Viral Kinetics in HBV

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Viral kinetics (VK) during treatment allows us to better understand and quantify the *in-vivo* anti-viral effect and the interaction between the virus, host, and therapy. Analysis of VK during treatment can be divided into a highly frequent and quantitative analysis of early VK during the first month or so of therapy and the analysis of VK patterns during long-term treatment. In both cases, it is important to analyze the kinetics per individual patients, since averaging over all patients often gives rise to misleading results.[1]

HBV-DNA kinetics are compatible with the assumption that the major early in-vivo effect of both polymerase-inhibitors and IFN is to partially block the production of virions.[1] The effectiveness (ε) in blocking virion production, which can be represented by the first phase HBV-DNA decline, varies from 1.0 to 2.2 logs for various polymerase-inhibitors and is on average 0.8 log for Peg-IFN. The mean half-life of the free virions (LN (2)/c), where c is the free-virus clearance rate, varies in different studies from 9 to 16 hours. Most patients have free virus half-life longer than 6 hours, in contrast to 2-4 hours for HCV and HIV, and this value needs to be further verified in non-treatment settings. The half-life of productively infected cells ($LN(2)/\delta$), where δ is the infected cells loss rate that can be approximately calculated from the second phase decline slope, varies from 2.5 days to longer than 70 days. There are no obvious differences between the various therapies in relation to this important rate of decline.

Unfortunately, the currently available results for early HBV VK during Peg-IFN therapy are only for HBeAg-negative patients, and it is not clear if the same results would be obtained for HBeAg-positive patients. More studies are needed to close the gaps in order to understand the role of a patient being HBeAg-negative or HBeAg-positive on HBV dynamics. There are additional important gaps in our knowledge about effects of baseline parameters on early HBV kinetics that need to be targeted. Notably, while the difference in VK between different genotypes of HCV is well understood, the effect of HBV genotype on viral kinetics was not yet studied. To that extent, HBV genotype is generally correlated with the race and/or region of the patients, and the latter are strongly correlated with mode and time of infection (at infancy versus adulthood). Better understanding of the effect of these various factors on viral dynamics may help to better individualize treatment.

In addition to HBV-DNA, the loss of HBeAg (or, more accurately, its decline below detection level) may be used as a VK marker in patients that were initially HBeAg-positive. However, interestingly, therapies that give rise to larger decline of HBV-DNA, e.g., more potent enzyme-inhibitors, do not in general give rise to a larger rate of HBeAg loss. A possible hypothesis to explain this data is that the loss of HBeAg is only a marker of the decline of infected cells below a certain threshold. A quantitative measurement of

HBeAg, as well as of HBsAg, should be used frequently during treatment in order to allow a real kinetic analysis of these important markers.

More importantly, recent findings show the existence of distinct kinetic patterns within each therapy group. In fact, a fraction of patients receiving placebo have no change in HBV-DNA during 48 weeks, as expected from an equilibrium between viral production and clearance. However, another large fraction of patients receiving placebo was reported to have extensive (1-5 logs) spontaneous declines (SPD) in HBV-DNA, in correlation with ALT elevations and HBeAg-loss. The identification of these SPDs, or their lack of, is clinically important for predicting the success of treatment and in determining an optimal time to start therapy.

Furthermore, also during treatment, a number of distinct HBV-DNA kinetic patterns are observed. During polymerase-inhibitor treatment, some of the patients have a flat partial response, while other patients have either a rapid bi-phasic or a slow multi-phasic HBV-DNA decline, and yet other patients show a staircase pattern. When Peg-IFN therapy is initiated, a fraction of patients have an immediate rapid HBV-DNA decline, while a considerable fraction have either a delayed response or no decline. Furthermore, a fraction of patients treated with Peg-IFN show viral rebound during treatment, while others have viral relapse at the end of treatment and yet others have a sustained response. Understanding these different VK patterns and their significance is important for planning strategies for individualization of treatment, and for optimization of combined therapies.

Lastly, the analysis of long-term HBV kinetics shows a disassociation between the early HBV kinetics and long-term kinetics in a large fraction of patients. Thus, simple analysis of early viral kinetics, unlike for HCV, might not be a good predictor of the outcome of treatment, especially for IFN-based therapy. A more general framework of modeling HBV viral kinetics is needed to allow prediction of the success of therapy.

References

1. Neumann AU, Hepatitis B viral kinetics—a dynamic puzzle still to be resolved. *Hepatology*, 42: 249-254 (2005).