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Hepatitis B (HBV) reactivation in patients receiving biologic therapy for chronic inflammatory diseases in clinical practice

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Abstract

Introduction and aim. Biologic treatment – particularly with the anti-TNF molecules – is frequently used in clinical practice to treat the severe form for both chronic rheumatic diseases and inflammatory bowel diseases. The immunosuppression induced by biologic therapies increases the risk of infections, including tuberculosis, as well as hepatitis B virus (HBV) reactivation may occur in inactive carriers or occult HBV infection (OBI) subjects during biologic therapy. This study aimed to update data on HBV prevalence and reactivation in patients receiving biologic therapy for either chronic rheumatic diseases or IBD, and to describe their management in clinical practice.

Materials and methods. This study was performed in 6 Italian centers (3 Rheumatology Units and 3 Gastroenterology Units). Clinical, biochemical and virological data, as well as follow up information, were recorded and analyzed.

Results. 984 patients were considered, including 817 with rheumatic disease and 167 with IBD. A total of 43 showed HBV infection (38 OBI and 5 carriers) accounting for a prevalence of 4%. Among OBI patients, 1 (2.6%) case of HBV reactivation occurred in a male patient with Crohn disease. Among the 5 HBV carriers, two patients (1 with spondyloarthritis and 1 with rheumatoid arthritis) did not received HBV antiviral therapy, and both experienced flare of hepatitis at 47 and 49 months following biologic therapy starting.

Discussion. Data of our study highlight that guidelines on management of HBV patients treated with biologic therapies should be still implemented in clinical practice when considering that, although infrequent, HBV reactivation could be potentially life-threatening.

Key words

- hepatitis virus B reactivation
- ulcerative colitis
- Crohn disease
- rheumatoid arthritis
- spondyloarthritis
- biologic therapy

INTRODUCTION

Biologic drugs are considered a cornerstone therapy for both chronic rheumatic diseases and inflammatory bowel diseases (IBD). Therefore, biologic treatment – particularly with the anti-TNF molecules – is frequently used in clinical practice to treat the severe form of these diseases. Unfortunately, the immunosuppression induced by biologic therapies increases the risk of infections, including tuberculosis. Moreover, hepatitis B virus (HBV) reactivation may occur in inactive carriers or occult HBV infection (OBI) subjects during biologic therapy [1-6]. In both cases, HBV reactivation may cause a severe form of hepatitis, which may remain subclinical or evolve in an acute liver failure and death

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[6]. Risk of reactivation does correlate with HBV-DNA levels pre therapy; by immunosuppressive therapeutic agents used and on the duration of treatment [7]. Usually, the normal immune function restoration developed after immunosuppressive treatment interruption cause immune-mediated liver inflammation and consequent hepatitis [6, 7] and hepatitis reactivation usually occur between 12- and 18-months from discontinuation [8].

Viral reactivation occurred in 39% out of 89 HBV carriers and in 5% of 168 patients with OBI, some cases develop a fulminant hepatitis and death [9]. Antiviral therapy is considered recommended for HBV carriers and a tight control advised in those with OBI in ongoing biologic therapy [8, 10-12]. However, the behavior of physicians on management of these patients in clinical practice has been reported to be at times different from recommendations of guidelines, as well as vaccination policies in these categories of patients are also not well defined.

This study aimed to update data on HBV prevalence and reactivation in patients receiving biologic therapy for either chronic rheumatic diseases or IBD, and to describe their management in clinical practice.

METHODS

This study was performed in 6 Italian centers (3 Rheumatology Units and 3 Gastroenterology Units). Diagnosis of chronic rheumatic diseases and IBD were established according to criteria recommended by international guidelines [9-12]. All patients were assuming biologic therapy.

HBV patients are stratified into the following categories according to serological, virologic and biochemical variables: a) occult HBV infection (OBI) [HBsAg-negativity, antibodies to the core antigen (anti-HBc) positivity and very low (<200 international units [IU]/ml), or absent HBV-DNA levels], with alanine aminotransferase (ALT) persistently within normal range, unless other potential hepatotoxic agents or conditions (i.e. obesity, alcohol, drugs) may increase this latter test; 2) overt carriers (HBsAg-positivity). This group of subjects is further subdivided into chronic HBV infection (the former inactive carrier), characterized by normal or minimally altered ALT value and HBV-DNA persistently below 2,000 IU/ml, and chronic HBV hepatitis (the former active carrier), based on the persistence of ALT elevation for at least 6 months and HBV-DNA higher than 2,000 IU/ml [6]. In overt HBsAg carriers, definition of reactivation is based on a ≥1 log10HBV-DNA increase as compared to the value before immunosuppression, or the *de novo* HBV-DNA detection in a previously negative subject [6]. Reactivation in OBI is defined by the seroreversion, consisting in HBsAg re-expression. This occurrence represents a relevant virologic and clinical event, associated with re-appearance of active viral replication [12].

