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• VIRAL HEPATITIS •

Gastric autoimmune disorders in patients with chronic hepatitis C before, during and after interferon-alpha therapy

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Abstract

AIM: To explore the prevalence of autoimmune gastritis in chronic hepatitis C virus (HCV) patients and the influence of α-interferon (IFN) treatment on autoimmune gastritis.

METHODS: We performed a prospective study on 189 patients with positive anti-HCV and viral RNA enrolled in a 12-month IFN protocol. We evaluated: a) the baseline prevalence of autoimmune gastritis, b) the impact of IFN treatment on development of biochemical signs of autoimmune gastritis (at 3, 6 and 12 months), c) the evolution after IFN withdrawal (12 months) in terms of anti-gastric-parietal-cell antibodies (APCA), gastrin, anti-thyroid, and anti-non-organ-specific antibodies.

RESULTS: APCA positivity and 3-fold gastrin levels were detected in 3 (1.6 %) and 9 (5 %) patients, respectively, at baseline, in 25 (13 %) and 31 (16 %) patients at the end of treatment (both $P<0.001$, *vs* baseline), and in 7 (4 %) and 14 (7 %) patients 12 months after withdrawal ($P=0.002$ and $P=0.01$ respectively, *vs* baseline; P=not significant *vs* end of treatment). The development of autoimmune gastritis was strictly associated with the presence of autoimmune thyroiditis ($P=0.0001$), no relationship was found with other markers of autoimmunity.

CONCLUSION: In HCV patients, IFN frequently precipitates latent autoimmune gastritis, particularly in females. Following our 12-month protocol, the phenomenon generally regressed. Since APCA positivity and high gastrin levels are associated with the presence of antithyroid antibodies, development of autoimmune thyroiditis during IFN treatment may provide a surrogate preliminary indicator of possible autoimmune gastritis to limit the need for invasive examinations.

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INTRODUCTION

Chronic hepatitis C virus (HCV) infection can lead to the development of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC)[1]. Chronic HCV patients frequently have a broad spectrum of autoantibodies and/or concurrent autoimmune disease[2-4], apparently not closely associated with the HCV genotype[5] or to the severity of liver disease[6]. Several studies have indicated that immunological abnormalities are sometimes unmasked by interferon-α (IFN) therapy[7-12]. Although autoimmune thyroiditis is one of the most common immunological side effects of IFN treatment, with very close monitoring, its presence is not an absolute contraindication for the therapy. A close association has been reported between autoimmune thyroiditis and autoimmune (i. e. type A) gastritis[13]. Autoimmune gastritis involves the fundus and the body of the stomach while sparing the antrum. It is associated with pernicious anemia, autoantibodies to gastric parietal cells, achlorhydria, low serum pepsinogen I with normal serum pepsinogen II concentrations[14] and high serum gastrin concentration, the latter is resulted from hyperplasia of gastrin-producing cells. It is thought that *Helicobacter pylori* (*H.pylori*) could be implicated in the development of autoimmune gastritis[15,16], since it induces antigenic mimicry[17] and antibodies against *H. pylori* can cross-react with both antral mucosal and gastrin-producing cells.

The frequencies of thyroiditis manifestations during IFN treatment of chronic hepatitis C infection are well documented[7,9,10]. However, the impact of IFN therapy on the development of autoimmune and other types of gastric disease is unknown. To address this issue, we designed a prospective study on 189 chronic HCV patients treated with IFN. In particular, we investigated: a) the baseline prevalence of autoimmune gastritis, b) the impact of IFN on the development of biochemical signs of autoimmune gastritis, c) the outcome of twelve months after withdrawal of IFN. We also examined the presence of antithyroid, antigastric parietal-cell and anti-non-organ-specific (anti-NOS) antibodies. Finally, we investigated whether the presence of *H. pylori* affected the development of autoimmune gastritis.

MATERIALS AND METHODS

Patients and study design

We prospectively studied a group of 189 consecutive IFN-treated chronic hepatitis C patients (95 males, 94 females, mean age 58±18 years) who entered an IFN therapeutic program at our institution from September 1996 to July 1998 (Table 1). Criteria for the diagnosis of chronic HCV infection were: 1) presence of anti-HCV antibodies and polymerase chain reaction (PCR) positivity for HCV-RNA, 2) histological confirmation of chronic hepatitis C, 3) exclusion of other causes of chronic liver diseases (alcoholism, Wilson's disease, drugs, hemochromatosis, a1 antitrypsin deficiency, autoimmune hepatitis, PBC). Criteria for inclusion in the IFN treatment program were the generally recognized ones (transaminase levels over two times the upper limit, age between 18 and 70

years, absence of pregnancy and psychiatric history or other chronic severely invalidating conditions). None of the patients had received immunosuppressive or immunostimulatory therapy before entry into the study. All the patients were negative for human immunodeficiency virus (HIV) antibodies and hepatitis B surface antigen (HBsAg). Disease activity and stage were evaluated according to Scheuer' s histological score. None of the patients were receiving proton pump inhibitors or anti-H_2 antagonist drugs. Informed consent was obtained from each patient and approval for the study protocol was granted by the Ethical Committee of our institution.

