

# Treatment of HBeAg negative chronic Hepatitis B: Treatment with Interferon or Pegylated Interferon

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## Abstract

As soon as alpha-interferon (IFN) became available it was used in chronic HBeAg negative chronic hepatitis B: at the beginning (1986-1990) 5-10 MU IFN for 16-24 weeks, thereafter 5-6 MU for 12-24 months. During therapy serum HBV-DNA and ALT decreased progressively and end of treatment response (HBV-DNA < 1-10 pg/ml and normal ALT) was obtained in 57 to 90% of the patients. After therapy (12-24 months) relapse rates ranged from 89 to 25%. HBeAg negative patients miss a hallmark of response, such as HBeAg to anti-HBe seroconversion and show a disease profile with wide fluctuations of HBV-DNA and ALT. Therefore variability of response to IFN was influenced also by monitoring criteria in addition to differences in treatment duration and study populations. After 2-4 years post-treatment follow-up sustained response ranged from 10 to 15% in 4-6 months treated and 22% to 30% in 12-24 months treated patients respectively. One to two thirds of sustained responders (36-66.6%) cleared serum HBsAg (with anti-HBs seroconversion in 50 to 77% of them) after 4.5-7 years. The long-term impact of IFN was investigated in 3 studies: overall progression of chronic hepatitis to cirrhosis was slower and end-stage complications of cirrhosis fewer. Prospective studies are needed to answer the question whether IFN may reduce the incidence of hepatocellular carcinoma.

## Introduction.

Anti-HBe positive chronic hepatitis B was firstly described and characterized in patients of the Mediterranean Basin, where about 20% of hepatitis B surface antigen (HBsAg) carriers with antibody to hepatitis B "e" antigen (HBeAg) show detectable serum levels of hepatitis B virus (HBV) DNA by hybridization assays and intrahepatic necro-inflammation (1-2). They are infected with HBV variants with mutations in the pre-core region which hamper HBeAg production. The G to A switch at nucleotide 1896 of the pre-core region is the most commonly described (3-4). Liver disease runs an indolent course for 3 to 4 decades reaching the stage of histological cirrhosis at a median age of 45 years (5); thereafter about 25% of the patients progress to end stage complications in 10 years (5).

In the recent years an increasing number of reports suggests a worldwide prevalence of the HBeAg negative form of chronic hepatitis B (6-7). However further virological and clinical studies are needed to warrant a complete characterization of the disease and to understand whether it shares common features with the anti-HBe positive chronic hepatitis B observed in Mediterranean patients, who are infected with genotype D HBV, bearing the stop codon at nucleotide 1896 (8). Because of the progressive course of HBeAg negative /anti-HBe positive chronic hepatitis B interferon (IFN) treatment was attempted as soon as the drug became available for treatment of chronic HBV infection (9-12). Most of available studies about interferon treatment of anti-HBe positive chronic hepatitis B were performed in Southern Europe (9-14) and more recently a few reports had been published from Asia (15-17).

## Aims of antiviral treatment and monitoring criteria.

In chronic hepatitis B antiviral treatment is aimed to cure liver disease by an efficacious and sustained

control of HBV infection. This can be obtained in progressive steps: inhibition of viral replication, HBeAg to anti-HBe seroconversion and eventually clearance of serum HBsAg and seroconversion to anti-HBs (6,18). Since HBsAg to anti-HBs seroconversion occurs months or years after the resolution of HBV induced liver damage it can not be used as a short term marker of response to treatment (19-20). Therefore, in HBeAg positive patients HBeAg to anti-HBe seroconversion is considered the hallmark of a successful control of HBV replication and it is used to monitor response to antiviral treatment. On the contrary, in anti-HBe positive chronic hepatitis B a hallmark event such as HBeAg to anti-HBe seroconversion is missing and a general consensus on alternative criteria to be used to monitor treatment has never been reached.

In addition, anti-HBe positive chronic hepatitis B shows variable profiles characterized by major fluctuations of both viremia and transaminases (HBV-DNA can fall below the 10<sup>5</sup> genomes/ml and ALT may normalize temporarily) in over 50% of the patients (5-6). These features hamper the precise identification of disease or hepatitis relapse when the detection limits for HBV-DNA are 10<sup>5</sup> a 10<sup>6</sup> genomes/ml, unless surrogate markers of HBV induced liver damage (IgM anti-HBc) and stringent monitoring criteria are used (5). All together these factors have significantly contributed to the variability of the response rate to interferon reported in the literature (21).

