REVIEW

Autoantibodies in chronic hepatitis C: A clinical perspective

Janaína Luz Narciso-Schiavon, Leonardo de Lucca Schiavon

Janaína Luz Narciso-Schiavon, Leonardo de Lucca Schiavon, Department of Internal Medicine, Gastroenterology Division, Federal University of Santa Catarina, Florianópolis, Santa Catarina 88040-900, Brazil

Author contributions: Both authors contributed to this manuscript.

Conflict-of-interest: None declared.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Janaína Luz Narciso-Schiavon, MD, PhD, Department of Internal Medicine, Gastroenterology Division, Federal University of Santa Catarina, R. Prof. Mª Flora Pausewang s/nº, 3º andar, Trindade, Florianópolis, Santa Catarina 88040-900, Brazil. janaina.narciso@uol.com.br
Telephone: +55-48-37219149
Fax: +55-48-37219014
Received: September 26, 2014
Peer-review started: September 28, 2014
First decision: December 17, 2014
Revised: January 16, 2015
Accepted: February 4, 2015
Article in press: February 9, 2015
Published online: May 18, 2015

Abstract

Non-organ-specific autoantibodies and thyroid auto-antibodies 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.

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.

Narciso-Schiavon JL, Schiavon LL. Autoantibodies in chronic hepatitis C: A clinical perspective. *World J Hepatol* 2015; 7(8): 1074-1085 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i8/1074.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i8.1074

INTRODUCTION

It is estimated that 2%-3% of the world's population is infected with the hepatitis C virus (HCV)[1]. HCV causes chronic hepatitis, cirrhosis, and hepatocellular carcinoma[2]. HCV has been implicated both in the triggering of autoimmune diseases and in the development of autoantibodies[3,4]. 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[3,4].

Until recently, the association of pegylated interferon-alfa (IFN) with ribavirin was the gold-standard treatment for hepatitis C[5,6]. IFN may induce autoimmune disorders or worsen pre-existing autoimmune disorders[7-14]. 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[6,15].

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

A high prevalence of thyroid dysfunction and anti-thyroid antibodies in patients with HCV infection has been described in the literature[27-29]. 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[10,11,30-34].

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[19,35-40].

From a clinical point-of-view, the presence of auto-antibodies 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], 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%[16-21,23-26, 33,42-44]. 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[13,16-21,23-26,33,42,44-47]. Among NOSA, anti-liver kidney microsome-1 (LKM1) is less frequent, with a prevalence of between 0% and 13%[3,5,7,9,11,13,18, 19,29,33,36,40,44]. The major concern regarding the presence of NOSA is the overlap with AIH in HCV-infected patients[21,26,48,49]. In AIH, the detection of NOSA, although not pathognomonic, remains the hallmark for

diagnosis[50]. However, most individuals with hepatitis C and NOSA do not meet the diagnostic criteria for AIH[41,49]. Although the actual prevalence of AIH in this group is unknown, it is estimated that only a minority present overlap[49]. AIH is treated with glucocorticoids and an immuno-suppressor such as azathioprine[50]. As a rule, such treatment is not recommended for patients with chronic HCV infections, as it generally increases the viremia levels[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]. 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]. 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[48,56]. However, a histological pattern demonstrating intense interface hepatitis has been reported in HCV patients[26,57,58]. 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[26,48,56,59].

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]. In such cases, biochemical and histologic improvement were achieved despite an apparent increase in the degree of viremia[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[16,19,21,65,66], probably reflecting the severity of the underlying liver lesions[20,25,44]. It has been proposed that ANA could be helpful in predicting a more rapid progression of fibrosis[45]. Nevertheless, previous reports have failed to demonstrate significant histological differences between NOSA-positive and NOSA-negative patients[17,19,46,47,65-67].

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

SMA: Smooth muscle antibody; ANA: Antinuclear antibody; LKM1: Anti-liver kidney microsome-1.

In terms of antiviral treatment outcome, a negative correlation between the efficacy of anti-viral treatment for HCV and the presence of NOSA[23,45,66,68,69] has been demonstrated, particularly for non-1 genotypes[65]. Conversely, baseline ANA status was not a consistent predictor factor of non-response in the majority of earlier studies[19,21,46,47,65,67,70,71]. 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[45,72]. Alanine aminotransferase (ALT) flares have been reported during IFN treatment in NOSA-positive individuals[45,69]. 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]. Autoimmune thrombocytopenic purpura is another possible complication in patients with high titers of ANA that have been exposed to IFN-based treatment[73].

NOSA titers may increase during treatment[23,65,68,74], or might also fade/become negative in some cases[23,65,68,69]; moreover, patients that were NOSA-negative prior to treatment may develop autoantibodies during treatment[23,65,69,74]. The increase of NOSA titers during IFN-based treatment has been correlated to poor sustained virological response (SVR) rates[23]. A careful monitoring of liver biochemistry and NOSA levels is recommended during treatment[33,45,68]. Autoantibodies should be screened every 3 mo, with monthly monitoring of ALT. High titers of autoantibodies

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[2]
Lopes et al[74]	Brazil	21	IFN-α	ANA, SMA, AMA, etc.	↑	ANA	N	N
Cassani et al[21]	Italy	144	IFN-α	ANA, SMA	N/A	N/A	N/A	N
Muratori et al[69]	Italy	22[1]	IFN-α	ANA, SMA, LKM1	N/A	ANA, SMA	2 ALT flare 7-10 xULN	Y
Wasmuth et al[66]	Germany	48	IFN-α + RBV	ANA, SMA, LKM1, AMA, ANCA	N/A	N/A	N/A	Y
Yee et al[47]	Europe multicenter	258	IFN-α	ANA	N/A	N/A	N/A	N
Stroffolini et al[19]	Italy	502	IFN-α + RBV	ANA, SMA, LKM1, AMA	N/A	N/A	N	N
Muratori et al[65]	Italy	143	IFN-α + RBV	ANA, SMA, LKM1	↑	Y	N	N
Gatselis et al[68]	Greece	57	IFN-α + RBV	ANA, SMA, LKM1, AMA, ANCA, etc.	↑	ANA, LKM1, ANCA	N	Y
Gatselis et al[23]	Greece	102	IFN-α/PEG + RBV	ANA, SMA, LKM1, AMA, ANCA, etc.	↑	Y	N	Y
Daryani et al[67]	Iran	52	IFN-α + RBV	ANA, SMA, LKM1, AMA	N/A	N/A	N/A	N
Narciso-Schiavon et al[46]	Brazil	234	IFN-α + RBV	ANA	N/A	N/A	N	N
Bai et al[76]	China	46	IFN-α	ANA, LKM1	N/A	N/A	N	N
Hsieh et al[45]	Taiwan	243	PEG + RBV	ANA, SMA, LKM1, AMA, ANCA	N/A	N/A	ALT flare	Y
Mauss et al[77]	Germany	12369	PEG + RBV	ANA, SMA, LKM1, AMA	N/A	N/A	N	N
Khairy et al[78]	Egypt	3673	PEG + RBV	ANA	N/A	N/A	N	N

[1]Children; [2]Higher 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; ALT: Alanine aminotransferase.

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] 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[79,80]. 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)[12,80-83].

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]. Graves' disease is an autoantibody-mediated autoimmune disease characterized by thyrotoxicosis. 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]. The ability of TRAb to provide differential diagnoses of overt hyperthyroidism is excellent, with a sensitivity and specificity above 90%[84]. Physical examination shows hyperthyroidism symptoms and goiter. Graves' disease is caused by direct stimulation of the thyroid epithelial cells by TRAb[84].

