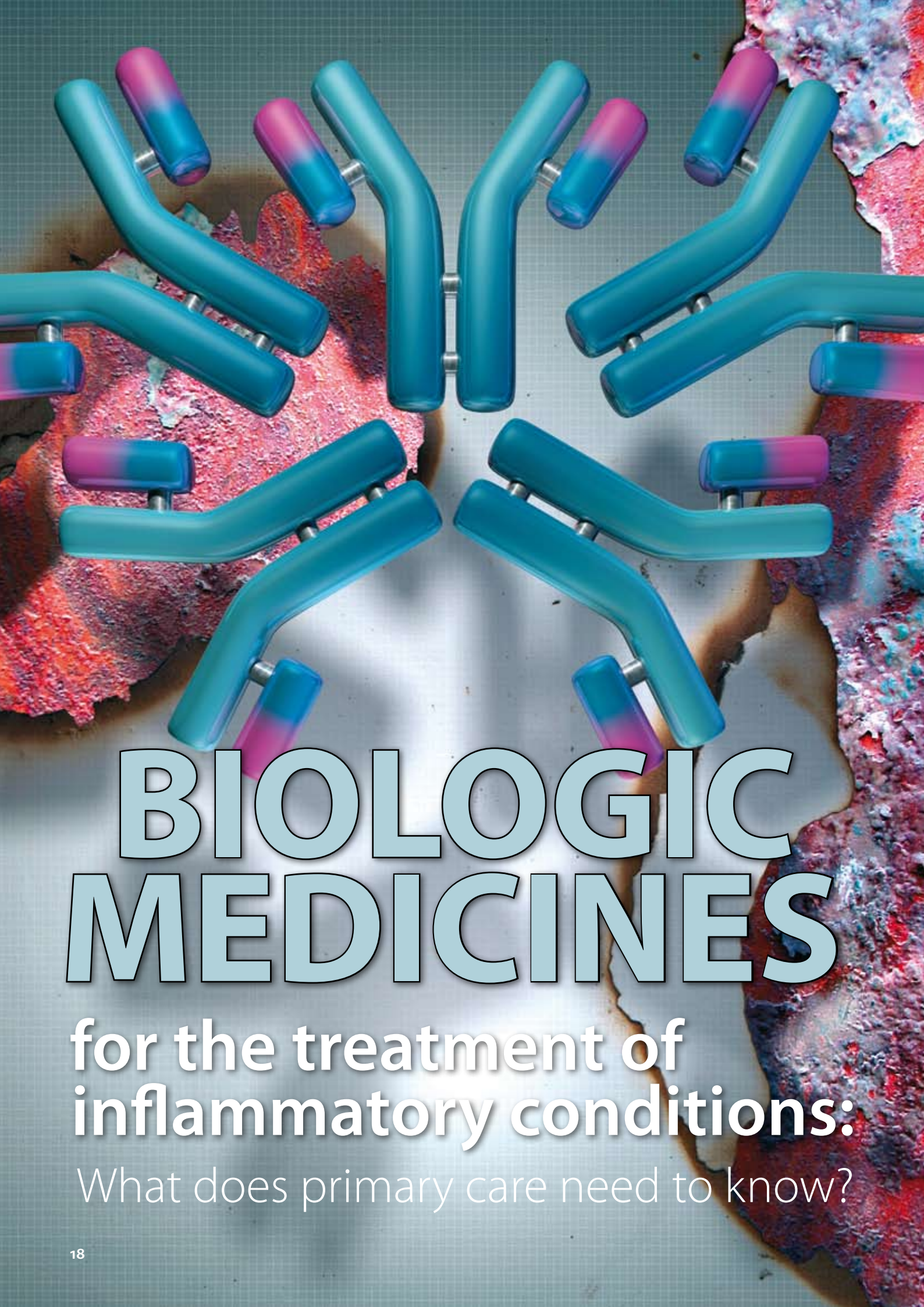

BIOLOGIC MEDICINES

for the treatment of inflammatory conditions:

What does primary care need to know?

