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Short- and long-term outcome of interferon therapy for chronic hepatitis B infection

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Abstract

Hepatitis B virus (HBV) infection is a serious clinical problem worldwide. Conventional interferon (IFN)- α has been approved for the treatment of chronic hepatitis B (CHB). Short-term studies have demonstrated that IFN-based therapy is moderately effective in inducing the loss of hepatitis e antigen (HBeAg) or seroconversion (30%-40%) in HBeAg-positive patients and also produces sustained HBV DNA suppression (20%-30%) in HBeAg-negative patients. Many studies have reported a correlation between the HBV genotype and response to IFN treatment. The highest response rate to IFN treatment was found in patients infected with HBV genotype A, followed by HBV genotypes B, C, and D. The long-term effect of IFN- α on CHB has not yet been elucidated. The ability of IFN- α treatment to prevent new cirrhosis, complications associated with cirrhosis, and development of hepatocellular carcinoma (HCC) is controversial. The beneficial effect of IFN- α treatment in reducing the development of HCC has mainly been observed in treatment responders who already have cirrhosis. These inconsistent findings may be attributed to the inevitable limitations of comparisons across stud-

ies, including differences in the baseline characteristics of the study and the moderate suppression of HBV replication by IFN- α relative to nucleoside/nucleos(t)ide analogs.

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Key words: Chronic hepatitis B; Hepatitis B virus; Interferon α ; Long-term outcome; Hepatocellular carcinoma

Core tip: The long-term ability of interferon (IFN)- α treatment of chronic hepatitis B virus (HBV) infections to prevent new cirrhosis, complications associated with cirrhosis, and development of hepatocellular carcinoma (HCC) is controversial. The beneficial effect of IFN- α treatment in reducing the development of HCC has mainly been observed in treatment responders who already have cirrhosis. These inconsistent findings may be due to the inevitable limitations of comparisons across studies, including differences in the baseline characteristics of the study and the moderate suppression of HBV replication by IFN- α relative to nucleoside/nucleotide analogs.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a major health problem that affects approximately 400 million people worldwide^[1]. The clinical manifestations of HBV infection can range from acute or fulminant hepatitis to various forms of chronic infection, including chronic hepatitis,

cirrhosis, and hepatocellular carcinoma (HCC). The age of acquisition of HBV plays an important role in determining the natural history of HBV infection and is best illustrated by the differences observed between Asian and Caucasian patients. The majority of Asian patients acquire HBV via vertical transmission or early horizontal transmission within the first few years after birth, whereas the majority of Caucasian patients acquire the infection during adolescence or in early adulthood. The course of patients infected early in life is characterized by a prolonged immunotolerant phase followed by a prolonged phase of immunoclearance, typically during the third and fourth decades of life. In contrast, the majority of patients infected during adolescence or early adulthood will immediately enter the immunoclearance phase without enduring an immunotolerant phase^[2]. Seventy-five percent of HBV carriers are from Asian countries, where the incidence of HCC is relatively high, at 14 to 36 per 100000 men compared to 5 to 10 per 100000 men in Europe and 2 to 5 per 100000 men in America, Australia, and New Zealand^[3].

The risk of developing HCC is 200-fold higher in patients with a chronic HBV infection than in those without^[4]. A large-scale cohort study reported that the risk of HCC is higher in hepatitis e antigen (HBeAg)-positive patients than in HBeAg-negative patients^[5]. The most significant risk factor for hepatic carcinogenesis may be the viral load. Active HBV replication is the key driving force of disease progression, including the development of cirrhosis and HCC^[6].

To date, ten HBV genotypes (A-J) have been identified^[7-10] based on an intergroup divergence of 8% or more in the complete genomic sequences. HBV genotypes influence long-term outcomes in patients with chronic hepatitis B. Genotype C is associated with more severe liver disease, a faster progression of liver fibrosis, and a higher risk of HCC than is genotype B, which may be because of the higher prevalence of basal core promoter mutations^[11,12]. The effects of genotypes and HBV DNA appear to be additive in the process of hepatic carcinogenesis^[13,14]. HBV genotypes correlate not only with clinical outcomes but also with the response to interferon (IFN) treatment.

The primary aim of therapy is to eliminate or permanently suppress HBV, to reduce the activity of hepatitis, and to slow or limit the progression of liver disease. The ultimate long-term goals of therapy are to achieve a sustained viral response (SVR) and to clear the surface antigen (HBsAg), thus preventing or reducing the development of hepatic decompensation, cirrhosis, or HCC as well as to prolong survival^[15].

