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Hepatitis B and C virus reactivations under biologic treatments in patients with rheumatic diseases: long-term results from a single-center

Belkis Nihan Coşkun[1], Burcu Yağız[2], Ezgi Sezen Özboz[3], Ayşe Nur Tufan[4], Selime Ermurat[5], Yavuz Pehlivan[1], Hüseyin Ediz Dalkılıç[1]

[1]*Department of Internal Medicine, Division of Rheumatology, Uludağ University School of Medicine, Bursa, Turkey*
[2]*Department of Rheumatology, Afyonkarahisar State Hospital, Afyonkarahisar, Turkey*
[3]*Department of Internal Medicine, Bornova Türkan Özilhan State Hospital, İzmir, Turkey*
[4]*Department of Rheumatology, Haseki Training and Research Hospital, İstanbul, Turkey*
[5]*Department of Rheumatology, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey*

ABSTRACT

Objectives: To find out the effects and prevalence of disease-modifying antirheumatic drugs (DMARDs) and anti-TNF agents on hepatitis B virus (HBV) reactivation in hepatitis B surface antigen (HBsAg)-positive patients with rheumatic diseases (RD).

Methods: This retrospective study was conducted on 1,548 RD patients. Patients' medical records regarding immunological profiles, clinical courses, and outcomes, were obtained. In this research, the patient used conventional DMARDs (cDMARDs) and biological DMARDs (bDMARDs). A drug exposure was considered when a patient was administered GC, cDMARDs, or bDMARDs for > 4 weeks. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were measured. HBsAg, HBV DNA assay, anti-HCV and HIV were identified.

Results: HBsAg was positive in 19 (37.3%) patients. Anti-HBs in 5 (9.8%) patients and anti-HBc IgG in 35 (68.6%) patients were positive. All patients with HBsAg positivity were receiving antiviral prophylaxis. Anti-HCV was positive in 25.5% (n = 13) of individuals . There was not any reactivation among the patients. No HBV reactivation was observed.

Conclusions: Screening before treatment and give prophylaxis to patients who have occult hepatitis or hepatitis B, may be an important factor in the absence of reactivation. Hepatitis screening should be performed in all patients prior to biological treatment is initiated.

Keywords: Hepatitis, rheumatic disease, reactivation, biologic treatment. Disease-modifying antirheumatic drugs, occult Hepatitis.

The primary cause of chronic hepatitis, end-stage liver disease, and hepatocellular carcinoma (HCC) is hepatitis B virus (HBV) infection [1-3]. Around 350 million people worldwide are afflicted with HBV, which causes between 0.5 and 1 million fatalities each year [4]. Similarly, hepatitis C virus (HCV) infects around 170 million people [5].

HBV infection is a significant issue for rheumatologists, as reactivation of HBV can occur as a side effect of immunosuppressive medications (ISDs) [6].

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Address for correspondence: *Belkis Nihan Coşkun, MD., Assistant Professor, Uludağ University School of Medicine, Department of Internal Medicine, Division of Rheumatology, Görükle, Nilüfer, 16059, Bursa, Turkey. E-mail: belkisnihanseniz@hotmail.com, Tel (Mobil): +90 533 225 55 13, Tel (Office): +90 224 295 15 53*

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Numerous conventional disease-modifying antirheumatic medications (cDMARDs), such as glucocorticoids, methotrexate (MTX), hydroxychloroquine, sulfasalazine, and leflunomide, as well as biological DMARDs, such as etanercept, adalimumab, golimumab, infliximab, certolizumab, tocilizumab, TNF-alfa is significant because it inhibits HBV replication and is capable of eradicating the virus [7]. Notably, rituximab, a B cell depleting drug, is frequently used to treat rheumatic disorders. However, prolonged use of potentially hepatotoxic DMARDs, such as MTX, is likely to result in HBV reactivation, and a link between anti-TNF therapy and HBV activation has been established [8, 9].

