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SAFETY OF ABATACEPT IN RHEUMATOID ARTHRITIS WITH SEROLOGICAL EVIDENCE OF PAST OR PRESENT HEPATITIS B VIRUS INFECTION

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List of abbreviations (in order of appearance)

hepatitis B virus (HBV)

rheumatoid arthritis (RA)

conventional syntetic disease-modifying anti-rheumatic drugs (csDMARDs)

biologic disease-modifying anti-rheumatic drugs (bDMARDs)

tumor necrosis factor alpha (TNFα)

cytotoxic T-lymphocyte antigen-4 (CTLA-4)

American College of Rheumatology (ACR)

disease activity score including 28 joint count (DAS28)

rheumatoid factor (RF)

anti-cyclic citrullinated protein antibody (ACPA)

liver function tests (LFT)

alanine aminotransferase (ALT)

aspartate aminotransferase (AST)

european association for the study of the liver (EASL)

adverse events (AE)

standard deviation (SD)

The European League Against Rheumatism (EULAR)

regulatory T cells (Tregs)

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Key words

rheumatoid arthritis, disease-modifying anti-rheumatic drugs (DMARDs), infection, abatacept, hepatitis B, HBV reactivation, safety

Conflict of Interest

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ABSTRACT

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 concerning the HBV reactivation following treatment with abatacept coming from anecdotal case reports. This observational retrospective study was aimed to assess the safety profile of abatacept in this particular clinical setting.

Methods. Eleven Italian rheumatologic centres provided data from patients with RA and positive HBV serology treated with intravenously abatacept. HBV markers, clinical and laboratory data were checked at follow up visits every 3 months.

Results. In total 72 patients were included in the study, 47 inactive carrier, 21 occult carries 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. 13 patients received prophylaxis with lamivudine and 4 treatment with

adefovir or tenofovir. At the end of 24 months period of follow up, 49 patients were being treated. Data from 316 follow up 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 follow up or adverse events not related to HBV infection.

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

Significance and Innovation

1. 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.

2. This manuscript 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 rheumatoid arthritis and HBV infection (with and without antiviral prophylaxis) in a 24 months follow up period. No patients experienced HBV reactivation.

Text Manuscript

Introduction

Hepatitis B virus (HBV) can cause chronic disease in 5% of immunocompetent adults with a worldwide prevalence of more than 350 million persons. It is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma, accounting 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 anti-rheumatic drugs (csDMARDs) could be associated with increased hepatotoxicity and biologic DMARDs (bDMARDs), in particular TNF-alfa blockers and anti-CD20 monoclonal antibodies but also 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 cytotoxic T-lymphocyte antigen-4 (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 co-stimulatory activation of T cells involved in RA pathogenesis 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, multicentre, retrospective observational study was to verify the safety of abatacept in a group of RA Italian patients with serological evidence of past or present HBV infection in a “real life” setting.

Methods and Materials

Eleven rheumatologic centres from different geographical areas of Italy were invited to participate providing retrospective data about patients fulfilling the 1987 revised criteria of the American College of Rheumatology (ACR) for RA [26] and HBV positive serology treated with abatacept. 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 data, disease duration, comorbidities, concomitant drugs, previous csDMARDs and bDMARDs, disease activity score (DAS28) [27], rheumatoid factor (RF) and anti-cyclic citrullinated protein antibody (ACPA) status, liver function tests (LFT) measured by alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (U/L), serological B hepatitis markers (HbsAg, HbsAb, anti-Hbe, HbcAb, HBV DNA (IU/mL) and HCV co-infection markers (anti-hepatitis C antibodies, HCV RNA). Antibody levels were determined using commercial immunoassays tests commonly used in each study centre. The most common was Abbott Architect system, Abbott Diagnostics, Ireland and Wiesbanden. Serum HBV-DNA was measured by polymerase chain reaction assay, by using different commercial kits in each study centre. The most commonly used were: 1) COBAS Amplicor HBV Monitor Test v2.0 Roche Diagnostics, Mannheim, Germany, with a lower limit of quantification of 71 IU/mL; 2) COBAS TaqMan HBV Test v2.0 Roche Molecular Systems, Inc., Branchburg, NJ, USA, with a lower limit of quantification of 12 IU/mL; 3) COBAS TaqMan HBV, CTM HBV test, Roche Diagnostics, Meylan, France, with a lower limit of quantification of 12 IU/mL; 4) Abbott Real Time HBV, Abbott m2000 with a lower limit of quantification of 4 UI/ml.

