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World J Gastroenterol 2006 September 28; 12(36): 5787-5792
World Journal of Gastroenterology ISSN 1007-9327

Prevalence of autoantibodies and the risk of autoimmune thyroid disease in children with chronic hepatitis C virus infection treated with interferon-α

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Received: 2006-06-06 Accepted: 2006-08-14

Abstract

AIM: To evaluate the prevalence of autoantibodies in chronic hepatitis C virus (HCV)-infected children focusing on thyroid autoimmunity.

METHODS: We investigated the prevalence of autoantibodies in 123 chronic HCV-infected children before, during and after monotherapy with interferon-alpha (IFN-α) or combined treatment with interferon-α or peginterferon-α and ribavirin. Besides antibodies against smooth muscle (SMA), nuclei (ANA), and liver/kidney microsomes (LKM), the incidence of anti-thyroid peroxidase antibodies as well as thyroid function parameters (TSH, FT3 and FT4) were determined.

RESULTS: We found that 8% of children had autoantibodies before treatment. During treatment, 18% of children were found positive for at least one autoantibody; 15.5% of children developed pathologic thyroid values during IFN-α treatment compared to only one child before therapy. Six children had to be substituted while developing laboratory signs of hypothyroidism.

CONCLUSION: Our data indicate a strong correlation between interferon-α treatment and autoimmune phenomena, notably the emergence of thyroid antibodies. The fact that some children required hormone replacement underlines the need of close monitoring in particularly those who respond to therapy and have to be treated for more than 6 mo.

Key words: Hepatitis C treatment; Children; Thyroid dysfunction; Autoantibodies

Gehring S, Kullmer U, Koeppelmann S, Gerner P, Wintermeyer P, Wirth S. Prevalence of autoantibodies and the risk of autoimmune thyroid disease in children with chronic hepatitis C virus infection treated with interferon-α. *World J Gastroenterol* 2006; 12(36): 5787-5792

http://www.wjgnet.com/1007-9327/12/5787.asp

INTRODUCTION

Since the discovery of the hepatitis C virus (HCV) in 1989[1], an increasing number of studies report an association of chronic HCV infection with autoimmune phenomena. In studies among adult patients, the prevalence of autoantibodies in chronic HCV-infected patients varies from 25% to 66%[2-5]. The most commonly detected autoantibodies are anti-smooth muscle antibodies (SMA), followed by anti-nuclear antibodies (ANA), and anti-liver/kidney microsomal antibodies (LKM). The latter have been associated with ALT flares during interferon-alpha (IFN-α) administration, leading to discontinuation of treatment[6]. The non-organ-specific autoantibodies (NOSA) ANA, SMA and LKM detected during chronic HCV infection are also found in patients with autoimmune hepatitis (AIH). A discrimination of HCV-related appearance of autoantibodies and AIH is usually possible based on the detection of viral RNA, the subtype of the examined autoantibodies, histology and response to treatment[4,7]. In rare occasions, an overlapping clinical and histological pattern of chronic HCV and AIH is found. In these cases, a careful assessment of either an immunosuppressive or anti-viral therapeutic approach is necessary[8].

Various studies in adult patients addressed the question of whether the presence of NOSA in chronic HCV infection influences the response to IFN-α treatment. NOSA detection correlates with significantly higher ALT levels and higher histological activity[3,4]. The majority of studies did not observe any effects of NOSA on the final outcome of treatment[4-6]. The limitation of most of these

studies is that they only deal with IFN-α monotherapy. A very recent study investigating the effects of NOSA in patients receiving combined treatment not only detected a significantly higher viral load and higher ALT levels, but also observed a poorer response to treatment[2]. Besides the detection of autoantibodies, the natural course of HCV infection is accompanied by an increased prevalence of autoimmune diseases[9,10].

One of the most common phenomena in chronic HCV infection is the appearance of autoantibodies against the thyroid[11-15]. A significant percentage of patients with anti-thyroid antibodies develop signs of thyroid dysfunction, predominantly hypothyroidism[12]. Several studies observed that IFN-α treatment increased the risk of thyroid dysfunction[13-15], whereas in most cases, thyroid dysfunction is reversed after discontinuation of IFN-α treatment. A recent study by Carella *et al*[16] observed the development of long-term thyroiditis following IFN-α therapy. It is important to note that IFN-α treatment itself is associated with autoimmune manifestations[17]. These are not only observed in the context of HCV treatment, but also when IFN-α is used as a therapeutic agent in various oncologic diseases[18].

