Original Article

Hepatitis B Virus Reactivation in Patients with Psoriasis on Biologic Therapies: A Retrospective Study

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Abstract

Background: There are limited data on the safety of biological therapies in psoriasis patients with hepatitis B virus (HBV) infection in the literature, and are still ongoing controversies about HBV reactivation in patients treated with biologics for psoriasis. **Aims:** This was aimed to investigate the demographic, clinical, and laboratory characteristics of the patients with HBV seropositive receiving biological treatment for psoriasis. **Study Design:** This was a retrospective observational study. **Materials and Methods:** Ninety-seven patients with psoriasis treated with biologics in the outpatient clinic were evaluated retrospectively. Of these, 16 patients with HBV seropositive were included in the study. Patients with positive HBV serology were divided into three groups as chronic HBV infection, past HBV infection, and isolated core antibody positivity (HBV core-specific antibody [HBcAb]). The demographic, clinical, and laboratory characteristics of the patients were obtained from the records. **Results:** Of the patients, 5 patients were female (31.2%), and 11 were male (68.8%). The mean age of the patients was 55.81 ± 11.05. Thirteen of the patients had past HBV infection, three had isolated HBcAb positive. Infliximab (n = 13) was the most common biologic agent used, followed by adalimumab (n = 6), secukinumab (n = 4), ustekinumab (n = 2), and etanercept (n = 2). The mean duration of treatment was 3.59 ± 2.76 years. The HBV reactivation occurred in only one patient with past HBV infection receiving infliximab (6.2%). **Conclusion:** It remains unclear how exactly the biologic drugs for psoriasis impact viral reactivation. For the safe use of biological agents in psoriasis patients with HBV seropositive, screening tests must be performed with a triple serology, including HBV surface antigen, HBV surface-specific antibody, and HBcAb. The patients who have positive HBV serology must be monitored closely with reactivation markers and receive antiviral prophylaxis if they are at moderate-to-high risk of HBV reactivation.

Keywords: Biologic agent, hepatitis B virus, psoriasis, reactivation

Introduction

In recent years, biological therapies play an important role in the treatment of moderate-to-severe psoriasis. It is said that biologics that target specific parts of the immune system that play a crucial role in the pathogenesis of psoriasis are usually well tolerated and have few side effects. However, biologics can cause reactivation of some infections, such as hepatitis B virus (HBV), through their immunomodulatory activity. At this point, there are very limited data on the safety of biological therapies in psoriasis patients with HBV infection in the literature and are still ongoing controversies about HBV reactivation in patients treated with biologics for psoriasis. Besides the limited data on the management of biologics in patients with HBV infection, most of these data have been obtained from studies with diseases other than psoriasis (e.g., rheumatological, gastroenterological).[1-3] In addition to these, there are many difficulties to find HBV reactivation rates in the real-world. For these reasons, we aimed to investigate the demographic, clinical, and laboratory characteristics of the patients with HBV seropositive receiving biological treatment for psoriasis with this study.

Materials and Methods

All patients with psoriasis who are treated with biologics reached to the outpatient clinic were evaluated retrospectively.

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A total of 97 patients with psoriasis were receiving biological therapy between August 2014 and September 2019. Of these, only HBV seropositive patients were included in the study. HBV status has been classified according to the European Association for the Study of Liver Disease:

1. Chronic HBV infection (HBV surface antigen [HBsAg]-positive)
2. Past HBV infection (HBsAg-negative, HBV surface-specific antibody [HBsAb]-positive, and HBV core-specific antibody [HBcAb]-positive)
3. Isolated core antibody positivity (HBsAg negative, HBsAb negative, and HBcAb positive).[4]

Demographic variables, medical history, type of psoriasis, previous or concomitant immunosuppressive therapies, use of antiviral prophylaxis, type and duration of biological therapy (adalimumab, etanercept, infliximab, ustekinumab, secukinumab) were recorded retrospectively from the patients' medical records. Laboratory data (HBsAg, HBsAb, HBcAb, HBV DNA, alanine aminotransferase, aspartate transaminase) was also extracted from the records to determine serologic status at baseline and during treatment at various intervals. We included all patients whose viral load was assessed at the beginning of biological therapy and in every 3 months during treatment.