Thyroid autoimmunity is a common characteristic of HCV infection[85,86]. A high prevalence of TAAb in chronic HCV carriers has been reported over the years, varying

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]
	14	9/66	> 50/100	France	1992	Pateron *et al*[159]
	12.5	9/76	-	France	1993	Tran *et al*[89]
	9.4	42/449	≥ 100	Taiwan	2012	Huang *et al*[88]
	9.7	7/72	-	Italy	2002	Carella *et al*[90]
	7	5/71	≥ 60	Greece	2011	Vasiliadis *et al*[10]
	6.7	14/207	-	Spain	1996	Marazuela *et al*[91]
	5.6	4/71	≥ 100	Italy	2006	Floreani *et al*[29]
	4.5	5/111	≥ 100	United Kingdom	1997	Metcalfe *et al*[92]
TPOAb	30.8	60/195	≥ 50	China	2011	Yang *et al*[28]
	21	132/630	> 150	Italy	2004	Antonelli *et al*[87]
	20	26/134	> 150	Spain	1998	Fernandez-Soto *et al*[95]
	16.3	51/312	> 35	China	2013	Shao *et al*[34]
	15	30/200	> 18	Greece	1997	Deutsch *et al*[94]
	14	9/66	> 50/100	France	1992	Pateron *et al*[159]
	10	3/32	> 100	Italy	1996	Roti *et al*[97]
	7.4	4/54	-	Brazil	2013	Marconcini *et al*[20]
	6.7	13/192	> 100	Spain	1995	Boadas *et al*[93]
	6.5	29/449	≥ 100	Taiwan	2012	Huang *et al*[88]
	5.4	9/168	-	France	2005	Moncoucy *et al*[96]
	3.5	9/254	> 60	Norway	2002	Dalgard *et al*[102]
TGAb	30.8	60/195	≥ 40	China	2011	Yang *et al*[28]
	17	108/630	> 150	Italy	2004	Antonelli *et al*[87]
	13.3	44/312	> 35	China	2013	Shao *et al*[34]
	11	15/134	> 200	Spain	1998	Fernandez-Soto *et al*[95]
	10	13/130	-	Taiwan	1999	Huang *et al*[98]
	8	13/162	-	France	2005	Moncoucy *et al*[96]
	7.6	5/66	≥ 50	France	1992	Pateron *et al*[159]
	5.8	13/449	≥ 100	Taiwan	2012	Huang *et al*[88]
	0	0/48	-	Brazil	2013	Marconcini *et al*[20]

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

from 4.5%-25%[10,27,29,87-92]. The prevalences of TPOAb and TGAb vary from 5.4%-30%[20,27,28,34,87,88,93-97] and 0%-30.7%[20,27,28,34,88,95,96,98], 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]. Environmental cofactors such as iodine intake or other infectious agents could also play an important role in the development of autoimmune thyroid disorders[100]. TAAb are more frequent among women[29,93-96,101], and their prevalence increases with age[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[87,101]. The prevalence of thyroid dysfunction in individuals with chronic hepatitis C varies from 3.6%-23%[33,87,90,93-96,98,102]. 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].

No relationship has been observed between serum concentrations of TSH or thyroid hormone and auto-antibody titers[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)[87,94,95,98].

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]. It has been long known that pretreatment-reactive TAAb represent a high risk for overt thyroid dysfunction during IFN-based therapy[27]. The pegylated form of IFN seems to have the same effects as standard IFN[103]. IFN dose and duration do not influence the development of IFN-induced thyroiditis[102,104], nor do they affect virological response[102]. Although some authors do not agree[90,98], 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]. The rate of development of TAAb secondary to IFN therapy varies from 1.9%-40.0%[27,90,91,93,94,97,104-110]. 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[12,96]. There are two recognized clinical forms of non-auto-immune thyroiditis: destructive thyroiditis[97,109] and non-autoimmune hypothyroidism[91,97,108], 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]. 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]. The reversibility of AITD after IFN withdrawal is controversial. Initially, the thyroid disorders induced by IFN were described as reversible[110]. Later, it was demonstrated that in more than one third of treated patients, hypothyroidism may persist[94-96]. Although it has been demonstrated that Graves' thyrotoxicosis may not be reversible with IFN withdrawal[108], in a recent cohort of 18 hepatitis C patients who developed thyroiditis during INF-based treatment, all cases recovered[112]. Late-onset thyroid dysfunction has also been observed after discontinuation of IFN-based treatment (6-mo post-treatment)[94,95]. Perhaps monitoring for thyroid disease could be safely ceased at the 6-mo follow-up, coinciding with the SVR review[112].

Finally, it has been reported that IFN-based therapy does not aggravate previous existing thyroid disease[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]. When hypothyroidism occurs, thyroxin therapy should be initiated promptly[100]. Hashi-moto's thyroiditis is rarely the reason for premature termination of therapy with IFN[12]. While in cases of symptomatic thyrotoxicosis, withholding IFN therapy should be considered only after consulting with an endocrinologist[108]. If thyrotoxicosis is suspected, and TRAb is negative, patients should undergo a thyroid scan to check for diffusely increased uptake[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].

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]. 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] 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[80,94,95,99,113].

CD ANTIBODIES

CD is a chronic, small-intestinal, immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed people[114]. CD is now considered to be a multisystemic disorder, rather than a sole gastrointestinal process[115]. CD is triggered by the ingestion of gluten, the protein component of wheat, rye, and barley[116,117]. Such exposure results in a variable degree of intestinal damage[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-EmA, IgA anti-tTG, and the more recent test for deamidated gliadin peptides (DGP)[119-121]. Positive serology with normal histology, formerly called latent CD[122], is now defined as potential CD[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], but is now defined as asymptomatic CD[114]. Once a diagnosis of celiac sprue has been established, the conventional treatment is a gluten-free diet[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[115,121,123].

Gliadins, the alcohol-soluble fraction of gluten, elicit a strong humoral response in CD, which originates in the submucosa[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[124,125]. Thus, AGA is no longer recommended for the primary detection of CD[126,127]. 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]. Selective IgA deficiency affects approximately 2%-5% of patients diagnosed with CD[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]. IgA and IgG enzyme-linked immunosorbent assay 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]. In patients with a high-probability CD and IgA deficiency, DGP IgG-based testing is advocated[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]. Some individual present abnormal liver tests, by the diagnosis of CD, that regularize with a gluten-free diet[130-135]. CD has been described in association with autoimmune liver diseases[136-140], and also with HCV[36,40,139,141-143]. In the

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]
	11	11/104	Sweden	1997	Sjöberg *et al*[141]
	6.3	37/583	France multicenter	2007	Thevenot *et al*[145]
EmA/tTG	3.5	7/195	Italy	2004	Durante-Mangoni *et al*[14]
	2.0	5/244	Italy	2007	Ruggeri *et al*[36]
	1.2	3/259	United States	2001	Fine *et al*[142]
	0	0/210	Italy	2012	Gravina *et al*[35]
EmA	5.8	3/52	Brazil	2013	Marconcini *et al*[20]
	0.2	1/623	France multicenter	2007	Thevenot *et al*[145]
	0	0/195	United States	2008	Hernandez *et al*[40]
tTG	1	2/195	United States	2008	Hernandez *et al*[40]
	0	0/34	Brazil	2013	Marconcini *et al*[20]
	0	0/41	France multicenter	2007	Thevenot *et al*[145]

AGA: Antigliadin antibody; EmA: Anti-endomysial antibody; tTG: Tissue transglutaminase; EmA: Endomysial antibodies.

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].

Few studies have evaluated the prevalence of celiac antibodies in the HCV population. AGA prevalence varies between 6.3% and 32%[141,142,145], while EmA prevalence varies between 0% and 5.8%[20,40,145], and tTG antibodies have been reported in between 0% and 1% of patients with HCV[20,40,145] (Table 4). Among patients with chronic liver disease, AGA positivity generally occurs at an increased frequency and may represent non-specific immune activation[141,142,145]. 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].

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]. Similarly, Hernandez *et al*[40] did not find evidence for a higher prevalence of HCV among individuals with CD and *vice versa*[40]. Silano *et al*[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]. Given these findings, there is little evidence to support the role of screening HCV patients for CD[40,146]. 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[147,148].

The activation of CD during IFN treatment has been reported in some cases. Patients may experience severe diarrhea with weight loss during IFN treatment[9,149-154], as well as dermatitis herpetiformis[9,155], hypoferritinemia[154,156,157], and refractory anemia that persist after treatment has stopped[149,152,154]. Treatment interruption has been reported[149,150,152]. However, early diagnosis of CD enables prompt management with a gluten-free diet, which can permit the completion of IFN-based treatment[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]. Late onset CD has also been observed after discontinuation of IFN-based treatment (various months post treatment)[8,37]. Intestinal diffuse large B cell lymphoma has been reported in an IFN-experienced elder non-adherent to a gluten-free diet[38].