Patients with severe immune-mediated inflammatory diseases, e.g. rheumatoid arthritis, Crohn's disease or psoriasis, often respond well and relatively quickly to treatment with biologic medicines such as tumour necrosis factor (TNF) inhibitors. For a patient to qualify for subsidy for these medicines, treatment must be initiated by a relevant specialist, e.g. Rheumatologist, Gastroenterologist or Dermatologist. The role of the primary care team is to facilitate discussion between the patient and the treating specialist, to reduce the risk of complications, e.g. serious infection, to provide repeat prescriptions and in some cases to monitor the patient's response to treatment. General Practitioners may also be involved in applications for the renewal of Special Authority subsidy for patients taking biologic medicines.

What are biologic medicines?

Biologics are a class of medicine that are derived from biological systems as opposed to being synthesised in a chemical process. The term includes a wide range of medical products such as immunomodulators, vaccines, blood products and chemotherapy agents. Biologic immunomodulators are often used to treat immune-mediated inflammatory disease, e.g. rheumatoid arthritis and inflammatory bowel disease. A feature of this type of medicine is that unlike other immunosuppressive medicines, e.g. methotrexate, specific cell signalling pathways involved in the disease are targeted. The most well known biologics used to treat immune-mediated diseases are the tumour necrosis factor (TNF) inhibitors (see: "What are TNF inhibitors?").

The effectiveness of biologic medicines can vary between patients

Treatment with biologic medicines can produce a marked beneficial response in many patients with inflammatory conditions. For example, in patients with rheumatoid arthritis, TNF inhibitor treatment can decrease synovitis and prevent joint erosions within months, and sometimes induce disease remission.[1] However, approximately one-third of patients do not respond to treatment.[2] A lack of response may be due to differences in the pathophysiology of the patient's condition, differences in genetics or the treatment being only effective at certain stages of a disease.

Patients may also develop antibodies against biologic medicines that limit their effectiveness. This is more likely to occur with the use of chimeric biologics, e.g. infliximab (Table 1, over page), which contain a combination of human and animal-derived amino acids, as opposed to humanised biologics which contain only human derived amino acids.[1] If a patient does not respond to one biologic medicine, they may respond to another.[1]

Biologic medicines subsidised in New Zealand to treat inflammatory diseases

In New Zealand several biologic medicines are funded under Special Authority criteria or subject to restrictions on the Hospital Medicines List (HML) for the treatment of immune-mediated inflammatory disease (Table 1). These medicines are usually initiated when patients have not responded sufficiently to conventional treatment and remain severely affected by an inflammatory condition. To qualify for subsidy the initial application for treatment must come from an appropriate named specialist, e.g. a Rheumatologist, Gastroenterologist or Dermatologist.

Supporting the treatment of patients with biologic medicines

When initiation of treatment with a biologic is being considered for a patient the role of the primary care team is to facilitate discussion between the patient and the treating specialist, to reduce the patient's risk of complications through the course of their treatment and to provide repeat prescriptions where appropriate.

Methotrexate is often co-prescribed with immunosuppressive biologic medicines. This is to reduce the development of antibodies that may neutralise the effectiveness of treatment and because an additional disease-modifying anti-rheumatic drug (DMARD) is likely to provide further clinical benefit.[1]

Table 1: Immunosuppressive biologic medicines available in New Zealand under Special Authority criteria and/or Hospital Medicines List (HML) restrictions for the treatment of inflammatory diseases[2, 3]

