

Obinutuzumab, a potent anti-B-cell agent, for rituximab-unresponsive IgM anti-MAG neuropathy

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Neurol Neuroimmunol Neuroinflamm 2018;5:e460. doi:10.1212/NXI.0000000000000460

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Anti-MAG demyelinating neuropathy is difficult to treat. All immunotherapies have failed except for rituximab, a chimeric B-cell-depleting monoclonal antibody against CD20, that helps up to 40% of patients based on 2 controlled and several uncontrolled series.^{1–3} Because the majority of these patients are left disabled, stronger anti-B-cell agents might be promising.

We describe clinical response and autoantibody changes after treatment with obinutuzumab (Gazyva), a new generation of humanized anti-CD20 monoclonal antibodies, in 2 patients with anti-MAG neuropathy who continued to worsen despite multiple courses of rituximab. Obinutuzumab, approved for chronic lymphocytic leukemia (CLL), exerts greater peripheral and lymphoid B-cell depletion⁴ and might be more effective in rituximab-refractory patients.

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Classification of evidence

This is a single observational study without controls and provides Class IV evidence that obinutuzumab is safe to use in patients with IgM anti-MAG demyelinating neuropathy.

Patients and treatments

Patient 1

A 71-year-old man developed feet paresthesias that progressed in 4 years to bilateral foot drop. Workup revealed distal demyelinating neuropathy, a benign IgMκ monoclonal gammopathy, elevated IgM levels, and high-titer anti-MAG antibodies (table). The gammopathy was benign including normal bone marrow biopsy. He received 3 monthly courses of IVIG without benefits. Rituximab, 2 g, was ineffective without affecting the IgM level or anti-MAG titers while his weakness continued to worsen. Obinutuzumab was then administered in 6 cycles over 6 months, as per the CLL protocol, as follows: day 1: 100 mg; day 2: 900 mg; days 8 and 18: 1,000 mg each; and 1,000 mg thereafter monthly for 5 months.

Patient 2

A 65-year-old man, developed distal leg numbness and paresthesias 13 years ago following successful therapy for colorectal cancer. The neuropathic symptoms gradually worsened with sensory ataxia and muscle weakness. Workup revealed a demyelinating neuropathy, an IgMκ gammopathy, normal bone marrow biopsy, and high-titer anti-MAG antibodies (table). His symptoms transiently improved with oral corticosteroids and IVIG. Over the following 7 years, he received 5 courses of rituximab, 2 g every year. His gait and stamina improved after the first 2 treatments, but there was no further benefit. He gradually progressed with more weakness, requiring MAFOs and canes for ambulation, and prominent hand tremors. The IgMκ spike and

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

The Article Processing Charge was funded by the authors.

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Table IgM levels and anti-MAG antibody titers before and after treatment with obinutuzumab in 2 patients with anti-MAG neuropathy

Patients	IgM levels (normal 40–230 mg/dL)	IgM monoclonal spike	Anti-MAG titers by EIA (normal ≤ 1:1600 units)
Patient 1			
Before obinutuzumab	524 mg/dL	Present	>1:102,400
After obinutuzumab	229 mg/dL	Present	<1:1,600 (normalized)
Patient 2			
Before obinutuzumab	420 mg/dL	Present	>1:102,400
After obinutuzumab	173 mg/dL	Present	<1:1,600 (normalized)

high anti-MAG antibody titers persisted. Because of severe disease worsening and continuing disability not responding anymore to rituximab, he was treated with obinutuzumab, administered for 6 months as described above.

Results

There was no clinical improvement or worsening in the patients' neuropathic symptoms 6 and 12 months after treatment with obinutuzumab. In patient 1, the neurologic deficits remained unchanged several months after therapy. Patient 2, 1 year after therapy, showed signs of progression in pace consistent with his pretreatment course; no accelerated worsening related to obinutuzumab was observed. Both patients tolerated the treatment well. Except for transient mild thrombocytopenia, there were no complications during the administration or the follow-up period.

Despite no clinical benefits, however, the IgM levels normalized and remained normal up to a year after obinutuzumab in both patients (table). Of interest, the anti-MAG antibody titers, 6 months after treatments, were also normalized and remained low up to 12 months; the IgM κ spike, however, remained unchanged without discernible differences in the light chain (table). In patient 2, 1 year after obinutuzumab, the anti-MAG titers started to rise, reaching now >70,000 units.

