

## Research article

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# Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: results from a cohort of 21 patients

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## Abstract

**Introduction** Reactivation of hepatitis B virus (HBV) infection in patients with past infection has been described in 5% to 10% of individuals undergoing immunosuppressive therapies. No data are available to date on the outcome of patients treated by tumour necrosis factor-alpha (TNF $\alpha$ ) inhibitors for chronic arthritis with a serological pattern of past HBV infection. The aim of our study was to monitor HBV markers in HBV surface antigen (HBsAg)-negative/anti-HBcAb-positive patients treated with a TNF $\alpha$  inhibitor for inflammatory arthritides.

**Methods** Twenty-one HBsAg-negative/anti-HBcAb-positive patients were included. HBV serological patterns were compared with those determined before starting TNF $\alpha$  inhibitors. Serum HBV DNA testing by polymerase chain reaction was additionally performed. Spearman correlation analysis was used and  $P < 0.05$  was chosen as the significance threshold.

**Results** Before starting therapy, mean anti-HBsAb titre was 725 IU/L, no patient had an anti-HBsAb titre  $< 10$  IU/L, and 18

patients had an anti-HBsAb  $> 100$  IU/L. At a mean time of 27.2 months following therapy introduction, mean anti-HBsAb titre was 675 IU/L and anti-HBsAb titre remained  $> 100$  IU/L in 17 patients. There was a strong correlation between the first and second anti-HBsAb titres ( $r = 0.98$ ,  $P = 0.013$ ). Moreover, no patient had an anti-HBsAb titre below 10 IU/L or HBV reactivation (HBsAg seroreversion or positive HBV DNA detection). However, the anti-HBsAb titre decreased by more than 30% in 6 patients. The mean anti-HBsAb titre at baseline was significantly lower ( $P = 0.006$ ) and the mean duration of anti-TNF $\alpha$  therapy, although non-significant ( $P = 0.09$ ), was longer in these six patients as compared to patients without a decrease in anti-HBsAb titre.

**Conclusions** Anti-TNF $\alpha$  treatments are likely to be safe in patients with past hepatitis B serological pattern. However, the significant decrease of anti-HBsAb titre observed in a proportion of patients deserves HBV virological follow-up in these patients, especially in those with a low anti-HBsAb titre at baseline.

## Introduction

Hepatitis B virus (HBV) reactivation is a life-threatening disease that is known to occur in HBV inactive carriers following polychemotherapy or immunosuppressive treatments. Thus,

HBV reactivation has been reported to occur in up to 50% of HBV surface antigen (HBsAg)-positive patients following polychemotherapy for haematological cancer [1], and in these patients, preventive anti-HBV therapy is recommended [2]. In

Ab: antibody; ALT: alanine transaminase; AS: ankylosing spondylarthritis; AST: aspartate transaminase; GGT: gamma-glutamyl transferase; HBsAg: hepatitis B virus surface antigen; HBV: hepatitis B virus; PCR: polymerase chain reaction; RA: rheumatoid arthritis; TNF $\alpha$ : tumour necrosis factor-alpha.

addition, several studies have pointed out that HBV reactivation was possible, though at a much lower frequency, in patients undergoing immunosuppressive chemotherapy and whose HBV serological patterns indicate past hepatitis B, as defined by HBsAg negativity and anti-HBV core antibody positivity resulting in severe acute hepatitis and significant morbidity and mortality rates despite antiviral therapy.

Tumour necrosis factor- $\alpha$  (TNF $\alpha$ ) inhibitors that are widely used in chronic inflammatory arthritides, inflammatory bowel diseases, and psoriasis treatment are likely to interfere with the natural history of chronic HBV infection. Production of TNF $\alpha$  has been shown to be elevated in the liver of patients chronically infected with HBV; TNF $\alpha$  participates in the clearance of HBV by promoting elimination of HBV-infected hepatocytes and inhibiting HBV replication. More recently, TNF $\alpha$  has been shown to play a key role in the control of the immune response directed against HBV. Thus, TNF $\alpha$  may inhibit the suppressive effect of regulatory T cells on the HBV-specific immune response and lack of TNF $\alpha$  induces impaired proliferation of HBV-specific cytotoxic T lymphocytes [3]. TNF $\alpha$  inhibitors are therefore likely to promote HBV replication and reactivation. In this view, some case reports have had a fatal outcome because of HBV reactivation following infliximab administration in HBsAg-positive patients [4-9]. In these patients, TNF $\alpha$  inhibitors should not be used without preventive anti-HBV therapy. Except for one case report [10], no data are available to date in the outcome of patients treated with TNF $\alpha$  inhibitors for chronic inflammatory arthritides with a serological pattern of past HBV infection, although this serological status is much more frequently encountered as compared with HBsAg positivity. In the present work, we aimed at detecting HBV reactivation in a cohort of patients with past HBV infection who underwent TNF $\alpha$  inhibitor treatment for chronic inflammatory rheumatism.

