Treatments for severe psoriasis

***John R Sullivan**, Dermatologist and Clinical Pharmacologist, Southderm Kogarah, Skin and Cancer Foundation Australia, St Vincent's Hospital, and University of New South Wales, and **Veronica A Preda**, Dermatology Research Officer, Skin and Cancer Foundation Australia, St Vincent's Hospital and University of New South Wales, Sydney*

Summary

Methotrexate, cyclosporin, acitretin and narrow-band ultraviolet B phototherapy help most patients with severe psoriasis. However, toxicity tends to limit the dose and duration of therapy, so other treatments are being developed. Biological therapies of proven benefit in severe psoriasis include etanercept, adalimumab and infliximab, which target tumour necrosis factor. Lymphocytes are the target of other therapies including efalizumab and alefacept. Biological therapies have a range of safety concerns which differ from, but overlap with, those of other systemic treatments for psoriasis. In Australia, the Pharmaceutical Benefits Scheme subsidises a therapeutic trial of approved biological therapies in severe psoriasis if traditional therapies are insufficiently effective or are contraindicated by intercurrent disease or adverse effects. Ongoing therapy is only subsidised for patients whose psoriasis significantly improves. Care must be taken when withdrawing efalizumab or cyclosporin in case of rebound disease.

Key words: adalimumab, efalizumab, etanercept, infliximab, ustekinumab.

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Introduction

Psoriasis is a chronic disorder characterised by erythematous plaques, patches and papules which may be pruritic and classically have silver scale. Morphologically there are varying forms, with 80–90% being of the plaque variety. Other less common psoriasis forms include inverse psoriasis (involving the skin folds), erythrodermic (from chronic plaque psoriasis or acute), pustular and guttate (with 'dewdrop' lesions).[1]

The peak onset of psoriasis occurs during the teenage and early adult years which means that most patients will be affected for the majority of their lives. This necessitates careful consideration as to the short-, medium- and long-term risks of psoriasis, its comorbidities and its treatments. The consequences of severe psoriasis are more than just skin deep. It may be associated with conditions such as arthritis, liver disease, cardiovascular disease and the metabolic syndrome. Severe psoriasis involves large areas of the skin's surface. Due to the chronic and very visual nature of this disease, there can be profound psychosocial consequences.[2]

The autoimmune lesions of psoriasis are hyperproliferative, hyperaemic, abnormally thick and shed increased amounts of highly visible scales. Psoriasis plaques are packed with enormous numbers of activated T cells which drive the inflammatory process, cause dysmaturation of epidermal cells and impair skin function. This results, for example, in the increased loss of water through the epidermis and makes psoriatic skin more susceptible to physical and chemical irritation, contributing to itching and irritation. The plaques are also prone to develop painful fissures and cracks.

Psoriasis involving sensitive skin areas such as genitals, groin and face or the glabrous skin of the hands and feet is often symptomatic. Involvement of these areas is particularly likely to adversely impact on activities of daily living, personal interactions, especially those involving skin contact, and the ability to work.

The aims and frustrations of therapy

Patients want a safe, convenient therapy that will rapidly clear their disease and keep it in remission. Surveys of patient support groups have found most patients were not satisfied with the control obtained with standard therapies. Around a third felt that their medical treatment was insufficiently aggressive. To add to their frustration, patients often trial a therapy for several months before their treatment is altered because of an inadequate response. Following a switch, the mean time to treatment failure is another 3–6 months.[3]

Untreated severe psoriasis tends to follow a fluctuating but persistent course. In contrast, the course of disease in mild to moderate psoriasis is generally one of relapse and remission.

Phototherapy and standard systemic drugs in severe psoriasis

Our standard therapies can control psoriasis in the majority of patients with severe psoriasis (Table 1), however potential therapy-related toxicities limit the dose and duration of

Table 1

Treatments for severe psoriasis

	Administration	Dosing	Induction therapy	Maintenance therapy
Standard				
Acitretin	Oral	10–50 mg daily	Low initial dose followed by dose escalation often used	May be daily, alternate days or less, used long-term, often years
Cyclosporin	Oral	2–5 mg/kg daily in two doses	3.5–5 mg/kg daily	2–4 mg/kg daily, 6–24 months
Methotrexate	Oral or intramuscular	5–25 mg weekly	Close clinical and blood monitoring needed	Long-term, often years
Phototherapy	In cabinet	3 times a week	Dosing tailored depending on skin type and response	6–12 week course, intermittent therapy
Biological				
Adalimumab	Subcutaneous	Fortnightly	80 mg followed by 40 mg one week later	40 mg fortnightly
Alefacept	Intravenous	Weekly	7.5 mg for 12 weeks	If the course is repeated there must be a gap of at least 12 weeks between courses
	Intramuscular	Weekly	15 mg for 12 weeks	
Efalizumab	Subcutaneous	1 mg/kg weekly	0.7 mg/kg first dose	Long-term, potentially years
Etanercept	Subcutaneous	Weekly or twice-weekly	50–100 mg weekly for up to 12 weeks*	50 mg weekly either continuously or 12 weeks on/12 weeks off, potentially years
Infliximab	Intravenous	5 mg/kg	Weeks 0, 2, 6, 12	6–8 weekly maintenance, potentially years

