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Individualized B cell-targeting therapy for neuromyelitis optica spectrum disorder

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ABSTRACT

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disease of the central nervous system characterized by severe attacks of optic neuritis (ON), longitudinally extensive transverse myelitis (LETM), and area postrema syndrome. The majority of patients with NMOSD are seropositive for autoantibodies against the astrocyte water channel aquaporin-4 (AQP4). As convergent clinical and laboratory-based investigations have indicated that B cells play a fundamental role in NMO immunopathology, B cells have become an attractive therapeutic target. Rituximab is a therapeutic monoclonal antibody against CD20 expressed on B cells and increasingly used for the treatment of NMOSD. Although there is robust evidence for the efficacy and safety of rituximab in NMOSD, considerable variability has been noted in biological and clinical responses in patients. Therefore, the focus now is on understanding the mechanisms underlying the variability in response to rituximab and optimizing the use of rituximab for NMOSD. Identification of biomarkers for prediction of clinical response, and effective dosing and timing of treatment may provide useful tools for patient-tailored treatment in NMOSD. Herein, we review current evidence on factors that affect biological and clinical responses to rituximab and highlight the importance of individualized therapies for NMOSD.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory disease of the CNS characterized by severe attacks of optic neuritis (ON), longitudinally extensive transverse myelitis (LETM), and area postrema syndrome (Wingerchuk et al., 2015). The discovery of disease-specific anti-aquaporin-4 (AQP-4) antibodies (Lennon et al., 2004) has marked a major advance in our understanding of this disease. Convergent clinical and laboratory-based investigations have indicated that B cells play a fundamental role in the immunopathogenesis of NMOSD (Bennett et al., 2015; Mitsdoerffer et al., 2013). Multiple mechanisms underlying NMOSD immunopathogenesis have been proposed, such as anti-AQP4 antibody production, enhanced proinflammatory B cell and plasmablast activity, aberrant B cell tolerance checkpoints, diminished B cell regulatory function, and loss of B cell anergy (Bennett et al., 2015). Therefore, biological agents that target B cells are hypothesized to modulate NMOSD disease activity. Rituximab is a chimeric monoclonal anti-CD20 antibody that produces rapid depletion of circulating $CD20^+$ B cells. Previous studies have reported that rituximab is an effective and well-tolerated therapy for NMOSD (Annovazzi et al., 2016; Bedi et al., 2011; Cabre et al., 2018; Cohen et al., 2017; Collongues et al., 2016; Cree et al., 2005; Damato et al., 2016; Evangelopoulos et al., 2017; Greenberg et al., 2012; Ip et al., 2013; Jacob et al., 2008; Kim et al., 2011, 2013, 2015b; Lin et al., 2018; Mealy et al., 2014; Nikoo et al., 2017; Pellkofer et al., 2011; Radaelli et al., 2016; Xu et al., 2014; Yang et al., 2013). However, biomarkers to stratify patients into those most likely to respond to rituximab versus other treatment options are lacking. Moreover, it remains unclear how to determine the optimal dose and frequency of rituximab required for the best response in individual patients. Herein, we review current evidence on factors that affect biological and clinical responses to rituximab and highlight the importance of individualized therapies for NMOSD based on currently available knowledge and the authors' experience.

2. Clinical response to rituximab

Since Cree et al. (2005) first reported the efficacy of rituximab in preventing relapse in eight patients with NMOSD in 2005, many studies employing treatment with rituximab in NMOSD have reported clinical efficacy and safety (Table 1). Twelve studies including at least 20 patients reported a relapse-free rate of 47–85% and disability stabilization

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Table 1
Protocols and outcomes of rituximab treatment in neuromyelitis optica spectrum disorder.

