Author’s response to reviews

Title: Cost-minimization analysis of the direct costs of TPE and IVIg in the treatment of Guillain-Barre syndrome

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Author’s response to reviews:

Dear Dr Galbraith,

Thank you and the reviewers for the constructive feedback concerning our manuscript. We have attempted to address the reviewers’ concerns. However, some of the requested economic analysis could not be performed due to a lack of appropriate data.

In addition to responding to the reviewers’ concerns, as outlined below, we have taken the opportunity to update the manuscript to include average cost data for our two institutions for 2010 as well as include the most recent CMS data. The subsequent analysis and the attached spreadsheet have been updated.

The specific changes to the manuscript and our response to the reviewers is as follows:

Response to Reviewers

Reviewer 1

The author assumed that serious adverse events (AEs) attributable to TPE or IVIg occur infrequently at similar rates and that associated costs would not directly affect this analysis. The author also assumed that the length of hospitalization would be equivalent between the two therapies given the equivalent time to response between the two. However, it’s debatable, a Dutch study reported a higher rate of complication with PE than IVIG; pneumonia, atelectasis, thrombosis, and hemodynamic difficulties occurred more often with PE than with IVIG. Sixteen of 73 patients (22%) had multiple complications with PE compared with 5 of 74 (7%) with IVIG. See: Van der Meché FGA, Schmitz PIM, Dutch Guillain-Barré Study Group. A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. N Engl J Med 1992;326:1123–1129. Also, another largest trial, adverse events occurred in 8 of 121 patients (7%) in the PE group (hypotension, septicemia,
pneumonia, malaise, abnormal clotting, and hypocalcaemia) and in 6 of 130 (5%) patients in the IVIG group (vomiting, meningism, renal failure, myocardial infarction, and infusion site erythema). The increased rate of complications with PE involve increased cost, from a pharmacoeconomic perspective. See: Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. Lancet 1997;349:225–230. Its means that more complication, more related and direct cost. Since the basic supposing is so debatable, therefore, analysis of the direct cost between TPE and IVIG seemed to be not so important and significant. The difference between Outpatient Hospital CMS 2010 Reimbursement TPE 8171, and Provider TPE Costs 4238 showed that there should be some bias and direct cost not emphasized by the author. The author should address the above questionable point to make the manuscript more perfect.

Response - The reviewer is correct that early trials indicated differences in complication rates between TPE and IVIG. However, as described on page 9 of our manuscript, there were problems with the study by van der Meché et al, which could have significantly influenced the complication rates. Specifically, the two treatment groups were not balanced, with those patients in the TPE group being older and more severely affected. This would have influenced the occurrence of complications with questionable attribution to TPE such as atelectasis and pneumonia. With regard to the frequency and types of complications that occurred in the larger Plasma Exchange/Sandoglobulin trial, the authors of this study make the following statement in the discussion:

“There were no significant differences between groups in the number of side effects attributed by the treating neurologist to the treatments or in the numbers of patients reported at 2 or 4 weeks after randomization to have infections requiring antibiotic treatment, abnormalities of liver enzymes, or cardiac arrhythmias.”

Later in the discussion, the authors further state:

“PE also removes immunoglobulins and clotting factors, which could in theory increase the risk of infection and haemorrhage, but neither occurred more frequently in the PE than IVIG group in this trial”.

Finally, the most recent Cochrane Database review of IVIG for the treatment of GBS found three trials of sufficient quality to examine the occurrence of adverse events related to treatment. Of note, the trial by van der Meché did not meet the criteria for inclusion. From these three trials, the relative risk of adverse events attributed to treatment was 0.84 for IVIG with a 95% confidence interval from 0.54 to 1.30. The fact that the confidence interval crosses 1 indicates that there is not a difference in reactions attributable to the two procedures. (see Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome (review) Cochrane Database Syst Rev 2006;(1):CD002063.) This has been added to the manuscript on page 4.
Recent articles examining the overall frequencies of the complications of TPE and IVIG, as referenced in our manuscript, have found similar frequencies and severity between the two treatments. In the early studies referenced by the reviewer, some of the complications associated with TPE are of questionable association such as atelectasis. Even pneumonia, postulated to result from decreased humoral immunity due to TPE, is of questionable association as this complication is rarely seen in clinical practice and has not been reported to occur in more recent TPE trials. Finally, it has been reported by the Canadian Apheresis Study Group that the frequency of complications due to TPE has decreased with time (0.8% in 1985 to 0.2% in 1998) (please see Rock GA, Clark W, Sutton D et al. The demographics of therapeutic plasma exchange. Transfusion 2001; 41 (Suppl.):40S). These findings indicate that applying the frequency and types of complications from these early trials in order to determine the costs of the treatment of these complications is not valid. We do not have access to contemporary data examining complication rate and severity for TPE and IVIG in order to determine the cost of treating complications and we, therefore, cannot perform the analysis requested by the reviewer. In the manuscript, on page 14, we have identified the assumption that the two treatments have similar frequency and severity of complications as a potential weakness of our paper. We have attempted to clarify that we are comparing direct costs and not total costs of the procedures by modifying the title of the manuscript and by explicitly stating this throughout the manuscript, including as a weakness of the study on page 16.

