Prevalence of Hepatitis B virus infection and risk of reactivation in a rheumatic population undergoing biological therapy

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Abstract

Objective

Hepatitis B (HBV) is a common comorbidity among rheumatic patients. The prevalence of HBV infection and the rate of reactivation remain unclear. The literature data suggested a higher risk in chronic than in past infection. Currently, the literature data are mostly focused on anti-TNF and rituximab. This retrospective observational study aimed to analyse the prevalence of HBV infection and the risk of viral reactivation in a population of rheumatic patients undergoing anti-TNF and non-anti-TNF agents.

Methods

We analysed 1216 rheumatic patients, treated with both csDMARDs and bDMARDs between 2006 and 2017. Serologic markers for HBV (HBsAg, anti-HBs, anti-HBc) were performed prior and during biologic treatment. Patients with chronic or resolved infection were monitored every 3 months.

Results

The prevalence of HBV in our cohort was 15.7% (chronic infection: 0.4%, resolved infection: 12.6%, anti-HBc positivity alone: 2.6%). 12 (6.2%) out of 191 HBV infected patients experienced a reactivation. All of them showed markers of past infection. One patient experienced HBV reactivation despite lamivudine. Only one patient experienced acute hepatitis, probably due to the interruption of immunosuppressors in anticipation of surgery, not preceded by any HBV prophylactic treatment.

Conclusion

HBV reactivation is a rare event in patients treated with a bDMARD and it can also occur while taking lamivudine, not only in chronic carriers (as per the literature data) but also in inactive ones. Regular screening followed by prompt treatment can prevent symptoms or complications. Due to the risk of hepatitis following the immune reconstitution, an antiviral therapy should be considered in the case of sudden discontinuation of csDMARDs or bDMARD.

Key words

autoimmune diseases, Hepatitis B infection, chronic infection, resolved infection, bDMARDs

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Introduction

Rheumatoid arthritis (RA), seronegative spondyloarthritis (SpA), including ankylosing spondylitis (AS) and psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS) and vasculitis are chronic rheumatic inflammatory diseases whose treatment has been recently revolutionised with the introduction of biologic drugs. The aetiology of these diseases is unknown, and the global prevalence is respectively 0.3–1% for RA, 0.5–0.7% for AS, 0.1–0.4% for PsA, and 0.09–0.1% for SLE (1).

The treatment was historically based on the use of non-specific immunosuppressive drugs, whose mechanism of action mainly consists of the prevention of cellular survival or division. These drugs include methotrexate, azathioprine, cyclophosphamide, cyclosporine, leflunomide and other conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) which can be combined with corticosteroids in various ways. During the last two decades, thanks to the introductions of biological drugs (bDMARDs) and recently, small molecules, targeting either Janus-Kinases (JAK-inhibitors) or phosphodiesterases, treatments have become more specific, thus targeting specific cellular molecules, cytokines and receptors involved in sustaining and perpetuating inflammation.

Hepatitis B virus (HBV) belongs to the family of *Flaviviridae and* consists of a DNA virus having both a lytic and a latent phase with a specific tropism for hepatocytes. In endemic areas (Africa and Asia) the prevalence of HBV infection varies between 2% and 10% *versus* <1% reported prevalence in non-endemic areas (Europe and North America) (2, 3).

Vaccination against HBV was introduced in 1982 and recommended by the World Health Organisation (WHO) for every new-born in the first months of life, leading to a significant decrease of the worldwide incidence of acute HBV infection (4). In Italy it has been mandatory for new-borns from 1979 onwards.

Table I summarises the HBV serology in the different infectious phases.

It is known that immunosuppressive therapies can reduce the surveillance against viruses. HBV can replicate in the hepatocytes of patients undergoing both csDMARDs and bDMARDs treatments with a higher efficiency. Furthermore, it has been shown that a sudden immunosuppressive therapy interruption in patients with a latent HBV infection may noteworthy increase the risk to develop an acute hepatitis, due to immune reconstitution (Fig. 1) (5). Therefore, HBV screening is mandatory for any rheumatic patient before and undergoing an immunosuppressive treatment, especially bDMARDs (6-9).

The exact prevalence of HBV infection in patients with rheumatic diseases is not known but it seems to be slightly higher than (or at least comparable to) the one reported in general population (10-12.

The risk of HBV reactivation depends on the type and length of immunosuppression and on the patient's virologic profile (13, 14).

