A RESEARCH REVIEW™
PRODUCT REVIEW

Ocrelizumab [Ocrevus®]

Making Education Easy 2018

About the reviewer

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After undergraduate training in medicine at the University of Auckland, Jennifer trained in neurology at Auckland City Hospital. Postgraduate training consisted of an MS research fellowship, with the Therapeutic Immunology Group in the Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK.

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This review summarises important pharmacological and clinical characteristics of ocrelizumab [Ocrevus®], a humanised monoclonal antibody that selectively depletes CD20+ B cells and has demonstrated efficacy in patients with multiple sclerosis (MS).[1-4] Ocrelizumab was registered for use in New Zealand in December 2017 for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) to suppress relapses and disease progression (clinical and subclinical disease activity).[5] Ocrelizumab is also indicated for the treatment of adult patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed. Ocrelizumab is not a PHARMAC funded medicine.

Multiple Sclerosis

MS is a chronic inflammatory demyelinating disease of the central nervous system (CNS).[6] While the etiology of MS is not fully understood, it is thought to involve a complex interplay between genetic and environmental factors resulting in immune-mediated tissue injury.[7] Traditionally considered a T-cell-mediated disorder, the contribution of B cells has been reassessed due to findings on the beneficial effect of B-cell-depleting therapies.[8]

Epidemiology and disease burden

MS predominantly affects individuals with Northern European ancestry.[7] In Western countries MS is the most common cause of neurological disability in young adults and is more prevalent in females than males, at a ratio of 3:1.[7] Worldwide MS prevalence rates vary greatly.[9] In New Zealand, 2006 data suggest an age-standardised prevalence rate of 73.1 per 100,000 population, with a rate of 24.2 per 100,000 population for Maori.[7] Longitudinal data also suggest that the overall prevalence of MS in New Zealand is increasing.[7] A striking latitudinal gradient in MS prevalence is evident, with those furthest from the equator in both hemispheres having the greatest risk.[7] In fact, in New Zealand, a 3-fold difference in 2006 age-standardised MS prevalence rates was evident between the North (50.8 per 100,00) and the South (134.6 per 100,000) Islands.[7]

While one-third of individuals in New Zealand are reported to experience only mild disability due to their MS, 50% experience moderate disability and 16% are severely disabled, being restricted to bed or chair.[7] Not surprisingly, MS has a profound effect on the socioeconomic and work status of individuals living with the disease and worldwide, unemployment rates as high as 80% have been reported.[7] New Zealand surveys report that up to 55% of individuals with MS are not in paid employment, largely due to fatigue, lack of mobility and lack of concentration associated with the disease, with loss of work status occurring early in the disease.[7] In 2006, the median annual personal income for the working age MS population was $NZ20,000 compared with $NZ34,750 for the general population and >30% received an invalid's benefit.[7] In 1999, the estimated annual national cost of MS in New Zealand was $NZ69.5 million (personal costs of $NZ45 million and government costs of $NZ24.5 million), but it is likely that the actual cost today is much higher.[10]

Diagnosis and classification

MS is diagnosed on the basis of clinical findings and supporting evidence from tests, such as magnetic resonance imaging (MRI) of the brain and spinal cord and examination of the cerebrospinal fluid.[11] The course of MS is highly varied and unpredictable. The US National Multiple Sclerosis Society recommends the following disease course definitions:[12]

Clinically Isolated Syndrome — a first symptomatic episode compatible with demyelination that could become MS if additional activity occurs.

Relapsing-Remitting MS (RMS) — episodes of acute worsening of neurologic functioning (new symptoms or the worsening of existing symptoms) with total or partial recovery.

Primary Progressive MS (PPMS) — steadily worsening neurologic function from the onset of symptoms with or without occasional relapses or remissions.

Secondary Progressive MS — following an initial relapsing-remitting course, the disease becomes more steadily progressive, with or without relapses.