## Materials and methods

### Patients

#### *Selection of anti-TNF $\alpha$ -treated patients and hepatitis B virus serological patterns*

Five hundred four patients followed in the department of rheumatology were tested for hepatitis B serological pattern between 2005 and 2006. Of them, 284 had a totally negative serology, 2 (0.4%) had a serology indicating chronic hepatitis B (HBsAg positivity), and 58 (13%) had an HBV serology indicating spontaneously cured hepatitis B (HBsAg-negative, anti-HBcAb-positive,  $\pm$  anti-HBeAb-positive); 54 of these 58 patients were anti-HBsAb-positive and the remaining 4 were anti-HBsAb-negative. In addition, 8 patients harboured isolated anti-HBcAb (without anti-HBsAb or anti-HBeAb). Finally, 152 patients had a serological pattern in agreement with HBV vaccination (isolated anti-HBsAb positivity). Twenty-four of the 58 patients with a serology indicating cured hepatitis B were treated for rheumatoid arthritis (RA) or spondylarthropathy by one or more anti-TNF $\alpha$ . Three of them could not be included

in this study: one died, one withdrew consent, and one was lost to follow-up. Finally, a total of 21 patients gave informed consent for the study and were included.

### Methods

Peripheral blood analyses, including blood count, transaminase activity (aspartate transaminase [AST] and alanine transaminase [ALT]), gamma-glutamyl transferase [GGT], bilirubin dosage, and hepatitis B serological pattern before anti-TNF $\alpha$  treatment and during follow-up, were compared. The mean duration between the two blood samples was 35 months (range 12 to 60 months). Additionally, HBV DNA detection using polymerase chain reaction (PCR) was performed in the last serological pattern determination.

#### *Detection of hepatitis B viral DNA*

Quantification of viral DNA was performed using a real-time PCR assay (Cobas Ampliprep/Cobas TaqMan 48 assay; Roche Diagnostics, Meylan, France). The detection threshold was 12 IU/L (1.08 log IU/mL, or 70 copies/mL).

#### *Anti-HBs antibody dosage*

Anti-HBsAb quantification was performed using the AxSYM Abbott immunoenzymatic assay (Abbott Diagnostics, Wiesbaden, Germany). An anti-HBsAb titre of less than 10 IU/L was considered negative. An anti-HBsAb titre of greater than 100 IU/L was considered to represent good protective immune status in a healthy subject, even if it is admitted that a greater than 10 IU/L titre is sufficient for conferring a protective effect against HBV after immunization [11]. HBsAg and anti-HBcAb were detected using AxSYM Abbott immunoenzymatic assays.

### Statistical analysis

The difference of anti-HBsAb titre between the first and second serum samples was analysed using a non-parametric test: the Spearman rank correlation coefficient. A *P* value of less than 0.05 was chosen as the significance threshold. AST, ALT, and GGT levels and bilirubin dosage were considered to increase when there was twofold elevation.

## Results

### **Baseline characteristics of the 21 patients included**

The baseline characteristics of the 21 patients before the first blood test analysis are as follows: the majority of patients (62%) were women, patients had a mean age  $\pm$  standard deviation of  $57.7 \pm 2.7$  years (range 38 to 81), and the disease duration was  $11 \pm 2.2$  years (range 1 to 30). Twelve patients suffered from RA, 5 from psoriatic arthritis, and 4 from ankylosing spondylarthritis (AS). At the end of the study, 4 patients were treated with infliximab, 14 with etanercept, and 3 with adalimumab. Thirteen patients received only one TNF $\alpha$  inhibitor: 8 were treated with etanercept, 3 with adalimumab, and 2 with infliximab. Because of non-response to one TNF $\alpha$  inhibitor, 6 patients had two types of TNF $\alpha$  inhibitors, and 2 patients

did not respond to two TNF $\alpha$  inhibitors but benefited from three TNF $\alpha$  inhibitors. TNF $\alpha$  inhibitor dosage was usual: 50 mg per week for etanercept, 40 mg twice a month for adalimumab, and 3 to 5 mg/kg for 8 weeks (RA patients) or 6 weeks (AS patients) for infliximab. Ten of the 21 patients also received methotrexate (7.5 to 15 mg per week). The mean duration of treatment was 27.2 months (range 7 to 56).