The American Association for the Study of Liver Diseases (AASLD)-recommended criteria for HBV reactivation were considered.[5] According to AASLD, HBV reactivation in HBsAg-positive, anti-HBc–positive patients is reasonably defined as one of the following:

1. A 2 log (100-fold) increase in HBV DNA compared to the baseline level
2. HBV DNA 3 log (1000) IU/mL in a patient with previously undetectable level (given that HBV-DNA levels fluctuate)
3. HBV DNA 4 log (10,000) IU/mL if the baseline level is not available.

For HBsAg-negative, anti-HBc–positive patients, the following criteria are reasonable for HBV reactivation:

1. HBV DNA is detectable or
2. Reverse HBsAg seroconversion occurs (reappearance of HBsAg).[5]

Approval for the study was obtained from the local ethics committee (Decision number 2019/92; 08/07/2019). Statistical analyses were conducted using STATA (version 13, StataCorp LLC College Station, Texas, USA) program. Data obtained by counting are expressed as numbers and percentages.

Results

A total of 97 patients with psoriasis receiving biological therapy were examined retrospectively, and 16 of them were included in the study. Five of all patients were female (31.2%) and eleven were male (68.8%). The mean age of the patients was 55.81 ± 11.05. The mean age of females was 62.2 ± 7.79, and 52.9 ± 11.37 for the male.

All patients had plaque-type psoriasis (mean duration of 21.31 years, range 6–45 years). The demographic, clinical, and laboratory characteristics of patients are shown in Tables 1 and 2.

Thirteen of the patients had past HBV infection, three had isolated HBcAb positive. No patient had chronic HBV infection and detectable serum HBV DNA at baseline. Out of 13 patients, only three patients with past HBV infection were receiving antiviral prophylaxis with *tenofovir* that were suggested by gastroenterologists [Table 2].

Table 1: Clinical characteristics of cases at baseline

Case	Age	Sex	Medical history	Psoriasis duration (years)	HBV status	Previous immunotherapy	Biologic therapies	Biological treatment duration (years)
1	40	Male	-	29	Isolated	MTX, CYS	INF	1
2	45	Male	-	15	Past	MTX, CYS	SEC	1
3	53	Female	HT	36	Past	MTX, CYS	INF, ETA, ADA*	10
4	34	Male	-	13	Past	MTX, CYS	ETA, INF, ADA, UST, SEC*	10
5	58	Male	-	45	Past	MTX, CYS	INF, ADA*	4
6	58	Male	DYS	12	Isolated	MTX	INF, SEC*	2
7	50	Male	-	11	Past	MTX	INF	3
8	65	Male	-	19	Past	MTX	INF	3
9	58	Female	DM, HT	30	Past	MTX	ADA, INF*	4
10	63	Female	-	25	Past	MTX, CYS	INF	2
11	66	Male	-	19	Isolated	MTX, CYS	INF, SEC*	4
12	68	Male	-	14	Past	MTX, CYS	INF	1
13	55	Male	-	34	Past	MTX, CYS	ADA	4
14	74	Female	HT	15	Past	MTX	INF, ADA*	4.5
15	43	Male	DM	18	Past	MTX, CYS	UST	2
16	63	Female	-	6	Past	MTX	INF	2

*Currently used biologics. ADA: Adalimumab, CYS: Cyclosporine, DM: Diabetes mellitus, DYS: Dyslipidemia, ETA: Etanercept, HBV: Hepatitis B virus, HT: Hypertension, INF: Infliximab, MTX: Methotrexate, PASI: Psoriasis Area and Severity Index, SEC: Secukinumab, UST: Ustekinumab

