case suggests that choroidal vasodilation could play an inciting role as increased levels of dopamine have been shown to cause choroidal vasodilation. The time course of effusion development in this case is similar to that with topiramate. This suggests that if bupropion use were causative, one of its major active metabolites, hydroxymethylbupropion or theobupropion (both with half-lives similar to that of topiramate), may be responsible. Both metabolites inhibit dopamine and norepinephrine reuptake; thus, norepinephrine could also have a role. Bilateral effusions have been reported with venlafaxine hydrochloride, a norepinephrine and serotonin reuptake inhibitor.

Bupropion is a common medication, and it is unclear why other cases have not been reported. If bupropion use were causative in this case, the absence of other similar reports may reflect underreporting; alternatively, this patient may harbor a rare, private polymorphism that causes bupropion or one of its metabolites to become a particularly potent choroidal vasodilator.

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Small Dose of Rituximab for Graves Orbitopathy: New Insights Into the Mechanism of Action

Rituximab has been used in the treatment of several autoimmune diseases. Preliminary studies from our laboratory, recently confirmed, have shown that 2 cycles of 1000 mg of rituximab induced peripheral CD20+ cell depletion and significant clinical improvement of active Graves orbitopathy (GO). We report an unexpectedly rapid therapeutic effect of 100 mg of rituximab observed in 3 patients as early as 1 to 7 days after therapy, with persistent inactivation of inflammation and total depletion of CD20+ and CD19+ B cells. Immunohistochemistry of orbital tissues from patients treated with rituximab has shown early recruitment of type 2 macrophages, which may be involved in rituximab-induced phagocytosis of B-cell targets in orbital tissues.

Methods. Patients with GO underwent rituximab infusion after premedication with acetaminophen, chlorpheniramine maleate, and 100 mg of hydrocortisone sodium succinate. Peripheral cell subpopulation analysis was performed at baseline, at the time of the acute reaction (60 minutes), and weekly thereafter by flow cytometry (Figure 1C). Orbital tissues after treatment with 100 mg of rituximab, treatment with steroids, and no treat-
ment of GO were studied by immunohistochemistry (Figure 2A). Lymphocytic infiltration was graded 1+, 2+, and 3+ if there were fewer than 10, more than 10, and more than 30 immunoreactive cells per high-power field (magnification ×400), respectively.

**Results.** Two women aged 43 and 67 years with primary myxedema and a 50-year-old woman with previous Graves hyperthyroidism treated with iodine 131 who were euthyroid while receiving levothyroxine and had active, moderate to severe GO with clinical activity scores (CASs) of 5/10, 6/10 (Figure 1A and B), and 6/7, respectively, were treated with rituximab. Infusion with 100 mg of rituximab was stopped at 60 minutes in 2 patients who had an infusion-related reaction with rapidly progressive, transient edema of soft orbital tissues and decrease of vision, and the patients were treated intravenously with 100 mg of hydrocortisone sodium succinate.

The first patient had edema and chemosis more pronounced in the left eye, with stretching of the optic nerve on orbital computed tomography due to marked periorbital tissue swelling (Figure 1B). Visual acuity returned to normal (10/10), and significant decreases of edema and inflammation (CAS decreased from 5 to 3) and proptosis in both eyes (decreasing from 24.5 to 23 mm OD and from 31 to 28 mm OS) were observed the next day. A week later, the disease was inactive (CAS of 2) (Figure 1A and B). The second patient had marked orbital edema (Figure 1B) and visual loss (counting fingers) in the more severely affected eye (the left eye). Orbital computed tomography showed only swelling of the retro-ocular tissue. Visual acuity improved in 60 minutes; 3 hours later, visual acuity was 10/10. A week later, inflammation improved bilaterally (CAS decreased from 6 to 3) (Figure 1A) and proptosis decreased (decreasing from 27.5 to 26 mm OD and from 29.5 to 27 mm OS) (Figure 1B). The third patient had no infusion-related effect, and the GO became inactive at 8 weeks (CAS decreased from 6 to 3). No disease relapse was observed in the patients at 32, 55, and 86 weeks of follow-up, respectively. Sixty minutes after

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CD20*</th>
<th>CD3*</th>
<th>CD68*</th>
<th>CD163*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>0</td>
<td>1+</td>
<td>2+</td>
<td>3+</td>
</tr>
<tr>
<td>Intravenous steroids</td>
<td>1+</td>
<td>2+</td>
<td>Focal</td>
<td>1+</td>
</tr>
<tr>
<td>Untreated</td>
<td>1+</td>
<td>1+</td>
<td>Focal</td>
<td>1+</td>
</tr>
</tbody>
</table>

**Figure 2.** Degree of infiltration (A) and characteristics of infiltrating cells (original magnification × 400) (B) in orbital tissues by immunohistochemistry in relation to the type of treatment. There was an absence of CD20* cells with rituximab treatment compared with marked infiltration with intravenous steroid treatment. There were focal CD3* infiltrates with rituximab treatment compared with marked expression with intravenous steroid treatment. There was evident CD68* cell infiltration with rituximab treatment compared with focal infiltration with intravenous steroid treatment and no treatment. There was markedly increased CD163* cell infiltration with rituximab treatment compared with focal infiltration with intravenous steroid treatment and no treatment.
Comment. We report, for the first time to our knowledge, that low-dose rituximab (100 mg) causes effective peripheral B-cell depletion and induces long-term remission of GO without further therapy. No data on the time for depletion after rituximab infusion have been previously reported in the literature. This observation was made after discontinuing rituximab treatment in 2 patients because of an important infusion-related reaction. Anaphylatoxins and cytokines might presumably be at the basis of the observed edema after rituximab treatment. Our data suggest that C3a and C5a anaphylatoxins and other inflammatory cytokines may have recruited CD68+ CD163+ CD1a− macrophages, no CD1a+ dendritic cells, and good expression of CD163, a marker of type 2 macrophages. Control patients had only focal CD68+ and CD163− cell infiltration.

Rituximab treatment of GO may induce a clinical response that can vary from patient to patient, occur at a very early stage of disease activity, and persist long term. The small number of patients in this study suggests the need for caution in drawing more general conclusions from our observations: should these findings be confirmed, we would envisage a new treatment option with low-dose rituximab, with fewer adverse effects and more cost-effectiveness.