

Total Serum IgE Levels in Chronic Hepatitis C: Influence of Interferon Alpha Therapy

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Key Words

IgE · Hepatitis C virus · Interferon- α

Abstract

Background: Liver disease has been considered a prominent cause of IgE elevation. No data on serum IgE levels in chronic hepatitis C have been reported. Interferon- α is a standard therapy for chronic hepatitis C. Cytokine use is a promising type of immunomodulation in the treatment of IgE-mediated diseases. The effects of interferon- α therapy on serum IgE have not been fully evaluated. The aim of the study was to evaluate both serum IgE levels in patients with chronic hepatitis C and the course of these levels after interferon- α therapy. **Patients and Methods:** Serum IgE was determined in 100 adult patients with chronic hepatitis C (24 atopics according to positive skin prick tests and 76 nonatopics) and in 75 healthy controls (25 atopics and 50 nonatopics). Serum IgE measurements were repeated at 1 and 3 months of therapy with recombinant interferon- α (3×10^6 units s.c. 3 times weekly) in 34 of these patients. **Results:** Serum IgE levels were similar in chronic hepatitis C patients and in controls when adjusted for atopic status. Among patients with chronic hepatitis C, serum IgE levels were unrelated to liver necroinflammatory activity. A modest but statistically significant increase of IgE values was

observed after interferon- α therapy, particularly in patients with no virological response. **Conclusions:** Chronic hepatitis C is not a significant cause of increased total serum IgE values. Serum IgE increase in some patients with liver disease may be related to the cause of liver injury and not to liver disease per se. Interferon- α therapy in patients with chronic hepatitis C is followed by no modification or even a moderate increase of serum IgE values.

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Introduction

Liver disease has been considered a prominent cause of IgE elevation [1]. However, significant differences may be observed depending on the cause of liver damage [2, 3]. Serum IgE levels are particularly increased in patients with alcoholic liver disease [2]. For viral hepatitis, increased IgE concentrations have been observed during acute hepatitis A and B [4–6]. Chronic hepatitis B carriers may also have high IgE levels [7]. IgE values in chronic hepatitis of undetermined origin have been reported as either high [8, 9] or normal [4]. The discovery of hepatitis C virus (HCV) in 1989 [10] identified the cause of many liver diseases which until then had been cryptogenic. Most cases of ‘non-A, non-B’ chronic hepatitis are now

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known to be chronic hepatitis C [11]. The average prevalence of chronic hepatitis C is estimated to be 3% (ranging from 0.1 to 5% worldwide) [12]. Most HCV-infected patients develop chronic hepatitis and 20% will proceed to cirrhosis [12]. HCV is, therefore, one of the leading causes of chronic liver disease. To our knowledge, there are no studies focused on serum IgE levels in chronic hepatitis C.

Interferon- α (IFN- α), a cytokine with antiviral, anti-proliferative and immunomodulatory properties [13], is a standard therapy for chronic hepatitis C [12]. In vitro, IFN- α is not only a potent IL-12 inducer but can switch Th cells from a Th2 to a Th1 profile [14–16], therefore decreasing IgE synthesis [17]. IFN- α inhibits gene expression of IL-13, a cytokine implicated in IgE synthesis [18]. Influencing the profile of cytokines could be a useful strategy for the treatment of immune diseases [13], including IgE-mediated disorders. In small series of patients, IFN- α therapy offered conflicting results concerning both the reduction of serum IgE levels and the clinical improvement of atopic diseases [19–28]. The effect of IFN- α on IgE levels in nonatopic adult patients has not been tested.

The present study was aimed to evaluate both serum IgE levels in chronic hepatitis C and the influence of IFN- α therapy on IgE values in these cases.

Patients, Materials and Methods

Characteristics of Patients and Controls

One hundred consecutive patients with chronic hepatitis C (80 males and 20 females, median age 34 years, range 21–67 years), studied in our department between June 1998 and August 1999, were included. All had histologically proven chronic hepatitis, positive serum HCV antibodies (Abbott EIA, Abbott, USA) and positive serum HCV-RNA by PCR (Cobas Amplicor HCV, Roche Diagnostic Systems, USA). The route of HCV transmission was blood transfusion in 4 cases (4%), unknown in 26 cases (26%) and prior intravenous drug use (IDU) in 70 cases (70%). A total of 83 patients (83%) were smokers, the rate being particularly high among ex-IDUs (67 out of 70 cases, 96%). Knodell's numerical scoring system was used to assess the histological activity of chronic hepatitis (periportal necrosis, intralobular necrosis, portal inflammation and fibrosis) [29]. Patients who had previously received antiviral therapy were excluded. Global liver function, reflected by prothrombin (Quick's) index and serum bilirubin, was normal or near-normal in all cases (table 1). Other causes of liver disease, particularly active hepatitis B virus (HBV) infection, autoimmunity and alcohol abuse, were excluded. Seventy-five patients (75%, 52 of them ex-IDUs) had serologic markers of past HBV infection (serum HBV core antibody with or without HBV surface antibody – IMx Abbott, Abbott, USA). Patients were neither HIV-infected nor current IDUs.