Follow up data were checked every 3 months for up to 24 months and included DAS28 scores, HBV markers (HbsAg, HbsAb, anti-Hbe, HbcAb, HBV DNA), LFT, antiviral therapy or prophylaxis ; all adverse events (AE) were recorded too. Abatacept was administered

intravenously accordingly to the approved manifactured schedules in agreement with standard of care, every 2 weeks for the first month and then monthly.

Following European Association for the Study of the Liver (EASL) 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 >2000 IU/mL, persistently or intermittently high LFT, HBeAg or anti-HBe positivity. Status of inactive carrier was defined as having persistent HBsAg positivity, anti-HBe positivity, HBV DNA levels <2000 IU/mL and normal LFT. Occult HBV carriers were defined as HBsAg negativity in serum with HBcAb reactivity or anti HBs reactivity in patients that did not received vaccination for HBV, with normal LFT and undetectable or low HBV DNA levels (below the sensitivity cut off of current assay).

A reactivation in a chronic carrier was defined as a switch to chronic hepatitis status; in an occult carrier the definition included also HBsAg seroconversion on follow up.

The qualitative variables were expressed as percentages of positivity; the quantitative variables were expressed as mean values ± standard deviation (SD).

Results

Demographic and clinical data of the patients are summarized in Table 1. Seventy-two patients (10 male and 62 female) mean age 62.6 (range 33-84), mean disease duration 12 ± 5 yrs with active disease (DAS28 = 6.44 ± 1.5 SD) were included. Before abatacept treatment, 45.8% had been previously treated with 2 bDMARDs, 19.4% with 3 and 23.6% with one. 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 hydroxicloroquine 8.3%), associated with low dose (≤ 7.5 mg/day prednisone equivalent) glucocorticosteroids (80.6%) or glucocorticosteroids 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 carries (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 titres >2000 IU/mL (range 12.000 IU/ml – 55.000 IU/ml). Thirteen patients (18%) received antiviral prophylaxis with lamivudine (9/47 inactive carriers and 4/21 occult carriers). The majority of inactive and occult carrier patients were treated with abatacept without antiviral prophylaxis. In all cases a tight lab and clinical control, in collaboration with the infectivologist, has been set in order to identify HBV reactivation and to promptly start antiviral therapy. Due to the retrospective design of the study, the decision about to start or not antiviral prophylaxis has been taken in each centre on the basis of local expert opinion and risk stratification. In all patients HBV-DNA undetectable and normal LFT were recorded at the baseline visit and at the follow up visits. 4 patients (5.6%) received antiviral treatment, 2 with adefovir and 2 with tenofovir (all of them were chronic hepatitis). No significance differences were observed in LFT, HBVDNA levels concomitant therapy and number of previous DMARDs between inactive carriers with and without lamivudine prophylaxis. Four patients (2 inactive carrier, 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 24 months period of follow up, a total of 316 follow up visits were performed, 49 patients (68%) were still on treatment with abatacept (Table 2), a reduction of DAS28 (average 2.3 ±1.9 SD) has been 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. 13 patients received lamivudine while taking abatacept for all the time and a 24 months follow up was available (13 person/years); 38 inactive carriers and 17 occult carriers received abatacept

without lamivudine prophylaxis corresponding to 32 person/years (respectively 16.2 and 15.8 person/years); 4 chronic active hepatitis patients received abatacept with concomitant antiviral treatment (2 tenofovir and 2 adefovir) for all the time, with a 24 months follow up available (4 person/years). LFT remained normal and HBV serology remained unchanged. In the 4 active carriers HBV DNA titres became undetectable between 4 and 6 month after antiviral treatment and abatacept initiation, remaining within the normal limits throughout the subsequent 18 months follow up. No differences have been observed between patients treated with combination therapy or monotherapy for RA. 5 patients discontinued treatment with abatacept for primary inefficacy, 7 for loss of efficacy, 5 for subject decision/lost at follow up, 6 for AE , none of them related to HBV (chronic infected skin ulcer, post-surgery acute renal failure for hip fracture, suspected demyelinating disease, urinary tract or respiratory recurrent infections) (Table 2).

