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**Autoantibodies in chronic hepatitis C: A clinical perspective**

Narciso-Schiavon JL *et al.* Autoimmunity in hepatitis C

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**Abstract**

Non-organ-specific autoantibodies and thyroid autoantibodies have been frequently found in chronic carriers of hepatitis C virus (HCV). With respect to endomysial antibodies and tissue transglutaminase, it is controversial whether the prevalence of gluten-related seromarkers is higher in patients with HCV. In such cases, in addition to acknowledging any currently existing autoimmune disease, recognizing the risk of the patient developing an autoimmune disease during interferon (IFN)-based treatment must be a principle concern. From a clinical point-of-view, the presence of autoantibodies arouses suspicion that an autoimmune disease may be present or may be precipitated by IFN-based HCV treatment. In this paper, we review the prevalence of autoantibodies in individuals with hepatitis C, the clinical significance of these autoantibodies, and the approach recommended for such situations.

**Key words:** Hepatitis C; Interferon-alpha; Autoimmunity; Antibodies; Antinuclear; Hepatitis; Autoimmune; Thyroid diseases; Hashimoto disease; Thyroglobulin; Celiac disease; Transglutaminases; Diarrhea

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**Core tip:** We review the prevalence of Non-organ-specific autoantibodies, thyroid autoantibodies, and gluten-related seromarkers and their significance in predicting autoimmune diseases in individuals with hepatitis C. Autoantibodies’ importance for treatment choice and possible complications due to their presence during interferon-based treatment are appraised.

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**INTRODUCTION**

It is estimated that 2%-3% of the world’s population is infected with the hepatitis C virus (HCV)[[1](#_ENREF_1)]. HCV causes chronic hepatitis, cirrhosis, and hepatocellular carcinoma[[2](#_ENREF_2)]. HCV has been implicated both in the triggering of autoimmune diseases and in the development of autoantibodies[[3](#_ENREF_3),[4](#_ENREF_4)]. HCV might be involved in the breaking of tolerance to self-antigens and thus in triggering autoreactivity. A number of extrahepatic manifestations have been described in association with chronic HCV infections, most of which can be mediated by immunological mechanisms, rather than being related to the infection of extrahepatic tissues[[3](#_ENREF_3),[4](#_ENREF_4)].

Until recently, the association of pegylated interferon-alfa (IFN) with ribavirin was the gold-standard treatment for hepatitis C[[5](#_ENREF_5),[6](#_ENREF_6)]. IFN may induce autoimmune disorders or worsen pre-existing autoimmune disorders[[7-14](#_ENREF_7)]. Therefore, it is advisable to screen autoantibodies prior to treatment; the diagnosis of an autoimmune disease may be a relative contraindication to IFN-based therapy[[6](#_ENREF_6),[15](#_ENREF_15)].

Non-organ-specific autoantibodies (NOSA), particularly smooth muscle antibodies (SMA) and antinuclear antibodies (ANA), among others, have been frequently found in chronic HCV carriers[[16-25](#_ENREF_16)]. In such cases, the principal concern is to discriminate between autoimmune hepatitis (AIH) and viral liver disease; this knowledge will influence treatment choices[[13](#_ENREF_13),[18](#_ENREF_18),[24](#_ENREF_24),[26](#_ENREF_26)].

A high prevalence of thyroid dysfunction and anti-thyroid antibodies in patients with HCV infection has been described in the literature[[27-29](#_ENREF_27)]. Furthermore, a major and common adverse effect of HCV IFN-based treatment is the development of thyroid disease during therapy. A broad spectrum of autoimmune thyroid diseases have been reported, including Graves’ disease, thyroiditis, and frank primary hypothyroidism[[10](#_ENREF_10),[11](#_ENREF_11),[30-34](#_ENREF_30)].

With respect to the presence of organ-specific antibodies, although it has been postulated that HCV can induce immunologic intolerance to gluten in susceptible individuals, whether the prevalence of celiac disease (CD), or the levels of endomysial antibodies (EmA) and tissue transglutaminase (tTG) antibodies, are higher in patients with hepatitis C, remains controversial[[19](#_ENREF_19),[35-40](#_ENREF_35)].

From a clinical point-of-view, the presence of autoantibodies arouses suspicion that an autoimmune disease may be present or may be precipitated by IFN-based hepatitis C treatment. Here we review the prevalence of autoantibodies in individuals with hepatitis C, the clinical significance of these autoantibodies, and the approach recommended for such situations.

**NOSA**

NOSA were first described in autoimmune disorders[[41](#_ENREF_41)], and are now frequently found in chronic HCV carriers. Their prevalence varies according to country, as does the titer considered as a cut-off point for positivity (Table 1). The autoantibody most commonly found in chronic hepatitis C is SMA, which exhibits a large variation in its prevalence, ranging between 4% and 78%[[16-21](#_ENREF_16),[23-26](#_ENREF_23),[33](#_ENREF_33),[42-44](#_ENREF_42)]. ANA, a marker for autoimmune liver disease and other inflammatory conditions, has been detected in 4%-54% of patients with chronic HCV infection in several studies[[13](#_ENREF_13),[16-21](#_ENREF_16),[23-26](#_ENREF_23),[33](#_ENREF_33),[42](#_ENREF_42),[44-47](#_ENREF_44)]. Among NOSA, LKM1 is less frequent, with a prevalence of between 0% and 13%[[3](#_ENREF_3),[5,7](#_ENREF_5),[9](#_ENREF_9),[11](#_ENREF_11),[13](#_ENREF_13),[18](#_ENREF_18),[19](#_ENREF_19),[29](#_ENREF_29),[33](#_ENREF_33),[36](#_ENREF_36),[40](#_ENREF_40),[44](#_ENREF_44)]. The major concern regarding the presence of NOSA is the overlap with AIH in HCV-infected patients[[21](#_ENREF_21),[26](#_ENREF_26),[48](#_ENREF_48),[49](#_ENREF_49)]. In AIH, the detection of NOSA, although not pathognomonic, remains the hallmark for diagnosis[[50](#_ENREF_50)]. However, most individuals with hepatitis C and NOSA do not meet the diagnostic criteria for AIH[[41](#_ENREF_41),[49](#_ENREF_49)]. Although the actual prevalence of AIH in this group is unknown, it is estimated that only a minority present overlap[[49](#_ENREF_49)]. AIH is treated with glucocorticoids and an immuno-suppressor such as azathioprine[[50](#_ENREF_50)]. As a rule, such treatment is not recommended for patients with chronic HCV infections, as it generally increases the viremia levels[[51](#_ENREF_51)]. Whereas IFN-based therapy is typically not recommended for patients with AIH, because the immune stimulation produced by such treatment may lead to exacerbation of disease activity[[52-54](#_ENREF_52)]. Thus, a careful distinction needs to be drawn between chronic HCV infection and AIH.

