Randomized Controlled Trial of Intravenous Immunoglobulin for Autoimmune Postural Tachycardia Syndrome (iSTAND)

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Disclosures

Dr. Vernino – Consultant for argenx, Antag,CSL Behring. Serves on a Data Safety Monitoring Board for Alterity. Receives research funding from Takeda and NIH

Steve Hopkins – Consultant for Theravance

Dr. Bryarly – Receives research funding from Theravance.

Roberto S. Hernandez – nothing to disclose

Amber Salter - receives research funding from Multiple Sclerosis Society of Canada, National Multiple Sclerosis Society, Consortium of MS Centers and the Department of Defense Congressionally Directed Medical Research Program and is a member of editorial board for Neurology. She serves as a consultant for Gryphon Bio, LLC and Abata Therapeutics. She is a member of the Data and Safety Monitoring Board for Premature Infants Receiving Milking or Delayed Cord Clamping (PREMOD2), Central Vein Sign: A Diagnostic Biomarker in Multiple Sclerosis (CAVS-MS), and Methotrexate treatment of Arthritis caused by Chikungunya virus (MARCH). She holds the Kenney Marie Dixon-Pickens Distinguished Professorship in Multiple Sclerosis Research.

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ABSTRACT

Objective: Assess response to intravenous immunoglobulin (IVIG) in presumed autoimmune postural orthostatic tachycardia syndrome (POTS)

Background: POTS predominantly affects young women and may be associated with systemic autoimmune disorders, serum autoantibodies or recent infection. Uncontrolled case studies suggest that IVIG is beneficial for treating autoimmune POTS. However, no previous randomized controlled trials have been conducted.

Methods: This single site randomized controlled clinical trial compared IVIG to intravenous albumin infusions. Albumin comparator ensured blinding and control for effects of volume expansion. Eligible POTS patients had COMPASS-31 score ≥ 40 and met pre-determined criteria suggesting autoimmunity. Over 12 weeks, participants received 8 infusions (0.4gm/kg each). Four infusions were given weekly followed by four infusions every other week. Primary outcome measure was improvement in COMPASS-31 two weeks after final infusion.

Results: 50 participants consented; 30 met inclusion criteria and received study drug (16 IVIG and 14 albumin; 29 female). Group baseline characteristics were well matched. 27 participants completed treatment protocol. Change in COMPASS-31 did not differ between groups (median change [IQR]; IVIG: -5.5 [-23.3, 2.5] vs. Albumin: -10.6 [-14.1, -4.7]; p-value = 0.629). Response rate was also not different between groups. Adverse events were common but usually mild and did not differ between treatment groups.

Conclusions: This first randomized controlled trial of IVIG in POTS found no difference in symptom response compared to albumin infusion. Both groups showed improvement possibly related to volume expansion obscuring other benefits. Future clinical trials may benefit from the use of POTS-specific clinical outcome measures sensitive to symptoms other than orthostatic intolerance.

INTRODUCTION

Postural tachycardia syndrome (POTS) is estimated to affect more than a million Americans.[1] POTS is defined by an excessive increase in heart rate on standing with orthostatic symptoms in the absence of hypotension[2], but other symptoms beyond orthostatic intolerance include cognitive difficulty, gastrointestinal distress, myalgia, and fatigue. The cause of POTS is likely heterogeneous and multifactorial. Typically, POTS affects young woman and there is an association with systemic autoimmune disorders, notably Sjogren's disease[3]. Other characteristics suggesting an autoimmune cause of POTS include subacute onset following infection, physical injury, immunization or surgery, a personal or family history of autoimmune disease, or laboratory evidence of autoimmunity.[4, 5] The latter includes antinuclear antibodies, Sjogren antibodies (SSA/SSB), antiphosholipid antibodies and autoantibodies against G-protein coupled receptors (GPCRs) including adrenergic and muscarinic acetylcholine receptors although the significance of these autoantibodies remains unclear.[6, 7] A subset of POTS patients have clinical features of small fiber neuropathy with evidence of reduced intraepidermal nerve fiber density on skin biopsy.

Immunomodulatory therapy (specifically intravenous immunoglobulin, IVIG) has been proposed as a treatment approach for immune-mediated dysautonomia. Beneficial responses to immunotherapy (including IVIG, subcutaneous IgG, plasma exchange) have been reported in isolated patients or case series.[8-11] Schofield et al.[10] retrospectively reported clinical improvement with IVIG treatment in 32 of 38 patients with presumed autoimmune dysautonomia (mostly POTS). Rodriguez et al.[9] reported 6 patients with refractory immune-mediated POTS who all responded to IVIG. All of the evidence for effectiveness of immunotherapy for POTS to date, however, are from retrospective uncontrolled studies. Reporting bias, selection bias, placebo effects and non-specific benefits of IVIG (including symptom improvement due to blood volume expansion) complicate the interpretation of the retrospective case reports. Randomized, blinded and controlled trials are needed.