Table 2: Laboratory characteristics of cases at baseline

Case	HBsAg	HBsAb* (mIU/mL) Baseline	HBsAb (mIU/mL) Follow up	HBcAb	Viral load (IU/mL) Baseline	Viral load (IU/mL) End	ALT (IU/L) Baseline	ALT (IU/L) End	AST (IU/L) Baseline	AST (IU/L) End	Antiviral PRX
1	Negative	0.83	10	Positive	<10	<10	40	30	24	25	-
2	Negative	12.64	16.86	Positive	<10	<10	26	28	37	25	-
3	Negative	160.39	151.63	Positive	<10	<10	19	17	17	17	-
4	Negative	672.02	1000	Positive	<10	<10	51	67	28	40	-
5	Negative	39.92	202.57	Positive	<10	<10	20	28	22	24	-
6	Negative	0.43	5.53	Positive	<10	<10	13	35	25	75	-
7	Negative	202.59	287.69	Positive	<10	<10	32	35	25	27	-
8	Negative	186.39	173.8	Positive	<10	<10	11	15	16	19	+
9	Negative	504.36	1000	Positive	<10	<10	19	11	12	11	+
10	Negative	130.17	184.25	Positive	<10	<10	22	10	22	21	-
11	Negative	6.34	4.78	Positive	<10	<10	10	14	32	27	-
12	Negative	16.53	15.83	Positive	<10	<10	14	13	16	14	-
13	Negative	1000	1000	Positive	<10	<10	26	16	29	22	-
14	Negative	53.14	39.98	Positive	<10	<10	39	46	26	36	-
15	Negative	101.6	111.63	Positive	<10	<10	37	27	18	21	+
16	Negative	64.89	47.49	Positive	<10	52000	16	32	18	26	-

*HBsAb levels above 10 IU/mL were considered positive. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBV: Hepatitis B virüs, HBcAb: HBV core antibody, HBsAb: HBV surface antibody, PRX: Prophylaxis

All the patients had the use of conventional drug at least, such as methotrexate and cyclosporine, before biological treatment. Infliximab (n = 13) was the most common biologic agent used, followed by adalimumab (n = 6), secukinumab (n = 4), ustekinumab (n = 2), and etanercept (n = 2). While nine patients had the use of only one biological agent, seven had a history of more than one biological agent used. The mean duration of biological treatment was 3.59 ± 2.76 years (range 1–10). The mean duration of treatment was 2 years for infliximab, 1.7 years for etanercept, 3.1 years for adalimumab, 2.5 years for ustekinumab, and 1.7 years for secukinumab.

The HBV reactivation occurred in only one patient with past HBV infection who did not receive antiviral prophylaxis. The patient developed detectable HBV DNA without reverse seroconversion to HBsAg positive. Her serum HBV DNA was measured as 52000 IU/mL [Table 2]. As soon as noticing the reactivation, the drug discontinued, and she was referred to the gastroenterologist. The reactivation rate was 6.2% among all patients, and 7.6% among the patients who did not receive antiviral prophylaxis. Three patients who were receiving antiviral prophylaxis did not develop reactivation during follow-up.

Discussion

Biological therapies have been playing an important role in the treatment of moderate-to-severe psoriasis in recent years. Biologic drugs can cause HBV reactivation due to their immunomodulatory effects. HBV infection is one of the most common infectious liver diseases in the World. There are >292 million carriers of HBV worldwide. In Turkey, the estimated number of HBV carriers is 3.3 million.[6]

Once the HBV enters the nucleus of the host hepatocytes, the viral DNA is transformed into a covalently closed circular DNA, which serves as a template for viral replication throughout the host's lifetime. Reactivation of HBV infection is characterized by an abrupt increase in HBV replication. Patients with seropositive HBV infection who receive immunosuppressive therapy are at risk for HBV reactivation. Reactivation most commonly occurs in patients with HBsAg (especially chronic active carriers). It can also rarely occur in patients with past or occult infections.[7]

