Arthritis Care & Research
Vol. 68, No. 6, June 2016, pp 738–743
DOI 10.1002/acr.22786

ORIGINAL ARTICLE

Safety of Abatacept in Rheumatoid Arthritis With Serologic Evidence of Past or Present Hepatitis B Virus Infection

MELISSA PADOVAN,[1] MATTEO FILIPPINI,[2] ANGELA TINCANI,[2] ELISABETTA LANCIANO,[3] ELEONORA BRUSCHI,[4] OSCAR EPIS,[4] PIETRO GARAU,[5] ALESSANDRO MATHIEU,[5] ELEONORA CELLETTI,[6] LEOPOLDO GIANI,[7] PAOLA TOMIETTO,[8] FABIOLA ATZENI,[9] PIERCARLO SARZI PUTTINI,[9] FRANCESCA ZULIANI,[10] SALVATORE DE VITA,[10] FRANCESCO TROTTA,[1] ANASTASIO GRILLI,[1] MASSIMO PUOTI,[4] AND MARCELLO GOVONI[1]

Objective. **Rheumatoid arthritis (RA) with concomitant hepatitis B virus (HBV) infection represents a therapeutic challenge due to the risk of HBV reactivation under immunosuppressive treatment. To date there are few data coming from anecdotal case reports that concern HBV reactivation following treatment with abatacept. This observational retrospective study was aimed to assess the safety profile of abatacept in this particular clinical setting.**

Methods. **Eleven Italian rheumatologic centers provided data from patients with RA and positive HBV serology treated with intravenous abatacept. HBV markers and clinical and laboratory data were checked at followup visits every 3 months.**

Results. **In total, 72 patients were included in the study: 47 inactive carriers, 21 occult carriers, and 4 chronic active carriers for HBV. At baseline all of the patients had normal liver function tests and low or undetectable HBV DNA levels, except for those with chronic active hepatitis. Thirteen patients received prophylaxis with lamivudine, and 4 received treatment with adefovir or tenofovir. At the end of the 24-month followup period, 49 patients were being treated. Data from 316 followup visits showed that abatacept was safe. No patients experienced reactivation of hepatitis B. Treatment withdrawals (23 patients) were due to lack of efficacy, subject decision/lost at followup, or adverse events not related to HBV infection.**

Conclusion. **Our study provides reassuring data about the safety profile of abatacept in RA with concomitant HBV infection without universal antiviral prophylaxis. Further prospective studies are needed to confirm these preliminary results.**

INTRODUCTION

Hepatitis B virus (HBV) can cause chronic disease in 5% of immunocompetent adults and has a worldwide prevalence of more than 350 million persons. It is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma, and accounts for more than 600,000 deaths every year (1). Treatment of rheumatoid arthritis (RA) patients with concomitant HBV is a clinical challenge. Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) could be associated with increased hepatotoxicity, and biologic DMARDs (bDMARDs), in particular tumor necrosis factor (TNF) blockers and anti-CD20 monoclonal antibodies, as well as newer drugs like tocilizumab and abatacept, should be closely monitored for the possible reactivation of B hepatitis (2–18). Abatacept is a soluble fusion protein of the extracellular domain of CTLA-4 and the Fc portion of IgG1 (19). CTLA-4 is naturally expressed on T cells for regulatory function and acts as a competitive inhibitor to prevent the costimulatory activation of T cells involved in RA pathogenesis

[1]Melissa Padovan, MD, PhD, Francesco Trotta, MD, Anastasio Grilli, MD, Marcello Govoni, MD: Università degli studi di Ferrara and Azienda Ospedaliero Universitaria S. Anna di Ferrara, Ferrara, Italy; [2]Matteo Filippini, MD, Angela Tincani, MD: Spedali Civili di Brescia, Brescia, Italy; [3]Elisabetta Lanciano, MD: Policlinico Universitario, Bari, Italy; [4]Eleonora Bruschi, MD, Oscar Epis, MD, Massimo Puoti, MD: A. O. Ospedale Niguarda Cà Granda, Milano, Italy; [5]Pietro Garau, MD, Alessandro Mathieu, MD: Policlinico Universitario Monserrato, Cagliari, Italy; [6]Eleonora Celletti, MD: Università G. D'Annunzio, Chieti-Pescara, Italy; [7]Leopoldo Giani, MD: Ospedale Civile, Legnano, Milano, Italy; [8]Paola Tomietto, MD: Azienda Ospedaliero-Universitaria Ospedali Riuniti di Trieste, Trieste, Italy; [9]Fabiola Atzeni, MD, PierCarlo Sarzi Puttini, MD: Ospedale Sacco, Milano, Italy; [10]Francesca Zuliani, MD, Salvatore De Vita, MD: Università degli studi di Udine, Udine, Italy.

