Emerging therapies in psoriasis

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There is no cure for psoriasis, but recent research has led to improved understanding of the disease. Several new biological therapies target specific steps in the pathogenesis of psoriasis, and enhancements in topical therapy and phototherapy have improved the armamentarium of effective suppressive treatments.

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Psoriasis is a chronic inflammatory, immune-mediated disease that predominantly presents with skin and joint manifestations. It is common, affecting 2% to 3% of the worldwide population.[1] Once psoriasis has appeared as a localised disease, it persists throughout life, manifesting at unpredictable intervals. It is not contagious.

There are several different phenotypes of psoriasis. The most common is plaque psoriasis, which is estimated to affect between 80% and 90% of people with psoriasis. Plaque psoriasis is characterised by thickened, well-demarcated erythematous skin lesions covered with silvery scales. The nails and, less often, the mucous membranes, may also be affected. Pathogenically, excessive growth and aberrant differentiation of keratinocytes is driven by T-cell infiltration and associated elevated cytokine levels. Although not considered life-threatening, plaque psoriasis is a medically significant disease that can have a profound impact on a patient's quality of life.

Recent research has led to improved understanding of psoriasis. Several new biological therapies have been developed that target specific steps in the pathogenesis of the disease. Enhancements in topical therapy and phototherapy have also improved the armamentarium of treatments for this disorder.

This article reviews both older and newer treatment options that are available for treating psoriasis (all forms) of different severity (see the box on page 71). The role of newer therapies is highlighted in two cases (see the boxes on pages 71 and 72).

TOPICAL THERAPIES

Corticosteroids

Corticosteroids are the most commonly prescribed topical agents for psoriasis. They have a rapid onset of action but psoriasis often recurs rapidly when treatment is ceased. Corticosteroids may exhibit tachyphylaxis (decreased response over time), which has resulted in some dermatologists recommending intermittent use.

Topical corticosteroids are available in a variety of potencies and delivery vehicles. The choice of formulation is based on disease severity, the site of the lesions and patient preference. Use of corticosteroids is limited by their side effects and short-term effectiveness.

Vitamin D_3 analogues

Topical vitamin D_3 analogues are used in the treatment of mild to moderate psoriasis. They act by binding nuclear vitamin D_3 receptors on genes involved in cellular proliferation, differentiation and inflammation. These agents have fewer side effects than corticosteroids and can be used long term.

The only vitamin D_3 analogue available in Australia is calcipotriol, which can be used as monotherapy or in combination

THERAPIES FOR PSORIASIS

Older therapies

Topical therapies: corticosteroids, coal tar, dithranol

Phototherapy: conventional PUVA and NB-UVB

Systemic therapies: methotrexate, cyclosporin, acitretin

Newer therapies

Topical therapies: calcipotriol (vitamin D_3 analogue, with or without betamethasone dipropionate), tazarotene (retinoid)

Phototherapy: excimer laser

Systemic therapies: biological therapies (adalimumab, etanercept, infliximab, ustekinumab)

ABBREVIATIONS: NB-UVB = narrow band ultraviolet B; PUVA = psoralens plus ultraviolet A.

with topical corticosteroids. A topical formulation containing both calcipotriol and betamethasone dipropionate has recently become available; this combination appears to be more effective and to have fewer side effects than calcipotriol alone.[2,3]

Retinoids

Tazarotene is a retinoic acid receptor-specific retinoid. It has demonstrated efficacy in the topical treatment of psoriasis.

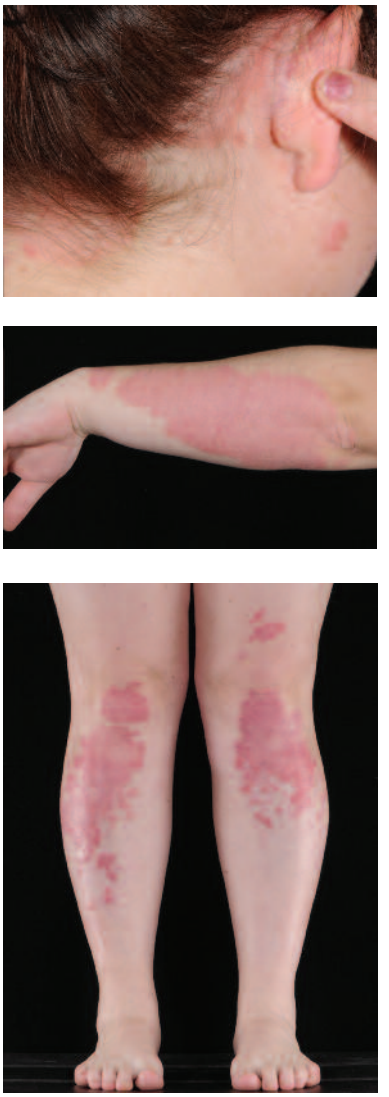
Tazarotene down-regulates keratinocyte differentiation, proliferation and inflammation. It also up-regulates the expression of three genes that appear to be specific for tazarotene *(RARRES1, RARRES2* and *RARRES3)*, which results in increased transcription of proteins involved in cellular differentiation and proliferation and may mediate an anti-proliferative effect.[4]