Durante-Mangoni *et al*[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], it is important to exclude other causes (mainly infectious and autoimmunity) prior to attributing the symptoms to IFN therapy[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[14,143,149-152,155,156,158]. 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[14,153], 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.

REFERENCES

1 **Lauer GM**, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001; **345**: 41-52 [PMID: 11439948 DOI: 10.1056/NEJM200107053 450107]

2 **Dore GJ**, Freeman AJ, Law M, Kaldor JM. Natural history models for hepatitis C-related liver disease: different disease progression parameters for different settings. *Antivir Ther* 2003; **8**: 365-372 [PMID: 14640382]

3 **Hadziyannis SJ**. Nonhepatic manifestations and combined diseases in HCV infection. *Dig Dis Sci* 1996; **41**: 63S-74S [PMID: 9011479]

4 **McMurray RW**, Elbourne K. Hepatitis C virus infection and autoimmunity. *Semin Arthritis Rheum* 1997; **26**: 689-701 [PMID: 9062950]

5 **Ghany MG**, Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; **54**: 1433-1444 [PMID: 21898493 DOI: 10.1002/hep.24641]

6 **Ghany MG**, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335-1374 [PMID: 19330875 DOI: 10.1002/hep.22759]

7 **Dumoulin FL**, Leifeld L, Sauerbruch T, Spengler U. Autoimmunity induced by interferon-alpha therapy for chronic viral hepatitis. *Biomed Pharmacother* 1999; **53**: 242-254 [PMID: 10424246 DOI: 10.1016/S0753-3322(99)80095-X]

8 **Martins EV**, Gaburri AK. Celiac disease onset after pegylated interferon and ribavirin treatment of chronic hepatitis C. *Arq Gastroenterol* 2004; **41**: 132-133 [PMID: 15543388]

9 **Ioniţă-Radu F**, Bucurică S, Costache R, Nuţa P, Stanciu S. An adult case with onset of celiac disease during chronic hepatitis C antiviral treatment. *Rom J Intern Med* 2010; **48**: 105-108 [PMID: 21180248]

10 **Vasiliadis T**, Anagnostis P, Nalmpantidis G, Soufleris K, Patsiaoura K, Grammatikos N, Orfanou-Koumerkeridou E, Kargiotis K, Slavakis A, Deliyiannidis A, Eugenidis N. Thyroid dysfunction and long-term outcome during and after interferon-alpha therapy in patients with chronic hepatitis C. *Ann Acad Med Singapore* 2011; **40**: 394-400 [PMID: 22065032]

11 **Czarnywojtek A**, Zgorzalewicz-Stachowiak M, Wasko R, Czepczynski R, Szczepanek-Parulska E, Waligorska-Stachura J, Kurdybacha P, Bereszynska I, Florek E, Stangierski A, Zdanowska J, Nikisch E, Sowinski J, Ruchala M. Patients with chronic hepatitis type C and interferon-alpha-induced hyperthyroidism in two-years clinical follow-up. *Neuro Endocrinol Lett* 2013; **34**: 154-161 [PMID: 23645313]

12 **Kozielewicz D**, Halota W. Interferon-induced thyroiditis during treatment of chronic hepatitis C. *Endokrynol Pol* 2012; **63**: 66-70 [PMID: 22378101]

13 **Rigopoulou EI**, Zachou K, Gatselis N, Koukoulis GK, Dalekos GN. Autoimmune hepatitis in patients with chronic HBV and HCV infections: patterns of clinical characteristics, disease progression and outcome. *Ann Hepatol* 2013; **13**: 127-135 [PMID: 24378276]

14 **Durante-Mangoni E**, Iardino P, Resse M, Cesaro G, Sica A, Farzati B, Ruggiero G, Adinolfi LE. Silent celiac disease in chronic hepatitis C: impact of interferon treatment on the disease onset and clinical outcome. *J Clin Gastroenterol* 2004; **38**: 901-905 [PMID: 15492610]

15 EASL recommendations on treatment of hepatitis C 2014. *J Hepatol* 2014; **61**: 373-395 [PMID: 24818984 DOI: 10.1016/j.jhep.2014.05.001]

16 **Peng YC**, Hsieh SC, Yang DY, Tung CF, Hu WH, Huang WN, Chen GH. Expression and clinical significance of antinuclear antibody in hepatitis C virus infection. *J Clin Gastroenterol* 2001; **33**: 402-406 [PMID: 11606858]

17 **Clifford BD**, Donahue D, Smith L, Cable E, Luttig B, Manns M, Bonkovsky HL. High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. *Hepatology* 1995; **21**: 613-619 [PMID: 7533120]

18 **Fried MW**, Draguesku JO, Shindo M, Simpson LH, Banks SM, Hoofnagle JH, Di Bisceglie AM. Clinical and serological differentiation of autoimmune and hepatitis C virus-related chronic hepatitis. *Dig Dis Sci* 1993; **38**: 631-636 [PMID: 8384981]

19 **Stroffolini T**, Colloredo G, Gaeta GB, Sonzogni A, Angeletti S, Marignani M, Pasquale G, Venezia G, Craxì A, Almasio P. Does an 'autoimmune' profile affect the clinical profile of chronic hepatitis C? An Italian multicentre survey. *J Viral Hepat* 2004; **11**: 257-262 [PMID: 15117328 DOI: 10.1111/j.1365-2893.2004.00489.x]

20 **Marconcini ML**, Fayad L, Shiozawa MB, Dantas-Correa EB, Lucca Schiavon Ld, Narciso-Schiavon JL. Autoantibody profile in individuals with chronic hepatitis C. *Rev Soc Bras Med Trop* 2013; **46**: 147-153 [PMID: 23740063 DOI: 10.1590/0037-8682-0039-2013]

21 **Cassani F**, Cataleta M, Valentini P, Muratori P, Giostra F, Francesconi R, Muratori L, Lenzi M, Bianchi G, Zauli D, Bianchi FB. Serum autoantibodies in chronic hepatitis C: comparison with autoimmune hepatitis and impact on the disease profile. *Hepatology* 1997; **26**: 561-566 [PMID: 9303483 DOI: 10.1002/hep.510260305]

22 **Czaja AJ**, Manns MP, Homburger HA. Frequency and significance of antibodies to liver/kidney microsome type 1 in adults with chronic active hepatitis. *Gastroenterology* 1992; **103**: 1290-1295 [PMID: 1397887]

23 **Gatselis NK**, Georgiadou SP, Koukoulis GK, Tassopoulos N, Zachou K, Liaskos C, Hatzakis A, Dalekos GN. Clinical significance of organ- and non-organ-specific autoantibodies on the response to anti-viral treatment of patients with chronic hepatitis C. *Aliment Pharmacol Ther* 2006; **24**: 1563-1573 [PMID: 17094775 DOI: 10.1111/j.1365-2036.2006.03165.x]

24 **Daschakraborty S**, Aggarwal A, Aggarwal R. Non-organ-specific autoantibodies in Indian patients with chronic liver disease. *Indian J Gastroenterol* 2012; **31**: 237-242 [PMID: 22941677 DOI: 10.1007/s12664-012-0247-4]

25 **Chrétien P**, Chousterman M, Abd Alsamad I, Ozenne V, Rosa I, Barrault C, Lons T, Hagège H. Non-organ-specific autoantibodies in chronic hepatitis C patients: association with histological activity and fibrosis. *J Autoimmun* 2009; **32**: 201-205 [PMID: 19324518 DOI: 10.1016/j.jaut.2009.02.005]

26 **Badiani RG**, Becker V, Perez RM, Matos CA, Lemos LB, Lanzoni VP, Andrade LE, Dellavance A, Silva AE, Ferraz ML. Is autoimmune hepatitis a frequent finding among HCV patients with intense interface hepatitis? *World J Gastroenterol* 2010; **16**: 3704-3708 [PMID: 20677344]

27 **Pateron D**, Hartmann DJ, Duclos-Vallée JC, Jouanolle H, Beaugrand M. Latent autoimmune thyroid disease in patients with chronic HCV hepatitis. *J Hepatol* 1993; **17**: 417-419 [PMID: 8315269]

