Consensus Guidelines for the Management of Plaque Psoriasis

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The *Canadian Guidelines for the Management of Plaque Psoriasis* were reviewed by the entire National Psoriasis Foundation Medical Board and updated to include newly approved agents such as ustekinumab and to reflect practice patterns in the United States, where the excimer laser is approved for psoriasis treatment. Management of psoriasis in special populations is discussed. In the updated guidelines, we include sections on children, pregnant patients or pregnant partners of patients, nursing mothers, the elderly, patients with hepatitis B or C virus infections, human immunodeficiency virus–infected patients, and patients with malignant neoplasms, as well as sections on tumor necrosis factor blockers, elective surgery, and vaccinations.

Arch Dermatol. 2012;148(1):95-102

Psoriasis skin manifestations have a wide range of presentations. The manifestations can be severe and widespread with signs and symptoms that greatly affect the patients' quality of life. Psoriatic arthritis, which can be severe and debilitating, is also present in many patients. Finally, psoriasis is associated with an increased risk of serious comorbidities, such as cardiovascular disease and the metabolic syndrome, that complicate management and increase the risk of early death.[1]

Inflammation driven by T cells is responsible for keratinocyte growth and angiogenesis in the psoriatic plaque.[2] Many of the newly introduced therapies for psoriasis were therefore devised to target T cells or their inflammatory mediators.[3,4] Indeed, many of the classic topical and systemic therapies and phototherapies also act at least in large part by interfering with this same immune response.

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MANAGEMENT OF MODERATE TO SEVERE PLAQUE PSORIASIS

Definitions of moderate to severe psoriasis in the literature are varied and contradictory. Moderate psoriasis is commonly distinguished from milder forms of the disease on the basis of scores on 1 or more clinical metrics, such as the Psoriasis Area and Severity Index (PASI); the percentage of the body surface area affected; and the Dermatological Life Quality Index (eAppendix, chapter 3, Table 2; http://www.archdermatol.com). Although numerical cutoffs are necessary in clinical trial design, they have little value in daily prac-

Table. Drugs Used in Treatment of Psoriasis

Drug Name	Classification/Mechanism of Action	Comments
Acitretin	Oral retinoid	First-line systemic drug for chronic palmoplantar or pustular psoriasis in patients of nonchildbearing potential Limited benefit for plaque psoriasis
Cyclosporine	Oral calcineurin inhibitor	Fast-acting systemic drug that is often used first-line for von Zumbusch pustular psoriasis or erythrodermic psoriasis For intermittent use in periods up to 12 wk as a short-term agent to control a flare of psoriasis
Methotrexate sodium	Inhibitor of folate biosynthesis	May be used as a first-line systemic drug for plaque psoriasis Compared with cyclosporine, has a more modest effect, but can be used continuously for years or decades
Adalimumab	TNF inhibitor	May be used as first-line systemic treatment of plaque psoriasis[5] Has higher efficacy and lower rate of adverse effects compared with methotrexate[6]
Etanercept	TNF inhibitor	Commonly used as a first-line systemic drug for chronic plaque psoriasis
Infliximab	TNF inhibitor	Intravenous infusion Fast-acting drug that is often used as a second- or third-line biological for chronic plaque psoriasis
Ustekinumab	Monoclonal antibody that binds the shared p40 protein subunit of IL-12 and IL-23	Favorable results when compared with etanercept in terms of efficacy and safety[7] May be used as first-line systemic treatment for chronic plaque psoriasis
Alefacept	Interacts with T-cell surface proteins; acts in part by triggering the death of pathogenic T lymphocytes	For intermittent use Little evidence to support use to achieve full clearance Often used in combination regimens May be used as first-line systemic drug for chronic plaque psoriasis

Abbreviations: IL, interleukin; TNF, tumor necrosis factor.

tice. For the purposes of these guidelines, 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.

Safety, Efficacy, and Tolerability of Various Therapeutic Options

For patients with moderate to severe psoriasis, the topical agents used in mild psoriasis remain useful adjuncts. Because it is assumed that the patient's condition is intractable with strictly topical therapy, these agents are not discussed herein unless they are to be used in combination regimens that include systemic therapies or phototherapies.

