hirsutism. However, they are not in general use in Australia. Flutamide may cause hepatotoxicity, while finasteride is teratogenic.

Management of long-term risks

Insulin resistance is important in the development of the metabolic syndrome and is associated with an increased risk of cardiovascular disease. There are no long-term clinical studies to assess the benefit of metformin in reducing adverse cardiovascular outcomes in women with polycystic ovary syndrome.[5] However, the findings of the Diabetes Prevention Program Research Group (which found lifestyle changes were more effective than metformin in reducing the incidence of type 2 diabetes in people at high risk) suggest that clinicians should persist in working with their patients to achieve lifestyle changes that will reduce body mass and improve insulin sensitivity.[6]

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 133)

9. In polycystic ovary syndrome, the combined oral contraceptive pill has more effect on acne than on hirsutism.
10. Metformin is the drug of choice in the treatment of polycystic ovary syndrome if there are no contraindications to its use.

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.

Agalsidase beta

Fabrazyme (Genzyme)

5 mL vials containing 5 mg powder for reconstitution

20 mL vials containing 35 mg powder for reconstitution

Approved indication: Fabry's disease

Australian Medicines Handbook section 10.6

Lysosomal storage diseases are caused by inborn errors of metabolism. The lack of a specific enzyme results in the substrate accumulating inside lysosomes. Fabry's disease results from an X-linked recessive genetic defect which causes a deficiency of α-galactosidase A. This deficiency leads to the accumulation of globotriaosylceramide in the lysosomes in blood vessel walls. Patients usually die of cerebrovascular disease, myocardial infarction, heart failure or renal failure.

Agalsidase beta is a recombinant form of α-galactosidase A produced by genetically engineered Chinese hamster ovary cells. To replace the deficient enzyme requires an intravenous infusion, for at least two hours, every two weeks.

The infused agalsidase is taken up by endothelial lysosomes and has an elimination half-life of 45–100 minutes. As agalsidase is broken down by peptide hydrolysis, impaired liver or renal function may have little effect on clearance.

As the incidence of Fabry's disease is less than 1 in 100 000 births, clinical trials involve only a few patients. In a placebo-controlled trial 29 adult patients were treated with agalsidase beta for 20 weeks. After 11 infusions, 69% of this group had no microvascular endothelial deposits of globotriaosylceramide in more than 50% of the capillaries seen on renal biopsy. Deposits were also significantly reduced in the skin and the heart. There was also a significant reduction in the amount of globotriaosylceramide in the urine.[1]

Agalsidase is a protein so infusion reactions are common. Approximately half the patients will have an adverse reaction on the day of the infusion. They may develop headache, fever, muscle pain and altered sensation. Oedema, hypertension, nausea and vomiting are also very common.

More than 80% of patients will develop IgG antibodies to agalsidase. The long-term consequences of the seroconversion are unknown, but no evidence of immune-complex glomerulonephritis was seen in the clinical trials. Although agalsidase improves the pathological appearance of tissue samples, its clinical benefits are unknown. Agalsidase did not reduce the pain experienced by patients with Fabry's disease significantly more than placebo.[1] Longer-term follow-up shows some improvement in pain and quality of life, but there were no statistically significant changes. The effect of agalsidase in children is unknown.

Agalsidase is likely to be expensive, but other companies are genetically engineering α-galactosidase A so competition may help to control costs. In the absence of clinical outcomes calculating cost-effectiveness could be a problem.

Reference †

1. International Collaborative Fabry Disease Study Group. Safety and efficacy of recombinant human α-galactosidase A replacement therapy in Fabry's disease. N Engl J Med 2001;345:9-16.

Agalsidase alfa

Replagal (Orphan)

vials containing 3.5 mL concentrate

Approved indication: Fabry's disease

Australian Medicines Handbook section 10.6

Agalsidase alfa is a recombinant form of α-galactosidase A approved in Australia for Fabry's disease. It is produced using human cell lines, but the process should ensure viral safety. Like agalsidase beta, agalsidase alfa is given by infusion every two weeks, however a shorter infusion time (40 minutes) is recommended.

In a six-month trial 14 men with Fabry's disease were randomised to receive agalsidase alfa and 12 were given placebo infusions. At the end of the trial renal biopsies showed a 21% increase in the proportion of normal glomeruli in patients given agalsidase and a 27% decrease in the placebo group. Renal function, assessed by creatinine clearance, decreased in the placebo group, but not in the active treatment group. Agalsidase also significantly reduced the urinary concentration of globotriaosylceramide (the glycosphingolipid which accumulates in Fabry's disease).[1]

Unlike the main trial of agalsidase beta[2], the effect of enzyme replacement on neuropathic pain was a major focus of the trial of agalsidase alfa. Patients given agalsidase had small but statistically significant changes in the severity of their pain and four were able to stop taking analgesics.[1]

Infusion reactions are the most common adverse effects of agalsidase alfa. These reactions may not develop until patients have had a few months of treatment. More than half the patients develop antibodies to the enzyme.

There are differences between the alfa and beta forms of agalsidase, but it is difficult to compare their effectiveness as the trials[1,2] had different designs.[3] The US Food and Drug Administration has approved agalsidase beta, but not agalsidase alfa. Further research is needed to determine the best use of these expensive products. For example, will they change the outcomes for patients if they are started early in the course of the disease?

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Iobenguane sulfate

MIBGen (ANSTO Radiopharmaceuticals)

vials containing 90–110 MBq/mL

Approved indication: tumour localisation

Iobenguane is meta-iodobenzylguanidine, an analogue of noradrenaline. Radiolabelling the iodine (I^{123}) in the molecule therefore enables investigation of the sympathetic nervous system. Iobenguane localises in the adrenal medulla so it can be used in diagnostic scintigraphy of phaeochromocytomas. It can also be used to locate ganglioneuroblastomas, ganglioneuromas and paragangliomas, and to detect end stage neuroblastomas.

Patients are given a slow intravenous injection. The radioactivity spreads around the body with a high uptake in hyperplastic adrenal glands. Most of the dose is excreted in the urine within four days.

In a trial involving 120 patients, radiolabelled iobenguane showed intense uptake in 21 of 24 phaeochromocytomas confined to the adrenals. The uptake was partly increased in the other three tumours, however partial uptake also occurred in 30% of the normal adrenal glands.[1]

In a preoperative study involving 16 patients with neuroblastoma, radiolabelled iobenguane showed the primary tumour in 15 cases.[2]

Although radiolabelled iobenguane is a sensitive technique its advantages over other imaging techniques and its role in diagnostic algorithms will need clarification.

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† 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).

NEW FORMULATIONS

Glatiramer acetate

Copaxone (Aventis Pharma)

20 mg solution in pre-filled syringes

Sodium cromoglycate

Intal CFC-free (Aventis Pharma)

1 mg/actuation metered dose aerosol

NEW STRENGTH

Levobupivacaine hydrochloride

Chirocaine (Abbott)

0.625 mg/mL and 1.25 mg/mL in 100 mL and 200 mL infusion bags

NEW BRANDS

Cefaclor monohydrate

Karlor CD (Aspen Pharmacare)

375 mg tablets

Cephalexin

Ialex (Aspen Pharmacare)

125 mg/5 mL and 250 mg/5 mL oral suspension

Gabapentin

Nupentin (Alphapharm)

100 mg, 300 mg and 400 mg capsules

Answers to self-test questions

1. False
2. True
3. True
4. False
5. True
6. True
7. False
8. False
9. True
10. False

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