Prophylaxis includes nucleos(t)ide analogues (NAs) lamivudine or tenofovir or Entecavir depending on the HBV titre. Guidelines recommended to continue prophylaxis at least 12 month after immunosuppressant interruption to avoid HBV reactivation (15, 16). Controversial exist regarding dose reduction or interruption (17, 18).

Despite having some cases reported, the use of csDMARDs (methotrexate, azathioprine, hydroxychloroquine, leflunomide, sulfasalazine, mycophenolate, cyclophosphamide) seems to be safe in HBV-infected patients, with a low risk of reactivation even in HBsAg-positive patients. However, rare cases of severe HBV reactivation and fulminant hepatitis following the use of methotrexate have been reported, suggesting that a prophylactic antiviral therapy could be considered in HBsAg-positive patients (19-25).

Data on HBV infection and bDMARDs mainly derive from the cohorts of patients treated with the oldest class, represented by anti-TNF agents. TNF-α has a key role in controlling viral infections; therefore, the use of anti-TNF agents significantly increases the risk of HBV reactivation which has been

Table I. Hepatitis B nomenclature and laboratory tests interpretation (adapted Trepo C. *et al*.) (3).

Nomenclature and interpretation of HBV laboratory tests	
HBV-DNA	Hepatitis B virus
HBsAg	Hepatitis B surface antigen: detectable in serum in case of active hepatitis B infection
HBeAg	Hepatitis B e antigen: detectable in serum in case of active viral replication
HBcAg	Hepatitis B core antigen: associated to active viral replication. No tests available.
Anti-HBs	Antibody *vs*. HBsAg: immunity due to past infection or vaccine or HBIG
Anti-HBe	Antibody *vs*. HBeAg: detectable in case of chronic infection with low titre of HBV
Anti-HBc	Antibody *vs*. HBcAg: detectable in case of past or ongoing infection
Anti-HBc IgM	IgM class antibody *vs*. HBcAg: detectable in case of recent infection (4-6 months)
Anti-HBc IgG	IgG class antibody *vs*. HBcAg: detectable 4–6 months after infection
HBIG	Hepatitis B immune globulin: high titre antibodies *vs*. HBV

HBV profile		HBsAg	anti-HBc IgG	anti-HBc IgM	Anti-HBs	HBeAg	anti-HBe	HBV-DNA
Acute HBV Infection *(Active Carrier)*	Acute infection (Active Carrier if HBV-DNA≥2000 IU/mL, ALT increased and liver damage present)	+	±	+	-	+	-	+
Chronic HBV Infection *(Chronic Carrier)*	Chronic infection with active viral replication	+	+	-	-	+	-	+
	Chronic Precore infection with low viral replication (Inactive carrier if HBV-DNA <2000 IU/mL, ALT normal, no Liver Damage)	+	+	-	-	-	+	+
Past infection	Past infection, recovered and immune	-	+	-	+	-	±	-
	Occult carrier	-	+	-	±	-	-	+
	False positive, infection in remote past	-	+	-	-	-	-	-
Immunity (vaccination)	Immune if titre is >10 mlU/ml	-	-	-	+	-	-	-

reported to be high to moderate (up to 64%) in HBsAg-positive patients who have not received antiviral prophylaxis (26). On the other hand, the reported rate of viral reactivation appears significantly lower in HBsAg-negative/antiHBc-positive patients (<5%) (25-34).

The concomitant administration of anti-TNF drugs and corticosteroids, as well as other non-biologic immunosuppressants is quite common and may increase the risk of HBV reactivation.

Rituximab is an anti-CD20 antibody with a powerful B-cell depleting effect and it has been classified as a highly immunosuppressive drug (34). Contrary to the onco-haematological setting, the risk of HBV reactivation in rheumatic patients treated with rituximab appears to be low due to different therapeutic protocols. However, even when used for autoimmune diseases, Rituximab may be considered a high-risk therapy for patients with HBsAg positivity, while the drug seems safer in HBsAg-negative/Anti-HBc-positive patients (25, 35-39).

There are limited and conflicting data for bDMARDs belonging to other classes. HBsAg-positive patients affected by SpA and treated with ustekinumab, a monoclonal antibody targeting the subunit p40 of IL-12 and IL-23, are reported to have 29% HBV reactivation without antiviral prophylaxis (40), while no case of reactivation has been observed in HBsAg positive patients who received antiviral prophylaxis (41) or in patients with resolved HBV infection without any anti-HBV prophylaxis (40, 42, 43).

HBV-infected RA patients were not included to clinical studies with tocilizumab (a monoclonal antibody targeting IL-6 receptor), therefore data on its safety in HBV patients are limited.

