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# Development of anti-CD20 Therapy for Multiple Sclerosis

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## Introduction

The first agent for the therapeutic targeting of B lymphocytes is a chimeric (i.e., retains mouse variable region sequences) monoclonal anti-CD20 antibody, rituximab (Rituxan$^{R}$, Mabthera$^{R}$), was originally developed for the treatment of the B-cell neoplastic disease, CD20+ Non-Hodgkins Lymphoma (NHL), in which the rationale for the targeting of the pathogenic B cells in this disease was unambiguous. In 2005, rituximab was also approved in the US for the treatment of patients with rheumatoid arthritis (RA) with inadequate response to TNFa blockers. Yet, RA is a chronic inflammatory disease that often results in joint deformities and disabilities, while pathogenesis has autoimmune features for which T cells were long believed to be dominant in pathogenesis [1].

The advent of B-cell targeted agents for autoimmune diseases has therefore also provided investigative opportunities to better understand what components are essential for driving the disease process, and for examination of the potential contributions of the different functional roles of B cells in these processes. While diverse cell types are involved in RA pathogenesis, in a majority of patients there is prominent autoantibody production, which include rheumatoid factors (antibodies to IgG constant regions), and more recently a range of autoantibodies to citrullinated proteins have been described.

As most plasma cells do not express CD20, and are therefore not directly targeted by anti-CD20 antibodies, the clinical benefits of this form of B cell targeted therapy is therefore likely to result from effects on B cell functions other than immunoglobulin synthesis. Similarly, even though intrathecal immunoglobulin production is a hallmark of multiple sclerosis (MS), T cells have long been considered as the main effectors of disease pathogenesis. In recent years, recognition of role of autoreactive B cells has changed this conventional view of the disease and also provided a rationale for studies of anti-CD20 therapy in MS [2–3]. In this review we will provide an overview on recent progress in studies of anti-CD20 therapy in multiple sclerosis.

## Role of B cells in pathogenesis of autoimmune disease

A large number of autoimmune diseases have been found to be associated with specific types of autoantibodies, which in many cases are routinely used to aid in diagnosis. While



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such findings clearly document the involvement of autoreactive B lymphocytes in pathogenesis, in many cases it has proven challenging to demonstrate that such autoantibodies are directly pathogenic, and there are certainly diseases with autoimmune features in which circulating autoantibodies cannot be detected. In fact, in addition to the secretion of antibodies/immunoglobulins, extensive data has been presented that B cells can play many other functional roles in health, which may have even more profound roles in pathogenesis in certain autoimmune diseases. While this topic has been recently reviewed extensively [4–5], the targeting of B cells with anti-CD20 therapy may provide clinical benefits through interference with these other pathways, which include the roles of autoreactive B cells as key antigen-presenting cells that sustain secondary immune responses. In fact, an antigen specific B cells can be 100-fold more efficient than a professional antigen-presenting cell (e.g., dendritic cell or macrophage) at antigen uptake of soluble antigens, or of immune-complexed antigens, which results in processing and presentation in the context of MHC molecules to autoreactive T cells, (especially under limited Ag conditions). When activated, B cells can also express costimulatory molecules that promote T cell activation, and also synthesize inflammatory cytokines (e.g., IL-6, IFNg, LTa) that activate T cells or other cell types, and chemokines that induce leukocyte infiltration. B cells therefore can also produce factors that initiate and sustain angiogenesis and granulation tissue formation, and contribute to ectopic lymphoid neo-organogenesis at sites of end-organ disease. Of course, B cells can release immunoglobulins and autoantibodies that can be directly or indirectly (via immune complex formation) destructive to tissues. Within the B cell compartment there are also memory B cells that maintain immune memory responses, including to autoantigens that sustain the chronic ongoing autoimmune disease process, which provides a great challenge to the goal of actually eradicating the autoimmune disease.