Table 1. Parameters of liver function and histological activity in the 100 patients with chronic hepatitis C, and their Spearman's rank correlation with IgE values

	Median	Correlation index with serum IgE
Serum bilirubin, mg/dl	0.6 (0.2–1.8)	–0.116
Prothrombin index, %	100 (63–100)	0.016
Serum albumin, g/dl	4.9 (3.5–5.7)	0.137
Serum ALT, U/l	76 (13–660)	–0.079
Serum AST, U/l	37 (11–221)	–0.026
Serum GGT, U/l	30 (9–461)	–0.060
Knodell score	7 (2–16)	–0.204
Periportal necrosis	1 (0–6)	–0.045
Intralobular necrosis	1 (0–4)	–0.216
Portal inflammation	3 (1–4)	–0.123
Fibrosis	1 (0–3)	0.010

Figures in parentheses represent range. Upper normal levels of serum ALT, AST and GGT are 29, 28 and 32 U/l, respectively. No correlation is statistically significant.

Seventy-five healthy HCV-negative volunteers (hospital staff and medical students) of a similar age (median 28 years, range 18–70 years) and gender distribution (61 males, 81% and 14 females, 19%) as HCV-infected patients were used as controls. Forty-five controls (59%) were smokers.

Patients and controls underwent an allergologic evaluation, including skin prick tests against aeroallergens (*Dermatophagoides pteronyssinus*, *Lolium perenne*, *Plantago lanceolata*, *Betula alba*, *Parietaria judaica*, dog and cat dander – ALK-Abelló, Spain). Standard technique and positivity criteria were used [30]. Cases with one or more positive skin prick tests were classified as atopic regardless of symptoms of disease. In our sample, 24 patients (24%) and 25 controls (33%) were atopic. *D. pteronyssinus* sensitization was present in 22 (92%) atopic patients and 20 (80%) atopic controls. Among atopics, 19 patients (79%) and 18 controls (69%) were entirely asymptomatic, the remainder being only mildly symptomatic, without pharmacologic therapy or current or previous specific immunotherapy. Evidence of parasitic infestation was absent in both patients and controls.

Total Serum IgE and Biochemical Assays

Total serum IgE was determined by chemiluminescent enzyme immunoassay (Immulite, Diagnostic Products, USA). Normal reference values for IgE are 0–170 IU/ml. Routine serum biochemical parameters were measured in a Hitachi 747 autoanalyzer (Boehringer-Mannheim, Germany).

Study Protocol

Informed consent for participating in the study was obtained in all cases. Baseline serum IgE was determined in both patients and controls. Atopic status was unknown prior to the inclusion in the study. A total of 42 patients began treatment with IFN- α during the study period. In accordance with our therapy protocol for chronic hepatitis C, they received 3 million units of recombinant IFN- α sub-

Table 2. Total serum IgE (IU/ml) in patients with chronic hepatitis C and healthy controls

	Chronic hepatitis C	Healthy controls	p value
All cases	52 (2–1,200) (n = 100)	43 (3–4,227) (n = 75)	0.65
Atopics	220 (27–1,200) (n = 24)	138 (28–4,227) (n = 25)	0.56
Nonatopics	35 (2–550) (n = 76)	30 (3–376) (n = 50)	0.22

Data are represented as median with the range in parentheses.

Table 3. Evolution of total serum IgE (IU/ml) in patients treated with IFN- α

	Baseline	1st month	3rd month
All cases (n = 34)	62 (2–1,200)	69 (1–1,450)*	84.5 (2–1,390)**
Atopics (n = 10)	155 (41–1,200)	181 (39–1,450)	164.5 (44–1,390)*
Nonatopics (n = 24)	43.5 (2–135)	54.5 (1–148)*	46 (2–149)*
Treated with IFN- α -2a (n = 13)	108 (2–1,200)	105 (1–1,450)	132 (2–1,390)*
Treated with IFN- α -2b (n = 21)	59 (2–166)	63 (2–188)**	75 (2–238)*
Responders (n = 20)	62 (2–1,200)	64.5 (1–1,450)	69 (2–1,390)
Nonresponders (n = 14)	73.5 (6–500)	97.5 (4–490)*	105.5 (5–760)**

Data are represented as median with the range in parentheses. Responders: patients with negative serum HCV-RNA at the 3rd month of IFN- α therapy. * $p < 0.05$; ** $p < 0.005$ vs. baseline values.

cutaneously 3 times per week. The treatment was maintained for 3 months unless serious toxicity occurred. Afterwards, HCV-RNA was tested in serum. If positive, the patient was considered a nonresponder and IFN- α therapy was interrupted. If negative, therapy was continued for up to 12 months. Thirty-four patients (10 atopics and 24 nonatopics), aged 25–51 years, completed at least 3 months of therapy with either IFN- α -2a (RoferonTM, Roche, Spain, 13 cases) or IFN- α -2b (IntronaTM, Schering Plough, Spain, 21 cases). The remainder either dropped out or were withdrawn from therapy because of significant side effects. Three patients received ribavirin (1,000 mg/day p.o.) along with IFN- α . A serum sample for IgE assay was obtained at 1 and 3 months of treatment in these 34 cases.

