Liver safety of non-tumour necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: an observational, controlled, long-term study

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Abstract

Objective

The risk of hepatitis B virus (HBV) reactivation with non-tumour necrosis factor inhibitor (non-TNFi) biologic agents in patients with rheumatic diseases and past HBV infection has not been definively elucidated. We assessed the comparative safety of non-TNFi and TNFi biologic agents in such patients in real-life clinical settings.

Methods

We carried out a retrospective cohort study from the Department of Rheumatology, University Hospital of Heraklion. Patients who received abatacept (ABA), tocilizumab (TCZ) or rituximab (RTX) during the period 2003–2016 and were HbsAg(-), anti-HBc(+), anti-HBs(±) at baseline, were monitored for HBV reactivation. Patients treated with TNFi agents during the same period were used as a control group.

Results

101 cases of non-TNFi (39 ABA, 32 RTX and 30 TCZ) and 111 cases of TNFi treatment were identified. In non-TNFi, 76 cases (75.2%) were anti-HBc(+)/anti-HBs(+) and 25 (24.8%) were anti-HBc(+)/anti-HBs(-), as compared to 82 (73.9%) and 29 (26.1%) in TNFi-treated, respectively. After a median (IQR) observation of 24.0 (34.7) months, two cases (2.0%) of HBV reactivation were identified in the non-TNFi group; one with ABA, successfully treated with entecavir, and one fatal case with RTX and prior exposure to cyclophosphamide. No reactivation was observed in the TNFi group (p=0.226 vs. non-TNFi). Anti-HBs titres were significantly reduced compared to baseline in the non-TNFi group [median (IQR) 203.9 (954.7) mIU/ml before treatment versus 144.9 (962.9) mIU/ml after treatment, p=0.03].

Conclusion

Two cases of HBV reactivation highlight the risk for this complication in patients with past HBV infection under biologic therapy.

Key words

HBV infection, reactivation, biologic agents, safety

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Introduction

Notwithstanding the effective vaccination and availability of several therapeutic regimens (1), hepatitis B virus (HBV) infection remains an important health issue. About one million deaths are recorded annually worldwide, owing to the various complications of the disease (cirrhosis, liver failure, hepatocellular carcinoma) (2).

Reactivation of HBV infection can occur in patients receiving immunosuppressive treatment for malignancies, autoimmune diseases or organ transplantation (3). The clinical expression of HBV reactivation is wide and extends from total absence of symptoms to life threatening conditions, such as fulminant hepatitis and liver failure. Although hepatitis B surface antigen (HBsAg) carriers have the highest risk, reactivation can also appear – although less often – in patients with evidence of past HBV infection (*i.e.* HBsAg(-), anti-HBc(+), anti-HBs(±)) (4-6).

Over the last decade, biologic agents have demonstrated significant efficacy and are thus included in the treatment armamentarium of autoimmune rheumatic diseases [rheumatoid arthritis (RA), spondylarthropathies (SpA), ANCA-positive vasculitides and systemic lupus erythematosus] (7-9). The extended use of TNF inhibitor (TNFi) biologics in clinical practice has provided substantial data on the prevalence of HBV reactivation in patients with past HBV infection who receive these agents (~1%) (10, 11). On the contrary, evidence regarding the safety of newer non-TNFi biologic drugs, such as rituximab (RTX), tocilizumab (TCZ) and abatacept (ABA), in rheumatic patients infected with HBV, and especially those with past HBV infection, is limited (12). Data from haematologic patients support a substantially increased risk of reactivation in patients receiving RTX (13, 14). Occasional cases of HBV reactivation in anti-HBc(+) rheumatic patients receiving RTX have been reported (15-17), albeit this has not been confirmed in small–size observational studies (18). Others and we have also reported on cases of HBV reactivation in patients with past infection following treatment with abatacept (19-21), but a recent multicentre study did not find an increased risk (22).