There is also increasing recent evidence that some B cells can produce the potentially anti-inflammatory factor, IL-10 [6–7], some B cells make regulatory IgM antibodies that bind apoptotic cells and these can block the inflammatory responses of macrophages and dendritic cells. The roles of some IgM antibody products to affect the capacity of innate immune cells for inflammatory responses of macrophages and dendritic cells[8].These recent observations have evoked an interest in understanding how B-cell targeted therapies may also affect these potentially protective pathways (reviewed [9]).

## Role of B cells in MS: rationale for B-cell targeted therapies

MS is an inflammatory demyelinating disease of the central nervous system (CNS), which occurs with distinct clinical presentations: The relapsing remitting form (RRMS) is characterized by relapsing periods of neurodegeneration followed by partial or complete period of remission. On the other hand, the primary progressive form of MS (PPMS) is associated with neurodegeneration that is progressive without interim clinical improvement. Secondary progressive MS initially presents as RRMS followed by more steady progression of symptoms.

Although intrathecal immunoglobulin production is found in more than 90% of patients and is considered a hallmark of the disease, until recently this was believed to be more of a bystander effect and B cells were not considered to be major players in disease pathogenesis. Investigations of the rodent animal model, experimental autoimmune encephalitis (EAE), have provided the bases for a better understanding of some aspects of these arguably related diseases. The emphasis on the role of T cells in MS pathogenesis and the controversy about role of B cells come from studies of the murine EAE model. EAE is induced by active immunization or passive transfer of myelin protein-specific CD4+ T cells but it is not induced by passive transfer of B cells or antibodies [10–11]. These findings led to initial

acceptance of the paradigm that CD4+ T cells with Th1 polarization are the major pathogenic drivers of the disease.

In humans, the pathologic MS plaques contain lymphocytic infiltrates that are predominantly T cells and macrophages. While intrathecal oligoclonal IgG production is commonly present, these levels do not change over time, and may not correlate with disease activity. Nonetheless, B cells and plasma cells are common in the parenchyma and cerebrospinal fluid (CSF). In fact, these oligoclonal immunoglobulins are seen in the CSF in 81% of patients at first clinical presentation of MS. There have also been reports of clonally expanded B cells in CSF and somatic hypermutation of the expressed antibody gene rearrangement, which has been cited as evidence of antigen-driven responses [12].

The antigen specificity of these B cell responses remains a topic of active investigation. Yet there have been reports of antibodies in the CSF react with antigens from measles, rubella, varicella zoster, and mumps, which has suggested that these viral pathogens may play some role in pathogenesis. Other studies have found antibody reactivity with several neuronal antigens. While myelin basic protein has long been known to be an immunodominant antigen, myelin oligodendrocyte glycoprotein (MOG) can also ne specifically recognized by B-cells in MS patients. MOG is a minor Ag compared with other myelin proteins, but localized on the outer surface of the myelin sheets which makes it more accessible and induces strong B-cell response [10]. Antibodies to MOG induce EAE in non-human primates, augment MBP-induced EAE in Lewis rats and accelerate EAE in mice. Studies also have demonstrated that both passive transfer of monoclonal abs to MOG and active immunization leads to demyelination and oligodendrocyte loss in EAE [13].

There have also been reports of antibody reactivity with neuronal structures, such as neurofascin, contactin-2/TAG-1 [14–15]. Together these findings have been cited as support for the hypothesis that disease is driven by a B-cell anti-myelin response, with the resulting antibody response playing a potential role in pathogenesis by recruitment of macrophages, complement-mediated phagocytosis and myelin destruction.

Based on histological analysis of CNS lesions, four patterns have been recognized [16]. The pattern II lesions Igs and complement fragments were colocalized with B cells which are always were found close to the venules. The infiltrating cells are primarily T cells and macrophages, which was seen in about 75% of the demyelinated lesions. Notably, patients with this histopathologic pattern are reported to better respond to plasma exchange, which supports a role for antibodies and/or immune complexes in pathogenesis [17].

