Neurol Ther (2023) 12:1375–1383
https://doi.org/10.1007/s40120-023-00481-w

BRIEF REPORT

Tailoring Rituximab According to CD27-Positive B-Cell versus CD19-Positive B-Cell Monitoring in Neuromyelitis Optica Spectrum Disorder and MOG-Associated Disease: Results from a Single-Center Study

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Received: May 2, 2022 / Accepted: April 12, 2023 / Published online: May 11, 2023

ABSTRACT

Introduction: B-cell-depleting agents have been widely used for neuromyelitis optica spectrum disorder (NMOSD) and MOG-associated diseases (MOGAD), but no consensus exists on the optimal dose and frequency of treatment administration. The aim of our study was to evaluate the effect of a Rituximab (RTX) personalized treatment approach based on CD27-positive B-cell monitoring on efficacy, safety, and infusion rates.

Methods: This is a retrospective, uncontrolled, single-center study including patients with NMOSD and MOGAD treated with RTX at a tertiary multiple sclerosis center at the San Luigi University Hospital, Orbassano, Italy. All the patients were treated with RTX induction, followed by maintenance infusion at the dosage of 1000 mg according to cell repopulation: initially according to total CD19-positive B-cell monitoring (> 0.1% of lymphocytes), and subsequently according to CD27-positive B-cell repopulation (> 0.05% of lymphocytes for the first 2 years, and subsequently > 0.1%). NMOSD and MOGAD activity was assessed as clinical or MRI activity. All patients were screened of the occurrence of severe adverse events (AEs).

Results: A total of 19 patients were included in the analysis. Median follow-up was 7.64 years (range 3.09–16.25). The annualized relapse rate

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(ARR) 1 year before RTX start was 2.37 [Standard deviation (SD), 1.34] and decreased to 0.08 (SD 0.11) in the subsequent years after RTX initiation. ARR did not differ before and after start of CD27 monitoring. Median inter-dose time was 8.80 (range 5.78–14.23) before CD27 monitoring and 15.93 months (range 8.56–35.37) after CD27 monitoring ($p < 0.001$). We observed no AEs.

Conclusion: Our findings suggest that in our cohort CD27-positive B-cell-based RTX reinfusion regimen was able to reduce the number of RTX reinfusions relative to CD19-positive B-cell monitoring, with comparable efficacy and safety profile. In order to achieve an even more individualized and effective treatment, the FCGR3A genetic polymorphisms could be evaluated when assessing RTX efficacy.

Keywords: Neuromyelitis optica spectrum disorder; MOG-associated diseases; Rituximab; CD27-positive B-cell

Key Summary Points
Why carry out this study?
Different treatment regimens exist for neuromyelitis optica spectrum disorder (NMOSD) and MOG-associated-antibody-diseases (MOGAD).
B-cell population monitoring is crucial for a personalized treatment approach.
CD27-positive B-cell monitoring could be more effective than B-cell monitoring.
What was learned from the study?
CD27-positive B-cell monitoring is safe and effective.
Lower infusion number could reduce treatment burden and risk of infectious events.

INTRODUCTION

NMOSD is an autoimmune inflammatory disease of the central nervous system mainly characterized by severe attacks of optic neuritis and transverse myelitis alone or in combination [1]. The majority of patients test positive for water channel aquaporin-4 autoantibodies (AQP4-IgG), and present frequently with the classic clinical phenotype [1]. A minority of patients with antibodies against myelin oligodendrocyte glycoprotein (MOG-IgG) has a distinct more variegate clinical phenotype defined as MOGAD [2]. Robust evidence exists regarding efficacy of B-cell-depleting agents, such as Rituximab (RTX), in NMOSD and, to a lesser extent, in MOGAD [3–5]. Different treatment regimens exist including, among others, fixed time-point (every 6 months) infusions or cell-monitoring-based reinfusion regimens [6]. The latter is further classified in maintenance regimens based on CD19-positive or blood CD27-positive B-cell monitoring. A treatment regimen based on blood CD27-positive B-cell dosage has been adopted in NMOSD to tailor RTX redosing with consistent results [3, 7]. Nevertheless, it remains unclear how to determine the optimal dose and frequency of RTX required for the best response in individual patients, in particular according to B-cell subtype monitoring [7].

