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Targeting B cells to modify MS, NMOSD, and MOGAD

Part 2

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Abstract

Ocrelizumab, rituximab, ofatumumab, ublituximab, inebilizumab, and evobrutinib are immunotherapies that target various B cell–related proteins. Most of these treatments have proven efficacy in relapsing and progressive forms of MS and neuromyelitis optica spectrum disease (NMOSD) or are in advanced stages of clinical development. Currently, ocrelizumab and inebilizumab are licensed for treatment of MS and NMOSD, respectively. This part of the review focuses on monoclonal antibody B cell–depleting strategies in NMOSD and the emerging related myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G–associated disease (MOGAD). Case series and phase 2/3 studies in these inflammatory disorders are assessed. The safety profile of long-term B-cell depletion in MS, NMOSD, and MOGAD will be highlighted. Finally implications of the current coronavirus disease 2019 pandemic on the management of patients with these disorders and the use of B cell–depleting agents will be discussed.

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Glossary

COVID-19 = coronavirus disease 2019; **IgG** = immunoglobulin G; **NEMOS** = Neuromyelitis Optica Study Group; **MOG** = myelin oligodendrocyte glycoprotein; **MOGAD** = MOG IgG–associated disease; **NMOSD** = neuromyelitis optica spectrum disease; **PML** = progressive multifocal leukoencephalopathy; **SARS-CoV2** = severe acute respiratory syndrome coronavirus 2.

NMOSD

Following identification of immunoglobulin G (IgG) antibodies to aquaporin 4 in some 75%–80% of patients, research in humans and animal models has implicated aberrant B-cell responses in the pathogenesis of neuromyelitis optica spectrum disease (NMOSD)[1–4] These include defects in central and peripheral tolerance mechanisms allowing emergence of pathogenic antibodies, impairment of B regulatory activity, heightened production of proinflammatory cytokines, and complement activation.

Rituximab

Relevant CD19– and CD20– B lymphocyte–depleting studies in NMOSD are summarized in the table. Most studies were observational and retrospective.[5–7] Rituximab has long been considered a first-line treatment in NMOSD.[8] This recommendation for many years relied on multiple smaller observational studies and expert opinion (Class IV evidence).[7,9,10] Two recent meta-analyses analyzed 438[5] and 577 patients[6] from some 25 interpretable studies. The largest multicenter retrospective study from Italy included 73 patients. Two regimens were mostly applied: either 375 mg/m^2 weekly for 3 weeks or 1 g every 2 weeks twice. Rituximab reduces relapse frequency and neurologic disability but does not alter the frequencies of autoreactive B cells and does not reset defective early B-cell tolerance checkpoints.[11] B cells remain depleted in the circulation for up to 12 months. Bimonthly assessment of CD19/CD27-positive memory B cells was proposed to determine the time point for reintroduction of rituximab therapy.[12–16] A multinational 14-center study reported real-world data on 67 children having aquaporin 4 antibody–positive NMOSD.[17] They had a median follow-up of 4 years. Their mean age at onset was 10.2 years. Twenty-nine children received rituximab, half of them first line and one-third second line. In the entire group, the annualized relapse rate dropped from 2.5 to 0.14 on treatment. The patients on first-line rituximab treatment experienced no further relapse; 24% had further attacks. Two patients were switched to ofatumumab due to severe infusion-related reactions. One child developed persistent neutropenia.[17]

Recently, a multicenter, randomized, double-blind, placebo-controlled clinical trial has been performed in Japan, proving its capacity to prevent relapses,[18] which can be considered a breakthrough.[19] Given the small size and some other methodological limitations, a larger, randomized, controlled phase 3 trial would need to be undertaken to validate these observations.

Strategies to individualize rituximab treatment by changing intervals of redosing rely on determining CD19-positive or CD19$^+$ CD27$^+$ memory B cells or switched memory B cells (CD19$^+$/CD27$^+$/IgM$^-$/IgD$^-$) as a percentage of peripheral blood mononuclear cells.[13,20]

Inebilizumab

Inebilizumab is a glycoengineered, afucosylated anti-CD19 antibody that was specifically designed to increase affinity to FcyRIIA and thereby enhance antibody-dependent cytotoxicity.[21,22] CD19 is more broadly expressed on cells of the B-cell lineage. Late-stage memory B cells and plasmablasts carry CD19 on their surface but are CD20 negative. Hence, it was predicted that depleting CD19 carrying cells would affect pathogenic autoantibody production more markedly than targeting CD20 cells. In vitro assays examining antibody-dependent cell-mediated cytotoxicity demonstrated B-cell depletion occurring at lower antibody concentrations than with rituximab.[21,23] Studies in preclinical models and phase 1 trails in systemic sclerosis and MS provided evidence for effective CD19 B-cell depletion.[23,24]