Table 1 Baseline characteristics of patients

Patients (*n*)	189	
Age (*year*) ± SD	58±18	
Sex (M / F)	95 / 94	
ALT (U / L) ± SE	142±8	
AST (U / L) ± SE	103±7	
Genotype 1-4 *vs* others	115 *vs* 74	61 *vs* 39%
Anti-*Hp* positive antibody	60	31.8%
Gastrin (pg / ml)(median±SE)	52.0±10.4	
TSH (UI / ml)	2.2±0.15	
ANA positive (*n*)	34	18%
AMA positive (*n*)	-	
ASMA positive (*n*)	57	30%
LKM positive (*n*)	1	0.5%
APCA positive (*n*)	3	1.6%
ATM positive (*n*)	15	7.8 %
Liver histology (*n*)		
CAH without cirrhosis (*n*)	138	73 %
CAH with cirrhosis (*n*)	51	27 %

All the patients received 6 MU of recombinant IFN daily for the first month, followed by 6 MU each alternate day for 5 months and then 3 MU each alternate day for a further 6 months. In the event of side-effects, the dosage was decreased. If side effects were severe or sustained, IFN treatment was suspended.

Serum samples were analyzed in all the patients for presence of gastric parietal cell autoantibodies and gastrin at the following time points: baseline, after 3 and 6 months of treatment, the end of IFN treatment (i.e. at 12 months, or at the time of suspension, if earlier), 12 months after suspension of IFN. Multiple endoscopic gastric biopsies were always performed when positive anti-gastric parietal cell autoantibodies and/or serum levels of gastrin were found to be over 3 times the normal upper limit, presence of gastrinoma was excluded by the secretin stimulation test. In all patients, *Helicobacter pylori* status was serologically tested before the start of treatment. Criteria for diagnosis of autoimmune gastritis were according to Sidney classification system[18,19].

Biochemical and virological assays

Serum samples were analyzed for routine biochemical liver function tests with a multichannel autoanalyzer. HBsAg and anti-HBs and anti-hepatitis B core (HBc) antibodies were tested using a commercial solid-phase radioimmunoassay (Abbott Laboratories, North Chicago, IL). HIV determination was done according to a standard enzyme-linked immunosorbent assay (ELISA) procedure (HIV ELISA, Abbott Laboratories, North Chicago, IL). Anti-HCV antibodies were tested using a second-generation ELISA procedure (ELISA-2, Ortho Diagnostic Test Systems, Raritan, NJ). HCV RNA was detected by nested PCR analysis using primers from the highly conserved 5' non-coding region of the HCV genome (Shindo *et al*, 1991). HCV genotype was determined by InnoLipa.

Immunoserological evaluation

Anti-nuclear, anti-mitochondrial, smooth-muscle and liver-kidney microsome-1 auto-antibodies (ANA, AMA, SMA and LKM-1) were determined using indirect immunofluorescence assays on unfixed cryostat frozen sections of mouse liver, kidney and stomach. Sera were screened for anti-parietal cell autoantibodies (APCA) by immunofluorescence reactivity with paraffin-embedded sections of mouse stomach and for H^+/K^+-ATPase autoantibodies by ELISA. A positive result required a titer of at least 1/40. Basal serum gastrin and thyroid serum hormone (TSH) concentration were measured by radioimmunological assay (RIA), which detects sulfated and non-sulfated human heptadecapeptide (hG-17), as well as human big gastrin (hG-34). Gastrin results were expressed as pg/ml. Thyroid microsomal and thyroglobulin autoantibodies (TMA and TGA) were analyzed using hemagglutination tests (Ames, Elkhart, IN, USA). The cut-off points for both TMA and TGA were 1:100.

H. pylori investigation

Serum immunoglobulin G (IgG) response to *H. pylori* purified antigens was measured by ELISA, the cut-off value used was an optical density ratio >1.0. The presence or absence of *H. pylori* was also defined by histological examination of multiple gastric biopsy specimens from the antrum, fundus, or cardia in all the patients with positive APCA and/or elevated levels of gastrin. All biopsy specimens were fixed in Hollande' s fixative and stained with H&E and Giemsa.

Statistical analysis

Intent-to-treat analysis was adopted. To analyze associations among groups the Fisher' s exact test and the χ^2 test with Yates' correction were used. A two-tailed *P* value less than 0.05 was considered significant.

