Tailoring B cell depletion therapy in MS according to memory B cell monitoring

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Abstract

Objective

We wanted to evaluate efficacy on inflammatory parameters of rituximab (RTX)-personalized reinfusion scheme using a memory B cell-based treatment regimen.

Methods

This is a prospective, uncontrolled, open-label study including patients with MS treated with RTX in 2 Italian MS units. All patients were treated with RTX induction, followed by maintenance infusion at the dosage of 375 mg/m², according to memory B cell repopulation (0.05% of peripheral-blood mononuclear cells [PBMCs] for the first 2 years, 0.1% of PBMC for the third year). MS activity was assessed as clinical or MRI activity.

Results

One hundred two patients were included in the analysis. Mean follow-up was 2.40 years (range 0.57–7.15 years). The annualized relapse rate (ARR) was 0.67 in the year before RTX start and decreased to 0.01 in the 3 years after RTX initiation (global ARR). The proportion of patient with MS activity (i.e., relapse or MRI activity) was 63.16% in the year before RTX start and decreased to 8.7% (0–6 months), 1.3% (6–12 months), 0% (12–24 months), and 0% (24–36 months). Annualized RTX infusion rates were 1.67 (95% confidence interval [CI]: 1.43–1.94), 0.76 (95% CI: 0.58–0.98), and 0.78 (95% CI: 0.52–1.12) for the first 3 years after RTX initiation, respectively. Patients were reinfused with a mean infusion interval of 367 days (range 181–839 days).

Conclusion

The results of this study show that the memory B cell-based RTX reinfusion protocol is able to reduce the mean number of RTX reinfusions with persistent reduction of disease activity.

Classification of evidence

This study provides Class IV evidence that for patients with MS, a memory B cell-based RTX reinfusion protocol can reduce the mean number of RTX reinfusions with persistent reduction of disease activity.

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Glossary

ARIR = annualized reinfusion rate; **ARR** = annualized relapse rate; **CI** = confidence interval; **EDSS** = expanded disability status scale; **mAb** = monoclonal antibody; **OCR** = ocrelizumab; **PBMC** = peripheral blood mononuclear cell; **PP** = primary progressive; **RR** = relapsing-remitting; **RTX** = rituximab; **SE** = standard error; **SP** = secondary progressive.

The MS therapeutic field has been recently widened by the approval of ocrelizumab (OCR) treatment as the first anti-CD20-depleting monoclonal antibody (mAb).¹ Rituximab (RTX), a first-generation anti-CD20 mAb, has also been adopted as an off-label treatment in MS,^{2,3} and it is currently used as standard of care therapy in some European countries.⁴ The standard treatment regimen of anti-CD20 mAbs usually consists of an “induction” phase, followed by regular fixed maintenance reinfusions (usually every 6 months). However, despite being a more practical approach in the daily practice, the fixed doses regimen could represent an overtreatment because B cells could be still depleted before each subsequent retreatment dose, as B cell immune reconstitution after B cell depletion ranges from 27 to 125 weeks with a median of 72 weeks.⁵ In addition, no data support the fact that resurgence (and/or normalization) of CD19⁺ B cells is strictly associated with an inflammatory activity (i.e., clinical relapse or MRI activity).

Furthermore, a subgroup of B cells called memory B cells (characterized by CD19 and CD27 co-expressions) have been recently implied as a putative target of many MS-approved treatments (including CD20-depleting mAbs).⁶ Peripheral blood memory B cell dosage has been extensively adopted in neuromyelitis optica to tailor RTX redosing with consistent results.^{7–10}

Consequently, evaluating peripheral blood memory B cells resurgence to tailor RTX retreatment in MS might optimize RTX redosing, reducing the number of infusions, possibly maintaining consistent efficacy on MRI and relapse activity, and potentially reducing risks of adverse events. To test our hypothesis, we conducted a pilot study in 2 MS centers in Italy to assess efficacy on inflammatory parameters (i.e., MRI activity and clinical relapses) of memory B cells–tailored RTX redosing in patients with MS.

Methods

We designed a proof-of-concept, uncontrolled, single-arm, open-label, prospective study where we enrolled patients with MS who were referred to our clinic and were treated, with an off-label indication, with RTX, since 2012. Database was locked in November 2019.

The primary research question was to evaluate efficacy on inflammatory parameters of RTX-personalized reinfusion scheme using a memory B cell–based treatment regimen.

Standard protocol approvals, registrations, and patient consents

The local ethic committee approved treatment regimen and data collection, and patients signed written informed consent before treatment initiation.

