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

Goran Rakocevic, MD, FAAN, Ubaldo Martinez-Outschoorn, MD, and Marinos C. Dalakas, MD, FAAN

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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.

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...
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 accel-
erated worsening related to obinutuzumab was observed.
Both patients tolerated the treatment well. Except for
transient mild thrombocytopenia, there were no compli-
cations during the administration or the follow-up period.

Despite no clinical benefits, however, the IgM levels normal-
ized 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 IgMk 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 sus-
tained depletion of memory B cells and affect antibody pro-
duction. These effects prompted us to evaluate its efficacy in
patients with rituximab-refractory anti-MAG–mediated neu-
ropyathy.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 nor-
malized 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 in-
effectiveness 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 obi-
nutuzumab might still be considered as an early treatment of
this difficult-to-treat neuropathy.

**Author contributions**

Dr. Rakovevic 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 in-
terpretation, 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

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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

<table>
<thead>
<tr>
<th>Patients</th>
<th>IgM levels (normal 40-230 mg/dL)</th>
<th>IgM monoclonal spike</th>
<th>Anti-MAG titers by EIA (normal ≤ 1:1600 units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Before obinutuzumab 524 mg/dL</td>
<td>Present</td>
<td>&gt;1:102,400</td>
</tr>
<tr>
<td></td>
<td>After obinutuzumab 229 mg/dL</td>
<td>Present</td>
<td>&lt;1:1,600 (normalized)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Before obinutuzumab 420 mg/dL</td>
<td>Present</td>
<td>&gt;1:102,400</td>
</tr>
<tr>
<td></td>
<td>After obinutuzumab 173 mg/dL</td>
<td>Present</td>
<td>&lt;1:1,600 (normalized)</td>
</tr>
</tbody>
</table>
References
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