Conclusion

Patients with bronchiectasis experience a lot of morbidity. The management requires attention to a diverse range of concerns, but each intervention is simple and generally easily available. A holistic management strategy will improve health outcomes and quality of life.

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Conflict of interest: none declared

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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.

Alglucosidase alfa

Myozyme (Genzyme)

vials containing 50 mg powder for reconstitution

Approved indication: Pompe disease

Australian Medicines Handbook Appendix A

Pompe disease is a rare inherited glycogen storage disease caused by a deficiency in the enzyme acid alglucosidase alfa, which breaks down glycogen to glucose. In patients who lack this enzyme, glycogen builds up in various tissues, particularly cardiac and skeletal muscle, leading to cardiomyopathy, progressive muscle weakness and impaired respiratory function. Early-onset disease typically leads to death from cardiorespiratory failure within the first year of life.

This recombinant form of human alglucosidase alfa is produced in Chinese hamster ovary cells. The recommended dose is 20 mg/kg given as an intravenous infusion every two weeks. Its elimination half-life is 2–3 hours.

The efficacy of recombinant alglucosidase alfa (20 mg/kg or 40 mg/kg fortnightly) has been assessed in 18 infants with Pompe disease (aged 7 months or younger) and compared to a historical cohort of 61 untreated infants. All patients given alglucosidase alfa survived until 18 months of age compared with only one of the 61 untreated controls. However, three of the treated infants required invasive ventilatory support during the study. Thirteen of the 18 treated infants had improved motor development by week 52 of treatment with seven of them being able to walk independently. In general, the higher alglucosidase alfa dose (40 mg/kg) did not seem to offer any clear advantage over the lower dose (20 mg/kg).[1]

In a similarly designed trial, 21 infants aged 3–36 months were given alglucosidase alfa 20 mg/kg fortnightly. Of the 16 infants who did not need invasive ventilatory support at enrolment, four had died, two required invasive ventilatory support and ten did not after a year of treatment. Of the five infants who needed ventilatory support at baseline, one had died and four still required ventilation. A historical comparison of the treated infants with 86 untreated infants showed no significant difference in mortality rate. The trial was inconclusive probably due to the heterogeneous study population.

Around half of the children treated with alglucosidase alfa had an infusion-related reaction, which included fever, rash, urticaria, cough, decreased oxygen saturation, vomiting, flushing and tachycardia. These were usually managed by slowing or interrupting the infusion or giving an antipyretic, antihistamine or corticosteriod. Life-threatening anaphylactic reactions have been reported. Pneumonia, respiratory failure or distress, intravenous catheter-related infection, respiratory syncytial virus infection and gastroenteritis have also occurred following treatment.[1]

There is an increased risk of cardiac arrhythmia and sudden death during general anaesthesia for central venous catheter replacement. This has been observed in patients with cardiac hypertrophy. Acute respiratory failure has also occurred in one

infant following an infusion of alglucosidase alfa. This was possibly associated with fluid overload.

Most infants developed antibodies to the recombinant alglucosidase alfa within three months of starting treatment. High antibody titres have been associated with reduced efficacy and an increased incidence of infusion reactions.[1]

Alglucosidase alfa replacement therapy is the only treatment available for improving the short-term survival of infants with Pompe disease. The long-term prognosis of these patients is not known. As there is a potential for serious adverse events, appropriate medical support, including resuscitation equipment, should be available when treating patients. The effectiveness of alglucosidase alfa in late-onset Pompe disease has not yet been established.

X manufacturer did not respond to request for data

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Duloxetine

Cymbalta (Eli Lilly)

30 mg and 60 mg capsules

Approved indication: major depression

Australian Medicines Handbook section 18.1.2

Duloxetine is a new antidepressant which selectively inhibits serotonin and noradrenaline reuptake. It also weakly inhibits dopamine uptake.

After oral administration of duloxetine, maximum plasma concentrations are reached after six hours. Duloxetine is extensively metabolised in the liver and has an overall half-life of about 12 hours. Most of the metabolites are excreted in the urine.

