Author's response to reviews

Title: Patient-Reported Treatment Burden of Chronic Immune Thrombocytopenia Therapies

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Author's response to reviews: see over
22 December 2011

Jo Appleford-Cook on behalf of
Miss Emilie Aime
The BioMed Central Editorial Team

Regarding: MS: 1997926655620042. Patient-Reported Treatment Burden of Chronic Immune Thrombocytopenia Therapies T. Michelle Brown PhD, Ruslan V Horblyuk MBA, Kelly M Grotzinger PhD, Axel C Matzdorff MD, PhD and Chris L Pashos PhD

Dear Ms. Appleford-Cook,

Thank you very much for your notification message and the valuable feedback that you have provided on our manuscript. We are pleased to accept your invitation to revise and resubmit the manuscript. Below are our responses to the points made by the reviewers.

We look forward to future correspondence, and will do our best to respond as quickly as we can.

Best wishes,
Chris

Chris L. Pashos, PhD
United BioSource Corp.

Responses to Referees’ Feedback

Referee 1:
Discretionary Revisions- side effects of corticosteroids may be related to the dose and duration of treatment, it would be helpful if the authors can provide data on steroids dose and treatment duration to see whether most of the side effects were reported by subjects on a higher dose of corticosteroids. >>>>>> Data to inform this issue were not collected, to avoid adding too much complexity to the retrospective data collection instrument. Therefore, it is not possible to determine what proportion of the 90% of patients receiving corticosteroid (CS) treatment received higher doses or longer duration therapy. Text has been added on page 12 to the discussion presenting this limitation and suggesting additional research into the particular effects of specific regimens of treatment (e.g., CS doses and duration).

Referee 2:
This is a well done survey of 589 patients using appropriate methodology, which provides novel information, albeit within the limitations of an online survey. >>>>>> Thank you for your kind words.

Comparing chronic therapy with steroids to acute therapy with IVIG and anti-D is inappropriate as they are very different. IVIG and anti-D are given over one or two days whereas steroids maybe given daily
for weeks - months. Splenectomy is a more appropriate comparison to steroids as it would be considered “long-term” therapy. I am not ruling out the comparison but it needs to be clear that you are comparing apples and oranges. A comment about the significant burden/side effects of long term steroids would be appropriate (although I am not clear for the manuscript if you are able to distinguish whether patients received a short course of steroids (which could rightfully be compared to IVIG and anti-D) or chronic steroids). This needs to be clearly stated as a limitation of this study.

We agree. As noted above in our response to Referee 1, data to inform this issue were not collected in our study, so it is not possible to report on the specifics of therapy. Text has been added on page 12 to the discussion presenting this limitation and recommending additional research into the particular effects of specific regimens of treatment (e.g., doses and duration).

Clarity of the statistics: “aggregate bother” is used throughout the manuscript and is not a term that clinicians will be familiar with. Please make this concept clearer.

We appreciate the opportunity to clarify this concept. “Bother” is a term common among those clinical researchers focused on patient health-related quality of life assessment. Specifically it refers to the amount of interference or negative impact an effect or condition has on a patient’s well-being. “Aggregate” refers to overall or average level of the bother across all effects noted or experienced by the patient. We have added text to this effect in the manuscript (“Survey Instrument” section).

Related to this table 2 and 3 will be uninterpretable for the average clinician – for instance why is an adjusted R^2 of 0.17 in gender for steroids statistically significant? Explain Beta estimates – again a term most clinicians are not familiar with.

Text has been added in the “Determinants of Treatment Type Bother” explaining the importance of the betas despite the relatively low adjusted R^2, which themselves indicate that other (“unobserved”) factors also contributed to the results.

Introduction:
1. first paragraph – change “rate” to “prevalence”
This has been done.

2. second paragraph – delete “achieve and maintain a platelet count that” as this is controversial.
This has been done.

3. 3rd paragraph - I have never heard of IVIG being associated with epistaxis – please delete and back pain is not a common problem. Please replace with more common side effects such as fever, rash or similar.
More commonly acknowledged effects have replaced the original text, based on input from a more recent and more relevant reference, which has replaced the original one.

4. 4th paragraph – delete sentence “given that long-term ... successfully: as this is controversial.
The phrase, “given that long-term ... successfully”, has been deleted.