The N-MOmentum trial was the largest ever conducted in NMOSD. This international multicenter double-blind, randomized placebo-controlled phase 2/3 study with an open-label extension period investigated the safety and efficacy of this CD19-depleting monoclonal antibody in aquaporin 4 IgG-positive and -negative patients with NMOSD. Of 231 patients,

Table Trials of CD20–and CD19-depleting monoclonal antibodies for NMOSD

Trial	Rituximab (CD20 cell depletion)	Inebilizumab (CD19 cell depletion)
Phase 2/3	RIN-1 study (UMIN000013453)[18] vs placebo n = 38 participants, AQP4 IgG positive No participant on rituximab vs 37% of participants in the placebo group developed an attack Group difference 36.8%, 95% CI 12.3–65.5; log-rank p = 0.0058	N-Momentum (NCT02200770)[25] vs placebo n = 230 participants, AQP4 IgG positive and negative 12% of participants receiving inebilizumab vs 39% of participants allocated to placebo developed an adjudicated attack Hazard ratio 0.272, 95% CI 0.150–0.496; p < 0.0001

Abbreviations: IgG = immunoglobulin G; NMOSD = neuromyelitis optica spectrum disease.

175 were randomized to inebilizumab and 56 to placebo. Ninety-two percent and 93% were aquaporin 4 IgG positive. The primary outcome was time to onset of an NMOSD attack determined by an adjudication committee. Secondary end points included worsening of Expanded Disability Status Scale from baseline, low-contrast visual acuity, cumulative number of active MR lesions (new gadolinium-enhancing or new or enlarging T2 lesions), and number of disease-related hospitalizations. Inebilizumab markedly reduced the risk of attacks, the main cause of disability in this crippling disease[25] (table). This trial was terminated early by an independent data-monitoring committee because of a clear demonstration of efficacy. Twelve percent of the patients receiving inebilizumab vs 39% of the patients receiving placebo encountered an attack ($p < 0.0001$; hazard ratio 0–272). Significant and robust B-cell depletion occurred within 4 weeks. Expanded Disability Status Scale worsening was less with inebilizumab; no difference was observed in low-contrast visual acuity, but post hoc analysis showed a lower risk of inebilizumab-treated patients to experience optic neuritis. Cumulative active MRI lesion count was lower in inebilizumab-treated participants as were NMOSD-related hospitalizations.[25]

Adverse events occurred at similar frequency in both treatment arms. Thus, CD19 depletion is a well-validated treatment option for NMOSD.[21–23,26] Further safety studies are needed as long-term CD19 depletion may be associated with an elevated risk of opportunistic infections.[27]

Perspective

A phase 1 study of ublituximab as an add-on therapy to methylprednisolone in an acute relapse of NMOSD suggests that CD20 depletion is safe in this regime and may improve neurologic outcome.[28] Further placebo-controlled studies are to confirm these findings. Studies that emphasize the efficacy of anti–interleukin 6 receptor antibodies, e.g., sartralizumab and tocilizumab, underline the importance of interleukin 6 as a B cell–activating factor in NMOSD.[29–31]

MOGAD

MOG, myelin oligodendrocyte glycoprotein, is a minor component of CNS myelin expressed on its outer layer. Conformation-dependent antibodies have been described in a number of CNS inflammatory disease, but recent evidence suggests that MOG IgG–associated disease (MOGAD), affecting children and adults, is a distinct clinical and pathologic entity with optic neuritis, myelitis, isolated brainstem, encephalitis, encephalopathic, or acute disseminated encephalomyelitis-like presentation. It runs a monophasic or more frequently relapsing course.[1,32–38] Pathologically, inflammation, demyelination, and preservation of astrocytes have been observed. Studies on the pathogenicity of MOG IgG have been largely undertaken in rodent models where antibodies and autoreactive T cells in isolation or in concert induce injury.[4,38–40] In 60% of 21 MOG IgG–positive patients, MOG-reactive B cells could be isolated. They displayed a heterogeneous pattern of antibody production.[41] In a flow cytometric study looking at B- and T-cell populations in 19 MOG IgG–positive patients, regulatory B cells were lower and memory B cells higher in number compared with controls.[42] A range of immunosuppressive and immunomodulatory drugs have been used, among them rituximab, mostly to prevent further attacks.

