Author's response to reviews

Title: Incidence and cost of Treatment-Emergent Comorbid Events in Insured Patients with Chronic Hepatitis C Virus Infection: A Retrospective Cohort Study

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Author's response to reviews: see over
We thank the editor for the opportunity to reply to the reviewer’s comments. The comments are reproduced below along with our responses.

**Reviewer 1**

**Minor Essential Revisions**

1. line 216 and 217 I think it is worth including incremental before the means in this paragraph. It occurs with the first one but is not present in the remainder.

   This change has been made.

2. Given that costs are usually distributed asymmetrically it would be useful to report the medians in figure 3

   This change has been made.

**Discretionary Revisions**

3. Why did you exclude patients with a Hep B diagnosis- co-infection is not uncommon and it is not obvious to me that the removal of this patients is entirely appropriate. Carrying on from this point, it may be worth actually giving the percentage for the portion who were excluded because of inadequate enrollment (line 186-187). Personally I would have liked to have seen Table 1 expanded to include the excluded patients.

   The reviewer raises an interesting point. We excluded patients who may have received interferon for an indication other than hepatitis C, including those with hepatitis B and certain hematologic malignancies. Of the 2526 excluded patients, 138 were excluded based on these diagnoses. A clarifying clause has been added in the Methods at line 120 -121, and the following text was added in the first paragraph of the Results:

   ‘The most common reason for exclusion (2,274 patients) was lack of continuous enrollment for 24 months. One hundred thirty-eight patients were excluded because of a co-occurring diagnosis of hepatitis B or a hematologic malignancy, 16 because they lacked an HCV diagnosis in the pre-index period, and 85 because they had an initial dose of PEG-IFN-alfa/ribavirin other than one of those recommended by the manufacturer.”

4. Dosing can be adjusted for current low WCC and platelets. It may be that low initial dosing corresponds to a higher rate and cost of anemia and thrombocytopenia- you may wish to comment on this or alternatively if you
included the recommended lower dosage for low platelets in the inclusion criteria you may wish to comment on that.

We appreciate the reviewers comment and agree that this may be the reason for some of the lower doses. Unfortunately, the database we used does not contain laboratory results for the majority of patients, so we cannot identify which patients this would apply to. Eighty-five patients were excluded based on having a dose not in the manufacturer’s recommended range, and this information has been added to the first paragraph of the Results section. (See response 3 above)

5. If I understand it correctly, participants who may have died in the first year after initiation of treatment would not have been included, if you had any information about this it might be useful to include. I assume it would have only been a very small portion of the excluded population.

Unfortunately, we do not have any information about this population – in the database (which derives from commercial insurance claims) is difficult (if not impossible) to determine whether a patient has died or disenrolled for another reason, therefore all patients without adequate enrollment were excluded.

6. Given your discussion about triple therapy in the introduction it might be worth mentioning it in the discussion- I assume given the timing of the pivotal trials that none of the patients in the paper received triple therapy.

We thank the reviewer for pointing out this oversight. A sentence has been added at line 301 addressing this.

7. On line 148 it may be worth adding "prescriptions" before "fills"

This change has been made.

8. One thing not commented on is when discontinuing the combined therapy what portion continued on one element or other of the therapy.

In lines 147 through 152 we provide a short description of how discontinuation was defined. In order to be considered a discontinuer, a patient must have had neither drug for at least 60 days. In some cases, one drug was available to the patient for a longer period than the other. Because we were analyzing prescription claims, and not actual medication use, it is difficult to interpret this as representing actual continuation of one medication versus the patient simply having a longer supply of one. For that reason we did no further analysis of this group.
Reviewer 2

Major Compulsory Revisions

1. The most important concern is that the article is reported by the employee of Bristol-Meyers Squibb and that the research was funded by this company. This company is releasing new oral anti-HCV direct acting antivirals (DAAs), the adverse events of which are reportedly much less. This article reported the negative aspect of PEG-IFN-based anti-HCV therapy emphasizing the high rate of TECs with the cost to treat them, and the authors described in conclusion as “Better-tolerated therapies that reduce the financial burden on the healthcare system and improve patient experience are needed”. In face of the release of new anti-HCV drugs with much less TECs, the company that release these new drugs reported the negative aspect the previous therapy. This reviewer does not determine whether this contains conflict of interest or other problems or not, this fact should be taken into consideration.

We appreciate the reviewers concern.

2. In relation with Major point #1, the new DAAs will be very costly despite much less TECs. Although the financial burden to treat TECs will be reduced when using new DAAs, the total cost to achieve the eradication of HCV (i.e., the cost to achieve sustained virologic response, SVR) may be higher than current PEG-IFN-based therapy even when the cost to treat TECs is included. When investigating the financial burden, the authors should analyze the total cost to achieve the eradication of HCV and should not focus on the cost to treat TECs. The report focusing on only the costs to treat TECs can be unfair and may result in a biased conclusion.

The reviewer makes the important point that a major component of cost is the cost of therapy itself, and that our estimates are only relevant in the context of total cost. We fully agree with this. It was beyond the scope of this study to examine total costs in HCV, and several published cost-effectiveness models have already done so. Rather, we intended to focus on one aspect of cost that may be overlooked. We hope that our real-world estimates of the cost of TECs will improve the ability of clinicians and researchers to understand total costs of care in HCV.

We have added the following to the discussion:

"This study was intended to examine only one aspect of cost, not total treatment costs or cost-effectiveness. HCV treatment with PEG-IFN-alfa/ribavirin costs between $23,000 and $78,000 per year, and newer treatments are substantially more expensive."

3. The value of the cost to treat TECs is largely different depending whether the patient achieve the eradication of HCV or not. Without the data on the final
treatment outcomes, it is difficult to obtain the conclusions that have meanings.