Medicine	Classification	Mode of action	Administration	**Subsidised indications** (inflammatory conditions)
Biologic medicines for inflammatory disease subsidised in the community and on the HML				
Etanercept	Human fusion protein	Decoy for soluble TNF-α receptors that competitively binds to TNF-α	Subcutaneous injection, once or twice weekly, in a community setting	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and severe plaque psoriasis
Adalimumab	Humanised monoclonal antibody	Binds to TNF-α	Subcutaneous injection, usually every two weeks, in a community setting	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (including fistulising) and severe plaque psoriasis
Biologic medicines for inflammatory disease subsidised on the HML only				
Infliximab	Chimeric monoclonal antibody containing approximately 25% mouse-derived amino acids[4]	Binds to TNF-α	Intravenous infusion at zero, two and six weeks, then every eight weeks, in a secondary care setting	Where treatment with adalimumab or etanercept has been intolerable or ineffective, used in combination with methotrexate (if possible) for: rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease (including fistulising), ulcerative colitis, severe plaque psoriasis and ocular inflammation
Rituximab	Chimeric monoclonal antibody	Binds to a CD20 protein mainly found on antibody-producing B cells	Intravenous infusion, in two-dose courses, in a secondary care setting	Rheumatoid arthritis where treatment with a TNF inhibitor has failed or is contraindicated
Tocilizumab	Humanised monoclonal antibody	Binds to interleukin-6 receptors	Intravenous infusion, every two weeks, in a secondary care setting	Systemic juvenile idiopathic arthritis

The New Zealand Formulary or Pharmaceutical Schedule has details of Special Authority subsidy criteria.

Precautions with the use of biologic medicines

Biologic medicines are usually contraindicated in patients with any of the following:[2, 6, 8]

- Severe active infections
- Moderate to severe heart failure
- Multiple sclerosis or optic neuritis
- Untreated or latent tuberculosis
- Hepatitis B
- Malignancy within the last five years

Testing for latent infection

Patients should be tested for latent tuberculosis infection prior to starting a biologic medicine using an interferon gamma release assay (QuantiFeron Gold).[8] This test is reported to be more sensitive in people who are immunocompromised than Tuberculin Skin Testing (TST/Mantoux), e.g. in patients who have been taking corticosteroids or methotrexate.[8] The specificity of the QuantiFeron Gold test is also higher than Mantoux testing in patients who have previously had a BCG vaccination and the test only requires one patient visit.[8] Infliximab is most frequently associated with tuberculosis reactivation, but reactivation can occur with other biologics.[9]

Check the patient's vaccination history

Before patients are prescribed biologic medicines they should have their immunisation status reviewed to ensure they have received all vaccinations recommended on the New Zealand immunisation schedule.

For some patients it may be necessary to plan an immunisation catch-up. Live vaccinations, e.g. varicella vaccine, tuberculosis (BCG) and measles, mumps rubella (MMR), are contraindicated in patients who are undergoing immunosuppressive treatment and should be completed in advance of treatment.[10, 11]

Hepatitis A and B vaccination is recommended in patients who will be taking biologic medicines who do not have confirmed immunity to viral hepatitis.[10, 11] Reactivation of hepatitis B in patients taking biologics is increasingly reported in the literature.

Influenza vaccination should be provided annually to people taking biologic medicines. People who are immunosuppressed, people aged over 65 years and people with rheumatoid arthritis are currently eligible for free annual influenza vaccinations. Vaccination against pneumococcal infection

What are TNF inhibitors?

Tumour necrosis factor (TNF) inhibitors are used to treat immune-mediated inflammatory diseases, e.g. rheumatoid arthritis, inflammatory bowel disease and psoriasis, by blocking the action of TNF-α, a pro-inflammatory cytokine.[2] TNF-α is a transmembrane protein that is cleaved by an enzyme to produce a soluble form of the protein.[5] Soluble TNF-α is released by activated T cells.[6] Both the soluble and transmembrane forms of TNF-α bind to TNF receptors causing activation of inflammatory genes that result in:[5, 6]

- Increased blood flow and permeability of blood vessels; and
- Guidance of neutrophils to sites of infection

Soluble TNF-α also:[6, 7]

