Author's response to reviews

Title: Patterns of Use, Dosing, and Economic Impact of Biologic Agent Use in Patients with Rheumatoid Arthritis: A Retrospective Cohort Study

Authors:

Thomas D Gilbert Jr (thomas.gilbert@ipsen.com)
Daniel Smith (dsmith@pharmetrics.com)
Daniel A Ollendorf (dollendorf@pharmetrics.com)

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Author's response to reviews:

Memo
To: BioMed Central Editorial Team
From: Daniel A. Ollendorf, Thomas D. Gilbert, Jr., and Daniel Smith
Date: August 19, 2004
Re: Response to Editorial Comments - Manuscript #1631230435382177

Thank you for considering our manuscript for publication. The purpose of this memorandum is to respond to reviewer's comments regarding the above-referenced manuscript ("Patterns of Use, Dosing, and Economic Impact of Biologic Agent Use in Patients with Rheumatoid Arthritis: A Retrospective Cohort Study"). The reviewers' comments are noted below, with our responses in italics.

Reviewer: Mark Nuijten
This is in general a solid study, which shows the real costs in daily practice of biologicals. This is especially relevant because of the high annual drug costs. It appears that biologicals are not used according to the label, and that actual costs are higher because of dose increase. The analysis shows that especially Remicade is used in higher dosage, which was found also in other studies. I recommend the authors including these references in the conclusion, because it strengthens their findings for Remicade. With regards to Enbrel, there are no studies, which show a dose increase. Therefore the small increase of Enbrel in this study should be considered with prudence, but further research is required.

References:

Page 6:
For example, a patient initially receiving infliximab and later receiving etanercept would be classified as an "infliximab" patient for the duration of the study period. This approach seems to be based on intention to treat, which is often ideal approach for cost-effectiveness studies. However, in this case the objective of the study is to assess the real costs associated with biologics in real practice compared with labeling information. The current approach is not suitable for calculation of this differences, when the Remicade analysis contains Enbrel patients and the Enbrel analysis contains Remicade patients. The current design compares first-choice treatment with Remicade with first choice treatment with Enbrel.

We disagree with the author's assertion that "intent to treat" is an invalid approach for this study. The intent of the study was to characterize all costs associated with patients initiated on an infliximab vs. etanercept regimen under conditions of typical clinical practice, which should in our view include the costs of other biologics received (including switch therapy). That said, the use of alternative biologic therapy in these two populations was miniscule, as indicated by the low average cost for etanercept among infliximab patients ($100-$200), and the similarly low cost for infliximab among etanercept patients ($200-$300). We therefore feel that inclusion of alternative therapy in our cost estimates might have slightly altered the magnitude, but would not have affected the direction of, our results. We have included text in the Results section to speak to the low use of alternative therapy.
Another pitfall may be that patients may increase the dose in case of lack of efficacy. However, lack of efficacy may also lead to a switch to another biological. The current analysis does not consider this option.

We have added text regarding this limitation to the Discussion section.

Page 7: Infliximab and etanercept doses reported at the third infusion/prescription respectively were considered to be the maintenance dose levels. There may have been already dose escalation during the initial start of the treatment. In this case maintenance treatment may already be higher than according to the label. I would recommend a table showing how many % of patients at the start of maintenance treatment have a dose, which is higher than the label.

In fact, the infliximab label has been modified to allow flexibility in dosing (from the original labeled dose of 3 mg/kg of body weight up to 10 mg/kg as necessary); our focus in the manuscript was to address the widespread perception that dosing patterns still follow the original label. These dosing guidelines are already addressed in the second paragraph of the Discussion section.

Page 9: Regression model should ideally contain a measure of severity of RA. However, the data base probably does not contain clinical measures of severity. Another important variable may be working status of the patient. Authors may address these variables, and explain, why these variables were not included.

The reviewer is correct; neither of these measures is available in the database. We have added text regarding this to the Discussion section.