Papalopoulos and colleagues evaluated 111 non anti-TNF patients including 30 RA patients treated with tocilizumab. They found no reactivation with this biologic (44*)*. Similar findings are report in a case report published by Nagashima *et al*. (45*)* showed that a chronic hepatitis B patient without any prior or concomitant antiviral therapy did not have viral reactivation while receiving tocilizumab.

However, in a retrospective study, two cases of HBV reactivation (11%) in a cohort of 18 patients treated with tocilizumab and with resolved HBV infection have been reported (46*)*.

HBV reactivation has been described during abatacept (an anti-CTLA4 fusion receptor) therapy in HBsAg positive (47*)* and HBsAg-negative/anti-HBc-positive RA patients (44*)*, although another retrospective study did not demonstrate HBV reactivation in 72 patients treated with abatacept (48, 49*)*.

Overall, the risk of non-anti-TNF drugs seems to be similar to anti-TNF agents. For recently approved JAK inhibitors tofacitinib and baricitinib, data are lacking even if some reports of HBV reactivation are present in the literature (50*)*.

There are no reports of HBV reactivation during therapy with the human monoclonal antibody inhibiting B-cell activating factor (BAFF), belimumab.

In this uncertain scenario, we aimed to provide in a real-life, monocentric, retrospective analysis, the HBV serology and infection outcome in an Italian cohort of patients.

