Biologics and psoriasis today

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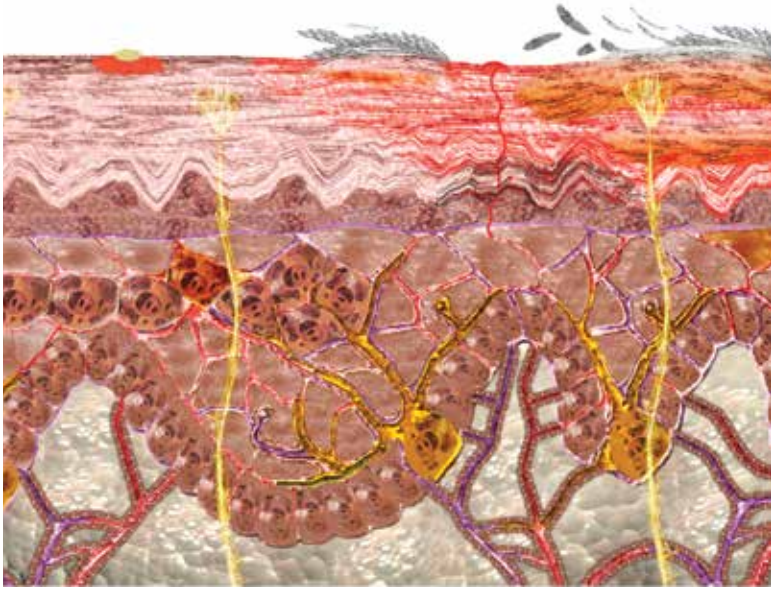
Biologic agents have emerged as alternative treatment options for patients with moderate-to-severe plaque psoriasis. These agents have shown good efficacy and are well tolerated.



Psoriasis is a chronic systemic immune-mediated inflammatory disease of unknown aetiology that manifests primarily in the skin. It affects approximately 2% of the Australian population and has a substantial negative impact on patients' quality of life. Patients with localised limited disease can usually be managed satisfactorily with topical agents, whereas those with moderate-to-severe disease often require systemic treatment.[1] Phototherapy and traditional systemic treatments, although often effective, can be associated with long-term cumulative toxicity. In addition, some patients have treatment-resistant disease, and patients themselves show high levels of dissatisfaction with standard approaches to treatment.[2]

Biologic agents are a significant breakthrough in the treatment of psoriasis, akin to the introduction of isotretinoin for acne or the discovery of the benefits of propranolol for infantile haemangiomas. They have higher efficacy rates and appear safer than the traditional treatment options, resulting in significant improvements in health-related quality of life for people with this potentially devastating condition. Some practice points regarding biologic agents and psoriasis are summarised in Box 1. The effects of biologic therapy in three patients with severe psoriasis are illustrated in Figures 1 to 3.

Psoriasis area and severity index

The Psoriasis Area and Severity Index (PASI) is a measure of overall disease severity in chronic plaque psoriasis. This score is calculated using the percentage of area coverage and the severity of the psoriatic plaques based on three clinical signs: erythema, thickness and scaling (each rated 0 to 4). Both the body surface area and the severity ratings are incorporated into a formula to calculate the PASI score on a nonlinear scale from 0 to 72. A score of 10 or more is considered moderate-to-severe psoriasis. A reduction in PASI score of at least 75% compared with baseline (termed a 'PASI 75' response) is considered the gold standard measure of treatment efficacy.[3,4]

Immunological basis of psoriasis

Psoriasis is a chronic, immune-mediated disorder that results from polygenic predisposition combined with environmental triggers. The underlying pathophysiology is mediated by T cells and involves the innate immune system stimulating the

1. BIOLOGICS AND PSORIASIS: PRACTICE POINTS

- Biologic agents are a recent advance in the treatment of patients with moderate-to-severe plaque psoriasis; they show good efficacy and are well tolerated.
- Pre-treatment screening for chronic infections is mandatory and age-appropriate screening for malignancy is recommended.
- Monitoring for infection and regular skin cancer surveillance are important during biologic therapy.
- The use of live vaccines is contraindicated while patients are receiving a biologic agent.
- The most common side effects that may prompt patients to seek GP advice include injection site reactions, nasopharyngitis and upper respiratory tract infections.
- The risks of biologic therapy during pregnancy and breastfeeding are not fully understood; current guidelines recommend ceasing therapy before conception and during pregnancy and breastfeeding.
- New promising biologic therapies are in development, offering more treatment options for patients with difficult to treat disease.

