

## Hepatitis B virus (HBV) reactivation in rheumatic patients with hepatitis core antigen (HBV occult carriers) undergoing anti-tumour necrosis factor therapy

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**Key words:** anti-tumour necrosis factor therapy, hepatitis B virus reactivation, hepatitis B virus occult carrier

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### ABSTRACT

**Objective.** *The aim of this study was to assess the effects of anti-tumour necrosis factor (TNF) agents on hepatitis B virus (HBV) reactivation in hepatitis B surface antigen (HBsAg)-negative and anti-hepatitis B core (HBc)-positive patients (HBV occult carriers) with rheumatic diseases.*

**Methods.** *Evidence of HBV reactivation after anti-TNF therapy in HBV occult carriers with a rheumatic disease was studied by summarising results and by performing meta-analysis.*

**Results.** *A total of 468 HBsAg-negative and anti-HBc-positive patients with a rheumatic disease undergoing treatment with an anti-TNF agent were identified in nine studies. The anti-TNF agents used were etanercept in 269 cases, adalimumab in 95, and infliximab in 100 cases, and these were administered for rheumatoid arthritis (RA) in 327 patients, ankylosing spondylitis in 49, and psoriatic arthritis (PsA) in 73 patients. Follow-up periods ranged from 6 to 60 months. HBV reactivation in patients on an anti-TNF agent was reported in 8 cases (8/468 = 1.7%). Seven of these patients had RA and 1 had PsA. Seven patients received etanercept and one adalimumab. HBV-DNA was detectable in 7 of these 8 cases. Antiviral treatment was administered in 6 of the 8 (lamivudine in 2, entecavir in 4) and clinical outcomes were satisfactory in all 8 patients.*

**Conclusions.** *HBV reactivation was found in 8 (1.7%) patients among 468 HBsAg-negative and anti-HBc-positive patients with rheumatic diseases treated with anti-TNF agents. Our data suggest that HBsAg-negative and anti-HBc-positive patients undergoing anti-TNF therapy need to be carefully monitored during anti-TNF therapy.*

### Introduction

Anti-tumour necrosis factor-alpha (TNF- $\alpha$ ) agents are increasingly being used for the effective treatment of autoimmune rheumatic diseases. However, they have been reported to increase the risk of infection, and in particular, to reactivate latent infections (1). Furthermore, an association between anti-TNF therapy and the activation of hepatis

tis B virus (HBV) has been described (2). TNF- $\alpha$  plays an important role in host defense, and patients treated with anti-TNF agents have a high susceptibility to infections. TNF- $\alpha$  suppresses HBV replication and plays a key role in eradicating HBV by stimulating HBV-specific cytotoxic T-cell responses (3). The blockade of TNF- $\alpha$  allows HBV to escape immune control, and thus, facilitates viral replication (4).

In patients with HBV infection, viral reactivation is well known after anti-TNF therapy (5). Prophylactic antiviral therapy has been demonstrated to be excellent at preventing HBV reactivation in hepatitis B surface antigen (HBsAg)-positive patients treated with anti-TNF agents, and thus, it has been proposed that antiviral therapy for chronic HBV infection be administered in rheumatic patients undergoing anti-TNF therapy (2). HBV reactivation has been also reported to occur in HBV occult carriers, who are HBsAg-negative and hepatitis B core antibody (anti-HBc) positive, regardless of the presence of anti-HBs antibodies (5). However, little data based on systematic approaches to the safety of anti-TNF agents in rheumatic patients with an HBV occult infection is available.

Accordingly, the aim of this study was to assess the effects of anti-TNF agents on HBV reactivation in HBsAg-negative and anti-HBc-positive patients (HBV occult carriers) with a rheumatic disease using a systematic analytical approach.

### Methods

#### Identification of eligible studies and data extraction

We performed an electronic search for studies that examined HBV reactivation after anti-TNF therapy in patients with rheumatic diseases. Literature searches were made using MEDLINE and the Cochrane databases to identify available articles (up to December 2011). The following key words and subject terms were used in the searches: 'hepatitis B virus,' 'etanercept,' 'adalimumab,' 'infliximab,' and 'HBV reactivation.' All references in the studies were also reviewed to identify additional studies not indexed by the above-mentioned electronic databases.