Seven agents have been approved to treat chronic hepatitis B, which include two immunomodulators (conventional IFN- α and pegylated IFN- α) and five nucleoside/nucleotide (NA) analogs (lamivudine, adefovir, entecavir, telbivudine, and tenofovir). IFN and NA, which are available therapies against chronic hepatitis B that suppress the activity of HBV, work either by stimulating

the immune system to eliminate virus-infected cells or to inhibit viral replication, respectively.

Prior to the recent approval of NA therapy, IFN- α was the first agent approved for chronic hepatitis B therapy. The main advantages of IFN- α over NA are the absence of resistance and the possibility of immune-mediated clearance of HBV. Unfortunately, side effects preclude the use of IFN- α in large numbers of patients, and prolonged maintenance therapy to suppress HBV is not feasible^[16].

All of the studies that have previously investigated the impact of IFN- α treatment on HBV-related liver disease progression were conducted with conventional IFN- α because pegylated IFN- α was recently licensed and long-term studies have not yet to be published.

Previous studies have shown that antiviral therapy can improve both the short-term and long-term outcomes of chronic hepatitis B. However, long-term follow-up studies of IFN- α treatment for chronic HBV infection have reported conflicting findings. The ability of the treatment to prevent cirrhosis and the development of HCC remains poorly understood.

SHORT-TERM STUDIES OF IFN- α

Alanine aminotransferase (ALT) levels, HBV DNA titers, and the degree of liver inflammation have been associated with predicting the IFN response in chronic HBV infection^[17,18]. Short-term studies have shown that IFN-based therapy is moderately effective in inducing the loss of HBeAg or seroconversion (30%-40%) in HBeAg-positive patients^[17,19-22] as well as in producing sustained HBV DNA suppression (20%-30%) in HBeAg-negative patients^[22-25].

Many studies have reported a correlation between the HBV genotype and response to IFN treatment. Table 1 summarizes the details of studies of the response to IFN-based treatment on HBV genotypes. Because most of the available information on HBV is from Asia, the United States, and Europe, the predominant genotypes of these countries, A, B, C, and D, are prominent in the literature. HBV genotype B was associated with a better response to IFN-based treatment compared to that of HBV genotype C (39% *vs* 17%, $P < 0.03$) in a Chinese study of 73 HBeAg positive patients^[26]. A study from Taiwan comprising 58 HBeAg positive patients also demonstrated a better response in HBV genotype B than in HBV genotype C infection (41% *vs* 15%, $P < 0.05$)^[27]. A small study, with only HBeAg negative patients treated with highly variable IFN doses of 3×1 MU to 3×8 MU weekly, suggested a better response rate in patients with HBV genotype A than with HBV genotype D or E^[28]. A study from Germany involving 144 patients with HBV genotype A or D (99 HBeAg positive and 45 HBeAg negative patients) investigated the sustained response (six months after treatment) rate to standard IFN- α therapy^[29]. The sustained response rate was higher in HBV genotype A- than in HBV genotype D-infected

Table 1 Summary of the studies of the response to interferon-based treatment on hepatitis B virus genotypes