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 toxic effects, but it is teratogenic and therefore inappropriate for many female patients of childbearing age. These drugs also have the potential for interactions with other drugs, which may limit their use in certain patients (**Table**).

The biological agents used to treat psoriasis represent significant recent additions to the dermatologist's toolkit. The safety records of the biologicals include multiple years of premarketing and postmarketing use. In the case of the tumor necrosis factor (TNF) antagonists, the safety record for psoriasis is supported by a longer history of use in other indications, such as rheumatoid arthritis (RA) or psoriatic arthritis. As described herein, the various biologicals have been linked to specific adverse events, but none is associated with common safety concerns, such as the end-organ toxic effects observed with cyclosporine and methotrexate. Therefore, no clinical reason supports reserving the biologicals for second-line use. In many cases, the safety of these agents and their relatively good tolerability represent deciding factors for their use. Monotherapies and combination regimens may be used to achieve complete or nearly complete clearance of psoriasis (eAppendix, chapter 6, Tables 1 and 2).

Oral Therapies

Acitretin is the only antipsoriatic retinoid available for systemic use in the United States and Canada. Retinoids are teratogenic, placing severe constraints on the use of acitretin in women of childbearing age. Common adverse effects include mucocutaneous dryness and elevation of triglyceride levels. The clinical use of acitretin has been limited because of its slow onset of action and persistence of residual plaque psoriasis even when plaque thinning is noted. The combination of acitretin with topical calcipotriene (calcipotriol) or biological therapy or phototherapy may increase rates of clearance. Acitretin is especially useful in patients with severely sun-damaged skin, in which it may suppress actinic keratoses and even invasive malignant neoplasms.

Cyclosporine is a calcineurin inhibitor used as an immunomodulator in a variety of indications, including psoriasis. Although it can be effective in the long term, continuous use of cyclosporine is associated with cumulative renal toxic effects. Cyclosporine can also cause hypertension and hypertriglyceridemia. The risk of squamous and basal cell carcinomas also increases with increasing duration of cyclosporine use. Cyclosporine should normally be reserved for intermittent use of no longer than 12 weeks as a short-term treatment agent to

control a flare of psoriasis, after which therapy is transitioned to something else for long-term maintenance. When used in this intermittent fashion, a course of cyclosporine treatment can induce an average decrease of more than 75% in psoriasis severity.

Methotrexate is an inhibitor of folate biosynthesis and therefore impairs DNA replication. Methotrexate was originally used to treat psoriasis because of its cytostatic properties, but the drug is now recognized to be directly anti-inflammatory because of its effects on T-cell gene expression patterns. Some of these effects are related to folate depletion. A recent study in RA confirmed that folate supplementation significantly reduced the incidence of toxic effects in the liver.[8] Without reducing efficacy, folate improves the tolerability of the gastrointestinal tract for methotrexate treatment. Thus, folate supplementation is advisable for patients taking methotrexate.

Compared with cyclosporine, methotrexate has a more modest effect on psoriasis severity, but it is valuable because it can be used continuously for many years with durable benefits. A major safety issue with methotrexate is the cumulative toxic effects to the liver, which were shown to be severe in nearly one-quarter of patients receiving the drug for 1 to 11 years.[9] Patients with comorbid diabetes mellitus were at particularly high risk of severe liver fibrosis and cirrhosis.

Guidelines have traditionally recommended routine pretreatment liver biopsies and subsequent biopsies every time a cumulative dose of 1.5 g is taken. However, pretreatment biopsies may not be appropriate in all cases. The most recent National Psoriasis Foundation guidelines have reduced the need for liver biopsies in patients without risk factors for hepatic fibrosis, such as obesity or diabetes, to every 3.5 to 4.0 g of total cumulative dose.[10]

Methotrexate is an abortifacient and a teratogen, and therapy is therefore contraindicated during pregnancy. Men and women should use contraception while taking the drug. Men should continue to use contraception for 3 months, and women should do so for at least 1 ovulatory cycle after discontinuing methotrexate therapy.

Biological Agents

The TNF inhibitors adalimumab, etanercept, and infliximab share a common mechanism of action that leads to safety concerns. Safety concerns include serious infections (ie, sepsis, tuberculosis, and viral infections), autoimmune conditions (lupus and demyelinating disorders), and lymphoma (Table). Causality is difficult to establish in specific patients who develop these conditions during treatment with TNF inhibitors.

