Editorial

Discontinuation of Long-Term Nucleos(T)ide Analogue (NA) Therapy in HBeAg-Negative Chronic Hepatitis B (CHB). Is it Feasible Strategy in 2016?

Hariklia Kranidioti1,2, George Kontos1, Melanie Deutsch1 and Spilios Manolakopoulos1*

12nd Academic Department of Internal Medicine, Hippokration General Hospital, University of Athens, Greece
2Department of Clinical and Experimental Sciences, University of Southampton, United Kingdom

ABBREVIATIONS

AASLD: American Association for the Study of Liver Diseases; ALT: Alanine Transaminase; APASL: Asian Pacific Association for the Study of Liver Diseases; CHB: Chronic Hepatitis B; EASL: European Association for the Study of the Liver; HBV: Hepatitis B Virus; NA: Nucleos(t)ide analogue; ULN: Upper Limit Normal

INTRODUCTION

The introduction of NAs for oral antiviral therapy has dramatically improved the clinical outcome in patients with CHB due to their ability to inhibit viral replication [1]. However, HBV eradication and the ideal goal of HBsAg loss is rarely met by NAs and virological relapse is common after discontinuation of treatment [1]. Both EASL and AASLD guidelines recommend long-term NA therapy until HBsAg seroclearance. Conversely, the APASL guidelines suggest that cessation of NAs can be considered after at least 2 years of treatment if HBV DNA remains undetectable on 3 separate occasions 6 months apart [1-3]. Whether NAs are able to induce a sustained off-treatment response in HBeAg-negative CHB patients is now an important area for research.

Outcome after discontinuation of NAs therapy

Studies with HBeAg-negative patients who stopped NA therapy are mainly retrospective with many differences in the design, the characteristics of the patients, the definitions of hepatitis relapse and the criteria for retreatment [4]. The majority of them are Asian trying to explore or justify the APASL criteria for stopping therapy [5,6]. Some studies have applied levels of HBV DNA >2000 IU/mL to define relapse. A relapse rate of 43-73% after 12 months of follow-up was also addressed in these studies [8-10].

If clinical relapse is considered as a combination of virological and biochemical relapse the results are slightly different. HBV DNA >2000 IU/mL and ALT >2ULN is a reasonable definition of clinical relapse as these levels used to guide initiation of treatment. In two studies [9,11] almost the half the patients relapsed during the 12 months off-treatment period, including one study in which the APASL stopping rules were used.

A prospective cohort study [12] of 33 patients who had been treated with ADV for 4-5 years and monitored for 5.5 years after cessation of treatment showed an overall relapse rate of 45% during the follow up period. The authors defined relapse, the HBV DNA >2000 IU/mL and ALT >x1 ULN, from 6th month post-treatment until the end of follow-up. Interestingly, in the same study 10 of 33 patients who achieved sustained response, 13 (72%) showed HBsAg clearance and 9 of 13 (69%) developed anti-HBs.

Most of the virological relapse occurs within the first 3-9 months after treatment discontinuation [7,8] and the majority of patients who eventually relapse have done so by the end of second year of follow up [13]. Thus 24 months off-treatment is a reasonable indicator of sustained response. Usually the biochemical relapse occurred 1-2 months or longer [12] after the virological relapse.

Risks of relapse and predictive factors

Cessation of antiviral treatment with NAs may be associated with a flare in viraemia, hepatitis and potential hepatic decompensation. These occur in approximately 10% of patients...
[14]. However, in general withdrawal of anti-viral therapy has proved relatively safe for patients under close monitoring during follow-up. It is worthy to mention that the majority of the studies included non-cirrhotic individuals. Jeng et al included 39 patients with cirrhosis and reported one case with decompensation with a successful retreatment with entecavir [11]. The therapeutic response was similar between retreatment and first-course therapy. Salvage therapy either with lamivudine or adefovir had a 100% response [12,13]. Concluding, flares after NA withdrawal are generally self-limiting and severe episodes can be managed with retreatment efficiently. However, patients with cirrhosis may be at risk of developing decompensation [15]. This has led to the suggestion that withdrawal of NA in individuals with cirrhosis should not be undertaken lightly and accompanied by stringent monitoring with a view to prompt retreatment.

Researchers have studied host and viral factors that predict relapse or sustained response after treatment cessation. Patient characteristics such as age and gender, or baseline clinical characteristics as stage of liver fibrosis, levels of ALT, HBV DNA and HBsAg and the kinetics of these during the treatment or the off-treatment period have been analyzed with conflicting results [5,6,8-13]. Additionally treatment-related factors, including the duration of consolidation therapy [5,8,11], type of NA [7,9,14] and virus related factors [7,10,11] as genotype and mutations have also been considered not significantly related with relapse.

CONCLUSIONS

Long-term treatment of chronic hepatitis B with NAs is efficient, safe and associated with a reduction in morbidity and mortality. On the other hand the compliance and the unknown side effects, the cost of the therapy and the rare achievement of the HBsAg clearance create the need of the potential NA therapy cessation or the developing of new drugs.

Maintenance on the inactive carrier state seems to be the most reasonable clinical endpoint for patients who stopped NA treatment. Transient post-treatment virological or biochemical relapse may be beneficial and lead to virological remission and even spontaneous clearance due to the efficient host immune response. As a result early unnecessary retreatment can drive to the loss of the long-lasting virological remission.

Definitely, there is a risk of relapse after treatment discontinuation with a variable range among the studies. The complications of relapse could be eliminated by a very close, individualized follow-up of patients who are willing to stop therapy and only at specialized centers. It is important that cirrhotic patients should avoid treatment discontinuation due to the risk of liver failure. To date consistent stopping rules with broad applicability remain elusive. Further research for predictive factors or new biomarkers of the disease that could identify those who remain in sustained off-treatment remission is needed.

REFERENCES