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Efficacy and safety of interferon alpha therapy in children with chronic hepatitis B

A long-term follow-up cohort study from China

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Abstract

Interferon-alpha (IFN-α) is currently the preferred antiviral treatment for children with chronic hepatitis B (CHB) aged >1-year-old. However, the evidence regarding the exact efficacy and safety in the real world is not sufficient. This study aimed to investigate the efficacy of IFN-α therapy in children with CHB and to provide a theoretical basis for practically identifying ideal antiviral therapies for CHB children.

Clinical manifestations, baseline characteristics, related laboratory tests, and adverse events were retrospectively analyzed in children with CHB who visited the Children's Hospital of Fudan University, were treated with IFN-α and were followed up from January 2003 to October 2018.

A total of 18 immune-active patients without advanced fibrosis were enrolled, and their average age at the start of treatment was 4.45 ± 2.75 years old. IFN α-2b was administered subcutaneously by body surface area (BSA) category, based on 3 MU/m^2, for a median 48 weeks. Before treatment, the alanine aminotransferase (ALT) range was 81 to 409 U/L (median 158 U/L). The median hepatitis B virus (HBV)-DNA load was 9.89×10^7 IU/mL, and the HBV-DNA load varied from 3.10×10^4 to 4.56×10^8 IU/mL. The ALT levels of 17 children became normal at an average of 12 weeks during treatment, and those of 1 child became normal at 6 weeks after IFN-α withdrawal. Sixteen (88.9%, 16/18) children became HBV-DNA negative (<10^3 IU/mL) at an average of 24 weeks during treatment, while 1 became negative at 96 weeks after IFN-α withdrawal and 1 remained HBV-DNA positive. HBV e antigen (HBeAg) seroconversion occurred in 13 of 14 (92.9%, 13/14) HBeAg-positive patients at an average of 12 weeks during treatment. HBV s antigen (HBsAg) loss or seroconversion occurred in 4 (22.2%, 4/18) patients at an average of 21 weeks during treatment. Only mild flu-like symptoms and transient neutropenia appeared in some children at the early treatment stage. No severe abnormal results were observed in other laboratory parameters.

The antiviral monotherapy of 48 weeks of IFN-α was well tolerated and good responded, which was associated with higher rates of HBeAg seroconversion and HBsAg clearance in the children in this study than in previously reported adults and pediatric patients.

Abbreviations: ALT = alanine aminotransferase, CHB = chronic hepatitis B, HBeAg = HBV e antigen, HBsAg = HBV s antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, IFN-α = interferon alpha.

Keywords: antiviral therapy, children, chronic hepatitis B, interferon-alpha

1. Introduction

Hepatitis B is an infectious disease caused by hepatitis B virus (HBV) that results in liver damage. Approximately 2 billion people worldwide are infected with HBV, including 240 million people with chronic HBV infection, according to the World Health Organization (WHO).[1] Approximately 650,000 people die from liver failure, cirrhosis and hepatocellular carcinoma (HCC) which are caused by HBV infection, every year.[2] Therefore, for both adults and children, the aims of treatment for chronic hepatitis B (CHB) are to maximize the long-term suppression of HBV replication; relieve inflammatory cell necrosis in the liver and liver fibrosis; delay and reduce liver failure, decompensated cirrhosis, HCC and other complications; improve patient quality of life; and prolong survival time.[3–5] Childhood infections often lead to CHB, and children are the main source of CHB patients in China nowadays.[2]

Safe and effective CHB treatment for children <12 years old remains an unmet medical need due to the particularities of children's growth and development.[6] The only drugs that can currently be used for HBV antiviral treatment in children are interferon-alpha (IFN-α), including polyethylene glycol interferon-alpha (Peg-IFN-α), and some nucleoside (acid) analogs (NAs), and these choices are limited. IFN-α is considered the preferred therapy for the antiviral treatment of CHB children aged ≥1-year-old.[6]

However, the evidence of the exact efficacy and safety of IFN-α in the real world is not sufficient.[6] The aims of this observational cohort study were primarily to analyze the clinical data of CHB children treated with IFN α-2b monotherapy and followed up at the Children's Hospital of Fudan University from January 2003

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to October 2018 and to estimate the efficacy and safety of IFN α-2b monotherapy.

2. Objects and methods

A cohort study was performed at the Children's Hospital of Fudan University. The study protocol was approved by the Ethics Committee of the hospital, and written informed consent was obtained from the children's parents.

