DISEASE EXACERBATION AFTER RITUXIMAB INDUCTION IN NEUROMYELITIS OPTICA
OPEN

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 reinfection 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. e4 had a relapse after RTX induction but before therapeutic depletion of CD20+ B lymphocytes was achieved. A similar relapse rate within 3 months of RTX was recorded by Javed et al. e1 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 women 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. e3 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
CD20 + cells from circulation occurs over 4–6 weeks, 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 resistantiae. 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.

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.

*These authors contributed equally to the work.

From the Department of Neurology (J.S.P.), Weill Cornell Medical College, New York, NY; and Department of Neurology (I.K., J. Howard, J. Herbert), New York University School of Medicine, New York, NY.

Author contributions: Jai Perumal: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. Ilya Kister: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. Joseph Herbert: drafting of the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Acknowledgments: The authors thank Dr. Adil Javed for sharing his experience with rituximab in NMO, Dr. Bibiana Bielekova for insightful comments, and Prof. Markus Reindl for carrying out anti-MOG antibody testing on patient 3. The authors are grateful to Ms. Tamar Bacon for her help with preparation of the figures. Study funding: No targeted funding reported.
Disclosure: J. Perumal has consulted for Biogen Idec; has received honoraria from Biogen Idec, Teva Neuroscience, Acorda Pharmaceuticals, and Genzyme; and is on the speakers’ bureau for Biogen Idec, Teva Neuroscience, and Acorda Pharmaceuticals. I. Kister is on the scientific advisory board for Biogen Idec and MS Franchise Data Generation; has consulted for Biogen Idec; and has received research support from Biogen Idec, Serono, Novartis, Guthy-Jackson Charitable Foundation, and National Multiple Sclerosis Society. J. Howard has received publishing royalties from Neurology Video Textbook. J. Herbert is on the scientific advisory board for Biogen and Genzyme; has received funding from Biogen and Genzyme; and has received research support from Novartis, Biogen Idec, Acorda, Roche, Genetech, Teva, Genzyme, and St. Barnabas Hospital. Go to Neurology.org/nii for full disclosures. The Article Processing Charge was paid by the authors.

Received June 25, 2014. Accepted in final form December 6, 2014.

Correspondence to Dr. Kister: ilya.kister@gmail.com

Disease exacerbation after rituximab induction in neuromyelitis optica
Neurol Neuroimmunol Neuroinflamm 2015;2;
DOI 10.1212/NXI.0000000000000061

This information is current as of February 5, 2015

Updated Information & Services
including high resolution figures, can be found at:
http://nn.neurology.org/content/2/1/e61.full.html

References
This article cites 7 articles, 0 of which you can access for free at:
http://nn.neurology.org/content/2/1/e61.full.html##ref-list-1

Citations
This article has been cited by 2 HighWire-hosted articles:
http://nn.neurology.org/content/2/1/e61.full.html##otherarticles

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Cohort studies
http://nn.neurology.org/cgi/collection/cohort_studies
Devic's syndrome
http://nn.neurology.org/cgi/collection/devics_syndrome

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://nn.neurology.org/misc/about.xhtml#permissions

Reprints
Information about ordering reprints can be found online:
http://nn.neurology.org/misc/addir.xhtml#reprintsus