

Autoimmunity in Hepatitis C Virus Infection – An Immunologist’s Perspective

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Abstract

Hepatitis C virus infection can be associated with the presence of auto antibodies and clinical disease which may have significant morbidity in this population. Manifestations can be systemic or organ specific. This review presents the current state of play on autoimmunity in Hepatitis C in the absence of interferon-alpha based treatment, from a clinical immunologist’s perspective.

Keywords: Hepatitis C virus; Autoimmunity; Thyroid disease; Arthropathy; Cryoglobulins; Sicca symptoms; Sjogren’s Immunity; Interferon

Abbreviations: AAb: Auto Antibodies; AECG: American-European Consensus Group; AIH: Autoimmune Hepatitis; AMA: Anti-Mitochondrial Antibody; ANA: Anti-Nuclear Antibody; ASMA: Anti-Smooth Muscle Antibody; CCP: Cyclic Citrullinated Peptide; DAA: Direct Acting Antivirals; GT: Genotype; HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; IF: Intrinsic Factor; IFN: Interferon; LDL: Low Density Lipoprotein; LKMA-1: Liver Kidney Microsomal Antibody 1; MC: Mixed Cryoglobulinaemia; MCV: Mutated Citrullinated vimentin Antibody; NOSA: Non-Organ Specific Autoantibody; pSS: primary Sjogren’s Syndrome; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; SP: Symmetric Polyarthropathy; SS: Sjogren’s Syndrome; sSS: Secondary Sjogren’s Syndrome; T3: Tri-Iodothyronine; T4: Thyroxine; TFT: Thyroid Function Test; Tg: Thyroglobulin; TPO: Thyroid Peroxidase; TSH: Thyroid Stimulating Hormone

Introduction

Hepatitis C Virus (HCV) infection is commonly thought of being associated with an increased incidence of autoimmunity. However, the immunological basis behind this heightened susceptibility to autoimmunity is not well understood. It is not clear whether HCV infection itself induces autoimmunity, how this differs compared to other viral hepatitis infections, or if the presence of autoimmunity is confounded by the previously widespread use of interferon-alpha based regimens for the treatment of HCV. Therefore, in the current era of interferon-free treatments based on direct acting anti-viral (DAA), do clinicians need to remain vigilant for autoimmune complications in their patients? This review summarises current evidence to assist clinicians with the management of subjects with HCV and when to suspect autoimmunity. As the majority of evidence in regards to HCV and autoimmunity is related to B cell mediated

autoimmunity, with the association of auto antibodies (AAb), this will be the focus of this review. Overall, while published evidence generally distinguishes between HCV with and without interferon treatment, there are only a few studies that include relevant healthy age and gender matched control populations.

HCV interferes with normal B cell regulation

Although HCV is primarily hepatotropic, there is evidence to suggest that the virus is able to directly infect lymphoid cells [1], including B cells [2] via interaction of HCV envelope protein E2 and the cell surface protein CD81. Following this, there is increased expression of the anti-apoptotic B cell survival factor Bcl-2 in B cells and protection of B cells from Fas-mediated apoptosis [3-6], implying prolonged B cell survival and protection from activation-induced death.

CD81 forms part of the B cell co stimulatory complex that includes CD19, CD21 and the IFN-inducible protein CD225 that can reduce the threshold for B cell activation following antigen-stimulation. Following HCV E2-CD81 binding, there are reports of up-regulation of co stimulatory markers CD80 and CD86 [6] on B cells leading to their non-specific polyclonal activation [7] resulting in hyper gamma globulinaemia. This is further supported by the high incidence (10-70%) of cryoglobulinaemia in subjects with chronic HCV infection [8].

The viral protein NS5A also increases the activity of the protein Fyn, which is a member of the Src family of kinases, leading to an increase in cell cycling and consequent B cell proliferation [9].

All of the above mechanisms are thought to contribute to B cell dysregulation, with the presumed potential for the induction of AAbs. Furthermore, there is also evidence to suggest that liver cirrhosis itself, leads to B cell abnormalities in the CD27+IgM+ memory B cell compartment [10].

AAbs in HCV-general considerations

AAbs are defined as antibodies directed against self. They can be directly pathogenic in the associated autoimmune disease, or “marker” antibodies that are not directly pathogenic [11].

Low levels of AAbs are commonly present in healthy subjects, often more so in females and also increase with age [12-16]. It is thought that the positive predictive value for clinical disease increases with higher titre and may precede clinical disease by more than five years [17-19]. Overall, the presence of AAbs in serum is not synonymous with presence of autoimmune disease, which is relevant in the context of HCV studies, as many looked at the presence of AAbs, but not clinical disease.