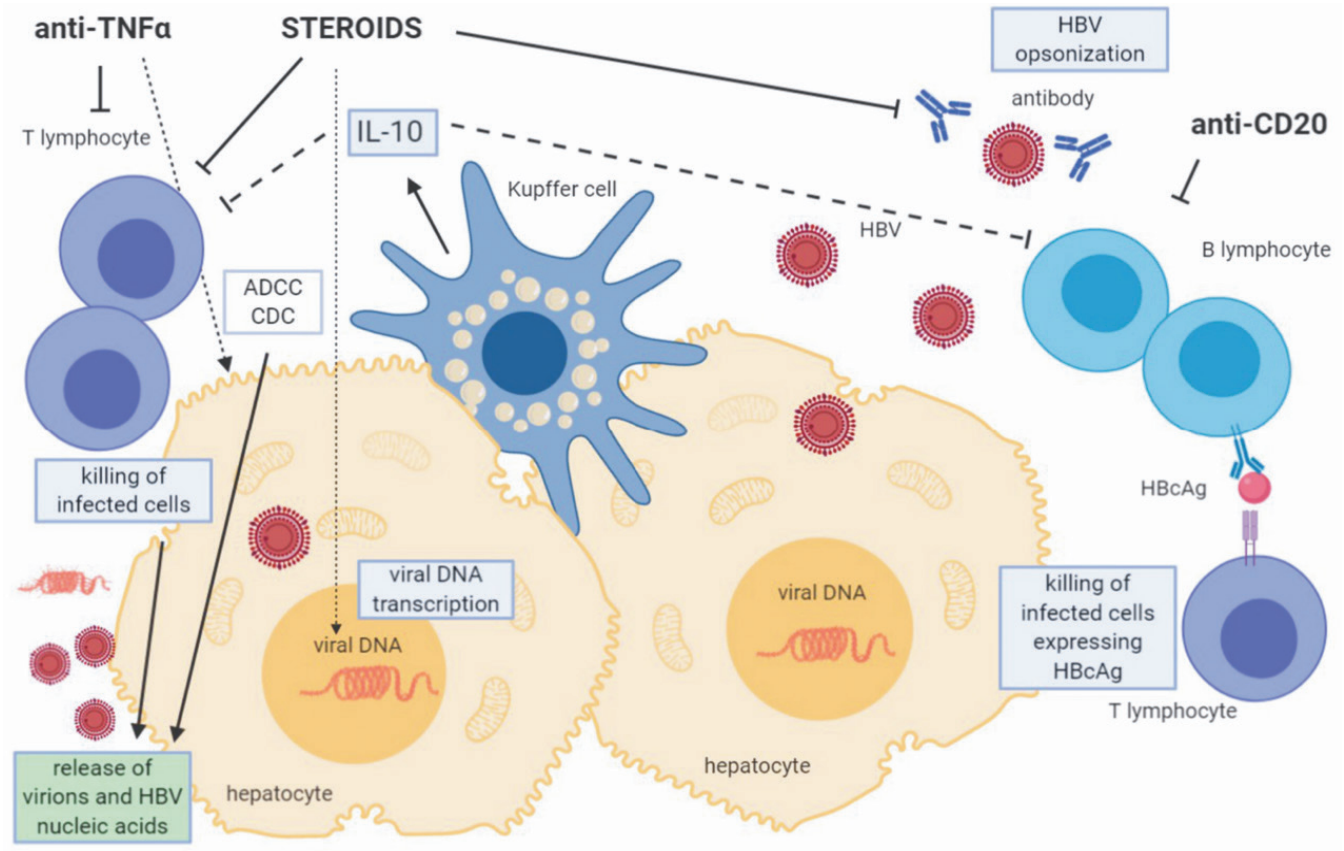

Fig. 1. The immunologic pathway occurring in hepatocytes during HBV infection and the effect of immunosuppressive agents (5).
Soon after the entry inside hepatocytes, HBV can undergo a lytic or latent phase. In the first case, the virus gives rise to a high number of virions, which destroy the cell and are released in bloodstream. Virions activate both T and B lymphocyte responses. T lymphocytes recognise viral antigens on hepatocytes and kill infected cells. B lymphocytes mature to plasma cell stage and synthesise antibodies opsonising extracellular HBV. In addition, the viral antigen HBcAg has a high tropism for B lymphocytes and can be presented to T cells, thus directing an immune response towards HBcAg-expressing hepatocytes. Finally, HBV-infected animal models showed that Kupffer cells may attenuate the activation of immune cells against infected hepatocytes by locally secreting IL-10 (5).
The use of immunosuppressive agents (*e.g.* steroids and biologic therapies like anti-TNF and anti-CD20 agents) may on the one hand lower the threshold of immunosurveillance or directly enhance the expression of viral sequences; on the other hand, it may counteract the setting of an immune response towards infected hepatocytes, which finally leads to an immune-mediated hepatitis. Moreover, monoclonal antibodies against TNF-alpha can induce the lysis of hepatocytes expressing transmembrane TNF, thus favouring hepatic inflammation and viral dissemination.
IL: interleukin; ADCC: antibody-dependent cell-mediated cytotoxicity; CDC: complement-dependent cytotoxicity; HBV: hepatitis B virus; TNFα: tumour necrosis factor alpha; CD: cluster of differentiation.

Materials and methods

We retrospectively collected demographical, clinical and laboratory data from a real-life cohort of rheumatic patients, treated with both csDMARDs and bDMARDs between 2006 and 2017. Every patients belonging to our Department sign a consent form to use these data for observational/retrospective studies. bDMARDs included anti-TNFα (infliximab, etanercept, adalimumab, golimumab, certolizumab pegol), abatacept, tocilizumab, rituximab, belimumab, anakinra, ustekinumab. Many patients had been treated with more than one bDMARD (from one to seven lines of therapy). Demographic data and line of therapy are summarised in Table II. Patients were screened for HBV serologic markers prior and during the biologic treatment. Screening tests included HBsAg, anti-HBs and anti-HBc titres. The research of HBV-DNA in peripheral blood samples was only performed in case of at least one positivity of the previous serologic tests and monitored every 3 months. Concomitant liver diseases, in particular HCV co-infection and cirrhosis, were also recorded.
All the patients were screened at baseline for HBV serologic markers. Those with negative results were followed-up yearly, while those with chronic and resolved infection or anti-HBc positivity monitored every 3 months.
The screening rate was 99.6%; 0.4% of patients were screened after the start of the biological therapy. The results are summarised in Figure 2.

Results

Of 1216 enrolled patients, 847 patients (69.6%) were negative for all the HBV serologic markers at the baseline and remained negative in every re-screening for all the parameters during therapy.

HBsAg-, anti-HBc-, anti-HBs+ (immune, vaccinated)

178 patients (14.6%) showed anti-HBs positivity at the baseline with negative findings for anti-HBc and HBsAg. The anti-HBs positivity was partly due to vaccination (104 patients were vaccinated according to the Italian vaccination policy introduced in 1991, manda-

Table II. Demographic data and line of therapy.

		n. of patients	Male/Female	Mean age
Diagnosis	**Rheumatoid arthritis**	640 (53.6%)	147/493	64.06 (DS±14.3)
	Spondyloarthritis	507 (41.6%)	304/203	55.94 (DS±13.46)
	- Psoriatic arthritis	188 (37%)		
	- Ankylosing spondylitis	135 (26.6%)		
	- IBD-related arthritis	86 (16.9%)		
	- Undifferentiated spondylitis	98 (19.3%)		
	Others	69 (5.6%)	24/45	50.14 (DS±15.25)
	- Systemic lupus erythematosus	18 (1.4%)		
	- Behçet's disease	15 (1.2%)		
	- Polymyositis	2 (0.1%)		
	- Sjögren's syndrome	9 (0.7%)		
	- Large-vessel vasculitis	7 (0.5%)		
	- ANCA-vasculitis	6 (0.4%)		
	- Still's disease	4 (0.3%)		
	- Familial mediterrean fever	1 (0.08%)		
	- UCTD	2 (0.1%)		
	- Recurrent polychondritis	1 (0.08%)		
	- Systemic sclerosis	3 (0.2%)		
	- Mixed connective tissue disease	1 (0.08%)		
Total		1216	429/787	59.72 (DS±14.9)