Address correspondence to Melissa Padovan, MD, PhD, Rheumatology Unit, Department of Medical Science, University of Ferrara and Azienda Ospedaliero-Universitaria Sant'Anna Hospital, Via Aldo Moro 8–44124 Cona-Ferrara, Italy. E-mail: melissa.padovan@unife.it.

Submitted for publication May 11, 2015; accepted in revised form November 3, 2015.

Significance & Innovations

- The management strategy of rheumatoid arthritis (RA) with concomitant hepatitis B virus (HBV) infection is still debated due to the risk of HBV reactivation under immunosuppressive treatment. This study adds significant information to the existing anecdotal literature and provides further evidence about the management of these cases.
- This article describes an Italian retrospective multicenter long-term observational study. This report, obtained in a "real-life" setting, provides encouraging data about a good safety profile of abatacept in a large case series of 72 patients with RA and HBV infection (with and without antiviral prophylaxis) in a 24-month followup period. No patients experienced HBV reactivation.

and in the modulation of HBV replication (20,21). Few and sometimes conflicting data concerning the safety of abatacept in RA patients with concomitant HBV infection arise from reviews of short medical records or anecdotal cases. A study found that it was safe and feasible only with antiviral prophylaxis in 4 of 8 patients (22). Two case reports described hepatitis B reactivation following treatment with abatacept (23,24). In a small case series of 9 RA patients, 1 case of HBV reactivation is described in a chronic inactive carrier (25).

The aim of this long-term, multicenter, retrospective observational study was to verify the safety of abatacept in a group of Italian RA patients with serologic evidence of past or present HBV infection in a "real-life" setting.

MATERIALS AND METHODS

Eleven rheumatologic centers from different geographic areas of Italy were invited to participate, i.e., provide retrospective data about patients fulfilling the 1987 revised criteria of the American College of Rheumatology for RA (26) and HBV-positive serology treated with abatacept. Medical history, clinical and laboratory data were retrieved from hospital records, patient folders, and clinical charts and stored in a dedicated database. Baseline data included demographic information, disease duration, comorbidities, concomitant drugs, previous csDMARDs and bDMARDs, Disease Activity Score in 28 joints (DAS28) (27), rheumatoid factor and anti–cyclic citrullinated protein antibody status, liver function tests (LFTs) measured by alanine aminotransferase and aspartate aminotransferase levels (units/liter), serologic B hepatitis markers (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [HBsAb], anti-HBe, hepatitis B core antibody [HBcAb], and HBV DNA [IU/ml]), and hepatitis C virus (HCV) co-infection markers (anti–hepatitis C antibodies and HCV RNA). Antibody levels were determined using commercial immunoassay tests commonly used in each study center (most common was Abbott Architect, Abbott Diagnostics). Serum HBV DNA was measured by polymerase chain reaction assay, using different commercial kits in each study center. The most commonly used were 1) COBAS Amplicor HBV Monitor Test, version 2.0, Roche Diagnostics, with a lower limit of quantification of 71 IU/ml; 2) COBAS TaqMan HBV Test, version 2.0, Roche Molecular Systems, with a lower limit of quantification of 12 IU/ml; 3) COBAS TaqMan HBV, CTM HBV test, Roche Diagnostics, with a lower limit of quantification of 12 IU/ml; and 4) Abbott Real Time HBV, Abbott m2000, with a lower limit of quantification of 4 UI/ml.

Followup data were checked every 3 months for up to 24 months and included DAS28 scores, HBV markers (HBsAg, HBsAb, anti-HBe, HBcAb, and HBV DNA), LFT, antiviral therapy, or prophylaxis, and all adverse events (AEs) were recorded as well. Abatacept was administered intravenously according to the approved manufacturer schedules in agreement with standard of care, every 2 weeks for the first month and then monthly.

