Treatment of rheumatoid arthritis in patients with concomitant chronic hepatitis C infection

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Abstract: Hepatitis C virus (HCV) infection is present in 1.8% of the general US population and its prevalence worldwide is estimated at 2–3%. HCV infected patients with concomitant rheumatoid arthritis (RA) pose a particular challenge to the rheumatologist because of the risks of treatment with disease-modifying medications in patients with chronic liver infection. In this paper the difficulties of diagnosing RA in HCV patients and the safety of RA treatment in patients with both conditions are discussed.

Keywords: biological-response modifiers, disease-modifying antirheumatic drugs, hepatitis C, rheumatoid arthritis

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Epidemiology and natural history of hepatitis C virus infection

Hepatitis C virus (HCV) is the primary cause of viral hepatitis in the US population and cirrhosis caused by HCV is the leading indication for liver transplant. Intravenous drug abuse is the most prevalent risk factor for HCV infection, with blood transfusion prior to 1992 the second most prevalent, and fully 10% of patients having no known risk factors [Murphy *et al.* 2000]. Iatrogenic transmission has essentially been eliminated in developed countries because of the screening of blood products. However, in developing countries, medical procedures remain the primary source of HCV infection because of the lack of screening of blood products and the use of nonsterile injections [Prati, 2006]. The majority of patients in Europe and the USA are infected with genotype 1, which is poorly responsive to treatment with interferon (IFN) and ribavirin. However, the new medications boceprevir and telaprevir double the efficacy of IFN-ribavirin for genotype 1 [McHutchison *et al.* 2010; Poordad *et al.* 2011; Bacon *et al.* 2011].

Acute HCV infections are almost always asymptomatic. Between 75% and 85% of acutely infected patients develop chronic infection and, of those, about 20% will progress to cirrhosis over the next 20–25 years. Cirrhotic patients are at high risk for developing endstage liver disease or hepatocellular carcinoma [Rustgi, 2007]. Chronic HCV infection is often clinically silent for years, with up to 50% of patients having normal transaminase levels at any given time, and 20–30% having normal transaminase levels for prolonged periods. However, transaminase levels do not accurately reflect liver damage as a significant number of patients with normal transaminase levels will develop hepatic fibrosis [Armstrong *et al.* 2006; Shiffman *et al.* 2006]

Extrahepatic manifestations are seen in patients with chronic HCV infection. These are primarily rheumatologic or lymphoproliferative, including arthralgias or arthritis, cryoglobulin-related vasculitis and glomerulonephritis, Sjogren-like sialadenitis, and non-Hodgkins lymphomas. As the hepatitis can be asymptomatic and transaminase levels normal, symptoms of extrahepatic disease are often the initial manifestations of HCV infection.

American College of Rheumatology (ACR) guidelines recommend screening for hepatitis B and C in patients with risk factors prior to initiating methotrexate (MTX) or leflunomide (LEF), which are contraindicated in patients with chronic hepatitis [Saag *et al.* 2008]. However, as about 10% of HCV-infected patients have no known risk factors, perhaps universal screening for HCV

Table 1. Child–Pugh [Pugh, 1973] class: A=5–6 points, B=7–9 points, C=10–15 points.

	1 Point	2 Points	3 Points
Ascites	None	Controlled	Refractory
Encephalopathy	Absent	Controlled	Dense
Albumin (g/L)	> 35	28–35	< 28
Bilirubin (micromol/L)	<34.2	34.2–51.3	>51.3
International Normalized Ratio	< 1.7	1.7–2.3	> 2.3

Table 2. Hepatitis C virus patients (n = 91) with polyarthralgias or polyarthritis (unpublished data).

Diagnosis	CCP+	CCP-
Definite RA	9	0
Possible RA	4	2
Inflammatory (SNSA, PMR, crystalline)	1 (diagnosis PMR)	13
Arthralgias (HCV, FM, OA)	2	60

CCP, citrullinated peptide; FM, fibromyalgia; HCV, hepatitis C virus; OA, osteoarthritis; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; SNSA, seronegative spondyloarthropathy.

would be appropriate. In addition, in those patients who do have chronic HCV, treatment of rheumatologic conditions is based on the Child–Pugh class, which designates the severity of liver disease (Table 1). As will be discussed below, many of the medications used to treat rheumatoid arthritis (RA), other than MTX and LEF, are considered safe in Child–Pugh class A, some in class B, but few are recommended to be used in class C.

Case report

A 60-year-old White man, a Vietnam veteran, presented with a 6-month history of pain and stiffness in his proximal interphalangeal (PIP) joints, metacarpophalangeal (MCP) joints, and wrists. On examination the affected joints were tender but not warm or swollen. Hand and wrist films were normal. Rheumatoid factor was positive at 619 and HCV-antibody testing was positive.