Ref.	Study type	Number of patients (treated/controls)	IFN	Region of origin	HBeAg-positive (%)	Treatment endpoint	Treatment endpoint by HBV genotype (%)	Significance (P value)
Wai <i>et al</i> ^[26]	Retrospective, unmatched controls	107 (73/34)	IFN α	China	100.0	HBeAg seroconversion	B: 39 C: 17	0.03
Kao <i>et al</i> ^[27]	Retrospective, unmatched controls	58 (58/0)	IFN α	Taiwan	100.0	Loss of HBeAg and HBV DNA 48 wk post-treatment	B: 41 C: 15	0.045
Zhang <i>et al</i> ^[28]	Retrospective, unmatched controls	35 (35/0)	IFN α	France	0.0	Normalization of ALT, loss of HBV DNA by a branched-DNA assay 6 mo post-treatment	A: 70 non-A: 40	0.001
Erhardt <i>et al</i> ^[29]	Retrospective, unmatched controls	165 (69/72)	IFN α	Germany, Mediterranean, Eastern Europe, Asia, Africa	A: 51.4 B: 5 C: 8.4 D: 31.9 E: 2.5 G: 0.8	HBeAg-positive: normalization of ALT, negative HBV DNA by a hybridization assay, and HBeAg seroconversion 6 mo post-treatment HBeAg-negative: loss of HBV DNA by a hybridization assay and the normalization of ALT 6 mo post-treatment	(overall) A: 49 D: 26 (HBeAg-positive) A: 46 D: 24 (HBeAg-negative) A: 59 D: 29	0.005 0.03 0.05
Flink <i>et al</i> ^[30]	Prospective, multicenter randomized controlled trials	266 (266/0)	Peg-IFN- α -2b +/- lamivudine	The Netherlands	100.0	Loss of HBsAg at the end of follow-up	A: 14 B: 9 C: 3 D: 2	0.006
Erhardt <i>et al</i> ^[32]	Retrospective, cohort	49 (23/26)	IFN α	Germany, Hong Kong, France	E: 47 F: 50 G: 50 H: 60	Normalization of ALT, decrease of HBV DNA < 4000 IU/mL 6 mo post-treatment	E: 36 F: 50 G: 20 H: 50	NA

IFN: Interferon; HBeAg: Hepatitis e antigen; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; NS: Not significant; NA: Not available.

patients (49% *vs* 26%, $P < 0.005$). The sustained response rate to IFN was 46% *vs* 24% ($P < 0.03$), respectively, in patients with HBeAg positive hepatitis and was 59% *vs* 29% ($P < 0.05$) for HBV genotype A and HBV genotype D, respectively, in patients with HBeAg negative hepatitis.

Large multicenter trials of pegylated IFN- α revealed a significant correlation between the viral genotype and sustained HBeAg loss in patients treated with pegylated-IFN- α -2b. The highest rate of HBeAg clearance at the end of the follow-up was observed in patients infected with genotype A (47%), followed by genotypes B (44%), C (28%), and D (25%). Further analyses of the same study population demonstrated that HBsAg clearance was also closely linked to the viral genotype and was the highest in genotype A (14%), followed by B (9%), C (3%), and D (2%)^[30]. A recent meta-analysis has provided compelling support of genotype A as the most treatment-responsive genotype in HBeAg-positive hepatitis B^[31].

The antiviral responses of HBV genotypes E-H have not been examined in detail. In a small study from Germany, 23 patients with HBV genotypes E-H received IFN- α ^[32]. A SVR was defined as the normalization of ALT and decrease in HBV DNA of < 4000 IU/mL 6 mo after treatment. SVR was 35% (8/23) for patients

treated with IFN- α . SVR was 36% (5/14) for HBV genotype E, 50% (2/4) for HBV genotype F or H, and 20% (1/5) for HBV genotype G. HBV genotype G/A co-infection was found in 40% of patients with HBV genotype G, whereas HBV genotype G/C co-infection was found in 30%. HBV genotypes E, F, and H appeared to be sensitive to IFN- α . The lower response rates to IFN- α observed in patients with HBV genotype G may be related to the frequent occurrence of double infection. In a study from Argentina, Marciano *et al*^[33] reported that although the available data were even more limited, HBV genotype F had a more similar response rate to pegylated IFN- α -2a than HBV genotype A.

The precore mutation (G₁₈₉₆A) and dual core promoter mutations (A₁₇₆₂T and G₁₇₆₄A) play an important role in the molecular virological factors that contribute to clinical outcome and therapy for chronic hepatitis B. These mutations are closely associated with the seroconversion of HBeAg^[34,35]. Although the rate of dual core promoter mutations has been shown to be higher in genotype C and closely related to the active progression of chronic liver disease and increased risk for HCC^[12,36-38], studies have reported a correlation between these mutations and a better response to IFN- α therapy^[39-41].