Ref.	No. of patients	Induction protocol	Maintenance protocol	Treatment duration (months)	% Anti AQP4 Ab seropositive	ARR before rituximab	ARR after rituximab	Patients relapse free (%)	Patients stabilized disability after rituximab (%)
Cree et al. (2005)	8	375/m^2, weekly, 4weeks	1000 mg twice, twice, 2 wks apart, when B cells became detectable.	mean 12	NA	median 2.6	median 0	75	88
Jacob et al. (2008)	25	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart, every 6–12 months or after relapse or when B cells became detectable	mean 19	70	median 1.7	median 0	52	80
Kim et al. (2011)	30	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	Whenever memory B cells ≥ 0.05% of PBMCs	mean 24	70	mean 2.4	mean 0.3	70	97
Kim et al. (2013)	30	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	Whenever memory B cells ≥ 0.05% of PBMCs during initial 2 years, and ≥0.1% of PBMCs thereafter	median 60	70	mean 2.4	mean 0.3	60	93
Kim et al. (2015a, 2015b)	100	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	Whenever memory B cells ≥ 0.05% of PBMCs during initial 2 years, and ≥0.1% of PBMCs thereafter	median 67	94	mean 2.4	mean 0.1	70	96
Pellkofer et al. (2011)	10	1000 mg, 2wks apart	1000 mg, 2wks apart, every 6–9 months	mean 27	100	median 1.3	median 0.3	40	60
Bedi et al. (2011)	23	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	375/m^2, weekly, 4 wks, every 12 months or 1000 mg, 2wks apart, every 6 months	median 33	72	median 1.9	median 0	74	100
Lindsey et al. (2012)	10	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	Retreatment at the discretion of the treating physician	median 17	60	median 2.0	median 2.0	30	60
Ip et al. (2013)	7	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart, every 6–9 months	mean 24	67	NA	NA	71	100
Yang et al. (2013)	5	100 mg, weekly, 3 wks	100 mg, 3 wks whenever B cells ≥ 1% of PBMCs	mean 12	80	mean 1.0	mean 0	100	100
Zephir et al. (2015)	32	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	375/m^2, 4 wks, 1000 mg, 2wks apart or 1000 mg once,	mean 29	88	mean 2.7	mean 0.1	84	NA
Mealy et al. (2014)	30	1000 mg, 2wks apart	1000 mg, 2wks apart, whenever B cells ≥ 0.1% of lymphocytes or every 6 months	median 20	90	mean 2.9	mean 0.3	67	NA
Torres et al. (2015)	32	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	375/m^2, weekly, 4 wks, or 1000 mg, 2 wks apart, every 6 months or after relapse or whenever B cells > 2%	mean 22	72	median 1.2	median 0.3	47	NA
Collongues et al. (2016)	21	Induction protocol was determined according to the habits of the treating physician.	Retreatment at the discretion of the treating physician (at least 6 months interval)	mean 31	91	mean 1.3	mean 0.4	52	81
Annovazzi et al. (2016)	73	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart, every 6 or after relapse or when B cells became detectable	median 27	NA	mean 2.3	mean 0.6	52	85
Radaelli et al. (2016)	21	375/m^2, weekly, 4 wks or 1000 mg, 2wks apart	1000 mg once, every 6–12 months or when B cells became detectable	mean 48	81	mean 2.1	mean 0.2	57	90
Evangelopoulos et al. (2017)	5	375/m^2, weekly, 4 wks	375/m^2, weekly, 4 wks every 2 months for the first two years/every 6–9 months for the following 4 years	median 72	100	NA	NA	100	100
Nikoo et al. (2017)	33	1000 mg, 2wks apart	Every 6 months	median 12	39	Mean 1.3	Mean 0.21	79	NA
Cabre et al. (2018)	32	375/m^2, weekly, 4 wks	1000 mg, 2 wks apart, whenever B cells ≥ 1% of PBMCs	24	63	Mean 1.34	Mean 0.56	53	72

No: Number; wks: weeks; AQP4: Aquaporin-4; ARR: Annualized relapse rate; NA: not available.

of 72–100% during median 1–5.6 years of rituximab treatment (Annovazzi et al., 2016; Bedi et al., 2011; Cabre et al., 2018; Chen et al., 2017; Cohen et al., 2017; Collongues et al., 2016; Jacob et al., 2008; Kim et al., 2015b; Mealy et al., 2014; Nikoo et al., 2017; Radaelli et al., 2016; Torres et al., 2015; Zephir et al., 2015). Owing to lack of definition of poor response to rituximab, heterogenous rituximab retreatment indication (preplanned 6–12 months interval, when repopulation of CD19 cells > 1–2% of peripheral blood mononuclear cells [PBMCs] or after relapse), and dosing (1000 mg once or 1000 mg twice with a 2-week interval), it is difficult to draw conclusions regarding the response rate in NMOSD. In addition, 9–32% of patients in four of the studies did not receive any retreatment after induction treatment (Annovazzi et al., 2016; Jacob et al., 2008; Radaelli et al., 2016; Zephir et al., 2015); therefore, the possibility of insufficient treatment cannot be ruled out in these patients.

