Author’s response to reviews

Title: Adherence with tobramycin inhaled solution and health care utilization

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Author’s response to reviews: see over
Dear Dr. Harold,

Please accept our revised manuscript “Adherence with tobramycin inhaled solution and health care utilization.” We believe this version is greatly improved due to the thoughtful recommendations from the reviewers and editors. Our responses to the reviewers are itemized below.

Reviewer 2

1) The methods are clear but for the non-US reader some further explanation of the healthcare system is required. Are these insurance claims from the employer or from the employee? (i.e., what does self-insure mean?) Is this a standard procedure in the states (i.e., might a patient move employer and then not be included)

A: The data come from the employer, and self-insurance is popular among large employers in the US. We have clarified the text: “The data come from approximately 45 large employers who self-insure their employees and dependents. Typically, large corporations or government entities use self-insurance as a way to manage their risk pool of sick and healthy employees rather than hire an insurance company. Self-insured employers have detailed data on the health care utilization of their employees and dependents.” (Page 5, 1st para)

2) Some more information about TSI is needed in the introduction. Particularly why was a one month on- one month off regimen decided on. This is a fairly unique regimen for a long term suppressive antibiotic therapy. Could it be that this unusual regimen is a factor in these poor levels of adherence (i.e., the families never settle into a routine?). This might be considered in the discussion.

A: The pivotal TIS study using the every other month treatment regimen was published in the New England Journal in 1993 by Ramsey et al. The rationale for this regimen was to reduce resistance, cost, and treatment burden while increasing convenience while maintaining lung function. While the reviewer is correct is proposing this unusual regimen might contribute to poor adherence, this is the recommended regimen by the manufacturer as well as the CF community as this is the only regimen that has been shown to be effective.

3) To highlight the poor levels in this study the authors should include data from studies that have used electronic data capturing (considered by most as the gold standard measure of adherence). For example, our study demonstrated mean adherence levels over 60% (McNamara, Journal of CF, 2009) to different inhaled CF regimens.
<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
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<tr>
<td>A</td>
<td>We have added this citation as suggested, but as the authors acknowledge, this was a relatively small, single center study. In addition, a recent paper accepted in Chest, uses the same electronic device, but found average adherence to TSI to be 37%. We added a caveat to the limitations section: “It should be noted, though, that studies using electronic data capturing methods have found a range of adherence rates with some reporting higher levels of TIS adherence in selected populations.” (Page 11, 3rd para)</td>
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<td>4)</td>
<td>Although numbers are good for this study, a concern is the relatively low number of patients (54) in the high utilization, 14 of whom were hospitalized. I think the authors should highlight these numbers with some caution when describing their main finding.</td>
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<td>A</td>
<td>We agree and have added this text: “Thus, our findings are consistent with the clinical trial results, and suggest that TIS use in routine clinical care and not within a clinical trial may also be associated with a reduction in hospitalizations. This finding deserves further study as the sample size of CF patients with high utilization was modest (n=54) and many factors besides TIS adherence contribute to hospitalization risk.” (Page 10, para 3)</td>
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<td>5)</td>
<td>In Background, I would rather have active than aggressive</td>
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<td>A</td>
<td>We changed the text as suggested. (Page 4, 1st para)</td>
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<td>6)</td>
<td>Methods, how do you know the patients were on TSI for the whole of the year chosen? (for example if a physician stops TSI, would their prescription be pulled immediately (that doesn’t happen in this country but we have a different system)</td>
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<td>A</td>
<td>We have data on all prescriptions dispensed for the study population during the period they are ENROLLED in this health care plan. Discontinuation of therapy does not result in missing data.</td>
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<td>7)</td>
<td>Discussion para 2, what is “national rate of use” and how did the CFF measure it? (why is the range up to 100% in 2006?)</td>
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<td>A</td>
<td>We clarified that statement as the “national AVERAGE rate of reported use”. The range shows that some individual CFF centers reported 100% rates of prescribing TIS for eligible patients. Please note that this may not reflect actual use, but rather prescriptions.</td>
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<td>8)</td>
<td>Para 3, as above need to be more equivocal about the finding supporting Ramsey et al. Are you simply identifying all round good adherers. Cannot assume that it is TSI alone (you need to be particularly careful here not to overegg your findings as the company have provided some support for this study)</td>
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<tr>
<td>A</td>
<td>We agree and have modified the text as described above in our response to Question 4: “Thus, our findings are consistent with the clinical trial results, and suggest that TIS use in routine clinical care and not within a clinical trial may also be associated with a reduction in hospitalizations. This finding deserves further study as the sample size of CF patients with high utilization was modest (n=54) and many factors besides TIS adherence contribute to hospitalization risk.” (Page 10, para 3)</td>
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<td>9)</td>
<td>Last para of discussion, quite a number of off-license drugs are prescribed to children, I don’t think the authors should make too much of this, shame it is the last sentence, much more important is to highlight the appalling overall levels of adherence to this therapy and possibly suggest some interventions to improve.</td>
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A: We deleted the sentence and have included the following: “One particular strength of these data is the ability to capture medication adherence as measured through prescription dispensing records; in this study, we found that persistent use of TIS was quite low and may deserve further investigation.” (Page 12, 2nd para) We are currently testing a randomized controlled trial to improve adherence in adolescents with CF at 19 CF Care Centers.

