B Cell Targeted Therapy in Multiple Sclerosis – New Possibilities

Report from a Satellite Symposium held at the 31st Congress of the European Committee for Treatment and Research in Multiple Sclerosis in Barcelona, Spain, 9 October 2015

Catherine Amey

Touch Medical Media, Reading, UK

The role of B cells in the pathogenesis of multiple sclerosis (MS) may not be simply related to their ability to produce antibodies. They are highly efficient antigen-presenting cells, producing cytokines that can change the microenvironment and can mediate negative effects through astrocyte populations. Furthermore, as well as producing antibodies, B cells produce ectopic lymphoid follicle-like aggregates that persist in the brains of MS patients. This improved understanding of the centrality of the B cell in the biology of MS presents greater opportunities for developing effective therapies. The lymphocyte antigen CD20 is not expressed at early stem and pro B cell stages, nor on most short- or long-lived plasma cells. This presents the possibility that anti-CD20 treatment could deplete the intermediate stage of B-cell development while preserving the ability of stem cells to repopulate and protecting pre-existing humoural immunity. Ocrelizumab is a humanised monoclonal antibody that depletes CD20+ B cells via multiple mechanisms. In the OPERA I and OPERA II trials, compared with interferon beta-1a (IFNβ-1a) treatment over 96 months, ocrelizumab significantly reduced: the annualised relapse rate, 12- and 24-week confirmed disease progression, T1 gadolinium-enhancing lesions and new and/or enlarging T2 lesions. Overall, in OPERA I and OPERA II, ocrelizumab had a similar safety profile to that of IFNβ-1a over the study period. The OPERA I and OPERA II studies therefore provide strong support of for the theory that targeting CD20+ B cells as a potential therapeutic approach in relapsing MS.

Keywords

Multiple sclerosis, B cells, OPERA I, OPERA II, ocrelizumab, interferon beta-1a

Disclosure: Catherine Amey is an employee of Touch Medical Media, Reading, UK. This article reports the proceedings of a sponsored satellite symposium held at the European Committee for Treatment and Research in Multiple Sclerosis in Barcelona 2015 and, as such, has not been subject to this journal's usual peer-review process. A member of the editorial board reviewed the report before publication. This report contains information about a non-authorised product(s)/investigational drug(s).

Received: 7 June 2016

Published Online: 26 July 2016

Citation: *European Neurological Review,* 2016;11(Suppl.1):5–9

Corresponding Author: Catherine Amey, Touch Medical Media, 4 Reading Road, Pangbourne, Reading, West Berkshire, RG8 7LY.

E: catherine.amey@touchmedicalmedia.com

Support: The publication of this article was supported by Roche.

Much progress has been achieved in the treatment of multiple sclerosis (MS), however, many important unmet needs remain. A large proportion of patients with MS experience disease activity despite treatment with disease-modifying therapies (DMTs), whereas the desired treatments would have the potential to impact neurodegeneration and promote re-myelination. For some treatments there may be a compromise between efficacy and safety, however, ideally treatments would be well tolerated, highly efficacious and have favourable benefit–risk profiles. The attributes of currently available treatments can present adherence challenges. Treatments with mechanisms of action that promote persistence and adherence are therefore needed. There are a number of treatments currently in development that may meet at least some of these needs and have interesting potential to improve outcomes in MS (*Table 1*).

