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REVIEW

Finite therapy of chronic hepatitis B infection: Pros

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Long-term monotherapy with a nucleos(t)ide analogue (NA) of high genetic barrier represents the main therapeutic option for patients with chronic hepatitis B (CHB), improving all their outcomes.[1,2] NA(s) have excellent tolerability and good safety profile but cannot achieve HBV eradication and rarely result in "functional cure" or HBsAg seroclearance, which currently represents the optimal feasible therapeutic end-point minimizing the risks of liver-related complications.[1,3] Thus, long-term, perhaps life-long, NA therapy is usually necessary to prevent relapses of HBV replication and liver disease exacerbation.[1,2] On the other hand, finite NA therapy is used in several countries mostly due to reimbursement limitations,[4] whereas NA(s) may be stopped in other countries by some patients for various reasons.[5] Thus, there is accumulating experience on NA(s) cessation in CHB. Currently, all guidelines agree that NA(s) can be discontinued in all patients with CHB who achieve HBsAg clearance as well as in patients without cirrhosis with HBeAg-positive CHB who achieve HBeAg/anti-HBe seroconversion and HBV DNA undetectability and complete $\geq$ 12 months (preferentially 36-month according to APASL) consolidation therapy.[1]

Therefore, this review focuses on the advantages of stopping NA(s) in patients who are HBsAg-positive with HBeAg-negative CHB, who represent the most controversial setting (Table 1).

INCREASING RATES OF HBsAg CLEARANCE

There has been accumulating evidence that the cumulative rates of HBsAg seroclearance increase after NA discontinuation.[6] Most data supporting such a concept, including 2 randomized controlled trials, come from studies in patients who are HBeAg-negative and CHB who have a very low probability of HBsAg clearance under NA(s).[5,7] HBsAg clearance rates have been reported to range between 10% and 24% at 2 years off-NAs in several European cohorts, whereas they have been lower in Asian cohorts in which they increase later exceeding 10%–20% at 5–6 years off-NA(s).[5,6] HBsAg clearance rates are undoubtedly associated with HBsAg levels at NA cessation, while their associations with different patient and viral characteristics (eg, race, HBV genotype), durations of treatment, and on-therapy virological remission and other parameters remain controversial.[5,6,8–10] In a multicenter large retrospective study, a high probability of HBsAg loss (>30% at 4 y off-NAs) was observed in Whites and Asians with end-of-therapy HBsAg levels $<$ 1000 and $<$ 100 IU/mL, respectively.[10] Since HBV investigational agents mainly aim to achieve functional cure, NA discontinuation seems to represent a reasonable control arm in clinical trials, including NA-treated patients with CHB.

PROBABILITY OF TRANSITIONING INTO CHRONIC HBV INFECTION WITHOUT TREATMENT

A substantial proportion ($>$ 60% at month 12) of patients who are HBeAg-negative and have CHB-stopping NA(s) remain in the HBeAg-negative chronic HBV infection phase without treatment (or "inactive carrier" state).[5,10] The probability of remaining in this phase depends on several factors, including the retreatment criteria,[5] while

Abbreviations: APASL, Asian Pacific Association for the Study of Liver; CHB, chronic hepatitis B; EASL, European Association for the Study of Liver; NA, nucleos(t)ide analogue.

TABLE 1 Arguments favoring discontinuation of NA therapy in patients with HBsAg-positive with HBeAg-negative chronic hepatitis B

- Increasing probability of HBsAg seroclearance (functional cure)
- Probability of transitioning into chronic HBV infection phase without treatment (or "inactive carrier" state)
- No risk for drug-related adverse events
- Lower cost
- Minimal risk of off-NA hepatic decompensation in patients without cirrhosis before treatment
- No increased risk for HCC; HCC surveillance for both treated and untreated patients
- No need for closer long-term monitoring; closer monitoring only for first 12 (mostly for first 3) months
- No need to better adherence to follow-up; adherence to follow-up is mandatory for both treated and untreated patients

