The potential role for ocrelizumab in the treatment of multiple sclerosis: current evidence and future prospects

Per Soelberg Sorensen and Morten Blinkenberg

Abstract: B cells play a central role in the pathogenesis in multiple sclerosis (MS), being involved in the activation of proinflammatory T cells, secretion of proinflammatory cytokines, and production of autoantibodies directed against myelin. Hence, the usage of B-cell-depleting monoclonal antibodies as therapy for autoimmune diseases including MS lay near at hand. Rituximab was the first therapeutic B-cell-depleting chimeric monoclonal antibody to be used successfully in MS. Ocrelizumab, a second-generation humanized anti-CD20 antibody, was explored in a large phase II, randomized, placebo-controlled multicentre trial in patients with relapsing–remitting disease. Compared with placebo, two doses of ocrelizumab (600 and 2000 mg on days 1 and 15) showed a pronounced effect on disease activity seen in magnetic resonance imaging (MRI) as gadolinium-enhanced lesions (89% and 96% relative reduction, both $p < 0.001$) and also had a significant effect on relapses. In exploratory analyses, both doses of ocrelizumab had better effect on gadolinium-enhanced lesions than interferon beta-1a intramuscularly that was used as a reference arm. Adverse effects were mainly infusion-related reactions, in particular during the first infusion. Serious infections occurred at similar rates in ocrelizumab and placebo-treated patients, and no opportunistic infections were reported. However, progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with anti-CD20 monoclonal antibodies for other indications.

Other anti-CD20 monoclonal antibodies have been tested as treatments for MS, including ofatumumab that has shown beneficial results in placebo-controlled phase II trials in patients with relapsing–remitting MS. Ocrelizumab is now in phase III development for the treatment of relapsing–remitting MS, as well as primary progressive MS, and the results of ongoing clinical trials are eagerly awaited and will determine the place of ocrelizumab in the armamentarium of MS therapies.

Keywords: anti-CD20 monoclonal antibodies, ocrelizumab, relapsing–remitting multiple sclerosis

The role of B cells in multiple sclerosis pathology

The central role of T cells in the pathogenesis of multiple sclerosis (MS) has long been established. This is supported by the association with human leukocyte antigen (HLA) class II genes, which are crucial in antigen presentation to CD4+ T cells [Patsopoulos *et al.* 2013]. Myelin-reactive T helper type 1 (Th1) cells secreting proinflammatory cytokines such as interferon (IFN)- γ and Th17 cells secreting interleukin (IL)-17 are thought to be pathogenic in MS [Sospedra and Martin 2005; Steinman, 2014; Weiner, 2009].

Other studies have indicated that cytotoxic CD8+ T cells as well play a crucial role, and CD8+ T cells outnumber CD4+ T cells in MS lesions [Friese and Fugger, 2007; Lassmann, 2011].

However, B cells also play an important role in the pathogenesis in MS. B cells can produce proinflammatory cytokines and are potent antigen-presenting cells being involved in the activation of proinflammatory T cells. Further, B cells may differentiate into plasma cells that can produce autoantibodies directed against myelin and cause complement-mediated attack on the myelin

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sheath [Archelos *et al.* 2000; Bar-Or *et al.* 2010; Disanto *et al.* 2012]. Furthermore, a recently discovered subset of CD4⁺ T cells, termed T follicular helper (T_{FH}) cells, which may be involved in the pathogenesis of MS [Crotty 2011; Romme *et al.* 2013; Tangye *et al.* 2013], are important for the activation of B cells in secondary lymphoid tissues, and a relationship between increased T_{FH} cell and B cell activation in blood from patients with MS has been shown, supporting that abnormal interactions between CD4⁺ T cells and B cells are involved in the immunopathogenesis of MS [Romme *et al.* 2013].

Studies of the pathology of MS have shown that ectopic lymphoid follicles resembling germinal centres containing B cells and plasma cells are present in the meninges of patients with secondary progressive MS [Serafini *et al.* 2004], indicating that B cells migrate to the brain. Although apparently restricted to late disease phases, the establishment of lymphoid-like structures in the brains of patients with MS suggest a pathophysiological role of B cells in MS.