1st line bDMARD	227 (18.6%)
2nd line bDMARD	618 (50.8%)
3rd line bDMARD	245 (20.1%)
4th and more line bDMARD	128 (10.5%)

tory for every person born after 1979), 55 patients were vaccinated because of job-related risk factors, travelling reasons or other elements; however, 19 anti-HBs positive patients did not remember vaccination or could not prove it with some certification. For one of these patients anti-HBs titres were positive at the baseline only but undetectable at the follow-up.

HBV infected

The prevalence of HBV infection was 15.7% (chronic infection: 0.4%, resolved infection: 12.6%, anti-HBc positivity alone: 2.6%).

– HBsAg+, anti-HBc+, anti-HBs- (chronic infection)

Five patients were classified as HBV carriers at baseline. For four of them the HBV profile at baseline was characterised by the anti-HBs-, anti-HBc+ and HBsAg+, and HBV-DNA-; one patient had HBsAg+ and HBV-DNA with undetectable anti-HBs and anti-HBc. All patients were treated with an antiviral therapy (4 patients with lamivudine, 1 with entecavir), prior to start and during bDMARDs therapy. No one showed HBV reactivation during the follow-up.

– HBsAg-, anti-HBc+, anti-HBs+ (past infection, recovered and immune)

154 patients (12.6%) showed a positivity for both anti-HBs and anti-HBc at the baseline so the research of HBV-DNA in peripheral blood was performed every 3–4 months. 8 out of 154 patients (5.1%) had a concomitant HCV infection. For each patient, liver ultrasound was performed; cirrhosis was found in 1 patient, steatosis in 17 patient, echinococcal cyst in 1 patient.

