation using specific streptococcal antigens.

### Persistence

Advances in psoriasis research continue to yield new approaches that promise ever more complete control of plaque psoriasis. The developments may well revolutionize care in coming years. However, they are unlikely to change the fundamental need, noted in the introduction, for active engagement with the patient to ensure that the selected treatment is used consistently and appropriately.<sup>47</sup> Our hard-won insights on the limits of treatment persistence in the real world will apply, no matter how subtly targeted the treatment options become. Even the most sophisticated drugs only work if the patient uses them.



## References

- Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006;55:598–606.
- Krueger GG, Langley RG, Leonardi C, et al. A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* 2007;356:580–92.
- Gottlieb AB, Griffiths CEM, Ho VC, et al. Oral pimecrolimus in the treatment of moderate to severe chronic plaque-type psoriasis: A double-blind, multicentre, randomized, dose-finding trial. *Br J Dermatol* 2005;152:1219–27.
- Krueger GG, Feldman SR, Camisa C, et al. Two considerations for patients with psoriasis and their clinicians: what defines mild, moderate, and severe psoriasis? What constitutes a clinically significant improvement when treating psoriasis? *J Am Acad Dermatol* 2000;43:281–5.
- Chalmers RJG, Kirby B, Smith A, et al. Replacement of routine liver biopsy by procollagen III aminopeptide for monitoring patients with psoriasis receiving long-term methotrexate: A multicentre audit and health economic analysis. *Br J Dermatol* 2005;152:444–50.
- Mrowietz U, Christophers E, Altmeyer P. Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. German Multicentre Study. *Br J Dermatol* 1998;138:456–60.
- Naldi L, Griffiths CE. Traditional therapies in the management of moderate to severe chronic plaque psoriasis: an assessment of the benefits and risks. *Br J Dermatol* 2005;152:597–615.
- Litjens NH, Rademaker M, Ravensbergen B, et al. Monomethylfumarate affects polarization of monocyte-derived dendritic cells resulting in down-regulated Th1 lymphocyte responses. *Eur J Immunol* 2004;34:565–75.
- Ormerod AD, Mrowietz U. Fumaric acid esters, their place in the treatment of psoriasis. *Br J Dermatol* 2004;150:630–2.
- Housman TS, McMichael AJ, Mellen BG, et al. Use of 0.12% betamethasone valerate foam vs 0.01% fluocinonide acetonide topical oil to treat scalp psoriasis: Quantitative assessment of patient preference and treatment efficacy. *Cosmet Dermatol* 2002;15:27–30.
- Bergstrom KG, Arambula K, Kimball AB. Medication formulation affects quality of life: a randomized single-blind study of clobetasol propionate foam 0.05% compared with a combined program of clobetasol cream 0.05% and solution 0.05% for the treatment of psoriasis. *Cutis* 2003;72:407–11.
- Feldman SR, Housman TS. Patients' vehicle preference for corticosteroid treatments of scalp psoriasis. *Am J Clin Dermatol* 2003;4:221–4.
- Yones SS, Palmer RA, Garibaldinos TT, Hawk JLM. Randomized double-blind trial of the treatment of chronic plaque psoriasis: efficacy of psoralen-UV-A therapy vs narrowband UV-B therapy. *Arch Dermatol* 2006;142:836–42.
- Saurat JH, Stingl G, Dubertret L, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008;158:558–66.
- Legat FJ, Hofer A, Wackernagel A, et al. Narrowband UV-B phototherapy, alefacept, and clearance of psoriasis. *Arch Dermatol* 2007;143:1016–22.
- Halsall JA, Osborne JE, Pringle JH, Hutchinson PE. Vitamin D receptor gene polymorphisms, particularly the novel A-1012G promoter polymorphism, are associated with vitamin D3 responsiveness and non-familial susceptibility in psoriasis. *Pharmacogenomics* 2005;15:349–55.
- Gottlieb AB, Cooper KD, McCormick TS, et al. A phase 1, double-blind, placebo-controlled study evaluating single subcutaneous administrations of a human interleukin-12/23 monoclonal antibody in subjects with plaque psoriasis. *Curr Med Res Opin* 2007;23:1081–92.
- Toichi E, Torres G, McCormick TS, et al. An anti-IL-12p40 antibody down-regulates type 1 cytokines, chemokines, and IL-12/IL-23 in psoriasis. *J Immunol* 2006;177:4917–26.
- Hider SL, Bruce IN, Thomson W. The pharmacogenetics of methotrexate. *Rheumatology (Oxford)* 2007;46:1520–4.
- Lew W, Lee E, Krueger JG. Psoriasis genomics: analysis of proinflammatory (type 1) gene expression in large plaque (Western) and small plaque (Asian) psoriasis vulgaris. *Br J Dermatol* 2004;150:668–76.