Patients

Patients were treated with RTX with two 1-g infusions 15 days apart as loading doses. Patients were then followed up quarterly with memory B cell evaluation (assessed as CD19⁺ and CD27⁺ cells). MRI assessment was performed within 6 months of RTX initiation, followed by additional scans at the end of each treatment year.

Treatment

Patients were reinfused with 375 mg/m² RTX when the percentage of memory B cells exceeded the predefined reinfusion cutoff: 0.05% of peripheral blood mononuclear cells (PBMC) for the first 2 years and 0.1% of PBMC for the third year with subsequent doubling for each year of treatment (maximum cutoff at the 7th year of treatment of 1.6% of PBMC). A year-by-year increase in the threshold for reinfusion was adopted to further reduce the number of RTX reinfusions with each year of treatment.

Statistical analysis

The Annualized relapse rate (ARR), defined as the total number of relapses divided by the total number of patient years, pre- and post-RTX start, and the annualized reinfusion rate (ARIR) after RTX initiation were compared by mixed-effect negative binomial models accounting for the repeated measures analysis, with *p*-values adjusted for multiple testing by the Bonferroni correction. SAS 9.3 (Institute Inc., Cary, NC) and R software (version 3.5.0) were used for the computation.

Data availability

Raw data are available on appropriate request.

Results

One hundred two patients were enrolled in the study: 34 patients (33.33%) had a relapsing-remitting (RR) phenotype, 29 (28.43%) a primary progressive (PP) phenotype, and 39 (38.24%) a secondary progressive (SP) phenotype. Eighty-two percent of RRMS individuals and 52% of progressive patients (regardless of a primary or secondary phenotype) displayed disease activity at MRI carried out in the year before RTX start. Complete demographic analysis is reported in

table. At database lock, the patient mean follow-up was 2.40 years (range 0.57–7.15 years). The annualized relapse rate was 0.43 (95% confidence interval [CI]: 0.35–0.53) in the 2 years before RTX initiation and increased to 0.67 (95% CI: 0.52–0.84) in the year before RTX initiation. As expected, ARR was dramatically reduced on RTX initiation to 0.01 (95% CI: 0.001–0.04) in the first year, 0.01 (95% CI: 0.001–0.06) in the second year, and 0.00 (95% CI: 0.00–0.10)

in the third year, with a 3-year global ARR of 0.01 (95% CI: 0.002–0.03) ($p < 0.0001$) (figure 1).

Of 60 patients (63.16%) with MRI evidence of activity (either Gd+ enhancing lesions or new enlarging T2/fluid attenuated inversion recovery lesions) in the year before RTX initiation, 28 patients (26.32%) had a RR phenotype, whereas the remaining 32 (33.68%) had a progressive phenotype.

Table Baseline characteristics for 102 patients with MS treated with RTX, grouped by MS subtype

