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Interferon in chronic hepatitis B[1]

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Abstract

In patients with typical chronic hepatitis B (HBsAg, HBeAg, HBV-DNA-positive), treatment with interferon-alpha must be carried out for 4–6 months on an alternate-day basis and dosage should be not less than 5 million units\square meter of body surface. The therapeutic response (i.e., clearance of replicative markers, transaminases normalization, histologic improvement) is achieved in about 40% of treated patients and the long-term beneficial effect is maintained in about 90% of them. Oriental HBV carriers, children, immunodeficient and highly viraemic patients are less likely to respond. Patients given combinations therapy (with steroids, antivirals, stimulators of the immune system) do not appear to gain more benefit from the association in comparison with treatment with interferon alone. Side-effects are usually minor (flu-like symptoms), but in a minority major adverse events have also been reported. In conclusion, interferon-alpha is effective in inhibiting viral replication but new therapeutic regimens and a better selection of patients are needed in order to induce persistent remissions and to reduce the cost\benefit ratio.

Key words: Hepatitis B, HBeAg; HBV-DNA; IFN-α; Interferon

1. Introduction

Chronic hepatitis B affects about 5% of the world's population and is the main cause of cirrhosis and hepatocellular carcinoma (Hoofnagle et al., 1984). The infec-

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tion is classically divided into two phases, the early replicative phase and the later low replicative/latent phase (Davis 1991). It is during the replicative phase that patients are most infectious and also at highest risk of progressive liver disease (Hoofnagle et al., 1986); this phase is characterized by the presence of the "e" antigen of the hepatitis B virus (HBeAg) and detectable HBV-DNA in the serum by dot blot assays (Davis 1984) and of HBcAg in the hepatocytes.

The main goals of antiviral and immunomodulatory therapies in patients with chronic hepatitis B are the clearance of markers of the replicative phase, the normalization of transaminases and the improvement of liver histology. The loss of the surface antigen of the Hepatitis B virus (HBsAg) is considered as the final evidence of a complete recovery.

Interferon-alpha (IFN-α) has proven to be the most effective drug to date and it results in HBeAg seroconversion in 30 to 61% of patients (Table 1). Most of the patients who clear HBeAg and HBV-DNA will eventually loose HBsAg (Korenman et al., 1991); however, more than half of the treated patients do not respond to IFN therapy.

The aim of this paper is to give an updated review on the most recent data regarding management of chronic HBeAg-positive hepatitis with IFN.

2. Patient selection

IFN is suggested for patients with abnormal alanineaminotransferase (ALT) values, with a histologic picture showing chronic hepatitis with detectable core antigen of the Hepatitis B virus (HBcAg) and with HBsAg, HBeAg and HBV-DNA in serum. The patient should have a compensated liver disease. Patients with decompensated cirrhosis may show beneficial response when treated with IFN (Hoofnagle

Table 1
Interferon in chronic hepatitis type B

Author (year)	IFN	Dosage	Duration	Clearance HBeAg (%)
Hoofnagle 1988	alfa 2b	10 MU 3/weekly	4 months	32%
Perrillo 1990	predn. + alfa2b	60–40–20 mg 5 MU/die	6 weeks 3 months	44%
Brook 1989b	lymph.	10 MU/m^2 3/weekly	3 months	35%
Saracco 1989	lymph.	5 MU/m^2 3/weekly	6 months	61%
Lok 1992	predn. + alfa2b	45–30–15 mg 10 MU t.i.w.	6 weeks 4 months	21.5%

et al., 1993), but side-effects are severe and sustained responses are rare. Finally, patients should not have other severe parallel diseases.

3. Treatment protocol

3.1. Single agent

Experience to date has shown that the optimal dose of IFN is at least 5 million units (MU) 3 times per week over 4 to 6 months. Usually, IFN is given in a single continuous course. A recent study (Janssen et al., 1992) suggested that a short primer course and prolongation of therapy (5 MU daily for 4 weeks, 4 weeks of rest, 5 MU daily for 16–30 weeks) may help to enhance the response rate.