### Hepatitis B serology, hepatitis B viral detection, and liver enzymes

#### Initial anti-HBsAb titre analysis

Three patients (one with RA and two with AS) had an anti-HBsAb titre of less than 100 IU/L at the first blood analysis: 16, 22, and 94 IU/L.

#### Anti-HBsAb titre evolution

The anti-HBsAb titre remained greater than 10 IU/L in all patients at the second blood analysis (the lowest titre was 12 IU/L). A tendency for the decrease of anti-HBsAb titre by an average of 48 IU/L (8%) in comparison with the first measurement was observed. No patient had an increase in anti-HBsAb titre. Before the start of therapy, the mean anti-HBsAb titre was 725 IU/L, and at the second sample, the mean anti-HBsAb titre was 675 IU/L. There was a strong correlation between the anti-HBsAb titre of the first and second blood samples ( $r = 0.98$ ,  $P = 0.013$ ) (Figure 1a, b). Only 1 of 21 patients experienced a decrease of anti-HBsAb level below 100 IU/L, from 256 to 80 IU/L. A subgroup of six patients experienced a significant decrease in anti-HBsAb titres, ranging from 30% to 70%. In these six patients, the mean anti-HBsAb titre at baseline was significantly lower ( $P = 0.006$ ), and although it did not reach significance, the mean duration of anti-TNF therapy was longer ( $P = 0.09$ ) as compared with patients who did not present a decrease in anti-HBsAb. Four of them had a therapeutic association with methotrexate (Table 1).

#### Hepatitis B virus reactivation

No hepatitis B reactivation, as defined by HBsAg or HBV DNA detection, was observed.

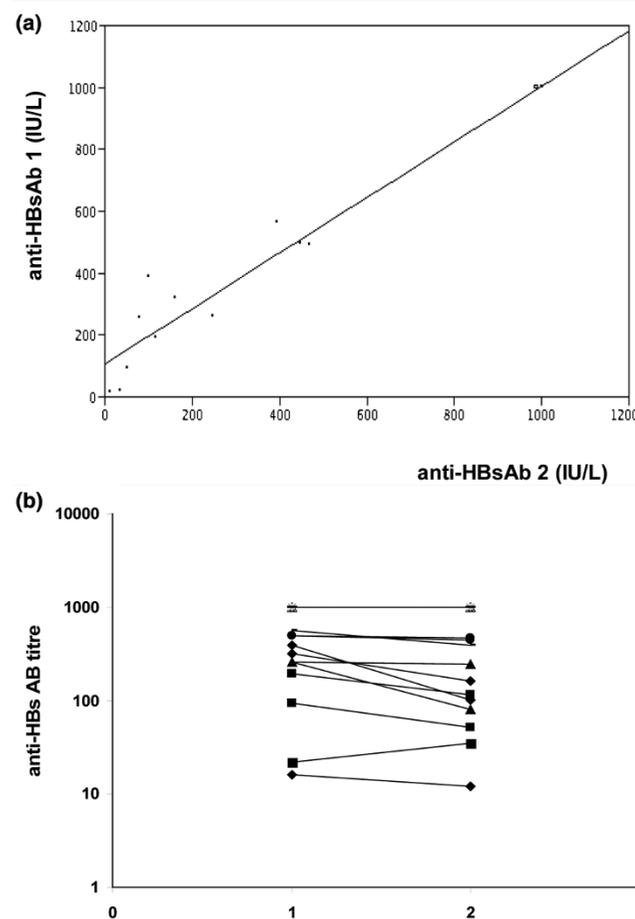
#### Liver enzyme evolution

At the beginning of the study, three patients had significant abnormalities of liver enzymes, even if only one of them had a methotrexate association. At the time of the second blood sample, only one patient (not one of the three previous patients) had significant abnormalities; she was treated with methotrexate. All patients had a normal platelet count.

### Discussion

The main result of the present work is that we did not observe HBV reactivation following TNF $\alpha$  inhibitor treatment in patients with a serological pattern of past HBV infection. This is a very important result. Indeed, although TNF $\alpha$  inhibitors are likely to interfere with the natural history of chronic HBV infec-

**Figure 1**



Correlation between group 1 and 2 anti-HBs Ab titre. (a) Correlation between anti-HBsAb titre of the first (baseline) and second (end of follow-up) dosages (anti-HBsAb 1 and anti-HBsAb 2, respectively). The coefficient of correlation is  $r = 0.98$ , and  $P = 0.013$  by the Spearman rank correlation. (b) Evolution of anti-HBsAb titre for each patient between the first (1) and second (2) dosages.

tion and HBV reactivation has been described in HBsAg-positive patients following TNF $\alpha$  inhibitors (including case reports with a severe or fatal outcome), no clear recommendation for the management of patients presenting a serological status of past HBV infection exists to date.