We agree with the reviewers point that efficacy is a crucial determinant of utility of a given medication. The intent of the study was not to determine the overall value of a given treatment or treatments, but rather to inform clinicians, policymakers, managed-care decision-makers and researchers about an important cost related to HCV care.

As noted above in response 2, we added text to the discussion to address this issue.

4. Although the authors assumed the discontinuation of the therapy based on the duration of the prescription of drugs, the duration of treatment would be changed based on the response of HCV to the therapy after the start of the therapy. Actually, the AASLD guidelines recommended “response-guided therapy (RGT)”, according to which the treatment duration of some patients with HCV genotype 1 should be elongated to 72 weeks based on the reduction of HCV after the start of the therapy. Therefore, some patients discontinued their therapy even the period of drug prescription was more than 48 weeks. Conversely, discontinuation of the therapy is recommended even the patient did not experience TECs, when the response of HCV is poor. With the lack of the response of HCV after the start of the therapy, it is difficult to determine whether the therapy was discontinued or not and the reason of discontinuation.

The reviewer has highlighted a crucial limitation of our study. The study database was derived from insurance claims, and as such contained little clinical information. Specifically, we did not have data on virologic response to therapy. We have modified the description of limitations to clarify this issue:

“Lack of clinical data can confound interpretation. In particular, HCV treatment duration is dictated by GT, which was unavailable for most patients in this study. HCV GT was available for a subset of 238 patients. In this subset, 81% had GT 1/4/6, which is similar to other US cohorts, suggesting that our data are representative of the US population [31,32]. According to standard treatment recommendations, these patients with predominately GT-1 would be expected to complete 48 weeks of treatment [33]. This subset of patients had discontinuation rates that were similar to the overall group, which suggests that our assumption that treatment duration was indicative of GT was reasonable. Furthermore, response guided therapy would lead some patients to have treatment recommended beyond 48 weeks. If these patients continued treatment up to 48 weeks, they might be clinically discontinuing therapy prematurely, whereas in our analysis they would not be considered to have done so. Conversely, discontinuation of
therapy may be recommended when virologic response is poor, and we could not distinguish between this and TECs as a cause of discontinuation.”

Minor Essential Revisions

1. Methods, Study population, page 6, 2nd paragraph: Why did the authors describe various kinds of leukemia uniquely as exclusion criteria, while other diseases were not described?

Hepatitis B and hematologic malignancies were considered exclusions since patients may receive interferon to treat these conditions. In an attempt to reduce confounding, we elected to eliminate these patients. We have modified the results section to indicate the number of patients eliminated as a result of this decision.

“The most common reason for exclusion (2,274 patients) was lack of continuous enrollment for 24 months. One hundred thirty-eight patients were excluded because of a co-occurring diagnosis of hepatitis B or a hematologic malignancy...”

Various hematologic malignancies were listed separately because they have multiple ICD – 9 – CM codes. We have added a clarification at line 120 – 121 in the Methods section.

2. Methods, Covariates, page 8: “Physicians specialty was assigned using claims from the preindex periods.” Can the specialty of the doctor who actually performed anti-HCV therapy really be determined with this method? The patient might have been referred hepatologist when receiving anti-HCV therapy.

We thank the reviewer for highlighting this issue common to all analyses using US insurance claims. The reviewer is correct that the specialty of the prescribing physician cannot be directly identified using claims. For this reason, we use a validated method to impute the specialty. Using the method of Hwang, et al, the specialist with the most visits in the pre-index period is assigned as the "usual physician." We have added a clarification in lines 161 – 162.

“The specialty of the physician prescribing therapy was not directly identifiable in the claims database. Instead, the method counts all claims for evaluation and management services and identifies the physician specialty with the largest plurality of such claims.”

3. Results, page 11, lines 208-209: “for medications to treat anemia and neutropenia" What kind of medications were prescribed? Please describe in details.
The medications included in this category were epoetin alfa, darbepoetin, filgastrim, and eltrombopag. This information has been added to the text at lines 223-224.

4. Results: page 11, lines 209-213 and Discussion, page 13, lines 259-261: “The increase in non-drug-related charges ...” and “Nonprescription costs accounted for most of the total costs ...”. Usually, the follow-up interval is closer during the first 12 weeks when treating patients with PEG-IFN regardless of TECs. Therefore, it is usual that non-drug-related charges were greatest during the first 12 weeks. The high nonprescription costs during the first 12 weeks do not mean that the patients who stopped treatment by 12 weeks frequently experienced TECs.

The reviewer makes an interesting point regarding follow-up interval. We agree that scheduled visits would not be evenly distributed throughout the post-index period. Two things decrease the likelihood that scheduled visits alone account for the difference in non-prescription costs observed. First, a typical charge for an office visit would be in the range of $100-250, and thus an inordinate number of visits would be required to account for the observed cost difference. Second, only visits that included a claim for one of the TECs listed in lines 138 – 147 were included in this calculation-- a visit for follow-up and evaluation would not be included. It is possible that more frequent scheduled visits increase the opportunities to identify and diagnose TECs.

We have added clarification to the Methods section at lines 132 and 136:

“The primary outcome variable was net incremental cost, which was calculated as the difference between preindex and postindex cost for a prespecified list of TECs (see following paragraph) and their treatments, excluding the cost of PEG-IFN-alfa/ribavirin therapy. Charges for TECs were taken from medical claims consistent with one of these events or pharmacy claims with National Drug Codes for medications to treat the events. Charges for visits lacking a code for one of the listed TECs were not included.”

5. The right column of Table 2 and Figure 1 overlap.

We are unable to address this, as we submitted the Tables and Figures as separate files. We assume the final version will be corrected.

6. Figure 1 can be deleted.

The figure has been deleted and the remaining figure renumbered.