## New perspectives on B-cell involvement in MS

Using immunohistochemistry, ectopic lymphoid follicles reminiscent of germinal centers containing B cells and plasma cells were demonstrated in the meninges of 40% of patients with secondary-progressive MS [18]. These ectopic follicles are preferentially localized to the subarachnoid space in the cerebral sulci and their presence correlated with severe cortical pathology and more severe clinical disease [19]. These observations suggest that ectopic lymphoid structures may provide the appropriate microenvironment for B-cell differentiation, local antibody production in the central nervous system and might be responsible for gray matter pathology in subset of MS patients.

Patients with CNS infiltrates with GC-like features was also associated with CD38high, CD77+, bcl2− centroblasts in the CSF that was not detectable in the peripheral blood mononuclear cells (PBMC), which suggested this was an organ-specific reaction [20]. These same patients also commonly displayed enrichment of CD27+ IgD− memory B cells with activated phenotype in CSF compared with PBMC [21].

Cytokines and chemokines important in B-cell homing and lymphoid neogenesis have also been evaluated in MS patients. Among these LTa, CXCL12 and CXCL13 were detected in CNS tissue [22]. CXCL13 expression in addition to intrameningeal follicles [18–19] and active lesions was also detected in the CSF at high concentrations MS patients [19]. High concentration of CXCL13 in CSF correlated with presence of follicles and active lesions [22–24]. In addition, the B cell survival factor, B-cell activating factor (BAFF) is produced by astrocytes and has been reported to be upregulated in active MS plaques [25]. Moreover, the presence of BAFF may synergize with the homeostatic chemokines CXCL12, CXCL13 and CCL19 to attract and protect prolonged local survival of B cells in the inflamed CNS. Nonetheless, the role of this process in MS pathogenesis and disease activity is not well understood. It remains unclear whether these pathways contributed to the disease progression in some MS patients. In a recent clinical trial patients who received treatment with Atacicept, a recombinant decoy receptor that blocks both BAFF and the related APRIL molecule had worsening of their disease, which led to the early termination of the trial (http://www.clinicaltrial.gov/ct2/show/NCT0064201) [26].

The identification of ectopic B-cell follicles in patients with MS led to suggestion that might be manifestation of an EBV- associated disease. Accumulation of EBV-infected cells were found in post-mortem brain tissue in 21 of 22 patients of MS particularly inside ectopic follicles and in the perivascular cuffs of acute and chronic demyelinated lesions [27]. Cross-reactivity between EBV and myelin antigens and immortalization of autoantibody-producing B-cell clones might be a possible trigger for autoimmunity [28–30]. Presence of EBV-infected B cells and plasma cells in the subarachnoid space suggests that the oligoclonal IgG in MS patients could be produced by randomly EBV infected memory B-cells and consequently would be heterogeneous [31–32].

## Regulatory B cells

Compared to healthy individuals, B cell from MS produced less IL-10 compared with healthy controls [33]. In the murine model, prophylactic treatment with an anti-CD20 antibody before EAE induction has been shown to result in more severe disease and a more profound influx of pathogenic T cells, and concurrent depletion of IL-10-secreting B cells. In contrast, B-cell depletion after EAE onset led to dramatic suppression of signs and symptoms [34].

In another study B-cell depletion with anti-CD20 treatment in mice reduced the frequency of CD4(+)CD25(+)Foxp3(+) regulatory T cells (Treg), and increased the proinflammatory polarizing capacity of remaining myeloid APCs. Clinical benefit from anti-CD20 treatment may relate to inhibition of proinflammatory B cell APC functions; however elimination of B cell that regulate T-cells and other APC might have undesirable effects in certain clinical settings [35].

