Reviewer's report

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

Version: 2
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Reviewer: Hidenori Toyoda

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This article by Sapra et al. reported the incidence and cost of treatment-emergent comorbid (TEC) events associated with peginterferon (PEG-IFN)-based antiviral therapy against chronic hepatitis C virus (HCV) infection. The research is original and may be useful. However, there are several concerns.

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.

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.

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.

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.

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?

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.

3. Results, page 11, lines 208-209: “for medications to treat anemia and neutropenia” What kind of medications were prescribed? Please describe in details.

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.

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

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.