Tofacitinib

Approved indication: rheumatoid arthritis
Xeljanz (Pfizer)
5 mg film-coated tablets
Australian Medicines Handbook section 15.1

Rheumatoid arthritis is now managed with disease-modifying antirheumatic drugs, such as methotrexate. If there is an inadequate response, a biological drug may be prescribed. These include the tumour necrosis factor (TNF) alpha antagonists, such as adalimumab and etanercept. The choice of treatment for moderate to severe active rheumatoid arthritis has now been expanded with the approval of tofacitinib. This is a Janus kinase inhibitor, which blocks the cytokine pathway that leads to the activation of lymphocytes. The Janus kinase inhibitors therefore have effects on immune and inflammatory processes.[1,2]

In contrast to adalimumab and etanercept, tofacitinib can be taken orally. Although a steady state is achieved after 24–48 hours of tofacitinib 5 mg twice daily, the maximum effect on lymphocytes takes 8–10 weeks. Most of the drug is metabolised, primarily by cytochrome P450 (CYP) 3A4. Tofacitinib is therefore contraindicated in severe liver disease and can interact with inducers and inhibitors of CYP3A4. As 30% of the drug is excreted unchanged, a dose reduction is recommended if the patient has a creatinine clearance below 50 mL/minute.

The clinical trials of tofacitinib assessed patients using the criteria of the American College of Rheumatology (ACR). The outcomes were measured by the reduction in the number of affected joints and improvements in other assessments. For example an ACR20 response represents a 20% change from baseline.

Tofacitinib monotherapy was studied in a trial of 611 patients who had had an inadequate response to a disease-modifying drug. Four different regimens were studied with efficacy assessed after three months. Among the patients taking the recommended dose of 5 mg twice daily, 59.8% achieved an ACR20 response compared with 26.7% of the placebo group. The corresponding results for an ACR70 response were 15.4% versus 5.8%.[3]

Another trial compared tofacitinib monotherapy with methotrexate in 956 patients who had not previously been treated with methotrexate. After six months 25.5% of the 369 patients who took tofacitinib 5 mg twice daily had achieved an ACR70 response. Only 12% of the 184 patients who took methotrexate achieved this response. X-rays showed significantly less disease progression with tofacitinib.[4]

Tofacitinib has also been studied in combination with methotrexate or other (non-biological) disease-modifying antirheumatic drugs. Patients who had had an inadequate response to previous treatment either added tofacitinib or a placebo. Most (79%) of the 795 patients were taking methotrexate. At six months an ACR20 response had been achieved by 52.1% of the 315 patients treated with tofacitinib and 30.8% of the 159 patients taking placebo.[5]

The combination of tofacitinib and methotrexate has been studied in a trial that investigated the radiological changes in the joints of 800 patients. After six months, 51.5% of the 321 patients who took tofacitinib 5 mg twice daily had achieved an ACR20 response compared with 25.3% of the 160 patients in the placebo groups. Compared to methotrexate alone, the combination resulted in less joint space narrowing and fewer erosions on X-ray. However, the 5 mg dose was not statistically superior to placebo at six months.[6]

For patients with arthritis that is not adequately controlled by methotrexate, adding a TNF antagonist may be considered. This strategy has been compared to adding tofacitinib in a trial involving 717 patients. There were five different regimens in this trial. Two involved starting patients on placebo before switching to tofacitinib. The comparison regimen was adalimumab injected every two weeks. At six months the ACR20 response was achieved by 51.5% of the patients taking tofacitinib 5 mg twice daily and 47.2% of the patients given adalimumab. This response was only achieved by 28.3% of the patients in the placebo groups.[7]

Tofacitinib has also been studied in patients who have had an inadequate response to TNF antagonists. The four regimens in the trial either added tofacitinib to methotrexate at the start of the study or after three months on placebo. There were 399 patients of whom 133 took tofacitinib 5 mg twice daily for six months. Most of the patients had previously tried adalimumab or etanercept. Three months after adding tofacitinib 5 mg the ACR20 response was 41.7% whereas only 24.4% of the 131 patients in the placebo groups had responded.[8]

As tofacitinib acts on the immune system, patients have a higher risk of serious infections. Hepatitis B and C, and tuberculosis should be excluded before treatment begins. Live vaccines should not be given. Serious infections in the trials included cellulitis, herpes zoster, pneumonia and urinary tract infections. Tofacitinib will reduce neutrophil and lymphocyte counts. Regular monitoring is required as neutropenia and lymphopenia may require treatment to be stopped. The patient's haemoglobin should

also be monitored as life-threatening anaemia has been reported.[7]

Routine monitoring of liver function is recommended and the patient's lipid concentrations will also need to be measured as tofacitinib increases cholesterol concentrations. Although the relationship to tofacitinib is unclear, serious adverse events have included gastrointestinal perforation, interstitial lung disease, lymphoma and skin cancer.