Following the European Association for the Study of the Liver guidelines (28), baseline patients' viral status profiles were classified as chronic active disease, carriers of inactive disease, or occult HBV carriers. Chronic active B hepatitis was defined as persistent HBsAg positivity, HBV DNA levels $>$2,000 IU/ml, persistently or intermittently high LFTs, and HBeAg or anti-HBe positivity. The status of inactive carrier was defined as having persistent HBsAg positivity, anti-HBe positivity, HBV DNA levels $<$2,000 IU/ml, and normal LFTs. The status of occult HBV carrier was defined as HBsAg negativity in serum with HBcAb reactivity or anti-HBe reactivity in patients that did not receive the HBV vaccination, with normal LFTs and undetectable or low HBV DNA levels (below the sensitivity cutoff of the current assay). A reactivation in a chronic carrier was defined as a switch to chronic hepatitis status; in an occult carrier the definition also included HBsAg seroconversion on followup.

The qualitative variables were expressed as percentages of positivity; the quantitative variables were expressed as mean $\pm$ SD.

RESULTS

Demographic and clinical data of the patients are summarized in Table 1. Seventy-two patients (10 male and 62 female), with a mean age of 62.6 years (range 33–84 years) and a mean $\pm$ SD disease duration of 12 $\pm$ 5 years with active disease (mean $\pm$ SD DAS28 score 6.44 $\pm$ 1.5), were included. Before abatacept treatment, 45.8% had been previously treated with 2 bDMARDs, 19.4% with 3, and 23.6% with 1 bDMARD. In 8 cases (11.1%) abatacept was the first bDMARD. In combination with abatacept, patients received csDMARDS (methotrexate 66.7%, leflunomide 6.9%, sulphasalazine 2.8%, or hydroxychloroquine 8.3%) associated with low-dosage ($\leq$7.5 mg/day prednisone equivalent) glucocorticoids (80.6%) or glucocorticoids alone (16.6%). Two patients received abatacept in monotherapy (2.8%).

Table 1 describes the baseline HBV status and treatment: 47 patients (65.3%) were categorized as inactive carriers and 21 patients (29.1%) as occult carriers (anti-core positive). Four patients (5.6%) had chronic active hepatitis.

At baseline all the patients had normal LFT and low or undetectable HBV DNA levels, except for those with chronic active hepatitis who had HBV DNA titers $>$2,000 IU/ml

Table 1. Baseline characteristics*

Demographic/clinical data	All	Inactive carrier	Occult carrier	Chronic active hepatitis
Patients	72	47 (65.3)	21 (29.1)	4 (5.6)
Female:male ratio	62:10	26:21	11:10	2:2
Mean age, years	62.6 (range 33–84)	62.8	62.3	62.6
Disease duration, mean ± SD years	12 ± 5	15 ± 2	12 ± 5	11 ± 3
DAS28, mean ± SD	6.44 ± 1.5	6.2 ± 1.5	6.6 ± 1.2	6.4 ± 1.4
RF positive	53 (73.6)	34 (72.3)	16 (76.1)	3 (75)
ACPA positive	51 (70.8)	33 (70.2)	15 (71.4)	3 (75)
2 previous biologic DMARDs	33 (45.8)	21 (44.6)	10 (47.6)	2 (50)
3 previous biologic DMARDs	14 (19.4)	9 (19.1)	4 (19)	1 (25)
1 prior biologic DMARD	17 (23.6)	11 (23.4)	5 (23.8)	1 (25)
No prior biologic DMARDs	8 (11.1)	6 (12.7)	2 (9.5)	0
Concomitant therapy				
Abatacept monotherapy	2 (2.8)	1 (2.1)	1 (4.7)	0
Steroids (alone)	12 (16.6)	6 (12.7)	2 (9.5)	4 (100)
Steroids associated with csDMARDs	58 (80.6)	40 (85.1)	18 (85.7)	0
HBV viral load				
HBV DNA >2,000 IU/ml	4 (5.6)	0	0	4 (100)
HBV DNA low or undetectable level	68 (94.4)	47 (100)	21 (100)	0
Antiviral prophylaxis/treatment				
Lamivudine	13 (18)	9 (19.1)	4 (19)	0
Adefovir/tenofovir (chronic active hepatitis)	4 (5.6)	0	0	4 (100)
Concomitant hepatitis C				
Anti-HCV antibodies	4 (5.6)	2 (4.2)	1 (4.7)	1 (25)
Detectable HCV RNA	0	0	0	0

