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REVIEW ARTICLE

Lamivudine and Chronic Hepatitis B; Questions to Be Answered.

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Hepatitis B virus (HBV) infection is a major cause of both acute and chronic liver disease world-wide, affecting approximately 350 million individuals (1). In Iran, hepatitis B is the most common cause of chronic liver disease (2). Chronic hepatitis B can be divided into two forms based on presence of the hepatitis B e antigen (HBeAg) and antibody (anti-HBe) (3). HBeAg-negative chronic hepatitis B represents a potentially severe and progressive form of chronic liver disease with very rare spontaneous remissions, frequent progression to cirrhosis and increased risk of the development of hepatocellular carcinoma (4) .

The objective of the treatment is to interrupt HBV replication. Three drugs are currently available and approved by FDA for treatment of chronic hepatitis B: interferon alpha (IFN), lamivudine, and adefovir dipivoxil. Lamivudine was found to have inhibitory effects on HBV replication when used against HIV. Several randomized controlled trials have shown the efficacy of lamivudine in the treatment of HBeAg-positive and negative chronic hepatitis B. A 12-month lamivudine course was found to achieve a loss of HBeAg in 17-32% of patients (5). The percentage of responders who maintain HBeAg seroconversion after the cessation of lamivudine varies between studies. The prolongation of lamivudine therapy for more than 2 years may gradually increase the HBeAg seroconversion rate, as a 2-year course has been found to achieve seroconversion in 27%, a 3-year course in 33% and a 4-year course in 47% of cases (6, 7). Lamivudine has a number of advantages over interferon alpha (IFN-alpha). The rate of HBeAg loss and sustained disappearance of serum HBV-DNA occur with comparable frequency to that observed with IFN-alpha (9, 10).

It is considerably more potent than IFN-alpha in reducing viral replication and is free of serious adverse effects, which make it particularly suitable for patients with decompensated cirrhosis. However, the rate of HBsAg seroconversion is lower with nucleoside analogs. This can be explained by the relative resistance of the covalently closed circular HBV-DNA to the effects of nucleoside derivatives and possibility that IFN-induced hepatocytolysis more effectively eliminates this genomic template. Patients who are successfully treated with lamivudine have less progression of fibrosis than do untreated controls (11). When patients are maintained on treatment for 2 or more years, there appears to be significant histologic improvement in pre-existing cirrhosis (12, 13).

On the other hand, the major downside of lamivudine has been the emergence of drug-resistant HBV variants when this agent is used as monotherapy. A high level of serum HBV-DNA is the best independent predictor that drug resistance will occur. Although the development and licensing of this drug has been a significant advance in the medical treatment of hepatitis B, the frequent occurrence of drug-resistant HBV mutants has led to questions on how long to treat and in what clinical situations this should be considered first line therapy. The rate of resistance increases with the duration of treatment, being detected in approximately 50% of patients after 3 years and 65 % to 70 % after 4 years of continuous treatment. (14)

Emergence of resistance has a negative impact on the efficacy of therapy in both HBeAg-positive and HBeAg-negative chronic hepatitis B patients (15, 16). Unfortunately, sustained off-therapy responses in HBeAg negative chronic hepatitis B are rare; biochemical and virological relapses are observed in most patients after the cessation of a 12-month lamivudine course (17).

In conclusion, the majority of treated patients develop a virological response with loss of serum HBV-DNA associated with normalization of serum ALT and histological improvement. The tolerability and safety of lamivudine are excellent. Antiviral effect of the drug is rapid. The major inconvenience of lamivudine is the high rate of viral resistance related to mutations in the YMDD motif. Usually, the breakthrough related to the occurrence of resistance is moderate, but severe cases have been reported in patients with cirrhosis. Another disadvantage of lamivudine therapy in HBeAg-negative chronic hepatitis B is that no course of finite duration has been shown to achieve sustained off-therapy responses in a sizeable proportion of patients and the optimal duration of therapy is currently unknown. (18) The course of HBeAg-negative chronic hepatitis B after the discontinuation of lamivudine, in patients who have remained in very prolonged complete on-therapy remission, is not known. The current data regarding treatment of chronic hepatitis B are not clearly pro lamivudine as a first line therapy.

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