The role of B cells in the pathogenesis in MS was strongly supported by clinical trials using B-cell-depleting monoclonal antibodies [Hauser *et al.* 2008; Kappos *et al.* 2011; Sorensen *et al.* 2014].

Ocrelizumab, a second-generation anti-CD20 monoclonal antibody with a humanized IgG1 tail, binds to a different but overlapping epitope than rituximab does. Since ocrelizumab is derived mostly from human antibodies, it induces less of an immune response to foreign antigens. As ocrelizumab is thought to bind more avidly to CD20 and expected to be less immunogenic than rituximab, it might have a more favourable benefit-to-risk profile [Dorner and Burmester, 2008].

Here we review the available data on the role of anti-CD20 monoclonal antibodies, and in particular ocrelizumab, in the treatment of MS, including its mechanisms of action and clinical efficacy data.

Mechanism of action of ocrelizumab

Ocrelizumab is a recombinant humanized antibody designed to selectively target cells that express the B lymphocyte antigen CD20 on their surface. The CD20 molecule is an activated glycosylated phosphoprotein expressed on a broad range of cells of the human B-cell lineage, with increasing concentrations from pre-B cell through

naïve and memory B cell, whereas CD20 is not expressed on stem cells, pro-B cells, or differentiated plasma cells [Stashenko *et al.* 1980]. Hence, antibodies targeting CD20 will not change the concentration of IgG and IgM antibodies in the blood or in the CSF. No ligand binding to CD20 has ever been discovered. Recently, several studies have suggested that CD20 is an amplifier of calcium signals that are transduced through the B-cell antigen receptor during antigen recognition by immature and mature B cells [Bubien *et al.* 1993]. However, CD20 knock-out mice deficient in CD20 do only reveal subtle differences compared with wildtype mice: decreased transmembrane Ca²⁺ movement in primary B cells has been reported [Uchida *et al.* 2004] and also reduced T-dependent humoral immunity [Morsy *et al.* 2013] that, however, was not found by others [Uchida *et al.* 2004].

Although the exact aetiology of B-cell depletion is unknown, three different mechanisms of action have been suggested: (1) complement-dependent cytotoxicity characterized by the formation of pores in the cell membrane causing breakdown of the cell membrane leading to cell lysis; (2) antibody-dependant cellular cytotoxicity involving macrophages, natural killer cells, and cytotoxic T cells that act together to cause cell destruction; and (3) apoptosis, which occurs through cross-linking membrane CD20 on the target cell surface [Anderson *et al.* 1997; Clynes *et al.* 2000; Mease 2008; Reff *et al.* 1994]. There are several potential benefits from using therapeutic antibodies targeting CD20: CD20 is not expressed in haematopoietic stem cell B cells; it is not expressed on plasma cells, which means that 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 internalized after antibody binding [van Meerten and Hagenbeek, 2009]. However, although CD20 is not expressed on plasma cells, anti-CD20 therapy with rituximab frequently induces a reduction of immunoglobulins, notably IgM and response to vaccination may be ineffective [Buch *et al.* 2011].

Rituximab was the first anti-CD20 monoclonal antibody to be approved specifically for the treatment of patients with refractory CD20-positive follicular non-Hodgkin's lymphoma [Maloney *et al.* 1994], and the first anti-CD20 monoclonal antibody to be used for treatment of MS [Bar-Or *et al.* 2008; Hauser *et al.* 2008]. Rituximab is a

glycosylated IgG1 chimeric anti-CD20 antibody. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain recruits immune effector cells that result in B-cell death. Rituximab is thought to deplete B cells by all three suggested mechanisms of action for anti-CD20 antibodies: antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and by induction of apoptosis [Clynes *et al.* 2000]. Despite rituximab concentration in the cerebrospinal fluid (CSF) being 10-fold less than the concentration achieved in the peripheral blood of patients with normal blood–brain barrier, it was shown to be active in the central nervous system (CNS) [Ruhstaller *et al.* 2000], which could be of interest when treating MS.

Compared with rituximab, ocrelizumab *in vitro* causes increased antibody-dependent cell-mediated cytotoxic effects and reduced complement-dependent cytotoxic effects [Kappos *et al.* 2011] and, hence, might modulate pathogenic response *in vivo* more effectively than rituximab does. As a humanized molecule, ocrelizumab is expected to be less immunogenic with repeated infusions causing less induction of human antihuman antibodies (HAHAs) compared with the formation of human antichimeric antibodies (HACAs) against rituximab, and could thus have a more favourable benefit-to-risk profile than rituximab.

