An Eye for an Eye: A Randomized Placebo-Controlled Trial of IVIG in Antibody-Mediated Encephalitis

Randomized Placebo-Controlled Trial of Intravenous Immunoglobulin in Autoimmune LGI1/CASPR2 Epilepsy

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Objective: Drug-resistant seizures are common in patients with leucine-rich, glioma-inactivated 1 (LGI1) immunoglobulin (IgG)-associated and contactin-associated protein-like 2 (CASPR2)-IgG associated encephalitis. We performed the first randomized double-blind placebo-controlled trial to evaluate efficacy of intravenous immunoglobulin (IVIG) in reducing seizure frequency. Methods: Our enrollment goal was 30 LGI1/CASPR2-IgG-seropositive adult patients with $\geq$2 seizures per week. Patients were randomized to receive IVIG (0.5 g/kg, day 1; 1 g/kg, day 2; 0.6 g/kg weeks 3 and 5) or volume-matched IV normal saline. Following the blinded phase, the nonresponders in the placebo group received IVIG. The primary clinical outcome was 50% reduction in seizure frequency from baseline to 5 weeks. Results: After enrollment of 17 patients (LGI1-IgG, 14; CASPR2-IgG, 3) over 34 months, the study was terminated due to slow enrollment. Six of 8 patients in the IVIG group were responders, compared to 2 of 9 in the placebo group (P = .044, odds ratio = 10.5, 95% confidence interval = 1.1-98.9). For the LGI1-IgG seropositive subgroup, 6 of 8 patients in the IVIG group were responders, compared to 0 of 6 in the placebo group. Two LGI1-IgG-seropositive patients receiving IVIG, but none receiving placebo, were seizure-free at the end of the blinded phase. Four of the 6 patients entering the open-label IVIG arm reported $\geq$50% reduction in seizure frequency. There were no correlations with LGI1/CASPR2-IgG1-4 subclasses. Interpretation: Superiority of IVIG to placebo reached statistical significance for the primary end point for all patients and the subset with LGI1-IgG. These results have to be interpreted with the caveat that the study did not reach its originally selected sample size.

Commentary

Autoimmunity is a recent addition to the list of causes of epilepsy recognized by the International League Against Epilepsy (ILAE).[1] Encephalitis associated with leucine-rich, glioma-inactivated 1 (LGI1), and contactin-associated protein-like 2 (CASPR2) antibodies is the second most frequent form of antibody-mediated encephalitis.[2-4] Clinical manifestations include seizures, behavioral changes, cognitive dysfunction, and sleep disorder. It remains a rare condition, with only a few hundred cases reported in the literature. Choosing an appropriate treatment thus mostly relies on observational data from uncontrolled retrospective and prospective case series.[5-7]

In these studies, different immune therapies were tried, including intravenous (IV) steroids, IV immunoglobulins (IVIG), plasma exchanges, and rituximab, an anti-CD20 antibody. Overall, they appeared superior to conventional ASMs to achieve seizure freedom.[7] In particular early treatment was associated with better outcome.[6,8,9] Which one of the immune therapies is the most effective is not known, although experience from the N-methyl-D- aspartate receptor antibody syndrome indicates that steroids alone might be inferior to the combination of steroids and IVIG or plasma exchange.[10] In any case, these data are subject to all the limitations of retrospective uncontrolled studies.

Dubey et al[11] thus performed the first double-blind randomized placebo controlled in the treatment of antibody-mediated encephalitis. Participants were randomized to receive either IVIG or placebo, which consisted in an infusion of normal saline fluid. The course of IVIG consisted of 0.5 mg/kg on day 1 and 1g/kg on day 2 of the first week, followed by 0.6 g/kg on day 1 of weeks 3 and 5, which is a rather unusual scheme. Participants were assessed after 5 weeks and subsequently unblinded. Participants in the placebo group with persistent symptoms at time of assessment were allowed to receive IVIG in an open-label fashion following the same scheme as in the active arm. The primary outcome measure was reduction in seizure frequency by at least 50% and secondary outcome measures included reduction in seizure frequency, seizure freedom, and change in cognitive status.

