Prescrire's proposals

Management of chronic hepatitis B

● For patients with chronic hepatitis B, signs of viral replication (detectable viral DNA or HBe antigen in the bloodstream) and histological signs of liver damage, the first-line treatment is peginterferon alfa-2a at a dose of one subcutaneous injection of 90 µg per week, usually for 24 weeks if HBe antigen is positive (48 weeks if it is negative). This treatment requires regular monitoring of blood cell and platelet counts, as well as thyroid function and mood. Sustained eradication of HBe antigen is obtained in 20% to 40% of cases, but DNA becomes undetectable in fewer than 20% of cases (detection threshold 400 copies/ml). No additional benefit is obtained by adding an antiviral agent to peginterferon alfa-2a.

● When peginterferon does not adequately affect viral load or is unacceptable, especially because of its adverse effects, continuous oral treatment with lamivudine or adefovir dipivoxil reduces the risk of complications of hepatitis B. Lamivudine seems to prevent clinical progression in 10% of patients with cirrhosis after three years of treatment. The choice between these two antivirals is not an easy one: lamivudine is less effective than adefovir dipivoxil on viral load, but less evidence is available concerning the effects of adefovir on complications of hepatitis B, and we have less experience in terms of longer-term adverse effects.

● Lamivudine therapy does not require specific laboratory monitoring. The nephrotoxicity of adefovir dipivoxil means that blood creatinine levels must be monitored. Patients must be warned that sudden deterioration can occur when these drugs are withdrawn, and that close monitoring at this time is preferable.

● If lamivudine fails, adefovir dipivoxil remains effective in some patients.

● If both lamivudine and adefovir dipivoxil fail or are poorly tolerated, continuous oral entecavir therapy can be tried, at a dose of 1 mg/day, but its adverse effects have not been adequately documented.

► patients on placebo (p<0.001). Hepatocellular carcinoma was diagnosed in 4% of patients on lamivudine group versus 7% of patients on placebo (p=0.047).

However, the Tyr-Met-Asp-Asp (YMDD) mutation, generally associated with viral resistance to lamivudine, occurred in half the patients on lamivudine. The incidence of mutations associated with antiviral resistance does not appear to be influenced by HBeAg status (12,14).

Most adverse effects of lamivudine are mild: abdominal pain, gastrointestinal disorders (diarrhoea, nausea), malaise, fatigue, and headache (1). Hepatitis sometimes recurs after treatment cessation. Pancreatitis and rare cases of lactic acidosis have been described in HIV infected patients taking lamivudine doses three times higher than those used in hepatitis B treatment (**d**)(1).

Lamivudine is an effective and well tolerated treatment for chronic hepatitis B. However, resistance frequently occurs after several months of treatment and is a major drawback.

Adefovir: an alternative to lamivudine

The final results of two clinical trials in 59 and 95 patients treated for about a year confirm that, in patients with lamivudine resistant mutations, high-level viraemia and elevated transaminase activity, adefovir, alone or in combination with lamivudine, has a greater effect on viral load than ongoing lamivudine therapy (**e**)(15,16).

Furthermore, at the end of a 48-week placebo-controlled trial, another randomisation of patients to either continuation of adefovir or adefovir withdrawal, with follow-up until 144 weeks, showed that viral replication increased when adefovir was withdrawn after a total of two years but not when it was continued (17). Viral mutations associated with resistance to adefovir occurred in 6% of patients treated for three years (**f**)(17).

In other follow-up studies of patients resistant to lamivudine, resistance to adefovir developed in 6% of cases at 1 year and 25% to 38% of cases at two years (18,19).

Virological efficacy lasting at least two years in 25% of patients. Adefovir has also been evaluated as first-line treatment in patients with chronic hepatitis B who had signs of viral replication and histological liver damage. In contrast, we found no trials versus interferon alfa or peginterferon alfa.

A two-year double-blind placebo-controlled trial in 515 HBeAg-positive patients compared adefovir 10 mg/day versus adefovir 30 mg/day (20). Two years after the end of treatment, 24% and 27% of patients on adefovir 10mg/day and 30mg/day no longer had signs of viral replication, compared to 11% of patients on placebo. Anti-HBe antibodies developed in 13% of patients on adefovir and in 6% of patients on placebo.

No mutations associated with treatment resistance occurred during this trial.

Dose-dependent nephrotoxicity. Experience with adefovir is relatively short. During clinical trials, the main adverse effect of adefovir was nephrotoxicity at high doses (2% to 5% of patients at 10 mg/day, 40% at 30 mg/day). The most frequent adverse effects are gastrointestinal disorders (nausea, flatulence, diarrhoea, dyspepsia and abdominal pain), headache and fatigue (21).

Rapid recurrence of hepatitis has been described following treatment cessation (**g**).

Entecavir: short follow-up

Entecavir is the third nucleoside/nucleotide analogue to be approved for the treatment of hepatitis B. Our literature search identified no trials comparing entecavir with interferon, peginterferon or adefovir.

Oral lamivudine and entecavir were compared in three 96-week clinical trials: two trials in previously untreated patients and the third in patients in whom lamivudine had failed. Entecavir was significantly more effective than