Human α-Interferon Therapy for Chronic Active Hepatitis B in Children

Dr. O. MAKHMUDOV, Dr. B. KADİROV, Dr. F. INOYATOVE, Dr. Sh. ABDUMADJİDOVA

Özet: *Yaşları 3-14 arasında olan kronik aktif hepatitli 40 çocukta biokimyasal, immunolojik ve radioimmunolojik değerledirmeler ve klinik gözlemlerimizin sonuçları bildirilmiştir. Olgulardan 20'si interferon ve komplex tedavi gördü (tedavi grubu), 20 olgu ise sadece klasik tedavi gördü. (kontrol grubu). Aynı yaş grubunda 24 çocuk sağlıklı çocuk grubu olarak oluşturuldu.*

Anahtar kelimeler: Kronik aktif hepatit, α interferon tedavisi

Summary: *We report our results of clinical observations, biochemical, immunologic and radioimmunologic exams of 40 children with chronic active hepatitis B, aged 3-14 years, 20 children of which received interferon additionally to the complex therapy and the other 20 patients had only basic therapy and were control gorup, 24 children of the same age formed the group of healthy children.*

Key words: Chronic active hepatitis, α interferon therapy

The treatment with leukocyte interferon has resulted in imrovement of some functional liver tests and changed the indices of cellular immunity. We suggested that the positive effect of interferon is associated with its immunomodulating action to the cellular immunity. However leukocyte interferon had no essential influence on serologic markers of hepatitis B virus. From the results we concluded that the higher dose of human leukocyte interferon and longer treatment schedule could be effective.

The problems of rational therapy, preventing the progress of pathological processes, remain actual in chronic viral hepatitis. The success of therapy for patients with chronic viral hepatitis depends on the time of the beginning. There are three major forms of chronic viral hepatitis; chronic hepatitis B, chronic non-A, non-B (type C) hepatitis and chronic delta hepatitis. These forms of chronic hepatitis are distinct from non-viral forms of chronic hepatites not only on the basis of serological tests and etiology, but also on the basis of natural history and response to antiviral and immunosup-pressive therapies. Therapeutic approaches that have been taken for chronic hepatitis B include: İmmunosuppression with corticosteroids (2,3) (1,12); immunostimulation with BCG vaccination or levamisole (5,9) (3,7), the use of plant extracts such as from phyllanthus amarus (8) and antiviral therapy with adenine-arabinoside monophosohate, lymphokin, acyclovir, viderabin and α,β-interferon, of all these human leukocyte α-interferon is the most promising agent at present. There is an opinion that long-term corticosteroid therapy is actually detrimental in chronic type B hepatitis, can worsen this disease by inducing an exacerbation of hepatitis B. Adenine arabinoside (Ara-A) and its monophosphate derivative (Ara-AMP) can transiently lower the serum level of HBV.

M. D., Proffessor, Scientific and Research Institute of Pediatrics, Republic of Uzbekistan.

Candidate of Medicine, Scientific and Research Institute of Pediatrics, Republic of Uzbekistan.

However, a longterm response requires permanent cessation of viral replication. The interferons are a series of host proteins made in response to virus infections and other antigenic stimuli. They are classified as alpha (leukocyte), beta (fibroblast) and gamma (Immune), based upon antigenicity and cell origin. The level of interferon production reflects the host total immunostimulant effect of interferon is significantly depended from dose and time parameters of such used agent as antigen, some characteristics of interferon itself (endo-or-exogenecity, the sourse and method of obtaining, degree of clearence). Interferon producers, especially endotoxin, have the whole range of immunotrope effects, many of which are independent from interferon. Lower doses of interferon induce stimulating effect and higher doses show negative effect (17,27).