During therapy it is necessary to monitor the white blood cell (WBC) count and the platelets (Plts) count (which usually decrease). An overall reduction of leukocytes (particularly neutrophils) and platelets is a very frequent event. This reduction does not result in clinical manifestations provided that the decrease is not too marked (below 1500 WBC and 60 000 Plts). Responders show very often an ALT flare up between the first and third month of therapy (Fig. 1), an event reported as predictive of clearance of HBeAg and HBV-DNA. Such patients complain of a hepatitis-like illness that is indistinguishable from acute viral hepatitis: their ALT values progressively decrease to normal, both HBV-DNA and HBeAg disappear and anti-HBe is found.

Clearance of HBsAg – when present – occurs often at a late stage during the follow-up.

3.2. Combination therapy

Attempts to obtain better results by using combination or sequential treatment protocols with other antiviral drugs (ribavirin, acyclovir, vidarabin, zidovudine) have not yet succeeded (Muller 1991; Janssen et al., 1993). Moreover, combination therapies are often more toxic than IFN used alone (Muller 1991).

Initially the use of a pulse of steroid followed by a standard IFN course appeared

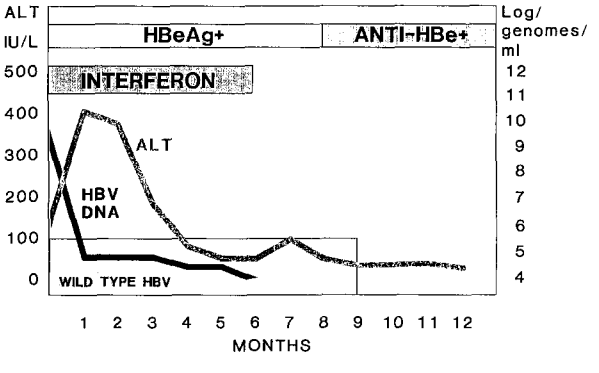

Fig. 1. Virologic, immunologic and enzymatic patterns of a treated patient responding to IFN.

to promise greater success in comparison with therapy with IFN alone (Perrillo et al., 1988) but a recent multicenter controlled trial performed in the USA (Perrillo et al., 1990) did not confirm the preliminary results. In this study the seroconversion rate of the HBeAg/anti-HBe system was found to be as high as 45%, but it did not differ significantly from that of a single agent treatment with IFN-α given at a dose of 5 MU for 4 months. According to the study, the sequential treatment (prednisone + IFN) should be reserved for patients with high levels of HBV-DNA and low ALT values only. In such patients the steroid withdrawal would enhance the immune response and in this phase IFN would be at its most effective. However, a recent randomized trial (Lok et al., 1992) showed that prednisone priming appears to have no benefit in patients with very low ALT levels (0%) and a marginal benefit over treatment with IFN alone in patients with elevated ALT levels (43% vs. 33%).

3.3. Predictive factors of response

Attempts have been made to identify predictive factors of response by univariate and stepwise logistic regression analysis (Brook et al., 1989a). The absence of Human Immunodeficiency Virus antibody (anti-HIV), an immunocompetent status, low baseline viraemia, elevated ALT levels and chronic active hepatitis (CAH) were all found to be associated with a higher rate of response to IFN. However, the same factors were predictive also of spontaneous seroconversion from HBeAg to anti-HBe. Thus, in this subset of patients IFN seems to accelerate or anticipate a forthcoming event.

Chinese patients have been usually considered poor responders to the drug (Lok et al., 1988) but this is probably due to the fact that the virus is transmitted principally by perinatal infection in the Chinese population rather than to ethnic factors. Most HBeAg-positive Chinese are infected perinatally with the subsequent creation of an immunotolerant status (high levels of viraemia, low/normal ALT values) which is incompatible with the action of IFN. Chinese patients in immunoelimination phase (low HBV-DNA levels, high ALT values) respond positively to the drug in the same way as Caucasian patients do (Lok et al., 1992).