Does the patient have RA?

Patients with HCV infection produce autoantibodies, with between 30% and 70% being rheumatoid factor (RF) positive, often in high titer [Clifford *et al.* 1995; Pawlotsky *et al.*1995]. However, unlike RF positivity, anticyclic citrullinated peptide (anti-CCP)-antibody positivity does not appear to be increased in HCV infection [Wener *et al.* 2004; Ezzat *et al.* 2011; Sanmarti *et al.* 2009; Orge *et al.* 2010; Sène *et al.* 2006; Lienesch *et al.* 2005; Bombardieri *et al.* 2004; Lu *et al.* 2007]. Our data also support this (Table 2, unpublished). In addition, polyarthralgias and polyarthritis are associated with HCV infection. Arthralgias may be the presenting symptom or can occur later in the course of HCV infection.

One pattern of polyarthralgia or polyarthritis in HCV resembles RA, with MCP, PIP, and wrist involvement [Olivieri *et al.* 2003]. The other common pattern of involvement is a mono- or oligoarthritis affecting primarily medium and large joints, which is often associated with cryoglobulinemia; this type of arthritis is beyond the scope of this paper. However, HCV arthritis is mild and nonerosive [Lovy *et al.*1996]. This type of joint involvement accompanied by RF positivity can easily be mistaken for RA, especially given that transaminases are normal in 20–50% of HCV patients, and hepatic manifestations of HCV are typically clinically silent until late in the course of the disease. It is likely that many such patients were given an incorrect diagnosis of RA before HCV testing became widely available in 1990.

So given this ambiguity, how does one distinguish between HCV arthritis and RA? If the patient has erosions, rheumatoid nodules, or positive anti-CCP, RA is the likely diagnosis [Zuckerman *et al.* 2000]. If the arthritis resolves with successful treatment of the HCV infection, then the patient likely had HCV arthritis. However, HCV arthritis does not always remit with clearing of the HCV infection. Also patients with HCV can develop

nonerosive, CCP-negative RA without nodules. So, while these factors can help confirm the diagnosis in such cases, it is not always possible to know with certainty whether an HCV-infected patient, such as the patient in the case above, has HCV arthritis or RA.

Treatment of HCV arthritis and RA

HCV arthritis is mild and nonerosive, so toxic medications should be avoided [Palazzi *et al*. 2008]. The use of nonsteroidal anti-inflammatory drugs (NSAIDs), low- to moderate-dose glucocorticoids, hydroxychloroquine (HCQ), or sulfasalazine (SSZ) could be considered. However, HCV patients with RA often require more aggressive therapy, including biologic medications.

Treatment with anti-inflammatory medications

NSAIDs can be used in HCV patients, exercising caution because of the potential for hepatotoxicity or variceal bleeding. Corticosteroids have been shown to increase viral load but without worsening of hepatitis. They are considered safe in low to moderate doses [Palazzi *et al*. 2008].

Treatment with nonbiologic disease-modifying antirheumatic drugs

HCQ is generally considered safe in patients with Child–Pugh classes A and B. However, there are three cases in the literature of severe acute hepatitis occurring in patients with no underlying hepatic disease, so it should be avoided in Child–Pugh class C [Giner Galvañ *et al*. 2007].

SSZ can cause hepatotoxicity so the ACR task force recommended avoiding prescribing it in Child–Pugh classes B and C. MTX and LEF should be avoided in all Child–Pugh classes [Saag *et al*. 2008].

Cyclosporin A (CSA) has been shown to have antiviral activity against HCV [Inoue *et al*. 2003; Galeazzi *et al*. 2006], so consideration could be given to using it as an immunosuppressant in HCV patients.

Treatment with biologic disease-modifying antirheumatic drugs

Tumor necrosis factor (TNF) inhibitors have been used safely in HCV patients with RA. However, when the TNF inhibitors became available, concerns arose over the safety of blocking TNF in patients with a chronic viral infection. On the other hand, it was recognized that inhibiting TNF might be beneficial in HCV. Serum and hepatic TNF-alpha levels are increased in patients with HCV [Gonzalez-Amaro *et al*. 1994]. Liver damage is caused by the immune response to the virus, not by the virus itself, with TNF-alpha triggering an inflammatory cascade, so perhaps inhibiting TNF might reduce hepatic injury [Nelson *et al*. 1997].