Etanercept therapy is initiated at a dosage of 50 mg twice weekly, which is reduced to 50 mg/wk after 12 weeks. This dosing is sufficient to achieve PASI 75 after 24 weeks in more than half the patients. However, higher rates of clearance or near clearance are observed in patients receiving a constant dosage of 50 mg twice weekly. For patients with an inadequate response at 24 weeks, the physician should consider maintaining a constant dosage at 50 mg twice weekly rather than stepping down the dose. This dosage has not been associated with any additional safety concerns.

Adalimumab offers effective control of plaque psoriasis. It is administered subcutaneously at a dosage of 40 mg every other week beginning 1 week after a loading dose of 80 mg. Clinical benefits with the PASI level of 75 or better were maintained for at least 1 year with continuous therapy.[5] Compared with methotrexate and placebo, adalimumab proved to have higher rates of 75%, 90%, and 100% PASI improvement and a lower rate of adverse events.[6]

Infliximab offers rapid and thorough suppression of psoriasis. The drug is administered in 3 intravenous infusions (5 mg/kg) across a 6-week induction period (at weeks 0, 2, and 6) followed by infusions every 8 weeks. Nearly half the infliximab-treated patients experience a decline of at least 90% in PASI score within 10 weeks.

Ustekinumab is a fully human monoclonal antibody that binds to the shared p40 subunit of interleukin 12 (IL-12) and IL-23. Ustekinumab normalizes IL-12– and IL-23–mediated cellular activation events by preventing human IL-12 and IL-23 interaction with their cell surface receptors. The recommended dose of ustekinumab is 45 mg administered subcutaneously at weeks 0 and 4, then every 12 weeks thereafter for patients weighing no more than 100 kg. For patients weighing more than 100 kg, 90 mg is recommended. Ustekinumab is efficacious and is approved for use in moderate to severe plaque psoriasis.[11,12] Phase 2 and 3 trials demonstrated statistically significant improvement of psoriasis and safety of ustekinumab when the drug was compared with placebo.[11,12] A PASI of 75 was achieved in 67% to 81% of patients with a prolonged response to treatment.[11,12] Improvements in psoriasis were seen quickly, with statistically and clinically higher proportions of patients achieving a PASI response of at least 50 at week 2.[12] Ustekinumab also demonstrated favorable results when compared with etanercept in terms of efficacy and safety in another phase 3 trial.[7]

Ustekinumab was well tolerated as demonstrated by its comparable safety profile to placebo in trials, although long-term safety data are not yet available. A potential for causing serious adverse events may exist, but no significant risk of malignant neoplasm or infection appears to exist based on the data from recent trials.[11,12]

Alefacept is currently the only biological approved for psoriasis that interacts directly with T-cell surface proteins. Alefacept acts in part by triggering the death of pathogenic T lymphocytes. No evidence suggests that alefacept increases the incidence of infections, cancers, or any other serious adverse outcome beyond background levels. However, alefacept may deplete CD4 T lymphocytes. The patient's CD4 cell counts must be monitored and treatment withheld when this cell population declines to less than 250/μL. In case of a persistent decline in CD4 count, alefacept therapy should be discontinued.

Alefacept is intended for intermittent use. A 12-week course of alefacept allows for a 50% to 75% reduction in PASI in approximately one-quarter of these patients, and this improvement may be maintained in some patients for periods beyond 1 year. Treatment courses may be repeated as often as twice a year. Although some patients benefit from repeated courses of alefacept, the number of such responders is difficult to estimate. Alefacept leads

to full clearance of symptoms and signs of psoriasis in only a small minority of patients. However, it has an excellent safety profile when CD4 counts are monitored. This biological is often used in combination regimens, such as with narrowband (NB) UV-B.

UV Light Therapies

Narrowband UV-B and psoralen–UV-A (PUVA) cause a rapid depletion of cell populations that are implicated in psoriasis pathogenesis, including dermal and epidermal lymphocytes, macrophages, and dendritic cells. Acute safety issues with phototherapy can include erythema or blistering. Because PUVA and UV-B therapy pose a risk of carcinogenesis, patients' cumulative exposure to therapeutic UV light should be limited.

