

## Retrospective Study

## Interferon therapy in hepatitis C leading to chronic type 1 diabetes

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### Abstract

**AIM:** To review the prevalence, clinical data and course of interferon-associated type 1 diabetes in chronic hepatitis C virus (HCV) infection.

**METHODS:** Search of all interferon (INF)-related

type 1 diabetes mellitus (T1DM) cases published in the English literature from 1992 to December 2013 according to the key words: chronic hepatitis C infection, diabetes mellitus type 1, insulin dependent diabetes mellitus, and interferon treatment. We found 107 cases and analyzed their clinical and laboratory data and long-term follow-up. Due to the predominance of cases described in Japanese literature, we analyzed separately cases of Caucasian and Japanese origin. In addition we describe a representative case with HCV who developed INF-related T1DM.

**RESULTS:** Our data show that INF treatment increases the risk of developing T1DM by 10-18 fold compared with the corresponding general population and the median age of onset was 43 years (range: 24-66 years) in Caucasians and 52 years (range: 45-63 years) in Japanese. Most patients developed T1DM during INF treatment, after a median time-period of 4.2 and 5.7 mo in Caucasian and Japanese groups, respectively. The clinical course was characterized by a fulminant course with abrupt severe hyperglycemia or ketoacidosis, a high titer of anti-islet autoantibodies and almost all patients (105/107) permanently required insulin therapy with a follow-up of up to 4 years. A substantial number of patients had evidence for other autoimmune disorders mainly thyroid diseases (25% and 31% in Caucasian and Japanese groups, respectively).

**CONCLUSION:** INF-associated T1DM in HCV has a fulminant course, often associated with other autoimmune diseases, and results almost inevitably in permanent insulin therapy requirement.

**Key words:** Interferon; Hepatitis C; Type 1 diabetes; Autoimmune diseases; Pancreatic autoantibodies

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**Core tip:** Interferon (INF) treatment is an important component of hepatitis C virus treatment. Although INF-associated type 1 diabetes mellitus was described more than 2 decades ago its importance is under-recognized. Based on a review of all published cases we found that this complication typically appears abruptly, is manifested by severe hyperglycemia accompanied by a high titer of anti-islet antibodies and is often associated with autoimmune thyroid disease. Most worrisome, almost all patients who develop this complication require permanent insulin treatment. With the emergence of new interferon-free therapies, this serious complication has to be taken into consideration especially in relatively young patients with mild to moderate disease.

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## INTRODUCTION

Pegylated interferon (INF) in combination with ribavirin (RBV) is still the standard of care for chronic hepatitis c virus (HCV) infection. INF treatment is known to cause numerous side effects in HCV patients<sup>[1-3]</sup>, however INF-induced type 1 diabetes mellitus (T1DM) is less well recognized and rarely taken into consideration before initiating therapy.

Both HCV infection and INF treatment can be involved in the pathogenesis of diabetes. Several studies and a meta-analysis have shown an increased prevalence of type 2 diabetes in HCV-infected patients compared with non-infected individuals or patients with chronic hepatitis B infection<sup>[4-6]</sup>. This increased prevalence is mediated by insulin resistance due to increased levels of proinflammatory cytokines such as tumor necrosis factor alpha or by direct effect of viral proteins on insulin signaling<sup>[7-9]</sup>. The prevalence of T1DM in HCV patients is much lower than T2DM. Fabris *et al*<sup>[10]</sup> described in 1992 the development of INF-induced T1DM in a patient with chronic HCV infection and this observation was followed later by additional cases, many of them from Japan<sup>[11-30]</sup>. The development of several other INF-induced autoimmune disorders suggests that autoimmunity is the underlying mechanism. Surprisingly, although T1DM is a serious medical condition, this adverse effect has not gained a lot of attention. We describe here a case treated in our hospital of a patient with chronic HCV hepatitis who developed INF-induced T1DM to demonstrate the clinical course and severity of this complication.

