

## References

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*Conflict of interest: none declared*

## Self-test questions

*The following statements are either true or false (answers on page 105)*

7. Thiazide diuretics are as effective as ACE inhibitors in reducing overall mortality in patients with hypertension.
8. Treatment with thiazide diuretics is associated with significantly more strokes than treatment with ACE inhibitors.

## New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been 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.

### Adalimumab

Humira (Abbott Australia)

vials/pre-filled syringes containing 40 mg solution

Approved indication: rheumatoid arthritis

Australian Medicines Handbook section 15.2.1

Modern treatment for rheumatoid arthritis aims to modify the disease process with drugs such as methotrexate.<sup>1</sup> In some patients treatment with disease-modifying drugs is unsuccessful and biological agents such as the inhibitors of tumour necrosis factor alpha (TNF- $\alpha$ ) may be needed.<sup>2</sup>

Adalimumab is a genetically engineered antibody. It is a 'humanised' antibody as its gene sequence is not derived from animals. Adalimumab binds to TNF- $\alpha$  preventing it from acting on receptors on the surface of cells. This blocks the inflammatory process and results in a rapid fall in the erythrocyte sedimentation rate and concentrations of C-reactive protein.

Although adalimumab only needs to be administered once every two weeks, it has to be injected. After subcutaneous injection it takes five days to reach the peak serum concentration. These concentrations are higher than the concentration in synovial fluid. Serum concentrations are

increased if the patient is also taking methotrexate.

Significantly more patients respond to adalimumab than to placebo. After 26 weeks 46% of patients will have had a 20% improvement compared to 19% of those given a placebo. A study of 36 patients who took adalimumab for two years found that there was no radiological progression of the arthritis in 15.<sup>3</sup>

Adalimumab has also been studied in combination with methotrexate. After 24 weeks there was a 20% improvement in 45 of the 67 patients taking methotrexate and adalimumab 40 mg. Only nine of the 62 patients who took methotrexate and a placebo had a similar response.<sup>4</sup>

As adalimumab has an immunosuppressant effect there is a risk of serious infection. Patients should be checked for latent tuberculosis before they start treatment. Caution is also needed if the patient has a demyelinating disease. Antibodies to adalimumab can develop during treatment and this tends to reduce the therapeutic response. Some patients experience hypersensitivity reactions.

During clinical trials 6.6% of patients discontinued treatment with adalimumab because of adverse effects. Common adverse effects include injection site reactions, dizziness and infections.

Treatment may reduce haemoglobin and increase lipid concentrations.

Although a 20% improvement was the outcome used to establish efficacy in trials<sup>4</sup>, patients may not notice much change. Less than one patient in four will experience a 70% improvement in their arthritis while taking methotrexate and adalimumab. Currently, there is limited information whether the modest benefits seen in the trials will translate into long-term prevention of disability. There is also concern that long-term inhibition of TNF- $\alpha$  could increase the risk of autoimmune diseases or cancer.

There are no direct comparisons of adalimumab with the other TNF- $\alpha$  inhibitors. A meta-analysis suggests that no product is clearly more efficacious than the others.<sup>5</sup>

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## Alefacept

Amevive (Biogen-Idec)

vials containing 7.5 mg and 15 mg as powder for reconstitution

Approved indication: chronic plaque psoriasis

Australian Medicines Handbook section 8.6

Some patients with severe psoriasis will require systemic treatment to control the inflammation. Sometimes this requires the use of immunosuppressants such as cyclosporin and methotrexate.

Alefacept is an immunosuppressant protein produced by genetic engineering. It binds to the CD2 receptor on T lymphocytes. This interferes with the lymphocyte activation which may contribute to the inflammation and proliferation of keratinocytes in psoriasis. Treatment with alefacept also reduces the lymphocyte count.

The recommended treatment regimen is 15 mg intramuscularly or 7.5 mg intravenously. Doses are given weekly for 12 weeks. Although there is limited information about the pharmacokinetics of alefacept, it has a half-life longer than 10 days after intravenous injection.

