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Treatment options in HBV

Antonio Craxì[1,*], Giorgio Antonucci[2], Calogero Cammà[1]

[1]*Clinica Medica I, Cattedra di Gastroenterologia, University of Palermo, Piazza delle Cliniche 2, 90127 Palermo, Italy*
[2]*Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani, Istituto di Ricovero e Cura a Carattere Scientifico, Roma, Italy*

The available evidence on interferon-alpha (IFN) treatment for chronic hepatitis B is sufficient to conclude that in patients with HBeAg positive chronic hepatitis, standard IFN therapy significantly improves clearance of HBeAg (number needed to treat [NNT] = 4), loss of HBV-DNA (NNT = 4) and clearance of HBsAg (NNT = 18). HBeAg positive patients with normal or slightly raised ALT should be treated only if there is histological evidence of progressive disease. In patients with HBeAg negative chronic hepatitis, less than 20% of subjects who have achieved an end-of-treatment virological response after a course of standard IFN mantain a sustained virological response in the long-term. IFN treatment could help to delay or prevent disease decompensation and liver-related deaths but further large studies are needed. Lamivudine is effective at reducing, and sometimes clearing, HBV replication in heavily immunosuppressed patients and can be safely administered to patients with advanced liver disease. Lamivudine should be continued over an undefined extended period of time, with a switch from lamivudine to adefovir if there is an HBV-DNA breakthrough under therapy. Adefovir, excluding cost, is preferable to lamivudine as a first-choice because there is less chance of inducing resistance. The long-term benefit of lamivudine and adefovir and the role of combinations is under investigation.

***Keywords*: Hepatitis B; HIV; Liver disease; Interferon; Lamivudine; Adefovir; Treatment**

1. Current therapies for chronic HBV infection

1.1. Interferon

1.1.1. Effects of IFN on 'surrogate' markers of response

Meta-analyses [1–4] of randomized controlled trials (RCTs) of interferon-((IFN) for chronic hepatitis B conclusively prove its effectiveness on 'surrogate' markers of response. Meta-analysis [3] of 24 RCTs comparing standard IFN to no treatment in adult patients with HBeAg positive chronic hepatitis B showed the following risk differences (RDs), all in favour of IFN:

- persistent ALT normalization: RD + 26.2% (95% CI: 18.3–34.0%); NNT 3.8;
- clearance of HBeAg: RD + 24.3% (95% CI: 8.3–30.4%); NNT 4.1;
- sustained loss of HBV-DNA: RD + 23.4% (95% CI: 17.9–28.8%); NNT 4.3;
- clearance of HBsAg: RD + 5.6% (95% CI: 3.5–7.6%); NNT 18.

The optimal cost-effectiveness ratio on surrogate end-points is reached by treating HBeAg positive patients with 9–10 MU of standard IFN tiw for 4–6 months.

Meta-analysis of seven RCTs [5–11] comparing standard IFN to no treatment, enrolling only patients infected by the HBe minus mutant, showed a significant effect of standard IFN on the combined outcome of sustained loss of serum HBV-DNA and persistent ALT normalization (RD + 21%; 95% CI: 6.8–35%). The dose and duration of IFN therapy for HBeAg positive chronic hepatitis B have not been standardized but prolonged treatment ($\geq$12 months) may result in higher and more durable sustained response [12].

* Corresponding author. Tel.: +39 091 6553248; fax: +39 091 6552156.
E-mail address: craxanto@unipa.it (A. Craxì).

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1.1.2. Long-term benefits of IFN treatment

Meta-analysis [3] of 12 long-term studies performed in the setting of HBeAg positive chronic hepatitis B showed the following distribution of probabilities:

- Loss of HBsAg: treated 11.4% (95% CI: 9.1–13.7%), controls 2.6% (95% CI: 1.8–3.4%); RD 8.8; NNT 11.4;
- Disease decompensation: treated 9.9% (95% CI: 7.7–12.1%), controls 13.3% (95% CI: 10.1–16.4%);
- Liver-related death: treated 4.9% (95% CI: 3.3–6.5%), controls 8.7% (95% CI: 6.1–11.3%).

Three long-term cohort studies [13–15] performed in the setting of HBeAg negative chronic hepatitis B showed that the response appeared to be less durable at long-term follow-up compared to HBeAg positive cases and that relapses can occur even years after therapy.

