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DISEASE EXACERBATION AFTER RITUXIMAB INDUCTION IN NEUROMYELITIS OPTICA

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Background. Rituximab (RTX), an anti-CD20 monoclonal antibody, was highly efficacious in reducing relapse rates in neuromyelitis optica (NMO) in several observational case series.^{1–7, e1–e3} Despite the favorable record, most series include 1 or more patients who experienced a relapse shortly after RTX induction.^{2, 5, 7, e1, e4–e6} We review clinical histories of 6 patients with NMO treated at the New York University Multiple Sclerosis Center who experienced a relapse within 1 week of RTX induction and discuss potential biological mechanisms that may account for apparent disease rebound.

Case series. Six of 17 (43%) patients with NMO at our center who received ≥ 1 dose of RTX experienced a relapse within 1 week of their first RTX infusion. Average age at RTX induction was 43.3 years (± 16.2 years; range 18–58 years), average disease duration was 7.2 years (± 7.2 years; range 0.3–20 years), and all patients were women. Five patients were NMO immunoglobulin G seropositive (Mayo Clinic Laboratories, Rochester, MN) and 1 was anti-myelin oligodendrocyte glycoprotein antibody seropositive (Prof. Reindl's laboratory, Innsbruck, Austria). Postinduction relapses were confirmed by MRI in all cases (figure e-1 at Neurology.org/nn), except for 2 patients in whom MRI was not performed. Relapse and treatment history for each of the 6 patients is shown in figure 1 and elaborated in the accompanying legend. All patients had a history of prior relapse within 3 months of RTX initiation, 2 within 2 weeks of induction. In all cases, the location of pre-RTX and postinduction relapse was the same—spinal cord in 4 patients and optic nerve in the other 2 patients. One patient also developed encephalopathy with multiple new gadolinium-enhancing lesions throughout the cerebrum (figure e-1, D and E).

Four patients received subsequent infusions of RTX; 3 of them experienced one relapse each after RTX, 1 patient within 1 week of the reinfusion and 2 within 2 weeks (figure 1).

Discussion. Although accumulating evidence supports the use of RTX in NMO,^{1–7, e1–e3} relapses after initiation of RTX have been reported in most series. Five of 25 patients treated by Kim et al.^{e1} had a relapse after RTX induction but before therapeutic depletion of CD27⁺ B lymphocytes was achieved. A similar relapse rate within 3 months of RTX was recorded by Javed et al.^{e2} Lindsey et al.^{e6} noted that 3 of 9 patients relapsed within 1 month of RTX, and 1 patient relapsed during the immediate post-RTX period on 3 separate occasions. Ayzenberg et al. reported 2 patients with NMO who had a relapse within days of RTX infusion and were then successfully treated with the anti-interleukin-6 (IL-6) receptor antibody tocilizumab.^{e4} Severe relapses within 1 month of RTX were also documented by Capobiano et al.^{e5} and Sanchez-Carteyron et al.,^{e8} whose case of a young woman with encephalopathy within 24 hours of RTX infusion shares striking similarity with our patient 1 (figure 1). On the other hand, none of the 23 patients with NMO in the series of Bedi et al.³ experienced a post-RTX relapse.

Our study focused on the relapses in the immediate postinduction period and examined them in relation to pre-RTX relapses. We observed that each of the 6 patients with a post-RTX relapse had a relapse within 3 months of drug induction, 2 of them within 2 weeks of induction. Intriguingly, post-RTX relapse affected the same location as pre-RTX relapse in all patients. Although occurrence of postinfusion relapse in the immediate post-RTX period in our patients with highly active NMO could be coincidental, the high proportion of our patients who relapsed (43%) as well as the close temporal—within days of first infusion—and spatial relation between pre- and post-RTX induction relapses raises the question of whether RTX can transiently exacerbate NMO in a susceptible patient. We hypothesize that the apparent rebound in disease activity may be due to RTX-induced increase in proinflammatory cytokines, such as tumor necrosis factor α (TNF- α), IL-6,^{e9} and B-cell activating factor (BAFF),^{e10, e11} which promote maturation and survival of anti-aquaporin-4 (AQP4) antibody-producing plasmablasts and B cells.^{e10–e12} Moreover, since elimination of pathogenic