In POTS patients with clinical and laboratory evidence of autoimmunity, we hypothesized that intravenous immunoglobulin (IVIG) would more efficacious when compared to intravenous albumin (volume expansion alone) in improving symptoms. Immunomodulatory therapy with IVIG may be particularly effective for dysautonomia in patients with clinical and laboratory features suggesting autoimmunity. We organized the first double-blind, parallel-design, randomized controlled trial to evaluate efficacy and safety of IVIG compared to intravenous albumin.

METHODS

The Institutional Review Board at UT Southwestern approved the protocol (IRB# 2018-005). Enrollment is summarized in Figure 1 (more detailed information about recruitment and prescreening is presented in the supplemental Figure). Potential research subjects were recruited from the UT Southwestern autonomic clinics and from community patients who responded to public information about the study. First participant was randomized and treated on July 25, 2019. Last participant completed last study visit on June 26, 2023. Enrollment of the study was

hampered by restrictions due to the COVID-19 pandemic but only one participant missed one scheduled infusion treatment due to COVID infection.

Eligible participants were adults (age ≥ 18 years) who met the clinical criteria for POTS with severe symptom burden (COMPASS-31 score ≥ 40)[12, 13] who also had clinical and laboratory evidence suggesting an autoimmune neuropathic etiology. Specific inclusion and exclusion criteria are listed in Table 1. All patients had autonomic testing including tilt table test during screening phase. Participants were required to meet the heart rate criteria for POTS on at least one active stand test or tilt test during the screening period (but were not required to meet the orthostatic HR criteria at every orthostatic assessment).

The study protocol (depicted in Figure 2) was a double-blind, parallel-design, randomized controlled trial to evaluate efficacy and safety of IVIG compared to intravenous albumin. Each infusion was 0.4 gm/kg of intravenous immunoblobulin (10% Gammunex-C, Grifols) or 0.4 gm/kg intravenous 10% albumin (Grifols). The timing and dose of the study infusions were chosen to reduce the likelihood of infusion side effects since patients with dysautonomia appear to be at higher risk for headache or aseptic meningitis when treated with high doses of IVIG (such as 1-2 gm/kg over 1-2 days). Intravenous albumin, at equal volume and concentration, was chosen as the comparator treatment to ensure blinding and to control for the effects of volume expansion.

At the initial screening visit, patients provided informed consent, were provided specific guidance for fluid and salt intake and educated to follow a structured exercise program (modified Levine protocol for reconditioning exercise) to continue during the study. Screening procedures included standard of care assessments (history and physical exam, autonomic testing, laboratory studies and skin biopsy for intraepidermal nerve fiber density) as well as research assessments (standing test with supine and standing catecholamines, symptom questionnaires).

After a screening and baseline stabilization period of at least 2 weeks, participants who met inclusion criteria were randomized with a 1:1 allocation to the two treatment groups. Randomization was performed by the research pharmacist; participants and research study personnel remained blinded to the treatment assignment. An autonomic neurologist who was not involved with study procedures served as a safety monitor to review unexpected or severe adverse events (and could obtain access to the treatment assignment if needed). Adverse events reported by patients at study visits or recorded in daily diaries were assessed for severity and temporal relationship to treatment.

The primary outcome was change in autonomic symptom severity (assessed by COMPASS-31) comparing baseline to the study week 13 assessment (2 weeks after the 8th study drug infusion). The COMPASS-31 measure is a validated assessment of patient reported autonomic symptoms comprising 31 questions in 6 domains.[12] Subdomain scores are scaled and summed to produce a full scaled score of 0 to 100 (higher scores indicating more severe autonomic symptoms). Subscores reflect orthostatic intolerance (0-40), vasomotor (0-5), gastrointestinal (0-25), secretomotor (0-15), bladder (0-10), and pupil (0-5) symptoms. Based on prior reports, clinical improvement was defined as a 20% decrease in the COMPASS-31 in sensitivity analysis.[11] Additional Secondary outcomes included an analysis of COMPASS-31 subscores, Vanderbilt

Orthostatic Symptom Score (VOSS) during standing test, and severity of patient-identified most concerning symptom (MCS). Orthostatic (standing) vitals and laboratory studies for safety and for exploratory biomarkers were collected at screening, baseline and weeks 5, 13 and 15.