To add to the existing knowledge, we aimed to assess the safety of non-TNFi biologic agents in patients with serologic evidence of past HBV infection in the real-life settings of a tertiary centre.

Patients and methods

Patients from the Department of Rheumatology, University Hospital of Heraklion, who received any of the three non-TNFi biologic agents ABA, RTX, or TCZ, during the period 2003–2016, were retrospectively evaluated for the identification of cases of past HBV infection and also HBV reactivation under treatment. To better characterise the risk of HBV reactivation with non-TNFi agents, patients with past HBV infection who received TNFi agents in our Department from 2001 to 2016 were used as a control group.

All patients initiating biologic agents in our centre are followed up on a regular basis (quarterly examinations) with physical examination and laboratory tests. As part of the standard of care, patients initiating or switching biologic therapy are screened for HBV infection with HBsAg, anti-HBs and anti-HBc. For the purpose of this study, we included patients with serologic evidence of previous exposure to HBV, *i.e.* HBsAg(-), anti-HBc(+), anti-HBs(±) at baseline. Our routine practice for the identification of possible HBV reactivation in this subset of patients, is to monitor with repeat liver function tests (LFT) every 3 months and HBsAg every 6 months, for detecting possible liver injury or seroconversion [*i.e.* from HBsAg(-) to HBsAg(+)], respectively. Despite the fact that HBV DNA levels may increase before ALT elevation in cases of HBV reactivation and thus regular monitoring of HBV DNA may allow for early detection (23), we do not routinely measure HBV DNA levels or anti-HBe due to cost limitations. Moreover, until recently ordering of HBV DNA was not compensated for, by public insurance funds in Greece. Instead, HBV DNA is measured in cases of HBsAg seroconversion, to confirm HBV reactivation. Prophylactic antivi-

ral therapy is individualised following consultation by a hepatologist. Withstanding the fact that antiviral therapy significantly reduces the risk for HBV reactivation, for this study we included all patients with evidence of past HBV infection, irrespective of whether they received prophylactic antiviral treatment or not, because we aimed to reflect real-life clinical practice. Additionally, some patients (described in Results) were treated with lamivudine, which is known to be associated with high resistance rates when used for prolonged periods (up to 30% at 2 years) (24).

During the study period, patients could have been treated with one or more biologic agents, according to standard practice and based on physician's judgment; HBsAg, anti-HBs and anti-HBc were assessed at every switch of biologic agent. For the purpose of this study, every change of biologic therapy in a given patient accounted for a different "case" of treatment.

HBV reactivation was defined as an increased alanine aminotransferase (ALT) >2-3 times the upper normal limit (ULN) accompanied by an increase of serum HBV DNA levels by >1 $\log_{10}$ compared with baseline, or a switch in HBV DNA detection from negative to positive (3, 25). In addition, for patients receiving non-TNFi agents who were anti-HBs(+) at baseline, changes in the levels of anti-HBs titres between baseline and most recent follow-up (or discontinuation of non-TNFi agents) were assessed, in cases these were available. Anti-HBs antibody was detected and quantified by using the Axsym Abbott immunoenzymatic assay (Abbott Diagnostics, Wiesbaden, Germany) assay; titres above 10 mIU/ml were considered positive. COBAS AMPLICOR assay (Roche Diagnostics, France) was used for quantification of serum HBV DNA in cases of HBV reactivation.

Statistical analysis

Values are presented as medians (interquartile range, IQR) for continuous variables and frequencies (percentages) for categorical variables. Differences between TNFi and non-TNFi groups were analysed using the non-parametric Kruskal-Wallis test and the chi-square test, as appropriate. For the comparison of serum anti-HBs levels before and after non-TNFi therapy, the non-parametric Wilcoxon signed rank test was used. A *p*-value (two-tailed) of less than 0.05 was considered significant for all comparisons. Statistical analyses were performed using SPSS statistics (v. 22.0, SPSS Inc, Chicago, Illinois, USA).

