Extending rituximab dosing intervals in patients with MS during the COVID-19 pandemic and beyond?

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Neurol Neuroimmunol Neuroinflamm 2020;7:e825. doi:10.1212/NXI.0000000000000825

Abstract

Objective
To evaluate disease activity in patients with relapsing-remitting MS (RRMS) receiving rituximab with an extended dosing interval.

Methods
In the context of COVID-19 pandemic, this was an interim analysis of an ongoing prospective observational study of patients who were stable on rituximab for at least 6 months and who had a planned extended dosing interval of 24 months. Only data for patients with active RRMS before rituximab were analyzed.

Results
Among 177 patients receiving rituximab, 33 had RRMS and MRI activity before rituximab and at least 8 months of follow-up after the last infusion. The mean (SD) age was 40 (14) years, 25 were females, the mean disease duration was 10 (6.8) years, the mean annual relapse rate (ARR) before rituximab was 1.7 (1.3), and the median Expanded Disability Status Scale (EDSS) score before rituximab was 4.5 (1–7). Before extended dosing, when rituximab was infused every 6 months, the mean (SD) ARR decreased to 0.04 (0.1) (p < 0.0001) and the EDSS score to 4 (0–7) (p = 0.04). At the time of this analysis, the median follow-up since the last infusion was 11 (8–31) months. No patient showed relapse or disability progression. In total, 30 patients had at least 1 MRI performed since the last infusion (median time between the last MRI and the last infusion 10 [8–31] months). No MRI showed activity. The CD19+ cell proportion was >1% for 10 of 25 patients at the last count (median time 8 [6–25] months).

Conclusions
An extended dosing interval for rituximab for patients with stable MS during the COVID-19 pandemic may be associated with a low risk of disease activity.

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the authors.

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In the emergency context of the COVID-19 pandemic, maintaining anti-CD20 therapy is problematic because of the well-known risk of severe infectious diseases developing in patients under this therapy.\(^1\) The wait-and-see option, involving a survey of the potential increase in the incidence of severe COVID-19 infection in patients receiving anti-CD20 therapy before changing recommendations, is unsafe and ethically questionable. One careful option would be to delay reinfusion during the pandemic to limit immunodeficiency during this period.\(^2\)

Anti-CD20 therapies are usually administered every 6 months, but their efficacy may be more prolonged in MS. In pivotal studies of rituximab in relapsing-remitting MS (RRMS),\(^3,4\) efficacy was maintained for 12 months. Recently, Juto et al.\(^5\) did not find any return of disease activity in patients interrupting rituximab for different reasons. However, most patients switched to another treatment after rituximab withdrawal.

All these studies suggest that extending the delay between 2 infusions to 12 months could be possible in MS. However, this possibility cannot exclude a potential return of disease activity after 12 months, especially in patients with highly active RRMS. This issue must be addressed before systematically considering postponing anti-CD20 reinfusion during the COVID-19 pandemic.

On March 15, 2020, at the beginning of the COVID-19 epidemic in France, an emergency meeting was organized in the tertiary MS center of Marseille to develop local recommendations for treatment management during this period. For suggesting an anti-CD20 therapy strategy, we decided to perform an interim analysis of the data from a larger ongoing monocentric prospective observational study of patients with MS receiving rituximab off-label with extended dosing. For this interim analysis, only data for patients with active RRMS just before rituximab were analyzed because of the highest risk of return of disease activity in these patients.

We limited this interim analysis to data concerning patients with RRMS showing disease activity confirmed by MRI performed during the year before rituximab initiation (new T2 lesion [nT2L] or contrast-enhancing lesion [CEL]) and with the last clinical follow-up at least 8 months after the last rituximab infusion.

**Lymphocyte count**
Flow cytometry immunophenotyping was used to count CD19\(^+\) lymphocytes. At least 5,000 lymphocytes were analyzed by Navios flow cytometry (Beckman Coulter, Miami, FL). The analysis was stopped when a minimum of 20 CD19\(^+\) events were detected. The maximum number of lymphocytes analyzed was 200,000. Lymphocyte counting was planned every 6 months.

**Standard protocol approvals, registrations, and patient consents**
This study was conducted within the framework of the national French registry designated as OFSEP (Observatoire Français de la Sclérose en Plaques; ClinicalTrials.gov no. NCT02889965). Patients enrolled in our OFSEP center provided written consent for participation. OFSEP received approval from the Comité Consultatif sur le Traitement de l’Information en matière de Recherche dans le domaine de la Santé and Commission nationale de l’informatique et des libertés for storing clinical, biological, and imaging data for research purposes. This study was covered by this general approval and did not require any additional procedure according to French laws.