* Values are the number (percentage) unless indicated otherwise. DAS28 = Disease Activity Score in 28 joints; RF = rheumatoid factor; ACPA = anti–citrullinated protein antibodies; DMARDs = disease-modifying antirheumatic drugs; csDMARDs = conventional synthetic DMARDs; HBV = hepatitis B virus; HCV = hepatitis C virus.

(range 12,000–55,000 IU/ml). Thirteen patients (18%) received antiviral prophylaxis with lamivudine (9 of 47 inactive carriers and 4 of 21 occult carriers). The majority of inactive and occult carrier patients were treated with abatacept without antiviral prophylaxis. In all cases, tight laboratory and clinical control, in collaboration with the infectologist, was set in order to identify HBV reactivation and to promptly start antiviral therapy. Due to the retrospective design of the study, the decision whether to start or not start antiviral prophylaxis was considered in each center on the basis of local expert opinion and risk stratification. In all patients HBV DNA was undetectable and normal LFTs were recorded at the baseline and followup visits. Four patients (5.6%) received antiviral treatment, 2 with adefovir and 2 with tenofovir (all 4 were chronic hepatitis). No significant differences were observed in LFTs, HBV DNA levels, concomitant therapy, and number of previous DMARDs between inactive carriers with and without lamivudine prophylaxis. Four patients (2 inactive carriers, 1 occult carrier, and 1 with chronic active hepatitis) were also anti–HCV positive without active viral replication (HCV RNA undetectable).

At the end of the 24-month followup period, a total of 316 followup visits were performed, and 49 patients (68%) were still on treatment with abatacept (Table 2); a decrease in the mean ± SD DAS28 score (2.3 ± 1.9) was

Table 2. Followup data*

	3 months	6 months	12 months	24 months
Patients being treated (ongoing)	67 (93)	62 (86.1)	55 (76.3)	49 (68)
DAS28, mean ± SD	4.66 ± 1.5	2.4 ± 1.8	2.10 ± 1.6	2.3 ± 1.9
HBV reactivation	0	0	0	0
LFTs increased	0	0	0	0
Abatacept withdrawal				
Primary inefficacy	4 (5.6)		1 (1.4)	
Loss of efficacy		3 (4.1)	1 (1.4)	3 (4.1)
AEs (unrelated to HBV)		2 (2.7)	1 (1.4)	3 (4.1)
Subject decision/lost to followup	1 (1.4)		4 (5.6)	

* Values are the number (percentage) unless indicated otherwise. DAS28 = Disease Activity Score in 28 joints; HBV = hepatitis B virus; LFTs = liver function tests; AEs = adverse events.

observed in those patients who continued the treatment. In 316 LFT determinations and 158 HBV DNA determinations recorded in 24 months, no patients experienced reactivation of B hepatitis. Thirteen patients received lamivudine while taking abatacept for all the time and a 24-months followup was available (13 person-years); 38 inactive carriers and 17 occult carriers received abatacept without lamivudine prophylaxis, corresponding to 32 person-years (16.2 and 15.8 person-years, respectively); 4 chronic active hepatitis patients received abatacept with concomitant antiviral treatment (2 tenofovir and 2 adefovir) for all the time, with a 24-month followup available (4 person-years). LFTs remained normal and HBV serology remained unchanged. In the 4 active carriers, HBV DNA titers became undetectable between 4 and 6 months after antiviral treatment and abatacept initiation, remaining within the normal limits throughout the subsequent 18-month followup. No differences have been observed between patients treated with combination therapy or monotherapy for RA. Five patients discontinued treatment with abatacept for primary inefficacy, 7 for loss of efficacy, 5 for subject decision/lost at followup, and 6 for AEs (none related to HBV; chronic infected skin ulcer, postsurgery acute renal failure for hip fracture, suspected demyelinating disease, and urinary tract or respiratory recurrent infections) (Table 2).