The study was approved by the Institutional Review Board of the University Hospital of Heraklion, Crete (decision number: 1476/20-03-2012).

Results

A total of 451 patients received at least one non-anti TNF agent during the 13-year period of the study (non-TNFi group). Of them, 71 patients (15.7%) were HBsAg(-), anti-HBc(+), anti-HBs(±) at the initiation of the first non-TNFi agent. ABA and TCZ were administered in patients with rheumatoid arthritis (RA) who were diagnosed according to 1987 ACR classification criteria or 2010 ACR/EULAR criteria (26); RTX was administered in patients with RA and also, in two patients with systemic vasculitis. Forty-seven patients received one non-TNFi agent, eighteen patients received two, and six patients received all three aforementioned non-TNFi agents, successively; this resulted in a total of 101 cases of non-TNFi biologic treatment in the context of past HBV infection (Fig. 1A). Of cases with RA, 69/101 (68.3%) had received ≥1 TNFi agent prior to the use of a non-TNFi biologic.

For the control group (TNFi group), we reviewed 560 patients who received one or more TNFi agent during the period 2001–2016. Of them, 85 patients (15.2%) had evidence of past HBV infection at baseline of the first TNFi agent (Fig. 1B). As expected, composition of the TNFi group was more heterogeneous; 69.4% of patients had a diagnosis of RA and the remaining were patients with different forms of spondylarthritis. Demographic and clinical characteristics of the patients are given in Table I. Age at diagnosis and disease duration were comparable between the TNFi and non-TNFi groups, while concomitant use of synthetic DMARDs and glucocorticoids during biologic treatment were more prevalent in the non-TNFi group.

Regarding prophylactic antiviral prophylaxis while on biologic therapy, antiviral agents were administered in seven cases from the non-TNFi group (7.0%, five cases of RTX and 2 of TCZ therapy). Four of these cases were anti-HBc(+), anti-HBs(-) and three were anti-HBc(+), anti-HBs(+); lamivudine was prescribed in four and entecavir in three cases. One patient had a concomitant HCV infection [anti-HCV(+), anti-HBc(+), anti-HBs(-)] and received entecavir for HBV and interferon for HCV, concomitantly with RTX for RA. She was lost to follow-up after 4 cycles of RTX, with no signs of active hepatitis at last follow-up. A single case in the TNFi group was treated prophylactically with lamivudine. All remaining cases in both groups were followed under close surveillance, without antiviral treatment.

Cases of HBV reactivation

We documented two cases of HBV reactivation during treatment with non-TNFi biologic agents; both cases were not receiving antiviral prophylaxis. The first case has been previously described (19) in a patient who experienced HBV reactivation 10 months following treatment with ABA as first biologic agent; treatment with tenofovir resulted in prompt elimination of HBV-DNA. HBV reactivation had been preceded by a transient ALT elevation four months earlier, attributed to isoniazide (INH) hepatotoxicity given for a latent tuberculosis infection, which normalised following INH discontinuation.

The second case, an 81-year-old man who was treated with RTX for refractory cryoglobulinaemic vasculitis, following lack of response to two monthly pulses of cyclophosphamide, was HBsAg(-), anti-HBc(+), anti-HBs(+) at baseline (baseline anti-HBs level: 546 mIU/ml). Following 5 cycles of preemptive RTX treatment (32 months after its initiation), while the patient was on prednisone 5 mg/day and his disease in remission for more than one year, routine HBsAg testing showed seroconversion to HBsAg(+); prompt order of HBV-DNA confirmed HBV reactivation (9.81×10^7 copies/ml). Both RTX

