Psoriasis: An update on effective therapies

New topical agents and biologics expand the armamentarium

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Over the past decade, new treatment options have surfaced in the management of psoriasis. These include topical treatments for mild to moderate cases and biologic therapy for moderate to severe cases. To ensure therapeutic success, proper patient education about the disease, the treatment options and adverse effects is essential. This will help alleviate the common problem of poor patient adherence, and inevitably result in better clinical outcomes.

New topical treatments

Topical agents form the cornerstone of initial management of psoriasis. They play a significant role as monotherapy in mild to moderate psoriasis, and are used predominantly as adjunctive therapy in moderate to severe forms of the disease. Over the past decade, topical treatment of psoriasis has evolved from the age-old applications, such as coal tar, to the more cosmetically acceptable and efficacious options of topical corticosteroids, vitamin D analogues and combination products. In addition to newer treatment options, in recent years a wider range of appropriately tailored vehicles and sophisticated delivery modes has also been developed.

Calcipotriol plus betamethasone dipropionate gel (Xamiol)

Xamiol is a lipophilic gel specially formulated for the scalp and contains the active ingredients calcipotriol 0.005% and betamethasone dipropionate 0.05%. Calcipotriol binds to the intracellular vitamin D receptor, which forms a heterodimer unit. These units migrate to the nucleus, where they bind the vitamin D response element, which directly regulates genes involved in epidermal proliferation, inflammation and keratinization.

Betamethasone dipropionate is a potent topical steroid that binds to glucocorticoid receptors in the cytoplasm, which rapidly translocate to the nucleus where they inhibit or stimulate genes that regulate inflammation. As a result, the production of cytokines (such as interleukin-1 and -8, tumour necrosis factor alpha and gamma interferon) is inhibited, and levels of nitric oxide, prostaglandins and leukotrienes are reduced. Both vitamin D and corticosteroids can increase the number of T regulatory cells that are diminished in psoriatic skin.

One study published in the *British Journal of Dermatology* in 2009 compared calcipotriol-betamethasone (207 patients) with calcipotriol alone (105). Dr. Knud Kragballe of the Marselisborg Center in Aarhus, Denmark, and colleagues found the proportion of patients with "clear" or "minimal" disease at week eight was significantly greater in the calcipotriol-betamethasone group (68.6%) than in the calcipotriol group (31.4%). Additionally, the rate of improvement was more rapid and adverse events were fewer with calcipotriol-betamethasone.

Another phase III study involving 2,920 patients investigated the clinical efficacy of calcipotriol-betamethasone after only one week of treatment. The study authors, led by Dr. Gregor Jemec, a dermatologist at the University of Copenhagen in Denmark, reported their results in the *Journal of the European Academy of Dermatology and Venereology* in January 2011. The percentage of patients who had "absent" or "very mild" disease was