### **Interferon schedules and evaluation of efficacy.**

In anti-HBe positive chronic hepatitis B 2 different treatment approaches had been used overtime: between 1986 and 1990, when IFN was firstly introduced for treatment of chronic hepatitis B, medium-high doses (5 –10 MU) of alpha-recombinant or lymphoblastoid interferon were given for 16-24 weeks, according to the schedules adopted for chronic HBeAg positive hepatitis B (9-13, 21); thereafter, longer treatment courses (12-24 months) were attempted with medium interferon doses (5-6 MU) (14,22-24). Therefore, to analyse the efficacy of IFN and its impact on disease outcome, the “duration of treatment” has to be considered in addition to factors such as disease variability and the different monitoring criteria used in the different studies.

During treatment response (DTR) has been described to be associated, independently of the IFN schedule, to a progressive decrease of serum HBV-DNA levels, followed by a parallel but slower ALT decrease (9-11,22). The occurrence of ALT flares, like those described in HBeAg positive responder patients during the 2<sup>o</sup>-4<sup>o</sup> month of treatment, had been described only in one study, where in 42% of responders serum HBV-DNA clearance was preceded by an ALT flare-up at least 2 times higher than the median pre-treatment value (12).

End of treatment response (ETR) (Figure n.1) is achieved in 57 to 90% of treated patients, when it was defined by the decrease of HBV-DNA levels below 1-10 pg/ml and ALT within the normal range at the time of treatment discontinuation (9-13). In only one study where more stringent criteria (HBV-DNA < 1 pg/ml and normal ALT values persistently in the last 6 months) were used, a lower rate of ETR (38%) was reported in spite of the longest treatment course (24 months) (14).

At 12-24 month post-treatment evaluation variable relapse rates were observed, ranging from 89 to 25% of cases (9-14, 21). Such a high variability appears to be influenced by many factors: 1) criteria used in the post treatment follow-up; 2) duration of treatment and 3) heterogeneity of the population

As previously pointed out a general consensus on the monitoring criteria (parameters to be measured and frequency of monitoring) of the post-treatment follow-up is missing.

This issue was been addressed in a multicenter study where 72 patients were followed-up for 18 months after treatment discontinuation by monthly monitoring of ALT, HBV-DNA and IgM anti-HBc (21). The authors showed that the most stringent criterion is the monthly monitoring of ALT plus every 3 months detection of IgM anti-HBc; whereas the every 3 months measurement of both ALT and IgM anti-HBc maintained an acceptable diagnostic accuracy, with a slightly lower sensitivity (Figure n.2). On the contrary, HBV-DNA detection proved less useful in the identification of relapsers, mainly because of the detection limits of hybridization assays; future studies should investigate the diagnostic accuracy of PCR based assays,

possibly defining the viremia levels of clinical relevance.

Duration of treatment: from available data it appears that the longer is the treatment the higher is the sustained response rate. Sixteen-twenty-four week treatments show a relapse rate ranging from 89 to 50%: the mean time of relapse was 6 months, with over 90% of cases relapsing within the first year of post-treatment follow-up, when monthly monitoring was adopted.

The hepatitis relapse were associated with an ALT flare-up in a significant proportion of patients (50 to 86% of cases) (9-11,13, 21). Three studies report a persistent clearance of markers of viral replication together with biochemical remission after the hepatitis relapse, showing the possibility of a “second intention” disease resolution (9,11,13,21) (Figure n.3).

Interestingly, the only study where a short course of IFN resulted in a lower relapse rate (37%), was the only one that reported the unusual association of ALT flare with response to treatment (12). These finding suggest a possible bias deriving from the selection of patients enrolled in the study and due to the heterogeneity of anti-HBe positive patient’s population.

Data from a 24 month treatment show a lower relapse rate (25%) at 22 months median post-treatment follow-up (14). A longer follow-up (54 months) of 101 patients treated with the same schedule demonstrated a slightly higher (35%) relapse rate (23). These data are consistent with the results of a multivariate analysis of 216 patients where a 1.64 times higher probability of sustained remission was found when 12 month courses were compared to shorter treatments (22). All the findings suggest that longer treatments prolong the remission time, but also the rate of sustained response.

Overall the sustained response rate after 2 to 4 years of post-treatment follow-up appears to be ranging from 10 to 15% in patients treated for 4-6 months (usually at 9-10 MU of interferon), 22% and 30% when 12 and 24 months of 5 MU of interferon were given.

Untreated patients, in spite of frequent temporary remissions recovered from their liver disease very uncommonly. The only study where a significant number (10% after 6 months, 17% after 18 months) of sustained remissions was reported over time in untreated patients showed also an unusually high rate of sustained response (53%) in spite of 6 month treatment (12).