Additional data were available for 28 patients who remained on treatment with abatacept for more than 24 months with no signs of HBV reactivation for up to 54 months of followup (reaching a total cumulative count of 812 followup visits). The prophylactic antiviral treatment was continued for all the period of exposure to abatacept and/or 6 months after treatment discontinuation (data not shown).

Data were also available for 20 of 23 patients who discontinued abatacept with no signs of HBV reactivation for up to 27 additional average months of followup. Six of these 20 patients switched to TNF blockers, 6 switched to tocilizumab, 4 to rituximab, and 4 to csDMARDs. In this group of patients, 18 were occult carriers and 2 were inactive carriers. The prophylactic antiviral treatment was continued in all patients in whom it was already ongoing (3 occult carriers and 1 inactive carrier) in those switching to TNF blockers or swapping to tocilizumab for all the time of exposure to the new biologic treatment and/or 6 months after treatment discontinuation. In 1 occult carrier who switched to rituximab, the prophylactic antiviral treatment with lamivudine was started at the moment of changing therapy.

DISCUSSION

Our report supports a favorable safety profile of abatacept in RA patients with positive HBV infection serology, either managed with HBV prophylaxis or treatment and without. To the best of our knowledge this is the first long-term, retrospective multicenter observational case series of patients concerning the use of abatacept in a "real-life" setting of RA patients with serologic evidence of past or present HBV infection.

The prevalence of hepatitis varies widely, but even in areas with low endemic levels it is essential to identify RA patients who are or have been infected with HBV, because present or past infection can have a considerable impact on morbidity and clinical outcomes (1). This is particularly true in the case of candidates for immunosuppressive treatment (5,29,30), which may increase viral load or lead to viral reactivation in patients with undiagnosed viral hepatitis (10,13,14).

Reactivation of HBV, even in occult carriers, is one of the emerging problems in RA patients undergoing immunosuppressive treatment, especially with old and newer bDMARDs (17). There have been reports about HBV reactivation in patients with a history of occult HBV infection (i.e., negative for HBsAg but positive for antibody anti-HBc and/or antibody to HBsAg) receiving immunosuppressive therapy and/or chemotherapy for autoimmune diseases, organ transplantation, or malignancy (2–18).

The management strategy of RA patients with a history of HBV infection receiving csDMARDs or bDMARDs is a still debated issue. Data from literature are conflicting. To date, no formal guidelines exist regarding screening, monitoring, and management in the field of rheumatology. Different scientific societies, in the fields of rheumatology, virology, and hepatology, have identified this focus as a substantial concern and each has provided their own recommendations (14,28–39).

The management varies according to immunosuppressive agent and HBV infection profile (chronic carrier or serologic sequelae of hepatitis B). If HBV infection is active or re-activated, in either case antiviral therapy must be initiated promptly, as soon as HBV DNA becomes detectable. Concomitant immunosuppressive treatment must be delayed or withdrawn.

The European League Against Rheumatism recommendations contraindicate each treatment with biologic drugs in patients with untreated chronic hepatitis B or with treated chronic hepatitis B with Child-Pugh class B or higher and advocate vaccination against hepatitis B in all patients (38,39).

Abatacept is a soluble fusion protein that binds the CTLA-4 extracellular domain to the Fc region of the IgG molecule. CTLA-4 is an inhibitory T cell receptor, with a molecular structure similar to CD28, expressed by activated and regulatory T cells (Tregs). CTLA-4 is constitutively expressed on CD4+ CD25+ Tregs, and such expression is important for Treg-mediated suppression of T cell proliferation (19). Through the inhibition of the co-stimulatory signaling of T cells in RA, abatacept has demonstrated clinical efficacy. It is well known that the outcome of HBV infection varies, depending on the efficiency of the immune response, a process that is regulated by a number of molecules, including CTLA-4 (13). However, the role of CTLA-4 in the pathogenesis of liver damage and hepatitis B replication is still unknown: single-nucleotide polymorphisms in the CTLA-4 gene may be associated with HBV progression and viral persistence, especially in the Asian population (40). There is also evidence that CTLA-4 blockade could form one arm of a therapeutic approach to modulate the different patterns of co-regulation of T cell exhaustion in this heterogeneous disease (41). Finally, in a case–control study, inactive carriers showed a higher increased inhibitory co-stimulation than subjects with chronic active hepatitis (42).