This study was powered to determine a difference between groups for the COMPASS-31 change from baseline assuming the IVIG group would have a 15 point decrease and the Albumin group would have a 4 point decrease with a pooled standard deviation of 10.0. These estimates were based on reported changes in POTS patients treated with IVIG.[8-10] Based on these, sample sizes of 15 per group achieved 82.8% power to detect this difference (effect size of 1.1) using a two-sided two-sample t-test and assuming a significance level of 0.05.

After a six-week washout, subjects who completed the protocol were allowed to cross-over to the other treatment arm (but both subjects and investigators remained blinded to treatment assignment). The crossover treatment option was included in the protocol to improve recruitment (but was not part of the primary study outcome). Analysis of data for the crossover phase (which included 24 of 30 participants) will be reported separately.

Data from all participants who began treatment were analyzed in an intention-to-treat analysis using Kruskal-Wallis test for COMPASS-31 score change (primary), MCS score change, and VOSS score change. Fisher exact tests were used for dichotomous variables such as symptomatic outcome (COMPASS-31 score improved/worsened by 20%). Summary statistics for continuous variables were reported with means and standard deviations if normally distributed, medians and interquartile range if non-normally distributed. Summary statistics for categorical variables were reported as counts and column percentages. Outcomes were evaluated both as "intention-to-treat" (ITT, including 28 evaluable participants) and "per-protocol" (including only the 27 who completed > 85% of study treatments).

RESULTS

Fifty patients consented to participate, and 30 met inclusion criteria, were randomized and started treatment. 16 received IVIG and 14 received intravenous albumin. There were no differences in the characteristics of the two study groups at screening or baseline (Table 2) except for orthostatic HR increase which was greater in the albumin group at baseline (p=0.033). The majority in both groups had elevated standing norepinephrine. Participants rated their most concerning symptom (MCS) on a 0-10 scale as 7.0 (median) which was not different between the groups at baseline. The type of MCS was also not different between the groups. Participants reported their MCS as fatigue (36%), lightheadedness (30%), tachycardia (17%), gastrointestinal issues (10%) and chest pain or dyspnea (7%). An established diagnosis of a systemic autoimmune disease was present in 8 participants (4 Sjogren's, 2 psoriatic arthritis, 1 mixed connective tissue disease, 1 celiac disease).

Overall, there was no difference in the clinical response between the two study groups as assessed by change in total COMPASS-31 score at week 13 compared to baseline (IVIG: -5.5 [-23.3, 2.5]; Albumin: -10.6 [-14.1, -4.7]; p-value: 0.629) or the change in the COMPASS-31 score excluding the orthostatic intolerance subscore (IVIG: -3.3 [-5.5, 4.2]; Albumin: -2.6 [-3.7, -0.7]; p-value: 0.872). Table 3 shows the analysis of 28 evaluable subjects who were randomized

according to study protocol, regardless of complete adherence ("intention to treat analysis"). Only one participant who completed the protocol (from the IVIG group) showed worsening based on COMPASS-31 score. Overall, both groups showed improvement COMPASS-31 as well as MCS severity and orthostatic symptoms during stand test (VOSS) with no difference between the two treatments.

Although the primary and secondary outcomes did not significantly differ between the two groups, the number of patients and frequency of improvement with IVIG was higher in both the ITT (IVIG: 7 (46.7%); Albumin: 5 (38.5%); p= 0.718) and per-protocol analysis (IVIG: 7 (46.7%); Albumin: 4 (33.3%); p= 0.696). Individual responses are shown in figure 3. In the IVIG group, there were 4 (25%) whose COMPASS-31 score decreased by more than 30% compared to none in the albumin group (per-protocol analysis, p=0.103, Fisher Exact test). The one participant assigned to the albumin group who showed a 43.5% decrease in COMPASS score had dropped out of the study and received IVIG off protocol prior to the primary outcome assessment.

One participant in each study group experienced a serious adverse event resulting in discontinuation of treatment protocol. One participant experienced increased headache after receiving 2 IVIG infusions. She presented to a community emergency department where an MRI of the brain was reported to show a cerebral venous sinus thrombosis. She was immediately removed from the study and seen urgently for evaluation. The neurological examination was normal, and subsequent review of the MRI images by the PI, safety monitor and neuroradiologist showed no convincing evidence of sinus thrombosis (the MRI was unchanged compared to a previous MRI completed before the study). Another participant, after 2 albumin infusions, was hospitalized with pneumonia and worsening gastrointestinal symptoms resulting in inability to maintain hydration and nutrition. She was removed from the study. These two participants were unable to complete study procedures and were lost to follow-up. A third participant (from albumin group) withdrew from the study after 5 infusions in order to receive IVIG infusions from another provider.