Clinical experience with ocrelizumab

The clinical experience with ocrelizumab has so far been limited to clinical trials, where the drug has been used for four different conditions: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), haematological cancer and MS. The development of ocrelizumab has been suspended in RA and SLE, since phase III trials were terminated as a result of an overall risk–benefit assessment, where ocrelizumab did not demonstrate additional benefit over existing therapies [Emery *et al.* 2014; Mysler *et al.* 2013]. Furthermore, serious infections were more frequent in RA patients treated with ocrelizumab in combination with methotrexate, which was also reported in SLE, when ocrelizumab was accompanied by glucocorticoids and mycophenolate mofetil [Emery *et al.* 2014; Mysler *et al.* 2013; Rigby *et al.* 2012; Tak *et al.* 2012].

In MS, ocrelizumab has been used as monotherapy, and the efficacy and safety has been explored

in a phase II, randomized, placebo-controlled multicentre trial in patients with relapsing–remitting disease course, assigned to either: (1) placebo administered at day 1 and day 15 in the first cycle and intravenous ocrelizumab 300 mg administered at day 1 and day 15 in the second cycle ($n = 54$); (2) low-dose cycles of intravenous ocrelizumab 300 mg administered at day 1 and day 15 in the first cycle and 600 mg administered at day 1 in the second cycle ($n = 56$); (3) high-dose cycles of intravenous ocrelizumab 1000 mg administered at day 1 and day 15 in the first cycle and 1000 mg administered at day 1 in the second cycle ($n = 55$); or (4) intramuscular injections of IFN- β 1a 30 μ g once weekly ($n = 55$) (Table 1) [Kappos *et al.* 2011]. The primary outcome of the study was the total number of gadolinium-enhanced lesions on MRI at weeks 12, 16, 20 and 24, which compared with placebo was significantly lower in both ocrelizumab groups: 5.5 for placebo; 0.6 for ocrelizumab 600 mg (89% relative reduction compared with placebo); and 0.2 for ocrelizumab 2000 mg (96% relative reduction compared with placebo), both $p < 0.001$; while total number of gadolinium-enhanced lesions was 6.9 for IFN- β 1a. An exploratory analysis furthermore showed that both groups were superior to IFN- β 1a. The clinical data showed that the annualized relapse rate (ARR) was significantly reduced in both ocrelizumab groups (0.13 with ocrelizumab 600 mg and 0.17 with ocrelizumab 2000 mg) compared with 0.64 in the placebo group. Results of an open-label extension phase of the study were reported, showing minimal MRI activity at week 144 and continued low AAR in both ocrelizumab groups [Kappos *et al.* 2012]. There were no major safety concerns reported in the double-blind phase II study or in the extension study, and especially no reports of opportunistic infections, including progressive multifocal leukoencephalopathy (PML). In the double-blind phase II study, serious adverse events and infections were comparable in all treatment groups, but there was one death in the high-dose ocrelizumab group, due to acute-onset thrombotic microangiopathy, where a possible relation to the study treatment could not be excluded. Infusion-related adverse events were increased in the two ocrelizumab groups (35% in low-dose ocrelizumab, 44% in high-dose ocrelizumab and 9% in placebo relative to the number of patients). In the extension study, infection rates were 6.5% for low-dose ocrelizumab and 11.1% for high-dose ocrelizumab, primarily due to respiratory and urinary tract infections.

Table 1. Clinical trials of anti-CD20 B-cell-depleting monoclonal antibodies in patients with multiple sclerosis.