Abatacept has only been associated with the reactivation of HBV infection in the few case reports mentioned above (22–25). In a retrospective analysis of 8 patients with RA and chronic hepatitis B (6 inactive carriers and 2

chronic active hepatitis B) treated with abatacept, the drug was shown to be safe in only 4 patients who were treated with antiviral prophylaxis (22). RA improved in these patients, as evidenced by a statistically significant decrease in DAS28 scores, and none of the patients had reactivation of hepatitis B. In the remaining 4 patients without antiviral prophylaxis, there was no significant decrease in the DAS28 scores and all of them experienced reactivation of hepatitis B. Two other case reports described hepatitis B reactivation following treatment with abatacept for RA. In one case the patient was an occult carrier with a previous history of long-term treatment with glucocorticoids, csDMARDs, and an anti-TNF agent. The HBV reactivation occurred after 9 months of treatment with abatacept associated with glucocorticoids and leflunomide, without antiviral prophylaxis (23). The other case was an occult carrier with a 2-year history of RA treated with csDMARDs for 1 year. The HBV reactivation occurred after 10 months of treatment with abatacept without antiviral prophylaxis (24).

In a recent Italian case series of 9 RA patients treated with abatacept (8 with resolved HBV infection and 1 chronic inactive carrier), 1 patient with chronic co-infection HCV started lamivudine for LFT elevation occurring 2 months after abatacept initiation, with a gradual improvement of laboratory levels along with persistently undetectable viral load, while 1 HBsAg-negative patient not receiving antiviral prophylaxis developed HBV DNA positivity without aminotransferase elevation at 12 months after starting abatacept (25).

There are no specific indications for management of HBV infection in abatacept-treated patients. Recently, some interesting recommendations for screening and treatment of HBV infection in anti-TNF– and rituximab-treated patients were proposed by Italian experts (43,44). The authors advised the need for HBV infection screening before starting anti-TNF therapy, as well as early treatment with nucleoside/nucleotide analogs and lamivudine prophylaxis in HBV active and inactive carriers. Occult carriers (anti-HBc–positive/HBsAg-negative patients) who have to undergo TNF inhibitors do not need prophylaxis, but a tight control is advised (HBsAg tests repeated every 3 months) in order to identify HBV reactivation and to start antiviral therapy as soon as possible (43). In the case of treatment with rituximab in occult patients, prophylaxis with lamivudine is recommended for those with oncohematologic diseases, whereas watchful monitoring of HBsAg/HBV DNA levels is advisable for all the other indications (44).

In our long-term, retrospective multicenter case series of 72 patients treated with abatacept in a "real-life" setting, we provide encouraging data about safety in RA patients with concomitant HBV-positive serology without universal antiviral prophylaxis. No reactivation of hepatitis B was observed in 47 inactive carriers and in 21 occult carriers treated with abatacept for, respectively, 15.8 and 16.2 person-years without lamivudine prophylaxis. On the basis of these observations, but taking into account a prudent risk stratification, it could be reasonable to set the management of patients with RA and HBV serology, who are candidates for treatment with abatacept, according to what has been previously proposed by the Italian experts for anti-TNF (43,44): 1) treatment with nucleoside/nucleotide analogs in patients with evidence of active hepatitis, 2) lamivudine prophylaxis in inactive carriers before starting abatacept, and 3) tight surveillance for the occult carrier. However, taking into account the results of this study, cost effectiveness of lamivudine prophylaxis in inactive carriers could be assessed after a careful risk stratification. More prospective data and shared expert opinion are needed to confirm these preliminary results.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Padovan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Padovan, Govoni.

Acquisition of data. Padovan, Filippini, Lanciano, Bruschi, Epis, Garau, Celletti, Giani, Tomietto, Atzeni, Zuliani, Govoni.

Analysis and interpretation of data. Padovan, Filippini, Tincani, Lanciano, Bruschi, Epis, Garau, Mathieu, Celletti, Giani, Tomietto, Atzeni, Puttini, Zuliani, de Vita, Trotta, Grilli, Puoti, Govoni.