RESULTS

Treatment outcome

The entire 12-month treatment schedule was completed by 168/189 (89 %) of patients. In 21 patients, the IFN dose was reduced due to the severity of side effects (severe thrombocytopenia and/or severe leukopenia with neutrophil count <800/mm^3, continuous fever unresponsive to paracetamol, or severe myalgia). At least three months of treatment were completed by all but two of the patients (one suspended due to severe depression and suicidal tendency, the other due to side effects coupled with lack of motivation). None of the patients who discontinued therapy was positive for APCA.

Abdominal symptoms

In 164/189 (87 %) patients, no abdominal symptoms were reported. The most frequently reported symptoms were epigastric pain and/or abdominal discomfort. Presence of abdominal symptoms was not affected by positivity/negativity for *H. pylori*.

APCA and hypergastrinemia outcome (Tables 2, 3)

At the start of treatment, APCA positivity was detected in 3 (1.6 %) patients, and hypergastrinemia (i.e. serum gastrin levels over three times the normal upper limit) was found in a further 9 (5 %). At the end of treatment, these incidences rose to 25 (13 %) and 31 (16 %) patients, respectively (both $P<0.001$ *vs* baseline values). Thus, 22 patients developed both APCA and hypergastrinemia, mostly by the third month of therapy. Twelve

months after suspension of IFN, APCA and hypergastrinemia were still present in 7 (4 %) and 14 (7 %) patients, respectively (P=0.002 and P=0.01, respectively, *vs* end of IFN treatment; both P=not significant *vs* baseline). During IFN treatment, females were more prone to have increased APCA (P=0.017) or increased serum gastrin levels (P=0.011) than males.

Serum gastrin levels (defined as median ± Standard Error) increased during administration of IFN (from 52±10.4 pg/ml to 57±17.2 pg/ml, P=0.001). Twelve months after withdrawal of therapy, serum gastrin levels (56±12.6 pg/ml) were still higher than those at baseline (P=0.001), although they were significantly lower than those at the end of treatment (P=0.001). Serum TSH levels increased during administration of IFN (from 2.6±0.13 MCU/ml to 3.2±0.17 MCU/ml, P=0.02), and subsequently remained higher than the baseline values at 12 months from withdrawal of therapy (3.2±0.3 MCU/ml, P=0.02 *vs* baseline, P =not significant *vs* withdrawal). As can be seen from Tables 2 and 3, the behavior of the antithyroid autoantibodies TPO was very similar to that of APCA. By contrast, IFN did not affect the non-organ-specific antibodies ANA, SMA and AMA.

Table 2 Variations of APCA positivity and hypergastrinemia in IFN treated patients

	Before IFN *n* (%)	IFN withdrawal *n* (%)	12 months after withdrawal *n* (%)
APCA positivity	3 (1.6%)	25 (13%)[a]	7 (4%)[b,d]
Hypergastrinemia	9 (5%)	31(16%)[a]	14 (7%)[c,d]

[a]P<0.001 *vs* before IFN; [b]P<0.002 *vs* IFN withdrawal; [c]P<0.01 *vs* IFN withdrawal; [d]P=not significant *vs* before IFN.

Table 3 Organ-specific and non-organ-specific autoantibodies

	Before IFN + (%)	IFN withdrawal + (%)	12 months after withdrawal+(%)
Organ-specific antibodies			
TPO	14 (8.0%)	39 (20.6%)[a]	23 (12.2%)
Non-organ-specific antibodies			
ANA	34 (18.0%)	45 (24.0%)	41 (22.0%)
SMA	56 (30.0%)	62 (33.0%)	60 (31.0%)
AMA	-	1 (0.5%)	1 (0.5%)
LMK 1	1 (0.5%)	3 (1.6%)	2 (1.1%)

[a]P<0.001 *vs* before IFN; P=0.036 *vs* 12 months after IFN withdrawal.

H. pylori status

At baseline, 61/189 (32.3 %) patients had a positive serum IgG response to *H. pylori* whole-cell antigen. These included 3 of the 9 (33.3 %) patients with autoimmune gastritis and 12 of the 31 (38.7 %) who developed biochemical signs of autoimmune gastritis during treatment.

Histology

Multiple endoscopic gastric biopsies were performed when positive APCA and/or serum levels of gastrin were found to be over 3 times the normal upper limit. At biopsy, all the patients with either baseline APCA positivity (n=3) or hypergastrinemia (n=9) showed a histological picture consistent with autoimmune gastritis. Among the 22 patients who developed both APCA positivity and hypergastrinemia during IFN therapy, the histology of the fundus was consistent with autoimmune gastric atrophy in 13 (59 %). Four other patients who were persistently consistent with presence of gastric atrophy maintained histological lesions at 12 months from IFN withdrawal.

