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*Conflict of interest: none declared*

**Self-test questions**

*The following statements are either true or false (answers on page 151)*

11. Eczema is a contraindication to BCG vaccine.
12. With the exception of babies under six months of age, Mantoux testing is recommended before patients are given BCG vaccine.

## Tuberculosis testing and immunisation in the Australian Defence Force

*Prepared by Air Vice-Marshal Bruce Short, Surgeon General, Australian Defence Force*

In the course of peacetime service in Australia, the exposure of Australian Defence Force personnel to tuberculosis, and hence risk of infection, is similar to that of the general population. However, when operationally deployed, particularly in Australia's region of interest, personnel may be exposed to infected people. This risk is heightened during humanitarian or peace-keeping operations.

In the past, the mainstay of prevention was immunisation with BCG vaccine. In recent times the widespread use of BCG vaccination has been shown to prevent few cases in regions with low incidence rates. The vaccine may also cause false positives in Mantoux tests and this may increase the difficulty in diagnosing tuberculosis infection.

The Australian Defence Force has followed the guidelines of the US Centers for Disease Control and Prevention and, therefore, does not recommend routine BCG vaccination.<sup>1</sup>

Within the Australian Defence Force, screening for tuberculosis is undertaken by skin testing all personnel on entry, using 10 units of tuberculin purified protein derivative. Tuberculin skin testing may also be performed in two steps if the initial induration is less than 15 mm diameter. It is not performed by using multiple puncture tests (Heaf test).<sup>2</sup>

The tuberculin skin test is also used to screen personnel after

redeployment or removal from a country with a high incidence of tuberculosis, provided that the period of redeployment has been at least three months. This testing is performed three months after the personnel return to Australia. A high incidence country is one in which the annual tuberculosis incidence is at least 49 per 100 000. For people visiting and residing in such an area for at least 3-12 months, incidence rates for tuberculosis infection have been reported as 1.8%.<sup>3</sup>

Personnel who have been exposed to high risk situations are also tested. This latter group includes those people who have spent a total of eight or more hours with an infected person in a confined environment, as well as healthcare workers who have had regular close contact with an index case.

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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 have been little experience in Australia of their safety or efficacy. However, the Editorial 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.

**Eptifibatide**

Integrilin (Schering Plough)

10 mL vial containing 2 mg/mL

100 mL vial containing 0.75 mg/mL

Approved indications: unstable angina, myocardial infarction, intracoronary stenting

Australian Medicines Handbook section 7.2.1

Eptifibatide is the latest of several glycoprotein IIb/IIIa receptor antagonists such as tirofiban and abciximab, to be marketed in Australia. These drugs work in acute coronary syndromes by inhibiting platelet aggregation.<sup>1</sup>

Patients with unstable angina or non-Q wave myocardial infarction are given an intravenous bolus of eptifibatide. This is followed by an infusion which continues, for up to 72 hours, until the patient has a coronary bypass or leaves hospital. In

most patients this regimen will inhibit more than 80% of platelet aggregation. The half-life of eptifibatide is 2.5 hours with half of the dose being cleared by the kidney.

The efficacy of eptifibatide was assessed in a study of 10 948 patients with acute cardiac ischaemia. They were given eptifibatide or a placebo, in addition to aspirin and heparin. Eptifibatide significantly reduced the number of patients who died or suffered a myocardial infarction within 30 days.<sup>2</sup>

Eptifibatide can also be used in patients who require intracoronary stenting. A trial randomised 2064 patients to receive two doses of eptifibatide and an infusion, or a placebo before the non-urgent percutaneous implantation of a stent. The primary end-point of the trial was a composite of death, myocardial infarction, urgent revascularisation and 'bailout glycoprotein IIb/IIIa inhibitor therapy'. This trial was stopped early because of a significant difference in the primary end-point between eptifibatide and placebo (10.5% versus 6.6%).<sup>3</sup>

Predictably, bleeding is an important adverse effect of eptifibatide. In the pivotal study 11.6% of patients needed a transfusion.<sup>2</sup> This bleeding most often occurred in patients who require coronary artery bypass grafting and was also a problem for the patients given a placebo. Approximately 9% of the patients given a placebo needed a transfusion.<sup>2</sup> Common sites for bleeding are the femoral artery access point, the genitourinary system and the gut.

Monitoring the patient includes checking their blood counts within six hours of starting treatment and then at least once a day. The activated clotting time should be measured in patients having percutaneous coronary interventions.