The prevalences of autoantibodies and risk to develop autoimmune diseases in children and adolescents with chronic HCV have only been investigated in three pediatric cohorts[7,19-21]. These studies have in common that they: (1) analyzed intensively the overall prevalence of autoantibodies in HCV-infected children; (2) correlated autoantibody appearance with IFN-α monotherapy; and (3) investigated the response of LKM-positive children to IFN-α treatment. However, they did not elucidate the emergence of NOSA and thyroid autoantibodies under combination treatment.

Based on our experience with children requiring thyroid hormone replacement during treatment for chronic HCV, a systematic surveillance is needed in order to avoid harmful clinical side effects.

We therefore aimed to investigate the prevalence and dynamics of the appearance of autoantibodies in our cohort of HCV-positive children that underwent IFN-α treatment with and without ribavirin, to analyze the risk of chronically HCV-infected children to develop clinical or laboratory signs of thyroid dysfunction, and to obtain follow-up data after ceasing therapy.

MATERIALS AND METHODS

Patients

We evaluated a total of 123 children with chronic HCV infection who underwent IFN-α treatment. The diagnosis of chronic hepatitis C was based on: (1) presence of abnormal alanine aminotransferase (ALT) levels; (2) detection of anti-HCV antibodies; (3) detection of HCV-RNA over a period of at least 6 mo; and (4) histological evidence of hepatitis in patients with available liver biopsy. None of the patients had serological evidence of co-infection with hepatitis B, delta hepatitis, HIV, or clinical signs of an autoimmune disease prior to treatment with IFN-α. After interferon first became available for treatment of children, 21 children were treated with IFN-α alone. Additionally, 102 chronically HCV-infected children received combined treatment of IFN-α or peginterferon-α and ribavirin[22,23]. Forty nine percent of the children were male. The predominant route of infection for the interferon-monotherapy treatment group was parenteral (57%), whereas, for the combined treatment group, parenteral and vertical infections were almost the same (41% *vs* 45%). The age ranged between 2-17 years at the beginning of treatment with a median age of approximately 9 years. The average time between diagnosis and start of treatment was 2.5 years (Table 1).

Table 1 Epidemiological, clinical, and biochemical baseline data for HCV-infected patients who underwent either IFN-α monotherapy or combined therapy with IFN-α or peginterferon-α plus ribavirin

	IFN-α (*n* = 21)	IFN-α + ribavirin (*n* = 40)	Peginterferon-α + ribavirin (*n* = 62)
Male/female (*n*)	12/9	19/21	29/33
Median age, yr (range)	9.5 (2-17)	8.1 (2-16)	10.6 (2-17)
Route of infection, *n* (%)			
Parenteral	12 (57%)	14 (35%)	28 (45.1%)
Vertical	9 (43%)	21 (52.5%)	25 (40.3%)
Unknown	-	5 (12.5%)	9 (14.6%)
Median time between diagnosis and treatment, yr (range)	2.8 (1-9)	2.5 (1-5)	Not determined
Response to treatment, *n* (%)			
Sustained	6 (29%)	24 (60%)	36 (59%)
Transient	3 (14%)	1 (2.5%)	7 (11%)
No response	12 (57%)	15 (37.5%)	19 (30%)
Median ALT level (U/L) (range)			
Before treatment	39 (13-386)	35.5 (7-90)	41.6 (11-293)
After treatment (24 mo)	35 (9-137)	22.1 (6-104)	23.1 (7-71)

Treatment

In addition to those mentioned above, inclusion criteria for treatment of chronic HCV infection were normal values for hemoglobin, platelets, white blood cells, bilirubin, glucose, and serum creatinine. Criteria for exclusion were underlying systemic disease, metabolic liver disorders, prior immune suppressive therapy, and severe neurologic impairment. The parents of each patient gave written consent and the University Ethics Committee approved the studies.