Early relapses after rituximab induction but before therapeutic depletion of B cells have been reported. Perumal et al. reported that six of 17 (43%) patients experienced a relapse within 1 week of their first rituximab infusion (Perumal et al., 2015). As the six patients experienced a relapse within 3 months of initiation of rituximab, the occurrence of relapse in the immediate post-rituximab period could be owing to ongoing disease activity before achieving depletion of B cells (Perumal et al., 2015). Autoantibody-producing plasma cells that do not express CD20 are not affected by rituximab treatment. In addition, the possibility of rebound disease activity after rituximab due to increased levels of proinflammatory cytokines such as IL-6 and B-cell activating factor (BAFF) has been suggested (Jones et al., 2014; Nakashima et al., 2011). In our previous study in 30 patients with NMOSD, five patients relapsed during early treatment stages, but their disease activity was well controlled by subsequent adequate retreatment (Kim et al., 2011). Therefore, it is premature to judge treatment failure merely by early relapse, although how we predict and prevent early relapse remains an open question.

Regarding predictors of response to rituximab in NMOSD, recent studies on the efficacy of rituximab have reported that it is not related to anti-aquaporin-4 (AQP4) antibody seropositivity (Cabre et al., 2018; Collongues et al., 2016; Kim et al., 2015b; Mealy et al., 2017). However, among patients that are anti-AQP4 antibody negative, some patients with anti-myelin oligodendrocyte glycoprotein (MOG) antibodies may show an insufficient response to rituximab. No predictive impact was found for age at onset, sex, time to rituximab, number and type of treatments used before rituximab, Expanded Disability Status Scale (EDSS) score and annualized relapse rate (ARR) before rituximab, or the presence of severe attacks before rituximab (Annovazzi et al., 2016; Collongues et al., 2016; Kim et al., 2015b, 2017). Collongues et al. have suggested that high body mass index (BMI) was associated with increased risk of disability worsening after rituximab, as BMI could drive a dose-effect response linked to the volume of rituximab dilution (Collongues et al., 2016). Greenberg and colleagues reported that low doses of rituximab induced depletion of B cells, but there was also a high rate of early B cell repopulation (Greenberg et al., 2012). These results suggest that low doses of rituximab require greater vigilance for early repopulation of B cells than do conventional doses. Thus, tighter monitoring and more frequent retreatment may be required to sustain depletion of B cells and clinical response when using low doses of rituximab.

3. Retreatment schedule of rituximab

The appropriate dose and number of infusions of rituximab are dependent on the clinical setting. For lymphoma, the approved dose is 375 mg/m^2 as an IV infusion for four weekly doses (Ghielmini et al., 2005). The dose being studied in adult rheumatoid arthritis (and most autoimmune diseases) is 1 g every other week for two doses (Ng et al., 2005). Although the optimal strategy for rituximab therapy has yet to be determined in NMOSD, the need for retreatment to prevent relapse has been recognized. NMO relapses can have a devastating impact on the patient owing to their severity. As such, awaiting the re-emergence of clinical symptoms before retreating carries unacceptable risks (Wingerchuk and Weinshenker, 2011). Retreatment with rituximab is more effective when it is offered before disease symptoms flare. An additional cycle of rituximab administered prior to B cell repopulation was shown to enhance B cell depletion and clinical responses. Common practice includes the repeated administration of a course (375 mg/m^2/week for 4 weeks or 1000 mg infused twice with 2 weeks between doses) every 6–12 months. However, given that the time for B-cell repopulation and disease activity shows inter-individual variability (Ellwardt et al., 2018; Kim et al., 2011; Pellkofer et al., 2011), retreatment at fixed intervals poses a risk of insufficient efficacy in some patients and overtreatment in others. Accordingly, reliable biomarkers must be identified for better stratification of repeated rituximab treatment to fit the needs of patients with NMOSD.

Anti-AQP4 antibody levels are reduced or maintained at a low level after rituximab treatment, consistent with the clinical response. However, delayed retreatment caused an increase in anti-AQP4 antibody levels (Kim et al., 2011). Most relapses were accompanied by an elevation of anti-AQP4 antibody levels during rituximab treatment but rising anti-AQP4 antibody levels were not always associated with clinical relapse (Kim et al., 2013). The threshold level of anti-AQP4 antibody that triggers clinical relapse differs widely within and between individuals (Bennett et al., 2015). Thus, the utility of monitoring anti-AQP4 antibody levels to predict relapse is limited (Valentino et al., 2017).