Although the effect of eptifibatide in acute ischaemia is statistically significant the absolute reduction is only 1.5%. (Eptifibatide reduces deaths and myocardial infarctions from 15.7% to 14.2%.<sup>2</sup>) In the stenting study the overall benefit was accounted for by a reduction in myocardial infarctions. The difference in mortality between eptifibatide and placebo was not significant. The benefits of eptifibatide need to be balanced against the cost of managing the extra haemorrhages it causes.

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### Escitalopram oxalate

Lexapro (Lundbeck)

10 mg and 20 mg tablets

Approved indication: major depression

Australian Medicines Handbook section 18.1

Citalopram is a selective serotonin reuptake inhibitor (SSRI). It is a racemic compound, but most of its activity is thought to reside in the S-isomer (escitalopram).

Starting doses of escitalopram are half those of citalopram. The isomers of citalopram have different pharmacokinetics, with escitalopram being metabolised by pathways which include cytochrome P450 2C19, 3A4 and 2D6. The metabolites are mainly excreted in the urine.

Escitalopram has been compared with placebo and citalopram, but not all of these studies have been published in full. One trial, involving 491 patients, found that escitalopram was more effective than placebo, but not significantly more effective than citalopram after eight weeks of treatment.<sup>1</sup> Another study lasting six months also found that 10 mg escitalopram was at least as efficacious as 20 mg of citalopram.

The adverse effects of escitalopram resemble those of citalopram and other SSRIs. In the comparative trial 4.2% of the patients taking 10 mg escitalopram discontinued treatment because of adverse effects.<sup>1</sup> These effects included nausea, diarrhoea, insomnia, dry mouth and ejaculation disorders.

There is insufficient published evidence to say that escitalopram should replace citalopram. The Health Research Group in the USA said that 'the primary purpose for developing escitalopram appears to be nothing more than a strategy to protect sales as citalopram nears the end of its patent protection'.<sup>2</sup>

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### Ezetimibe

Ezetrol (Merck Sharp & Dohme)

10 mg tablets

Approved indications: hypercholesterolaemia and sitosterolaemia

Australian Medicines Handbook section 6.6

Familial hypercholesterolaemia is caused by a mutation in the gene which codes for the receptors for low density lipoprotein (LDL) cholesterol. The homozygous form of the disorder results in very high concentrations of cholesterol in the blood. This greatly increases the patient's risk of cardiovascular disease.

Sitosterolaemia (phytosterolaemia) is another genetic disorder which can cause hypercholesterolaemia. There is increased absorption of cholesterol and plant sterols from the gut.

Ezetimibe may benefit homozygous patients with familial hypercholesterolaemia or sitosterolaemia because it selectively inhibits absorption of cholesterol and phytosterols from the small intestine. The drug is taken once a day and its absorption is not affected by food. It is metabolised in the small intestine and mostly excreted in the faeces. The half-life of ezetimibe and its main metabolite is approximately 22 hours.

Monotherapy with ezetimibe reduces concentrations of LDL cholesterol by approximately 17%. As patients with hypercholesterolaemia are often treated with an HMG CoA reductase inhibitor, ezetimibe has been studied in combination with these 'statins'.

In a study of 50 patients with homozygous familial hypercholesterolaemia 12 weeks of treatment with ezetimibe and either atorvastatin or simvastatin had greater efficacy than statin therapy alone. Combined treatment reduced LDL cholesterol by 20.7% while high-dose (80 mg/day) statin therapy reduced it by 6.7%.<sup>1</sup> Adding ezetimibe to the treatment regimen of 37 patients with homozygous sitosterolaemia reduced their sitosterol concentrations by 21% and their campesterol concentrations by 24%.

Caution is needed when prescribing ezetimibe to patients who are being treated with a bile acid binding resin such as cholestyramine. The drugs interact resulting in reduced concentrations of ezetimibe. Combined therapy with fibrates is not recommended. When ezetimibe is combined with a statin the patient's liver enzymes should be checked. The combination is contraindicated in patients with altered liver function.

Although 5% of patients treated with ezetimibe may complain of myalgia, there are currently no reports of rhabdomyolysis. Other symptoms reported in clinical trials include abdominal pain, diarrhoea, chest pain, headache and dizziness.

Ezetimibe does improve patients' lipid profiles, but it will be several years before any effect on morbidity and mortality emerges. Familial hypercholesterolaemia is a relatively uncommon form of primary hypercholesterolaemia. Although ezetimibe has also been approved for other forms of primary hypercholesterolaemia its use for this indication will probably be limited to patients who cannot tolerate statins.