In the US, the reimbursement for IVIG involves primarily drug and nursing time. Since 2005, due to legislation under the Medicare Modernization Act (MMA), reimbursement formula for IVIG changed from AWP-based reimbursement (that included a high mark-up of 20% above cost) to ASP-based reimbursement that is Average Selling Price plus 6%) thus, significantly narrowing the delta between IVIG cost and reimbursement. At the same time in the past 10 years, while the cost for IVIG had doubled that for albumin has essentially remained the same, thus contributing to the lower direct costs for TPE that involves the use of albumin. In addition, albumin is reimbursed under a different formula by Medicare, as a blood replacement product and offers better reimbursement, creating a favorable delta for TPE.

Finally, for TPE, besides reimbursement of over $856 for the procedure, there is also separate payment in the hospital outpatient department for “vascular access” or for placement of central venous access line, which is not the case with IVIG that is administered intravenously with marginal reimbursement for nursing time. Hospital nurses being salaried, (fixed costs as FTEs) there is not a significant additional cost associated with TPE access. Hence the differences between TPE costs and reimbursement are much wider as shown than with IVIG especially now due to the very low delta between the very high cost of IVIG and the reduced reimbursement from Medicare.
1. The main issue relates to the fact that the authors compared only direct cost. In this reviewer's opinion, the primary comparison should be total cost and then direct and indirect costs separately.

Response - The purpose of our article is to point out that because of the dramatic changes in costs of IVIG and albumin over the past two decades, the direct costs of TPE and IVIG administration have changed. Frequently, assumptions are made, based upon early trials comparing the two modalities at a time when costs were dramatically different, that IVIG is "cheaper". Our goal was not to compare total costs of the two treatments. In order to compare direct costs, it would be necessary to determine the frequency and severity of complications of each treatment and the costs associated with these. The data to determine this is not available as described in our response to Reviewer 1.

2. Though systematic reviews and meta-analysis found that plasma exchanges and IVIg had similar effects on recovering muscle strength and function, they also showed that there were more patients relapsing within the first year in the TPE treated patients. This higher relapsing rate may increase treatment costs.

Response – The most recent Cochrane Database review of the use of IVIG in GBS examined relapse rates in TPE and IVIG. Three studies were included in the analysis including the van der Meché trial, the Sandoglobulin Trial, and a trial by Nomura. The relative risk of relapse for IVIG compared to TPE was 0.89 but the 95% confidence interval was 0.42 to 1.89. The fact that the confidence interval crosses 1 suggests that there is not a difference in relapse rates for the two procedures. (see Hughes RAC, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome (review) Cochrane Database Syst Rev 2006;(1):CD002063.) As our manuscript only looks at direct costs and not total costs and the evidence but does not confirm a difference in relapse rates, we have not added this to the manuscript.

3. RCTs also suggested that in GBS patients who did not lose the capability to walk, 2 sessions of TPE are sufficient and in the remainders 4 sessions had similar effects than 6 sessions. Thus, the total number of TPE may likely be further reduced lowering associated cost.

Response – The study by the French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome found that four plasma exchanges was superior to two in patients who did not need respiratory assistance. In more severely affected patients, six was equivalent to four except for the frequency of hypotension. (see French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome. Appropriate number of plasma exchanges in Guillain-Barré Syndrome. Ann Neurol 1997;41:298-306.) Statements indicating this have been added to page 5. We have not revised the analysis, however, as this would require considering multiple different potential TPE treatment regimens. We have assumed worst-case scenario, five TPEs, based upon the above findings as well as
published guidelines.

4. The authors have made the assumption that substitution fluids for TPE included albumin and crystalloids. Nevertheless, a number of institution are now using albumin and synthetic colloids mainly starch solution. This practice may likely increase the cost of TPE. It may be worth for the authors to present sensitivity analyses using the different scenario for the practical modalities of TPE (i.e. varying the number of sessions and varying the type of fluids substitution).

Response - The reviewer is correct that alternate replacement solutions can be used. These solutions are primarily used due to the fact that they are less expensive than albumin (e.g. pentastarch and hetastarch solutions) which would further decrease the cost of TPE. In addition to the use of colloid solutions, some institutions also use more crystalloid and less albumin (e.g. 60% albumin and 40% saline or even 50% albumin and 50% saline). Each of these strategies, while further reducing the costs of TPE, also increases the frequency of complications of TPE (e.g. increased frequency of hypotensive reactions with 50/50 albumin and saline, intractable pruritis with starch solutions, etc). In addition, the use of these alternate solutions or the use of less than 70% albumin is not consistent with guidelines published by the American Society for Apheresis. Other guidelines such as those of the American Academy of Neurology do not address technical issues such as this. For this reason, in our analysis we assumed a worst-case scenario that maximizes the direct expenses of the TPE, an 80% albumin/20% saline replacement. It is not feasible to perform calculations for all of the various permutations of the various colloid replacement fluids and the various percentages of albumin to saline. We have indicated on pages 6 and 15 that alternate colloid replacement fluids can be used as well as alternate percentages of albumin and that this would further decrease the direct costs of TPE. We have, however, indicated that these come with increased costs due to reactions and complications of the TPE and that the use of these other fluids are not consistent with the guidelines published by the American Society for Apheresis.

We hope that our responses address the reviewers’ concerns. If we can be of further assistance, please do not hesitate to contact me.

Sincerely,

Jeffrey L. Winters, M.D.