

Hepatitis C and Rheumatic Disease:

2008

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I. LARGE OBSERVATIONAL STUDIES

1. Cacoub P, Poynard T, Ghillani P, Charlotte F, Olivi M, Piette JC, et al. Extrahepatic Manifestations of Chronic Hepatitis C. *Arthritis & Rheumatism* 1999; 42: 2204-12.

[PUB MED LINK](#)

This prospective study of 1,614 patients with chronic Hepatitis C virus (HCV) infection assessed the prevalence of clinical and biological extra-hepatic manifestations. Only five clinical manifestations, including arthralgia (23%), paresthesia (17%), myalgia (15%), pruritis (15%), and sicca syndrome (11%) had a prevalence >10%. The authors cited a significant prevalence of cryoglobulins (40%), antinuclear antibodies (10%), and anti-smooth muscle antibodies (7%).

2. Buskila D, Shnaider A, Neumann L, Lorber M, Zilberman D, Hilzenrat N, et al. Musculoskeletal Manifestations and Autoantibody Profile in 90 Hepatitis C virus Infected Israeli Patients. *Seminars in Arthritis and Rheumatism* 1998; 28: 107-113.

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Examining 90 HCV positive patients, rheumatic manifestations were found in 31%, the most prevalent being arthralgias (9%), arthritis (4%), cryoglobulinemia (11%), sicca symptoms (8%), and myalgias (24%). Sixty-nine percent of patients had at least one auto-antibody detected, including RF (44%), ANA (38%), and aCL (22%).

II. EXTRA-HEPATIC CLINICAL MANIFESTATIONS

A. Sicca Syndrome

3. Haddad J, Deny P, Munz-Gotheil C, Ambrosini JC, Trinchet JC, Pateron D, et al. Lymphocytic sialadenitis in Sjogren's syndrome associated with chronic hepatitis C virus liver disease. *Lancet* 1992; 339: 321-3. [PUB MED LINK](#)

First major publication postulating a possible relationship between HCV and sjogren's symptoms, showing histologic changes characteristic of Sjogren's syndrome were more common in HCV-infected patients (57%) versus controls (5%).

4. Ramos-Casals M, Loustaud-Ratti V, De Vita S, Zeher M, Bosch JA, Toussirot E, et al. Sjogren Syndrome Associated With Hepatitis C Virus. A Multicenter Analysis of 137 Cases. *Medicine* 2005; 84: 81-89. [PUB MED LINK](#)

Comparison of 137 SS-HCV patients with 400 Primary SS controls found a higher mean age, higher percentage of vasculitis (likely 2/2 cryoglobulins), less SS-A/SS-B antibodies, higher prevalence of cryoglobulinemias and hypocomplementemia in the SS-HCV group.

5. Koike K, Moriya K, Ishibashi K, Yotsuyanagi H, Shintani Y, Fujie H, et al. Sialadenitis histologically resembling Sjogren syndrome in mice transgenic for hepatitis C virus envelope genes. *Proc. Natl. Acad. Sci. US* 1997; 94: 233-6. [PUB MED LINK](#)

Two independent transgenic mouse lines, expressing envelope genes from HCV of genotype 1b, were found to have lymphocytic infiltration in the salivary glands resembling that found in human sjogren's syndrome, suggesting a relationship between chronic HCV infection and Sjogren's-like sialadenitis.

6. King PD, McMurray RW, Becherer PR. Sjogren's syndrome without mixed cryoglobulinemia is not associated with hepatitis C virus infection. *American Journal of Gastroenterology* 1994; 89: 1047-50. [PUB MED LINK](#)

Evaluation of 48 patients with a diagnosis of Sjogren's syndrome, without cryoglobulinemia and with detectable SS-A/SS-B autoantibodies, found no patient with evidence of hepatitis C viremia or hepatitis C antibodies, indicating that patients with defined Sjogren's syndrome rarely have HCV infection (although this varies greatly in different reports, from 0-19%). It is actually part of the exclusion criteria to diagnose Primary SS (see below).

