

Medical Writers' Circle

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a series of articles
written by medical
professionals about
the management
and treatment of
hepatitis C

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Overview of Treatment of Hepatitis B

Interferon alpha (5 million units/day or 10 million units tiw) is associated with HBeAg loss in 30-40% of patients, and in early trials, approximately 10% lost HbsAg (A CURE!). If a patient loses HBeAg during interferon therapy, HbsAg loss follows in approximately 80% of patients followed for a decade. In addition, improved survival, complication-free survival, and a reduction in the frequency of hepatocellular carcinoma have been documented or suggested in interferon responders. Interferon therapy is more effective in patients with low-level HBV DNA 100,000–40 million copies per mL, elevated ALT (esp if >200 IU/mL), immunocompetence, normal liver function (albumin, bilirubin and coagulation), and acquisition of infection in adulthood. Early studies suggested that the efficacy of interferon was low in patients with pre-core-mutant HBV infection (HBeAg negative strains), but recent observations have renewed interest in interferon for this indication. Emerging data on PEG interferon may result in the first line use of PEG products alone or in combination with oral agents.

Lamivudine

Lamivudine is associated with a 4-log suppression of HBV DNA at daily oral doses of ≥ 100 mg. In phase-III, prospective, controlled

clinical trials among North American, European, and Asian patients with HbeAg+ and elevated ALT, 12 months of lamivudine therapy was associated with almost universal suppression of hybridization-assay-detectable HBV DNA (<100,000 copies per mL), approximately 30% HBeAg loss, approximately 16%-18% HBeAg seroconversion (HbeAg + to - and antiHBe- to +), sustained ALT normalization in approximately 40%-50%, and liver histologic improvement in approximately 50%. Hepatitis B e antigen loss/seroconversion achieved during therapy is maintained in approximately 70-80% over the immediate months and up to >2 years after therapy. Among those treated for two years, liver histology improved and fibrosis was reduced. Trials in which lamivudine and interferon were administered in combination (**2-month lead-in period** of lamivudine monotherapy, followed by a 4-month period of combination therapy) failed to show a statistical benefit of combination therapy. In addition, in a head-to-head comparison of 12-months of lamivudine versus 4 months of interferon, the two regimens achieved comparable results although long term data is still pending.

Clinical and laboratory side effects during lamivudine therapy cannot be distinguished from those during placebo treatment. In placebo-controlled trials, when lamivudine therapy was discontin-

ued, aminotransferase elevations occurred in approximately a quarter of patients, but these were self-limited and unassociated with jaundice or hepatic decompensation. However, there have been rare reports of deaths occurring after discontinuation of lamivudine due to severe flares of hepatitis. Current experience with lamivudine suggests that losses of HbsAg are extremely rare. Among patients with pre-core HBV mutations, suppression of HBV replication can be achieved almost universally with lamivudine, and histologic improvement occurs in the majority of treated patients, but reactivation is the rule when therapy is stopped.

Mutations in the YMDD polymerase motif of HBV DNA emerge in approximately 20% of patients treated with lamivudine for a year, and the frequency of these mutations increases each year (>67% at 4 years). Generally, immunocompetent patients with these viral variants tend to be asymptomatic and to maintain lower levels of HBV DNA and ALT than baseline levels before therapy for one year, but by 3 years the histology and ALT values are back to baseline or worse and severe cases of hepatitis have occurred when this mutant emerges.

Adefovir

Recently completed placebo-controlled, randomized clinical trials of adefovir dipivoxil monotherapy

(orally administered 10 mg/d) in patients with wild-type and pre-core-mutant chronic hepatitis B have demonstrated histologic, virologic, and biochemical improvements comparable to those achieved with lamivudine monotherapy but with a much lower rate of resistance. In HBeAg-reactive patients, HBeAg seroconversions occurred during the first year of adefovir therapy (12%)—which is similar to lamivudine therapy (16-

others. The efficacy of interferon is being re-addressed, now that more potent, longer-acting, pegylated interferons are available.

Summary:

Interferon requires only four to six months of therapy, achieved a 30+% HBeAg loss, perhaps a 10% HBsAg loss, and long-term improvements in natural history without HBV mutations are important issues to consider. However,

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18%)—and very rare resistance to antiviral therapy emerging during adefovir monotherapy has been reported (EASL 2003 2% at 2 years). The eAg seroconversion rate continues to increase at years 2 and 3 of therapy. In addition, adefovir was found to be safe and well tolerated in clinical trials, and the treatment-limiting nephrotoxicity seen when this drug was used at higher doses for patients with HIV infection was not encountered among patients in HBV trials at 10mg per day. Dose adjustments of Adefovir must take place if the patient has renal insufficiency. Adefovir has been shown to inhibit HBV replication in lamivudine-treated patients with YMDD variants in clinical trials among both immunocompetent patients and liver-allograft recipients. Approval of this drug by the FDA was granted in 2002 and this medication is now a serious contender for first line therapy for patients who are not interferon candidates (approximately 80-90% of patients).

Other agents

Clinical trials are in progress on a series of other potent inhibitors of HBV replication, including emtricitabine, entecavir, clevudine, HepaVir, Ld4T and L-dT among

interferon requires inconvenient injection therapy, is associated with side effects, is no better than lamivudine in head-to-head comparisons for eAg seroconversion, and is of limited value in certain subgroups although it is the only medication that offers a chance at a cure! Lamivudine and adefovir are both safe and convenient to take, achieve a 30+% HBeAg loss, histologic improvement in the majority of patients (not limited to HBeAg responders, as is the case for interferon), and achieve every benefit observed in interferon-treated patients, as shown in direct-comparison trials. Importantly, lamivudine requires longer-duration therapy and is associated with the emergence of viral variants that are rarely seen with adefovir therapy.

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