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**Lutropin alfa**

Luveris (Serono)

vials containing 75 IU as powder for reconstitution

Approved indication: gonadotrophin deficiency

Australian Medicines Handbook section 10.6.1

Some women with infertility have a severe deficiency of follicle stimulating hormone (FSH) and luteinising hormone (LH). To induce ovulation they can be treated with these hormones, but the preparations may be derived from urine. Urinary human chorionic gonadotrophin (HCG) is often used to mimic LH as it has a similar structure and action.

Genetic engineering has now enabled the production of recombinant LH. A double-blind trial randomised 259 infertile women to receive either recombinant LH or urinary HCG for the induction of ovulation. There were no significant differences between the treatments in the number of oocytes retrieved or the number of subsequent pregnancies.<sup>1</sup>

Lutropin alfa is a recombinant form of LH. It is genetically engineered using Chinese hamster ovary cells. There are only slight differences in the structure of lutropin and the hormone derived from urine.

The recommended regimen for lutropin is designed to assist the development of one follicle, but HCG is still used to induce

ovulation. Patients have daily subcutaneous injections of lutropin and FSH. The patient's response is assessed by oestrogen secretion and measuring the follicle size with ultrasound. When an optimal response is obtained HCG is given 24–48 hours after the previous injection of lutropin. Approximately 70% of the women taking a daily lutropin dose of 75 IU respond to this regimen.

The response has to be carefully monitored because of the risk of ovarian hyperstimulation syndrome. Other adverse effects include injection site reactions, abdominal or pelvic pain, breast pain and nausea.

Infertility due to gonadotrophin deficiency is rare, so lutropin has been studied in relatively few patients. It will initially be reserved for women with a severe deficiency (LH less than 1.2 IU/L) because those with a less severe deficiency may respond to FSH alone.

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**Omalizumab**

Xolair (Novartis)

vials containing 150 mg as powder for reconstitution for injection

Approved indication: asthma

Australian Medicines Handbook section 14.1.4

Inflammation of the airways plays an important part in the pathogenesis of asthma. Allergens stimulate the production of IgE which then binds to mast cells resulting in the release of inflammatory mediators. Omalizumab is a recombinant monoclonal antibody which forms complexes with free IgE to prevent it binding to mast cells.

The concentration of free IgE is reduced within a few hours of a subcutaneous injection, even though it takes six to ten days for the drug to reach its peak plasma concentration. As well as slow absorption omalizumab has a slow clearance. Its half-life is approximately three weeks. Some patients may only need one injection a month depending on their weight and IgE concentration.

Two doses of intravenous omalizumab were compared with placebo injections in 317 patients who required corticosteroids for the control of allergic asthma. After a period of dose titration, patients were injected every two weeks for 20 weeks. In the later part of the study attempts were made to reduce the patients' doses of corticosteroids. Treatment reduced the patients' free IgE concentrations by 95% and resulted in a reduction of asthma symptoms. Half the patients given omalizumab were able to reduce their dose of inhaled steroids and 33–43% of those taking oral steroids were able to stop them. During the study period there were fewer exacerbations in the patients receiving omalizumab.<sup>1</sup>

Another study also found that subcutaneous omalizumab reduced exacerbations and enabled some patients to reduce or stop their inhaled corticosteroids.<sup>2</sup>

Omalizumab is generally well tolerated, but as it is a protein there is a risk of anaphylaxis and other allergic reactions. The most common adverse effects are reactions at the injection site.

Although omalizumab improves the symptoms of asthma it does not have a profound effect on lung function. In the trial of intravenous omalizumab FEV<sub>1</sub> increased by approximately 2%, while subcutaneous omalizumab resulted in a 4% improvement.

Omalizumab is only approved for subcutaneous injection into patients with moderate allergic asthma who have a raised IgE concentration and are already taking steroids. It is therefore not indicated for the majority of patients with asthma who have a normal IgE concentration and no history of allergy. Childhood asthma often has an allergic component, however, although omalizumab has been studied in children<sup>3</sup>, it is not approved for patients less than 12 years old.