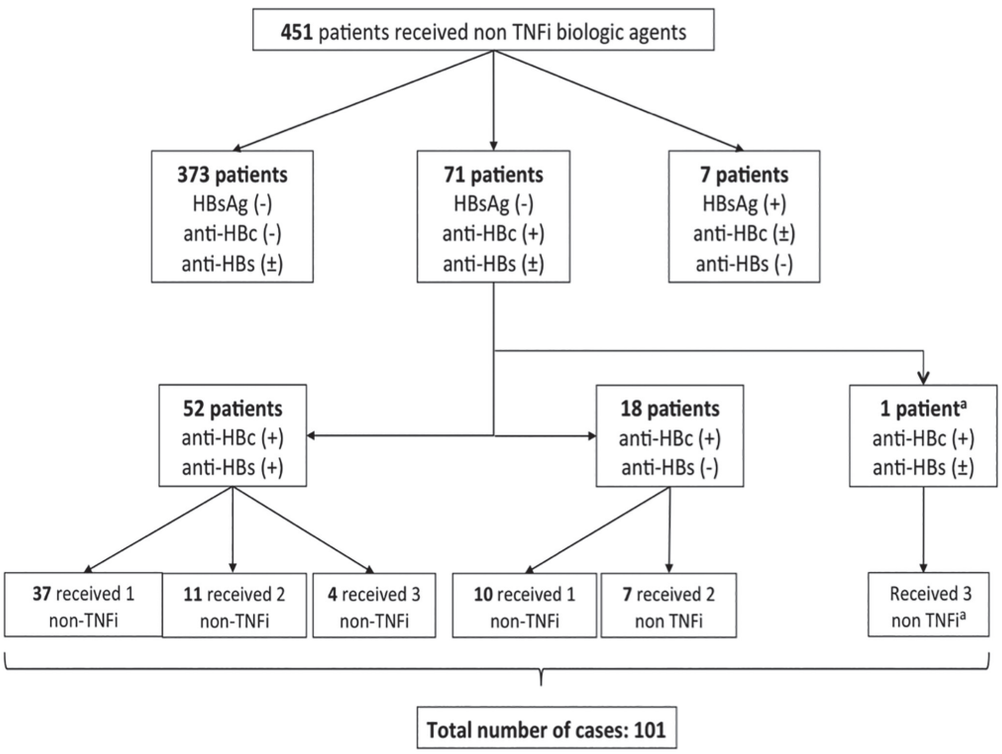

Fig. 1A. Flow chart of patients receiving non-TNFi biologic agents during the period 2003-2016 and their baseline HBV status.
[a]This patient who received three non-TNFi biologics was anti-HBs(+) at the initiation of the first two non-TNFi and anti-HBs(-) at the initiation of the third.