Page 10: Most patients in the sample were members of an HMO or PPO product; however, the use of infliximab was much lower in the HMO group compared to etanercept (30% vs. 45% respectively) and substantially higher among PPO patients (49% vs. 35% respectively). Is there an explanation for this remarkable result, when considering financial systems between HMO and PPO?

It may be that HMO plans, who traditionally have more restrictive formularies, are placing greater constraints on the use of infliximab (which, even in the absence of dose escalation, is more costly to acquire and administer than etanercept). It should be noted that the major purpose in stratification by plan type was to examine the effects of plan type on dose escalation, however; while HMO plans trended towards a lower likelihood of escalation, there was not a statistically significant effect.

Page 14: Therefore, these results may not reflect the true amount of infliximab utilized and may in fact understate the rate of dose escalation, as a patient who increases from 1.2 to 1.7 vials will be shown to have utilized 2 vials in both instances. This may indeed underestimate real use, especially for patients with a weight just over 70 kg, who just have to use 3 vials. They need 2,1 vial, but have to increase to 3,1 vials in order to need an extra vial. Consequently a lot dose increases are masked. Authors may add estimation for this effect.

We are hesitant to attempt to estimate what actual dosing might be in the absence of data on actual units administered and body weight. In fact, our reliance on billed vials may either under- or overestimate actual use, depending on the dose increase required (as the second reviewer notes below). We have amended our description of this effect in the Discussion section.

Reviewer: Paul Emery
This is a retrospective analysis of the direct cost of anti-TNF drugs used in RA undertaken by a particular reimbursement agency in the US. As such, it is a relatively crude analysis of infliximab versus etanercept, knowing that there is a licensed indication to increase dose on infliximab but not to etanercept. Not surprisingly the finding is that the dose of infliximab increases whereas etanercept (with its absence of indication for increased dosing) does not.

It is important to recognize that we included all patients in the database who received infliximab after it received its indication for RA in the US (June 2000); the change in labeling to allow flexibility in dosing did not occur until several years later. However, the phenomenon of dose escalation has been documented before the labeling change took effect.

Points
* The numbers of patients are significant
* The inclusion criteria included 5 infusions or prescription of the index medication.

We are unsure if these statements require a response.
No indication that the data collected is validated is included in the methodology.

The data used for this study come from final, adjudicated record from health plans. We are unsure if the reviewer is speaking about clinical validation for patterns of care or validation of recorded data. Nevertheless, we have added text to the Discussion section regarding the fact that our data may have been subject to coding errors.

* The authors suggest that they under-estimated the increase in infliximab because it would be impossible to increase the dose from 1.5 vs. to 1.7 vs. with no detectable change in the reimbursement. In fact it is also possible that the reverse is true, that they have over-estimated the change because of a small increase in either weight or dose might require the patient to move from 1.9 vs. to 2.1 vs. The reimbursement cost would appear to be much larger under these circumstances.

We agree with this assessment and have amended the Discussion section accordingly.

* Because of the reimbursement situation arrangement may artificially raise the cost of infliximab. In practice, in large units the vials are shared to minimize this effect.

In the US, the manufacturer of infliximab prohibits its re-use; providers are expected to discard unused medication following the infusion. Even if this differs somewhat in practice, it is not likely that providers would change their billing practices - in other words, the actual amount of medication used would be rounded up to the next whole vial amount.

* The patients are not closely matched for age (for very understandable reasons reimbursement etc.) however this may have a major impact on the likelihood of increasing dose.

While it is true that we did not match our populations on age, age was controlled for in multivariate analyses of dose escalation. It does not appear in the final model specification (Table 3) because its effect was not significant at a p-value level <0.15 (and therefore did not enter the final model).

* The lack of ability to distinguish switching and labelling patients according to their initial therapy is also a major limitation.

We are unsure what is meant by this comment. If the reviewer is concerned about mixing patients who are naive to biologic therapy and those switching between drugs, our two cohorts were "inception" cohorts - i.e., they had neither claims for infliximab nor etanercept in the pre-index period.

We appreciate the opportunity to respond to these comments. Please feel free to contact us if there are further questions or concerns.