Adverse events (AE) were common in both treatment groups (Table 4), and there was no difference between the groups in the frequency or type of AEs. 90% of participants reports one or more AEs; however, AEs were generally mild and self-limited. The majority of AEs were categorized as treatment-related based on the temporal relationship to infusion and the known association with IVIG infusion. Headache, lasting 1-2 days after infusion, was the most common AE.

CONCLUSIONS

This first randomized controlled trial evaluating IVIG as a treatment for immune-mediated POTS did not show a significant difference in response between IVIG and control treatment (IV albumin), and results were consistent for secondary outcomes. However some findings, namely the higher frequency of strong responders in the IVIG group, indicate that larger randomized controlled trials are warranted.

This study demonstrates the feasibility of randomized double-blind controlled trials of IVIG for POTS and provides important practical data on effect size to guide power calculations for future studies. The use of an appropriate control group is critical for separating the immunomodulating effects of IVIG from placebo effects and non-specific effects of volume expansion (which reduces orthostatic intolerance symptoms). Symptomatic improvement was seen in both treatment groups, and it is possible that the lack of a difference between groups was due to reduction in orthostatic symptoms in the albumin group. The primary outcome measure (COMPASS-31) is heavily weighted toward orthostatic symptoms, and hence, the improvement in orthostatic intolerance may have obscured a differential response in other domains. Future studies could consider using three arms (IVIG, albumin and placebo/saline), and using POTS-specific outcome measures that better reflect the overall severity and symptom burden beyond orthostatic intolerance. This study included an exploratory outcome measure (the severity of self-reported most concerning symptom). Although there was no difference in change in MCS between the treatment groups, such "personalized" patient reported outcomes may have merit given the heterogeneity in POTS. Better understanding of the responsiveness of these potential outcome measures are critical to designing future clinical trials.

Despite using inclusion criteria to select patients with probable immune-mediated POTS, the clinical response to IVIG in our trial (47%) was lower than expected based on previous case series. The overestimate of treatment response may have led to underpowering of this study to detect differences compared to the albumin comparator. A closer assessment of the criteria used to defined "autoimmune POTS" is warranted, although the number of participants in this study is too small for such an analysis.

Consistent with previous experience with this patient population, infusion treatment-related side effects were very common. However, using a more frequent dosing schedule appeared to be better tolerated than high-dose monthly infusion protocols reported previously. The drop-out rate in this study (10%) was lower than expected with no discontinuations directly attributable to treatment-emergent side effects.

In summary, this small single center study did not find a difference in symptomatic response comparing IVIG with albumin. However, meaningful clinical responses were seen, and the data suggest that larger, randomized controlled trials are warranted. Further secondary analyses from this study may help inform criteria used to identify POTS patients most likely to have an immune-mediated pathophysiology.

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Table 1: Inclusion/exclusion criteria

Inclusion Criteria
1) 18 years or older and able to provide informed consent 2) Diagnosis of POTS at screening visit - Orthostatic Symptoms ≥ 6 months duration - HR increase ≥ 30 bpm within 10 min of standing (or head-up tilt) with symptoms - Absence of orthostatic hypotension 3) COMPASS-31 total scaled score ≥ 40 4) Clinical/laboratory evidence of autoimmunity (requiring at least 3 of the following 5 features): - One or more serum autoantibodies or inflammatory markers * - Formal diagnosis of one or more systemic autoimmune disorders - Clear history of a subacute onset of POTS following infection, immunization, injury/concussion, surgery or pregnancy - Severe gastrointestinal symptoms (with either formal diagnosis of GI dysmotility or symptoms interfering with ability to maintain nutrition) - Evidence of small fiber neuropathy (with either reduced intraepidermal nerve fiber density on skin biopsy or reduced sweat volumes on QSART) 5) Stable medications for at least 30 days prior to baseline visit (and intention to remain on current medications throughout the study)
Exclusion criteria
1) Resting supine tachycardia (>100 bpm) 2) Current or prior treatment with intravenous immunoglobulin 3) Current intravenous treatment with saline, albumin or total parenteral nutrition 4) IgA deficiency or other known contraindication to study drugs (such as unstable cardiac or renal disease) 5) Current use of immunosuppressive or biological immunomodulatory drugs (topical medications and stable dose of hydroxychloroquine or low dose oral steroids were allowed) 6) Inadequate venous access for infusion 7) History of deep venous thrombosis
* This inclusion item required one or more of the following positive antibody results: ANA (≥ 1:160), gAChR antibody (> 0.2 nmol/L), Extractable Nuclear Antigen (including SSA/SSB), lupus anticoagulant, antiphopholipid/cardiolipin, tissue transglutaminase, or gliadin **AND/OR** inflammatory markers: CRP (> 2), low complement C3

