New drugs

Belimumab

Approved indication: systemic lupus erythematosus
Benlysta (GlaxoSmithKline)
120 mg or 400 mg powder in vials
Australian Medicines Handbook section 15.4

Systemic lupus erythematosus is a complex autoimmune disease which can affect the skin, joints, kidneys, heart and central nervous system. Belimumab is a monoclonal antibody that blocks the B lymphocyte stimulator (BLyS), a soluble protein that binds to B cells. This molecule, which is overexpressed in people with lupus, promotes the survival and differentiation of B cells. Inhibiting it therefore aims to reduce antibody-producing B cells.

Belimumab is indicated as an add-on therapy for adults with active disease despite standard therapy. The recommended dose is 10 mg/kg by intravenous infusion every two weeks for the first six weeks and then monthly after that. Its terminal half-life is 18 days.

The approval of this drug is based on results from one phase II trial[1] and two phase III trials[2,3] totalling 2133 patients. Patients had to be already taking corticosteroids, non-steroidal anti-inflammatories, antimalarials or immunosuppressants for their disease. People with severe active lupus nephritis or central nervous system disease were excluded from the trials.

In the phase II placebo-controlled trial of 449 patients, disease activity was measured using the SELENA-SLEDAI score (Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index). This scoring system, which is usually only used in clinical trials, measures organ involvement and includes items such as seizure, visual disturbance, hair loss, new rash, muscle weakness and arthritis. Laboratory tests such as urinalysis, blood counts and serum autoantibodies are also measured. Scores can vary from 0 to 105, but scores over 6 indicate active disease. Patients with disease scores of 4 or more were enrolled in the phase II trial. Belimumab (1 mg, 4 mg or 10 mg/kg) did not reduce disease activity compared to placebo after a year and there was no difference in the time to the first flare or the incidence of flares between groups.[1]

A post hoc analysis in the phase II trial showed that patients with antinuclear antibodies (titre ≥1:80) or anti-double stranded DNA antibodies (>30 IU/mL) at screening seemed to respond better to belimumab.[1]

Therefore in the phase III trials only seropositive patients with a disease score of 6 or above were enrolled.[2,3] To be considered a responder in the trials, patients had to have met three criteria:

- at least a four-point reduction on the SELENA-SLEDAI score
- no change on the British Isles Lupus Assessment Group (BILAG) A organ domain score, or no more than one point increase on the BILAG B score, and
- no decline in the physician's global assessment score.

Based on this composite endpoint, significantly more patients responded to belimumab 10 mg/kg than to placebo after 52 weeks (see Table).[2,3] However at 76 weeks, this effect had been lost and there was no difference in response rates between groups.[3]

The most common adverse events (≥5% participants) with belimumab include nausea, diarrhoea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain, depression, migraine and pharyngitis. In the trials 13% of participants had a hypersensitivity reaction to belimumab and 0.6% developed anaphylaxis. Infusion reactions were the most common adverse event that resulted in treatment discontinuation (1.6% with belimumab vs 0.9% with placebo). Depression, insomnia, anxiety, suicide attempts (4 patients) and suicide (2 patients) have occurred with this drug so patients should be warned to report psychiatric problems.

Fourteen people died in the trials – 3/675 (0.4%) in the placebo groups versus 11/1458 (0.75%) in

Table **The efficacy of belimumab for systemic lupus erythematosus in two phase III trials**

Phase III trial	Response rate at 52 weeks (and 76 weeks)‡		
	placebo	belimumab 1 mg/kg	belimumab 10 mg/kg
BLISS-52 (867 patients)[2]	43.6%	51.4%	57.6%
BLISS-76 (819 patients)[3]	33.5% (32.4%)	40.6% (39.1%)	43.2% (38.5%)

‡ Based on assessments using the SELENA-SLEDAI score (Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index), the BILAG score (British Isles Lupus Assessment Group) and the physician's global assessment score

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 from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

the belimumab groups. Causes of death included infection, cardiovascular disease and suicide.

In the trials, 70% of patients who received belimumab had an infection compared to 67% who received placebo. Upper respiratory and urinary tract infection, nasopharyngitis, sinusitis, bronchitis and influenza were the most common. Treatment may need to be interrupted if a patient develops an infection. Likewise, it should not be given to patients being treated for a chronic infection. Live vaccines should not be given with belimumab.

Because of its mechanism of action, belimumab could increase the risk of malignancy although this was not observed in the trials.

Although clinical data in pregnant women are limited, belimumab is known to cross the placenta. Contraception should therefore be used during treatment and for four months afterwards. There is also a lack of data in people over 65 years of age so caution is urged in this group.

There have been no drug interaction studies with belimumab. It is therefore not known how safe concomitant use is with other biological therapies or cyclophosphamide.

Belimumab is a new class of drug for lupus. It appears to have modest efficacy over placebo, with significantly more seropositive patients (with active disease) responding to belimumab after 52 weeks but not after 76 weeks. It is unclear how clinically relevant these responses were. A four-point reduction in the SELENA-SLEDAI score was considered to be clinically meaningful in the phase III trials whereas the American College of Rheumatologists have defined at least a seven-point reduction to be clinically meaningful.[4]

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REFERENCES †

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).