Current disease-modifying therapies for MS

Managing patients with MS requires a multidisciplinary approach, coordinated by primary care and supported in some regions by specialist nurses.[13] Treatment goals are to reduce symptoms, improve quality of life, and minimise adverse events.[13] Individuals with active RMS or whom have experienced a single demyelinating event and are at risk of developing clinically definite MS (based on MRI findings) may be treated with disease-modifying

agents. These therapies interfere with immunological mechanisms to reduce rates of relapse, accumulation of disease burden measured by MRI, and decline in neurological function.[14,15] However, current disease-modifying therapies do not slow accrual of disability once progressive MS is established. It is recommended that disease-modifying therapies are started as early as possible in eligible patients.[15] Individualised therapy is advocated when selecting a disease-modifying treatment.[14] Methods such as stratifying patients on the basis of estimated risk for future disability, weighing patient specific factors and preferences, and using objective outcomes to assess treatment success are recommended.[16]

According to the Association of British Neurologists (ABN) guidelines, disease-modifying agents in MS can be divided into two broad classes: agents of moderate efficacy with an average relapse reduction of 30-50% (interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate and fingolimod) and agents of high efficacy with an average relapse reduction substantially more than 50% (natalizumab).[15] The side effect profiles of these agents vary considerably.[15] According to the ABN guidelines, patients may be started on either an `escalation' strategy which involves starting with the drug that is considered least toxic but will control the patient's disease and escalating to more potent agents in the event of continued disease activity, or an `induction' strategy involving giving a more powerful drug with significant side effects, upfront and early in the disease.[15] A recent systematic review investigating the timing of high-efficacy therapy in RMS suggests that treatment with high-efficacy immunotherapies is more potent in suppressing relapse activity when initiated early versus with a delay after the diagnosis of MS, however, the evidence reported for MRI outcomes and disability is inconclusive.[17]

In New Zealand, the following disease-modifying agents are currently available under Special Authority for the treatment of MS.[6]

Drugs of moderate efficacy[15]

Interferon beta

Interferon beta [Avonex®; Betaferon®], a naturally occurring polypeptide with immunomodulatory and anti-inflammatory effects, is administered by injection.[5,18] Phase III trials of interferon beta in RMS have shown reduction in the annualised relapse rate (ARR) by 30-34%, and reduction in the progression of disability as well as MRI disease activity.[19,20] Most patients (50-75%) experience transient flu-like symptoms, including muscle aches, fever, chills, headache and back pain after injection. Liver enzymes may be elevated and bone marrow function may be depressed.[5,19,20]

Teriflunomide

Teriflunomide [Aubagio®] is an oral immunomodulatory agent with anti-inflammatory properties that selectively and reversibly inhibits pyrimidine synthesis.[5] The therapeutic effect in MS is thought to be mediated by a reduction of circulating lymphocytes.[5] Phase III trials in RMS showed that teriflunomide, compared to placebo, reduced the annualised relapse rate by 31-36%, the rate of disability progression by 26-27% and MRI gadolinium enhancing lesions by about 80%.[21,22] Common adverse events include upper respiratory tract infection, urinary tract infection, paraesthesia, diarrhoea, nausea, hair thinning, alanine aminotransferase increase, reduction in blood leucocytes and increase in blood pressure.[5,21,22]

Dimethyl fumarate

Dimethyl fumarate [Tecfidera®] is administered orally and has immunomodulatory and anti-inflammatory properties.[5] Phase III trials in RMS showed that dimethyl fumarate, compared to placebo, reduced the ARR by 44-53%, the rate of disability progression by 22-32% and MRI gadolinium-enhancing lesions by about 75-94%.[23,24] Common adverse events include flushing, nausea, diarrhoea and abdominal pain.[5] The treatment may also reduce white blood cell counts and give elevations of hepatic transaminases.[5]

Glatiramer acetate

Glatiramer acetate [Copaxone®] is a pool of synthetic peptides resembling sequences of myelin basic protein also administered by injection.[5,25] The mode of action is thought to be by activation of suppressor T cells in the periphery.[25] Glatiramer acetate trials in RMS showed a significant reduction in ARR (29%) and a reduction in gadolinium-enhanced MRI activity compared to placebo.[26,27] Glatiramer acetate-associated adverse reactions include injection site reactions, vasodilation, hypersensitivity, rash, dyspnoea and chest pain.[5]

Fingolimod

Fingolimod [Gilenya®], is administered orally and prevents lymphocyte trafficking through the lymph node and causes a reversible lymphopenia.[28] Phase III trials in relapsing MS showed that fingolimod, compared to placebo, reduced the ARR by 48-55%, the rate of disability progression by 25-30% and MRI gadolinium-enhancing lesions by more than 80%.[29,30] Possible side effects include first-dose bradycardia, macular oedema, liver function abnormalities and increased risk of infections.[5]