MedicineToday 2016; 17(4): 57-66

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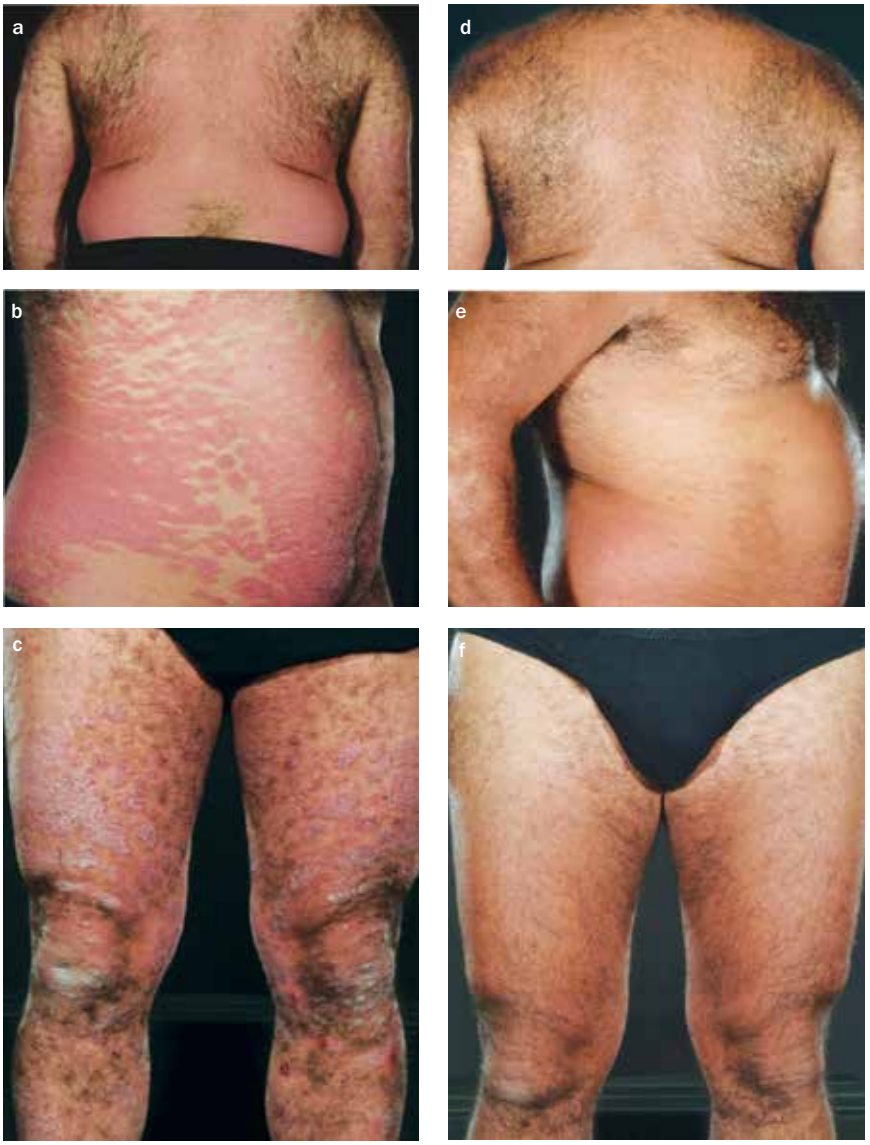


Figures 1a to f. A 39-year-old man with a 25-year history of severe psoriasis. a to c (left top, middle and bottom). Before treatment. d to f (right top, middle and bottom). After 24 weeks of biologic therapy, showing a decrease in the Psoriasis Area and Severity Index (PASI) from 25.3 to 1.8.

production of proinflammatory mediators, perpetuating an inflammatory loop.[5] Cellular components of the innate immune system that have been linked to the pathophysiology of psoriasis include dendritic cells, macrophages and neutrophils. Cytokines produced by immune cells that appear to play major roles in the development of psoriasis include interferon (IFN)-α, tumour necrosis factor (TNF)-α, interleukin (IL)-12, IL-17 and IL-23.[4-6]

When stressed (e.g. by trauma or infection), keratinocytes in the skin induce the production of IFN-α by plasmacytoid dendritic cells and release TNF-α. The latter activates dermal dendritic cells, which migrate and activate naïve T cells, promoting their differentiation into T helper (Th) cells.[5] IL-12 and IL-23 are key drivers of this T cell differentiation and the consequent production of chemokines and other inflammatory cytokines that act on the epithelium and epidermis. IL-12 and IL-23 are produced primarily by antigen-presenting dendritic cells and macrophages, and under their influence naïve T cells differentiate into Th1 and Th17 cells, respectively, the latter producing IL-17 and IL-22.[4-6] IL-17 was recently implicated as a central proinflammatory cytokine in the pathogenesis of psoriasis.[5,6]

Biologics and psoriasis

Biologic agents targeting specific immune mediators have emerged as alternative treatment options for patients with moderate-to-severe plaque psoriasis who are unresponsive to, intolerant of or have contraindications to nonbiologic systemic agents.[7] Unlike traditional systemic therapies (e.g. cyclosporin and methotrexate), biologics act in a targeted way, affecting various proinflammatory molecules involved in the immunopathogenesis of psoriasis.