In an EU Pediatric Demyelinating Disease Consortium study, 102 children received rituximab first, second, or third line. The majority continued to relapse despite effective peripheral B-cell depletion.[43] An Australian multicenter study of 33 children and 26 adult patients with relapsing MOG IgG–associated demyelination found 1 of 7 patients not responding to rituximab, although B cells were depleted. The German Neuromyelitis Optica Study Group (NEMOS) reported relapses in 6 of 9 patients receiving rituximab.[32] In a prospective French study of 16 adult patients with MOG IgG, one-third of patients relapsed in the presence of less than 0.05% memory B cells.[44] In the largest international cohort retrospectively analyzing data from 121 patients, relapse rates on rituximab declined by 37%. After 2 years, 33% were predicted to remain relapse free.[45] Effect size was largest with first-line administration and higher in adult compared with pediatric patients. In summary, rituximab has shown efficacy in up to two-thirds of patients with MOGAD, but a sizable fraction continued to have attacks with full B-cell depletion.

CD20/CD19 B-cell depletion in MS, NMOSD, and MOGAD: adverse events and safety profiles

The biggest concerns with immune cell depletion therapies are the occurrence of serious infections, opportunistic infections, and malignancies as consequences of lymphopenia and impaired lymphocyte function.[46]

Three controlled phase 2 and phase 2/3 trials and retrospective series are available for determining the safety of rituximab in MS,[46] NMOSD, and MOGAD. Overall, rituximab was well tolerated apart from infusion-related reactions, which tended to diminish in severity with repeat infusion. The largest observational study with a retrospective design comes from Sweden where rituximab has been commonly used as preferred high-efficacy disease-modifying treatment of MS. In 2016, safety results from 822 rituximab-treated patients (557 relapsing-remitting, 198 secondary progressive, and 67 primary progressive MS) were reported.[47] Again, infusion-related reactions were the most frequent adverse events occurring during 7.8% of infusions. They were usually mild. Importantly, 76 infections developed in 72 patients. A 2-center retrospective study from the United States recognized infections at a rate of 38.6/1,000 patient-years in 907 patients studied.[48] A comparative study of infection risks among patients on various disease-modifying agents again from the Swedish national MS registry cohort

associated rituximab use with the highest incidence of infections.[49] Most common were upper respiratory and lower urinary tract infections and pneumonia. In this study of 3,260 patients receiving rituximab, 2 cases of carry-over progressive multifocal leukoencephalopathy (PML) were diagnosed. In a study from Finland of 72 patients with MS, rituximab caused severe neutropenia in 2 requiring discontinuation.[50] In the US study referred to above, neutropenia of less than 500 cells/mm^3 was noted in 1.2% of patients on rituximab.[48] The same group of investigators observed low values of IgG evolving over a mean treatment period of 31.1 months and a mean cumulative dose of 4,012 mg in 6%.[48]

When the FDA Adverse Event Reporting Database was recently interrogated,[51] 623 and 7,984 reports for rituximab and ocrelizumab, respectively, were identified. Serious adverse events were more commonly reported for rituximab as were adverse events related to blood, lymphatic, and immune system. On the other hand, infections, although mild or moderate such as nasopharyngitis and upper respiratory tract infection, were twice as frequent with ocrelizumab whose safety profile was in line with published data. The authors of this report speculated about a different or more extensive depletion of B cells by ocrelizumab underlying these observations but also admitted a number of methodological limitations[51] inherent in interpreting data from such a registry.

Linking data from the Swedish national MS registry and Swedish Cancer registry, Alping et al.[52] did not find a higher incidence of invasive cancers in 4,187 first-ever treated rituximab MS patients. These data are in line with the long-term experience of over 11 years in the Rheumatoid Arthritis Global Clinical Trial Program that enrolled 3,595 patients receiving a mean of 4 courses.[53]

In essence, safety data for rituximab in NMOSD are comparable. A systematic review and meta-analysis of 46 studies published between 2000 and 2015 encompassing 438 patients found infusion-related adverse events in 10.3%, infections in 9.1%, persistent leukopenia in 4.6%, and posterior reversible encephalopathy in 0.5%.[5] A single-center prospective observational study from Milan recorded serious infections in 5 of 21 patients who had leukopenia and hypogammaglobulinemia.[10]