Previous studies in NMOSD have reported that persistent depletion of B cells was associated with clinical remission. CD19$^+$ B cells in peripheral blood have been monitored in an attempt to guide treatment decisions based on different threshold values to determine the timing of re-treatment (0.1% of lymphocytes, 1% of PBMCs, or 10 cells/μL) (Cabre et al., 2018; Jacob et al., 2008; Lindsey et al., 2012; Mealy et al., 2014; Pellkofer et al., 2011; Torres et al., 2015). However, the definition of these B cell depletions is arbitrary and not based on evidence of correlation with clinical responses. A considerable number of relapses occurred below the therapeutic target of B cell depletion. Lindsey et al. suggested that relapses with low CD19$^+$ cell count (< 10 cells/μL) indicated a disease process that was independent of circulating B cells (Lindsey et al., 2012). A study in France reported that nine (27%) of 33 relapses occurred in patients with PBMCs below 1%, which was their therapeutic target (Cabre et al., 2018). Radaelli et al. also reported that four (19%) of 21 patients experienced a concomitant CD19$^+$ B cell count < 1% (Radaelli et al., 2016). A lower limit of 1% of PBMCs has often been regarded as the depletion of B cells in studies of rituximab treatment in NMOSD. By use of standard methods such as Ficoll–Paque density gradient centrifugation for PBMC, isolation recoveries yield on average 0.5–2 × 10^3 cells/μL blood taken (Ulmer and Flad, 1979). Thus, a lower limit of 1% of PBMCs is calculated to be approximately 5–20 cells/μL. In 2011, we first suggested retreatment with rituximab with depletion of memory B cells as a therapeutic target (< 0.05% of PBMCs during the initial 2 years, < 0.1% of PBMCs thereafter) over 2 years in 30 patients with NMOSD (Kim et al., 2011) and then reported the outcome of 5 years rituximab treatment in succession (Kim et al., 2013). In our previous study of the initial 2 years, CD19$^+$ B cell counts at relapse were 2.8 cells/μL (Kim and Kim, 2012; Kim et al., 2011). In the extension study of 5 years (Kim et al., 2013), we observed that 12 (60%) and 13 (65%) of 20 relapses occurred in patients with CD19$^+$ B cell counts less than 10 cells/μL or less than 0.5% of PBMCs, which were considered as a state of B cell depletion in previous studies. Thus, the threshold for defining B cells less than 1% of PBMCs or 10 cells/μL may not be sensitive enough to prevent relapse in patients with NMOSD. In rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), more stringent definitions of B cell depletion using highly sensitive flow cytometry with a threshold set at < 1 cell/μL have been suggested based on correlations between the threshold and clinical response (Dass

et al., 2008; Vancsa et al., 2013; Vital et al., 2011).

Memory B cells provide enhanced antibody production when re-stimulated and are characterized by isotype switching and affinity maturation (Tangye and Good, 2007). Depletion of memory B cells can indirectly affect the production of anti–AQP4 antibodies by short-lived plasma cells. In addition, memory B cells play important roles in autoimmunity through cytokine production and antigen presentation to T cells. IL-6 secretion by proinflammatory memory B cells in NMOSD may aggravate disease activity by promoting pathogenic Th17 differentiation (Bennett et al., 2015). Moreover, cooperation between AQP4-specific B cells and AQP4-specific T cells may be particularly important in antibody-secreting cell differentiation and the production of anti-AQP4 antibodies. Therefore, we retreated with rituximab targeting depletion of $CD27^+$ memory B cells (Kim et al., 2011, 2013, 2015b). After induction therapy, a single infusion of rituximab (375 mg/m^2) as maintenance therapy was administered whenever the frequency of reemerging $CD27^+$ memory B cells in PBMCS exceeded 0.05% in the first 2 years and 0.1% thereafter. Although our threshold for depletion of memory B cells was also arbitrary based on our clinical experience, the results of our previous studies suggested the relevance of this value as a quantitative threshold to determine retreatment. The depletion of memory B cells in peripheral blood was associated with a clinical response to rituximab (Kim et al., 2011, 2013, 2015b). Despite rituximab treatment, an insufficient depletion or unexpected rapid repopulation of memory B cells was associated with occurrence of relapse (Kim et al., 2011).