This was a retrospective study on data available for clinical practice in which clinical records of all patients in ongoing biologic therapy were reviewed. Data were anonymously collected in each center and were cumulatively gathered in an electronic database for analysis. Patients were not required to give informed consent to the study because the analysis used anonymous data that were obtained after each patient agreed to being followed up and to collect clinical records by institutions. No experimental procedures, novel devices or experimental drugs were used, as well as no founds were received. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

RESULTS

Data of 984 patients were considered, including 817 with rheumatic disease (83%) and 167 with IBD (17%). A total of 43 patients had HBV infection (38 OBI and 5 carriers) accounting for a prevalence of 4%. In detail, the prevalence was 3% (95% CI: 1.3-6.8) in IBD and 4.7% (95% CI: 3.4-6.4) in rheumatic disease patients. Clinical characteristics of these patients are summarized in *Table 1*.

Among OBI patients, 1 (2.6%) case of HBV reactivation occurred in a male patient with Crohn disease *(Table 2)*. Biologic therapy was stopped, and antiviral therapy with tenofovir performed until normalization of liver enzymes and undetectable HBV-DNA was achieved. The patient is actually on therapy with both adalimumab and entecavir without experience further HBV flare-up. In this group of patients, a prophylactic therapy with lamivudine was introduced in a patient with spondyloarthritis before starting biologic therapy with sekukinumab.

Among the 5 HBV carriers, two patients (1 male with spondyloarthritis and 1 female with rheumatoid arthritis) did not received HBV antiviral therapy, and both experienced flare of hepatitis at 47 and 49 months after biologic therapy initiation *(Table 3)*. Biologic therapy was therefore stopped and antiviral therapy with entecavir started, achieving remission of hepatitis. Then, biologic and entecavir co-therapy was continued without further hepatitis flare-up. In the other 3 patients, antiviral therapy was performed with lamivudine in two cases and with entecavir in the remaining patient. Two out of these patients were receiving a combo therapy with abatacept and methotrexate. None of these patients experienced HBV reactivation or side-effects.

DISCUSSION

Table 1
Clinical characteristics of patients with HBV

Parameter	Number
Sex (M/F)	20/23
Age (Years ± SD)	58.4 ± 14.2
Diagnosis (UC/CD/RA/SPA)	2/2/15/24
Therapy (infliximab/adalimumab/abatacept/enbrel/etanercept/others	6/6/9/7/8/7
Combo therapy with methotrexate (No/Yes)	24/19
HBV Status (OBI/Carrier)	38/5
Time of biologic therapy exposure (months SD)	50.5 ± 39

UC: ulcerative colitis; CD: Crohn disease; RA: rheumatoid arthritis; SPA: spondyloarthritis; OBI: occult b infection.

Table 2
Characteristics of patient with reactivation of occult HBV infection

Parameter	Status
Sex	Male
Age	52 years
Diagnosis	Crohn's disease
Treatment	Adalimumab
HBV status before starting biologic therapy	HBsAg negative HBcAb positive HBsAb: 6 UI/ml HBV DNA: <10 UI/ml
Time of biologic therapy exposure before reactivation	41 months
Time from therapy discontinuation	13 months
HBV status at reactivation	HBsAg positive HBcAb positive HBsAb negative HBV-DNA: 980 UI/ml
HBV treatment	Tenofovir
HBV status after 6 months from starting antiviral treatment	HBsAg positive HBcAb positive HBsAb negative HBV-DNA: <10 UI/ml

Table 3
Characteristics of HBV carriers who experienced flare of hepatitis

Parameter	Status
Sex (M/F)	1/1
Age; years	73/56
Diagnosis	RA/SPA
Treatment*	Abatacept
HBV Status before starting biologic therapy*	HBsAg positive HBcAb positive HBsAb negative HBV DNA >10 UI/ml
Time of biologic therapy exposure before reactivation	49/41 months
Time from therapy discontinuation	14/15 months
HBV treatment*	Entecavir

*Similar in both patients. RA: rheumatoid arthritis, SPA: spondyloarthritis.