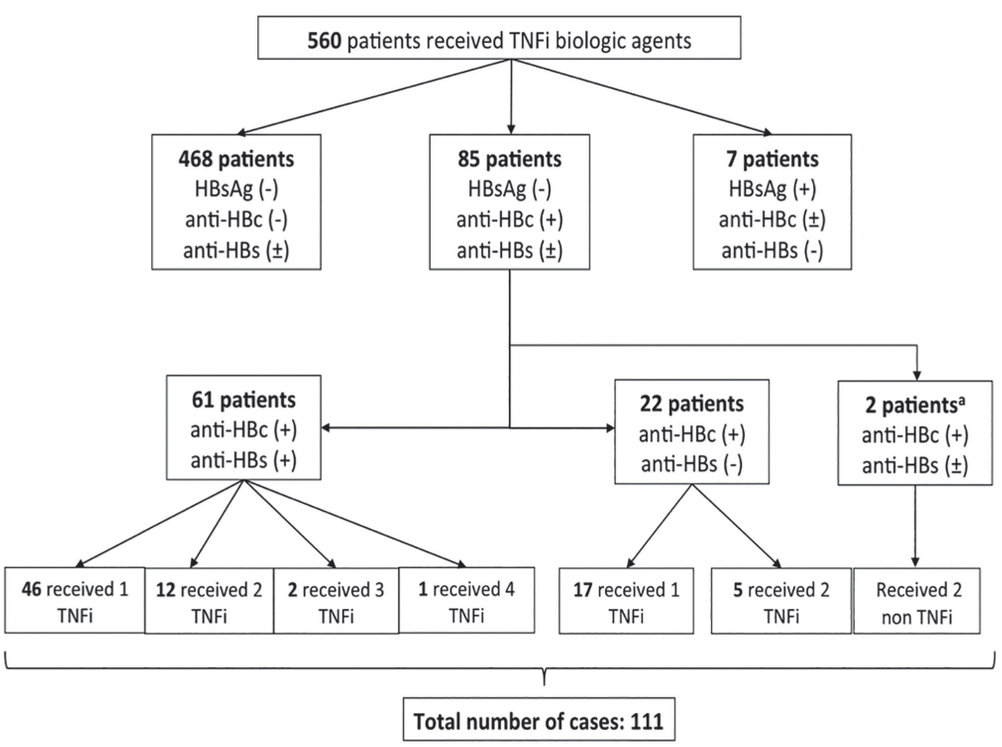

Fig. 1B. Flow chart of patients receiving TNFi biologic agents during the period 2001-2016 and their baseline HBV status.
[a] These patients who received two TNFi agents each, were anti-HBs negative at the initiation of the first TNFi and anti-HBs positive at the initiation of the second.

and glucocorticoids were discontinued and after hepatologist's consultation the patient was started on entecavir, while LFT progressively reached 10x ULN. Following a transient improvement in laboratory parameters during the first month of anti-viral treatment (ALT/AST 6x ULN, HBV DNA 2.85 x10^5), the patient was soon readmitted with a deteriorated clinical condition and eventually died from multiple organ dysfunction syndrome, two months after the diagnosis of HBV reactivation. No evidence of active vasculitis was evident.

No cases of HBV reactivation were documented in the TNFi control group. The difference in HBV reactivation rates between the two groups (2.0% in non-TNFi *vs*. 0% in TNFi) did not reach statistical significance (p=0.226, Fisher's exact test).

Table I. Clinical characteristics of cases with past HBV infection, who received non TNFi and TNFi biologic agents.

	Non-TNFi	TNFi	*p*-value
Age at disease diagnosis, median (IQR) years	54.6 (16.2)	52.0 (21.5)	0.259
Age at biologic agent initiation, median (IQR) years	65.1 (11.2)	62.1 (11.3)	**0.040**
Disease duration at biologic agent initiation, median (IQR) years	7.7 (9.6)	6.2 (9.3)	0.154
Female/Male gender, n (%)	58/13 (81.7/18.3)	53/32 (62.4/37.6)	**0.008**
Diagnosis	69 RA 2 Other • 1 GPA • 1 cryoglobulinaemic vasculitis	59 RA 26 Other • 12 AS • 7 PsA • 6 uSpA • 1 Enteropathic SpA	**<0.001**
Biologic agent used	39 ABA 30 TCZ 32 RTX	48 INF 34 ETN 15 ADA 10 GOL 4 CER	
Number of TNFi agents received prior to index biologic, median (IQR)	1 (1)	0 (1)	**<0.001**
Concomitant use of sDMARDs with biologic therapy, n (%)	94 (92.1) • 52 MTX • 25 LEF • 1 CsA • 1 MMF • 15 combination	90 (82.6) • 46 MTX • 26 LEF • 1 HCQ • 17 combination	**0.040**
Concomitant use of glucocorticoids with biologic therapy and dose, n (%)	53 (52.5) • 28 (53): ≥7.5 mg/d • 25 (47): <7.5 mg/d	37 (33.9) • 26 (70): ≥ 7.5 mg/d • 11 (30): < 7.5 mg/d	**0.007**
Duration of follow-up, median (IQR) months	24.0 (12.5-47.1)	27.0 (9.5-63.5)	0.544
Titre of anti-HBs antibodies at baseline, IU/ml*	207.1 (951.3)	256.4 (900.8)	0.242
Antiviral prophylaxis, n (%)	7 (6.9)	1 (0.9)	**0.020**

