

Treatment of Chronic Hepatitis B in Children with Prednisolone Withdrawal Followed by Recombinant Interferon Alpha

Hyo Sin Kim, Je Woo Kim, and Ki Sup Chung

Steroid withdrawal followed by interferon therapy is an alternative approach for treating chronic hepatitis B virus infection when there has been no therapeutic response to interferon alone. The effectiveness of steroid withdrawal followed by interferon therapy and factors predictive of the response were evaluated in 35 children with biopsy-proven chronic hepatitis B. Patients had received a 1-month course of prednisolone, 1mg/kg per day orally, followed by a 2-week rest, and then were treated with interferon alpha 3 MU three times per week for 4-6 months. The serum aminotransferase values normalized in 80%, and negative seroconversion rates of HBeAg and HBV-DNA were 69% and 66%. The good response rate was associated with a pretreatment HBV-DNA level lower than 100 pg/ml and a posttreatment ALT level more than 200 IU/L. Normalization of ALT values usually took 5 months, and the clearance of HBV-DNA and HBeAg took 7.8 and 6.7 months, respectively. These results suggest that steroid withdrawal followed by interferon therapy is useful in the treatment of chronic hepatitis B in children, and that a good response rate can be expected in children with lower pretreatment HBV-DNA levels (<100 pg/ml).

Key Words: Interferon, prednisolone, chronic hepatitis B, children

Chronic hepatitis B (CHB) in childhood may progress to cirrhosis, liver failure and hepatocellular carcinoma later in adulthood (Wu *et al.* 1987). The chronicity of HBV infection is associated with the age from infection: approximately 90% of children acquired the infection during the perinatal period, 10~20% during the age of 1~3 years, and less than 5% acquired the infection later in childhood (Beasley *et al.* 1983; Chang *et al.* 1988). Therefore, early antiviral treatment for CHB in children appears

warranted.

Interferon (IFN) alpha, which reduces viral replication and enhances the immune response to HBV, has proved to be an effective therapy for carriers infected in adult life, with response rates of 30~40% (Hoofnagle *et al.* 1988; Perrillo *et al.* 1990; Utili *et al.* 1994). It has been proposed that the response rate to IFN may be enhanced by a priming course of corticosteroid (Perrillo *et al.* 1988). This has led to alternative approaches, such as the combination of steroid withdrawal followed by interferon therapy in children when there is no therapeutic response to IFN alone (Utili *et al.* 1994).

Accordingly, this study was performed to evaluate the therapeutic efficacy and the factors predictive of a good response to prednisolone withdrawal followed by interferon alpha treatment in children.

Received March 27, 1998

Accepted July 27, 1998

Department of Pediatrics, Yonsei University College of Medicine, Seoul, Korea

Address reprint request to Dr. K.S. Chung, Department of Pediatrics, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea. Tel: 361-5510, 5519, Fax: 393-9118 e-mail: kschung58@yumc.yonsei.ac.kr

MATERIALS AND METHODS

Sixty-five children with chronic HBV infection who were admitted to the Department of Pediatrics, Yonsei University College of Medicine between October 1992 and May 1996, were enrolled in this study. All patients had CHB, documented by the presence of HBsAg, HBeAg, HBV-DNA and elevated alanine aminotransferase (ALT) values in serum for at least 6 months. Of the total 65 children, the treated group included 35 patients who had undergone percutaneous liver biopsy with pathologic examination, and who received prednisolone withdrawal followed by IFN- α . Thirty patients who refused liver biopsy and had no IFN therapy, were assigned to the untreated group.

The treated group received a 4-week course of prednisolone, 1mg/kg per day orally, followed by a 2-week rest, and then were treated with interferon- α -2a (Intermax- α [®], LG Co. Seoul) 3 MU three times weekly for 4~6 months. The untreated group were managed conservatively or left untreated during the follow-up period.

Patients in the treated group were followed up monthly during IFN therapy, and then every 3 months for at least 6 months after the completion of treatment. Patients in the untreated group were followed up every 3~6 months for more than 12 months. During the follow-up period, aspartate aminotransferase (AST) and ALT values were measured. After the normalization of aminotransferases, tests for HBeAg, anti-HBe and HBV-DNA were performed every 1~6 months. The mean follow-up period was 16 ± 7 months in the treated group, while it was 63 ± 44 months in the untreated group. The therapeutic efficacy was evaluated using the following criteria; loss of HBV-DNA, HBeAg clearance, and anti-HBe seroconversion. As the prognostic factors, we used pre- and posttreatment aminotransferase and pretreatment HBV-DNA levels. We defined the "pretreatment" state as the period before receiving prednisolone and the "posttreatment" state as the period after termination of prednisolone treatment.