In our recent report of 100 patients (Kim et al., 2015b), relapse-free condition was observed in 70% of patients, and disability improved or stabilized in 96% of patients over median 67 months in which clinical outcomes of rituximab treatment appeared to be superior to that seen previously in other studies (e.g., retreatment with rituximab every 6–9 months or whenever $CD19^+$ B cells > 1% of PBMCs) (Annovazzi et al., 2016; Cabre et al., 2018; Collongues et al., 2016; Jacob et al., 2008; Radaelli et al., 2016; Torres et al., 2015). A recent study in France that monitored memory B cells reported that all 17 patients had disability stabilization over mean 38 months (Lebrun et al., 2018). These results suggest that when the timing of rituximab retreatment is tailored to the individual patient with more appropriate therapeutic targets, the real proportion of poor responders to rituximab may be smaller than that reported in previous studies (Capobianco et al., 2007; Lindsey et al., 2012). Our results are in accordance with reports of RA, wherein, it was demonstrated that reconstitution with higher memory B cells correlates with earlier relapse of disease (Dass et al., 2008; Sellam et al., 2011).

Reconstitution of $CD19^+$ B cells is not necessarily proportional to $CD27^+$ memory B cells, and the reemergence of $CD27^+$ memory B cells above the therapeutic target occurs even in $CD19^+$ B cells at less than 0.1% of PBMCs (Kim et al., 2013). It should be noted that even if $CD19^+$ B cells were depleted to < 1% of PBMCs, reconstitution of memory B cells above our threshold may lead to an incomplete clinical response (Kim et al., 2013). Over mean 67 months of treatment, a median of seven single reinfusions (375 mg/m^2) after induction were administered; the mean interval was 23 weeks (range, 8–56 weeks) during the initial 2-year study, and 37 weeks (range, 15–81 weeks) thereafter. The cumulative dose in our group was much lower than that achieved with the conventional practice of one or two reinfusions (1000 mg) of rituximab every 6–9 months. Our findings suggest that tighter control of disease activity by sustaining a predefined therapeutic target before disease activity flares up can enable control of disease activity with a lower dose (Kim et al., 2013). Recently, Cohen et al. compared the two rituximab maintenance regimens (1000 mg every 6 months or 1000 mg whenever memory B cells reached > 0.05% of PBMCs) directly over 1 year in 40 patients with NMOSD. They concluded that memory B cell-based administration of rituximab allowed personalized treatment administration with lower cumulative doses without loss of efficacy when compared to retreatment with a 6-month interval (Cohen et al., 2017).

4. Optimal dosing regimen of rituximab

Two induction treatment protocols have been used: 375 mg/m^2 IV per week for 4 weeks or 1000 mg IV twice, 2 weeks apart. Although a recent study in Italy reported that high dose pulses (1000 mg IV twice, 2 weeks apart) may be more effective than a more fractioned dose (375 mg/m^2 IV per week for 4 weeks) for NMOSD, the results must be interpreted with caution as the subsequent retreatment schedules were not controlled between the two induction protocols (Annovazzi et al., 2016). Previously, we reported no difference in efficacy between the two induction regimens once retreatment was properly performed based on pre-planned B cell monitoring (Kim et al., 2011). The optimal retreatment dosage for rituximab in NMOSD has also not been determined. Lower dosing of rituximab appeared to be associated with early repopulation of B cells (Greenberg et al., 2012). Cohen and colleagues used the same treatment regimen (whenever memory B cells were > 0.05% of PBMCs) that we used in the previous study. However, there was a slightly longer retreatment interval (mean 7 months over 1 year) in Cohen's study than in our study (mean 23 weeks during the initial 2 years), which may be associated with the higher dosing of the retreatment protocol in Cohen's study than in our protocol (1000 mg single infusion vs. 375 mg/m^2 single infusion) (Cohen et al., 2017; Kim et al., 2015b). Recent studies in China suggested the possibility of low-dose rituximab therapy. Yang et al. first reported the efficacy of low-dose rituximab (100 mg infusion for 3 consecutive weeks when $CD19^+$ B cells exceeded 1%) in five patients with NMOSD (Yang et al., 2013); however, the reliability of the study outcome is questionable due to the small number of patients, irregular B cell monitoring, and unclear frequency of reinfusion (Kim and Kim, 2014). Li et al. also reported the 1-year outcome of low dose-rituximab therapy (100 mg infusion for 3 consecutive weeks when the $CD19^+$ B cells exceeded 1%) in 19 patients with NMOSD, but only 78.9% of patients showed significant reduction of relapse rate (Li et al., 2018) which was a lower response rate compared to that observed in our study, wherein 94% of our 100 patients showed a marked reduction in the relapse rate over median 5 years (Kim et al., 2015b). It is not clear whether this lower response rate in their study is due to low dose or threshold for determining retreatment (< 1% of PBMCs). Ellwardt et al. recently reported that a larger body surface area (BSA) is associated with faster repopulation of B cells, even when treatment is adapted to the BSA (Ellwardt et al., 2018). Taken together, these results suggest that patients with high disease activity and/or high BSA may be more likely to fail in low-dose therapy associated with rapid reconstitution of B cells after rituximab. Further studies are required to individualize the dose of administration to maximize efficacy while minimizing overtreatment and cost in NMOSD.

