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• *RAPID COMMUNICATION* •

Histological outcome of chronic hepatitis B in children treated with interferon alpha

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Abstract

AIM: To evaluate the effect of interferon alpha (IFN-α) treatment on the liver histology in children with chronic hepatitis B and to evaluate the usefulness of various histological scoring systems of liver histology in this group of patients.

METHODS: Fibrosis stage and inflammation grade were assessed according to Batts and Ludwig, Ishak *et al*, and METAVIR (only fibrosis stage) before and 12 mo after IFN-α treatment termination in 93 children aged 2-16 years with chronic hepatitis B.

RESULTS: None of the three numerical scoring systems for liver fibrosis showed statistically significant differences in liver fibrosis, while evolution of inflammatory activity revealed statistically significant improvement in the whole group of children with chronic hepatitis B treated with IFN-α and in responders. Significantly positive correlations were found between fibrosis stage and inflammation grade in the respective scoring systems.

CONCLUSION: Treatment with IFN-α did not improve histological fibrosis but decreased inflammatory activity in children with chronic hepatitis B. The three semiquantitative scoring systems seem to be comparable in the estimation of the inflammation grade and fibrosis stage in this group of children.

Key words: Children; Chronic hepatitis B; Interferon alpha; Fibrosis stage, Inflammation grade; Semiquantitative scoring systems

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INTRODUCTION

Interferon alpha (IFN-α) is currently used as a standard treatment for chronic hepatitis B in children. According to Bortolotti[1], the clearance of HBeAg and HBV DNA from serum, normalization of serum ALT activity and improvement of liver histology within 12 mo after treatment discontinuation are considered as the most important endpoints in therapy efficacy evaluation.

Several semiquantitative histological scoring systems have been used in the morphological evaluation of chronic viral hepatitis. The most widely used are the scoring systems according to Ishak *et al*[2], Batts and Ludwig[3], Desmet *et al*[4] and METAVIR[5], which is contrary to the scale proposed by Knodell *et al*[6], definitely separate inflammation grade from fibrosis stage.

The aim of the study was to evaluate the effect of IFN-α treatment on liver histology in children with chronic hepatitis B and to assess the usefulness of different scoring systems of liver histology in pediatric patients. This is the first morphological analysis using different histological semiquantitative scoring systems performed on such a large material obtained from children.

MATERIALS AND METHODS

Patients

The study was carried out prospectively on 93 consecutive children (range 2-16 years, mean age 7.1 years; 69 boys and 24 girls) with biopsy-verified chronic hepatitis B (HBs/+/, HBe/+/, DNA/+/ for at least 12 mo; mean 39±27 mo). Mean ALT activity was 95±79 IU/L. Patients with diagnosed autoimmune hepatitis, liver cirrhosis or HCV coinfection were excluded from the study. None of the children were treated with antiviral or immunomodulating drugs during the 12-mo period before entering the study. IFN-α was applied in the dose of 3 MU thrice a week subcutaneously for 20 wk (this schedule is accepted for children in Poland by Polish Interferon Study Group[7]). The presence of HBeAg/antiHBe seroconversion 1 year after therapy discontinuation was considered to be the criterion of treatment efficacy. Informed consent was obtained from all parents of the patients. The study protocol was approved by the local ethical committee.

Table 1 Morphological evaluation of liver biopsies in children with chronic hepatitis B treated with IFN-α (*n* = 93)

Scoring system	Baseline biopsy	Final biopsy
Batts grade	1.516±0.619	1.312±0.51[a]
Batts stage	1.892±0.598	1.839±0.631
Ishak grade	4.054±1.683	3.344±1.514[b]
Ishak stage	2.462±1.006	2.398±1.034
METAVIR stage	1.667±0.712	1.645±0.702

[a]$P<0.05$ *vs* baseline biopsy; [b]$P<0.01$ *vs* baseline biopsy.

