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LETTER TO THE EDITOR

iSTAND trial of IVIG in POTS: a step in the right direction, but more studies are needed

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The authors of the study, "Randomized controlled trial of intravenous immunoglobulin for autoimmune postural tachycardia syndrome (iSTAND)," conducted by Vernino et al., are to be commended for undertaking a challenging and important trial of intravenous immunoglobulin (IVIG) in patients with postural orthostatic tachycardia syndrome (POTS) [1]. However, we have notable concerns about the multiple limitations of this study, which raise questions about its conclusion. The authors' claim that IVIG is not superior to albumin in this context seems premature and could be misleading, potentially affecting future patients.

Although this small study found no significant benefit of IVIG versus albumin infusions in patients with POTS, the IVIG group had a trend toward a higher response rate than the albumin group, suggesting that the true benefit of IVIG may not have been captured in this likely underpowered study. Nevertheless, it is important to examine the discrepancy between the iSTAND results and the positive outcomes found via the anecdotal experience observed in our patients and numerous reported case series in the literature [2–5].

First, the IVIG dosage administered in the study is lower than that used in standard clinical practice for patients with autoimmune diseases. Following a short induction, the maintenance dose given was only 0.8 g/kg/month, compared to the widely accepted 1–2 g/kg/month dose in patients with autoimmune diseases [6, 7]. In our anecdotal experience, the average "lowest most effective" maintenance dose in this patient population is approximately 1.3 gm/kg/month [8]. The low doses used in this study likely impacted the study's ability to reflect the true efficacy of IVIG in patients with POTS and other autoimmune dysautonomias.

Second, the relatively short duration of the study, with a focus on a 3-month time frame and an assessment of outcomes at 2 weeks after the IVIG infusion cycle, may not adequately capture the full spectrum of therapeutic effects associated with IVIG. From the chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) literature [9, 10], autoimmune small-fiber neuropathy literature [11], and our collective experience in patients with autoimmune small-fiber neuropathy and POTS, patients often require monthly IVIG treatments for at least 3 months, but often 6 months or longer to exhibit significant improvement, and in some cases, up to 12–18 months to see the full benefits of the therapy.

Third, the argument posited in the study regarding a potential volume expansion effect also requires scrutiny. The absence of documented time to improvement and of serial assessments of improvement throughout the trial duration raises questions about the validity of this assertion. If volume expansion due to albumin infusions were the primary factor driving improvement, one would expect an immediate response to therapy rather than the need for a 3-month treatment. The average time for patients with autoimmune dysautonomias treated with our published IVIG protocol to note the first signs of improvement was 5–6 weeks and ranged from 2 to 12 weeks [8]. Additionally, many of these patients were treated with intravenous fluids as a bridge to IVIG due to the severity of their illness, which strongly argues against the benefits of IVIG being due to its transient volume expansive effects.

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Fourth, the nature of "the comparator" may be a confounding factor in this study of patients with POTS, where one of the major pathophysiological mechanisms is hypovolemia. Although albumin as a comparator has been utilized in other double-blinded controlled trials, albumin was described in some studies as a non-neutral product which could have physiological effects in itself, including immunomodulatory, anti-inflammatory, and antioxidant effects [12–15], which is particularly problematic in this study. While the circulatory half-life of albumin is about 16–18 h, the overall half-life of albumin is considered to be 14–20 days in healthy adults [15], suggesting that IV albumin can also extend its benefits way beyond its expected temporary time frame. Even a more neutral comparator consisting of normal saline may have also resulted in confounding the study results due to blood volume expansion [16]. To bypass this major issue of placebo infusion as a confounding factor in patients with hypovolemia-driven disorders, future studies might need two control groups: one with intravenous saline administered from a covered saline bag and another one with no fluids administered from a covered IV bag. Such a setting could provide the most effective way to study IVIG in patients with POTS in a blinded placebo-controlled trial while also controlling for the volume expansion confounder in the placebo group.

Fifth, the selection criteria for patients in the study lack clarity. In our experience, IVIG treatments are typically reserved for patients with standard treatment-refractory POTS, after addressing their autonomic symptoms and coexisting etiologies, e.g., metabolic, infectious, mitochondrial disorders, and for some of the authors, mast cell activation syndrome, and establishing persistent antibody positivity and clinical evidence of associated autoimmune disease. The study does not provide sufficient information on whether these criteria were rigorously applied, leaving uncertainties about the patient cohort's suitability for IVIG treatment. In fact, it appears from Table 2 that prior to treatment, the IVIG group had less functional impairment than the albumin group, with the RAND-36 score being more than twice as high in the IVIG group (median score 45) as in the albumin group (median score 20) and the energy score being only 10 in the albumin versus 17 in the IVIG group [17].