Current biologics available for psoriasis in Australia include:

- monoclonal antibodies specific to TNF (infliximab, adalimumab)
- fusion proteins targeting TNF (etanercept)
- monoclonal antibodies to the p40 subunit of IL-12 and IL-23 (ustekinumab)
- monoclonal antibodies to IL-17 (secukinumab).[8]

Efalizumab, a humanised monoclonal antibody that inhibits activation of T cells, was withdrawn from global markets including Australia in 2009. This followed three confirmed and one suspected case of progressive multifocal leukoencephalopathy in patients with chronic plaque psoriasis who were continuously treated with efalizumab for three or more years.[8]

Current PBS-approved biologics

Five biologic agents are currently PBS-listed for the treatment of severe chronic plaque psoriasis (Table):

- three TNF-α inhibitors – adalimumab, etanercept, infliximab (etanercept also inhibits TNF-β)

- one IL-12 and IL-23 inhibitor – ustekinumab
- one IL-17 inhibitor – secukinumab.

These biologic agents are subsidised only for patients with severe chronic plaque psoriasis who have had lesions present for at least six months from the time of initial diagnosis and have failed to achieve an adequate response (i.e. have a PASI score of 15 or higher) after a minimum of six weeks of therapy with at least three of four conventional therapies: phototherapy, cyclosporin, methotrexate and acitretin, unless contraindicated or a toxicity develops to treatment (Box 2).

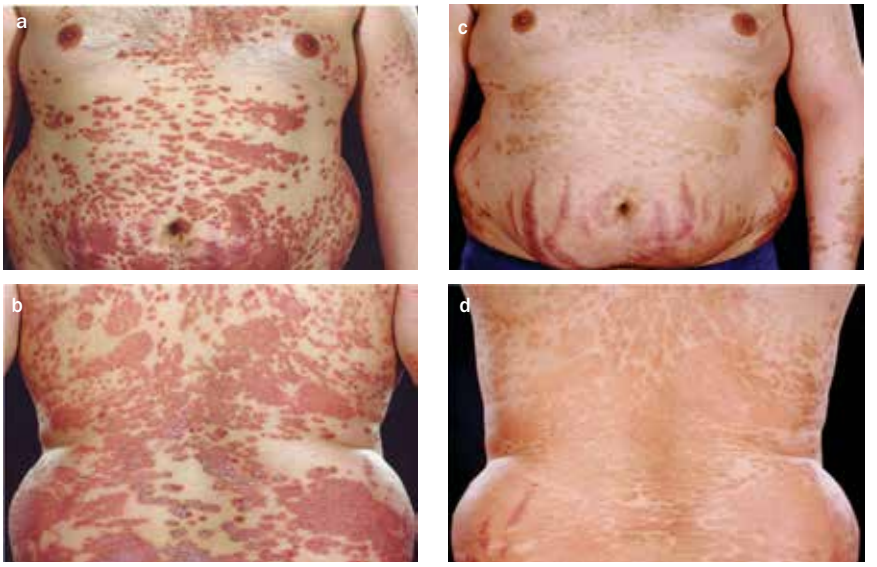
In addition, adalimumab, etanercept and infliximab are PBS-listed for the treatment of severe active psoriatic arthritis. Ustekinumab has TGA approval for treating psoriatic arthritis but is awaiting PBS listing for this indication after receiving a positive PBAC recommendation. Recently published trial data have shown secukinumab to also be effective in patients with psoriatic arthritis.[9]

The PBS listing for the biologic therapies requires that patients be treated by a dermatologist and does not permit variation in dosing schedule. The choice of biologic is individualised for the patient. Over time, all the biologics may decrease in efficacy. This may manifest as a worsening of residual psoriasis or some return of clinical disease in the lead up to the next dose. The managing dermatologist may choose any of a number of options, including increasing the dose, shortening the dose interval (neither are possible on the PBS), adding additional therapy (topical agents, phototherapy or methotrexate) or switching agents.

