A RESEARCH REVIEW™
SPEAKER SERIES

Ocrevus® (ocrelizumab)
An update and practical issues for neurologists, nurses and others

Making Education Easy 2020

About the speaker

Professor Bruce Taylor

Bruce Taylor is Professor of Neurological Research at the Menzies Institute for Medical Research, University of Tasmania, where he leads the MRFF-funded, Multiple Sclerosis Research Flagship Program. He is also a consultant neurologist at the Royal Hobart Hospital, where he has a special interest in neuroimmunology and neuromuscular diseases. He has a strong research interest in multiple sclerosis, particularly the personal environmental and genetic factors associated with onset and progression of multiple sclerosis.

This publication summarises an educational meeting presented by Professor Bruce Taylor on Monday 9th March 2020. Professor Taylor reviewed published data on Ocrevus® (ocrelizumab) for the treatment of multiple sclerosis, and discussed his 10 years of experience with using the drug for patients with relapsing forms of multiple sclerosis and primary progressive multiple sclerosis in Australia. Also included is a short commentary on Ocrevus and COVID-19, the NZ perspective, provided by Dr Jennifer Pereira on 18th May 2020. The meeting was sponsored by Roche Products (New Zealand) Limited.

Ocrevus 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), and for the treatment of adult patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed.[1] From December 2019, Ocrevus has been funded by PHARMAC for the treatment of RMS in patients who meet predefined criteria.[2] It is not funded for the treatment of PPMS.

Mechanism of action

Multiple sclerosis (MS) was traditionally considered to be a T-cell mediated disease, but it is now understood that B cells play a key role in MS disease activity.[3] B cells are present in all forms of MS,[4] and the density of CD20+ B cells correlates with the activity of demyelinating lesions.[5] Selectively targeting CD20+ B cells may preserve reconstitution and long-term immune memory.[6,7] Ocrevus is a recombinant humanised monoclonal antibody that targets CD20-expressing B cells.[8,9] It binds to an epitope on an extracellular loop of CD20.[10] The percentage of human protein in Ocrevus is 90-95%, higher than that found in chimeric antibodies.[10] Ocrevus may deplete CD20+ B cells via multiple mechanisms, including antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, complement-dependent cytotoxicity and induction of apoptosis.[8,11]

Pharmacodynamic and pharmacokinetic properties

CD19+ cells represent a measure of B-cell counts in Ocrevus-treated patients, as the presence of Ocrevus interferes with assay detection of CD20.[1] Treatment with Ocrevus leads to rapid and prolonged depletion of CD19+ B cells in blood by 14 days post-treatment.[12] The median time to B-cell repletion is 72 weeks, with 90% of patients showing B-cell counts returned to the lower limit of normal or baseline by approximately 2.5 years after the last infusion of Ocrevus.[1] The extent and duration of B-cell depletion is consistent in patients with RMS and PPMS.[1] In phase III trials, up to 5% of patients showed B-cell repletion (greater than lower limit of normal or baseline), at least at one time point, between doses of Ocrevus.[1] The terminal half-life of Ocrevus is 26 days.[1]

Ocrelizumab and MS during COVID-19 in NZ (Commentary from Dr Jennifer Pereira)

The risk of coronavirus infection in New Zealand is currently reducing. This pandemic has brought with it added concern for those over 70, people with co-morbidities and for individuals with suppressed immune systems. PwMS on disease modifying treatment are potentially at an increased risk of becoming infected and having more significant complications – although this is a theoretical risk based on DMT impact immune function and the known risk from other infections.

In New Zealand we have an array of effective immunotherapies for the treatment of active relapsing multiple sclerosis. Ocrelizumab was funded from the 1st of December 2019 and available even earlier for many patients due to compassionate supply from the drug company. This treatment is mostly prescribed for those who are JCV positive with aggressive disease. Prior to the availability of ocrelizumab, natalizumab was the only available high efficacy drug and for some this came with a 1/100 per annum risk of the viral brain disease, PML. The switch to or initiation of ocrelizumab brings with it a different of risk, with moderate systemic immunosuppression.

This moderate systemic immunosuppression brought with it concerned added risk from coronavirus infection. Following recommendations from the Italian MS group and development of ANZAN guidelines, we delayed the start and retreatment with ocrelizumab where possible. Advice for those already treated was to self-isolate and strictly adhere to WHO hand hygiene and physical distancing advice when contact was required. Ocrelizumab is administered by intravenous infusion 6 monthly. The infusion takes approximately 6 hours and for the majority of patients this is given in a hospital setting. Due to the potential risk of coronavirus exposure when attending hospital in an already compromised state, where possible we delayed retreatment. Most individuals remain B cell depleted for many months beyond the 6-month retreatment mark. Cell markers which look to see if the B cells have begun to repopulate can be measured and if these remain low an individual is effectively treated and retreatment can be delayed. With the move to Alert level 2 we have now mostly returned to Ocrelizumab treatment as per normal practice. It is likely that definitive statistics regarding the risk of coronavirus for those on Ocrelizumab will come out of registries set up as the pandemic unfolded. To date, anecdotally the risk looks likely to be lower than initially postulated.