The efficacy of duloxetine (60 mg/day) has been compared to that of escitalopram (10 mg/day) and placebo in a randomised study of 684 patients (randomised in a 2:2:1 ratio). The onset of efficacy was defined as a 20% sustained reduction in the patient's score on the Hamilton Rating Scale for Depression Maier subscale, by the second week of treatment. The probability of meeting these criteria was 42.6% in patients given duloxetine, 35.2% in patients given escitalopram and 21.5% in patients given placebo. After eight weeks, the probability of responding to treatment (defined as a 50% improvement from baseline on the Hamilton Rating Scale for Depression) was not statistically different between patients given active drug or placebo. Response rates were 48.7% for duloxetine, 45.3% for escitalopram and 36.9% for placebo.[1]

In a review analysing efficacy data from nine duloxetine trials, the number needed to treat for a duloxetine dose of 60 mg/day or more was 6 for a response (based on the Hamilton Rating Scale for Depression), 7–9 for remission and 6–7 for a Clinical Global Impression-defined improvement by eight weeks. For fluoxetine or paroxetine (20 mg/day), the number needed to treat was 7 for a response, 11 for remission and 8 for a Clinical Global Impression-defined improvement.[2]

A safety analysis revealed significantly more nausea, dry mouth, vomiting and yawning reported by patients on duloxetine treatment compared to those on escitalopram or placebo. Nausea was the most common adverse event occurring in 23.8% of patients taking duloxetine, 12% of patients taking escitalopram and 8.8% of patients taking placebo. There were considerably more dropouts due to nausea in the duloxetine group than in the escitalopram group. Mean changes in blood pressure and heart rate after treatment were higher for duloxetine than escitalopram.[1]

Fatal cases of liver failure have been reported with duloxetine so it is contraindicated for patients with hepatic impairment and should not be given to patients who are drinking substantial amounts of alcohol. A lower dose of 30 mg/day should be used in patients with end-stage renal disease.

The concomitant use of monoamine oxidase inhibitors with duloxetine is contraindicated. Duloxetine should be started at least 14 days after finishing monoamine oxidase inhibitor treatment.

The metabolism of duloxetine involves cytochrome P450 1A2 and 2D6 therefore concomitant administration of P450 1A2 inhibitors such as ciprofloxacin should be avoided. Caution should be used when giving duloxetine with drugs that are metabolised by P450 2D6. Thioridazine should be avoided.

If tolerability is a concern, patients can be started on a dose of 30 mg/day before increasing to 60 mg/day. If patients do not respond to 60 mg/day, there is little evidence to suggest that they will respond to a higher dose. When discontinuing duloxetine after more than one week of treatment, tapering of the dose is recommended.

The short-term effectiveness of duloxetine is comparable to low-dose escitalopram but its tolerability is less. There appear to be no published studies comparing duloxetine to other drugs that inhibit the reuptake of noradrenaline and serotonin, such as venlafaxine and reboxetine. There are limited data about the long-term use of duloxetine.

T manufacturer provided only the product information

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Ibandronic acid

Bondronat (Hospira)

vials containing 6 mg/6 mL

Approved indications: hypercalcaemia, bony metastases of breast cancer

Australian Medicines Handbook section 10.3.1

Bisphosphonates can reduce the hypercalcaemia of malignant disease by inhibiting the resorption of bone. Clodronate, pamidronate and zoledronic acid are already available for this indication. They are now joined by ibandronic acid which has been approved for patients, with or without metastases, who have tumour-induced hypercalcaemia. It is also approved for the treatment of metastatic bone disease in patients with breast cancer.

When ibandronic acid is given intravenously, it should be diluted and infused over two hours. For hypercalcaemia the dose is determined by the serum calcium, after correction for the albumin concentration. Patients with metastatic breast cancer can be given an intravenous infusion every four weeks or a daily oral dose. Ibandronic acid should not be taken with food as this reduces its bioavailability by 90%. The tablets must be swallowed whole with water and the patient must not lie down for 30 minutes afterwards.

About half of the dose is absorbed by bone. The remainder is excreted unchanged in the urine. No dose adjustment is suggested for hepatic impairment, but the dose should be reduced in patients with severe renal impairment.

