Efficacy and safety of tocilizumab combined with cyclosporine A in a patient with rheumatoid arthritis and concomitant chronic hepatitis C virus infection

Sirs,

It is known that 0.65–7.6% of rheumatoid arthritis (RA) patients also carry hepatitis C virus (HCV) (1), arising a therapeutic challenge because immunosuppression may promote viral replication. Furthermore, the disease-modifying anti-rheumatic drugs are associated with hepatotoxicity (2). An exception seems to be cyclosporine-A (CSA) demonstrated to control HCV replication by inhibition of cyclophilin-B (while the inhibition of calcineurin causes immunosuppressive effect) and to be safe in patients with autoimmune disorders and concomitant HCV infection (3). We also showed its ability to reduce serum HCV-RNA (4) even with anti-tumour necrosis factor (TNF) α agents (5), while viraemia remained almost unchanged in patients treated with anti-TNF-α alone (6).

To date, only 3 cases have been reported about tocilizumab (TCZ) safety in monotherapy in RA patients with HCV infection (7-9). Instead, one case of HCV reactivation (10) in a RA asymptomatic carrier, has been recently reported.

Here, we describe a 58-year-old male diagnosed in 2001 with RA according to the 1987 American College of Rheumatology (ACR) criteria and then confirmed by the 2010 ACR/EULAR classification criteria. Both rheumatoid factor and anti-cyclic-citrullinated-peptide antibodies tested positive. He was firstly treated with methotrexate then discontinued for incomplete clinical response and elevation of liver enzymes. At the pre-anti-TNF-α therapy work-up, the patient was incidentally found HCV-infected (viraemia = 364767 IU/ml). Previous hepatic ultrasonographies were reported as unremarkable. According to our experience, a combined therapy with CSA (3 mg/kg/die), Infliximab and low dose prednisone was introduced (September 2008). In the following months, RA achieved remission, the clinical course of HCV disease remained benign with normality of aminotransferases, and absence of liver or systemic impairment.

On December 2011, arthritis flared and Infliximab was discontinued. TCZ with CSA (3 mg/kg/die) and Prednisone (5 mg/die) were started. At baseline, disease-activity score for 28 joints (DAS28) was 4.74, Health Assessment Questionnaire (HAQ) resulted 2.25, HCV-load was 850906 IU/ml. Ultrasonography showed an increased liver volume with homogeneous echostructure, no ascites, liver masses, focal lesions or cirrhosis.

His RA remarkably improved with DAS28 scoring 1.89 and HAQ 1.75 at last visit in December 2012, HCV-load was 66687 IU/ml (-92% from baseline), aminotransferases remained normal, no disturbances of the synthetic liver function, nor adverse events were recorded during the 12-month follow-up (Fig. 1). Liver ultrasonography did not change after one-year-treatment.

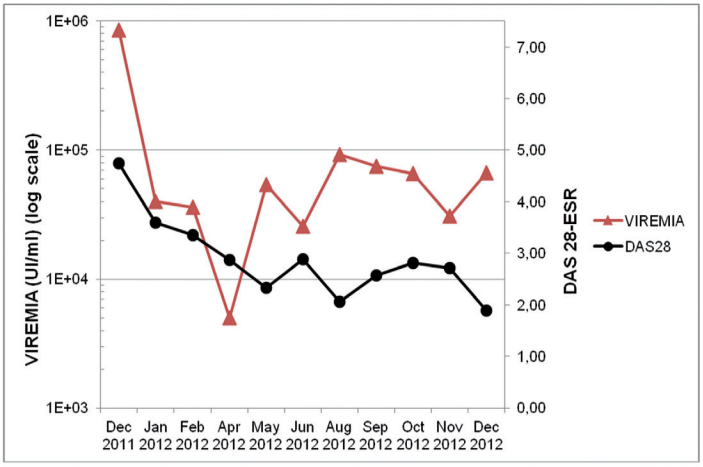

Fig. 1. HCV-RNA levels and DAS28 score based on the erythrocyte sedimentation rate (ESR) during the TCZ-CSA combination therapy – 1 year follow-up.

Nagashima *et al*. (7) reported on a HCV-positive male with RA treated with TCZ for 6 months with unchanged serum viral load and liver function, hospitalised for cellulitis of left foot.

Iebba *et al*. (8) described a 71-year-old HCV-positive female with RA with a rapid response to TCZ with early remission, no adverse events and normal aminotransferases during a 6-month follow-up (HCV-RNA reported only at baseline).

Dragonas *et al*. (9) reported on a RA HCV-positive male who safely received TCZ during a 12-month follow-up and whose liver function tests and viral load remained stable.

In contrast, Mori *et al*. (10) described HCV-reactivation in a 65-year-old female with RA occurring within the first-year TCZ-therapy, suggesting that treatment with tacrolimus before TCZ could have promoted viral reactivation.

The peculiarity of our case is the combination therapy TCZ-CSA in a RA patient with concomitant chronic HCV infection, that, to the best of our knowledge, has never been reported before. Such an association was efficacious for RA and possibly also responsible for the significant decrease in viral load not seen in the previous cases, perhaps mediated by different mechanisms of action.

Our case report further supports the safety and efficacy of TCZ in these patients, reasonably suggesting that the association TCZ-CSA may better control viral infection compared to TCZ monotherapy.

Additional reporting of such cases is advisable to further evaluate an issue still poorly investigated. However, close clinical monitoring, regular testing of liver function tests and viral load is needed to detect HCV reactivation immediately.

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