EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2017.17003

Original Article

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

Sultana Abdulaziz[1], Hussein Halabi[2], Mohammed A. Omair[3], Suzan Attar[4], Abdullah Alghamdi[5], Mohammed Shabrawishi[2], Abdulwahab Neyazi[6], Haneen Alnazzawi[6], Nuha Meraiani[2], Hani Almoallim[6,7,8]

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-ribonuecleic 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 detoriation 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

Cite this article as: Abdulaziz S, Halabi H, Omair MA, Attar S, Alghamdi A, Shabrawishi M. Biological therapy in arthritis patients with hepatitis B or C infection: a multicenter retrospective case series. Eur J Rheumatol 2017; 4: 194-9.

[1] Unit of Rheumatology, Department of Medicine, King Fahd Hospital, Jeddah, Saudi Arabia
[2] Department of Medicine, King Faisal Specialist Hospital, Jeddah, Saudi Arabia
[3] Division of Rheumatology, Department of Medicine, King Saud University College of Medicine, Riyadh, Saudi Arabia
[4] Department of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[5] Unit of Gastroenterology, Department of Medicine, King Fahd Hospital, Jeddah, Saudi Arabia
[6] Department of Medicine, Umm Alqura University School of Medicine, Makkah, Saudi Arabia
[7] Department of Medicine, Dr. Soliman Fakeeh Hospital, Jeddah, Saudi Arabia
[8] Alzaidi Chair of Research Diseases, Umm Alqura University School of Medicine, Makkah, Saudi Arabia

Address for Correspondence: Sultana Abdulaziz, Unit of Rheumatology, Department of Medicine, King Fahd Hospital, Jeddah, Saudi Arabia

E-mail: drsabdulaziz@yahoo.com

Submitted: 2 January 2017
Accepted: 10 April 2017

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 (Humaira; 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 arthriris 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.

Table 1. Characteristics and treatment in 10 arthritis patients with Hepatitis B infection on biologics

No	Age /Sex	Rheumatic Disease	Duration (Months)	HBsAg	HBV markers (BL)	HBV DNA (BL) IU/ML	ALT,AST (BL)	HBV DNA before treatment	B-DMARD	Duration of biologics months	HBO' A ntiviral	Duration of Antiviral (Months)	HB \ DNA followup	HBVr	Follow-up months	DMARDS	Steroids	Multiple biologics
1	61/F	RA	300		HBsAg HBcAb HBeAb	3298	Normal	ND	ETA	60	ETV	72	3969	Yes	71	MTX HCQ	Yes	No
2	34/F	RA SLE	58		HBsAg HBcAb HBeAb	ND	Normal	ND	RIT	60	LMV ETV	>30 28	ND	No	60	SSZ HCQ MME	Yes	No
3	85/M	RA	276		HBsAg	26	Normal	NE ETA	ADA 16	38	ETV	52	ND	No	53	MTx HCQ	Yes	Yes
4	641E	HIV related arthritis	52		1-1BsAg HBcAb HBeAb	4.5 million	ALT 139 AST 175	ND	ETA ADA	11 43	TFV	72	ND	No	75	HCQ	Yes	Yes
5	64.P	RA	51		IffisAb HBcAb	ND	Normal	ND	ADA ETA	9 28	ETV	37	ND	No	51	MD:	Yes	Yes
6	51/F	BA	43		HBeAb HBcAb	NE	Normal	NE	TOC	27	NO	NF	NF	No	27	MTh HCQ	Yes	No
7	52'M		108		HBsAg HBeAb	380	Normal	NE	ETA	14	ETV	24	20 113	No	48	HCQ SSZ	NF	No
8	54/F	RA	144		HBsAg	15	Normal	ND	ETA	60	ETV	60	NF	No	60	HCQ MTX	Yes	No
9	42'F	RA	48		HBsAg	6726	Normal	NE	ETA	11	ETV	60	6653	Yes	72	NE	NF	No
10	35/F	RA	216		HBsAg HBeAb	467	Normal	NE	ETA	19	ETV	14	<20	NO	19	MTX	Yes	No

F: female; M: male; BL: baseline; Ast: aspartate transaminases; Alt: alanine transaminases; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; ND: not detected; NF: not found; ETN: etanercept; INF: infliimab; RTX: rithiximab; ADA: adalimumab; ABA: abatacept; TOC: toclizumab; LMV: lamivudine; EVT: entecavir; TFV: tenofovir; LEF: leflunomide; MTX: methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine; AZA: azathioprine; CyA: cyclosporine; DMARD: disease-modifying antirheumatic drug; B-DMARD: biological disease-modifying antirheumatic drug; HBV: HBV reaction