28 **Yang R**, Shan Z, Li Y, Fan C, Li C, Teng W. Prevalence of thyroid autoantibodies in hepatitis C and hepatitis B infection in China. *Intern Med* 2011; **50**: 811-815 [PMID: 21498927]

29 **Floreani A**, Betterle C, Carderi I, Presotto F, Pedini B, Moscon A, Andrea O, Chiaramonte M. Is hepatitis C virus a risk factor for thyroid autoimmunity? *J Viral Hepat* 2006; **13**: 272-277 [PMID: 16611194 DOI: 10.1111/j.1365-2893.2005.00699.x]

30 **Prummel MF**, Laurberg P. Interferon-alpha and autoimmune thyroid disease. *Thyroid* 2003; **13**: 547-551 [PMID: 12930598 DOI: 10.1089/105072503322238809]

31   **Carella C**, Mazziotti G, Amato G, Braverman LE, Roti E. Clinical review 169: Interferon-alpha-related thyroid disease: pathophysiological, epidemiological, and clinical aspects. *J Clin Endocrinol Metab* 2004; **89**: 3656-3661 [PMID: 15292282 DOI: 10.1210/jc.2004-0627]

32   **Tomer Y**, Blackard JT, Akeno N. Interferon alpha treatment and thyroid dysfunction. *Endocrinol Metab Clin North Am* 2007; **36**: 1051-1066; x-xi [PMID: 17983936 DOI: 10.1016/j.ecl.2007.07.001]

33   **Muratori L**, Bogdanos DP, Muratori P, Lenzi M, Granito A, Ma Y, Mieli-Vergani G, Bianchi FB, Vergani D. Susceptibility to thyroid disorders in hepatitis C. *Clin Gastroenterol Hepatol* 2005; **3**: 595-603 [PMID: 15952102]

34   **Shao C**, Huo N, Zhao L, Gao Y, Fan X, Zheng Y, Wang L, Lu H, Xu X, Guo X. The presence of thyroid peroxidase antibody of IgG2 subclass is a risk factor for thyroid dysfunction in chronic hepatitis C patients. *Eur J Endocrinol* 2013; **168**: 717-722 [PMID: 23419250 DOI: 10.1530/EJE-12-0775]

35   **Gravina AG**, Federico A, Masarone M, Cuomo A, Tuccillo C, Loguercio C, Persico M, Romano M. Coeliac disease and C virus-related chronic hepatitis: a non association. *BMC Res Notes* 2012; **5**: 533 [PMID: 23009068 DOI: 10.1186/1756-0500-5-533]

36   **Ruggeri C**, La Masa AT, Rudi S, Squadrito G, Di Pasquale G, Maimone S, Caccamo G, Pellegrino S, Raimondo G, Magazzù G. Celiac disease and non-organ-specific autoantibodies in patients with chronic hepatitis C virus infection. *Dig Dis Sci* 2008; **53**: 2151-2155 [PMID: 18231858 DOI: 10.1007/s10620-007-0146-1]

37   **Aguancha I**, Valera JM, Hurtado C, Smok G, Brahm J. [Chronic hepatitis C and celiac sprue: an infrequent association]. *Gastroenterol Hepatol* 2004; **27**: 408-410 [PMID: 15461939]

38   **Coban S**, Palabiyikoğlu M, Ensari A, Idilman R, Köklü S, Yolcu OF, Ormeci N. Intestinal B cell lymphoma associated with chronic hepatitis C and celiac disease. *Dig Dis Sci* 2005; **50**: 2359-2361 [PMID: 16416190 DOI: 10.1007/s10620-005-3063-1]

39   **Thevenot T**, Boruchowicz A, Henrion J, Nalet B, Moindrot H. Celiac disease is not associated with chronic hepatitis C. *Dig Dis Sci* 2007; **52**: 1310-1312 [PMID: 17372827 DOI: 10.1007/s10620-006-9360-5]

40   **Hernandez L**, Johnson TC, Naiyer AJ, Kryszak D, Ciaccio EJ, Min A, Bodenheimer HC, Brown RS, Fasano A, Green PH. Chronic hepatitis C virus and celiac disease, is there an association? *Dig Dis Sci* 2008; **53**: 256-261 [PMID: 17549632 DOI: 10.1007/s10620-007-9851-z]

41   **Vergani D**, Alvarez F, Bianchi FB, Cançado EL, Mackay IR, Manns MP, Nishioka M, Penner E. Liver autoimmune serology: a consensus statement from the committee for autoimmune serology of the International Autoimmune Hepatitis Group. *J Hepatol* 2004; **41**: 677-683 [PMID: 15464251 DOI: 10.1016/j.jhep.2004.08.002]

42   **Daryani A**, Basu S, Becker W, Larsson A, Risérus U. Antioxidant intake, oxidative stress and inflammation among immigrant women from the Middle East living in Sweden: associations with cardiovascular risk factors. *Nutr Metab Cardiovasc Dis* 2007; **17**: 748-756 [PMID: 17145175 DOI: 10.1016/j.numecd.2006.07.011]

43   **Rigopoulou EI**, Mytilinaiou M, Romanidou O, Liaskos C, Dalekos GN. Autoimmune hepatitis-specific antibodies against soluble liver antigen and liver cytosol type 1 in patients with chronic viral hepatitis. *J Autoimmune Dis* 2007; **4**: 2 [PMID: 17274827 DOI: 10.1186/1740-2557-4-2]

44   **Squadrito G**, Previti M, Lenzi M, Le Rose EP, Caccamo G, Restuccia T, Di Cesare E, Pollicino T, Raimondo G. High prevalence of non-organ-specific autoantibodies in hepatitis C virus-infected cirrhotic patients from southern Italy. *Dig Dis Sci* 2003; **48**: 349-353 [PMID: 12643614]

45   **Hsieh MY**, Dai CY, Lee LP, Huang JF, Chuang WL, Hou NJ, Lin ZY, Chen SC, Hsieh MY, Wang LY, Chang WY, Yu ML. Antinuclear antibody titer and treatment response to peginterferon plus ribavirin for chronic hepatitis C patients. *Kaohsiung J Med Sci* 2012; **28**: 86-93 [PMID: 22313535 DOI: 10.1016/j.kjms.2011.10.031]

46   **Narciso-Schiavon JL**, Freire FC, Suarez MM, Ferrari MV, Scanhola GQ, Schiavon Lde L, de Carvalho Filho RJ, Ferraz ML, Silva AE. Antinuclear antibody positivity in patients with chronic hepatitis C: clinically relevant or an epiphenomenon? *Eur J Gastroenterol Hepatol* 2009; **21**: 440-446 [PMID: 19382301]

47   **Yee LJ**, Kelleher P, Goldin RD, Marshall S, Thomas HC, Alberti A, Chiaramonte M, Braconier JH, Hall AJ, Thursz MR. Antinuclear antibodies (ANA) in chronic hepatitis C virus infection: correlates of positivity and clinical relevance. *J Viral Hepat* 2004; **11**: 459-464 [PMID: 15357653 DOI: 10.1111/j.1365-2893.2004.00530.x]

48   **Czaja AJ**, Carpenter HA. Histological findings in chronic hepatitis C with autoimmune features. *Hepatology* 1997; **26**: 459-466 [PMID: 9252159 DOI: 10.1002/hep.510260229]

49   **Antonaci S**, Giannelli G, Simone B, Vella FS. [Syndrome of overlap: Chronic hepatitis C/autoimmune hepatitis: fact or fancy?]. *Recenti Prog Med* 2005; **96**: 27-31 [PMID: 15789635]

50   **Zachou K**, Muratori P, Koukoulis GK, Granito A, Gatselis N, Fabbri A, Dalekos GN, Muratori L. Review article: autoimmune hepatitis -- current management and challenges. *Aliment Pharmacol Ther* 2013; **38**: 887-913 [PMID: 24010812 DOI: 10.1111/apt.12470]

51   **Magrin S**, Craxi A, Fabiano C, Simonetti RG, Fiorentino G, Marino L, Diquattro O, Di Marco V, Loiacono O, Volpes R. Hepatitis C viremia in chronic liver disease: relationship to interferon-alpha or corticosteroid treatment. *Hepatology* 1994; **19**: 273-279 [PMID: 8294085]