METHODS

Study Design

This is a retrospective, uncontrolled, single-center study including patients with NMOSD and MOGAD treated with RTX from January 2008 to January 2022 at the Regional Reference Centre for Multiple Sclerosis (C.RE.S.M.), San Luigi University Hospital, Orbassano, Italy. The aims of this study are to report a single-center experience of RTX treatment in patients with

NMOSD and MOGAD, and to evaluate the effect of a personalized treatment approach based on CD27-positive B-cell monitoring on efficacy, infusion rates, and safety.

Compliance with Ethics Guidelines

This study was notified and approved by the local ethical committee (approval number 9583/2019), and patients signed written informed consent before treatment monitoring, and for collection and storage of blood samples at CRESM Biobank (approval number 18390/2019). This study was conducted in accordance with the Declaration of Helsinki.

Patients

Patients were included in the analysis if they had: (1) a diagnosis of NMOSD based on 2015 diagnostic criteria, independently of autoantibody status (e.g., AQP4-IgG, or double-negative) [1] or a diagnosis of MOGAD; and (2) if they had reached at least 1 year of follow-up after CD27 monitoring start. AQP4-IgG and MOG-IgG autoantibodies were all measured at San Luigi University Hospital laboratory. Commercial fixed cell-based immunofluorescent assay was used for AQP4-IgG (Euroimmun), while home-made live cell-based fluorescent cell-counter assay (FACS) was used to detect MOG-IgG.

Patients have been described both as a whole cohort and divided according to their different disease phenotype (NMOSD and MOGAD). Patients were all treated with RTX with two 1000-mg infusions 15 days apart every 6 months for the first year as induction doses, and subsequently with a maintenance dose of 1000 mg according to B-cell monitoring. Patients were then followed-up monthly with CD19-positive B-cell evaluation, and, starting from January 2020, with CD27-positive B-cell evaluation. Disease activity was assessed clinically and radiologically by the treating neurologist as part of standard clinical care. A relapse was defined as a new neurological disturbance that increased the Expanded Disability Status Scale (EDSS) score by at least half a point, or when the worsening of 1 point in 2 functional systems, or 2 points in 1 functional system, occurred and lasted for at least 24 h in the absence of fever or infection. If a new neurological change accompanied a corresponding new magnetic resonance imaging lesion, it was also considered to be relapse, regardless of disability change. Relapses were treated with high-dose intravenous methylprednisolone, intravenous immunoglobulin and plasma exchange, alone or in combination, depending on relapse severity and response to methylprednisolone. Patients were monitored for the whole study for the occurrence of adverse events (AE) defined according to Common Terminology Criteria for Adverse Events. B-cell subtypes were assessed using BD FACS Lyric™.

Treatment

The majority of patients were started on RTX before the availability of BD FACS Lyric™, and thus without B-cell subtype monitoring. In this period, different treatment regimens were used, mainly represented by fixed time-point maintenance infusions every 6 months. When B-cell subtype monitoring became available, patients were reinfused with a 1000-mg RTX maintenance dose when the percentage of CD19-positive B-cells exceeded 0.1% of lymphocytes. After CD27-positive B-cell monitoring implementation, patients were reinfused with 1000 mg RTX when CD27-positive B-cells exceeded the following cutoff: 0.05% of lymphocytes for the first 2 years and subsequently 0.1% [8]. Median time between infusions was then calculated.