* Australian Medicines Handbook and product information give 50 mg twice weekly as an option for initial treatment

therapy. This has led to intermittent, sequential, rotation and combination therapies which aim to maintain reasonable disease control while reducing the risk of treatment-specific cumulative toxicities. Other than acitretin (an oral retinoid) all systemic treatments, including biological therapies, are immunosuppressive and are contraindicated in patients with cancer or infections. Only around a third of patients with chronic plaque psoriasis achieve and maintain good disease control when acitretin is used as monotherapy although its efficacy in pustular and erythrodermic psoriasis is higher.

Narrow-band phototherapy is generally administered three times a week. Moderate psoriasis can usually be cleared with around six weeks of phototherapy and will normally result in around 3–6 months of improved disease control. Onset of significant change usually occurs within 20–25 treatments (at approximately three weeks into therapy). Phototherapy can be combined with topical therapy. Concurrent acitretin can speed up and increase the response to phototherapy. Once adequate clearance has been achieved, phototherapy is normally stopped. Phototherapy can cause erythema, pruritus and nausea. High cumulative doses increase the risk of skin cancer.[4]

Cyclosporin usually works quickly to clear psoriasis (6–12 weeks) and is generally very effective in maintaining disease remission. Depending on the dose required for maintaining control, hypertension, nephrotoxicity, malignancy and metabolic concerns usually limit the total duration of cyclosporin therapy to 12–24 months.

Methotrexate is generally slower at clearing psoriasis than cyclosporin partly because of cautious initial dosing. It often takes three or more months to induce remission, but if tolerated and there is no haematological or hepatic toxicity methotrexate can often be continued for many years to maintain good disease control. The dose is titrated to the lowest dose that balances safety concerns and disease control. Monthly or more frequent monitoring is needed for the first six months when starting or increasing the dose of methotrexate. Second monthly monitoring of full blood count, liver function tests, urea and electrolytes needs to be continued long-term to help avoid preventable toxicities. Taking folate supplements daily (5 mg folic acid) may help prevent a number of potential toxicities such as gastrointestinal adverse effects and bone marrow toxicity and is the standard of care in Australia.[5]

Biological therapies

Biological therapies for severe psoriasis either target T cells or block pro-inflammatory cytokines. Efalizumab is a recombinant humanised monoclonal antibody against cells with the CD11a marker. Binding interferes with T cell activation in lymph nodes and T cell trafficking to skin and interferes with their activation and reactivation in the skin. Alefacept binds to the CD2 receptor

on lymphocytes. It reduces the number of T lymphocytes and interferes with their activation. Etanercept, infliximab and adalimumab bind with tumour necrosis factor (TNF), a key pro-inflammatory cytokine in psoriasis. Ustekinumab is a human monoclonal antibody against interleukin-12 and interleukin-23. It is thought to rebalance the T cell response away from the psoriatic diathesis.

Biological therapies appear to work in severe psoriasis irrespective of the response to standard therapies. However, there must have been an inadequate response or significant intolerance to at least three treatments before patients can use a biological therapy subsidised by the Pharmaceutical Benefits Scheme (PBS). There are no markers, other than a trial of therapy, to help us identify responders to biological therapies.

Most patients start to improve by four weeks and achieve good reductions in disease severity by 12 weeks. Infliximab is associated with the best response rates as 80% of patients achieve a 75% improvement in their psoriasis area and severity index which equates closely to disease clearance. The greatest improvements in quality of life are with infliximab followed by etanercept.[6]

To date the literature on combination therapy involving biologicals is extremely limited. This area needs to be further explored to improve patient outcomes and important drug safety issues such as skin cancer.

Safety

The efficacy and safety of the biological therapies requires long-term disease-specific data. The effects associated with psoriasis and the toxicities of previous therapies are likely to influence the frequency and severity of the harm associated with long-term treatment, particularly when using an immunosuppressive drug.