RA: rheumatoid arthritis; GPA: granulomatosis with polyangiitis; AS: ankylosing spondylitis; PsA: psoriatic arthritis; SpA: spondylarthropathy; uSPA: undifferentiated spondylarthropathy; ABA: abatacept; TCZ: tocilizumab; RTX: rituximab; INF: infliximab; ETN: etanercept: ADA: adalimumab; GOL: golimumab: CER: certolizumab; MTX: methotrexate; LEF: leflunomide; CsA: cyclosporine A; HCQ: hydroxychloroquine: MMF: mycophenolate mofetil
*For patients who were anti-HBs(+) at initiation of non-TNFi (*i.e.* anti-HBs titres > 10 IU/ml)

Kinetics of anti-HBs levels during treatment with non-TNFi biologic agents

In the non-TNFi group, 76 cases were anti-HBs(+) at baseline. Of these, and after excluding the patient who experienced HBV reactivation under RTX, anti-HBs levels at most recent follow-up were available in 39 cases (51.3%; 17 cases with ABA, 11 with RTX and 11 with TCZ). Median (IQR) duration was 35.1 (33.6) months. Anti-HBs levels fell significantly during non-TNFi biologic therapy [median (IQR) 203.9 (954.7) mIU/ml before treatment *vs*. 144.9 (962.9) mIU/ml after treatment, *p*=0.03)]. Reduction in anti-HBs was more pronounced in patients who received ABA [median (IQR) 207.1 (964.0) mIU/ml before treatment *vs*. 154.7 (969.2) mIU/ml after treatment, *p*=0.003); no statistically significant difference was observed in patients who received RTX [median (IQR) 234.0 (929.4) mIU/ml before treatment *vs*. 196.0 (926.4) mIU/ml after treatment, *p*=0.49] or TCZ [median (IQR) 56.3 (791.9) mIU/ml before treatment *vs*. 122.5 (513.3) mIU/ml after treatment, *p*=0.50]. Of note, in one case that received TCZ, anti-HBs titre at last follow-up fell below 10 mIU/ml, the cut-off for protective immunity to HBV (baseline value 18.9 mIU/ml), corresponding to a frequency of 2.6% (of 39 cases of non-TNFi treatment who had available titres).

In the TNFi group, from a total of 82 anti-HBs positive cases at baseline, repeated antibody titres were available in 16 cases (19.5%; 9 cases with infliximab, 5 with etanercept, 1 with certolizumab and golimumab). In a median (IQR) follow-up time of 40.0 (55.3) months, anti-HBs levels showed non-significant increase from a median (IQR) 285.0 (893.3) mIU/ml before treatment to 628.2 (937.8) mIU/ml after treatment (*p*=0.158).

Discussion

Biologic therapy for rheumatic diseases carries a potential risk of reactivation of latent infections. In this longitudinal real-life study in a single tertiary centre, we identified two cases of HBV reactivation among 101 cases with past HBV infection, following treatment with

Table II. Cases of HBV reactivation following non-TNFi administration in patients with rheumatic diseases and past HBV infection.

Reference	Age/Gender/Diagnosis	Baseline HBV status	Concomitant therapies	Non-TNFi	Timing of reactivation following biologic initiation	HBV DNA at reactivation (copies/ml)	Treatment of HBV reactivation	Outcome/ Duration of f/u
Papalopoulos *et al*.	68/F/RA	anti-HBc (+)/ anti-HBs(-)	MTX	ABA	10 months	$1.1x10^8$	Tenofovir	Good/5 months
Papalopoulos *et al*.	83/M/Cryoglobulinaemic vasculitis	anti-HBc (+)/ anti-HBs(+)	(-)	RTX	32 months	$9.8x10^7$	Entecavir	Death/3 months
Germanidis *et al*. (20)	72/F/RA	anti-HBc (+)/ antiHBs (+)/	LEF	ABA	6 months	$4.3X10^5$	Tenofovir	Good/4 months
Talotta *et al*. (21)	66/M/RA	anti-HBc (+)/ antiHBs (-)/	MTX	ABA	23 months	$3.2x10^2$	Lamivudine	Good/23 months
Ghrenassia *et al*. (15)	78/M/RA	anti-HBc (+)/ anti-HBs(?)	PRE 10 mg/d	RTX	9 months	10^7	Entecavir	Good/6 months
Gigi *et al*. (16)	64/F/RA	anti-HBc (+)/ anti-HBs(+)/	MTX	RTX	24 months	$1.1x10^8$	Entecavir	Good/4 months
Salman-Monte *et al*. (17)	77/M/RA	anti-HBc (+)/ antiHBs(?)	PRE 15 mg/d	RTX	17 months	$>10^8$	Entecavir	Good/18 months