It has been suggested that the management of patients with a possible HCV-AIH overlap syndrome must start with the determination of the predominating entity, thus enabling the selection of the appropriate form of therapy[[55](#_ENREF_55)]. Although no single histological feature is pathognomonic of either HCV or AIH, distinct composite histological patterns have been described for each entity. Patients with AIH are more likely to have severe lobular necrosis and inflammation, piecemeal necrosis, multinucleated hepatocytes, and broad areas of parenchymal collapse. Whereas patients with HCV are more likely to have bile duct damage, bile duct loss, steatosis, and lymphoid cell follicles within portal tracts[[48](#_ENREF_48),[56](#_ENREF_56)]. However, a histological pattern demonstrating intense interface hepatitis has been reported in HCV patients[[26](#_ENREF_26),[57](#_ENREF_57),[58](#_ENREF_58)]. In this pattern, a rosette formation of periportal hepatocytes may not always be considered suggestive of autoimmune injury, since it reflects hepatic regeneration activity as a consequence of greater necroinflammatory activity, and can be observed in other etiologies of liver diseases[[26](#_ENREF_26),[48](#_ENREF_48),[56](#_ENREF_56),[59](#_ENREF_59)].

In the past, at a time when the treatment of choice for hepatitis C was being defined in the literature, when NOSA and histological features of AIH were present, many scientists administered corticosteroids (and sometimes azathioprine) as a first-line treatment of HCV-AIH overlap syndrome[[60-64](#_ENREF_60)]. In such cases, biochemical and histologic improvement were achieved despite an apparent increase in the degree of viremia[[60](#_ENREF_60)]. Whether these patients should be further treated with IFN while they were in biochemical remission and receiving steroids was already under debate at this time.

Today, despite much research, the real relevance of the presence of NOSA in individuals with chronic HCV infection remains a matter of discussion.

Several authors have described higher serum levels of liver tests in HCV patients who test positive for NOSA[[16](#_ENREF_16),[19](#_ENREF_19),[21](#_ENREF_21),[65](#_ENREF_65),[66](#_ENREF_66)], probably reflecting the severity of the underlying liver lesions[[20](#_ENREF_20),[25](#_ENREF_25),[44](#_ENREF_44)]. It has been proposed that ANA could be helpful in predicting a more rapid progression of fibrosis[[45](#_ENREF_45)]. Nevertheless, previous reports have failed to demonstrate significant histological differences between NOSA-positive and NOSA-negative patients[[17](#_ENREF_17),[19](#_ENREF_19),[46](#_ENREF_46),[47](#_ENREF_47),[65-67](#_ENREF_65)].

In terms of antiviral treatment outcome, a negative correlation between the efficacy of anti-viral treatment for HCV and the presence of NOSA[[23](#_ENREF_23),[45](#_ENREF_45),[66](#_ENREF_66),[68](#_ENREF_68),[69](#_ENREF_69)] has been demonstrated, particularly for non-1 genotypes[[65](#_ENREF_65)]. Conversely, baseline ANA status was not a consistent predictor factor of non-response in the majority of earlier studies[[19](#_ENREF_19),[21](#_ENREF_21),[46](#_ENREF_46),[47](#_ENREF_47),[65](#_ENREF_65),[67](#_ENREF_67),[70](#_ENREF_70),[71](#_ENREF_71)]. Nowadays, IFN-based therapy is considered to be effective and safe in NOSA-positive chronic hepatitis C patients for whom the major diagnosis of probable autoimmune hepatitis has been ruled out[[45](#_ENREF_45),[72](#_ENREF_72)]. ALT flares have been reported during IFN treatment in NOSA-positive individuals[[45](#_ENREF_45),[69](#_ENREF_69)]. Some cases may remit with the suspension of the drug and there have been reports of AIH being triggered by IFN, with subsequent of immunosuppression[[69](#_ENREF_69)]. Autoimmune thrombocytopenic purpura is another possible complication in patients with high titers of ANA that have been exposed to IFN-based treatment[[73](#_ENREF_73)].

NOSA titers may increase during treatment[[23](#_ENREF_23),[65](#_ENREF_65),[68](#_ENREF_68),[74](#_ENREF_74)], or might also fade/become negative in some cases[[23](#_ENREF_23),[65](#_ENREF_65),[68](#_ENREF_68),[69](#_ENREF_69)]; moreover, patients that were NOSA-negative prior to treatment may develop autoantibodies during treatment[[23](#_ENREF_23),[65](#_ENREF_65),[69](#_ENREF_69),[74](#_ENREF_74)]. The increase of NOSA titers during IFN-based treatment has been correlated to poor sustained virological response (SVR) rates[[23](#_ENREF_23)]. A careful monitoring of liver biochemistry and NOSA levels is recommended during treatment[[33](#_ENREF_33),[45](#_ENREF_45),[68](#_ENREF_68)]. Autoantibodies should be screened every 3 mo, with monthly monitoring of ALT. High titers of autoantibodies during treatment, with normal ALT, should be monitored, but without great concern. ALT exacerbations should be interpreted with caution, especially if the titers of autoantibodies are high, as they may (or may not) reflect autoimmunity. Differential diagnosis in these cases include drug hepatotoxicity (by IFN or some other drug the individual may have taken during treatment) or another viral infection, among others. Table 2 details the influence of NOSA on interferon-based treatment outcome in several studies.