Table 2 Morphological evaluation of liver biopsies in children with chronic hepatitis B treated with IFN-α in the subgroups of responders (*n* = 35) and nonresponders (*n* = 58)

Scoring system	Subgroups	Baseline biopsy	Final biopsy
Batts grade	Nonresponders	1.431±0.596	1.379±0.524
	Responders	1.657±0.639	1.2±0.473[b]
Batts stage	Nonresponders	1.793±0.554	1.81±0.606
	Responders	2.057±0.639	1.886±0.676
Ishak grade	Nonresponders	3.81±1.503	3.43±1.403
	Responders	4.457±1.899	3.2±1.694[b]
Ishak stage	Nonresponders	2.293±0.878	2.431±0.901
	Responders	2.743±1.146	2.343±1.255
METAVIR stage	Nonresponders	1.62±0.644	1.638±0.667
	Responders	1.743±0.816	1.657±0.764

[b]$P<0.01$ *vs* baseline biopsy.

Table 3 Correlations between staging and grading according different histological scoring systems

Scoring system	Batts grade	Batts stage	Ishak grade	Ishak stage	METAVIR stage
Batts grade	-	$r = 0.385$ $P = 0.00014$	$r = 0.825$ $P = 0.0000001$	$r = 0.392$ $P = 0.0001$	$r = 0.405$ $P = 0.00005$
Batts stage	$r = 0.385$ $P = 0.00014$	-	$r = 0.522$ $P = 0.0000001$	$r = 0.713$ $P = 0.0000001$	$r = 0.713$ $P = 0.0000001$
Ishak grade	$r = 0.825$ $P = 0.0000001$	$r = 0.522$ $P = 0.0000001$	-	$r = 0.409$ $P = 0.000045$	$r = 0.41$ $P = 0.000045$
Ishak stage	$r = 0.392$ $P = 0.0001$	$r = 0.713$ $P = 0.0000001$	$r = 0.409$ $P = 0.000045$	-	$r = 0.758$ $P = 0.0000001$
METAVIR stage	$r = 0.405$ $P = 0.00005$	$r = 0.713$ $P = 0.0000001$	$r = 0.41$ $P = 0.000045$	$r = 0.758$ $P = 0.0000001$	-

Histological analysis

The percutaneous liver biopsies were obtained immediately before the treatment and 12 mo after the end of the IFN-α treatment. The liver biopsies were fixed in 10% buffered formalin and embedded in paraffin. Four-micrometer histological sections were prepared and stained with hematoxylin and eosin, Masson's trichrome, Masson's-Goldner and reticulin stain. Fibrosis stage and inflammation grade were assessed in a blinded fashion by a single pathologist according to Batts and Ludwig[3] and Ishak *et al*[2]; METAVIR scoring system[5] was additionally used for assessing only fibrosis.

Statistical analysis

The results were expressed as mean±SD. Differences in the respective groups were analyzed using Wilcoxon's test for pairs. Spearman's correlation coefficient was used to define correlations between the examined scoring systems. Differences were considered statistically significant at $P<0.05$.

RESULTS

Table 1 shows the results of morphological evaluation of hepatic inflammation and fibrosis in children with chronic hepatitis B prior to the IFN-α treatment (baseline biopsy) and 12 mo after IFN-α therapy discontinuation (final biopsy).

There was a significant improvement of histological inflammation both in the system of Batts and Ludwig ($P = 0.039$) and Ishak *et al* ($P = 0.0019$). However, there were no significant differences in liver fibrosis of the three semiquantitative scoring systems used.

HBeAg/antiHBe seroconversion 12 mo after therapy termination was observed in 38% of treated children. Therefore, two subgroups were distinguished: responders (35 children) and nonresponders (58 children).

The results of morphological examinations of liver biopsy before the treatment in both subgroups showed more severe intensification (although statistically insignificant) of the inflammation grade and the stage of fibrosis in the subgroup of responders. There was significant improvement of histological inflammation only in the subgroup of responders ($P = 0.0058$ according to Batts and Ludwig; $P = 0.0039$ according to Ishak *et al*), but there were no significant changes in liver fibrosis in either subgroup according to the three respective scoring systems (Table 2).

Significantly positive correlations were found between fibrosis stage and inflammation grade in the respective systems (Table 3).