Psoralen–UV-A refers to a variety of therapeutic techniques that use 5- or 8-methoxypsoralen to sensitize cells to 320- to 400-nm UV light. Psoralen may be administered orally or topically, by bathing in a psoralen solution or by painting the compound on the affected skin. Oral psoralen can cause nausea but is usually well tolerated, and in general PUVA is highly effective.

In fair-skinned individuals, PUVA leads to skin aging and freckling and has been associated with squamous cell carcinoma and less frequently with basal cell carcinoma. This heightened risk correlates with the patient's cumulative dose, increases dramatically in individuals who have undergone more than 200 treatments, and persists for as long as 15 years after PUVA is discontinued.[13]

One large prospective study in the United States has identified an additional risk of melanoma with increasing cumulative UV-A doses.[14] In a Scandinavian cohort, however, no such effect on melanoma risk could be detected.[15] The basis for this difference in outcome is not known. Patients with a history of PUVA use and multiple squamous cell carcinomas may be inappropriate for subsequent treatment with cyclosporine, which could allow the emergence of squamous and basal cell carcinomas.

Narrowband UV-B can also lead to full clearance of psoriasis. Thrice-weekly NB UV-B treatment is as effective as twice-weekly PUVA, whereas twice-weekly NB UV-B treatment is less likely to lead to clearance.

Despite the extensive history of this treatment, the long-term safety of UV-B remains a matter of speculation. Although it has not yet been established whether UV-B is carcinogenic, future studies may show otherwise.

The addition of acitretin to PUVA or to UV-B can significantly reduce total UV exposure compared with PUVA or UV-B alone. Topical calcitriol and tazarotene can be combined with UV treatment. Both of these agents used in combination with NB UV-B can significantly reduce the UV dose needed to achieve clearance.[16]

The excimer laser emits monochromatic 308-nm radiation, which has effects similar to those of NB UV-B. The main advantage for its use is the restriction of exposure to psoriatic skin. In a multicenter trial of 80 patients, 72% achieved a 75% reduction of their psoriasis in an average of 6.2 treatments.[17] Erythema and transient hyperpigmentation were the only adverse effects.

SPECIAL POPULATIONS AND CIRCUMSTANCES

Pregnancy

Fortunately, many women may require minimal treatment while pregnant because hormonal changes during pregnancy result in symptomatic improvement for more than half these patients. For pregnant patients who require treatment, some effective options are relatively safe. Topical corticosteroids, calcitriol, or anthralin may be used to control mild disease, whereas UV-B is an option in more severe disease. Cyclosporine, bath PUVA, and biologicals may be considered when the benefits outweigh the risks.

Hepatitis B Virus Infection

Patients with hepatitis B virus (HBV) infection should be referred to a hepatologist to be classified as active, inactive, or occult carriers. Methotrexate should not be prescribed to patients with HBV because of the drug's potential hepatotoxicity. Although the organ failure and fatal outcome cannot be definitively linked to the use of methotrexate, it is prudent for patients with HBV infection to avoid this drug.

Isolated instances of HBV reactivation have been observed in patients undergoing treatment with TNF antagonists. In addition, a few cases of hepatic complications have been described in HBV-seropositive patients treated with infliximab, with or without methotrexate, for Still disease, ankylosing spondylitis, or RA; however, there was no evidence of HBV reactivation or exacerbation of hepatitis symptoms in any of these cases. 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 antagonists can be safely used in patients with HBV infection.

Patients with psoriasis who are candidates for a TNF antagonist should undergo screening for HBV before initiating treatment. In patients who are seropositive for HBV surface antigen with inactive disease, a course of antiviral therapy is recommended, starting 2 to 4 weeks before the TNF antagonist therapy. All HBV-seropositive patients receiving anti-TNF therapy should undergo close monitoring of liver function and viral load.