Table 2 Summary of the long-term follow-up studies of interferon- α treatment on hepatitis B virus-related liver disease progression

Ref.	Study type	Number of patients (treated/controls)	Region of origin	HBeAg-positive	Treatment follow-up (yr)	Cirrhosis development (% treated vs % controls)	Significance (P value)	Cirrhosis complication development (% treated vs % controls)	Significance (P value)
Lin <i>et al</i> ^[19]	Prospective, randomized, controlled	89 (60/29)	Taiwan	100%	7.4	13.3 vs 17.2	NS	9.0 vs 14.7	NS
Lin <i>et al</i> ^[42]	Retrospective, matched controls	466 (233/233)	Taiwan	100%	6.8	17.8 vs 33.7	0.041	NA	NA
Krogsgaard <i>et al</i> ^[43]	Retrospective, multicenter controlled trials	253 (histologically evaluated)	Europe	100%	4.7	10 vs 10	NS	NA	NA
Tangkijvanich <i>et al</i> ^[44]	Retrospective, unmatched controls	139 (69/72)	Thailand	100%	5.0	10.4 vs 22.2	NS	NA	NA
Truong <i>et al</i> ^[46]	Retrospective, matched controls	62 (27/35)	Japan	59.6%	6.5	11 vs 6	NS	NA	NA
Yuen <i>et al</i> ^[47]	Prospective, matched controls	411 (208/203)	Hong Kong	100%	8.9	NA	NA	4.3 vs 1.0	0.062

HBeAg: Hepatitis e antigen; NS: Not significant; NA: Not available.

LONG-TERM OUTCOME ON LIVER DISEASE PROGRESSION

Long-term follow-up studies after a 4- to 6-mo course of IFN therapy in HBeAg-positive patients showed a reduction in the progression of fibrosis, especially in patients with sustained HBeAg seroconversion^[17,19,20]. Table 2 summarizes the details of long-term follow-up studies of IFN- α treatment on HBV-related liver disease progression.

Lin *et al*^[19] conducted follow-up of 101 HBeAg-positive male Taiwan patients. In 89 patients without any evidence of cirrhosis on admission, cirrhosis developed in 1 (4.2%) of the 24 seroconverters and 7 (19.4%) of the 36 nonseroconverters in the treated group, and 5 (23.8%) of the 21 nonseroconverters in the untreated group, whereas cirrhosis did not develop in any of the 8 seroconverters in the untreated group ($P > 0.05$). No significant differences were observed in the incidence of new cirrhosis (13.3% of treated patients vs 17.2% of untreated patients) and in complications of cirrhosis (9.0% of treated patients vs 14.7% of untreated patients) between the two groups of patients.

The study expanded their sample population by including patients from other nonrandomized studies in Taiwan^[42]. This large study compared 233 IFN-treated HBeAg-positive patients with 233 well-matched untreated patients and reported a reduction in the cumulative incidence of cirrhosis (17.8% vs 33.7% in the controls; $P = 0.041$) after a median follow-up of 6.8 (1.1-16.5) years.

Krogsgaard *et al*^[43] conducted a follow-up study of 469 HBeAg-positive patients from three multicenter European trials. 253 patients were histologically evaluated. No significant difference was observed in progression to cirrhosis between the treated and untreated groups (10% vs 10%).

Tangkijvanich *et al*^[44] conducted follow-up of 139

HBeAg-positive patients in a retrospective study in Thailand. The baseline ALT levels of the two groups were unmatched, which were higher in the treated group ($P = 0.001$). Progression to cirrhosis was observed in 4.2% of sustained responders and 14% of nonresponders, whereas 22.2% of controls. The overall incidence of new cirrhosis in sustained responders was significantly lower than that in the control group ($P = 0.04$).

Papatheodoridis *et al*^[45] prospectively followed-up 406 non-randomized HBeAg-negative patients in Greece. The baseline ALT levels in the treated patients were significantly higher than those in the untreated patients ($P < 0.001$), and no significant differences were observed in survival or complication-free survival between IFN- α -treated patients and untreated patients ($P = 0.62$ and $P = 0.14$, respectively). Survival and complication-free survival were significantly better in sustained responders than in non-sustained responders ($P = 0.027$ and $P = 0.019$, respectively) or untreated patients ($P = 0.048$ and $P = 0.012$, respectively).

In a follow-up study of 62 Japanese patients conducted by Truong *et al*^[46], the baseline ALT levels of the two groups were unmatched, which were significantly higher in the treated group than in the untreated group ($P < 0.05$). No significant difference was observed in HBeAg seroconversion, ALT normalization, and undetectable HBV DNA between the two groups of patients. Progression to cirrhosis was observed in 3 treated patients (11%) and 2 untreated patients (6%).