A 21-year-old female without prior medical problems and with normal glucose levels and thyroid function tests was found during pregnancy screening to have positive

HCV antibodies on January 2004. An initial PCR test was negative for HCV (the lower limit of detection was 600 IU/mL at that time) and liver function tests were normal and she received no treatment. In September 2008 repeat testing found a viral load of  $1 \times 10^6$  IU/mL and genotype 1b. Treatment with pegylated (Peg) INF- $\alpha$  2b 80  $\mu$ g subcutaneously and RBV 400 mg *bid* was commenced. On December 2008 she developed hypothyroidism followed later by thyrotoxicosis with positive thyroid peroxidase and thyroid stimulating autoantibodies for which she received propylthiouracil. On April 2009 she was hospitalized for diabetic ketoacidosis: pH 7.13, urine acetone +3, glucose 535 mg/dL, anion gap 25. Islet cell and insulin autoantibodies were positive, C-peptide 122 pmol/L (normal > 500 pmol/L). She was diagnosed with T1DM and started treatment with multiple daily insulin injections and soon after with an insulin pump. Anti-viral therapy was discontinued. A repeat episode of ketoacidosis triggered by pneumonia occurred on April 2011. She continues to be followed at a diabetes clinic and at her last visit on September 2013 she was still treated with an insulin pump with good glycemic control (hemoglobin A1c 6.4%). The patient remained HCV positive with slightly abnormal liver tests.

In order to evaluate the prevalence, clinical and laboratory characteristics of INF-induced T1DM in HCV patients we performed a literature search of all cases described in the English literature during the last 21 years.

## MATERIALS AND METHODS

We conducted a search of all INF-related T1DM cases published in the English language literature from 1992 to December 2013 using the key words: chronic hepatitis c infection, diabetes mellitus type 1, insulin dependent diabetes mellitus, and interferon treatment. Due to the predominance of Japanese patients, all reviewed cases were divided into two groups: Caucasian (mostly from Italy and the remainder from other European countries) and Japanese patients.

## RESULTS

### Epidemiology

Two large retrospective studies investigated the side effects of INF therapy in HCV patients. In a study from Italy, Fattovich *et al*<sup>[3]</sup> collected data from 73 centers and included 11241 INF-treated HCV patients. They found 10 cases (0.09%) that developed “insulin dependent diabetes” during therapy, 18-fold higher than the annual incidence of insulin dependent diabetes (0.005%), reported in the general Italian population. Similar results were observed in a recently published Japanese national survey of INF-related T1DM. The prevalence of DM among INF treated patients was estimated to be 0.34%, which is 10-fold higher than that reported in the general Japanese population<sup>[11]</sup>.

In another small study from the Netherlands, 5

**Table 1 Clinical and laboratory characteristics of 107 patients with interferon-induced type 1 diabetes mellitus *n* (%)**

Variable	Caucasian <i>n</i> = 20	Japanese <i>n</i> = 87
Age (range), yr	43 (24-66)	52 (45-63)
Males	13 (65)	48 (52)
HCV genotype		
Type 1b	1 (5)	28 (32)
Non- type 1b	7 (32)	6 (7)
Unavailable data	12 (63)	53 (61)
Type of therapy		
Non-Peg INF- $\alpha$	10 (50)	39 (45)
Peg INF- $\alpha$	10 (50)	45 (52)
Other types of INF	-	3 (3)
Combination with ribavirin	15 (75)	54 (62)
Patients who developed DM during INF treatment	17 (85)	63 (72)
Patients who developed DM after INF cessation	3 (15)	24 (28)
Time-period between INF initiation and T1DM onset mo	4.2 (1.8-8.5)	5.7 (2.8-14.6)
Time-period between INF cessation and T1DM onset (mo)	3.6 (3.0-4.0)	6.3 (1.6-13)
Ab positive before INF treatment	10 (62)	0 (0)
Ab negative before INF treatment	6 (38)	4 (100)
Not done	4 (20)	83 (95.4)
Insulin therapy at end of follow-up	20 (100)	85 (98)

HCV: Hepatitis C virus; Peg INF- $\alpha$ : Pegylated interferon  $\alpha$ ; T1DM: Type 1 diabetes mellitus.