Table 2: Baseline characteristics of study participants

	Group assignment			
	IVIG (N=16)	Albumin (N=14)	Total (N=30)	P-value
Age, Mean (SD) (Range)	31.7 (8.75) (20-49)	31.9 (9.99) (18-55)	31.8 (9.19) (18-55)	0.944[2]
BMI, Median [IQR] (Range)	24.1 [19.6, 30.3] (14-49)	22.7 [20.2, 27.7] (15-42)	23.8 [20.0, 28.1] (14-49)	0.708[1]
Supine HR, Mean (SD) (Range)	74.2 (9.51) (59-90)	74.4 (12.39) (54-96)	74.3 (10.75) (54-96)	0.967[2]
Supine SBP, Mean (SD) (Range)	118.9 (11.72) (105-144)	118.2 (19.48) (91-172)	118.6 (15.53) (91-172)	0.708[2]
Orthostatic HR increase, Mean (SD) (Range)	35.0 (10.98) (12-58)	45.1 (13.55) (23-64)	39.7 (13.07) (12-64)	**0.033**[2]
VOSS, Median [IQR] (Range)	21.5 [14.0, 28.5] (7-55)	18.5 [11.0, 38.0] (3-49)	20.5 [11.0, 31.0] (3-55)	0.603[1]
Screening COMPASS-31, Median [IQR] (Range)	55.5 [50.6, 66.4] (42-76)	57.4 [53.2, 65.0] (46-88)	56.8 [52.6, 66.3] (42-88)	0.648[1]
Baseline COMPASS-31, Median [IQR] (Range)	55.8 [53.5, 62.6] (50-76)	51.8 [46.7, 67.7] (34-92)	55.1 [51.2, 64.2] (34-92)	0.244[1]
Beighton score, Median [IQR] (Range)	4.0 [3, 6] (1-8)	3.5 [2, 6] (1-9)	4.0 [3, 6] (1-9)	0.634[1]
Main symptom score (0-10), Median [IQR] (Range)	7.0 [6, 8] (5-9)	7.0 [7, 8] (6-9)	7.0 [7, 8] (5-9)	0.285[1]
Standing norepinephrine, Mean (SD) (Range)	611.4 (231.25) (97-1112)	702.1 (316.51) (235-1196)	653.8 (273.29) (97-1196)	0.385[3]
Presence of systemic autoimmune disease	5 (31%) 3 Sjogren	3 (21%) 1 Sjogren	8 (27%)	0.689[4]

[1]Kruskal-Wallis p-value; [2]Equal variance two sample t-test; [3]Unequal variance two sample t-test; [4]Fisher Exact Test

IQR = interquartile range; VOSS (Vanderbilt Orthostatic Symptom Score)

Table 3: Comparison of treatment outcomes ("intention to treat analysis")

	Group assignment			
	IVIG (N=15)	Albumin (N=13)	Total (N=28)	P-value
Change in full COMPASS-31[3] Median [IQR] (Range)	-5.5 [-23.3, 2.5] (-27 to 21)	-10.6 [-14.1, -4.7] (-28 to 2)	-10.1 [-15.4, 0.0] (-28 to 21)	0.629[1]
Change non-OI COMPASS-31[3,4] Median [IQR] (Range)	-3.3 [-5.5, 4.2] (-11 to 6)	-2.6 [-3.7, -0.7] (-2 to 6)	-2.6 [-5.2, -0.1] (-28 to 6)	0.872[1]
COMPASS-31 % change[3] Median [IQR] (Range)	-10.3 [-38.6, 4.5] (-47.4 to 39.1)	-15.4 [-20.7, -10.0] (-43.5 to 3.1)	-14.6 [-23.8, 0.7] (-47.4 to 39.1)	0.800[1]
COMPASS improved 20%, n (%)	7 (46.7%)	5 (38.5%)	12 (42.9%)	0.718[2]
COMPASS worsened 20%, n (%)	1 (6.7%)	0 (0.0%)	1 (3.6%)	1.000[2]
Change in MCS score[3,5] Median [IQR] (Range)	-1.0 [-3.0, 0.0] (-6 to 3)	-1.0 [-3.0, -0.5] (-5 to 3)[*]	-1.0 [-3.0, 0.0] (-6 to 3)	0.692[1]
Change in VOSS total, Median [IQR] (Range)	-4.0 [-7.0, 1.0] (-20 to 12)	-3.0 [-11.0, 0.0] (-39 to 32)	-4.0 [-8.5, 0.5] (-39 to 32)	0.927[1]