5. Long-term maintenance strategy

Rituximab is expensive, and the long-term safety of repeated rituximab treatment is unclear. Thus, any effective treatment strategy that minimizes unnecessary exposure to the drug and allows significant cost savings and safety would be beneficial. Regarding long-term maintenance strategy, we postulated that after disease activity has stabilized, less frequent re-treatment relative to that during the early stage of treatment may be sufficient to prevent a relapse in NMOSD. Based on our hypothesis, we extended the monitoring interval (from every 6–8 weeks during the initial 2 years to every 10 weeks thereafter) and increased the therapeutic threshold of $CD27^+$ memory B cells (from < 0.05% of PBMCs during initial 2 years to < 0.1% of PBMCs thereafter) after completion of the initial 2-year treatment. Control of disease activity was maintained in most patients with longer re-treatment intervals after 2 years (Kim et al., 2013).

Recently, we investigated the immunological phenotypes of repopulated peripheral blood B cells over multiple courses of rituximab in 47 patients with NMOSD for at least 7 years (Kim et al., 2018). After repeated cycles of rituximab, there was an additive effect of repeated

treatments targeting memory B cells, with delays in reconstitution of memory B cells in the peripheral blood despite unchanged cutoff for the therapeutic target after the initial 2 years of treatment. Thus, 7-month intervals at 3 years of treatment extended to 9-month intervals after 6 years of treatment. Despite significant repopulation of $CD19^+$ B cells (consisting predominantly of $CD27^-$ naïve B cells) which increased up to a median 4.6% of PBMCs following 7 years of treatment, sustained depletion of memory B cells (targeting < 0.1% of PBMCs) enabled to maintain clinical response during a median 9.2 years of rituximab treatment; indeed, 62% of patients became relapse-free and disability improved or stabilized in 98% of patients (Kim et al., 2018). These results suggest that the degree of $CD27^+$ memory B cell depletion as opposed to $CD19^+$ B cells is a more robust biomarker of rituximab response, and that the outcome of rituximab therapy depends on the balance between protective and pathogenic B cell populations rather than depletion of total absolute number of B cells. Given these results, conventional retreatment strategy (every 6–9 months or whenever < 1% of PBMCs) may lead to unnecessarily frequent retreatment following 5 years of rituximab treatment.

