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EDITORIAL

Sequential combination therapies for HBeAg-positive chronic hepatitis B: the search continues

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Total eradication of the hepatitis B virus (HBV) is still elusive, as even if HBsAg is lost, covalently closed circular DNA (cccDNA) often persists in the hepatocytes. The currently available drugs for treatment of chronic hepatitis B (CHB) are not able to give sustained off-treatment HBsAg loss (functional cure) in most of the patients, which is the ultimate goal of therapy of CHB and is closest to eradication. In the absence of functional cure, Hepatitis B e antigen (HBeAg) seroconversion and undetectable HBV DNA are taken as end-points of antiviral therapy in HBeAg-positive CHB.

At present, monotherapy with potent nucleot(s)ide analogues (NAs) (directly inhibit HBV DNA polymerase) or pegylated interferon alpha (Peg-IFN) (immune modulator) is recommended as the first-line therapy for HBeAg-positive CHB. Long-term potent NA treatment has excellent viral suppression (more than 95% at 5 years) [1], but relapse is common after stopping NAs. Therefore, prolongation of potent NAs therapy over long period maintains the initially high virological remission rates. The rationale for Peg-IFN use is to induce immunological control with a finite duration of therapy [2]. However, the response to Peg-IFN treatment is highly variable and it has more side effects as compared to NAs. Among HBeAg-positive CHB patients, Peg-IFN therapy leads to higher HBeAg seroconversion and HBsAg seroclearance rates as compared to NAs, but the sustained virologic response rates at 6 months following 12 months of Peg-IFNa therapy are ~ 20–30% [3]. Baseline predictors for good response to Peg-IFN treatment include lower HBV DNA levels (< 7 log10 IU/ml) and higher ALT levels (2–3 times ULN) [1].

Many investigational agents are in pipeline with varied mechanisms of actions including interference with specific steps in HBV replication or acting as host cellular targeting agents or as immune modulators. However, these drugs are currently not approved for clinical use. Therefore, novel therapeutic concepts involving the currently approved therapies, such as combination of agents with differential mechanisms of actions on HBV (e.g., NAs plus Peg-IFN) are being explored to achieve higher rates of HBsAg loss.

The combination of NAs and Peg-IFN has been studied in CHB patients. The approaches to combination therapy include: simultaneous administration of Peg-IFN and NA or sequential administration of Peg-IFN and NA (either starting with NA for a variable period, followed by 'switch to' or 'add-on' Peg-IFN; or starting with Peg-IFN followed by addition of NA). At present, the optimal combination therapy to obtain the best treatment outcomes remains undefined due to differences in study designs and case–control selection.

There is no robust evidence that a simultaneous combination of Peg-IFN and NA is superior compared to Peg-IFN or NA alone in treatment naïve patients. The main theoretical advantage of this approach is the possible synergy of the different mechanisms of the 2 drugs and simplicity of the regime. In one recent randomized-controlled trial, HBsAg loss rates at 72 weeks were superior in the Peg-IFN and tenofovir (TDF)-treated patients as compared to patients receiving Peg-IFN alone or TDF alone (9% vs. 3% vs. 0%), but the overall rates were low and mainly in genotype A patients [4].

Because high viral loads lead to blunting of immune responses to HBV, viral load reduction by NAs leads to increased immune responses against HBV, which then followed by immune modulation by addition of Peg-IFN results in increase in r HBV virus-specific cytotoxic T-cell activity [5]. In CHB patients on NA treatment, Peg-IFN can be used as a 'switch to' or 'add-on' strategy. Studies have shown higher HBeAg seroconversion rates using 'switch to' or 'add-on' strategies [6, 7].

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In this issue of Hepatology International, Xu et al. evaluated the efficacy of Peg-IFN–NA sequential optimization therapy (SOT) in HBeAg-positive CHB patients as compared to Peg-IFN alone [8]. Starting with Peg-IFN followed by addition of NA achieved more HBsAg levels drop; higher rates of HBsAg ≤ 100 IU/mL, undetectable HBV DNA, and ALT normalization compared with Peg-IFN monotherapy [7]. Starting with Peg-IFN first was probably because of the better efficacy of Peg-IFN treatment in the setting of ALT levels (patients with ALT > 2 times ULN were included in this study). Unlike many previous studies, the protocol of therapy in this study was adjusted based on early response. The previously established early on-treatment predictors can be used as tools to individualize the treatment strategy, thus helping to discontinue Peg-IFN early in those with a low likelihood of long-term response. Recent studies suggest that HBsAg quantification serves as a useful marker for predicting treatment response and making decisions about sequential combination therapy. A recent meta-analysis demonstrates that based on HBsAg levels, early Peg-IFN discontinuation should be considered in HBeAg-positive genotype B/C patients at weeks 12 or 24 of treatment (if HBsAg > 20,000 IU/mL at week 12), while patients with a decline of HBsAg levels below 1,500 IU/mL at 12 weeks can be continued on Peg-IFN (positive predictive value of 50% as a predictor of HBeAg seroconversion) [3, 9]. Other studies have also found that baseline and on-treatment HBsAg levels can help predict HBsAg decline or loss during interferon-based combination therapy [10].

Optimizing therapeutic regimens based on early response and individual characteristics would ensure that only patients who fail to achieve a good response with Peg-INF monotherapy would receive combination therapy, thereby enhancing virological response, decreasing the economic burden, and conserving medical resources. In the current study, patients with partial response at 48 weeks were given a further 24 weeks of Peg-IFN. Extending the duration of Peg-IFN therapy beyond 48 weeks has been shown to achieve higher sustained virological responses and HBsAg loss in HBeAg-negative CHB patients [11, 12].

The majority of patients who achieve sustained off-treatment responses after Peg-IFN therapy maintain such responses during long-term follow-up of at least 5 years. HBsAg loss rates increase after the end of Peg-IFN therapy in initially HBeAg-positive CHB patients with sustained virological responses (approaching 50% at 5 years after the end of therapy) [13]. The long-term effects on HBsAg clearance using the approach used in the current study remain to be seen.

Thus, in the treatment of HBeAg-positive CHB patients, the approach of starting with Peg-IFN and using a response-based approach to adding NA is exciting. Whether this approach will be useful in patients with genotypes other than B and C (i.e., A and D), and patients with initial high viral loads and lower levels of ALT (< 2 times ULN) remains to be evaluated in future studies. Also, the effect on long-term HBsAg loss remains to be seen. Also, total eradication of the hepatitis B virus (HBV) is still elusive, as even if HBsAg is lost, covalently closed circular DNA (cccDNA) and integrated HBV DNA often persist in the hepatocytes.

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Compliance with ethical standards

Conflict of interest Ankur Jindal and Manoj Kumar have no conflict of interest.

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