[1]Kruskal-Wallis test; [2]Fisher Exact test; [3]Negative value reflects improvement; [4]Partial COMPASS-31 score includes all scaled subscales except orthostatic intolerance (full score 60 points); [5]MCS = most concerning symptom (0-10); [*]N=12. VOSS = Vanderbilt Orthostatic Symptom Score

Table 4: Adverse Events[1]

	Group assignment		
	IVIG (N=16)	Albumin (N=14)	Total (N=30)
Any adverse event, n (%)	15 (93.8%)	12 (85.7%)	27 (90.0%)
Treatment related AE, n (%)	13 (81.3%)	11 (78.6%)	24 (80.0%)
Serious adverse event, n (%)	1 (6.3%)	1 (7.1%)	2 (6.7%)
Headache, n (%)	11 (68.8%)	9 (64.3%)	20 (66.7%)
Fatigue, n (%)	6 (37.5%)	5 (35.7%)	11 (36.7%)
Pain, n (%)	6 (37.5%)	7 (50.0%)	13 (43.3%)
Dermatological/Rash[2], n (%)	6 (37.5%)	1 (7.1%)	7 (23.3%)
Gastrointestinal, n (%)	5 (31.3%)	5 (35.7%)	10 (33.3%)
Fever, n (%)	2 (12.5%)	1 (7.1%)	3 (10.0%)
Infection, n (%)	1 (6.3%)	0 (0.0%)	1 (3.3%)

[1]86 total adverse events reported among 27 participants;
No significant differences between groups; [2]p=0.09, Fisher exact test

Figure Legends:

Figure 1: Enrollment Consort Diagram

Figure 2: Treatment Protocol Diagram

Figure 3: Individual treatment responses. Primary outcome (% change in COMPASS-31) is shown for each participant who completed the protocol. A 20% decrease was defined as clinical improvement. The IVIG treated group showed broader range of response compared to albumin. One IVIG-treated patient worsened and 4 showed greater than 30% reduction in COMPASS-31.