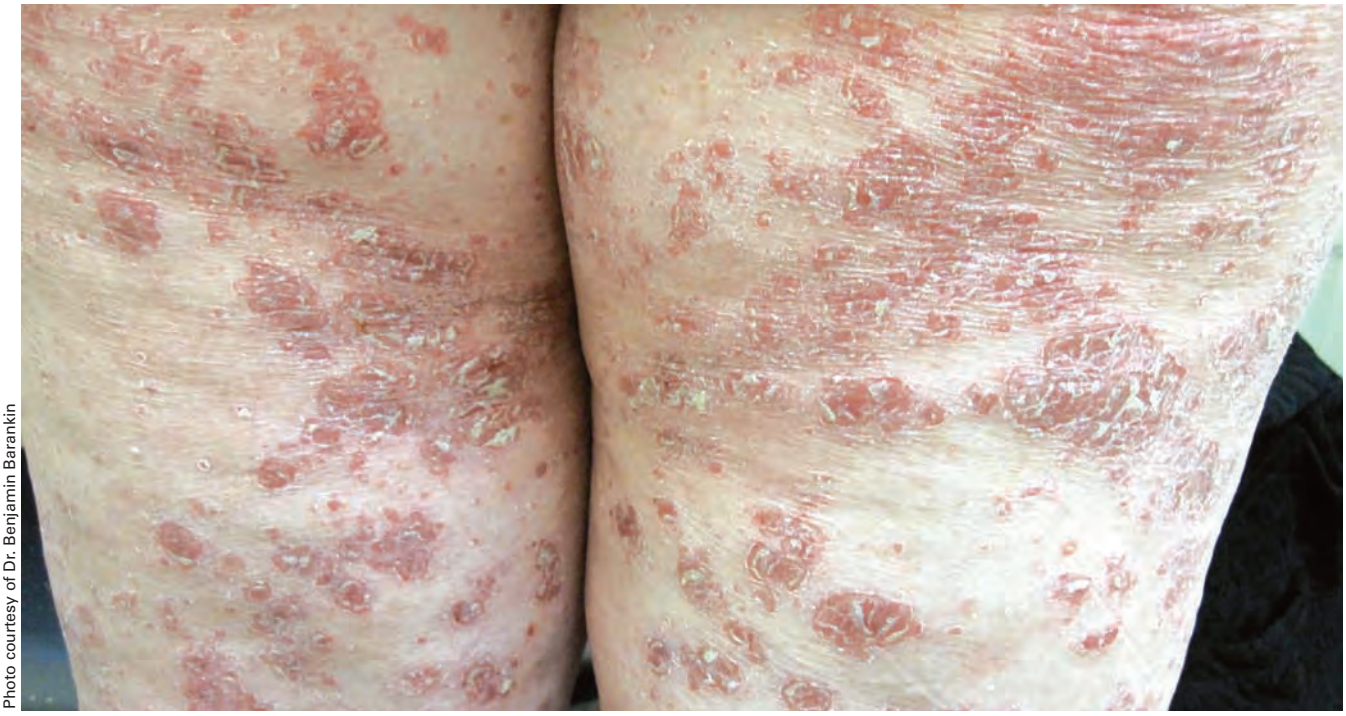


Photo courtesy of Dr. Benjamin Barankin

Newer formulations of clobetasol propionate (CP) have been found to be roughly equal in efficacy to conventional ointments and cream formulations in clinical trials. The CP spray may be particularly useful in the treatment of large areas of affected skin (up to 15% to 20% of body surface area), expanding the range of topical therapy treatment in psoriasis patients.

significantly higher with the two-compound scalp formulation (30.6%) compared with betamethasone alone (24.1%), calcipotriol alone (10.0%) or vehicle (6.9%). Calcipotriol-betamethasone worked more quickly in treating scalp psoriasis than either of the individual components.

Calcitriol 3 mcg/g ointment (Silkis)

Topical vitamin D modulators are among the most widely used medications for the treatment of psoriasis. Calcitriol 3 mcg/g ointment is a synthetic topical vitamin D analogue considered to be as effective as other vitamin D analogues, but calcitriol has the advantage of increased tolerability in sensitive areas such as the face, hairline and postauricular and flexural areas. The use of a tolerable vitamin D3 analogue in sensitive areas may minimize corticosteroid use in these areas and allow for better individualization of a psoriasis regimen.

Calcitriol ointment has been extensively evaluated for the treatment of chronic plaque-type psoriasis and has been shown to be effective, safe and well-tolerated in a number of short-term and long-term clinical trials. Pharmacokinetic studies in patients with psoriasis and healthy control subjects have demonstrated that topical calcitriol ointment produces little systemic absorption of calcitriol and does not result in systemic hypercalcemia even when applied to approximately one-third of the body surface area.

In two randomized, double-blind clinical trials led by Dr. Mark Lebwohl of the Mount Sinai School of Medicine in New York, patients were randomized to calcitriol ointment (419 patients) or its vehicle (420) twice daily for up to eight weeks. Treatment with calcitriol ointment for eight weeks resulted in clearing or minimal residual psoriasis in 34.4% and 33.3% of patients in studies one and two, respectively, compared with 22.5% and 12.3% of patients treated with vehicle ointment in the two studies. The calcitriol ointment was shown to have a local safety profile comparable to its vehicle. Treatment-related side-effects were relatively minor and included erythema, pruritus and general skin discomfort.

Clobetasol propionate 0.05% spray and shampoo (Clobex)

Ultrapotent topical corticosteroids are the most widely used psoriasis treatments, and new formulations provide efficacious, safe and tolerable options that may increase patient satisfaction and adherence to therapy. Although skin moisturizing is often described as an important benefit of ointments, the available evidence suggests that reduction of inflammation achieved with the anti-inflammatory agent is the key factor driving improvement in outcomes, such that the newer clobetasol propionate (CP) formulations are roughly equal in efficacy to conventional ointments and cream formulations in clinical trial settings.