52   **Black M**, Peters M. Alpha-interferon treatment of chronic hepatitis C: need for accurate diagnosis in selecting patients. *Ann Intern Med* 1992; **116**: 86-88 [PMID: 1727098]

53   **García-Buey L**, García-Monzón C, Rodriguez S, Borque MJ, García-Sánchez A, Iglesias R, DeCastro M, Mateos FG, Vicario JL, Balas A. Latent autoimmune hepatitis triggered during interferon therapy in patients with chronic hepatitis C. *Gastroenterology* 1995; **108**: 1770-1777 [PMID: 7768382]

54   **Shindo M**, Di Bisceglie AM, Hoofnagle JH. Acute exacerbation of liver disease during interferon alfa therapy for chronic hepatitis C. *Gastroenterology* 1992; **102**: 1406-1408 [PMID: 1551549]

55   **Schiano TD**, Te HS, Thomas RM, Hussain H, Bond K, Black M. Results of steroid-based therapy for the hepatitis C-autoimmune hepatitis overlap syndrome. *Am J Gastroenterol* 2001; **96**: 2984-2991 [PMID: 11693337 DOI: 10.1111/j.1572-0241.2001.04672.x]

56   **Bach N**, Thung SN, Schaffner F. The histological features of chronic hepatitis C and autoimmune chronic hepatitis: a comparative analysis. *Hepatology* 1992; **15**: 572-577 [PMID: 1551632]

57   **Roudot-Thoraval F**, Bastie A, Pawlotsky JM, Dhumeaux D. Epidemiological factors affecting the severity of hepatitis C virus-related liver disease: a French survey of 6,664 patients. The Study Group for the Prevalence and the Epidemiology of Hepatitis C Virus. *Hepatology* 1997; **26**: 485-490 [PMID: 9252163 DOI: 10.1002/hep.510260233]

58   **Pasquale G**, Sagnelli E, Coppola N, Onofrio M, Scarano F, Scolastico C, Bellomo PF, Lettieri A, Mogavero AR, Caprio N, Sagnelli C, Piccinino F. [An attempt to improve classification of HCV-correlated chronic hepatitis]. *Infez Med* 2005; **13**: 16-22 [PMID: 15888977]

59   **Czaja AJ**, Carpenter HA. Sensitivity, specificity, and predictability of biopsy interpretations in chronic hepatitis. *Gastroenterology* 1993; **105**: 1824-1832 [PMID: 8253358]

60   **Bellary S**, Schiano T, Hartman G, Black M. Chronic hepatitis with combined features of autoimmune chronic hepatitis and chronic hepatitis C: favorable response to prednisone and azathioprine. *Ann Intern Med* 1995; **123**: 32-34 [PMID: 7762911]

61   **Magrin S**, Craxì A, Fiorentino G, Fabiano C, Provenzano G, Pinzello GB, Palazzo U, Almasio P, Pagliaro L. Is autoimmune chronic active hepatitis a HCV-related disease? *J Hepatol* 1991; **13**: 56-60 [PMID: 1717543]

62   **Magrin S**, Craxi A, Fabiano C, Fiorentino G, Almasio P, Palazzo U, Pinzello G, Provenzano G, Pagliaro L, Choo QL. Hepatitis C virus replication in 'autoimmune' chronic hepatitis. *J Hepatol* 1991; **13**: 364-367 [PMID: 1725529]

63   **Provenzano G**, Almasio P, Fabiano C, Magrin S, Pinzello G, Vaccaro A, Craxi A. Interferon and steroid treatment in patients with chronic hepatitis C and antinuclear or anti-liver-kidney microsomal antibodies. *Ital J Gastroenterol* 1996; **28**: 377-380

[PMID: 8937938]

64   **Calleja JL**, Albillos A, Cacho G, Iborra J, Abreu L, Escartín P. Interferon and prednisone therapy in chronic hepatitis C with non-organ-specific antibodies. *J Hepatol* 1996; **24**: 308-312 [PMID: 8778197]

65   **Muratori P**, Muratori L, Guidi M, Granito A, Susca M, Lenzi M, Bianchi FB. Clinical impact of non-organ-specific autoantibodies on the response to combined antiviral treatment in patients with hepatitis C. *Clin Infect Dis* 2005; **40**: 501-507 [PMID: 15712070 DOI: 10.1086/427285]

66   **Wasmuth HE**, Stolte C, Geier A, Dietrich CG, Gartung C, Lorenzen J, Matern S, Lammert F. The presence of non-organ-specific autoantibodies is associated with a negative response to combination therapy with interferon and ribavirin for chronic hepatitis C. *BMC Infect Dis* 2004; **4**: 4 [PMID: 15040810 DOI: 10.1186/1471-2334-4-4]

67   **Daryani NE**, Bahrami H, Haghpanah B, Jalili M, Hashtroudi A, Mohammad, Bashashati, Sayyah A. The frequency of non-organ-specific autoantibodies in patients with chronic hepatitis C and its relation with disease severity and response to therapy. *IJCID* 2006; **1**: 5-10

68   **Gatselis NK**, Georgiadou SP, Tassopoulos N, Zachou K, Liaskos C, Hatzakis A, Dalekos GN. Impact of parietal cell autoantibodies and non-organ-specific autoantibodies on the treatment outcome of patients with hepatitis C virus infection: a pilot study. *World J Gastroenterol* 2005; **11**: 482-487 [PMID: 15641130 DOI: 10.3748/wjg.v11.i4.482]

69   **Muratori P**, Muratori L, Verucchi G, Attard L, Bianchi FB, Lenzi M. Non-organ-specific autoantibodies in children with chronic hepatitis C: clinical significance and impact on interferon treatment. *Clin Infect Dis* 2003; **37**: 1320-1326 [PMID: 14583865 DOI: 10.1086/379018]

70   **Noda K**, Enomoto N, Arai K, Masuda E, Yamada Y, Suzuki K, Tanaka M, Yoshihara H. Induction of antinuclear antibody after interferon therapy in patients with type-C chronic hepatitis: its relation to the efficacy of therapy. *Scand J Gastroenterol* 1996; **31**: 716-722 [PMID: 8819224]

71   **Wada M**, Kang KB, Kinugasa A, Shintani S, Sawada K, Nishigami T, Shimoyama T. Does the presence of serum autoantibodies influence the responsiveness to interferon-alpha 2a treatment in chronic hepatitis C? *Intern Med* 1997; **36**: 248-254 [PMID: 9187562]

72   **Hass HG**, Klein R, Nehls O, Kaiser S. Thyroid disorders and occurrence of nonorgan-specific autoantibodies (NOSA) in patients with chronic hepatitis C before and during antiviral induction therapy with consensus interferon (interferon alfacon-1). *J Clin Gastroenterol* 2009; **43**: 470-476 [PMID: 19247202 DOI: 10.1097/MCG.0b013e318184a470]

73   **Kim SR**, Imoto S, Kudo M, Nakajima T, Ando K, Mita K, Fukuda K, Hong HS, Lee YH, Nakashima K, Shoji I, Nagano-Fujii M, Hotta H, Hayashi Y. Autoimmune thrombocytopenic purpura during pegylated interferon α treatment for chronic hepatitis C. *Intern Med* 2010; **49**: 1119-1122 [PMID: 20558927]

74   **Lopes EP**, Silva AE, Sette Junior H, Guimarães RX, Ferraz ML. Autoantibodies before, during and after administration of recombinant interferon-alpha for chronic viral hepatitis. *Rev Inst Med Trop Sao Paulo* 1995; **37**: 455-460 [PMID: 8729757]

75   **De Luca A**, Bianco C, Rossetti B. Treatment of HCV infection with the novel NS3/4A protease inhibitors. *Curr Opin Pharmacol* 2014; **18**: 9-17 [PMID: 25117198 DOI: 10.1016/j.coph.2014.07.016]

76   **Bai L**, Feng ZR, Lu HY, Li WG, Yu M, Xu XY. Prevalence of antinuclear and anti-liver-kidney-microsome type-1 antibodies in patients with chronic hepatitis C in China. *Chin Med J* (Engl) 2009; **122**: 5-9 [PMID: 19187609]