Hepatitis C Virus Infection

Available data concerning psoriasis treatment in patients with hepatitis C virus (HCV) infection are lacking, but the limited findings to date suggest that TNF antagonists may be safe in this population. Etanercept may act as an adjuvant to standard antiviral therapies for HCV, although at least 1 case study has identified an exacerbation of HCV symptoms with etanercept therapy for RA.[18] However, a larger study of 24 HCV-seropositive patients receiving etanercept or infliximab for RA showed no significant adverse events or increases in liver enzyme levels or viral load.[19] A similar lack of HCV exacerbation was seen in a study of 2 patients whose psoriasis was treated with alefacept.[20] For HCV-seropositive

patients receiving long-term treatment with biologicals, screening for hepatocellular carcinoma and regular monitoring of serum aminotransferase and HCV RNA levels are recommended.

Cyclosporine may also be a useful treatment option in patients with comorbid psoriasis and HCV infection because in vitro evidence suggests that cyclosporine can suppress replication of HCV. This finding is supported by a case study in which a single patient exhibited a dramatic improvement in psoriasis with cyclosporine treatment but did not experience any exacerbation of HCV symptoms.[21]

Human Immunodeficiency Virus Infection

Psoriasis is not necessarily more common in individuals who are seropositive for human immunodeficiency virus (HIV), but psoriasis in the HIV-seropositive patient is more likely to be more severe than in the HIV-seronegative patient.

Because HIV/AIDS is a disease of immunosuppression, the use of immunosuppressive agents in this population is concerning. Many of these concerns may be exaggerated in the current era when highly active antiretroviral therapy is widely used in HIV-seropositive patients, reducing overall viral loads and improving immune status. However, vigilance is important when prescribing an immunosuppressive agent to an HIV-seropositive individual regardless of the patient's antiviral therapy.

Because HIV selectively attacks $CD4^+$ T cells, cyclosporine, which also suppresses CD4 cells, has generally been avoided in HIV-seropositive patients.

Methotrexate is considered inappropriate for HIV-seropositive patients because of several reports of rapid progression of immunosuppression, some with fatal outcomes. Methotrexate should not be used in this population unless absolutely necessary.

Tumor necrosis factor may be intimately involved in HIV pathogenesis. Tumor necrosis factor 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 expression in cultured cells. Conversely, exogenous TNF enhances HIV replication. Inhibition of TNF in HIV-associated psoriasis is therefore a theoretically appealing strategy that could not only ameliorate the symptoms of psoriasis but also have potential antiviral effects. However, there have been concerns that inhibiting TNF in patients who are already immunocompromised may leave them even more vulnerable to opportunistic infections. Several trials have examined the potential role of TNF inhibition in HIV-associated psoriasis. In 3 randomized trials of infliximab or etanercept in HIV-seropositive patients,[22-24] 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 tuberculosis.[24]

Despite these encouraging safety findings, the role of TNF inhibitors in HIV-associated psoriasis is a matter of debate. Although HIV-associated psoriasis is responsive to alefacept, which acts generally on T cells and appears to be safe in this population, the efficacy of the TNF antagonists in this population has not been established. Ustekinumab has not been studied in patients with HIV-associated psoriasis.

Exposure to UV-B has no significant effect on plasma HIV-1 levels. The addition of psoralens to UV-A leads to viral inactivation in cultured cells. Therapy with UV-B does not generally lead to opportunistic infections or malignant neoplasms, and no evidence suggests that PUVA causes viral activation. Psoralen–UV-A should be used with caution because of the potential for carcinogenesis in this immunocompromised patient population. The most widely used phototherapy in this population is UV-B, which is an effective treatment. The response to UV-B in HIV-seropositive individuals is identical to that of matched seronegative controls, and no deterioration of immune status or other significant adverse events have been observed.

TNF Antagonists and Elective Surgery

Because of a potential increased risk of postsurgical infection, RA experts recommend that TNF antagonists be withheld for at least 1 week before and 1 week after surgery. Several European studies have examined complication rates for patients with RA undergoing elective foot and ankle surgery[25] or other elective surgery. It does not appear that the use or preoperative discontinuation of TNF antagonist therapy influences the rates of surgical complications, including incidence of infections. However, because no such analysis has been published outside the setting of RA, the conservative choice of suspending TNF antagonist treatment should still be considered for patients with psoriasis who are undergoing elective surgery. The optimal period of suspension is not known. When following recommendations for patients with RA, consider discontinuation of the TNF antagonist therapy for a period of 4 half-lives before surgery, including 12 days for etanercept, 39 days for infliximab, and 56 days for adalimumab. Although ustekinumab has not been studied in patients undergoing surgery, discontinuation of therapy before and after surgery should be considered. The half-life of ustekinumab ranges from 15 to 46 days.

