Success and Failure in the Therapeutic Control of HBV

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Q. What, in your view, are the therapeutic successes of HBV control?

Long-term oral therapy with third generation nucleos(t)ide analogues (NUC), i.e. ETV and TDF, has revolutionized the landscape of HBV therapy. Ten years of clinical studies have convincingly demonstrated that long-term administration of these drugs leads to maintained virological and biochemical responses in >95% of patients, histological regression of fibrosis and early cirrhosis[1,2]. From the clinical point of view, progression to cirrhosis as well as decompensation are prevented, portal hypertension improved, and the HCC risk reduced[1,2]. Improved survival has been also recently demonstrated. The drugs are easy to use, cost is not a major issue as they are both generics, monitoring is limited to two times a year, safety is not a relevant issue. All in all, this treatment strategy is highly effective and simple though it does not lead to HBsAg loss, i.e. functional cure, in the vast majority of patients[1,2].

Q. What are the remaining gaps for this antiviral strategy?

There are a few remaining gaps, namely safety in some TDF treated patients, residual HCC risk, HBsAg clearance rates and stopping rules[1,2].

Q. How safe are these drugs in the long term?

As far as safety is concerned, less than 5% of TDF treated patients experienced a significant renal problem, while up to 50% may have chronic asymptomatic tubular dysfunction as assessed by sensitive urinary markers. Chronic glomerular and tubular damage may lead to osteoporosis a condition that significantly impacts not only on quality of life but also costs, for example for hospitalization, and cardiovascular outcomes. Among different available strategies such as a proactive dose reduction of TDF and switch to ETV for selected patients, TAF may represent the best treatment strategy to prevent or to rescue patients with TDF induced renal and bone damage as controlled studies have shown that its renal and bone profiles are safer than that of TDF[1,2]. However, a significant limitation to the widespread use of TAF is represented by its cost, which is approximately 5 times higher than that of TDF and ETV. Moreover, the real-life data with TAF are still very limited.

Q. Does long-term therapy reduce the risk of HCC?

It has been shown that NUC therapy reduces by approximately 50% the risk of HCC compared to untreated HBV patients[1,3]. However, patients remain at a substantial risk of HCC despite effective oral therapy, the annual

incidence rates are 0.4-1% and 3-5% in patients without and with compensated cirrhosis, respectively[1,3]. Continuous surveillance with semiannual US with or without AFP is recommended. HCC remains almost the only liver specific complication in patients treated long term with ETV or TDF[1].

Q. Is "functional cure" an achievable goal with current therapies?

Long-term NUC treatment does not significantly affect HBsAg levels, with this marker declining approximately 0.5 log IU/ml every 5 years. HBsAg loss rates are <5% after 10 years of oral therapy in most populations, i.e. HBeAg negative CHB and HBeAg positive CHB in Asians, with the notable exception of selected genotype A patients with HBeAg positive CHB where rates of functional cure peak 20%[1,2]. There is no evidence that TAF monotherapy may change this situation. Four strategies aimed to accelerate HBsAg loss have been proposed: continuous administration of NUC, as longer viral replication is suppressed lower HBsAg levels will become. Peg-IFN as add-on or as switch to has proved to accelerate by 5-10 times HBsAg decline compared to NUC treated patients, but few patients ultimately clear HBsAg loss, not forgetting the side-effects of this strategy. Stopping therapy before HBsAg might induce HBsAg loss in 10-20% of patients, but with all the problems, risks and limitations of strict monitoring and retreatment of these patients after NUC discontinuation[4]. Recent studies suggest that HBsAg <100 IU/ml might represent a good stopping rule before HBsAg.

Q. Do we need new therapies for HBV? Are there any new promising therapeutics?

New therapeutic approaches may serve the purpose of increasing HBsAg rates in long-term NUC treated patients or shortening the duration of therapy in untreated ones[1,5]. Off-treatment HBsAg loss coupled with undetectable HBV DNA, recently redefined as "functional cure" may further decrease the risk of HCC. Entry inhibitors, CAM, cccDNA targeting drugs, RNA interference, NAP and immunomodulators are currently tested in phase I and II studies[1,5]. Many companies are testing these compounds either as monotherapy or in combination. Results are encouraging but still very preliminary as only few candidate drugs have entered phase II studies, yet most present as a monotherapy or in combination with NUC as the backbone[5].

This task is challenging for several reasons: currently oral therapy is effective, safe and cheap; HBsAg production may derive mainly from integrated HBV DNA, at least for HBeAg negative patients; safety must be excellent and costs must be reasonable; strategies must be based on oral therapies or, eventually, sc administration; ALT flares should be avoided or at least minimized. The minimal requirements for any new strategy are therefore challenging: a safe, short-term and only relatively expensive but easy to administer therapy which leads to HBsAg clearance in at least 30-40% of patients in 24 weeks. However, diagnostics of HBV are evolving in parallel[1,5]. New quantitative viral markers such as HBsAg fragments, HBcrAg, HBV-RNA, anti-HBc and HBeAg may represent additional tools in the race to achieve a "functional cure" of HBV[1,5].

References

1. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection, J Hepatol 2017;67:370-398.
2. Terrault NA, Lok ASF, McMahon BJ et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. Hepatology 2018;67:1560-1599.
3. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
4. Lampertico P and Berg T. Less Can Be More: A Finite Treatment Approach for HBeAg-Negative Chronic Hepatitis B. Hepatology. 2018;68(2):397-400
5. Testoni B, Durantel D, Zoulim F. Novel targets for hepatitis B virus therapy. Liver Int 2017;37 Suppl 1:33-39