During the post-treatment follow-up (median follow-up 4.5 to 7 years) 31.6 to 66.6% of sustained responders lost serum HBsAg with anti-HBs seroconversion in 50 to 77% of cases (5, 22-24). Interestingly, more than 50% of patients who cleared serum HBsAg had levels of HBV-DNA < 400 cp/ml as compared to 25% of sustained responders without HBsAg loss (22), suggesting a stronger control of HBV infection in patients who experience the clearance of HBsAg.

### **Long term impact of interferon treatment.**

Long term studies to evaluate the influence of IFN on the outcome of chronic hepatitis should analyse separately the early and late phase of the disease, as the impact of many factors, including treatment, may vary during such a prolonged course of the disease. In addition, the heterogeneity of criteria used to monitor the patients and to define response to therapy may hamper the possibility to compare the results of different studies. Furthermore, all available studies with an untreated control group were not randomized, therefore the data have to be taken cautiously. So far, the impact of IFN on the progression of anti-HBe positive chronic hepatitis B had been evaluated in 3 studies where 669 (413 treated and 256 untreated) patients had been followed-up for 4.5 - 6 years (5, 23-24).

In a study where the achievement sustained response required persistently undetectable HBV-DNA (<10 pg/ml), IgM anti-HBc and normal ALT at multivariate analysis interferon treatment, independently of the response, appears to be able to slow by 2.5 fold disease progression and to reduce terminal events (5). None of the long term responders showed disease progression, which was observed instead in 20% of relapsers or non-responders, however the difference was not statistically significant because of the low rate

(14.6%) of SR. Interferon proved useful to reduce the progression of chronic hepatitis to cirrhosis (5) and to reduce the occurrence of end stage complications in cirrhotic patients (5). Improved long-term outcome and reduction of liver-related morbidity had been confirmed in biochemical (24) or biochemical and virological (23) sustained responders in the other 2 studies. The impact of therapy on hepatocellular carcinoma (HCC) remains debated: the results of the 2 studies addressing this question being contradictory (23-24). The cumulative analysis of the available data (5,23,24) indicates that 3 of 102 (2.9%) of sustained responders developed HCC as compared to 27 of 311 (8.7%) treated patients with relapse or non response ( $p=0.086$ ,  $\chi^2 2.954$ ). Therefore, studies in larger cohorts of patients with adequate follow-up and stratification by diagnosis at baseline (chronic hepatitis and cirrhosis) are needed to see whether interferon may eventually reduce the incidence of HCC slowing the progression of chronic hepatitis to cirrhosis or by hampering the oncogenetic process in cirrhotic patients.

### **Factors influencing disease outcome and predicting response to interferon.**

When factors influencing disease progression were evaluated by multivariate analysis older age resulted to be associated with the worst outcome both in treated and untreated patients (5,24). In addition when chronic hepatitis and cirrhotic patients were analysed separately it appears that factors implicated in the pathogenesis of liver damage such as high levels of viral replication (more frequently observed in those patients with an unremitting biochemical disease profile) and steatosis were associated with progression of chronic hepatitis to cirrhosis. Flares ups of IgM anti-HBc serum levels, that are the hallmark of hepatitis B exacerbations were associated with progression of cirrhosis to end stage complications (5).

Factors predicting a higher chance of response to interferon are not well defined: starting therapy at the time of increasing serum levels of IgM anti-HBc was reported to be associated with a higher sustained response rate in a pilot study (25). Recently, a larger study showed an association between sustained response and higher IgM anti-HBc levels and undetectable HBV-DNA levels with sustained response (23). In addition when baseline serum levels were measured by quantitative PCR, median baseline levels HBV-DNA were significantly lower in sustained responders (22). These findings suggest the possibility that starting treatment immediately after a hepatitis exacerbation could increase the chance of sustained response. During treatment an early achievement of both virological and biochemical response was associated with a 3.45 times higher probability of sustained response (22).

### **Conclusion and perspectives**

In conclusion interferon represents the bench mark of antiviral treatment for anti-HBe positive chronic hepatitis B. However, optimization of treatment schedules is awaited.

Early treatment appears to be indicated in patients with disease profiles associated with faster progression, nevertheless interferon appears to be able to slow also end stage complications in cirrhotics.

The availability of pegylated interferons in monotherapy or combination with antivirals could improve and prolong the suppression on HBV replication or favor a more efficacious control of HBV infection. Future studies should be addressed to study the kinetics of both viral replication and immune response under combination therapy to warrant a synergistic effect on both the antiviral and the immune-modulatory activities of interferon.