Serum HBsAg, anti-HBs, HBeAg and anti-HBe were measured by an enzyme immunoassay with commercial kit (Enzygnost, Behring, Marburg, Ger-

many), and serum HBV-DNA was measured using a chemiluminescent molecular hybridization assay with commercial kit (Digene Hybrid Capture System, Digene, Beltsville, MD, USA).

Written informed consent was obtained from each patient. Statistical analysis was made by the student *t* test and Mann-Whitney *U* test using SPSS 7.0 for Windows. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

Age and sex distribution on admission

The treated group consisted of 35 children with a mean age of 11.5 ± 3.3 years (range, 1.3 to 16.4 years): less than 5 years in 3 children, 5 to less than 10 years in 6, and 10 years and older in 26. There were 24 males and 11 females. The untreated group consisted of 30 children with a mean age of 7.1 ± 4.5 years (range, 0.2 to 19.2 years): less than 5 years in 10 children, 5 to less than 10 years in 9, and 10 years and older in 11. There were 21 males and 9 females (Table 1).

Pathologic types of chronic hepatitis B

The pathologic types in the treated group included chronic lobular hepatitis (CLH) in 4 (11%), chronic persistent hepatitis (CPH) in 19 (54%) and chronic active hepatitis (CAH) in 12 (34%) cases. The untreated group included 30 children whose histopathologic examinations were not done (Table 2).

Pretreatment clinical characteristics of patients and pathologic type

Pretreatment serum aminotransferase values were higher in children with CAH than in children with CLH or CPH. The treated and untreated groups were comparable with respect to total serum bilirubin, prothrombin time, total cholesterol, and alkaline phosphatase as biochemical tests. The mean follow-up period for the treated group was 16 ± 7 months after the completion of interferon α , and that for the untreated group was 63 ± 44 months (Table 3).

Outcome of serum ALT, AST, HBV-DNA, HBeAg and anti-HBe value after treatment

Normalization of transaminases was observed in 28 (80%) of the 35 children in the treated group and in 19 (63%) of the 30 children in the untreated group, which showed no significant difference between the 2 groups ($p=0.13$).

Seroconversion of HBV-DNA occurred in 23 (66%) children in the treated group and in 8 (38%) of 21 in the untreated group, which showed a significantly higher clearance rate of HBV-DNA in the treated group than in the untreated group ($p=0.04$). HBeAg seroconversion occurred in 24 (69%) children in the treated group and in 11 (37%) of 30 in the untreated group, which showed a

significantly higher clearance rate of HBeAg in the treated group than in the untreated group ($p=0.01$). Seroconversion of anti-HBe occurred in 21 (60%) children in the treated group and in 7 (23%) of 30 in the untreated group, which showed a significantly higher seroconversion rate of anti-HBe in the treated group than in the untreated group ($p=0.01$) (Table 4).

Outcome of serum aminotransferases, HBV-DNA, HBeAg, anti-HBe value after treatment and pathologic types

Normalization of aminotransferases, seroconversion of HBV-DNA, HBeAg and anti-HBe were

Table 1. Age and sex distribution on admission

Age(years)	Treated group	Untreated group	Total
< 5	3 (1)	10 (7)	13 (8)
5~10	6 (5)	9 (9)	15 (14)
>10	26 (18)	11 (5)	37 (23)
Total	35 (24)	30 (21)	65 (45)
Male			

Table 2. Pathologic types of chronic hepatitis B

	Treated group(%)	Untreated group(%)
CLHB	4 (11.4)	—
CPHB	19 (54.3)	—
CAHB	12 (34.3)	—
Undetermined	—	30 (100.0)
Total	35 (100.0)	30 (100.0)

CLHB: chronic lobular hepatitis B, CPHB: chronic persistent hepatitis B, CAHB: chronic active hepatitis B