77   **Mauss S**, Berger F, Schober A, Moog G, Heyne R, John C, Pape S, Hueppe D, Pfeiffer-Vornkahl H, Alshuth U. Screening for autoantibodies in chronic hepatitis C patients has no effect on treatment initiation or outcome. *J Viral Hepat* 2013; **20**: e72-e77 [PMID: 23490392 DOI: 10.1111/jvh.12011]

78   **Khairy M**, El-Raziky M, El-Akel W, Abdelbary MS, Khatab

H, El-Kholy B, Esmat G, Mabrouk M. Serum autoantibodies positivity prevalence in patients with chronic HCV and impact on pegylated interferon and ribavirin treatment response. *Liver Int* 2013; **33**: 1504-1509 [PMID: 23763380 DOI: 10.1111/liv.12227]

79   **Weetman AP**. Determinants of autoimmune thyroid disease. *Nat Immunol* 2001; **2**: 769-770 [PMID: 11526381 DOI: 10.1038/ni0901-769]

80   **Mandac JC**, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. *Hepatology* 2006; **43**: 661-672 [PMID: 16557537 DOI: 10.1002/hep.21146]

81   **Tunbridge WM**, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T, Smith PA. The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol* (Oxf) 1977; **7**: 481-493 [PMID: 598014]

82   **Knudsen N**, Jorgensen T, Rasmussen S, Christiansen E, Perrild H. The prevalence of thyroid dysfunction in a population with borderline iodine deficiency. *Clin Endocrinol* (Oxf) 1999; **51**: 361-367 [PMID: 10469017]

83   **Vanderpump MP**. The epidemiology of thyroid disease. *Br Med Bull* 2011; **99**: 39-51 [PMID: 21893493 DOI: 10.1093/bmb/ldr030]

84   **Barbesino G**, Tomer Y. Clinical review: Clinical utility of TSH receptor antibodies. *J Clin Endocrinol Metab* 2013; **98**: 2247-2255 [PMID: 23539719 DOI: 10.1210/jc.2012-4309]

85   **Andrade LJ**, Atta AM, D'Almeida Junior A, Paraná R. Thyroid dysfunction in hepatitis C individuals treated with interferon-alpha and ribavirin--a review. *Braz J Infect Dis* 2008; **12**: 144-148 [PMID: 18641852]

86   **Antonelli A**, Ferri C, Ferrari SM, Colaci M, Sansonno D, Fallahi P. Endocrine manifestations of hepatitis C virus infection. *Nat Clin Pract Endocrinol Metab* 2009; **5**: 26-34 [PMID: 19079271 DOI: 10.1038/ncpendmet1027]

87   **Antonelli A**, Ferri C, Pampana A, Fallahi P, Nesti C, Pasquini M, Marchi S, Ferrannini E. Thyroid disorders in chronic hepatitis C. *Am J Med* 2004; **117**: 10-13 [PMID: 15210382 DOI: 10.1016/j.amjmed.2004.01.023]

88   **Huang JF**, Huang CK, Yu ML, Dai CY, Huang CF, Hung WW, Yeh ML, Hsieh MH, Yang JF, Hsieh MY, Lin ZY, Chen SC, Wu SS, Chuang WL. Thyroid autoantibodies and dysfunction do not impact the treatment efficacy of peginterferon and ribavirin combination therapy in chronic hepatitis C. *Hepatol Int* 2011; **6**: 613-619 [PMID: 22020824 DOI: 10.1007/s12072-011-9308-5]

89   **Tran A**, Quaranta JF, Benzaken S, Thiers V, Chau HT, Hastier P, Regnier D, Dreyfus G, Pradier C, Sadoul JL. High prevalence of thyroid autoantibodies in a prospective series of patients with chronic hepatitis C before interferon therapy. *Hepatology* 1993; **18**: 253-257 [PMID: 7687977]

90   **Carella C**, Mazziotti G, Morisco F, Rotondi M, Cioffi M, Tuccillo C, Sorvillo F, Caporaso N, Amato G. The addition of ribavirin to interferon-alpha therapy in patients with hepatitis C virus-related chronic hepatitis does not modify the thyroid autoantibody pattern but increases the risk of developing hypothyroidism. *Eur J Endocrinol* 2002; **146**: 743-749 [PMID: 12039693]

91   **Marazuela M**, García-Buey L, González-Fernández B, García-Monzón C, Arranz A, Borque MJ, Moreno-Otero R. Thyroid autoimmune disorders in patients with chronic hepatitis C before and during interferon-alpha therapy. *Clin Endocrinol* (Oxf) 1996; **44**: 635-642 [PMID: 8759175]

92   **Metcalfe RA**, Ball G, Kudesia G, Weetman AP. Failure to find an association between hepatitis C virus and thyroid autoimmunity. *Thyroid* 1997; **7**: 421-424 [PMID: 9226214]

93   **Boadas J**, Rodríguez-Espinosa J, Enríquez J, Miralles F, Martínez-Cerezo FJ, González P, Madoz P, Vilardell F. Prevalence of thyroid autoantibodies is not increased in blood donors with hepatitis C virus infection. *J Hepatol* 1995; **22**: 611-615 [PMID: 7560854]

94   **Deutsch M**, Dourakis S, Manesis EK, Gioustozi A, Hess G, Horsch A, Hadziyannis S. Thyroid abnormalities in chronic viral hepatitis and their relationship to interferon alfa therapy. *Hepatology* 1997; **26**: 206-210 [PMID: 9214471 DOI: 10.1002/hep.510260127]

95   **Fernandez-Soto L**, Gonzalez A, Escobar-Jimenez F, Vazquez

R, Ocete E, Olea N, Salmeron J. Increased risk of autoimmune thyroid disease in hepatitis C vs hepatitis B before, during, and after discontinuing interferon therapy. *Arch Intern Med* 1998; **158**: 1445-1448 [PMID: 9665354]

96   **Moncoucy X**, Leymarie F, Delemer B, Lévy S, Bernard-Chabert B, Bouché O, Jolly D, Diebold MD, Cadiot G, Thiéfin G. Risk factors and long-term course of thyroid dysfunction during antiviral treatments in 221 patients with chronic hepatitis C. *Gastroenterol Clin Biol* 2005; **29**: 339-345 [PMID: 15864192]

97   **Roti E**, Minelli R, Giuberti T, Marchelli S, Schianchi C, Gardini E, Salvi M, Fiaccadori F, Ugolotti G, Neri TM, Braverman LE. Multiple changes in thyroid function in patients with chronic active HCV hepatitis treated with recombinant interferon-alpha. *Am J Med* 1996; **101**: 482-487 [PMID: 8948271]

98   **Huang MJ**, Tsai SL, Huang BY, Sheen IS, Yeh CT, Liaw YF. Prevalence and significance of thyroid autoantibodies in patients with chronic hepatitis C virus infection: a prospective controlled study. *Clin Endocrinol* (Oxf) 1999; **50**: 503-509 [PMID: 10468911]

99   **Marcellin P**, Pouteau M, Benhamou JP. Hepatitis C virus infection, alpha interferon therapy and thyroid dysfunction. *J Hepatol* 1995; **22**: 364-369 [PMID: 7608489]

100   **Antonelli A**, Ferri C, Fallahi P, Ferrari SM, Ghinoi A, Rotondi M, Ferrannini E. Thyroid disorders in chronic hepatitis C virus infection. *Thyroid* 2006; **16**: 563-572 [PMID: 16839258 DOI: 10.1089/thy.2006.16.563]

101   **Bjøro T**, Gaarder PI, Smeland EB, Kornstad L. Thyroid antibodies in blood donors: prevalence and clinical significance. *Acta Endocrinol* (Copenh) 1984; **105**: 324-329 [PMID: 6702401]

102   **Dalgard O**, Bjøro K, Hellum K, Myrvang B, Bjøro T, Haug E, Bell H. Thyroid dysfunction during treatment of chronic hepatitis C with interferon alpha: no association with either interferon dosage or efficacy of therapy. *J Intern Med* 2002; **251**: 400-406 [PMID: 11982739]

103   **Tran HA**, Attia JR, Jones TL, Batey RG. Pegylated interferon-alpha2beta in combination with ribavirin does not aggravate thyroid dysfunction in comparison to regular interferon-alpha2beta in a hepatitis C population: meta-analysis. *J Gastroenterol Hepatol* 2007; **22**: 472-476 [PMID: 17376035 DOI: 10.1111/j.1440-1746.2006.04771.x]

