Effect of Rituximab in Patients With Leucine-Rich, Glioma-Inactivated 1 Antibody–Associated Encephalopathy

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IMPORTANCE This observational study describes the efficacy and safety of rituximab in 5 patients with voltage-gated potassium channel (VGKC)–complex/leucine-rich, glioma-inactivated 1 (LGI1) antibody-associated encephalopathy. Rituximab is a monoclonal antibody that targets CD20 and is used to treat other neurologic and nonneurologic diseases.

OBSERVATIONS This case series reports sequential seizure frequencies, modified Rankin Scale scores, and VGKC-complex antibody titers in 5 adult patients (median age, 65 years; range, 48-73 years) treated with rituximab. Median time from symptom onset to rituximab initiation was 414 days (range, 312-851 days). One patient showed a rapid clinical improvement after treatment with rituximab alone and experienced a rituximab-responsive clinical relapse. Another showed possible improvement on neuropsychometric memory indexes after rituximab therapy. In contrast, all patients showed robust responses to treatment with glucocorticoids, intravenous immunoglobulins, and/or plasma exchange at some point in their illness. Treatment with glucocorticoids—less so with intravenous immunoglobulins and plasma exchange—was associated with the most marked reductions in VGKC-complex antibodies. The only patient who did not receive glucocorticoids showed the poorest clinical and serologic responses.

CONCLUSIONS AND RELEVANCE Rituximab was well tolerated in this predominantly older adult patient population and may be an effective option for some patients with LGI1 antibody-associated encephalopathy. Glucocorticoid therapy appears particularly efficacious. Earlier rituximab administration and randomized trials are required to formally assess efficacy.

Voltage-gated potassium channel (VGKC)–complex/leucine-rich, glioma-inactivated 1 (LGI1) antibody–associated encephalopathy has a subacute onset with features that include cognitive impairment, seizures of medial temporal lobe origin, faciobrachial dystonic seizures (FBDS), and serum hyponatremia.1-3 Leucine-rich, glioma-inactivated 1 antibody–associated encephalopathy is a treatable differential diagnosis within the rapidly progressive dementias.4 Most patients improve with glucocorticoid therapy, which is often accompanied by treatment with intravenous immunoglobulins (IVIG), plasma exchange (PLEX), or both.1-3 Despite this, residual cognitive impairment is common (B.M.B., J.M.G., S.R.I., John Neuhaus, PhD, Sven Forner, BSc, Chris Hess, BSc, and M.D.G., unpublished data, June 27, 2013).5 Nevertheless, only a few patients are offered additional immunotherapy, such as azathioprine sodium, methotrexate sodium, and mycophenolate mofetil hydrochloride. The effect of rituximab administration has not, however, to our knowledge, been described in detail for the treatment of LGI1 antibody–associated encephalopathy.

Rituximab is a monoclonal antibody directed against CD20, which is expressed on naïve and mature B cells that are depleted by rituximab infusion.6 CD20 is not found on plasma cells, which are the main cell type that secrete antibodies. Because LGI1 antibodies are likely to be directly pathogenic, it is therefore plausible that rituximab should not have a therapeutic effect in this putative autoantibody-mediated encephalopathy. Nevertheless, in neuromyelitis optica, another putative autoantibody-mediated disease of the central nervous system, rituximab has proved efficacious in reducing relapse rates.7

To better understand the efficacy of rituximab in LGI1 antibody–associated encephalopathy, we report the long-term clinical and serologic outcomes of 5 patients with LGI1 antibody–associated encephalopathy who were treated with rituximab.

Methods

This study was approved by the University of California, San Francisco, Committee on Human Research. Written in-
formed consent was obtained from participants and/or surrogates. We reviewed our database on rapidly progressive dementia for all patients with VGKC-complex/LGI1 antibody-associated encephalopathy treated with rituximab.

Of 14 patients with VGKC-complex antibody–associated encephalopathy seen at the University of California, San Francisco, between January 1, 2006, and October 31, 2013, five had received rituximab (Table). In addition to medical and research record reviews, we performed retrospective in-person interviews (n = 4) and telephone (n = 1) interviews of these 5 patients and their relatives or caregivers, all of whom had compiled chronological notes of their respective patient’s illness. These notes determined sequential modified Rankin Scale (mRS) scores, seizure or FBDS frequencies, timing of immunotherapies received, and VGKC-complex antibody results (Figure; parts A-E correspond to patients A-E). In patient A, the last 3 rituximab infusions were 500 mg each; all other infusions were 1 g twice, 2 weeks apart. Intravenous (IV) methylprednisolone sodium succinate, 100 to 250 mg, was administered before all rituximab infusions. All patients showed near-complete CD19 cell depletion after rituximab administration. Some data from patient A were published previously (patient 1 in Geschwind et al).2

### Results

All 5 patients had VGKC-complex and LGI1 antibodies and showed typical features of the associated encephalopathy (Table). Median time from symptom onset to rituximab initiation was 414 days (range, 312-851 days).