- Papp KA, Bissonnette R, Rosoph L, et al. Efficacy of ISA247 in plaque psoriasis: a phase 3, randomized, multicenter, double-blind, placebo-controlled study. *Lancet* 2008;371:1337–42.
- Kreuter A, Sommer A, Hyun J, et al. 1% pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone in the treatment of intertriginous psoriasis: a double-blind, randomized controlled study. *Arch Dermatol* 2006;142:1138–43.
- Chan JR, Blumenschein W, Murphy E, et al. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *J Exp Med* 2006;203:2577–87.
- Piskin G, Sylva-Steenland RM, Bos JD, Teunissen MB. In vitro and in situ expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. *J Immunol* 2006;176:1908–15.
- Cargill M, Schrodi SJ, Chang M, et al. A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. *Am J Hum Genet* 2007;80:273–90.
- Nickoloff BJ. Cracking the cytokine code in psoriasis. *Nat Med* 2007;13:242–4.
- Reddy M, Davis C, Wong J, et al. Modulation of CLA, IL-12R, CD40L, and IL-2/Ralpha expression and inhibition of IL-12- and IL-23-induced cytokine secretion by CNTO 1275. *Cell Immunol* 2007;247:1–11.
- Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008;371:1665–74.
- Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008;371:1675–84.
- Kimball AB, Gordon KB, Langley RG, et al. Safety and efficacy of ABT-874, a fully human interleukin 12/23 monoclonal antibody, in the treatment of moderate to severe chronic plaque psoriasis: results of a randomized, placebo-controlled, phase 2 trial. *Arch Dermatol* 2008;144:200–7.
- Chen Y, Langrish CL, McKenzie B, et al. Anti-IL-23 therapy inhibits multiple inflammatory pathways and ameliorates autoimmune encephalomyelitis. *J Clin Invest* 2006;116:1317–26.
- Gaston JS. Cytokines in arthritis — the 'big numbers' move centre stage. *Rheumatology (Oxford)* 2008;47:8–12.
- Helfrich YR, Kang S, Hamilton TA, Voorhees JJ. Topical bexocalcidiol for the treatment of psoriasis vulgaris: a randomized, placebo-controlled, double-blind, multicentre study. *Br J Dermatol* 2007;157:369–74.
- Berth-Jones J, Todd G, Hutchinson PE, et al. Treatment of psoriasis with oral liarozole: a dose-ranging study. *Br J Dermatol* 2000;143:1170–6.
- Bovenschen HJ, Otero ME, Langewouters AMG, et al. Oral retinoic acid metabolism blocking agent Rambazole for plaque psoriasis: an immunohistochemical study. *Br J Dermatol* 2007;156:263–70.
- Roberts C, Ivins S, Cook AC, et al. Cyp26 genes a1, b1 and c1 are down-regulated in Tbx1 null mice and inhibition of Cyp26 enzyme function produces a phenocopy of DiGeorge Syndrome in the chick. *Hum Mol Genet* 2006;15:3394–410.
- Kneuer C, Ehrhardt C, Radomski MW, Bakowsky U. Selectins — potential pharmacological targets? *Drug Discov Today* 2006;11:1034–40.
- O'Neill LAJ. Targeting signal transduction as a strategy to treat inflammatory diseases. *Nature Reviews Drug Discovery* 2006;5:549–63.
- Gupta SN, Taylor CR. 308-nm Excimer laser for the treatment of scalp psoriasis. *Arch Dermatol* 2004;140:518–20.
- Taylor CR, Racette AL. A 308-nm excimer laser for the treatment of scalp psoriasis. *Lasers Surg Med* 2004;34:136–40.
- Morison WL, Atkinson DF, Werthman L. Effective treatment of scalp psoriasis using the excimer (308 nm) laser. *Photodermatol Photoimmunol Photomed* 2006;22:181–3.
- Neumann NJ, Mahnke N, Korpusik D, et al. Treatment of palmoplantar psoriasis with monochromatic excimer light (308-nm) versus cream PUVA. *Acta Derm Venereol* 2006;86:22–4.
- Sezer E, Erbil AH, Kurumlu Z, et al. Comparison of the efficacy of local narrowband ultraviolet B (NB-UVB) phototherapy versus psoralen plus ultraviolet A (PUVA) paint for palmoplantar psoriasis. *J Dermatol* 2007;34:435–40.
- Nistico SP, Saraceno R, Stefanescu S, Chimenti S. A 308-nm monochromatic excimer light in the treatment of palmoplantar psoriasis. *J Eur Acad Dermatol Venereol* 2006;20:523–6.
- Mafong EA, Friedman PM, Kauvar ANB, et al. Treatment of inverse psoriasis with the 308 nm excimer laser. *Dermatol Surg* 2002;28:530–2.
- Johnston A, Gudjonsson JE, Sigmundsdottir H, et al. Peripheral blood T cell responses to keratin peptides that share sequences with streptococcal M proteins are largely restricted to skin-homing CD8(+) T cells. *Clin Exp Immunol* 2004;138:83–93.
- Ali SM, Brodell RT, Balkrishnan R, Feldman SR. Poor adherence to treatments: A fundamental principle of dermatology. *Arch Dermatol* 2007;143:912–5.