In a case-controlled study of IFN- α vs no treatment in patients recruited from 4 previous randomized controlled trials in Hong Kong, Yuen *et al*^[47] conducted follow-up of 208 HBeAg-positive patients treated with IFN- α and compared them to 203 controls. No significant differences were observed in the HBeAg seroconversion rate or undetectable HBV DNA by PCR assay

Table 3 Summary of the long-term follow-up studies of interferon α treatment on the development of hepatitis B virus-related hepatocellular carcinoma

Ref.	Study type	Number of patients (treated/controls)	Region of origin	HBeAg-positive (%)	Cirrhosis (%)	Treatment follow-up (yr)	HCC development (% treated vs % controls)	Significance (P value)
Lin <i>et al</i> ^[19]	Prospective, randomized, controlled	101 (67/34)	Taiwan	100	12.5	7.4	1.5 vs 11.8	0.043
Lin <i>et al</i> ^[42]	Retrospective, matched controls	466 (233/233)	Taiwan	100	9.4	6.8	2.7 vs 12.5	0.011
Ikeda <i>et al</i> ^[49]	Retrospective, unmatched controls	313 (94/219)	Japan	36	100	6.9	17.0 vs 30.8	0.012
Krogsgaard <i>et al</i> ^[43]	Retrospective, multicenter controlled trials	308 (210/98)	Europe	100	6.1	4.7	0.96 vs 1.0	NS
International IFN- α HCC Study Group ^[50]	Retrospective, multicenter, matched controls	146 (49/97)	Italy, Argentina	NA	91	6.5	16 vs 19	NS
Mazzella <i>et al</i> ^[51]	Prospective, randomized, controlled	64 (33/31)	Italy	0	0	6.9	3.0 vs 6.4	NS
Tangkijvanich <i>et al</i> ^[44]	Retrospective, unmatched controls	139 (69/72)	Thailand	100	20.1	5.0	4.7 vs 12.5	NS
Papatheodoridis <i>et al</i> ^[45]	Retrospective, unmatched controls	404 (209/195)	Greece	100	30.9	6.0	8.1 vs 7.7	NS
Truong <i>et al</i> ^[46]	Retrospective, matched controls	62 (27/35)	Japan	59.6	1.6	6.5	3.7 vs 0.0	NS
Yuen <i>et al</i> ^[47]	Prospective, matched controls	411 (208/203)	Hong Kong	100	NA	8.9	2.4 vs 0.0	NS
			Number of analyzed studies		RD/RR		95%CI	Significance (P value)
Cammà <i>et al</i> ^[52]	Meta-analysis	853/652	7 Studies		RD = -6.4% (overall) RD = -4.8% (European)		-2.8%-(-10%) -11.1%-1.5%	< 0.001 NS
Miyake <i>et al</i> ^[53]	Meta-analysis	553/750	8 Studies		RD = -5.0% (overall) RD = -8.5% (Asian)		-9.4%-(-0.5%) -13.6%-(-3.6%)	0.028 0.001
Sung <i>et al</i> ^[54]	Meta-analysis	1292/1458	12 Studies		RR = 0.66		0.48-0.89	0.006
Yang <i>et al</i> ^[55]	Meta-analysis	1006/1076	11 Studies		RR = 0.59		0.43-0.81	0.001
Zhang <i>et al</i> ^[56]	Meta-analysis	176/171	2 Studies		RR = 0.23		0.05-1.04	NS
Jin <i>et al</i> ^[57]	Meta-analysis	1291/1048	9 Studies		RR = 0.274		0.059-1.031	NS

IFN: Interferon; HBeAg: Hepatitis e antigen; HCC: Hepatocellular carcinoma; NS: Not significant; NA: Not available; RD: Risk difference; RR: Relative risk.

between the two groups of patients. Complications associated with cirrhosis developed in 9 treated patients (4.3%) and in only 2 untreated patients (1.0%) ($P = 0.062$).

LONG-TERM OUTCOME ON THE DEVELOPMENT OF HCC

Studies on the long-term effect of IFN on the prevention of HCC in patients with HBV have yielded conflicting results. The utility of IFN- α in preventing HBV-related HCC, unlike its effect on hepatitis C virus (HCV)-related HCC, is highly variable among different studies. Most studies are limited by a relatively small sample size, short duration of follow-up, and lack of a control group for comparisons. Table 3 summarizes the details of long-term follow-up studies of IFN- α treatment on the development of HBV-related HCC.