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### **Peginterferon alfa-2a (with ribavirin)**

Pegasys (Pegasys-RBV) (Roche)

pre-filled syringes containing 135 microgram/0.5 mL and 180 microgram/0.5 mL

(Pegasys-RBV is packaged as pre-filled syringes with 200 mg tablets of ribavirin)

Approved indication: chronic hepatitis C

Australian Medicines Handbook section 14.2.2

The interferons are cytokines which can enhance the immune response. They have been used to treat patients with hepatitis to try and halt the progression to cirrhosis. To prolong the effect of a dose of interferon the genetically engineered molecule has been conjugated to polyethylene glycol. Peginterferon alfa-2b and ribavirin is an effective combination for treating chronic hepatitis C.<sup>1</sup>

Peginterferon alfa-2a has also been studied as a treatment for hepatitis C. One trial compared weekly injections of peginterferon alfa-2a with thrice weekly interferon alfa-2a in 531 previously untreated patients. After 48 weeks of treatment and a further 24 weeks of follow-up, 38% of the peginterferon group and 17% of the interferon group had normal aminotransferase concentrations and no detectable viral RNA. Liver biopsies showed a response in 63% of the peginterferon group and 55% of the interferon group.<sup>2</sup>

Peginterferon alfa-2a has also been compared with interferon alfa-2b. All 444 patients randomised to take interferon alfa-2b

and 453 of the patients randomised to take peginterferon alfa-2a also received ribavirin. The other 224 patients took peginterferon alfa-2a and a placebo for up to 48 weeks. When the patients were assessed at 72 weeks, 56% of the patients treated with peginterferon alfa-2a and ribavirin had no detectable viral RNA. This was significantly greater than the sustained virological response seen in patients taking a placebo (29%) or interferon alfa-2b and ribavirin (44%).<sup>3</sup> The sustained response rate in patients with genotype 1 virus was lower (46%), but still significantly greater than in the other groups.

Doses of peginterferon alfa-2a are injected subcutaneously into the abdomen or thigh. The serum concentration peaks after 6–8 days and accumulates during the first two months of treatment. As the half-life is 50–130 hours the serum concentrations are sustained between each weekly injection.

Injection site reactions are among the many common adverse reactions reported in clinical trials. Other common complaints are fever, fatigue, myalgia and headache. Treatment was discontinued by 22% of the patients taking peginterferon alfa-2a with ribavirin and 32% of these withdrawals were because of adverse events. Laboratory abnormalities accounted for another 12% of withdrawals.<sup>3</sup> These abnormalities included neutropenia and thrombocytopenia, so it is important that haematological and biochemical tests are monitored during treatment. Peginterferon alfa-2a may also alter thyroid function and exacerbate autoimmune disease. It can also cause depression and patients' quality of life reduces during the 48 weeks of treatment.

While peginterferon alfa-2a may be superior to interferon alfa-2b<sup>3</sup>, peginterferon alfa-2b can also induce sustained virological responses in more than 50% of patients<sup>1</sup> so a direct comparison of their effectiveness would be useful. Both drugs should be used in combination with ribavirin unless ribavirin is contraindicated or not tolerated. Even if the treatment is tolerated, it should probably be stopped if it has not significantly reduced viral RNA within 12 weeks.

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### **Pimecrolimus**

Elidel (Novartis)

15 mg tubes containing 1% cream

Approved indication: atopic dermatitis

Australian Medicines Handbook section 8.1

Sirolimus and tacrolimus are immunosuppressants that can be used to prevent the rejection of kidney transplants. These drugs act by inhibiting the activation of T-lymphocytes. Pimecrolimus acts in a similar way and prevents the release of

inflammatory mediators from mast cells. It has therefore been studied in conditions such as atopic eczema.

As atopic eczema is common in children, pimecrolimus cream has been compared with placebo in 186 infants. After a six-week double-blind trial the dermatitis had improved in 55% of the infants given pimecrolimus and in 24% of those given a placebo cream.<sup>1</sup> Pooled results of short-term studies in older children show the eczema cleared in 35% of those given pimecrolimus and 18% of those given placebo.

In other studies, pimecrolimus has been compared with corticosteroid creams. An early study suggested that the efficacy of pimecrolimus 1% cream was less than that of betamethasone 0.1% cream.<sup>2</sup> Another trial studied 713 patients for up to one year to see if pimecrolimus could stop their eczema flaring up. They applied pimecrolimus or its vehicle and added topical corticosteroids if the eczema flared up. The eczema was controlled in 28% of patients given the vehicle and in 51% of those applying pimecrolimus.<sup>3</sup> The drug has therefore been given approval for intermittent long-term treatment, as well as short-term use.