Drugs of high efficacy[15]

Natalizumab

Natalizumab [Tysabri®] is a monoclonal antibody against α4-integrin that prevents adherence of activated leucocytes to inflamed endothelium, thus inhibiting the migration of inflammatory cells into the CNS.[31] It is administered by intravenous infusion once every 4 weeks.[5] The pivotal phase III trial in RMS showed that natalizumab monotherapy reduced the ARR by 68%, the rate of disability progression by 54% and MRI gadolinium-enhancing lesions by more than 90% compared to placebo.[31] Although natalizumab is generally well tolerated, the treatment is associated with an increased risk of developing progressive multifocal leukoencephalopathy (PML), a serious and potentially life-threatening condition.[5] The risk for PML in John Cunningham virus (JCV)-positive patients ranges from 0.1-10/1000 patients depending upon anti-JCV antibody level, but is lower in JCV-negative patients (<0.09/1000).[5]

Ocrelizumab – a new agent for RMS and PPMS

In March 2017, the US FDA approved ocrelizumab for the treatment of adult patients with RMS or PPMS. Ocrelizumab was registered for use in New Zealand in December 2017 for the treatment of adult patients with RMS to suppress relapses and disease progression (clinical and subclinical disease activity) and for the treatment of adult patients with PPMS to delay disease progression and reduce deterioration in walking speed.

The precise mechanism by which ocrelizumab exerts its therapeutic effects in MS is unknown. Research suggests it involves binding to CD20, a cell surface antigen present on pre-B and mature B lymphocytes, selectively depleting CD20-expressing B cells while preserving the capacity for B-cell reconstitution and pre-existing humoral immunity.[1,2] B-cell depletion may be achieved by several mechanisms, including antibody-dependent cell-mediated phagocytosis, antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and induction of apoptosis.[2] In a review of CD20-targeted therapy, van Meerten et al., highlights the potential benefits from using therapeutic antibodies targeting CD20.[32] CD20 is not expressed in haematopoietic stem cell B cells and it is not expressed on plasma cells, therefore antibody therapy might not significantly decrease the immunoglobulin production against pathogens. CD20 does not circulate in the plasma, it is not shed from the cell surface and it is not internalised after antibody binding. In addition, CD20-targeted therapy does not affect total numbers of the innate immune system and total T-cell numbers.[32]

Pharmacodynamics

CD19+ cells represent a measure of B-cell counts in ocrelizumab treated patients as the presence of ocrelizumab interferes with the detection of CD20 by the assay.[5] The level of CD19+ cells in peripheral blood decreased to negligible levels with ocrelizumab treatment by week 2.[3] A Phase III study reported treatment of PPMS patients with ocrelizumab lead to a decrease of 2 to 6% from baseline in peripheral-blood counts of CD3+ or CD8+ cells, at week 2. An additional 6% decrease was observed from week 2 to week 120 for CD8- expressing cells. It was noted that T cells remained stable throughout the treatment period.[4] A phase III study found antidrug-binding antibodies developed in three of 825 RMS patients (0.4%) who received ocrelizumab, with neutralising antibodies developing in one patient.[3] Neutralising anti–interferon beta-1a antibodies were detected in 21.3% of the patients.[3]

Pharmacokinetics

The pharmacokinetics of ocrelizumab were investigated in a phase I/II dose-escalation trial of ocrelizumab in patients with relapsed/refractory follicular lymphoma (n = 18).[33] The researchers showed ocrelizumab had a mean terminal

half-life of 23-28 days and a slow systemic clearance (0.19-0.71 L/day) at steady state. The steady-state volume of distribution was low and ranged between 5.4 and 6.1 L. Maximum serum concentration and total area under the serum concentration time curve for the dosing interval at steady-state increased with increasing doses. The researchers noted steady-state values for half-life, clearance and volume of distribution for ocrelizumab were generally comparable across dose levels.

Administering ocrelizumab

The product information for ocrelizumab should be consulted for detailed information on dosage, administration, contraindications and adverse events.