Additionally, it appears, based on data presented in Table 4, that the IVIG group had improvement of the change in orthostatic heart rate increase median (−2) compared to worsening of the change in orthostatic heart rate increase median (4.5) in the albumin group. It should be noted, however, that although orthostatic heart rate is used for diagnosis of POTS, a caveat to this statement is that there are no good data to demonstrate that follow-up assessments correlate either to clinical improvement or to therapeutic efficacy.

Finally, it is important to emphasize that the study was likely underpowered to detect the benefits of IVIG over albumin. In the power analysis, the authors report that they based their analysis on a *t*-test and an effect size of 1.1 [1]. While the *t*-test aspect may be appropriate, the effect size is large, which can be problematic because a power analysis will estimate fewer required patients with increasing effect size. The study's power analysis asserts that 14 patients per group can confidently discern a significant effect when the differences are quite large. Additionally, the confidence intervals reported in the tables appear wide, which may further indicate an underpowered study. Specifically, there is a lot of variation in the data, and not enough patients to make reliable estimates [1].

In conclusion, while the study represents a commendable effort and a step in the right direction, it is imperative that the limitations are acknowledged and mitigated in future trials. Currently, accessibility of IVIG for patients with severe POTS is significantly restricted, which represents a major barrier to patient care; as such, we believe that third-party payers should not rely on this study as a basis for coverage decisions. Further research with large, multicenter, randomized controlled trials of longer duration, addressing the above concerns and limitations, is needed to provide a comprehensive and objective assessment of the efficacy of immunoglobulin therapy in patients with standard treatment-refractory POTS, given the trend of positive response in the IVIG group in this small study.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Vernino S, Hopkins S, Bryarly M, Hernandez RS, Salter A (2024) Randomized controlled trial of intravenous immunoglobulin for autoimmune postural orthostatic tachycardia syndrome (iSTAND). Clin Auton Res 34(1):153–163. https://doi.org/10.1007/s10286-024-01020-9
2. Kesterson K, Schofield J, Blitshteyn S (2023) Immunotherapy with subcutaneous immunoglobulin or plasmapheresis in patients with postural orthostatic tachycardia syndrome (POTS). J Neurol 270(1):233–239
3. Pitarokoili K et al (2021) Maintenance therapy with subcutaneous immunoglobulin in a patient with immune-mediated neuropathic postural tachycardia syndrome. J Transl Autoimmun 4:100112. https://doi.org/10.1016/j.jtauto.2021.100112
4. Rodriguez B et al (2021) Immunomodulatory treatment in postural tachycardia syndrome: a case series. Eur J Neurol 28(5):1692–1697
5. Schofield JR, Chemali KR (2019) Intravenous immunoglobulin therapy in refractory autoimmune dysautonomias: a retrospective analysis of 38 patients. Am J Ther 26(5):570–582
6. Cornblath DR et al (2018) A randomised, multi-centre phase III study of 3 different doses of intravenous immunoglobulin 10% in patients with chronic inflammatory demyelinating

polyradiculoneuropathy (ProCID trial): study design and protocol. J Peripher Nerv Syst 23(2):108–114
7. Dalakas MC (2021) Update on intravenous immunoglobulin in neurology: modulating neuro-autoimmunity, evolving factors on efficacy and dosing and challenges on stopping chronic ivig therapy. Neurotherapeutics 18(4):2397–2418
8. Schofield JR, Chemali KR (2018) How we treat autoimmune small fiber polyneuropathy with immunoglobulin therapy. Eur Neurol 80(5–6):304–310
9. Nobile-Orazio E et al (2020) An international multicenter efficacy and safety study of IqYmune in initial and maintenance treatment of patients with chronic inflammatory demyelinating polyradiculoneuropathy: PRISM study. J Peripher Nerv Syst 25(4):356–365
10. Hughes RA et al (2008) Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. Lancet Neurol 7(2):136–144
11. Liu X et al (2018) IVIg for apparently autoimmune small-fiber polyneuropathy: first analysis of efficacy and safety. Ther Adv Neurol Disord 11:1756285617744484
12. Aubin E et al (2011) Immunomodulatory effects of therapeutic preparations of human albumin. Vox Sang 101(2):131–137
13. O'Brien AJ et al (2014) Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. Nat Med 20(5):518–523
14. Casulleras M et al (2020) Albumin internalizes and inhibits endosomal TLR signaling in leukocytes from patients with decompensated cirrhosis. Sci Trans Med 12(566):eaax5135
15. Pompili E, Zaccherini G, Baldassarre M, Iannone G, Caraceni P (2023) Albumin administration in internal medicine: a journey between effectiveness and futility. Eur J Intern Med 117:28–37. https://doi.org/10.1016/j.ejim.2023.07.003
16. Blitshteyn S, Doherty TA (2023) Intravenous saline may not be a placebo in patients with small fiber neuropathy. Muscle Nerve 67(6):E25-e26
17. Hays RD, Morales LS (2001) The RAND-36 measure of health-related quality of life. Ann Med 33(5):350–357