All of the newer topical CP formulations produce clearing or near-clearing of psoriasis for a large proportion of patients within two to four weeks, with response, safety and tolerability rates that are at least comparable to those observed with older topical CP ointments and creams.

A study by Dr. Serena Mraz, a clinician at Dow Pharmaceutical Sciences in Petaluma, Calif., and colleagues noted CP spray is the only CP 0.05% formulation currently approved for treatment up to four weeks for those moderate-to-severe plaque psoriasis patients whose benefit/risk ratio supports the additional two weeks of treatment. In their study, published in the *Journal of Dermatological Treatment* in 2008, 77 patients were randomized to receive either CP foam (two weeks) or CP spray (four weeks). The findings indicated the additional two weeks of treatment with CP spray increased clinical efficacy (clearing of lesions) significantly without adversely affecting the drug's safety profile. As such, the CP spray may have an important role in the treatment of large areas of affected skin (up to 15% to 20% body surface area), widening the range of topical therapy treatment in psoriasis patients. Patients using the spray also reported vast improvements in quality of life scores when compared with those using other formulations.

CP 0.05% shampoo is also effective and safe for the management of all severities of scalp psoriasis. CP shampoo effectively prevents relapse of scalp psoriasis and the short-contact (15 minutes) shampoo formulation of CP can be used for extended periods without leading to notable side-effects. This treatment also leads to high patient satisfaction, which may increase adherence and result in even greater overall treatment efficacy.

Steroid foams have been shown to be more effective vehicles of treatment that are absorbed more rapidly than lotions and creams. These advantages may lead to improved compliance and efficacy of treatment.

Steroid foams

Despite the availability of numerous topical agents for the treatment of relatively localized psoriasis, patients are frequently not satisfied with their prescribed treatment due to a lack of efficacy and difficulty of use. Psoriatic patients' compliance is reported to be low (approximately 60%) and is associated with complaints that treatments interfere with their life. Steroid foam preparations are newer formulations that provide commonly prescribed topical steroids in a low-residue vehicle.

Foam formulations of corticosteroids offer cosmetic advantages over traditional topical vehicles (ointments and creams), including quality-of-life variables such as quick-drying, ease of application and lack of fragrance. In other findings, patients using foam spent less time applying medication compared with other topical medications, and no significant difference in cost was found between foam and cream/lotion after controlling for body surface area.

In preliminary studies, steroid foams have also been shown to be more effective vehicles of treatment that are absorbed more rapidly and demonstrate greater total absorption than lotions and creams. These advantages may lead to improved compliance and efficacy of treatment. The most frequently reported adverse events with steroid foam preparations are application-site reactions such as burning, stinging or itching. However, ethanol-free versions of steroid foams are also being formulated to minimize the side-effects.

As of this writing, there are no steroid foams available in Canada, although several are planned for this market in 2011.

Biological therapy

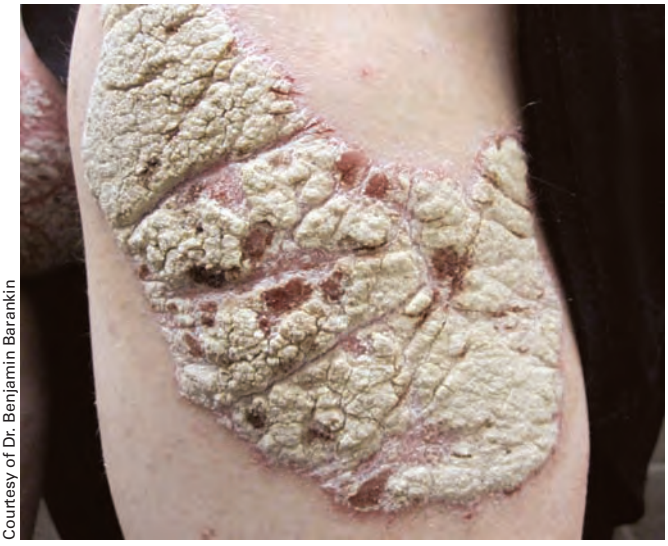
For the management of moderate to severe psoriasis, biological therapy has recently become more popular to control severe psoriatic lesions and has been found to greatly improve patients' quality of life. Biological agents are proteins produced from animal tissue or via recombinant DNA technology. These drugs are particularly useful in patients for whom phototherapy or other systemic medications have failed or are unsuitable. Current biologics on the market for psoriasis include the tumour necrosis factor-alpha blockers etanercept (Enbrel), infliximab (Remicade) and adalimumab (Humira). One of the newest biologics is ustekinumab (Stelara), a human monoclonal antibody directed against interleukin (IL)-12 and IL-23.