In addition it should be investigated whether a treatment timed at specific phases of disease could increase the rate of sustained response.

As far the impact of interferon on HCC is concerned prospective studies are needed to answer the question whether IFN may reduce the its incidence.

**Figure 1: End of treatment response in 5 randomized controlled studies (9,10,11,12,14).**

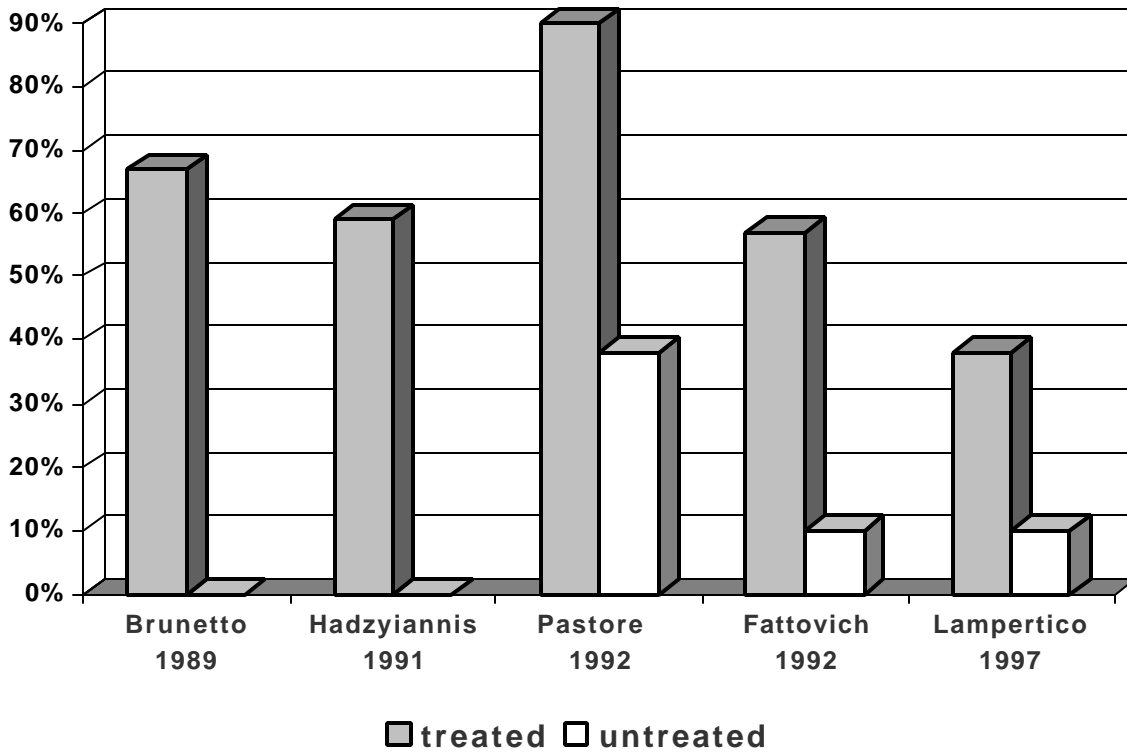


Figure 2: Control of HBV infection and resolution of chronic hepatitis following a relapse after the end of IFN treatment.