7. Jorgensen C, Legouffe MC, Perney P, Coste J, Tissot B, Segarra C, et al. Sicca syndrome associated with hepatitis C virus infection. *Arthritis & Rheumatism* 1996; 39: 1166-71. [PUB MED LINK](#)

HCV-positive sicca syndrome patients were seronegative for SS-A/SS-B antibodies and had HCV RNA present in their saliva (83%) when compared to HCV-negative sicca patients (0%), emphasizing the difference between HCV-associated sicca and primary Sjogren's syndrome.

8. Scott CA, Avellini C, Desinan L, Pirisi M, Ferraccioli GF, Bardus P, et al. Chronic lymphocytic sialoadenitis in HCV related chronic liver disease: comparison of Sjogren's syndrome. *Histopathology* 1997; 30: 41-8. [PUB MED LINK](#)

To morphologically characterize sialoadenitis in patients with HCV, minor salivary gland biopsies from 22 patients with HCV and 10 patients with primary sjogren's were compared. While histopathology and lymphocyte typing were similar in the two groups, there was a lesser degree of inflammation in the HCV group.

9. Pawlotsky JM, Ben Yahia M, Andre C, Voisin MC, Intrator L, Roudot-Thoraval F, et al. Immunological disorders in C virus chronic active hepatitis: a prospective case-control study. *Hepatology* 1994; 19: 841-8. [PUB MED LINK](#)

HCV-associated sicca syndrome had similar salivary gland lesions as those seen in primary Sjogren's syndrome (SS), but duct walls were intact with pericapillary rather than periductal lesions predominating.

10. Coll J, Gambus G, Corominas J, Tomás S, Esteban JI, Guardia J. Immunohistochemistry of minor salivary gland biopsy specimens from patients with Sjogren's syndrome with and without hepatitis C virus infection. *Annals of the Rheumatic Diseases* 1997; 56: 390-92. [PUB MED LINK](#)

HCV-infected sicca patients have a predominance of CD4 over CD8 T cells (similar to primary SS), predominance of CD20 positive cells, but low epithelial cell expression of CD25.

11. Ramos-Casals M, Garcia-Carrasco M, Cervera R, Rosas J, Trejo O, de la Red G, et al. Hepatitis C Virus Infection Mimicking Primary Sjogren Syndrome. A Clinical and Immunologic Description of 35 Cases. *Medicine* 2001; 80: 1-8. [PUB MED LINK](#)

SS-HCV patients had a lower prevalence of parotidomegaly, a higher mean age, higher prevalence of liver involvement, cryoglobulinemia and hypocomplementemia when compared to patients with primary SS.

12. Ramos-Casals M, Garcia-Carrasco M, Cervera R, Filella X, Trejo O, de la Red G, et al. Th1/Th2 Cytokine Imbalance in Patients with Sjogren Syndrome Secondary to Hepatitis C Virus Infection. *Seminars in Arthritis and Rheumatism* 2002; 32: 56-63. [PUB MED LINK](#)

Patients with HCV-SS have a poor Th1 response (low levels of IL-2) and an enhanced Th2 response (higher levels of IL-6 and IL-10) compared to primary SS patients.

13. Ramos-Casals M, Civita L, De Vita S, Solans R, Luppi M, Medina F, et al. Characterization of B Cell Lymphoma in Patients with Sjogren's Syndrome and Hepatitis C Virus Infection. *Arthritis & Rheumatism* 2007; 57: 161-170. [PUB MED LINK](#)

The first study to characterize the clinical and immunologic manifestations of patients with SS-HCV who developed a B-cell lymphoma. In comparison to patients with SS-HCV without lymphoma, those with lymphoma were characterized by a higher frequency of parotid enlargement and vasculitis, RF positivity, and the presence of mixed type II cryoglobulins. MALT lymphomas predominated.

14. Vitali C, Bombardieri S, Johnson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Annals of the Rheumatic Diseases* 2002; 61: 554-558. [PUB MED LINK](#)

HCV infection is in the exclusion criterion for the diagnosis of Primary SS.