Coal tar

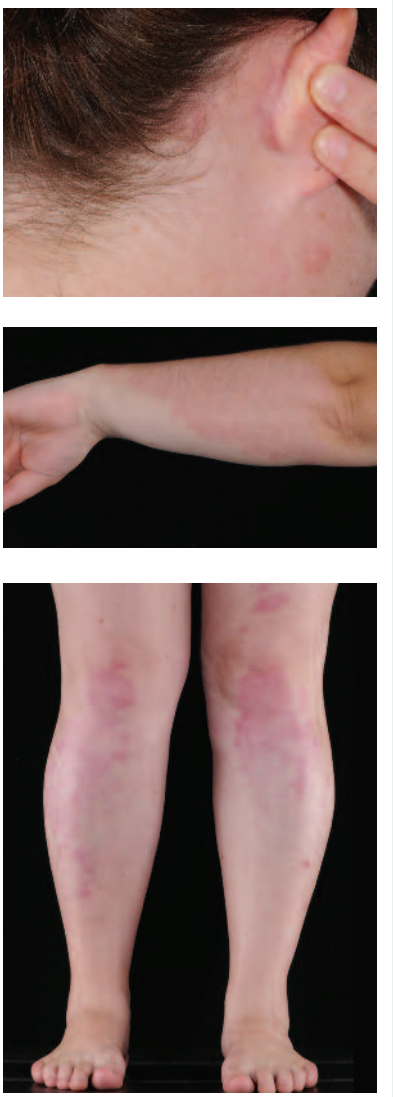
Coal tar, one of the few remaining old-fashioned therapies for psoriasis, is still

CASE 1: SKIN-DIRECTED THERAPIES FOR LOCALISED PSORIASIS

A 55-year-old woman presented with an 18-month history of classic psoriatic lesions on her scalp, extensor elbows and knees (Figures 1a to c). She was diagnosed with mild to moderate chronic plaque psoriasis, which was managed satisfactorily with topical agents – combination calcipotriol and betamethasone dipropionate, applied once daily (Figures 2a to c).



Figures 1a to c. The patient's localised psoriasis on the scalp, elbow and knees at presentation.

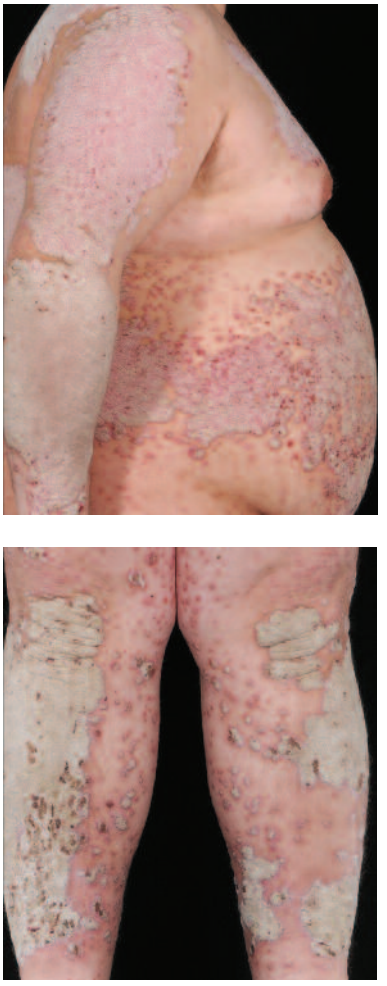


Figures 2a to c. The patient's psoriasis about eight weeks after commencing treatment with once daily combination calcipotriol and betamethasone dipropionate.

