Hepatitis C virus-related arthritis: Characteristics and response to therapy with interferon alpha

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Abstract

Objective
To characterize hepatitis C virus (HCV)-related arthropathy and to evaluate the response to treatment with interferon-α (INF-α).

Methods
We studied 28 HCV-infected patients with arthritis. All patients underwent complete clinical, laboratory and radiological evaluation, including assessment and follow-up by a rheumatologist. Twenty-five patients were treated with INF-α for a median period of 12 months.

Results
All patients were HCV-RNA positive (genotype 1b in 65%). The mean duration of arthropathy-related symptoms prior to the diagnosis of HCV infection was 12 months. 19 patients (68%) had symmetric polyarthritis and 19 (68%) had morning stiffness ≥ 60 min. None of the patients had erosive disease or subcutaneous nodules. 12 (43%) had detectable cryoglobulin (mean cryocrit: 3.6 ± 3.5%), 17 (61%) had rheumatoid factor (RF) (median titer: 1:80), and only 15 (54%) had elevated ESR. 14 patients (50%) had 4 ACR (American College of Rheumatology) criteria for the diagnosis of rheumatoid arthritis (RA), 9 of whom were mistakenly diagnosed and previously treated as RA patients. Only 3 patients had a satisfactory response to previous treatment with anti-inflammatory or disease modifying drugs. Complete or partial response of arthritis-related symptoms in INF-α treated patients was observed in 44% and 32%, respectively. Cryoglobulin became undetectable in 9 of 12 patients. However, a complete biochemical and virological end-of-treatment response was achieved in only 8 (36%) and 5 patients (20%), respectively.

Conclusion
HCV arthropathy should be considered in the differential diagnosis of any patient with arthritis, even in the absence of liver disease. Treatment with interferon-α may lead to substantial clinical improvement of HCV-related arthritis even without a complete biochemical or virological response.

Key words
Hepatitis C virus, arthritis, treatment, interferon-alpha.

Introduction
The hepatitis C virus (HCV) is the major etiologic agent of post-transfusion and sporadic non-A, non-B chronic hepatitis (1,2) and has become one of the most important known causes of liver disease world-wide. In addition to its being hepatotropic, HCV has been increasingly recognized as a cause of rheumatologic disease and autoimmune phenomena, including mixed cryoglobulinemia (MC) and sicca syndrome, and is frequently associated with the presence of various autoantibodies (3-11). In addition, chronic HCV infection has recently been recognized to be associated with chronic inflammatory polyarthritis with or without mixed cryoglobulinemia (12-19).

Many patients with HCV-related arthritis satisfy the American College of Rheumatology (ACR) criteria for the classification of rheumatoid arthritis (RA) (20). These patients, with polyarthritis and positive rheumatoid factor (RF) may be diagnosed mistakenly as RA patients and thus may be treated with corticosteroids and cytotoxic drugs, which may worsen HCV viremia (21, 22). HCV-related arthropathy and its response to treatment with interferon alpha have not been completely characterized. Thus, we conducted this study in order to characterize HCV-related arthritis and to assess its response to treatment with interferon alpha (INF-α). To the best of our knowledge, this is the largest group thus far of HCV-infected patients with arthritis who have been systematically studied and reported in the English literature.

Materials and methods
Subjects
Twenty-eight HCV-infected patients with arthritis attending both the Liver and Rheumatology Clinics at B’nai Zion Medical Center were studied. Patients referred for consultation to the Rheumatology Clinic who were either: (i) rheumatoid factor positive, without subcutaneous nodules nor radiographic joint erosions, and who had not responded to standard anti-inflammatory therapy, or (ii) arthritis patients with mild aminotransferases elevations, were tested for HCV. Those found to be positive were referred to the Liver Clinic. In addition, HCV-infected patients in consultation at the Liver Clinic were referred to the Rheumatology Clinic if they complained of significant arthralgia or arthritis. Patients with inflammatory arthritis of other etiologies such as chronic pseudogout, psoriatic arthritis, etc. were excluded.

The study group included 20 men and 8 women, with a mean age of 51.5 years (range 27-70 years), diagnosed as having clinical arthritis of the peripheral joints by a rheumatologist (23, 24). All patients tested positive for anti-HCV antibody and HCV RNA and negative for anti-HIV antibody and hepatitis B surface antigen. Each patient underwent a complete clinical assessment by a hepatologist and a rheumatologist, radiological evaluation, and a laboratory work-up including determination of the complete blood count, erythrocyte sedimentation rate (ESR), C3 and C4 levels, rheumatoid factor (RF), antinuclear antibodies, cryoglobulin, and anti-HCV antibody, HCV-RNA and HCV genotype. A liver panel including serum albumin, globulin, alkaline phosphatase, bilirubin, lactic dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and prothrombin activity (PT) was also obtained in all patients, of whom 22 underwent a liver biopsy.