The safety data from a cohort of patients treated with efalizumab continuously for longer than 2.5 years is a reassuring beginning and suggests that efficacy is well maintained.[7] However, this cohort differs significantly in their disease severity and previous treatments from those currently qualifying for therapy subsidised by the PBS. Serious adverse events with efalizumab include infections and severe arthritis.

Long-term efficacy and safety data are more limited for the therapies which act on TNF. When TNF inhibitors are used to treat rheumatoid arthritis the patients' already elevated risk of lymphoma may increase. There is also a risk of serious infections including tuberculosis reactivation. These therapies can also worsen congestive cardiac failure. New neurological symptoms such as visual disturbance and paraesthesia warrant stopping treatment if a demyelinating cause is suspected. There are rare reports of demyelinating disease, such as optic neuritis, and exacerbations of multiple sclerosis occurring in patients taking TNF inhibitors.

Risk of disease rebound

A rebound in psoriasis can occur after stopping a drug or therapy. In a rebound episode the disease becomes unstable and rapidly more severe than before therapy. It may also affect previously uninvolved body regions or change its form, for example becoming erythrodermic or pustular. The risk of rebound varies with the treatment.

Ceasing efalizumab appears to have a significant risk of causing severe and unstable disease that can result in prolonged hospitalisation. Efalizumab should only be stopped under the guidance of a dermatologist familiar with its use. To minimise risks of a disease rebound when switching therapy, these patients need to be closely monitored. Combination therapy may be needed during the transition period. Pharmacogenetics show promise for helping to predict and prevent this adverse effect in subpopulations of patients.

Renal and cardiovascular problems

Patients with severe psoriasis have several factors that place them at increased risk of clinically significant renal and cardiovascular disease. They are more likely to smoke, with the number of cigarettes smoked per day correlating with disease severity. They are also more likely to have hypertension, hyperuricaemia, nephrocalcinosis and hyperlipidaemia. Although most of the evidence is from transplantation medicine, calcium antagonists are nephroprotective when used for small increases in blood pressure occurring during the first 1–2 months of cyclosporin therapy. An increase in blood pressure after this time warns of cyclosporin nephrotoxicity, especially if associated with an elevated creatinine or an increase in the patient's creatinine of more than 30% above baseline. If this fails to settle with dose reduction, cyclosporin should be stopped before significant permanent renal damage can occur.

The liver and obesity

Patients with severe psoriasis have an increased risk of liver disease including non-alcoholic steatohepatitis and cirrhosis due to associated comorbidities. Methotrexate and acitretin therapy can contribute to these liver problems.

Lifestyle interventions can reduce the risk of medically significant liver-associated comorbidities. Health professionals should regularly counsel all patients, but particularly those with severe psoriasis, about the importance of maintaining a healthy weight, regularly exercising, having a diet with a low glycaemic index and low fat plus moderation of their often excessive alcohol consumption. Patients with psoriasis should be offered vaccination for hepatitis A and B.

Malignancy

Patients with severe psoriasis are at increased risk of skin cancer and this increases further if phototherapy is followed

or combined with cyclosporin or methotrexate. Education about the importance of sun protection, sun avoidance, skin monitoring and lifelong regular (at least annual) full skin examinations is warranted.

It is unclear if immunosuppressive therapies further increase the risk of skin cancer. They are likely to increase the risk of oncogenic virus-related malignancies including human papillomavirus-related cervical, vulval and penile cancer, warranting regular check-ups. Patients with psoriasis should be regularly counselled regarding lifestyle modification and interventions to reduce the impact of associated comorbidities and exposures known to increase malignancy including smoking, obesity and diet.

Good long-term control of the inflammation due to severe psoriasis could theoretically reduce the background risk of malignancy such as lymphoma. However, this is likely to be counterbalanced by the immunosuppressive actions of therapies for severe psoriasis. All appropriate recommendations for cancer screening should be followed.

Periodontal disease

Good dental hygiene and regular dental review are important for everyone on immunosuppressive therapy. Cyclosporin carries the greatest risks for causing as well as worsening periodontal disease, including acute and chronic gingivitis and gingival hypertrophy.

