Treatment of HBeAg-Positive Chronic Hepatitis B with Conventional or Pegylated Interferon

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INTRODUCTION

Despite the introduction of an effective hepatitis B vaccine in the early 1980s, infection with hepatitis B virus (HBV) is not a problem to be consigned to the past. Although the prevalence of chronic HBV is relatively low in Western Europe and the United States, it is 2-7% in southern and eastern Europe and 8-15% in Africa, some parts of Asia, and the western Pacific. Chronic HBV infection currently affects an estimated 400 million people, making it one of the world's most common infectious diseases, and it is among the world's 10 leading causes of death [1]. Unfortunately, the hepatitis B vaccine is not an option for patients who are already chronically infected with HBV; currently antiviral therapy is the only recourse [1].

The aim of this review is to provide practicing physicians with a brief, pragmatic overview of current concepts regarding treatment strategies in hepatitis Be antigen (HBeAg)-positive patients, the role of interferon in the strategy and the potential of pegylated interferon which is likely to be available for use in the near future.

NATURAL HISTORY AND PATIENT CLASSIFICATION

Chronic HBV infection is defined by the persistence of serum hepatitis B surface antigen (HBsAg) for 6 months or longer and accounts for most HBV-related morbidity and mortality. The onset of chronic HBV is characterized by persistent HBV DNA, HBsAg, and HBeAg in serum following infection. Patients with chronic HBV can be classified according to several phases of viral replication and immunologic responsiveness. When acquired in childhood, chronic HBV starts with the "immune tolerance" phase. In this high-replicative phase, HBeAg and high levels of HBV DNA are detectable, but ALT is normal, histological activity is minimal, and the patient is asymptomatic [2]. This phase may persist for 20-30 years. The second phase, which typically occurs between ages 15-35, is termed the "immune clearance" phase and is characterized by declining rates of HBV replication, transient alanine aminotransferase (ALT) elevation (hepatic flares), and hepatic necroinflammatory disease and fibrosis. Transition to the third phase is marked by seroconversion of HBeAg to HBeAg antibody (anti-HBe). Following seroconversion, ALT levels usually normalize, and hepatic damage is repaired. This third phase of "immune control" is characterized by persistent serum HBsAg, undetectable HBeAg, HBV DNA $<10^5$ copies/mL and normal serum ALT and is now widely called the "inactive HBsAg carrier state" [3].

The "inactive HBsAg carrier state" is usually associated with disease remission for decades, but, according to recent observations, mainly in patients with genotype A. In contrast, patients, particularly those living in Asia and southern Europe and with HBV genotype B, C or D, may develop reactivation of hepatitis with persistent or intermittent ALT elevations; they remain HBeAg-negative while simultaneously showing elevated levels of serum HBV DNA. This fourth phase due to "immune escape" is known as chronic HBeAg-negative HBV, this is the second of the two major forms of the disease and is also potentially progressive [4].

It is also noteworthy that each year, 5-15% of patients with chronic HBV seroconvert spontaneously [3]. By the time seroconversion occurs, however, the disease will already have progressed to cirrhosis in a proportion of patients [5], a fact that provides an implicit rationale for intervention.

DESIRABLE END-POINTS OF THERAPY AND TREATMENT OPTIONS

Ideally, the objective of treatment in chronic HBV is complete viral eradication. However, due to the difficulty of eliminating viral DNA from affected hepatocytes, it is unclear whether this is an attainable goal [6]. From a practical perspective, the main objective of therapeutic intervention is to stop progression of disease-related liver injury. This objective will be nearly achieved when the patient is brought into and maintained in the "inactive HBsAg carrier state", characterized by persistent serum HBsAg, undetectable HBeAg, HBV DNA $<10^5$ copies/mL and normal serum ALT. The increasing awareness that the disease may reactivate is changing the desired goal of treatment to complete serologic resolution of chronic hepatitis B, characterized by the additional clearance of serum HBsAg. After HBsAg seroconversion reactivation is rare and the long-term outcome is further improved [3, 6].