After the initial assessment, 25 patients were treated with INF-α (2a or 2b), 3 million units injected subcutaneously 3 times per week for a median of 12 months (range 4-16). INF-α treatment was given to these patients mainly for chronic HCV-related liver disease. However, 7 patients received treatment mainly for arthritis-related symptoms (with or without cryoglobulinemia): 3 had no liver disease (normal ALT), whereas 4 were older than 60 years (older than the cut-off age for treatment of HCV liver disease). During a mean follow-up period of 14 ± 3 months (range 7-18), patients were evaluated every 4 to 8 weeks by both a rheumatologist and a hepatologist.

All participants gave their written informed consent, and the study was approved by the Institutional Review Board of the B’nai Zion Medical Center.
**Immunologic assessment**

Rheumatoid factor was assayed by the 2-minute hemagglutination slide test (Wampole Laboratories, NJ). A test at 1:10 dilution was considered positive. ANA was determined by immunofluorescence using Hep-2 cell slides. SMA was determined using rat stomach and kidney slides (Immunofix Kit; Helena Laboratories, Beaumont, TX, USA).

**Assessment of HCV infection**

Anti-HCV was detected using a second-generation enzyme immunosorbent assay (ELISA II) (Abbot Laboratories, North Chicago, IL). HCV RNA in the serum was measured by a reverse transcription-polymerase chain reaction assay (AMPLICOR HCV test; Roche Molecular Systems, Somerville, NJ) as previously described (25). HCV genotyping was performed on all HCV RNA-positive specimens using genotype specific primers from the HCV core region under conditions as previously described (26).

**Clinical rheumatologic assessment**

The clinical assessment was based on the patient’s report of pain, morning stiffness, and systemic symptoms (fatigue); the physician’s evaluation of joint swelling and tenderness, and laboratory measurements of acute phase reactants (ESR, CRP). Remission was defined as per the criteria for clinical remission in RA (27). Improvement or lack of improvement in the arthritis status was determined by the global assessment of the rheumatologist, where several but not all of the criteria for remission were met. An additional criterion evaluated was NSAID usage; those whose average daily NSAID dose was reduced by half or more were considered responders by this criterion.

**Cryoglobulin detection and analysis**

Venous blood samples were collected into pre-warmed tubes after overnight fasting and allowed to clot at 37°C. After centrifugation, the sera were incubated at 4°C for 3 days. The cryocrit was evaluated by centrifugation of the serum in haematocrit tubes at 4°C. The cryoprecipitates were further analyzed and characterized by immunofixation electrophoresis (Immunofix Kit; Helena Laboratories, Beaumont, TX, USA).

**Statistical analysis**

Proportions were compared using Fisher’s exact test. A two-tailed p value of 0.05 or less was considered to be significant.

**Results**

Twenty-eight patients who met the entry criteria - the presence of clinical arthritis and HCV positivity - were studied.

**Assessment of HCV-related arthritis**

Table I summarizes the clinical and laboratory findings in the HCV-infected patients of the study group. Symmetric, non-deforming polyarthritis was observed in 19 patients (68%). The joints most commonly involved were the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, wrists and ankles. In the other 9 patients, asymmetric oligoarthritis (6 patients) or monoarthritis (3) was observed, most commonly involving the wrists, shoulders, ankles and knees. Synovial fluid analysis in 3 patients revealed 15,000-55,000 WBC/ml (mainly neutrophils). The mean duration of arthritis-related symptoms prior to the diagnosis of HCV infection was 12 months (range 2 - 60). Nineteen patients (68%) had morning stiffness for a duration of 60 minutes or more. Rheumatoid factor, usually at a low titer (median titer: 1:80), was present in 17 patients (61%), while low levels of C3 and C4 were found in 4 (14%) and 11 (39%) patients, respectively. Twelve patients (43%) had detectable cryoglobulin in the serum (type II in all) with a mean cryocrit of 3.6% (range 0.9-11.5%). None of the patients with HCV-related arthritis had erosions (by X-ray) or subcutaneous nodules, and only 15 patients (54%) had an elevated ESR with a mean of 52 mm/hour. Antinuclear and anti-smooth muscle antibodies were present in 8 (28%) and 6 (21%) patients, respectively. Fourteen patients (50%) met 4 or more of the ACR criteria for the diagnosis of RA.