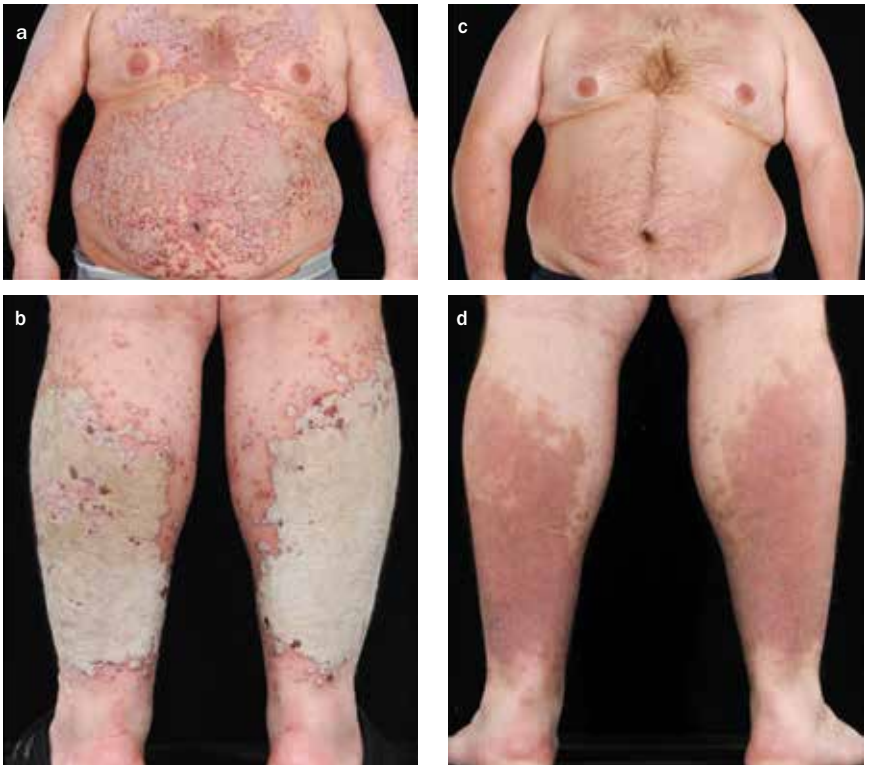
All companies that market biologics in Australia provide nursing support programs to educate and instruct patients how to self inject. They also provide support websites.

TNF inhibitors

TNF is a proinflammatory cytokine produced by a wide variety of cell types, including keratinocytes and T lymphocytes.[10]



Figures 2a to d. A 32-year-old man with a 14-year history of severe psoriasis. a and b (left top and bottom). Before treatment. c and d (right top and bottom). After 10 weeks of biologic therapy, showing a decrease in erythema score from 4 to 0. After therapy there was only post-inflammatory pigmentation and striae, the latter caused by long-term topical corticosteroid use.



Figures 3a to d. A 25-year-old man with a five-year history of severe psoriasis. a and b (left top and bottom). Before treatment, with a PASI of 43.3 and a scale score of 4. c and d (right top and bottom). After 24 weeks of biologic therapy, there was an 85% reduction in PASI and a decrease in the scale score to 0 (trunk) and 1 (lower limbs).

TABLE. PBS-APPROVED BIOLOGICS FOR THE TREATMENT OF SEVERE CHRONIC PLAQUE PSORIASIS

Drug	Class	Dosing schedule	Common side effects	Contraindications	Warnings	Pregnancy and breastfeeding	PBS approval date	Doses per script
Adalimumab	Anti-TNF-α	Adults 80 mg (2 x 40 mg injections) initial dose, then 40 mg fortnightly (subcutaneous)	• Infection • Injection site reactions	• Live vaccines • Tuberculosis • Sepsis • Malignancy	• Serious infection	• TGA pregnancy category C • Caution in breastfeeding (insufficient data)	June 2009	2
Etanercept	Anti-TNF-α and β	Adults 50 mg weekly (subcutaneous)	• Infection • Injection site reactions	• Live vaccines • Tuberculosis • Sepsis • Malignancy • Cyclophosphamide	• Serious infection	• TGA pregnancy category B2 • Caution in breastfeeding (insufficient data)	August 2006	4
Infliximab	Anti-TNF-α	Adults 5 mg/kg at weeks 0, 2, 6, then every 8 weeks (intravenous)	• Infection • Infusion reactions	• Live vaccines • Tuberculosis • Sepsis • Malignancy	• Serious infection	• TGA pregnancy category C • Compatible with breastfeeding	December 2007	1
Ustekinumab	IL-12 and IL-23 inhibitor	Adults 45 mg at weeks 0, 4, then every 12 weeks If >100 kg, 90 mg (2 x 45 mg) may be prescribed (subcutaneous)	• Infection • Injection site reactions	• Live vaccines • Tuberculosis • Sepsis • Malignancy	• Serious infection	• TGA pregnancy category B1 • Caution in breastfeeding (insufficient data)	March 2010	1
Secukinumab	IL-17 inhibitor	Adults 300 mg at weeks 0, 1, 2, 3, then every month from week 4	• Infection • Injection site reactions	• Live vaccines • Tuberculosis • Sepsis • Malignancy	• Serious infection • Active Crohn's disease	• TGA pregnancy category C • Caution in breastfeeding (insufficient data)	September 2015	1

Abbreviations: IL = interleukin; TNF = tumour necrosis factor.

TNF inhibitors are a class of systemic biologic agents used to treat patients with a range of inflammatory autoimmune diseases, including psoriasis, rheumatoid arthritis, ankylosing spondylitis and Crohn's disease.[8] In chronic psoriasis, TNF inhibition can reverse epidermal hyperplasia and cutaneous inflammation. Three anti-TNF therapies are approved in Australia for the treatment of chronic plaque psoriasis: adalimumab, etanercept and infliximab.