Results
There is duplication with table 1 – please delete any repetition – for instance delete the gender row from the table.
The gender row in the table has been deleted. The remainder of the table now provides details while the text provides overall highlights.
The first sentence of “Impact of Effects” is not clear, please revise.

We have separated the first sentence into two, and the text is much easier to understand now.

Tables

1. Under “Dry bleeds” “bruising” is misspelled.

This has been corrected.

2. Table 2 change title to Regression model predicting aggregate bother among patients with at least one side effect – taken from the text as this is clearer than the current title. Alter the text so that it is not identical to the table title.

These two changes have been implemented.

Referee 3:

P8 Statistical Methods (and elsewhere): please, define clearly the outcome and predictors of all the regression models you employed. From your description and the legend of some Tables, I understand that at least some models had treatment (0-1), bother (1-5) and a treatmentXbother interaction as predictors.

Was the treatmentXbother interaction modeled as continuous? What is the clinical interpretation of this interaction for the purpose of the present study? (I suppose that main effects were also in the models when this interaction was employed - is this right?)

More text has been added in the Methods to clarify the analyses. We apologize for the notation and the associated confusion. We have now clarified that the term in question is not an interaction term. Also, yes, it was treated as continuous. We did not include the main effects because they were not applicable given that the bother score was not obtained among those not receiving a given treatment. To interpret the variables, it is accurate to read each as: among those receiving a treatment, an increase in the bother score increased the perceived limitation of disease. A value of 0 represents no bother (no effect). Text was added to expand on the model.

P21 (and elsewhere) Some data reported as mean (SD) are unlikely to be normally distributed although this is difficult to tell without the raw data. Platelet count is a good example: its SD is 85980 vs a mean of 62230. A median would be a better descriptor of central tendency for these data.

We agree that platelet count was not normally distributed, and that the mean is therefore insufficiently informative. Accordingly we have removed mean (SD) platelet counts from Table 1, and replaced those data with more informative counts in the text: Results: Patient Demographic and Clinical Characteristics.

P22 (and elsewhere): the regression coefficients given in Table 2 were obtained using ordinary least squares regression. The outcome variable is a 5-level ordinal variable that is unlikely to be normally distributed. More importantly, it is unlikely that regression residuals are homoskedastic. You should formally check the assumptions of linear regression before accepting these coefficients and especially their standard errors / 95% confidence intervals - please, report SE or 95%CI in the Tables. Some ways to get around this potential problem: use robust or bootstrap confidence intervals, use robust regression (of which many varieties exist), use quantile regression to model the 50th centile as a function of the predictors of interest.

We reexamined the data and have added standard errors to the tables to provide a more complete understanding of the findings.
P23 (and elsewhere): weighted bother was obtained by multiplying mean bother by its frequency. Median bother may be better for the reasons reported above.

Since we conducted no analyses with the weighted bother data, we deleted the weighted bother column. As noted by the reviewer, it does not add to this communication of results.

P4 Please give a reference for the last phrase.

References are provided for the first phrase and the last phrase.

P6 It appears that the face validity of the study questionnaire was adequately addressed. Do you have any data on other validity dimensions of the questionnaire?

The clinician author provided confirmation of content validity. No formal psychometric testing was conducted on the survey instrument.

P7 (and elsewhere) The Likert scale gives much information that is lost by dichotomizing it when performing logistic regression. Ordinal logistic regression may be used to recover much more information from the data.

The dependent variables in these analyses were dichotomous. Text has been added in the Methods section to clarify this aspect of the analysis and to help avoid misunderstanding.

P9 589 patients completed the survey. But how many patients were sent the questionnaire? Please report the respondent rate.

No one was sent the questionnaire. Instead, this was a collaboration with the Platelet Disorder Support Association (PDSA), a patient support group in the United States. PDSA invited its members (who include patients with different platelet disorders) to participate if they had chronic ITP. Those members who were interested in participating in a study on chronic ITP opted into the survey by going to the secure portal, qualifying in, and completing the data collection instrument. It is not known how many chronic ITP patients were eligible and aware of the survey (to serve as a denominator population). So, unfortunately we are unable to report a meaningful respondent rate.