Reviewer's report

Title: Meta-analysis: implication of IL28B polymorphisms in spontaneous and treatment-related clearance for hepatitis C patients

Version: 3 Date: 29 June 2012

Reviewer: Jaime Peters

Reviewer's report:

The authors have undertaken a very large review of the evidence. Although there are many results reported, there needs to be more consideration of the studies and the assumptions made in the analysis when reporting these results. Below are my suggestions for helping to improve the manuscript.

Major compulsory revisions

1. There are a lot of results and figures presented. The penultimate paragraph of the Discussion section clearly identifies the considerations needed to interpret the results of this meta-analysis. To help the reader fully acknowledge how the different reported results should be interpreted, as well as giving an idea of which ones we can place more confidence in, there should be more text to guide the reader through the Results section itself. For instance,

p10 rs12979860 a) Race: It would be helpful to point out that three of these subgroup results are based on results from a very small number of studies, therefore there is uncertainty associated with the estimates reported.

p11 rs12979860 b) HCV genotype: Point out that the difference between genotype 1/4 and 2/3 is statistically significant here.

p11 rs8099917 a) Race: Make clear that there is still a great deal of heterogeneity within the Asian subgroup (i.e. I2 = 66%).

p11 rs8099917 b) HCV genotype: Some interpretation needed so reader can get an idea of how much confidence to place in these estimates.

p11 rs8099917 c) Type of viral infection: As above, point out since heterogeneity within HCV monoinfected subgroup (I2=65%), only three studies in HCV/HIV coinfected subgroup.

p12 rs12980275 a) Race and b) HCV genotype: Point out only 2 or 3 studies in each subgroup.

2. The authors state that meta-analyses were conducted following PRISMA guidelines. PRISMA is for the reporting of systematic review and meta-analyses, not for conduct. The authors should check that their methods comply with guidelines for systematic review and meta-analysis methods such as Cochrane Handbook, Centre for Reviews and Dissemination handbook, published texts (e.g. Sterne et al Systemati Reviews in Healthcare (BMJ Books) or Sutton et al Methods for Meta-analysis in Medical Research (Wiley)), the HuGENetTM HuGE review handbook, specifically for meta-analyses of genetic association studies.
3. Related to point 2 above, there does not seem to be any report of critical appraisal of these studies. This is a serious omission as it is not clear to the reader whether the studies on which the meta-analyses are based are highly likely to be susceptible to bias or not. The authors should provide details on the quality of the included studies to aid interpretation of the meta-analysis results.

4. I suggest the authors be VERY careful about omitting studies just because they are different to the rest of the studies (p10, a) Sustained virologic response and p13 b) Spontaneous clearance). If the authors could supply an explanation for why these 2 studies should be excluded (Smith for SVR and Dring for SC) on the basis of population characteristics etc, I would be much more confident about this part of their methods. However, as it stands, I would advise the authors to report the results of these meta-analyses with Smith and Dring included, and report their influence sensitivity analyses after this. It is not good practice to exclude studies just because their estimates are different to the others. This practice could easily introduce bias into the meta-analysis and provide misleading results.

5. I am not convinced that excluding those SNPs where only one study provides evidence is appropriate. I realise that the focus of the paper is the meta-analysis, but this paper also represents the most-up-to-date review of the evidence in this area and so reporting these results, even though they can’t be included in a meta-analysis, would be very useful. For rs8099917, meta-analysis of only 2 studies is reported and I’m not sure this is any more informative than just reporting results from an individual study.

6. The methods section reports that searches were conducted up until October 2011, yet in the results section (p9) it is reported that publication year ranged from 2009 to 2012 – could the inclusion of 2012 articles be clarified by the authors?

7. p10 Publication bias test results: I would also add in this section that it is very difficult to tell whether publication bias is present for rs12979860 (SC) and rs12980275 (SVR) as there are only a few studies reporting on these. Therefore, publication bias cannot be ruled out and this should be made clear to readers. Recommendations indicate that such methods should not be used when there are fewer than 10 studies (see Sterne et al BMJ 2011; 342: d4002 or Cochrane Handbook).

8. Related to 7 above, the authors should qualify their statements of publication bias not being detected when only a handful of studies are included in the analyses. In particular, last sentence of page 13: it should be pointed out that you would not expect to find publication bias in a sample of 2 studies as the methods are not powerful enough (again see Sterne et al BMJ).

9. Bottom of page p15 “Both studies individually showed a significant association, but this significance was lost after performing the meta-analysis” Could the authors provide an explanation of why this is seen?

Minor essential revisions

2. Define IFN in abstract (Conclusions)
3. Main text suggests fixed and random effects meta-analysis models used, but abstract only reports that random effects models were used – this should be clarified.

4. p9, first line of second paragraph: use of “near IL28B” – the term “adjacent” was used in the inclusion criteria section. Do near and adjacent mean the same in this context? If so, perhaps one or other term could be used throughout for consistency.

Discretionary revisions

1. p9, 3rd paragraph: providing the number of studies as well as the number of individuals for each genotypes could be helpful to the reader.

2. p18, last paragraph: typographical error: - “row” should be “raw”.

Quality of written English: Acceptable

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

Declaration of competing interests:

I declare that I have no competing interests.