REFERENCES

1. World Health Organization. Hepatitis B fact sheet 2014. URL: http://www.who.int/mediacentre/factsheets/fs204/en/index.html.
2. Charpin C, Guis S, Colson P, Borentain P, Mattei JP, Alcaraz P, et al. Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: results from a cohort of 21 patients. Arthritis Res Ther 2009;11:R179.
3. Caporali R, Bobbio-Pallavicini F, Atzeni F, Sakellariou G, Caprioli M, Montecucco C, et al. Safety of tumor necrosis factor α blockers in hepatitis B virus occult carriers (hepatitis B surface antigen negative/anti–hepatitis B core antigen positive) with rheumatic diseases. Arthritis Care Res (Hoboken) 2010;62:749–54.
4. Perez-Alvarez R, Diaz-Lagares C, Garcia-Hernandez F, Lopez-Roses L, Brito-Zeron P, Perez-de-Lis M, et al. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. Medicine (Baltimore) 2011;90:359–71.
5. Urata Y, Uesato R, Tanaka D, Kowatari K, Nitobe T, Nakamura Y, et al. Prevalence of reactivation of hepatitis B virus replication in rheumatoid arthritis patients. Mod Rheumatol 2011;21:16–23.
6. Tamori A, Koike T, Goto H, Wakitani S, Tada M, Morikawa H, et al. Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. J Gastroenterol 2011;46:556–64.
7. Kato M, Atsumi T, Kurita T, Odani T, Fujieda Y, Otomo K, et al. Hepatitis B virus reactivation by immunosuppressive therapy in patients with autoimmune diseases: risk analysis in hepatitis B surface antigen negative cases. J Rheumatol 2011;38:2209–14.
8. Marignani M, Gigante E, Begini P, Marzano A, di Fonzo M, Deli I, et al. Patients with hematological malignancies and serological signs of prior resolved hepatitis B. World J Gastrointest Oncol 2012;4:37–45.
9. Lee YH, Bae SC, Song GG. Hepatitis B virus (HBV) reactivation in rheumatic patients with hepatitis core antigen (HBV occult carriers) undergoing anti-tumor necrosis factor therapy. Clin Exp Rheumatol 2013;31:118–21.
10. Cantini F, Boccia S, Goletti D, Iannone F, Leoncini E, Panic N, et al. HBV reactivation in patients treated with antitumor necrosis factor-α (TNF-α) agents for rheumatic and dermato-