HBV reactivation in patients receiving immunosuppressive biologic therapy has been reported in HBV carriers and, with less extent, in those with OBI [2-8]. Recent guidelines [9-12] advice to perform a complete HBV status screening before starting biologic therapy. In detail, patients with OBI should be, in the majority of cases, only monitored without anti-HBV prophylaxis, whilst HBV carriers should receive anti-HBV therapy before immunosuppressive therapy starting. In these case, anti-HBV drugs with a high resistance barrier, such as entecavir or tenofovir, should be preferred over low-barrier agents as lamivudine.

This study analyzes data of a large cohort of patients receiving biologic therapy, in whom a complete HBV status screening and a close follow-up were performed. We found that the overall prevalence of HBV infection was 4% in these patients. These high prevalence rates could be explained for different reasons: 1) the present is a population intensively screened for HBV infection and 2) the cohort studied come from different countries, including regions at high HBV infection prevalence. HBV reactivation occurred in 2.6% OBI patients and was successfully treated with antiviral therapy. This finding confirms that a close monitoring in OBI patients treated with biological therapy is mandatory [2-8]. Of note, our patient was HBsAb positive with a titer of 6 UI/ml. Few recent observations reported that HBV reactivation did not occur in those OBI patients with an anti-HBs titer >100 IU/mL [13]. Therefore, attention needs to be reserved for those patients with low anti-HBs titer. On the other hand, although the presence of anti-HBs might not prevent HBV reactivation, anti-HBs titer may be useful for surveillance given that the loss of anti- HBs may be a predictor of HBV reactivation [13]. Surprisingly, lamivudine prophylaxis was performed in 1 patient of this group, despite such an approach was not suggested by guidelines [9-12]. Conversely, among the HBV carriers, 2 out of 5 patients did not receive antiviral prophylactic therapy, and both experienced hepatitis. Moreover, in the 3 patients who were on antiviral therapy, only 1 received a high resistance barrier antiviral drug as suggested by guidelines [9-12], whilst the remaining 2 patients were on lamivudine therapy. All these observations highlight that the behavior of physicians on management of these patients in clinical practice remains occasionally different from recommendations of guidelines. All patients, candidates to immunosuppressive therapy should be tested for HBV infection before starting treatment. In our opinion this should considered a tricky point needing of further implementation, considering that often HBV infection is unknown by patient, and many physicians are not fully aware the need of preventing HBV reactivation in patients undergoing immunosuppressive therapy [14].

Guidelines recommend that HBV-negative patients before starting immunosuppressive biologic therapy should be managed with HBV vaccination [9, 15], whereas HBV vaccination of subjects with isolated anti-HBc positivity remains, although rationale, still debated [16]. HBsAg-positive carriers must be treated with antivirals according to their categories, while pOBI, considering their lower risk of reactivation [17-21], should be monitored during and after treatment with immunosuppressive drugs (especially those under biologic treatments), in order to promptly detect a reactivation. A different management should be considered if drugs at high risk of reactivation such as rituximab in rheumatological setting are adopted. In this condition the behavior should be like the one adopted in hematological setting [12, 17-21]. Treatment for both rheumatic disease and inflammatory bowel disease is generally lifelong, but HBV status (HBVDNA and HBsAg) should be

continued in OBI if, in case of remission of the disease, immunosuppressive treatments are stopped [6]. Adherence to guidelines remains an extremely important issue. As this study shows, the different management by clinicians of the same type of patient determines sometimes different outcomes. Therefore, sensitization actions are necessary for a homogeneous management of HBV infection in gastro/rheumatological patients as well as possibly further studies.

In conclusion, data of our study highlight that guidelines on management of HBV patients treated with biologic therapies should be still implemented in order to improve the management of these patients. In fact, it should strongly consider that, although infrequent, HBV reactivation could be potentially fatal and life-threatening. Patients suffering of HBV infection should be promptly identified and referred to specialist for a full evaluation of liver disease. Moreover, a close collaboration between rheumatologist/gastroenterologist and hepatologist should be considered mandatory and therefore strongly encouraged in order to obtain the better and safe management of HBV infection. Finally, the role of vaccination of seronegative patients is increasing and is considered highly recommended.

Authors contribution

Ridola L: conception and design, drafting of the article, critical revision of the article for important intellectual content, final approval of the article; Zullo A: drafting of the article, critical revision of the article for important intellectual content, final approval of the article; Laganà B, Lorenzetti R, Migliore A, Pica R, Picchianti Diamanti A, Gigliucci G, Scolieri P: acquisition of data; Bruzzese V: critical revision of the article for important intellectual content, final approval of the article.

Conflict of interest statement

None.

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