104   **Watanabe U**, Hashimoto E, Hisamitsu T, Obata H, Hayashi N. The risk factor for development of thyroid disease during interferon-alpha therapy for chronic hepatitis C. *Am J Gastroenterol* 1994; **89**: 399-403 [PMID: 8122653]

105   **Imagawa A**, Itoh N, Hanafusa T, Oda Y, Waguri M, Miyagawa J, Kono N, Kuwajima M, Matsuzawa Y. Autoimmune endocrine disease induced by recombinant interferon-alpha therapy for chronic active type C hepatitis. *J Clin Endocrinol Metab* 1995; **80**: 922-926 [PMID: 7883851 DOI: 10.1210/jcem.80.3.7883851]

106   **Carella C**, Mazziotti G, Morisco F, Manganella G, Rotondi M, Tuccillo C, Sorvillo F, Caporaso N, Amato G. Long-term outcome of interferon-alpha-induced thyroid autoimmunity and prognostic influence of thyroid autoantibody pattern at the end of treatment. *J Clin Endocrinol Metab* 2001; **86**: 1925-1929 [PMID: 11344186 DOI: 10.1210/jcem.86.5.7459]

107   **Lisker-Melman M**, Di Bisceglie AM, Usala SJ, Weintraub B, Murray LM, Hoofnagle JH. Development of thyroid disease during therapy of chronic viral hepatitis with interferon alfa. *Gastroenterology* 1992; **102**: 2155-2160 [PMID: 1587439]

108   **Wong V**, Fu AX, George J, Cheung NW. Thyrotoxicosis induced by alpha-interferon therapy in chronic viral hepatitis. *Clin Endocrinol* (Oxf) 2002; **56**: 793-798 [PMID: 12072050]

109   **Preziati D**, La Rosa L, Covini G, Marcelli R, Rescalli S, Persani L, Del Ninno E, Meroni PL, Colombo M, Beck-Peccoz P. Autoimmunity and thyroid function in patients with chronic active hepatitis treated with recombinant interferon alpha-2a. *Eur J Endocrinol* 1995; **132**: 587-593 [PMID: 7749499]

110   **Baudin E**, Marcellin P, Pouteau M, Colas-Linhart N, Le Floch JP, Lemmonier C, Benhamou JP, Bok B. Reversibility of thyroid dysfunction induced by recombinant alpha interferon in chronic hepatitis C. *Clin Endocrinol* (Oxf) 1993; **39**: 657-661 [PMID:

8287583]

111   **Paraná R**, Cruz M, Santos-Jesus R, Ferreira K, Codes L, Cruz T. Thyroid disease in HCV carriers undergoing antiviral therapy with interferon plus ribavirin. *Braz J Infect Dis* 2000; **4**: 284-290 [PMID: 11136525]

112   **Tran HA**, Jones TL, Ianna EA, Reeves GE. The natural history of interferon-α induced thyroiditis in chronic hepatitis c patients: a long term study. *Thyroid Res* 2011; **4**: 2 [PMID: 21214950 DOI: 10.1186/1756-6614-4-2]

113   **Nair Kesavachandran C**, Haamann F, Nienhaus A. Frequency of thyroid dysfunctions during interferon alpha treatment of single and combination therapy in hepatitis C virus-infected patients: a systematic review based analysis. *PLoS One* 2013; **8**: e55364 [PMID: 23383326 DOI: 10.1371/journal.pone.0055364]

114   **Ludvigsson JF**, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, Hadjivassiliou M, Kaukinen K, Kelly CP, Leonard JN, Lundin KE, Murray JA, Sanders DS, Walker MM, Zingone F, Ciacci C. The Oslo definitions for coeliac disease and related terms. *Gut* 2013; **62**: 43-52 [PMID: 22345659 DOI: 10.1136/gutjnl-2011-301346]

115   **Rodrigo L**. Celiac disease. *World J Gastroenterol* 2006; **12**: 6585-6593 [PMID: 17075969]

116   **Janatuinen EK**, Pikkarainen PH, Kemppainen TA, Kosma VM, Järvinen RM, Uusitupa MI, Julkunen RJ. A comparison of diets with and without oats in adults with celiac disease. *N Engl J Med* 1995; **333**: 1033-1037 [PMID: 7675045 DOI: 10.1056/NEJM199510193331602]

117   **Vader LW**, de Ru A, van der Wal Y, Kooy YM, Benckhuijsen W, Mearin ML, Drijfhout JW, van Veelen P, Koning F. Specificity of tissue transglutaminase explains cereal toxicity in celiac disease. *J Exp Med* 2002; **195**: 643-649 [PMID: 11877487]

118   **Marsh MN**. Gluten, major histocompatibility complex, and the small intestine. A molecular and immunobiologic approach to the spectrum of gluten sensitivity ('celiac sprue'). *Gastroenterology* 1992; **102**: 330-354 [PMID: 1727768]

119   **van der Windt DA**, Jellema P, Mulder CJ, Kneepkens CM, van der Horst HE. Diagnostic testing for celiac disease among patients with abdominal symptoms: a systematic review. *JAMA* 2010; **303**: 1738-1746 [PMID: 20442390 DOI: 10.1001/jama.2010.549]

120   **Abdulkarim AS**, Murray JA. Review article: The diagnosis of coeliac disease. *Aliment Pharmacol Ther* 2003; **17**: 987-995 [PMID: 12694080]

121   **Ludvigsson JF**, Bai JC, Biagi F, Card TR, Ciacci C, Ciclitira PJ, Green PH, Hadjivassiliou M, Holdoway A, van Heel DA, Kaukinen K, Leffler DA, Leonard JN, Lundin KE, McGough N, Davidson M, Murray JA, Swift GL, Walker MM, Zingone F, Sanders DS. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut* 2014; **63**: 1210-1228 [PMID: 24917550 DOI: 10.1136/gutjnl-2013-306578]

122   **Ciclitira PJ**, King AL, Fraser JS. AGA technical review on Celiac Sprue. American Gastroenterological Association. *Gastroenterology* 2001; **120**: 1526-1540 [PMID: 11313324]

123   **Haines ML**, Anderson RP, Gibson PR. Systematic review: The evidence base for long-term management of coeliac disease. *Aliment Pharmacol Ther* 2008; **28**: 1042-1066 [PMID: 18671779 DOI: 10.1111/j.1365-2036.2008.03820.x]

124   **Fasano A**, Catassi C. Current approaches to diagnosis and treatment of celiac disease: an evolving spectrum. *Gastroenterology* 2001; **120**: 636-651 [PMID: 11179241]

125   **Rostami K**, Kerckhaert J, Tiemessen R, von Blomberg BM, Meijer JW, Mulder CJ. Sensitivity of antiendomysium and antigliadin antibodies in untreated celiac disease: disappointing in clinical practice. *Am J Gastroenterol* 1999; **94**: 888-894 [PMID: 10201452 DOI: 10.1111/j.1572-0241.1999.983_f.x]

126   **Rubio-Tapia A**, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterol* 2013; **108**: 656-676; quiz 677 [PMID: 23609613 DOI: 10.1038/ajg.2013.79]

127   **Vial T**, Descotes J. Clinical toxicity of the interferons. *Drug Saf* 1994; **10**: 115-150 [PMID: 7516663]

128   **Cataldo F**, Marino V, Bottaro G, Greco P, Ventura A. Celiac disease and selective immunoglobulin A deficiency. *J Pediatr*

1997; **131**: 306-308 [PMID: 9290622]

129   **Wakim-Fleming J**, Pagadala MR, McCullough AJ, Lopez R, Bennett AE, Barnes DS, Carey WD. Prevalence of celiac disease in cirrhosis and outcome of cirrhosis on a gluten free diet: a prospective study. *J Hepatol* 2014; **61**: 558-563 [PMID: 24842303 DOI: 10.1016/j.jhep.2014.05.020]

130   **Lance P**, Gazzard BG. Ulcerative enteritis and liver disease in a patient with coeliac disease. *Gut* 1983; **24**: 433-437 [PMID: 6840617]

