

**2034** histologic responses; consolidation of virologic and biochemical benefit in the ensuing years after therapy; and improvement in the natural history of chronic hepatitis B. Standard IFN has been supplanted by long-acting PEG IFN (see below), and IFN nonresponders are now treated with one of the newer oral nucleoside analogues.

### LAMIVUDINE

The first of the nucleoside analogues to be approved, the dideoxynucleoside lamivudine inhibits reverse transcriptase activity of both HIV and HBV and is a potent and effective agent for patients with chronic hepatitis B. Although generally superseded by newer, more potent agents, lamivudine is still used in regions of the world where newer agents are not yet approved or are not affordable. In clinical trials among patients with HBeAg-reactive chronic hepatitis B, lamivudine therapy at daily doses of 100 mg for 48–52 weeks suppressed HBV DNA by a median of approximately  $5.5 \log_{10}$  copies/mL and to undetectable levels, as measured by PCR amplification assays, in approximately 40% of patients. Therapy was associated with HBeAg loss in 32–33%; HBeAg seroconversion (i.e., conversion from HBeAg-reactive to anti-HBe-reactive) in 16–21%; normalization of ALT in 40–75%; improvement in histology in 50–60%; retardation in fibrosis in 20–30%; and prevention of progression to cirrhosis. HBeAg responses can occur even in subgroups who are resistant to IFN (e.g., those with high-level HBV DNA) or who failed in the past to respond to it. As is true for IFN therapy of chronic hepatitis B, patients with near-normal ALT activity tend not to experience HBeAg responses (despite suppression of HBV DNA), and those with ALT levels exceeding  $5 \times$  the upper limit of normal can expect 1-year HBeAg seroconversion rates of 50–60%. Generally, HBeAg seroconversions are confined to patients who achieve suppression of HBV DNA to  $<10^4$  copies/mL (equivalent to  $\sim 10^3$  IU/mL). Lamivudine-associated HBeAg responses are accompanied by a posttreatment HBsAg seroconversion rate comparable to that seen after IFN-induced HBeAg responses. Among Western patients who undergo HBeAg responses during a year-long course of therapy and in whom the response is sustained for 4–6 months after cessation of therapy, the response is durable thereafter in the vast majority ( $>80\%$ ); therefore, the achievement of an HBeAg response represents a viable stopping point in therapy. Reduced durability has been reported in Asian patients; therefore, to support the durability of HBeAg responses, patients should receive a period of consolidation therapy of  $\geq 6$  months in Western patients and  $\geq 1$  year in Asian patients after HBeAg seroconversion. Close posttreatment monitoring is necessary to identify HBV reactivation promptly and to resume therapy. If HBeAg is unaffected by lamivudine therapy, the current approach is to continue therapy until an HBeAg response occurs, but long-term therapy may be required to suppress HBV replication and, in turn, limit liver injury; HBeAg seroconversions can increase to a level of 50% after 5 years of therapy. Histologic improvement continues to accrue with therapy beyond the first year; after a cumulative course of 3 years of lamivudine therapy, necroinflammatory activity is reduced in the majority of patients, and even cirrhosis has been shown to regress to precirrhotic stages in as many as three-quarters of patients.

Losses of HBsAg have been few during the first year of lamivudine therapy, and this observation had been cited as an advantage of IFN-based over lamivudine therapy; however, in head-to-head comparisons between standard IFN and lamivudine monotherapy, HBsAg losses were rare in both groups. Trials in which lamivudine and IFN were administered in combination failed to show a benefit of combination therapy over lamivudine monotherapy for either treatment-naïve patients or prior IFN nonresponders.