2.1. Inclusion and exclusion criteria

Inclusion criteria:

(1) Children diagnosed with CHB conforming to the "Guidelines for treatment of chronic hepatitis B (2015)" from the Chinese Medical Association[3] and aged ≥ 1-year-old;
(2) Children in the immune-active phase with antiviral treatment indications;
(3) Children with CHB who chose antiviral monotherapy with IFN-α after their parents were informed of all the regimens;
(4) Liver biopsy and pathology examination, including liver inflammatory activity grading (G) and fibrosis staging (S), performed within 6 months before antiviral treatment; and
(5) The antiviral treatment period lasted for at least 24 weeks, and patient information was relatively complete.

Exclusion criteria:

(1) Patients were ineligible if they had cirrhosis (METAVIR F4 or equivalent); tested positive for hepatitis A, C, or D or human immunodeficiency virus (HIV); had a history or evidence of a chronic liver disease other than CHB or had a suspicion of HCC.
(2) Patients with a history of psychiatric disorder, significant chronic pulmonary or cardiac disease, poorly controlled thyroid disease or diabetes, previous solid organ or stem-cell transplant, or evidence or history of malignancy were also excluded.
(3) Patients with other liver diseases, such as autoimmune hepatitis, or Wilson's disease, were eliminated by the detection of an autoimmune anti-hepatitis antibody or copper blue protein.[7]

2.2. Treatment and follow-up

The enrolled children aged ≥1 year received IFN α-2b (3 MU/m^2, 3 times per week, subcutaneous administration) for antiviral treatment and dosing was based on body surface area (BSA) categories.

Serum levels of HBV e antigen (HBeAg), HBV s antigen (HBsAg), anti-HBe antibodies, anti-HBs antibodies (measured by enzyme-linked immunosorbent assays) and HBV-DNA levels (measured by real-time quantitative PCR [qPCR]; limit of detection, 1000 IU/mL) were measured at baseline and every 12 weeks thereafter.

The safety evaluation included the incidence of adverse events, laboratory assessments, growth parameters, and vital signs. Safety was assessed at baseline; weeks 1, 2, 3, 4, 8, 12, and every 12 weeks thereafter during treatment; and weeks 8, 16, 24, 48, 72, 96, and every 48 weeks thereafter during follow-up. The laboratory assessments included standard hematology, coagulation function, blood chemistry, and thyroid function (triiodothyronine [T3], tetraiodothyronine [T4], free triiodothyronine [FT3], free tetraiodothyronine [FT4] and thyroid-stimulating hormone [TSH]).

3. Results

3.1. Baseline characteristics

Eighteen treatment-naïve CHB children (8 boys and 10 girls) with a mean age of 4.45 ± 2.75 years old at the beginning of treatment and who had regular follow-up and relatively complete data were enrolled in this study. The median follow-up period length was 4.29 ± 3.58 years.

All children had no obvious symptoms. Fourteen children were HBeAg positive and 4 (patients 3, 9, 16, and 18) were HBeAg negative. HBV genotyping was performed with 13 patients, and 8 were infected with HBV genotype C, while 5 had HBV-B infections. Liver biopsy was performed in all children before antiviral treatment.

The antiviral period lasted from 24 to 64 weeks (median 48 weeks). The antiviral period of 9 patients lasted for 48 weeks, that of 2 patients (patients 6 and 12) lasted for 64 weeks, that of 2 patients (patients 7 and 9) lasted for 40 weeks, and that of patients 1, 4, 11, 13, and 15 lasted for 24, 30, 32, 52, and 56 weeks, respectively.

The baseline characteristics such as sex, age, duration, and follow-up period are summarized in Table 1.

3.2. Alanine aminotransferase (ALT)

Before treatment, the ALT levels exhibited a range of 81 to 409 U/L (median 158 U/L) (Table 1). The ALT levels of 17 children fell into the normal range at an average of 12 weeks during treatment, and the ALT level of 1 child fell at 6 weeks after IFN α-2b withdrawal.