Assessments prior to first dose of ocrelizumab

Hepatitis B virus (HBV) screening is required prior to initiating ocrelizumab.[5] Ocrelizumab is contraindicated in patients with active HBV confirmed by positive results for HBsAg and anti-HBV tests.[5] For patients who are negative for surface antigen and positive for HB core antibody or who are carriers of HBV, consultation with liver disease experts is recommended.[5] Vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion.[5] Immunisations should be administered at least 6 weeks prior to initiation of ocrelizumab.[5]

Preparation before every infusion

Patients should be assessed for active infection prior to every infusion of ocrelizumab.[5] In the case of active infection, infusion is to be delayed until the infection resolves.[5] Pre-medicate with 100 mg of intravenous methylprednisolone (or an equivalent corticosteroid) and an antihistamine approximately 30-60 minutes prior to each ocrelizumab infusion to reduce the frequency and severity of infusion reactions.[5] Antipyretic administration may also be considered.[5]

Dosage and administration

The initial 600 mg dose of ocrelizumab is administered as two separate intravenous infusions; one 300 mg infusion, followed by a second 300 mg infusion two weeks later.[5] Subsequent doses thereafter are administered as a single 600 mg intravenous infusion every 6 months (**Table 1**).[5] Observation is recommended for at least one hour after the completion of the infusion.[5]

Table 1. Recommended dose, infusion rate and infusion duration for RMS and PPMS[5]

		Quantity of ocrelizumab to be administered	Infusion Instructions
Initial Dose (600 mg) divided into 2 infusions	Infusion 1	300 mg in 250 mL	• Initiate the infusion at a rate of 30 mL/hr • Thereafter the rate can be increased in 30 mL/hr increments every 30 minutes to a maximum of 180 mL/hr • Each infusion should be given over approximately 2.5 hrs
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent Doses (600 mg) once every 6 months	Single infusion	600 mg in 500 mL	• Initiate the infusion at a rate of 40 mL/hr • Thereafter the rate can be increased in 40 mL/hr increments every 30 minutes to a maximum of 200 mL/hr • Each infusion should be given over approximately 3.5 hrs

Dose modifications

Dose modifications in response to infusion reactions depend on the severity.[5] Life-threatening infusion reactions require immediate cessation and permanent discontinuation.[5] In the case of severe infusion reactions ocrelizumab infusion is to be immediately interrupted and the appropriate supportive treatment administered.[5] The infusion is to be restarted only after all symptoms have resolved.[5] Upon restarting, the infusion rate is to be half of the infusion rate at the time of onset of the infusion reaction. If this rate is tolerated, the infusion can be increased to the initial infusion rate. Mild-to-moderate infusion reactions require the infusion rate to be reduced to half the rate at the onset of the infusion reaction and maintained for at least 30 minutes.[5] If this rate is tolerated, the infusion rate can be increased to the initial infusion rate.

Adverse events

In phase III trials of ocrelizumab in MS, overall rates of adverse events did not differ significantly between the ocrelizumab group and the placebo group or the comparator (interferon beta-1a).[3,4] Safety data from a meta-analysis of four RCTs in rheumatoid arthritis patients have shown similar findings with rates of serious adverse events comparable between the ocrelizumab and placebo groups.[34] However, infusion-related reactions were significantly higher in ocrelizumab recipients compared with placebo recipients (RR = 2.13; 95% CI 1.69-2.68, $p < 0.00001$). An updated safety analysis from controlled and open-label extension periods from the clinical trials of ocrelizumab in RMS and PPMS involving 2279 patients (5711 patient-years of exposure) has revealed an adverse event rate of 242 per 100 patient-years (95% CI 238-246): serious adverse events 6.97 per 100 patient-years (95% CI 6.30-7.69), infections 73.6 (95% CI 71.4-75.9), serious infections 1.80 (95% CI 1.47-2.19), malignancy 0.440 (95% CI 0.263-0.589).[35]

Infusion-related reactions

At least one infusion-related reaction was reported by 39.9% of PPMS patients who received ocrelizumab (n = 488) compared with 25.5% of those who received placebo (n = 244).[4] In the phase III trials in RMS 34.3% of patients in the ocrelizumab group (n = 821) had at least one infusion-related reaction compared to 9.7% of patients in the interferon beta-1a comparator group (n = 835).[3] Most infusion-related reactions were mild to moderate and decreased in both rate and severity with subsequent administration. Notably, in the phase III RMS trial, one patient in the ocrelizumab group had a life-threatening episode of bronchospasm during the first infusion; the patient recovered with treatment. The most frequent symptoms of infusion related reaction with ocrelizumab included pruritus, rash, throat irritation, and flushing.[3]