(2.65%) INF treated HCV- patients developed T1DM based on antibody positivity and the need for insulin treatment<sup>[12]</sup>.

### Clinical and laboratory characteristics in patients with INF-induced T1DM

The clinical and laboratory data of 107 patients with INF-induced T1DM (20 Caucasian and 87 Japanese origins) found in our literature search are presented in Table 1<sup>[10-30]</sup>.

The median age at onset of type 1 diabetes was 43 years (range: 24-66 years) in the Caucasian group and 52 years (range: 45-63 years) in the Japanese patients. In the Caucasian group there were 65% male and 35% female patients and in the Italian group the male/female ratio of 1.6 was similar to the ratio found in patients with T1DM in the general Italian population<sup>[31]</sup>. This male/female difference was not observed in the Japanese patients<sup>[32]</sup>.

HCV genotype 1b was found in only one out of eight patients in the Caucasian group, compared with the Japanese patients in whom among those tested, the majority had genotype 1b. In the Caucasian group 75% of patients received combination therapy of INF and RBV. There was a similar distribution of patients receiving Peg INF and non-Peg INF treatment in both Caucasian and Japanese groups.

Most patients in the two study groups developed T1DM during INF treatment (85% and 72% in the Caucasian and Japanese groups, respectively) after a median time period from treatment initiation of 4.2 and

5.7 mo in Caucasian and Japanese groups, respectively. A quarter of patients in the Japanese group developed T1DM after INF treatment cessation. The longest time period between INF treatment cessation and T1DM was 13 mo with a median of 3.6 mo (range: 3.0-4.0 mo) and 6.3 mo (range: 1.6-13 mo), in Caucasian and Japanese groups, respectively.

In the Caucasian group, pancreas-associated autoantibody status was known in 16/20 patients before INF treatment initiation. Ten of these patients (62%) had at least one positive antibody. In the Japanese group, pancreas-associated autoantibodies were measured before INF initiation in only 4/87 patients and in all of these cases it was negative. Anti-glutamic acid decarboxylase (GAD) antibodies were most commonly tested. Due to lack of sufficient data in most patients, especially in the Japanese group, the pancreatic autoantibody conversion rate could not be determined. There was also insufficient data available regarding human leukocyte antigen typing and family history of diabetes.

The majority of the patients had acute onset of diabetes characterized by severe hyperglycemia often with ketoacidosis. In addition, very high titers of pancreatic autoantibodies, mainly anti-GAD, were found (up to 10,000-fold higher than the normal range). Almost all of these patients remained insulin-dependent for up to four years of follow-up from cessation of INF treatment. There were only two cases in which insulin was discontinued<sup>[26,27]</sup>.

Other autoimmune disorders in patients with INF-induced T1DM are described in Table 2.

About a third of patients also developed clinical and biochemical evidence of thyroid dysfunction during or after INF therapy in both study groups.

## DISCUSSION

In the current review we summarized 107 patients treated with INF for chronic HCV hepatitis who developed T1DM, 81% of Japanese origin and the rest from European countries mainly Italy. According to this limited epidemiological data, the incidence of T1DM in INF-treated HCV patients is 10-18 fold higher than in the general population<sup>[3,11,12]</sup>. Data from other populations are not available but we assume that INF-induced T1DM is globally under-reported. Interestingly, INF-induced T1DM has been rarely described in patients receiving this treatment for multiple sclerosis<sup>[33]</sup>.

The typical presentation of INF-induced T1DM is fulminant, occurring several months after INF initiation in most patients but it can also occur after INF therapy cessation. Most patients in both cohorts presented with ketoacidosis within one week to three months after the onset of hyperglycemic symptoms, with a high titer of pancreatic autoantibodies and severe insulin deficiency demonstrated by low levels of C-peptide. The markedly high titer of anti-GAD antibodies at presentation was significantly higher than what is usually reported in

**Table 2 Other autoimmune disorders in Caucasian and Japanese patients with interferon-induced type 1 diabetes mellitus *n* (%)**

Disorder	Autoantibodies	Caucasian	Japanese	Ref.
Autoimmune thyroid disease	Anti TPO	5 (25)	27 (31)	[11,12,18,19,21,22,25,28,29]
	Anti TG			
	TSI			
Stiff person syndrome	Anti-GAD	1		[21]
Insulin resistance	Anti-insulin receptor	1		[22]
Neuromyelitis optica	Anti AQP-4		1	[30]
Sjogren's syndrome	SS-A, SS-B		1	[26]

TPO: Thyroid peroxidase; TG: Thyroglobulin; GAD: Glutamic acid decarboxylase; TSI: Thyroid-stimulating immunoglobulins; AQP-4: Aquaporin-4.