Furthermore, the sensitivity and specificity of the autoantibody result depends on the assay and antigenic target that was used to measure the autoantibody; newer assays are generally more sensitive and use more specific targets [20-22]. Therefore, older studies using historical assays may not be easily reproduced with the newer assays.

Table 1: Auto antibodies described in Hepatitis C infection.

System	AAb	Associated Autoimmune Disease
Organ specific Thyroid Gastrointestinal Joints Haematological	TPO (thyroid peroxidase) Tg (thyroglobulin) IF (intrinsic factor) AMA (anti-mitochondrial) ASMA (anti-smooth muscle) LKMA-1 (liver kidney microsomal antibody 1) CCP (cyclic citrullinated peptide) MCV (mutated citrullinated dementin) Anti-platelet N/A	Thyroiditis (hyper/hypothyroidism) Pernicious anaemia Primary biliary cirrhosis Autoimmune hepatitis type 1 Autoimmune hepatitis type 2 Rheumatoid arthritis Rheumatoid arthritis Immune thrombocytopenia Autoimmune haemolytic anaemia
Non-organ specific	ANA (anti-nuclear antibodies) SS-A/Ro, SS-B/La RF (rheumatoid factor)	SLE, Systemic sclerosis, Sjogren's syndrome, autoimmune hepatitis Sjogren's syndrome, congenital heart block, neonatal lupus Associated with rheumatoid arthritis, infection/inflammation

Several AAbs have been described at increased frequency in HCV infection; for most of these the level of evidence is Level 3 or 4. Table 1 summarises the antibodies studied and their clinical disease associations.

Hepatitis C and thyroid disease

It is well established that thyroid autoimmunity, whether subacute or clinically manifest, may emerge during the course of HCV infection, even in the absence of IFN-α treatment. Between 2% and 48% of patients with chronic HCV infection manifest anti-thyroid antibodies, with the variability in prevalence attributed to a number of factors including geography, study population ethnicity [23,24], iodine intake [25] and HCV genotype (GTs) [26-28].

One of the earliest and largest studies to demonstrate thyroid autoimmunity assessed 630 chronic HCV-infected subjects, presenting to clinic prior to IFN-α treatment, for the presence of abnormal thyroid function test (TFT) including free thyroxine (T4), free tri-iodothyronine (T3) and thyroid stimulating hormone (TSH), TPO antibodies and anti-thyroglobulin (Tg) antibodies [29]. This study also included three control groups selected retrospectively from a general population registry and comprising 389 subjects from an iodine deficient area, 268 subjects from an area of iodine sufficiency, and 86 subjects over the age of 40 with chronic HBV infection. There was a significantly higher incidence of hypothyroidism in the subjects with HCV infection (13% versus 3-5% of the controls). 21% of HCV-infected subjects had anti-TPO antibodies versus 10-13% of

the controls, and 17% had anti-thyroglobulin antibodies versus 9-10% of controls. These findings were confirmed by further studies [30] and three meta-analyses verified a significant association between HCV infection and thyroid autoimmunity [31,32]. Overall, female gender and anti-TPO antibody positivity was associated with a raised risk of hypothyroidism [25,33] in these studies. Nevertheless, an increased risk of thyroiditis associated with HCV infection was also demonstrated in a cohort study of predominantly male subjects (97%) attending US Veterans Affairs Health Care facilities from 1997-2004 [34].

Thyroid autoimmunity has been studied in the presence of mixed cryoglobulinaemia (MC). Although few in number, these studies suggest that MC-positive HCV-infected subjects have a higher incidence of autoimmune thyroid disease as compared to MC-negative HCV-infected subjects; this is most pronounced in females with TPOAAbs, leading to the recommendation that female subjects with MC-positive HCV infection should be screened for thyroid autoimmunity [30].

Importantly, several studies suggest that chronic HCV infection and thyroid autoimmunity may be associated with a higher rate of papillary thyroid cancer. Antonelli, et al. [35] described a higher prevalence of this papillary thyroid cancer in 139 HCV-infected subjects compared to controls [35] while another case control study for various cancers noted an association between HCV and thyroid cancer (OR 2.8 $p=0.01$) [35,36]. The increased risk for thyroid cancer is also true for HCV-infected subjects with MC [37]. Significant lymphocytic infiltrates in the thyroid tissue were seen in the cases of HCV-associated thyroid cancer; supporting the notion that autoimmune thyroiditis may be a predisposing factor [38,39]. Case studies have also reported that more aggressive thyroid cancers can be seen within HCV-infected subjects [40], leading to clinical recommendations to monitor HCV-infected subjects with thyroid disease for the development of thyroid cancer.