Infections and vaccination

Patients with severe psoriasis should keep their immunisations up to date. In general, vaccinations are recommended before commencing biological therapy. The standard of care that is appropriate to follow may be similar to that of organ transplantation where pneumococcal, hepatitis A and B, influenza and tetanus-diphtheria vaccines are recommended before starting immunosuppressive therapy.[1] Live vaccines should not be given without specialist advice if the patient is taking immunosuppressive therapy. All patients should be screened for tuberculosis before immunosuppressive therapy especially when starting a TNF inhibitor.[8]

When a patient with psoriasis presents with sepsis while on systemic therapy, always consider atypical infections. Careful consideration is also required regarding ongoing therapy for their psoriasis. In contrast to efalizumab, a TNF inhibitor can be stopped, given the absence of the risk of rebound on cessation. Thought needs to be given to the possible ongoing immunosuppressive effect of the biological therapies; etanercept has a short half-life of days, but the half-life of adalimumab and infliximab is considerably longer, up to weeks in duration.

When taking a medication history for a patient presenting with potential sepsis, remember to ask about injectable drugs, including the biological therapies.

Pregnancy and lactation

Effective pregnancy prevention advice and precautions need to be regularly provided and checked when women of childbearing age are taking systemic psoriasis therapies. Should pregnancy occur, all systemic psoriasis drugs should be stopped immediately and specialist advice sought. The risk of disease rebound with efalizumab has to be balanced against the uncertain risk to the fetus. Acitretin and methotrexate have significant proven adverse effects on the fetus. The long half-life of acitretin means that a planned pregnancy must be postponed for several years after stopping treatment. Cyclosporin has been used in pregnancy when severe psoriasis has not responded to other therapies. The safety of biological therapies in pregnancy and breastfeeding is unknown.

Psoriatic arthritis

Approximately 10% of patients with psoriasis also have psoriatic arthropathy. Drugs which improve the skin may have less effect on the arthritis.

The treatment of psoriatic arthritis is similar to that of other joint diseases and may involve disease-modifying drugs. If there is no response to drugs such as sulfasalazine and methotrexate, biological therapies may be considered. Adalimumab, etanercept, infliximab and ustekinumab can be used to treat severe active psoriatic arthritis.

Conclusion

Biological therapies for psoriasis are proving valuable for achieving and maintaining disease control in patients with severe psoriasis. They complement rather than replace our standard therapies. They also provide alternatives in resistant disease and greater therapeutic choice should allow better tailoring of treatment to the patient's needs. Treatment choice should take into consideration the order in which drugs are prescribed, a person's stage in life, associated comorbidities and variation in disease severity. The best use of biological therapies will be guided by the ongoing collection of data on their long-term safety.

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Further reading

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Conflict of interest: Dr Sullivan has served on advisory committees for Schering and Wyeth, and has received (unconditional) educational grants from Merck Serono. Dr Preda: none declared.

Self-test questions

The following statements are either true or false (answers on page 27)

1. Patients with severe psoriasis may experience a flare-up of the disease when treatment with efalizumab is ceased.
2. Women taking acitretin should not plan to become pregnant until at least two years after stopping treatment.

Patient support organisation

Psoriasis Australia

Psoriasis Australia provides information about psoriasis, and support to people with psoriasis, to enable informed decisions on treatment choices and lifestyle. It provides pamphlets and other material for health professionals and the public. Although based in Victoria it is a national organisation.

Website: http://home.vicnet.net.au/~psorias/
Email: info@psoriasisaustralia.org.au
Phone: (03) 9813 8080 Thursdays 10 am – 1pm
Address: 334 High Street ASHBURTON VIC 3147

Dental notes

*Prepared by **Michael McCullough**, Chair, Therapeutics Committee, Australian Dental Association*

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Dentists have become increasingly aware of the effects that systemic medications can have on the oral cavity. Cyclosporin has long been known to be associated with gingival enlargement, and the degree of enlargement appears to be associated with both the daily dose and length of time the drug is taken. This was first observed in patients with renal transplants and these patients remain the group most commonly affected by cyclosporin-induced gingival hyperplasia.[1] However, cyclosporin and other immunomodulatory drugs are commonly used for patients with severe psoriasis. Cyclosporin-induced gingival enlargement resolves following cessation of the drug and, in some patients, it will also resolve following a reduction in drug dosage.[2]

A recent study has shown that isotretinoin (a retinoid used for severe acne) has significant oral adverse effects with a decrease in salivary flow and a concomitant increase in the number of decayed, missing or filled teeth.[3] It is possible that acitretin (a retinoid used for severe psoriasis) could have a similar effect. Acitretin is known to cause dry mouth and gingivitis. Patients taking methotrexate also have a decrease in salivary function, although this has not been studied in patients with severe psoriasis. People taking medication for severe psoriasis require very high levels of oral hygiene and regular professional cleaning to prevent or minimise deterioration of their periodontal structures. It would be advisable for these measures to start at the same time they begin their treatment for psoriasis.

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