- Causes macrophages to phagocytose pathogens
- Stimulates leukocytes and endothelial cells in blood vessels to release cytokines
- Increases expression of cell-surface attachment molecules for neutrophils
- Increases production of leukotrienes (cell signalling molecules that cause contraction of smooth muscle)

TNF-α levels are increased in areas of immune-mediated inflammation in people with conditions such as rheumatoid arthritis.[4] TNF inhibitors block the pro-inflammatory action of TNF-α and usually reduce the severity of the patient's symptoms, and sometimes induce disease remission.[1] Each TNF inhibitor blocks binding of both soluble and membrane forms of TNF-α to TNF receptors resulting in any one, or combination, of the following events occurring:[2]

1. Neutralisation of soluble TNF, therefore reducing inflammation. This action mimics the body's own ability to prevent fatal shock during infection and inflammation via the production of endogenous soluble receptors.
2. Cell lysis through serum protein-dependent or antibody-dependent cell-mediated cytotoxicity
3. Intracellular signalling which can reduce cytokine production, reduce cell growth or induce apoptosis (programmed cell death) of inflammatory cells following binding to membrane receptors

The adverse effects of the TNF inhibitors can be serious because they potentially involve all the immune-mediated pathways that interact with TNF-α (Page 22).

is also recommended, but not funded, for patients taking biologics. To achieve a maximum immune response against pneumococcal infection the Immunisation Advisory Centre recommends that Prevenar 13 (unsubsidised) be given eight weeks before Pneumovax 23, in patients at high-risk of an infection.[12] Patients at high-risk of infection should also receive a second Pneumovax 23 vaccine after three to five years.

Varicella vaccination is recommended by New Zealand gastroenterology guidelines for patients who will be taking biologic medicines who do not have demonstrated varicella immunity.[10] However, rheumatology guidelines do not make this recommendation as greater than 90% of the adult population are reported to have evidence of serological immunity and most instances of varicella infection are due to reactivation.[13]

HPV vaccination is recommended before beginning treatment with biologic medicines for females aged nine to 26 years, based on current guidelines.[10] This vaccine is fully subsidised for females prior to their twentieth birthday.

The New Zealand Immunisation Schedule has advice and examples to help plan an immunisation catch-up programme. See: **www.health.govt.nz/publication/immunistion-handbook-2011**

For further information see: "How to plan a catch-up immunisation", BPJ 45 (Aug, 2012).

The safety of biological medicines during pregnancy

The use of biologic medicines in women who are pregnant is not recommended as their safety has not been established.[13] Most guidelines suggest females treated with biologics be prescribed effective contraception during treatment and also for several months after treatment has been discontinued.[3, 13] In the event of a pregnancy occurring while a female is being treated with a biologic, the decision to discontinue the medicine should take into account the current activity of the condition being treated, the risks of a flare if treatment is discontinued and the potential for harm to the foetus.[13] However, there is a lack of data and consensus regarding the adverse effects of biologics during pregnancy. There have been reports in the literature of an increased risk of miscarriage and foetal abnormality but also instances where the pregnancy has progressed normally and there has been no harm to the infant.[13]

Monitoring patients being treated with biologics

Reducing the risk of infection in patients taking biologics is an important role for the primary care team. Patients prescribed biologics should be made aware that they have an increased risk of acquiring infections and to report any symptoms early. Strategies such as good food hygiene to reduce the likelihood of food-borne infections, e.g. listeria, and good personal hygiene to reduce the risk of opportunistic infection, e.g. candidiasis, can be discussed.[13] Once the patient is stabilised on treatment, General Practitioners will be involved with ongoing monitoring for adverse effects.

Monitoring for adverse events during administration

Subcutaneous administration of adalimumab and etanercept is usually performed by the patient themselves, but may be performed by a Practice Nurse. The most frequent reactions include: redness, rash, swelling, itching and bruising, however, more severe gastrointestinal and cardiovascular effects can also occur.[3, 10] To reduce injection site reactions patients can be advised to space each new injection site at least 3 cm from the previous site and to apply a damp towel or ice pack to the site for ten to fifteen minutes after the injection, if required.