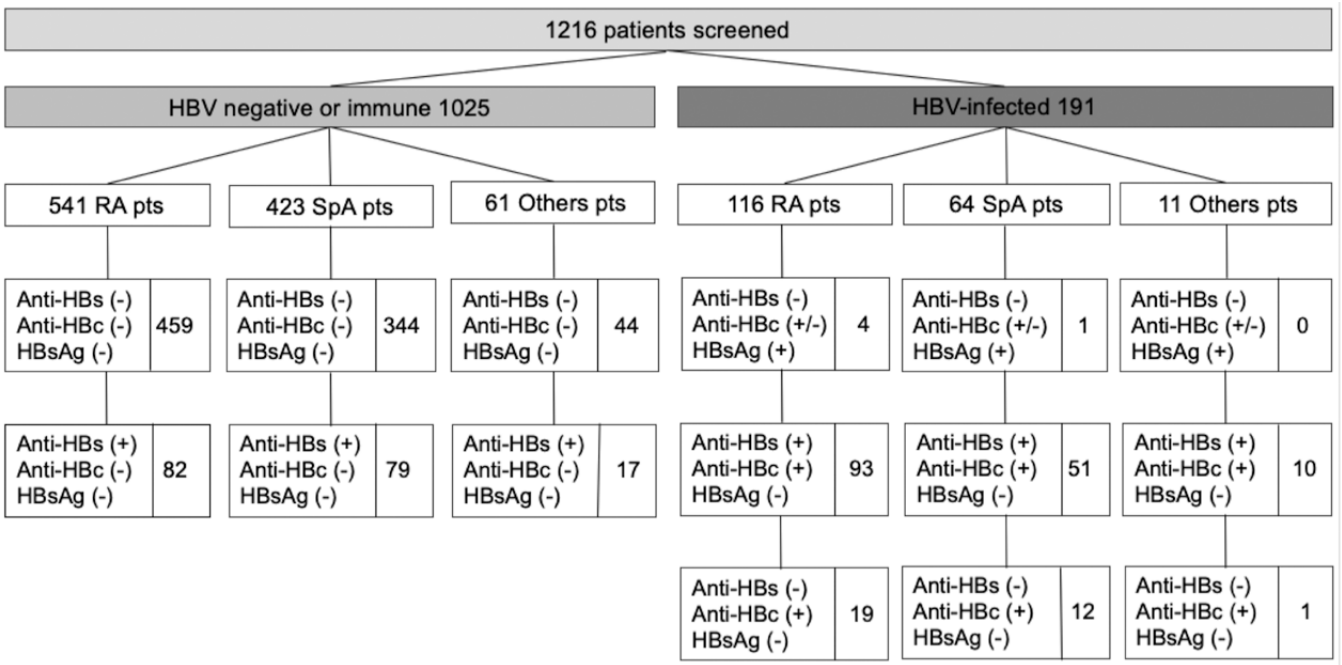

Fig. 2. Flow chart of Hepatitis B profile distribution at baseline.
RA: rheumatoid arthritis; SpA: seronegative spondyloarthritis.

8 patients were treated with antiviral before starting bDMARDs, according to hepatological prescription and 7 out of 8 patients interrupted prophylaxis undergoing biological therapy without consequences.

In particular in this group, one female patient affected by polymyositis started entecavir before rituximab.

One male patient affected by SpA undergoing infliximab was prophylaxed with Lamivudine, because of a concomitant HCV infection with cirrhosis.

Other 2 patients (a female patient affected by PsA, prophylaxed with lamivudine before starting bDMARDs and a male patient affected by AS prophylaxed with entecavir) had a concomitant HCV infection as well.

– HBsAg-, anti-HBs-, anti-HBc+ (past infection, false positive, infection in remote past)

32 patients (2.5%) showed the solely positivity for anti-HBc-IgG at baseline.

In our HBV cohort including 191 patients (chronic and past infected), patients who did not experience HBV-reactivation (179, 93.7%) were distributed as it follows: 85 patients in the first line of therapy, 57 in the second line, 21 in the third, 11 in the fourth, 7 in the fifth; 99 out of 180 patients (55%) assumed both bDMARDs and methotrexate (median dosage 12.2 mg/w); in this scenario, HBV-reactivated patients were reported to be 5 in the first biological line of treatment and 7 in the second line; 9 out of 12 patients (75%) concomitantly assumed methotrexate (mean dosage 10 mg/w).

HBV reactivated (HBV-DNA+, HBsAg ±)

In two patients (only anti-HBc+) HBV-DNA and HBV-DNA/HBsAg became detectable respectively during routine screening. An anti-viral therapy was introduced without the further development of hepatic signs or symptoms.

In 10 patients with resolved infection (HBsAg-, anti-HBc+, anti-HBs+), HBV-DNA became detectable during the observational period. In 9 patients, HBV-DNA elevation was not accompanied by either symptoms or AST/ALT elevation/ or HBsAg detection; 7 out of 9 patients received prophylactic treatment with lamivudine and 1 with entecavir without any consequences; 1 out of 9 patients was not treated due to low HBV-DNA titres which was not detected during the following measurement.

In 3 patients, HBV-DNA titres were associated with HBsAg and AST and ALT increase in serum. One of these patients was a 69-year-old man affected by RA and treated with etanercept. He was promptly treated with entecavir; no symptoms or signs appeared, and the HBV-DNA titres became undetectable in 3 months. The second one was an 80-year-old male patient affected by RA, treated at baseline with lamivudine, which was then swapped to entecavir due to a detectable increase in HBV-DNA titres. He started intravenous abatacept in 2009. At baseline, while undergoing lamivudine, HBV-DNA and HBsAg were negative, while anti-HBs and anti-HBc were positive. His screening results remained unchanged until 2012, when HBV-DNA became detectable (>20000 copies/mL) with a slight increase in AST and ALT. HBV-DNA became undetectable after one month of therapy with entecavir. No change in rheumatic therapy was made and no symptoms were experienced.

On the contrary, the third patient manifested symptoms of acute hepatitis. She was a 64-year-old woman affected by RA and treated with methotrexate (15 mg/w) and golimumab (50 mg/m). She interrupted the therapy in forecast of a surgical procedure. After 2 months, she was admitted at the emergency room with nausea, fatigue, vomiting, abdominal pain, loss of appetite. Laboratory tests showed hypertransaminasaemia (AST 377 IU/mL, ALT 929 IU/mL), elevation in CRP levels (6 mg/L, upper normal value <5 mg/L), HBsAg 30.189 IU/ml, HbeAg 677.06 IU/ml, Anti-HBe 15.67 IU/ml, anti-HBc 11.95 IU/ml, HBV-DNA 3.419.944 copies and 1.002.921 UI/ml. She was hospitalized and treated with tenofovir 245 mg/d. However, despite an initial improvement and HBV-DNA reduction, hypertransaminasaemia persisted with jaundice and abdominal pain, probably due to an intense immunologic response against hepatocytes determined by concomitant anti-TNF agent and methotrexate interruption (immune reconstitution-derived hepatitis). In addition, RA worsened, and a severe flare occurred (DAS28 5.2). Golimumab was reintroduced as per clinical needs with a sudden improvement in RA signs, symptoms and laboratory tests. After 5 months of therapy, HBV-DNA was undetectable (Table III).