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

Data were also available in 20 out of 23 patients who discontinued abatacept with no signs of HBV reactivation for up to 27 additional average months of follow up. 6 of them switched to TNF blockers, 6 swapped to tocilizumab, 4 to rituximab and 4 to csDMARDs. In this group of patients 18 were occult carriers and 2 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 treatments discontinuation. In one occult carrier who swapped to rituximab, the

prophylactic antiviral treatment with lamivudine was started at the moment of changing therapy.

Discussion

Our report supports a favourable 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 serological 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 carrier, is one of the emerging problems in RA patients with 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 been indentified this focus as a substantial concern and each of them has provided their own recommendations [14, 28-39].

The management varies according to immunosuppressive agent and HBV infection profile (chronic carrier or serological sequelae of hepatitis B). When HBV infection is active or re-activated, anyhow, 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 (EULAR) recommendations contraindicate each treatment with biologic drug 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 which 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 rheumatoid arthritis, 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: SNPs in the CTLA-4 gene may be associated with HBV progression and viral persistence, especially in the Asian population [40]; there are also evidences 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 resulted safe only in 4 patients who were treated with antiviral prophylaxis [22]. In these patients RA improved as evidenced by a statistically significant decrease in DAS28 scores, and none 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. Others two case reports described hepatitis B reactivation following treatment with abatacept for RA. In a case the patient was an occult carrier with a previous history of long term treatment with glucocorticosteroids, csDMARDs and anti-TNFα agent. The HBV reactivation occurred after 9 months of treatment with abatacept associated with glucocorticosteroids 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 prophilaxis [24].

In a recent Italian case series of 9 RA patients treated with abatacept (8 with resolved HBV infection and 1 chronic inactive carrier), one patient with chronic co-infection HCV started lamivudine for liver function tests elevation occurring 2 months after abatacept initiation, with a gradual improvement of lab levels along with persistently undetectable viral load, whilst 1 patient HbsAg negative 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-TNFα- and rituximab-treated patients were proposed by Italian experts [43-44]. The authors advised the need for HBV infection screening before starting anti-TNFα therapy as well as early treatment with nucleoside/nucleotide analogues and lamivudine

prophylaxis in HBV active and inactive carriers. Occult carriers (Anti-HBc positive/HBsAg negative patients) who have to undergo TNFα 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 onco-hematological 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 provides encouraging data about safety in RA patients with concomitant HBV positive serology also 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 candidate for treatment with abatacept, accordingly to what has been previously proposed by the Italian experts for anti-TNFα [43,44]: a) treatment with nucleoside/nucleotide analogues in patients with evidence of active hepatitis; b) lamivudine prophylaxis in inactive carriers before starting abatacept; c) tight surveillance for 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 experts opinion are needed to confirm these preliminary results.

References

[1] WHO, “Hepatitis B,” Fact Sheet 204, 2014, http: //www.who.int/mediacentre/factsheets fs204 /en/index.html.

[2] Charpin C, Guis S, Colson P, Borentain P, Mattéi JP, Alcaraz P, et al. Safety of TNFblocking 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 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 2010; 62:749–54.

[4] Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-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; 46:556–564.

[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: 2209–2214.

[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-Alpha (TNF-α) Agents for Rheumatic and Dermatologic 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. European Journal of Internal Medicine 2014; 25: 482–484

[12] Tsutsumi Y, Yamamoto Y, Shimono J, Ohhigashi H, Teshima T. Hepatitis B virus reactivation with rituximab-containing regimen. World J Hepatol. 2013 Nov 27; 5(11):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 Dec; 81(6):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 of Systematic Reviews 2011, Issue 2. Art. No.: 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 March 27; 7(3): 344-361.

[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: 1504-1514 [PMID: 23436730 DOI: 10.1002/acr.21990]

[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; 78:11258–11262

[21] Carroll MB. The impact of biologic response modifiers on hepatitis B virus infection. Expert Opin Biol Ther 2011; 11:533–544. Erratum in: Expert Opin Biol Ther 2011; 11:825.

[22] Kim P, Ho G, Prete P, Furst D. Safety and efficacy of abatacept in eight rheumatoid arthritis patients with chronic hepatitis B. Arthritis Care & Research 2012; 64:1265–1268.

[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 Jun; 56(6):1420-1421.

[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 Jan; 53(1):195-196.

[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. Ann Rheum Dis 2014; 73: 499 [DOI: 10.1136/annrheumdis2014-eular.5021]

[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;31:315–324.

[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; 38:44–48.