Abbreviation: NA, nucleos(t)ide analogue.

the reported off-NA(s) remission rates also depend on many factors, including the relapse definitions.[11] The probability of relapse seems to be inversely associated with end-of-therapy HBsAg levels, but these associations are much weaker compared to HBsAg loss.[5,6] The reported cumulative probabilities of relapse usually overestimate the actual relapse rates at certain time points after the first months off-NA(s), as the transient course of many relapses cannot be considered by such statistical estimations.[5,11] The annual retreatment probability is higher during the first year off-NA(s), whereas the cumulative retreatment probability increases over time (30% at year 1 and 55% at year 4), but a substantial proportion of patients remains untreated.[10]

NO RISK FOR DRUG-RELATED ADVERSE EVENTS

Although the safety profile of NA(s) is very good,[1] there is no doubt that the safety of no therapy is superior than the safety of any, especially long-term, therapy.

LOWER COST

The cost of monitoring, including frequent HBV DNA determinations, increases during the first few months after NA cessation when it may approach the cost of NA use. However, the frequency and thus the cost of monitoring decrease over time, especially after 6–12 months, in patients remaining untreated (Figure 1).[5]

MINIMAL RISK OF HEPATIC DECOMPENSATION

The main argument against NA discontinuation has been the risk of severe HBV reactivation and clinical exacerbation following the almost universal virological relapses. However, in patients with CHB without pretreatment cirrhosis, alanine aminotransferase flares with jaundice and hepatic decompensation are extremely rare (< 0.05% annually) in patients under close follow-up.[5,10] Thus, the possibility for NA(s) discontinuation in patients who are HBeAg-negative without cirrhosis and with CHB with long-term on-NA virological remission has now been included not only in APASL but EASL guidelines as well.[2,4] The risk of hepatic decompensation (4%) and death is higher in patients with pretreatment cirrhosis[9,10] and therefore only APASL guidelines consider the possibility of NA discontinuation in patients with cirrhosis with careful monitoring.[4]

LOW RESIDUAL RISK FOR HEPATOCELLULAR CARCINOMA

A concern in patients who discontinue NA(s) has been the potential effect of relapsing HBV replication on HCC risk. However, all existing data do not support such an effect on HCC risk,[9,12] which was recently shown to be reduced after NA cessation even in patients who are HBeAg-negative with cirrhosis.[13] In any case, HCC surveillance should continue in both treated and untreated patients who remain at increased HCC risk.[5]

NO NEED FOR CLOSER LONG-TERM MONITORING

Another argument favoring NA continuation has been the need for closer monitoring and good adherence to off-NA(s) follow-up[5] compared to the 6–12 month monitoring during NA(s).[2,4] The monitoring is closer during the first 12 months off-NA(s) (monthly until month 3 and every 3 months until month 12), but it becomes similar to that of NA therapy after month 12 (Figure 1).[5]

NO NEED FOR BETTER ADHERENCE TO FOLLOW-UP

Good adherence to follow-up is mandatory for patients stopping NA(s), but also for patients under long-term NA (s), in whom adherence rates decrease over time. In fact, poor (< 90%) adherence to medication has been associated with increased mortality and risks for liver-related complications, particularly among patients with cirrhosis.[14] Thus, planned finite NA courses may improve compliance with treatment and prevent potentially harmful unplanned patient-driven NA discontinuations.