## Rituximab trials in patients with MS

The evolution of disease activity and disability can follow more than one overall pattern. Relapsing remitting form of MS (RRMS) is the most common, and this subset of patients are characterized by periods of neurological deterioration (relapses) and partial or complete recovery (remission), with (secondary progressive) or without (relapsing remitting MS) progression between exacerbations. RRMS is seen in more than 80% of MS patients. The remaining subset of patients presents with gradually increasing neurological disability, primarily affecting ambulation, without obvious relapses, called primary progressive MS (PPMS).

The HERMES trial (Helping to Evaluate Rituxan in Relapsing-Remitting Multiple Sclerosis) [36] was designed to evaluate the potential safety and clinical utility in MS of rituximab in a randomized double blind, placebo controlled trial. In this multicenter (US and Canada) phase II trial, 104 relapsing remitting MS (RRMS) were enrolled, of which 69 received RTX and 35 received placebo treatment. Patients received rituximab 1000 mg i.v. or placebo on day 1 and day 15, and were followed for a period of 48 weeks. Patients enrolled in the study were aged 18–55 with a documented history of relapsing-remitting MS, and at least one relapse in the preceding year. Patients were excluded if they had received cyclophosphamide or mitoxantrone within 1 year, glucocorticoids within 30 days, or treatment with interferon, glatiramer acetate, natalizumab, plasmapheresis or IVIg within 60 days.

The study was based on an intention to treat (ITT) analysis and it was anticipated that patients would develop 8 new lesions on average, which was based on a statistical model in which it was anticipated that such patients would on average have 8 new detectable Gad MRI lesions between 12–24 wks in the placebo treated group, and the data and were assumed to follow a negative binomial distribution. In addition, baseline disease severity was determined according to Expanded Disability Status Scale (EDSS).

The primary end point involved whether there were differences in the total number at wks 12, 16, 20 and 24 weeks of Gadolinium (Gad) enhancing CNS lesions on serial T1 weighted magnetic resonance images (MRI). Also, if the lesions persisted > 4 wks, they were counted more than once. The secondary end points included the proportion of patients with clinical relapses between enrollment (i.e., wk 0) and wk 24, as well the annual relapse rate, the total number of new Gad enhancing MRI lesions, and the change CNS lesion volume on T2 weighted MRI images from baseline to wk 24.

This study succeeded in attaining its primary endpoint, and found a reduction of total number of Gad lesions in the RTX group at wk 12, 16, 20, 24 ($p=0.003$ to $p<0.001$). In addition, the mean number of Gad lesions was 0.5 in the rituximab-treated group vs 5.5 in the control group at wk12, 16, 20, 24, which represented a 91% mean reduction), and was sustained up to 48 wks. However, it should also be noted that at baseline the proportion of patients with Gad enhancing lesions was greater in the placebo group compared to the rituximab-treated group (85.7% vs 63.8%, $p=0.02$).

With regard to the secondary end points, the rituximab-treated group also demonstrated a significantly lower clinical relapse rate wk 24 (14.5% vs 34.3%, $p=0.02$), as well as at wk 48 (20.3% vs 40.0%, $p=0.04$). In addition, new Gad enhancing lesions were also reduced wk 12, 16, 20 and 24 (mean 0.2 vs 4.5, $p<0.001$). Rituximab treatment was also associated with a reduction of the lesions volume on T2 wk 24 ($p=0.008$) and at wk 48 ($p=0.004$).

With regard to the biologic effect of treatment, the results were comparable to those found in RA patients, as rituximab treatment resulted in a >95% reduction from baseline of blood CD19+ cell levels from wk 2-wk 24, and by wk 48 there was a mean 30.7% return of B cells, indicating the effect of the therapeutic antibody was waning. In these patients, median IgM, IgG and IgA remained within normal limits even after rituximab treatment.