Children treated with IFN-α received recombinant 5 mU IFN-α-2b/m^2 of body surface inoculated subcutaneously (sc) 3 times weekly over a period of 12 mo. Children treated with IFN-α combined with ribavirin received the same dose of IFN-α or 1.5 μg/kg peginterferon-α-2b once a week and 15 mg/kg ribavirin twice daily orally over 12 mo. Patients who remained HCV-RNA seropositive 6 mo after the beginning of treatment discontinued therapy. Complete sustained virologic response was defined as normalization of serum aminotransferase levels and undetectable HCV RNA during the course of treatment and persisting during the entire post-therapy follow-up.

Screening for auto-antibodies and thyroid markers

Serum samples were taken at the time of primary

Table 2 Positive[1] autoantibodies in the two treatment groups before, during and 12 mo after treatment

Group		Before treatment			During treatment			After treatment		
	n	LKM[2]	SMA[3]	ANA[4]	LKM[2]	SMA[3]	ANA[4]	LKM[2]	SMA[3]	ANA[4]
IFN-monotherapy	21	1	0	0	2	0	2	1	1	2
IFN /ribavirin-combined treatment	18	0	0	2	0	2	1	0	0	0
Total	39	1	0	2	2	2	3	1	1	**2**

[1]Antibody titer was considered positive at values ⩾ 1:40; [2]Liver kidney microsomal antibody; [3]Anti-smooth muscle antibody; [4]Antinuclear antibody.

diagnosis, before, during and after treatment. During treatment, samples were taken at 3 mo intervals. Antinuclear antibodies (ANA), anti-smooth-muscle antibodies (SMA), and antibodies against liver/kidney microsomes (LKM) were assessed by indirect immunofluorescence (IFL) on cryostat sections of rat liver and kidney specimens. ANA-positive samples were subsequently tested by IFL on Hep-2 cells. Antibody titers ⩾ 1:40 were considered positive. Along with testing auto-antibodies, thyroid function was evaluated by measuring the serum levels of free triiodothyronine (FT3; normal values: 1.8-4.6 ng/L), free thyroxine (FT4; normal values: 0.9-1.7 ng/dL) and thyroid-stimulating hormone (TSH; normal values: 0.3-4.2 mU/L). The sera were analyzed on site using commercially available kits. Furthermore, we determined anti-thyroglobulin antibody (TGA; normal values < 50 U/L) and anti-thyroid peroxidase antibodies (TPO; normal values: < 35 IU/mL) in the samples.

Statistical analysis

Results were analyzed using the SigmaStat 3.0 statistics program (Jandel Scientific, San Raael, CA). When comparing more than two groups, a one-way ANOVA was performed, followed by a Dunn's test to determine which groups differed significantly. $P < 0.05$ was considered statistically significant.

RESULTS

Duration of treatment

Of the 21 children treated with IFN-α-2b monotherapy, 12 (57%) remained HCV-RNA-positive and therefore discontinued after 6 mo, 3 patients showed a transient response with reappearance of viral RNA, and 6 (29%) children had a sustained response. Thus, 9 individuals were treated for 12 mo (Table 1). Forty children were enrolled in the second study that consisted of a combination treatment with IFN-α and ribavirin[22]. Fifty seven percent of the treated children and adolescents displayed a transient or sustained virologic response and were treated for 12 mo. With introduction of peginterferon-α into the combined treatment group, the percentage of children with sustained response remained at a similar level. A total of 39 (63%) individuals were treated for 12 mo[23].

Prevalence of non-organ specific autoantibodies

A total of 39 children had a complete record of their autoantibody status (Table 2). Before treatment, 3 of the 39 (8%) were positive for autoantibodies. One child was positive for LKM and two children were positive for SMA. All measured antibody titers were in a low range between 1:40 and 1:80. None of the children had any apparent signs of autoimmune disease. The child found positive for LKM antibodies had slightly elevated ALT levels (56 U/L) and was closely monitored.