Outcome of HCV infection

At baseline, 115/189 (61.0 %) patients were found to be infected with HCV genotype 1 or 4, while the remaining 74 (39.0 %) were infected with more IFN-responsive strains. Overall, 37/189 (19.5 %) patients showed a long-term virological response to IFN (at 12 months from withdrawal). In particular, long-term response was observed in 8/109 (7.3 %) patients with genotype 1, 21/39 (35 %) with genotype 2, 7/14 (50 %) with genotype 3, and 1/6 (16 %) with genotype 4, respectively. No difference in responsive rate was observed among the patients who developed hypothyroidism and/or hypergastrinemia and those who did not. No relationships were observed between HCV genotype and the development of autoimmune gastritis.

DISCUSSION

The prevalence of autoimmune gastritis in chronic HCV patients is currently unknown. Autoimmune gastritis can be associated with thyroid autoimmune abnormalities. The hypothesis that IFN therapy encourages the development of autoimmune gastritis in these patients has never been tested.

In this prospective study, we investigated the occurrence of autoimmune gastritis in 189 chronic HCV patients treated with IFN. The baseline prevalence of biochemical signs and histological features of autoimmune gastritis was similar to that found in the general population. However, the number of patients who displayed biochemical and/or histological signs of autoimmune gastritis significantly increased during IFN treatment. By 12 months after interruption of IFN, the number of patients showing these signs had partially regressed, although it still remained higher than the baseline value. Seven more patients continued to have elevated APCA and gastrinemia, all with histological evidence of autoimmune gastritis. These findings are in line with the hypothesis that IFN can unmask patients with latent autoimmune gastritis and sometimes may even induce permanent alterations consistent with autoimmune gastritis. Our findings also support the concept that these abnormalities are more frequent in females.

Patients with autoimmune gastritis have a 3-fold increased risk of gastric carcinoma and a 13-fold higher risk of gastric carcinoid tumours[20]. However, it is not known whether hypergastrinemia or mucosal damage plays a dominant etiologic role[21]. Evidence exists that endogenous hypergastrinemia is associated with stimulation of rectal[21] and liver cell proliferation[22,23], as also occurs in conditions that are known to raise the risk of colon cancer and HCC. HCV patients are at increased risk of developing HCC anyway[1] but IFN treatment seems to prevent or delay its onset[24]. Hence, the implications of the occurrence of hypergastrinemia followed by autoimmune gastritis during IFN treatment of HCV infection require careful consideration.

Although 13/22 of our patients developed histological signs of autoimmune gastritis during the 12-month period of therapy, in the majority of cases, these signs regressed in the following year. Persistent histological and biochemical hallmarks of autoimmune gastritis were only eventually found in 4 % (7 of 189) of our patients. The relatively short duration of immunostimulation by IFN may explain why the autoimmune gastritis regressed in most cases. Therefore, our findings may only be applicable to the effects of short-term treatment.

The presence of antithyroid antibodies does not absolutely contraindicate the use of IFN[25], even though it has to be remembered that IFN leads to permanent thyroid alterations in more than one-fifth patients[26,27]. Likewise, although the presence of autoimmune gastritis does not contraindicate IFN treatment, it has to be considered that some patients may develop permanent gastric alterations.

In the present study, we also investigated the possibility that *H. pylori* infection might play a pathogenetic role in the onset of autoimmune gastritis in IFN-treated chronic HCV patients[15,16]. Our data provided no support for this hypothesis. Indeed, in our series of patients, there was no observable difference in the frequencies of autoimmune gastritis between chronic HCV patients with and without *H. pylori* infection, either before, during or after IFN treatment.

Furthermore, we were unable to find any association between the presence of non-organ specific antibodies and that of antithyroid antibodies or APCA. This finding is of clinical interest because positivity for antithyroid antibodies or APCA reveals autoimmune thyroid or gastric disease, whereas the presence of anti-NOS antibodies may only refer to an autoimmune epiphenomenon. This underlines the importance of testing antithyroid antibodies and APCA as well as the anti-NOS ones.

In conclusion, IFN treatment for chronic hepatitis C does appear to be associated with frequent occurrence of autoimmune gastritis, particularly in female patients. In the majority of cases, autoimmune gastritis in the wake of our protocol appeared to be a transient phenomenon. However, this may depend on the limited (12 month) duration of treatment, and this point requires further investigation, especially in regard to the effects of long-term treatment. Autoimmune gastritis is an asymptomatic disease, but in the long run increases the risk for developing a variety of tumors especially in the stomach. Our experience underlines the importance of measuring APCA and/or gastrin levels in chronic HCV patients treated with IFN, and especially those who develop thyroid dysfunction. Development of autoimmune thyroiditis during IFN treatment might provide a surrogate indicator of possible autoimmune gastritis, limiting the need for invasive gastric procedures.

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