Supplemental data
at Neurology.org/nn

Figure 1 Relapse and rituximab history

The figure shows rituximab (RTX) treatment history as well as relapse history for 100 days prior to the first RTX dose until the last follow-up. The shaded area shows the time period of interest—10 days after the initial RTX infusion (vertical lines). Note that the time scale for the shaded area is different from the rest of the chart in order to resolve the temporal relation between RTX infusion and relapse. Patient 1 is a 19-year-old Moroccan-born woman who experienced 2 relapses within 2 months of RTX treatment. Her last pre-RTX relapse was longitudinally extensive transverse myelitis (LETM), which was treated with IV methylprednisolone and 6 courses of plasmapheresis (PLEX). Due to failure to improve, she was given an infusion of RTX 10 days after PLEX, while on prednisone taper. She developed symptoms of worsening myelopathy and new-onset encephalopathy within 2 days of RTX. Brain MRI before and after RTX is shown in figure e-1, D and E. The patient was lost to follow-up after her discharge from the hospital 2 months later. Patient 2 is a 32-year-old African American woman who experienced LETM while on mycophenolate mofetil (MMF). Immunosuppression was then stopped. She received her first RTX treatment 3 months later and experienced another episode of LETM within 4 days of the infusion (figure e-1, A-C). She was then continued on MMF from 2009 to 2013 and had 2 relapses, the second of which was bilateral optic neuritis (ON) treated with IV methylprednisolone, PLEX, a single dose of IV cyclophosphamide, and a short course of filgrastin due to severe neutropenia. She received a dose of RTX—her second ever—1 month after cyclophosphamide and developed myelitis within 5 days of infusion, which was treated with IV methylprednisolone. She has subsequently received 3 doses of RTX without adverse reaction. Patient 3 is 39-year-old Caucasian woman who is anti-myelin oligodendrocyte glycoprotein antibody seropositive (1:5,120, Prof. Markus Reindl's laboratory, Innsbruck Medical University, Austria) and who experienced 3 relapses within 3 months of RTX. The last relapse was left ON for which she received IV methylprednisolone, 2 courses of PLEX, one dose of mitoxantrone, and then one dose of RTX. Despite "pretreatment" with mitoxantrone, the patient experienced recurrence of severe left ON with new area of enhancement of optic nerve on MRI within 3 days of infusion (figure e-1, F-H). She has subsequently received 5 courses of RTX and had only one mild episode of ON 2 weeks after the third RTX dose. Patient 4 is a 52-year-old Hispanic woman who experienced LETM while on azathioprine. She received IV methylprednisolone and was on prednisone at the time of her first RTX infusion, which was followed by recurrence of LETM 7 days later. She was subsequently maintained on MMF but had 2 relapses. Patient 5 is a 60-year-old Haitian-American woman who continued to have relapses despite treatment with mitoxantrone and azathioprine. Immunosuppression was stopped 5 months prior to RTX. Three months prior to RTX, she experienced bilateral ON and received IV methylprednisolone and PLEX. The first infusion of RTX was followed by recurrence of ON within 3 days. She subsequently received 2 more courses of RTX, and the last course was followed by recurrence of ON 2 weeks later. The patient died of sepsis 2 years after her last RTX dose. Patient 6 is a 58-year-old Afro-Caribbean woman with long-standing neuromyelitis optica who experienced 2 relapses of myelitis within 6 months while on azathioprine and discontinued immunosuppression 2.5 months before RTX. She had severe cervical myelitis within 1 week of her first RTX infusion. She was continued on RTX and remained remarkably relapse-free for 7 years, when she experienced a mild myelitis attack 2 weeks after regularly scheduled RTX. EDSS = Expanded Disability Status Scale.

CD20⁺ cells from circulation occurs over 4–6 weeks,⁶¹ the immediate postinduction period is characterized by a lack of protection from RTX as well as a potentially more proinflammatory milieu, with increased levels of IL-6, BAFF, and anti-AQP4 antibodies. We speculate that the RTX-induced surge of proinflammatory cytokines and pathogenic antibodies superimposed on an incompletely repaired blood-brain barrier following a recent relapse could lead to recurrence of inflammation in *locus minoris resistentiae*. It is interesting that some of our patients were able to tolerate subsequent dosing of RTX without complications; perhaps this is due to their relative inability to mount cytokine release once CD20⁺ cell counts are diminished or absent.⁶⁹

Although our observational data are insufficient to make recommendations on how to preempt post-RTX relapses, it seems plausible that premature termination of prior immunosuppression, which occurred in 3 of our cases, could put patients at increased risk for post-RTX relapse. Perhaps overlap of prior immunosuppression with RTX would yield better results, especially in patients with recent disease activity. We did not observe any protective effect of

recent IV steroids on post-RTX relapse. More effective strategies to optimize use of RTX in NMO are needed. One possibility would be to test whether levels of TNF- α , IL-6, BAFF, and anti-AQP4 antibody titers prior to induction of RTX are predictive of a post-RTX relapse.

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