Active treatment	Comparator	Patients	Primary endpoint	Status	Relative reduction in primary endpoint
Ocrelizumab 600 mg [#] i.v. (<i>n</i> = 54)	Placebo (<i>n</i> = 55)	Relapsing MS	Total number of Gd+ lesions on MRI at weeks 12, 16, 20, and 24	Published [Kappos <i>et al.</i> 2011]	89% reduction* (<i>p</i> < 0.001)
Ocrelizumab 2000 mg [#] i.v. (<i>n</i> = 56)	IFN-β 1a i.m. (<i>n</i> = 55)				96% reduction* (<i>p</i> < 0.001)
Ocrelizumab 600 mg i.v. every 24 weeks	IFN-β 1a s.c.	Relapsing MS	Annualized relapse rate by 2 years	Ongoing	NA
Ocrelizumab 600 mg [#] i.v. every 24 weeks	IFN-β 1a s.c.	Relapsing MS	Annualized relapse rate by 2 years	Ongoing	NA
Ocrelizumab 600 mg [#] i.v. every 24 weeks	IFN-β 1a s.c.	Primary progressive MS	Annualized relapse rate by 2 years	Ongoing	NA
Rituximab 2000 mg [#] i.v. (<i>n</i> = 69)	Placebo (<i>n</i> = 35)	Relapsing–remitting MS	Total number of Gd+ lesions on MRI at weeks 12, 16, 20, and 24	Published [Hauser <i>et al.</i> 2008]	91% reduction* (<i>p</i> < 0.001)
Ofatumumab 200 mg [#] (<i>n</i> = 8), 600 mg [#] (<i>n</i> = 11), 1400 mg [#] (<i>n</i> = 7) i.v.	Placebo (<i>n</i> = 12)	Relapsing–remitting MS	Number of new Gd+ lesions on MRI from week 8 to week 24	Published [Sorensen <i>et al.</i> 2014]	99.8% reduction** (<i>p</i> < 0.001)
Ofatumumab s.c. 3 mg, 30 mg, 60 mg every 12 weeks or 60 mg every 4 weeks	Placebo	Relapsing–remitting MS	Cumulative number of new Gd+ lesions from week 4 to week 12	Reported [Bar-Or <i>et al.</i> 2014]	>90% reductions* for each dose ≥30 mg (<i>p</i> < 0.001)

#Divided into two doses separated by 2 weeks.

*Compared with placebo.

**All ofatumumab doses compared with placebo.

i.v., intravenously; s.c., subcutaneously; Gd+, gadolinium-enhanced; MS, multiple sclerosis; IFN, interferon.

Currently, three phase III trials are ongoing, two of which are randomized, double-blind, double-dummy, parallel-group studies evaluating the efficacy and safety of ocrelizumab 300 mg in comparison with IFN-β 1a subcutaneously in patients with relapsing MS [ClinicalTrials.gov identifier: NCT01412333, NCT01247324], and one is a randomized, parallel-group, double-blind, placebo controlled study evaluating the efficacy and safety of ocrelizumab in patients with primary progressive MS [ClinicalTrials.gov identifier: NCT01194570] (Table 1).

As efficacy measures of the phase II study were impressive compared with available first-line

disease-modifying treatments, the results of these phase III studies are awaited with anticipation.

Other B-cell-depleting drugs

The first study using B-cell depletion for treatment of MS was a phase II, double-blind, placebo-controlled trial with the chimeric human–mouse anti-CD20 antibody rituximab (Table 1) [Hauser *et al.* 2008]. The study comprised 102 patients with relapsing MS, and compared with placebo rituximab showed a significant reduction in total number of gadolinium-enhanced lesions of 91% (*p* < 0.001) and a significant reduction of ARR of 58% at week 24

($p = 0.04$) and 50% at week 48 ($p = 0.08$). More patients in the rituximab group had infusion-related adverse events within the first 24 hours, but after the second infusion, the numbers of adverse events were similar in the two groups. Most adverse events were mild-to-moderate and there were no major safety concerns.

A phase II/III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study in primary progressive MS failed to reach the primary endpoint, since time to confirmed disease progression, was not reduced at 96 weeks [Hawker *et al.* 2009]. Although one secondary MRI endpoint, reduction in T2 lesion volume, was reached, the other, brain volume change, was not different from placebo. Subgroup analysis showed that time to confirmed disease progression was delayed in patients younger than 51 years of age and gadolinium-enhanced lesions were also reduced in the same subgroup. This led the authors to conclude that B-cell depletion with rituximab may be efficacious in younger progressive MS patients with inflammatory lesions. Whether this is true has yet to be confirmed. Regarding safety, there were no differences between adverse events between the two groups, but serious infections were more pronounced in the rituximab group (4.5% of rituximab and <1.0% of placebo patients). Infusion-related events were predominantly mild to moderate, and more common with rituximab during the first course, but decreased to rates comparable with placebo on successive courses. Disease modification with rituximab has also been reported in smaller studies and clinical observations [Castillo-Trivino *et al.* 2013], but further exploration of efficacy in relapsing MS has not been carried out in phase III trials.

