# Short-Term Course of Chronic Hepatitis B and C Under Treatment with Etanercept Associated with Different Disease Modifying Antirheumatic Drugs without Antiviral Prophylaxis

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***ABSTRACT.*** ***Objective.*** To evaluate the short-term course of chronic hepatitis B and C under treatment with etanercept (ETN) associated with different disease modifying antirheumatic drugs (DMARD).

***Methods.*** Patients with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) receiving anti-tumor necrosis factor-α (TNF-α) were retrospectively reviewed for the presence of hepatitis B or C serology, liver function tests, liver biopsy findings, and the relevant outcomes in terms of viral load.

***Results.*** We identified 5 relevant cases receiving ETN, 3 RA patients with chronic hepatitis C, another RA patient with dual infection by B and C, and one AS patient with hepatitis B. Four patients met the American College of Rheumatology criteria for RA. The patient with AS fulfilled the modified New York diagnostic criteria for AS. In Case 1, ETN was started after having discontinued α-interferon and ribavirin due to viral clearance of hepatitis C. These patients had not received prophylactic antiviral therapy while being treated with ETN. Viral replication increased in 2 patients to an insignificant level, remained negative in 2, and decreased in the remaining one. No significant rise in patients' liver transaminases could be determined during followup.

***Conclusion.*** We observed reactivation of hepatitis C virus infection in 2 of 4 patients while they were receiving ETN with DMARD without antiviral prophylaxis. (First Release Jan 15 2008; J Rheumatol 2008;35:421–4)

*Key Indexing Terms:*
ETANERCEPT HEPATITIS B HEPATITIS C
RHEUMATOID ARTHRITIS ANTI-TUMOR NECROSIS FACTOR-α

Treatment of patients with coexisting rheumatoid arthritis (RA) and hepatitis C virus (HCV) or hepatitis B (HBV) poses a difficult therapeutic challenge because of the risk that treatment of RA could aggravate hepatitis and increase viremia. The literature on the safety of anti-tumor necrosis factor-α (TNF-α) in the setting of chronic viral infections is insufficient. There are reports describing HBV reactivation[1,2] after anti-TNF-α therapy as well as others showing lack of reactivation[3]. In general, prophylaxis with lamivudine is recommended[4]. In HCV, the literature is unclear. In particular, it has been reported that etanercept (ETN) does not increase viral load[5,6]. However, lack of viral load increase does not confer any protection from advancement of disease. There is little correlation between HCV viral load and disease progression[7].

We describe the short-term course of 3 patients with RA and 1 patient with ankylosing spondylitis (AS) with hepatitis C and B, respectively, and 1 RA patient with dual infection with hepatitis B and C in terms of the changes occurring in the liver transaminases and viral load.

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## MATERIALS AND METHODS

Three RA patients with hepatitis C, 1 RA patient with combined hepatitis B and C, and 1 AS patient with hepatitis B were selected for evaluation. Four patients met the American College of Rheumatology criteria for RA[8]. The patient with AS fulfilled the modified New York diagnostic criteria for AS[9]. Their disease durations, treatment details, liver transaminases, viral loads, and liver biopsy findings were reviewed retrospectively (Table 1). These patients underwent liver function tests and then were assessed once every 2 months. After DNA extraction with a QiaGen kit, HBV DNA was determined by real-time polymerase chain reaction (PCR; Arthus, Corbett Research, Sydney, Australia). After RNA extraction with an Abbott kit, HCV RNA was determined by real-time PCR. Although liver biopsies of 3 patients had already been performed in other hospitals, we had their histological examinations carried out in our hospital. We were unable to perform 2 patients' Knodell scores, defined by histology activity index consisting of periportal and/or bridging necrosis, intralobular degeneration and focal necrosis, portal inflammation, and fibrosis[10], due to insufficient amount of material harvested for biopsy. Whether antiviral prophylaxis was necessary was determined by 2 different hepatologists employed in 2 other hospitals.