With this in mind, Zein and colleagues treated 50 HCV patients (who did not have RA) with IFN and ribavirin plus etanercept or placebo for 48 weeks [Zein *et al*. 2005]. The severity of liver damage at baseline varied in both groups from minimal hepatitis to cirrhosis. HCV RNA was absent at 24 weeks in 63% of the etanercept patients and 32% of the placebo patients ($p = 0.04$). At 48 weeks there was less fibrosis on liver biopsy in the etanercept group than in the placebo group, but the improvement in inflammation did not differ between the two groups. Etanercept did not worsen hepatitis when given with IFN-ribavirin and there was a suggestion of benefit with etanercept. The ACR recommends avoiding the TNF inhibitors in Child–Pugh classes B and C [Saag *et al*. 2008].

Several case reports and small series have investigated the safety of TNF inhibitors in a total of 93 RA patients with HCV (Table 3). No safety concerns were raised in the vast majority of those cases. However, one reported reactivation of HCV in two patients who were HCV-antibody positive but polymerase chain reaction (PCR) negative [Cansu *et al*. 2008]. Based on this, it is advised that the use of TNF inhibitors be avoided in patients whose HCV has been successfully treated.

Rituximab

Although the ACR advises against the use of all biologics in Child–Pugh classes B and C, rituximab has been used to treat cryoglobulinemic vasculitis in HCV patients with good clinical response, no hepatotoxicity, and few side effects [Cacoub *et al*. 2008; DeVita *et al*. 2007]. Petrarca and colleagues used rituximab to treat HCV-associated cryoglobulinemia in 19 patients with severe liver disease, 15 of whom had cirrhosis [Petrarca *et al*. 2010]. No worsening of liver disease was noted. In fact, albumin levels increased and ascites decreased in the patients with more advanced disease. Based on these reports, consideration might be given to prescribing rituximab for RA in patients with Child–Pugh class B or C liver disease.

Table 3. Safety of the tumor necrosis factor inhibitors in hepatitis C virus-infected patients with rheumatoid arthritis: summary of the published data. (Adapted with permission from Jill Gibson, M.D.)

Author Year	Study design	Number of patients	Duration (months)	Δ Viral load, Δtransaminases
Peterson *et al*. [2003]	Prospective	8	3	No,
Peterson *et al*	Retrospective	16	1–34	No, No
Parke and Reveille [2004]	Retrospective	5	8–49	Yes, No
Oniankitan *et al*. [2004]	Case report	1	12	No, –
Vauloup *et al*. [2006]	Prospective	6	3.5	No, No
Roux *et al*. [2006]	Retrospective	3	6–39	Yes, No
Cavazzana *et al*. [2008]	Prospective	4	14	No, No
Ferri *et al*. [2008]	Prospective	31	11–33	No, No
Cansu *et al*. [2008]	Retrospective	4	13–23	2 reactivated, No
Giannitti *et al*. [2009]	Prospective (tumor necrosis factor and cyclosporin A)	7	Not reported	No, No
Li *et al*. [2009]	Retrospective	8	3–60	1: Yes, Yes 7: No, No

However, six HCV patients with cryoglobulinemia in another series were reported to have had severe reactions after rituximab infusions. Severe flares of cryoglobulinemic vasculitis were noted early and serum sickness occurred later in the course. Affected patients tended to be those with higher cryoglobulin titers and were more likely to have received the high dose (1000 mg every 2 weeks × 2) than the low dose (375 mg/m^2 weekly × 4) regimen. So caution should be used when treating RA in HCV patients with cryoglobulinemia. Plasma exchange prior to rituximab infusion should be considered in patients with high titers of cryoglobulins. Also the low-dose regimen might be advantageous in HCV cryoglobulinemia [Sène *et al*. 2006].

Abatacept

There is one report in the literature of two HCV patients with RA unresponsive to other therapies who were given abatacept. Neither had an infusion reaction or persistent worsening of hepatic function or viral load. Abatacept lost efficacy after 1 year in one of the patients but had ongoing efficacy in the other patient after 4 years [Mahajan *et al*. 2010].

Summary

RA in the setting of HCV infection can be difficult to distinguish from HCV polyarthritis. The presence of HCV infection limits to some degree the therapeutic options for treating RA. NSAIDs and corticosteroids can be used with caution. HCQ and SSZ can be used in milder hepatic disease. CSA is safe in HCV and might have antiviral effect. TNF inhibitors might reduce harm to the liver and are considered safe except in PCR-negative HCV disease. Rituximab is safe in HCV patients, but plasmapheresis should be considered before administering it in patients with high titer cryoglobulins. In addition there are case reports of the safe use of abatacept in HCV.

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Conflict of interest statement

None declared.

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