[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; 70:1701–1703

[31] Pham T, Bachelez H, Berthelot JM, et al. TNF alpha antagonist therapy and safety monitoring. Joint Bone Spine 2011; 78:15–85.[8]

[32] Giemza A, Olesin´ska M, S´wierkocka K, Szewczyk E, Haładyj E. Treatment of rheumatic diseases and hepatitis B virus coinfection. Rheumatol Int DOI 10.1007/s00296-014-3195-8

[33] Pham T, Bachelez H, Berthelot JM, et al. Abatacept therapy and safety manage-ment. Joint Bone Spine 2012; 79:3–84.

[34] Saag KG, Teng GG, Patkar NM, 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. DigDis 2012; 30:408–14.[47]

[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, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2012. Ann Rheum Dis2013; 72:ii2–34.

[38] Smolen JS, Landewé 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 M F, Dougados M et al. EULAR recommendations for vaccination in adult patients with autoimmune infl ammatory rheumatic diseases. Ann Rheum Dis 2011; 70:414–422.

[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 Jun; 41(3):559-67.

[41] Schurich A, Khanna P, Lopes AR, Han KJ, Peppa D, Micco L, Nebbia G, Kennedy PT, Geretti AM, Dusheiko G, Maini MK. Role of the coinhibitory receptor cytotoxic T lymphocyte antigen-4 on apoptosis-Prone CD8 T cells in persistent hepatitis B virus infection. Hepatology. 2011 May; 53(5):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. 2014Mar; 63(3):217-29.

[43] Viganò M, Degasperi E, Aghemo A, Lampertico P, Colombo M. Anti-TNF drugs in patientswith hepatitis B or C virus infection: safety and clinical management. Expert Opin Biol Ther 2012; 12:193–207.

[44] Viganò M, Mangia G, Lampertico P. Management of patients with overt or resolved epatitis B virus infection undergoing rituximab therapy. Expert Opin Biol Ther 2014; 14:1019-31.

Tables

Table 1. Baseline characteristics				
	All	**Inactive carrier**	**Occult carrier**	**Choronic active hepatitis**
Demographic and clinical data	**N (%)**	**N (%)**	**N (%)**	**N (%)**
N° Patients	72	47 (65.3)	21 (29.1)	4 (5.6)
F:M	62:10	26:21	11:10	2:2
Mean age (ys)	62.6 (range 33-84)	62.8	62.3	62.6
Mean disease duration (ys)	12 ± 5	15 ± 2	12 ± 5	11 ± 3
DAS28	6.44 ± 1.5	6.2 ± 1.5	6.6 ± 1.2	6.4 ± 1.4
N° RF positive (%)	53 (73.6)	34 (72.3)	16 (76.1)	3 (75)
N° ACPA positive (%)	51 (70.8)	33 (70.2)	15 (71.4)	3 (75)
2 previous bDMARDs (%)	33 (45.1)	21 (44.6)	10 (47.6)	2 (50)
3 previous bDMARDs (%)	14 (19.4)	9 (19.1)	4 (19)	1 (25)
1 prior bDMARD (%)	17 (23.6)	11 (23.4)	5 (23.8)	1 (25)
No prior bDMARDs (%)	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 to csDMARDs	58 (80.6)	40 (85.1)	18 (85.7)	0
HBV viral load				
HBV-DNA > 2000 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

Legend
DAS28: disease activity score; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibodies ; bDMARDs: biologic disease modifying anti-rheumatic drugs ; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; HBV:hepatitis B virus; HCV:hepatitis C virus

Table 2. Follow up data				
	3 months	**6 months**	**12 months**	**24 months**
	No (%)	**No (%)**	**No (%)**	**No (%)**
patients being treated (ongoing)	67 (93)	62 (86.1)	55 (76.3)	49 (68)
Mean DAS28	4.66±1.5	2.4±1.8	2.10 ±1.6	2.3±1.9
HBV reactivation	0	0	0	0
LFT increased	0	0	0	0
abatacept withdrawal	**No (%)**	**No (%)**	**No (%)**	**No (%)**
Primary inefficacy	4 (5.6)		1 (1.4)	
Loss of efficacy		3 (4.1)	1 (1.4)	3(4.1)
AEs (HBV unrelated)		2 (2.7)	1 (1.4)	3 (4.1)
Subject decision/lost at follow up	1 (1.4)		4 (5.6)	

Legend
DAS28: disease activity score; HBV:hepatitis B virus; LFT:liver function tests; AEs: adverse events