## RESULTS

*Case 1.* The first case was a 55-year-old woman with RA and chronic hepatitis C. Sulfasalazine (SSZ), hydroxychloroquine (HCQ), and prednisolone (PRED) had been used between

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*Table 1.* Patients' characteristics and levels of liver aminotranferases and viral loads before and during etanercept treatment.

| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|---|---|---|---|---|---|
| Age, yrs/sex | 55 F | 62 F | 58 F | 48 F | 38 F |
| Rheumatic disease | RA | RA | RA | RA | AS |
| RA duration since diagnosis, yrs | 9 | 6 | 8 | 9 | 10 |
| Viral disease | HCV | HCV | HCV | HCV + HBV | HBV |
| Duration of viral disease since diagnosis, yrs | 7 | 3 | 5 | 3 | 3 |
| Duration of anti-TNF-α treatment, mo | 21 | 23 | 22 | 13 | 12 |
| DMARD before anti-TNF-α | SSZ + HCQ | SSZ + MTX + LFN | MTX + HCQ | MTX + SSZ | SSZ |
| DMARD with anti-TNF-α | HCQ | SSZ | MTX | MTX | — |
| Viral load (copies/ml) | | | | | |
| Baseline† | Negative | Negative 150,816 (at 5th) | Negative | 131,023/—* | Negative |
| End of followup | Negative | 363,154 | 270,069 | 14,018/514* | 36 |
| AST, IU/ml | | | | | |
| Baseline | 26 | 41 | 14 | 30 | 21 |
| During followup, median (range) | 21 (13–26) | 44 (41–66) | 21 (15–58) | 44 (34–54) | 15 (12–34) |
| End of followup | 20 | 42 | 21 | 54 | 12 |
| ALT, IU/ml | | | | | |
| Baseline | 20 | 50 | 15 | 25 | 25 |
| During followup, median (range) | 15 (13–21) | 46 (13–83) | 34 (13–39) | 40 (33–45) | 15 (15–21) |
| End of followup | 14 | 20 | 37 | 45 | 11 |

† Viral loads were determined 6 and 10 months before initiation of ETN in Cases 2 and 3, respectively. * Second levels show HBV viral load. RA: rheumatoid arthritis; HCV: hepatitis C virus; TNF: tumor necrosis factor; SSZ: sulfasalazine; MTX: methotrexate; HCQ: hydroxychloroquine; LFN: leflunomide; DMARD: disease modifying antirheumatic drugs.

1999 and 2000. At the end of 2000, anti-HCV antibody was found to be positive, but her transaminases remained at normal levels until 2004, therefore only PRED was discontinued; SSZ and antimalarial drug were continued. AST and ALT were found to be 48 IU/l and 54 IU/l in 2004. Viral load was 22,398 copies/ml. A liver biopsy was performed. Activity, fibrosis, and Knodell scores were 1, 1, and 8, respectively. There was also piece-meal necrosis. She was given ribavirin and α-interferon (α-IFN) 2b. After 12 months of treatment, viral load was negative. Ribavirin and IFN were discontinued and because SSZ and antimalarial drug were ineffective, ETN had to be administered at the dosage of 25 mg twice a week. Serum aminotransferases were normal and viral load was still negative at the end of 21 months of the followup therapy.

*Case 2.* The second case was a 62-year-old woman with RA. She was given SSZ in 2001 and methotrexate (MTX) was added to her treatment in 2003. During followup between 2001 and 2003, her transaminase levels were normal. Because of lack of response to SSZ and MTX, leflunomide (LFN) was added to her treatment in 2004. Eight months later, her laboratory testing showed high aminotransferase levels (AST 1128 IU/ml, ALT 959 IU/ml). Serological testing revealed anti-HCV positivity. Viral load was negative. In the liver biopsy, activity, fibrosis, and Knodell scores were 9, 3, and 12, respectively. MTX and LFN were discontinued. After 6 months, AST and ALT returned to nearly normal levels (AST 41 IU/ml, ALT 50 IU/ml). ETN was administered at a dosage of 25 mg twice a week in addition to SSZ. After 5 months, AST and ALT were 66 and 83, respectively; viral load was 150,816 copies/ml. After 23 months, viral load increased to 363,154 copies/ml. Her serum aminotransferase levels changed, varying between 66 and 42 for AST and between 83 and 29 for ALT.

