

rate of sustained response (6 months after treatment) than is achieved with oral nucleoside/nucleotide analogue therapy, the comparison is confounded by the fact that oral agents are not discontinued at the end of 1 year. Instead, taken orally and free of side effects, therapy with oral agents is extended indefinitely or until after the occurrence of an HBeAg response. The rate of HBeAg responses after 2 years of oral-agent nucleoside analogue therapy is at least as high as, if not higher than, that achieved with PEG IFN after 1 year; favoring oral agents is the absence of injections, difficult-to-tolerate side effects, and laboratory monitoring as well as lower direct and indirect medical care costs and inconvenience. The association of HBsAg responses with PEG IFN therapy occurs in such a small proportion of patients that subjecting everyone to PEG IFN for the marginal gain of HBsAg responses during or immediately after therapy in such a very small minority is questionable. Moreover, HBsAg responses occur in a comparable proportion of patients treated with early-generation nucleoside/nucleotide analogues in the years after therapy, and, with the newer, more potent nucleoside analogues, the frequency of HBsAg loss during the first year of therapy equals that of PEG IFN and is exceeded during year 2 and beyond (see below). Of course, resistance is not an issue during PEG IFN therapy, but the risk of resistance is much lower with new agents ($\leq 1\%$ up to 3–6 years in previously treatment-naïve, entecavir-treated and tenofovir-treated patients; see below). Finally, the level of HBV DNA inhibition that can be achieved with the newer agents, and even with lamivudine, exceeds that which can be achieved with PEG IFN, in some cases by several orders of magnitude.

In HBeAg-negative chronic hepatitis B, a trial of PEG IFN- α 2a (180 μg weekly for 48 weeks versus comparison arms of lamivudine monotherapy and of combination therapy) in 564 patients showed that PEG IFN monotherapy resulted at the end of therapy in suppression of HBV DNA by a mean of 4.1 \log_{10} copies/mL, undetectable HBV DNA (<400 copies/mL by PCR) in 63%, normal ALT in 38%, and loss of HBsAg in 4%. Although lamivudine monotherapy and combination lamivudine–PEG IFN therapy were both superior to PEG IFN at the end of therapy, no advantage of lamivudine monotherapy or combination therapy was apparent over PEG IFN monotherapy 6 months after therapy—suppression of HBV DNA by a mean of 2.3 \log_{10} copies/mL, undetectable HBV DNA in 19%, and normal ALT in 59%. In subjects involved in this trial followed for up to 5 years, among the two-thirds followed who had been treated initially with PEG IFN, 17% maintained HBV DNA suppression to <400 copies/mL, but ALT remained normal in only 22%; HBsAg loss increased gradually to 12%. Among the half followed who had been treated initially with lamivudine monotherapy, HBV DNA remained <400 copies/mL in 7% and ALT normal in 16%; by year 5, 3.5% had lost HBsAg. As was the case for standard IFN therapy in HBeAg-negative patients, only a small proportion maintained responsiveness after completion of PEG IFN therapy, raising questions about the relative value of a finite period of PEG IFN, versus a longer course with a potent, low-resistance oral nucleoside analogue in these patients. Moreover, the value of PEG IFN for HBeAg-negative chronic hepatitis B has not been confirmed. In the only other controlled clinical trial of PEG IFN for HBeAg-negative chronic hepatitis B, the hepatitis C regimen of PEG IFN plus ribavirin was compared to PEG IFN monotherapy. In this trial, HBV DNA suppression (<400 copies/mL) occurred in only 7.5% of the two groups combined, and no study subject lost HBsAg.

In patients treated with PEG IFN, HBeAg and HBsAg responses have been associated with *IL28B* genotype CC, the favorable genotype identified in trials of PEG IFN for chronic hepatitis C. Also, reductions in quantitative HBsAg levels have been shown to correlate with and to be predictive of responsiveness to PEG IFN in chronic hepatitis B. If HBsAg levels fail to fall within the first 12–24 weeks or to reach $<20,000$ IU/mL by week 24, PEG IFN therapy is unlikely to be effective and should be discontinued.