OPERA I and OPERA II trials

The phase III OPERA I and OPERA II trials investigated the efficacy and safety of Ocrevus, compared with interferon beta-1a, in patients with RMS.[12] The two trials were identical randomised (1:1), double-blind, double-dummy, parallel-group studies.[12] Patients received an Ocrevus 600 mg infusion every 24 weeks or subcutaneous interferon beta-1a three times a week for 96 weeks.[12] The initial dose of Ocrevus was administered as two separate 300mg infusions given 2 weeks apart.[12] MRI scans were assessed by a blinded, central MRI reader.[12]

The primary endpoint of the OPERA I and OPERA II trials was the annualised relapse rate (ARR) at 96 weeks, and a number of important secondary endpoints were also assessed.[12] Relapse was defined in the trial protocols as new or worsening neurological symptoms persisting for >24 hours attributable to MS immediately preceded by a stable or improving neurological state for ≥30 days.[13]

In OPERA I, 821 patients were randomised and formed the intention-to-treat population, 817 received treatment with Ocrevus or interferon beta-1a and formed the safety population, and 706 completed the 96-week study.[12] Corresponding numbers for OPERA II were 835, 834, and 680 patients.[12] There were a greater number of withdrawals in the interferon beta-1a group compared with the Ocrevus group in both trials.[12] Baseline demographic and disease characteristics between the assigned groups in the two studies were similar.[12] The mean age of patients was approximately 37 years, and approximately two-thirds were female.[12] Mean duration of MS symptoms was approximately 6.6 years, and mean Expanded Disability Status Scale (EDSS) score was approximately 2.8.[12]

Safety

In OPERA I and OPERA II, the percentage of patients reporting any adverse event was very similar in both treatment groups (see **Table 1**).[12] The rates of any serious adverse events, and serious infections and infestations, were lower in patients treated with Ocrevus compared with interferon beta-1a in both the OPERA I and OPERA II trials.[12]

No cases of progressive multifocal leukoencephalopathy (PML) were reported in OPERA I and OPERA II,[12] and there have been no reported cases of this adverse event to date across all clinical trials of Ocrevus.[1] However, a risk of PML cannot be excluded.[1]

	OPERA I		OPERA II	
	Interferon beta-1a (n = 409)	Ocrevus (n= 408)	Interferon beta-1a (n = 417)	Ocrevus (n = 417)
Any adverse event	80.9%	80.1%	85.6%	86.3%
Adverse event leading to discontinuation	6.4%	3.2%	6.0%	3.8%
≥1 Infusion-related reaction	7.3%	30.9%	12.0%	37.6%
Infections	54.3%	56.9%	52.5%	60.2%
System Organ Class infection and infestation	52.8%	56.6%	52.0%	60.2%
Herpes infections:				
Herpes zoster	1.0%	2.2%	1.0%	1.9%
Oral herpes	2.0%	2.2%	2.2%	3.6%
Malignancies	0.2%	0.7%	0.2%	0.2%
Death	0.2%	0	0.2%	0.2%
Any serious adverse event	7.8%	6.9%	9.6%	7.0%
Serious infections and infestations	2.9%	1.2%	2.9%	1.4%

Table 1. Adverse events in the safety population of OPERA I and OPERA II.[12]

The most common adverse events with Ocrevus were infusion-related reactions, nasopharyngitis, upper respiratory tract infection, headache and urinary tract infection.[12] The most common adverse events with interferon beta-1a were influenza-like illness, injection-site erythema, headache, urinary tract infection and upper respiratory tract infection.[12]

Across OPERA I and OPERA II, malignancies occurred in two patients treated with interferon beta-1a (1 case each of mantle cell lymphoma and squamous cell carcinoma) and four patients treated with Ocrevus (2 cases of ductal breast carcinoma, 1 case of renal cell carcinoma, and 1 case of malignant melanoma).[12] There were two deaths in patients treated with interferon beta-1a (1 due to suicide and 1 due to mechanical ileus), and one death in a patient treated with Ocrevus due to suicide.[12]

Efficacy

In a prespecified pooled analysis of OPERA I and OPERA II over 96 weeks, patients treated with Ocrevus had a 46.5% reduction in ARR compared to those treated with interferon beta-1a (0.156 vs 0.291, respectively; p<0.001).[12] The pooled analysis was comparable to data from the individual OPERA I and OPERA II studies, which found relative reductions in ARR of 46% and 47%, respectively.[12] The reduction in ARR was significant at week 8, and at every timepoint tested over the 96-week treatment period.[12] The cumulative probability of patients experiencing a relapse over 96 weeks was 19% with Ocrevus and 32% with interferon beta-1a in the pooled analysis (p<0.001).[12]

Also in the pooled analysis, the risk of confirmed disease progression (CDP) at 12 weeks was reduced by 40% with Ocrevus vs interferon beta-1a (hazard ratio 0.60; 95% CI 0.45-0.81; p<0.001), and time to onset of CDP ≥12 weeks was delayed by >5 weeks.[12] At 24 weeks, the risk of CDP was also reduced by 40% with Ocrevus vs interferon beta-1a (hazard ratio 0.60; 95% CI 0.43-0.84; p<0.01), and time to onset of CDP ≥24 weeks was delayed by >4 weeks.[12]

Ocrevus had a significantly better impact on patients' physical functioning compared with interferon beta-1a in the pooled analysis, as measured by Short-Form 36 physical component summary score (difference in adjusted mean from baseline to 96 weeks 0.918; 95% CI 0.135-1.702; p<0.05).[12]