3.3. HBV-DNA

Before treatment, the median HBV-DNA load was 9.89×10^7 IU/mL, and the HBV-DNA load varied from 3.10×10^4 to 4.56×10^8 IU/mL (Table 1). Sixteen children became HBV-DNA negative ($<10^3$ IU/mL) at an average of 24 weeks during treatment, although transient HBV-DNA positivity occurred in 1 (patient 2) of these patients after withdrawal, and HBV-DNA measurements became positive several times in 4 of these patients (patients 6, 8, 12, and 18) after withdrawal. One child became HBV-DNA negative at 96 weeks after withdrawal, and transient HBV-DNA positivity was observed at 12.5 years after treatment. One child remained HBV-DNA positive, and only transient HBV-DNA negativity was observed at 24 weeks of treatment (Table 2 and Fig. 1).

3.4. HBeAg

HBeAg seroconversion occurred and was maintained in 13 of the 14 HBeAg-positive patients (92.9%, 13/14) at an average of 12 weeks during treatment, and 1 patient (patient 6) exhibited persistent HBeAg positivity. The other 4 HBeAg-negative children (patients 3, 9, 16, and 18) remained HBeAg negative (Table 2 and Fig. 2).

3.5. HBsAg

HBsAg loss or seroconversion occurred in 4 patients (22.2%, 4/18) (patients 5, 10, 11, and 13) at an average of 21 weeks during treatment (Table 2). Two (patients 5 and 11) of these patients experienced HBsAg seroconversion at 12 weeks during

Table 1

Baseline Characteristics (n = 18).

Patient No.	Gender	Liver biopsy		HBV genotype	Age	Duration of IFN-α, weeks	Follow-up period
		Grade	Stage				
1	M	1	2	C	2y9m	24	14y6m
2	F	2	2	/	9y11m	48	8y
3	F	2	3	/	1y	48	9y2m
4	F	3	2	/	3y7m	30	1y11.5m
5	F	3	1	B	7y	48	1y
6	F	2	0	B	8y5m	64	1y11m
7	M	2	2	C	9y2m	40	2y11m
8	F	3	2	C	4y3m	48	8y7m
9	M	2	2	B	2y1m	40	4y10m
10	M	3	2	C	4y7m	48	8y5m
11	F	2	1	/	2y1m	32	8m
12	M	3	2	B	7y9m	64	7y2m
13	F	2	2	B	2y	52	4y11m
14	F	3	2	C	2y6m	48	2y6m
15	F	4	4	C	1y6m	56	3y3m
16	M	2	3	C	5y2m	48	5y8m
17	M	0	0	/	2y8m	48	3y10m
18	M	3	4	C	2y3m	48	5y6m

" / " = no testing, F = female, M = male, m = month, y = year.

treatment and maintained HBsAg seroconversion. One child (patient 10) became HBsAg negative at 36 weeks during treatment but exhibited recurrence with a low level of HBsAg positivity at 48 weeks after withdrawal. One child (patient 13) became HBsAg seroconverted at 24 weeks during treatment and exhibited HBsAg-positive recurrence at 8 weeks after IFN-α withdrawal, with the HBsAg level showing a rising trend.

3.6. Adverse events

Only mild flu-like symptoms, such as pyrexia (low grade), and rhinorrhea, and transient neutropenia appeared in some children at the early stage of treatment. No treatment reduction or withdrawal was performed for the children with flu-like symptoms, and the transient neutropenia disappeared rapidly. No patients reported adverse events of hypothyroidism or hyperthyroidism or required dose modification for thyroid function abnormalities. No severe abnormal results were observed in other laboratory assessments.

4. Discussion

This observational and open cohort study was conducted in children and adolescents aged 1 to <18 years old with CHB in the immune-active stage. IFN α-2b monotherapy administered per the BSA category-based dosing regimen provided comparable exposure across BSA categories, showed an acceptable safety profile and was efficacious in pediatric patients without advanced

Table 2

Summary of Response to IFN-α Therapy (n = 18).