Supplemental Figure: Additional Recruitment Detail Diagram

Figure 1

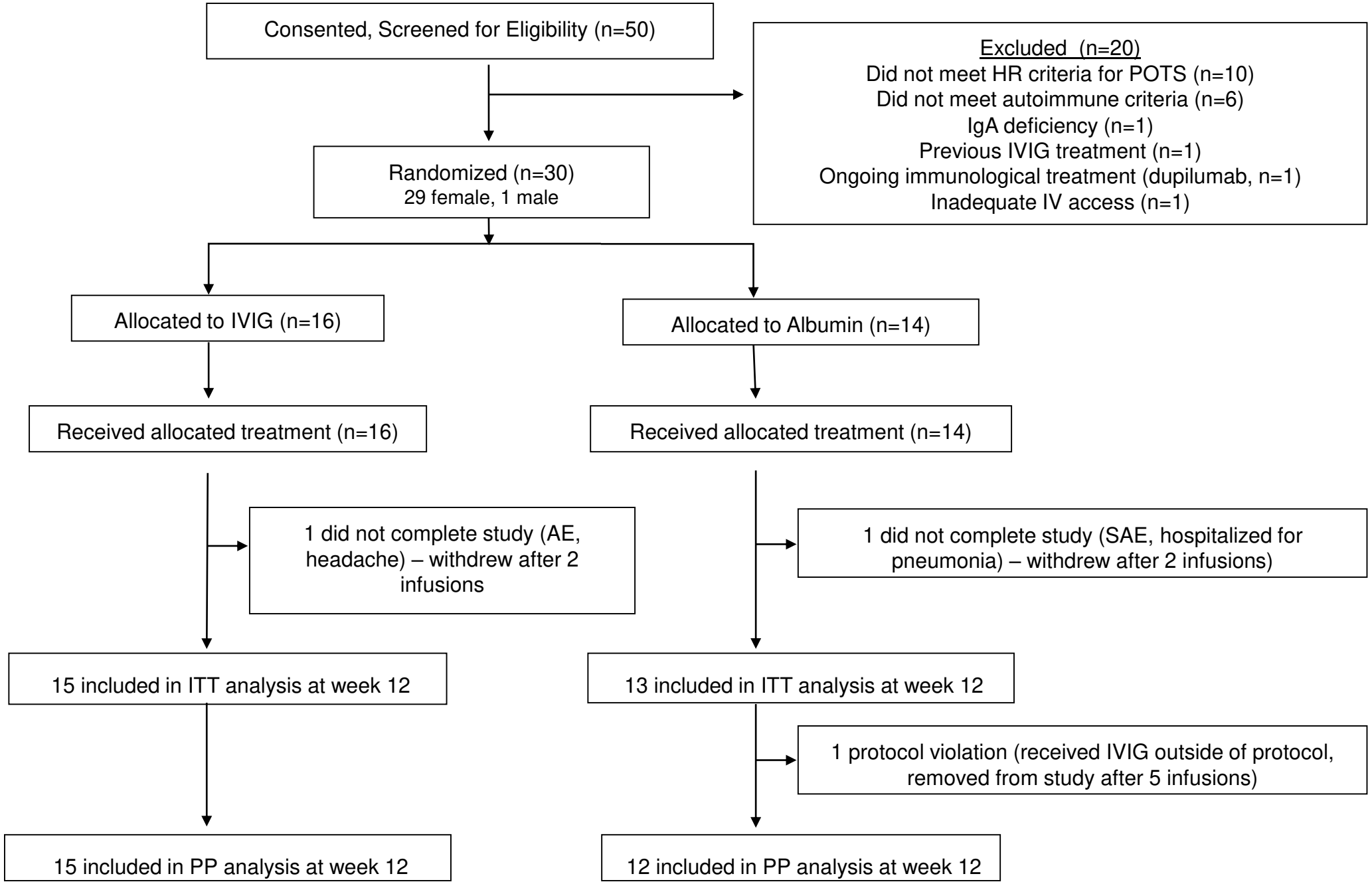

Consented, Screened for Eligibility (n=50)
Excluded (n=20)
Did not meet HR criteria for POTS (n=10)
Did not meet autoimmune criteria (n=6)
IgA deficiency (n=1)
Previous IVIG treatment (n=1)
Ongoing immunological treatment (dupilumab, n=1)
Inadequate IV access (n=1)
Randomized (n=30)
29 female, 1 male
Allocated to IVIG (n=16)
Allocated to Albumin (n=14)
Received allocated treatment (n=16)
Received allocated treatment (n=14)
1 did not complete study (AE, headache) – withdrew after 2 infusions
1 did not complete study (SAE, hospitalized for pneumonia) – withdrew after 2 infusions)
15 included in ITT analysis at week 12
13 included in ITT analysis at week 12
1 protocol violation (received IVIG outside of protocol, removed from study after 5 infusions)
15 included in PP analysis at week 12
12 included in PP analysis at week 12