The role of B cells in multiple sclerosis

Derived from haematopoietic stem cells residing in the bone marrow or liver, pre-B cells can evolve into mature naïve cells that can migrate throughout the body into secondary lymphoid tissue (*Figure 1*). If they encounter an antigen that can activate or cross-link their B-cell receptors, they are activated and can move into germinal centres, where they receive help from dendritic cells and T-cells to proliferate, clonally expand and undergo further antigen-driven maturation of the B-cell receptor. This then ultimately yields plasmablasts and memory B cells. The plasmablasts can move into other tissues, in particular, the bone marrow, and continue to produce antibodies for years, potentially decades. The memory B cells also circulate and can mediate surveillance of the entire body, in this case, they can enter the brain and, again, if their B-cell receptors encounter appropriate antigens, they can become activated and receive T-cell help to undergo further clonal expansion. The cells that are clonally expanded can become long-lived in the central nervous system (CNS), ultimately developing the follicle-like aggregates that characterise the brain of MS patients with chronic disease. The result is development of plasmablasts and plasma cells, which are believed to be the source of oligoclonal bands seen in the cerebrospinal fluid of patients with MS. In addition, the CNS-educated B cells can recirculate. Research carried out at the University of San Francisco using a deep sequencing technique to identify the lineage of individual B cells indicates that it is possible to identify B cells in the periphery that are derived from the same clonal lineage as those residing chronically in the brain. The findings suggest that the B-cell population is moving rapidly back and forth across the blood–brain barrier and, further, it appears that B cells are undergoing more clonal expansion in the periphery.

Table 1: Emerging therapies for multiple sclerosis

Generic name	Target	Study phase (route of administration)	MS disease course
Daclizumab	CD25	III (SC)	RRMS
Ocrelizumab	CD20	III (IV) III (IV)	RMS PPMS
Laquinimod	Inhibits cytokines and lymphocyte migration into the CNS	III (Oral) II (Oral)	RMS PPMS
Siponimod	Sphingosine-1-phosphate 1/5 receptors	III (Oral)	SPMS
Ponesimod	Sphingosine-1-phosphate 1/5 receptor	III (Oral)	RMS
Ofatumumab	CD20	II (IV) II (SC)	RRMS RRMS
ATX-MS-1467	Reduces T-cell response to myelin	II (ID)	RMS
Secukinumab	IL-17A	II (IV)	RRMS
Ibudilast	Phosphodiesterases, leukotrienes, nitric oxide synthesis	II (Oral)	PMS
BIIB033	LINGO-1	II (IV)	RRMS or SPMS
Vatelizumab	VLA-2	II (IV)	RRMS

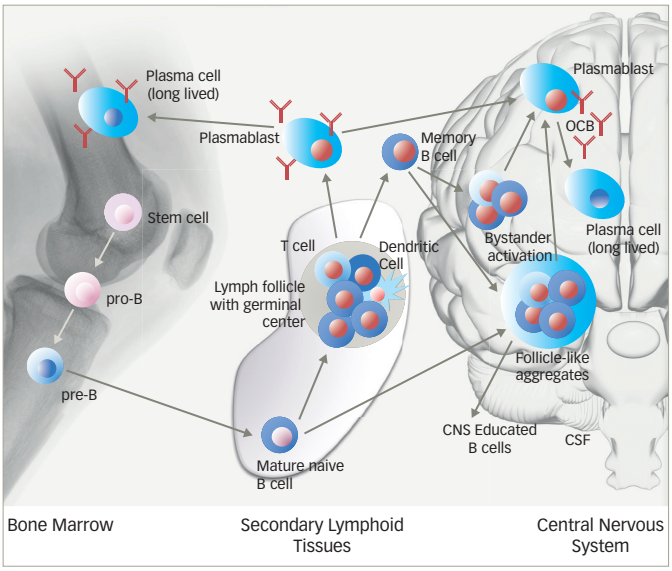
CNS = central nervous system; ID = intradermal; IV = intravenous; MS = multiple sclerosis; PPMS = primary progressive MS; RMS = relapsing MS; RRMS = relapsing remitting MS; SC = subcutaneous; SPMS = secondary progressive MS.