6. Variability in depletion and clinical response to rituximab

In NMOSD, the clinical response to rituximab was shown to depend on the degree of B cell depletion, regardless of the dose of rituximab used. Therefore, until sufficient treatment with rituximab with complete B cell depletion is ensured and a solid rationale for switching is provided, we should be cautious when drawing conclusions about treatment failure and switching to another treatment. When patients have a relapse on rituximab treatment, clinicians should check the depletion status of B cells in the peripheral blood. Relapses occurring with ineffective depletion of B cells may be related to insufficient treatment (insufficient frequency or dose). In this case, more frequent administration of rituximab targeting depletion of memory B cells may induce better clinical response. However, ongoing relapses associated with insufficient depletion of B cells despite frequent administration of rituximab can be considered as rituximab resistance. The degree and durability of B cell depletion by rituximab treatment is variable (Cohen et al., 2017; Kim et al., 2011, 2013). The reason for which rituximab appears to show such variation in its ability to deplete peripheral B cells is not completely understood. Rituximab-coated B cells are eliminated by antibody-dependent cell cytotoxicity (ADCC) by natural killer cells, complement-dependent cytotoxicity, and apoptosis. In particular, the prevailing mechanism of B cell depletion is believed to be ADCC, mediated by effector cells that engage the fragment c portion of rituximab via the fragment c gamma receptor (FCGR), which is present on natural killer cells (Cornec et al., 2012). A valine (V)/phenylalanine (F) substitution at position 158 of *FCGR3A* is the polymorphism that affects the affinity of receptors in human IgG binding and the 158F allele has a lower affinity for human IgG (Bruhns et al., 2009). Polymorphisms of *FCGR3A* are associated with poor response to rituximab therapy in hematologic disease (Cartron et al., 2002; Weng and Levy, 2003). Recently, we suggested that the *FCGR3A-F* genotype was associated with a risk of relapse while receiving rituximab treatment and insufficient memory B cell depletion in NMOSD (Kim et al., 2015b). However, we demonstrated that the influence of this genetic variation on rituximab response may be overcome by individualized treatment strategies in NMOSD, which involves more frequent retreatment (Kim et al., 2015b). Development of human antichimeric antibodies (HACA) has been suggested as one mechanism of rituximab resistance in other autoimmune diseases, particularly SLE (Looney et al., 2004; Merrill et al., 2010). HACA production may induce less effective B cell depletion and a rapid drop in rituximab levels. However, in RA, HACA does not seem to affect the efficacy of rituximab in B cell depletion and clinical efficacy (Mok, 2013). A recent study on multiple sclerosis (MS) reported that a high degree of HACA was associated with efficacy of B cell depletion, but the clinical relevance of HACA remains uncertain (Dunn et al., 2017). Li et al. reported that HACA-rituximab antibodies were observed in 7/19 (36.9%) NMOSD patients and the presence of HACA was associated with short-lived B cell depletion and the requirement for increased frequency of rituximab reinfusion to maintain treatment response (Li et al., 2018). However, direct functional effects of HACA-rituximab antibodies on B cell depletion were not observed in another study with 17 NMOSD patients (Lebrun et al., 2018). Further studies are required to determine the true effect of HACA on rituximab response in NMOSD.

Another important question is why some relapses occurred following depletion of memory B cells. An inadequate clinical response despite effective depletion represents 'treatment failure'. In our study, although most relapses were associated with the repopulation of memory B cells, some relapses occurred below the therapeutic target (Kim et al., 2015b). The reason for this finding is unclear. Although the CD27 marker has been used to represent human memory B cells, recently appearing memory B cells can be further fractionated based on the expression of IgD, IgM, and CD27 as $IgM^+IgD^+CD27^+$ memory B cells, IgM^-only memory B cells, IgD^- only memory B cells, $IgM^-IgD^-CD27^+$ memory B cells (class-switched $CD27^+$ memory B cells), and $IgM^-IgD^-CD27^-$ memory B cells (class-switched $CD27^-$ memory B cells) (Klein et al., 1998). Thus, targeting more refined biomarkers may improve treatment efficacy. Autoreactive long-lived plasma cells resistant to rituximab can maintain autoimmunity and inflammatory processes (Hiepe et al., 2011).

There is only limited evidence regarding therapeutic options for patients in whom rituximab has failed, namely, a small case series with tocilizumab (IL-6 receptor antibody) (Ringelstein et al., 2015; Ayzenberg et al., 2013) and two open-label pilot studies of eculizumab (Pittock et al., 2013) and bortezomib add on therapy (Zhang et al., 2017). In our previous study (Kim et al., 2011), there was one patient with rituximab treatment failure with ongoing relapses and insufficient depletion of memory B cells despite frequent retreatment with rituximab. We switched from rituximab to mitoxantrone (monthly 12 mg/m^2 up to a maximum cumulative dose of 72 mg/m^2) followed by mycophenolate mofetil in this rituximab-refractory patient. With regard to preventive treatment of NMOSD, randomized clinical trials using monoclonal immunoglobulin G antibody targeting CD19 (Inebilizumab), interleukin-6 (Satralizumab), and complement protein C5 (Eculizumab) are underway. Effective therapeutic protocols for patients resistant to rituximab are still required.

7. Safety concerns

For chronic diseases such as NMOSD, the long duration of immunosuppressive treatment may expose patients to higher risk of adverse events such as opportunistic infections. The tolerability of rituximab is well established in other autoimmune diseases, especially RA. The most frequent adverse events are infusion reactions. Infusion reactions become less common during subsequent infusions. They are usually mild to moderate, but may require therapeutic intervention (additional paracetamol, antihistamines, or glucocorticoids). In RA, a pooled analysis of the long-term safety of rituximab in global clinical trials recently reported that among 3595 patients who had received up to 20 rituximab courses over 11 years, the rate of serious infections (3.76/100 patient-years) remained static over time and multiple courses of administration (van Vollenhoven et al., 2015). Even after development of low immunoglobulin levels, serious opportunistic infections remained rare (van Vollenhoven et al., 2015). In our cohort, after 7 years of rituximab treatment, 49%, 32%, and 23% of patients exhibited low IgM, IgG, and IgA levels, respectively; but no serious infections leading to discontinuation were observed (Kim et al., 2018). However, low baseline IgG level was a risk factor for severe infections after rituximab treatment (van Vollenhoven et al., 2013); thus, monitoring of the immunoglobulin levels at baseline and longitudinally before each rituximab cycle is recommended. No cases of progressive multifocal leukoencephalopathy in rituximab-treated NMOSD patients