A randomised phase II trial studied 174 cancer patients with hypercalcaemia.[1] These patients were given ibandronic acid in one of three different doses. The best response to treatment was seen in the patients given the highest dose (2 mg). In this group of 55 patients, 37 became normocalcaemic. Patients with higher baseline concentrations of calcium also responded better to the highest dose.

The efficacy of intravenous ibandronic acid, given every 3–4 weeks, was assessed in a placebo-controlled trial of 466 women with breast cancer and bony metastases. Their median time in the study was 13 months with placebo and 18 months with ibandronic acid. Although a 2 mg dose was not statistically different from placebo, the rate of skeletal complications was reduced in women given ibandronic acid 6 mg. At that dose there were 2.65 'bone events' per patient compared with 3.64 in the placebo group. (These events included fractures and other bony complications requiring treatment.) The women taking ibandronic acid 6 mg also had less bone pain.[2]

Oral ibandronic acid was assessed in 435 women with bony metastases randomised to take 20 mg, 50 mg or a placebo daily for up to 96 weeks. The mean number of bone events per patient was 1.36 with 20 mg, 1.43 with 50 mg and 2.23 with placebo. Although the two doses of ibandronic acid had similar efficacy the higher dose is recommended for clinical use.[3]

The adverse effects of oral treatment include dyspepsia, oesophagitis, abdominal pain, nausea and hypocalcaemia. Intravenous ibandronic acid is associated with fever or a flu-like illness, asthenia, diarrhoea, vomiting, headache and myalgia. Calcium and renal function should be monitored during treatment. The patient must have an adequate intake of calcium and vitamin D if there is a risk of hypocalcaemia. They should also have a dental check-up before treatment because of the association between bisphosphonates and osteonecrosis of the jaw.

A Cochrane review has concluded that bisphosphonates are effective treatment for the bony metastases of breast cancer, although they have no effect on survival. It did not report if ibandronic acid had a clinical advantage over other bisphosphonates.[4] An analysis in the UK found that oral ibandronic acid is more cost-effective than intravenous pamidronate or zoledronic acid, but this could reflect the cost of infusions rather than greater efficacy.[5] Comparative trials are needed.

T T T manufacturer provided all requested information (provided by Roche)

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Pramipexole

Sifrol (Boehringer Ingelheim)

125 microgram, 250 microgram and 1 mg tablets

Approved indications: Parkinson's disease, restless legs syndrome

Australian Medicines Handbook section 16.2.1

In Parkinson's disease, there is a reduced concentration of dopamine in the nigrostriatal system. Dopamine agonists, such

as bromocriptine, therefore have a role in the treatment of Parkinson's disease. Pramipexole is a non-ergoline dopamine agonist which acts on D_2 and D_3 receptors (see 'Dopamine – clinical applications i. neurology', Aust Prescr 1994;17:21-3).

Levodopa (combined with a decarboxylase inhibitor) remains the first-line drug treatment for Parkinson's disease of moderate severity. In advanced disease, the effect of this therapy starts to wear off. Maintaining the stimulation of dopamine receptors may alleviate this disabling complication.

When pramipexole was added to levodopa treatment, in a double-blind trial of 291 patients with advanced disease, it was more effective than placebo. Pramipexole improved motor function and decreased 'off' time. The patients' self-assessments also suggested that the severity of the 'off' time was reduced by pramipexole. Compared to placebo, the biggest changes were seen in rigidity, resting tremor, hand movements and finger tapping. At the end of the 32-week trial, the dose of levodopa required by the patients taking pramipexole had been significantly reduced.[1]

In the trial, the maximum dose was 4.5 mg a day. Usually pramipexole is given in divided doses, beginning with 125 microgram three times a day. The dose is increased every week if the patient is improving without adverse effects. While the dose is being titrated, the dose of levodopa can be reduced.