There is another evolving concept in the cellular aetiology of MS. The brain is not an 'immune desert' and, in fact, 40–60% of cells in the brain are members of the innate immune system, i.e., astrocytes, which express class I and II major histocompatibility complex; and can internalise and process antigens and present them to T-cells (*Figure 2*).[1–7] There is an emerging model suggests that this T-cell–B-cell interaction may be more complicated than formerly believed. This is based on two key processes. Firstly, B cells that internalize antigen that bind to their B-cell receptor are highly efficient antigen-presenting cells, being up to 10,000 times more efficient than dendritic cells. B cells may consequently be the primary antigen-presenting cell in an MS plaque that activate T cells, resulting in the inflammatory cascade. Secondly, there appears to be involvement of astrocytes, the innate immune cells Interleukin-1β and interferon-γ activate astrocytes to become type II astrocytes that upregulate inducible nitric oxide synthase (iNOS) and produce tumour necrosis factor, leading to axonal injury and oligodendrocyte and neuronal death. This means that there may be two steps with two different targets in the immune cascade, i.e., in both the innate and adaptive immune system. Whether purified B cells from MS patients could themselves damage the brain has been the subject of much exploration. CD19+ B lymphocytes from treatment-naive patients with MS-induced demyelination of cerebellar slices derived from mice, suggesting that B-cells have a direct effect on the brain.[8] Although we currently consider the approved therapies as working via T cells, all therapies have now been reported to have B cell effects.

New possibilities with B cell targeted therapy

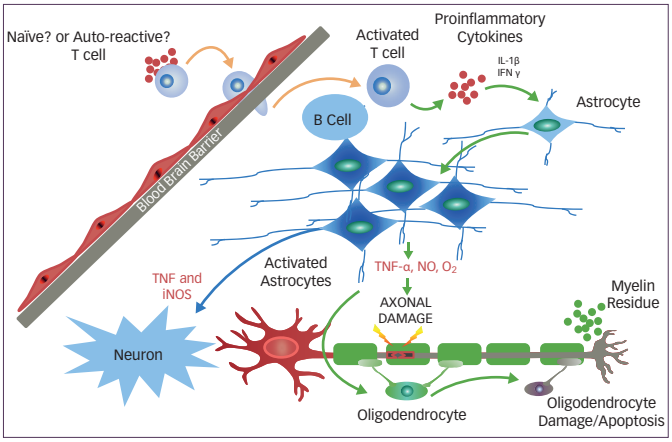
Along the B cell lineage, starting as stem cells, B cells differentiate into pro B cells and then undergo, a process of diversification that occurs mostly in secondary lymphoid organs, which results in antigen-triggered memory B cells, plasmablasts and short- and long-lived plasma cells (*Figure 3*).[9–12] B cells are also characterised by a variety of surface markers, which serve as guides to B-cell differentiation staging. The CD20 surface marker is a membrane-spanning protein that is expressed at the intermediate stage of B cell differentiation. CD20 is not expressed at the earlier stem and pro B cell stage or on most short-lived plasma cells or any long-lived plasma cells. This poses the possibility that anti-CD20 treatment could deplete the intermediate stage of B-cell development while preserving the ability of stem cells to repopulate and protecting pre-existing humoural immunity.

Figure 1: B cells and the brain



CNS = central nervous system; CSF = cerebrospinal fluid; OCB = oligoclonal band.

Figure 2: B cell-mediated inflammatory pathway in multiple sclerosis



IFN = interferon; iNOS = inducible nitric oxide synthase; IL = interleukin; TNF = tumour necrosis factor.

Figure 3: B cells express different surface markers throughout development

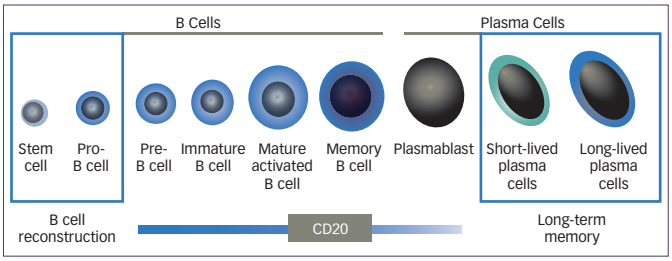
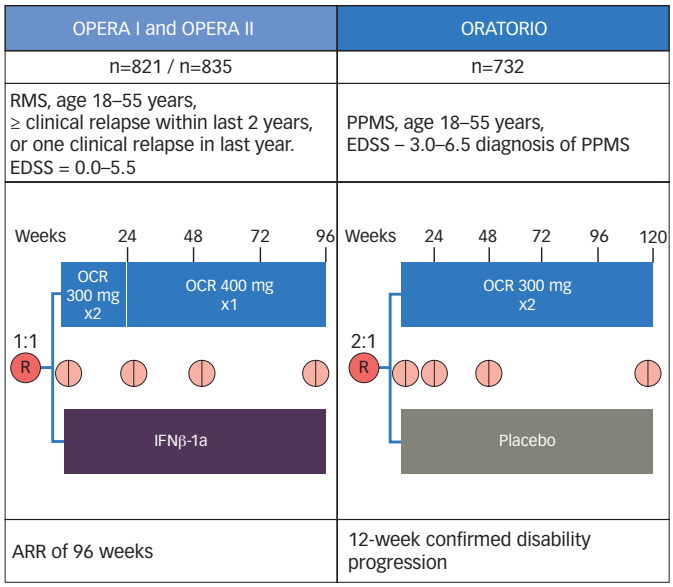


