Interferon Therapy for Chronic Hepatitis B

JMAJ 47(5): 247–252, 2004

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Abstract: Interferon has been used to treat chronic hepatitis B in Japan for more than 10 years, but the duration of treatment has been limited to only 1 month by the health insurance system in Japan. The efficacy of daily 28-day therapy is unsatisfactory, with seroconversion occurring in less than 30% of hepatitis B e antigen-positive patients. The insurance system has recently begun to cover interferon therapy for 6 months, and the longer treatment is expected to increase the seroconversion rate above 30% and to decrease viral proliferation more effectively. Interferon therapy, instead of other treatment modalities, such as lamivudine, is mostly indicated for chronic hepatitis B in naïve young patients. Newer anti-viral agents are expected to increase the diversity and efficacy of treatment.

Key words: Hepatitis B virus; Anti-viral therapy; Gene mutation; Lamivudine

Introduction

The pathophysiology of chronic hepatitis B reflects the balance between proliferation of the hepatitis B virus (HBV) and the host’s immunological response against the virus. Most cases of hepatitis B in Japan and Southeast Asian countries are diagnosed in HBV carriers beginning in infancy. During childhood, immune tolerance keeps these carriers symptom-free (no hepatic inflammation). However, after puberty, when the immune system becomes mature, immune clearance of HBV begins in these HBV carriers, with liver cell destruction and the onset of chronic hepatitis. When the immunological response is stronger than the proliferative potential of the HBV, virus proliferation is controlled, leading to seroconversion of HBeAg (hepatitis B e antigen) and remission of hepatitis. The natural history of HBV is thought to typically follow such a course.

HBV attempts to escape from the host’s immune attack by inducing mutations within itself (in the pre-core and core promoter regions, etc.). When this occurs, there may be renewed interplay between the variant HBV and the immune system, possibly resulting in modification of the above-mentioned natural history of HBV in individual cases. During the natural history of HBV infection in chronic HBV carriers, the transaminase levels sometimes show a flare. When viewed histologically, fibrosis advances episodically during such a flare, depending on the magnitude of the flare.
antiviral therapy for chronic hepatitis B is aimed at keeping HBV absent from the blood and alleviating hepatitis. In other words, the treatment should be aimed at normalizing the transaminase levels, reducing the serum HBV DNA level to below the detectable level (always less than $10^5$ copies/ml in Western countries), achieving disappearance of the HBeAg from the blood, and alleviating the hepatocellular inflammation. The only antiviral drugs currently covered by the Health Insurance system in Japan for the treatment of chronic hepatitis B are interferon (IFN)-α, IFN-β, and lamivudine.

IFN Therapy for Chronic Hepatitis B

Although IFN has been shown to suppress the proliferation of hepatitis viruses and reduce the severity of hepatic inflammation, the response of cases of chronic hepatitis B to IFN therapy has been poor. The effect of IFN against hepatitis B is only transient, and treatment with the drug given according to currently employed regimens yields rather unsatisfactory results. In Japan, IFN therapy for chronic hepatitis B is covered by the Health Insurance if it is administered to HBeAg positive cases of chronic active hepatitis for 28 consecutive days (one month) at the maximum.

Chronic hepatitis B in Japan mostly develops in HBV carriers who have contracted the infection by vertical mother-child transmission. In such cases with prolonged HBV infection, it is difficult to successfully eradicate the virus by IFN therapy or any other currently available antiviral therapy. That is, the percentage of cases in which the HBsAg (hepatitis B surface antigen) disappears from the serum, with the appearance of anti HBsAg antibody, during the natural course of HBV infection or following antiviral therapy is only up to about 5% in this country. Cases of chronic active hepatitis with elevated serum transaminase levels should be

\[\text{Severity of fibrosis} \quad \text{Time}\]

Fig. 1

In cases of chronic hepatitis B, a flare in the transaminase levels is associated with histological deterioration of the liver, and episodic exacerbation of fibrosis. The ALT levels normalize as the flare subsides, but the reserve function of the liver, represented by the total bilirubin (TB) level, diminishes after the flare. Thus, hepatitis progresses episodically towards cirrhosis following cycles of appearance and remission of the flares.
considered as candidates for treatment, even when the HBeAg cannot be detected in the serum.

1. IFN therapy in Japan

In Japan, IFN has been administered to HBeAg positive cases of chronic active hepatitis for a maximum period of one month due to the restrictions imposed by the Health Insurance system. IFN therapy thus has not yielded satisfactory results, and the number of cases receiving IFN therapy for chronic hepatitis B has been on the decline.