**Assessment of liver disease**

Table II summarizes the clinical data related to liver disease in the HCV-infected patients with arthritis. Twenty-four patients (86%) had abnormal liver tests while 4 (14%) patients had no evidence of liver disease. In 14 patients (50%) liver biopsy showed chronic hepatitis with a mean hepatitis activity index of 12 ± 3, while 10 (36%) had cirrhosis.

**Table I. Clinical and laboratory characteristics of patients with HCV-related arthritis (n=28).**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, yrs (range)</td>
<td>51.5 (22-70)</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>20 (71)</td>
</tr>
<tr>
<td>Mean duration of arthritis (months)*, (range)</td>
<td>12 (2-60)</td>
</tr>
<tr>
<td>Arthritis pattern</td>
<td></td>
</tr>
<tr>
<td>Symmetric polyarticular (%)</td>
<td>19 (68)</td>
</tr>
<tr>
<td>Oligo- or monoarticular (%)</td>
<td>9 (32)</td>
</tr>
<tr>
<td>Morning stiffness &gt; 60 min (%)</td>
<td>19 (68)</td>
</tr>
<tr>
<td>Erosive changes (X-ray)</td>
<td>None</td>
</tr>
<tr>
<td>Sub-cutaneous nodules</td>
<td>None</td>
</tr>
<tr>
<td>≥ 4 ACR classification criteria for RA (%)</td>
<td>14 (50)</td>
</tr>
<tr>
<td>Cryoglobulin (%)</td>
<td>12 (43)</td>
</tr>
<tr>
<td>Mean cryocrit, % (range)</td>
<td>3.6 (0.9-11.5)</td>
</tr>
<tr>
<td>Positive rheumatoid factor (%)</td>
<td>17 (61)</td>
</tr>
<tr>
<td>Median titer</td>
<td>1.80</td>
</tr>
<tr>
<td>Positive anti-nuclear antibody (%)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Positive anti-smooth muscle antibody (%)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Elevated erythrocyte sedimentation rate (%)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>Mean (mm/hr)</td>
<td>52</td>
</tr>
<tr>
<td>Low C3 level (%)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Low C4 level (%)</td>
<td>11 (39)</td>
</tr>
</tbody>
</table>

*Mean duration of arthritis prior to the diagnosis of hepatitis C virus infection.
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Table II. Clinical data related to liver disease in patients with HCV-related arthritis (n = 28).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Liver disease (%)</th>
<th>Chronic hepatitis C (%)</th>
<th>Risk factor for HCV infection (%)</th>
<th>Abnormal ALT (%)</th>
<th>Mean (IU/L)</th>
<th>HCV genotype*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis (%)</td>
<td>10 (36)</td>
<td>14 (50)</td>
<td>20 (71)</td>
<td>24 (86)</td>
<td>84</td>
<td></td>
</tr>
</tbody>
</table>

HCV genotype:
- 1b (%): 15 (65)
- 2a (%): 3 (13)
- 2b (%): 1 (4)
- Mixed: 1b + 2a (%): 2 (8)
- 4 (%): 1 (4)

*HCV genotyping was performed in 23 of 28 patients with HCV-related arthritis.

HCV: hepatitis C virus; ALT, alanine aminotransferase.

Table III. Response to treatment with interferon-alpha in patients with HCV-related arthritis (n = 25).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Previous treatment*</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[NSAIDs (n=22), MTX (4)]</td>
<td>25 (100)</td>
<td></td>
</tr>
<tr>
<td>HC (3), AZA (1), Sulfasalazine (2), CS (12), gold salts (3), colchicine (2)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interferon co-treatment (NSAIDs, HC)</td>
<td>10 (40)</td>
<td></td>
</tr>
</tbody>
</table>

Arthritis-related symptoms:
- CR: 11 (44)
- PR: 8 (32)
- NR: 6 (24)

Arthritis with cryoglobulinemia (n=12):
- CR: 7 (58)

Arthritis without cryoglobulinemia (n=13):
- CR: 4 (31)

Response of cryoglobulin (n=12):
- CR: 9 (75)
- PR: 3 (25)

Biochemical response (ALT) (n=22):
- CR: 8 (32)
- NR: 14 (67)

Virological response (n=25): 5 (20)


*Treatment for HCV-related arthritis prior to therapy with interferon alpha.