Studies were considered eligible if:

1) they included patients with a rheumatic disease (rheumatoid arthritis [RA], ankylosing spondylitis [AS], psoriatic arthritis [PsA], and spondyloarthropathy [SpA]),

2) intervention consisted of anti-TNF agents,

3) if patient were HBsAg-negative and anti-HBc-positive, regardless of anti-HBs antibody status, and

4) if the study presented sufficient data on the effect of anti-TNF agents on HBV reactivation. Reviews and case reports were excluded.

The following information was extracted from each study: first author, year of publication, number of patients, study design, age, sex, disease for which the anti-TNF therapy was administered, transaminase levels, HBV markers, HBV-DNA levels, anti-TNF agent, antiviral prophylaxis, length of follow-up, other treatments, and outcomes.

## Results

### *Studies included in the meta-analysis*

Thirty-six studies were identified by electronic or manual searching and 12 were selected for full-text review based on title and abstract details (6-17). However, three of the 12 were excluded; two were case reports (15, 16) and the other for other than a rheumatic disease (17). Thus, nine studies met the inclusion criteria (6-14). These 9 studies involved

a total of 468 patients with a resolved HBV infection; six were prospective studies and 3 were retrospective studies. The numbers of each anti-TNF agent were not identified in two of the nine studies. The anti-TNF agents used were etanercept in 269 cases, adalimumab in 95, and infliximab in 100. In all studies, except for the study that did not detail RA and SPA patient numbers (11), anti-TNF agents were administered for RA in 327 patients, AS in 49, and PsA in 73 patients. Follow-up period was available in 6 of the 9 studies and ranged from 6 to 60 months. Antiviral prophylaxis was administered in one of the 9 studies (11). Alanine aminotransferase/aspartate aminotransferase (ALT/AST) levels were normal in 7 studies, in one of the two other studies, three (14) and one patients (7), respectively, had an increased ALT/AST level. HBV-DNA levels were available in 7 studies; in one of the other studies 4 patients had a detectable HBV-DNA level (6). Details of the studies included in this review are provided in Table I.

### *HBV reactivation in patients with a resolved HBV infection (anti-HBc + patients)*

Of the 468 patients with a resolved HBV infection and treated with anti-TNF agents, HBV was reactivated in 8 (1.7%). The characteristics of these 8 patients are summarised in Table II.

Seven patients had RA and 1 had PsA. Seven of the 8 received etanercept and one adalimumab, both without antiviral prophylaxis. Follow-up periods were available for 6 of the 8 and ranged from 1 to 18 months. HBsAg data was available for 3, and 2 were HBsAg positive. HBV-DNA was detected in 7 of the 8. Antiviral treatment was administered in 6 cases (lamivudine in 2 and entecavir in 4), but not in the remaining two. Kim *et al.* (12) showed that 14 patients showed a 2-fold or greater increase in ALT/AST after anti-TNF therapy, but did not confirm HBV reactivation. Clinical outcomes were satisfactory in all 8 cases of HBV reactivation.

## Discussion

The HBV affects nearly 400 million people worldwide. After acute infection, most patients eliminate the virus (resolved or occult HBV infection), as demonstrated by the absence of HBsAg and positivity for anti-HBc in serum (18, 19). However, about 10% of patients develop chronic HBV infection. TNF- $\alpha$  is a proinflammatory cytokine that plays a key role in immune response against infectious agents. Furthermore, TNF- $\alpha$  inhibits HBV replication, but in patients with chronic hepatitis, this cytokine contributes to liver injury (20). TNF- $\alpha$  inhibition facilitates HBV replication by allowing the virus to escape host antiviral immune defense