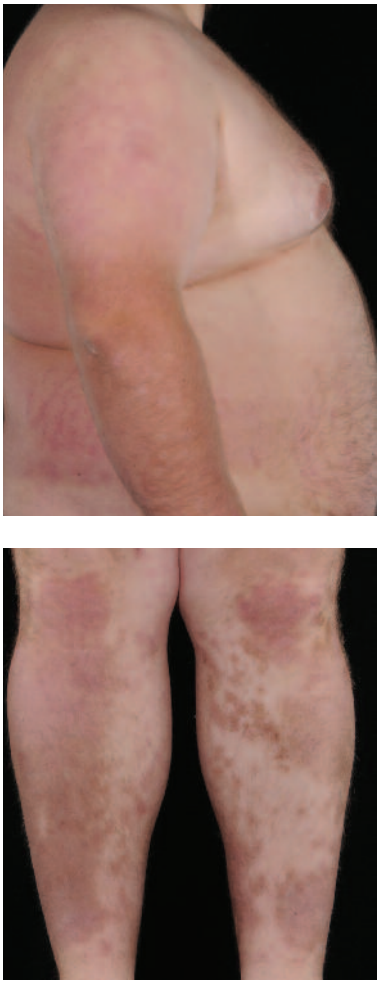
CASE 2: SYSTEMIC BIOLOGICAL THERAPY FOR WIDESPREAD PSORIASIS

A 36-year-old man presented with moderate to severe chronic plaque psoriasis that had failed to respond to traditional 'standard' systemic therapies, including phototherapy (Figures 3a and b). He was treated with a systemic biological agent (infliximab).

The patient's response to treatment with the biological agent was assessed using the Psoriasis Area and Severity Index (PASI) – see the box on page 74. A good response was observed, with PASI score reduction from 36.3 to 2.7 (93%), which comfortably surpasses the benchmark of 75% for assessing improvement (PASI 75). Figures 4a and b show the patient 10 weeks after commencing treatment with infliximab. His quality of life improved dramatically as a result of the successful treatment.



Figures 3a and b. The patient's widespread psoriasis at presentation.



Figures 4a and b. The patient's psoriasis 10 weeks after commencing treatment with infliximab.

effective. However, the smell of coal tar, its staining properties and its potential for irritation may impair patient acceptance of this therapy. Tar shampoos are frequently used to treat scalp psoriasis.

Dithranol

Dithranol, an anthracene derivative, is used topically to treat psoriasis. It has a slower onset of action than corticosteroids but does not cause rebound upon withdrawal. Dithranol induces apoptosis of keratinocytes in psoriasis through disruption of mitochondrial function and structure.

Dithranol may be used alone, in combination with salicylic acid or in addition to tar. Side effects include skin irritation and staining of the skin and hair.

PHOTOTHERAPY

Conventional phototherapy

Conventional phototherapy is a mainstay in the treatment of psoriasis. It is available in two modalities: psoralens plus ultraviolet A (PUVA) and narrow band ultraviolet B (NB-UVB). Both modalities cause depletion of dermal and epidermal inflammatory cells, including lymphocytes, macrophages and dendritic cells. They may also have a role in decreasing keratinocyte hyperproliferation.

Systemic PUVA phototherapy is associated with an increased risk of squamous cell carcinoma and possibly Merkel cell carcinoma and melanoma; for this reason, NB-UVB has largely replaced PUVA. NB-UVB is most effective when undertaken three times per week for six to eight weeks. Phototherapy requires strict compliance and long-term toxicity associated with it includes photocarcinogenesis.

Excimer laser

The excimer laser offers effective and safe treatment for small but stubborn areas of psoriasis. This type of laser produces ultraviolet radiation at a specific wavelength (308 nm), which is almost

PSORIASIS AREA AND SEVERITY INDEX

The Psoriasis Area and Severity Index (PASI) is a scale for quantifying the global severity of a patient's psoriasis based on area coverage and severity (plaque appearance).[9] The severity is calculated by measuring three clinical signs – erythema (redness), induration (thickness) and desquamation (scaling) – with each sign being assigned a number from 0 to 4 (4 being worst). Then the extent of involvement of four regions of the body is determined and assigned a number (0 to 6). Compiling these numbers gives a PASI score in the range of 0 to 72.

An improvement in PASI score of at least 75% compared to baseline (PASI 75) is considered the gold standard measure of treatment efficacy.

PASI calculators are available online (see www.pasi.corti.li or www.pasitraining.com/calculator/step_1.php).

identical to the wavelength of NB-UVB phototherapy (312 nm). Excimer laser treatment requires fewer patient visits than conventional phototherapy and targets the affected areas of the skin while sparing the surrounding uninvolved skin.