The American Gastroenterological Association (AGA) Institute emphasized the possibility of HBVr infection associated with chemotherapeutic treatments and immunosuppressive medicines in 2015 [10-11]. As a result, immunocompromised patients should be evaluated for HBV and HCV infection [12]. The prophylactic antiviral medication is extremely useful since it prevents HBV reactivation in HBsAg-positive patients receiving anti-TNF or DMARD therapy [7]. The purpose of this study is to determine the effect and prevalence of DMARDs and anti-TNF medications on HBV and HCV reactivation in patients with rheumatic illnesses who are HBsAg positive.

METHODS

Patients

Between January 2006 and December 2012, we retrospectively analyzed 1,548 individuals with RD who had available HBsAg and HCV data at a university hospital. Without taking anti-HBV prophylaxis, 19 patients tested positive for HBsAg at the time of diagnosis or prior to immunosuppressive treatment. We received medical documents pertaining to immunological profiles, clinical courses, and results.
The inclusion criteria for our patients to participate in the present research were (i) patients with RD (rheumatoid arthritis [RA], ankylosing spondylitis [AS], psoriatic arthritis [PsA], spondyloarthropathy [SpA], vasculitis, systemic lupus erythematosus, behcet disease, and systemic sclerosis); (ii) the intervention consisted of anti-TNF agents, Rituximab, Tocilizumab, Abatacept, Ustekinumab, Tofacitinib, Cyclophosphamide, and DMARDs; (iii) sufficient data on patience regarding the effects of anti-TNF agents or DMARD on HBV reactivation.

Immunosuppressive Therapy

Methotrexate, hydroxychloroquine, and sulfasalazine were used as cDMARDs in this study. Anti-TNF medicines, rituximab (anti-CD20 monoclonal antibody), tocilizumab (anti–interleukin 6 receptor monoclonal antibody), and abatacept (cytotoxic T lymphocyte–associated antigen 4 immunoglobulin) were listed among the bDMARDs. When a patient got GC, cDMARDs, or bDMARDs for a period of more than 4 weeks, exposure to medicines was assessed.

Serological Tests of Viral Hepatitis Markers

We determined serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin using a 24-factor automated chemical analyzer and standard reagents. The Architect-plus 2001 chemiluminisans method was used to determine the hepatitis B surface antigen. Plasma samples from patients were purified using the automated m2000sp (Abbott Molecular, USA) instrument for DNA extraction. The acquired DNA was amplified using the Real-Time PCR on a m2000rt (Abbott Molecular, USA) equipment using an Abbott Real-Time HBV kit.

The study protocol was approved by the Local Clinical Research Ethics Committee (decision number: 2021-6/43).

Statistical Analysis

Statistical analysis was performed with the SPSS program, version 23. The demographic data of the patients were presented as frequency and percentage for qualitative variables and mean and standard deviation for qualitative variables. For all tests, probability values (values) of < 0.05 were considered to indicate statistical significance.

RESULTS

The mean age of the 51 patients was 50.9 ±13.51 years (range: 20-69 years). Out of 51 patients, 58.8% of them were females and 41.2% of them were males (see Appendix 1 for patient characteristics).

HBsAg positivity was observed in 37.3% of pa-

tients (n = 19), Anti-HBs positivity was observed in 9.8% of patients (n = 5), and Anti-HBc IgG positivity was observed in 68.6% of patients (n = 35). It is worth noting that data for Anti-HBc IgG were absent. There were no patients who tested positive for Anti-HBc IgM. All patients with HBsAg positivity were receiving antiviral prophylaxis.

HBsAg was negative in 68.6% of patients (n = 35), although Anti-HBc IgG was positive (occult hepatitis). Anti-HCV was positive in 25.5% of individuals (n = 13). Among the patients, 19 were tested for HIV, and the results revealed that none of the patients had the virus.

When the patients were investigated, eight unique diagnoses were made: RA (35.3%), AS (33.3%), PsA (13.7%), Vasculitis (7.8%), Systemic Lupus Erythematosus (5.9%), Behcet Disease (2%), and Systemic Sclerosis (2%).

Our data indicated that eleven distinct immunosuppressive agents were present in the patients: Etanercept (33.3%), Infliximab (15.7%), Rituximab (15.7%), Adalimumab (9.8%), Golimumab (5.9%), Tocilizumab (5.9%), Abatacept (3.9%), Cyclophosphamide (3.9%), Certolizumab (2%), Ustekinumab (2%), and Tofacitinib (2%). Table 1 summarizes the duration of biological treatment, the duration of steroid treatment, and the steroid doses.