Statistical Analysis

Normality of data was explored with the Kolmogorov–Smirnov test. Continuous variables were reported as means and standard deviation (SD) or medians and range, as appropriate. Wilcoxon signed rank tests were used to assess differences in median interval dose time before and after CD27-positive B-cell monitoring. All statistical analyses were performed using SPSS 27 (v.27; IBM).

RESULTS

A total of 31 patients were screened, of whom 13 were excluded from the analysis due to different treatment regimens ($n = 7$), incomplete data ($n = 2$), early treatment discontinuation ($n = 1$), and insufficient follow-up ($n = 2$). The patient excluded for early treatment discontinuation was diagnosed as having monophasic MOGAD. Thus, 19 patients with NMOSD and MOGAD were retained for the analysis. Baseline demographic and clinical characteristics of the study population are shown in Table 1, which describes the whole cohort (NMOSD and MOGAD patients), Table 2 describes the NMOSD patients and Table 3 the MOGAD patients. For the whole cohort, mean age was 52.74 years (SD 17.60), 84.20% were female, median EDSS at last clinical evaluation was 2.5 (range 0–7.5), and median follow-up was 7.64 years (range 3.09–16.25). A total of 8 patients were immunosuppressant-naïve and 13 received 1 or more immunosuppressants before beginning RTX therapy. During RTX treatment, one patient also received methotrexate for concomitant undifferentiated connective tissue disease. None of the other patients received concomitant immunosuppressive medications. Data describing treatment regimens before B-cell monitoring implementation are displayed in Table 4: 13/19 patients (68.4%) were already under treatment with RTX with a median interdose time of 3.23 months (0.47–24.3); the wide interval is due to a single patient who initially refused re-treatment and did not experience any relapses during the off-treatment period. The annualized relapse rate (ARR) 1 year before RTX start was 2.37 (SD 1.34) and, as expected, decreased to 0.08 (SD 0.11) in the subsequent years after RTX initiation. Table 5 displays data regarding B-cell monitoring treatment regimens: the ARR and EDSS were similar during CD19- and CD27-positive B-cell monitoring [ARR: 0.02 (SD 0.11) vs. 0.03 (SD 0.13) n.s.; EDSS: 2.5 (1–7.5), 2.5 (1–7.5), n.s.]. We observed only two relapses in two different patients in the year before and after CD27-positive B-cell monitoring: one patient had MOG-IgG antibodies, presented with retrobulbar optic neuritis, and was treated with high-dose intravenous methylprednisolone with excellent clinical response; the other patient had double-negative NMOSD and presented with a truncal relapse which was treated with high-dose intravenous methylprednisolone and plasma exchange with incomplete clinical response, for both patients, CD19- and CD27-positive B-cells were below 0.01% at the time of the relapse.

Table 1 Demographic and clinical characteristics of the whole cohort of patients

Patients, *n*	19
AQP4-IgG, *n* (%)	12 (63.16)
MOG-IgG, *n* (%)	3 (15.79)
Double-negative, *n* (%)	4 (21.05)
Age, years (SD)	52.74 (17.60)
Female, *n* (%)	16 (84.20%)
Disease duration, years (SD)	12.13 (5.84)
EDSS pre-RTX start, (range)	2.0 (0–7.5)
EDSS after RTX start (range)	2.5 (0–7.5)
ARR 1 year before RTX start (SD)	2.37 (1.34)
ARR after RTX start (SD)	0.08 (0.11)
Relapse free time, years (SD)	7.92 (4.35)
Previous treatments, *n* (range)	1 (0–4)
Previous immunosuppressive treatment history, *n* (%)	11 (57.89)
Naive	8
Azathioprine	7
Prednisone	3
Interferon beta-1a	3
Methotrexate	2
Mychophenolate mofetil	2
Cyclophosphamide	1
Mitoxantrone	1
Follow-up time from RTX start, years (range)	7.64 (3.09–16.25)

