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Conflict of interest: none declared

New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Dutasteride

Avodart (GlaxoSmithKline)

500 microgram capsules

Approved indication: benign prostatic hyperplasia

Australian Medicines Handbook section 13.2.2

Although surgery is the definitive treatment for benign prostatic hyperplasia, some patients can be managed with drugs (see 'Drug treatment of benign prostatic hypertrophy', *Aust Prescr* 1995;18:30-2). The drug treatments include finasteride which inhibits the conversion of testosterone to dihydrotestosterone. This androgen is thought to be responsible for stimulating the growth of the prostate.

Like finasteride, dutasteride is a 5-alpha reductase inhibitor. Finasteride mainly inhibits the type II enzyme found in the prostate, while dutasteride also inhibits the type I enzyme found in the liver and skin. After two weeks of treatment with dutasteride there is a reduction of up to 90% in the concentration of dihydrotestosterone.

The bioavailability of the drug varies from 40% to 94% and it is extensively metabolised. Although cytochrome P450 3A4 is involved in the metabolism, few specific studies of interactions have been carried out in patients. There is a potential for interactions with other drugs metabolised by this enzyme. Most of the metabolites are excreted in the faeces. The half-life of the drug is up to five weeks so it remains in the body for several months after treatment stops. The onset of the full treatment effect is also slow.

In placebo-controlled clinical trials the efficacy of dutasteride has been evaluated using symptom scores in 4325 men. At the

start of the studies the average score was 17/35. After two years of treatment this score was significantly reduced by 4.5 points. Dutasteride significantly reduced the volume of the prostate gland. It also significantly improved the urinary flow rate and reduced the risk of acute urinary retention.¹ These effects continued during a two-year open-label extension of the trials.²

Dutasteride has adverse effects on sexual function. Patients may develop a decreased libido, ejaculation disorders or impotence. Serum testosterone may increase, but prostate specific antigen concentrations will be reduced by dutasteride.

As dutasteride may affect the development of a male fetus the capsules should not be handled by pregnant women.

Like finasteride (see 'The price of urine', *Aust Prescr* 1995;18:26-7), the effect of dutasteride is modest. A placebo can improve a patient's symptom score by 2.3 points and the statistically significant change in urinary flow rate is only 1.3 mL/second greater than placebo.¹ Drug treatment should therefore only be used if self-management strategies do not work.

T manufacturer provided only the product information

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Eculizumab

Sorilis (Alexion)

30 mL vials containing 10 mg/mL

Approved indication: paroxysmal nocturnal haemoglobinuria

Australian Medicines Handbook Appendix A

Paroxysmal nocturnal haemoglobinuria is a rare cause of haemolytic anaemia. Patients have stem cells with a somatic mutation which results in red blood cells being unable to anchor a complement inhibitory protein to their cell membrane. The absence of this protein makes the affected red blood cells vulnerable to complement-induced haemolysis. This haemolysis results in haemoglobinuria and anaemia. Patients are also prone to thrombosis, and thromboembolism is a common cause of death.

Blocking the action of complement on the abnormal cells could reduce haemolysis. Eculizumab achieves this by binding to complement protein C5.

Eculizumab is a humanised monoclonal mouse antibody (IgG). After infusion over 35 minutes, eculizumab rapidly reduces complement activity. This infusion is given weekly for five weeks and then repeated every two weeks. The half-life of eculizumab is approximately 11 days and maintaining the serum concentration above 35 microgram/mL suppresses haemolysis.

A preliminary study treated 11 patients for 12 weeks. Concentrations of lactate dehydrogenase, a marker of haemolysis, fell after the first dose of eculizumab. Haemolytic activity was completely blocked in patients whose serum concentration remained above 35 microgram/mL.¹ These patients continued in a 52-week extension study and nine showed complete blockade of haemolysis throughout. This reduction in haemolysis raised the proportion of affected cells, as a proportion of the total number of red cells, from 37% at baseline to 58% at 64 weeks.²

To investigate the effect of eculizumab on transfusion requirements 87 patients were randomised in a double-blind controlled trial. After 26 weeks haemoglobin concentrations had stabilised in 49% of the patients given eculizumab and 51% had not required a blood transfusion. The haemoglobin did not stabilise in the placebo group and they all needed transfusions. The mean number of units of packed cells used was three in the eculizumab group and 11 in the placebo group. Patients given eculizumab had an improved quality of life.³

An open-label study, with less stringent inclusion criteria, then treated 97 patients for 52 weeks. Haemolytic activity was suppressed in 89 patients throughout the study. The survival of the affected cells increased their proportion in the red cell population from 39% to 55%. Transfusions reduced from an annual mean of 12 units of packed cells to six units. There were 49 patients who did not need a transfusion while being treated with eculizumab.⁴

During this study the most frequent adverse effects were headache, upper respiratory tract symptoms, nausea and fever. These symptoms tended to be less frequent during the second six months of treatment.⁴ Infections are common, but usually mild, however eculizumab increases susceptibility to meningococcal infections because of its effect on the complement system. Patients should therefore be given a meningococcal vaccine before starting treatment.

Patients can develop antibodies to eculizumab, but so far these have not reduced the effect of the drug. There is still a potential for infusion reactions.

An analysis of the thromboembolism rate in the studies found that it fell from 7.37 events/100 patient years to 1.07 events/100 patient years with treatment.⁵ While the reduction is significant, there is not yet enough evidence to change the management of patients being treated with anticoagulants. The effect of eculizumab on survival is currently unknown.