Eight patients received Rituximab (RTX) (15.7%). The average length of RTX use was 39.87 ± 27.48 months (range from 6 to 96 months). Antiviral prophylaxis was administered to all eight individuals. In none of the eight patients was reactivation observed.

DISCUSSION

Hepatitis virus infections are a significant issue for rheumatologists, given the difficulties associated with treatment [12-15]. Numerous studies have demonstrated that methotrexate and biologic treatments, such as infliximab, etanercept, adalimumab, and rituximab, can reactivate HBV in dormant HBV carriers [16-21]. Thus, the ACR recommends screening for HBV and HCV prior to initiating immunosuppressive medication, whether non-biologic or biologic [12]. Although other studies have demonstrated HBV reactivation in patients receiving immunosuppressive therapy for cancer or transplantation at a rate of 20-50%, our investigation found no evidence of HBV reactivation in any of our 51 patients (n = 51) [22].

Notably, TNF-a is required for immunological responses as a pro-inflammatory cytokine. Thus, when TNF-a inhibitors are administered, the virus is able to evade the host's immune protection systems against infection [9]. Prior to initiating treatment, all patients with rheumatic illnesses should be tested for HBV, as HBsAg carriers must get antiviral prophylaxis [6, 7, 11]. Chronic autoimmune illnesses require long-term immunosuppressive medication, but chemotherapy is frequently used for brief periods [23]. It is worth noting that, despite immunosuppressive therapy's benefits, long-term use is likely to compromise host immunological functioning. Lee *et al*. conducted a review of nine studies that comprised 122 individuals with rheumatic illness who tested positive for HBsAg. 15 (12.3%) of 122 individuals acquired HBVr [6]. Etanercept (33.3%), Infliximab (15.7%), Adalimumab (9.8%), Golimumab (5.9%), and Certolizumab (5.9%) were utilized by 34 individuals (2%). There was no evidence of reactivation in any of the patients.

Although Rituximab is the most hazardous medicine due to its HBVr-related side effects, a study found that due to its longer dose interval, Rituximab therapy was safe in individuals with RD [24]. Another study

Table 1. Period of treatment and steroid dose

	Period of biological treatment (month)	Period of steroid treatment (month)	Steroid dose (mg)
HBsAg positive	36.89 ± 19.55 (6-72)	41.89 ± 110.93 (0-480)	1.71 ± 2.89 (0-10)
HBsAg negative Anti-HBc IgG positive	48.47 ± 30.76 (4-120)	54.36 ± 109.36 (0-480)	3.42 ± 4.72 (0-20)
Anti-HCV positive	29.07 ± 25.22 (3-96)	138.84 ± 183.17 (0-552)	2.69 ± 2.78 (0-7.5)

found that the incidence of HBVr was 40% to 100% in HBsAg positive RA patients receiving rituximab without or with GC therapy, arguing in favor of antiviral prophylaxis in HBsAg positive RA patients receiving rituximab [25]. The surprising finding in this study was the absence of reactivation among the 51 patients, notably among the eight individuals who received antiviral prophylaxis for a period spanning from 6 to 96 months. This finding implies that appropriate antiviral prophylaxis is critical for the health of patients.

Tocilizumab and Abatacept are likely to have an influence on the patient's immune response to HBV, as mentioned in the literature. However, we should keep in mind that the majority of GC research on HBVr in patients treated with tocilizumab or abatacept has been hampered by small sample sizes [25]. As a result, additional research with a larger cohort of patients is required.

ISDs (e.g., biologics, steroids, and MTX) are highly likely to reactivate HBV. It is worth noting that assessing the risk of reactivation for each treatment is critical for preventing HBV reactivation [12-23].

In a case–control study including RA patients approved by the US Food and Drug Administration, the odds ratio for HBV reactivation was 2.3 for steroids and much lower for TNF blockers than for steroids or MTX [26].