In this study, rituximab also displayed an attractive safety profile as there were no significant differences in infusion reactions, malignancies or infections, in the two groups. Significantly, at wk 48, 16 out of 65 rituximab treated patients (i.e., mean 24.1%) had detectable antibodies to rituximab (i.e., human anti-chimeric antibodies, HACA). This HACA level in MS patients is much higher than found in RA patients, but this may reflect the routine of methotrexate as a background agent in RA. Nonetheless, HACA host responses are always a concern, as there can be an association with decreased biologic and

clinical activity as well as serious allergic reactions on reexposure of the sensitized host. Hence, the finding of such a high frequency of HACA in rituximab-treated MS patients may provide a rational for the development of fully human anti-CD20 therapeutic antibodies.

In summary, the effect of rituximab treatment was very rapid, with reduction of the inflammatory lesions on MRI within 4 wks. These findings suggested that anti-CD20 therapy may affect the development of the lesions in acute disease, which as previously discussed are thought to be T- cell mediated for which B cells may serve as APCs and as cytokine producers that drive pathogenic T cells. However, this study did not address the longterm effect on disability.

## Addition of rituximab therapy for breakthrough activity in RRMS

A single center Phase II trial was conducted with 52 wk follow up in patients with breakthrough clinical symptoms with relapsing remitting disease (investigator initiated, single center trial) [37]. Herein, 30 MS patients were studied who had suffered clinical relapse within 18 month while on disease modifying agents, with MRI evidence of at least one Gad-enhancing lesion. Patients received the original NHL treatment regimen of weekly infusions of rituximab 375mg/m2 weekly for four weeks, in addition to background treatment of therapeutic interferon treatments or glatiramer, although glucocorticoids were not permitted. Starting at 12 weeks after the first infusion, patients were evaluated by MRI every month for three months. Blinded MRI found that while at baseline 26% of patients had Gad-enhancing lesions, 74% of patients of the rituximab treated patients had no lesions found after rituximab treatment. These findings provided additional evidence that anti-CD20 may provide benefits in some MS patients.

To assess the biologic effect of such treatments, a small open label study of a small series of 21 MS patients examined cerebrospinal fluid (CSF) from lumbar puncture one week before treatment and 24–30 wks after rituximab treatment. These investigators found that rituximab treatment resulted in a reduction in the levels of both B cells and T cells in CSF of 81% of patients. In fact, B (CD19+) cells were reduced in 20 pt ($p=0.0001$), while 6 had undetected B cells before and after. Overall, the mean reduction in CSF cellularity for B cells was 95%, while CD80 and CD86 levels on B cells were significantly increased ($p=0.01$), while there was no difference in CD25, CD38 and CD138. Importantly, rituximab also resulted in a decrease in CD3+ T cells in 21/26 patients ($p=0.0001$), with an overall decrease of 50%.

In this study, 17 chemokines were measured in CSF samples, and only 9 was detected. There was also evidence that anti-CD20 treatment also reduced B-cell chemokines, CXCL13, CCL19 ($p=0.002$ and $p=0.03$) levels in the CSF. Moreover, the levels of CXCL13 correlated with the decline in levels of total T cells in CSF. There was no correlation between changes in CXCL13 or CCL19 in serum and CSF for individual patients. There was weak correlation between T cells and CXCL13 ($r=0.45$ and $p=0.03$) and negative correlation with MCP1 ($r=-0.46$, $p=0.03$) [38].

These findings suggested that the representation and perhaps that the mechanisms responsible for the recruitment of disease-associated T cells is directly linked to B cell recruitment into the CSF of MS patients. Notably, comparisons of pre- and post treatment CSF samples showed that rituximab treatment had no effect on levels of IgG. These findings may be explained by the lack of direct effect of rituximab on plasma cells responsible for the local production in the CNS of IgG, or of the IgG index that compares blood and CSF levels, the detection of oligoclonal bands or of anti-MOG), or of anti-MBP antibodies in the CSF.

## Primary Progressive MS (PPMS)

Although less common, PPMS is a clinical form of MS for which there are no proven disease- modifying treatments that slow disease course. The OLYMPUS Trial was a double-blinded, placebo-controlled trial, Phase II/III, conducted at 60 centers in the US and Canada [39]. This large study enrolled 439 patients with PPMS. Enrolment inclusion criteria required evidence of intrathecal IgG, while 35% had received prior IFN, or glatiramer that is only approved for the treatment of RRMS.