15. Smyth C, McKieran S, Hagan R, Pilkington R, O'Regan M, Lawlor E, et al. Chronic hepatitis C infection and sicca syndrome: a clear association with HLA DQB1*02. *European Journal of Gastroenterology & Hepatology* 2007; 19: 493-98. [PUB MED LINK](#)

*Human Leukocyte antigen DQB1*02 was significantly associated with the development of sicca syndrome in HCV positive patients.*

B. Arthritis

16. Rosner I, Rozenbaum M, Toubi E, Kessel A, Naschitz JE, Zuckerman E. The Case for Hepatitis C Arthritis. *Seminars in Arthritis Rheumatism* 2004; 33:375-387. [PUB MED LINK](#)

A comprehensive review on hepatitis C arthritis outlining clinical features, pathogenesis, differential diagnosis, prevalence, and therapeutics.

17. Maillefert JF, Muller G, Falgarone G, Bour JB, Ratovohery D, Dougados M, et al. Prevalence of hepatitis C virus infection in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases* 2002; 61:635-37. [PUB MED LINK](#)

Of 309 patients with RA, two patients (0.65%) had positive anti-HCV serology, and only one had a remarkable hepatitis C viral load.

18. Rivera J, Garcia-Monforte A, Pineda A, Millán Núñez-Cortés J. Arthritis in patients with chronic hepatitis C virus infection. *Journal of Rheumatology* 1999; 26: 420-4. [PUB MED LINK](#)

A study of two patient populations: one with arthritis and ALT elevation and another with an established diagnosis of RA. Both groups were checked for HCV antibodies. Twenty-eight patients with arthritis had anti-HCV antibodies, seven of whom fulfilled the criteria for RA. 7 patients had an intermittent arthritis, of which a significant percentage (86%) had mixed cryoglobulinemia. The cases of mixed cryoglobulinemia had a distinct clinical picture with an intermittent, large joint, non-destructive oligoarthritis. Among the patients with an established RA diagnosis, 7.6% had HCV antibodies and only 2.3% had active infection by viral RNA PCR.

19. Lovy MR, Starkebaum G, Uberoi S. Hepatitis C infection presenting with rheumatic manifestations: a mimic of rheumatoid arthritis. *Journal of Rheumatology* 1996; 23: 979-83. [PUB MED LINK](#)

Hepatitis C infection can present with a small joint, symmetric polyarthritis that is difficult to distinguish from RA. 15 of 19 patients in this study with Hepatitis C virus infection fulfilled diagnostic criteria for RA.

20. Zuckerman E, Keren D, Rozenbaum M, Toubi E, Slobodin G, Tamir A, et al. Hepatitis C virus-related arthritis: characteristics and response to therapy with interferon alpha. *Clinical Experimental Rheumatology* 2000; 18: 579-84. [PUB MED LINK](#)

Greater than 60% of HCV patients with arthritis had symmetric polyarticular symptoms and >1 hour of AM stiffness, but none had erosions or subcutaneous nodules. Approximately 50% had an elevated ESR and met ACR criteria for RA. Response of HCV-associated arthritis to IFN-alpha was between 30-40%, even though a smaller percentage of patients achieved a complete virological response.

C. Fibromyalgia

21. Narvaez J, Joan M, Valverde-Garcia J. Lack of Association of Fibromyalgia with Hepatitis C Virus Infection. *Journal of Rheumatology* 2005; 32:1118-21. [PUB MED LINK](#)

This study investigated a possible association between HCV and Fibromyalgia (FM). There was no statistical difference in the prevalence of HCV infection in a series of 115 FM patients with the prevalence of HCV in the general population. This does not support a significant association with HCV and FM, but suggests the two processes have similar symptoms, sometimes complicating the diagnostic picture.