T1DM in the general population<sup>[34]</sup>. Moreover, unlike the natural history of autoimmune T1DM, in which the appearance of autoantibodies precedes the manifestation of insulin insufficiency by years, in INF-induced T1DM humoral autoimmune markers seem to develop relatively within a short-time prior to diagnosis. Taken together, these clinical characteristics suggest that INF therapy leads to a severe autoimmune process that within a short-time period results in massive  $\beta$ -cell destruction. The correlation between a high titer of anti-GAD antibodies and more severe insulin deficiency was described also in latent autoimmune diabetes in adults<sup>[35]</sup>. Of special concern are the data presented in this review that almost all patients remained insulin dependent up to 4 years of follow-up unrelated to HCV status. In the only two patients in which insulin was discontinued there was no long-term follow-up to rule out the possibility that insulin cessation was related to the “honeymoon” phenomenon, well described in new onset T1DM<sup>[26,27]</sup>.

Can INF-induced T1DM be predicted by pancreatic antibody measurement? Due to incomplete data on autoimmunity status before treatment in many of these cases, no definite conclusion can be made. However, Betterle *et al*<sup>[36]</sup> assessed the presence of autoantibodies in 70 HCV patients. The frequency of pancreatic autoantibodies was not significantly different when compared with healthy control subjects, except for the low titer of insulin autoantibodies (IAA) in 41% patients. IAA levels did not change during the course of INF treatment, and none of the IAA-positive patients developed T1DM. Previous data show that both the positive and negative predictive value of  $\beta$ -cell autoantibodies seem to be too low to identify patients at high risk or to effectively rule out the possibility of developing interferon-associated T1DM<sup>[37]</sup>. Therefore INF-associated T1DM is still an unpredictable severe complication of interferon treatment even today, two decades since its first description<sup>[10]</sup>.

In our review we found that many of the patients with T1DM had also autoimmune thyroid disease and a few cases also had other autoimmune disorders including neuromyelitis optica, Sjogren's syndrome, severe insulin resistance with insulin receptor antibodies, and stiff person syndrome. In HCV patients treated by INF other autoimmune disorders have been described, including autoimmune gastritis, rheumatoid arthritis,

psoriasis, interstitial pneumonitis and rare diseases such as myasthenia gravis, Raynaud's syndrome and Vogt-Koyanagi-Harada disease<sup>[3,38-43]</sup>.

### Pathogenesis

The role of INF in the pathogenesis of T1DM in the general population is supported by the findings, that only INF- $\alpha$  was significantly over-expressed in islets of T1DM patients amongst a panel of evaluated cytokines and elevated INF- $\alpha$  levels were also detected in blood samples<sup>[44-46]</sup>. One of the molecular mechanisms underlying INF- $\alpha$ -induced T1DM induced by viral infection is  $\beta$ -cell apoptosis. Viral double-stranded RNA activates the production of INF- $\alpha$  in various cells, which is directly cytotoxic to  $\beta$ -cells. INF- $\alpha$  also induces apoptosis by activating the oligoadenylate synthase-ribonuclease L and the protein kinase R pathway. Apoptotic materials induce more INF- $\alpha$  and activate the immune system<sup>[47]</sup>. Furthermore, interferon- $\alpha$  is known to increase major histocompatibility complex class I antigen expression on cell membranes and to activate T cells and natural killer cells<sup>[48]</sup>. Interestingly, INF- $\alpha$ -neutralizing antibody prevented type 1 diabetes development in transgenic mice expressing INF- $\alpha$  in their  $\beta$ -cells<sup>[49]</sup>.