NON-BIOLOGICAL SYSTEMIC THERAPIES

Non-biological systemic therapies for psoriasis may be effective but they can be associated with significant short- and long-term toxicities. Most patients with moderate to severe disease achieve satisfactory disease control (i.e. significant or complete clearing of disease) in the short term with at least one of the non-biological systemic agents currently available.

Methotrexate

Methotrexate is the most commonly used systemic agent for psoriasis. It is a folic acid antagonist with immunosuppressive and cytostatic effects. Close patient monitoring is necessary during treatment because methotrexate can cause hepatotoxicity and myelosuppression.

Cyclosporin

Cyclosporin works by inhibiting T-cell transcription of interleukin-2. The long term use of cyclosporin is limited by concerns about nephrotoxicity, hypertension and cutaneous malignancies, particularly SCC. Cyclosporin is ideally suited for crisis intervention, but it should be replaced by other treatment modalities for long-term disease management. It is currently recommended that cyclosporin not be used for more than two years in dermatology patients.[5,6]

Acitretin

Acitretin is an oral retinoid that is effective in treating psoriasis and often used in combination with phototherapy. Acitretin works by inhibiting excessive cell growth and keratinisation. The efficacy and side effects of acitretin appear to be dose-related. Mucocutaneous side effects such as cheilitis and hair loss are the most common dose-dependent side effects. Acitretin is a potent teratogen, so there are strict requirements for pregnancy prevention during and after its use.

BIOLOGICAL THERAPIES

The biological therapies for psoriasis use genetically engineered drugs that target specific steps in the pathogenesis of the disease that involve T cells and cytokines (e.g. TNF-alpha and interleukin-23). Currently, three biological TNF-alpha inhibitors (adalimumab, etanercept and infliximab) and one anti-interleukin-12/23 agent (ustekinumab) are approved by the TGA and listed on the PBS for chronic plaque psoriasis.

When treatment with a biological therapy is commenced, there is a risk of tuberculosis emerging from reactivation of latent *Mycobacterium tuberculosis* infection. Therefore, pre-treatment screening for tuberculosis is mandatory, with chest radiography and Quantiferon-TB Gold testing. Regular monitoring of liver function and full blood is recommended.[7,8] Patients taking biological therapies should be monitored for early signs and symptoms of infection through-out treatment.

The use of PASI scores to assess the treatment efficacy of the biological therapies is explained in the box on this page.[9]

Adalimumab

Adalimumab is a fully human monoclonal antibody that binds to TNF-alpha, preventing it from activating TNF receptors. It is administered subcutaneously at weeks zero and one, and fortnightly thereafter. About 70% patients of patients treated with adalimumab achieve PASI 75 at week 16. Interrupted therapy may result in loss of treatment response. Anti-adalimumab antibodies develop in 8.4% of patients and are associated with increased clearance and reduced efficacy of adalimumab.[10]

Etanercept

Etanercept was the first TNF antagonist approved for use in psoriasis in Australia.

It is a genetically engineered fusion protein composed of a dimer of the extracellular portions of human TNF receptor 2 fused to the Fc domain of human IgG1. Etanercept binds both soluble and transmembrane forms of TNF, and also binds lymphotoxin (TNF-beta). About one-third of patients achieve PASI 75 at week 12; this response rate increases to at least 50% of patients at week 24 with continuous dosing.[11]

Etanercept is administered subcutaneously as a weekly fixed dose. There appears to be little loss of efficacy over time.

Infliximab

Infliximab is a chimeric human–murine monoclonal antibody and the only biological agent approved for psoriasis that is administered intravenously. It is infused at weeks zero, two and six and every eight weeks thereafter. About 80% of patients treated with infliximab achieve PASI 75 at week 10.[12] There may be some loss of efficacy over time, presumably due to development of neutralising antibodies against the murine component or to enhanced metabolism. Methotrexate may be administered concurrently to reduce loss of efficacy.

Ustekinumab

Ustekinumab, a human monoclonal antibody that inhibits interleukins 12 and 23, is the newest biological agent to be approved in Australia. Ustekinumab is administered subcutaneously at weeks zero and four, and 12-weekly thereafter. It has a PASI 75 response rate of over 70% that is maintained long-term.[13]

CONCLUSION

Plaque psoriasis is a chronic skin condition and treatment must be individualised according to age, gender, stage in life, disease severity and associated comorbidities. There is no cure for psoriasis, but effective suppressive treatments are available that aim to induce a remission or reduce the psoriasis to an amount that is tolerable to the patient.

Three basic treatment modalities exist for psoriasis – topical agents, phototherapy and systemic agents (including biological therapies); these may be used alone or in combination. MT

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