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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 83)

7. Most dental pain is caused by tooth infection.
8. Most of the bacteria causing dental infections are resistant to penicillin.

Patient support organisation

The Australian Lung Foundation

The Australian Lung Foundation promotes understanding, management and relief of lung disease. It has over 100 patient support groups in metropolitan and regional areas of all the states and territories. For patients and carers the Foundation produces a range of fact sheets and illustrations, written in non-scientific language, about respiratory diseases and lung health. These fact sheets can be ordered or downloaded from the website, which also contains lists of pulmonary rehabilitation programs, internet support groups, links to further information, and materials for healthcare professionals.

Contacts

Phone 1800 654 301
Website www.lungnet.com.au
Email enquiries@lungnet.com.au

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.

Darunavir

Prezista (Janssen-Cilag)

300 mg tablet

Approved indication: HIV infection

Australian Medicines Handbook section 5.4.3

Darunavir is a new protease inhibitor that can be used in combination with other antiretroviral drugs to treat patients infected with HIV.[1] It works by selectively inhibiting the cleavage of viral polyproteins in infected cells, which prevents the formation of mature virus.

Darunavir is extensively metabolised by CYP3A. Ritonavir inhibits this enzyme and, when co-administered, increases the bioavailability of darunavir 14-fold. After an oral dose of 600 mg darunavir with 100 mg ritonavir, peak plasma concentrations are reached within 2.5–4 hours. The terminal half-life is around 15 hours and most of the drug is excreted in the faeces. This drug should be taken with ritonavir and food to increase its bioavailability.

The efficacy of darunavir (with ritonavir 100 mg) has been compared to other protease inhibitors in a phase II dose-finding trial. The 318 patients who were enrolled had previously been treated with antiretroviral drugs and many of them had HIV that was resistant to commercially available protease inhibitors. Before the patients were allocated to a treatment group, they were prescribed an optimised background regimen of two

or more nucleoside analogue reverse transcriptase inhibitors with or without enfuvirtide. Patients were then randomised to receive darunavir or another protease inhibitor (lopinavir, saquinavir, fosamprenavir, atazanavir or indinavir) selected by the investigator. After 24 weeks of treatment, 53% (32) of patients taking 600 mg darunavir (twice daily) had less than 50 viral copies/mL of blood compared to 18% (11) of patients taking another protease inhibitor. Corresponding to this, mean CD4 cell counts increased by 124 cells/microlitre of blood in the darunavir group and 20 cells/microlitre in the comparator group.[2]

Viral resistance to darunavir has been noted in patients previously treated with other protease inhibitors. This is associated with amino acid substitutions in the viral proteases. HIV strains that are resistant to darunavir may also have decreased susceptibility to other protease inhibitors.

Headache and gastrointestinal symptoms are the most common adverse events associated with darunavir. Skin rashes have also been reported.

Darunavir interacts with many drugs as it is metabolised by CYP3A. It must not be prescribed with drugs that rely on this enzyme for their clearance such as ergot derivatives and midazolam and triazolam. Darunavir can also interact with complementary medicines such as St John's wort. Other antiretroviral drugs (lopinavir/ritonavir and saquinavir) also affect the bioavailability of darunavir.

Darunavir is indicated in combination with other antiretroviral drugs for the treatment of HIV in heavily pre-treated adults who already have resistance to multiple protease inhibitors. So far, it has only been tested in a limited number of patients. The effectiveness of this drug depends on the treatment history of the individual patient and the genotype of their HIV strain.

[X] manufacturer declined to supply data

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Laronidase

Aldurazyme (Genzyme)

5 mL vials containing 100 U/mL

Approved indication: mucopolysaccharidosis I

Mucopolysaccharidosis I is a lysosomal storage disease caused by an inborn error of metabolism. Severe cases are also known as Hurler disease. The patient has a deficiency of the enzyme α–L–iduronidase which leads to an accumulation of substrates inside the lysosomes. This gradually impairs cell function and results in developmental delay, hepatosplenomegaly, joint stiffness, neurological problems, airway obstruction and abnormal facial features. Children with Hurler disease usually die before the age of 10 years, less severe cases may live into their 20s.

Laronidase is a recombinant form of the deficient enzyme. It is genetically engineered, using Chinese hamster ovary cells, to have exactly the same amino acid sequence as the human enzyme.