DISCUSSION

The improvement of liver morphology evaluated not earlier than 12 mo after treatment discontinuation in

comparison to the baseline biopsy is one of the criteria of IFN-α therapy efficacy.

The comparison of three histological scoring systems used to evaluate chronic hepatitis in children with HBV infection revealed a high coefficient of positive correlation between the respective scales. Thus, the systems seem comparable in the estimation of the inflammation grade and stage of fibrosis in children and therefore they can be used according to the preferences of a hepatological center. In adults, Rozario and Ramakrishna[8] were in agreement with our results; they concluded that concordance between Ishak and METAVIR scoring systems was good for necroinflammatory change and excellent for fibrotic change. We also showed a close correlation between liver fibrosis and inflammatory activity, which is in agreement with Lu *et al*[9]. Assy and Minuk[10] also confirmed good correlation between the previously and currently used histological assessment of chronic hepatitis, according to the International Group[11] and Desmet *et al*[4]. As no comparative analysis of the above systems in children have been known to the authors, the current study may inspire further analysis performed on a large group of patients in order to make up the standard morphological estimation of liver biopsy in childhood.

We found no significant changes in the stage of liver fibrosis in children with chronic hepatitis B, neither in responders nor in nonresponders to IFN-α, while a statistically significant decrease was noted in the intensification of necrotic-inflammatory process in the whole group and in the subgroup of responders.

The inhibition of HBV replication was most widely discussed in the previous reports on the treatment of HBV infections in children[12,13]. Considerably less attention was paid to the changes in the morphological picture of liver biopsy after antiviral therapy (changes in necrotic-inflammatory process intensification were mainly evaluated); single reports discuss the changes of liver fibrosis. So far, a statistically significant decrease has been reported in the inflammation grade[14-20], which is in agreement with our analysis. In literature, the reduction in inflammatory activity in IFN-α treated children is estimated at 80%[16,17].

Only a few studies in the world literature analyze the effect of IFN-α therapy on the stage of fibrosis in children with chronic hepatitis B. Most authors did not show improvement of the stage of liver fibrosis caused by antiviral treatment[14,20,21]. Gregorio *et al*[15] found significant improvement only in staging in the responders. But these trials included a relatively small number of liver biopsies. Further studies by Ruiz Moreno *et al*[19] were conducted on a representative group of 60 children with chronic hepatitis B treated with IFN-α, who underwent two liver biopsies (baseline and final). They found that when biopsies were obtained within 12 mo after HBeAg clearance, the degree of histological fibrosis was significantly higher than that seen in biopsies taken after 12 mo. These data seem to indicate that in order to achieve a reliable evaluation of final hepatic fibrosis, histological examination should be performed not earlier than 12 mo after HBeAg/antiHBe seroconversion. In the present study, the liver biopsies were taken not earlier than after 12 mo of IFN-α therapy discontinuation, as this length of time seems sufficient to evaluate the therapy efficacy determined by histopathological analyses.

Studies conducted on the population of adults with chronic hepatitis B and C also do not provide a satisfactory answer to the question whether IFN-α treatment reduces the stage of liver fibrosis. Many authors have shown no significant changes of liver fibrosis due to this cytokine[22-24]; others, however, have proved a beneficial effect of IFN-α therapy on the reduction of the stage of fibrosis[25-29], particularly in responders[30-32]. Yet, they all underline the effect of IFN-α on the reduction of inflammation grade. The analysis of natural history of HBV infection shows that the inflammatory process in the liver is a triggering mechanism preceding fibrosis. It also seems that the IFN-α-induced reduction in fibrosis is preceded by the regression of inflammatory activity. Considerable divergence in the evaluation of the effect of IFN-α on fibrotic lesions in the liver of patients with chronic viral hepatitis seems to suggest that longer observation period (a few years) prior to the final biopsy is necessary to properly evaluate therapy-induced changes in fibrotic processes.

In conclusion, the treatment with IFN-α did not improve histological fibrosis but decreased inflammatory activity in children with chronic hepatitis B. The various semiquantitative histological scoring systems seem to be comparable in the estimation of the inflammation grade and fibrosis stage in this group of children.

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