**Table I.** Characteristics of individual studies included in review.

Study (Ref)	Study type	Disease	Case number	Anti-TNF agent	Follow-up (months)	Antiviral prophylaxis	ALT/AST*	HBV-DNA	HBV reactivation (%)
Lan <i>et al.</i> 2011 (6)	Retrospective	RA	70	E:31, A:39	NA	No	N	+ (4 pts)	1 (1.4)
Mori 2011 (7)	Prospective	RA	39	E 18, A 2, I 19	NA	No	†(1 pt)	–	1 (2.6%)
Urata <i>et al.</i> 2011 (8)	Prospective	RA	60	E 38, A 7, I 15	12	No	N	–	5 (8.3)
Tamori <i>et al.</i> 2011 (9)	Prospective	RA	42	E 19, A 2, I 21	12-32	No	N	–	0
Cassano <i>et al.</i> 2011 (10)	Retrospective	PsA	62	E 44, A 10, I 8	6-55	No	N	–	1 (1.6)
Vassilopoulos <i>et al.</i> 2010 (11)	Prospective	RA, SPA	19 (RA: 50.4%)	E 39%, A 37%, I 35%	1.8 yrs	Yes	N	NA	0
Kim <i>et al.</i> 2010 (12)	Retrospective	RA, AS, PsA	88 (45, 41, 2)	E 60, A 16, I 12	NA	No	N	NA	0**
Caporali <i>et al.</i> 2010 (13)	Prospective	RA, AS, PsA	67 (59, 4, 4)	E 23, A 19, I 25	up to 36	No	N	–	0
Charpin <i>et al.</i> 2009 (14)	Prospective	RA, AS, PsA	21 (12, 4, 5)	NA	12-60	No	†(3 pts)	–	0

TNF: tumour necrosis factor; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HBV: hepatitis B virus; RA: rheumatoid arthritis; SPA: spondyloarthropathies; AS: ankylosing spondylitis; PsA: psoriatic arthritis; E: etanercept; A: adalimumab; I: infliximab; NA: not available; pts: patients. ALT/AST\*: N = normal, †<500 IU/L; \*\*14 patients had a 2-fold or greater increase of ALT/AST after anti-TNF therapy.

**Table II.** Characteristics of patients with HBV reactivation after anti-TNF therapy.

Patient (Ref)	Disease	Age / sex	Anti-TNF agent	DMARDs	ALT/AST*	Follow-up (months)	sAg/eAg	sAb/eAb	HBV-DNA	Treatment	Outcome
1 (6)	RA	54/F	Etanercept	MTX	↑	12	+/+	NA/NA	+	Lamivudine	Satisfactory
2 (8)	RA	65/NA	Etanercept	None	N	5	NA/NA	NA/NA	+	Entacavir	Satisfactory
3 (8)	RA	46/NA	Etanercept	MTX, tacrolimus	N	1	NA/NA	NA/NA	+	Entacavir	Satisfactory
4 (8)	RA	49/NA	Etanercept	Bucillamine	N	18	NA/NA	NA/NA	+	Entacavir	Satisfactory
5 (8)	RA	60/NA	Etanercept	Leflunomide	N	1	NA/NA	NA/NA	+	None	Satisfactory
6 (8)	RA	75/NA	Etanercept	MTX	N	2	NA/NA	NA/NA	+	Entacavir	Satisfactory
7 (7)	PsA	NA/NA	Etanercept	NA	N	NA	+/NA	NA/NA	-	Lamivudine	Satisfactory
8 (10)	RA	80/F	Adalimumab	MTX	N	NA	-/NA	NA/NA	+	-	Satisfactory

HBV: hepatitis B virus; TNF: tumour necrosis factor; DMARDs: disease-modifying anti-rheumatic drugs; ALT: alanine aminotransferase; AST: aspartate aminotransferase; RA: rheumatoid arthritis; PsA: psoriatic arthritis; F: female; NA: not available; MTX: methotrexate; NA: not available; ALT/AST\*: N = normal, †<500 IU/L.

mechanisms. The use of TNF- $\alpha$  inhibitors in patients with rheumatic diseases has been associated with HBV reactivation (5). It is well known that anti-TNF therapy increases the risk of HBV reactivation in HBsAg-positive patients with a rheumatic disease. Antiviral prophylaxis against HBV reactivation is required in HBsAg carriers administered anti-TNF agents (2). However, the risk of HBV reactivation and the need for antiviral prophylaxis in HBV occult carriers taking anti-TNF agents remains unclear.

