Reviewer's report

Title: Triple therapy for hepatitis C improves viral response but also the risk of severe infections and anaemia: a frequentist meta-analyses approach.

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Reviewer: cALOGERO Cammà

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The authors have attempted a meta-analysis of the available literature in order to evaluate efficacy and safety of triple therapy (TT) with first generation PI (boceprevir and telaprevir) in comparison with dual therapy. Ten RCTs were assessed. Grouped rather than individual patient data were used. Authors concluded that triple therapy with boceprevir and telaprevir increases both the proportion of SVR and the occurrence of SAEs.

Although this analysis was conducted with rigorous methodology and there is some valuable information contained in this paper regarding the issue of TT tolerability which is of interest to hepatologists, it does not add any novel observations. The authors do not make a sufficiently convincing case that this study will add significantly to clinical practice and to future research. I am not sure whether the data presented in this meta-analysis is necessarily stronger than data of the RCTs and several meta-analyses that have been previously published.

The studies pooled in this meta-analysis are heterogeneous in terms of baseline features of patients included, schedules of treatment, making it more difficult to draw firm conclusions and limiting the conclusions that may be drawn regarding the efficacy and safety of TT. Ideally, a meta-analysis would include individual patient data with up-dated follow-up. Unfortunately, the overall interest of the study is limited by the clinical heterogeneity among the included studies, which limits the conclusions that may be drawn regarding the benefit of first-generation PI treatments and the authors are very fair in pointing out the resultant limitations on the conclusion that may be drawn from these data.

Another problem with this meta-analysis is that there are limitations in the data, which are beyond the authors’ control, but nevertheless compromise the value of the study. In particular, the lack of data on IL28B prevalence hampers the validity of the pooled estimates of the effect size.

Several important methodological issues must also be reconsidered.

1. A major concern of this meta-analysis is that trials of naive and experienced patients were pooled. So, the studies selected are heterogeneous from a clinical point of view. I agree that it is correct to test for quantitative heterogeneity. The significant statistical heterogeneity observed in many of the performed analyses is a valid reason for choosing a random effect over a fixed effect model. The random-effect model should take care of the quantitative heterogeneity.
However, whichever statistical method is chosen one needs to be confident that clinical diversity is not so great that the studies should not be combined at all. If there is substantial clinical heterogeneity, it is preferable not to pool the studies. Therefore, when a significant heterogeneity of baseline risk is found, more detailed treatment comparisons could be achieved by a meta-analysis of individual patient data only. Referee suggests that the authors may be looking to perform a quantitative method to assess combinability of RCTs in meta-analysis according to Aiello et al (Assessing covariate imbalance in meta-analysis studies) Stat Med. 2011 Sep 30;30(22):2671-82.

2. Any meta-analysis is susceptible to publication bias. One can sympathize with the authors when they included studies published as full paper only. The authors restricted the literature search excluding abstracts. However, many of those performing meta-analysis include abstracts in the literature search in order to contain all the work in the field. The authors may need to justify themselves.

3. Meta-analysis of multi-arm trials has been used increasingly in recent years. Referee suggests to include in the analysis only the most relevant treatment group of multi-arm RCT, using effect size estimates calculated from observations on that measure. So, the statistical analysis should use only independent estimators of effect size as suggested by Hedges and Olkin (Statistical Methods for Metaanalysis. San Diego, Calif: Academic Press; 1985.)

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.