	All N = 102	RR N = 34	PP N = 29	SP N = 39
Age at MS onset, y, mean (SD)	30.90 (10.25)	28.71 (7.38)	39.29 (9.98)	26.58 (9.02)
Gender (female), n (%)	67 (65.69)	21 (61.76)	18 (62.07)	28 (71.79)
MS duration, y, mean (SD)	11.29 (8.61)	7.68 (6.97)	6.63 (5.47)	17.92 (7.71)
Comorbidity, n (%)	37 (36.27)	15 (44.12)	8 (27.59)	14 (35.90)
Autoimmune comorbidity, n (%)	9 (8.82)	3 (8.82)	2 (6.90)	4 (10.26)
EDSS 6 mo pre-RTX, median (range)	5 (0–8.5)	2.5 (0–7)	5 (1.5–6.5)	6 (1.5–8.5)
EDSS at RTX start, median (range)	5 (1–8.5)	3 (1.0–7.5)	5 (1.5–6.5)	6.5 (3–8.5)
No. relapse 2 y pre-RTX, median (range)	1 (0–4)	1.5 (0–4)	0 (0–3)	0 (0–2)
No. relapse 1 y pre-RTX, median (range)	0 (0–3)	1 (0–3)	0 (0–2)	0 (0–2)
Presence of active MRI 1 y pre-RTX, n (%)	60/95 (63.16)	28 (82.35)	12/23 (52.17)	20/38 (52.63)
Presence of spinal lesions 1 y pre-RTX, n (%)	37/90 (41.11)	23 (67.65)	7/18 (38.89)	7/38 (18.42)
Naïve patients, n (%)	18 (17.65)	7 (20.59)	9 (31.03)	2 (5.13)
Previous treatments, median (range)	2 (0–7)	2 (1–5)	1 (1–4)	3 (1–7)
Last DMT before RTX, n (%)	84 (82.35)	27 (79.41)	20 (68.97)	37 (94.87)
Cyclophosphamide	6 (7.14)	1 (3.70)	2 (10.00)	3 (8.11)
Daclizumab	1 (1.19)	1 (3.70)	0 (0.00)	0 (0.00)
Dimethyl fumarate	5 (5.95)	2 (7.41)	3 (15.00)	0 (0.00)
Fingolimod	30 (35.71)	10 (37.04)	3 (15.00)	17 (49.95)
Glatiramer acetate	8 (9.52)	3 (11.11)	1 (5.00)	4 (10.81)
Interferons	11 (13.10)	4 (14.81)	3 (15.00)	4 (10.81)
Natalizumab	11 (13.10)	3 (11.11)	2 (10.00)	6 (16.22)
Teriflunomide	2 (2.38)	1 (3.70)	1 (5.00)	0 (0.00)
Other	10 (11.90)	2 (7.41)	5 (25.00)	3 (8.11)
Reasons for changing to RTX, n (%)	84 (82.35)	27 (79.41)	20 (68.97)	37 (94.87)
Inefficacy	54 (64.29)	19 (70.37)	15 (75.00)	20 (54.05)
Intolerance/adverse event	11 (13.10)	2 (7.41)	4 (20.00)	5 (13.51)
JCV+	8 (9.52)	2 (7.41)	1 (5.00)	5 (13.51)
Pregnancy	1 (1.19)	1 (3.70)	0 (0.00)	7 (18.92)
Other	10 (11.90)	3 (11.11)	0 (0.00)	0 (0.00)

Abbreviations: DMT = disease-modifying treatment; EDSS = expanded disability status scale; JCV+ = positive for John Cunningham virus; PP = primary progressive; RR = relapsing remitting; RTX = rituximab; SP = secondary progressive.

Figure 1 Trend of annualized relapse rate in the 2 years preceding rituximab treatment and in the 3 years after rituximab initiation

Such a proportion declined to 8.70% (8/92 patients) in the first 6 months after therapy initiation (4 RR patients and 4 progressive patients) and then to 1.28% (1/78 PP patient) in the subsequent 6 months (till month 12), 0% (0/59 patients) in the second year, and 0% in the third year (0/32 patients). To date, none of the patients with a follow-up longer than 3 years experienced relapses or disease activity during the subsequent years of follow-up.

Nine of 102 patients (8.82%) (4 RR, 4 PP, and 1 SP) had inflammatory activity (defined as relapse and/or MRI activity) during the first 6 months after therapy initiation, probably as a consequence of a carryover activity from previous disease-modifying treatments (mainly natalizumab or fingolimod) and because of delayed onset of RTX maximum efficacy.

Interestingly, ARIR was consistently reduced year by year: during the first year, ARIR was 1.67 (95% CI: 1.43–1.94), 0.76 (95% CI: 0.58–0.98) in the second year, and 0.78 (95% CI: 0.52–1.12) in the third year ($p < 0.0001$). The results are consistent with those obtained analyzing only the 41 patients who have completed at least 3 years of follow-up: ARIR was 1.75 (95% CI: 1.38–2.19) in the first year, 0.87 (95% CI:

0.62–1.20) in the second year, and 0.78 (95% CI: 0.52–1.12) in the third year (figure 2).

The median number of memory B cells before reinfusions was 2 cells/mm³ (range 1–53 cells/mm³) in the first year, 2 cells/mm³ (range 1–21 cells/mm³) in the second year, and 3 cells/mm³ (range 1–18 cells/mm³) in the third year of treatment.

The median (range) baseline expanded disability status scale (EDSS) score was 3.0 (1.0–7.5) in patients with RRMS, 6.5 (3.0–8.5) in patients with SPMS, and 5.0 (1.5–6.5) in patients with PPMS. The median time to progression was 1.65 years (0.38–7.15).

The proportion of patients with a 6-month confirmed EDSS progression after 3 years from RTX start was 8.82% (standard error [SE] = 0.02) in the RRMS group, 17.95% (SE = 0.05) in the SPMS group, and 48.28% (SE = 0.09) in the PPMS group.

Patients were reinfused with a mean infusion interval of 367 days (range 181–839 days).