Hepatitis C and autoimmune arthritis

Arthralgia is a common symptom in subjects with HCV infection [41] and asymptomatic inflammatory joint changes have been described in the majority of subjects in an HCV-infected cohort when screened by joint ultrasonography [42]. Clinically manifest arthritis in HCV-infected subjects is seen in approximately 4% [43]. HCV-associated arthritis usually manifests as a symmetric polyarthritis (SP) or an intermittent oligoarthritis (IMO) of medium to large joints; the latter often in patients with MC.

Compared to thyroid autoimmunity, autoantibody profiling for HCV-associated arthropathy is less studied. Anti-cyclic citrullinated peptide (CCP) antibodies, which are highly specific for rheumatoid arthritis (RA) and are found in 60% to 75% of patients with RA [44,45], but can be also seen in a small proportion of patients with HCV-related arthritis (4.5% to 7%) [46-48]. The majority of HCV-related arthritis is, however,

thought to be CCP negative. This is supported by a recent study [49] investigating the prevalence of anti-mutated citrullinated vimentin (MCV) antibodies, CCP antibodies, rheumatoid factor (RF) and mixed cryoglobulinaemia (MC) in 45 subjects with HCV (GT4) infection-associated arthritis compared to 30 RA subjects. The most frequent clinical presentation was a symmetric polyarthropathy (SP), which in RA subjects was associated with CCP antibodies but not in HCV-infected subjects. Other antibodies studied such as MCV (30% in HCV-infected subjects versus 93.3% in RA subjects) did not aid further clinical distinction between RA and HCV-associated arthritis. In this particular study the level of RF positivity was high in both cohorts 73.3% in HCV arthropathy versus 86.7% in RA subjects. A potential role for CCP antibodies in distinguishing HCV-associated SP from RA was identified in further studies (0% to 11.7% CCP positivity in HCV-associated disease depending on demographics of the population studied) [48,50-52]. Finally, a large nation-wide study from Taiwan revealed that in the Taiwanese population chronic HCV infection alone was associated with an increased risk for SP (hazard ratio 2.03). Due to the nature of the study no distinction between HCV-associated SP and RA was made and no data on anti-CCP antibody profiles were provided [53].

Hepatitis C and Sjogren's syndrome

Sjogren's syndrome (SS) is a chronic, auto immune exocrinopathy characterised by reduced salivary and lacrimal gland function causing dry eyes and mouth ("sicca symptoms"), and extra-glandular manifestations affecting multiple organ systems [54]. It may present by itself, primary SS (pSS), or in association with another autoimmune disease such as SLE or RA, termed secondary SS. Hepatitis C virus is sialotropic with HCV RNA found in both saliva and salivary epithelial cells it has been questioned whether HCV is directly responsible for the manifestations of sicca symptoms seen as a common extra-hepatic manifestation of HCV infection [55-58] or whether the sicca symptoms and sialadenitis associated with HCV identify a subset of patients with pSS (potentially with HCV as a trigger for immune dysregulation). Epidemiological data on the association of HCV with SS depends on the criteria used which have changed over time and also depends on the background prevalence of HCV, and the geographical location. The prevalence of HCV in patients with SS varies from 0-19%. Patients are now considered to have a secondary form of SS if there is concurrent HCV infection [59].

Sjogren's syndrome is associated with the presence of AAbs to SS-A/Ro and SS-B/La antigens and has inflammatory cell infiltrates within the salivary glands that appear to vary with disease course or severity of disease [60]. Positivity for SS-A/Ro and SS-B/La antibodies in patients with HCV infection and sicca symptoms has been reported in up to 25% of HCV patients [61].

However, while some subjects with HCV have very similar features compared with non-HCV pSS [61], sialadenitis in the context of HCV generally shows sufficient aetiological,

histopathological and genetic differences to allow differentiation between the two states [62,63].

From a practical perspective, a predominantly B cell infiltrate in the salivary glands is strongly associated with hyper gamma globulinaemia, autoantibody production and clinical manifestations of salivary gland swelling. Both hypo complementaemia and glandular swelling are risk factors in SS for lympho proliferative disease [64-66]. Patients who otherwise satisfy American-European Consensus Group (AECG) criteria for pSS, but who are HCV positive, also have a high frequency of parotid enlargement and vasculitis are RF positive with MC, have higher extra-nodal involvement in organs where HCV replicates, and a predominance of mucosa-associated lymphoid tissue lymphomas [67]. The presence of sicca symptoms in patients with HCV therefore remains a red flag to monitor for lympho proliferative disease.

