Ocrelizumab

Aust Prescr 2018;41:125–6
https://doi.org/10.18773/austprescr.2018.028
First published 12 June 2018

Approved indication: multiple sclerosis

Ocrevus (Roche)
vials containing 300 mg/10 mL concentrate
Australian Medicines Handbook section 16.5

Multiple sclerosis is an autoimmune disease caused by immune cells attacking the central nervous system resulting in demyelination. Commonly the disease has a relapsing-remitting course, but some patients have a more progressive type of multiple sclerosis. During the past 20 years immunotherapy has been increasingly used to reduce rates of relapse.[1] The available options include genetically engineered monoclonal antibodies, such as alemtuzumab and natalizumab which target different parts of the immune system. Ocrelizumab is a monoclonal antibody that binds to the CD20 antigen on B lymphocytes. The resulting lymphocyte depletion modulates the immune response, but the exact mechanism of action of ocrelizumab in multiple sclerosis is currently uncertain.

Ocrelizumab concentrate has to be diluted and then slowly infused intravenously. The recommended regimen is to give half the usual dose then repeat the infusion after two weeks and then give the usual dose (600 mg) every six months. As an antibody, ocrelizumab is subsequently cleared by catabolism. It has a terminal elimination half-life of 26 days.

In a phase II placebo-controlled trial, 220 patients were randomised to receive high- or low-dose ocrelizumab or interferon beta-1a. These patients had the relapsing-remitting type of multiple sclerosis and their response to treatment was primarily assessed by the number of gadolinium-enhancing lesions seen on MRI of the brain. After 24 weeks the mean number of new lesions was 6.6 in the placebo group, 7.2 in the interferon group and 0.8 with both doses of ocrelizumab. Ocrelizumab also reduced the total number of lesions significantly more than placebo or interferon.[2] The lower dose (600 mg) regimen was used in the subsequent phase III trials.

Two trials (OPERA I and II) compared ocrelizumab infusions with subcutaneous interferon beta-1a in 1656 patients with relapsing multiple sclerosis. When these patients were assessed after 24 weeks there was a lower risk of disability progression in the ocrelizumab group. At 96 weeks the annualised relapse rate was lower with ocrelizumab. MRI revealed that the total number of new or enlarged lesions in the brain was also significantly lower (see Table).[3]

There are currently no effective treatments for primary progressive multiple sclerosis. The efficacy of ocrelizumab for this condition was compared with placebo infusions in 732 patients. They were treated for at least 120 weeks, but the primary end point of the trial was the progression of disability at 12 weeks. It progressed in 32.9% of the 488 patients given ocrelizumab and in 39.3% of the 244 given placebo. The corresponding figures at 24 weeks were 29.6% and 35.7%. There was a small reduction (3.4%) in the volume of lesions seen on MRI in patients given ocrelizumab while there was an increase (7.4%) with placebo.[4]

Drugs that reduce the immune response expose patients to an increased risk of infection or reactivation of previous infections. Patients should be screened for hepatitis B before treatment. In the clinical trials, herpes infections and upper respiratory tract infections were more frequent with ocrelizumab than with interferon beta-1a.[3] Immunomodulation can increase the risk of cancer. In the OPERA trials of relapsing multiple sclerosis, four cancers developed in patients taking ocrelizumab compared with two in the interferon groups.[3] Similar to rituximab, another CD20 antibody, ocrelizumab may reduce neutrophil counts. Immunoglobulins are decreased and live vaccines are not recommended. Some patients develop antibodies to ocrelizumab. Infusion-related reactions are common and can be life-threatening.

Table **Efficacy of ocrelizumab in relapsing multiple sclerosis**

Trial	Numbers of patients		Annualised relapse rate at 96 weeks	Proportion with disability progression at 24 weeks	Proportion with no evidence of disease activity at 96 weeks	Total mean number of new or newly enlarged brain lesions at 96 weeks
OPERA I	Ocrelizumab	410	0.16	5.9%	47.9%	0.32
	Interferon beta-1a	411	0.29	9.5%	29.2%	1.41
OPERA II	Ocrelizumab	417	0.16	7.9%	47.5%	0.33
	Interferon beta-1a	418	0.29	11.5%	25.1%	1.90

Source: reference 3

NEW DRUGS

Patients need to be given steroids and antihistamines before ocrelizumab is infused.

The drug should not be used in pregnancy and conception should be avoided for at least six months after stopping treatment. The safety of ocrelizumab in lactation is unknown.

Ocrelizumab is approved for primary progressive and relapsing forms of multiple sclerosis. There are now at least 10 drugs available to manage the relapsing forms. Some require injection, others can be taken by mouth. Other monoclonal antibodies have reduced relapse rates more than interferons, so the results of the ocrelizumab trials are not surprising. An analysis, supported by rival pharmaceutical companies, calculated the numbers of patients who need to be treated to prevent one relapse, relative to interferon therapy. These were four or five for alemtuzumab and eight for ocrelizumab. To prevent one patient having worsening disability at six months requires 13–15 to be treated with alemtuzumab and 21–23 to be treated with ocrelizumab.[5] In primary progressive disease ocrelizumab does have advantages over placebo, but some of them are small and not significant.[4] No cases of progressive multifocal leucoencephalopathy appeared in the clinical trials, but the long-term safety and efficacy of ocrelizumab will require further study to establish its place in therapy.

REFERENCES

1. Taylor I, Coleman J. Treatment of multiple sclerosis with newer immune-modulating drugs. Aust Prescr 2002;25:32-5. https://doi.org/10.18773/austprescr.2002.033
2. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011;378:1779-87. https://doi.org/10.1016/S0140-6736(11)61649-8
3. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376:221-34. https://doi.org/10.1056/NEJMoa1601277
4. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G, et al; ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017;376:209-20. https://doi.org/10.1056/NEJMoa1606468
5. Comi G, Alroughani R, Berkovich R, Limmroth V, Macdonell RAL, Moreau T. Number needed to treat analyses to assess clinical outcomes in patients with relapsing-remitting multiple sclerosis treated with alemtuzumab or ocrelizumab (P6.384). Neurology 2017;88:(Suppl 16).

T manufacturer provided the product information

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA and the European Medicines Agency.