Ocrevus had a profound effect on MRI markers, reducing T1 Gd-enhancing lesions over 96 weeks vs interferon beta-1a by 94% and 95%, respectively, in the OPERA I and OPERA II trials (both p<0.001).[12] By weeks 48 and 96, Ocrevus also prevented the occurrence of new or enlarging T2 lesions in OPERA I and OPERA II.[12] Over the 96-week treatment period, T2 lesions were reduced with Ocrevus vs interferon beta-1a by 77% and 83%, respectively, in the OPERA I and OPERA II trials (both p<0.001).[12]

Ocrevus was associated with a significant reduction in brain volume loss vs interferon beta-1a in OPERA I (22.8%; p<0.01), but not in OPERA II (14.9%; p=0.09).[12] Pooled data from OPERA I and OPERA II showed that Ocrevus was associated with a significant improvement in Symbol Digit Modalities Test score over 96 weeks compared with interferon beta-1a (p<0.05).[14]

By week 96, there was an overall decrease in mean EDSS score for patients treated with Ocrevus, compared with a slight increase in patients treated with interferon beta-1a.[12] Adjusted mean difference was -0.17 in favour of Ocrevus in OPERA I and -0.19 in OPERA II (both p<0.01).[12]

Open-label extension

The open-label extension phase enrolled 678 patients from OPERA I and 647 patients from OPERA II, of whom 82.3% completed 4 years of follow up.[15] All patients received Ocrevus 600 mg every 24 weeks.[15] No increased safety signals have been detected during the open-label extension, said Professor Taylor, including no cases of PML.

In patients who received continuous Ocrevus, the ARR remained consistently low over the 4-year follow-up period.[15] Switching from interferon beta-1a to Ocrevus was associated with a reduction in ARR, which was maintained throughout the 4-year follow-up period (see **Figure 1**).[15]

Starting treatment with Ocrevus rather than interferon beta-1a may have a long-term advantage in terms of CDP ≥24 weeks, as the proportion of patients with CDP ≥24 weeks was significantly lower in those who received continuous Ocrevus

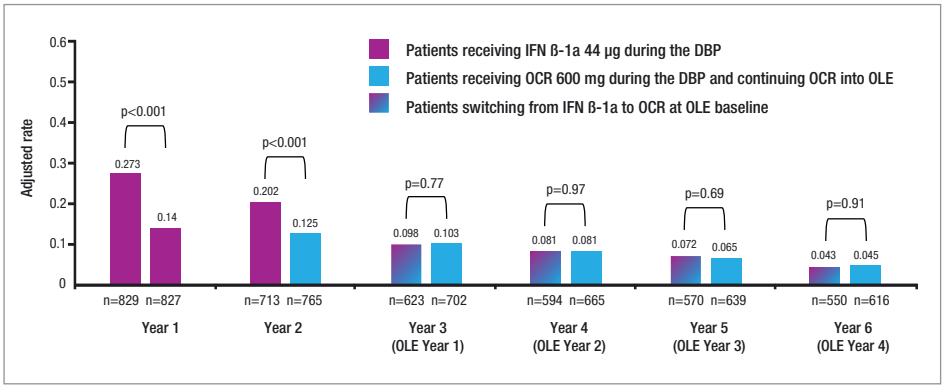

Figure 1. Annualised relapse rate in the double-blind and open-label extension phases of the OPERA trials.[15] DBP = double-blind phase; IFN = interferon; OCR = Ocrevus; OLE = open-label extension.

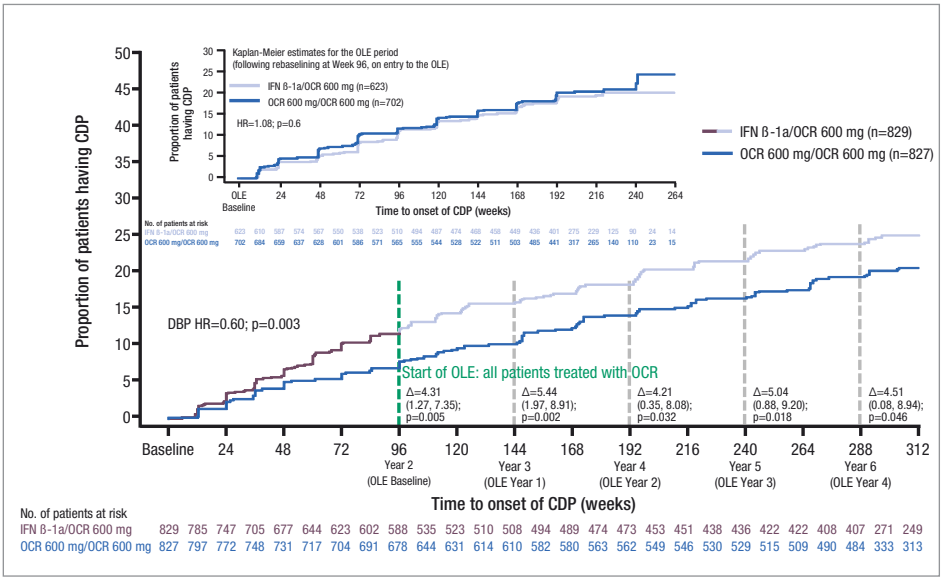

Figure 2. Time to onset of confirmed disability progression ≥24 weeks in the double-blind and open-label extension phases of the OPERA trials.[15] CDP = confirmed disability progression; DBP = double-blind phase; HR = hazard ratio; IFN = interferon; OCR = Ocrevus; OLE = open-label extension.