Figure 4: OPERA I and II study design



ARR = annualised relapse rate; EDSS = Expanded Disability Status Scale; IFNβ-1a = interferon beta-1a; OCR = ocrelizumab; PPMS = primary progressive multiple sclerosis; RMS = relapsing multiple sclerosis.

Ocrelizumab is a humanised monoclonal antibody that depletes CD20+ B cells via multiple mechanisms.[13–15] The predominant mechanism is believed to be stimulation of cell-mediated antibody-dependent cellular phagocytosis and antibody-dependent cellular cytotoxicity. Ocrelizumab also depletes CD20+ B cells by complement-dependent cytotoxicity and by direct apoptosis, but it is thought that the cell-mediated mechanisms predominate. This may explain some of the characteristics in terms of infusion-related reactions (IRR) associated with ocrelizumab. The humanised, rather than chimeric nature of the antibody is another potential advantage.

There is a new understanding of a very dynamic recirculation of B cells from the blood into the brain out into secondary lymphoid tissues (*Figure 1*). It is thought that activation and stimulation of clonally specific B cells is occurring on both sides of the blood–brain barrier. These cells are released from the protective cytokine-rich lymphoid niches that are present in most secondary lymphoid organs and it is mostly these motile B cells that are targeted by ocrelizumab. It is believed that with anti-CD20 therapy, there is a fairly rapid depletion of the circulating memory B cells and the egressing CNS-educated B cells which is substantially greater than any effects on secondary lymphoid tissue.

In phase II and III trials, ocrelizumab has been studied in over 1500 MS patients with over 4000 patient-years of experience.[16] The OPERA I and OPERA II studies were double-blind, double-dummy controlled trials with interferon beta-1a (IFNβ-1a) 44 µg three times per week subcutaneously as a comparator and ocrelizumab given as 4 doses four cycles at 24-week intervals. The initial cycle was administered as two 300-mg infusions on Days 1 and 15 for the first dose, and as a single 600-mg infusion thereafter (*Figure 4*). An infusion of 100 mg of methylprednisolone was given 30 minutes prior to each ocrelizumab dose. The objective of OPERA I and OPERA II was to evaluate the efficacy and safety of ocrelizumab compared with IFNβ-1a in patients with relapsing MS (RMS). The primary endpoint was the annualised relapse rate (ARR) at 96 weeks and key secondary endpoints included: pooled 12- and 24-week confirmed disability progression (CDP), number of gadolinium (Gd)-enhancing lesions and the number of new and/or emerging T2 lesions at weeks 24, 48 and 96.

Over 85% of patients completed the OPERA I and OPERA II studies. Slightly more patients withdrew in the IFNβ-1a arms compared with the ocrelizumab arms in both studies (OPERA I: 17% versus 10%, respectively and OPERA II: 23% versus 14%, respectively). Nearly all (96%) patients entered the open-label extension phase. Patients who withdrew for any reason were then moved into a safety follow-up phase. MS disease history and baseline characteristics were balanced between the treatment arms in both OPERA I and II, and were representative of a typical RMS population. Mean time since onset of MS was six or more years and mean age was approximately 37 years old. Gender dimorphism (66% of patients in both studies were female) was as expected for MS, and the mean Expanded Disability Status Scale (EDSS) was 2.8. Over 70% of patients were untreated in the past 24 months. There was a 46% reduction in ARR with ocrelizumab compared with IFNβ-1a ($p<0.0001$) in OPERA I and a 47% reduction favouring ocrelizumab in OPERA II ($p<0.0001$ in both studies). The adjusted ARR for ocrelizumab was <0.16 in both trials compared with 0.292 and 0.290, for IFNβ-1a in OPERA I and OPERA II, respectively. Consistency was a hallmark between the OPERA I and OPERA II study results. There was also a significant reduction in CDP in the pre-specified pooled analysis of pooled data from OPERA I and OPERA II. For both time to 12-week CDP and 24-week CDP there was a risk reduction of 40% favouring ocrelizumab, which was consistent across the two studies.

