Hepatitis C virus (HCV) infection is a major public health problem, with an estimated prevalence of 2-3% of worldwide population. Because Tumour Necrosis Factor (TNF) seems to have an important role in the immune response to HCV infection by inducing apoptosis of the infected cells, suppression by TNF inhibitors may pose a potential threat of excessive viral replication and worsening of chronic HCV infection. Although previous reports have shown that treating HCV infected patients with TNFi does not lead to worsening of hepatocyte lesion/liver disease, in the short-term, guidelines recommend screening for anti-HCV antibodies before starting a biological agent and making treatment decisions only after consulting a gastroenterologist.

We report 3 cases of patients with chronic HCV infection and advanced liver disease, treated with a TNFi, etanercept (ETN), for a period ranging from 4 months to 4 years, without hepatitis C therapy, and in two of them, during concomitant therapy with direct-acting antiviral agents (DAA) and continued afterwards.

**CASE 1**
Male with rheumatoid arthritis (RA) and HCV-compensated cirrhosis, Child-Pugh score 5, initiated ETN 50mg/week, after maintaining high disease activity with combination of conventional synthetic disease modifying anti-rheumatic drugs (cDMARD) and systemic corticoids. He was medicated for almost 4 years with ETN 50mg/week without HCV therapy and maintained stable transaminase levels and viral load (Table I). In 2015, he started a 24 week course of sofosbuvir and daclatasvir with clearance of the virus, sustained at 12 and 24 weeks after treatment cessation. During these 24 weeks of concomitant medication there was a good tolerance, without adverse events. Three years after HCV treatment, the patient maintains ETN with good control of RA and the viral load remains negative.

**CASE 2**
Male with severe polyarticular Psoriatic Arthritis (PsA) and HCV infection at cirrhotic stage, initiated at 2008, treatment with ETN 50mg/week, after failure of cDMARD and PUVA phototherapy. Over 2 years, without HCV therapy, there was no progression of the liver disease, maintaining HCV viral load and transaminases levels stable (Table I). This patient deceased in 2010, following an ischemic stroke, before DAA became available.

**CASE 3**
Female diagnosed with PsA (peripheral arthritis and dactylitis) and HCV infection in cirrhosis stage (Table I), initiated ETN 50mg/week, after failure and intolerance to cDMARDs. After 4 months on ETN without hepatitis C therapy there was no change in transaminase levels and the viral load decreased (Table I). In 2015, she was treated with a 24 week course of sofosbuvir and daclatasvir with clearance of the virus, persistent at 12 and 24 weeks after treatment cessation. As in case 1, concomitant medication with ETN, sofosbuvir and daclatasvir was well tolerated, without adverse events, and the viral load remained negative three years after the treatment and under ETN.

Although increasing number of clinical reports support the short-term safety and efficacy of TNFi in patients with HCV, some uncertainties remain regarding long-term safety of these agents. The 3 cases reported, with considerable follow-up time, suggests that the risk of HCV reactivation related to ETN remains low even without concomitant antiviral therapy. Nevertheless, a strict collaboration between rheumatologists and gastroenterologists/hepatologists, allied to clinical and laboratory monitoring throughout the treatment period is advised. The new DAA, highly effective and very well tolerated are, at present date, the standard of care for
HCV patients. Our results also showed a good tolerance and efficacy when used concomitantly with ETN in patients 1 and 3.

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**REFERENCES**
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<table>
<thead>
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<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Rheumatic disease</th>
<th>HCV genotype</th>
<th>Previous HCV therapy</th>
<th>Viral load at baseline*</th>
<th>Viral load 3 or 6 months after ETN*</th>
<th>Previous csDMARDs</th>
<th>Exposure time to anti-TNF**</th>
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<td>MTX, Cyclosporine, LEF, SSZ</td>
<td>4 months</td>
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RA, Rheumatoid Arthritis; PsA, Psoriatic Arthritis; HCV, hepatitis C virus; DMARDs, disease-modifying anti-rheumatic drugs; MTX, methotrexate; LEF, leflunomide; SSZ, sulfasalazine; ETN, Etanercept. Etanercept was used alone in all patients. Patient 1 met the ACR criteria for RA. *The values are the log10 copies/ml. **Exposure time to anti-TNF without therapy for Hepatitis C.