The efficacy of IFN therapy has been reported to increase with increasing duration of administration of the drug. At our facility, the percentage of patients found to be HBeAg negative at the end of one year after IFN-α (9 MIU) therapy for a month was 28.6% (n = 28). Kanai et al. reported that among cases in which IFN-α (9 MIU) was administered for 14 consecutive days followed by thrice weekly dosing for 22 weeks (6 months in total), 52% became HBeAg negative by 6 months after the end of therapy. They further reported that the percentage of cases becoming HBeAg negative rose further when IFN was administered for 26 additional weeks.1) Iino et al. compared the efficacy of IFN therapy administered for 4, 12, and 24 weeks, and reported that the percentage of patients who became seronegative for HBV DNA was the highest (21%) in the 24-week dosing group.2) At our facility also, the percentage of patients who became HBeAg negative was significantly lower in the 28-day consecutive dosing group than in the 28-week, once weekly dosing group, for the same cumulative dose.

Currently, there is no restriction on the period of IFN therapy for cases of chronic hepatitis C under the Health Insurance system in Japan. For cases of chronic hepatitis B, administration of IFN for a maximum period of 6 months is also now deemed to be possible under the Health Insurance system (this interpretation began to be adopted 2 years ago). The results of 6-month IFN therapy for chronic hepatitis B can therefore be expected to be published in the near future in Japan.

2. IFN therapy in foreign countries

A meta-analysis was carried out of the results of several published studies on IFN therapy administered for 3–6 months to HBeAg positive cases of chronic hepatitis B. This analysis revealed that the percentage of patients showing disappearance of HBeAg following IFN therapy was as high as 30–40%, as compared to only 5–6% among untreated patients. This result leads one to conclude that IFN may be effective in HBeAg positive cases of chronic hepatitis B.

The meta-analysis conducted by Wong et al.3) involved 15 randomized controlled trials. Of the 837 patients included in these 15 trials, 498 received IFN-α (5–10 MIU) thrice weekly for 4–6 months, and 339 received no IFN-α therapy (control group). Wong et al. reported that following IFN therapy, the percentage of cases showing disappearance of HBV DNA was 37% in the treated group as compared to 17% in the control group, the HBeAg disappearance rate was 33% in the treated group as compared to 12% in the control group, and the HBsAg disappearance rate was 8% in the treated group as compared to 1% in the control group. Krogsgaard et al.4) recommended that IFN be administered at a cumulative dose level of over 100 mega-IU.

3. Indications for treatment and prediction of efficacy

A near-consensus has been reached among the Asian Pacific Association for the Study of Liver (APASL), the European Association for the Study of the Liver (EASL) and Japanese hepatologists about the suitable candidates for IFN therapy among patients with chronic hepatitis B. It is clearly agreed that IFN therapy is not indicated in patients with normal transaminase levels. Patients who are seropositive for HBV DNA and whose transaminase levels are
twice as high or more than the upper limit of the normal range are considered to be suitable candidates for IFN therapy, while lamivudine rather than IFN is recommended for patients whose transaminase levels are closer to five times the upper limit of the normal range. IFN therapy has also been recommended in young patients with chronic active hepatitis.

Regarding the prediction of efficacy of IFN therapy, it has been reported that female patients are likely to respond better to IFN therapy than male patients, and that cases with higher histological activity levels more frequently become HBeAg negative following IFN therapy. Regarding the relationship between the efficacy of IFN and the pre-treatment levels of the transaminases, virus load, etc., it has been reported that the HBe antigen disappearance rate increase as the HBV DNA load decrease and the serum ALT levels rise.

4. Responses of HBeAg negative cases to IFN therapy

Some cases of chronic hepatitis B have active hepatitis while being HBeAg negative. The absence of HBeAg in these cases is thought to be attributable to mutation of the HBV (mutation of the pre-core and core promoter regions of the HBV gene).

In regard to the effectiveness of IFN therapy in these patients, the author found that 38 to 90% of the cases became seronegative for HBV DNA immediately after IFN therapy for 6–12 months, as compared to 0–37% in the untreated group. The percentage of patients who were seronegative for HBV DNA at the end of one year after treatment was 10–47% in the IFN therapy group (0% in the untreated group). These results indicate that the suppressive effect on the proliferation of HBV often persists even after the end of IFN therapy.

Thus, IFN therapy may be a valid strategy for treating cases of chronic hepatitis B, irrespective of the serum HBeAg status. However, the indications for this therapy need to be determined based on a thorough evaluation of such factors as the serum ALT levels, HBV DNA levels, and the histological features.

5. HBV gene mutation and response to IFN therapy

In general, the genomes of viruses often undergo mutation since they lack a sophisticated mechanism to verify replication. However, analysis of these mutations often gives the impression that these mutations do not occur at random. It seems likely that viruses undergo mutations of their own genes (including mutations of amino acids) to escape the stress of immune attacks of the host. HBV is one of such viruses to frequently exercise this ability to undergo mutations. Mutations of HBV, seemingly aimed at escaping from the effects of IFN therapy have also been noted. Such a mutant virus is called “escape mutant.” Antigens present on the surface (S) of viruses include three proteins: large S, middle S, and small S proteins. The gene region encoding large S is called Pre S. If this Pre S region is partially defective, an HBV escape mutant is sometimes formed. Cases in which gene mutations have taken place in other regions (including the core region) after IFN therapy have been reported. These variants of HBV are considered to serve as escape mutants against IFN therapy.