During the follow-up, 14/102 (13.72%) experimented an infusion-related reaction (IRR), all occurring during the first 3

Figure 2 Trend of annualized rituximab reinfusion rate in the 3 years after rituximab initiation for the whole population enrolled (blue) and for the 41 patients who have completed at least 3 years of follow-up (red)

infusions, and 75/102 (73.53%) patients developed AE and 19 patients developed a serious AE (see supplementary appendix 1, links.lww.com/NXI/A290). At the 2-year follow-up, among patients with known immunoglobulin levels ($n = 46$), hypogammaglobulinemia (immunoglobulin G levels lower than 5.6 g/L) developed in 2 patients, whereas for 2 patients, it was pre-existent and one patient developed hypogammaglobulinemia after 6 years of treatment. One patient died during the follow-up because of an undifferentiated mediastinal tumor lesion.

Discussion

In this pilot, uncontrolled study, we show that the RTX reinfusion protocol based on memory B cells might be feasible and able to reduce ARIR and drug dosage, preserving efficacy on inflammatory parameters (i.e., relapses and MRI activity).

This proposed scheme moves toward a personalized medicine approach in MS, a paradigm shift that is much needed in the field, especially considering emerging data on long-term safety of fixed doses reinfusion schemes for CD20-depleting antibodies.¹¹ Our protocol might confirm the putative role of memory B cells in MS pathogenesis, addressing relevant questions on the mechanism of action of some disease-modifying treatments in MS. Notably, we show that, with our reinfusion scheme, RTX reinfusions could be performed less than once per year at the second year of treatment, representing a 50% reduction in reinfusion rates, compared with

classical schemes with a significant saving of drug and subsequent economical advantage possibly arising from the reduction of the yearly infused drug and from the decrement of the use of healthcare system resources.

For patients with progressive MS (either SP or PP), our findings suggest that our regimen could reduce the chance of disability accrual through a reduction in the inflammatory activity. However, similar to other approved CD20-depleting therapies (i.e., OCR), it is reasonable to speculate that this treatment regimen will not be able to completely abolish disability progression driven by ongoing neurodegeneration.

The main limit of our study is represented by the lack of a control group that is required for disability progression analysis and is warranted for the comparison of composite outcomes, such as no evidence of disease activity. In addition, a control group is needed to compare the adverse event's occurrence (including hypogammaglobulinemia), although a lower intensity regimen of B cell depletion might warrant a safer risk profile. To date, many patients completed at least 2 years of treatment without emergence of MS activity, and therefore, it is reasonable that a reinfusion cutoff of 0.05% memory B cell is safe and potentially applicable to everyday clinical practice.

Finally, we hope that our data might prompt the conduction of randomized clinical trial to assess the efficacy and safety of tailored reinfusion schemes for CD20-depleting mAbs.

Study funding

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Disclosure

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Name	Location	Contribution
Giovanni Novi, MD	University of Genova, Genova, Italy	Major role in the acquisition of data, interpreted the data, design and conceptualized study, analyzed the data, and drafted the manuscript
Francesca Bovis, PhD	University of Genova, Genova, Italy	Analyzed the data and revised the manuscript for intellectual content
Sabrina Fabbri, MD	Antero Micone Hospital, Genova	Major role in acquisition of data
Francesco Tazza, MD	University of Genova, Genova, Italy	Major role in acquisition of data
Paola Gazzola, MD	Antero Micone Hospital, Genova	Major role in acquisition of data
Ilaria Maietta	University of Genova, Genova, Italy	Analyzed the data
Daniela Currò, MD	University of Genova, Genova, Italy	Major role in acquisition of data
Nicolò Bruschi, MD	University of Genova, Genova, Italy	Major role in acquisition of data
Luca Roccatagliata, MD, PhD	University of Genova, Genova, Italy	Major role in acquisition of data
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Appendix (continued)

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Maria Cellerino, MD	University of Genova, Genova, Italy	Major role in acquisition of data
Claudio Solaro, MD	Antero Micone Hospital, Genova	Major role in acquisition of data
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Elisabetta Capello, MD	University of Genova, Genova, Italy	Major role in acquisition of data
Gianluigi Mancardi, MD, PhD	University of Genova, Genova, Italy	Major role in acquisition of data
Mariapia Sormani, PhD	University of Genova, Genova, Italy	Analyzed the data and revised the manuscript for intellectual content
Matilde Inglese, MD, PhD	University of Genova, Genova, Italy	Analyzed the data and revised the manuscript for intellectual content
Antonio Uccelli, MD	University of Genova, Genova, Italy	Analyzed the data and revised the manuscript for intellectual content

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