Regarding ocrelizumab, the safety profile has recently been systematically reviewed.[54] Data on longer-term side effects, particularly relating to reactivation of infections and induction of malignancies following completion of the pivotal trials, have been presented at conferences and in a recent report of the 5-year open-label extension pooled analysis of the twin OPERA (Study of Ocrelizumab in Comparison With Interferon Beta-1a (Rebif) in Participants With Relapsing Multiple Sclerosis) studies in relapsing MS.[55] These analyses did not identify new safety signals among the approximately 150,000 patients who had been treated with ocrelizumab worldwide (180,000 patient-years) (Roche, data on file, March 2, 2020).[56] In the pivotal clinical trials, 11 cancer cases occurred in patients with PPMS on ocrelizumab in the placebo-controlled phase. These included 4 cases of breast cancer and 3 cases of basal cell carcinoma, as well as 1 case each of endometrioid adenocarcinoma, anaplastic large cell lymphoma, malignant fibrous histiocytoma, and pancreatic carcinoma.

The open-label extension study reported 1 case of basal cell carcinoma and 1 case of squamous cell carcinoma. The placebo group included 1 basal cell carcinoma and 1 cervical adenocarcinoma in situ.[57] Among patients with relapsing MS receiving ocrelizumab, there were 2 cases of breast cancer, 1 renal cell carcinoma, and 1 malignant melanoma compared with the placebo group, which reported 1 mantle cell carcinoma and 1 squamous cell carcinoma case. The ocrelizumab open-label extension study reported 2 cases of breast cancer, 2 cases of basal cell carcinoma, and 1 case of malignant melanoma.[58] A more recent analysis of 5,051 patients who received ocrelizumab in controlled trials and open-label extensions for up to 6.5 years presented the latest available data set at the 2020 EAN Meeting. Thirty-six patients with breast cancer (benign, malignant, and nonspecified) were recorded and 4 patients with malignant melanoma. Single cases of other malignancies were observed. However, these rates were in the range of incidence data from the Danish MS Registry and the US National Cancer Institute SEER (Surveillance, Epidemiology, and End Results) general population database and hence do not signify a specific malignancy signal associated with ocrelizumab.[58]

In the phase 3 trials, patients with relapsing MS treated with ocrelizumab, compared with interferon beta-1a, exhibited a higher incidence of varicella zoster infections (17 vs 8, respectively[78]), and patients with PPMS receiving ocrelizumab, compared with placebo, had a higher prevalence of oral herpes infections (2.3% vs 0.4%, respectively).[58] Case reports highlight the relevance of hepatitis reactivation in the setting of CD20 cell depletion[59,60] and emphasize the need for and the benefits of patient risk stratification before the start of therapy.[e1]

Similarly to its precursor, the chimeric CD20 monoclonal antibody rituximab,[e2] the postauthorization use of ocrelizumab increased the risk of developing late-onset neutropenia,[e3,e4] tumefactive demyelinating lesions,[e5] and PML. As of January 31, 2020, when 150,000 patients were on ocrelizumab worldwide, 9 confirmed PML cases were reported.[54,57,58] Eight patients developed PML on ocrelizumab after switching from previous disease-modifying therapies, while to date, only 1 case of non–carry-over PML has been reported in an elderly patient who had low T lymphocyte counts before starting ocrelizumab. He finally passed away.[e6] Isolated case reports of herpes simplex type 2 encephalitis,[e7] B19 parvovirus infection,[e8] and 2 cases of meningitis[e9] have been published in patients treated with ocrelizumab.[e9] Ocrelizumab therapy is unlikely to be associated with an elevated risk of tuberculosis infection.[e10] Secondary immunoglobulin deficiency can precipitate serious infections.[e11] A review investigating potential associations of B-cell depletion treatment with rituximab and the risk of developing hypogammaglobulinemia or infection failed to identify any significant risk factors.[e12] Ongoing data analyses examine the incidence

over time of hypogammaglobulinemia in patients treated with ocrelizumab. Over the 5 years of the double-blind pooled OPERA trials in relapsing MS and their open-label extension up to 5 years, IgG levels were lowered below lower limit of normal in 5.4%, IgA in 5.1%, and IgM in 29.5% of patients.[55] A drug reaction with eosinophilia and systemic symptoms after ocrelizumab therapy has also been described.[e13]

There were no specific safety concerns (i.e., spontaneous abortions or fetal malformations) in pregnant women who underwent CD20 depletion with rituximab during the first 6 months of pregnancy.[e14] A current study suggests that monoclonal antibodies may be safe in breastfeeding.[e15] Although a retrospective analysis of patients with neuroimmunologic diseases who underwent rituximab therapy over a period of 7 years[e16] and a meta-analysis of patients with rheumatoid arthritis[e17] confirm rituximab's good safety profile, the effects of long-term B-cell depletion still remain unclear.