Infections

A higher proportion of ocrelizumab-treated patients experienced infections compared to patients taking interferon beta-1a or placebo. In RMS trials, 58% of patients treated with ocrelizumab experienced one or more infections compared to 52% of patients treated with interferon beta-1a. In the PPMS trial, 70% of ocrelizumab-treated patients experienced one or more infections compared to 68% of patients on placebo. Ocrelizumab increased the risk of respiratory tract infections, skin infections, and herpes-related infections.[33] There were no reports of PML in MS patients treated with ocrelizumab in clinical trials.[1] JCV infection resulting in PML has been observed in patients treated with other anti-CD20 agents.[1]

Malignancies

An increased number of malignancies (including breast cancers) have been observed in clinical trials in patients treated with ocrelizumab, compared to control groups.[36] However, the incidence was within the background rate expected for an MS population.

Special patient groups

Safety and effectiveness of ocrelizumab in pregnant women, geriatric and pediatric patients have not been established. It is recommended women of childbearing potential use contraception while receiving ocrelizumab and for 6 months after the last infusion.[5]

Clinical efficacy and tolerability

The efficacy and safety of ocrelizumab was assessed in a phase II, placebo-controlled trial in patients with RMS.[37] The researchers investigated the effect of two dose regimens of ocrelizumab on the total number of gadolinium enhancing T1 lesions observed on brain MRI scans. They reported the number of gadolinium-enhancing lesions was 89% lower in the 600 mg ocrelizumab group than in the placebo group, and 96% lower in the 2000 mg group. They also found both 600 mg and 2000 mg ocrelizumab groups were better than interferon beta-1a for gadolinium-enhancing lesion reduction. On the basis of these findings phase III studies were conducted in RMS and PPMS.

The phase III parallel-group trials OPERA I and OPERA II investigated the efficacy and safety of ocrelizumab, compared with subcutaneous interferon beta-1a, in patients with RMS.[3] Ocrelizumab was associated with significantly lower ARR than interferon beta-1a, during the 96-week treatment period. In addition, ocrelizumab was associated with a lower rate of disability progression and significantly greater suppression of development of new areas of inflammation and new or newly enlarged plaque formation. Another phase III study (ORATORIO) investigated the efficacy and safety of ocrelizumab in patients with PPMS and found ocrelizumab was associated with lower rates of clinical and MRI progression than placebo.[4] The authors of the phase III studies highlighted the need for additional and extended studies to determine the long-term safety and efficacy of ocrelizumab.

The following are summaries of the two pivotal ocrelizumab clinical trials with commentary on how the study findings define the role of ocrelizumab in the management of MS.

Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis[3]

Authors: Hauser SL et al.

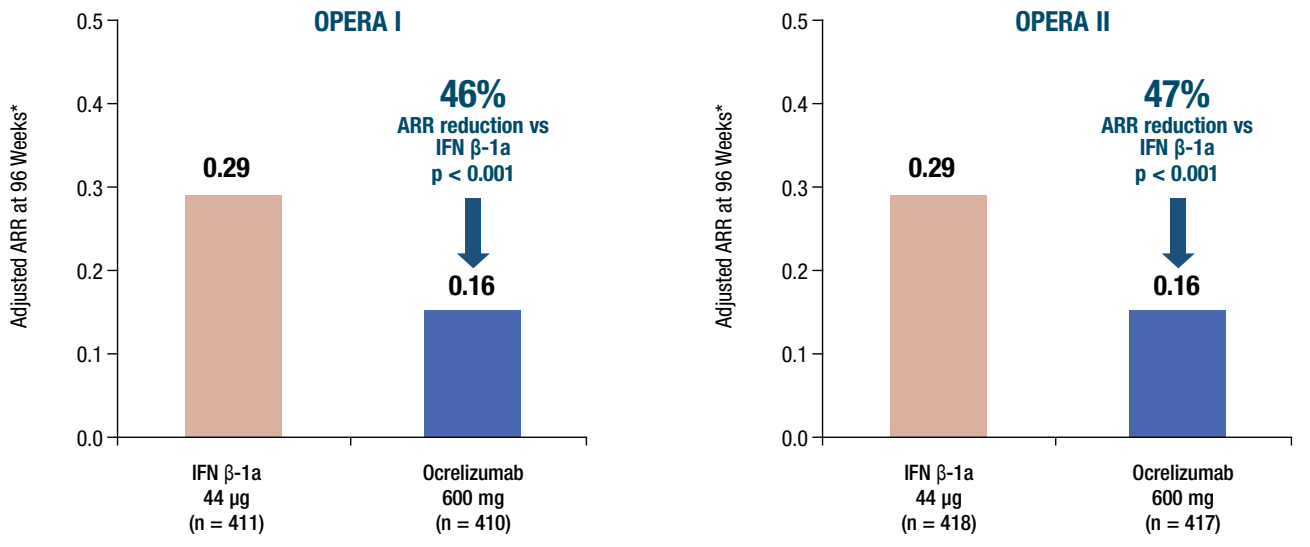
Aim: The OPERA I and OPERA II trials investigated the efficacy and safety of ocrelizumab, compared with interferon beta-1a, in patients with RMS.