## APPENDIX: TRADE NAME/GENERIC NAME TRANSLATOR

Because generic names are used throughout these Guidelines, text searches of the electronic document using trade names for drugs will not identify the relevant pages. Readers who are uncertain of the correct generic name of a drug may consult the table below to identify a searchable drug name.

Although this list is as thorough as possible, it is provided as a guide only; it is not guaranteed to be complete.

Trade name or trivial name	Generic name	Notes
Abelcet	Amphotericin B	
Adalat	Nifedipine	
Alkeran	Melphalan	
Ambisome	Amphotericin B	
Amevive	Alefacept	
Amphotec	Amphotericin B	
Anthraforte	Anthralin	
Anthranol	Anthralin	
AnthraScalp	Anthralin	
Apo-Atenidone	Atenolol	Formulated as atenolol plus chlorthalidone
Apo-Atenol	Atenolol	
Apo-Azathioprine	Azathioprine	
Apo-Ciproflox	Ciprofloxacin	
Apo-Cyclosporine	Cyclosporine	
Apo-Digoxin	Digoxin	
Apo-Fenofibrate	Fenofibrate	
Apo-Hydroxyquine	Hydroxychloroquine sulfate	
Apo-Lithium Carbonate	Lithium	Formulated as lithium carbonate
Apo-Methotrexate	Methotrexate	
Apo-Metoprolol	Metoprolol	
Apo-Nifed	Nifedipine	
Apo-Phenylbutazone; Apo Phenylbutazone	Phenylbutazone	
Apo-Propranolol	Propranolol	
Apo-Sulfasalazine; Apo Sulfasalazine	Sulfasalazine	
Apo-Sulfatrim	Trimethoprim/sulfamethoxazole combination product; cotrimoxazole (also search by names of component drugs)	Formulated as trimethoprim plus sulfamethoxazole
Apo-Theo-La	Theophylline	
Apo-Timol	Timolol	
Apo-Timop	Timolol	
Apo-Trimethoprim	Trimethoprim	



Trade name or trivial name	Generic name	Notes
Apo-Zidovudine; Apo Zidovudine	Zidovudine	
Arava	Leflunomide	
Aristocort	Triamcinolone	Formulated as triamcinolone acetonide
AZT	Zidovudine	
BCI-Atenolol	Atenolol	
Benuryl	Probenecid	
Betaderm	Betamethasone	Formulated as betamethasone valerate
Betaject	Betamethasone	Formulated as betamethasone 21-disodium phosphate plus betamethasone acetate
Betaloc	Metoprolol	
Betnesol	Betamethasone	Formulated as betamethasone sodium phosphate
Bezalip	Bezafibrate	
Caduet	Amlodipine	Formulated as amlodipine besylate plus atorvastatin
Carbolith	Lithium	Formulated as lithium carbonate
Celestone Soluspan Injectable	Betamethasone	Formulated as betamethasone sodium phosphate plus betamethasone acetate
Cellcept	Mycophenolate mofetil	
Cerebyx	Fosphenytoin sodium	
Ciloxan	Ciprofloxacin	
Cipro	Ciprofloxacin	
Clobex	Clobetasol	
CO Atenolol	Atenolol	
Colchicinum	Colchicine	
Combigan	Timolol	Formulated as timolol maleate plus brimonidine tartrate
Combivir	Zidovudine	Formulated as zidovudine plus lamivudine
Cosopt	Timolol	Formulated as timolol maleate plus dorzolamide hydrochloride
Cutivate	Fluticasone propionate	
Cyclocort	Amcinonide	
Denorex	Coal tar	Formulated as coal tar plus chloroxylenol and menthol
Dermovate	Clobetasol	
Digibind	Digoxin	
Dilantin	Phenytoin	