*Case 3.* A 58-year-old woman with an 8-year history of RA and 2-year history of hepatitis C was admitted to our hospital with active RA manifestations in 2004. Serum aminotransferases were normal. Viral load was negative. MTX, HCQ, and PRED were started. After 10 months, ETN was administered in addition to MTX. At that time, serum aminotransferases were normal once again, and remained normal during the 22-month followup period. In February 2007, AST and ALT were 58 IU/l and 39 IU/l, respectively. The viral load increased to 270,069 copies/ml. Her liver biopsy showed mild piece-meal necrosis and focal hepatocellular necrosis without fibrosis. MTX was interrupted while ETN was continued.

*Case 4.* A 48-year-old woman with RA associated with dual infection by hepatitis C and B was referred to our hospital in 2004. Serum transaminases were normal. Viral load for HBV was negative, but viral load for HCV could not be determined from the hospital file. Her liver biopsy revealed chronic hepatitis without Knodell score. MTX, SSZ, and HCQ were started sequentially. At the beginning of 2006, ETN was added to the aforementioned disease modifying antirheumatic drugs (DMARD). Before adding the ETN, transaminases were normal; however, viral load for hepatitis C was 131,023 copies/ml, but it was negative for hepatitis B. After 6 months, MTX was stopped due to leukopenia. During the treatment with ETN, AST and ALT levels fluctuated between 35 and 54

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IU/ml and between 33 and 45 IU/ml. After 13 months, viral load for HBV increased slightly (514 copies/ml). Viral load for HCV decreased to 14,018 copies/ml.

*Case 5.* A 38-year-old woman with AS had chronic hepatitis B. Before being referred to us, she had taken salazopyrin, then LFN after discontinuation of SSZ. Her HBsAg and anti-HBe were positive. Serum aminotransferases were normal. Viral load was negative. We discontinued LFN and started ETN because of increased disease activity. During 12 months' followup, AST and ALT remained within normal limits. Viral load changed little (36 copies/ml).

## DISCUSSION

Although there are acceptable preventive medications for HBV, no consensus guidelines have been achieved for strategies towards preventing HCV while patients are under immunosuppressive treatments[11]. Serum TNF-α levels are highly correlated with viral load and parallel degree of liver inflammation and damage[12]. Low baseline TNF-α level is an independent predictor of sustained response to IFN and ribavirin treatment[13]. Administering soluble TNF-α receptor treatment increases peripheral T-cell reactivity to several microbial antigens, and results in a significant increase in the production of IFN-γ[14]. IFN-γ is the major cytokine in hepatocyte viral clearance[11].

The number of reports on the use of anti-TNF-α in patients with hepatitis C is insufficient. Peterson, *et al* measured viremia in 22 patients with RA (19 received ETN, 3 infliximab) at the start of treatment and after median 9 months followup[5]. They showed that liver-related blood tests and viral load measurements did not change substantially. Parke and Reveille retrospectively reviewed 5 patients known to have RA requiring anti-TNF-α therapy as well as established HCV infection. They concluded that anti-TNF-α therapy appears to be safe and well tolerated without apparent influence on the underlying HCV infection[6]. Anti-TNF-α agents were used concomitantly with cyclosporin A in the treatment of 2 patients with RA accompanied by hepatitis C by Bellisai, *et al*[15]. The liver transaminases and HCV-RNA serum levels remained unchanged during the treatment that lasted for over a year.

As for anti-TNF-α therapy in patients with HBV, Roux, *et al* also retrospectively reviewed 6 patients, 2 of them RA with hepatitis B, one with spondyloarthropathy (SpA) with chronic hepatitis B, and 3 RA with chronic hepatitis C[16]. All the HBV patients were given lamivudine. MTX was administered with anti-TNF-α therapy in 3 cases. In one patient only, viral load was consistently high throughout the study with the exception of some fluctuations, while serum aminotransferases remained normal. Oniankitan, *et al* reported 2 cases with RA and AS accompanied by hepatitis C and hepatitis B, respectively[3]. The patient with AS was given lamivudine throughout the infliximab treatment. No worsening in the liver function or virologic status was observed. In an RA patient with amyloidosis, Anelli, *et al* reported improvement in renal function and disappearance of HBV-DNA following a treatment with infliximab[17].