Table 2 Demographic and clinical characteristics of NMOSD patients

Patients, *n*	16
AQP4-IgG, *n* (%)	12 (63.16)
Double-negative, *n* (%)	4 (21.05)
Age, years (SD)	55.63 (16.08)
Female, *n* (%)	13 (81.30)
Disease duration, years (SD)	13.42 (5.87)
EDSS pre-RTX start, (range)	2.0 (0–7.5)
EDSS after RTX start (range)	2.5 (0–7.5)
ARR 1 year before RTX start (SD)	2.44 (1.31)
ARR after RTX start (SD)	0.07 (0.10)
Relapse free time, years (SD)	8.66 (4.22)
Previous treatments, *n* (range)	1 (0–4)
Previous immunosuppressive treatment history, *n* (%)	9 (56.25)
Naïve	7
Azathioprine	5
Prednisone	2
Interferon beta-1a	2
Methotrexate	2
Mychophenolate mofetil	2
Cyclophosphamide	1
Mitoxantrone	1
Follow-up time from RTX start, years (range)	8.21 (3.09–16.25)

Age, disease duration, relapse free time, and ARR are expressed as mean; previous treatments, EDSS, and follow-up time are expressed as median

Median time between RTX infusions before CD27-positive B-cell monitoring was 8.80 months (range 5.78–14.23) and increased to 15.93 months (range 8.56–35.37) after CD27-positive B-cell monitoring (Wilcoxon test $Z - 3.82$; $p < 0.001$). We observed no AEs during treatment.

Table 3 Demographic and clinical characteristics of MOG-IgG patients

MOG-IgG patients, *n*	3
Age, years (SD)	39.56 (22.84)
Female, *n* (%)	3 (100)
Disease duration, years (SD)	7.50 (1.98)
EDSS pre-RTX start, (range)	1.0 (0–4)
EDSS after RTX start (range)	1.0 (0–4)
ARR 1 year before RTX start (SD)	2.00 (1.73)
ARR after RTX start (SD)	0.13 (0.13)
Relapse free time, years (SD)	3.97 (3.09)
Previous treatments, *n* (range)	0 (0–1)
Previous immunosuppressive treatment history, *n* (%)	1 (33.33)
Naïve	2
Azathioprine	1
Follow-up time from RTX start, years (range)	5.17 (3.67–7.43)

Age, disease duration, relapse free time, and ARR are expressed as mean; previous treatments, EDSS, and follow-up time are expressed as median

MOG-IgG myelin oligodendrocyte glycoprotein, *EDSS* Expanded Disability Status Scale, *ARR* annualized relapse rate, *RTX* Rituximab

DISCUSSION

Treatment with RTX in NMOSD and MOGAD requires an individualized approach. No consensus exists about the administration regimen for induction and maintenance therapy, nor about the most sensitive biological marker for monitoring treatment efficacy [7]. In this work, we have evaluated the effect on efficacy, infusion rates, and safety of two reinfusion regimens based on CD19- or CD27-positive B-cell monitoring in NMOSD and MOGAD. Among different treatment induction regimens (100 mg/week for 3 weeks, 375 mg/m^2 once, 500 mg/week for 4 weeks, 375 mg/m^2 weekly for 4 weeks, and 1000 mg twice with 2 weeks apart),

Table 4 Characteristics of patient treatment regimens before CD19 B-cell monitoring implementation

Patients, *n*	13
AQP4-IgG, *n* (%)	10 (76.9)
MOG-IgG, *n* (%)	1 (7.7)
Double-negative, *n* (%)	2 (15.4)
ARR until CD19 B-cell monitoring (SD)	0.24 (0.35)
Follow-up time until CD19-B cell monitoring, years (range)	4.1 (0.9–8.5)
Interdose time until CD19 B-cell monitoring, months (range)	3.23 (0.47–24.3)

