To the Editor:
We read with great interest the paper by Ning et al. [1] about the efficacy of switching from entecavir to PegIFN alfa-2a in patients with HBeAg-positive chronic hepatitis B (CHB). In this prospective study, hepatitis B e antigen-positive CHB patients who had received entecavir for 9–36 months were randomized 1:1 to switch to PegIFN alfa-2a or to continue with entecavir for 48 weeks. It showed that only 14.9% patients achieved HBeAg seroconversion and 8.5% patients achieved HBsAg loss in the Peg-IFN alfa-2a cohort at week 48. The authors indicated that HBeAg loss and seroconversion were less likely to occur in patients with prior long-time exposure to a nucleos(t)ide analogue (NUC) compared with treatment-naïve patients. However, “add-on” PegIFN alfa to a current NUC therapy has been shown to lead to a high rate of HBsAg loss in some small cohort studies [2,3]. Moreover, the complete response (HBsAg loss and HBV DNA <2000 IU/ml) and HBsAg loss rates were much higher in patients with sequential combination therapy in our recent retrospective study. In the sequential combination therapy cohort, PegIFN alfa-2a was added to HBeAg-positive CHB patients who had received NUC for at least two years. It showed that complete response and HBsAg loss rates in the “add-on” PegIFN alfa-2a cohort were 60.2% and 27.7% at week 72 (48 week treatment and 24 week follow-up), respectively [4]. Since the study design and inclusion criteria are different, we can hardly draw the conclusion that sequential combination therapy with PegIFN alfa (“add-on”) is better than “switch-to” PegIFN alfa in patients with prior long-time exposure to NUC.

Nevertheless, some recent studies have further found that PegIFN alfa therapy may benefit more from the combination therapy with NUC. First, PegIFN alfa therapy induced the expansion of natural killer (NK) cell populations, which was detrimental to CD8 T cells [5,6] and conversely, NUC playing a role in the restoration of adaptive antiviral responses had already been proven in an earlier study [7]. Thus, it was suggested that the combination with NUC addresses the limitation of the PegIFN alfa therapy. Second, chronic HBV patients became refractory to multiple doses of PegIFN alfa, which could be reduced by the combination of PegIFN alfa and tenofovir [8]. Third, the combination therapy might avoid the replenishment of nuclear cccDNA after degradation [9]. Although early and recent clinical trials showed no extra benefit of simultaneous combination therapy compared to PegIFN alfa monotherapy, more evidence had shown that sequential combination therapy with late “add-on” PegIFN alfa to an ongoing NUC treatment instead of simultaneous combination therapy might be more beneficial [10]. With increasing data finding an extra benefit of combination therapy, we suggest that “add-on” may be more suitable than “switch-to” PegIFN alfa therapy for patients with prior exposure to NUC in clinical practice. Obviously, large clinical trials are needed to further clarify the above hypothesis and its underlying mechanism.

Conflict of interest
The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

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