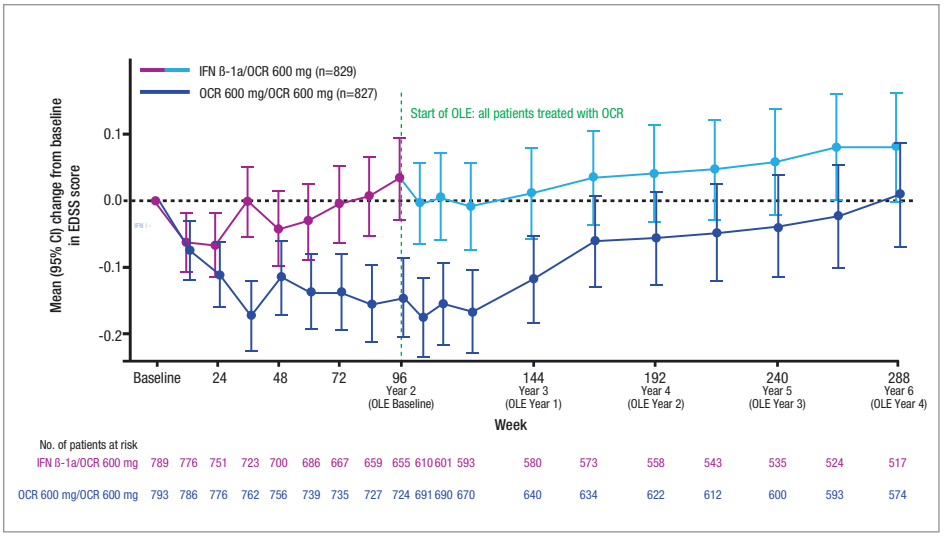

Figure 3. Change in Expanded Disability Status Scale score vs baseline in the double-blind and open-label extension phases of the OPERA trials.[15] EDSS = Expanded Disability Status Scale; IFN = interferon; OCR = Ocrevus; OLE = open-label extension.

compared with those who switched from interferon beta-1a at each year of follow-up in the open-label extension (see **Figure 2**).[15]

After 6 years of continuous treatment with Ocrevus, mean EDSS score returned to baseline (see **Figure 3**).[15] However, in patients switched to Ocrevus at the start of the open-label extension, EDSS score remained higher at each year of the 4-year follow-up compared with patients who received continuous Ocrevus.[15]

Systematic review and network meta-analysis

A recently published systematic review and network meta-analysis compared the efficacy and safety of Ocrevus with those of all disease-modifying therapies approved by the European Medicines Agency for the treatment of RMS as of July 2017.[16] Ocrevus was compared with 17 different treatments, including placebo, for 12-week CDP, ARR and serious adverse events, and with 18 different treatments, including placebo, for discontinuation due to adverse events.[16]

Ocrevus was more effective in reducing the risk of 12-week CDP than 10 other treatments, including placebo (see **Figure 4**).[16] The probability that Ocrevus was more effective than the 6 remaining treatments was greater than 50% in each case, and there was no evidence to suggest that any treatment was more effective than Ocrevus.[16]

Ocrevus was also more effective in reducing the ARR than 12 other treatments, including placebo (see **Figure 4**).[16] The probability that Ocrevus was more effective than the two of the four remaining treatments was greater than 50% in each case, and there was no evidence to suggest that any treatment was more effective than Ocrevus.[16]

With regard to the risk of serious adverse events and discontinuation due to serious adverse events, there was no evidence of a difference between Ocrevus and any other disease-modifying therapies (see **Figure 5**).[16]

A surface under the cumulative ranking curve (SUCRA) radar plot was used to generate treatment rankings based on the two key efficacy outcomes and the two key safety outcomes (see **Figure 6**).[16] Ocrevus demonstrated a consistently high probability of being ranked as the most effective or well tolerated treatment across all four outcomes.[16]