Characteristics of patients' treatment regimens before CD19 B-cell monitoring implementation
ARR is expressed as mean and SD; follow-up time and interdose time are expressed as median and range
AQP4-IgG Aquaporin-4 autoantibodies, *MOG-IgG* myelin oligodendrocyte glycoprotein, *ARR* annualized relapse rate

Table 5 Differences between CD19- and CD27-positive B-cell monitoring in the whole cohort

	CD19 monitoring	**CD 27 monitoring**	***p* value**
Follow-up time, years (range)	3.53 (1.21–5.85)	1.41 (1.21–1.62)	< 0.001
Interdose time, months (range)	8.80 (5.78–14.23)	15.93 (8.56–35.37)	< 0.001
Relapse, *n*	1	1	n.s.
ARR during B-cell monitoring (SD)	0.02 (0.11)	0.03 (0.13)	n.s.
EDSS (range)	2.5 (1–7.5)	2.5 (1–7.5)	n.s.
AEs, *n*	0	0	n.s.

Follow-up time, interdose time, and EDSS are expressed as median and range; ARR is expressed as mean and SD
ARR annualized relapse rate, *EDSS* Expanded Disability Status Scale, *AEs* severe adverse events, *n.s.* not significant

we decided to start RTX treatment with two 1000-mg infusions 2 weeks apart, since it has been shown to be more effective in achieving rapid disease control [6, 9]. This is of utmost importance, especially in NMOSD, since disability accrual is mainly due to severe relapses with incomplete recovery [1]. The clinical effectiveness of RTX in our study was confirmed by the significant drop in ARR before and after treatment start (2.37 vs. 0.08) and EDSS stabilization [7, 8].

When we applied re-treatment criteria based on B-cell monitoring (CD19-positive B-cell vs. C27-positive B-cell), we found that CD27-positive B-cell monitoring was safe and effective with less frequent RTX reinfusion than CD19-positive B-cell monitoring (median infusion interval 15.93 vs. 8.80 months, $p < 0.001$) and similar ARR and EDSS with only two relapses in the year before and after CD27-positive B-cell monitoring. This was unexpected, since CD19-positive B-cell monitoring sensitivity has been reported to be inferior compared to CD27-positive B cell monitoring [3]. However, patients of our cohort were relatively stable, while previously treated patients non-responding to RTX were already switched to other immunosuppressive drugs (such as Tocilizumab); for this reason, they were not included in the analysis, thus possibly overestimating CD19-positive B-cell monitoring sensitivity. Another issue (the evaluation of which was beyond the aim of this paper) is represented by RTX resistance mechanisms in NMOSD and MOGAD. For example, therapeutic activity of RTX could decrease depending on the persistence of long lived CD19-positive B-cell clusters not efficiently depleted by RTX [10]. Moreover, the fragment c gamma receptor 3A gene (FCGR3A) polymorphisms could result in a low-antibody affinity of natural killer cells and decreased RTX-coated B cells elimination by antibody-dependent cell cytotoxicity [3]; data about FCGR3A polymorphisms were not available in our cohort. On the other hand, our results about longer interdose times are in line with the conclusions drawn from other works [3, 6, 11], which hypothesize an immunological shift from CD27-positive B-cells to naïve B-cells that occurs with repeated cycles of RTX. This shift towards naïve B-cells in the reconstituted B-cell population is associated with sustained clinical remission, and thus requiring less

frequent re-treatments [8], despite significant reconstitution of CD19-positive B-cells [12]. This suggest that the degree of CD27-positive B-cell depletion, as opposed to CD19-positive B-cells, is a more robust biomarker of RTX response, and that the outcome of RTX therapy depends on the balance between protective and pathogenic B-cell populations, rather than depletion of total absolute number of B-cells [12]. For chronic diseases such as NMOSD, long exposure to immunosuppressant drugs may lead to an increased AE rate, especially infectious ones. During our study we detected no AEs. This is in line with the well-established RTX safety profile in NMOSD and other autoimmune diseases [7, 13]. Usually, the most commonly reported AE are infusion reactions [7, 13], which were not evaluated or included in our study. Even if it is not demonstrated by our data, it might be that a lower number of infusions and cumulative doses of RTX results in a lower induction of AEs in the long term, in particular infectious diseases, and in reducing the number of patients developing iatrogenic hypogammaglobulinemia [14].