IV infusions of infliximab, rituximab and tocilizumab are administered in secondary care. Patients require monitoring during the procedure and for one hour afterwards.[10] Infusion reactions are rare, but can be marked and may occur up to 12 days following treatment including: hypertension, hypotension, headache, skin rashes and urticaria and flu-like symptoms.[3, 10]

Monitoring for complications

If a patient taking a biologic medicine develops symptoms of a serious disease or infection then prompt action is required; the treating specialist should be contacted and the possibility of withdrawing the biologic discussed.[13]

Patients taking biologic medicines have an increased risk of developing serious infections. For example, in the first six months of treatment there is an increased likelihood of pneumonia, soft tissue infections and opportunistic infection, particularly latent infections that have been controlled by the production of granulomas (foreign material surrounded by macrophages), e.g. *Mycobacterium tuberculosis* and *Listeria monocytogenes*.[6] Depending on the type and severity of the infection, there may be a lower threshold for prescribing antibiotics.[2] The rate of infection is dependent on baseline risk and is also influenced by age, other medicine use and co-morbidities, e.g. chronic obstructive pulmonary disease (COPD).[6]

Heart failure may occur or be exacerbated in patients taking biologic medicines.[13] Treatment with biologics should be discontinued if heart failure develops and patients with mild heart failure should be regularly monitored and treatment withdrawn if the condition worsens.[13] Etanercept and infliximab are known to be associated with an increased risk of heart failure.[13] It is not known if there is an association between adalimumab use and heart failure as no trials have been conducted, however, it is generally assumed a similar risk is associated with its use.[13]

Interstitial lung disease is associated with rheumatoid arthritis and can be life threatening. Patients should be monitored for shortness of breath or dry cough.[14] The incidence of interstitial lung disease is increased with the use of etanercept, infliximab and adalimumab.[13] It is likely that the risk of a patient developing interstitial lung disease is also influenced by the concomitant use of methotrexate,[13] which can itself cause pulmonary fibrosis.

A periodic skin examination for non-melanoma skin cancer is appropriate for patients who are at increased risk, e.g. patients with a history of psoriasis or those treated with photochemotherapy (PUVA).[14]

People with rheumatoid arthritis are also approximately 2 – 2.5 times more likely than people in the general population to develop lymphoma.[13] In addition, there have been studies suggesting that the risk of developing lymphoma may be increased in patients taking biologics for inflammatory conditions, however, the overall evidence for this is mixed.[13]

The use of etanercept, infliximab and adalimumab has been associated with both peripheral and central demyelination.[13] These medicines should not be prescribed to patients with multiple sclerosis and should be used with caution in patients with a history of other demyelinating diseases.[13]

Treatment with biologics has also occasionally been associated with autoimmune diseases, e.g. lupus-like syndrome, autoimmune uveitis, vasculitis or inflammatory bowel disease.[13, 15]

Laboratory investigations

Guidance varies on the type and frequency of laboratory tests required for patients taking biologic medicines. Laboratory tests may include:[16]

- CRP – to monitor the inflammatory response
- FBC – the use of biologics has been associated with various cytopaenias, e.g. neutropaenia, thrombocytopaenia
- LFTs – due to reports of hepatotoxicity
- Creatinine and electrolytes – as a baseline, particularly prior to IV infusion

Depending on the clinical situation, laboratory testing should be repeated every three to six months, or more frequently if the patient is being treated with other DMARDs.[14] When interpreting the results it is important to note that although the absolute laboratory values are important, any consistent trend in values, such as a steady downward pattern or a rapid fall or rise in a parameter may signal the need for clinical assessment and further investigations.[14]