Patient No.	HBsAg	HBeAg	ALT initial (U/L)	ALT before EOT (U/L)	HBV DNA initial (IU/mL)	HBV DNA before EOT (IU/mL)	HBeAg loss	HBeAb	HBsAg loss	HBsAb
1	positive	positive	145	70	1.24E+06	<1000	YES	positive	NO	NO
2	positive	positive	100	10	6.03E+07	<1000	YES	positive	NO	NO
3	positive	negative	381	10	4.56E+08	<1000	negative	positive	NO	NO
4	positive	positive	328	24	3.88E+06	<1000	YES	positive	NO	NO
5	positive	positive	159	11	6.12E+08	<1000	YES	positive	YES	YES
6	positive	positive	204	13	1.00E+08	1.00E+08	NO	negative	NO	NO
7	positive	positive	158	66	8.81E+06	<1000	YES	positive	NO	NO
8	positive	positive	145	25	2.65E+06	1.04E+03	YES	positive	NO	NO
9	positive	negative	81	26	3.29E+08	<1000	negative	positive	NO	NO
10	positive	positive	409	46	1.16E+06	<1000	YES	positive	YES	NO
11	positive	positive	107	6	2.91E+06	<1000	YES	positive	YES	YES
12	positive	positive	150	99	1.00E+08	1.30E+03	YES	positive	NO	NO
13	positive	positive	175	14	5.71E+06	<1000	YES	positive	YES	NO
14	positive	positive	219	16	1.71E+07	<1000	YES	positive	NO	NO
15	positive	positive	111	26	1.00E+08	<1000	YES	positive	NO	NO
16	positive	negative	86	27	3.10E+04	<1000	negative	positive	NO	NO
17	positive	positive	271	19	7.45E+06	<1000	YES	positive	NO	NO
18	positive	negative	317	16	5.01E+07	1.24E+04	negative	positive	NO	NO

EOT = end-of-treatment.

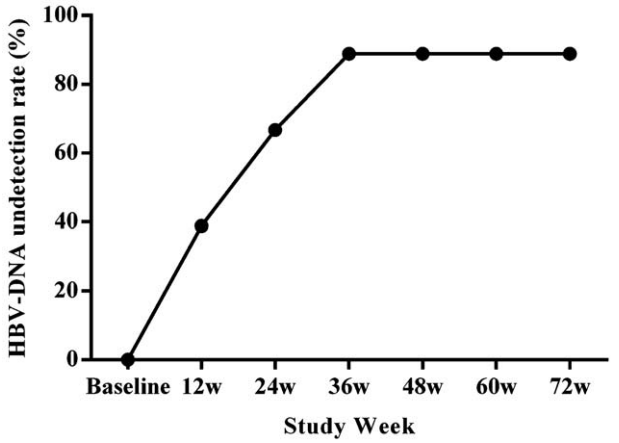

Figure 1. HBV-DNA undetection rate. HBV-DNA undetection rate was maximum at 36 weeks during IFN-α treatment. HBV-DNA undetection rate of 12 weeks treatment (early virological response) was 38.9%.

fibrosis. The primary efficacy assessments included ALT normalization, HBV-DNA suppression, and HBeAg loss or seroconversion in HBeAg-positive patients; HBsAg loss or seroconversion was the ultimate goal.

In this study, 18 children with naïve CHB were treated with IFN α-2b for a median of 48 weeks, and the results of this study confirmed the significantly high HBeAg seroconversion rate in patients treated with IFN α-2b (92.9%) observed in previous reports.[8] The rate of HBsAg loss or seroconversion (22.2%) was higher than that reported in adults (2.3%–3.3%) and previous pediatric studies.[6,8–13]

Sustained HBsAg clearance is considered the ideal endpoint in CHB because it is associated with complete remission, lack of disease progression, and reduced risk of HCC.[14,15] However, HBsAg clearance is difficult to achieve in practice,[16,17] and spontaneous HBsAg clearance is considered a rare event in childhood (0%–1%/year).[15,18,19] In this study, 4 patients (22.2%) achieved HBsAg loss or seroconversion at an average of 21 weeks during treatment. Two of these patients achieved HBsAg seroconversion at 12 weeks during treatment and maintained the HBsAg seroconversion. One became HBsAg negative at 36 weeks during treatment and recurred low-level HBsAg positivity at 48 weeks after withdrawal. One became HBsAg seroconverted at 24 weeks during treatment but exhibited recurrent HBsAg positivity at 8 weeks after withdrawal, and the HBsAg level showed a rising trend.

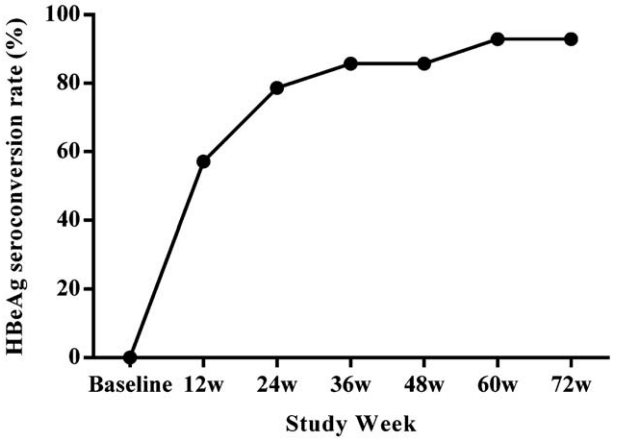

Figure 2. HBeAg seroconversion rate. HBeAg seroconversion rate was maximum at 60 weeks during IFN-α treatment. HBeAg seroconversion rate of 12 weeks treatment was 57.1%.