Considering the above, IFN-free regimens[[75](#_ENREF_75)] are the logical choice for patients with high titers of NOSA and histological findings that suggest HCV-AIH overlap syndrome, despite the fact that no clinical trials have specifically evaluated this issue.

**THYROID AUTOANTIBODIES**

Autoimmune thyroid diseases (AITD) are a group of disorders characterized by loss of immunological self-tolerance, whose most common forms include Graves’ disease and Hashimoto’s thyroiditis[[79](#_ENREF_79),[80](#_ENREF_80)]. AITD are characterized by the presence of thyroid autoantibodies (TAAb), such as thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TGAb), and thyroid stimulating hormone (TSH) receptor antibodies (TRAb)[[12](#_ENREF_12),[80-83](#_ENREF_80)].

Hashimoto’s thyroiditis is the most common clinical manifestation of AITD. The disease manifests itself through subclinical hypothyroidism (elevated TSH levels, normal free thyroxin (fT4) levels), or clinically apparent hypothyroidism (elevated TSH, low fT4). Goiter occurs in some patients. The disease is diagnosed on the basis of hypothyroidism symptoms and the presence of TPOAb and/or TgAb[[12](#_ENREF_12)]. Graves’ disease is an autoantibody-mediated autoimmune disease characterized by thyrotoxicosis. Graves’ disease is caused by direct stimulation of the thyroid epithelial cells by TRAb[[84](#_ENREF_84)]. Physical examination shows hyperthyroidism symptoms and goiter. Graves’ ophthalmopathy may be apparent. Laboratory tests show a characteristic decrease in TSH levels, an increase in fT4 and free triiodothyronine (fT3) levels, and the presence of TRAb[[12](#_ENREF_12)]. The ability of TRAb to provide differential diagnoses of overt hyperthyroidism is excellent, with a sensitivity and specificity above 90%[[84](#_ENREF_84)].

Thyroid autoimmunity is a common characteristic of HCV infection[[85](#_ENREF_85),[86](#_ENREF_86)]. A high prevalence of TAAb in chronic HCV carriers has been reported over the years, varying from 4.5%-25%[[10](#_ENREF_10),[27](#_ENREF_27),[29](#_ENREF_29),[87-92](#_ENREF_87)]. The prevalences of TPOAb and TGAb vary from 5.4%-30%[[20](#_ENREF_20),[27](#_ENREF_27),[28](#_ENREF_28),[34](#_ENREF_34),[87](#_ENREF_87),[88](#_ENREF_88),[93-97](#_ENREF_93)] and 0%-30.7%[[20](#_ENREF_20),[27](#_ENREF_27),[28](#_ENREF_28),[34](#_ENREF_34),[88](#_ENREF_88),[95](#_ENREF_95),[96](#_ENREF_96),[98](#_ENREF_98)], respectively (Table 3). Such a remarkable variation may be attributable to the different methods used, and/or to the different geography, race, age, and sex of the populations targeted in these reported studies[[99](#_ENREF_99)]. Environmental cofactors such as iodine intake or other infectious agents could also play an important role in the development of autoimmune thyroid disorders[[100](#_ENREF_100)]. TAAb are more frequent among women[[29](#_ENREF_29),[93-96](#_ENREF_93),[101](#_ENREF_101)], and their prevalence increases with age[[101](#_ENREF_101)].

The presence of TAAb does not always reflect the presence of AITD; many individuals may be asymptomatic with normal levels of thyroid hormones. The presence of TAAb may indicate subclinical thyroid disease and an increased risk of developing clinical thyroid disease[[87](#_ENREF_87),[101](#_ENREF_101)]. The prevalence of thyroid dysfunction in individuals with chronic hepatitis C varies from 3.6%-23%[[33](#_ENREF_33),[87](#_ENREF_87),[90](#_ENREF_90),[93-96](#_ENREF_93),[98](#_ENREF_98),[102](#_ENREF_102)]. Several possible explanations exist for these wide variations in the incidence of reported TAAb in IFN-treated patients, including the various assays used to test for TAAb, the cut-offs used to define serum positivity, and the variability in ethnicity of the patients studied[[80](#_ENREF_80)].

No relationship has been observed between serum concentrations of TSH or thyroid hormone and autoantibody titers[[100](#_ENREF_100)]. Nonetheless, the high prevalence of AITD (*i.e.*, Hashimoto’s thyroiditis, atrophic autoimmune thyroiditis, and Graves’ disease) in patients with chronic HCV infections is often associated with humoral thyroid autoimmunity (TAAb serum levels above normal values)[[87](#_ENREF_87),[94](#_ENREF_94),[95](#_ENREF_95),[98](#_ENREF_98)].