Table 3. Pretreatment clinical characteristics of patients and pathologic types

	Treated group (Mean \pm SD)				Untreated group (Mean \pm SD)	P value*
	CLHB	CPHB	CAHB	Total		
No. of patients	4	19	12	35	30	
Age (years)	12.1 \pm 0.8	10.7 \pm 3.9	12.6 \pm 2.4	11.5 \pm 3.3	7.1 \pm 4.5	
Duration of history (month)	65 \pm 117	28 \pm 31	24 \pm 33	31 \pm 47	12 \pm 15	
AST (IU/L)	45 \pm 7	48 \pm 29	133 \pm 131	77 \pm 88	69 \pm 48	0.67
ALT (IU/L)	84 \pm 7	65 \pm 34	213 \pm 218	118 \pm 145	102 \pm 71	0.59
HBVDNA (pg/ml)	537 \pm 338	735 \pm 556	504 \pm 617	634 \pm 559	808 \pm 699 [†]	0.37
T.bilirubin (mg/dl)	0.5 \pm 0.1	0.5 \pm 0.1	0.7 \pm 0.3	0.6 \pm 0.2	0.7 \pm 0.8	0.47
Prothrombin time (% of normal)	93 \pm 14	89 \pm 9	86 \pm 7	88 \pm 9		—
Cholesterol (mg/dl)	167 \pm 34	179 \pm 51	152 \pm 23	169 \pm 42	170 \pm 38	0.94
ALP (IU/L)	317 \pm 14	231 \pm 97	291 \pm 64	262 \pm 86	232 \pm 66	0.25
Follow-up (months)	18 \pm 6	14 \pm 8	19 \pm 5	16 \pm 7	63 \pm 44	—

*: P value between total patients of treated group and untreated group, Student t-test: AST, ALT, T.Bilirubin, Cholesterol, ALP, Mann-Whitney test(Rank sums)test: HBV-DNA. [†]: Only 15 of a total 30 cases were checked for HBV-DNA.

observed in 4 (100%), 4 (100%), 4 (100%) and 3 (75%) of the 4 children with CLH; 15 (79%), 11 (58%), 11 (58%) and 10 (53%) of the 19 children with CPH; 9 (75%), 8 (67%), 9 (75%) and 8 (67%) of the 12 children with CAH, respectively. Children with CAH showed a more favorable response to the therapy than children with CPH. But the number of children with CLH was so small that the comparison with other pathologic types could not be made (Table 5).

Seroconversion of HBeAg, HBV-DNA and pretreatment peak ALT values

HBeAg seroconversion was observed in 12 (67%)

Table 4. Outcome of patients treated with prednisolone withdrawal followed by interferon alpha therapy

	No. of patients(%)		
	Treated group(n=35)	Untreated group(n/N*)	P-value (X ² test)
Normalization of transaminase	28 (80)	19/30 (63)	0.13
Negative conversion of HBV-DNA	23 (66)	8/21 (38)	0.04
Negative conversion of HBeAg	24 (69)	11/30 (37)	0.01
Positive conversion of anti-HBe	21 (60)	7/30 (23)	0.01

*n/N: no. of cases / total patients

Table 5. Outcome of patients treated with prednisolone withdrawal followed by interferon alpha therapy and pathologic types

	No. of patients (%)			
	CLH (n=4)	CPH (n=19)	CAH (n=12)	Total (n=35)
Normalization of transaminase	4 (100)	15 (79)	9 (75)	28 (80)
Negative conversion of HBV-DNA	4 (100)	11 (58)	8 (67)	23 (66)
Negative conversion of HBeAg	4 (100)	11 (58)	9 (75)	24 (69)
Positive conversion of anti-HBe	3 (75)	10 (53)	8 (67)	21 (60)

of the 18 children with pretreatment peak ALT values below 100 IU/L, in 8 (73%) of the 11 with ALT between 100 IU/L and 200 IU/L, and 4 (67%) of the 6 with ALT over 200 IU/L. Seroconversion of HBV-DNA occurred in 11 (61%) of the 18 children with pretreatment peak ALT values below 100 IU/L, in 8 (73%) of the 11 with ALT between 100 IU/L and 200 IU/L, and in 4 (67%) of the 6 with ALT over 200 IU/L. There was no significant difference between seroconversion of HBeAg, HBV-DNA and pretreatment peak ALT levels (Table 6).