22. Palazzi C, D'Amico S, D'Angelo A, Nucera A, Petricca A, Olivieri I. Hepatitis C virus infection in Italian patients with fibromyalgia. *Clinical Rheumatology* 2008; 27: 101-103. [PUB MED LINK](#)

There was no statistically significant difference in the prevalence of HCV in 152 patients suffering from FM and 152 patients with osteoarthritis, negating a significant pathogenic role of HCV in FM.

D. Cryoglobulinemia

23. Saadoun D, Landau DA, Calabrese LH, Cacoub PP. Hepatitis C-associated mixed cryoglobulinemia: a crossroad between autoimmunity and lymphoproliferation. *Rheumatology (Oxford)*2007; 46: 1234-1242. [PUB MED LINK](#)

An extensive review outlining the clinical course, complications, pathophysiology and treatment of HCV-associated cryoglobulinemia, the main points of which are: 1. circulating mixed cryoglobulins (MC) are present in 40-60% of HCV-infected patients, while <10% develop MC-associated vasculitis; 2. MC represents a monoclonal expansion of B cells; 3. disease expression can be variable, including palpable purpura, arthralgias, membranoproliferative glomerulonephritis, and neuropathy; 3. treatment primarily consists of antiviral therapy +/- rituxan.

24. Saadoun D, Delluc A, Piette JC, Cacoub P. Treatment of hepatitis C-associated mixed cryoglobulinemia vasculitis. *Current Opinion in Rheumatology* 2008; 20:23-28. [PUB MED LINK](#)

Review outlining the therapeutic approach for HCV-associated cryoglobulinemia vasculitis, a combination of anti-viral therapy with treatment aimed at cryoglobulin-producing B-cells (Peg-IFN/ribavirin plus rituxan).

25. Saadoun D, Resche-Rigon M, Thibault V, Piette JC, Cacoub P. Antiviral Therapy for Hepatitis C Virus-Associated Mixed Cryoglobulinemia Vasculitis. *Arthritis & Rheumatism* 2006; 54: 3696-3706. [PUB MED LINK](#)

This study evaluated the long-term efficacy of IFN (PEG or non-PEG) in a large cohort of MC patients. Overall rates of complete clinical and virologic response of HCV-MC vasculitis was approximately 60%. 26.7% of the complete clinical responders were not sustained virologic responders. Renal insufficiency was a negative predictor and an early virologic response was a positive predictor for a complete clinical response. Although this approach had a satisfactory response rate, this study emphasized the need for additional therapy in certain cases (i.e. renal failure and those without an early viral response).

26. Landau DA, Saadoun D, Halfon P, Martinot-Peignoux M, Marcellin P, Fois E, et al. Relapse of Hepatitis C Virus-Associated Mixed Cryoglobulinemia Vasculitis in Patients with Sustained Viral Response. *Arthritis & Rheumatism* 2008; 58:604-611. [PUB MED LINK](#)

This study investigated the clinical characteristics and outcomes in 8 patients who experienced a relapse of MC vasculitis despite achieving a sustained viral response (negative HCV viral load) to treatment with antiviral agents (PEG-IFN and ribavirin). The relapse was not related to persistence of virus (negative viral load), appeared soon after antiviral treatment was discontinued (mean of 3 months), had mild symptoms (purpura and arthralgias most frequent), and was short-lived in all but 3 patients. In 2 of the 3 patients, B cell lymphoma was diagnosed, emphasizing the need to seek an alternate diagnosis in patients with persistent MC vasculitis symptoms following anti-viral therapy.

27. Cacoub P, Renou C, Kerr G, Hùe S, Rosenthal E, Cohen P, et al. Influence of HLA-DR Phenotype on the Risk of Hepatitis C Virus-Associated Mixed Cryoglobulinemia. *Arthritis & Rheumatism* 2001; 44: 2118-2124. [PUB MED LINK](#)

HLA-DR11 was significantly more frequent in patients with type II MC than in those without MC, regardless of the presence of MC-associated vasculitis, while HLA-DR7 appeared to protect against the production of type II MC.