Various antiviral and immunomodulatory agents have been evaluated for the treatment of chronic HBV. However, until 2004, only interferon, lamivudine and adefovir have been judged to be sufficiently safe and effective to warrant approval in most countries. In the last year large randomized trials have been completed that document the safety and effectiveness of pegylated interferon and submission for regulatory approval of two forms of pegylated interferon is currently ongoing. For the practicing physician it is important to summarize the results of the trials performed in HBeAg-positive chronic hepatitis B and to describe the advantages and disadvantages of interferon-based therapy versus treatment with nucleoside analogs.

INTERFERON

Interferons are potent, naturally occurring cytokines that have antiviral, immunomodulating, and antiproliferative effects. Their complex scope of activity is mediated through a variety of inhibitory mechanisms that may affect most steps of viral replication. For many viruses, inhibition of protein synthesis appears to be the major inhibitory mechanism.

The predominant cause of viral persistence during HBV infection is generally thought to involve a weak immune response to viral

antigens. Immune tolerance to high viral burdens almost certainly plays a key role in chronicity following neonatal acquisition of HBV, but the specific basis for inhibited viral clearance in adult-acquired disease is less well-defined. One of several abnormalities found in the immunologic profile of patients with chronic HBV infection is deficient production or attenuated response to interferon [7]. This, coupled with the fact that some patients with chronic HBV respond to exogenous interferon, provides the basis for clinical use of the agent. The effects of natural interferon in the treatment of chronic HBV infection were first reported in small studies in the late 1970s. The recombinant product interferon has received extensive clinical use in the treatment of chronic hepatitis B for at least a decade.

EFFICACY FOR SEROLOGIC END-POINTS

A 1993 meta-analysis of 15 well-controlled studies [8] is the most frequently cited report on interferon in the treatment of chronic HBV. The aggregate population described included 837 HBeAg-positive adults with compensated liver disease who were treated with doses of 5-10MU three times weekly for 4-6 months. The primary indices of efficacy were loss of HBsAg and HBeAg. In this meta-analysis, interferon was associated with significant treatment effects on both efficacy indices. A significant treatment effect was also shown for normalization of ALT. Overall, loss of HBsAg and HBeAg in interferon-treated patients was about 6% and 20% respectively more frequent than that occurring spontaneously in the control group.

There is evidence that elevated ALT at baseline is an important predictor of favorable response to interferon (Table 1).

Baseline ALT	Placebo (n=196)	Interferon† (n=68)
>1 x ULN	20/171 (11%)	14/66 (21%)
>2 x ULN	16/112 (14%)	11/42 (26%)
>3 x ULN	7/28 (25%)	4/10 (40%)

Table 1: Rates of seroconversion (loss of HBeAg + anti-HBe) with interferon-alpha at week 52.
†Treatment duration=16 weeks
From Perrillo RP et al. [20].

Although interferon has been widely used in the treatment of chronic HBV for more than a decade, the optimal treatment duration remains uncertain. The typical recommendation is for a 16-week course of 10MU three times per week. However, a recent European Concerted Action on Viral Hepatitis (EUROHEP) study found that a second 16-week course in patients who remained HBeAg-positive at the conclusion of the first course produced a higher rate of seroconversion compared to a control group who received no additional treatment (28% vs. 12%, respectively; *P*=0.04) [9].