CONCLUSIONS

NA(s) may be stopped not only in the few patients who clear HBsAg but also in selected patients who are HBeAg-

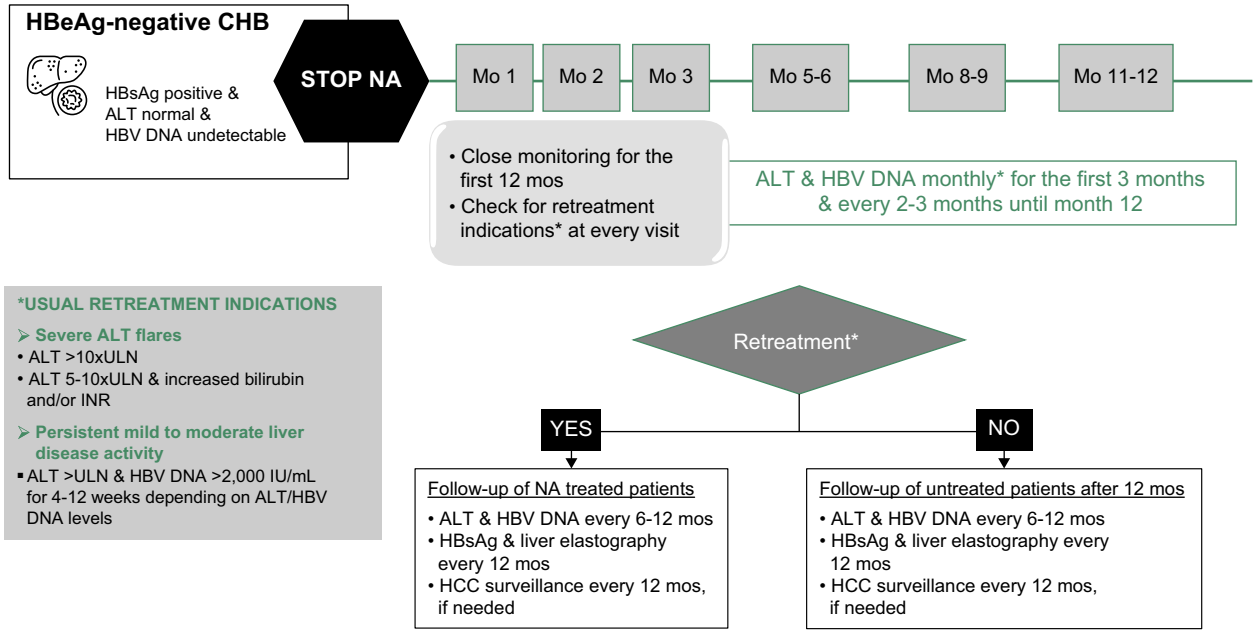

FIGURE 1 Algorithm for the optimization of follow-up of patients with CHB without pre-existing cirrhosis who discontinue long-term therapy with NA(s) before HBsAg loss. Abbreviations: ALT, alanine aminotransferase; CHB, chronic hepatitis B; ULN: upper limit of normal; mo(s): month (s); NA(s), nucleos(t)ide analogue(s).

negative and have CHB who remain HBsAg-positive. All such patients should have achieved long-term on-therapy virological remission and should comply with strict off-NA (s) follow-up. Post-NA(s) virological relapses will occur in the majority and biochemical relapses in a proportion of patients, but progressively increasing HBsAg clearance rates are observed and substantial proportions of patients remain in the chronic HBV phase without treatment. If indications develop, prompt retreatment can introduce virological and biochemical remission without safety concerns in patients without pretreatment cirrhosis, although reasonable clinical judgment may be applied in cases with mild relapses as early retreatment may impede HBsAg clearance.[9] The off-NA(s) probability of HBsAg loss and remission is higher in patients with end-of-therapy HBsAg levels < 100–1000 IU/L, but remission may be maintained in variable proportions of untreated patients regardless of HBsAg levels.

CONFLICTS OF INTEREST

George Papatheodoridis advises, is on the speakers' bureau for, and received grants from AbbVie and Gilead. He advises and is on the speakers' bureau for AstraZeneca, Elpen, Genesis, GlaxoSmithKline, Janssen, Ipsen, Merck Sharp & Dohme, Novartis, Novo Nordisk, and Roche. He advises and received grants from Takeda. He advises Albireo. He received grants from Vianex. Margarita Papatheodoridi has no conflicts to report.

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