Etanercept

Etanercept was the first TNF antagonist approved for use in Australia in patients with psoriasis. Etanercept 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 immunoglobulin G subclass IgG1.[4] Etanercept binds both soluble and transmembrane forms of TNF and also binds lymphotoxin (TNF-β). Etanercept is administered subcutaneously as a weekly fixed dose. About 34% of patients achieve a PASI 75 response at week 12.[2,3,11] The maximal effect may take up to 24 weeks of therapy with etanercept. At this time point, at least 50% of people will have achieved a PASI 75 response.[10] Etanercept is the only biologic that is PBS-listed for patients with psoriasis younger than 18 years.

Adalimumab

Adalimumab is a fully human monoclonal antibody that binds to TNF-α, preventing it from activating TNF receptors.[10] It is administered subcutaneously at weeks zero and one, and fortnightly thereafter. Onset of action is rapid, with significant improvement seen within four weeks and maximum disease response between weeks 12 and 16. About 70% of patients achieve a PASI 75 response by week 16.[11] Efficacy data show long-term responses for up to three years, with no evidence of significant loss of

2. PBS CRITERIA FOR USE OF BIOLOGIC THERAPY IN PATIENTS WITH PSORIASIS (INITIAL TREATMENT)*

To qualify for PBS authority approval for the initial treatment of chronic plaque psoriasis, the following conditions must be met:

- Patients must have a diagnosis of chronic plaque psoriasis where lesions have been present for at least six months from the time of initial diagnosis with a baseline PASI score greater than 15

OR

- Severe chronic plaque psoriasis of the face, palm or sole of the foot where lesions have been present for at least six months from the time of initial diagnosis **AND**
  EITHER
  - Two of the three PASI symptom subscores are rated severe (3) or very severe (4)

  OR
  - The affected skin is 30% or more of the face, palm of a hand or sole of a foot

AND

- The patient must have failed to achieve an adequate response, as indicated by PASI assessment (PASI score greater than 15) or the development of contraindications or intolerance, following at least six weeks' treatment with at least three of the following four treatments:
  - Phototherapy consisting of a minimum three treatments per week
  - Methotrexate at a dose of at least 10 mg weekly
  - Cyclosporin at a dose of at least 2mg per kg per day
  - Acitretin at a dose of at least 0.4 mg per kg per day

* Note: Patients must be aged 18 years or older (except in the case of etanercept) and must be treated by a dermatologist.

response over that time.[10] Interrupted therapy may result in loss of treatment response because of the formation of antibodies.[8,11]

Infliximab

Infliximab is a chimeric human–murine monoclonal antibody and the only intravenously administered biologic agent approved for psoriasis.[10] It is infused at weeks 0, 2 and 6, and then every eight weeks thereafter. Onset of action is rapid, with evidence of significant improvement within the first two weeks of treatment and maximum benefit by week 10, with 79% of patients achieving PASI 75.[11] Loss of efficacy correlates with development of antibodies to infliximab, which occurs in approximately 28% of patients treated.[10]

Interleukin inhibitors

IL-12 and IL-23 are inflammatory cytokines that play a crucial role in T cell differentiation and production of chemokines and other inflammatory cytokines that act on the epithelium and epidermis. In addition, IL-17 has recently been implicated as a central proinflammatory cytokine in the pathogenesis of psoriasis.[5,6] IL-17 stimulates keratinocytes to secrete chemokines and other proinflammatory mediators that recruit additional inflammatory cells.[12]

Ustekinumab

Ustekinumab is the only PBS-approved IL-12/IL-23 inhibitor for the treatment of chronic plaque psoriasis. Meta-analyses of clinical trial data have shown ustekinumab response rates of over 70% after 12 to 28 weeks of treatment.[3] Ustekinumab is a human monoclonal antibody that inhibits IL-12 and IL-23 by binding with high affinity to the p40 protein subunit.[10] It is administered subcutaneously at weeks 0 and 4 and then every 12 weeks thereafter. Onset of action is within two weeks, with 72% of patients achieving a PASI 75 response by week 12.[11] Disease responses are maintained long-term with continued therapy. On cessation of therapy, median time to relapse is 15 weeks.