EFFICACY FOR CLINICAL END-POINTS

The long-term effects of interferon therapy on morbidity and mortality are less well defined and are more controversial. Most studies compared the survival of interferon treated patients with that of untreated controls [10-14]. Three studies [10, 11, 13] found prolonged survival and a decreased incidence of hepatocellular carcinoma or complications in general after HBeAg clearance; in two studies [12, 14] this effect was not demonstrated. The difference between the results of these studies may be explained by the limited follow-up or the low rate of complications in general due to the inclusion of mainly young patients with less advanced disease. In a recent study of 165 HBeAg-positive patients responders to interferon therapy were compared to non-responders [15]. Response to treatment was defined as HBeAg loss within 12 months after the end of therapy, thus

separating interferon-induced responses from later spontaneous HBeAg loss. Median follow-up was 8.8 years. Fifty-four patients (33%) responded to interferon treatment. Relapse (HBeAg reactivation) was observed in 7 (13%) responders. Loss of HBsAg occurred in 52% of responders compared to 9% of the initial 111 non-responders (Figure 1). Hepatocellular carcinoma was found in 8 patients, 6 of whom were non-responders and one relapser. Multivariate analysis showed significantly improved survival and reduced risk of developing hepatocellular carcinoma in responders. These results provide further support that the response to interferon therapy increases survival and reduces the risk of developing hepatocellular carcinoma.

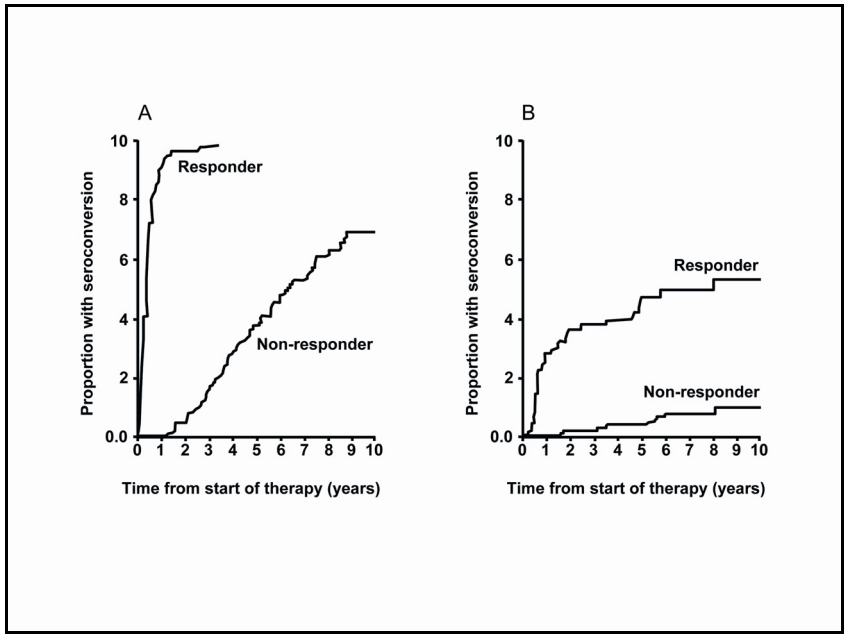

Figure 1: Time to HBeAg loss (A) and HBsAg loss (B) of responders to interferon therapy compared to non-responders. Response was defined as loss of HBeAg within 12 months after the end of interferon therapy.

STRENGTHS AND DRAWBACKS

The advantages of interferon are that treatment is given for a limited time, viral resistance does not occur, and drug-induced seroconversion is sustained in 80-90% of patients. Most importantly, response to interferon is associated with clinically proven reductions in HCC and increased survival [10, 11, 13, 15].

Interferon therapy is not without drawbacks. Interferon can only be administered by subcutaneous injection. Moreover, doses of 5-10MU are usually associated with an acute influenza-like syndrome that may include fever, chills, headache, myalgia, and gastrointestinal disturbances. Tolerance to these effects develops in most patients, but additional toxicities, such as depression and other central nervous system (CNS) disturbances, thyroid dysfunction, and blood cytopenias, may also occur. A large meta-analysis found that dose reduction of interferon was required in approximately 20% of patients; however, adverse events necessitated treatment withdrawal in only about 5% [8].