Before summarizing the key findings of the study, some aspects of the trial deserve to be discussed. First, while the choice of IVIG might seem obvious from the available

literature—It is the second most prescribed treatment in auto-immune encephalitis after steroids, and it comes in relatively limited supply and shortages occur at times. I wonder why an alternative treatment was not chosen, such as steroids, which was used in almost all cases reported so far in the literature, or even rituximab, which is prescribed increasingly more often.[7] Second, opting for a placebo control arm might be questionable. Given the consistent—albeit low-quality—evidence from the literature, in LGI1, CASPR2, and other autoimmune encephalitis, I think most physicians would resort to immune therapies in these conditions. Spontaneous resolutions are exceedingly rare, or at least rarely reported, and early treatment with immune therapies is associated with better outcome, in particular in the LGI1 syndrome.[12] That being said, the duration of the blinded phase was relatively short and it seems unlikely that deferring treatment for 5 weeks might have compromised recovery. I still wonder if a randomized controlled trail (RCT) with an active control arm (IVIG vs steroids or IVIG vs subcutaneous IG) and a cross-over design could not have been feasible.[13] That would have avoided the ethical issue of the placebo arm, perhaps increased enrollment (some patients declined participation because they did not want to receive a placebo), allowed to study both treatments, in isolation or in sequence, and permitted a more prolonged observation period until assessment.

It is quite challenging to run an RCT in a rare condition at a single center. Not surprisingly, despite a rather low target enrollment of 30 participants, the study was terminated before reaching its goal. Seventeen patients were enrolled over a period of almost 3 years. Nine patients received IVIG and 8 received placebo. Participants were thoroughly investigated from an immunological and genetic standpoint. They all had either LGI1 (n = 14) or CASPR2 (n = 3) immunoglobulin 4 antibodies, and their HLA phenotypes matched those known to be associated with respective antibodies.[14] Seizure frequency was high in most patients, as expected, with 11 of 17 reporting more than 10 seizures a day. Half had faciobrachial dystonic seizures, a hallmark of the anti-LGI1 syndrome.[15] Sixteen patients had abnormal cognitive functions.

At the time of assessment, 6 (75%) of 8 patients in the IVIG arm showed a 50% reduction in seizure frequency, which was statistically better than 2 (22%) of 9 in the placebo arm. Only 2 patients became seizure-free in the IVIG arm, and this was not better than in the placebo arm. Seven patients in the placebo arm subsequently received IVIG in the open-label phase of the study. Nearly all showed an improvement in seizure frequency, although none became seizure-free. These results thus demonstrate the efficacy of IVIG for seizure control in LGI1 and CASPR2-antibody encephalitis and confirm findings from prior observational studies.[5-7] Although undeniable, the effect on seizure control is less striking than in these retrospective studies, in which seizure freedom was achieved in nearly 90% patients. This is perhaps due to report bias from retrospective studies or to the relatively short observation period until assessment. In prior studies, the median time to achieve seizure freedom from the start of immunotherapy was nearly 1 month.[6,8,9]

Of note, one patient with a CASPR2 antibody had a nearly complete resolution of his symptoms while receiving placebo, indicating the (rare) possibility of self-remission. Whether or not this remission is definitive or transient remains unclear. Also, one patient with LGI1 antibody in the placebo arm had to be unblinded because of rapid worsening of her condition. Overall, though, the treatment was well tolerated with only one patient developing drug-related headache during the open-label phase.

Cognitive functions improved or stabilized in all patients who received IVIG, but this was not better than in the placebo arm. Again, the relatively short time from enrollment to assessment might contribute to underestimating the effect of treatment, as cognitive improvement tends to occur later than seizure control.[6,8,9]

In the subgroup of patients with LGI1 antibody, the effects of IVIG on seizure control and cognitive measures were slightly more significant than in patients with CASPR2 antibody, although the small sample size should temper any hasty conclusion on differences in sensitivity to immune treatment in the 2 conditions.

Long-term outcome was available in 15 patients. Of those, 9 required additional immune therapies, including IV steroids (n = 9), oral prednisolone (n = 5), additional IVIG (n = 2), mycophenolate mofetil (n = 1), plasmapheresis (n = 1), and 5 of 9 ultimately became seizure-free. This suggests that IVIG alone might not be sufficient to achieve complete remission or that remission might be delayed. Long-term outcome was not available.

Overall, the authors should definitely be commended for undertaking this trial. We now have level 1b evidence supporting the use of IVIG for seizure control in patients with LGI1 and CASPR2 encephalitis. How this will translate into clinical practice will largely depend on local availability of IVIG. I suspect steroids will remain the first line of treatment in many places. Further studies should investigate the duration of remission following IVIG and future RCT should explore other treatment options, such as IV steroids, subcutaneous IG, or rituximab.

By Nicolas Gaspard 🄸🄳

ORCID iD

Nicolas Gaspard 🄸🄳 https://orcid.org/0000-0003-1148-6723

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