Bone marrow transplantation can cure the condition, but donors are scarce and the procedure has significant risks. Eculizumab can reduce haemolysis, but the outcome of long-term treatment is uncertain. As treatment increases the proportion of affected cells in the circulation, people may have a high risk of serious haemolysis when they stop the drug. While eculizumab will reduce the need for treatments such as transfusion, these savings will not offset the high cost of the drug.

manufacturer did not respond to request for data

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Tocilizumab

Actemra (Roche)

4 mL, 10 mL and 20 mL vials containing 20 mg/mL

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2

Patients with moderate to severe rheumatoid arthritis, which does not respond to disease-modifying antirheumatic drugs, can be treated with biological therapies such as the inhibitors of tumour necrosis factor alpha (see 'Tumour necrosis factor alpha inhibitors for the treatment of adult rheumatoid arthritis', *Aust Prescr* 2004;27:43–6). One of the actions of tumour necrosis factor is regulating the production of pro-inflammatory molecules such as the interleukins. High concentrations of interleukin-6 have been associated with inflammatory disorders including rheumatoid arthritis. The inflammatory action may be blocked by antibodies against interleukin-6 receptors, such as tocilizumab.

Tocilizumab is a humanised monoclonal antibody (IgG) produced in Chinese hamster ovary cells by genetic engineering. It binds to the interleukin-6 receptors throughout the body leading to rapid reductions in erythrocyte sedimentation rate and concentrations of C-reactive protein.

Tocilizumab has to be diluted and given by infusion over one hour. The infusion is repeated every four weeks. Although clearance is concentration dependent, the pharmacokinetics of tocilizumab may be nonlinear at low concentrations. At steady state the half-life of the drug is 8–14 days, but this is prolonged at higher concentrations. The activity of cytochrome P450 1A2, 2C9, 2C19 and 3A4 may increase with tocilizumab, potentially affecting the metabolism of other drugs.

After development in Japan, a phase II trial was carried out in Europe. It randomised 359 patients who had experienced an inadequate response to methotrexate. They were given tocilizumab 2 mg, 4 mg or 8 mg/kg, with or without methotrexate, or methotrexate alone, for 16 weeks. Using the criteria of the American College of Rheumatology, a 20% improvement occurred in 41% of the patients taking methotrexate, 31–63% of those taking tocilizumab and 63–74% of those taking both drugs.¹

Phase III studies then used doses of 4 mg or 8 mg/kg. In one randomised study 418 patients received these doses and 204 had placebo infusions. Although the patients had had an inadequate response, they all continued their weekly doses of methotrexate for the 24 weeks of the trial. The response to the combined treatment was significantly greater than to methotrexate alone. A 20% improvement was achieved by 59% of the patients taking tocilizumab 8 mg/kg, 48% of those taking 4 mg/kg, but only 26% of the control group.²

Another trial included patients whose rheumatoid arthritis

had persisted despite treatment with disease-modifying antirheumatic drugs. A group of 805 patients were randomised to add tocilizumab 8 mg/kg while 415 added a placebo. The patients were treated every four weeks for 24 weeks. A 20% improvement was obtained by 61% of the tocilizumab group and 25% of the placebo group. Concentrations of C-reactive protein fell to normal within two weeks of starting tocilizumab.³

The SAMURAI study in Japan compared the radiological effects of tocilizumab monotherapy to those of disease-modifying antirheumatic drugs. A total of 265 patients were treated for 52 weeks. There was no progression of joint damage in 56% of the patients given tocilizumab compared with 39% of the others.⁴

Tocilizumab has also been studied in patients whose rheumatoid arthritis had not responded to tumour necrosis factor inhibitors. These drugs were stopped, and the 499 patients were given methotrexate for at least 12 weeks before being randomised to also have infusions of tocilizumab (4 mg or 8 mg/kg) or placebo every four weeks. After 24 weeks, there had been a 20% improvement in 50% of the patients given 8 mg/kg, 30% of those given 4 mg/kg, but only 10% of those who took methotrexate and placebo. This response was not influenced by whichever tumour necrosis factor inhibitors had been used previously.⁵

As tocilizumab affects the immune system, patients are at risk of infections. There may be a decline in the neutrophil count (and platelets) so the full blood cell count should be monitored. Serious infections, such as pneumonia and cellulitis, are more common with the higher doses of tocilizumab. Patients should be tested for latent tuberculosis before starting treatment.

There is an increased risk of cancer in patients with rheumatoid arthritis and this could be elevated by tocilizumab. In the SAMURAI study three cancers were found in the tocilizumab group with none in the group given disease-modifying antirheumatic drugs.⁴

As tocilizumab is an immunoglobulin some patients will have infusion reactions, including anaphylaxis. Approximately 6% of the patients given 8 mg/kg had infusion reactions.

Gastrointestinal disorders are common. Although they are mainly mouth ulceration and gastritis, a few patients have suffered perforation of the gut, mainly as a complication of diverticulitis.

Particularly when given with methotrexate, tocilizumab can alter liver function. Regular monitoring of liver function is required and the dose should be adjusted according to the results. It is uncertain if treatment increases overall cardiovascular risk, but tocilizumab can cause a rise in lipids and blood pressure.

Tocilizumab appears to work best in combination with other drugs. It is therefore approved for use with methotrexate or non-biological disease-modifying antirheumatic drugs when previous therapy has been unsatisfactory or not tolerated.

Monotherapy can be used if the patient has moderate to severe disease and cannot take methotrexate. The long-term safety of monthly infusions is unknown, but studies are continuing.

T T T manufacturer provided clinical evaluation

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The T-score (**T**) is explained in 'New drugs: transparency', *Aust Prescr* 2009;32:80-1.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

[†] At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.emea.europa.eu).

Answers to self-test questions

- | | | | |
|----------|----------|----------|----------|
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| 2. True | 4. False | 6. False | 8. False |

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