Some evidence suggests that Chinese patients may have lower rates of response to interferon than other groups [14]. However, differences in variables predictive of response to interferon probably play a role in the between-group differences attributed to race. For example, HBeAg-positive Asians with high baseline levels of ALT respond to interferon as well as other ethnic groups, but patients with low baseline ALT tend to respond poorly to interferon regardless of ethnicity [4]. However, in Asia many patients who acquire HBV during the perinatal period have low ALT during the protracted, immune-tolerance phase of the disease.

PEGYLATED INTERFERON

Pegylated versions of interferon were recently developed to address the short plasma half-life of interferon. The covalently attached polyethylene glycol moiety improved the pharmacokinetic properties of the molecule [16], resulting in greater efficacy, a more convenient once-weekly dosing schedule, and a similar safety profile in patients with chronic HCV infections [17]. Pegylated interferon has already been approved for the treatment of hepatitis C.

Preliminary studies in patients with chronic hepatitis B infections suggest that pegylated interferon will be more effective than interferon in these patients as well.

In the first large randomized controlled trial published in 2003 [18], 194 patients with chronic HBeAg-positive hepatitis, who had not been previously treated with interferon, were randomized to 3 doses of pegylated interferon-alpha-2a given weekly by subcutaneous injection or to conventional interferon-alpha-2a given three times weekly. The treatment duration was 24 weeks, with a 24 week follow-up. At the end of follow-up HBeAg was no longer detectable in 37%, 35% and 29% of patients receiving pegylated interferon 90μg, 180μg and 270μg, respectively, compared to 25% of patients on standard interferon. Two patients on pegylated interferon cleared HBsAg during treatment and remained negative for HBsAg to the end of follow-up. ALT normalization at the end of follow-up was observed in 43%, 35%, and 31% of patients on pegylated interferon 90μg, 180μg and 270μg, respectively, and in 26% of patients on standard interferon.

Additional favorable outcomes were the low proportion of patients who prematurely discontinued study medication (2% and 4% for pegylated interferon and standard interferon, respectively). The incidence of pyrexia, myalgia, severe fatigue, anorexia, insomnia and dizziness was similar for pegylated interferon and standard interferon, whereas headache, alopecia, nausea and diarrhoea were reported more frequently in patients receiving pegylated interferon. Dose modifications for laboratory abnormalities (usually neutropenia or elevated ALT values) occurred in 22-30% of patients receiving pegylated interferon vs. 10% of patients on standard interferon.

In patients with cirrhosis, adverse effects were not more prevalent, whereas 54% of 13 patients receiving pegylated interferon lost HBeAg (none of 4 cirrhotic patients on standard interferon had an HBeAg response). Other baseline factors known to be predictive of nonresponse (low ALT, high HBV DNA, genotype C) may also be less important with pegylated interferon therapy, since the 10% difference in response rates between pegylated interferon and conventional interferon was maintained in all subgroups, according to preliminary findings.

The conclusion that pegylated interferon is more advantageous than conventional interferon is not generally accepted in view of the,

according to the critics, low dose of conventional interferon used. It should be noted that licensed dose regimens differ for different interferons and different parts of the world; also, in retrospect, the superiority of the commonly used schedule of 10MU t.i.w. is hardly based on robust dose-response studies. When pharmocodynamics are investigated, pegylated interferon appears to have a greater antiviral effect than conventional interferon, at 4.5 or 10MU t.i.w. (Figure 2).