Seroconversion of HBeAg, HBV-DNA and pretreatment HBV-DNA values

Seroconversion of HBeAg was observed in 4 (80%) of 5 children with pretreatment HBV-DNA values below 100 pg/ml, in 13 (68%) of the 19 with HBV-DNA between 100 pg/ml, and 1000 pg/ml, and in 4 (57%) of the 7 with HBV-DNA over 1000 pg/ml. Loss of HBV-DNA occurred in 4 (80%) of the 5 children with pretreatment HBV-DNA values below 100 pg/ml, in 12 (63%) of the 19 with HBV-DNA between 100 pg/ml, and 200 pg/ml, and in 4 (57%) of the 7 with HBV-DNA over 200 pg/ml. There was no significant difference between the seroconversion rate of HBeAg, HBV-DNA and pretreatment HBV-DNA levels, but children with pretreatment peak HBV-DNA values of less than 100 pg/ml were more likely to clear HBeAg and HBV-DNA (Table 7).

Table 6. Pretreatment peak ALT values and the clearance of HBeAg and HBV-DNA

ALT (IU/L)	Clearance (No. of patients)	
	HBeAg (%)	HBV-DNA (%)
< 100 (n=18)	12 (67)	11 (61)
100~200 (n=11)	8 (73)	8 (73)
> 200 (n=6)	4 (67)	4 (67)
Total (n=35)	24 (69)	23 (66)

Table 7. Pretreatment HBV-DNA values and the clearance of HBeAg and HBV-DNA

HBV-DNA (pg/ml)	Clearance (No. of patients)	
	HBeAg (%)	HBV-DNA (%)
< 100 (n=5)	4 (80)	4 (80)
100~1000 (n=19)	13 (68)	12 (63)
> 1000 (n=7)	4 (57)	4 (57)
Total (n=31)	21 (68)	20 (65)

Seroconversion of HBeAg, HBV-DNA and posttreatment peak ALT values

Seroconversion of HBeAg was observed in 4 (67%) of the 6 children with posttreatment peak ALT values below 100 IU/L, in 10 (63%) of the 16 with ALT between 100 IU/L and 200 IU/L, and in 10 (77%) of the 13 with ALT over 200 IU/L. Loss of HBV-DNA occurred in 4 (67%) of the 6 children with posttreatment peak ALT values below 100 IU/L, in 10 (63%) of the 16 with ALT between 100 IU/L and 200 IU/L, and in 9 (69%) of the 13 with ALT over 200 IU/L. There was no significant difference between the seroconversion rate of HBeAg, HBV-DNA and posttreatment ALT levels, but children with higher posttreatment peak ALT levels were more likely to clear HBeAg and HBV-DNA (Table 8).

Duration of improvement after completion of treatment

The normalization of serum AST and ALT values

Table 8. Posttreatment peak ALT values and the clearance of HBeAg and HBV-DNA

ALT (IU/L)	Clearance (No. of patients)	
	HBeAg (%)	HBV-DNA (%)
< 100 (n=6)	4 (67)	4 (67)
100~200 (n=16)	10 (63)	10 (63)
> 200 (n=13)	10 (77)	9 (69)
Total (n=35)	24 (69)	23 (60)

Table 9. Duration of improvement after prednisolone withdrawal followed by interferon alpha therapy

	Duration (months: mean \pm SD)
Normalization of transaminase	5.0 \pm 3.7
Negative conversion of HBV-DNA	7.8 \pm 4.2
Negative conversion of HBeAg	6.7 \pm 4.5
Positive conversion of anti-HBe	8.3 \pm 4.2

took 5.0 \pm 3.7 months after completion of treatment. Seroconversion of HBV-DNA and HBeAg took 7.8 \pm 4.2 and 6.7 \pm 4.5 months, respectively. Seroconversion of anti-HBe took 8.3 \pm 4.2 months (Table 9).

DISCUSSION

Interferons are a complex family of cellular proteins with antiviral, immunomodulatory, and antiproliferative effects. Interferons not only act at multiple sites in the cycle of viral replication and limit virus spread, but they also have immunomodulatory effects to increase the expression of HLA class I antigen that is important for the recognition of viral epitopes by sensitized, cytotoxic T lymphocytes. Interferon also increase natural killer cell activity and induce maturation of cytotoxic T cells via rearrangement of the T cell receptor (Perrillo *et al.* 1990).

Since Greenberg *et al.* first reported the effect of buffy-coat-derived leukocyte interferon in the suppression of serum DNA polymerase and HBV-DNA values, interferons have been applied in the treatment of chronic hepatitis B (Greenberg *et al.* 1976). And the advent of recombinant gene technology made mass-production of interferons possible, and today interferons are widely used.