M: fale; F: female; RA: rheumatoid arthritis; ABA: abatacept; RTX: rituximab; MTX: methotrexate; LEF: leflunomide; PRE: prednisone; f/u: follow-up.

non-TNFi biologic agents. Notably, TNFi treatment in our cohort was not associated with HBV reactivation. This difference (2% *vs*. 0%) between the study groups did not reach statistical significance, although a larger sample size (387 cases in each group) would be required to ensure adequate (80%) power (α-error=0.05).

All non-TNFi biologic agents are not considered to carry the same risk for HBV reactivation (published cases of reactivation in rheumatic patients summarised in Table II). A clearly increased risk has been reported for patients receiving RTX as part of multidrug chemotherapy regimens for lymphoproliferative diseases (5, 27). Observational studies in patients with autoimmune rheumatic diseases have not confirmed high reactivation rates (18, 28-30). Of note, a safety report from multiple clinical trials of RTX in RA found no cases of reactivation in 131 anti-HBc(+) patients who had received up to 16 therapy cycles of RTX (28). Nevertheless, our patient who experienced fatal HBV reactivation under RTX is the fourth described case in the literature, regarding rheumatic patients with past HBV infection (the remaining three had a favorable outcome) (15-17). Although he had not discontinued glucocorticoids (which have occasionally been implicated for HBV reactivation (31)) at the time of HBsAg seroconversion, and he had also received cyclophosphamide before B-cell depletion, the potential contribution of RTX therein cannot be excluded. In this regard, the recently published American Gastroenterological Association (AGA) guidelines concluded on a high risk of HBV reactivation in anti-HBc(+) patients following RTX treatment (16.9%) (32) and recommend universal prophylactic antiviral therapy in all patients receiving B-cell depleting therapies. Notably, other experts recommend measuring baseline HBV DNA levels before RTX initiation and prescribing antiviral prophylaxis only in cases of DNA positivity (34). Our report reflects mostly the clinical practice before the publication of the AGA guidelines, including the group of patients treated with rituximab. In the absence of clear recommendations and given the absence of cases of HBV reactivation in patients with rheumatic diseases, a strategy of close monitoring prevailed over antiviral therapy at the time.

Data regarding safety of ABA and TCZ are scarce. For ABA, although case reports of HBV reactivation in anti-HBc(+) patients have been published (13-15), a recent retrospective study from Italy detected no HBV reactivation among 7 patients with past infection and even 17 HBsAg carriers who received ABA without prophylaxis (22). These conflicting data hinder the inference of solid conclusions regarding ABA safety in HBV infection. Our patient had a transient INH-induced LFT elevation prior to HBV reactivation and, albeit one could speculate some form of "synergy" between a hepatotoxic drug and HBV, direct contribution of INH-related transient liver injury to the subsequent HBV reactivation could not be established. A weak recommendation in favour of universal prophylaxis is provided in the AGA guidelines (21); nevertheless, the option of no therapy for patients who prefer to take the rather small risk of HBV reactivation over long-term antiviral therapy is also accepted as "reasonable"(21). The choice of routine prophylaxis *versus* careful observation in patients receiving ABA may be decided on an individual basis, following hepatologic consultation and assessment of comorbidities.