Trade name or trivial name	Generic name	Notes
Diprolene Glycol	Betamethasone	Formulated as betamethasone dipropionate
Diprosalic	Betamethasone	Formulated as betamethasone dipropionate plus salicylic acid
Diprosone	Betamethasone	Formulated as betamethasone dipropionate
Dithranol	Anthralin	
Doak Oil	Coal tar	
Dom-Fenofibrate	Fenofibrate	
Dom-Metoprolol	Metoprolol	
Dom-Propranolol	Propranolol	
Dom-Timolol	Timolol	
Dovobet	Calcipotriol/betamethasone combination product (also search by names of component drugs)	Formulated as betamethasone dipropionate plus calcipotriol
Dovonex	Calcipotriol	
Duotrav	Timolol	Formulated as timolol maleate plus travoprost
Duralith	Lithium	Formulated as lithium carbonate
Efudex	Fluorouracil	
Elidel	Pimecrolimus	
Enbrel	Etanercept	
Exorex	Coal tar	
Fenomax	Fenofibrate	
Fluoroplex	Fluorouracil	
Fungizone	Amphotericin B	
Gen-Azathioprine	Azathioprine	
Gen-Clobetasol	Clobetasol	
Gen-Hydroxychloroquine	Hydroxychloroquine sulfate	
Gen-Metoprolol	Metoprolol	
Gluconorm	Repaglinide	
Humira	Adalimumab	
Hydrea	Hydroxyurea	
Imuran	Azathioprine	
Inderal	Propranolol	
Kenalog	Triamcinolone	Formulated as triamcinolone acetonide
Lanoxin	Digoxin	

Trade name or trivial name	Generic name	Notes
Lidemol	Fluocinonide	
Lidex	Fluocinonide	
Lipidil	Fenofibrate	
Lithane	Lithium	Formulated as lithium carbonate
Lithium Benziocum	Lithium	Formulated as lithium benzoate
Lithium Carbonicum	Lithium	Formulated as lithium carbonate
Lopresor	Metoprolol	
Lyderm	Fluocinonide	
Mazon Medicated Cream	Coal tar	Formulated as coal tar plus resorcinol and salicylic acid
Medi-Dan Shampoo	Coal tar	Formulated as coal tar plus benzalkonium chloride and salicylic acid
Med-Timolol	Timolol	
Metoject	Methotrexate	
Multi-Tar Plus Shampoo	Coal tar	Formulated as coal tar plus juniper tar, pine tar, and pyrithione zinc
Neoral	Cyclosporine	
Nerisalic	Diflucortolone valerate	Formulated as diflucortolone valerate plus salicylic acid
Nerisone	Diflucortolone valerate	
Norvasc	Amlodipine	
Novo-Azathioprine	Azathioprine	
Novo-AZT	Zidovudine	
Novo-Chloroquine	Chloroquine	
Novo-Clobetasol	Clobetasol	
Novo-Fenofibrate	Fenofibrate	
Novo-Metoprol	Metoprolol	
Novo-Phenytoin	Phenytoin	
Novo-Pranol	Propranolol	
Novo-Theophyl	Theophylline	
Novo-Timol	Timolol	
Novo-Trimel	Trimethoprim/sulfamethoxazole combination product; cotrimoxazole (also search by names of component drugs)	Formulated as trimethoprim plus sulfamethoxazole
Nu-Cotrimox	Trimethoprim/sulfamethoxazole combination product; cotrimoxazole (also search by names of component drugs)	Formulated as trimethoprim plus sulfamethoxazole

Trade name or trivial name	Generic name	Notes
Nu-Fenofibrate	Fenofibrate	
Nu-Metop	Metoprolol	
Nu-Propranolol	Propranolol	
Nu-Timol	Timolol	
Odans Liquor Carbonis Detergens	Coal tar	
Oxipor	Coal tar	Formulated as coal tar plus benzocaine and salicylic acid
P&S Plus	Coal tar	Formulated as coal tar plus salicylic acid
Pekana-colchicinium	Colchicine	
Pentrax	Coal tar	
PHL-Lithium Carbonate	Lithium	Formulated as lithium carbonate
PHL-Fenofibrate	Fenofibrate	
PHL-Metoprolol	Metoprolol	
Plaquenil	Hydroxychloroquine sulfate	
Plendil	Felodipine	
PMS-Bezafibrate	Bezafibrate	
PMS-Lithium Carbonate	Lithium	Formulated as lithium carbonate
PMS-Digoxin	Digoxin	
PMS-Metoprolol	Metoprolol	
PMS-Polytrimethoprim	Trimethoprim	Formulated as trimethoprim sulfate plus polymyxin B sulfate
PMS-Propranolol	Propranolol	
PMS-Sulfasalazine	Sulfasalazine	
PMS-Theophylline	Theophylline	
PMS-Timolol	Timolol	
PMS-Vancomycin	Vancomycin	
Prevex B	Betamethasone	Formulated as betamethasone valerate
Pro-Hydroxyquine	Hydroxychloroquine sulfate	
Protopic	Tacrolimus	
Protrin	Trimethoprim/sulfamethoxazole combination product; cotrimoxazole (also search by names of component drugs)	Formulated as trimethoprim plus sulfamethoxazole
Psoriasin	Coal tar	
Pulmophylline	Theophylline	
Purinethol	Mercaptopurine	
Rambazole	Talarozole	Not available in Canada
Raptiva	Efalizumab	Removed from Canadian market in 2009