HBV reactivation in patients with serological tests of past HBV infection (that is, HBsAg-negative, anti-HBcAb-positive with or without anti-HBsAb) has been previously described following immunosuppressive therapies or polychemotherapy, especially those including biotherapies such as rituximab [12]. In these cases, HBV reactivation is explained by the persistence of HBV DNA inside the hepatocyte nucleus [13]. This allows the reappearance of HBV replication in a context of immune suppression [14]. The risk of HBV reactivation following TNF $\alpha$  inhibitors in such patients is therefore a concern and was recently underlined [4].

**Table 1****Comparison of group 1 and group 2 patients**

Patient characteristics	Group 1 (n = 6)	Group 2 (n = 15)
Mean age, years	56	57
Percentage of female patients	77	77
Percentage of patients with rheumatoid arthritis	77	53
Mean anti-HBsAb titre, IU/L	302	753
Mean duration of disease, years	13	10
Mean duration of treatment, months	34	24
Association with methotrexate (mean dosage: 10 mg/week)	4	6
Association with corticosteroid	1	4
Two successive anti-TNF $\alpha$ inhibitors	2	4
Three successive anti-TNF $\alpha$ inhibitors	0	2

Group 1 patients underwent a strong decrease in anti-HBsAb and group 2 patients did not. TNF $\alpha$ , tumor necrosis factor-alpha.

Moreover, this serological profile is frequently encountered. The rates of prevalence of this serological profile in the general population in France in 2004 were estimated to be 9.7% for men and 6.7% for women [15]. Thus, in the present study, 13% of the 504 patients from the department of rheumatology presented with an HBV serology indicating spontaneously cured hepatitis B.

The present work is the first to assess the safety of TNF $\alpha$  inhibitors in a cohort of patients with a serological pattern of past HBV infection, and although a larger number of patients should be necessary to draw a firm conclusion, it strongly suggests that the risk of TNF $\alpha$  inhibitor-related HBV reactivation is very low in these patients, even after several years of therapy. A longer follow-up of these patients, however, should be mandatory. Hence, although anti-HBsAb titre always remained higher than 10 IU/L and a very strong correlation between the first and second anti-HBsAb titres could be observed for each patient ( $r = 0.98$ ,  $P = 0.013$ ), a large decrease (30% to 70%) of anti-HBsAb titres could be noted in a significant proportion (6 of 21 patients) of TNF $\alpha$  inhibitor-treated patients, especially those presenting with a low anti-HBsAb at baseline. This point should be taken into consideration because such a decrease in anti-HBsAb titre has been shown to precede HBV reactivation in patients treated for haematological cancer or following immunosuppressive therapy [16], stressing the need for a closer follow-up of these patients. Although the difference did not reach significance, it is noteworthy that the mean duration of anti-TNF $\alpha$  therapy was longer in these six patients than in those in whom anti-HBsAb titre remained stable. A more prolonged follow-up of these patients will therefore be necessary. This decrease in anti-HBsAb titre might also be related to the underlying chronic disease itself as well as other coincidental factors such as concurrent immunosuppressive therapy. In this view, it is worth noting that four of six patients with a large

decrease in anti-HBsAb titres were also treated with methotrexate. Further studies will also be necessary to assess the risk of HBV reactivation in patients undergoing biotherapies other than anti-TNF $\alpha$  treatment.

## Conclusions

Although further studies that include more patients with a longer follow-up are necessary, it is likely that anti-TNF $\alpha$  treatments can be safely used in patients treated for chronic inflammatory arthritides with an HBV serological pattern indicating past hepatitis B. Thus, no HBV reactivation was observed after a mean of 27 months of anti-TNF $\alpha$  treatment. In addition, anti-HBsAb titre remained above 10 IU/L for all patients. However, the decrease of anti-HBsAb titre observed in a significant proportion of patients suggests that HBV virological follow-up should be considered during anti-TNF $\alpha$  therapy in patients with past HBV infection.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

CC and SG participated in patient recruitment, data acquisition and data analysis and helped to draft the manuscript. PC participated in serological data acquisition and data analysis and helped to draft the manuscript. PB, J-PM, PA, NB, BT, and JR participated in data analysis and patient recruitment. RG conceived of the study and participated in its design and coordination. All authors read and approved the final manuscript.

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