**Statistical analysis**
JMP 14.1.0 (SAS Institute Inc., Cary, NC) was used for statistical analyses. Changes in the mean relapse rate and Expanded Disability Status Scale (EDSS) score were assessed by the Wilcoxon signed-rank test. The proportion of patients with MRI activity was compared by the Fisher exact test. Because of multiple comparisons for the primary outcome (annual relapse rate [ARR] before, during, and after every 6-month infusion of rituximab), the p value was considered significant at 0.01 (Bonferroni correction).

**Methods**

**Protocol and participants**
In 2018, our department initiated change in clinical practice concerning the dosing interval used for off-label rituximab in RRMS. All neurologists (A.M., A.R., C.B., S.D., J.P., and B.A.) have extended the interval between 2 infusions to 24 months, maintaining clinical visits every 6 months and MRI monitoring at least annually. Extending dosing was used for only patients showing no disease activity since the last rituximab infusion 6 months ago. This decision was based on the absence of standardized administration scheme for rituximab in RRMS as demonstrated by the heterogeneity of dosing intervals reported in the literature\(^3,4,6,7\) along with our experience with patients stopping rituximab for various reasons and to limit the potential infectious side effects related to hypogammaglobulinemia.\(^8\) Particularly, the 24-month interval was chosen according to a recent study finding a potential slight waning of the rituximab effect at 24 months after the last infusion.\(^6\)

**Glossary**

ARR = annual relapse rate; CEL = contrast-enhancing lesion; EDSS = Expanded Disability Status Scale; nT2L = new T2 lesion; OFSEP = Observatoire Français de la Sclérose en Plaques; RRMS = relapsing-remitting MS.
For secondary outcomes (EDSS score and MRI lesions), \( p \) values are presented with effect size assessed by \( r \) rank correlation score for paired quantitative values (according to \( r = \sqrt{t^2}/\sqrt{t^2 + df} \) where \( t \) is the \( t \)-ratio of the test and \( df = n - 1 \), \( n \) is the number of observations) and with Cohen \( w \) for qualitative parameters (according to \( w = 2/N \), \( N \) is the total sample size). An effect size 0.1–0.3 was considered small, 0.3–0.5 medium, 0.5–0.8 large, and >0.8 very large.

**Results**

**Study population**

The flow of participants is shown in figure 1, and the characteristics of the population are shown in the table. Since the onset of the new administration scheme, only 1 patient showed disease activity after the first infusion and did not receive the extended dosing. This patient did not show depleted CD19+ cells after the second infusion and was positive for anti-rituximab antibodies. In total, 33 patients were included in the analysis. All patients, except 1 who previously received natalizumab were positive for JC virus and required highly effective therapy. The patient who previously received natalizumab showed MS disease activity despite this therapy. Up to June 2019, some planned 6-month rituximab infusions were administered in only some patients because we needed time to inform and convince patients about the rationale of this new administration scheme.

**Disease activity during rituximab treatment before extended dosing**

In total, 29 of the 33 patients received rituximab every 6 months before starting the standardized extended dosing protocol (median [range] 6 [2–9] cycles) (table and figure 2). The induction consisted of 1,000 mg infused twice at a 2-week interval. Maintenance treatment consisted of a single infusion of 1,000 mg. During treatment with 6-month interval dosing, the mean (SD) ARR decreased from 1.7 (1.3) to 0.04 (0.1) \( (p < 0.001, r = 0.79) \) and the median (range) EDSS score from 4.5 (1–7) to 4 (0–7) \( (p = 0.04, r = 0.37) \). Five relapses...
occurred in 4 patients at 4, 5, 5, 10, and 15 months after rituximab onset. All patients underwent MRI. The mean (range) number of MRI sessions per patient was 3 (1–7). The mean (SD) time between rituximab onset and the first MRI was 5.5 (3.5) months, between the first and second MRI was 9 (3.6) months, and between the second and third MRI was 11 (5) months. MRI activity was found in only 5 patients at 1 month (nT2L and CEL), 3 months (nT2L and CEL), 3 months (nT2L no CEL), 3 months (nT2L no CEL), and 8 months (nT2L no CEL) after rituximab initiation.

### Disease activity during extended dosing

At the time of this interim analysis (between March 18 and 25, 2020), the median (range) interval between the last follow-up...
and the last rituximab infusion was 11 (8–31) months (table and figure 2). Only 1 patient reached the 24-month time point (31 months). This patient refused new reinfusion, arguing neurologic stability and that rituximab worsened his psoriasis. During the follow-up, no patients showed relapse or disability progression. During this period, 30 patients had at least 1 MRI and 22 of these had at least 1 MRI at least 6 months after the last rituximab treatment. The median (range) interval between the last MRI and the last rituximab infusion was 10 (8–31) months. No MRI showed activity (nT2L or CEL).

CD19+ B-lymphocyte count was measured in 25 patients. The mean (range) CD19 proportion was 1.7% (0–6.7) of total lymphocytes at the last count performed after the last rituximab infusion (median [range] interval 8 [6–25] months). CD19 proportion was >1% in 10 of 25 patients and >0.1% in 13 of 25.