Managing patients who require surgery

There is some evidence that the risk of peri-operative infection is increased in patients taking biologics, although this varies, e.g. with the type of surgical procedure and the co-morbidities of the patient. There is a potential for a flare of the condition being treated when treatment is withheld, e.g. in rheumatoid arthritis activity, however, most guidelines advocate stopping TNF inhibitors before and after surgery.[13]

It is recommended that if patients require major surgery during treatment with biologics the medicine should be withheld prior to surgery for three to five times the half-life of the medicine being used.[13] The half-life of the most commonly used biologics is: 100 hours for etanercept, 15 – 19 days for adalimumab and 8 – 9.5 days for infliximab.[13] For example, a patient undergoing a major procedure should have etanercept withdrawn for 13 – 21 days and adalimumab 45 – 95 days prior to the operation. The medicine can be resumed 10 – 14 days after surgery provided there are no signs of infection and the wound is healing satisfactorily. The risk of post-operative infection is likely to be influenced by the type of procedure the patient is undergoing and the presence of comorbidites. Infection risk should therefore be assessed on a case-by-case basis.

Application for renewal of Special Authority subsidy

Special Authority subsidy for the treatment of inflammatory conditions with biologics can be renewed by General Practitioners who have written confirmation from a relevant specialist recommending that treatment be continued. This is dependent on specific renewal criteria (Table 2, over page). For some General Practitioners renewal may also involve monitoring a patient's clinical response to treatment when patient access to specialist assessment is limited or difficult, e.g. a rural location. For example, in patients with rheumatoid arthritis this may include: a regular clinical assessment of the

number of inflamed joints, any improvements in the patients daily function, the need for any additional anti-inflammatory agents and requests for laboratory tests, e.g. CRP, FBC and LFTs.[1, 16]

Patients who require specialist assessment prior to the renewal of a Special Authority need to be seen by the treating specialist before the approval expires. Most renewals are valid for six months.

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Table 2 : Special Authority renewal criteria for biologic medicines for the treatment of inflammatory conditions[3, 17]

Condition	Medicine	Renewal criteria*
Rheumatoid arthritis	Etanercept or adalimumab	At least a 50% decrease in active joint count (number of swollen or tender joints) from baseline. After the initial response the patient is assessed six-monthly and treatment withdrawn if a response is not maintained.
Juvenile idiopathic arthritis	Etanercept or adalimumab	At least a 50% decrease in active joint count following three to four months of treatment and improvement in overall clinical condition
Ankylosing spondylitis	Etanercept or adalimumab	At least a 50% decrease in active joint count from baseline, or at least four points on the ten point Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). For further information on calculating BASDAI see: www.basdai.com
Crohn's disease	Adalimumab	A reduction in the Crohn's Disease Activity Index (CDAI) of 100 points or a score of 150 or less. Patients with fistulising Crohn's disease require additional confirmation from a Gastroenterologist that there has been a decrease in the number of open draining fistulae by at least 50%, or a marked reduction based on the Fistula Assessment score in addition to a decrease in induration and pain.† For further information on calculating CDAI see: www.ibdjohn.com/cdai
Chronic plaque psoriasis	Etanercept or adalimumab	Requirements vary. Patients with "whole body" severe chronic plaque psoriasis prior to treatment require an ongoing reduction in the Psoriasis Area and Severity Index (PASI) of 75% or more. Patients with localised disease, e.g. of the face or sole of the foot at the start of treatment, must have a reduction in the PASI symptom subscore for erythema, thickness and scaling compared to baseline or a reduction of 75% or more in the area affected. For further information on calculating PASI see: www.dermnetnz.org
Psoriatic arthritis	Etanercept or adalimumab	A clinically significant result and at least a 50% reduction in active joint count after three to four months of treatment

* Including written confirmation from the treating specialist. † A form to calculate a fistula assessment score is available from: **www.pharmac.health.nz/ckeditor_assets/attachments/435/fistula-assessment-form-nz.pdf**

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