After a dose-ranging study in early Parkinson's disease[2], pramipexole was compared with levodopa in a double-blind trial involving 301 patients. Those randomised to receive pramipexole took longer to develop problems with the effect wearing off, on-off fluctuations or dyskinesia.[3]

Pramipexole also has an indication for restless legs syndrome. It was compared with placebo in a 12-week trial involving 344 patients. On a 40-point symptom rating scale, there was a mean improvement of 9.3 points with placebo and a 12.8 point improvement in people taking pramipexole 250 microgram daily. While 75% of patients responded to this dose of pramipexole, the response in the placebo group was 51%.[4]

In Parkinson's disease, lower doses of pramipexole are required if the patient has renal impairment as the drug is mainly excreted unchanged in the urine. The elimination half-life is increased from 8 to 12 hours in elderly patients. Renal clearance is also reduced by cimetidine which is thought to inhibit secretion in the renal tubules. This mechanism also creates the potential for interactions between pramipexole and ranitidine, diltiazem, verapamil, digoxin, triamterene and trimethoprim.

Some of the adverse effects of pramipexole can be predicted because of its stimulation of dopamine receptors. For example, up to 17% of patients will develop hallucinations. Other common adverse effects include nausea, insomnia, somnolence and dyskinesia. A few patients have fallen asleep suddenly, including when driving, and others have become compulsive gamblers while taking pramipexole.

Pramipexole should be withdrawn gradually over several days. Sudden cessation of antiparkinson drugs can cause neuroleptic malignant syndrome.

There are few published comparative studies of the dopamine agonists. A study in which pramipexole compared favourably with bromocriptine did not have enough power to show a statistical difference.[5] There is limited information about the long-term use of pramipexole. This is important because, for example, retinal degeneration has been seen in long-term studies of rats. Although fewer patients given pramipexole develop dopaminergic motor complications, patients given levodopa have a greater improvement in their early Parkinson's disease. While both drugs cause an initial improvement, after two years the patients' quality of life scores decline significantly less with levodopa.[3]

T T manufacturer provided additional useful information

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Sitaxentan sodium

Thelin (CSL)

100 mg tablets

Approved indication: pulmonary hypertension

Australian Medicines Handbook section 6.7.2

Pulmonary hypertension results from intimal hypertrophy narrowing small pulmonary arteries. The increase in pulmonary vascular resistance leads to right ventricular failure. Primary pulmonary hypertension is less common than the pulmonary hypertension associated with other conditions such as connective tissue diseases. The choice of treatment has expanded over recent years[1] with the approval of drugs such as bosentan, epoprostenol and treprostinil.

Patients with pulmonary arterial hypertension have increased concentrations of endothelin 1. This peptide acts on the endothelin A receptor to cause vasoconstriction and on the endothelin B receptor to cause vasodilation. Sitaxentan antagonises the endothelin A receptor, so the arterial pressure should reduce.

The daily dose of sitaxentan is well absorbed. The molecule is metabolised by cytochrome P450 2C9 and 3A4. As warfarin is also metabolised by P450 2C9, sitaxentan can increase the anticoagulant effect. Sitaxentan's metabolites are excreted in the urine and faeces, with an elimination half-life of eight hours.

There have been three placebo-controlled trials of sitaxentan involving a total of 516 patients. One trial lasted for 12 weeks and the others for 18 weeks. All three trials used changes in the distance patients could walk in six minutes as an outcome measure. At the start of the 12-week study, the patients could walk approximately 400 metres in six minutes. By the end of the study, patients given sitaxentan 100 mg could walk 35 metres further than the placebo group in six minutes. At the start of the18-week studies, the patients could walk 322–361 metres. After treatment, those given sitaxentan 100 mg could walk 25–31 metres further than those in the placebo group. There was an improvement in the severity of the condition in 12–25% of the patients. Although patients with less severe disease were included in the trials, the approval of sitaxentan is limited to patients with class III disease, according to the World Health Organization's classification. The approval also specifies primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.

Peripheral oedema, headache, insomnia, nasal congestion and epistaxis were common adverse events which occurred more frequently with sitaxentan than with placebo. Liver function must be checked before and during treatment with sitaxentan as hepatitis can develop. A rise in liver enzymes may require treatment to be stopped. Sitaxentan may also cause a decline in haemoglobin.

It is not clear if sitaxentan has any advantage over bosentan, another endothelin antagonist. Patients who do not respond to bosentan are unlikely to respond to sitaxentan.

T manufacturer provided only the product information

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The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2007;30:26–7.

* 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

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

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