Concise Report

Etanercept treatment for three months is safe in patients with rheumatological manifestations associated with hepatitis C virus

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Objective. The treatment of the rheumatological manifestations associated with hepatitis C virus (HCV) remains difficult. To examine the safety of anti-tumour necrosis factor-α (TNF-α) treatment, nine patients having rheumatological manifestations associated with HCV were treated with etanercept 25 mg twice a week for 3 months.

Methods. Five patients had a positive viral load at study entry (Group I), four were negative (Group II). Clinical data recorded were: disease duration, painful and swollen joint count, patient global and physician global assessment, the number of 18 specified fibromyalgia tender points and the Health Assessment Questionnaire score. Laboratory studies included checking for the presence of cryoglobulinaemia and transaminase levels. Quantitative HCV viral RNA was performed by real-time polymerase chain reaction (PCR).

Results. At 3 months, no patient was found to have evidence of increased hepatic inflammation based on serial serum transaminase levels. In the five patients from Group I with detectable HCV RNA, no significant viral load increase was observed. No reactivation was observed in the four patients from Group II with undetectable HCV RNA. The effect on the clinical rheumatological manifestations was more heterogeneous but appears to be lower than that observed in rheumatoid arthritis.

Conclusion. In this phase II open short-term study, etanercept appeared to be safe in patients with articular manifestations associated with HCV.

KEY WORDS: Rheumatological manifestations, Hepatitis C, Etanercept, Safety.

Introduction

Hepatitis C virus (HCV) infection is the most common blood-borne infectious disease [1]. The most obvious and well-known consequences of HCV are related to hepatocyte destruction leading to cirrhosis and hepatocellular carcinoma. Rheumatological manifestations are common and two subsets have been previously described: a rheumatoid arthritis (RA)-like symmetrical, inflammatory polyarthritis involving mainly small joints, but without destruction, and a mono- or oligo-arthritis involving medium-sized and large joints, with often an intermittent course and the presence of cryoglobulinaemia [2, 3]. The treatment of these rheumatological manifestations is not standardized as for RA [4]. Methotrexate has been described to be effective in some cases without alteration of the liver function or modification of the viraemia [2].

Elevated tumour necrosis factor-α (TNF-α) levels have been documented in patients with HCV and are associated with a worse prognosis, but the exact role of TNF-α in the pathogenesis of this disease is unclear [5]. Anti-TNF-α treatment is effective in chronic inflammatory joint diseases such as RA [6]. Preliminary results have suggested the interest of anti-TNF therapy in HCV-related liver disease [7] and the pathogenesis of hepatocyte destruction in chronic HCV may be mediated by the up-regulation of inflammatory cytokines including TNF-α [8, 9].

Based on these data, we investigated the safety of etanercept in patients with rheumatological manifestations related to HCV.

Patients and methods

Nine patients [median age (range) 57 yr (46–63 yr), eight females] with rheumatological manifestations were prospectively enrolled in this study, and they signed an informed consent, which had been approved by the local ethical committee of Lyon B. In all the patients, HCV infection was defined by at least a positive HCV viral load (at inclusion or at the time of diagnosis) and the detection of antibodies by ELISA. Eligible patients were at least 18 yrs of age, with chronic stable HCV infection (defined as the absence of clinical evidence of late-stage liver disease), normal albumin and normal prothrombin time (PT). Concomitant treatment with stable dose of steroids was permitted and non-steroidal anti-inflammatory drug (NSAID) doses could not exceed the maximum recommended dose. Patients having received NSAID previously or on therapy for HCV infection were accepted. No patient was enrolled who was human...
immunodeficiency virus (HIV) or hepatitis B virus (HBV) positive, had a current bacterial infection, was pregnant or had significant alcohol consumption. Patients are divided into two groups according to viral load detection at study entry: five positive patients in Group I and four negative patients in Group II. Group II was used to investigate if treatment could reactivate HCV.

At enrolment, patient age, sex, disease duration, current disease-modifying antirheumatic drug (DMARD) treatment, NSAID use, joint and swollen joint counts of 28 joints according to the disease activity score (DAS28) score, patient and physician global disease activity visual analogue scale, the number of 18 specified fibromyalgia tender points and the Health Assessment Questionnaire (HAQ) score were recorded. Hand and wrist X-rays were analysed for the presence of erosions. Biology follow-up include blood cell count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), rheumatoid factor (RF), antinuclear antibodies (ANA), erythrocyte sedimentation rate, C-reactive protein and PT. Quantitative HCV viral RNA was performed by real-time polymerase chain reaction (PCR) (Roche Molecular Diagnostics, Indiana, IN, USA) with a reference range of 10–10000000 IU/ml. Cryoglobulinaemia determination was obtained after storage of blood samples at 37°C until complete clotting occurs and then centrifugation. Serum was kept at 4°C for 7 days and if a cryoprecipitate was visible, the sample was centrifuged at 4°C for 15 min. Cryoglobulins were purified by washing at 4°C and characterized using immunofixation electrophoresis.

Etanercept was given by subcutaneous injections of 25 mg twice a week. Etanercept was used alone, particularly without methotrexate. Clinical and biological parameters were recorded at each visit at entry, 2 weeks and 3 months.