After IV methylprednisolone administration, patient A showed cessation of FBDS, a fall of 2 mRS points, and no reduction in VGKC-complex antibody levels (Figure, A). Her mRS score rose during the next year despite treatment with PLEX, IVIG, IV methylprednisolone, oral prednisone, and myco-phenolate mofetil. For the 6 months before initiation of rituximab treatment, during which she was not receiving immunotherapy, she was increasingly somnolent and did not interact with her caregivers or family (mRS score rose to 5). A few days after receiving her first course of rituximab, more than 2 years into her illness, she became markedly more communicative and even began beating her caregivers at chess again. This effect was sustained for 1 year, after which a relapse of gradual cognitive deterioration with FBDS was successfully retreated with rituximab alone, which was subsequently administered on 3 more occasions for maintenance.

Six months after symptom onset, during 4 weeks of treatment with prednisone, 60 mg daily, patient E showed marked improvement in seizure frequency and an ongoing fall in her mRS score (to 1). Because of persistent memory impairment 316 days after onset, she received IV methylprednisolone followed by 2 months of prednisone, without symptomatic benefit. At day 348, cognitive testing (eTable in the Supplement) showed markedly impaired verbal learning and memory (first percentile on the 16-item California Verbal Learning Test [CVLT-II]; z score, −2.5). Rituximab was administered 414 days after symptom onset. Results of cognitive testing at day 418 showed improvement in her CVLT-II score, with persistent impairments (30th percentile; z score, −0.5). At day 544, despite no change in her mRS score, cognitive testing revealed normalization of verbal learning and memory (70th percentile; z score, 0.5).

In the other 3 patients, rituximab therapy appeared to have no or only marginal clinical benefit in reducing seizure frequency or the mRS score (Figure, B-D; results before and after neuropsychometry were not available). After rituximab therapy, patient B had 2 seizures and patient C demonstrated an increase in FBDS (Figure, B and C, respectively). In contrast, the most consistent reductions in seizure (including FBDS) frequency were associated with glucocorticoid or IVIG administration (Figure). Improvement on the mRS appeared to be most consistently associated with glucocorticoid administration (Figure, B-E). In addition, patient D, who received IVIG, PLEX, and rituximab but no glucocorticoids (because of poorly controlled diabetes mellitus), showed the poorest outcome (mRS score of 2; neuropsychometry results not shown) and the highest antibody titers despite 5 years of follow-up (Figure, D).

Although precise comparisons of antibody levels are limited by inconsistent sampling times, falls in VGKC-complex antibody titers appeared to be most temporally associated with glucocorticoid therapy and less so with IVIG, PLEX, and rituximab therapy. Other than a single patient who developed an

### Table. Clinical Features of Patients With LGI1 Antibody–Associated Encephalopathy

<table>
<thead>
<tr>
<th>Patient No./Sex/Age at Diagnosis, y</th>
<th>Seizures</th>
<th>MTL Appearance on First MRI</th>
<th>Lowest Serum Sodium Level, mEq/L</th>
<th>Rule Out Other Confounding Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/F/73</td>
<td>FBDS</td>
<td>Normal*</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>B/F/69</td>
<td>FBDS and MTL</td>
<td>Normal</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>C/M/65</td>
<td>GTCS</td>
<td>T2/FLAIR hyperintense</td>
<td>121</td>
<td></td>
</tr>
<tr>
<td>D/F/62</td>
<td>MTL and GTCS</td>
<td>T2/FLAIR hyperintense</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>E/F/48</td>
<td>MTL</td>
<td>Possible FLAIR hyperintense</td>
<td>129</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FBDS, faciobrachial dystonic seizures; FLAIR, fluid-attenuated inversion recovery; GTCS, generalized tonic-clonic seizures; LGI1, leucine-rich, glioma-inactivated 1; MRI, magnetic resonance imaging; MTL, medial temporal lobe.

† Reference range, 135-145 mEq/L.

* When assessed before receiving a diagnosis, all patients exhibited amnesia and disorientation.