In patients with *HBeAg-negative chronic hepatitis B* (i.e., in those with precore and core-promoter HBV mutations), 1 year of lamivudine therapy results in HBV DNA suppression and normalization of ALT in three-quarters of patients and in histologic improvement in approximately two-thirds. Therapy has been shown to suppress HBV DNA by approximately  $4.5 \log_{10}$  copies/mL (baseline HBV DNA levels are lower than in patients with HBeAg-reactive hepatitis B)

and to undetectable levels in approximately 70%, as measured by sensitive PCR amplification assays. Lacking HBeAg at the outset, patients with HBeAg-negative chronic hepatitis B cannot achieve an HBeAg response—a stopping point in HBeAg-reactive patients; almost invariably, when therapy is discontinued, reactivation is the rule. Therefore, these patients require long-term therapy; with successive years, the proportion with suppressed HBV DNA and normal ALT increases.

Clinical and laboratory side effects of lamivudine are negligible and indistinguishable from those observed in placebo recipients. Still, lamivudine doses should be reduced in patients with reduced creatinine clearance. During lamivudine therapy, transient ALT elevations, resembling those seen during IFN therapy and during spontaneous HBeAg-to-anti-HBe seroconversions, occur in one-fourth of patients. These ALT elevations may result from restored cytolytic T cell activation permitted by suppression of HBV replication. Similar ALT elevations, however, occur at an identical frequency in placebo recipients, but ALT elevations associated with HBeAg seroconversion are confined to lamivudine-treated patients. When therapy is stopped after a year of therapy, two- to threefold ALT elevations occur in 20–30% of lamivudine-treated patients, representing renewed liver-cell injury as HBV replication returns. Although these posttreatment flares are almost always transient and mild, rare severe exacerbations, especially in cirrhotic patients, have been observed, mandating close and careful clinical and virologic monitoring after discontinuation of treatment. Many authorities caution against discontinuing therapy in patients with cirrhosis, in whom posttreatment flares could precipitate decompensation.

Long-term monotherapy with lamivudine is associated with methionine-to-valine (M204V) or methionine-to-isoleucine (M204I) mutations, primarily at amino acid 204 in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of HBV DNA polymerase, analogous to mutations that occur in HIV-infected patients treated with this drug. During a year of therapy, YMDD mutations occur in 15–30% of patients; the frequency increases with each year of therapy, reaching 70% at year 5. Ultimately, patients with YMDD mutants experience degradation of clinical, biochemical, and histologic responses; therefore, if treatment is begun with lamivudine monotherapy, the emergence of lamivudine resistance, reflected clinically by a breakthrough from suppressed levels of HBV DNA and ALT, is managed by adding another antiviral to which YMDD variants are sensitive (e.g., adefovir, tenofovir; see below).

Currently, although lamivudine is very safe and still used widely in other parts of the world, in the United States and Europe, lamivudine has been eclipsed by more potent antivirals that have superior resistance profiles (see below); it is no longer recommended as first-line therapy. Still, as the first successful oral antiviral agent for use in hepatitis B, lamivudine has provided proof of the concept that polymerase inhibitors can achieve virologic, serologic, biochemical, and histologic benefits. In addition, lamivudine has been shown to be effective in the treatment of patients with decompensated hepatitis B (for whom IFN is contraindicated), in some of whom decompensation can be reversed. Moreover, among patients with cirrhosis or advanced fibrosis, lamivudine has been shown to be effective in reducing the risk of progression to hepatic decompensation and, marginally, the risk of HCC. In the half decade following the introduction in the United States of lamivudine therapy for hepatitis B, referral of patients with HBV-associated end-stage liver disease for liver transplantation was reduced by  $\sim 30\%$ , supporting further the beneficial impact of oral antiviral therapy on the natural history of chronic hepatitis B.

Because lamivudine monotherapy can result universally in the rapid emergence of YMDD variants in persons with HIV infection, patients with chronic hepatitis B should be tested for anti-HIV prior to therapy; if HIV infection is identified, lamivudine monotherapy at the HBV daily dose of 100 mg is contraindicated. These patients should be treated for both HIV and HBV with an HIV drug regimen that includes or is supplemented by at least two drugs active against HBV; antiretroviral therapy (ART) often contains two drugs