have been reported to date. Previously, we investigated the change in anti-John Cunningham virus (JCV) antibody serostatus following rituximab treatment in 78 Korean patients with NMOSD (Kim et al., 2015a). Over 4 years of rituximab treatment, none of the initially seronegative patients converted to seropositive, whereas 11% of 54 initially seropositive patients converted to seronegative. Previous studies reported fatal outcomes in several rituximab-treated patients with NMOSD, but deaths among patients with NMOSD receiving rituximab have mostly been associated with the disease itself (severe relapse involving the medulla oblongata) rather than rituximab-related opportunistic infection (Annovazzi et al., 2016; Zephir et al., 2015). Especially, the deaths mainly occurred in patients with preexisting severe disability (Annovazzi et al., 2016; Zephir et al., 2015). Furthermore, serious infection associated with leukopenia in rituximab-treated patients could result from the effects of immunosuppressive therapy prior to rituximab: leukopenia was detected before the initiation of rituximab therapy (Radaelli et al., 2016). Thus, long-term treatment with rituximab is well-tolerated for NMOSD. Further larger prospective studies are required to identify potential adverse effects of long-term rituximab treatment.

8. New monoclonal antibodies targeting B cells

The new generations of anti-CD20 antibodies and anti-CD19 antibodies have gained great interest as potential alternatives to rituximab for B cell depleting therapy in NMOSD. Two monoclonal antibodies directed against a CD20 antigen, ocrelizumab and ofatumumab, vary in the extent of humanization and have different ADCCs and complement-dependent cytotoxicities (CDCs). Ocrelizumab is now approved for relapsing and primary progressive forms of MS and ofatumumab has shown efficacy in the treatment of hematological malignancy and rheumatoid arthritis. However, there is no published evidence regarding the treatment of NMOSD with ocrelizumab and ofatumumab. Inebilizumab (MEDI-551) is an anti-CD19 monoclonal antibody that is designed to deplete all B-lineage cells including pro-B cells, plasmablasts, and some plasma cells. In a recently published small phase I MS study, treatment with inebilizumab resulted in prolonged B cell depletion and had benefits in reducing lesions on magnetic resonance imaging (Agius et al., 2017); this drug is currently in the late phase of randomized clinical trials for treatment of NMOSD. It remains to be determined whether these next-generation antibodies will have greater clinical activity than rituximab.

9. Conclusion

Treatment with rituximab for NMOSD requires an individualized regimen. Optimization of the frequency and dosage of administration will help to maximize efficacy while minimizing overtreatment, cost, and serious adverse events. A better understanding of the mechanisms underpinning interindividual variability in response to rituximab is important to optimize the use of this therapy and improve treatment outcomes. Heterogeneity of patient characteristics such as Fc receptor polymorphisms, disease characteristics, and development of immunogenicity to rituximab may independently have an impact on interindividual responses to rituximab. Identification of biomarkers that are associated with rituximab response and that allow for better stratification with regard to response to B cell depletion would be ideal. $CD27^+$ memory B cells may be useful as biomarkers for planning repeated courses of rituximab. Further research is needed to confirm the threshold or find other biomarkers and optimal dosage for more efficient rituximab treatment.

Conflicts of interest

Kim SH has received a grant from the National Research Foundation of Korea. Hyun JW reports no disclosure. Kim HJ has lectured, consulted, and received honoraria from Bayer Schering Pharma, Biogen, Celltrion, Eisai, Genzyme, HanAll BioPharma, MedImmune, Merck Serono, Novartis, Teva-Handok and UCB; received a grant from the Ministry of Science & ICT; accepted research funding from Genzyme, Kael-Gemvax, Merck Serono, Teva-Handok and UCB; serves on a steering committee for MedImmune; is a coeditor for the Multiple Sclerosis Journal—Experimental, Translational and Clinical, and an associate editor for the Journal of Clinical Neurology.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2018.11.022.

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