Assessment of response to treatment

Twenty-five patients were treated with anti-inflammatory or disease-modifying drugs for a variable duration prior to the diagnosis of HCV infection (Table III). These regimens included non-steroidal anti-inflammatory drugs (NSAIDs) (22 patients), corticosteroids (CS) (12), gold salts (3), methotrexate (4), azathioprine (1), hydroxychloroquine (3), sulfasalazine (2) and colchicine (2), alone or in combination. In only 3 patients was a satisfactory response achieved with these drugs. In contrast, 11 (44%) of the 25 interferon-treated patients had significant improvement of arthritis-related symptoms (p = 0.025), with the resolution of synovitis and a decrease in the duration of morning stiffness [from a mean of 48 min to a mean of 16 min (P < 0.05)], most commonly occurring within 6 to 12 weeks of treatment (Table IV). Eight patients (32%) only had partial or minor improvement, while 6 patients (24%) did not respond to interferon. Of the 25 interferon-treated patients, 12 had cryoglobulinemia and 13 had no detectable cryoglobulin at baseline.

Table IV. Clinical characteristics in HCV-infected patients with a complete response to interferon-alpha therapy.

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Sex/age</th>
<th>Cryoglobulin</th>
<th>Sustained response*</th>
<th>Duration of remission</th>
<th>Relapse of arthritis</th>
<th>ALT (IU/L)</th>
<th>HCV-RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/52</td>
<td>yes</td>
<td>No</td>
<td>2 months</td>
<td>Yes</td>
<td>57</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>F/53</td>
<td>no</td>
<td>?</td>
<td>2 months</td>
<td>No</td>
<td>78</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>M/58</td>
<td>no</td>
<td>No</td>
<td>2 months</td>
<td>Yes</td>
<td>44</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>F/65</td>
<td>yes</td>
<td>Yes</td>
<td>5 months</td>
<td>No</td>
<td>158</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>F/48</td>
<td>yes</td>
<td>Yes</td>
<td>5 months</td>
<td>No</td>
<td>98</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>M/61</td>
<td>yes</td>
<td>No</td>
<td>7 weeks</td>
<td>Yes</td>
<td>70</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>F/51</td>
<td>no</td>
<td>Yes</td>
<td>4 months</td>
<td>No</td>
<td>55</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>F/58</td>
<td>yes</td>
<td>?</td>
<td>3 months</td>
<td>No</td>
<td>47</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>F/44</td>
<td>no</td>
<td>Yes</td>
<td>3 months</td>
<td>No</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>10</td>
<td>M/60</td>
<td>yes</td>
<td>No</td>
<td>2 months</td>
<td>Yes</td>
<td>110</td>
<td>38</td>
</tr>
<tr>
<td>11</td>
<td>F/50</td>
<td>yes</td>
<td>?</td>
<td></td>
<td></td>
<td>66</td>
<td>+</td>
</tr>
</tbody>
</table>

* Sustained response of arthritis related symptoms. ** ALT, normal values: 0-40 IU/L.

Patients 2, 8 and 11 are still being treated with interferon-α; patients 4, 5, 7 and 9 are in sustained remission after discontinuation of interferon treatment; patients 1, 3, 6 and 10 had a relapse of arthritis after discontinuation of interferon and were retreated. Duration of remission refers to post-interferon therapy.
line. There was no significant difference among the complete responders between those with and those without cryoglobulinemia: 7 of 12 patients (58%) compared to 4 of 13 (31%), respectively (p = 0.2). Cryoglobulinemia became undetectable in 9 of 12 (75%) patients within 4 to 8 weeks of interferon therapy and remained undetectable during treatment. In the other 3 patients with cryoglobulinemia, no response or only a partial response was observed. A complete end-of-treatment biochemical response (normalization of ALT) was achieved in 36% of the patients who had abnormal ALT prior to treatment with interferon. However, an end-of-treatment virological response (undetectable HCV RNA by PCR) was observed in only 5 (20%) of the interferon-treated patients.

Ten of the 25 interferon-treated patients who were partial or non-responders were co-treated with hydroxychloroquine and/or NSAIDs for additional relief of arthritis-related symptoms. Two other patients were co-treated with a stable low dose of corticosteroids (less than 10 mg daily) throughout the period. In 8 responders to interferon, therapy was discontinued after 7 to 12 months. However, relapse of arthritis was observed in 4, necessitating the re-administration of interferon with a favorable response. In the other 4 responders the virological response was maintained, while all remained symptom-free at 3 to 5 months post-interferon treatment. We could not demonstrate a correlation between the severity of liver disease and either the severity of arthritis or the response to interferon therapy.

Discussion
Since its initial description in 1989 (1), it has become evident that HCV is associated with a variety of extra-hepatic rheumatic disorders, including arthritis (3-19). However, HCV-related arthritis is still not well characterized as data are limited and based mainly on case reports or small series (14-19). To our knowledge, the present report represents one of the largest studies in which a cohort of patients with HCV-related arthritis has been systematically studied and characterized. Moreover, this is the first study in which the response to treatment with interferon alpha in a relatively large number of patients and for a relatively long period of follow-up has been documented.