Discussion

Twenty years after the introduction of innovative and high specific agents in rheumatology, the HBV screening remains mandatory before starting the treatment even though the risk of acute hepatitis seems to be very low (14, 30, 31). Although vaccination was implemented last year, the rate of vaccinated patients remains low. In our cohort, only 14% of rheumatic patients were vaccinated, and they were mostly born after 1979, undergoing mandatory childhood vaccination schemes.

Data about prevalence of HBV infection (resolved or chronic) in rheumatic diseases are extrapolated by registries and cross-sectional studies. Results from COMORA (COMOrbidities in Rheumatoid Arthritis), an international, cross-sectional study including 4,586 patients from 17 countries and focusing on RA showed that HBV infection is more frequent in Italy (9%) than in other countries [2.8% (95% CI 2.3–3.3%)] (13). Similar results were obtained from the international cross-sectional ASAS-COMOSPA study, which is focused on SpA and includes 3,984 patients from 22 countries from four continents. The HBV infection prevalence was 3.5% (95% CI 2.9 to 4.0), with the highest prevalence observed in China and Turkey (12%) (12). A higher prevalence was registered in Asia with 1.1% patients with RA and 0.3% patients with SLE positive for HBsAg, and 25.2% patients with RA and 13.7% patients with SLE positive for anti-HBc (10).

Koutsianas *et al*. showed that the prevalence of chronic HBV infection differs between countries with the highest rate in sub-Saharan Africa and East Asia (5–10%) whilst the lowest value is observed in Western Europe and North America (<1%) (2); likewise, the preva-

Table III. HBV-reactivated patients.

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9	Pt 10	Pt 11	P 12
Gender	F	F	F	M	M	F	F	F	F	F	F	M
Age	80	64	60	71	68	71	64	68	64	53	47	82
Diagnosis	RA	RA	RA	RA	RA	RA	RA	RA	RA	SSj	SpA	RA
csDMARD	MTX	MTX	MTX	MTX	MTX	MTX	MTX	MTX	-	MTX	-	-
bDMARD	ABA	GOL	CTZ	ETA	ABA	ETA	ABA	ABA	ABA	RTX	GOL	ABA
bDMARD-line	2	2	1	1	2	1	2	2	2	1	2	1
Previous bDMARD	IFX	IFX	na	na	GOL	na	TCZ	IFX	ETA	na	ADA	na
ALT baseline	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
AST baseline	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Anti-HBs baseline	Pos	Pos	Neg	Pos	Pos	Neg	Pos	Pos	Pos	Pos	Pos	Pos
Anti-HBc baseline	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos	Pos
HBsAg baseline	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg	Neg
NUCs baseline	-	-	-	-	-	-	-	-	-	-	-	LVD
ALT reactivation	Normal	High	Normal	High	Normal	Normal	Normal	Normal	Normal	Normal	Normal	High
AST reactivation	Normal	High	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	High
HBsAg reactivation	Neg	Pos	Pos	Pos	Neg	nd	nd	Neg	Neg	Neg	Neg	Pos
HBV-DNA reactivation	Detectb	Detectb	Detectb	Detectb	Detectb	Detectb	Detectb	Detectb	Detectb than undetec without therapy after 1 month	Detectb	Detectb	Detectb
NUCs	LVD	TDF	LVD	ETV	LVD	LVD	ETV	LVD	-	LVD	LVD	ETV

Pt: patient; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; bDMARD: biological disease-modifying anti-rheumatic drug; RA: rheumatoid arthritis; SSj: Sjögren's syndrome; SpA: spondyloarthritis; MTX: methotrexate; ABA: abatacept; GOL: golimumab; IFX: infliximab; CTZ: certolizumab; TCZ: tocilizumab; RTX: rituximab; NUCs: nucleoside/nucleotide analogue; LVD: lamivudine; ETV: entecavir; TDF: tenofovir; Detect.: detectable.

lence of resolved HBV infection was 5% in North America while the rate exceeds 50% in endemic areas (14, 51, 52).