Although initially not sufficiently powered to detect a treatment effect on CDP in each of the individual studies, the OPERA trials individually, but this was investigated in exploratory analysis, which revealed a consistent reduction in 12- and 24-week CDP. On imaging endpoints, a significant reduction was observed in the number of T1 Gd+ lesions with ocrelizumab treatment compared with IFNβ-1a (94% and 95% ARR reduction versus IFNBeta-1a in OPERA I and II, respectively; $p<0.0001$). There was a striking 94% reduction ($p<0.0001$) in the mean number of T1 GD+ lesions favouring ocrelizumab in OPERA I and in OPERA II, this was 95% ($p<0.0001$). This remarkable effect was consistent and sustained across the 96-week treatment period. There was also a significant reduction in the number of new and/or enlarging T2 hyperintense lesions compared with IFNβ-1a (77% and 83% for OPERA I and OPERA II, respectively). This result was also highly statistically significant ($p<0.0001$) and there was significant improvement associated with ocrelizumab versus IFNβ-1a in terms of the exploratory endpoints of rate of brain volume loss from baseline to week 96 (23.5% and 23.8% reduction in OPERA I and II, respectively; $p< 0.0001$) and no evidence of disease activity (NEDA) (64% and 89% improvement in OPERA I and II, respectively; $p< 0.0001$).

OPERA I and II – safety outcomes

Adverse events (AEs) over 96 weeks in the OPERA I and II studies are shown in *Table 2*. The number of patients with one or more AEs was similar the IFNβ-1a and ocrelizumab arms. Similarly, the total number of patients with one or more AEs occurring at a frequency of at least 5% in either arm was virtually identical in the two treatment arms (*Table 2*). There were more general disorders and administration site reactions in the group treated with IFNβ-1a. Slightly more infections (mainly upper respiratory tract) occurred in the ocrelizumab arms versus IFNβ-1a (58.4% vs. 52.4%), although other AEs were well balanced between treatments. There were slightly fewer patients with one or more serious AEs (SAEs) in the ocrelizumab group compared with IFNβ-1a (*Table 3*).

During OPERA I and OPERA II, three deaths occurred (in the IFNβ-1a arm, one case of suicide and one of mechanical ileus and in the

Table 2: Adverse events over 96 weeks in OPERA I and II

n (%)	Interferon beta-1a 44 µg (n=826)	Ocrelizumab 600 mg (n=825)
Total number of patients with ≥ 1 adverse event (AE)	**688 (83.3)**	**687 (83.3)**
Total number of patients with ≥ 1 AE occurring at a frequency ≥ 5% in either arm	**539 (65.3)**	**544 (65.9)**
Injury, poisoning and procedural complications	**155 (18.8)**	**333 (40.4)**
Infusion-mediated reaction	80 (9.7)	283 (34.3)
Generalized disorders and administration-site conditions	**396 (47.9)**	**173 (21.0)**
Influenza-like illness	177 (21.4)	38 (4.6)
Injection-site erythema	127 (15.4)	1 (0.1)
Fatigue	64 (7.7)	64 (7.8)
Injection-site reaction	45 (5.4)	2 (0.2)
Infections and infestations	**433 (52.4)**	**482 (58.4)**
Upper respiratory tract infection	87 (10.5)	125 (15.2)
Nasopharyngitis	84 (10.2)	122 (14.8)
Urinary tract infection	100 (12.1)	96 (11.6)
Sinusitis	45 (5.4)	46 (5.6)
Bronchitis	29 (3.5)	42 (5.1)
Nervous system disorders	**252 (30.5)**	**224 (27.2)**
Headache	124 (15.0)	93 (11.3)
Psychiatric disorders	144 (17.4)	149 (18.1)
Depression	54 (6.5)	64 (7.8)
Insomnia	38 (4.6)	46 (5.6)
Musculoskeletal and connective tissue disorders	**207 (25.1)**	**204 (24.7)**
Back pain	37 (4.5)	53 (6.4)
Arthralgia	51 (6.2)	46 (5.6)