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Serial measurements of modified Rankin Scale (mRS) scores, voltage-gated potassium channel (VGKC)-complex antibodies (Abs), and faciobrachial dystonic seizures (FBDS) or more typical medial temporal lobe seizure semiologies. Administered immunotherapies are shown at the top of each graph. The number 5 denotes administration of methylprednisolone, 5 g, in 5 consecutive daily infusions. The VGKC-complex antibody titers were determined by radioimmunoassay in picomolar (B) and scaled to axes after dividing by 10 (C through E) or by 100 (A). For any one patient and for internal consistency, results from a single laboratory were plotted. Quantitative VGKC-complex antibody levels were tested by radioimmunoassay at Mayo Laboratories (Rochester, Minnesota), Athena Diagnostics (Worcester, Massachusetts), or Oxford University (Oxford, England). The LGI1 antibodies were determined as positive or negative by cell-based assays in the laboratories of Josep Dalmau, MD, PhD (University of Pennsylvania, Philadelphia, or University of Barcelona, Barcelona, Spain), Angela Vincent, FRS (University of Oxford, Oxford, England), or Athena Diagnostics. Patient A was described previously in Geschwind et al.² (A). IV indicates intravenous.

²FBDS relapse.
itchy throat during a single rituximab infusion, no other adverse effects were noted.

**Discussion**

From this retrospective observational study of 5 patients with LGI1 antibody–associated encephalopathy, therapy with rituximab alone produced a clear benefit in both the mRS score and FBDS frequency 2 years into the illness of 1 patient after failed readministration of glucocorticoids. This effect was reproduced on disease relapse. Another patient had a possible improvement in verbal memory with rituximab therapy 1 year into the illness after a less-marked effect of repeated treatment with glucocorticoids.

Accumulating evidence suggests that LGI1 antibodies mediate this encephalopathy. Rituximab, however, does not target the CD20-negative antibody-producing plasma cells. This mechanism may explain the apparent clinical and serologic ineffectiveness of rituximab therapy in 3 of our patients and 2 previously reported LGI1 antibody-positive patients. Furthermore, its efficacy in 2 patients may reflect modulation of antibody-independent B-cell actions. Based on its promising effect in patients with muscle-specific kinase-antibody myasthenia gravis, treatment with rituximab may be particularly effective in diseases associated with antibodies of IgG4 subclass predominance, such as LGI1 antibodies. Further research is needed to determine if LGI1 antibody-positive patients who respond to rituximab have a higher level of IgG4 subclass-predominant antibodies compared with nonresponders.

The lack of clear efficacy observed in 3 of our 5 patients, however, might result from administration of rituximab too late into their illness, although the 2 rituximab-responsive patients received treatment even later than these 3 patients. Furthermore, although validated by the caregivers’ records, many clinical outcome measures were assessed retrospectively, which might have influenced our findings. In addition, the administration of multiple immunotherapies in individual patients, including methylprednisolone as rituximab infusion premedication, means that our retrospective observations do not precisely disentangle individual drug effects. The rituximab response in patients A and E, however, is unlikely to relate to corticosteroid premedication because both patients were previously unresponsive to greater and more prolonged doses of glucocorticoids. In patient E, however, the normalization of memory index scores may reflect the delayed action of glucocorticoid therapy. Nevertheless, the frequently observed rapid effects of glucocorticoids are consistent with previous reports in patients with LGI1 antibodies. Systematic clinical studies—ideally, randomized clinical trials—are required to formally address the efficacy of rituximab in this and related antibody-associated encephalopathies.

After this manuscript was accepted, a sixth of our 14 patients received a course of rituximab. This 65-year-old man with LGI1 antibody-associated encephalopathy had previously been treated with IV methylprednisolone, oral prednisone, and, later, IVIG, all with mild improvement. He received 1 round of IV rituximab, 2 doses of 1000 mg given 2 weeks apart, at 15 months and continued to receive prednisone, 20 mg/d. At the 18-month follow-up, LGI1- and VGKC-complex antibodies were undetectable, and he had clear incremental improvement in cognitive function and emotional stability.

In summary, we present long-term follow-up data suggesting that rituximab may be of use in some patients with LGI1 antibody-associated encephalopathy despite administration late in the illness and that rituximab is well tolerated in this predominantly older adult population. Earlier treatment with rituximab in VGKC-complex antibody-associated disorders, such as LGI1 antibody-associated encephalopathy, needs to be explored because it might help avoid the use of frequent administration of, and the potential complications associated with, glucocorticoid, PLEX, and IVIG therapy.

**ARTICLE INFORMATION**

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Study concept and design: Irani, Gelfand, Geschwind.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Irani.
Critical revision of the manuscript for important intellectual content: All authors.
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**REFERENCES**