Methods: The two trials were identical phase III, randomised, double-blind, double-dummy trials but were conducted independently at non-overlapping trial sites. The OPERA I trial randomised 821 patients from 141 trial sites across 32 countries between 2011 and 2013. The OPERA II trial randomised 835 patients from 166 trial sites across 24 countries between 2011 and 2013. Patients with RMS were randomly assigned, in a 1:1 ratio, to receive intravenous ocrelizumab (600 mg every 24 weeks) or subcutaneous interferon beta-1a (44 µg three times weekly) for 96 weeks. All patients received a matching subcutaneous or intravenous placebo.

Results: The primary end point, the ARR at 96 weeks (**Figure 1**), was 46% lower with ocrelizumab than with interferon beta-1a in OPERA I (0.16 vs 0.29; $p < 0.001$) and 47% lower in OPERA II (0.16 vs 0.29; $p < 0.001$). The authors reported the percentage of patients with disability progression confirmed at 12 weeks was significantly lower with ocrelizumab than with interferon beta-1a (9.1% vs 13.6%; HR 0.60; 95% CI 0.45-0.81, $p < 0.001$). Disability progression remained significantly lower at 24 weeks (6.9% vs 10.5%; HR 0.60; 95% CI 0.43-0.84, $p = 0.003$). The mean number of gadolinium-enhancing lesions per T1-weighted MRI scan was 94% lower with ocrelizumab than with interferon beta-1a in OPERA I (0.02 vs 0.29, $p < 0.001$) and 95% lower in OPERA II (0.02 vs 0.42, $p < 0.001$). Infusion-related reactions occurred more in patients treated with ocrelizumab (34.3%) than in the interferon beta-1a group (9.7%). In patients treated with ocrelizumab the most common adverse events were infusion-related reaction, nasopharyngitis, upper respiratory tract infection, headache, and urinary tract infection. With interferon beta-1a the most common adverse events were influenza-like illness, injection-site erythema, headache, urinary tract infection and upper respiratory tract infection.

Expert comment:

The results from OPERA I and II have proven the efficacy of ocrelizumab, a B cell depleting monoclonal antibody for the treatment of patients with RMS. The results of these phase III trials have been awaited since the phase II trial using rituximab showed a positive result in 2008. The efficacy of B cell therapy in RMS was novel at that time as although B cells were known to play a role, MS was believed to be a T cell predominant auto-immune disease. Ocrelizumab reduces relapses by 46-47% compared to interferon beta. The rates of disability progression and new lesion formation on MRI are also reduced. This supports that B cells, likely in their role as antigen presenters, cytokine producers and through the production of antibodies, play a key role in MS pathogenesis. In New Zealand we have six funded medications for patients with RMS who meet PHARMAC criteria. Ocrelizumab will likely join these and treating neurologists will have further choice. Although the long-term side-effect profile remains to be fully determined, it likely offers a safer alternative to natalizumab in our JCV positive MS population with more aggressive disease. Evidence that ocrelizumab slows disability progression in patients with PPMS also suggests that it may have a role in those with active progressive MS although this is unproven.



*Adjusted ARR calculated by negative binomial regression and adjusted for baseline EDSS score (<4.0 vs ≥4.0), and geographic region (US vs ROW).
ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; IFN = interferon; ROW = rest of the world.