logic conditions: a systematic review and meta-analysis. Int J Rheumatol 2014;2014:926836.
11. Biondo MI, Germano V, Pietrosanti M, Canzoni M, Marignani M, Stroffolini T, et al. Lack of hepatitis B virus reactivation after anti-tumour necrosis factor treatment in potential occult carriers with chronic inflammatory arthropathies. Eur J Intern Med 2014;25:482–4.
12. Tsutsumi Y, Yamamoto Y, Shimono J, Ohhigashi H, Teshima T. Hepatitis B virus reactivation with rituximab-containing regimen. World J Hepatol 2013;5:612–20.
13. Shouval D, Shibolet O. Immunosuppression and HBV reactivation. Semin Liver Dis 2013;33:167–77.
14. Lunel-Fabiani F, Masson C, Ducancelle A. Systemic diseases and biotherapies: understanding, evaluating, and preventing the risk of hepatitis B reactivation. Joint Bone Spine 2014;81:478–84.
15. Tsutsumi Y, Ogasawara R, Kamihara Y, Ito S, Yamamoto Y, Tanaka J, et al. Rituximab administration and reactivation of HBV. Hepat Res Treat 2010;2010:182067.
16. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, MacDonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011;2:CD008794.
17. De Nard F, Todoerti M, Grosso G, Monti S, Breda S, Rossi S, et al. Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologic treatment: extending perspective from old to newer drugs. World J Hepatol 2015; 7:344–61.
18. Droz N, Gilardin L, Cacoub P, Berenbaum F, Wendling D, Godeau B, et al. Kinetic profiles and management of hepatitis B virus reactivation in patients with immune-mediated inflammatory diseases. Arthritis Care Res (Hoboken) 2013; 65:1504–14.
19. Davis PM, Nadler SG, Stetsko DK, Suchard SJ. Abatacept modulates human dendritic cell-stimulated T-cell proliferation and effector function independent of IDO induction. Clin Immunol 2008;126:38–47.
20. Thio CL, Mosbruger TL, Kaslow RA, Karp CL, Strathdee SA, Vlahov D, et al. Cytotoxic T-lymphocyte antigen 4 gene and recovery from hepatitis B virus infection. J Virol 2004;78: 11258–62.
21. Carroll MB. The impact of biologic response modifiers on hepatitis B virus infection. Expert Opin Biol Ther 2011;11: 533–44.
22. Kim PS, Ho GY, Prete PE, Furst DE. Safety and efficacy of abatacept in eight rheumatoid arthritis patients with chronic hepatitis B. Arthritis Care Res (Hoboken) 2012;64:1265–8.
23. Germanidis G, Hytiroglou P, Zakalka M, Settas L. Reactivation of occult hepatitis B virus infection, following treatment of refractory rheumatoid arthritis with abatacept. J Hepatol 2012; 56:1420–1.
24. Fanouriakis A, Vassilopoulos D, Repa A, Boumpas DT, Sidiropoulos P. Hepatitis B reactivation following treatment with abatacept in a patient with past hepatitis B virus infection. Rheumatology (Oxford) 2014;53:195–6.
25. De Nard F, Todoerti M, Grosso V, Rossi S, Caporali R, Montecucco C. Safety of the newer biological DMARDs, tocilizumab and abatacept, in rheumatoid arthritis patients with a history of HBV infection: a real life experience. Proceedings of the European League Against Rheumatism Congress; 2014 June 11–14; Paris, France.
26. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
27. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38: 44–8.
28. EASL Clinical Practice Guidelines. Management of chronic hepatitis B. J Hepatol 2012;57:167–85.
29. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008;57:1–20.
30. Winthrop KL, Calabrese LH. Let the fog be lifted: screening for hepatitis B virus before biological therapy. Ann Rheum Dis 2011;70:1701–3.
31. Pham T, Bachelez H, Berthelot JM, Blacher J, Bouhnik Y, Claudepierre P, et al. TNFα antagonist therapy and safety monitoring. Joint Bone Spine 2011;78:15–185.
32. Giemza A, Olesinska M, Swierkocka K, Szewczyk E, Haladyj E. Treatment of rheumatic diseases and hepatitis B virus coinfection. Rheumatol Int 2015;35:385–92.
33. Pham T, Bachelez H, Berthelot JM, Blacher J, Claudepierre P, Constantin A, et al. Abatacept therapy and safety management. Joint Bone Spine 2012;79:3–84.
34. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59:762–84.
35. Rahier JF. Prevention and management of infectious complications in IBD. Dig Dis 2012;30:408–14.
36. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. Hepatology 2009;49:2087–97.
37. Furst DE, Keystone EC, So AK, Braun J, Breedveld FC, Burmester GR, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. Ann Rheum Dis 2013;72 Suppl 2:ii2–34.
38. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2013;0:1–18.
39. Van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 2011;70:414–22.
40. Xu H, Zhao M, He J, Chen Z. Association between cytotoxic T-lymphocyte associated protein 4 gene +49 A/G polymorphism and chronic infection with hepatitis B virus: a meta-analysis. J Int Med Res 2013;41:559–67.
41. Schurich A, Khanna P, Lopes AR, Han KJ, Peppa D, Micco L, et al. Role of the coinhibitory receptor cytotoxic T lymphocyte antigen-4 on apoptosis-Prone CD8 T cells in persistent hepatitis B virus infection. Hepatology 2011;53:1494–503.
42. Zhong B, Huang MP, Yin GQ, Gao X. Effects of costimulation on intrahepatic immunopathogenesis in patients with chronic HBV infection. Inflamm Res 2014;63:217–29.
43. Vigano M, Degasperi E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patients with hepatitis B or C virus infection: safety and clinical management. Expert Opin Biol Ther 2012;12:193–207.
44. Vigano M, Mangia G, Lampertico P. Management of patients with overt or resolved hepatitis B virus infection undergoing rituximab therapy. Expert Opin Biol Ther 2014;14:1019–31.