A trial, using a range of intravenous doses, compared alefacept with placebo in 229 patients. As judged on the 0–72 scale of the psoriasis area and severity index, there were significant improvements in the patients given alefacept. Overall, 19 (11%) of the 170 patients randomised to take alefacept, but none of the placebo group, were clear of psoriasis at the end of the course of injections. Compared to their baseline measurements, 60% of the patients given 0.075 mg/kg had a 50% reduction in their psoriasis score.<sup>1</sup>

Another placebo-controlled trial investigated intramuscular alefacept (10 mg or 15 mg) in 507 patients with chronic plaque psoriasis. Twelve weeks of treatment resulted in 57% of the patients given 15 mg alefacept having a reduction of at least 50% in their psoriasis scores. The peak effect of the drug occurred after the course of injections was completed.<sup>2</sup>

Although the improvement in the patients' psoriasis can continue after treatment, some may benefit from a second course. A two course regimen was studied in a trial of 553 patients with chronic plaque psoriasis. These patients were randomised to receive two courses of intravenous alefacept 12 weeks apart, or a course of alefacept followed by placebo, or a course of placebo injections followed by alefacept. Two weeks after completion of the second course, 55% of the 183 patients who had received two courses of alefacept had a greater than 50% reduction in their psoriasis scores. Only 25% of the 142 who had received a placebo in their second course achieved the same outcome. The median duration of the response, in patients who responded well to their first course of alefacept, was more than seven months.<sup>3</sup>

Although symptoms such as chills and injection site reactions are common problems with alefacept, it has the potential for more serious adverse effects. Patients need their differential lymphocyte count checked every other week because of the risk of lymphopaenia. Alefacept should be withheld if the CD4 lymphocyte count is below normal.

The immunosuppressive effects of alefacept increase the risk of infections, particularly if the course is repeated. Some patients developed malignancies, such as lymphoma, during the clinical trials.

Psoriasis is a chronic disease, but the safety and efficacy of more than two courses of alefacept is unknown. While alefacept has a greater effect than placebo, up to 35% of patients will improve while taking a placebo.<sup>2</sup> As alefacept is likely to be expensive, it would be useful to know which patients will respond. Approximately nine patients need treatment to achieve clearance of one person's psoriasis.<sup>1</sup> Phototherapy and drugs such as topical corticosteroids were prohibited during the

trials, so it would be interesting to know how these treatments compare with alefacept.

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## Atomoxetine hydrochloride

Strattera (Eli Lilly)

10 mg, 18 mg, 25 mg, 40 mg and 60 mg capsules

Approved indication: attention deficit hyperactivity disorder

Australian Medicines Handbook section 18.5

Controversy surrounds the diagnosis of attention deficit hyperactivity disorder and its treatment with stimulant drugs (see *Aust Prescr* 1995;18:60-4). Prescribers now have the option of treating patients with atomoxetine, a non-stimulant drug.

Atomoxetine inhibits the reuptake of noradrenaline by presynaptic neurons, but it is uncertain if this explains the therapeutic effects. The drug is well absorbed, but its bioavailability varies with each patient's oxidative metabolism. The bioavailability is higher in patients with reduced metabolism and their plasma concentrations of atomoxetine are also higher because metabolic clearance is reduced. As the metabolism of atomoxetine involves cytochrome P450 2D6 there is a potential for interactions with other drugs metabolised by this enzyme system. The half-life of atomoxetine is 5.2 hours, but this increases to 21.6 in poor metabolisers. Most of the metabolites are excreted in the urine.