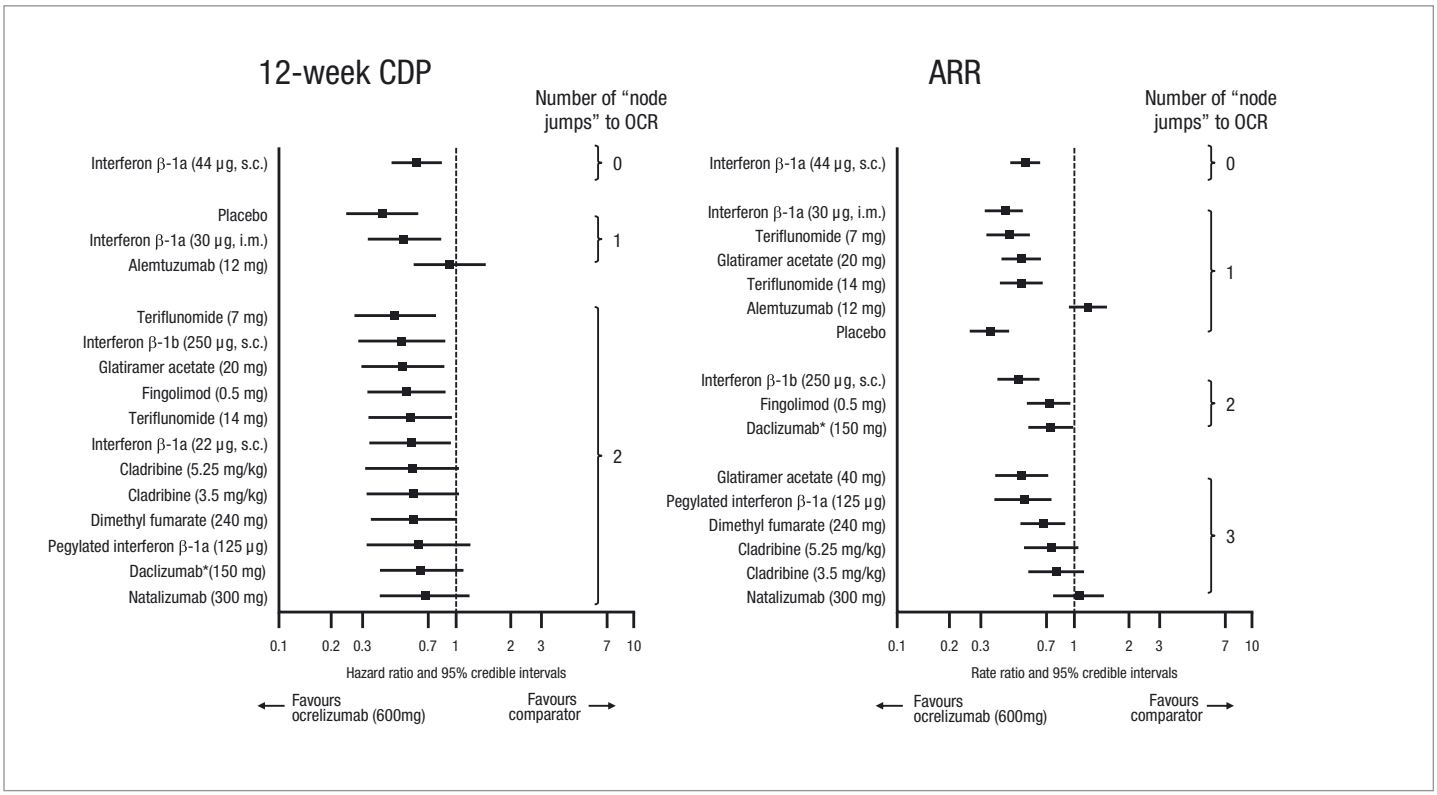

Figure 4. Base-case forest plots for efficacy of Ocrevus vs other disease-modifying therapies in patients with relapsing multiple sclerosis.[16] "Node jumps" are the number of jumps in the network between Ocrevus and the other treatments. ARR = annualised relapse rate; CDP = confirmed disability progression; OCR = Ocrevus.

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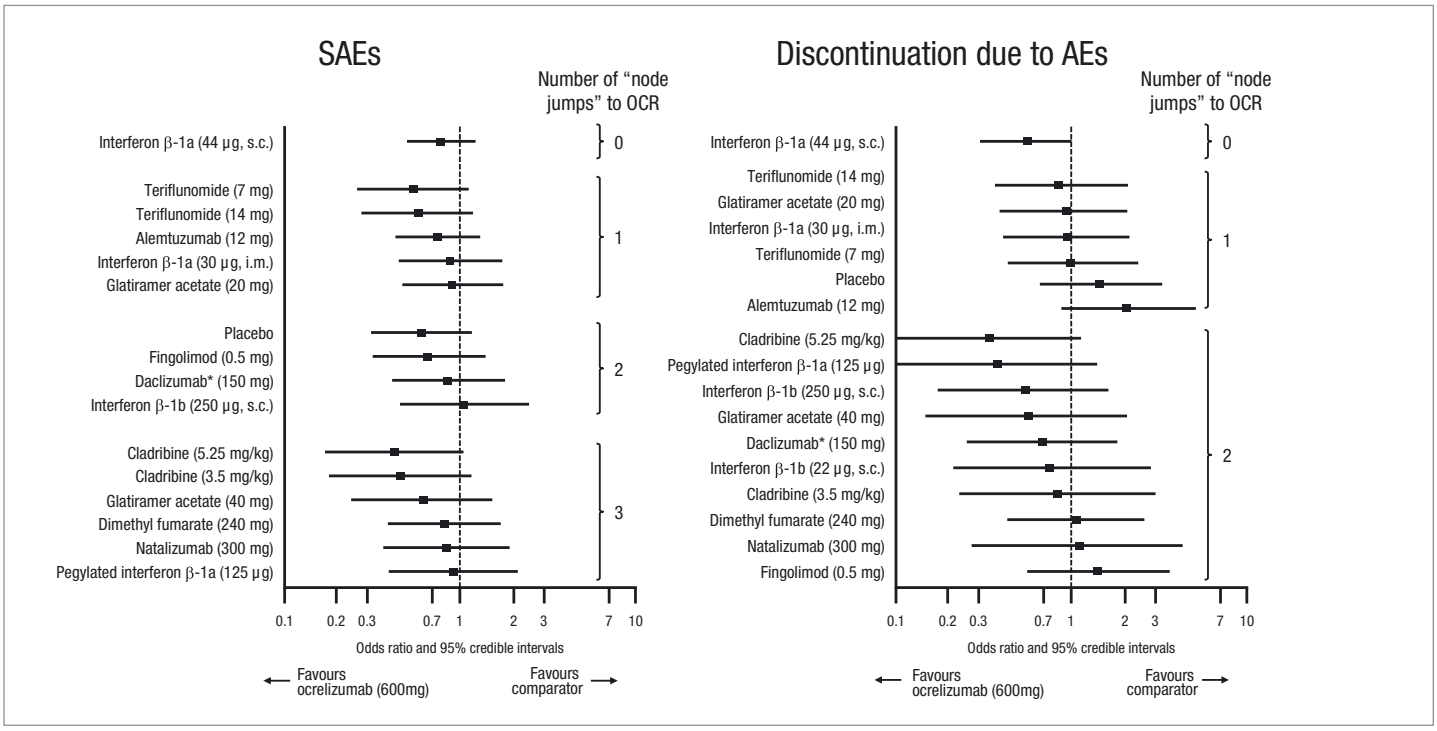

Figure 5. Base-case forest plots for safety of Ocrevus vs other disease-modifying therapies in patients with relapsing multiple sclerosis.[16] "Node jumps" are the number of jumps in the network between Ocrevus and the other treatments. AEs = adverse events; SAEs = serious adverse events; OCR = Ocrevus.