Fukuda *et al*. [23] found that MTX had a reduced risk ratio for HBV reactivation than steroids and biologics. The time period between ISD onset and HBV reactivation varied, and the clinical outcome following reactivation was not always aggressive [23]. Chen *et al*.'s [24] study discovered that HBVr is prevalent in HBsAg-positive RA patients, even more so when combined immunosuppressive therapies with GC are used. Physicians in particular should exercise caution, as antiviral treatment must be justified in light of the risk of HBVr infection in rheumatic patients receiving various immunosuppressive regimens [25, 27].

The literature is unanimous in recommending that all patients initiating DMARD medication be screened for HCV infection using anti-HCV antibodies. If the test results are positive, HCV RNA testing should be performed to validate the finding. Patients who have been infected with HCV for an extended period of time should be referred to a hepatologist. It's important emphasizing two critical points: I it is critical to understand the severity of the underlying chronic HCV infection before making a therapy option. These patients could be assessed for advanced fibrosis or cirrhosis. (ii) When a hepatologist diagnoses HCV, he or she should determine whether or not to initiate antiviral medication [8, 12, 28].

Limitations

Our study has some limitations. A retrospective study, for instance, was described. Second, the sample size for HBV carriers was limited to 19 individuals with RD. This is because hepatitis screening has become more prevalent in recent years. However, multicenter trials with a larger number of patients can provide more trustworthy findings.

CONCLUSION

In summary, HBV infection is screened for all patients receiving immunosuppressive therapy for rheumatic diseases, and antiviral prophylaxis should be administered if necessary.

Authors' Contribution

Study Conception: BNC, BY, HED, YP; Study Design: BNC, HED, YP; Supervision: BNC, HED, YP; Funding: N/A; Materials: N/A; Data Collection and/or Processing: ESÖ, ANT; Statistical Analysis and/or Data Interpretation: YP, SE, ANT; Literature Review: HED, ESÖ, SE; Manuscript Preparation: BNC, BY and Critical Review: BNC, BY, HED, YP, SE, ANT, ESÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Appendix 1. **Patient characteristics**

No	Age/Sex	Diagnosis	Serological markers				AST/ALT (IU/L)	HBV DNA (IU/mL)	HCV RNA (IU/mL)	Steroid dose	Steroid duration (months)	ISD	IST Duration (months)	Hepatitis Treatment
			HBsAg	Anti-Hbs	Anti-HBc IgG	Anti-HCV								
1	28/M	PsA	-	-	+	-	17/25	ND		5	48	ADA	50	-
2	49/M	AS	+	-	+	-	14/8	112		-	-	INF	6	TNV
3	53/M	GPA	-	-	+	-	16/17	NEG		5	48	RTX	48	-
4	37/F	AS	-	-	+	-	39/97	NEG		-	-	ETA	42	LAM
5	48/F	SLE	-	-	ND	+	19/23		504.544	5	552	RTX	36	-
6	66/F	AS	-	-	-	+	22/21		35.064	-	-	ETA	19	-
7	36/F	PsA	-	-	+	-	14/11	NEG		-	-	ETA	21	ENT
8	59/M	PAN	+	-	+	-	30/48	NEG		5	480	RTX	45	LAM
9	66/F	RA	-	-	+	-	18/9	NEG		5	480	ABA	35	-
10	25/M	AS	+	-	+	-	22/26	NEG		-	0	GOL	39	TNV
11	20/F	SLE	-	+	-	+	24/18		NEG	5	72	RTX	6	-
12	36/M	AS	-	-	+	-	27/46	NEG		-	0	ADA	25	-
13	46/F	RA	+	-	+	-	19/9	NEG		-	0	ETA	48	TNV
14	57/M	EGPA	-	-	+	-	14/7	ND		5	32	RTX	31	-
15	45/M	PsA	+	-	-	-	19/27	NEG		-	0	UST E	24	LAM
16	31/M	SLE	-	-	-	+	28/42		NEG	7.5	60	CYC	4	-
17	29/F	PsA	-	-	-	+	11/7		NEG	5	48	ETA	36	-
18	69/F	RA	+	-	+	-	19/20	418		5	101	TOCI	37	LAM
19	56/F	RA	+	-	ND	-	22/30	48.1		-	0	ETA	13	TNV
20	63/F	PsA	+	-	+	-	19/14	NEG		-	0	TOCI	72	LAM
21	65/F	RA	+	-	ND	ND	28/24	NEG		2.5	86	ABA	32	LAM
22	63/F	RA	-	-	+	-	29/27	ND		5	106	RTX	96	-
23	53/F	Ssc	+	+	+	-	17/7	NEG		5	66	CYC	9	LAM
24	65/F	RA	-	+	+	+	53/65		1.239.342	5	384	ETA	3	IFN + RBV
25	66/F	PsA	-	-	+	-	16/2	NEG		5	84	ADA	60	-
26	52/M	AS	+	-	+	-	18/9	30		-	0	ETA	60	TNV
27	55/F	RA	-	-	-	+	16/12		NEG	-	240	ETA	36	-
28	36/F	AS	-	-	+	-	14/15	NEG		-	0	ADA	39	-
29	67/M	AS	-	-	+	-	21/21	ND		-	0	INF	85	-
30	45/M	BD	-	-	-	+	41/102		NEG	15	52	INF	32	-