In this study, 292 received rituximab and 147 were in the placebo controlled group, who were followed for 96 wks. The study was powered to detect 50% relative reduction in progression rate in disease activity during the 2 year followup. The study was designed based on findings from the earlier PROMise trial of glatiramer acetate in PPMS, and therefore assumed there would be a confirmed disease progression rate for the placebo arm of 32% at 96 wks. Enrolled patients had mean disease duration of 9.1 years 65% had not received prior therapies, with significant EDSS of 4.8 and 25% of patients had evidence of Gad-enhancing lesions at baseline. In the active arm, patients received 1000 mg rituximab infusions on days 1 and 15 then every 24 wks, with the last treatments on wk 72 and 74.

The primary end point was based on disease activity as measured by time to confirmed disease progression using the Expanded Disability Status Scale (EDSS). There was also a planned subgroup analysis based on patient age and change in Gad-enhancing lesions by MRI. The planned secondary end point was for measured change in brain volume by MRI from baseline to wk 96 and volume change of the lesions documented in T2 weighted MRI.

At 96 weeks, the same proportion of patients completed the trial (i.e., 84.4% in placebo and 82.5% in rituximab treatment group). After 122 wks of safety follow up, treatments were well tolerated without significant differences in infusion reactions, or serious infections. There were 3 Deaths, with one in the placebo group from pneumonia, while the rituximab group included one death from pneumonia in a patient with a history of a brainstem lesion, and another death due to cardiopulmonary failure.

The study failed to make its primary endpoint as there was no difference in the time to conformed disease progression ($p=0.1442$) although patients in the rituximab treated group tended to delay CDP, (i.e., at 96 wk 38 % in placebo and 30.2 % in rituximab-treated). The predefined secondary endpoint was attained, as from baseline to wk 96, patients in the rituximab group had significantly less (p, 0.001) increase in T2 lesion volume, but the brain volume change was similar ($p=0.62$).

From planned subgroup analyses, it appeared that the age of the patient influenced the responsiveness to the therapeutic intervention. In the rituximab-treated group, patients less than 51 years of age (HR=051, $p=0.010$) had better responses. In addition, if such younger patients had at least 1 Gad enhancing lesion at baseline ($n=72$), anti-CD20 therapy significantly reduced the risk of disease progression by 2/3 (hazard ration 0.33). This group also displayed a more favorable outcome based on T2 MRI lesion volume. Yet there were no significant differences in such younger patients if they did not have at least one Gad enhancing lesion at baseline.

The outcome of this trial was informative as this cohort had significantly disabled PPMS patients with relatively long-standing disease. There was also evidence that the primary pathology in these patients was in the spinal cord in this disease group, which clearly is not reflected by MRI studies of the brain used to evaluate outcome. However, although this study did not meet the primary endpoint, the preplanned subgroup analysis suggested that in younger patients with MRI evidence of inflammatory disease rituximab might substantially

reduce the risk of disease progression. This is important because there is no proven disease modifying agent (DMARD) for the PPMS patients. These findings support the notion that MS pathogenesis can involve both an immune and neurodegenerative components. Rituximab might be beneficial early on in the disease when the inflammatory component dominates and might halt or prevent neurodegeneration.

## Rituximab in neuromyelitis optica

Neuromyelitis optica is a demyelinating disease of CNS that primarily affects the optic nerves and spinal cord. Pathogenesis is believed to commonly involve an autoantibody against the water channel protein, aquaporin-4. The clinical test for the anti-aquaphorin-4 antibody has been shown to have moderate clinical utility in aiding this diagnosis[40]. It is believed that this autoantibody also has pathologic relevance, as an open-label study of 8 patients treated with rituximab and followed for 6–18 month found no relapses seen in 6 patients after this treatment [41]. A retrospective analysis of 25 patients also found evidence of clinical efficacy [42]. The changes in the anti-aquaporin-4 levels following rituximab therapy were not assessed in these studies.