Table 3: Serious adverse events were low over 96 weeks in OPERA I and II

n (%)	Interferon beta-1a 44 µg (n=826)	Ocrelizumab 600 mg (n=825)
Overall patients with ≥1 serious adverse event	72 (8.7)	57 (6.9)
Infections and infestations	24 (2.9)	11 (1.3)
Nervous system disorders	11 (1.3)	8 (1.0)
Injury, poisoning and procedural complications	10 (1.2)	6 (0.7)

ocrelizumab arm, one case of suicide). Six malignancies were reported (in the IFNβ-1a arm: mantle cell lymphoma and squamous cell carcinoma, and in the ocrelizumab arm: renal cancer, melanoma and two breast cancers).

The most common AE associated with ocrelizumab was the IRR, which were mostly mild to moderate in intensity (less than 2% were severe in intensity). Eleven patients (1.3%) withdrew from ocrelizumab treatment due to an IRR during the first infusion.

Conclusions

- The role of B cells in the pathogenesis of MS may not be simply related to their ability to produce antibodies.
- B cells are likely to be important in MS because of their ability to be highly efficient antigen-presenting cells. They also produce cytokines that can change the microenvironment and can mediate negative effects through astrocyte populations, as well as producing antibody that may have a role in addition to producing ectopic lymphoid follicle-like aggregates that persist long term in the brains of MS patients.
- This improved understanding of the role of B cells in MS presents greater opportunities for developing effective therapies.
- Compared with IFNβ-1a, ocrelizumab significantly reduced:
  - ARR;
  - 12- and 24-week CDP;
  - T1 GD+ lesions; and
  - new and/or enlarging T2 lesions.
- In exploratory analysis compared with IFNβ-1a, ocrelizumab:
  - reduced brain volume loss; and
  - increased proportion of patients with NEDA.
- Ocrelizumab is the first investigational treatment for MS to significantly reduce, in two separate phase II studies:
  - Both 12- and 24-week CDP against any comparator
  - CDP versus active comparator.
- OPERA I and OPERA II showed that targeting CD20+ B cells is a potential therapeutic approach in RMS.
- Overall, in OPERA I and OPERA II, ocrelizumab had a similar safety profile compared with IFNβ-1a over 96 weeks.
- AEs occurred with similar frequency in the ocrelizumab and IFNβ-1a groups, with the following exceptions:
  - IRRs associated with ocrelizumab;
  - infections and infestations: IFNβ-1a (52.4%), ocrelizumab (58.5%); and
  - influenza-like illness and local cutaneous reactions associated with IFNβ-1a.
- Overall, the proportion of patients reporting an adverse event in the controlled treatment period was identical:
  - IFNβ-1a (83.3%) ocrelizumab (83.3%).
- The proportion of patients reporting a SAE in the controlled treatment period was low and similar between groups:
  - IFNβ-1a (8.7%), ocrelizumab (6.9%).
- Targeting CD20+ B cells may preserve B cell reconstitution and long-term immune memory (*Figure 3*), which may account for the favourable safety and tolerability profile observed for ocrelizumab.
- In summary, B-cell targeted therapy, such as ocrelizumab, offers exciting possibilities for the treatment of MS. ❑