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 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). In the HBV infection group (Table 2), the mean age was 51 (34-85) years and 80% were females. Eight (80%) HBV patients had rheumatoid arthritis (RA), one patient (10%) had RA/systemic lupus erythematosus, and one patient (10%) had human immunodeficiency virus related-arthritis (Table 3). Seven (70%) HBV patients were in chronic inactive HBsAg carrier states with undetectable HBV-DNA, and three 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 (Table 3). One patient who was HBsAg-positive, anti-HBs-positive, anti-HBe-positive, and had undetectable HBV-DNA was not given antiviral therapy. The majority (80%) of HBV patients received a biological treatment consisting of etanercept (ETA) (8 episodes), adalimumab (ADA) (3 episodes), tociluzumab (TOC) (Actemra; Genetech, USA) (1 episode), and rituximab (RIT) (Mabthera; Genetech, USA) (1 episode). Synthetic disease-modifying antirheumatic drugs (s-DMARDs) were prescribed in all except one (with missing data) and consisted of methotrexate (9 episodes), sulfasalazine (4 episodes), hydroxychloroquine (8 episodes), azathioprine (1 episode), mycophenolate (1 episode), and cyclophosphamide (1 epi-

Table 2. Patients characteristics of 10 arthritis patients with Hepatitis C infection on biologics

Case No.	Age/ Sex years	Rheumatic. Disease	Duration of RD (Months)	HCV PCR (BL) Genotype	ALT/ AST (BL)	HCV antiviral	HCVRNA before Biologic	B-DMARDS	Length of biologic (months)	Presence of flare	Follow up (months)	Follow up HCVRNA III/ml	DMARDS	Steroids	Multiple biologics
1	69/F	RA	100	Positive	Normal	PEG-RIB	ND	RIT	65	No	70	NF	MTx	No	No
2	41/F	RA	101	Positive	Normal	PEG-RIB	ND	RIT	84	No	90	NF	MTx	No	No
3	79/F	RA	178	11 m IU/mL Genotype 4	Normal	PEG-RIB (SE)	2million	INF ADA TOC ABA	NF NF 22 4	Yes Elevated HCVRNA	40	6m	Mtx LEF	Yes	Yes
4	68/F	RA	228	8 m IU/mL Genotype 1,4	Normal	PEG-RIB non responder	2million	ADA RIT	12 8	No	36	599	Mtx LEF	Yes	Yes
5	57/F	RA	108	4 million Genotype 4	Normal	PEG-RIB	ND	RIT	50	No	52	ND	SSZ HQC	Yes	No
6	60/F	RA Cryoglobulinemia Vasculitis	168	>3 m IU/mL Genotype 3,4	ALT197 AST177	PEG-RIB SOF-RIB	ND	RIT ABA	26 11	Yes Elevated HCVRNA	37	<2 m	No	Yes	Yes
7	23/F	RA Sickle cell anemia	60	62340 IU/mL	ALT49 AST57	PEG-RIB	ND	ETA ADA RIT	10 20 2	Yes Elevated HCVRNA	41	1.2	MTX,CyA	Yes	Yes
8	63/F	RA	180	2011883 IU/MI	Normal	PEG-RIB	NF	ETA	48	No	52	NF	MTXSSZ HOC	NF	No
9	77/F	RA	NF	162726 IU/m1	Normal	Not given	NF	ETA ADA	72 12	No	NF	NF	HQC	Yes	Yes
10	63/F	RA	180	280861 IU/mL Genotype 1	Normal	PEG-RIB	164046	ETA	72	NF	72	NF	HQC MTXSSZ Gold	Yes	No

F: female; M: male; BL: baseline; m: million; Ast: aspartate transaminases; Alt: alanine transaminases; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; ND: not detected; NF: not found; ETN: etanercept; INF: inflimab; RTX: rithiximab; ADA: adalimumab; ABA: abatacept; TOC: tocilizumab; LMV: lamivudine; EVT: entecavir; TFV: tenofovir; LEF: leflunomide; MTX: methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine; AZA: azathioprine; CyA: cyclosporine; DMARD: disease-modifying antirheumatic drug; B-DMARD: biological disease-modifying antirheumatic drug; PEG-INF: pegylated interfone; RBV: ribavarin; SOF: sofosbuvir

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 (20)	TOC (n)	2
Biological therapy		RIT (n)	6
ETA (n)	8	ABA (n)	2
ADA (n)	3	IFX (n)	1
TOC (n)	1	Duration of biological therapy (mean)(range) months	62 (2-72)
RIT(n)	1	Elevation of HCV RNA (n) %	3 (30%)
Duration of biological therapy (mean) (range) months	40 (11-60)	Duration of follow-up/ years (mean)(range) months	54 (36-72)
Reactivation (n)%	2	DMARDs	
Duration of follow- up (mean) (range) months	54 (19-75)	MTX (n)	7
DMARDs		LEF (n)	2
MTX (n)	9	SSZ (n)	3
SSZ (n)	4	HQC (n)	4
HCQ (n)	8	GOLD (n)	1
AZA (n)	1	CyA (n)	1
MMF (n)	1	Steroids (n)	6
Cyclophosphamide	1	Multiple Biologics (n) %	5 (50)
Steroids (n)	9		
Multiple biologics (n)%	3 (30)		

