Biological therapy in arthritis patients with hepatitis B or C infection: a multicenter retrospective case series

Sultana Abdulaziz, Hussein Halabi, Mohammed A. Omair, Suzan Attar, Abdullah Alghamdi, Mohammed Shabrawishi, Abdulwahab Neyazi, Haneen Alnazzawi, Nuha Meraiani, Hani Almoallim

Abstract

Objective: Reactivation of viral hepatitis B (HBV) and C (HCV) has been reported in various case reports of patients with arthritis on biological therapy. The objective of this study was to describe the clinical characteristics and outcomes of arthritis patients with HBV or HCV treated with biological therapy.

Material and Methods: This is a retrospective case series including all patients above 13 years of age with arthritis patients from four centers in Saudi Arabia with concurrent chronic viral hepatitis infection (HBV or HCV) who received biological agents in the rheumatology clinics during their course of their disease from duration of the disease onset until last outpatient visit up to November 2015. Demographic information, full details about the hepatitis status of each patient, rheumatic disease diagnosis and different therapies used were reviewed.

Results: We identified 10 cases each with HBV and HCV on biological therapy. The mean age in the HBV group was 51 (34–85) years and 80% were females. Eight patients had rheumatoid arthritis (RA), one patient had RA/systemic lupus erythematosus, and one had human immunodeficiency virus related arthritis. Seven were chronic inactive HBsAg carriers and three had chronic active HBV. Nine HBV patients received prophylactic antiviral therapy. Two cases with chronic HBV had reactivation with no elevation of the transaminases.

The mean age in the HCV group was 54 (23–79) years and all were female RA patients. Three had detectable hepatitis C virus-ribonucleic acid (HCV-RNA) before the start of biological therapy. Nine HCV patients received antiviral treatment and seven had a sustained virologic response (SVR) before start of biological treatment. Three patients had detectable HCV-RNA during the course of biological therapy. One of the three was a non-responder and two were relapsers. One of the patients with HCV relapse was started on sofosbuvir plus ribavirin and achieved SVR on follow-up.

Conclusion: We report the successful use of biological therapy in arthritis patients with hepatitis B infection with antiviral therapy with no deterioration of their viral status. Due to the lack of sufficient prospective studies demonstrating the rate of HCV flare on biological therapy, caution should be exercised and careful monitoring with liver enzymes and viral load is mandated in vulnerable HCV RNA patients. Treatment should be individualized by the rheumatologist in collaboration with the hepatologist to minimize complications.

Keywords: Arthritis, hepatitis B, hepatitis C, biologics, biological therapy

Introduction

Biological disease-modifying antirheumatic drugs (b-DMARDs) are considered a potent second-line treatment after the failure of first-line immunosuppressive therapy in several rheumatological, dermatological, and gastroenterological autoimmune diseases. Biological agents consist of proteins and protein fragments derived from living sources, such as humans, animals, or microorganisms (1). Since the introduction in 1999 of tumor necrosis factor (TNF) inhibitors (i.e., anti-TNF)—which demonstrated efficacy and safety in decreasing disease activity, mortality, and morbidity, and improving quality of life (2, 3)—biological agents have continued to gain popularity. To date, the U.S. Federal Drug Administration approved five anti-TNF agents: infliximab (Remicade; Janssen Biotech Inc. [formerly Centocor Biotech, Inc.], USA), adalimumab (Humira; Abbvi, USA); etanercept (Embril; Amgen and Pfizer, USA), golimumab (Simponi; Janssen Biotech, USA), and certolizumab (Cimzia; UCB biopharmaceutical, USA) (3).

However, as with most medications, these biological agents come with a number of reported side effects ranging from minor (e.g., rash, myalgias, fever, and headache) to serious (e.g., worsening heart failure, demyelinating disorders, liver enzyme abnormalities, and increasing susceptibility to infections or reactivation of existing infections) (2, 4, 5). The latter brings a need for complete screening for infections such as tuberculosis, hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus, and herpes virus, as well as prophylactic treatment and an up-to-date immunization status prior to the use of anti-TNF (2, 6). Studies by Toussaint (2), Calabrese (4), and Pompili (6) indicate the possibility of the reactivation of HBV infection during anti-TNF therapy.