A major concern about the presence of TAAb, besides the current existence of AITD, is to recognize the risk of the patient developing thyroid disease during IFN-based treatment[[27](#_ENREF_27)]. It has been long known that pretreatment-reactive TAAb represent a high risk for overt thyroid dysfunction during IFN-based therapy[[27](#_ENREF_27)]. The pegylated form of IFN seems to have the same effects as standard IFN[[103](#_ENREF_103)]. IFN dose and duration do not influence the development of IFN-induced thyroiditis[[102](#_ENREF_102),[104](#_ENREF_104)], nor do they affect virological response.[[102](#_ENREF_102)] Although some authors do not agree[[90](#_ENREF_90),[98](#_ENREF_98)], several studies have shown that IFN-based treatments of hepatitis C can either induce the production of TAAb, or cause a significant increase in TAAb levels, in individuals who were positive for TAAb prior to IFN therapy. Seropositivity for LKM1 may also predispose patients receiving IFN therapy for hepatitis C to develop AITD[[33](#_ENREF_33)]. The rate of development of TAAb secondary to IFN therapy varies from 1.9%-40.0%[[27](#_ENREF_27),[90](#_ENREF_90),[91](#_ENREF_91),[93](#_ENREF_93),[94](#_ENREF_94),[97](#_ENREF_97),[104-110](#_ENREF_104)]. Besides immunomediated thyroid dysfunction, it is noteworthy that TAAb are not detected in approximately 50% of patients with thyroid function disorders during IFN therapy. This finding indicates the direct toxic effect of IFN on thyroid cells, without the participation of immunological factors[[12](#_ENREF_12),[96](#_ENREF_96)]. There are two recognized clinical forms of non-autoimmune thyroiditis: destructive thyroiditis[[97](#_ENREF_97),[109](#_ENREF_109)] and non-autoimmune hypothyroidism[[91](#_ENREF_91),[97](#_ENREF_97),[108](#_ENREF_108)], which will not be addressed here since they are beyond the scope of this article.

IFN-induced thyroiditis is a major clinical problem for patients who receive IFN therapy, with complications such as thyrotoxicosis being especially severe[[97](#_ENREF_97)]. Symptoms of thyroid dysfunction can easily be mistaken for adverse effects of the HCV therapy, and could remain undiagnosed if patients do not undergo routine periodic screening of TSH and fT4 levels[[111](#_ENREF_111)]. The reversibility of AITD after IFN withdrawal is controversial. Initially, the thyroid disorders induced by IFN were described as reversible[[110](#_ENREF_110)]. Later, it was demonstrated that in more than one third of treated patients, hypothyroidism may persist[[94-96](#_ENREF_94)]. Although it has been demonstrated that Graves’ thyrotoxicosis may not be reversible with IFN withdrawal[[108](#_ENREF_108)], in a recent cohort of 18 hepatitis C patients who developed thyroiditis during INF-based treatment, all cases recovered[[112](#_ENREF_112)]. Late-onset thyroid dysfunction has also been observed after discontinuation of IFN-based treatment (6-mo post-treatment)[[94](#_ENREF_94),[95](#_ENREF_95)]. Perhaps monitoring for thyroid disease could be safely ceased at the 6-mo follow-up, coinciding with the SVR review[[112](#_ENREF_112)].

Finally, it has been reported that IFN-based therapy does not aggravate previous existing thyroid disease[[94](#_ENREF_94)], although some patients treated with thyroid medication before IFN treatment may require increased doses during therapy, and decreased doses after IFN therapy has been completed[[107](#_ENREF_107)]. When hypothyroidism occurs, thyroxin therapy should be initiated promptly[[100](#_ENREF_100)]. Hashimoto’s thyroiditis is rarely the reason for premature termination of therapy with IFN[[12](#_ENREF_12)]. While in cases of symptomatic thyrotoxicosis, withholding IFN therapy should be considered only after consulting with an endocrinologist[[108](#_ENREF_108)]. If thyrotoxicosis is suspected, and TRAb is negative, patients should undergo a thyroid scan to check for diffusely increased uptake[[80](#_ENREF_80)]. Patients with destructive thyroiditis should be closely monitored for the development of hypothyroidism, which typically follows the hyperthyroid phase within a few weeks[[80](#_ENREF_80)].

Regardless of symptoms, all patients should be screened for TAAb (TPOAb, TGAb, TRAb) and thyroid function (serum TSH, fT4) prior to starting IFN therapy[[80](#_ENREF_80)]. In patients with TAAb positivity, the choice of an IFN-based therapy must be made cautiously, taking into account the potential benefit of IFN treatment and the high risk of thyroid disease. IFN-free regimens[[30](#_ENREF_30)] are likely to be more suitable in such cases. In patients without TAAb, thyroid function and the presence of TAAb must be systematically tested (every 2-3 mo) during IFN therapy, particularly in women[[80](#_ENREF_80),[94](#_ENREF_94),[95](#_ENREF_95),[99](#_ENREF_99),[113](#_ENREF_113)].

**CELIAC DISEASE ANTIBODIES**

CD is a chronic, small-intestinal, immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed people[[114](#_ENREF_114)]. CD is now considered to be a multisystemic disorder, rather than a sole gastrointestinal process[[115](#_ENREF_115)]. CD is triggered by the ingestion of gluten, the protein component of wheat, rye, and barley[[116](#_ENREF_116),[117](#_ENREF_117)]. Such exposure results in a variable degree of intestinal damage[[118](#_ENREF_118)]. Since many patients have minor but chronic symptoms long before the full-blown malabsorption pattern develops, it may be readily possible to identify these patients at an earlier stage of the disease process by accurate screening blood tests: *e.g.*, IgA anti-endomysial antibodies (EmA), IgA anti-tissue transglutaminase antibodies (tTG), and the more recent test for deamidated gliadin peptides (DGP)[[119-121](#_ENREF_119)]. Positive serology with normal histology, formerly called latent CD[[122](#_ENREF_122)], is now defined as potential CD[[114](#_ENREF_114)]. Positive serology and characteristic morphological changes in the small intestinal biopsy, in the absence of clinical signs and symptoms, was previously classified as silent[[122](#_ENREF_122)], but is now defined as asymptomatic CD[[114](#_ENREF_114)]. Once a diagnosis of celiac sprue has been established, the conventional treatment is a gluten-free diet[[122](#_ENREF_122)]. Adherence to a gluten-free diet and mucosal healing may not only relive symptoms and improve the patient’s quality of life, but also prevent or ameliorate CD-associated complications, such as intestinal lymphoma and the emergence of other autoimmune diseases[[115](#_ENREF_115),[121](#_ENREF_121),[123](#_ENREF_123)].