Statistical Analysis

The majority of numerical variables did not fulfil criteria of normality in the Kolmogorof test. They were, therefore, expressed as median and range, and nonparametric tests (Mann-Whitney U test for unpaired data, Wilcoxon test for paired data, and Spearman's rank correlation) were used to analyze them. All tests were two-tailed. A p value of less than 0.05 was considered significant.

Results

Total Serum IgE in Chronic Hepatitis C

Total serum IgE levels were similar in patients with chronic hepatitis C and healthy volunteers, both among atopic and among nonatopic patients (table 2). Among

patients with chronic hepatitis C, no correlation was observed between serum IgE values and either parameters of liver function or liver necroinflammatory activity (table 1). Total serum IgE levels were similar in patients with or without past HBV infection, either in atopics (median 213 IU/ml and range 41–1,200 IU/ml vs. median 237 IU/ml and range 27–509 IU/ml, $p = 0.90$), or in nonatopics (median 34 IU/ml and range 2–192 IU/ml vs. median 46 IU/ml and range 5–550 IU/ml, $p = 0.39$). IgE levels were also similar in patients with or without a past history of IDU, either among atopics (median 220 IU/ml and range 27–1,200 IU/ml vs. median 227 IU/ml and range 41–500 IU/ml, $p = 0.93$) or among nonatopics (median 35 IU/ml and range 2–467 IU/ml vs. median 30 IU/ml and range 4–550 IU/ml, $p = 0.80$).

Influence of IFN- α Therapy on IgE Levels

A modest but statistically significant IgE increase was observed in HCV-infected patients treated with IFN- α (table 3). Twenty patients (59%) had a virological response to IFN- α at the 3rd month. Serum transaminases became normal in all patients with a virological response. No significant IgE change was observed in patients who responded to IFN- α , whereas a significant IgE increase was observed in nonresponders. Changes in IgE values

after IFN- α treatment were similar in both atopic and nonatopics. IgE elevation was similar in cases treated with IFN- α -2a or IFN- α -2b (table 3). No modifications of clinical symptoms of IgE-mediated diseases were observed throughout the study period.

Discussion

According to the results presented, chronic hepatitis C is not a prominent cause of increased serum IgE values. Many HCV-infected patients were ex-IDUs and the proportion of smokers in this group was higher than in controls. IDU [31] and smoking [32] are associated with increased IgE levels. Despite this, serum IgE values were similar in patients and controls when adjusting by atopic status. Furthermore, cessation of HCV replication and normalization of serum transaminases in patients responding to IFN- α therapy was not followed by a decrease of serum IgE levels. Serum IgE values were unrelated to parameters of liver damage in HCV-infected cases. In contrast to previous reports [33], IgE levels were similar in cases with and without serologic markers of past HBV infection.

Several features indicate that liver damage is not always associated with increased IgE levels, as previously suggested [1]. In this series, chronic hepatitis C was not associated with IgE increase. Serum IgE levels are commonly increased in patients with alcoholic cirrhosis, but not in cases of liver cirrhosis of a different origin [2, 3]. Serum IgE increase in alcoholics is unrelated to the severity of liver dysfunction [2, 34–36]. Moreover, low IgE levels have been observed in primary biliary cirrhosis [3]. As a whole, these data suggest that the cause of liver disease and not liver disease per se may underly IgE increase. Cytokine imbalance induced by ethanol could be the cause of increased serum IgE levels in alcoholics [35]. In contrast, primary biliary cirrhosis is characterized by a predominant Th1 response [37], which could explain the low IgE levels observed in this disease.