Given that viral hepatitis remains endemic in Saudi Arabia (7, 8), statistics of blood donors by Babanejad (9) suggest that the prevalence of HBsAg was found to be 1.5-2.6% in adult populations, and the prevalence rate of anti-HCV in Saudi nationals was estimated by Liakina et al. (10) to be 0.74%. It is not uncommon that
rheumatologists come across patients with arthritis with concomitant HBV or HCV in their daily practice. This study describes our experience with patients with arthritis with concurrent chronic HBV infection in 10 patients and HCV infection in 10 patients who received biological agents in Saudi Arabia.

Material and Methods
Acute HBV infection is defined by the presence of hepatitis B surface antigen (HBsAg), high titers of class-M immune-globulin (IgM) antibodies against the core antigen (i.e., IgM anti-hepatitis B core [HBc]), and abnormal levels of aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]). Chronic HBV infection is defined by the persistence of the virus in the host’s blood circulation for more than six months (HBsAg-positive). However, these virologic conditions may change during immunosuppression (2, 4, 11). The presence of chronic HCV infection is confirmed in patients with anti-HCV antibodies by using more sensitive molecular nucleic acid testing methods like polymerase chain reaction, with which the quality and the quantity of HCV-RNA is calculated (12).

We retrospectively reviewed the medical records of all arthritis patients with HBV or HCV infection who received biological therapy during the course of their disease in four medical centers in Saudi Arabia: King Faisal Specialist Hospital and Research Center, King Fahd Hospital, and King Abdulaziz University Hospital in Jeddah, and King Khalid University Hospital in Riyadh. We reviewed the charts of patients with arthritis and viral hepatitis on biological therapy from time period of their rheumatic disease onset until last outpatient visit up to November 2015. We obtained approval from the institutional ethics review board for the research protocol in all four centers. Being a retrospective study, consent was not obtained from the patients.

We included all patients above 13 years of age with the following features: confirmed clinical diagnosis of autoimmune rheumatic disease by a qualified rheumatologist and confirmed diagnosis of HBV or HCV by serological and molecular methods. HBV reactivation is defined as the reappearance of an active necro-inflammatory disease in a person known to have an inactive HBsAg carrier state or resolved HBV infection. HCV relapse is defined as a reappearance of serum HCV-RNA after end of HCV treatment. We excluded children younger than 13 years of age, hepatitis cases not linked to HBV or HCV, and HCV antibodies positive but HCV-RNA negative patients.

| No | Age | Sex | RA | HBO' Antiviral | Duration of biologics | DMARDs | Duration of DMARDs | Multiple biologics | Follow-up | Antiviral | Multiple | Steroids | Antiviral | Follow-up | Antiviral | Multiple | Steroids |
|----|-----|-----|----|---------------|----------------------|--------|-------------------|------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 1  | 61F | RA  | 300 | ETA           | 60                   | No     | No                | No               | 71        | ND        | No        | MTX       | Yes       | No        | No        | <20       | No        | No        |
| 2  | 34F | RA  | 58  | RIT           | ND                   | No     | No                | No               | 60        | LFV       | ND        | No        | No        | LFV       | ND        | <20       | LFV       | ND        |
| 3  | 85M | RA  | 276 | ADA           | 38                   | ND     | ND                | ND               | 52        | ND        | No        | MTX       | No        | MTX       | ND        | ND        | MTX       | ND        |
| 4  | 64F | RA  | 4.5 million | ETV              | 72                   | ND     | ND                | ND               | 52        | ND        | No        | LFV       | No        | LFV       | ND        | ND        | LFV       | ND        |
| 5  | 54F | RA  | 139 | ADA           | 28                   | ND     | ND                | ND               | 37        | ND        | No        | MTX       | No        | MTX       | ND        | ND        | MTX       | ND        |
| 6  | 51F | RA  | 4.5 million | ETA           | 27                   | ND     | ND                | ND               | 24        | ND        | No        | MTX       | No        | MTX       | ND        | ND        | MTX       | ND        |
| 7  | 52F | RA  | 6726 | ADA           | ND                   | ND     | ND                | ND               | 60        | ND        | No        | MTX       | No        | MTX       | ND        | ND        | MTX       | ND        |
| 8  | 35F | RA  | 216 | ADA           | 27                   | ND     | ND                | ND               | 216       | ND        | No        | MTX       | No        | MTX       | ND        | ND        | MTX       | ND        |