Discussion

These results suggest that the option to delay rituximab during the COVID-19 pandemic in RRMS could be considered. We reveal that patients with RRMS with a high level of activity before rituximab initiation did not demonstrate any return of disease activity after rituximab withdrawal during a period of 8–31 months. Importantly, no disease activity was found whatever the number of rituximab cycles previously administered. Moreover, of particular note, there was no switch to any other treatment.

Maintenance of the efficacy of rituximab during a relatively long period is not fully understood. Of note, B-cell counts during the extended dosing period showed significant re-emergence of B cells in more than half of tested patients. Nevertheless, none of these patients experienced disease activity, which suggests that the effect of rituximab in MS is maintained after B-cell repopulation. This situation contrasts with other pathologies such as AQP4 antibody disease, which tends to relapse when B cells repopulate.9,10

This study is not without limitations. First, the sample size was small, which limits the robustness of the findings. However, the population selected was homogeneous, including only patients with highly active RRMS, which facilitates generalization to patients with lower disease activity. Second, the number of patients with a long follow-up (≥12 months) after the last rituximab infusion was low (n = 14), inherent to the interim aspect of the study. However, no patient in this group showed relapse, which suggests that the potential for fast return to disease activity after rituximab withdrawal is unlikely. Third, the relatively short follow-up prevents any definitive conclusion about the potential effect of low dosing on medium-term disability progression suggested by 1 previous
study. Finally, lack of exhaustive assessment of CD19+ lymphocyte counts due to organization failure and memory B-cell monitoring limits the interpretation of the present findings.

In this emergency context of the COVID-19 pandemic, lack of knowledge of the potential consequences of anti-CD20 therapy on prognosis with this infection warrants careful consideration by neurologists. The present findings suggest that extended interval dosing for stable patients with MS receiving rituximab during the COVID-19 pandemic may be associated with a low risk of relapse or MRI activity. A randomized clinical trial of extended interval dosing is required.

**Study funding**
No targeted funding reported.

**Disclosure**
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

**Publication history**
Received by Neurology: Neuroimmunology & Neuroinflammation April 30, 2020. Accepted in final form May 27, 2020.

**Appendix**

| Name                  | Location                                | Contribution                                      |
|-----------------------|-----------------------------------------|--------------------------------------------------|
|marine Perriguey, MD   | Aix Marseille University, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques | Major role in the acquisition of data             |
| Audrey Rico, MD, PhD   | Aix Marseille University, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques | Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content |
| Sarah Demortiere, MD, PhD | Aix Marseille University, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques | Major role in the acquisition of data             |
| Jean Pelletier, MD, PhD | Aix Marseille University, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques | Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content |
| Bertrand Audoin, MD, PhD | Aix Marseille University, APHM, Hôpital de la Timone, Pôle de Neurosciences Cliniques | Designed and conceptualized the study; analyzed the data; and drafted the manuscript for intellectual content |

**References**

1. Luna G, Alping P, Burman J, et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. JAMA Neurol 2020;77:184.
2. Brownlee W, Bourdette D, Broadley S, Killestein J, Ciccarelli O. Treating multiple sclerosis and neuromyelitis optica spectrum disorder during the COVID-19 pandemic. Neurology 2020;94:949–952. doi: 10.1212/WNL.0000000000009507.
3. Bar-Oz A, Calabresi PAJ, Arnold D, et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. Ann Neurol 2008;63:395–400.
4. Hausser SL, Wisbant E, Arnold DI, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008;358:676–688.
5. Juto A, Fink K, Al Nimer F, Piehl F. Interrupting rituximab treatment in relapsing-remitting multiple sclerosis; no evidence of rebound disease activity. Mult Scler Relat Disord 2020;37:101468.
6. de Flon P, Guerassimov M, Laurel K, et al. Reduced inflammation in relapsing-remitting multiple sclerosis after therapy switch to rituximab. Neurology 2016;87:141–147.
7. Salzer J, Swaneningson R, Alping P, et al. Rituximab in multiple sclerosis. Neurology 2016;87:2074–2081.
8. Barmettler S, Ong MS, Farmer JR, Choi H, Walter J. Association of immunoglobulin levels, infectious risk, and mortality with rituximab and hypogammaglobulinemia. JAMA Netw Open 2018;1:e184169.
9. Kim S, Huh S, Lee S, Jeong A, Kim H. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurol 2013;70:1110–1117.
10. Durand P, Rico A, Boutiere C, et al. Comparison of the response to rituximab between myelin oligodendrocyte glycoprotein and aquaporin-4 antibody diseases. Ann Neurol 2020;87:256–266.
11. Kletzl H, Gievansky E, Petry C, et al. Pharmacokinetics, pharmacodynamics and exposure-response analyses of ocrelizumab in patients with multiple sclerosis (N4.001). Neurology 2019;92:N4.001.
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DOI 10.1212/NXI.0000000000000825

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