Ustekinumab (Stelara)

The cytokines IL-12 and IL-23 play key roles in the up-regulation of the immune response seen in psoriasis, including the activation of IL-17-producing T cells, which are pro-inflammatory and cause epidermal proliferation. Ustekinumab is a fully human monoclonal antibody that binds with high specificity and affinity to IL-12 and IL-23, thereby suppressing IL-12- and IL-23-mediated inflammation associated with psoriasis. Ustekinumab has been approved in Canada since December 2008.

In two large, phase III trials in patients with moderate to severe plaque psoriasis (PHOENIX 1 and PHOENIX 2), significantly more ustekinumab recipients than placebo recipients achieved a 75% improvement on the Psoriasis Area and Severity Index (PASI 75) at 12 weeks. Both were published in the *Lancet* in 2008.

PHOENIX 1 was led by Dr. Craig Leonardi, an associate clinical professor of dermatology at St. Louis University Medical School in Missouri. It had a parallel, double-blind, placebo-



Courtesy of Dr. Benjamin Barankin

Skin discomfort from thick plaques can involve itching, burning, cracking and bleeding. In severe cases, patients may find it difficult to sleep and focus on daily activities.

controlled design that included 766 patients with moderate to severe psoriasis. Participants were randomly assigned to receive ustekinumab 45 mg or 90 mg subcutaneously at weeks zero and four and then every 12 weeks, or placebo at weeks zero and four, with subsequent crossover to the study drug at week 12. By week 12, 67% of the patients receiving ustekinumab 45 mg achieved PASI 75, 66% of those receiving 90 mg and 3% of those receiving placebo. At week 40, long-term response was achieved by 150 patients in the 45 mg group and 172 patients in the 90 mg group. Furthermore, PASI 75 response was better maintained to at least one year in those who underwent maintenance therapy (treatment every 12 weeks) than in those who withdrew at week 40.

PHOENIX 2, led by Dr. Kim Papp, an assistant clinical professor of medicine at the University of Western Ontario in London, involved 1,230 patients with moderate to severe psoriasis. Subjects were randomly assigned to receive ustekinumab 45 mg or 90 mg subcutaneously at weeks zero and four and then subsequently every 12 weeks, or placebo. A total of 67% of patients receiving ustekinumab 45 mg, 76% of patients receiving ustekinumab 90 mg and 4% of the placebo group achieved PASI 75 at week 12. Furthermore, among partial responders at week 28, those who received ustekinumab 90 mg in an advanced schedule every eight weeks achieved PASI 75 more often than those who continued to be treated every 12 weeks. The study authors concluded that, although treatment with ustekinumab every 12 weeks is effective for most patients with moderate to severe psoriasis, increasing the dosage to once every eight weeks might help those who had partial responses to the initial regimen.

Ustekinumab has successfully established its superiority over placebo and over currently available psoriasis therapies. Not only have more patients achieved PASI 75 scores with it than with other biologics, but its rapid onset of action and better dosing profile also make this agent a potentially valuable alternative for psoriasis patients. Those with refractory psoriasis who have failed to respond to other systemic and/or biologic agents could potentially benefit most from ustekinumab. As additional clinical data become available, the target population for this drug will be more clearly defined. Because of its convenient dosing schedule as an infrequent monotherapeutic agent, it may translate into lower costs and better compliance.

To date, adverse events related to ustekinumab have been relatively minor. Overall rates of serious infections, malignancies, cardiovascular events and injection site reactions are reported as low. However, further investigations evaluating long-term efficacy and safety data are needed before ustekinumab can be considered the therapy of choice in the biologics market. Also, future ustekinumab studies should provide a detailed assessment on the clinical effects on psoriatic arthritis.

Conclusion

The outlook for effectively managing milder cases of psoriasis with newer topical therapies and more severe cases with innovative biologic agents looks positive. To ensure therapeutic success, proper patient education about the disease, available treatment options, assorted vehicle options and adverse effects is essential. Focusing on these areas will help to better address the primary reasons for poor patient adherence, and inevitably result in more optimal clinical outcomes.

Disclosures

The authors have no conflicts of interest to disclose in relation to this article.

For further reading

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