Gliadins, the alcohol-soluble fraction of gluten, elicit a strong humoral response in CD, which originates in the submucosa[[120](#_ENREF_120)]. Anti-gliadin antibodies (AGA), which have been used for decades, have moderate sensitivity but are far less specific than tests for IgA antiendomysial antibodies[[124](#_ENREF_124),[125](#_ENREF_125)]. Thus, AGA is no longer recommended for the primary detection of CD[[126](#_ENREF_126),[127](#_ENREF_127)]. Endomysium is a connective tissue protein found in the collagenous matrix of human tissue. The test to detect EmA is based on the immunofluorescence findings of reticular staining when EmA binds to the endomysium. Although highly specific when positive, EmA will be absent in individuals with CD with IgA deficiency[[120](#_ENREF_120)]. Selective IgA deficiency affects approximately 2%-5% of patients diagnosed with CD[[128](#_ENREF_128)]. tTG is a cytosolic protein that is released by the injured epithelium and serves as a cross-linker of various extracellular matrix proteins, including gliadin[[120](#_ENREF_120)]. IgA and IgG enzyme-linked immunosorbent assay (ELISA) tests are available with high sensitivity and specificity for the diagnosis of CD. Optimal results were achieved by combining a positive EmA test result and a positive IgA-tTG test result, with a sensitivity of 0.81 and a specificity of 0.99[[119](#_ENREF_119)]. In patients with a high-probability CD and IgA deficiency, DGP IgG-based testing is advocated[[126](#_ENREF_126)].

Liver involvement in CD has been widely described in case reports and case series. CD is at least twice as common in cirrhotic patients than in the general population[[129](#_ENREF_129)]. Some individual present abnormal liver tests, by the diagnosis of CD, that regularize with a gluten-free diet[[130-135](#_ENREF_130)]. CD has been described in association with autoimmune liver diseases[[136-140](#_ENREF_136)], and also with HCV[[36](#_ENREF_36),[40](#_ENREF_40),[139](#_ENREF_139),[141-143](#_ENREF_141)]. In the presence of intestinal inflammation, liver disease may be driven by lymphocytes generated in the intestine, which enter the portal circulation and trigger hepatic inflammation upon reactivation. This enterohepatic pathway is facilitated by the aberrant expression of adhesion molecules and chemokines that, under normal conditions, are restricted to either the gut or liver[[144](#_ENREF_144)].

Few studies have evaluated the prevalence of celiac antibodies in the HCV population. AGA prevalence varies between 6.3% and 32%[[141](#_ENREF_141),[142](#_ENREF_142),[145](#_ENREF_145)], while EmA prevalence varies between 0% and 5.8%[[20](#_ENREF_20),[40](#_ENREF_40),[145](#_ENREF_145)], and tTG antibodies have been reported in between 0% and 1% of patients with HCV[[20](#_ENREF_20),[40](#_ENREF_40),[145](#_ENREF_145)] (Table 4). Among patients with chronic liver disease, AGA positivity generally occurs at an increased frequency and may represent non-specific immune activation[[141](#_ENREF_141),[142](#_ENREF_142),[145](#_ENREF_145)]. Therefore, in the presence of liver disease, AGA testing is not useful in screening for CD. Whereas the EmA test seems to be highly specific for CD[[141](#_ENREF_141)].

A French multi-center study failed to demonstrate an association between HCV and CD, perhaps due to the low prevalence of CD in that country[[145](#_ENREF_145)]. Similarly, Hernandez *et al*[[40](#_ENREF_40)] did not find evidence for a higher prevalence of HCV among individuals with CD and *vice versa*[[40](#_ENREF_40)]. Silano *et al*[[146](#_ENREF_146)] identified a low prevalence (0.91%) of reactive anti-HCV in individuals with CD. In a recent Italian study, CD serologic screening was negative in all HCV patients; the prevalence of HCV infection among celiac patients was 1.54%, comparable to that reported in the Southern Italy population[[35](#_ENREF_35)]. Given these findings, there is little evidence to support the role of screening HCV patients for CD[[40](#_ENREF_40),[146](#_ENREF_146)]. Even if there is no association between the two diseases (and this question is yet to be definitively answered), the main concern is that patients may present severe cases of overt CD during HCV treatment, leading to IFN discontinuation. It is not clear whether the development of CD during IFN-based therapy is due to the general increased risk of developing autoimmunity or is specifically related to the role of IFN in promoting T helper cell type 1 responses in the small intestine in CD[[147](#_ENREF_147),[148](#_ENREF_148)].

The activation of CD during IFN treatment has been reported in some cases. Patients may experience severe diarrhea with weight loss during IFN treatment[[9](#_ENREF_9),[149-154](#_ENREF_149)], as well as dermatitis herpetiformis[[9](#_ENREF_9),[155](#_ENREF_155)], hypoferritinemia[[154](#_ENREF_154),[156](#_ENREF_156),[157](#_ENREF_157)], and refractory anemia that persist after treatment has stopped[[149](#_ENREF_149),[152](#_ENREF_152),[154](#_ENREF_154)]. Treatment interruption has been reported[[149](#_ENREF_149),[150](#_ENREF_150),[152](#_ENREF_152)]. However, early diagnosis of CD enables prompt management with a gluten-free diet, which can permit the completion of IFN-based treatment[[151](#_ENREF_151)]. Some individuals with a previous diagnosis of CD while following a gluten-free diet may experience symptoms such as diarrhea during IFN treatment, while other individuals may experience no symptoms[[39](#_ENREF_39)]. Late onset CD has also been observed after discontinuation of IFN-based treatment (various months post treatment)[[8](#_ENREF_8),[37](#_ENREF_37)]. Intestinal diffuse large B cell lymphoma has been reported in an IFN-experienced elder non-adherent to a gluten-free diet[[38](#_ENREF_38)].

Durante-Mangoni *et al*[[14](#_ENREF_14)] retrospectively evaluated 534 hepatitis C patients during IFN treatment. Prior to treatment, tTG were detected in 1.3% of hepatitis C patients and in 0.4% of controls (not significant). Eighty-six percent of patients with tTG showed activation of CD while receiving IFN-based treatment. Overall, 1.3% of IFN-treated patients had discontinued treatment of a CD-like condition.