Hepatitis C and cryoglobulinaemia

Hepatitis C is frequently associated with cryoglobulinaemia. Cryoglobulins are cold insoluble immune complexes that precipitate at temperatures below 37 °C and resolubilise on warming [8,68]. They are classified according to the type of immunoglobulin in the cryoprecipitate [68,69]: Type I cryoglobulins are typically monoclonal and associated with B cell lymphoproliferative disease; MC are Type II or III. Type II cryoglobulins are a mixture of polyclonal immunoglobulin IgG and a commonly monoclonal IgM immunoglobulin with reactivity for RF; Type III are polyclonal immunoglobulins (IgG, IgM, IgA) or polyclonal IgG with RF reactivity. Type II and III are those associated with (50 – 60%) chronic viral infections, including HCV. The reported frequency of cryoglobulins in chronic HCV-infected subjects ranges from 12 to 56%, with the highest prevalence reported in Mediterranean climates [69]. Although not a classical AAbs mediated immune disease, cryoglobulinaemia can present with a wide range of clinical features mimicking autoimmunity.

Symptoms associated with MC are variable ranging from Raynaud's phenomenon, small to medium-sized vessel vasculitis, purpura, arthralgia and asthenia to severe neurologic and renal involvement.

Other extra-hepatic manifestations of Hepatitis C associated with the presence of AAbs

Aside from the more common extra-hepatic manifestations, auto immunocytopenias have been described in association with AAbs in HCV-infected subjects [70]. In chronic HCV-infected subjects autoimmune hemolytic anemia is associated with ANA and MC positivity while subjects with HCV-infection and autoimmune thrombocytopenia had been observed to have anti-platelet antibodies.

AAbs to oxidized LDLs that have also been described and are thought to be serological marker for severity of atherosclerosis;

in addition an association of these AAbs with severity of hepatitis steatosis in chronic HCV-infected subjects has been described.

Systematic Autoantibody profiling in HCV-infected subjects

The prevalence of non-organ-specific AAbs (NOSAs; specifically ASMA, ANA and anti-liver kidney microsomal type 1 antibody (LKMA-1); Table 1) has been examined in several studies with varying results. Some authors have examined the prevalence of NOSAs versus age- and sex-matched HCV-negative subjects and found no significant difference in the NOSAs between cases and controls (18% versus 10%) [71].

Others however have shown higher prevalence in the HCV-infected subjects (25%) and with chronic liver disease than in age- and sex-matched controls, including normal healthy (6%) and HBV controls (7%; HbsAg positive). NOSAs seen in this study were generally low titre and not directed against well defined-antigens (e.g. F-actin in ASMA) [72]. This is similar to findings from Granito, et al. [73] in which none of the HCV-infected subjects tested by IIF had detectable ASMA VGT (VGT=vascular, glomerular and tubular) staining; a pattern usually associated with F-acting antibodies as opposed to ASMA V or ASMA VG staining, which are less specific for autoimmune hepatitis (AIH). Of note, many studies in HCV-infected subjects do not distinguish between these patterns despite their differing clinical predictive value for AIH.

NOSA positive individuals however may have higher levels of alkaline phosphatase, lower levels of platelets and prothrombin activity and increased prevalence of significant fibrosis suggesting possible association between NOSA positivity and biochemical and histological profile of HCV [74]. In a US population, a retrospective review of AAbs (as above and with the addition of RF, AMA and MC) in HCV-exposed subjects with elevated serum amino transferases (n=117) showed a high prevalence of positivity, particularly for ASMAs (66%) and RF (76%), in both men and women [75]. However, the study did not appear to include age- or sex-matched controls.

In a recent Egyptian paediatric population with chronic HCV GT4 infection (n=80), tested for the same set of NOSAs, 40% exhibited evidence of low to moderate titre ASMA without associated ANA or LKMA-1 but non-typical clinical features usually associated with the presence of ASMA. Nevertheless, it was found that HCV infected subjects with ASMA had higher levels of total bilirubin, albumin, immunoglobulins, alkaline phosphatase, and gamma-glutamyl transferase levels [76]. In addition, adult data suggests there may also be an association between ASMA antibody and degree of liver fibrosis [77].

ANA positivity (titre ≥ 80) appears to be an immunological epiphenomenon that does not influence clinical, biochemical or histological features of chronic hepatitis, or predict response to anti-viral treatment [78]. A large UK study of 963 chronic HCV

positive subjects reported a significant relationship between ASMA positivity and interface hepatitis in males, and that ANA was associated with increased age consistent with the frequencies reported in blood donors. The outcome of these reports suggests that ASMA may be associated with histological features of liver damage, while the association between ANA and clinical correlates remain unclear [77-80].

Conclusion

This review reflects on the current evidence for AAbs in HCV from a Clinical Immunology aspect. Although there is clear evidence for certain types of autoimmune disease in HCV-infected subjects, less is known about additional predisposing risk factors. Based on the current evidence, routine screening for thyroid autoimmunity and MC is recommended, however, the role of screening for other types of autoimmunity beyond these is less clear and should be performed only if the clinical suspicion of an autoimmune disease arises. Further studies in the field are urgently needed, as the time of initiation of treatment with DAAs may be critical to prevent future life-long autoimmune disease in some subjects.

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