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Dr Reutens has received conference sponsorship from Novo Nordisk. Dr Shaw has received research funding, and honoraria for lectures and consultancies, from Lilly Pharmaceuticals, Novo Nordisk, Merck Sharp & Dohme and Novartis.

Self-test questions

The following statements are either true or false
(answers on page 111)

9. The nausea associated with exenatide can persist for more than a year.
10. The main effect of drugs acting on the incretin system is a reduction in postprandial glucose concentrations.

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.

Fosaprepitant dimeglumine

Emend IV (Merck Sharp & Dohme)

vials containing 115 mg as powder for reconstitution

Approved indication: chemotherapy-induced nausea and vomiting

Australian Medicines Handbook section 12.3.4

Aprepitant is an oral antiemetic which was marketed for use in chemotherapy in 2004 (see 'New drugs' 2004;27:76–9). Fosaprepitant is an intravenous formulation of aprepitant which can be given on the first day of chemotherapy. The dose is infused over 15 minutes, 30 minutes before chemotherapy.

Fosaprepitant is a prodrug. It is rapidly converted by many tissues into aprepitant. An intravenous dose of 115 mg fosaprepitant is equivalent to an oral dose of 125 mg aprepitant.[1] Although the concentrations are similar after 24 hours, the maximum concentration of aprepitant is higher when fosaprepitant is used.

There appear to be few published clinical trials of fosaprepitant. Its product information only contains pivotal efficacy studies of aprepitant. The adverse effects of the two drugs are similar, but fosaprepitant has some extra warnings: the intravenous formulation is incompatible with Hartmann's or Ringer's lactate solution.

A dose of fosaprepitant does not stop vomiting, immediately after cisplatin-based chemotherapy, in as many patients as ondansetron, but it does reduce delayed emesis.[2] A similar result occurred when intravenous fosaprepitant and dexamethasone, followed by oral aprepitant, were compared to ondansetron and dexamethasone, followed by placebo.[3]

As aprepitant is metabolised by the cytochrome P450 system, especially 3A4, fosaprepitant can interact with other drugs with similar metabolism such as cyclosporin and tacrolimus. Aprepitant can reduce concentrations of warfarin and oral contraceptives. Inhibition of P450 3A4 by ketoconazole will increase concentrations of aprepitant.

T T manufacturer provided additional useful information

References

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3. Van Belle S, Lichinitser MR, Navari R, Garin AM, Decramer MLA, Riviere A, et al. Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869. A randomized controlled trial. Cancer 2002;94:3032-41.

Idursulfase

Elaprase (Genzyme)

5 mL glass vials containing 2 mg/mL concentrate solution for infusion

Approved indication: Hunter syndrome

Australian Medicines Handbook Appendix A

Hunter syndrome is a very rare lysosomal storage disease. Patients have a deficiency of the enzyme iduronate sulfatase and this leads to an accumulation of mucopolysaccharides. (Hunter syndrome is also known as mucopolysaccharidosis II.) Early onset of this X-linked disorder results in developmental delay, coarse facial features, impaired vision, deafness, stiff joints, hepatosplenomegaly and cardiorespiratory problems.

Idursulfase is a genetically engineered form of iduronate sulfatase. A solution of the enzyme is diluted and infused over 1–3 hours. Although it only has a half-life of approximately 45 minutes, idursulfase only needs to be infused once a week.

The efficacy of enzyme replacement therapy was assessed in 96 patients with a median age of approximately 14 years (range 5–31 years). These patients were randomised to receive a weekly infusion of idursulfase or placebo or an infusion of idursulfase every other week. After a year, liver volume had decreased by approximately 25% with enzyme replacement. Lung function (absolute forced vital capacity) improved, but was only significantly better than placebo with weekly infusions. From a baseline mean of 396 metres, the distance the patients could walk in six minutes increased by 44 metres with weekly infusion, 30 metres with infusions every other week and 7 metres with placebo.[1]

Adverse reactions which occurred more frequently with idursulfase than with placebo included headache, abdominal pain, arthralgia and rashes. Many reactions were infusion-related so the infusion may need to be slowed or stopped. Life-threatening anaphylaxis has been reported and these reactions may have a delayed onset. Patients who develop antibodies to idursulfase have an increased incidence of infusion reactions.

While the evidence shows that weekly infusions improve walking capacity, more research is needed to show if idursulfase has any effect on the progression of Hunter syndrome. The main trial of idursulfase did not report on the neurological aspects of the syndrome.[1] It is also unclear if the development of antibodies will eventually lead to a loss of efficacy. Although idursulfase replaces the deficient enzyme, it cannot be regarded as a cure for Hunter syndrome.

T manufacturer provided only the product information

Reference *†

1. Muenzer J, Wraith JE, Beck M, Giugliani R, Harmatz P, Eng CM, et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med 2006;8:465-73.

Paricalcitol

Zemplar (Abbott)

1 microgram, 2 microgram and 4 microgram capsules

5 microgram/mL in 1 mL and 2 mL ampoules

Approved indication: secondary hyperparathyroidism

Australian Medicines Handbook section 10.3.2

In chronic renal failure there is reduced production of calcitriol, the active form of vitamin D. This affects calcium homeostasis and leads to increased secretion of parathyroid hormone. High concentrations of parathyroid hormone increase bone resorption leading to renal osteodystrophy. Secondary hyperparathyroidism can be treated with calcitriol, but it may cause hypercalcaemia and hyperphosphataemia. This has led to research into vitamin D analogues, such as paricalcitol.

