A Randomized Trial Comparing Intravenous Immune Globulin (IVIG) and Plasma Exchange (PLEX) in Guillain-Barre Syndrome

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At the time of this trial, acute treatment for GBS (other than supportive measures) with PLEX had been studied in a number of clinical trials and was indicated in patients who presented within the first few weeks of disease onset and with major deficits at the time of presentation. At the same time, however, additional trials had also alluded to the benefit of high-dose IVIG in the treatment of CIDP, suggesting that IVIG could potentially serve as an effective acute treatment for GBS as well. Notably, IVIG also possessed several treatment advantages over PLEX (e.g., ubiquitous availability, high tolerability), so an analysis of its efficacy for acute GBS, relative to PLEX, was indicated. For this reason, the goal of this study was to determine whether acute treatment with IVIG was of equal efficacy as PLEX at improving the clinical course of patients with GBS.

Experimental design and statistics: Patients were eligible for enrollment if 1) they fulfilled criteria for GBS, 2) possessed an inability to walk 10m independently, and 3) were able to enter the study within 2wks of symptom onset. Exclusion criteria are noted below.[1] Eligible patients were then stratified by study center and then randomized to receive either PLEX (200-250mL/kg, 5 sessions over 7-14 days) or IVIG (0.4g/kg/day on 5 consecutive days) as soon as possible after randomization. Following an initial round of treatment, patients were able to repeat a second round of their same treatment if they showed deterioration after 1wk of clinical improvement or stability (i.e., showed a treatment-related fluctuation). Patients were followed for a total of 6 months after randomization, with 16 total follow up assessments. At the time of entry and at each follow up assessment, patients were given both a functional score (7-point scale of motor function[2]) and a Medical Research Council motor summary score[3]. Both scores were determined by an investigator blinded to each patient's treatment group, since treatment blinding during treatment administration was otherwise not feasible. The primary outcome for comparison was improvement by $\geq$1 grade on the functional score at 4wks post-randomization, as compared to that at the time of randomization. Secondary outcomes included the time to achieve this level of functional improvement, as well as the time needed to regain independent locomotion. Over the course of the trial, a stopping rule was set in place, such that study enrollment could be discontinued if one treatment was found to be significantly more effective than the other. Otherwise, the primary outcome was compared between the two treatment groups via Chi Square and Mann-Whitney U analyses. Secondary outcomes were analyzed via Kaplan Meier curves.

Results: A total of 150 eligible patients were initially randomized to receive either IVIG or PLEX. Three patients were later found to be ineligible after randomization, which led to a final study sample of 147 patients (73 = PLEX, 74 = IVIG). Baseline functional impairments at study entry were similar between the two groups (Table 1). Regarding the primary outcome, 34% of patients in the PLEX group and 53% of patients in the IVIG group achieved the primary outcome at 4wks ($p = 0.024$). As shown in Figure 3, group differences related to achieving the primary outcome were seen early after randomization (within 4wks), during which more medical complications and a higher percentage of mechanical ventilation

[1] Exclusion criteria: age <4yrs, a prior episode of GBS, IgA deficiency, prior severe reactions to blood products, pregnancy, treatment with immunosuppressants, severe concurrent medical disease, inability to follow up in 6 months

[2] Functional score ranged from 0-6, with 0 denoting healthy and 6 denoting dead. Scores in between denote different levels of functional loss/lack of independent ambulation.

[3] Medical Research Council summary scores provided scores for 6 bilateral muscle groups, yielding a summary score range from 0 – 60.

occurred in the PLEX vs. the IVIG group (for MV: 42% vs. 27%, PLEX vs. IVIG). Additionally, in terms of the secondary outcomes, the median times to functional grade improvement by >1pt were 41 and 27 days in the PLEX and IVIG groups, respectively ($p = 0.05$, Figure 1), and the median times to recovery of independent locomotion were 69 and 55 days in the PLEX and IVIG groups, respectively ($p = 0.07$, Figure 2). IVIG also appeared to be safe and well-tolerated, with only mild, infusion-related reactions (dyspnea, hypotension, hematuria) as well as mild, residual AST/ALT elevations after treatment. Overall, a total of 10 patients did undergo a 2nd round of treatment due to clinical fluctuations after 1 round of treatment, 6 in the IVIG group and 4 in the PLEX group. Finally, 2 patients in the PLEX group and 1 in the IVIG group died during follow up due to cardiovascular or respiratory complications.

Conclusions: Overall, this study was the first to show that IVIG was at least as effective as PLEX in improving the clinical course of patients with GBS. In fact, more patients in the IVIG group achieved early functional improvement (e.g., by 4wks post-randomization) as compared to PLEX, and fewer patients in the IVIG group experienced medical complications (including the need for MV). The mechanism underlying this difference in complication rates was unclear, though the study authors posed that it could have been related to the more frequent need for patients to discontinue a PLEX treatment session (16% vs. no treatment interruptions with IVIG). Regardless, as the goal of this trial was to confirm the utility of IVIG in GBS management, the major contribution of this study was the identification of IVIG as a safe and equally, if not more, efficacious acute treatment option for GBS.

Additional Reading, if interested:

1) Leonhard, S.H., et. al., **Diagnosis and Management of Guillain-Barre syndrome in ten steps**. Nature Reviews Neurology (2019), 15: 671 – 683.

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