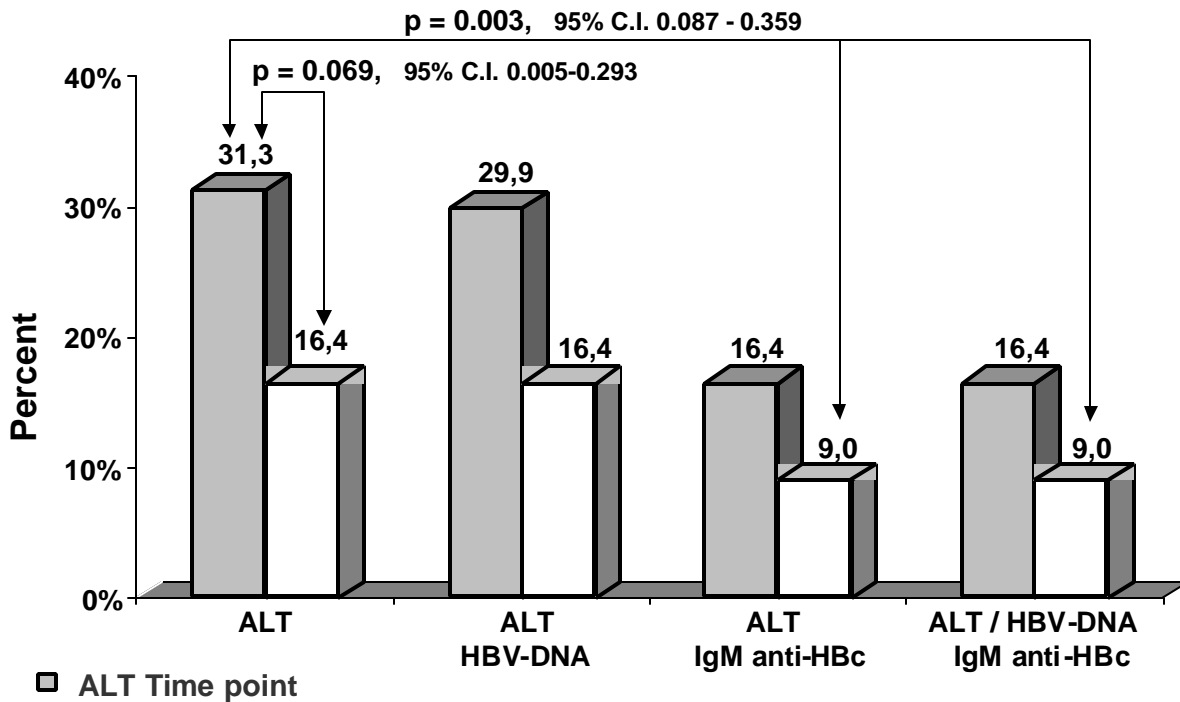
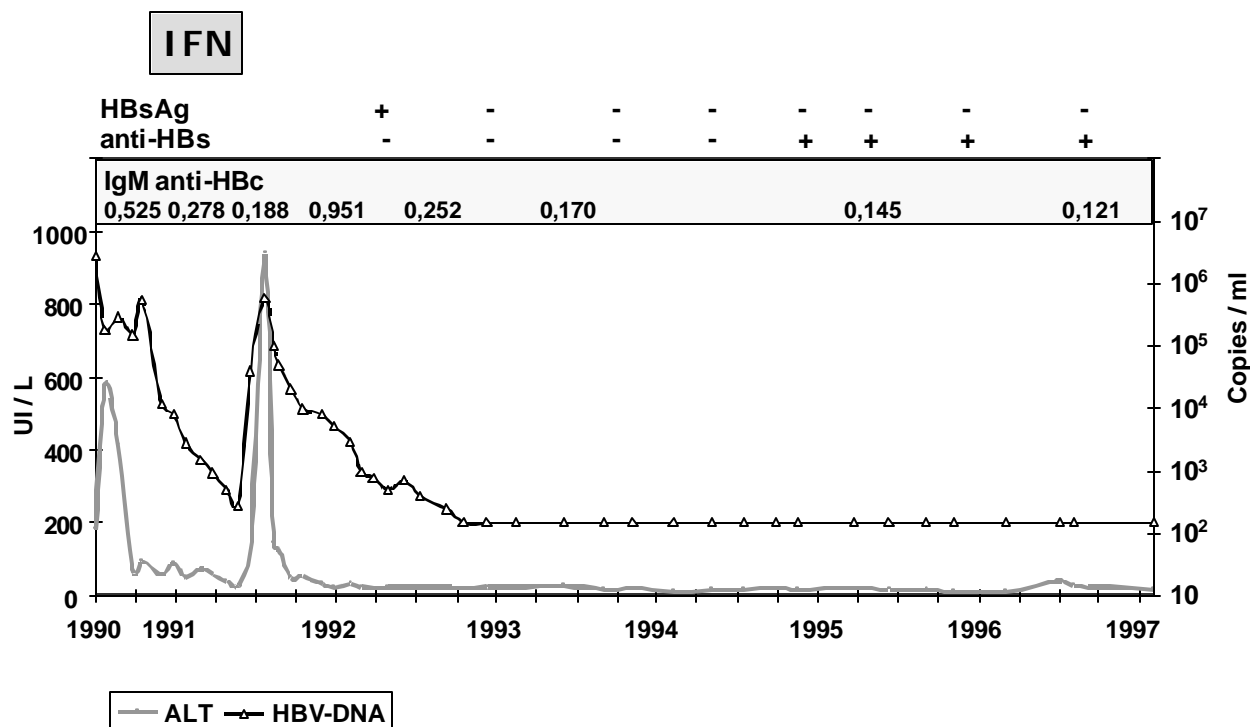


Figure 3: Rate of SR after 12 month post treatment follow-up according to different monitoring criteria (21). HBV-DNA and IgM anti-HBc were measured every 3 months.



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