Interferons are divided into three classes, alpha, beta, and gamma, according to the cells of production. All these interferons have antiviral effects, but in the treatment of hepatitis B, alpha form is generally used. In the first stage, human lymphoblastoid α -interferon was employed and more recently interferon alpha-2a (Roferon, Intermax-alpha) and interferon alpha-2b (Intron A) has become widely applied. In this study we used interferon alpha-2a (Intermax- $\alpha^{\text{®}}$, LG Co.).

Therapeutic doses and duration of IFN have not yet been established in children. The usual doses are 3 MU, 5 MU or 10 MU of IFN given three times weekly for 4 to 6 months. No effects are expected in a dose of less than 2.5 MU/m², and the effects of immunosuppression are seen in a dose of more than 10 MU/m² (Mora *et al.* 1987).

The therapeutic end point of interferons in chronic hepatitis B has generally been the sustained elimination of circulating markers for viral replication such as HBeAg, HBV-DNA and DNA polymerase. Seroconversion of HBeAg is accompanied by the disappearance of DNA polymerase and HBV-DNA in the serum, marked reduction in aminotransferase values, and improvement in histologic findings of the liver (Perrillo, 1993). In recent studies, seroconversion of HBeAg and HBV-DNA occurred in about 30~40% of adults (Hoofnagle *et al.* 1988; Perrillo *et al.* 1990), but the seroconversion rate of HBeAg and HBV-DNA ranges from 17% to 78% in children (Lai *et al.* 1987; Utili *et al.* 1991; Burczynska and Madalinski, 1994; Utili *et al.* 1994; Ruiz-Moreno *et al.* 1995; Gregorio *et al.* 1996; Vajro *et al.* 1996). There are various patient-related variables to influence the response to antiviral therapy in chronic hepatitis B. It is known that a high histological activity, a low percentage of HBcAg-stained hepatocytes, and high pretreatment serum AST and ALT levels are associated with a good response to IFN therapy (Ruiz-Moreno *et al.* 1995).

One approach to increasing the response rate to antiviral therapy involves the use of an antecedent course of corticosteroids (Scullard *et al.* 1981). A distinct trend existed for patients with low pretreatment aminotransferase values, which showed a more frequent response to the combination regimen (Krogsgaard, 1994; Perillo and Mason, 1994; Vajro *et al.* 1996). The rationale for the combination regimen is based on the fact that withdrawal of corticosteroid therapy frequently results in an acute hepatitis-like elevation of serum aminotransferase levels, which is thought to represent an "immunologic rebound" that results in a transient decline in markers of viral replication (Perrillo *et al.* 1985; Omata and Uchiumi, 1986). While corticosteroid withdrawal is well tolerated in clinically-stable patients, clinicians have been advised that it should never be used in patients with overt hepatic decompensation (Omata and Uchiumi, 1986).

In this study, 35 children received a 1-month course of prednisolone, 1mg/kg per day orally, followed by a 2-week rest, and then were treated with IFN alpha-2a 3 MU three times weekly for 4 to 6 months. The total follow-up was 16 ± 7 months. The seroconversion rates of HBeAg and HBV-DNA were 69% and 66% respectively in 35 children. Our overall success rate was much higher than other trials in children; by 13% of Lok *et al.* by 41% of Utili *et al.* by 44% of Giacchino *et al.* by 44% of Vajro *et al.* by 35% of Gregorio *et al.* and in adults by 36% of Perrillo *et al.* (Lok *et al.* 1989; Perrillo *et al.* 1990; Utili *et al.* 1994; Giacchino *et al.* 1995; Gregorio *et al.* 1996; Vajro *et al.* 1996). The relatively low efficacy of IFN in Chinese children (Lai *et al.* 1987; Lok *et al.* 1989) may be due to the fact that most Chinese children may have acquired the infection by perinatal transmission and may have developed an immunological "tolerance" to HBV, characterized by high viral replication and low disease activity (Utili *et al.* 1994).