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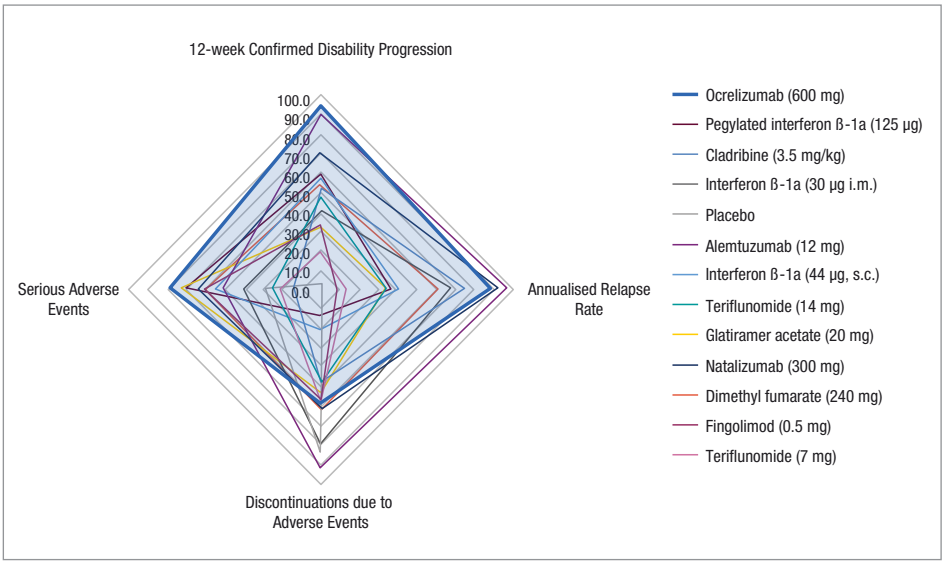

Figure 6. Radar plot of treatment rankings for relapsing multiple sclerosis based on SUCRA values for key efficacy and safety outcomes.[16] SUCRA = surface under the cumulative ranking curve.

Australian personal experience

In Australia, Ocrevus was registered for use in July 2017 for both RMS and PPMS,[17] with a Product Familiarisation Program initiated at the end of 2017. It has been funded under the Pharmaceutical Benefits Scheme, for the treatment of RMS in patients who meet predefined criteria, since February 2018.[18] Professor Taylor has been involved in research on Ocrevus since 2010, and to date has started more than 75 patients with RMS on treatment with Ocrevus at the Royal Hobart Hospital. Approximately 10 patients with PPMS are also receiving treatment with Ocrevus.

Adverse events have been in line with those seen in clinical trials, with no new adverse events or serious adverse events described. Professor Taylor has seen no evidence of neutralising antibody development in the patients he has treated (one patient in the OPERA II trial developed neutralising antibodies to Ocrevus).[12] Three RMS patients have discontinued Ocrevus due to perceived inefficacy; these patients had a high EDSS at baseline and continued to progress on treatment. Professor Taylor has observed that perceived efficacy may be delayed for several months, particularly in patients switching from natalizumab. One patient at the Royal Hobart Hospital discontinued treatment with Ocrevus due to continued significant infusion reactions. The main complaint Professor Taylor receives about Ocrevus is that the infusions take too long.

Before starting Ocrevus

Prior to treatment with Ocrevus, patients at the Royal Hobart Hospital are screened for infection, including hepatitis B, hepatitis C, human immunodeficiency virus (HIV), varicella zoster virus (VZV), cytomegalovirus, toxoplasma and tuberculosis (using the QuantiFERON-TB Gold test). Patients also undergo a full blood count, urea and electrolyte tests, and liver function tests.

Immunisation status should be reviewed, as live or live-attenuated vaccines are not recommended during treatment with Ocrevus.[1,17] Furthermore, other vaccines may be less effective when given during treatment with Ocrevus.[1,17] Immunisation against VZV is critically important, as is hepatitis B in patients at increased risk. Several patients at the Royal Hobart Hospital have required VZV vaccination. One patient had eradication of hepatitis C, and two patients were treated for latent tuberculosis infection, delaying commencement of Ocrevus by 3 months in one patient and 6 months in another.

All vulnerable individuals in Tasmania are immunised against meningitis B and pneumococcus, but these immunisations should be reviewed prior to commencement of Ocrevus, particularly in those at risk.

Switching to Ocrevus

When switching patients to treatment with Ocrevus, a number of factors must be considered, including:

- Does the previous disease-modifying therapy affect the lymphocyte count?
- Is there a risk of carry-over PML?
- Are there any infection screenings or immunisations that need to be undertaken?