In contrast to these data, the use of anti-TNF-α agents can result in unfavorable results for some rheumatologic diseases. Ostuni, *et al* described a patient with RA treated with infliximab plus MTX who carried the HBsAg and subsequently developed acute hepatitis due to HBV reactivation after 16 months of treatment with infliximab[2]. The patient's liver functions and viral load with lamivudine returned to normal. Michel, *et al* reported a patient with Still's disease who developed fulminant hepatitis B 2 weeks after having started the second infliximab infusion[18]. Esteve, *et al* reported that the activity of HBV infection increased in 2 patients with Crohn's disease[19]. One of these patients died of severe hepatic failure. Wendling, *et al* reported a case with severe SpA who developed reactivation of a latent precore mutant HBV-related chronic hepatitis during her infliximab treatment[1].

Our patients with RA had used DMARD consisting of MTX, SSZ, LFN, and HCQ as well as PRED in dosages of 5–10 mg until ETN was started. Viral load increased in 2 patients (Cases 2 and 3), but decreased in one (Case 4). In Case 2, viral load had already been determined 6 months before ETN was started. In general, because viral load increase is associated with elevation in the liver aminotransferases in immunosuppressed patients[20,21], viral load was not determined just before initiation of ETN because the patient's aminotransferases were normal. With combination therapy of ETN and SSZ, viral load increased, although not significantly, associated with fluctuations in aminotransferases. Because there was no clinical evidence showing the relationship between viral replication and SSZ use, the viral load increase seems to be related to ETN in Case 2.

In Case 3, the combination of MTX and LFN was associated with an increase in aminotransferase without measurable viral load increase before ETN administration. Although we could not exclude the possibility that MTX may have had a part in the viral load increase in Case 3, we speculate that the increase in viral load could be the result of ETN or a combination of both MTX and ETN. On the other hand, without treatments, viral loads are known to fluctuate significantly in some cases[22]. Changing levels of viremia during TNF-α blockade must, therefore, be compared with the expected rate of spontaneous variations[5]. The cutoff level for significant viral load for HCV is accepted to be 800,000 copies/ml[23]. As for our patients, the viral load remained below 400,000 copies/ml.

The fourth case is the first patient with RA in the literature to have dual infection with hepatitis B and C receiving anti-TNF-α. Considering that we did not observe any significant changes in the liver aminotransferases and viral load of Case 4, who had simultaneous HBV and HCV, it may be thought that presence of HCV led to a stable hepatitis B viral load. Interestingly, Case 5 showed no increase in hepatitis B viral

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load either, despite having only HBV. Therefore, it does not look very likely that presence of HCV in Case 4 could have significantly affected hepatitis B viral load.

Baseline liver biopsy samples were obtained from 3 patients with RA prior to ETN treatment. In the fifth case, liver biopsy was not performed. In all 5 cases, no significant changes were seen in serum transaminases or clinical status, apart from Case 3 (Table 1). Liver biopsy is known as a standard evaluation method for the assessment of changes in activity of HCV hepatitis. Unfortunately, because we had not harvested serial biopsy samples from the patients, we could not compare baseline liver biopsy results with posttreatment biopsy samples. Nevertheless, the levels of transaminases and other liver function tests allowed us to assess conditions of the liver indirectly[5]. On the other hand, patients with hepatitis C infection have been shown to have biopsy evidence of inflammation, necrosis, and fibrosis despite persistently normal ALT levels. Therefore, assessing the condition of the liver with serial liver biopsies with liver function tests could have been invaluable for our study, if performed.

We observed reactivation of the HCV infection in 2 patients while they were receiving ETN. ETN in combination with a DMARD without prophylactic antiviral therapy may result in an increase, albeit not significant, in viral load in patients with RA affected by HBV and HCV. Further studies showing the longterm effect of anti-TNF therapy on viral hepatitis, especially HCV, are needed to reach valid conclusions in clinical practice.

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