Trade name or trivial name	Generic name	Notes
Ratio-Amcinonide	Amcinonide	
Ratio-Clobetasol	Clobetasol	
Ratio-Ectosone	Betamethasone	Formulated as betamethasone valerate
Ratio-Fluticasone	Fluticasone propionate	
Ratio-Methotrexate Sodium	Methotrexate	
Ratio-Theo-Bronc	Theophylline	Formulated as theophylline plus guaifenesin, potassium iodide, and pyrilamine maleate
Ratio-Topilene	Betamethasone	Formulated as betamethasone dipropionate
Ratio-Topisalic	Betamethasone	Formulated as betamethasone dipropionate plus salicylic acid
Ratio-Topisone	Betamethasone	Formulated as betamethasone dipropionate
Ratio-Triacomb	Triamcinolone	Formulated as triamcinolone acetonide plus gramicidin, neomycin sulfate, and nystatin
Remicade	Infliximab	
Renedil	Felodipine	
Retrovir	Zidovudine	
Rhoxal-Timolol	Timolol	
Riva-Metoprolol	Metoprolol	
Rivasone Scalp	Betamethasone	Formulated as betamethasone valerate
Rolene	Betamethasone	Formulated as betamethasone dipropionate
Rosone	Betamethasone	Formulated as betamethasone dipropionate
S J Liniment	Coal tar	Formulated as coal tar plus ammonium hydroxide, menthol, and methyl salicylate
Salazopyrin	Sulfasalazine	
Sandoz Cyclosporine	Cyclosporine	
Sandoz Felodipine	Felodipine	
Sandoz Metoprolol	Metoprolol	
Sandoz Timolol	Timolol	
Sebcur	Coal tar	Formulated as coal tar plus salicylic acid
Septra	Trimethoprim/sulfamethoxazole combination product; cotrimoxazole (also search by names of component drugs)	Formulated as trimethoprim plus sulfamethoxazole
Soriatane	Acitretin	

Trade name or trivial name	Generic name	Notes
Stelara	Ustekinumab	
Sterex	Coal tar	Formulated as coal tar plus salicylic acid, sulfur, and/or hydrocortisone
T Gel; T/Gel Therapeutic Shampoo	Coal tar	
Tardan	Coal tar	Formulated as coal tar plus salicylic acid and triclosan
Targel	Coal tar	
Taro-Sone	Betamethasone	Formulated as betamethasone dipropionate
Taro-Amcinonide	Amcinonide	
Taro-Clobetasol	Clobetasol	
Taro-Phenytoin	Phenytoin	
Tazorac	Tazarotene	
Tegison	Etretinate	Removed from Canadian market in 1996
Tersa Tar Shampoo	Coal tar	
Theraderm	Triamcinolone	Formulated as triamcinolone acetonide plus gramicidin, neomycin sulfate, and nystatin
Tiamol	Fluocinonide	
Topactin	Fluocinonide	
Topsyn	Fluocinonide	
Trasicor	Oxprenolol	Discontinued in 2007
Tremytoin	Phenytoin	
Triaderm	Triamcinolone	Formulated as triamcinolone acetonide
Trizivir	Zidovudine	Formulated as zidovudine plus lamivudine and abacavir sulfate
Ultravate	Halobetasol propionate	
Vancocin	Vancomycin	
Vepesid	Etoposide	
Viaderm KC	Triamcinolone	Formulated as triamcinolone acetonide plus gramicidin, neomycin sulfate, and nystatin
Xamiol	Calcipotriol/betamethasone combination product (also search by names of component drugs)	Formulated as betamethasone dipropionate plus calcipotriol
X-Seb T-Plus Conditioning Shampoo	Coal tar	Formulated as coal tar plus menthol and salicylic acid
Zanidip	Lercanidipine	Not available in Canada
Zym-Metoprolol	Metoprolol	