It has been suggested that the stimulant effect of interferon, type II, is mediated by T cells and suppressive effect is due to the direct action to the B lymphocytes. More marked and persistent immunostimulant effect of interferon is expressed on natural killer-cells and macrophages. Beneficial indices of interferon therapy such as the low virus ability to induce interferogenesis (22,23), the low production of interferon in patients (3,14,19), the mild cytotoxicity of natural killer-cells (19,25) take an important role in the formation of antiviral immunity at the early stage of disease, the activity of which is induced by interferon. It has been found that the disorder of cell immunity in viral hepatitis B is characterised by the development of secondary suppressive immunideficiency (5), that the virus of hepatitis B ise a weak interferon producer, and a stable insufficiency of interferonogenesis is one of important factors of disease duration (14,19). The important advantage of interferon is the low toxicity. The interferon production in children is lower than in adults (7,10,18), and probably is one of the reasons of children sensibility to virus infections and development of hepatitis B chronic froms. While studying the therapeutic effect of α-interferon in patients with chronic viral hepatitis it has been found that the state of patients has gradually improved, function tests and immunity indices had tended to be normalized. The final effect reached its peak under the follow-up in a 3-6 months.

In chronic viral hepatitis the result of therapy depends clinical form of disease. The interferon therapy is more successful in benign chronic viral hepatitis. The 19-days course of interferon therapy for chronic active hepatitis improves only the subjective and objective state and leds to transient remission for 3-4 weeks. After 9-days course of interferon retreatment there were improvement of subjective state and indices of cellular immunity, but objective state was almost not changed in the patients. Perhaps permanent daily injection of interferon during a month or more is required for chronic active viral hepatitis. Intramuscular injections might be more effective in doses of 3-10 million units per injection.

MATERIALS and METHODS

Among 40 patients who fulfilled the criteria for the diagnosis of chronic hepatitis B, aged 3-14 years, 20 patients were treated with human leukocyte interferon additionally to the complex therapy (treated group) and the others received only basic therapy and were controls. Duration of disease in observed children was 3,02 ± 0,3 years. The diagnosis of chronic hepatitis was based on duration of disease (more than 6 months) as well as on appropriate clinical and laboratory criteria, data of sonography, radioisotope scanning of liver and punch biopsy. The two study groups were similar with respect to age, sex, known duration of hepatitis, history of concominant diseases before treatment. Criteria for selection of patients were: progressive course of disease, presence of marked intoxication, cytolysis syndrome, detection of HBsAg in the serum, lack of correlation between cellular and humoral immunity values. Human leukocyte α–interferon was obtained in A.F. Gamaleya Scientific and Research Institute of Epidemiology and Microbiology (Moscow).

Table I: Results of comparison among blood biochemical data from children with chronic active hepatitis B treated with basic therapy with and without interferon (M ± m).

Biochemical tests	Treated group Acute condition :	Remission	Control group Acute condition:	Remission	Normal children
Total blood bilirubin /Mmol/L/	29,1 ± 2,9	19,4 ± 1,52*	26,55 ± 2,01	18,01 ± 1,96*	8,33 ±0,37
ALT, mcmol/sec.l	2,76 ± 0,39	1,49 ± 0,19*	2,57 ± 0,23	1,8 ± 0,36*	0,31 ± 0,04
AST, mcmol/sec.l	2,39 ± 0,35	0,94 ± 0,11*'**	2,04 ± 0,32	1,33 ±0,11*	0,22 ± 0,33
Thymol turbidity test, U.	10,81 ± 0,48	6,81 ± 0,54*	9,89 ± 0,9	7,11 ± 0,62*	3,56 ± 0,25
Total blood protein, g/l	58,4 ± 4,77	70,25 ± 1,06*	58,49 ± 2,29	64,35 ± 2,95*	78,33 ± 3,4
Albumin, %	43,2 ± 2,04	54,4 ± 1,4*'**	41,94 ± 1,18	48,47 ± 1,19*	61,53 ± 1,59
Gamma-globulin	31,4 ± 1,5	19,3 ± 0,81*'**	30,96 ±1,16	22,75 ± 1,34*	14,07 ± 0,7

Notes: * - result of comparison between treated group, control group and normal children, p<0,05 - <0,001
** - result of comparison between treated and control groups, p<0,05 -<0,001.