## New anti-CD20 agents and MS

Recognizing the potential limitations of a chimeric antibody, which may be associated with greater risk for host immunity and associated adverse events, a number of newer generation anti-CD20 antibodies are currently also in development. These newer generation anti-CD20 mAbs, Ocrelizumab and Ofatumumab, have different pharmacological profiles and as they are humanized or fully human antibodies they may have advantages over a chimeric antibody due to lower immunogenicity. Ocrelizumab is a humanized IgG1 that binds to a CD20 epitope somewhat distinct from that recognized by rituximab. Early randomized clinical trials have also shown comparable efficacy of ocrelizimab for RA [43], however clinical trial were suspended following recommendation of the independent Ocrelizumab RA & Lupus Data and Safety Monitoring Board (DSMB) based on their assessment of the studies in RA (SCRIPT, FEATURE, FILM and STAGE) and lupus (BELONG and BEGIN). The DSMB concluded that the safety risk outweighs the benefits observed in these specific patient populations at this time. The DSMB review detected an infection related safety signal which included serious and opportunistic infections, some of which were fatal. Ocrelizumab may remain a viable candidate for MS, given the precedent for serious infection associated with Tysabri as an acceptable risk in this patient population. Controlled trials in rheumatoid arthritis demonstrated efficacy comparable to rituximab, however in at Asian sites in this multicenter trial there was a higher incidence of mycobacterial infections [44]. Otherwise this agent was generally well tolerated.

In a partially blinded, open label Phase II multicenter trial for RRMS performed at centers in the US, 250 patients were enrolled and distributed into groups that received either of 2 doses of Ocrelizumab (600 mg and 2000 mg) with standard of care of weekly IFN beta1, or standard of care alone. Patients received ocrelizumab on days 1 and 14, and were followed for 24 wks. Although not yet published, a preliminary report indicated that this study was successful at meeting the primary endpoint that was the same as used for the above described HERMES trial. The results have not yet been published.

Ofatumumab is a new anti-CD20 antibody that is a fully human IgG1 designed to have greater complement mediated cytotoxicity. In 2009, it was reported that this agent succeeded in a phase III for RA to meet its primary endpoint (press release). Although direct comparisons were not performed, overall it appeared to have similar efficacy to rituximab, with a comparable safety profile.

Ofatumamab is also currently being evaluated in MS patients in a European multicenter, randomized, placebo-controlled Phase I/II RRMS trial, which was started in June 2008. A total of 324 patients were assigned to one of four groups, representing ofatumamab infusions of 100 mg, 300 mg or 700 mg with standard of care, with comparisons to a placebo group that received only standard of care. It is anticipated that this study will be completed in Sept 2012.

## Concluding remarks

Recent progress in studies of anti-CD20 therapeutic interventions has demonstrated that this approach may provide clinical benefits in some MS patients that equal or surpass currently approved approaches. Yet not all patients may benefit from this approach, and results from the OLYMPUS trial of PPMS suggested that younger patients with evidence of an inflammatory component may respond best. While only a limited number of MS patients have been enrolled in these studies, and followup periods have been limited, there has not yet been a reported case of progressive multifocal leukoencephalopathy. This often fatal condition can be seen in patients treated with nataluzimab, an agent that interferes with leukocyte trafficking. However, although the data are also still limited, the rate of development of human anti-chimeric antibodies (HACA) in MS patients appears much higher than has been reported in RA patients treated with rituximab. Speculatively, this may reflect the routine usage of the background agent, methotrexate, in RA patients that receive rituximab, while this is not commonly used for the treatment of MS. This finding may become part of the rationale for the future development of fully human anti-CD20 antibodies for the treatment of MS.

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