Secukinumab

Secukinumab is the only PBS approved IL-17 inhibitor for the treatment of chronic plaque psoriasis.[12] It is a human monoclonal antibody that binds to and inhibits IL-17. Secukinumab is administered subcutaneously at weeks 0, 1, 2 and 3, and then monthly thereafter from week 4. Onset of action is within two weeks, with 81% of patients achieving a PASI 75 response by week 12.[12] This agent has only been commercially available since early 2015, but response is maintained at least to 12 months, based on published data.[12]

3. PRE-THERAPY SCREENING FOR PATIENTS COMMENCING BIOLOGIC THERAPY

Blood tests

- Full blood count, urea, electrolytes and creatinine levels, liver function tests, antinuclear antibody
- Hepatitis B and C screening
- HIV serology
- Interferon gamma release assay (for tuberculosis)

Imaging

- Chest x-ray

Other

- Age-related cancer screening (e.g. prostate-specific antigen testing, mammography)

Pre-therapy screening

Patients should be thoroughly screened and fully vaccinated before commencing biologic therapy. All patients starting a biologic should be screened for serious infections, malignancy and a history of chronic illness.[7,10] Recommended pre-therapy screening includes baseline blood tests and hepatitis and HIV serology (Box 3). Pre-treatment screening for tuberculosis is mandatory. A pre-treatment chest x-ray and interferon gamma release assay currently remain the preferred screening tests.[10] Patients with signs to suggest tuberculosis, a history of previous treatment for tuberculosis or positive screening test results should be referred to a physician specialising in tuberculosis.

Biologics should be used with caution in patients with chronic infection or a history of recurrent infection. Additional baseline investigations may include lipid and

4. VACCINES CONTRAINDICATED IN PATIENTS RECEIVING BIOLOGIC THERAPY

Live attenuated bacterial vaccines

- Bacille Calmette–Guérin (BCG)
- Oral typhoid

Live attenuated viral vaccines

- Japanese encephalitis
- Poliomyelitis (oral)
- Rotavirus
- Rubella (measles–mumps–rubella, measles–mumps–rubella–varicella)
- Varicella
- Yellow fever
- Zoster

glucose levels (as people with moderate-to-severe psoriasis have higher rates of hyperlipidaemia and diabetes) and syphilis, strongyloides and varicella serology.

Treating clinicians must ensure patients are fully vaccinated before starting biologic therapy. Recommended vaccines include influenza, hepatitis A, hepatitis B, pneumococcal, diptheria, pertussis and tetanus vaccines.[10]

Drug interactions

Biologic agents have few drug interactions and concerns are mainly to prevent excessive immunosuppression. The use of other immunosuppressive agents should be considered carefully. Concurrent use of cyclophosphamide with etanercept is not recommended.

The use of live vaccines with any biologic agent is contraindicated (Box 4).[10] Patients should not receive live or live attenuated vaccinations less than two weeks before, during or less than five drug half-lives after discontinuation of biologic therapy.[10] Inactivated vaccines are safe to administer concurrently with biologic therapy. However, where possible, inactivated vaccines should be administered at least two weeks before starting biologic therapy to ensure an optimal immune response. Patients should be advised to receive pneumococcal vaccine and annual influenza vaccine while receiving biologic therapy.[10]

Monitoring

Access to ongoing PBS reimbursement requires formal specialist monitoring of response (Box 5). After the initiation period, patients need to see their dermatologist approximately every 24 weeks for assessment of PASI response and monitoring of side effects. Because biologics inhibit cellular immune responses, there is a possibility that these agents can impair defences against infections and increase the risk of malignancies.

All treating doctors should be aware of the possibility of infection. In the case of serious infections, biologic treatment should be suspended until the infection resolves. Patients with latent or previous serious infection should be carefully monitored. Regular liver function tests and full blood examination are recommended.

Side effects

Biologics are generally well tolerated with no cumulative end-organ toxicity. The most common side effects that may prompt patients to seek GP advice include injection site reactions, pruritus, rash, gastrointestinal symptoms and infections such as nasopharyngitis and upper respiratory tract infections.[7] Unless there is a suggestion of significant infection, biologic therapy can be continued.

Injection site reactions

Injection site reactions are localised areas of erythema, induration, pruritus and tenderness at the sites of subcutaneous injections of biologics, considered to be immunological in nature. Most frequently they occur a day or two after an injection and tend to last three to five days. They are usually mild and can be treated with cool compresses, topical corticosteroids, antihistamines and/or paracetamol. They usually do not require cessation of therapy and typically decrease in frequency over time, although a persistent or worsening reaction has been described. Patients are advised to rotate the site of injection. It is important to explain to patients that injection site reactions will resolve and are not related to the disease process.

5. PBS CRITERIA FOR USE OF BIOLOGIC THERAPY IN PATIENTS WITH PSORIASIS (CONTINUING TREATMENT)*

To qualify for PBS authority approval for the continuing treatment of chronic plaque psoriasis, the following conditions must be met:

- Patient must have a documented history of severe chronic plaque psoriasis

AND

- Patient must have received this drug as their most recent course of PBS-subsidised treatment with a biologic agent for this condition in the treatment cycle

AND

- Patient must have demonstrated an adequate response to their most recent course of treatment with this drug (PASI score reduced by 75%)

AND

- The treatment must be as systemic monotherapy (other than methotrexate)

AND

- Patient must not receive more than 24 weeks of treatment per continuing treatment course authorised under this restriction

* Note: Patients must be aged 18 years or older (except in the case of etanercept) and must be treated by a dermatologist.