Recent data show that the time-period to the development of INF-induced T1DM was shorter in patients that received combination therapy of Peg-INF and ribavirin compared to non-Peg INF, suggesting that the longer duration of Peg-INF and the deviation to the Th1-type immune response by RBV may increase the risk of developing T1DM<sup>[11]</sup>.

### Clinical implications and future therapies

Based on the data presented in this review with a follow-up of up to 4 years, it appears that INF-induced T1DM is a serious irreversible complication of the current therapy of chronic HCV hepatitis leading to permanent insulin requirement. This being so, is this a reasonable risk to be taken in all HCV patients?

It is well established that HCV hepatitis can cause cirrhosis and its related complications, including end-stage liver disease and hepatocellular carcinoma, and is a major cause for liver transplantation in the United States and Europe<sup>[50]</sup>. However, in cohorts of women



of childbearing age who received contaminated anti-D in Germany there was a small risk for liver-related mortality<sup>[51]</sup>, and only 2% developed severe fibrosis after 25 years<sup>[52]</sup>. Data from France demonstrate that age at infection is important. In patients infected when younger than 20 years, it took 44 years to develop cirrhosis. In those infected at the age of 31-40 years, it required 30 years, and those older than 50 years when infected, developed cirrhosis after 12 years<sup>[53]</sup>. This observation is in accordance with the data that increasing age is a strong risk factor for increased fibrosis<sup>[54]</sup>. There has recently been a debate on the need to recommend antiviral therapy in HCV hepatitis and the reliance of a sustained virologic response (SVR) as a surrogate marker for treatment success<sup>[55]</sup>.

Characterization of HCV-encoded proteins and their functions has enabled development of treatments that interrupt HCV replication-direct acting antivirals. In 2011 the FDA approved 1<sup>st</sup> generation NS3/4A protease inhibitors telaprevir and boceprevir. At the end of 2013 sofosbuvir, a NS5B RNA polymerase inhibitor and simeprevir, a 2<sup>nd</sup> generation protease inhibitor, were approved for therapy, but most regimens still include INF treatment. Recently, INF-free regimens with a high SVR have been reported for genotype 1 HCV<sup>[56]</sup> and genotypes 1, 2 and 3<sup>[57]</sup>. In addition, there are NS5A inhibitors, NS5B polymerase inhibitors and combination strategies without INF in development. It is likely that several of these agents will be available for use in 2015.

Thus for young patients diagnosed with chronic HCV hepatitis with mild to moderate fibrosis, the possibility of delaying treatment until INF-free regimens are available has to be seriously considered. In many of these patients with untreated HCV hepatitis, the natural course is more benign than that of type 1 diabetes, a disease with significant acute and chronic complications and shortened life expectancy<sup>[58]</sup>. It may be appropriate to delay therapy for these patients until INF-free regimens become available.

## COMMENTS

### Background

Interferon (INF) in combination with ribavirin is still the standard of care for hepatitis C virus (HCV) infection in many countries. Although INF-associated type 1 diabetes mellitus (T1DM) was first described two decades ago, this serious adverse event is still under-recognized and seldom taken into consideration before initiating therapy.

### Research frontiers

Recently, INF-free regimens with a high response rate have been reported for HCV genotypes 1, 2 and 3.

### Innovations and breakthroughs

The present review summarizes the cases of INF-associated T1DM reported and demonstrates that: this complication develops abruptly; is mediated by a prominent autoimmune process; and on the basis of up to 4 years follow-up, almost inevitably results in permanent insulin treatment requirement.

### Applications

In young patients diagnosed with chronic HCV hepatitis with mild-to-moderate fibrosis, the possibility of delaying treatment until INF-free regimens are available, has to be seriously considered.

## Terminology

T1DM is a mediated by an autoimmune process that leads to severe and permanent  $\beta$ -cell failure and interferon has a central role in this process.

## Peer review

The natural course of untreated chronic HCV hepatitis with mild-to-moderate fibrosis is more benign than the course of INF-associated T1DM as described in this review.

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