Appendix 1. Continued

No	Age/Sex	Diagnosis	Serological markers				AST/ALT (IU/L)	HBV DNA (IU/mL)	HCV RNA (IU/mL)	Steroid dose	Steroid duration (months)	ISD	IST Duration (months)	Hepatitis Treatment
			HBsAg	Anti-Hbs	Anti-HBc IgG	Anti-HCV								
31	66/M	RA	-	-	+	-	23/21	NEG		5	96	GOL	27	-
32	54/F	PsA	-	-	+	-	27/17	ND		5	88	CERTO	34	-
33	66/F	RA	-	-	+	-	19/10	NEG		5	168	TOFA	33	-
34	62/F	RA	-	+	-	+	18/15		NEG	-	0	TOCI	42	-
35	27/M	AS	-	-	+	-	17/43	NEG		-	0	INF	48	-
36	63/F	AS	+	-	+	-	26/21	NEG		-	0	GOL	50	LAM
37	47/M	AS	+	-	+	-	15/10	18171		-	0	ETA	34	TNV
38	49/M	AS	+	-	+	-	20/20	238		-	0	ETA	48	TNV
39	59/F	AS	-	-	+	-	35/56	NEG		-	0	INF	60	TNV
40	53/F	AS	+	-	+	-	19/13	NEG		-	0	ETA	52	LAM
41	57/F	RA	-	-	-	+	29/42		NEG	2.5	360	ETA	8	-
42	38/M	PsA	+	-	+	-	20/18	114		-	0	ETA	12	TNV
43	63/F	PAN	-	-	-	+	25/22		NEG	-	21	RTX	45	IFN+ RBV
44	63/F	RA	-	+	-	+	26/21		NEG	5	2	ETA	96	-
45	47/F	RA	-	-	+	-	12/18	ND		15	15	INF	4	-
46	29/M	AS	+	-	+	-	32/35	NEG		0	0	INF	48	LAM
47	66/M	RA	+	-	ND	-	20/16	275		10	15	RTX	12	LAM
48	48/M	AS	-	-	+	-	19/12	NEG		-	0	INF	120	-
49	35/M	AS	-	-	+	-	14/10	ND		-	0	ETA	96	-
50	62/F	RA	-	ND	ND	+	16/13		NEG	-	24	ETA	15	-
51	56/F	RA	+	-	+	-	19/21	90		5	48	ADA	60	TNV

PsA = Psoriatic Arthritis, AS = Ankylosing Spondylitis, GPA = Granulomatous Polyangiitis, SLE = Systemic Lupus Erythematosus, PAN = Polyarteritis nodosa, RA = Rheumatoid Arthritis, EGPA = Eosinophilic granulomatosis with polyangiitis, SSc = Systemic Sclerosis, BD = Behcet Disease, ISD = Immunosuppressive drug, ADA = Adalimumab, INF = Infliximab, RTX = Rituximab, ETA = Etanercept, ABA = Abatacept, GOL = Golimumab, USTE = Ustekinumab, CYC = Cyclophosphamide, TOCI= Tocilizumab, CERTO = Certolizumab, TOFA = Tofacitinib, TNV = Tenofovir, LAM = Lamivudine, ENT = Entecavir, IFN+RBV = Interferon+ribavirin.