Ofatumumab is a fully human anti-CD20 antibody, binding to a different epitope than rituximab and ocrelizumab, and thereby depleting B cells by both complement-dependent and antibody-dependent cell-mediated cytotoxicity. Interestingly, this cytotoxic effect may be superior to rituximab, since *in vitro* studies have shown that ofatumumab also depletes B-cell lines resistant to rituximab [Wierda *et al.* 2011].

Results of a phase II, randomized, double-blind, placebo-controlled study of 38 relapsing MS patients receiving two ofatumumab intravenous infusions (100, 300 or 700 mg) or placebo 2 weeks apart, showed a substantial reduction of new brain MRI lesion activity (>99%) in the first

24 weeks after ofatumumab administration (all doses), as well as significant reductions of new T1 gadolinium-enhanced lesions, total enhanced T1 lesions, and new and enlarged T2 lesions (Table 1) [Sorensen *et al.* 2014]. Treatment was not associated with any unexpected safety concerns and was generally well tolerated. The most common adverse events were infusion reactions, infections, rash, erythema, throat irritation, fatigue and flushing.

A recently reported larger phase II, double-blind, placebo-controlled, parallel-group study (MIRROR) of subcutaneous administrations of ofatumumab comprised 232 subjects with relapsing MS randomized to one of five treatment groups: placebo, ofatumumab 3 mg every 12 weeks, ofatumumab 30 mg every 12 weeks, ofatumumab 60 mg every 12 weeks or ofatumumab 60 mg every 4 weeks (Table 1). All subjects continued in the study for 24 weeks of treatment and in follow up until B-cell repletion. The cumulative number of new T1 gadolinium-enhanced lesions for each ofatumumab dose regimen from baseline to week 12 was reduced by 65% [$p < 0.001$], and the corresponding data analysis of weeks 4–12 estimated $\geq 90\%$ reductions for each dose ≥ 30 mg ($p < 0.001$). A dose-dependent CD19 B-cell depletion was seen across regimens. The rate of repletion of B cells following cessation of dosing was similar, with a delay of approximately 4 weeks in the 60 mg every 4 weeks group [Bar-Or *et al.* 2014].

GSK have transferred the development of ofatumumab to Novartis and nobody knows anything about the fate of ofatumumab in MS.

A phase III trial of ofatumumab has been carried out in RA patients stable on methotrexate treatment [Taylor *et al.* 2011], who were randomized to two infusions of 700 mg ofatumumab or placebo. There were no unexpected safety findings and the most common adverse events for ofatumumab compared with placebo were skin rash (21% *versus* <1%) and urticaria (12% *versus* <1%), primarily occurring on the first infusion day. First-dose infusion reactions were 68% for ofatumumab and 6% for placebo, described as mild to moderate, but second-dose infusion reactions were markedly reduced (<1% and 0%). Serious adverse events were reported in 5% of patients receiving ofatumumab compared with 3% of placebo patients. Infection rates were 32% and 26% (serious infections <1% and 2%),

respectively, and one death (interstitial lung disease), presumably unrelated to study drug, was reported on ofatumumab treatment. Ofatumumab is currently approved for treatment refractory chronic lymphocytic leukaemia (CLL) and has been studied in several other haematological conditions without major safety concerns [Gupta and Jewell, 2012].