Paradoxical psoriasis

Paradoxically, new-onset psoriasis may appear for the first time, primarily when biologic therapy is used for indications other than psoriasis. This is an uncommon side effect, and the pathophysiology is poorly understood. The clinical appearance may be of typical plaque psoriasis or an atypical form such as pustular psoriasis, particularly involving palms and soles. Paradoxical psoriasis is an indication for dermatological review.

Serious infections

Serious infections and reactivation of latent infections such as tuberculosis have been reported in clinical trials of biologic agents. The most common infections about which patients may seek GP advice include nasopharyngitis and upper respiratory tract infections.[6] There are no known interactions between biologics and antibiotics used to treat infections. Choice of antibiotic is determined by the clinical situation, not the biologic the patient is taking. For mild infections, the biologic should be continued. For more significant infections or infections slow to respond to antibiotics, consideration should be given to temporarily suspending biologic administration.

Patients receiving biologic therapy should be monitored for early symptoms and signs of infection throughout treatment. Each review should include a detailed systems review, asking about symptoms such as fevers, night sweats and prolonged cough, prompting investigation where indicated. In addition, at each review clinicians should re-emphasise the risk of infection and the need for patients to have a lower threshold for seeking medical attention if they develop symptoms or signs of infection.

Hepatitis B

Reactivation of hepatitis B infection has been reported with anti-TNF therapy.[7] Current guidelines recommend that, in general, anti-TNF therapy should not be used in patients who are chronic carriers of hepatitis B virus.

Hepatitis C

TNF plays a role in hepatitis C-induced hepatocyte injury and treatment resistance to IFN-α2b. TNF antagonists have been used in the treatment of rheumatological disease and psoriasis in hepatitis C-positive patients with no increase in rates of hepatotoxicity or viral replication.[7,13]

Human immunodeficiency virus

The safety of biologic therapy in patients with HIV infection is unknown. Particular caution should be exercised in this group given the risk of opportunistic infections.[7]

Candida

In trials, rates of candida infection were higher in participants receiving secukinumab than in those receiving placebo or etanercept.[12] All reported cases of candida infection were mild to moderate, involving skin or mucosal surfaces, and responded to topical or oral therapies. No participants withdrew from the trials because of candida infection.[12] Any patients who develop thrush during biologic therapy should be treated with topical or oral agents as indicated, in the same manner as patients not receiving biologic therapy.

Malignancy

Any immunosuppressant agent has the potential to increase the risk of malignancy. However, to date there is no robust evidence of increased risk of malignancy with TNF inhibitors in patients with psoriasis. Data from clinical trials of their long-term use in rheumatology populations show no increased risk of solid tumours and lymphoma compared with traditional disease-modifying antirheumatic drug (DMARD) therapy.[10]

Nevertheless, all patients should be fully assessed before and during biologic therapy regarding their past or current history of malignancy and future risk of malignancy. Age-appropriate malignancy screening should be undertaken as per national guidelines for the general population.

Biologic therapy should be used with caution in patients with a history or a high risk of malignancy. It should be avoided in patients with current malignancy or a recent past history of malignancy unless the malignancy was diagnosed and treated more than five years previously and the likelihood of cure is high.[10]

Regular comprehensive dermatological assessment for skin cancer, including melanoma, is recommended before and at regular intervals during therapy, especially in patients who have an increased risk of skin cancer at baseline.[10] This monitoring is typically undertaken by the prescribing dermatologist.

Cardiovascular disease

TNF antagonist therapy should be avoided in patients with severe cardiac failure (NYHA class III or IV). Patients with well-compensated cardiac failure (NYHA class I or II) should have a screening echocardiogram, and those with an ejection fraction less than 50% of normal should not commence TNF antagonist therapy.[10] Furthermore, treatment should be withdrawn at the onset of new symptoms or worsening of pre-existing heart failure.[10]

Long-term safety

Biologic agents have shown good efficacy for the treatment of moderate-to-severe plaque psoriasis and are well tolerated in short-term trials.[7] In contrast, conventional therapies for moderate-to-severe plaque psoriasis can be associated with long-term side effects.[7] Cyclosporin has been shown to increase blood pressure, induce renal toxicity and increase the risk of nonmelanoma skin cancer. Long-term treatment with methotrexate may lead to hepatotoxicity. Retinoids have been linked to teratogenicity.[7]

A review of long-term safety data (one year or longer) on etanercept, infliximab, adalimumab and ustekinumab from randomised controlled trials, open-label extension studies and meta-analyses found no long-term safety concerns. However, the data are limited and further ongoing evaluation of the long-term safety profile of these drugs is required.[7] Infusion reactions, demyelination and a lupus-like syndrome are rare side effects of anti-TNF therapy.[10] Injection site reactions are frequent but generally mild.[10]

Secukinumab was well tolerated in phase 3 trials over 52 weeks.[12] The most common adverse events reported were nasopharyngitis, headache and upper respiratory tract infection.[12] Candida infections were more common in patients receiving secukinumab but resolved on

their own or with standard therapy.[12] Crohn's disease exacerbations were observed in clinical trials; caution is required when prescribing secukinumab to patients with active Crohn's disease.[14]

Use in pregnancy and breastfeeding

No studies have assessed the safety of biologic treatments for moderate-to-severe plaque psoriasis during pregnancy. According to manufacturers' guidelines, women should discontinue biologics for five drug half-lives before conceiving.[7] Drug half-lives vary from 2.9 days for etanercept up to 21 days for ustekinumab.