The aim of treatment is to metabolise the stored substrate and prevent further accumulation. To achieve this laronidase is diluted and given as an infusion over four hours. Although the half-life of laronidase is 2–4 hours, only a weekly dose is required. The molecule is metabolised by peptide hydrolysis.

In a 52-week study of 10 patients there was a 25% decrease in the size of the liver and a 20% decrease in the size of the spleen. There was a 63% reduction in the amount of substrate appearing in the urine. The range of joint movement increased and the prepubertal patients showed improved growth. Lung function also improved.[1]

A larger double-blind trial randomised 22 patients to receive laronidase and 23 to receive a placebo for 26 weeks. Active treatment resulted in a significant reduction in liver size and the excretion of substrates.

Infusing patients with peptides can cause hypersensitivity reactions. As 32% of patients may have a reaction to the infusion, it is important that they are given antipyretics and antihistamines before their infusions. Many patients will produce antibodies to laronidase, but they can also develop an immune tolerance.[2] It is therefore unknown if these antibodies will alter the long-term effectiveness of treatment.

Although the efficacy studies show some improvements for patients, not all of the benefits are statistically significant. In the larger trial the forced vital capacity significantly improved, but there was no significant change in the apnoea/hypopnea index. Although, after 26 weeks of treatment, the patients could walk nearly 20 metres further in six minutes, the advantage over placebo was not statistically significant. The effect of laronidase on the nervous system is uncertain and it is only indicated for non-neurological manifestations of the disease.

Although bone marrow transplantation can be helpful it will not be an option for many patients. Treatment with laronidase will be an expensive alternative and the long-term outcomes will remain unknown for many years.

[T] manufacturer provided only the product information

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Olmesartan medoxomil

Olmetec (Schering-Plough)
20 mg and 40 mg tablets

Olmetec Plus (Schering-Plough)
20 mg olmesartan medoxomil/12.5 mg hydrochlorothiazide tablets
40 mg olmesartan medoxomil/12.5 mg hydrochlorothiazide tablets
40 mg olmesartan medoxomil/25 mg hydrochlorothiazide tablets

Approved indication: hypertension

Australian Medicines Handbook section 6.4.5

Olmesartan is the sixth angiotensin receptor antagonist to be marketed in Australia. Like the other members of its class it blocks the binding of angiotensin II to the angiotensin (AT_1) receptor (see 'Angiotensin receptor antagonists for the treatment of hypertension', Aust Prescr 1998;21:95–7).

As olmesartan medoxomil is a prodrug it has to be converted to active olmesartan. This metabolism occurs during absorption. The bioavailability is 26%, but this is unaffected by food. Up to half of the absorbed drug is excreted in the urine. Renal and hepatic impairment will increase concentrations of olmesartan.

The efficacy of the drug has been shown in several placebo-controlled trials. Approximately 70% of patients with hypertension will respond. The mean reductions in ambulatory blood pressures with a daily dose of 20 mg olmesartan are 11 mmHg diastolic and 14 mmHg systolic.[1] The maximum effect of olmesartan occurs by the eighth week of treatment.

Olmesartan has been compared with other antihypertensive drugs. Olmesartan 20 mg had a greater effect on blood pressure than 50 mg losartan, 150 mg irbesartan and 8 mg candesartan.[2]

When combined with hydrochlorothiazide the efficacy of olmesartan is similar to that of atenolol and hydrochlorothiazide. The combination product should only be used when the patient's hypertension has not been controlled by olmesartan or hydrochlorothiazide alone.

The most common adverse effect of olmesartan is dizziness. Cough does not appear to be a major problem, but angioedema has been reported. Like other angiotensin receptor antagonists and ACE inhibitors caution is needed when prescribing for patients who may have renal impairment or be volume depleted by diuretics. Similarly, taking a non-steroidal anti-inflammatory drug with olmesartan could cause renal failure.

Hypertension is a chronic disease, but most trials of efficacy only last a few months. Although it may have a greater effect on blood pressure, the long-term effects of olmesartan are uncertain. As currently available angiotensin receptor antagonists have been more widely used and as some have also been approved for heart failure and diabetic renal disease, olmesartan should probably not become the first choice until it has more outcome data.

