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Editorial

Lamivudine: fading into the mists of time

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See Article on Page 331

The treatment goal for patients with chronic hepatitis B (CHB) is reducing liver related mortalities from cirrhosis and hepatocellular carcinoma (HCC). For the past 20 years, single or combination regimen of nucleos(t)ide analogues (NUCs) has been widely used for this purpose and partly achieved the treatment goal in CHB patients. Hepatitis B e antigen (HBeAg)-negative CHB has been regarded as challenging to treat owing to the rapid and aggressive progression of the disease.[1] Since the phase 3 study by Lai et al.[2] entecavir has been widely used in treatment-naïve HBeAg-negative CHB patients and showed its higher efficacy than lamivudine in the real world data.[3] International guidelines also recommend entecavir as the preferred choice for first-line agent for CHB patients along with tenofovir disoproxil fumarate, rather than lamivudine.[4-6]

Although the higher efficacy of entecavir compared with lamivudine has reported in previous randomized trial,[2] Lee et al. conducted a randomized controlled trial to compare the 'long-term' efficacy and safety during 5 years in treatment-naive HBeAg-negative Korean CHB patients whose genotype are mostly genotype C.[7] In the current issue of Clinical and Molecular Hepatology, this study showed long-term entecavir treatment was superior to lamivudine as quite well expected. Virologic response, defined according to the AASLD guidelines,[4] was achieved in 95.0% of entecavir-treated patients and 47.6% of lamivudine-treated patients (P<0.0001) after 240 weeks of treatment. Notably, 26 (42.6%) of lamivudine-treated patients occurred virologic breakthrough until week 96, whereas only one patient of entecavir-treated patient developed virologic breakthrough. This patient with virologic breakthrough at week 48 did not have resistance to entecavir and was found to have undetectable HBV DNA at week 60 and 192. The demerit of Lee's study is the small sample size and high drop-out rate as the authors mentioned in discussion. According to the study flow depicted in figure 1, most common cause of drop-out was treatment failure/lack of efficacy (n=24) and belonged to lamivudine-treated group. However, these high drop-outs might be expected in consequence of the lower efficacy and high virologic breakthrough in lamivudine-treated group.

Regarding the safety and tolerability, Lee's study reported both entecavir and lamivudine were well tolerated with a low incidence of adverse events which were not related to the study drugs through 5 year of study period. This accumulates supporting

Abbreviations:
CHB; chronic hepatitis B, HCC; hepatocellular carcinoma, NUCs; nucleos(t)ide analogues

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evidence for long-term use of entecavir in terms of safety concern considering the need of almost indefinite treatment with NUC until more potent antiviral agent appears.

We previously conducted a large historical cohort study with 5,374 CHB patients (1785 HBeAg-negative patients: 33.2%).[8] In this study, entecavir showed a low risk of death or transplantation than lamivudine, which fulfills in part the treatment goal in CHB patients, albeit the development of HCC did not differ between two groups.[8] Based on previous reports including our large historical cohort study and Lee's randomized study, lamivudine should not be considered any more as an option for NUCs in treatment-naïve CHB patients. Next research questions we might have is whether the long-term outcomes differ or not between entecavir and tenofovir, which are equivalent in terms of antiviral potency in the setting of treatment naive CHB patients.

Lamivudine, which is the first NUC for CHB patients, showed its efficacy in preventing liver disease progression but was also responsible for emerging drug-resistant mutants causing more severe hepatitis flares, disease progression, and death due to the low genetic barrier to resistance.[9] No international guidelines recommend its use as a first-line option in CHB patients any more. Lamivudine, this old star is fading into the mists of time.

Authors' contribution

All authors contributed to drafting of the manuscript and approved the final version for submission.

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Conflicts of Interest

The authors have no conflicts to disclose.

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