28. Saadoun D, Beiche I, Authier FJ, Laurendeau I, Jambou F, Piette JC, et al. Role of Matrix Metalloproteinases, Proinflammatory Cytokines, and oxidative Stress-Derived Molecules in Hepatitis C Virus-Associated Mixed Cryoglobulinemia Vasculitis Neuropathy. *Arthritis & Rheumatism* 2007; 56: 1315-1324. [PUB MED LINK](#)

This study examined the expression profile of genes involved in inflammatory vascular damage in patients with HCV-MC vasculitis versus those with PAN or a noninflammatory neuropathy, confirming the role of matrix metalloproteinases and other pro-inflammatory cytokines in the pathogenesis of HCV-MC vasculitis.

III. AUTOANTIBODY PRODUCTION

A. Antiphospholipid Antibodies

29. Harada M, Fujisawa Y, Sakisaka S, Kawaguchi T, Taniguchi E, Sakamoto M, et al. High Prevalence of anticardiolipin antibodies in hepatitis C virus infection: lack of effects on thrombocytopenia and thrombotic complications. *Journal of Gastroenterology* 2000; 35:272-277. [PUB MED LINK](#)

The prevalence of anticardiolipin antibodies in hepatitis C patients was significantly higher than patients with hepatitis B, PBC, or healthy controls. There was no significant correlation between anticardiolipin antibody-positivity and thrombocytopenia, and all but one antibody-positive patient were negative for phospholipid-dependent anti-B2 glycoprotein I antibodies. There was no significant difference between the thrombotic complications between the antibody-positive and negative patients and the presence of anticardiolipin antibodies did not correlate with the severity of liver disease.

30. Sthoeger Z, Fogel M, Smirov A, Ergas D, Lurie Y, Bass DD, et al. Anticardiolipin autoantibodies in serum samples and cryoglobulins of patients with chronic hepatitis C infection. *Annals of the Rheumatic Diseases* 2000; 59: 483-86. [PUB MED LINK](#)

Patients with HCV had a higher prevalence (44%) of IgG aCL antibodies vs. hepatitis B patients (20%) and controls (0%). Anticardiolipin antibody positivity was significantly associated with hepatitis C viremia (100% vs. 58%), and showed no B2 glycoprotein dependency or correlation to thrombotic events.

B. Anti-CCP and Rheumatoid Factor (RF)

31. Koga T, Migita K, Miyashita T, et al. Determination of anti-cyclic citrullinated peptide antibodies in the sera of patients with liver diseases. *Clinical Experimental Rheumatology* 2008; 26; 121-4. [PUB MED LINK](#)

Rheumatoid factor and anti-CCP antibodies were measured from patients with HCV (n=45), PBC (n=73), AIH (n=55), rheumatoid arthritis (n=48), and healthy controls (n=23). No HCV patients had positive anti-CCP antibodies.

32. Lienesch D, Morris R, Metzger A, Maeda Y, Nakamura M, Abiru S, et al. Absence of Cyclic Citrullinated Peptide Antibody in Nonarthritic Patients with Chronic Hepatitis C Infection. *Journal of Rheumatology* 2005; 32: 489-93. [PUB MED LINK](#)

In a series of 50 non-arthritic HCV patients, 54% were seropositive for RF, while only one patient had a marginally elevated anti-CCP antibody (2%).

33. Liu F, Chao Y, Hou T, Chen HC, Shyu RY, Hsieh TY, et al. Usefulness of anti-CCP antibodies in patients with hepatitis C virus infection with or without arthritis, rheumatoid factor, or cryoglobulinemia. *Clinical Rheumatology* 2008; 27: 463-467. [PUB MED LINK](#)

HCV patients, without RF and/or cryoglobulinemia, may have positive anti-CCP antibodies, as demonstrated by 3 of 34 patients with HCV that had low-titer positive anti-CCP antibodies.