Pregnancy should be avoided in patients with psoriasis receiving biologic therapy. The drugs are not thought to be teratogenic; however, patients who become pregnant while receiving biologic treatment should be referred to a specialist obstetrician for further assessment, and consideration should be given to stopping biologic therapy.[10]

Biologic agents are excreted in breast milk but are not orally absorbed; currently there is no evidence about the risk they pose. Current guidelines advise that breastfeeding should be avoided in patients receiving biologic therapy.[15]

Use of biologics before surgery

Although there is no conclusive evidence that biologics increase the risks associated with surgery, the known increase in risk of infections associated with biologics has prompted caution in the lead up to surgery. Current guidelines recommend discontinuation of therapy before surgery based on each agent's half-life and dosing interval. It is also recommended that biologic therapy is restarted postoperatively, provided that wound healing is satisfactory and there is no evidence of infection.[7]

Biologics and travel

Patients treated with systemic biologic therapy can easily travel provided there is adequate planning and preparation. Patients should ensure they have sufficient supplies of the drug to last the duration of the trip. Patients receiving intravenous therapy may find it more difficult to travel for long periods because of the need to attend an infusion centre regularly but benefit from the eight-week interval between doses.

All biologic medications must be packed in carry-on luggage to avoid extreme temperatures. Airlines will generally have a policy about how injectable medications can be carried and stored in flight. Patients need to understand that, in general, systemic biologics must be stored at 2 to 8°C to maintain their efficacy. The rules around taking medical supplies into other countries vary widely. Patients must check well in advance with the relevant authorities. Documentation including an explanatory letter from a medical professional is generally required.

Before international travel, patients should receive all necessary inactivated vaccinations. Live vaccines must not be administered. As yellow fever vaccine is a requirement for entry to some countries, patients receiving biologic therapy are precluded from travel to these countries unless they have received the vaccine before starting treatment. If patients wish to take a break from treatment during a holiday, the treating doctor must assess their PASI and document the response so that they can recommence treatment on their return.

Indications for stopping therapy

Biologic therapy should be discontinued when patients fail to achieve an adequate response after an adequate duration of therapy or when treatment response is not maintained. Withdrawal of therapy is also indicated in response to the following events:

- a serious adverse event, including malignancy (excluding nonmelanoma skin cancer)
- severe drug-related toxicity
- severe infection (temporary withdrawal)
- pregnancy (temporary withdrawal)
- elective surgical procedures (temporary withdrawal).[10]

Future for biologics

Despite the progress made to date with targeted therapies for psoriasis, not all will be effective for every patient.[16] New promising therapies for psoriasis are in development that offer treatment options for patients with difficult to treat disease and those who have failed previous biologic therapy. The advances to date have revealed new information on the immunopathogenesis of psoriasis, with a specific focus on Th17 cells and the central role of IL-17A as an effector cytokine.[5,16] These new biologics include an IL-17 antagonist (ixekizumab) and IL-23 antagonists (guselkumab and tildrakizumab).[16]

Conclusion

Psoriasis is a chronic systemic immune-mediated inflammatory disease. Biologic therapy has emerged as a safe and efficacious alternative treatment for patients with moderate-to-severe psoriasis. Patients receiving biologic therapy need monitoring for infection and regular skin cancer surveillance. The most common side effects that may prompt patients to seek GP advice include injection site reactions, nasopharyngitis and upper respiratory tract infections. New promising biologic therapies are in development, offering more treatment options for patients with difficult to treat disease. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Associate Professor Foley has served as a consultant, investigator, speaker and/or advisor for and/or received travel grants from Galderma, LEO/Peplin, Ascent, Clinuvel, Janssen-Cilag, Eli Lilly, Australian Ultraviolet Services, Roche, CSL, 3M/iNova/Valeant, GSK/Stiefel, Abbott/AbbVie, BiogenIdec, Merck Serono, Schering-Plough/MSD, Wyeth/Pfizer, Amgen, Novartis, Celgene, Aspen and BMS. Dr Meani has been a subinvestigator for clinical trials sponsored by Janssen-Cilag, Eli Lilly, Roche, Abbott/AbbVie, Merck Serono, Wyeth/Pfizer, Amgen, Novartis and Celgene.

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