Reviewer 3

1/ Intro; need to insert a paragraph or two about the US healthcare system for non-US readers.

A: We have added this paragraph: “In the US, patients with CF often receive their health care through a network of over 100 cystic fibrosis care centers and affiliated programs that are located nationwide. These centers are usually located in teaching and community hospitals with a variety of medical provider partners. Most of the health care services and products received by patients with CF are paid for through employer-based health insurance that is offered to employees and their dependents as part of the employment benefit package. Detailed insurance claims are generated for every prescription drug, hospitalization, and physician service received by patients with CF and thus claim-based databases are one of the most comprehensive sources for assessing the overall health care utilization of this patient population in the US” (Page 5, 1st para)

2/ Methods, data; health care claims needs to be expanded on for clarity again for non-US readers.

A: As described above, “The data come from approximately 45 large employers who self-insure their employees and dependents. Typically, large corporations or government entities use self-insurance as a way to manage their risk pool of sick and healthy employees rather than hire an insurance company to do it. Self-insured employers have detailed data on the health care utilization of their employees and dependents.” (Page 5, 1st para)

3/ Encounter data needs an explanation.

A: We added this text: “Encounter data describe the individuals who are covered within the database …The encounter data include age, sex, geographic residence, and eligibility information.

4/ Measure of health care utilisation; needs to be written more clearly for non-US readership

A: We revised that section to read: “Hospitalization was determined by any admission to an inpatient care setting. Total costs were summed over the year and categorized into two main settings of care (i.e., inpatient care and outpatient care), and prescription drugs.”

5/ Demographic and health measures; needs to be written more clearly for non-US readership

A: We revised that section to read: “We evaluated demographic characteristics, including age, gender, and the 4 US geographic regions of residence (i.e., Northeast, Midwest, South, and West), and type of health insurance plan (i.e., comprehensive, Health maintenance organization, preferred provider organization, and other).”

Reviewer 1
Discretionary Revisions: The prescription of TSI is indicated for patients with chronic P. aeruginosa infection and an FEV1 between 25-75% predicted. Several comments are made regarding physician prescribing patterns within the U.S. Some comment on the use of TSI within or outside of the indicated range of lung function would be helpful in the broader analysis. The degree of compromised lung function of individuals with CF also represents a potential significant comorbidity in this population. Some comment on the health of the studied population (or the lack of that data) would be helpful in the interpretation of the data.

While we agree that it is likely that TIS is used outside of the range of FEV1 % predicted, we cannot comment on the lung function of the subjects in this study and feel that the suggested revisions are beyond the scope of the manuscript.

The authors also identified two other major comorbidities: P. aeruginosa infection and failure to thrive/growth failure. The rate of failure to thrive (4.4%) reported in this trial seems extremely low compared to CFF registry data. Do the authors have any comment regarding this?

A: We addressed this on page 12: “Second, *P. aeruginosa* infection and the rate of failure to thrive may be under-coded due to lack of financial incentive to include these diagnoses to billing records.”

Thank you for your consideration,

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