The dose and frequency of paricalcitol are determined by the patient's concentrations of parathyroid hormone, calcium and phosphorus. The oral formulation is well absorbed whether or not it is taken with food. Paricalcitol is extensively metabolised by several enzymes including cytochrome P450 3A4. Most of the metabolites are excreted in the faeces. In healthy people the half-life of paricalcitol is 4–7 hours, but this increases to 14–20 hours in patients with chronic kidney disease. Haemodialysis has little effect on the elimination of paricalcitol.

Three placebo-controlled trials enrolled a total of 220 patients with secondary hyperparathyroidism due to chronic kidney disease. In one study patients took capsules once a day, in the others patients took them three times a week. The treatment period was 24 weeks and 83% of patients took the drug for at least 16 weeks. The trial end point (two consecutive decreases in parathyroid hormone greater than 30% of the baseline concentration) was achieved by 91% of the patients randomised to paricalcitol compared with 13% of the placebo group. Only two patients given paricalcitol developed hypercalcaemia.[1]

An open-label study has followed 164 patients, with end-stage renal failure, for up to 13 months. Intravenous doses of paricalcitol given two or three times a week at the end of haemodialysis decreased the concentrations of parathyroid hormone. Mean concentrations of calcium and phosphorus were controlled, but hypercalcaemia occurred in 10% of the patients. Drug-related adverse events affected 26% of patients and 9% withdrew from the study because of adverse events.[2]

Adverse events which occur more frequently with paricalcitol than with placebo include fever, chills, sepsis, pneumonia, oedema, nausea and vomiting. Patients require regular monitoring for hypercalcaemia.

Although the main trials of paricalcitol gave several doses a week this may not be essential. A small study has found that a weekly intravenous dose may be effective in reducing concentrations of parathyroid hormone.[3]

The advantages of paricalcitol over calcitriol, seen in an historical study, need confirmation. In approximately 67 000 patients having haemodialysis the mortality rate was 0.223 per person-year in patients receiving calcitriol and 0.18 per person-year in patients receiving paricalcitol.[4]

T manufacturer provided only the product information

References *

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4. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus M, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med 2003;349: 446-56.

Temsirolimus

Torisel (Wyeth)

vials containing 25 mg/mL concentrate

Approved indication: advanced renal cell carcinoma

Australian Medicines Handbook section 14.2.3

About 30% of patients with renal cell carcinoma have advanced or metastatic disease at the time of diagnosis. Chemotherapy is generally ineffective and nephrectomy is the mainstay of treatment for disease confined to the kidney. Treatment with drugs such as interferon alfa, interleukin-2 and the tyrosine kinase inhibitors sunitinib and sorafenib may benefit some patients.[1]

Temsirolimus is a kinase inhibitor derived from sirolimus (rapamycin) (Aust Prescr 2002;25:97–8). It works by inhibiting the action of an enzyme called 'mammalian target of rapamycin' or mTOR. Inhibition prevents the division of cancerous cells, slowing the growth and spread of the cancer.

Following intravenous administration, temsirolimus is extensively metabolised by CYP3A4, with the main metabolite being sirolimus. The half-life is 17 hours for temsirolimus and 55 hours for sirolimus. Metabolites are primarily eliminated in the faeces.

The efficacy of temsirolimus in advanced renal cell carcinoma was first assessed in a dose escalation trial of 111 previously treated patients. After a weekly dose of 25, 75 or 250 mg (for a median of 5.6 months), 7% of the patients had a complete or partial response to temsirolimus, but this was not dose-dependent.[2] In a larger trial of 626 previously untreated patients, median overall survival was longer in patients treated with temsirolimus (25 mg each week) than those treated with interferon alfa (10.9 months vs 7.3 months). Adding interferon alfa to temsirolimus did not improve the overall survival time and was associated with more serious adverse events than temsirolimus alone.[3]

In the trials, rash, fatigue, mucositis, nausea, oedema, anaemia and anorexia were common adverse events in patients receiving temsirolimus. The most frequent laboratory test abnormalities were hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypophosphataemia, thrombocytopenia, leucopenia and elevated alkaline phosphatase, serum creatinine and aspartate aminotransferase.[2,3]

Approximately 5% of the participants in the larger trial had a hypersensitivity reaction to temsirolimus so patients should be given intravenous antihistamine approximately 30 minutes before temsirolimus is administered. If a hypersensitivity reaction develops, the temsirolimus infusion should be stopped.

Cases of interstitial lung disease have occurred in patients taking temsirolimus and patients should be advised to seek medical attention if they develop worsening respiratory symptoms. Other rare but serious adverse events that have been reported include fatal bowel perforation and renal failure. Patients with central nervous system tumours and/or taking anticoagulants may have an increased risk of intracerebral bleeding.

Immunosuppression may occur with temsirolimus, so be vigilant for infections. Also, live vaccines and contact with people who have recently had them should be avoided. Temsirolimus may delay wound healing and should not be given to patients in the peri-surgical period.

Drugs that induce or inhibit the CYP3A4 enzyme should be avoided in patients taking temsirolimus. Concomitant use of sunitinib can result in dose-limiting toxicities such as serious maculopapular rash and gout or cellulitis requiring hospitalisation. Angioneurotic oedema-type reactions have been observed in patients who were receiving temsirolimus concomitantly with an angiotensin converting enzyme inhibitor. Some patients on temsirolimus and interferon alfa have developed cataracts.

Temsirolimus provides another option for patients with advanced renal cell carcinoma. However, its relative efficacy compared to tyrosine kinase inhibitors is not known.

T T T manufacturer provided clinical evaluation

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

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