Reviewer's report

Title: Long-term outcomes after nucleos(t)ide analogues discontinuation in chronic hepatitis B patients with HBeAg-negative

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Reviewer: George Papatheodoridis

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The possibility of nucleos(t)ide analogues (NAs) discontinuation in patients with HBeAg-negative chronic hepatitis B (CHB) is very timely and therefore the subject of this study is interesting. The number of patients included is not very large but it is adequate for such a study and the duration of post-treatment follow-up is satisfactory. However, there are issues which need to be clarified and/or improved.

Comments

1. The definition of CHB reported in this study is suboptimal and not consistent with the scientific guidelines. For example, did the authors consider an HBeAg-negative patient with ALT 1.2xULN perhaps just on one occasion and HBV DNA 2200 IU/ml as a definite CHB case without a liver biopsy? If they started antiviral therapy in marginal cases with mild ALT elevations and relatively low HBV DNA levels, they should comment on this in their discussion. This is a limitation which might have resulted in the inclusion of grey-zone HBeAg-negative CHB cases and may have affected the high off-treatment sustained response rate they report. Otherwise, they should rephrase the definition of CHB.

2. The definition of virological off-therapy relapse is unclear. The authors report that “Virological relapse was defined as an elevation of HBV DNA levels of 1 log10 IU/mL off-therapy in at least two determinations more than 4 weeks apart”. Since the patients who discontinued therapy had undetectable serum HBV DNA, the authors should clarify what they exactly mean by 1 log10 f HBV DNA elevation. If this means 1 log10 f HBV DNA elevation from the detection limit (200 IU/ml) of the assay used, then they should better state that “Virological relapse was defined as HBV DNA levels >2,000 IU/mL off-therapy in at least two determinations more than 4 weeks apart”, which is an acceptable definition of post-therapy relapse. If they mean something else, then they should change the definition and reanalyse their data.

3. The numbers of most patient subgroups according to the different type of NAs therapy are very small (particularly the telbivudine and entecavir treated patients) and therefore any comparisons between these subgroups are meaningless. The authors may report the type of NAs used but they should substantially limit the presentations of such comparisons. Figure 1D may be better removed.
4. The post-treatment ALT and HBV DNA levels of the patients with relapse should be presented more clearly; not only the ratios with baseline levels but the absolute levels should be also described. The outcomes of these patients should be also described in more details. Is there any chance that the relapse was only temporary, as it has been previously reported by others? Were they retreated?

5. It is strange that the “last date of follow-up was January 1, 2012”.

6. The manuscript needs substantial linguistic improvement.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

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