Three studies have reported the beneficial effect of IFN on HBV-related HCC prevention^[48]. The first report

by Lin *et al*^[19] was a follow-up study of 101 HBeAg-positive male patients in Taiwan. When recruited, cirrhosis was present in 10.3% of the treated patients and 14.7% of the untreated patients. HCC developed in 1 of the treated patients (1.5%) and 4 of the untreated patients (11.8%) ($P = 0.043$).

The second report was a large matched control study of HBeAg-positive patients with active chronic hepatitis B conducted by the same group of investigators who subsequently extended their study population in Taiwan^[42]. This large study compared 233 IFN-treated HBeAg-positive patients with 233 well-matched untreated patients and showed a reduction in the incidence of HCC (2.7% vs 12.5% in the controls, $P = 0.011$) after a median follow-up of 6.8 (1.1-16.5) years. When recruited, 8.1% of the treated patients and 10.7% of the untreated patients had cirrhosis. Significant reduction in the incidence of HCC was only observed in patients with cirrhosis of the liver on recruitment (19.7% for treated patients and 58.9% for untreated patients; $P < 0.01$). The reduction in

the incidence of HCC was not observed in the patients without cirrhosis (2.1% for treated patients and 2.3% for untreated patients, not significant). Both of the studies did not show the significant relationship between HBV DNA suppression and HCC development with IFN- α treatment.

The third study to demonstrate that IFN- α was useful in reducing the incidence of HCC was conducted in patients with cirrhosis only in Japan^[49]. Cumulative occurrence rates of HCC were 4.5%, 7.0%, and 17% at the end of 3, 5, and 10 years, respectively, for IFN-treated patients, 13.3%, 19.6%, and 30.8% for controls. The IFN- α treatment significantly decreased the rate of HCC development ($P = 0.0124$). The Cox proportional hazard model revealed that IFN- α treatment was an independent contributing factor that lowered the rate of carcinogenesis (OR = 0.39, $P = 0.031$) even after a correction by significant covariates in multivariate analysis. In this study, the reduction in the incidence of HCC by the IFN- α treatment was significantly higher in patients with a viral load higher than 10^6 copies/mL.

Seven studies did not show any beneficial effect of IFN on the progression of HCC^[48]. Krogsgaard *et al*^[43] conducted follow-up study of 469 HBeAg-positive patients from three multicenter European trials. HCC developed in three patients (1%) during the follow-up period: 2 were treated with IFN and 1 was untreated. The distribution of clinical events (progression to cirrhosis, HCC and liver-related deaths) was unrelated to response to IFN- α treatment.

The International Interferon- α Hepatocellular Carcinoma Study Group retrospectively recruited 913 patients positive for the anti-HCV antibody and/or HBsAg from 21 centers in Italy and Argentina^[50]. In 146 of the HBV-infected patients, eight (16%) of 49 treated patients and 18 (19%) of 97 untreated patients developed HCC (RR = 0.98, 95%CI: 0.33-2.92). The risk reduction by IFN- α treatment was apparently greater for patients with chronic hepatitis C and no evidence of HBV infection.

Mazzella *et al*^[51] conducted follow-up study of 33 HBeAg-positive Italian patients treated with IFN- α and compared them to 31 controls. IFN- α treatment accelerated the loss of HBeAg (90.9% in treated *vs* 61.3% in control patients, $P < 0.007$) and HBsAg (36.4% *vs* 9.8%, $P < 0.017$), whereas 1 (3.0%) treated patient and 2 (6.4%) controls developed HCC. IFN- α treatment did not have beneficial effect on the loss of HBV DNA (78.9% *vs* 58.1%, $P = 0.106$).

Tangkijvanich *et al*^[44] conducted follow-up study of 139 HBeAg-positive patients in Thailand. HCC appeared in 11 cirrhotic patients: 9 (12.5%) in the control group and 2 (4.7%) of the nonresponders ($P > 0.05$). None of the sustained responders ($n = 24$) developed HCC. Investigators reported that IFN- α treatment might prevent the progression of cirrhosis and development of HCC in sustained responders. However, the lack of significant P values renders the conclusions insufficient.

Papatheodoridis *et al*^[45] conducted prospective follow-

up study of 404 non-randomized HBeAg-negative patients in Greece. The baseline ALT levels in the treated patients were significantly higher than those in the untreated patients ($P < 0.001$), and HCC appeared in 17 (8.1%) treated (16 in nonresponders) and 15 (7.75%) untreated patients. IFN- α improved long-term outcome (liver decompensation and/or HCC) in patients with sustained biochemical remission, even in the presence of cirrhosis and old age.