Future place of ocrelizumab in the treatment of MS

Although no comparative studies have been performed with ocrelizumab or any other anti-CD20 monoclonal antibody against the current first-line or second-line MS therapies and the results of the phase III trials of ocrelizumab are not available one can only speculate about the future place of ocrelizumab in the treatment of MS. The results of phase II trials of rituximab and ocrelizumab suggest that the efficacy of B-cell depletion is closer to that of natalizumab or even alemtuzumab than that of the current available first-line therapies. The effect on clinical disease activity seem also to be of the same magnitude compared with that of fingolimod and natalizumab, as in the phase II trial the relative reduction in the annualised relapse rates over 24 weeks was 73–80% lower in the ocrelizumab groups than in the placebo group, while the effect on gadolinium-enhanced lesions was a relative reduction in gadolinium-enhanced lesions of 89–96% in the two ocrelizumab groups compared with placebo and approximately 90% compared with IFN- β 1a [Kappos *et al.* 2011].

Overall, ocrelizumab was well tolerated with mild or moderate infusion reactions during the first infusion as the most common adverse effect. The major safety concern has been the risk of PML. No opportunistic infections were reported in the clinical trials in MS, but in the phase III rheumatoid arthritis trials high rates of serious and opportunistic infections were seen with ocrelizumab treatment, some of which resulted in death [Barun and Bar-Or, 2012; Emery *et al.* 2014]. PML has also been reported in RA patients treated with rituximab, who, however, had received additional immunosuppressive treatment prior to or concurrent with rituximab therapy [Molloy and Calabrese, 2009; Paues and Vrethem, 2010]. Another safety issue is that response to vaccination may be ineffective. Patients considered for anti-CD 20 antibody therapy should receive all indicated vaccines at least 4 weeks before

treatment. There might also be a potential risk of vaccination with live vaccines, which are therefore not recommended for patients treated with anti-CD20 antibodies [Buch *et al.* 2011].

For treatment of MS, ocrelizumab will probably be an alternative to natalizumab and alemtuzumab; based on the available data from clinical trials in MS, ocrelizumab seems to have a more favourable risk–benefit profile compared with natalizumab in JC virus antibody-positive patients, whereas natalizumab in JC virus antibody-negative patients appears safer. Hence, ocrelizumab could be an attractive option among second-line therapies in patients who are JC virus antibody-positive, whereas natalizumab or alternatively oral fingolimod would be the first choice among second-line therapies in JC virus antibody-negative patients. The same considerations apply when a second-line drug is preferred as first-line therapy in patients with very active relapsing–remitting MS.

Another application for ocrelizumab therapy would be in patients experiencing breakthrough disease activity on a second-line therapy, i.e. patient experiencing disease activity on natalizumab therapy and JC virus antibody-positive patients experiencing disease activity on fingolimod therapy. However, it should be taken into consideration that the risk of PML associated with long-term ocrelizumab treatment is unknown.

As anti-CD20 monoclonal antibodies seem to cross the blood–brain barrier in measurable quantities, ocrelizumab may be of value in the treatment of progressive forms of MS. Indeed *post hoc* analyses in the rituximab primary progressive trial, that overall did not show a significant effect in delaying disability progression, suggested that the drug could be effective in patients with rapidly progressing primary progressive MS [Hawker *et al.* 2009]. As treatment of progressive MS, small studies of intrathecal administration of rituximab have been reported or are ongoing [Bonnar *et al.* 2014; Svenningsson *et al.* 2015].

However, it needs to be emphasized that long-term data on the safety of ocrelizumab in the treatment of MS is warranted, and therefore post-marketing safety programmes will be needed. One caveat would be that there is only limited experience with repeated ocrelizumab therapy over long time, both regarding efficacy and adverse effects. Long-standing B-cell depletion may lead to serious adverse effects that were not

observed in short-term trials of 1 or 2 years duration. Another unsolved question is whether ocrelizumab therapy should be applied at fixed intervals, e.g. every 6 months or re-treatment should be guided by the recovery of CD19-positive B cells.

Conclusions

The results of the published and reported studies of ocrelizumab and other anti-CD20 B-cell-depleting monoclonal antibodies for treatment of relapsing MS have shown remarkable therapeutic effects, in particular on MRI measures of disease activity. The largest phase II trial of ocrelizumab also showed promising effect on relapse rates and would suggest a therapeutic effect of ocrelizumab comparable with the most effective of the currently available treatments. However, the results of two phase III studies in relapsing MS and one phase III study in primary progressive, all with IFN- β 1a subcutaneously as an active comparator, using double-dummy study design are awaited with anticipation and will determine the place of ocrelizumab in the current armamentarium of MS therapies.

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