Therefore, although the literature data shows that the prevalence of HBV in rheumatic patients does not differ from that of the general population (especially in Europe) (2, 10-12) in our cohort it appeared to be higher with a value of 15.7% if all the patients are considered, while it decreases to 14.1% considering Italian people only. The prevalence seems to be higher in RA patients (18.1%) than SpA patients (12.6%) probably due to the higher age in the RA group (mean 64.06, DS±16.35 *vs.* mean 56.07, DS±13.77). Regardless of the literature data, we observed a higher prevalence of HBV reactivation amongst patients with inactive occult infection than chronic carriers. One possible explanation could be that all the patients who resulted to be chronic carriers underwent antiviral therapy before starting biological therapies. However, HBV reactivation was a rare event; since a close monitoring and a prompt treatment in case of HBV-DNA detection were performed, no serious events occurred. The only patient that showed an acute hepatitis was found to have interrupted both anti-TNF and methotrexate therapy thus leading to HBV reactivation and to an immuno-reconstitution-mediated liver damage (5).

The most available literature data on biological therapy and HBV are focused on anti-TNF agents 27-30, 32-34, 53, 54) and rituximab (36-38). Reports appear to be controversial about the association of HBV reactivation risk and abatacept. From one retrospective cohort study the risk of HBV reactivation seems higher for anti-TNF (0%) treated patients than non anti-TNF patients (2%, 1 patient treated with rituximab and 1 patient treated with abatacept) (44). Few circumstantial case reports/case series on HBV-reactivation in chronic and occult patients are also published (47, 55, 56). On the other hand, an Italian observational retrospective study including 72 RA patients treated with abatacept, 47 of which were inactive carriers, 21 occult carriers, and 4 chronic active carriers showed that no patient experienced HBV reactivation after 24 months of therapy (49).

To our knowledge this work appears to be the very first with a such large cohort from a single centre concerning the prevalence of HBV amongst patients either in therapy with biologics with different targets.

Contrary to available literature data, our study is focused on the patient rather than on the single drug, better reflecting the real life clinical practice. However, considering that most of HBV patients were treated with more than just one line of biologic, a carry-over effect cannot be excluded.

In our cohort, at the time of HBV reactivation, 6 patients were treated with an anti-TNF agent (3 etanercept, 1 adalimumab, 1 golimumab, 1 certolizumab pegol), 1 was treated with rituximab while 4 were treated with abatacept (47). Five of twelve HBV-reactivated patients were in the first line with bDMARD, while seven of twelve were on second line.

Many studies confirmed that lamivudine is sufficient to prevent HBV reactivation in HBsAg+ patients treated with anti-TNF agents. In our cohort, one patient undergoing lamivudine and abatacept experienced HBV reactivation with undetectable HBV-DNA after entecavir proving that tenofovir and entecavir rather than lamivudine should be preferred in case of a concomitant therapy with abatacept.

High serum level of liver enzymes, performed every 3–4 months to monitor drug toxicity, could be considered a red flag of HBV reactivation but can also remain normal at the onset, so the research of HBV-DNA in periph-

eral blood appears to be the only reliable test to promptly start an antiviral therapy in order to avoid any further complication. HBV reactivation is a very rare but not impossible event in patients starting a bDMARD treatment and previously undergoing prophylaxis with lamivudine. In these cases that the follow-up should be as tight as for past infected patients.

Despite reports of safe biologic interruption in case of resolved infection never prophylaxed with anti-viral therapy is reported (44), our data, due to the risk of hepatitis following the immune reconstitution, strongly suggest that an antiviral therapy should be considered especially in case of sudden discontinuation of csDMARD or bDMARD therapy. This event is not so uncommon, considering the high rate of rheumatic patients undergoing surgery procedures who require drugs discontinuation and the lack of guidelines about immunosuppressive therapy interruption.

Key messages

- Hepatitis B screening is required before starting immunosuppressive therapies due to the risk of viral reactivation.
- Our work appears to be the very first concerning the prevalence of HBV amongst patients either in therapy with anti-TNFα or with other biologic drugs.
- Our study shows that all the patients with viral reactivations were inactive carriers; there was no episode coming from chronic carriers, even though in the literature the prevalence of HBV is reported to be higher for this group. This element proves the importance of monitoring both categories of patients.
- Furthermore, there were no complications nor clinical manifestations in patients with reactivations due to a regular screening and a timely treatment.
- Peculiar attention is required however for all the patients who are about to go into surgery or in case of situations (such as comorbidities, other pathologies, etc.) for which therapies with csDMARDs and b-DMARDs are to be suspended.

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