A placebo-controlled dose-response study titrated twice-daily doses of atomoxetine at weekly intervals in 297 children. It found that, after eight weeks, a total daily dose of 1.2 mg/kg improved the children's symptoms on a variety of rating scales. This dose reduced the score on the Attention-Deficit/Hyperactivity Disorder Rating Scale (ADHD RS) by 13.6, from a baseline score of 39.2, while placebo achieved a reduction of 5.8 from a baseline score of 38.3.<sup>1</sup>

Another trial compared once-daily doses with placebo for six weeks in 171 children. Atomoxetine reduced the mean score on the ADHD RS by 12.8 from a baseline of 37.6, while placebo reduced the score by 5.0 from a baseline of 36.7. This suggests single daily doses have similar efficacy to divided doses.<sup>2</sup>

Atomoxetine has been compared with methylphenidate in a 10-week, randomised, open-label trial. In the 178 children who took atomoxetine, the ADHD RS score decreased from 39.4 to 20.0, while it decreased from 37.6 to 19.8 in the 40 children who took methylphenidate.<sup>3</sup>

Atomoxetine is approved for use in children over six years old and adolescents, but it can also be used in adults. A small double-blind, crossover study found that a daily dose of 80 mg atomoxetine reduced the ADHD RS from 30.0 to 21.5 while a placebo had no effect.<sup>4</sup> Two larger randomised placebo-controlled trials showed that 10 weeks treatment with atomoxetine produced greater reductions in the investigators' ratings of the patients' condition. In the trial involving 280 adults, it reduced the total symptom score from 33.6 to 17.6 while placebo reduced it from 33.2 to 23.9. In the other trial (256 adults) atomoxetine reduced the mean score from 34.9 to 17.6 while placebo reduced it from 34.2 to 22.6.<sup>5</sup>

Most of the trials were relatively short, so the long-term efficacy and safety is uncertain. Common complaints from children were abdominal pain and vomiting, while adults reported constipation, nausea, dry mouth and reduced appetite. Atomoxetine increases the pulse rate and blood pressure, but some patients will develop postural hypotension. In adults there may be urinary hesitancy or retention and atomoxetine can impair sexual function. As atomoxetine may affect growth, height and weight should be monitored during the treatment of children.

Atomoxetine has the advantage of not being a controlled drug and it does not appear to cause dependence. However, a therapeutic advantage over stimulants has not been shown.

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## Fenofibrate

Lipidil (Laboratoires Fournier SA)

67 mg capsules

160 mg film-coated tablets

Approved indication: dyslipidaemia

Australian Medicines Handbook section 6.6

Although HMG CoA reductase inhibitors are the drugs of choice for patients with hypercholesterolaemia, fibrates are sometimes considered if the high density lipoprotein (HDL)-cholesterol is low. Fibrates such as fenofibrate are more likely to be used for hypertriglyceridaemia as their main action is to decrease serum triglycerides.

After absorption fenofibrate is rapidly metabolised to fenofibric acid. By acting on the peroxisome proliferator activated receptor, fenofibric acid reduces total cholesterol, low density lipoprotein (LDL)-cholesterol, triglycerides, apolipoprotein B and very low density lipoprotein (VLDL). Fenofibric acid increases HDL. These effects make fenofibrate suitable, as an adjunct to diet, for the treatment of type II, III, IV and V dyslipidaemia, and the dyslipidaemia associated with type 2 diabetes. It can also be prescribed if dietary changes have not controlled hypercholesterolaemia.

Several placebo-controlled trials have confirmed the effect of fenofibrate on lipids. Some trials have compared fenofibrate with HMG CoA reductase inhibitors. In one study of 265 patients with primary hyperlipidaemia, fenofibrate was as effective as pravastatin in reducing total cholesterol and LDL-cholesterol. Fenofibrate had a greater effect than pravastatin on HDL-cholesterol (13.2% versus 5.6% increase) and triglycerides (38.7% versus 11.8% decrease).<sup>1</sup> Another 12-week trial of 181 patients found that fenofibrate increased HDL-cholesterol more than atorvastatin (13.3% versus 5.3%).<sup>2</sup> In patients with type 2 diabetes and mixed hyperlipoproteinaemia the increase in HDL-cholesterol was similar with fenofibrate and atorvastatin (10% versus 11%), but atorvastatin caused a greater reduction in total cholesterol (24% versus 16%).<sup>3</sup> Although gemfibrozil is currently the first-choice fibrate for hypertriglyceridaemia, there are no published comparisons with fenofibrate.

