Benefit of stopping finite nucleos(t)ide analogues therapy in chronic hepatitis B patients

The article of Liem *et al*[1] addressed important issues of finite nucleos(t)ide analogues (NUC) therapy in mostly Asian (>95%) patients with chronic hepatitis B. It is a randomised controlled trial (RCT) on this issue second to that of the first but a smaller one involving mainly (85%–90%) Caucasian patients.[2] Whereas recent controlled and cohort studies in pretherapy HBeAg-negative patients have provided evidence of much increased HBsAg loss rate after stopping NUC therapy,[2–6] the reasons of the contradictory conclusion of this study and several critical points of this trial deserve clarification and further discussion.

First, only 42% of the 159 patients agreed to be enrolled. Are there any bias comparing those enrolled and those declined? Second and most importantly, similar to the strategy of several reported studies involving smaller number of pretherapy HBeAg-negative patients, this trial also included both HBeAg-positive (n=18) and HBeAg-negative (n=27) patients. It is well known that HBeAg-positive and HBeAg-negative patients have inherent differences, not only in the virus (wild vs mutant, HBV DNA and HBsAg levels) but also in the host such as age difference. Their findings that, by the same predefined criteria, much more pretreatment HBeAg-positive patients required retreatment and HBsAg loss only in pretreatment HBeAg-negative patients also self-explained that they were different. It seems not appropriate to lump them together for this kind of study. Perhaps it is more appropriate to compare the results of their 27 pretherapy HBeAg-negative patients with those of earlier RCT[2] and other studies addressing HBsAg loss after stopping NUC.[3–6] It would be most informative to compare with the 59 pretherapy HBeAg-negative patients who might have detailed relevant data available for comparisons in a published study led by the same senior author.[7] Third, the median HBsAg decline in the Stop versus Continuation group should not be interpreted as 'similar' because their data showed two times higher HBsAg decline in the Stop arm (0.2 vs 0.1 $\log_{10}$ IU/mL) with a p value of 0.04 indicating statistically significant difference. Fourth, our large cohort study involving 691 pretherapy HBeAg-negative patients showed that the cumulative HBsAg loss rate was only 1% by year 1 and 2% by year 2 then accelerated to 13% by year 6 after stopping NUC.[4] Obviously, a follow-up duration of 1.5 year (72 week) is too short to see significant and/or greater difference in both the magnitude of HBsAg decline and HBsAg loss rate between Stop and to Continuation group, especially when the number of patients was small. Furthermore, >95% of their patients were Asians. Studies have shown much lower Off-NUC HBsAg loss rate than Caucasians, as summarised elsewhere.[8]

With these discussed problems in the results of the study, it can be concluded that it is too early to suggest that stopping NUC therapy in chronic hepatitis B has limited benefit. If the benefit of finite NUC therapy in HBeAg-negative patients elaborated in earlier studies is still questioned, RCTs in substantial number of patients with off-NUC follow-up >3 years are needed.

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