Author's response to reviews

Title: Thyroid disease is a favorable prognostic factor in achieving sustained virologic response in chronic hepatitis C undergoing combination therapy: A nested case control study

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Author's response to reviews: see over
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ADRIAN ALDCROFT  
EXECUTIVE EDITOR  
BMC SERIES JOURNALS  
BIOMED CENTRAL

Dear Adrian,

MS:  1307502268439239  
Thyroid disease is a favorable prognostic factor in achieving sustained virologic response in chronic hepatitis C undergoing combination therapy: A nested case control study Huy A Tran, Robert Gibson and Glenn E M Reeves

Thank you for your email dated November 20\(^{th}\), 2010 with valuable comments from the editor and reviewers. Thank you also for the extension of the revised manuscript. Please find attached the revised version. The detailed responses to the comments are as follow:

**Editorial requests:**

#1 Ethics: As the study is a retrospective analysis of treatments that are clinically indicated, we have been advised that no ethic approval was required. All HCV patients who undergo treatment at our unit by default consent to the study. A supporting statement from the Ethics Chairperson can be provided if required.

#2: Author contributions: This has been revised to meet the Journal’s requirement.

#3: The revised manuscript has been reformatted to conform with the journal style as required.

**Reviewer 1 (Professor Alessio Aghemo):**

**Major revisions:**

#1: The subjects were matched for genotypes which happened to be 1 & 3. Table 1 has been updated to include liver staging as either non-cirrhotic or cirrhotic. No liver biopsy results were available as these cases postdate histology requirement. The cirrhosis status was determined clinically by the treating hepatology team.

#2: The breakdown of IFN-a2a and IFN-a2b treated groups and the dose of ribavirin have been included and matched. The results are then re-analysed.

#3: The data on RVR is incomplete and thus only EVR and ETR have been included in the revision.
#4: There was no other predictor of SVR at a multivariate analysis as all other parameters were matched. We have elected to retain the analyses for both HCV-1 and HCV-3 despite all of the latter achieved SVR. All results are then available for the readers to inspect and form their own opinions.

**Minor essential revisions:**

The doses for PegIFNa2a and RBV have been clarified. The RBV doses have been reviewed and indeed follow the label when it comes to PegIFNa2b.

Patients were divided in two treatment groups with PegIFNa2a and PegIFNa2b. The reviewer’s comment regarding the different immunogenicity of the two types of IFNs is highly valuable and has been incorporated into the discussion.

Similarly, a comment has also been included regarding IL-28B SNPs and its place as a major predictor of treatment outcome. The clinical significance of this new discovery remains to be determined however.

**Reviewer 2 (Professor Guiseppe Montalto):**

#1: A multivariate analysis was performed to assess thyroid disease as a positive prognostic marker of therapeutic outcome. All revised 19 patients were retrieved from our treatment unit over a 5 year period which involved 512 patients. The point on cirrhotic patients was a little unclear but non-TD cirrhotic patients have been also included as control subjects.

#2: It is unfortunate that the point on adjuvant thyroxine therapy is misunderstood and perhaps it was not made very clear. The point is to simulate the exposure of HCV patients to high tetraiodothyronine concentrations similar to that of thyrotoxic concentration in the hyperthyroid phase of the thyroiditis. It is our hypothesis that supraphysiological concentrations of fT4 is HCV virocidal and therefore influences the final SVR although this is purely speculative and is yet to be proven.

**Minor concerns:**

The introduction section: the 5-10% prevalence of thyroid disease has been referenced as requested.

Line 3-4: the sentence has been reworded because as pointed out, it is misleading. The reviewer is correct in that the prevalence is now controlled but yet the sequelae are expected to increase due the lag-time effect.

The total number of patients who were conclusively proven to have thyroid disease has been revised to 19.

Third line: this has been referenced as requested.

Therapy: as per reviewer 1, the type of PegIFNa has been clarified.
Under “Patients and controls participants” it is said that “All (pts) were reviewed at monthly intervals, including those who developed TD with TSH levels...”: It is unclear what is required here. All patients (controls and TD) were indeed reviewed at monthly intervals to monitor progress.

Under “Thyroid disease definition”: The decision to perform the pertechnetate uptake scan is entirely with the treating endocrinology unit and is based on the clinical assessment. It is not based on TSH value alone. There is no published or agreed definition of thyroiditis. The authors summarise best of what appear to be the consensus of the literature.

Result section: The first paragraph has been removed as directed.

All revised 19 thyroid disease patients were assessed to have thyroiditis with the exception of one. The biochemical fT4 and fT3 concentrations vary between patients. With regards to TD, all patients were managed mutually and independently. That is IFN or RBV doses might have been modified or ceased because of TD. All TD patients were confirmed to indeed have thyroid disease, and not just a condition of non-thyroidal illness.

Discussion section

At the end of the first paragraph the AA say: “The relationship between TD and SVR was only scarcely addressed and in our solitary meta-analysis, the outcome was negative (8). Why to insist!” The authors are not clear about this comment. We think it is worthwhile to explore this hypothesis further, especially if open up another potential therapeutic option for HCV patients.

Statistical review: Yes – Comment: One of the authors, GEMR is a qualified medical statistician.

Further comment(s): T L Jones has been added to the author list.

With kind regards and please let us know of any more requirements.

Yours Sincerely

HuyATran

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