Figure 1. The primary endpoint, the ARR at 96 weeks, in the Opera I and II trials.[38]

Ocrelizumab versus placebo in primary progressive multiple sclerosis[4]

Authors: Montalban X et al.

Aim: The ORATORIO study investigated the efficacy and safety of ocrelizumab in patients with PPMS.

Method: The phase III, randomised, parallel-group, double-blind, placebo-controlled trial randomly assigned 732 PPMS patients in a 2:1 ratio to receive intravenous ocrelizumab (600 mg) or placebo every 24 weeks.

RESULTS: The primary end-point, percentage of patients with 12-week confirmed disability progression (**Figure 2**) was 32.9% with ocrelizumab versus 39.3% with placebo (HR 0.76; 95% CI 0.59-0.98, p = 0.03). The 24-week confirmed disability progression was 29.6% with ocrelizumab versus 35.7% with placebo (HR 0.75; 95% CI 0.58-0.98, p = 0.04). The authors observed 3.4% decrease in the total volume of brain lesions on T2-weighted MRI with ocrelizumab and an increase by 7.4% with placebo (p < 0.001). They also reported percentage of brain-volume loss was 0.90% with ocrelizumab versus 1.09% with placebo (p = 0.02). An exploratory analysis indicated that progression in a 9-hole peg test of ≥20% occurred in 27.0% of placebo versus 17.0% of ocrelizumab recipients at 12 weeks (HR 0.56; 95% CI 0.41–0.78, p < 0.001) and in 23.4% vs 14.2% at 24 weeks (HR 0.55; 95% CI 0.38–0.77, p < 0.001). Overall, the rates of adverse events did not differ significantly between the ocrelizumab group and the placebo group. The most frequently reported adverse event among ocrelizumab-treated patients was infusion related reaction: 39.9% of those who received ocrelizumab versus 25.5% of those who received placebo. Upper respiratory tract infections, and oral herpes infections were also more frequent with ocrelizumab than with placebo.

Expert comment:

The results of the ORATORIO trial have led to a wave of optimism through the MS world. This is the first time that a drug has demonstrated phase III clinical trial evidence of efficacy in PPMS. The benefit is clinically relevant to the population treated in the trial but overall could be looked at as modest. Those treated with ocrelizumab 600 mg every 24 weeks for at least 120 weeks showed a relative risk of disability progression of 25% less than those in the placebo group. This result is exciting, however, prescribing neurologists need to act cautiously, using this medication only in appropriate patients. The inclusion and exclusion criteria and safety profile from the ORATORIO trial should be used to inform prescribing. Patients included were aged 18-55 and with an Expanded Disability Status Scale (EDSS) score of 5 or less with disease duration of less than 15 years. Those included with an EDSS of 5 or more were required to have a disease duration less than 10 years. The benefit has to be weighed against the potential risk of infection and malignancy. It will be helpful to see how both the efficacy and safety trial data translates into real world experience. This result will also inform research into the pathogenesis of progressive MS. We now have confirmation that a B cell therapy impacts on neurodegeneration indicating it is directly or indirectly linked to B cell activity.