In the clinical trials the most common complaint was abdominal pain, but laboratory tests revealed that 75% of patients develop liver function abnormalities. Liver function should be monitored, as cholestatic and chronic active hepatitis have occurred during treatment. As fenofibrate is metabolised in the liver and excreted in the urine, it is contraindicated in patients with hepatic or severe renal dysfunction.

Fenofibrate affects the clotting process<sup>3</sup> and will prolong the prothrombin time. Patients taking warfarin will need to reduce their dose of anticoagulant. Although fibrates rarely cause rhabdomyolysis themselves, concomitant treatment with an HMG CoA reductase inhibitor should usually be avoided because of the increased risk of muscle damage.

Although fenofibrate has been available overseas for several years, there is not much information about its effect on cardiovascular disease. It should probably not be the first-choice fibrate until more outcome data are available.

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## Granisetron

Kytril (Mayne Pharma)

ampoules containing 3 mg/3 mL

2 mg tablets

Approved indications: nausea and vomiting

Australian Medicines Handbook section 12.3.4

Granisetron is another 5HT<sub>3</sub> antagonist (dolasetron, ondansetron and tropisetron are already available). It is approved for the prevention and treatment of nausea and vomiting due to cytotoxic drugs or surgery. Although it is approved for prevention, there are limited data to support the use of granisetron in the treatment of nausea and vomiting due to radiotherapy.

Chemotherapy releases serotonin from the gut and this results in stimulation of vagal nerve terminals and the chemoreceptor trigger zone. Granisetron acts by antagonising the peripheral and central 5HT<sub>3</sub> receptors (see 'Serotonin receptor agonists and antagonists' *Aust Prescr* 1991;14:46-51).

Granisetron is diluted then infused over five minutes, shortly before the cytotoxic therapy is given. A 3 mg dose will prevent vomiting in 50–70% of adult patients given cisplatin. If this preventive regimen does not work, the infusion may be repeated twice in 24 hours. The addition of a corticosteroid increases the effectiveness of granisetron.

To prevent postoperative nausea and vomiting in adults, 1 mg is slowly injected before the anaesthetic is given. A single dose is also effective in treating established postoperative nausea and vomiting.

The tablets can be given before chemotherapy and then continued for up to one week. This formulation has a bioavailability of 60% with peak plasma concentrations

being reached two hours after a dose. The half-life of granisetron is approximately nine hours with most of the drug being metabolised by the liver. No dosage adjustment is recommended for patients with hepatic or renal impairment. Headache is the most frequent adverse reaction, but patients may also complain of constipation or sleepiness. Granisetron promotes liver cancer in rats, but the clinical significance is uncertain. Altered liver function has been reported in humans. Serotonin antagonists may be no more effective than a regimen of metoclopramide and dexamethasone, but they are usually easier to give. Practitioners will now have to decide whether to prescribe dolasetron, ondansetron, tropisetron or granisetron. The drugs appear to be similar in effectiveness, so the choice of treatment may be influenced by its price.

- \* At the time the comment was prepared, information about this drug was available on the web site of the Food and Drug Administration in the USA ([www.fda.gov](http://www.fda.gov)).
- † At the time the comment was prepared, a scientific discussion about this drug was available on the web site of the European Agency for the Evaluation of Medicinal Products ([www.emea.eu.int](http://www.emea.eu.int)).

## NEW FORMULATIONS

### Galantamine

Reminyl (Janssen-Cilag)

8 mg, 16 mg and 24 mg prolonged release capsules

### Mesalazine

Pentasa (Ferring)

1 g/100 mL enemas and 1 g suppositories

Salofalk (Orphan)

500 mg tablets

### Olanzapine

Zyprexa IM (Eli Lilly)

10 mg powder for injection (vials)

### Risperidone

Risperdal Quicklet (Janssen-Cilag)

0.5 mg, 1 mg and 2 mg wafers

## Answers to self-test questions

- |          |          |          |          |
|----------|----------|----------|----------|
| 1. False | 3. False | 5. False | 7. True  |
| 2. True  | 4. True  | 6. False | 8. False |

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