ABA: abatacept; ADA: adalimumab; AZA: azathioprine; CyA: cyclosporine A; DMARD: disease-modifying antirheumatic drug; ETV: entecavir; ETN: etanercept; HCQ: hydroxychloroquine; IFX: infliximab; LMV: lamivudine; LEF: leflunomide; MTX: methotrexate; MMF: mycophenolate mofetil; PsA: psoriatic arthritis; RA: rheumatoid arthritis; RTX: rituximab; SLZ: sulfasalazine; SLE: systemic lupus erythematosus; TFV: tenofovir; TOC: tocilizumab

sode). Steroids were given to nine patients of the HBV infection group. The duration of follow-up was 54 (19–75) months. Two of the three patients with chronic active HBV infection had persistent HCV-DNA elevation with normal liver enzymes. Multiple biologics were used for the three patients (Table 3).

The mean age in HCV group (Table 3) was 54 (23–79) years and all were female RA patients. Three had detectable HCV-RNA before the start of biologics. Nine HCV patients received antiviral treatment in the form of pegylated interferon (PEG-INF) and ribavirin (RIB), and seven patients had sustained virologic responses (SVR) 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.

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). Abdo (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 had persistently mild elevation of HBV at less than 2000 IU/mL that was present even before the start of biological therapy; had no further elevation of transaminases during follow-up at 72 months and 60 months with antiviral 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

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 Xuan 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, Vigano (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-α 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 directly acting antiviral therapy have minimal toxicity and side effects, with reported cure rates of 93–100% 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 theraphy. 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.

Author Contributions: Concept - S.A., H.A; Design - S.A., H.A.; Supervision - S.A., H.A.; Resources - H.A., S.A.; Materials - S.A., H.H., M.O., S.Attar.; Data Collection and/or Processing - M.S., A.N., H.A., N.M.; Analysis and/or Interpretation - M.S., S.A., H.A.; Literature Search - M.S., S.A., H.A.; Writing Manuscript - S.A., M.S.; Critical Review - S.A, A.A., H.A., H.H., M.O., S.A.; Other - S.A., H.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The study was supported and funded by the Alzaidi Chair for Rheumatic Disease, Um Alqura University, Makkah, Saudi Arabia.

References

1. Pucino F Jr, Harbus PT, Goldbach-Mansky R. Use of biologics in rheumatoid arthritis: where are we going? Am J Health Syst Pharm 2006; 63(Suppl 4): S19-41. **[CrossRef]**

