Safety of Anti-Tumor Necrosis Factor Agents in Rheumatic Potential Carriers of Occult Hepatitis B Virus

To the Editor:

We read with interest the article by Kim, *et al*[1] regarding the possible reactivation of potential occult hepatitis B virus (HBV) infection by use of tumor necrosis factor-α (TNF-α) blockers in the treatment of rheumatic diseases. We describe our recent experience and review the literature, in order to illustrate the problem of the treatment of autoimmune patients who also have chronic or resolved HBV infection, and the difficulty of its resolution.

It is well known that immunosuppressive agents can induce viral reactivation[2], but data on the rate of HBV reactivation in patients with chronic HBV infection treated with anti-TNF agents are limited. Even fewer data are available on HBsAg-negative anti-HBc-carriers, who are considered potential occult carriers of HBV, and no recommendations are available for treatment of this type of patient.

Our experience consists of 12 Italian patients included in a prospective study. Their demographic and clinical characteristics are reported in Table 1. HBV infection was not discovered until the routine investigation leading up to anti-TNF-α therapy. This therapy became necessary because of loss of efficacy of disease-modifying antirheumatic drugs or appearance of adverse events, including liver toxicity in some cases. Patients' serology results indicated they were potential occult carriers of HBV[3]. All were HBV-DNA-negative and in no case was antiviral prophylaxis given. Blood analyses (blood cell counts, aminotransferase levels, hepatitis B serological patterns, HBV-DNA testing by polymerase chain reaction) were performed before anti-TNF-α treatment and subsequently at least every 3 months. During the followup period (mean 41.08 ± 33.93 months, range 9–104 months), no patient had raised levels of aminotransferases or HBV reactivation (HBsAg or HBV-DNA detection).

Only 2 case reports of TNF antagonist-related HBV reactivation in HBsAg-negative, anti-HBc-positive patients have been described[4,5]. Kim, *et al*[1] described 88 patients with potential occult HBV infection, who were found to have a significantly higher risk to develop persistent abnormal liver function tests, compared to the HBcAb-negative group. Kim and colleagues could not confirm the association of abnormal liver function tests with a reactivation of occult HBV infection, since they did not perform HBV-DNA testing.

On the other hand, other authors do not confirm the same findings. Raftery, *et al*[6] described a woman with rheumatoid arthritis who was HBsAg-negative, anti-HBc-positive, and anti-HBs-positive. She was given etanercept combined with methotrexate without lamivudine or adefovir, with no complications or evidence of HBV reactivation even after 2 years of treatment. Vassilopoulos, *et al*[7] did not detect elevated levels of aminotransferases or HBsAg or HBV-DNA positivity in 19 rheumatic patients with resolved HBV infection during anti-TNF treatment.

Similar findings were reported by Charpin and colleagues[8] in a recent study of 21 rheumatic patients whose HBV serology suggested the carrier status, treated with TNF-α inhibitors during a 3-year period. Jansen[9] confirmed these results in patients with a past hepatitis B serological pattern. Moreover, Caporali, *et al*[10] recently found no HBV reactivation during a followup period of 42.52 ± 21.33 months in 67 anti-HBc carriers who had chronic arthritis treated with anti-TNF-α therapy without lamivudine prophylaxis.

In agreement with these reports[6,7,8,9,10], our case series results confirm the substantial safety of TNF-α blockers in rheumatic patients previously exposed to HBV receiving no HBV prophylaxis.

On the whole, all these data do not completely resolve the problem of the safety of anti-TNF agents in rheumatic patients with potential occult HBV infection, and suggest that close monitoring of clinical signs and transaminase levels and/or viral load is essential throughout the anti-TNF treatment period in order to detect early viral reactivation; its occurrence is probably unlikely, but represents a risk to be identified and that cannot be totally ruled out.

Further reporting of such cases is important to inform and clarify a subject for which there is still a paucity of data, and to find common guidelines for management of this particular group of patients.

Table 1. Baseline demographic and clinical features of patients.

Characteristic	
Sex, men:women	5:7
Age, mean ± SD yrs	53.00 ± 11.69
Diagnosis	
Rheumatoid arthritis	5
Psoriatic arthritis	5
Seronegative arthritis	1
Entero-spondyloarthropathy	1
Disease duration, mean ± SD 101.67 ± 63.40 months (range 23 to 226)	
Previous therapies*, no. patients	
Methotrexate	9
Cyclosporine	6
Sulfasalazine	4
Hydroxychloroquine	4
Leflunomide	3
Gold salts	2
Anti-TNF treatment duration, mean ± SD 41.08 ± 33.93 months (range 9 to 104)	
Type of TNF inhibitor, no. patients	
Etanercept	7
Adalimumab	5
Concomitant DMARD, no. patients	
Methotrexate	3
Sulfasalazine	1

* Since some patients were treated with more than one agent, the cumulative number exceeds 100%. TNF: tumor necrosis factor; DMARD: disease modifying antirheumatic drug.

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