The cream is applied twice a day. Only a small amount is absorbed through the skin. Most of the absorbed drug is metabolised by the liver and excreted in the faeces.

Nearly half the infants dropped out of the placebo-controlled clinical trials. This was mainly because of a poor response to the placebo. In the long-term study 52% of the control group dropped out compared with 32% of the pimecrolimus group.<sup>3</sup> Suspected drug-related adverse effects occurred in 25% of the patients given pimecrolimus and 19% of the control group.<sup>3</sup> Burning at the site of application is a common complaint with pimecrolimus, but it is also associated with skin infections such as folliculitis. Although phototoxicity was not a major problem in clinical trials, pimecrolimus enhanced the carcinogenicity of ultraviolet light in animal studies. Patients should therefore minimise their exposure to sunlight.

Although pimecrolimus will reduce the need to expose children to the adverse effects of topical corticosteroids, it may expose them to other risks of immunosuppression. In long-term studies fever and viral infections such as influenza occurred more frequently in association with pimecrolimus. Lymphomas and thyroid adenomas have occurred in animal studies. Long-term therapy should therefore be restricted to intermittent use by patients who cannot be managed with topical corticosteroids, which cost less. If there is no response to six weeks of treatment pimecrolimus should be stopped.

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## Thalidomide

Thalidomide Pharmion (Pharmion)

50 mg capsules

Approved indication: erythema nodosum leprosum, multiple myeloma

Australian Medicines Handbook section 14

Thalidomide was originally marketed as a sedative, but was withdrawn in 1961 because of its association with birth defects. The drug was still made available for research purposes, and by chance it was found to be effective in erythema nodosum leprosum. This prompted further research into thalidomide's effects on inflammation and the immune system. Despite this research, the mechanism of action remains unclear and our knowledge of thalidomide's pharmacokinetics is incomplete.

Patients with leprosy may develop painful papules on the limbs. In more severe cases this erythema nodosum leprosum can be more widespread and make the patient systemically ill. Studies in the 1960s found that 66–75% of patients would respond to a seven-day course of thalidomide. Although thalidomide is effective for the cutaneous manifestations of erythema nodosum leprosum, it has no known action on *Mycobacterium leprae*.

The birth defects associated with thalidomide may have been related to its inhibition of angiogenesis. As neovascularisation occurs in the bone marrow of patients with multiple myeloma, thalidomide has been tried after other treatments have failed. A study of 84 patients with refractory multiple myeloma found that 32% responded to a course of thalidomide (median duration of treatment 80 days).<sup>1</sup> Despite this response rate, the hypothesis of thalidomide acting by inhibiting angiogenesis was not supported. There was no significant difference in the microvascular density of the bone marrow between patients who responded and those who did not.

Patient responses in studies of multiple myeloma are primarily judged by changes in the concentrations of paraprotein. It is not certain how these responses correlate with survival. The median event-free survival for the 84 patients was three months. After a year 58% of the patients were still alive.<sup>1</sup> An Australian study, which had an overall response rate of 28%, found that the median overall survival was 14.6 months. Increasing age may be associated with a poorer outcome.<sup>2</sup>

The optimum dose for thalidomide in refractory multiple myeloma is not yet clear. Many patients in the clinical trials were not able to increase their dose according to the maximum planned in the study design.<sup>1,2</sup> Higher doses are associated with an increased frequency of adverse effects.

Some of the adverse effects of thalidomide, such as sedation, are predictable. Before the drug was withdrawn in the 1960s there had been reports associating it with peripheral neuropathy, which may be irreversible. In the Australian study 29% of patients developed a degree of motor neuropathy and 47% developed some sensory neuropathy.<sup>2</sup> Patients need regular checks to detect early signs of neuropathy. The white blood cell count also needs regular monitoring as thalidomide may

cause neutropenia. Fatigue and constipation are the most frequent adverse effects of thalidomide.

Women of childbearing age who are prescribed thalidomide must not have intercourse or should use two types of contraception. As it is unknown if thalidomide is present in the semen of male patients they must use barrier contraception, even if they have had a vasectomy. As even a single dose may cause birth defects prescription of thalidomide will be tightly controlled. Only specialists and pharmacists registered with the Pharmion Risk Management Program will be allowed to prescribe and dispense thalidomide. Patients will need to give written informed consent before treatment.

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\* 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)).

**Answers to self-test questions**

1. True	3. True	5. True
2. True	4. True	6. True
7. False	9. True	11. True
8. True	10. True	12. True

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