T manufacturer provided only the product information

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Ranibizumab

Lucentis (Novartis)

1.8 mg/0.3 mL or 3.0 mg/0.3 mL in single-dose vials

Approved indication: neovascular age-related macular degeneration

Australian Medicines Handbook section 11.7

Age-related macular degeneration is the leading cause of irreversible blindness in Australia. It is a progressive disease that causes loss of 'straight ahead' vision. Approximately 10% of people with this condition have the neovascular or 'wet' form. This is caused by abnormal blood vessels under the macula leaking fluid and bleeding, which eventually leads to scarring. Using fluorescein angiography, these lesions can be classified as 'classic' or 'occult'.[1] One current treatment for this disease in Australia is verteporfin, which is given intravenously and then followed by photodynamic therapy (see New drugs, Aust Prescr 2000;23:137–9).

Ranibizumab is a humanised monoclonal antibody fragment which blocks vascular endothelial growth factor A (VEGF-A), a key mediator in neovascular age-related macular degeneration.

Following intravitreal injection very little ranibizumab is absorbed systemically and any that is, is rapidly cleared. The terminal half-life of ranibizumab in the vitreous humour is approximately 10 days.

Most of the published efficacy data for ranibizumab comes from two randomised controlled trials. One trial compared monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg) with sham injections (pressing a needleless syringe against the conjunctiva) in 716 patients with age-related macular degeneration. Patients had either occult or minimally classic choroidal neovascularisation. After 12 months of treatment, around 94% of patients given ranibizumab and 62% of patients receiving a sham injection maintained their vision. This was defined as losing less than 15 letters of visual acuity on the chart used in the Early Treatment Diabetic Retinopathy Study. The chart consists of 14 rows of 5 letters each. For patients in the ranibizumab groups, visual acuity increased by an average of 6.5 letters for the 0.3 mg dose and 7.2 letters for the 0.5 mg

dose and decreased by an average of 10.4 letters in the sham injection group. After 24 months of treatment visual improvements were largely maintained in the patients receiving ranibizumab, whereas vision continued to decline in patients receiving sham injections.[2]

In the other efficacy trial, monthly injections of ranibizumab (0.3 mg or 0.5 mg) were compared with an active treatment, verteporfin photodynamic therapy, in 423 patients who mostly had predominantly classic neovascular age-related macular degeneration. After 12 months of treatment, around 95% of patients given ranibizumab and 64% of patients receiving verteporfin therapy maintained their vision. On average, visual acuity in patients receiving ranibizumab increased by 8.5 letters in the 0.3 mg group and 11.3 in the 0.5 mg group and decreased by 9.5 letters in the verteporfin group.[3]

Within both of these trials, the difference between the efficacy of ranibizumab and the sham injection or verteporfin therapy was statistically significant, whereas the difference between the two ranibizumab doses was not.[2,3]

In the larger efficacy trial, serious uveitis, endophthalmitis and retinal tear occurred in the ranibizumab groups but not in the sham group. Increases in intraocular pressure (of 30 mmHg or more) occurred more often after ranibizumab injections than sham injections.[1] In both trials, non-ocular haemorrhage was more common in patients treated with ranibizumab compared to control patients.[2,3] Some trials have reported an increase in arterial thromboembolism in patients given intravitreal ranibizumab.

After two years of treatment, 4.4% of patients given 0.3 mg of ranibizumab and 6.3% of those given the 0.5 mg dose tested positive for circulating antibodies to ranibizumab. This did not seem to affect the efficacy of ranibizumab.[2]

Doctors should be aware that only one eye should be injected at each visit. As ranibizumab is injected into the vitreous cavity, aseptic technique is important and patients should be monitored during the week following treatment in case infection occurs. Advise patients to administer antimicrobial eye drops for three days before and after the injection.

Increases in intraocular pressure and changes in perfusion of the optic nerve head may occur within 60 minutes of the injection and so these should be monitored. Ranibizumab can temporarily affect vision and patients should be warned not to drive or operate machinery if this occurs.

Ranibizumab seems to offer a promising alternative to current therapy for neovascular age-related macular degeneration. Ongoing trials are investigating whether patients can have the same benefit from less frequent injections of ranibizumab.[4]

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).

Withdrawal of thioridazine

Thioridazine is an old antipsychotic drug. Its use has declined partly because of concerns about it causing serious cardiac arrhythmias.

The current manufacturer is ceasing production of thioridazine in Australia. It is expected that stocks will be exhausted in August 2007.

No protocol has been published to assist prescribers switch patients to other therapy. Some information was made available to Canadian prescribers when thioridazine sales ceased in Canada during 2005 (see www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2005/thioridazine_hpc-cps_e.html).