Systemic Treatments and Vaccination

Because most of the traditional and biological 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 exception of acitretin, the package inserts for the systemic agents or biologicals note the possibility that psoriasis treatment will affect the outcome of vaccinations. For patients receiving a biological, methotrexate, or cyclosporine, inactivated or subunit-based vaccines are generally safe. However, the efficacy of the vaccination may be compromised when patients are concurrently taking these medications that can suppress the immune system reaction.

Although no data show 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 because of the theoretical risk that a live immunization agent could produce an infection when introduced into an altered immune environment. Some examples of live-attenuated vaccines include measles, mumps, rubella, varicella, yellow fever, nasal-spray flu, rabies, BCG, and typhoid.

Comorbid Cardiovascular Disease

Patients with psoriasis are at elevated risk of cardiovascular disease, coronary artery calcification, and the metabolic syndrome. The metabolic syndrome is associated with an increased risk of myocardial infarction (MI). The association between psoriasis and the metabolic syndrome is stronger in individuals with earlier age at onset or with more severe skin disease. A large-scale epidemiological study in the United Kingdom[26] showed that, compared with the general population, the relative risk of obesity in individuals with psoriasis was 1.3 to 1.8, depending on the severity of the psoriasis. For hypertension and dyslipidemia, relative risks were approximately 1.2 and 1.3, respectively; for diabetes mellitus, the relative risk was as much as 1.9 for those with severe psoriasis.[26]

Given these cardiovascular risk factors, cigarette smoking may be particularly worrisome in the psoriatic population, and the rate of smoking[27] is also elevated in this group. Smoking has been shown to be a risk factor for the onset and exacerbation of psoriasis and palmoplantar pustulosis. Patients who smoke more than 20 cigarettes a day have been reported to be at a greater than 2-fold increased risk of severe psoriasis relative to nonsmokers. Clinicians should advocate smoking cessation programs and any other steps to correct modifiable cardiovascular risk factors.

Psoriasis has been identified as an independent risk factor for MI, especially in patients with an early age at onset and more severe disease. In one large study comparing the incidence of MI in a control population and in patients with different levels of psoriasis severity, psoriasis emerged as an independent risk factor for incidence of MIs.[1] When expressed as a relative risk, this effect was most striking in younger individuals, a finding similar to other cardiovascular risk factors, such as metabolic syndrome. Psoriasis significantly predisposed patients to MI in other age groups as well. This increased MI incidence is directly related to cardiovascular mortality, which occurs at an elevated rate in individuals with severe psoriasis. The increased risk of major cardiovascular events appears to be most clinically significant in patients with more severe disease, with only very modest elevations in risk associated with mild disease.

CONCLUSIONS

Advances in psoriasis research continue to yield new approaches that promise ever more control of plaque psoriasis. The developments may well revolutionize care in coming years. However, they are unlikely to change the fundamental need for active engagement with the patient to ensure that the selected treatment is used appropriately. 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 work only if the patient uses them.