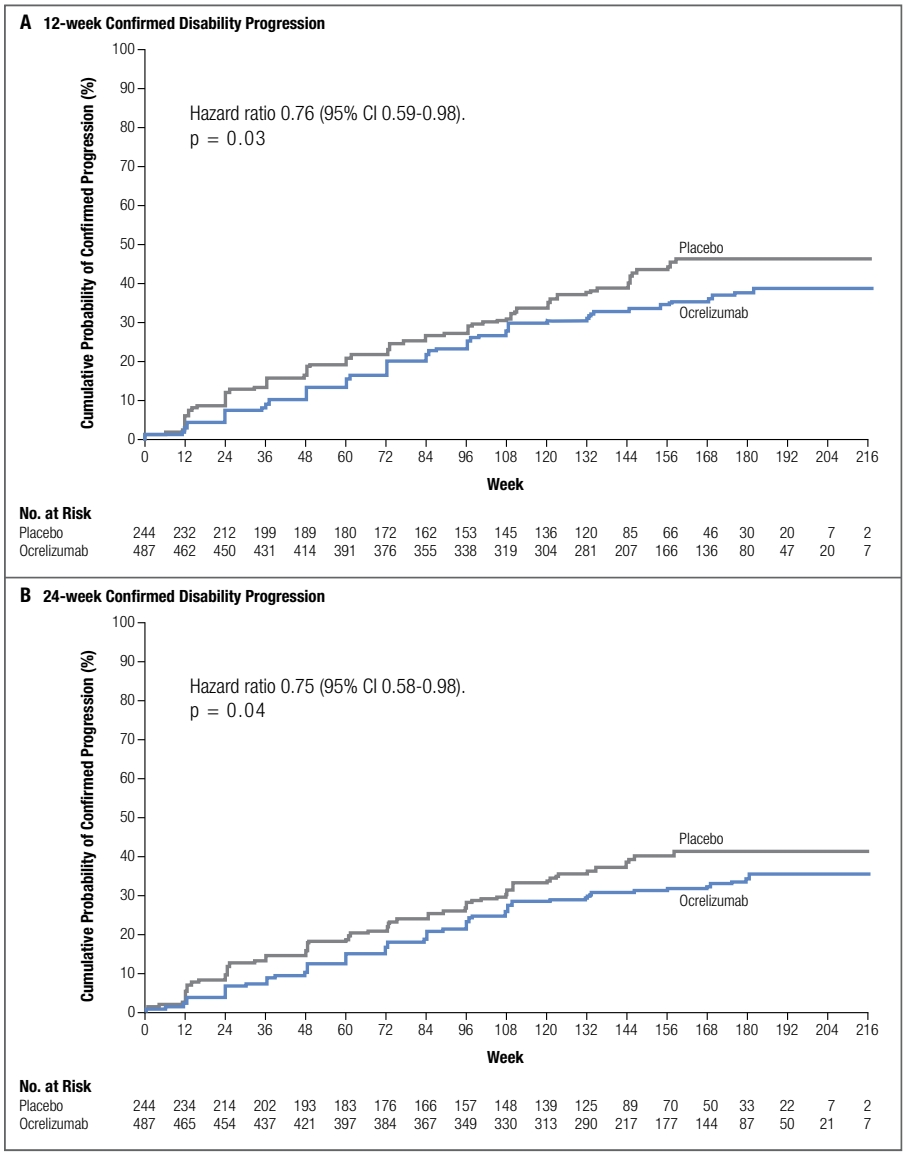


Figure 2. Cumulative probability of clinical disability progression that was confirmed after at least 12 weeks (Panel A) and at least 24 weeks (Panel B). Disability progression was defined as an increase from the baseline EDSS score of at least 1.0 point (or 0.5 points if the baseline EDSS score was >5.5) that was sustained for at least 12 or 24 weeks.[4]

EXPERT'S CONCLUDING COMMENTS

The results of the phase III ocrelizumab trials offer additional therapies for patients with RMS and the first ever proven disease-modifying treatment for those with PPMS. With time, ocrelizumab will find its niche in the MS clinic amongst other available treatments for RMS. The substantial efficacy in RMS, 6-monthly infusion protocol, lower JCV risk and efficacy in primary progressive disease point to where it will sit. Its use will likely be in those patients with more aggressive disease, those who are JCV positive and those showing signs of clinical progression. The limited safety data in pregnancy and breastfeeding make its use in women of childbearing age challenging. The appropriate group of patients with PPMS to treat should be directed by the inclusion and exclusion criteria of the trials, however, in New Zealand eligibility for funded therapy will be directed by PHARMAC criteria which are yet to be determined.

TAKE-HOME MESSAGES

- Ocrelizumab is a humanised monoclonal antibody that selectively depletes CD20+ B cells and has a unique mechanism of action for the treatment of MS.[1]
- Ocrelizumab is the first drug approved by Medsafe for both RMS or PPMS.
- The recommended administration of ocrelizumab is by intravenous infusion on Day 1, Week 2 and subsequent infusions every 6 months.[5]
- In two phase III studies of RMS, ocrelizumab was associated with lower rates of disease activity, relapses and progression than interferon beta-1a.[3]
- In a phase III study of PPMS, ocrelizumab was associated with lower rates of clinical and MRI progression than placebo.[4]
- Ocrelizumab has an acceptable side effect profile. The most common side effects include infusion-related reaction, upper respiratory tract infection and nasopharyngitis.[3,4]
- Extended observation is required to determine the long-term safety and efficacy of ocrelizumab.[3,4]

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