Interferon was injected intramuscularly at a dose of 3 million units three times a week for 30 days. To estimate the efficacy of α-interferon therapy besides clinical examinations alanine aminotransferase (ALT) and asparate aminotransferase (AST) activities, content of total bilirubin and its fractions, thymol turbidity test, content of total blood protein and its fractions, fibrinogen, prothrombin index, level of alkaline phosphatase, cholesterin and blood lipids were also determined in two groups.

Biochemical tests were performed with standard methods. Immune status was examined by the determination of T-lymphocytes/E-RFC/by M. Gondal et al (1972), B-lymphocytes/EAC-RFC/ by N. F. Mendes et al (1973), theophylline-resistant/TPR E-RFC/ and theophylline-sensitive /TPS E-RFC/ cells, indirect indicative cells of T-lymphocyte helper and suppressive activity according to the method of S. Limatibule et al (1978). Antigen-binding lymphocyte reaction was used for determination of lymphocyte viral sensibilization. Serum immunoglobulins in the peripheral blood were tested by Manchini (1965). HBV infection markers (HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc) were determined by radioimmunoassay with the use of diagnostic kits of "Abbott" firm.

RESULTS

Positive effect of α-interferon therapy was observed in 18 of 20 study children with active chronic hepatitis. To the end of therapy the activity of disease has been considerably improved. In treated group as compared with controls there were rapid improvement of intoxication symptoms, thus duration of flaccidity was shorter 1,7 times, the frequency of nausea and vomiting decreased 1,4 times. Anorexia disappeared in children receiving interferon and having basic therapy in 14,8 ± 1,3 days and 18,6 ± 1,2 days respectively. Duration of weakness in treated and control group was 19,2 ± 1,5 and 22,4 ± 1,4 days respectively, paleness- 17,2 ± 1,6 and 20,5 ± 1,6 days respectively, irritation 7,1 ± 0,5 and 10,2 ± 2,3 days respectively. Repeated nasal hemorrhage was longer than 1,6 times in controls. The average jaundice duration in children of treated and control groups was 23,0 ± 1,1 days and 26,2 ± 1,5 days respectively. Icteric sclera in treated group was observed during 25,7 ± 3,0 days, and in controls- during 29,3 ± 2,4 days. Reduction of liver size in children with chronic active hepatitis B was found in treated group: the liver was extended more than 5 cm below the costal margin after the treatment in 30% of control group, and only in 20% of treated group, from 3 to 5cm- in 45% and 30%, and to 3 cm- in 25% and 45% respectively. No significant differences in contraction of spleen size were in two groups. Rapid reduction of intoxication period and other symptoms of disease due to interferon therapy promoted to shorten of patient's stay in hospital. Mean children's stay in hospital in treated and control group was 27,0 ± 2,1 days and 31,6 ± 1,8 days respectively, clinical effect of human leukocyte interferon treatment was accompanied by tendency to rapid improvement of liver function tests. Before treatment the two study groups were similar with respect to biochemical param-

Table II: Comparisons among immunologic data in children with chronic acute hepatitis B receiving basic therapy with and without interferon /M ± m/.