C. Antinuclear Antibody (ANA)

34. Yee LJ, Kelleher P, Goldin R.D., Marshall S, Thomas HC, Alberti A, et al. Antinuclear antibodies (ANA) in chronic hepatitis C virus infection: correlates of positivity and clinical relevance. *Journal of Viral Hepatitis* 2004; 11: 459-464. [PUB MED LINK](#)

There was no correlation between ANA status and duration of HCV infection, age, genotype, fibrosis, inflammatory score or response to interferon therapy.

35. Peng Y, Hsieh S, Yang D, Tung CF, Hu WH, Huang WN, et al. Expression and Clinical Significance of Antinuclear Antibody in Hepatitis C Virus Infection. *Journal of Clinical Gastroenterology* 2001; 33: 402-406. [PUB MED LINK](#)

Eleven of 48 HCV-infected patients (23%) were positive for ANA, with a predominance of speckled pattern.

36. Hsieh M-Y, Dai C-Y, Lee L-P, Huang JF, Tsai WC, Hou NJ, et al. Antinuclear antibody is associated with a more advanced fibrosis and lower RNA levels of hepatitis C virus in patients with chronic hepatitis C. *Journal of Clinical Pathology* 2008; 61: 333-337. [PUB MED LINK](#)

A total of 614 HCV-infected patients were evaluated in a prospective, hospital-based study. ANA-positivity was significantly correlated with more advanced liver fibrosis, lower viral load, higher mean ALT levels, and older patient age.

D. Anti-ENA Antibodies

37. Omagari K, Ohba K, Kadokawa Y, Hayashida K, Isomoto H, Takeshima F, et al. Anti-extractable Nuclear Antigens (ENA) Antibodies in patients with Chronic Hepatitis C before and after Treatment with Interferon. *Autoimmunity* 2003; 36: 269-273.

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36% of chronic HCV patients had evidence of anti-ENA antibodies (2 anti-RNP, 1 anti-SS-A, 10 anti-SS-B, and 5 anti-Scl-70) versus 16% of non-HCV infected patients with liver disease (p=.0290).

IV. TREATMENT OF AUTOIMMUNE DISEASE IN A PATIENT WITH HCV

38. Mok MY, Ng WL, Yuen MF, Wong RW, Lau CS. Safety of disease modifying anti-rheumatic agents in rheumatoid arthritis patients with chronic viral hepatitis. *Clinical Experimental Rheumatology* 2000; 18: 363-8. [PUB MED LINK](#)

The use of DMARDs in RA and chronic viral hepatitis results in hepatotoxicity. This includes drugs like hydroxychloroquine, which are generally believed to be less hepatotoxic.

39. Peterson JR, Hsu FC, Simkin PA, Wener MH. Effect of tumor necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. *Annals of the Rheumatic Diseases* 2003; 62: 1078-1082. [PUB MED LINK](#)

In a retrospective survey of 24 HCV infected patients with RA, who had received either Etanercept or Infliximab, there was no change in liver-related blood tests or hepatitis C viral load, suggesting relative safety in using an anti-TNF medication for treatment of autoimmune disease in HCV-infected patients.

40. Parke F, Reveille JD. Anti-Tumor Necrosis Factor Agents for Rheumatoid Arthritis in the Setting of Chronic Hepatitis C Infection. *Arthritis & Rheumatism* 2004; 51: 800-804. [PUB MED LINK](#)

Looking at the effect of anti-TNF therapy in 5 patients with RA and HCV, study authors found no patient with sustained liver test abnormality or increase of viral load over a mean follow-up period of 41 months. Again, this confirms the relative safety of using anti-TNF therapy in the setting of HCV infection.

V. DEVELOPMENT OF AUTOIMMUNE DISEASE WITH ANTIVIRAL THERAPY

41. Niewold T, Swedler W. Systemic lupus erythematosus arising during interferon-alpha therapy for cryoglobulinemic vasculitis associated with hepatitis C. *Clinical Rheumatology* 2005; 24: 178-181. [PUB MED LINK](#)

Reviews the (sparse) literature on the development of SLE during IFN-alpha therapy for HCV.