Autoantibodies and interferon treatment

During interferon treatment, there was a significantly higher number of autoantibody-positive children. Altogether, 7 of 39 (18%) children were positive for either LKM, SMA, or ANA. In all cases, the patients were positive for only one of the autoantibodies tested. The antibody titers were higher than that measured before treatment (maximum = 1:320). None of the children had any clinical signs of autoimmune disease, which would cause interferon treatment to be discontinued. Both children, who were LKM-positive, displayed stable ALT levels during treatment. When correlating ALT levels and autoantibody prevalence, we found slightly higher ALT values in autoantibody-positive children (average ALT level 54.5 U/L *vs* 40.9 U/L). Autoantibody prevalence did not correlate with treatment outcome.

Influence of interferon on thyroid function

None of the children with chronic HCV prior to treatment had clinical signs of thyroid dysfunction. Except for two children, all had normal values for TGA, TPO, TSH, FT3, and FT4 (Table 3). In the case of one child, TSH was slightly elevated (5.45 mU/L) without any apparent clinical sign or laboratory value of thyroid dysfunction. The other child had borderline thyroid antibody levels, with an otherwise normal laboratory and clinical evaluation. During treatment, 19 (15.5%) children had at least one pathologic thyroid parameter. When these children were further analyzed, significant increases in serum TPO and TSH levels were observed (Table 4). Of the 14 children that became positive for TPO antibodies, 12 also displayed increased serum TSH values. The increase in TSH was accompanied by a 50% decrease in serum FT3 and a slight decrease in FT4. Because of pathologic thyroid values, 6 children received a weight-adjusted dose of L-thyroxin until completion of treatment. The substitution could be discontinued in 4 cases during the follow-up period. Two children required hormone supplementation 12 mo after the cessation of the ribavirin/IFN-α treatment. Despite significant increases in pathologic thyroid values, the interferon-treated children did not reveal any clinical signs of hypo- or hyperthyroidism upon physical examination.

Table 3 Thyroid function tests in the two treatment groups before, during and 12 mo after treatment

Group		Before treatment				During treatment				After treatment			
	n	TGA[1]	TPOAb[2]	TSH[3]	FT3[4]/FT4[5]	TGA[1]	TPOAb[2]	TSH[3]	FT3[4]/FT4[5]	TGA[1]	TPOAb[2]	TSH[3]	FT3[4]/FT4[5]
IFN-mono-therapy	21	0	0	1	0	3	5	3	0	0	0	0	0
IFN/ribavirin-combined treatment	40	0	0	0	0	5	2	3	1	1	0	0	0
Peginterferon-α + ribavirin	62	ND	1	0	ND	ND	7	6	ND	ND	3	0	ND
Total	123	0	1	1	0	8	14	12	1	1	3	0	0

[1]Thyroglobulin antibody (normal range < 50 U/L); [2]Thyroid peroxidase antibody (normal range < 35 IU/mL); [3]Thyroid-stimulating hormone (normal range 0.3-4.2 mU/L); [4]Free triiodothyronine (normal range: 1.8-4.6 ng/L); [5]Free thyroxine (normal range 7-19 ng/L). ND = not determined.

Table 4 Overview of the thyroid function and auto-antibody titers of the 12 children who developed pathologic values during the course of IFN-α treatment Median (range)

Treatment	TGA[1]	TPOAb[2]	TSH[3]	FT3[4]	FT4[5]
Before	29.0 (9.4-53.0)	3.2 (0-41.0)	2.7 (1.0-5.5)	3.15 (2.1-5.3)	1.2 (1.1-1.3)
During	100.0 (8.0-141.0)	82.5[a] (4-3 909)	7.3[a] (1.7-76.0)	2.12 (1.1-4.3)	1 (0.4-1.3)
After	40.0 (13-163.0)	4.5 (0-289.0)	2.2 (0.9-4.2)	4.0 (2.0-5.3)	1.1 (1.0-1.3)

[a]$P < 0.05$ *vs* before and after treatment. [1]Thyroglobulin antibody (normal range < 50 U/L); [2]Thyroid peroxidase antibody (normal range < 35 IU/mL); [3]Thyroid-stimulating hormone (normal range 0.3-4.2 mU/L); [4]Free triiodothyronine (normal range 1.8-4.6 ng/L); [5]Free thyroxine (normal range 7-19 ng/L).