Limitations

Our study is not without limitations. First there is the nature of the retrospective analysis and, due to the rarity of the disease, only a small number of MOGAD patients were included. Second, data about the mechanisms of RTX resistance influencing treatment response (such as FCGR3A polymorphism) were not available for our patients. Third, some patients were previously treated with different treatment regimens, due to the absence of standardized guidelines and treatment schedule, or due to specific comorbidities (e.g., one patient was previously treated for non-Hodgkin lymphoma with shorter intervals between infusions). Analyzing data regarding the period before B-cell monitoring treatment regimens, we found that the median interdose time was 3.23 months (0.47–24.3) and was close to a fixed time-point infusion every 6 months; moreover, not all patients were previously treated with RTX without a B-cell monitoring strategy (13/16 patients). In order to avoid any biases, all the patients were included in the analysis, and time between infusion was calculated only when their treatment regimen complied with the infusion regimens described in "Methods".

CONCLUSIONS

Our findings suggest that, in our cohort, the CD27-positive B-cell-based RTX reinfusion regimen was able to reduce the number of RTX reinfusions relative to CD19-positive B-cell monitoring, with comparable efficacy and safety profile. In order to achieve an even more individualized and effective treatment, the FCGR3A genetic polymorphisms could be evaluated when assessing RTX efficacy.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Conceptualization: Nicolò Bruschi, Marco Alfonso Capobianco, Simona Malucchi. Methodology: Nicolò Bruschi, Marco A. Capobianco, Paola Valentino, Simona Malucchi, Maria Malentacchi, Francesca Sperli, Arianna Sala, Marisa Pautasso. Formal analysis and investigation: Nicolò Bruschi, Paola Valentino, Serena Martire. Writing-original draft preparation: Nicolò Bruschi, Marco A. Capobianco. Writing-review and edit: Nicolò Bruschi, Paola Valentino, Serena Martire, Marco A. Capobianco. Supervision: Marco A. Capobianco, Paola Valentino, Simona Malucchi, Antonio Bertolotto.

Disclosures. Dr. Nicolò Bruschi has nothing to disclose. Dr. Maria Malentacchi received fees from Novartis and Biogen Idec for speaking in scientific meetings. Dr. Simona Malucchi received fees from Merck Serono, Biogen Idec, Novartis and Bristol Meyers for participation in advisory boards and for speaking in scientific meetings. Dr. Francesca Sperli received fees from Merck Serono, Biogen Idec, Novartis and Sanofi for participation in advisory boards and for speaking in scientific meetings. Dr. Arianna Sala has nothing to disclose. Dr. Paola Valentino received speaker honoraria from Roche, Biogen and Novartis,research support from Merck and grant support from Quanterix. Dr. Serena Martire has nothing to disclose. Dr. Antonio Bertolotto received honoraria for contribution in research, consultancy activity and activity of lectures from Almirall, Bayer, Biogen, Genzyme, Merck, Sanofi, Novartis, FISM, TEVA. Dr. Marisa Pautasso has nothing to disclose. Dr. Marco Alfonso Capobianco served on advisory board for Merck Serono, Biogen, Sanofi Genzyme, Roche, Novartis. Received honoraria from Almirall, Biogen, Novartis, Merck Serono, TEVA, Sanofi Genzyme.

Compliance with Ethics Guidelines. This study was notified and approved by the local ethical committee (approval number 9583/2019) and patients signed written informed consent before treatment monitoring and for collection and storage of blood samples at CRESM Biobank (approval number 18390/2019). This study was conducted in accordance with the Declaration of Helsinki.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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