Discussion

The clinical success of first-generation glycoengineered type-I, anti-CD20-mediated, B-cell-depleting, monoclonal antibodies in autoimmune neurologic and rheumatological disorders has provided the rationale for using more potent next-generation anti-CD20 agents. For example, ocrelizumab and ofatumumab seem more effective than rituximab in progressive and relapsing MS.^{5,6} Obinutuzumab, a third-generation, glycoengineered type-II, humanized anti-CD20 monoclonal antibody approved for CLL, has increased binding affinity to the Fc receptor on B cells and enhanced complement and antibody-dependent cytotoxicity resulting in extensive B-cell lysis of peripheral B cells, including some within the lymphoid tissues; because it

also affects IL-6 production, it is expected to cause more sustained depletion of memory B cells and affect antibody production. These effects prompted us to evaluate its efficacy in patients with rituximab-refractory anti-MAG-mediated neuropathy.³ Obinutuzumab, administered for 6 months, was safe but did not improve the patients' symptomatology even up to a year of follow-up. In contrast to rituximab, however, it normalized the IgM level and anti-MAG antibody titers (table). This observation suggests an effect beyond B-cell depletion; B cells play a key role in antigen presentation, complement activation, and cytokine production, such as IL-1, IL-6, and IL-10, that affect immunoregulatory B and T cells and antibody production by plasma cells.⁷ These preliminary results, even in a limited number of 2 patients, suggest that the IgM anti-MAG antibodies, despite being pathogenic,⁸ do not seem to correlate with clinical response. Whether this is related to our patients' advanced disease and severe axonal degeneration or to ineffectiveness of obinutuzumab is unclear. The good tolerance of the drug, however, the more profound induction of B-cell depletion, and effect on antibodies, as demonstrated with normalization of IgM and anti-MAG titers, suggest that obinutuzumab might still be considered as an early treatment of this difficult-to-treat neuropathy.

Author contributions

Dr. Rakocevic and Dr. Martinez: study concept and design, acquisition of data, analysis and interpretation, and critical revision of the manuscript for important intellectual content. Dr. Dalakas: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, and study supervision.

Study funding

No targeted funding reported.

Disclosure

M. Dalakas served on the scientific advisory board of Novartis, Baxalta, and Octapharma; received travel funding and/or speaker honoraria from Merck/Serono, Octapharma, and Pfizer AG; served on the editorial board of/as an editor of *Neurology*, *BMC Neurology*, *Acta Myologica*, *Acta Neurologica*

Scandinavica, and *Therapeutic Advances in Neurology*; consulted for Therapath, Baxter, Octapharma, CSL, and the Dysimmune Diseases Foundation; received institutional support to Thomas Jefferson University and University of Athens from Merck Serono, Genzyme, Novartis, the Guillain-Barré Syndrome/CIDP Foundation, Dysimmune Diseases Foundation, CSL, Biogen, and Newfactor; G. Rakocevic reports no disclosures. U. Martinez-Outschoorn served on the editorial board of the *American Journal of Pathology*; received research support from Otsuka Pharmaceuticals and the NIH/NCI. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

Received January 8, 2018. Accepted in final form March 5, 2018.

References

1. Dalakas MC, Rakocevic G, Salajegheh M, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Ann Neurol* 2009;65:286–293.
2. Ferfoglia R, Guimarães-Costa R, Viala K, et al. Long-term efficacy of rituximab in IgM anti-myelin-associated glycoprotein neuropathy: RIMAG follow-up study. *J Peripher Nerv Syst* 2016;21:10–14.
3. Dalakas MC. Rituximab an anti-MAG neuropathy: more evidence for efficacy and more predictive factors. *J Neurol Sci* 2017;377:224–226.
4. Dalakas MC. B cells as therapeutic targets in autoimmune neurological disorders. *Nat Clin Pract Neurol* 2008;4:557–567.
5. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 2017;376:209–220.
6. Bar-Or A, Grove R, Austin D, et al. The MIRROR Study: a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to investigate the safety and MRI efficacy of subcutaneous ofatumumab in subjects with relapsing-remitting multiple sclerosis. *Neurology* 2014;82:S23.006.
7. Li R, Rezk A, Healy LM, et al. Cytokine-defined B cell responses as therapeutic targets in multiple sclerosis. *Front Immunol* 2015;6:626.
8. Latov N. Pathogenesis and therapy of neuropathies associated with monoclonal gammopathies. *Ann Neurol* 1995;37:S32–S42.

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