Accepted for Publication: September 12, 2011.
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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design*: Hsu, Papp, Lebwohl, and Feldman. *Acquisition of data*: Hsu, Papp, Lebwohl, Crowley, Kalb, Michelon, and Stein Gold. *Analysis and interpretation of the data*: Hsu, Papp, Lebwohl, Bagel, Blauvelt, Callis Duffin, Crowley, Eichenfield, Feldman, Fiorentino, Gelfand, Gottlieb, Jacobsen, Kalb, Kavanaugh, Korman, Michelon, Morison, Ritchlin, Stone, Strober, Van Voorhees, Weiss, Wanat, and Bebo. *Drafting of the manuscript*: Hsu, Papp, Lebwohl, Blauvelt, Crowley, Feldman, Gottlieb, Michelon, Stein Gold, and Weiss. *Critical revision of the manuscript for important intellectual content*: Hsu, Papp, Lebwohl, Bagel, Blauvelt, Callis Duffin, Crowley, Eichenfield, Feldman, Fiorentino, Gelfand, Gottlieb, Jacobsen, Kalb, Kavanaugh, Korman, Krueger, Michelon, Morison, Ritchlin, Stein Gold, Stone, Strober, Van Voorhees, Weiss, Wanat, and Bebo. *Statistical analysis*: Papp. *Obtained funding*: Papp and Lebwohl. *Administrative, technical, or material support*: Papp, Lebwohl, Gottlieb, Jacobsen, Kalb, Morison, and Bebo. *Study supervision*: Hsu, Papp, Lebwohl, and Strober.
Financial Disclosure: Dr Bagel has consulted (includes advisory boards, editorial advice, podium presentations, and travel grants) for Abbott Laboratories, Amgen, Centocor Ortho Biotech Inc, Galderma, Leo Pharma, and Neostrata and performed contract research for Abbott Laboratories, Amgen, Astellas, Celegene, and Centocor Ortho Biotech Inc. Dr Blauvelt has consulted for Abbott Laboratories, Amgen, Anacor, Centocor Ortho Biotech Inc, Lilly, Novartis, Macrogenics, and Takeda; performed clinical studies for Abbott Laboratories, Celgene, Centocor Ortho Biotech Inc, Lilly, Novartis, Novo Nordisk, and Pfizer; and performed contract research for Abbott Laboratories, Centocor Ortho Biotech Inc, and Genentech. Dr Callis Duffin has consulted for Amgen and performed investigator-initiated studies for Abbott Laboratories, Amgen, and Centocor Ortho Biotech Inc. Dr Crowley has consulted for 3M, Abbott Laboratories, Amgen, and Centocor Ortho Biotech Inc and performed contract research for Abbott Laboratories, Amgen, Centocor Ortho Biotech Inc, and Lilly. Dr Eichenfield has consulted for Galderma, Leo Pharma, and Stiefel and performed contract research for Amgen, Galderma, and Leo Pharma. Dr Feldman has consulted for Abbott Laboratories, Amgen, Astellas, Bristol-Meyers Squibb, Caremark, Centocor Ortho Biotech Inc, Coria, Galderma, Leo Pharma, Pharmaderm, Photomedex, Novartis, Merck, Stiefel, Suncare Research, and Warner Chilcott and performed contract research for Abbott Laboratories, Amgen, Astellas, Aventis Pharmaceuticals, Bristol-Myers Squibb, Centocor Ortho Biotech Inc, Coria, Galderma,