Comparing the two treatment groups, there were more patients with TPO antibodies in the interferon monotherapy group (23%) than in the combined treatment group (9%). This difference was also apparent, but not as prominent, with regards to pathologic TSH values, which were 14% in the monotherapy group *versus* 10% in the group that underwent combined treatment. Notably, the prevalence of thyroid antibodies increased over the treatment period, particularly in the second half. While only 4.9% of children were positive after 3 mo, 12.8% were positive after 9 mo of medication.

DISCUSSION

In this study, we investigated the prevalence of autoimmune phenomena in chronic HCV-infected children treated in Germany. As we reported recently, over 50% of children and adolescents treated with IFN-α plus ribavirin displayed a sustained virologic response[22,23]. In the present study, we also incorporated HCV-positive children treated solely with IFN-α before the implementation of combination therapy. Concordant with other reports, these children had a sustained response in 29% of all cases[24]. Of the 39 children with complete autoantibody evaluation, 3 (2 ANA/1 LKM) were positive for autoantibodies before treatment. The overall prevalence of non-organ-specific autoantibodies (8%) was significantly lower than that found in the three published pediatric cohorts (32.5%-65%)[7,19,21]. Surprisingly, none of our children was SMA-positive before IFN-α treatment, compared to 17%-67% of the children in the aforementioned studies[7,19,21]. The number of autoantibody-positive children increased to 23% during treatment, which is still significantly lower than previously reported, then dropped to an approximate 10% after treatment completion. In contrast to the other pediatric cohorts, the two patients that were LKM-positive did not develop any significant ALT flare during IFN-α treatment.

Two possible factors might explain the differences observed in autoantibody prevalence: (1) the methodology used and cut-off for positive results, and (2) geographic differences and, therefore, differences in genetic predisposition. Interestingly, all the published pediatric cohorts came from various regions in Italy; the majority of the patients in our cohort were from Germany or Eastern Europe. It is well known that autoimmune diseases are influenced by genetic background and HLA type[25-27]. We compared liver enzyme levels in the sera of autoantibody-positive and -negative children. Average ALT levels were higher in the autoantibody-positive group, though the difference was not statistically significant. This finding correlates with similar observations in pediatric and adult cohorts[4,7]. As in the majority of adult studies, we could not detect any connection between autoantibody appearance and treatment outcome[4-6]. A very recent study in adults observed a better response in autoantibody-negative patients treated with IFN-α plus ribavirin[2]. We did not observe a similar tendency in children that received combined treatment.

To the best of our knowledge, this is the first pediatric study that investigates the correlation between chronic HCV infection and thyroid dysfunction. Before initiation of treatment, all children were euthyroid and only one child had low levels of TPO antibodies. This finding differs significantly from most adult studies, which report 4.8%-21% TPO autoantibody prevalence in their patient cohorts and up to 13% of patients with thyroid dysfunction[11,12,15]. A very recent publication by Mandac *et al*[28] emphasizes again the clinical significance of thyroiditis in patients receiving interferon therapy and suggests the classification as autoimmune type and non-autoimmune type. During the course of IFN-α treatment, 11% of the children became positive for antibody

specific for TPO. The prevalence of TPO antibody was accompanied by a significant increase in TSH levels and a decrease in FT3 values. Six children became hypothyroid and had to be treated. The risk of developing signs of thyroid dysfunction became particularly prominent during the 2nd half of the treatment period. Overall, the number of HCV-infected children with thyroid dysfunction was significantly lower and strongly associated to IFN-α treatment, which is in contrast to adult studies that reported a high prevalence of thyroid dysfunctions even before IFN-α treatment.

In summary, we found a lower prevalence of non-organ-specific, as well as thyroid-specific autoantibodies than reported in related pediatric and adult cohorts. The prevalence of NOSA and thyroid antibodies strongly correlated with IFN-α treatment; six children developed signs of hypothyroidism. Since serum thyroid antibodies and TSH levels increased significantly in the second 6-mo treatment period, some individuals may require thyroid hormone substitution. It must be emphasized that close monitoring of thyroid function is mandatory, especially in children who respond to therapy and have to be treated for more than 6 mo.

ACKNOWLEDGMENTS

We are grateful to Stephen H Gregory (Department of Medicine, Rhode Island Hospital, Providence, RI, USA) for his help in editing this manuscript.

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