Although IFN-based therapy *per se* can cause diarrhea in up to 10% of patients[[127](#_ENREF_127)], it is important to exclude other causes (mainly infectious and autoimmunity) prior to attributing the symptoms to IFN therapy[[154](#_ENREF_154)]. Given the difficulty in determining the cause of new symptoms while on IFN-based therapy, baseline screening for celiac-associated antibodies prior to the commencement of therapy is likely to be beneficial in guiding further investigations and disease management in patients who develop symptoms that may be attributable to CD during therapy[[14](#_ENREF_14),[143](#_ENREF_143),[149-152](#_ENREF_149),[155](#_ENREF_155),[156](#_ENREF_156),[158](#_ENREF_158)]. For patients with positive antibodies, IFN-free therapies should be considered. If IFN-based therapy is the first choice, a gluten-free diet must be started preemptively[[14](#_ENREF_14),[153](#_ENREF_153)], considering the risk of developing overt CD.

In conclusion, autoantibodies are extremely important in the follow-up of chronically infected HCV individuals, in determining the choice of treatment, and in IFN-based treatment management. Positive autoantibodies require careful consideration of IFN-free regimens. If IFN-free regimens are not available, NOSA and TAAb must be tested every 2-3 mo and physicians should be aware of the risk of the onset of an autoimmune disease.

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**Table 1 Prevalence of non-organ specific autoantibodies in patients with chronic hepatitis C**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Antibody** | **%** | ***N*** | **Titer** | **Country** | **Year** | **Ref.** |
| SMA | 78 | 25/40 | - | Taiwan | 2001 | Peng[[16](#_ENREF_16)] |
| 74.5 | 76/102 | > 1:80 | Greece | 2007 | Gatselis *et al*[[23](#_ENREF_23)] |
| 66.2 | 43/65 | > 1:20 | Germany | 1995 | Clifford *et al*[[17](#_ENREF_17)] |
| 55 | 34/62 | > 1:20 | United States | 1993 | Fried *et al*[[18](#_ENREF_18)] |
| 27.3 | 137/502 | > 1:40 | Italy multicenter | 2004 | Stroffolini *et al*[[19](#_ENREF_19)] |
| 26 | 9/35 | > 1:40 | India | 2012 | Daschakraborty *et al*[[24](#_ENREF_24)] |
| 26.7 | 12/45 | > 1:40 | Brazil | 2013 | Marconcini *et al*[[20](#_ENREF_20)] |
| 20 | 59/290 | > 1:40 | Italy | 1997 | Cassani *et al*[[21](#_ENREF_21)] |
| 17.8 | 62/348 | > 1:40 | Italy | 2005 | Muratori *et al*[[33](#_ENREF_33)] |
| 15 | 28/186 | > 1:80 | France | 2009 | Chrétien *et al*[[25](#_ENREF_25)] |
| 12.7 | 36/283 | > 1:40 | Italy | 2003 | Squadrito *et al*[[44](#_ENREF_44)] |
| 9.6 | 7/52 | > 1:40 | Iran | 2006 | Daryani *et al*[[67](#_ENREF_67)] |
| 5.4 | 5/92 | - | Brazil | 2010 | Badiani *et al*[[26](#_ENREF_26)] |
| 4.3 | 6/138 | > 1:40 | Greece | 2007 | Rigopoulou *et al*[[43](#_ENREF_43)] |
| ANA | 54 | 55/102 | > 1:80 | Greece | 2007 | Gatselis *et al*[[23](#_ENREF_23)] |
| 32 | 60/186 | > 1:80 | France | 2009 | Chrétien *et al*[[25](#_ENREF_25)] |
| 22.9 | 11/48 | > 1:50 | Taiwan | 2001 | Peng *et al*[[16](#_ENREF_16)] |
| 21 | 13/62 | > 1:80 | United States | 1993 | Fried *et al*[[18](#_ENREF_18)] |
| 20 | 7/35 | > 1:80 | India | 2012 | Daschakraborty *et al*[[24](#_ENREF_24)] |
| 19.9 | 79/502 | > 1:40 | Italy multicenter | 2004 | Stroffolini *et al*[[19](#_ENREF_19)] |
| 14 | 13/92 | > 1:80 | Germany | 1995 | Clifford *et al*[[17](#_ENREF_17)] |
| 12 | 11/92 | > 1:80 | Brazil | 2010 | Badiani *et al*[[26](#_ENREF_26)] |
| 11.5 | 6/52 | > 1:40 | Iran | 2006 | Daryani *et al*[[67](#_ENREF_67)] |
| 9.4 | 22/234 | > 1:80 | Brazil | 2009 | Narciso-Schiavon *et al* [[46](#_ENREF_46)] |
| 9.0 | 26/290 | > 1:40 | Italy | 1997 | Cassani *et al*[[21](#_ENREF_21)] |
| 7.8 | 50/645 | > 1:40 | Europe multicenter | 2004 | Yee *et al*[[47](#_ENREF_47)] |
| 7.7 | 22/283 | > 1:40 | Italy | 2003 | Squadrito *et al*[[44](#_ENREF_44)] |
| 7.6 | 5/66 | > 1:40 | Brazil | 2013 | Marconcini *et al*[[20](#_ENREF_20)] |
| 6 | 21/348 | > 1:40 | Italy | 2005 | Muratori *et al*[[33](#_ENREF_33)] |
| 5.8 | 14/243 | > 1:80 | Taiwan | 2012 | Hsieh *et al*[[45](#_ENREF_45)] |
| 3.6 | 5/138 | > 1:40 | Greece | 2007 | Rigopoulou *et al*[[43](#_ENREF_43)] |
| anti-LKM1 | 13 | 18/138 | > 1:40 | Greece | 2007 | Rigopoulou *et al*[[43](#_ENREF_43)] |
| 8 | 28/348 | > 1:80 | Italy | 2005 | Muratori *et al*[[33](#_ENREF_33)] |
| 6.8 | 3/44 | > 1:40 | Brazil | 2013 | Marconcini *et al*[[20](#_ENREF_20)] |
| 6 | 18/290 | > 1:40 | Italy | 1997 | Cassani *et al*[[21](#_ENREF_21)] |
| 3 | 3/102 | > 1:40 | Greece | 2007 | Gatselis *et al*[[23](#_ENREF_23)] |
| 2.2 | 11/502 | > 1:40 | Italy multicenter | 2004 | Stroffolini *et al*[[19](#_ENREF_19)] |
| 2 | 1/41 | > 1:10 | Germany | 1995 | Clifford *et al*[[17](#_ENREF_17)] |
| 1.9 | 1/52 | - | Iran | 2006 | Daryani *et al*[[67](#_ENREF_67)] |
| 0.7 | 2/283 | > 1:40 | Italy | 2003 | Squadrito *et al*[[44](#_ENREF_44)] |
| 0.5 | 1/186 | > 1:40 | France | 2009 | Chrétien *et al*[[25](#_ENREF_25)] |
| 0 | 0/35 | > 1:80 | India | 2012 | Daschakraborty *et al*[[24](#_ENREF_24)] |
| 0 | 0/92 | - | Brazil | 2010 | Badiani *et al*[[26](#_ENREF_26)] |
| 0 | 0/62 | - | United States | 1993 | Fried *et al*[[18](#_ENREF_18)] |
| 0 | 0/24 | > 1:10 | United States | 1992 | Czaja *et al*[[22](#_ENREF_22)] |