Our results show that HBV reactivation can occur in HBV occult carriers with a rheumatic disease being treated with anti-TNF agents. Of the 468 patients with a HBV occult infection receiving anti-TNF agents included in the present study, HBV was reactivated in 8 (1.7%). Seven received etanercept and adalimumab without antiviral prophylaxis. The risk of HBV reactivation may be influenced by anti-TNF agent type. However, it is unclear whether different anti-TNF agents affect HBV reactivation in HBV occult carriers to differing extents. Our findings are probably affected by publication bias because etanercept was used more frequently in rheumatic patients with an occult HBV infection. In a previous meta-analysis, 255 HBV positive patients were treated with an anti-TNF agent, and HBV reactivation occurred in 33 of 87 HBsAg positive patients but in only 9 of 168 anti-HBc positive patients (36% vs. 5%,  $p < 0.001$ ) (5). The present analysis differs from a previous analysis on

HBV reactivation in patients receiving TNF-targeted therapy performed by Perez-Alvarez *et al.* (5), and this previous study included autoimmune diseases, including psoriasis, inflammatory bowel disease, and case reports, whereas we excluded case reports, due to possible publication bias, and non-rheumatic diseases to reduce study heterogeneity of studies, and included rheumatic diseases. In the present study, 9 clinical studies were included, and the number of HBV occult carriers with rheumatic diseases included was much larger than in the study conducted by Perez-Alvarez *et al.* (5) (468 vs. 168).

Since HBV reactivation occurs in a few cases, it is important to identify predictors other than HBV-DNA which is a biomarker that fluctuates much more frequently and higher than serum antibody levels in chronically infected occult HBV patients. Important a few questions are needed to answer; 1) Is there any relation of the titers of anti-HBc reactivity and the risk of reactivation? 2) Is there any relation between detection of low levels of serum HBV-DNA by sensitive polymerase chain reaction and anti-HBc serum levels? 3) Is there any relation between presence or absence of coincident anti-HBs positivity together with anti-HBc and HBV reactivation? To the best of our knowledge, there were no enough data to answer the first and second questions, but there were data on the third question. Lan *et al.* investigated the risk of HBV reactivation in 12 anti-HBc-positive patients without anti-HBs and 58 anti-HBc-positive pa-

tients with anti-anti-HBs during the 12-month anti-TNF therapy (6). Baseline viral loads were detectable in four of 12 patients who had anti-HBc-positive and anti-HBs-negative status, and one developed HBV reactivation, while there was no HBV reactivation in 58 patients with both anti-HBc and anti-HBs positivity. This result was consistent with the finding of a previous study showing that anti-HBs may prevent HBV reactivation in recipients of liver grafts from donors with anti-HBc (21). It is likely that coincident anti-HBs positivity together with anti-HBc may decrease the risk of HBV reactivation.

The risk of HBV reactivation in HBV occult carriers during anti-TNF treatment implies the need for careful screening and monitoring. In rheumatic patients who are candidates for anti-TNF therapy, HBsAg and anti-HBc status tests should be conducted. Routine prophylaxis is not recommended in anti-HBc-positive patients with rheumatic diseases, but nevertheless, these patients should be monitored during anti-TNF treatment.

In the present meta-analysis, we included 468 HBsAg-negative and anti-HBc-positive patients with a rheumatic disease treated with an anti-TNF agent. HBV reactivation was found to occur in 8 (1.7%) of these patients. Accordingly, our data show that there is a risk of HBV reactivation in HBsAg-negative and anti-HBc-positive patients, and thus, we recommend that these patients be carefully monitored while on anti-TNF therapy.

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