A retrospective study demonstrated that the incidence of infusion-associated reactions was significantly reduced when histamine antagonists and oral fluid were also administered.[e18] There are very limited data available on the intrathecal administration of CD20 B cell–depleting monoclonal antibodies.[e19]

Given the aggregate evidence, it makes sense to perform regular clinical surveillance including routine blood work of patients with MS undergoing CD20 cell–depleting therapies.[e20–e22]

Implications of the COVID-19/SARS-CoV2 pandemic

There is concern that B cell–depleting agents may increase the risk of viral diseases, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV2)/coronavirus disease 2019 (COVID-19). Rituximab has in the past not been associated with an elevated risk of developing viral infections.[e23] Initially, evidence suggested there was not a more severe course of COVID-19 in ocrelizumab-treated patients with MS.[e24] This is based on a pharmacovigilance analysis conducted by Roche. As of 30 April 2020, 26 suspected and 74 confirmed cases of patients with MS on ocrelizumab contracting SARTS-CoV2 were identified. The great majority were asymptomatic, mild, or moderately affected and 64 of 64 patients fully recovered.[77]

In line with these observations are a case report of a patient with MS receiving ocrelizumab who had a mild COVID-19 infection[e25] and a case series of 60 patients under CD20 depletion from Spain.[e26] A recently published large case series from France found that rituximab- and ocrelizumab-treated patients with MS who got infected with SARS-CoV2 have a milder course of COVID-19.[e27] However, a cross-sectional survey in Iran revealed that B-cell depletion may increase the susceptibility to contracting COVID-19.[e28] A recent large scale study of some 200 people with MS and confirmed COVID-19 infection from Italy noted a higher infection frequency among patients on anti-CD20 monoclonal antibody therapy and a more severe course.[e29] Of interest, a patient with MS on fingolimod who developed a severe COVID-19 infection benefitted from short-term interleukin 6 receptor blockage with tocilizumab.[e30] Practitioners may consider a temporary delay of lymphocyte-depleting therapies in patients with MS.[e31] Clearly, management of inflammatory demyelinating CNS diseases with immunomodulatory and immunosuppressive treatments needs to take into account the potential impact of COVID-19, and it will be important to explore responsiveness to SARS-CoV2 vaccines in these patients.[e36,e37] The implications of the current pandemic on neurologic diseases have recently been discussed.[e32,e33]

Open issues and conclusion

Regarding MS, further studies are needed to better understand the mode of action and safety profile of (long-term) CD20 depletion. Publication of the 2 completed phase 3 trials of ofatumumab in MS may provide crucial evidence as it is still unknown whether a complete B-cell depletion is necessary for a therapeutic effect. Oral Bruton's tyrosine kinase inhibitors may be a promising therapy in the future, but phase 3 studies must prove a beneficial effect on clinical parameters. Today, it remains uncertain if CD19 depletion may be an option in patients with MS not responding to CD20 depletion.[24,e34] Of interest, 1 report suggested that cladribine preferentially depletes B cells producing only a modest diminution of circulating T cells.[e35]

Regarding NMOSD, the CD19 cell–depleting antibody inebilizumab is the first B cell–directed treatment licensed. It enlarges the therapeutic arsenal for this disabling disease. Controlled trials are desirable in MOGAD. Clearly, for both conditions, development of evidence-based treatment algorithms is highly desirable.

In summary, much has been achieved in the treatment of MS, NMOSD, and MOGAD in recent years. The approval of ocrelizumab constituted another important step toward the effective treatment of patients with MS. Ofatumumab has just been licensed for the treatment of relapsing forms of MS in the United States and is expected to receive market authorization in the EU early 2021. Importantly, ocrelizumab is the first drug shown to be effective in the treatment of PPMS.

Rigorous pharmacovigilance, analysis of registry data, and the results of phase 3b and 4 trials and real-world data are indispensable. There is also a strong case for further mechanistic studies to clarify the effects of CD19 and CD20 B-cell depletion. Ublituximab and kinase inhibitors are promising new immunotherapies, which may open a path toward more individualized treatment of MS and related inflammatory demyelinating disorders of the CNS.

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Additional e-references (e1-e37) available at: links.lww.com/NXI/A347.

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