**Statistical analysis**

Comparisons of differences between mean values were performed by the paired *t*-test using the StatView statistical software. Differences were interpreted as significant at *p* < 0.05, without adjustment for multiple comparisons. For comparisons of changes in clinical or biological parameters over time, paired two-tailed *t*-test were performed. Changes in HCV viral load were converted to log values before statistical analysis.

**Results**

Nine patients were included (Table 1). Five patients are enrolled in Group I defined by a detectable HCV viraemia and four in the Group II with undetectable viraemia at entry. All patients had longstanding rheumatological manifestations. The median disease duration of rheumatological manifestations after HCV diagnosis was 10 yrs (3–18 yrs). In Group I, two patients had a more aggressive joint disease with arthritis and biological inflammation, and one met the American college of rheumatology (ACR) criteria for RA. Only that patient had erosions on hand and wrist X-rays. Two patients had RF, none had ANA and four had cryoglobulinaemia (two type II and two type III). In Group II, three out of four patients had only arthralgias. One patient had RF, none had ANA and two had cryoglobulinaemia (type III). Out of the nine patients, six had been previously treated for HCV infection: five with interferon-α and ribavirin and one with interferon-α alone. Among these six patients, four were sustained responders (all Group II), and one a relapser (Group I) and one a non-responder (Group I).

The primary purpose of this study was to look for the worsening of hepatitis or increased viraemia when receiving etanercept. In Group I, no variation was observed for viral load during etanercept therapy (Table 1). In Group II, no reactivation of HCV viral load was observed. In the same way, serum tests showed no significant differences in AST, ALT and PT (Table 2). In one patient (patient 5) from Group I, the cryoglobulinaemia observed at baseline was not found at 3 months.

An evaluation of the effect on rheumatological manifestation improvement was also performed but remained difficult because of the small size of the population. The clinical results showed the same beneficial trend for all items (Table 2) in the two groups. The patient who met the ACR criteria for RA at entry had an ACR 20 response at 3 months.

**Discussion**

The treatment of rheumatological manifestations associated with HCV remains a difficult therapeutic challenge. In addition, there is always the risk that the treatment of these manifestations will aggravate hepatitis and increase viraemia. Methotrexate was proposed for rheumatological manifestations associated with HCV. In a previous study, methotrexate appeared effective without hepatotoxicity [2, 10]. TNF-α antagonists, such as etanercept, have no known direct liver toxicity. Although there is a consensus on the exacerbation of infections, the effects of etanercept on the course of HCV infection remain to be clarified. Previous case-report studies have explored the safety of TNF-α antagonists in RA patients [11, 12], psoriatic arthritis [13] or Crohn’s disease [14]. They reported no progression of HCV viraemia or worsening hepatitis in accordance with our results. These results are in contrast with exacerbation of hepatitis and the

### Table 1. Demographic and biological characteristics of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>HCV genotype</th>
<th>Previous HCV therapy</th>
<th>Cryoglobulinaemia</th>
<th>Type of cryoglobulinaemia</th>
<th>RF</th>
<th>Viral load at baseline</th>
<th>Viral load at 3 months</th>
<th>Previous DMARD</th>
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<tbody>
<tr>
<td>I</td>
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<td>Yes</td>
<td>III</td>
<td>Positive</td>
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<td>5.28</td>
<td>HQ-SG-DP-MTX</td>
</tr>
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<td>F</td>
<td>58</td>
<td>1</td>
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<td>Undetectable</td>
<td>No</td>
</tr>
<tr>
<td>I</td>
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<td>48</td>
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<td>No</td>
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<td>6.18</td>
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<td>4.90</td>
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<td>58</td>
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</table>

IFN, interferon-α; HCV, hepatitis C virus; RF, rheumatoid factor; DMARDs, disease-modifying antirheumatic drugs; HQ, hydroxychloroquine; SG, salt gold; DP, α-penicillamine; MTX, methotrexate. Etanercept was used alone in all patients.

Patient I met the ACR criteria for RA.

Group I was defined by a detectable RNA HCV and Group II by an undetectable RNA HCV at study entry. All patients were positive when HCV diagnosis was made.

*The values are the log10 copies/ml.
high levels of HCV viraemia in patients following aggressive immunosuppression [15]. Laboratory data consisting of serum transaminase levels and HCV viral load were analysed for evidence of hepatic parenchymal inflammation and viral proliferation, respectively. In this study, we were not able to evaluate a positive effect on liver disease as suggested in a recent study [7]. It is known that the lack of elevated transaminase levels does not necessarily exclude active liver disease. Patients with chronic HCV infection have been shown to have biopsy evidence of inflammation, necrosis and fibrosis despite persistent normal transaminase values.

Obviously, long-term safety issues remain to be clarified. In particular, the context of B-cell activation in these HCV patients implies a concern regarding the occurrence of B-cell non-Hodgkin’s lymphoma, as already discussed in RA.

Regarding efficacy, the small size of the study limits the interpretation. No flare was observed. If a positive trend was observed, the treatment efficacy of etanercept appears to be lower than that observed in RA, where a 60–70% response rate is commonly observed. Additional studies are needed to clarify the efficacy issue.

In conclusion, short-term administration of etanercept appeared to be safe in patients with HCV associated with articular manifestations.

The authors have declared no conflicts of interest.

References