Immunologic tests	Treated group		Control group		Normal children
	Acute period	Remission	Acute period	Remission	
T-Lymphocytes/%/	39,76 ± 0,82	52,29 ± 1,40*'**	38,14± 0,63	46,38 ± 0,83*	62,33 ±0,91
E-RFC/cells/mcl.	925,1± 55,75	1499,75± 94,4*	864,84± 35,75	1316,59± 62,50*	1768,83± 74,35
TRC E-RFC/%/	33,53± 0,93	37,88± 1,13*	33,23± 0,63	36,83± 0,98*	44,04± 1,08
/cells/mcl	789,52± 51,23	1050,61± 47,92*	741,44± 30,7	1013,92± 49,46*	1244,99 ±52,61
TSC E-RFC /%/	6,0 ±0,15	14,35± 1,40*'**	5,32± 0,26	10,80± 0,55*	18,29± 0,61
/cells/mcl.	135,54± 19,14	448,02 ±50,1**	119,41± 8,44	298,71± 20,57*	523,84± 31.20
TRC	6,29± 0,32	3,0± 0,1*'**	7,27± 0,36	3,90± 0,41*	2,49± 0,12
TSC					
ABL with HBsAg /%/	6,92± 0,65	6,31 ±0,46*	6,81± 0,49	7,44± 0,73*	1,20 ± 0,22
/cells/mcl.	190,64 ±12,65	171,69 ±14,39*	187,4 ±15,1	190,79± 31,33*	39,77± 12,15
B-Lymphocytes/%/	22,41± 0,96	19,23± 0,46*	23,8 ±1,17	20,9± 0,72*	16,42± 0,55
EAC-RFC/cells/mcl.	711,94 ±40,64	567,89± 47,09*'**	774,9± 57,2	713,1± 49*	465,57± 24,22
Ig A mg %	194,6± 11,7	163± 7,3*	207,26 ±4,73	168,78± 4,74*	107,97 ±3,59
Ig G mg %	1882± 81,18	1674,88± 88,58*	1970,81± 105,67	1641,78 ± 29,64*	938,30 ±17,59
Ig M mg %	180,53± 9,90	166,18± 9,71*	185,47± 3,59	146,78 ±4,14*	90,70± 2,80

eters. Their changes had differences only in some parameters throughout the therapy (Table I). Serum asparate aminotransferase /AST/ ($p<0,02$) activity, albumin ($p<0,05$) levels tended to be normalized in children receiving interferon additionally to the complex therapy, although all indices in spite of the treatment didn't achieve the values of normal children. There were more significant differences in the values of cell immunity between treated and untreated groups throughout the interferon therapy (Table II). Evident increase of E-RFC ($p<0,01$), TPS E-RFC ($p<0,05$; $<0,02$) was observed in children from treated group compared with controls. Ratio of theophylline-resistant and theophylline-sensitive lymphocytes and net content of B-lymphocytes in the treatment group were evidently lower ($p<0,05$), than in controls. There were no significant differences in the mean ABL content to HBsAg from the pretreatment levels and between treated and untreated groups throughout the therapy. The absence of change in the levels of antigen-binding lymphocytes to HBsAg is apparently associated with short course of completed treatment schedule. Dynamics of humoral immunity changes didn't differ significantly in two study groups, that is the evidence of different effect of T and B lymphocytes, theophylline-resistant and theophylline-sensitive lymphocytes and the ratio of theophylline-resistant L/theophylline-sensitive L confirm possible immunnomodulatory effect of interferon on the cellular immunity. Perhaps the beneficial therapeutic effects of interferon is associated with its immunomodulatory action on cellular level of immunity. Our observations show that this treatment schedule of interferon didn't influence significantly on the changes of serologic markers of hepatitis B virus. Seroconversion from HBsAg to anti-HBs was found at one case in the treated group, but in control group there were no anti-HBs throughout the therapy. Seroconversion from HBe to anti-HBe was detected at 10% of cases in treated group, and at 5%-in controls. After the interferon therapy there were no differences in the frequency of anti-HBs expression between the two groups. Side effect of interferon therapy was observed as a fever in two children in 3-4 hrs after injection and lasted 2 hrs. Results of our observations, comparisons of clinical, biochemical, immunologic and serologic findings in their dynamics suggested that in chronic active hepatitis B human leukocyte interferon therapy promoted to rapid control of intoxication, to improvement of biochemical and immunologic indices, to shortening of clinical symptom duration and active period of disease consequently. However insufficient clearness in the changes of markers throughout the therapy indicates to insufficient affect of completed treatment regime with α-interferon. Our present study suggests the possible afficacy of higher dose of human leukocyte interferon and longer treatment schedule.

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