Finally, the type of viral population has been shown to affect the response to IFN. Recently, various studies have described a strain of HBV with a mutation in the pre-core region which allows for viral replication but blocks synthesis (Carman et al., 1989; Brunetto et al., 1989). This mutant virus is usually undetectable (or only in low amounts) in HBeAg-positive patients responding to IFN. However, recent data (Brunetto et al., 1993) have shown that HBeAg-positive patients circulating a mixed viral population have a low chances of responding to therapy if the "e-minus" population represents more than 20% of total viraemia. For this reason, HBeAg-positive patients should be treated as early as possible before the pre-core mutant HBV becomes as prominent or prevalent.

3.4. Follow-up

To evaluate whether remissions of chronic hepatitis B induced by IFN are of long duration, researchers from the National Institute of Health (Bethesda, Maryland, USA) followed-up 23 patients who responded to the drug for 3 to 7 years (Koren-

man et al., 1991). Their conclusion was that remissions are of long duration (relapse rate: 13%) and that the loss of HBsAg results in the disappearance of all evidence of residual virus replication. These data were confirmed by a French study (Loriot et al., 1992) that has found low amounts of HBV-DNA (detected by polymerase chain reaction) in 83% of patients who had lost HBeAg 12 months before and in 15% of those who had lost HBsAg 1 year earlier. These findings demonstrate that a reduced level of hepatitis B virus replication persists in most of the patients after HBeAg to anti-HBe seroconversion and that – in contrast – hepatitis B virus replication progressively disappears in most of the patients after HBsAg to anti-HBs seroconversion.

A recent study (Perrillo et al., 1991) reported the histologic and immunohistochemical changes in long-term responders. The portal inflammation and the piecemeal necrosis were the histologic aspects most affected by the IFN therapy. Interestingly, the degree of reduction of hepatic inflammatory changes appeared to depend on the timing of liver biopsy: if follow-up liver biopsy is performed 6 months after the end of therapy, a 23% mean improvement is seen in responders; a 50% improvement is seen if liver biopsy is performed 2 years after the completion of treatment; a 83% improvement is found when the second biopsy is done at intervals of 4 or more years.

4. Side-effects

All the known IFN-related side-effects are reported on Table 2. They are usually minor and reversible. The most frequent include fever, chills, myalgias, headache and nausea during the early treatment period and weight and hair loss during prolonged treatment; bone marrow suppression is nearly always present.

The most dangerous side-effects are psychological changes including depression, irritability and even emotional lability (that can induce suicide attempts).

Autoimmune reactions or autoimmune diseases (haemolytic anaemias, thrombocytopenic purpura, autoimmune thyroiditis) may be triggered by IFN therapy but they usually improve after therapy suspension.

Table 2
Side-effects of IFN

Frequent	Unfrequent
Fever	Nausea and vomiting
Fatigue	Diarrhoea
Muscle aches and pains	Sleep disturbances
Anorexia	Abdominal pains/cramps
Hair loss	Anxiety
Dizziness	Psychosis
Difficulty concentrating	Seizures
Emotional lability	Bacterial infections
Bone marrow suppression	Autoimmune diseases

5. Non responders

To date, many trials have had as their objective an improvement in the initial response rate but no reports have yet been published regarding the retreatment of non-responders. An Eurohep multicenter trial on the treatment of chronic hepatitis B with recombinant IFN in patients previously treated with any type of IFN is currently being conducted by Drs. Quiroga and Carreno but no preliminary results are yet available. Only an anecdotical report has been recently published (Giacchino et al., 1992) showing that repeated courses of IFN therapy in children are ineffective. We retreated 4 of our 12 non-responders using a 4 month course of lymphoblastoid IFN given at the dosage of 10 MU t.i.w. preceded by a 6-week pulse of prednisone (escalating the dose from 60 mg/die up to 20 mg/die); no response was observed in any of them. In conclusion, patients who do not respond to a course of IFN should probably be followed up without retreatment or alternatively should be retreated if their ALT values increase and if there is a concomitant decrease in serum HBV-DNA levels (Hoofnagle 1990).

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