There are diverse opinions for the therapeutic efficacy of IFN alone or after prednisolone priming. In adults, Perrillo *et al.* reported that there was no difference in HBeAg seroconversion between combined regimen and IFN alone (Perrillo *et al.* 1990). In children, Lok *et al.* reported that the seroconversion rate of HBeAg was higher in combined regimen (13%) than in IFN alone (3%)

(Lok *et al.* 1989). However, the seroconversion rate of HBeAg was higher in IFN alone than in combined regimen by Giacchino *et al.*, with 53% vs 44%, and by Gregorio *et al.* with 40% vs 35% (Giacchino *et al.* 1995; Gregorio *et al.* 1996). We also reported the therapeutic efficacy of IFN alone in children with CHB previously (Jeong and Chung, 1997). In our previous IFN-alone study and in this combined regimen study, the overall seroconversion rate of HBeAg was higher in IFN alone (75%) than in combined regimen (66%), but it was higher in combined regimen (67%) than in IFN alone (55%) in children below 100 IU/L of serum ALT levels. This indicated that combined regimen may be more effective than IFN alone in cases of low serum ALT levels.

Factors predictive of a favorable response to IFN therapy in patients with chronic hepatitis B are pre- and posttreatment aminotransferase and pretreatment HBV-DNA values. It is known that seroconversion of HBeAg and HBV-DNA were significantly increased in patients with pretreatment peak ALT values over 100 IU/L and pretreatment peak HBV-DNA values below 100 pg/ml (Perrillo *et al.* 1990; Utili *et al.* 1994; Gregorio *et al.* 1996; Vajro *et al.* 1996). In our study, there was no significant difference in the clearance rates of HBeAg and HBV-DNA in association with pretreatment peak ALT and HBV-DNA values. However, the seroconversion rate of HBeAg and HBV-DNA were higher in children with pretreatment HBV-DNA values under 100 pg/ml (80% in each) than in children with values over 1000 pg/ml (57% in each). As well, the seroconversion rate of HBeAg was higher in children with posttreatment peak ALT values over 200 IU/L (77%) than in children with values under 100 IU/L (57%). In our previous study (1997), however, the seroconversion rate of HBeAg with IFN monotherapy was 55% in children with pretreatment peak ALT values less than 100 IU/L, while it was 67% in this study (Jeong and Chung, 1997). These results indicated that a higher therapeutic effect of steroid withdrawal after IFN priming can be expected in children with pretreatment peak ALT values less than 100 IU/L compared with IFN monotherapy inducing "immunologic rebound" by steroid withdrawal.

It is known that early side effects include fever,

headache, fatigue, myalgia and arthralgia. Our patients were well tolerated with combined therapy without any dose reduction. There were no patients who experienced late side effects such as bone marrow suppression, alopecia, changes in mood and impaired concentration.

In summary, our study shows that prednisolone withdrawal followed by IFN therapy is useful in the treatment of chronic hepatitis B in children. The seroconversion rates of HBeAg and HBV-DNA were 69% and 66% respectively, which were outstanding compared to those of other reports. We believe that a higher therapeutic effect of steroid withdrawal after IFN priming can be expected in children with higher posttreatment peak ALT values (>200 IU/L) and lower pretreatment HBV-DNA values (<100 pg/ml).

REFERENCES

- Beasley RP, Lee GY, Roan CH, Hwang LY, Lan CC, Hwang FY: Prevention of perinatally transmitted hepatitis B virus infection with hepatitis B immunoglobulin and hepatitis B vaccine. *Lancet* 2: 1099-1102, 1983
- Burczynska B, Madalinski K: The value of quantitative measurement of HBeAg and HBsAg before IFN alpha treatment of chronic hepatitis B in children. *J Hepatol* 21: 1097-1102, 1994
- Chang MH, Hwang LY, Hsu HC, Lee CY, Beasley RP: Prospective study of asymptomatic HBsAg carrier children infected in the perinatal period: clinical and liver histologic studies. *Hepatology* 8: 374-377, 1988
- Giacchino R, Main J, Timitilli A, Giambartolomeni G, Facco F, Cirillo C, Jacina MR, Brook MG, Callea F, Kariyannis P, Terragna A, Thomas HC: Dual-centre, double-blind, randomized trial of lymphoblastoid interferon alpha with or without steroid pretreatment in children with chronic hepatitis B. *Liver* 15: 143-148, 1995
- Greenberg HB, Pallard RB, Lutwick LI, Gregory PB, Robinson WS, Merigan TC: Effect of human leukocyte interferon on hepatitis virus infection in patients with chronic active hepatitis. *N Engl J Med* 295: 517-522, 1976
- Gregorio GV, Jara P, Hierro L, Diaz C, de la Vega A, Vegnente A, Iorio R, Bortolotti F, Crivellaro C, Zancan L, Daniels H, Portmann B, Mieli-Vergani G: Lymphoblastoid interferon alpha with or without steroid pretreatment in children with chronic hepatitis B: a multicenter controlled trial. *Hepatology* 23: 700-