Table 1. Characteristics and Treatment in 10 arthritis patients with Hepatitis B infection on biologic.
From each case, we collected the demographic information of the patient, full details about his/her hepatitis status including type, duration, serological and liver enzymes tests, imaging, and antiviral agents as well as rheumatic disease diagnosis, different therapies used including onset, duration of biological agents and any other medications that the patient received. Each drug-specific index date was defined as a treatment episode (World Health Organization Center for Health Development). Patients given different drug therapies are contributed to more than one treatment episode. Statistical analysis of the collected data was performed with the Statistical Package for Social Science 16 (SPSS Inc.; Chicago, IL, USA). Categorical data parameters were presented as frequencies and percentages, and descriptive statistics were presented as means for quantitative variables.

Results
We identified 20 patients with viral hepatitis and arthritis that were on biological therapy, including 10 patients with HBV infection (Table 1) and 10 patients with HCV infection (Table 2). Among the HBV patients (106), 80% had rheumatoid arthritis (RA), one patient (10%) had RA/systemic lupus erythematosus, and one patient (10%) had human immunodeficiency virus-related arthritis (Table 3). HBV patients (30%) had chronic active hepatitis B with HBV-DNA of >2000 IU/mL and mild elevation of transaminases in one of them.

Antiviral therapies were given to nine (90%) of the HBV patients on biological therapy. Entecavir was given to seven patients, lamivudine followed by entecavir was given to 1 patient, and tenofovir was given to 1 patient. Elevation of transaminases was observed in one patient who was HBsAg-positive, anti-HBs-positive, and had undetectable HBV-DNA.

The majority (80%) of HBV patients received a biological treatment consisting of etanercept (ETA) (8 episodes), adalimumab (ADA) (3 episodes), tocilizumab (TOC) (1 episode), and rituximab (RIT) (1 episode). S-DMARDs were prescribed in all except one (with missing data) and consisted of methotrexate (9 episodes), sulfasalazine (8 episodes), azathioprine (1 episode), and cyclophosphamide (1 episode).
Multiple biologics (n)% 3 (30)
Steroids (n) 9
Cyclophosphamide 1
MMF (n) 1
AZA (n) 1
HCQ (n) 8
SSZ (n) 4
MTX (n) 9

DMARDs (range) months 54 (19–75)
Duration of follow-up (mean) (range) months 40 (11–60)
Reactivation (n)% 2
Duration of follow-up (mean) (range) months 54 (19–75)

Hepatitis B DNA + (n) % 7 (70)
Antiviral therapy (n) % 9 (90)
Elevated transaminases (n) % 2 (13)

Biological therapy
ETA (n) 8
ADA (n) 3
TOC (n) 1
RIT (n) 1

Duration of biological therapy (mean) (range) months 62 (2–72)
Elevation of HCV RNA (n) % 3 (30%)
Duration of follow-up/years (mean) (range) months 54 (36–72)

DMARDs
MTX (n) 7
LEF (n) 2
SSZ (n) 3
HQC (n) 4
GOLD (n) 1
CyA (n) 1
Steroids (n) 6
Multiple Biologics (n) % 5 (50)

Table 3. Results of arthritis patients with HBV and HCV infection on biologics

HBsAg-positive total cases 10 HCV-RNA positive total cases 10

Age (mean) (range) 51 (34–85) Age (mean) (range) 54 (23–79)
Female (n)% 8 (80) Female (n)% 10 (100)
Rheumatic disease Rheumatic Disease
RA (n) % 8 RA (n) % 10 (100)
RA/SLE (n) % 1 Duration of disease (months) 144
HIV-related arthritis (n) % 1 Antiviral therapy (n) % 9 (90)
Duration of disease (months) 130 (43–276) PEG-RIB 9
Hepatitis B DNA + (n) % 7 (70) SOF-RIB 1
Antiviral therapy (n) % 9 (90) Elevated transaminases (n) % 2 (13)
LMV (n) 1 Biological therapy
ETV (n) 8 ETA (n) 4
TFV (n) 1 ADA (n) 4
Elevated transaminases (n) % 2 (13)
Biological therapy
ETA (n) 8 ABA (n) 2
ADA (n) 3 IFX (n) 1
TOC (n) 1
RIT (n) 1