Leo Pharma, Novartis, Ortho Pharmaceuticals, Pharmaderm, Photomedix, Roche, Stiefel, and Warner Chilcott. Dr Fiorentino has consulted for Centocor Ortho Biotech Inc, Pfizer, Seattle Genetics, Biogen, and Rigel; performed contract research for Amgen, Basilea, Celegene, Centocor Ortho Biotech Inc, Medimmune, and Mediquest; and performed investigator-initiated studies for Celegene. Dr Gelfand has consulted for Abbott Laboratories, Amgen, Celgene, and Centocor Ortho Biotech Inc and performed investigator-initiated studies for Abbott Laboratories, Amgen, Pfizer, and Novartis. Dr Gottlieb has consulted for Abbott Laboratories, Actelion, Alnylam, Amgen, Beiersdorf Inc, Bristol-Myers Squibb, Celgene, Centocor Ortho Biotech Inc, Cytokine Pharmasciences Inc, DermiPsor, Dermipsor Ltd, Immune Control, Incyte, Magen Biosciences, Novo Nordisk, Ono, PureTech, Pfizer, Schering, Teva, UCB, and Wyeth Pharmaceuticals and performed contract research for Abbott Laboratories, Amgen, Celgene, Centocor Ortho Biotech Inc, Immune Control, Incyte, Novo Nordisk, Pfizer, and Wyeth. Dr Hsu has consulted for Abbott Laboratories, Amgen, Biogen Idec, Centocor Ortho Biotech Inc, and Genentech and performed contract research for Centocor Ortho Biotech Inc. Dr Kalb has consulted for Abbott Laboratories, Amgen, Centocor Ortho Biotech Inc, Leo Pharma, and GlaxoSmithKline. Dr Kavanaugh has performed contract research for Abbott Laboratories, Amgen, BMS, Celgene, Centocor Ortho Biotech Inc, Genentech, UCB, and Roche. Dr Korman has consulted for Abbott Laboratories, Centocor Ortho Biotech Inc, and Eli Lilly; performed investigator-initiated studies for Celgene; and performed contract research for Abbott Laboratories, Amgen, Astellas, Centocor Ortho Biotech Inc, ESAL, and TenX BioPharma. Dr Krueger has consulted for Abbott Laboratories, Almirall, Amgen, Anacor, Astellas, Barrier Therapeutics, Boehringer Ingleheim, Bristol-Myers Squibb, Centocor Ortho Biotech Inc, CombinatoRX, Exelixis, Genzyme, Isis, Lilly, L'Oreal, Lupin Limited, Magen Biosciences, MedaCorp, Medicis, Novartis, NovaNordisk, Pfizer, Schering Plough, Somagenics, Synvista, theDerm.org, UCB, Warner Chilcott, and ZARs. Dr Lebwohl has consulted for Abbott Laboratories, Amgen/Pfizer, Astellas, Biosynexus, Celgene, Centocor/Janssen, DermaGenoma, DermiPsor, Galderma, GlaxoSmithKline-StiefelNovartis, Leo Pharma, and Pharmaderm. Dr Morison has consulted for Photomedix Inc. Dr Papp has consulted for 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, Merck Serono SA, and Schering-Plough Canada Inc; performed investigator-initiated studies for Merck Serono SA; performed contract research for Abbott Laboratories, Amgen Canada Inc, Centocor Ortho Biotech Inc, EMD Serono Canada Inc, Galderma Canada Inc, Isotechnika Inc, Leo Pharma, Merck Serono SA, and Schering-Plough Canada Inc; and owns company stocks in Isotechnika Inc. Dr Ritchlin has consulted for Abbott Laboratories, Amgen, Centocor Ortho Biotech Inc, Genentech, and Wyeth. Dr Stein Gold has consulted for Galderma, Leo Pharma, Merz, Stiefel, and Warner Chilcott and performed contract research for Abbott Laboratories, Galderma, Novartis, and Stiefel. Dr Stone has consulted with Celgene and Stiefel; performed contract research for Abbott Laboratories, Centocor Ortho Biotech Inc, and Pfizer; and served as a speaker for Abbott Laboratories, Amgen/Pfizer, and Centocor Ortho Biotech Inc. Dr Strober has consulted for Abbott Laboratories, Amgen, Centocor Ortho Biotech Inc, Celegene, Galderma, Leo Pharma, Maruho, Novartis, Ono, and Pfizer; performed contract research for Abbott Laboratories, Amgen, Celgene, Centocor Ortho Biotech Inc, Pfizer, Sirtris, and Vascular Biogenics; and performed investigator-initiated studies for Celgene. Dr Van Voorhees has consulted for Abbott Laboratories, Amgen, Centocor Ortho Biotech Inc, Connetics, Genentech, Incyte, Leo Pharma, Synta, Warner Chilcott, and VGX and performed contract research for Amgen. Dr Weiss has consulted for Abbott Laboratories and Stiefel Laboratories; performed contract research for Abbott Laboratories and Stiefel Laboratories; and served as a speaker for Abbott Laboratories, Stiefel Laboratories, and Warner Chilcott.

Funding/Support: The Canadian Guidelines were supported by Abbott Laboratories, Amgen Canada Inc, Astellas Pharma Canada Inc, Isotechnika Inc, Janssen-Ortho Inc, Leo Pharma, Schering-Plough Canada Inc, and Wyeth. The updated North American Guidelines were supported by the National Psoriasis Foundation.

Role of the Sponsors: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript. Sponsors were not involved in any aspects of the guidelines development or informed of the makeup of the guidelines committee.

Online-Only Material: The eAppendix of the North American Guidelines is available at http://www.archdermatol.com.

Additional Contributions: Helen Leask, PhD, John Ashkenas, PhD, Shareen Joseph, BSc, Meenkashi Kashyap, PhD, Oreon Traub, MD, PhD, and Sarah von Riedemann, MSc, contributed to the production of the original Canadian Guidelines.

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