In a follow-up study of 62 Japanese patients, Truong *et al*^[46] found that although one (3.7%) treated patient developed HCC, none of the controls developed HCC. The baseline ALT levels in the treated patients were significantly higher than those in the untreated patients ($P < 0.05$). Most patients continued to have detectable HBV DNA by PCR assay after HBeAg seroconversion.

In a case-control study of IFN- α *vs* no treatment in patients recruited from 4 previous randomized controlled trials in Hong Kong, Yuen *et al*^[47] followed-up 208 HBeAg-positive patients treated with IFN- α and compared them to 203 controls. The development of HCC was observed in five (2.4%) treated patients and none of the untreated patients.

Six meta-analyses^[52-57] on the effect of IFN- α treatment on the development of HBV-related HCC have been reported. Studies by Cammà *et al*^[52] and Miyake *et al*^[53] calculated the risk difference (RD), whereas the other four studies^[54-57] calculated the relative risk (RR). Cammà *et al*^[52] reported a different incidence of HCC between treated and untreated HBV-related Child A cirrhotic patients (overall RD = -6.4%; 95%CI: -2.8%-(10%), $P < 0.001$); however, no preventive effect of HCC was shown for HBV when data from European studies were evaluated (overall RD = -4.8%; 95%CI -11.1 - 1.5%, not significant). Therefore, it was concluded that IFN did not appear to affect the rate of HCC in HBV-related cirrhosis.

Miyake *et al*^[53] demonstrated the preventive effect of IFN treatment in an Asian population (RD = -8.5%; 95%CI: -13.6-(3.6), $P = 0.0012$), but not in a European population. These findings indicate that IFN treatment suppressed the development of HCC in patients with chronic hepatitis B virus infection, especially in HBeAg-positive Asians.

Sung *et al*^[54] showed that the risk of HCC after IFN treatment was reduced by 34% (RR = 0.66, 95%CI: 0.48-0.89) and that this effect was significantly strongly in patients with early cirrhosis than in those without cirrhosis.

Yang *et al*^[55] reported a difference in the incidence of liver cirrhosis and HCC between treated and untreated patients (RR = 0.65, 95%CI: 0.47-0.91, RR = 0.59, 95%CI: 0.43-0.81, respectively). These findings indicated that IFN prevents or delays the development of liver cirrhosis and HCC in patients with chronic hepatitis B.

Zhang *et al*^[56] demonstrated that IFN did not significantly affect the overall rate of HCC in HBV-infected patients; however, IFN therapy slightly ameliorated the rate of HCC (RR = 0.23, 95%CI: 0.05-1.04, $P = 0.056$).

Jin *et al.*⁵⁷¹ reported that IFN was associated with significant preventive effects on HCC according to the DerSimonian-Laird method (RR = 0.470, 95%CI: 0.260-0.850) and Bayesian methodology, with an adjustment for the underlying risk [RR = 0.249, 95% Bayesian credible intervals (BCI): 0.049-0.961] but not according to a Bayesian meta-analysis (RR = 0.274, 95%BCI: 0.059-1.031). These findings indicate that additional evidence is needed to support the role of IFN in delaying the progression of chronic hepatitis B.

Long-term follow-up studies of IFN- α treatment on the development and progression of HCC show inconsistent results. The preventive effect on HCC of IFN- α treatment has mainly been observed in sustained responders to the treatment who already have cirrhosis. However, IFN- α may lead to severe liver decompensation when used in patients with cirrhosis, and only less than 35% of treated patients are sustained responders. Almost all current guidelines suggest that patients with HBV-related cirrhosis should receive nucleoside/nucleotide analog therapy. These inconsistent findings may be attributed to the inevitable limitations of comparisons across studies, including differences in the baseline characteristics of the study and the moderate suppression of HBV replication by IFN- α relative to nucleoside/nucleotide analogs.

CONCLUSION

The ability of IFN- α treatment to prevent new cirrhosis, complications associated with cirrhosis, and development of HCC over the long-term is controversial. These inconsistent findings may be due to the inevitable limitations of comparisons across studies, including differences in the baseline characteristics of the study and the moderate suppression of HBV replication by IFN- α relative to nucleoside/nucleotide analogs.

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