The most frequently analyzed type of mutations in the HBV genome involve the pre-core and core promoter regions. Mutations of these regions yield HBV variants that lack the potential to produce HBeAg. These mutants are responsible for cases of active hepatitis B who remain HBeAg negative. Several reports have been published concerning the relationship between mutations in the pre-core region and the effectiveness of IFN therapy. While some investigators have reported that these mutants are more sensitive to IFN, others have reported that they are resistant to IFN therapy. According to Japanese reports, the sensitivity of these mutants to interferon therapy was enhanced as the number of mutations increased. Before arriving at any definitive conclusion regarding
this relationship, it would be important to analyze the relationship between the effectiveness of IFN therapy and such parameters as the route of infection, length of interval from the time of infection to the start of treatment, genotype, virus level, and dosing method of IFN.

Mutations in the core promoter region may also influence the effectiveness of IFN therapy. Mutations in this region seem to be associated with the duration of inflammations and resistance to IFN.7 Recently, Kao et al.8 reported that HBV genotype C underwent more frequent mutations of the core promoter region than HBV genotype B, and that the former was also more resistant to IFN therapy. Their findings suggest a correlation between the genotype of HBV and the response to IFN therapy. Some investigators, however, have reported that the genotype of HBV has no clinical significance.9

6. Adverse reactions to IFN

When compared to the adverse reactions to IFN reported among patients with other diseases, no noteworthy adverse reactions to IFN specific to patients with chronic hepatitis B have been reported. As stated above, in Japan many cases of chronic hepatitis B receive this drug for 28 consecutive days in accordance with the dosing regimen covered by the Health Insurance system. However, when IFN-β is administered thus, the incidence of proteinuria is considerably high. On the other hand, in consecutive treatment with IFN-α, almost no cases of proteinuria have been reported. However, both IFN-α and IFN-β are associated with problems such as reduced WBC and platelet count, when administered at high dose levels or in elderly patients. Unlike with IFN therapy administered for treatment of chronic hepatitis C, late adverse reactions such as depression, alopecia, and thyroid dysfunction are seldom associated with IFN therapy for chronic hepatitis B, unless the drug is used for prolonged periods.

Conclusion

Only results of limited value have been obtained with IFN therapy for chronic hepatitis B. Although dynamic correlations have been shown between the effectiveness of IFN therapy and HBV gene mutations, such as in the case of escape mutants, no definite conclusions have been arrived at yet concerning the correlation between the efficacy of IFN therapy and any particular mutation of the HBV gene.

In Japan, long-term IFN therapy has recently begun to be used. It would be interesting to monitor the methods of dosing that might be developed to enhance the therapeutic efficacy of IFN. If peg-IFN were clinically introduced, and if more prolonged use (more than 6 months) of this drug were to be covered by the Health Insurance, the antiviral efficacy of IFN therapy against HBV may be further enhanced.

Lamivudine, a nucleoside analog serving as a reverse transcriptase inhibitor, has recently been introduced as a drug targeted against HIV and has been listed as a drug covered by the Health Insurance. Most cases treated with lamivudine showed normalization of the transaminase levels, disappearance of the HBV DNA from blood, and a high HBeAg seroconversion rate. Furthermore, this drug can be administered orally, which would allow a high compliance rate of the patients with this therapy. Lamivudine with these features has made a significant impact as a new antiviral drug against HBV.

This drug, however, cannot eradicate the complete-length HBV DNA invading the nuclei of the hosts’ liver cells. For this reason, HBV may resume proliferative activity when lamivudine is discontinued. Strains of HBV resistant to this drug have also appeared following prolonged use of the drug. It would be desirable for a new drug to be developed with this problem resolved. Since IFN also exerts antiviral activity against lamivudine-resistant strains of HBV (YMDD mutants), study of prolonged IFN therapy to deal with lamivudine-resistant
HBV has been proposed. In the near future, the new antiviral agents entecavir and adefovir are expected to become commercially available. When this occurs, treatment of chronic hepatitis B with IFN will decrease markedly. However, long-term IFN therapy is still considered to be useful in many situations, e.g., in dealing with lamivudine-resistant HBV, and in combined therapy with other antiviral agents. Since adequate immune potential of the host is considered to be indispensable for complete eradication of HBV, IFN with immunomodulating activity in addition to antiviral activity may provide a valid means of complete eradication of the virus if used optimally. In this respect, clinical introduction of peg-IFN, suitable for long-term use, would be desirable.

REFERENCES