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Letter to the Editor

Combination therapy for chronic hepatitis B: The future and beyond

To the Editor:

We read with great interest the article entitled "Phase IV randomized clinical study: Peginterferon alfa-2a with adefovir or entecavir pre-therapy for HBeAg-positive chronic hepatitis B." by Hsu et al. in the December 2017 online edition.[1] Over the past decades, antiviral therapies have dramatically improved long-term outcomes of chronic hepatitis B (CHB). For HBeAg-positive patients, early HBeAg seroconversion is an important treatment end point for a promising outcome. Through immune modulatory effect, pegylated interferon (PEG-IFN) achieved higher rates of HBeAg seroconversion than nucleos(t)ide analogues (NA). However, the response rate of PEG-IFN is unsatisfactory. Therefore, combination therapies may have potential benefits.

In this paper, the authors demonstrated that PEG-IFN monotherapy and sequential a short course of NA therapy followed by PEG-IFN monotherapy were comparable in efficacy and safety. Thus, they concluded that PEG-IFN combined with a short-term NA therapy is not superior to PEG-IFN monotherapy. However, the optimal combination strategy remains elusive and deserves further discussion. First, the rationale of 4-week NA pre-therapy in the sequential combination therapy requires further clarification. The long-term NA therapy can restore HBV-specific adaptive immune response. The additional PEG-IFN on long-term NA therapy could enhance the function of HBV specific T-cell after restoration.[2] In a recent meta-analysis including 24 studies, patients receiving PEG-IFN at least 48 weeks after the beginning of NA had significantly greater HBsAg loss than patients who treated with simultaneous initiation of PEG-IFN and NA.[3] These findings indicate that additional PEG-IFN might achieve better responses than PEG-IFN monotherapy after long-term administration of NA. The Second issue is to determine the baseline factors associated with responses of combination therapy. In line with previous studies, the authors found that on-treatment HBsAg levels of PEG-IFN therapy were associated with rate of HBeAg seroconversion. Several studies suggested that PEG-IFN add-on or switch treatment in HBeAg-positive patients with low levels of HBsAg during long-term NA therapy increased rates of HBeAg seroconversion or HBsAg loss.[4] In current study, HBsAg levels at week 4 were significantly lower in the NA pre-therapy group than in the placebo group. Accordingly, it would be interesting to know whether HBsAg levels at week 4 was associated with treatment efficacy.

In summary, current evidence indicates that the efficacy of PEG-IFN and NA combination therapy still remains unproven. The selection of CHB patients who would benefit from combination therapy with PEG-IFN and NA will be clinically valuable in the era of precision medicine.

Conflict of interest

The author has no conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jfma.2018.04.006.

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