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EDITORIAL
Breaking the tolerance or the virus?
Toleransı veya virusu kırmak?

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The natural history of perinatally acquired HBV infection is well described (1). After primary infection, an immunotolerant phase characterized by a very high rate of viral replication but with no liver injury takes place. During this phase, HBeAg is positive and ALT levels are persistently normal. The mechanism of this tolerance is not completely understood. It is believed that before birth, HBeAg acts as a tolerogen viral protein in the fetus, and thus virus specific T cells undergo deletion. This phase lasts weeks to years depending on the age at acquisition. After years/decades, this tolerance is somehow broken down and immune attack against infected hepatocytes begins to cause liver damage. During this immune clearance phase ALT levels increase and HBV DNA levels begin to decrease. Immune attacks to infected hepatocytes result in HBeAg/HBeAb seroconversion and this seroconversion is usually associated with sustained remission of liver disease. This inactive carrier state can be life-long but some patients may develop exacerbation of their liver disease with increased viral replication. This reactivation phase is traditionally attributed to some specific viral variants, especially pre-core and core-promoter mutants. However, these mutations can also be observed in inactive carriers. In addition, reactivation can occur without these mutant infections (2).

Current approved treatment options of chronic HBV infection are interferon and nucleoside analogues, lamivudine and adefovir. Interferon acts primarily as an immunomodulatory agent, while nucleoside analogues have essentially antiviral effects. According to current consensus, treatment candidates are patients with active liver disease which is characterized by persistently elevated ALT levels and by detectable HBV DNA (10^5copy/ml) by most commercial assays, irrespective of their HBeAg/Ab status (3). These statements are in light of the results of studies reporting less efficacy of interferon or lamivudine in HBeAg+ patients with normal/near normal liver enzymes despite the presence of a high rate of viral replication. HBeAg-negative inactive carriers do not need any treatment because of the absence of viral replication and liver injury. Thus, patients in immune clearance phase (HBeAg+ or -) or in reactivation phase (HBeAg-) are candidates for the treatment with currently available drugs.

In this issue of The Turkish Journal of Gastroenterology, Yalcin et al. reports the results of a three-month lamivudine therapy in immunotolerant HBV-infected subjects (4). They report 3rd (end of treatment), 12th and 24th month results of therapy and observe no benefit of lamivudine in 13 treated patients when compared to 33 untreated patients with regard to HBe seroconversion, HBV DNA loss/decrease and complete ALT normalization. Three of 13 treated subjects, one of whom developed HBe seroconversion, had ALT elevation during the treatment. The seroconverted subject had HBe reversion even after an additional six months of lamivudine therapy. Unfortunately, histological activity worsened in this subject. One of the other two patients with ALT elevation developed HBe seroconversion during the long-term follow-up. In the control group, three patients developed ALT elevation and one patient HBe seroconversion during follow-up. In summary, one of 13 (0.7%) treated, and 1 of 33 (0.3%) untreated patients developed HBe seroconversion during long-term follow-up.

The idea of the investigators for the treatment of immunotolerant patients is that HBV-infected patients can develop hepatocellular carcinoma (HCC) even in the absence of advanced liver disease and cirrhosis. Their aim with a three-month course of lamivudine seems to break the tolerance and activate the immune response against infected hepatocytes while reducing viral load. Another reason for the preference of short-term lamivudine

therapy is to avoid development of lamivudine-resistant mutants. However, the current strategy with lamivudine treatment is prolonged therapy until HBe loss/seroconversion since most patients relapse after cessation of therapy (4, 5, 6). HBe seroconversion rate with one-year lamivudine treatment is about 18%, even in patients with elevated ALT levels (5, 6). This seroconversion rate is expected to be lower in patients with normal liver enzymes because ALT seems to be the most important predictor of HBe seroconversion with lamivudine (7). Therefore, there is no reason to introduce short-term lamivudine in these individuals. As expected, investigators could not reach their aim of clearance of the virus by breaking the tolerance. Lamivudine was the first drug to provide in vivo evidence of T cell tolerance induction by high viral load and viral antigen expression in humans. By reducing viral load and viral antigen expression with lamivudine, hyporesponsiveness of T cells to viral proteins has been shown to be reduced (8). However, subsequent studies showed that this effect is transient (9) and that this short-term treatment is unlikely to gain a sufficient and sustained (until clearance) induction of immune response. Possibly another boost for immune induction (endogenous or exogenous) is needed for viral clearance. Furthermore, predictors of effective induction of immune response by a treatment agent cannot be easily and practically documented and may need to be investigated via sophisticated immunological studies.

An ideal treatment agent should provide HBsAg/Anti-HBs seroconversion and cure of the disease in all, or at least in most, of the patients. Unfortunately, for now, we do not have such a powerful drug. Currently approved agents need endogenous immunoreactivity against the virus because only patients with elevated ALT levels (presumably reflecting ongoing anti-viral immune response) respond (not perfect but at an acceptable ratio) to these drugs (10).

Unfortunately, in the very early (immediately after primary infection) or early (immunotolerant phase) stages of the infection, our patients do not have a chance for disease cure with currently available drugs. Clearance of the virus at the early stage of infection may be critical because viral genome integrates into the cellular genome with time and clearance of a perfectly regulated pool of viral cccDNA becomes more difficult. An important consequence of chronic HBV infection is the development of HCC even in the absence of cirrhosis in some cases. This scenario necessitates discovery of a treatment strategy which can be effective during the early stages (immune tolerance) of the infection. An immunomodulatory drug alone is unlikely to work because there is no remarkable immune response to boost at this stage. In fact, interferon is effective in only one-third of the patients even in the presence of endogenous anti-viral responses (10). DNA polymerase inhibitors and nucleoside/nucleotide analogues can effectively suppress viral replication but development of drug resistant mutations in highly replicating virus (immune tolerance phase) is very likely. Another potential problem is the development of toxic injury to cellular/mitochondrial DNA with the more powerful polymerase inhibitor. Besides these potential problems, clearance of cccDNA seems to be essential for clearance of infection (11, 12). None of the known nucleoside/nucleotide analogues have been shown to effectively decrease the cccDNA pool in vivo. Loss of infected hepatocytes (cytolytic) or cytokine-mediated inhibition of viral genome (non-cytolytic) seems to be major routes for the clearance of cccDNA (11, 12). Even in the situation of effective inhibition of viral replication and prevention of newly synthetized hepatocytes from infection by nucleoside/nucleotide analogues, quiescent infected hepatocytes (in the absence of liver injury and hepatocyte regeneration) during the immune tolerant phase will not easily be replaced with newly born protected hepatocytes. In addition, intracellular activation and efficacy of nucleoside analogues may be directly related to the cell turnover (13). Therefore clearance of liver from infected hepatocytes will take a longer period of time in immunotolerant patients because of a low rate of cell turnover. This time period might be enough for the development of drug resistant mutants and/or cellular toxicity with a powerful nucleoside/nucleotide analogue.

Finally, well-targeted gene therapy based strategies may overcome these potential problems in the future. This type of strategy may aim to create defective viruses not capable of replication as opposed to the strategy attempted in this study which consisted of immune tolerance breakdown by viral load reduction.

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