Tofacitinib should not be used in pregnancy or lactation, or by women trying to conceive. It does not affect the pharmacokinetics of combined oral contraceptive pills.

While tofacitinib produces a 20% improvement in ACR criteria for some patients, there is less evidence about its effect on the long-term progression of rheumatoid arthritis. The potential advantages of tofacitinib have to be balanced against the risk of possibly fatal adverse reactions. Whether the risk of harm is greater than with other biological drugs is currently unclear. The combination of tofacitinib with other biological or immunosuppressive drugs is contraindicated. Longer term study will be needed to establish the place of tofacitinib in the treatment of rheumatoid arthritis. It will probably be reserved for specialist use in patients with arthritis that has not responded to other disease-modifying drugs.

T manufacturer provided the AusPAR and the product information

REFERENCES *A

1. Kubler P. Janus kinase inhibitors: Mechanisms of action. Aust Prescr 2014;37:154-7.
2. Walker J, Smith M. Janus kinase inhibitors in rheumatoid arthritis: Clinical applications. Aust Prescr 2014;37:158-60.
3. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al.; ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012;367:495-507.
4. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al.; ORAL Start Investigators. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014;370:2377-86.
5. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med 2013;159:253-61.
6. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al.; ORAL Scan Investigators. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 2013;65:559-70.
7. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al.; ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508-19.
8. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al.; ORAL Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013;381:451-60.

First published online 14 October 2015

Vedolizumab

Approved indication: inflammatory bowel disease
Entyvio (Takeda)
vials containing 300 mg powder for reconstitution
Australian Medicines Handbook section 12.6

In Crohn's disease and ulcerative colitis there is an influx of inflammatory cells into the gut. Conventional treatments, such as corticosteroids, aim to reduce this inflammation. The development of biological drugs such as adalimumab and infliximab has increased the options for managing inflammatory bowel disease that has not responded to conventional treatment. Vedolizumab is a monoclonal antibody that binds to a human integrin. It reduces inflammation by inhibiting the adhesion of T lymphocytes to gastrointestinal tissues.

Vedolizumab is given by intravenous infusion. An induction regimen is followed by infusions every eight weeks. The half-life of the antibody is approximately 25 days, but how it is eliminated is uncertain. No studies have been carried out in people with renal or hepatic impairment. There have also been no studies of drug interactions.

The main trial of vedolizumab in ulcerative colitis investigated induction and maintenance therapy in patients whose previous treatments had been unsuccessful. In a double-blind part of the trial, 225 patients were randomised to vedolizumab and 149 to placebo. A second cohort included 521 patients who were given open-label vedolizumab. Induction infusions were given two weeks apart. Patients from either cohort who showed a response to vedolizumab after six weeks were randomised to receive further infusions of vedolizumab every four weeks or eight weeks, or placebo, for up to one year.

In the first cohort, after six weeks, 47.1% of the vedolizumab group and 25.5% of the placebo group had a clinical response. In the second, open-label cohort there was a response in 44.3% of patients. After a year, 41.8% (51/122) of the patients treated every eight weeks and 44.8% (56/125) of those treated every four weeks were in clinical remission. Only 15.9% (20/126) of the placebo group went into remission. Sigmoidoscopy showed mucosal healing in 19.8% of the placebo group, 51.6% of the eight-weekly group and 56% of the four-weekly vedolizumab group.[1]

The main trial of vedolizumab in Crohn's disease had a similar design. It enrolled patients who had not tolerated or not responded to other drugs. One cohort compared vedolizumab and placebo while another took open-label vedolizumab for induction. Patients who responded to vedolizumab after six weeks were then randomised to continue receiving it every four or eight weeks, or to switch to placebo for up to a year.[2]