1. De Jager PL, Hafler DA, New therapeutic approaches for multiple sclerosis, *Annu Rev Med*, 2007;58:417–32.
2. Lassmann H, Models of multiple sclerosis: new insights into pathophysiology and repair, *Curr Opin Neurol*, 2008;21:242–7.
3. Markiewicz I, Lukomska B, The role of astrocytes in the physiology and pathology of the central nervous system, *Acta Neurobiol Exp*, 2006;66:343–58.
4. Nair A, Frederick TJ, Miller SD, Astrocytes in multiple sclerosis: a product of their environment, *Cell Mol Life Sci*, 2008;65:2702–20.
5. Van der Walt A, Butzkueven H, Kolbe S, et al., Neuroprotection in multiple sclerosis: a therapeutic challenge for the next decade, *Pharmacol Ther*, 2010;126:82–93.
6. Weiner HL, A shift from adaptive to innate immunity: a potential mechanism of disease progression in multiple sclerosis, *J Neurol*, 2008;255(Suppl 1):3–11.
7. Zhang D, Hu X, Qian L, et al., Astrogliosis in CNS pathologies: is there a role for microglia?, *Mol Neurobiol*, 2010;41:232–41.
8. Harlow DES, Saul KE, Jackson LJ, et al., Laquinimod reduces CNS pathology and demyelination induced by B lymphocytes from multiple sclerosis patients in a novel brain slice model of MS. 31st CONGRESS OF THE EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS (ECTRIMS); 9 October; Barcelona, Spain, 2015.
9. Stashenko P, Nadler LM, Hardy R, Schlossman SF, Characterization of a human B lymphocyte-specific antigen, *J Immunol*, 1980;125:1678–85.
10. Loken MR, Shah VO, Dattilio KL, Civin CI, Flow cytometric analysis of human bone marrow. II. Normal B lymphocyte development, *Blood*, 1987;70:1316–24.
11. Tedder TF, Engel P, CD20: a regulator of cell-cycle progression of B lymphocytes, *Immunol Today*, 1994;15:450–4.
12. 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;180:361–71.
13. Jaglowski SM, Alinari L, Lapalombella R, et al., The clinical application of monoclonal antibodies in chronic lymphocytic leukemia, *Blood*, 2010;116:3705–14.
14. Winiarska M, Glodkowska-Mrowka E, Bil J, Golab J, Molecular mechanisms of the antitumor effects of anti-CD20 antibodies, *Front Biosci* (Landmark Ed), 2011;16:277–306.
15. Klein C, Lammens A, Schafer W, et al., Epitope interactions of monoclonal antibodies targeting CD20 and their relationship to functional properties, *MAbs*, 2013;5:22–33.
16. Kappos L, Li D, Calabresi PA, et al., Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial, *Lancet*, 2011;378:1779–87.

Panel discussion and audience Q&A: evolving treatment options and strategies

Moderated by Gavin Giovannoni

Chair, Queen Mary University of Neurology, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University London, 4 Newark Street, London E1 2AT, UK; Department of Neurology, Royal London Hospital, Barts Health NHS Trust, London, UK

For what kind of patient would you use ocrelizumab?

Every patient should be considered on a case-by-case basis though early MS patients appear to have a very effective response. Ocrelizumab could be considered for first-line treatment though while the side effect profile looks extremely good, longer-term safety data are needed. Experience with rituximab may be helpful.

Why are the atrophy rates with ocrelizumab not as good as those seen with alemtuzumab?

This may be a reflection of different the various magnetic resonance imaging (MRI) techniques used to assess atrophy.

Given the striking magnetic resonance imaging (MRI) findings, why are the ARR data not even better than observed?

This will be investigated further. It will be interesting to assess to what degree these relapses might represent pseudo-attacks, attacks in regions not interrogated by MRI or true attacks that somehow doesn't declare itself on the current metrics used for MRI.

Does ocrelizumab treatment increase the risk of progressive multifocal leukoencephalopathy (PML)?

This would seem unlikely as CD8 cytotoxic T lymphocytes, which protect against PML, are left intact with B cell depletion.

Why wasn't there a placebo arm in OPERA I and II?

Now patients would not be recruited into studies using placebo that last longer than a few months.

Can ocrelizumab be combined with IFN?

Caution is needed to consider mechanisms of action of combined drugs. It would be surprising if these drugs are combined early in treatment although re-myelination therapy may be a future option for combination. ❑