NOSA: Non-organ specific autoantibody; SMA: Smooth muscle antibody; ANA: Antinuclear antibody; LKM1: Anti-liver kidney microsome-1.

**Table 2 The influence of non-organ specific autoantibodies in interferon based treatment outcome in patients with chronic hepatitis C**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | ***N*** | **Treatment** | **NOSA evaluated in the study** | **Titers of NOSA increased during treatment** | **Development of NOSA during treatment** | **Autoimmune disease triggered during treatment** | **Influence on SVR**b |
| Lopes *et al*[[74](#_ENREF_74)], 1995 | Brazil | 21 | IFN-α | ANA, SMA,  AMA, *etc.* | ↑ | ANA | N | N |
| Cassani *et al*[[21](#_ENREF_21)], 1997 | Italy | 144 | IFN-α | ANA, SMA | N/A | N/A | N/A | N |
| Muratori *et al*[[69](#_ENREF_69)], 2003 | Italy | 22a | IFN-α | ANA, SMA, LKM1 | N/A | ANA,  SMA | 2 ALT flare 7-10 xULN | Y |
| Wasmuth *et al*[[66](#_ENREF_66)], 2004 | Germany | 48 | IFN-α + RBV | ANA, SMA, LKM1, AMA, ANCA | N/A | N/A | N/A | Y |
| Yee *et al*[[47](#_ENREF_47)], 2004 | Europe multicenter | 258 | IFN-α | ANA | N/A | N/A | N/A | N |
| Stroffolini *et al*[[19](#_ENREF_19)] | Italy | 502 | IFN-α + RBV | ANA, SMA, LKM1, AMA | N/A | N/A | N | N |
| Muratori *et al*[[65](#_ENREF_65)], 2005 | Italy | 143 | IFN-α + RBV | ANA, SMA, LKM1 | ↑ | Y | N | N |
| Gatselis *et al*[[68](#_ENREF_68)],2005 | Greece | 57 | IFN-α + RBV | ANA, SMA, LKM1,  AMA,  ANCA, *etc.* | ↑ | ANA, LKM1,  ANCA | N | Y |
| Gatselis *et al*[[23](#_ENREF_23)], 2006 | Greece | 102 | IFN-α / PEG+ RBV | ANA, SMA, LKM1,  AMA,  ANCA, *etc.* | ↑ | Y | N | Y |
| Daryani *et al*[[67](#_ENREF_67)], 2006 | Iran | 52 | IFN-α + RBV | ANA,  SMA,  LKM1,  AMA | N/A | N/A | N/A | N |
| Narciso-Schiavon *et al*[[46](#_ENREF_46)] | Brazil | 234 | IFN-α + RBV | ANA | N/A | N/A | N | N |
| Li *et al*[[76](#_ENREF_76)], 2009 | China | 46 | IFN-α | ANA,  LKM1 | N/A | N/A | N | N |
| Hsieh *et al*[[45](#_ENREF_45)], 2012 | Taiwan | 243 | PEG + RBV | ANA, SMA, LKM1,  AMA,  ANCA | N/A | N/A | ALT flare | Y |
| Mauss *et al*[[77](#_ENREF_77)], 2013 | Germany | 12369 | PEG + RBV | ANA, SMA, LKM1,  AMA | N/A | N/A | N | N |
| Khairy *et al*[[78](#_ENREF_78)], 2013 | Egypt | 3673 |  |  | N/A | N/A | N | N |

aChildren; bHigher sustained virological response rates in NOSA negative group. NOSA: Non-organ specific autoantibodies; IFN-α: Interferon alpha; SVR: Sustained virological response; ANA: Antinuclear antibody; SMA: Smooth muscle antibody; xULN: Times the upper limit of normality; RBV: Ribavirin; AMA: Anti-mitochondrial antibodies; LKM1: Liver kidney microsomal type 1 antibody; ANCA: Anti-neutrophil cytoplasmic antibody; PEG: Pegylated interferon alpha; ↑: Increase; N: No; Y: Yes; N/A: Not available.