Figure 2

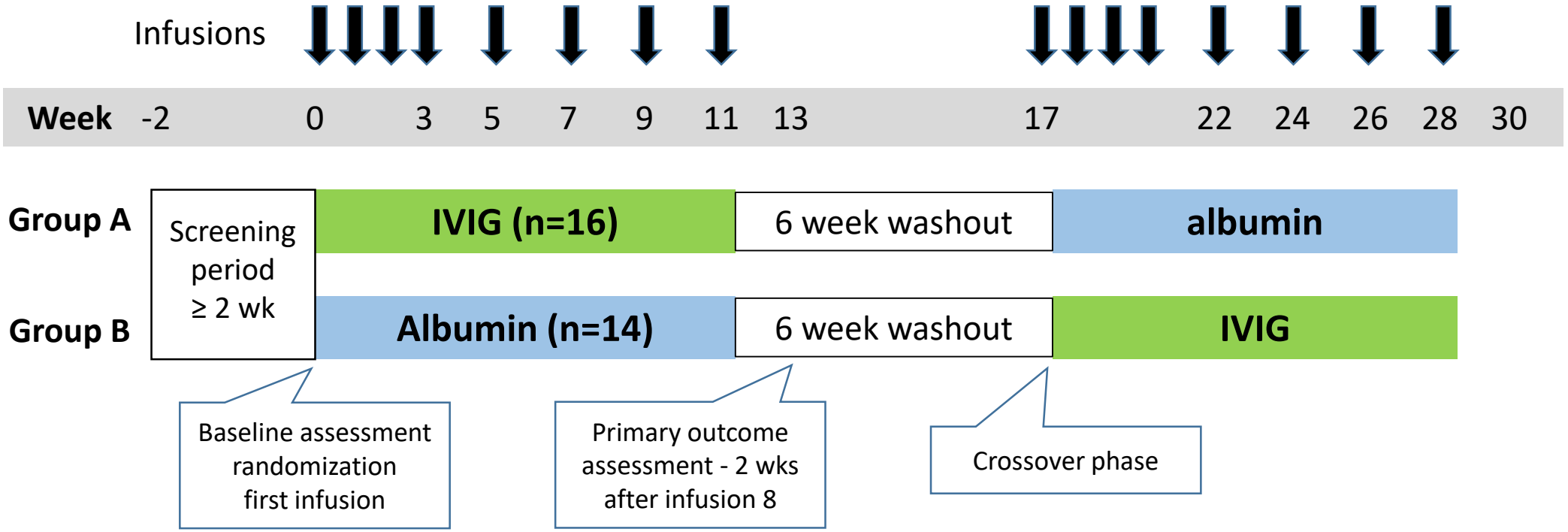
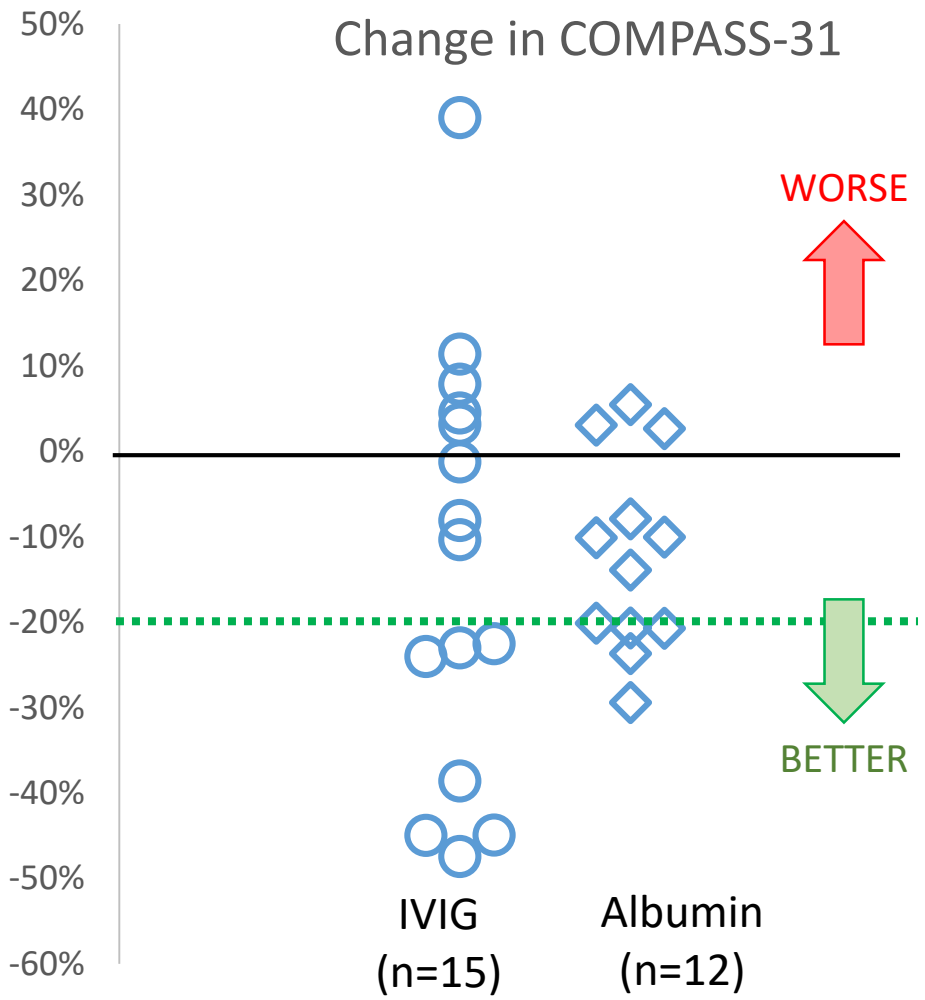

Infusions
Week -2 0 3 5 7 9 11 13 17 22 24 26 28 30
Group A
Screening period ≥ 2 wk
IVIG (n=16)
6 week washout
albumin
Group B
Albumin (n=14)
6 week washout
IVIG
Baseline assessment randomization first infusion
Primary outcome assessment - 2 wks after infusion 8
Crossover phase

Figure 3


Change in COMPASS-31
50%
40%
30%
20%
10%
0%
-10%
-20%
-30%
-40%
-50%
-60%
WORSE
BETTER
IVIG
(n=15)
Albumin
(n=12)

Supplementary Figure