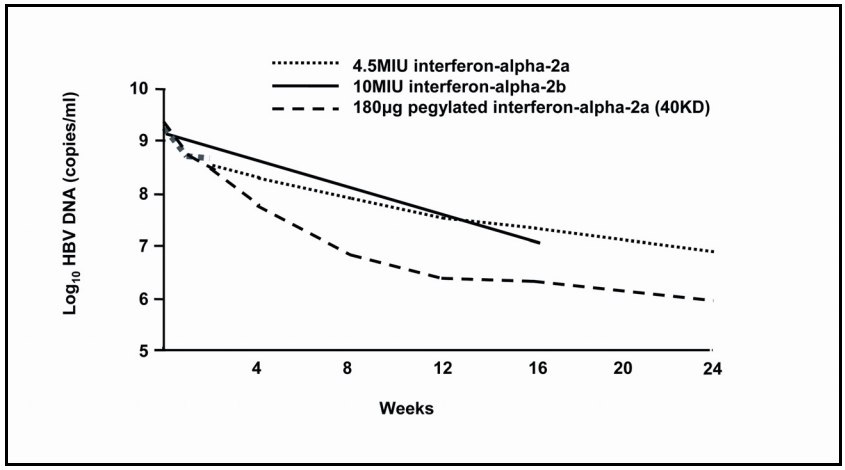

Figure 2: Pharmocodynamics of 180µg of pegylated interferon-alpha-2a compared to two standard regimens of conventional interferon-alpha-2a and alpha-2b in chronic hepatitis B. Note the steeper decline in serum HBV DNA levels in patients receiving pegylated interferon (data derived from Cooksley [18] and the EUROHEP study reported by Janssen [9]).

In a preliminary report from a second large trial [19], 266 patients with HBeAg-positive chronic hepatitis B and serum ALT levels at least twice the upper limit of normal, were randomized to pegylated interferon-alpha-2b 100µg/week and lamivudine 100mg/day or pegylated interferon-alpha-2b and placebo. Treatment was given for 52 weeks; however, the dose of pegylated interferon was reduced to 50µg at 32 weeks.

About 80% of patients completed therapy on the full dose; and dose reduction was about 10% in the first 8 weeks and another 10% between week 8 and week 26; thereafter dose reduction was rare. Ten percent of patients prematurely discontinued pegylated interferon, mainly between weeks 0 and 32; and this percentage was similar to the 9% discontinuation rate with conventional interferon for 16-32 weeks in 162 control patients participating in a multicenter randomized trial comparing short- and prolonged interferon therapy between 1994-1998. Psychiatric disturbances (3%: depression, psychosis), cytopenias (1%: anemia, neutropenia, thrombocytopenia) and flu-like syndrome (1%) were the causes with multiple discontinuations.

Thirty-five percent of patients receiving pegylated interferon lost HBeAg after the end of follow-up and there was no difference between the group receiving pegylated interferon alone and that receiving pegylated interferon plus lamivudine. Response rates (loss of HBeAg) varied by genotype: genotype A, 47%; genotype B, 44%; genotype C, 28%; and genotype D, 25%.

Together, these studies in 501 patients with chronic hepatitis B from both Asia and Europe suggest excellent tolerance of pegylated interferon therapy up to 1 year. The verdict on increased efficacy in comparison to conventional interferon awaits further study with stratification for genotype.

DISCUSSION

Effective management of the millions of patients chronically infected with HBV remains an important clinical objective. The introduction of nucleoside analogs such as lamivudine and adefovir represents an important advancement for tolerance, but questions persist about its long-term efficacy compared to interferon. Given the controversy about the durability of response and the significance of emergent drug resistance with nucleoside analogs, it seems premature to dismiss interferon-based treatment as an outmoded therapy. In fact, for many patients interferon or pegylated interferon may be the first choice of treatment.

Despite the success with interferon-based and nucleoside analogue monotherapy in a proportion of patients with chronic HBV, clinical and epidemiologic realities raise the question of how this problem can be managed more effectively. From a long-term perspective, one can speculate that the definitive treatment approach

will be based on the discovery of the reason(s) why 5% of immunocompetent adults exposed to HBV develop chronic infection, whereas 95% do not. Further investigation is needed to determine how immune control can be induced and - as important - can be maintained in patients with genotypes B, C, and D. Given the high prevalence of chronic HBV, clinicians who address this important disease need to make the most of the various options at hand.

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