707, 1996

- Hoofnagle JH, Peters M, Mullen KD, Jones DB, Rustgi V, Di Bisceglie A, Hallahan C, Park Y, Meschievitz C, Jones EA: Randomized, controlled trial of recombinant human alpha interferon in patients with chronic hepatitis B. *Gastroenterology* 95: 1318-1325, 1988
- Jeong IS, Chung KS: The therapeutic effect of interferon-alpha treatment in children with chronic hepatitis B. *J Korean Pediatr Soc* 40: 955-964, 1997
- Krogsgaard K: Does corticosteroid pretreatment enhance the effect of alpha interferon treatment in chronic hepatitis B? *J Hepatol* 20: 159-162, 1994
- Lai CL, Lin HJ, Yeoh EK, Lik ASF, Wu PC, Yeung CY: Placebo-controlled trial of recombinant alpha-2-interferon in Chinese HBsAg carrier children. *Lancet* ii: 870-880, 1987
- Lok ASF, Lai CL, Wu PC, Lan JYN, Leung EKY, Wong LSK: Treatment of chronic hepatitis B with interferon: experience in Asian patients. *Semin Liver Dis* 9: 249-253, 1989
- Mora I, Porres JC, Bartolome J: Changes of hepatitis B virus markers during prolonged recombinant interferon alpha-2A treatment of chronic HBV infection. *J Hepatol* 4: 29-36, 1987
- Omata M, Uchiumi K: Combination of prednisolone withdrawal and antiviral agents (adenine arabinoside, interferon) in chronic hepatitis B. *J Hepatol* 3(suppl 2): S65-69, 1986
- Perrillo RP: Interferon in the management of chronic hepatitis B. *Dig Dis Sci* 38: 577-593, 1993
- Perrillo RP, Mason AL: Therapy for hepatitis B virus infection. *Gastroenterol Clin North Am* 23: 581-601, 1994
- Perrillo RP, Regenstien FG, Bodicky CJ, Campbell CR, Sanders GE, Sunwoo YC: Comparative efficacy of adenine arabinoside 5'-monophosphate and prednisolone withdrawal followed by adenine arabinoside 5'-monophosphate in the treatment of chronic active hepatitis type B. *Gastroenterology* 88: 780-786, 1985
- Perrillo RP, Regenstien FG, Peters MG, DeSchryver-Kecskemeti K, Bodicky CJ, Campbell CR, Kuhns MC: Prednisolone withdrawal followed by recombinant alfa interferon in the treatment of chronic type B hepatitis. *Ann Intern Med* 109: 95-100, 1988
- Perrillo RP, Schief ER, Daris GL: A randomized, controlled trial of interferon alpha-2b alone and after prednisolone withdrawal for the treatment of chronic hepatitis B. *N Engl J Med* 323: 295-300, 1990
- Ruiz-Moreno M, Camp T, Jimenez J, Lopez R, Castillo I, Bartolome J, Carreno V: Factors predictive of response to interferon therapy in children with chronic hepatitis B. *J Hepatol* 22: 540-544, 1995
- Scullard GH, Smith CI, Merigan TC, Robinson WS, Gregory PB: Effects of immunosuppressive therapy on viral markers in active chronic hepatitis B. *Gastroenterology* 81: 987-991, 1981
- Utili R, Sagnelli E, Gaeta GB, Galanti B, Nardiello S, Felaco F, Pasquale G: Treatment of chronic hepatitis B in children with prednisolone followed by alfa-interferon: a controlled randomized study. *J Hepatol* 20: 163-167, 1994
- Utili R, Sagnelli E, Galanti B: Prolonged treatment of children with chronic hepatitis B with recombinant α_2 -Interferon: A controlled, randomized study. *Gastroenterology* 86: 327-330, 1991
- Vajro P, Tedesco M, Fontanella A, De Vincenzo A: Prolonged and high dose recombinant interferon alpha-2b alone or after prednisolone priming accelerates termination of active viral replication in children with chronic hepatitis B infection. *Pediatr Infect Dis J* 15: 223-231, 1996
- Wu TC, Tong MJ, Hwang B, Lee SD, Hu MM: Primary hepatocellular carcinoma and hepatitis B infection during childhood. *Hepatology* 7: 46-48, 1987