ENTECAVIR

Entecavir, an oral cyclopentyl guanosine analogue polymerase inhibitor, appears to be the most potent of the HBV antivirals and is just as well tolerated as lamivudine. In a 709-subject clinical trial among

HBeAg-reactive patients, oral entecavir, 0.5 mg daily, was compared to lamivudine, 100 mg daily. At 48 weeks, entecavir was superior to lamivudine in suppression of HBV DNA (mean 6.9 versus 5.5 \log_{10} copies/mL), percentage with undetectable HBV DNA (<300 copies/mL by PCR; 67% versus 36%), histologic improvement (≥ 2 -point improvement in necroinflammatory HAI score; 72% versus 62%), and normal ALT (68% versus 60%). The two treatments were indistinguishable in percentage with HBeAg loss (22% versus 20%) and seroconversion (21% versus 18%). Among patients treated with entecavir for 96 weeks, HBV DNA was undetectable cumulatively in 80% (versus 39% for lamivudine), and HBeAg seroconversions had occurred in 31% (versus 26% for lamivudine). After 3–6 years of entecavir, HBeAg seroconversions have been observed in 39–44% and HBsAg loss in 5–6%. Similarly, in a 638-subject clinical trial among HBeAg-negative patients, at week 48, oral entecavir, 0.5 mg daily, was superior to lamivudine, 100 mg daily, in suppression of HBV DNA (mean 5.0 versus 4.5 \log_{10} copies/mL) and in percentage with undetectable HBV DNA (90% versus 72%), histologic improvement (70% versus 61%), and normal ALT (78% versus 71%). No resistance mutations were encountered in previously treatment-naïve, entecavir-treated patients during 96 weeks of therapy, and in a cohort of subjects treated for up to 6 years, resistance emerged in only 1.2%. Entecavir-induced HBeAg seroconversions are as durable as those achieved with other antivirals. Its high barrier to resistance coupled with its high potency renders entecavir a first-line drug for patients with chronic hepatitis B.

Entecavir is also effective against lamivudine-resistant HBV infection. In a trial of 286 lamivudine-resistant patients, entecavir, at a higher daily dose of 1 mg, was superior to lamivudine, as measured at week 48, in achieving suppression of HBV DNA (mean 5.1 versus 0.48 \log_{10} copies/mL), undetectable HBV DNA (72% versus 19%), normal ALT (61% versus 15%), HBeAg loss (10% versus 3%), and HBeAg seroconversion (8% versus 3%). In this population of lamivudine-experienced patients, however, entecavir resistance emerged in 7% at 48 weeks. Although entecavir resistance requires both a YMDD mutation and a second mutation at one of several other sites (e.g., T184A, S202G/I, or M250V), resistance to entecavir in lamivudine-resistant chronic hepatitis B has been recorded to increase progressively to 43% at 4 years; therefore, entecavir is not as attractive a choice as adefovir or tenofovir for patients with lamivudine-resistant hepatitis B.

In clinical trials, entecavir has an excellent safety profile; in addition, on-treatment and posttreatment ALT flares are relatively uncommon and relatively mild in entecavir-treated patients. Doses should be reduced for patients with reduced creatinine clearance. Entecavir does have low-level antiviral activity against HIV and cannot be used as monotherapy to treat HBV infection in HIV/HBV co-infected persons.

TELBIVUDINE

Telbivudine, a cytosine analogue, is similar in efficacy to entecavir but slightly less potent in suppressing HBV DNA (a slightly less profound median 6.4 \log_{10} reduction in HBeAg-reactive disease and a similar 5.2 \log_{10} reduction in HBeAg-negative disease). In its registration trial, telbivudine at an oral daily dose of 600 mg suppressed HBV DNA to <300 copies/mL in 60% of HBeAg-positive and 88% of HBeAg-negative patients, reduced ALT to normal in 77% of HBeAg-positive and 74% of HBeAg-negative patients, and improved histology in 65% of HBeAg-positive and 67% of HBeAg-negative patients. Although resistance to telbivudine (M204I, not M204V, mutations) was less frequent than resistance to lamivudine at the end of 1 year, resistance mutations after 2 years of treatment occurred in up to 22%. Generally well tolerated, telbivudine has been associated with a low frequency of asymptomatic creatine kinase elevations and with a very low frequency of peripheral neuropathy; frequency of administration should be reduced for patients with impaired creatinine clearance. Its excellent potency notwithstanding, the inferior resistance profile of telbivudine has limited its appeal; telbivudine is neither recommended as first-line therapy nor widely used.