Although it is reported that HBV genotype C is a difficult-to-treat genotype, the HBeAg seroconversion rate in our children with this genotype was 100% (6/6), and this rate was significantly higher than that in previous adult (27.6%-39.0%) and pediatric (4.3%–38.2%) studies.[6,8–13,20] This finding may be associated with the young age of the children in this study. The interpretation of results from the genotype A and D subgroups was limited by low patient numbers.

A Chinese study of 49 HBeAg-negative cases of 1 to 7-year-old children with CHB treated with IFN-α found that, the liver of most of the children exhibited active inflammation and relatively severe fibrosis, and the authors suggested that children patients can obtain a higher HBsAg clearance rate if they receive antiviral treatment before 3 years of age.[21] In our study, the histological scores of the 4 HBeAg-negative patients were G2S3, G2S2, G2S3 and G3S4 before antiviral treatment, which indicated relatively serious disease. Their ages at the beginning of antiviral treatment were 1 year old, 2 years and 1 month old, 5 years and 2 months old, 2 years, and 3 months old, respectively. The antiviral treatment durations were 48 weeks, 40 weeks, 48 weeks, and 48 weeks, respectively. The time at which the elevated ALT level fell into the normal was week 20, week 16, week 48, and week 36 during treatment, respectively. HBV-DNA became undetectable by 36 weeks, 24 weeks, 24 weeks, and 36 weeks, respectively. HBeAg remained negative, and no cases of HBsAg loss or seroconversion occurred.

The main adverse events to IFN-α antiviral therapy include influenza-like syndrome, granulocytopenia, mental abnormalities (anxiety, depression, illusion, and so on), autoimmune diseases, and so on.[22] In this study, only mild flu-like symptoms such as pyrexia (low grade), and rhinorrhea, and transient neutropenia appeared in some children at the early stage of treatment. No severe abnormal results were observed in other laboratory assessments. No treatment reduction or withdrawal was performed with the children with flu-like symptoms, and transient neutropenia disappeared rapidly. Due to the incomplete data for height and weight, the evidence of treatment effects on growth in this study is insufficient, and this lack of data was 1 of the limitations of our study.

Currently, mother-to-child transmission is the dominant transmission method in China due to the use of disposable medical consumables and strict management of disinfection. Therefore, children with CHB are currently the main source of the CHB population in China. Antiviral treatment is not usually considered due to the particularities of children's growth and development, and infants and young children are often in the phase of immune tolerance when they are infected with HBV. According to some recent studies, scientists from China, which has a high prevalence of CHB, have suggested that children with CHB should be given antiviral treatment as soon as they enter the immune clearance phase and have antiviral indications. Of course, further long-term clinical research is needed, and more samples are needed to confirm the concrete antiviral therapy and antiviral treatment duration, efficacy, adverse reactions, resistance, etc. for children with CHB and to provide more evidence for guidelines for the antiviral treatment of children.

No 1 drug currently achieves reliable complete eradication of HBV. The treatment of chronic HBV infection in children should be individualized. The purpose of treatment is to reduce viral replication, which is defined as undetectable HBV-DNA levels in the serum and the development of anti-HBe antibodies. Seroconversion changes the disease to an inactive form. Currently, treatment is indicated for only patients who are in the immune-active phase. The use of IFN-α is limited due to the subcutaneous administration method, the duration of treatment for 24 weeks, and possible side effects. IFN-α treatment cannot be used for decompensated cirrhosis.[23]

The sample size of our study was small, which was 1 of the limitations of this study, and the sample size needs to be expanded in the future studies. Moreover, in adverse events monitoring, the growth parameters were not measured or recorded completely to monitor the impact of the antiviral treatment on children's growth and development.

In conclusion, the antiviral monotherapy of 48 weeks of IFN-α was well tolerated and good responded, which was associated with higher rates of HBeAg seroconversion and HBsAg clearance in the children in this study than in previously reported adults and pediatric patients.

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