Viral infections can change immune function [38]. IgE elevation in patients with HIV infection is associated with enhanced Th2 cytokine production [39]. Similarly, elevated IgE levels are observed during Epstein-Barr virus-induced infectious mononucleosis [40], measles [41], respiratory infections [42, 43], and hepatitis A or B [4–6]. In our experience, this is not the case for chronic hepatitis C. Increased intrahepatic expression of Th1-type cytokines and decreased expression of Th2-type cytokines are observed in chronic hepatitis C [44, 45]. Conversely, in

chronic hepatitis B intrahepatic T cells are Th0-like, capable of producing IL-4 [44]. Theoretically, IFN- α therapy for chronic HCV infection could decrease IgE synthesis. IFN- α shares properties with IFN- γ , a potent inhibitor of IgE synthesis [14, 15, 17]. IFN- γ therapy can improve severe atopic dermatitis and decrease IgE levels in these cases [46]. IFN- α favors Th1 responses [14–18]. In patients with chronic hepatitis C, IFN- α diminishes the Th2 cytokine (IL-4 and IL-10) response [47]. To our knowledge, the present study is the largest series focused on serum IgE changes after IFN- α therapy. Recombinant IFN- α (either 2a or 2b) at a dose of 3 million units administered subcutaneously 3 times weekly for 3 months induced either no change or even a modest increase in total serum IgE levels, both in atopic and nonatopic adult HCV-infected individuals.

Previous studies of the effect of IFN- α on atopic diseases and serum IgE levels gave conflicting results [19–28] (table 4). The cause of this discrepancy is not clear but could be related to differences in the age of the patients studied, the associated diseases, the dose administered, and the type of IFN- α used. Clinical response to IFN- α in atopic dermatitis or hyper-IgE syndrome ranged from marked improvement [19–21] to moderate benefit [22–24], no change [25, 27] or even worsening [26] of skin lesions. The most striking improvement was reported by Kimata et al. [21] after administration of large doses of natural IFN- α therapy to children. The type of IFN- α was not stated in the studies of Souillet et al. [20] and Pung et al. [19], which also reported a marked improvement in patients with atopic dermatitis and/or hyper-IgE syndrome. In the studies of Kimata et al. [21] and Souillet et al. [20], a significant decrease in serum IgE levels was reported. Conversely, all studies using recombinant IFN- α uniformly showed either moderate transient benefit or no effect of IFN- α on atopic diseases, along with no significant change of serum IgE levels [22, 23, 25–28] (table 4). It is important to consider that IFN- α are actually a family of 13 closely related cytokines with different immunomodulatory properties [48, 49]. The so-called natural IFNs are obtained from cultures of virus-infected cells and, therefore, contain a mixture of IFN- α molecules, in contrast to recombinant INF- α [50]. Further studies are needed to compare the effect of natural and recombinant IFN- α on IgE synthesis. Until now, no study has reported an IgE increase during IFN- α therapy. It should be noted that our series is larger, and a significant increase might become apparent when there is an increase in the number of patients under study. IgE elevation was similar in both atopics and nonatopics. However, IgE increase was only

Table 4. In vivo effects of IFN- α therapy on atopic diseases and serum IgE levels; review of the English literature

Reference	Cases	Age years	Atopic disease	IFN- α type	IFN- α dose	Improvement of disease	Effect on serum IgE
20	1	17	Hyper-IgE	NS	3 MU b.i.w.	Marked	Decrease
21	5	8–13	AD ^a	Natural	3–6 MU/day	Marked	Decrease
19	2	2–22	AD	NS ^b	0.5–3 MU/m ² t.i.w.	Marked	NS
22	9	18–39	AD	r-2a	3 MU/day	Moderate	No change
23	13	18–31	AD	r-2a	3 MU t.i.w.	Variable	No change
24	7	22–35	AD	r-2b	3 MU t.i.w.	Transient	Decrease
25	8	22–39	AD	r-2b	3–9 MU t.i.w.	No	No change
26	8	20–44	AD	r-2b	9–15 MU/week	No	No change
27	2	24–41	AD	NS	3 MU t.i.w.	No	No change
28	4	4–11	Asthma	r-2a	2 MU t.i.w.	No	No change
Present study	34	25–51	No ^c	r-2a/r-2b	3 MU t.i.w.	–	No change or increase

AD = atopic dermatitis; NS = not stated; r-2a = recombinant IFN- α -2a; r-2b = recombinant IFN- α -2b; b.i.w. = twice per week; t.i.w. = 3 times per week; MU = million units.

^a Atopic dermatitis was associated with chronic myeloid leukemia in one case, with HBV infection in two cases, and with HCV infection in two cases.

^b Following prior therapy with IFN- γ .

^c Patients with HCV infection; 20 were nonatopics, and 14 were either asymptomatic or mildly symptomatic atopics.

significant in patients without virological response to IFN- α . In responders to IFN- α , no IgE change was observed. This is an intriguing phenomenon for which we have no explanation. Anti-IFN-neutralizing antibodies can be found in healthy people [51] and may develop under IFN therapy, this being a reason for treatment fail-

ure [52]. Anti-IFN antibodies were not determined in the present study but are unlikely to account for the variation of IgE levels as they are usually of the IgG and not of the IgE class [52]. Further studies are needed to clarify the different in vivo immunomodulatory responses to IFN- α therapy.

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