While the incidence of HCV-associated arthritis may vary with the patient population, it appears that 2-20% of HCV-infected patients are affected by arthritis (19, 28-30). The 28 patients with arthritis in this study were identified from 245 (11.4%) HCV-infected patients attending the Liver Clinic at B’nai Zion Medical Center in Haifa, Israel. However, more than 50% of the patients with arthritis were referrals from the Rheumatology Unit or the Rheumatology Clinic. This bias is possibly responsible for a somewhat higher incidence of frank arthritis in our study population, along with a more severe form of disease than that reported by others (13, 16, 19).

Similar to findings in other studies (13, 16, 18, 19), all of our patients had non-deforming, non-erosive disease. The majority had seropositive rheumatoid-like arthritis, 50% of them satisfying the ACR criteria for the classification of RA. In fact, 9 patients were previously diagnosed as having RA and were treated accordingly. Such patients may add to the existing clinical confusion in diagnosing "true" RA with co-existent chronic HCV infection as distinct from "atypical" arthritis with autoantibodies and markers of HCV infection. Recent findings lend support to the distinction of HCV arthritis patients from classical RA in that the HCV population lacks antikeratin antibodies (31).

Although the majority of our patients had polyarticular disease, one-third had mono- or oligoarticular arthritis, a finding infrequently reported by others (12-19). Interestingly, one of these patients had severe, refractory, cryoglobulinemia-negative monoarthritis of the knee (with 55,000 WBC/ml in the synovial fluid) which dramatically resolved after 6 weeks of interferon therapy, in parallel with the disappearance of HCV RNA from the serum.

Our experience suggests that HCV-related arthropathy should be considered in the differential diagnosis of any patient with chronic inflammatory arthritis. Perrot et al. (30) found that as many as 10% of patients presenting with polyarthritis to their clinic were HCV-positive. Accurate and early diagnosis is important, as these patients can benefit from treatment with interferon. Although the optimum treatment of HCV-related arthritis has not yet been established, concerns may be raised about the use of corticosteroids to control the symptoms as they may worsen the HCV viremia (21, 22). Moreover, treatment with methotrexate or other hepato-toxic drugs in patients with pre-existing HCV-related liver disease may also be problematic.

In the experience of Lovy et al. (13), treatment with hydroxychloroquine and low doses of oral corticosteroids was effective in controlling arthritis-related symptoms in HCV-infected subjects. In our study, the majority of the patients had previously failed to respond to this combination or to other anti-inflammatory drugs. This may possibly be related to the more severe joint disease in our patients. Based on our experience reported herein, it may be suggested that once the diagnosis of HCV-associated arthritis is made, interferon therapy (especially in the presence of cryoglobulin) could form part of the therapeutic armamentarium unless there are contraindications. With the above protocol, we achieved a favorable response in 76% of our patients, most having moderate to severe joint disease. It is worth noting that in a few of our patients interferon was prescribed mainly for arthritis-related symptoms and not for liver disease. These patients had normal ALT (3 patients) or were older than 60 years (4), conditions where interferon treatment is usually not indicated.

Interestingly, interferon was effective in controlling the arthritis-associated symptoms even without achieving a complete biochemical or virological response. This effect is possibly related to a decrease in the viral load, as well as to the enhancement of anti-inflammatory cytokine production by peripheral blood leukocytes induced by interferon-α (32).

The pathogenesis of HCV-associated arthritis is far from clear. In many cases the development of arthritis can be attributed to the presence of cryoglobulinemia, which is associated with HCV infection. However, 57% of our patients had no cryoglobulin detected in their serum, thus possibly indicating a differ-
ent mechanism for the development of HCV-related synovitis. Moreover, treatment with interferon led to the clearance of HCV RNA from the serum in 5 patients: 2 patients with and 3 without cryoglobulinemia. Disappearance of HCV-RNA was associated with a complete resolution of the arthritis. The anti-viral effect of interferon in these cases may thus support the assumption that HCV could play a role in the development of arthritis via other pathways, independently of cryoglobulinemia.

In conclusion, HCV-related arthropathy should be considered in the differential diagnosis of any patient with chronic inflammatory arthritis. HCV-related arthritis often mimics RA, but is not typically associated with erosive disease or sub-cutaneous nodules. A favorable response to interferon-α therapy can be achieved in the majority of patients even without a complete biochemical or virological response. Further prospective studies involving larger numbers of patients and a longer period of follow-up will be required to determine the optimal therapy for patients with HCV-related arthritis.

References