Discussion
Hepatitis B and HCV infections are considered serious worldwide public health problems. According to the World Health Organization (WHO), as of 2010 around 1 million annual deaths occurred due to viral hepatitis infections (13). Abdoo (7) showed that in 2007, viral hepatitis ranked as the second most common viral infection in Saudi Arabia, with around 9,000 newly diagnosed cases reported (52% with HBV, 32% with HCV, and 16% with hepatitis A virus). The WHO (13) has reported that viral hepatitis infections are the leading cause of liver cancer in the world, accounting for 78% of cases. Reactivation of viral hepatitis infection presents a concern associated with the increasing use of biological agents to treat arthritis and other conditions. However, our results showed only two of ten (20%) patients who had persistently mild elevation of HBV at less than 2000 IU/mL that was present even before the start of biological therapy. In both patients, ETA was used as biological therapy. One patient with RA and resolved HBV infection (HBsAg-negative, HBc-antibody-positive and HBs-antibody-positive and undetectable HBV-DNA) treated with TOC was not given antiviral therapy. During follow-up at 27 months, no increase in transaminases or in the viral load was noted in this patient. Three of ten patients in the HCV group (30%), two HCV relapsers, and one patient who did not complete the PEG-INF treatment because of side effects, continued to have normal liver function tests before the start of biological treatment. Three patients had detectable HCV-RNA during the course of biological therapy. One of the three patients was a non-responder, and two patients were relapsers. One of the relapsers received direct acting antiviral treatment (DAAT) in the form of sofosbuvir and RIB and achieved sustained SVR. All patients with SVR and relapsers received biologics. The responders in the HCV group had undetectable HCV-RNA and normal liver transaminases during biological treatments. Also, the relapsers had stable liver function tests and enzymes in spite of persistent elevation of HCV-RNA (Table 3). The biologics used were ETA, ADA, TOC, RIT, abatacept (Orencia; Bristol-Myers Squibb, USA) (ABA), and INF. The duration of the follow-up was 54 (36–72) months. The s-DMARDs used were methotrexate (7 episodes), leflunomide (2 episodes), sulfasalazine (3 episodes), hydroxychloroquine (4 episodes), gold (1 episode), and cyclosporine (1 episode). Steroids were used in six patients. Multiple biologics were used in five of the patients with arthritis in the HCV group.
and enzymes in spite of persistent elevation of HCV-RNA. All three patients were genotype 4, which is the common genotype in Saudi Arabia (14) and has been shown by Sarasin-Filipowicz (15) to be resistant to interferon-based regimens.

The American College of Rheumatology (ACR), the American Gastroenterology Association (AGA) and the American Association for the Study of Liver Diseases (AASLD) recommend that all patients that need biologics and other immunosuppressive therapy should be screened for HBsAg (16-18). If there is evidence of past or present HBV infection, the quantitative HBV-DNA viral load should be determined and prophylactic antiviral therapy should be given. The ACR (16) and AASLD (18) recommend that patients with resolved HBV infection (i.e., HBC-antibody-positive, normal liver function tests, HBC-antibody-positive, and HBsAg-negative) should receive the same biological treatment as unexposed patients as long as the patient's viral load is monitored regularly (i.e., at least every 6–12 months). The AGA classifies immunosuppressive therapy into low-, moderate-, or high-risk groups based on estimates of reactivation and the available evidence (17). Rituximab is categorized in the high-risk group defined by expected incidence of HBV reactivation in >10% of HBsAg-positive/HBC-antibody-positive or HBsAg-negative/HBC-antibody-positive patients. ETN, ADA, certolizumab, IFX, ABA, and ustekinumab are categorized in the moderate-risk group, with an expected incidence of reactivation in 1–10% of patients. The AGA suggests antiviral prophylaxis for patients at moderate risk of reactivation undergoing immunosuppressive drug therapy and biological therapy rather than monitoring and that antivirals should be continued for six months after the cessation of immunosuppressive therapy.