From first generation disease-modifying therapies

When switching from interferons and glatiramer acetate, there is no real need to have a significant washout period. However, it is necessary to confirm immunity to VZV and to check hepatitis B and C status. Immunisation can take months for hepatitis B, so the level of exposure risk should be considered. Negativity for HIV and tuberculosis should also be confirmed.

From oral disease-modifying therapies

Fingolimod and dimethyl fumarate have been associated with an increased risk of PML.[19,20] Therefore, if the patient is switching to Ocrevus because of new MRI activity, a careful assessment of PML risk should be undertaken, including lumbar puncture if there is any concern. Determination of John Cunningham virus (JCV) antibody status can also be useful.

Immunisation status and immunosuppression bloods should also be considered.

Most MS neurologists would like to see the lymphocyte count return to normal (ie. ≥0.8 lymphocytes/µL) before starting treatment with Ocrevus. This may take some time, particularly for patients who have been receiving fingolimod.

From teriflunomide

Teriflunomide remains in the system for up to 3 months and affects lymphocyte function, primarily T-cell function.[21] Sequential administration of Ocrevus may result in pan lymphopenia, which can persist for months, is associated with significant infection risk and should be avoided.

If a rapid switch to Ocrevus is required on clinical grounds, washout with activated charcoal or cholestyramine can rapidly accelerate clearance of teriflunomide and should be considered.

Immunisation status and immunosuppression bloods should also be considered.

From natalizumab

One of the most common reasons for switching patients from natalizumab to Ocrevus at the Royal Hobart Hospital is the development of anti-JCV antibodies. This presents issues with carry-over PML, and can be a difficult transition to make. Professor Taylor plans for a 6-week switch with an MRI performed immediately prior to commencement of Ocrevus. If there is any doubt about PML, a lumbar puncture may be required.

Immunisation status and immunosuppression bloods should also be considered.

Switching from Ocrevus

Patients should be made aware that Ocrevus is not a drug that clears from the system quickly. If switching is required, a therapy that does not also deplete B-cell populations should be chosen. Natalizumab can be used in JCV-negative patients, and Category one injectable agents are another alternative. However, the failure rate of Ocrevus after the first 6 months of treatment is very low, and tolerability is very good. For those concerned about infusion-related reactions, Professor Taylor recommends at least two infusions of Ocrevus, as reactions diminish with each subsequent infusion.

Pregnancy and breastfeeding

Ocrevus has a pregnancy category C rating, meaning that use in pregnancy should be avoided, unless the benefits outweigh the risks.[1,18] The Ocrevus data sheet recommends effective contraception while receiving treatment with Ocrevus and for 6 months after the last infusion, which corresponds to 7 half-lives of the drug.[1,17]

The Ocrevus data sheet also advises patients not to breastfeed while receiving treatment with Ocrevus.[1,17]

Professor Taylor said that Ocrevus's prolonged effect on B cells means that patients with RMS wishing to become pregnant could be protected from relapse for a period of at least 2 years after cessation of the drug, providing a window for conception, pregnancy and breastfeeding. B-cell counts can be monitored during this time, and an alternative disease-modifying therapy started if necessary.

In general, Professor Taylor would only start patients on another disease-modifying therapy during the conception/pregnancy period if they were considered high risk (eg. difficult-to-control disease on Ocrevus or new MRI activity). He would use natalizumab in such cases, although the JCV titre should be considered.

Unanswered questions

According to Professor Taylor, there are still some unanswered questions regarding use of Ocrevus in MS:

- How long do we need to treat?
- Does Ocrevus have an immune reconstitution effect in MS?
- What is the ideal dosing interval; is 6-monthly too frequent?
- Will prolonged use of Ocrevus result in hypogammaglobulinemia?

REFERENCES:

1. Medsafe. New Zealand Data Sheet. Ocrevus 300 mg in 10 mL concentrate for solution for infusion. Available at: https://www.medsafe.govt.nz/profs/Datasheet/o/Ocrevusinf.pdf [Accessed March 2020].
2. PHARMAC. Online Pharmaceutical Schedule – March 2020. Ocrelizumab Special Authority SA1867. Available at: https://www.pharmac.govt.nz/2019/12/01/SA1867.pdf [Accessed March 2020].
3. Bittner S, Ruck T, Wiendl H, et al. Targeting B cells in relapsing-remitting multiple sclerosis: from pathophysiology to optimal clinical management. Ther Adv Neurol Disord. 2017 Jan;10(1):51-66.
4. Cepok S, Rosche B, Grummel V, et al. Short-lived plasma blasts are the main B cell effector subset during the course of multiple sclerosis. Brain. 2005 Jul;128(Pt 7):1667-76.
5. Frischer JM, Bramow S, Dal-Bianco A, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009 May;132(Pt 5):1175-89.
6. Martin F, Chan AC. B cell immunobiology in disease: evolving concepts from the clinic. Annu Rev Immunol. 2006;24:467–496.
7. DiLillo DJ, Hamaguchi Y, Ueda Y, et al. Maintenance of long-lived plasma cells and serological memory despite mature and memory B cell depletion during CD20 immunotherapy in mice. J Immunol. 2008;180(1):361–371.
8. Klein C, Lammens A, Schäfer W, et al. Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties. MAbs. 2013;5(1):22–33.
9. Genovese MC, Kaine JL, Lowenstein MB, et al. Ocrelizumab, a humanized anti-CD20 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I/II randomized, blinded, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008;58(9):2652–266.
10. Hammadi M, Pers JO, Berthou C, et al. A new approach to comparing anti-CD20 antibodies: importance of the lipid rafts in their lytic efficiency. Onco Targets Ther. 2010;3:99–109.
11. Jaglowski SM, Alinari L, Lapalombella R, et al. The clinical application of monoclonal antibodies in chronic lymphocytic leukemia. Blood. 2010;116(19):3705–3714.
12. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221–2.
13. Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3): Supplementary Material (Protocol).
14. Miller AE, de Seze J, Hauser SL, et al. The effect of ocrelizumab on cognitive functioning in relapsing multiple sclerosis: analysis of the phase 3 interferon-beta-1a-controlled OPERA studies. Presented at the 2017 Consortium of Multiple Sclerosis Centers (CMSC) Annual Meeting, 24-27th May 2017, New Orleans, Louisiana, USA. Poster DX09.
15. Giovannoni G, Kappos L, Hauser SL, et al. Long-term reduction of relapse rate and confirmed disability progression after 6 years of ocrelizumab treatment in patients with relapsing multiple sclerosis. Presented at the 35th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), 11-13th September 2019, Stockholm, Sweden. Poster P1015.
16. McCool R, Wilson K, Arber M, et al. Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis. Mult Scler Relat Disord. 2019;29:55–61.
17. Therapeutic Goods Administration. Australian Product Information. Ocrevus® (ocrelizumab). Available at: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2017-PI-02089-1&d=202003171016933 [Accessed March 2020].
18. Pharmaceutical Benefits Scheme. Ocrelizumab. Available at: http://www.pbs.gov.au/medicine/item/11237K-11242Q [Accessed March 2020].
19. Medsafe. New Zealand Data Sheet. Gilenya® 0.5 mg capsules. Available at: https://www.medsafe.govt.nz/Profs/Datasheet/g/gilenyacap.pdf [Accessed March 2020].
20. Medsafe. New Zealand Data Sheet. Tecfidera® dimethyl fumarate 120 mg modified release capsules. Tecfidera® dimethyl fumarate 240 mg modified release capsules. Available at: https://www.medsafe.govt.nz/profs/Datasheet/t/tecfideracap.pdf [Accessed March 2020].
21. Medsafe. New Zealand Data Sheet. Aubagio 14 mg film coated tablet. Available at: https://www.medsafe.govt.nz/Profs/Datasheet/a/aubagiotab.pdf [Accessed March 2020].

Ocrevus® Abridged Prescribing Information (API)

Ocrevus (ocrelizumab) 300 mg/10 mL concentrate solution for IV infusion is a **Prescription Medicine** indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) to suppress relapses and disease progression (clinical and subclinical disease activity) and for the treatment of adult patients with primary progressive multiple sclerosis (PPMS) to delay disease progression and reduce deterioration in walking speed.
Dose and Method of Administration: Please refer to the Ocrevus Data Sheet for information.
Contraindications: Patients with known hypersensitivity to ocrelizumab or any of the excipients.
Special Warnings and Precautions for Use: ***Infusion-related reactions (IRRs)***: IRRs may present as pruritus, rash, urticaria, erythema, throat irritation, oropharyngeal pain, dyspnoea, pharyngeal or laryngeal oedema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia and anaphylaxis. Premedicate patients before each Ocrevus infusion (see Data Sheet) and observe for at least one hour post-infusion. Life-threatening IRRs: Immediately stop the Ocrevus infusion and permanently discontinue. See Data Sheet for the management of mild to moderate and severe IRRs. ***Hypersensitivity reactions***: If a hypersensitivity reaction is suspected, stop the infusion immediately and permanently discontinue. ***Infections***: Delay administration in patients with an active infection until resolved. ***Progressive Multifocal Leucoencephalopathy (PML)***: Be vigilant for early signs and symptoms of PML. If PML is suspected, withhold dosing. If PML is confirmed, discontinue permanently. ***Hepatitis B reactivation***: Perform HBV screening in all patients before initiation of treatment. Patients with active HBV infection should not be treated. ***Treatment with other immunosuppressants***: Exercise caution and consider the pharmacodynamics of other disease-modifying therapies. ***Vaccinations***: Immunisation with live or live-attenuated vaccines is not recommended during treatment and not until B-cell repletion. Review patient immunisation status before starting treatment. Complete vaccinations at least 6 weeks prior to treatment initiation. ***Pregnancy Category C***: Avoid treatment during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. Women of child bearing potential should use effective contraception during treatment and for 6 months after the last infusion. ***Use in lactation***: Discontinue breast-feeding during therapy.
Undesirable Effects: See Data Sheet for full list. IRRs; upper respiratory tract infections (nasopharyngitis; sinusitis); bronchitis; influenza; gastroenteritis; herpes (oral, zoster, simplex, genital); viral infection; conjunctivitis; cellulitis; cough; catarrh. ***Laboratory abnormalities***: Decrease in total immunoglobulins driven by reduced IgM. An apparent association between decreased level of immunoglobulins and serious infections (SI), which is most apparent for IgG (0.5% of patients had a SI during a period with IgG < LLN). Decreased neutrophils (majority transient, Grade 1 and 2). Grade 3 or 4 neutropenia observed in~1% of patients.

Ocrevus is a PHARMAC funded medicine for patients with relapsing multiple sclerosis (RMS) who meet pre-defined criteria. Prescription and doctor's fees may apply.
Ocrevus is not PHARMAC funded for primary progressive multiple sclerosis (PPMS).

Before prescribing, please review the Ocrevus Data Sheet available at www.medsafe.govt.nz.

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