Evidence regarding safety of TCZ are even scarcer and this is reflected in the absence of a specific recommendation regarding IL-6 inhibition in the AGA guidelines (32). To our knowledge, our

study includes the largest number of cases (n=30) of TCZ administration in individuals with past HBV infection. The lack of HBV reactivation during TCZ treatment in our cohort corroborates data from previous observational studies; no case of HBV reactivation has been reported in anti-HBc(+) patients, only a transient mild elevation of HBV DNA in detectable levels in two Japanese patients, which subsided without treatment (33). Thus, monitoring patients receiving IL-6 inhibition regularly for signs of HBV reactivation, over prophylactic antiviral treatment, seems prudent with current knowledge (34).

Importantly, and similar to previous studies from Europe (30, 35), we found no cases of HBV reactivation in a similarly sized cohort of patients treated with TNFi agents (34). Most of the previously published cases (8 total) have been reported in patients originating from Asian countries (36), which could probably be explained by differences in geoepidemiology, as the prevalence of past HBV infection seems to be significantly higher in Asia than in Europe (30% *vs*. ≤15% anti-HBc(+) patients). Interestingly, a recent study showed that in chronic viral infections, signaling through TNF receptors could induce inhibitory signals in CD4(+) cells and, thus, T-cell dysfunction. Moreover, inhibition by anti-TNF monoclonal antibody (infliximab) was able to reverse T-cell dysfunction, supporting a potential therapeutic effect of TNF inhibition in chronic viral diseases (37). Although the risk for HBV reactivation may persist during the months following TNFi agent withdrawal (during the phase of immune reconstitution), we observed no cases of reactivation even after TNFi therapy was ceased. Interestingly, both patients in our cohort who experienced HBV reactivation had not received TNF inhibition prior to non-TNFi agents.

Several limitations of our study need to be acknowledged. Albeit significant for a single centre, our total number of cases is not sufficient to reach solid conclusions regarding the need for universal prophylactic antiviral therapy during non-TNFi treatment. Moreover, we chose to assess each treatment with a different biologic as an independent treatment case. Although not proven to date, a "carry-over effect" regarding the risk for HBV reactivation cannot be ruled out when using sequential biologic therapies. Thus, one cannot be certain whether sequential biologic therapies can actually be considered as different, independent treatment cases (38, 39). Of note, both patients who experienced HBV reactivation had not received TNF inhibition prior to non-TNFi agents; ABA and RTX were the sole biologic agents in each case, respectively. Finally, we did not follow a prespecified protocol for the administration of preemptive antiviral therapy during non-TNFi therapy, however all cases were discussed among staff physicians. Given the paucity of data regarding HBV reactivation during the study period, in most cases we chose to monitor patients for signs of viral reactivation; antiviral treatment was given in a minority following hepatologic consultation.

Notwithstanding these limitations, our study reflects real-life clinical practice in a tertiary referral centre of southern Europe, wherein past HBV infection pertains to a significant proportion of the population. To our knowledge, it is the largest reported cohort from a single centre, which evaluates all three non-TNFi biologic agents together and in comparison to TNFi biologics, with a median follow-up period that reaches two years. Considering the aforementioned limitations, the two cases of HBV reactivation highlight the risk for this complication in patients with past HBV infection under biologic therapy. While the optimal means of surveillance is still a matter of debate, we believe that at least for rheumatic patients initiating rituximab (which carries the highest risk, based on literature from haematologic patients), baseline HBV DNA testing should be ordered and its levels followed prospectively, at least in highly endemic regions for HBV. For abatacept and tocilizumab, as well as anti-TNF agents, literature suggests that the risk is considerably lower. However, in endemic areas, HBV DNA testing seems justified at least at baseline. In all cases, detection of HBV DNA should prompt initiation of preemptive antiviral therapy.

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