To date, few studies have been carried out in rheumatic disease patients with previous HBV infection treated with anti-TNF (11, 19). A review by Xu et al. (19) of all cases published in the literature up to 2012 identified 25 HBsAg-positive patients suffering from rheumatic disease treated by anti-TNF without antiviral prophylaxis. HBV reactivation occurred in 13 cases, including three cases that resulted in fulminant hepatitis, one death, and one liver transplantation, which may alternatively have been related to Still's disease or an idiopathic drug reaction. In the previous stated study, one patient reported with HBV reactivation after the third infusion of infliximab required drug withdrawal, and the patient was treated with entecavir for three months, which decreased ALT levels to normal (19). However, infliximab is associated with a greater risk of reactivation of HBV in HBsAg-positive patients compared with etanercept or adalimumab. The risk of HBV reactivation in HBsAg-negative/anti-HBc-positive patients is low. In a literature review, Vignani (20) showed a total of 214 patients suffering from rheumatological disorders or IBD with HBsAg-negative/HBC-antibody-positive carriers were treated with IFX, ETN, and ADA. In only three cases with reported HBV reactivation followed by a hepatitis flare-up, the drug was withdrawn and antiviral medication started. The currently recommended protocol includes prophylaxis with lamivudine of all inactive carriers (HBsAg negative HBC antibody positive patients) during therapy and for 6–12 months following therapy with TNF-a inhibitors and quarterly monitoring of HBsAg (2, 18). A prospective study by Caporali et al. (21) of fewer than 100 patients with occult HBV infection (HBC-antibody-positive without HBsAg) showed no HBV reactivation with anti-TNF therapy. Reactivation of occult HBV infection has been observed in patients treated with RTX by Gigi et al. (22) and ABA by De Nard et al. (23). Several other studies reported reactivation in both rheumatic and non-rheumatic patients by biological therapy (24-30).

In the context of HCV infection, the risk of flare-up during anti-TNF treatment is controversial. In a comprehensive literature review conducted by Pompili et al. (6) between January 2000 and August 2013, a total of 216 patients with HCV were observed for a cumulative total of 260 patients / years of anti-TNF treatment. Only three cases of drug withdrawal due to suspected worsening of HCV liver were reported. Short-term use of anti-TNF appears safe, but insufficient long-term safety data exist. The authors studied 153 patients on etanercept observed for a median duration of 1.14 years. Three cases showed elevation of ALT/AST, five cases reported elevation of HCV-RNA, and two cases withdrew the drug due to toxicity. Forty patients were on infliximab, including two reported cases with elevation of AST/ALT and four cases with elevation of HCV-RNA. One of those patients withdrew drug therapy due to liver toxicity. The last group of 23 patients was on ADA with no complications (6).

With the availability of highly effective antiviral treatments for HCV, rheumatologists should collaborate with the hepatologists to determine if the patient is a candidate for antiviral treatment. The EASL and the AASLD-IDSA recommend that the new interferon-free regimes of HCV with direct- acting antiviral therapy have minimal toxicity and side effects, with reported cure rates of 95–100% in all HCV genotypes (12, 31). Biologics such as anti-TNF and RTX have been usefully employed without significant side effects in HCV-RNA-positive RA patients (32-34). The limitations of this study include the retrospective nature of the study and the small number of patients due to the rarity of patients diagnosed with arthritis and hepatitis B/C infection requiring biologic therapy. Well-designed prospective studies are required to confirm the safety of biological therapy in this subset of patients.

In conclusion, patients with arthritis with concomitant HBV or HCV infections commonly present to rheumatologists. Given the risk of reactivation or relapse during or after the use of biological treatment, screenings should be undertaken for all patients. Patients with active HBV infections as well as chronic inactive carriers should be monitored regularly and prophylactic antiviral therapy started. Due to the lack of sufficient prospective studies demonstrating the rate of HCV flare-up on biological therapy, caution should be exercised and careful monitoring of liver enzymes and viral load is mandated in vulnerable HCV-RNA patients. However, the risk of HCV relapse does not preclude the use of biologics. The new directly DAAT may be more effective in reaching SVR of HCV-RNA in all genotypes. Treatment of the complex combination of rheumatic disease and viral hepatitis should be individualized by rheumatologists in collaboration with hepatologists to minimize mortality and morbidity.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of medical research studies department, Directorate of health affairs, Jeddah, Saudi Arabia.

Informed Consent: Written informed consent was not obtained due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.


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References