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| **Table 3 Prevalence of serum thyroid autoantibodies in patients with chronic hepatitis C** | | | | | | |
| **Autoantibody** | **%** | ***N*** | **Positive values (U/mL)** | **Country** | **Year** | **Ref.** |
| TAAb | 25 | 132/630 | > 150 | Italy | 2004 | Antonelli *et al*[[87](#_ENREF_87)] |
| 14 | 9/66 | > 50/100 | France | 1992 | Pateron *et al*[[159](#_ENREF_159)] |
| 12.5 | 9/76 | - | France | 1993 | Tran *et al*[[89](#_ENREF_89)] |
| 9.4 | 42/449 | ≥ 100 | Taiwan | 2012 | Huang *et al*[[88](#_ENREF_88)] |
| 9.7 | 7/72 | - | Italy | 2002 | Carella *et al*[[90](#_ENREF_90)] |
| 7 | 5/71 | ≥ 60 | Greece | 2011 | Vasiliadis *et al*[[10](#_ENREF_10)] |
| 6.7 | 14/207 | - | Spain | 1996 | Marazuela *et al*[[91](#_ENREF_91)] |
| 5.6 | 4/71 | ≥ 100 | Italy | 2006 | Floreani *et al*[[29](#_ENREF_29)] |
| 4.5 | 5/111 | ≥ 100 | United Kingdom | 1997 | Metcalfe *et al*[[92](#_ENREF_92)] |
| TPOAb | 30.8 | 60/195 | ≥ 50 | China | 2011 | Yang *et al*[[28](#_ENREF_28)] |
| 21 | 132/630 | > 150 | Italy | 2004 | Antonelli *et al*[[87](#_ENREF_87)] |
| 20 | 26/134 | > 150 | Spain | 1998 | Fernandez-Soto *et al*[[95](#_ENREF_95)] |
| 16.3 | 51/312 | > 35 | China | 2013 | Shao *et al*[[34](#_ENREF_34)] |
| 15 | 30/200 | > 18 | Greece | 1997 | Deutsch *et al*[[94](#_ENREF_94)] |
| 14 | 9/66 | > 50/100 | France | 1992 | Pateron *et al*[[159](#_ENREF_159)] |
| 10 | 3/32 | > 100 | Italy | 1996 | Roti *et al*[[97](#_ENREF_97)] |
| 7.4 | 4/54 | - | Brazil | 2013 | Marconcini *et al*[[20](#_ENREF_20)] |
| 6.7 | 13/192 | > 100 | Spain | 1995 | Boadas *et al*[[93](#_ENREF_93)] |
| 6.5 | 29/449 | ≥ 100 | Taiwan | 2012 | Huang *et al*[[88](#_ENREF_88)] |
| 5.4 | 9/168 | - | France | 2005 | Moncoucy *et al*[[96](#_ENREF_96)] |
| 3.5 | 9/254 | > 60 | Norway | 2002 | Dalgard *et al*[[102](#_ENREF_102)] |
| TGAb | 30.8 | 60/195 | ≥ 40 | China | 2011 | Yang *et al*[[28](#_ENREF_28)] |
| 17 | 108/630 | > 150 | Italy | 2004 | Antonelli *et al*[[87](#_ENREF_87)] |
| 13.3 | 44/312 | > 35 | China | 2013 | Shao *et al*[[34](#_ENREF_34)] |
| 11 | 15/134 | > 200 | Spain | 1998 | Fernandez-Soto *et al*[[95](#_ENREF_95)] |
| 10 | 13/130 | - | Taiwan | 1999 | Huang *et al*[[98](#_ENREF_98)] |
| 8 | 13/162 | - | France | 2005 | Moncoucy *et al*[[96](#_ENREF_96)] |
| 7.6 | 5/66 | ≥ 50 | France | 1992 | Pateron *et al*[[159](#_ENREF_159)] |
| 5.8 | 13/449 | ≥ 100 | Taiwan | 2012 | Huang *et al*[[88](#_ENREF_88)] |
| 0 | 0/48 | - | Brazil | 2013 | Marconcini *et al*[[20](#_ENREF_20)] |

TAAb: Thyroid autoantibodies; TPOAb: Anti thyroperoxidase; TGAb: Antithyroglobulin antibody.

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| **Table 4 Prevalence of celiac disease autoantibodies in patients with chronic hepatitis C** | | | | | |
| **Autoantibody** | **%** | ***N*** | **Country** | **Year** | **Ref.** |
| AGA | 32 | 82/359 | United States | 2001 | Fine *et al*[[142](#_ENREF_142)] |
| 11 | 11/104 | Sweden | 1997 | Sjöberg *et al*[[141](#_ENREF_141)] |
| 6.3 | 37/583 | France multicenter | 2007 | Thevenot *et al*[[145](#_ENREF_145)] |
| EmA/tTG | 3.5 | 7/195 | Italy | 2004 | Durante-Mangoni *et al*[[14](#_ENREF_14)] |
| 2.0 | 5/244 | Italy | 2007 | Ruggeri *et al*[[36](#_ENREF_36)] |
| 1.2 | 3/259 | United States | 2001 | Fine *et al*[[142](#_ENREF_142)] |
| 0 | 0/210 | Italy | 2012 | Gravina *et al*[[35](#_ENREF_35)] |
| EmA | 5.8 | 3/52 | Brazil | 2013 | Marconcini *et al*[[20](#_ENREF_20)] |
| 0.2 | 1/623 | France multicenter | 2007 | Thevenot *et al*[[145](#_ENREF_145)] |
| 0 | 0/195 | United States | 2008 | Hernandez *et al*[[40](#_ENREF_40)] |
| tTG | 1 | 2/195 | United States | 2008 | Hernandez *et al*[[40](#_ENREF_40)] |
| 0 | 0/34 | Brazil | 2013 | Marconcini *et al*[[20](#_ENREF_20)] |
| 0 | 0/41 | France multicenter | 2007 | Thevenot *et al*[[145](#_ENREF_145)] |

CD: Celiac disease; AGA: Antigliadin antibody; EmA: Anti-endomysial antibody; tTG: Tissue transglutaminase.