We combined by meta-analysis [16] 11 controlled trials including 2560 patients with HBV-related cirrhosis that reported the rate of HCC in treated and untreated patients. Overall, regarding HBV-related cirrhosis there is no evidence from trials to support a recommendation for widespread use of IFN to prevent HCC in these patients.

1.2. Lamivudine

1.2.1. Effects of lamivudine on 'surrogate' markers of response

The original observations on the anti-HBV efficacy of lamivudine came from the treatment of HIV-infected subjects who were also HBsAg positive [17,18]. We have analyzed the results of RCTs of lamivudine in immunocompetent HBV infected patients [19–24], all but one [24] including patients with HBeAg positive chronic hepatitis treated with different doses (25–300 mg daily) of lamivudine for periods of 4 weeks to 1 year. The optimal dosage, found by a dose-ranging trial [19] and confirmed by one RCT [21] is 100 mg daily. At the end of treatment the rate of HBeAg seroconversion (defined as loss of HBeAg and appearance of anti-HBe) ranged from 0 to 19%. The durability of HBeAg seroconversion beyond 52 weeks was evaluated in several papers [25–29] with a sufficient follow-up (up to 3 years): all showed a relapse rate ranging from 36 to 57.4% with the highest percentage in Asian patients.

The only published RCT including HBeAg negative patients used a schedule of 52 weeks of therapy [24]. At the end of treatment, 65% of patients had undetectable serum HBV-DNA. However, in this clinical setting there are two major issues with lamivudine treatment: the occurrence of YMDD mutants under therapy and the stability of viral suppression after drug discontinuation.

In patients with HBeAg positive chronic hepatitis, two RCTs evaluated the combination of lamivudine with standard IFN [23,30] and two RCTs assessed the efficacy and the safety of lamivudine with pegylated IFN given for 48–52 weeks [31,32]. In HBeAg negative patients, only one RCT compared [33] pegylated IFN 40 kDa in combination with lamivudine to lamivudine alone or to pegylated IFN alone, all treatments given for 48 weeks.

Overall, in patients with HBeAg positive as well as HBeAg negative chronic hepatitis, pegilated IFN monotherapy shows significantly higher response rates 24 weeks after therapy for both biochemical and virological response compared with lamivudine monotherapy. Combination of pegylated IFN plus lamivudine did not improve the post-therapy response rates compared with pegylated IFN alone. The appearance of YMDD mutant was significantly lower with combination therapy than with lamivudine alone.

1.2.2. Long-term benefits of lamivudine treatment

Two studies of long-term follow-up are available. The first, a recently published RCT [34] compared 436 Asian patients treated with lamivudine for a median of 32 months with 215 untreated controls. HBeAg was present at randomization in 58% of these patients. The Child-Pugh score increased in 3.4% of the patients receiving lamivudine and 8.8% of those receiving placebo (hazard ratio, 0.45; $P=0.02$), whereas HCC occurred in 3.9% of those in the lamivudine group and 7.4% of those in the placebo group (hazard ratio, 0.49; $P=0.047$). YMDD mutations developed in 49% of the patients treated with lamivudine, and the Child-Pugh score was more likely to increase in patients with these mutations than in the other patients treated with lamivudine (7% vs. $<1\%$).

The second retrospective study [35] included 656 anti-HBe positive, HBV-DNA positive Italian patients on long-term lamivudine, 54% with chronic hepatitis, and 46% with cirrhosis. On therapy (median 22 months, range 1–66) HBV-DNA suppression was obtained in 616 patients (93.9%). The rate of sustained virological suppression was 39% after 4 years. The overall incidence of HCC among cirrhotic patients was 4.6, 8.7, 19.8 and 22.1% at 1, 2, 3 and 4 years of therapy. The likelihood of developing HCC was significantly less for cirrhotic patients with sustained virological suppression.

1.3. Adefovir dipivoxil

Two phase III multicenter RCTs, one in HBeAg positive [36] and one in HBeAg negative patients [37] have been published.

In the first RCT [36], 1515 patients worldwide with HBeAg positive chronic hepatitis B were randomized to receive 10 mg or to 30 mg of adefovir or placebo for 48 weeks. The observed reduction of HBV-DNA levels was 4.76 log copies/ml with 30 mg vs. 3.52 log copies/ml with 10 mg of adefovir, in both cases a significantly greater suppression than with placebo. The rates of biochemical and histological improvement were comparable for the two adefovir regimens (59% vs. 53% and 55% vs. 48%, respectively). HBeAg seroconversion, although significantly more common in patients receiving adefovir