131   **Mitchison HC**, Record CO, Bateson MC, Cobden I. Hepatic abnormalities in coeliac disease: three cases of delayed diagnosis. *Postgrad Med J* 1989; **65**: 920-922 [PMID: 2616433]

132   **Bonamico M**, Pitzalis G, Culasso F, Vania A, Monti S, Benedetti C, Mariani P, Signoretti A. [Hepatic damage in celiac disease in children]. *Minerva Pediatr* 1986; **38**: 959-962 [PMID: 3807839]

133   **Bardella MT**, Fraquelli M, Quatrini M, Molteni N, Bianchi P, Conte D. Prevalence of hypertransaminasemia in adult celiac patients and effect of gluten-free diet. *Hepatology* 1995; **22**: 833-836 [PMID: 7657290]

134   **Volta U**, De Franceschi L, Lari F, Molinaro N, Zoli M, Bianchi FB. Coeliac disease hidden by cryptogenic hypertransaminasaemia. *Lancet* 1998; **352**: 26-29 [PMID: 9800742]

135   **Korpimäki S**, Kaukinen K, Collin P, Haapala AM, Holm P, Laurila K, Kurppa K, Saavalainen P, Haimila K, Partanen J, Mäki M, Lähdeaho ML. Gluten-sensitive hypertransaminasemia in celiac disease: an infrequent and often subclinical finding. *Am J Gastroenterol* 2011; **106**: 1689-1696 [PMID: 21502996 DOI: 10.1038/ajg.2011.134]

136   **Logan RF**, Ferguson A, Finlayson ND, Weir DG. Primary biliary cirrhosis and coeliac disease: an association? *Lancet* 1978; **1**: 230-233 [PMID: 74661]

137   **Sorensen HT**, Thulstrup AM, Blomqvist P, Nørgaard B, Fonager K, Ekbom A. Risk of primary biliary liver cirrhosis in patients with coeliac disease: Danish and Swedish cohort data. *Gut* 1999; **44**: 736-738 [PMID: 10205215]

138   **Sima H**, Hekmatdoost A, Ghaziani T, Alavian SM, Mashayekh A, Zali MR. The prevalence of celiac autoantibodies in hepatitis patients. *Iran J Allergy Asthma Immunol* 2010; **9**: 157-162 [PMID: 20952805]

139   **Freeman HJ**. Hepatic manifestations of celiac disease. *Clin Exp Gastroenterol* 2010; **3**: 33-39 [PMID: 21694844]

140   **Drastich P**, Honsová E, Lodererová A, Jarešová M, Pekáriková A, Hoffmanová I, Tučková L, Tlaskalová-Hogenová H, Spičák J, Sánchez D. Celiac disease markers in patients with liver diseases: a single center large scale screening study. *World J Gastroenterol* 2012; **18**: 6255-6262 [PMID: 23180946 DOI: 10.3748/wjg.v18.i43.6255]

141   **Sjöberg K**, Lindgren S, Eriksson S. Frequent occurrence of non-specific gliadin antibodies in chronic liver disease. Endomysial but not gliadin antibodies predict coeliac disease in patients with chronic liver disease. *Scand J Gastroenterol* 1997; **32**: 1162-1167 [PMID: 9399399]

142   **Fine KD**, Ogunji F, Saloum Y, Beharry S, Crippin J, Weinstein J. Celiac sprue: another autoimmune syndrome associated with hepatitis C. *Am J Gastroenterol* 2001; **96**: 138-145 [PMID: 11197243 DOI: 10.1111/j.1572-0241.2001.03464.x]

143   **Nadir A**, Van Thiel DH. Celiac disease in patients with HCV genotype 1A. *Am J Gastroenterol* 2003; **98**: 940-941 [PMID: 12738488 DOI: 10.1111/j.1572-0241.2003.07366.x]

144   **Trivedi PJ**, Adams DH. Mucosal immunity in liver autoimmunity: a comprehensive review. *J Autoimmun* 2013; **46**: 97-111 [PMID: 23891169 DOI: 10.1016/j.jaut.2013.06.013]

145   **Thevenot T**, Denis J, Jouannaud V, Monnet E, Renou C, Labadie H, Abdelli N, Nguyen-Khac E, Dumouchel P, Bresson-Hadni S, Chousterman M, DI Martino V, Cadranel JF. Coeliac disease in chronic hepatitis C: a French multicentre prospective study. *Aliment Pharmacol Ther* 2007; **26**: 1209-1216 [PMID: 17944735 DOI: 10.1111/j.1365-2036.2007.03499.x]

146   **Silano M**, Volta U, Vincentini O, De Vincenzi M. Clinical features of chronic C virus hepatitis in patients with celiac disease. *Eur J Clin Microbiol Infect Dis* 2009; **28**: 1267-1269 [PMID: 19529964 DOI: 10.1007/s10096-009-0769-6]

147   **Monteleone G**, Pender SL, Alstead E, Hauer AC, Lionetti P, McKenzie C, MacDonald TT. Role of interferon alpha in promoting T helper cell type 1 responses in the small intestine in coeliac disease. *Gut* 2001; **48**: 425-429 [PMID: 11171837]

148   **Di Sabatino A**, Corazza GR. Coeliac disease. *Lancet* 2009; **373**: 1480-1493 [PMID: 19394538 DOI: 10.1016/s0140-6736(09)60254-3]

149   **Bardella MT**, Marino R, Meroni PL. Celiac disease during interferon treatment. *Ann Intern Med* 1999; **131**: 157-158 [PMID: 10419441]

150   **Adinolfi LE**, Durante Mangoni E, Andreana A. Interferon and ribavirin treatment for chronic hepatitis C may activate celiac disease. *Am J Gastroenterol* 2001; **96**: 607-608 [PMID: 11232725 DOI: 10.1111/j.1572-0241.2001.03574.x]

151   **Vasudevan A**, Lubel JS. New-onset of celiac disease during interferon-based therapy for hepatitis C. *Gastroenterol Rep* (Oxf) 2015; **3**: 83-85 [PMID: 25212692 DOI: 10.1093/gastro/gou060]

152   **Cammarota G**, Cuoco L, Cianci R, Pandolfi F, Gasbarrini G. Onset of coeliac disease during treatment with interferon for chronic hepatitis C. *Lancet* 2000; **356**: 1494-1495 [PMID: 11081540 DOI: 10.1016/s0140-6736(00)02880-4]

153   **Bourlière M**, Oulés V, Perrier H, Mengotti C. Onset of coeliac disease and interferon treatment. *Lancet* 2001; **357**: 803-804 [PMID: 11253998 DOI: 10.1016/s0140-6736(05)71230-7]

154   **Lim EJ**, Watson K. Unmasking of coeliac disease on interferon treatment for hepatitis C. *Intern Med J* 2010; **40**: 85-87 [PMID: 20561373 DOI: 10.1111/j.1445-5994.2009.02087.x]

155   **Borghi-Scoazec G**, Merle P, Scoazec JY, Claudy A, Trepo C. Onset of dermatitis herpetiformis after treatment by interferon and ribavirin for chronic hepatitis C. *J Hepatol* 2004; **40**: 871-872 [PMID: 15094241 DOI: 10.1016/j.jhep.2004.01.026]

156   **Casella G**, Bardella MT, Perego D, Baldini V. Should routine screening for coeliac disease be considered before starting interferon/ribavirin treatment in patients affected by chronic hepatitis C? *Eur J Gastroenterol Hepatol* 2004; **16**: 429 [PMID: 15028979]

157   **Colombo E**, Cermesoni L, Morganti D. Celiac sprue: another autoimmune syndrome associated with hepatitis C? *Dig Liver Dis* 2003; **35**: 64-65 [PMID: 12725613]

158   **Nejad MR**, Alavian SM. Should routine screening for celiac disease be considered before starting interferon/ribavirin treatment in patients affected by chronic hepatitis C or not? *Bratisl Lek Listy* 2012; **113**: 251 [PMID: 22502761]

159   **Pateron D**, Hartmann DJ, Duclos-Vallee JC, Jouanolle H, Beaugrand M. Latent autoimmune thyroid disease in patients with chronic HCV hepatitis. *J Hepatol* 1992; **16**: 244-245 [PMID: 1484160]

Baishideng®