2. Toussaint NC, Maman Y, Kohlbacher O, Louzoun Y. Universal peptide vaccines - optimal peptide vaccine design based on viral sequence conservation. Vaccine 2011; 29: 8745-53. [CrossRef]
3. Efe C. Drug induced autoimmune hepatitis and TNF-alpha blocking agents: is there a real relationship? Autoimmun Rev 2013; 12: 337-9. [CrossRef]
4. Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. Ann Rheum Dis 2006; 65: 983-9. [CrossRef]
5. Carlsen KM, Riis L, Madsen OR. Toxic hepatitis induced by infliximab in a patient with rheumatoid arthritis with no relapse after switching to etanercept. Clinical rheumatol 2009; 28: 1001-3. [CrossRef]
6. Pompili M, Biolato M, Miele L, Grieco A. Tumor necrosis factor-alpha inhibitors and chronic hepatitis C: a comprehensive literature review. World J Gastroenterol 2013; 19: 7867-73. [CrossRef]
7. Abdo AA, Sanai FM, Al-Faleh FZ. Epidemiology of viral hepatitis in Saudi Arabia: are we off the hook? Saudi J Gastroenterol 2012; 18: 349-57. [CrossRef]
8. Alfaleh FZ, Nugrahini N, Matičič M, Tolmane I, Alzaabi M, Hajarizadeh B, et al. Strategies to manage hepatitis C virus infection disease burden. JVH 2015; 22: 42-65. [CrossRef]
9. Babanejad M, Izadi N, Najafi F, Alavian SM. The HBsAg Prevalence among blood donors from Eastern Mediterranean and Middle Eastern countries: a systematic review and meta-Analysis. Hepat Mon 2016; 16: e35664. [CrossRef]
10. Liakina V, Hamid S, Tanaka J, Olafsson S, Sharara AI, Alavian SM, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries. JVH 2015; 22: 4-20. [CrossRef]
11. Ferri C, Cacoub P, Mascia MT, Saadoun D. Cryoglobulinemia and systemic manifestations of hepatitis C virus. EULAR Compendium on Rheumatic Diseases. BMJ Publishing Group Ltd: London; 2009.
12. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015; 63: 199-36. [CrossRef]
13. World Health Organization (WHO). Hepatitis: frequently asked questions. 2010. Available`-from: http://www.who.int/csr/disease/hepatitis/world_hepatitis_day/question_answer/en/.
14. Al Traif I, Al Balwi MA, Abdulkarim I, Handoo FA, Alqhamdi HS, Alotaibi M, et al. HCV genotypes among 1013 Saudi nationals: a multicenter study. Ann Saudi Med 2013; 33: 10-2. [CrossRef]
15. Sarasin-Filipowicz M. Interferon therapy of hepatitis C: molecular insights into success and failure. Swiss Med Wkly 2010; 140: 3-11.
16. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016; 68: 1-26. [CrossRef]
17. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015; 148: 215-9; quiz e16-7.
18. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016; 63: 261-83. [CrossRef]
19. Xuan D, Yu Y, Shao L, Wang J, Zhang W, Zou H. Hepatitis reactivation in patients with rheumatic diseases after immunosuppressive therapy--a report of long-term follow-up of serial cases and literature review. Clin rheumatol 2014; 33: 577-86. [CrossRef]
20. Viganò 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 on Biol Ther 2012; 12: 193-207. [CrossRef]
21. Caporali R, Bobbio-Pallavicini F, Atzeni F, Sakellariou G, Caprioli M, Montecucco C, et al. Safety of tumor necrosis factor alpha 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. [CrossRef]
22. Gigi E, Georgiou T, Mougiou D, Boura P, Raptopoulou-Gigi M. Hepatitis B reactivation in a patient with rheumatoid arthritis with antibodies to hepatitis B surface antigen treated with rituximab. Hippokratia 2013; 17: 91-3.
23. De Nard F, Todoerti M, Grosso V, Rossi S, Caporali R, Montecucco C. FRI0314 Safety of the newer biological Dmards, TOCILIZUMAB and Abatacept, in rheumatoid arthritis (RA) patients with a history of HBV infection: A real life experience. Ann Rheum Dis 2014; 73: 499. [CrossRef]
24. 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 2011; 90: 359-71. [CrossRef]
25. Burton MJ, Curtis JR, Yang S, Chen L, Singh JA, Mikuls TR, et al. Safety of biologic and nonbiologic disease-modifying antirheumatic drug therapy in veterans with rheumatoid arthritis and hepatitis B virus infection: a retrospective cohort study. Arthritis Res Ther 2015; 17: 136. [CrossRef]
26. Lee YH, Bae SC, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. Int J Rheum Dis 2013; 16: 527-31. [CrossRef]
27. Nagashima T, Minota S. Long-term tocilizumab therapy in a patient with rheumatoid arthritis and chronic hepatitis B. Rheumatology 2008; 47: 1838-40. [CrossRef]
28. Tsuboi H, Tsujii A, Nampei A, Yoshihara H, Kawano K, Takeuchi E, et al. A patient with rheumatoid arthritis treated with tocilizumab together with lamivudine prophylaxis after remission of infliximab-reactivated hepatitis B. Mod Rheumatol 2011; 21: 701-5. [CrossRef]
29. Nakamura J, Nagashima T, Nagatani K, Yoshio T, Iwamoto M, Minota S. Reactivation of hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. Int J Rheum Dis 2016; 19: 470-5. [CrossRef]
30. Pyrpasopoulou A, Douma S, Vassiliadis T, Chatzimichailidou S, Triantafyllou A, Aslanidis S. Reactivation of chronic hepatitis B virus infection following rituximab administration for rheumatoid arthritis. Rheumatol Int 2011; 31: 403-4. [CrossRef]
31. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015; 62: 932-54. [CrossRef]
32. Zein NN, Etanercept Study G. Etanercept as an adjuvant to interferon and ribavirin in treatment-naive patients with chronic hepatitis C virus infection: a phase 2 randomized, double-blind, placebo-controlled study. J Hepatol 2005; 42: 315-22. [CrossRef]
33. Ferri C, Ferraccioli G, Ferrari D, Galeazzi M, Lapadula G, Montecucco C, et al. Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. J Rheumatol 2008; 35: 1944-9.
34. Ferri C, Cacoub P, Mazzaro C, Roccatello D, Scaini P, Sebastiani M, et al. Treatment with rituximab in patients with mixed cryoglobulinemia syndrome: results of multicenter cohort study and review of the literature. Autoimmun Rev 2011; 11: 48-55. [CrossRef]