As can be understood, the risk of HBV reactivation in patients receiving immunosuppressive treatment is higher in patients with HBsAg positive than negatives. American Gastroenterological Association (AGA) defined risk levels for HBV reactivation in patients receiving immunosuppressive agents.[8] The risk for HBV reactivation is categorized into high risk (>10%), moderate risk (1%–10%), and low risk (<1%) depending upon the serological status and the type of immunosuppressive therapy.[9] According to this classification of AGA, the reactivation rates in patients with HBsAg-negative and HBcAg-positive receiving biologic drugs vary between medium and low risk (1%–10%).[8] However, it may be said that the risk of reactivation is very low in patients with HBsAg-negative and HBcAb-positive, receiving biologics for psoriasis.[9] The probable reason for this is that while biologic drugs are generally used in combination with other immunosuppressive treatments in rheumatological, gastroenterological diseases, are usually used alone in dermatological diseases.

There are limited data on the safety of biologic drugs in psoriasis patients with HBV infection in the literature. Current guidelines do not recommend the use of biological

drugs in patients with active HBV infection due to the risk of reactivation.[10-12] However, prior or current HBV infection is not necessarily an absolute contraindication to biological treatment for the treatment of psoriasis. Psoriasis patients with HBV infection may receive biologic drugs, but they should be evaluated carefully, closely monitored for signs of reactivation, and managed in conjunction with a gastroenterologist.[9] Available data on the management and treatment of psoriasis with biologics in patients with HBV infection are based on few prospective studies, some retrospective studies, lots of case series, and reports in the literature.[13] Table 3 shows the findings of various studies investigating reactivation in psoriasis patients with positive HBV serology receiving biological therapy.

In this study, the psoriasis patients who have past HBV infection or isolated HBcAb positivity were at low risk for reactivation with biologics. However, HBV reactivation occurred in only one patient who was taking infliximab, and also had past HBV infection. This patient had also taken methotrexate for a long time. The use of prior immunosuppressive therapy may have also impacted the risk of reactivation in the patient. In 2011, a review published by Pérez-Alvarez *et al*. analyzing 257 cases reported the risk of reactivation is 5% in 168 HBcAb positive patients treated with anti-tumor necrosis factor (TNF) agents.[14] A systematic review including 175 patients with HBcAb positive treated with biologic drugs reported a reactivation rate of 1.14%.[15] Another systematic review involving 712 rheumatic patients with past HBV infection treated with biologic drugs found that the reactivation rate was 1.7%.[16] A recent study in Turkey, including 29 patients with past HBV infection or isolated HBcAb positivity treated with biologic drugs, found that five of all patients (4 had psoriasis, one had rheumatoid arthritis) developed HBV reactivation.[17] It is intriguing that a very high reactivation rate of 17.2% was found for a low-risk group in this study. It is seen that there are several studies showing the HBV reactivation rates in patients receiving biologic drugs are quite variable [Table 3]. This is because both these studies and ours had a low number of cases. Hence, there is a strong need for larger studies on this issue.

All patients had HBcAb positive in this study, and been consulted to gastroenterologists for the requirement of antiviral prophylaxis before treatment with biologic drugs. Despite there were 10 patients with past HBV infection, only 3 of them were initiated antiviral prophylaxis by gastroenterologists before biological treatment. Although all the patients in this study were at low risk for HBV reactivation with biologics, while antiviral prophylaxis was recommended in some patients, and were not recommended in some patients. Unfortunately, no guidelines exist for this particular issue with clear suggestions. It seems that while some gastroenterologists prefer antiviral prophylaxis over monitoring for patients with HBcAb positive receiving biologic drugs, some prefer monitoring over antiviral prophylaxis. It is understood that the decision to administer antiviral prophylaxis for patients with HBcAb positive depends on the physician's discretion, unless the risk of HBV reactivation in patients with HBsAg negative and HBcAb

Table 3: Summary of reports and studies describing hepatitis B virüs reactivation in patients psoriasis on biologic therapies

Study	Disease, *n*	HBsAg+ (inactive carriers), *n*	HBcAb+ HBsAb± (past or isolated), *n*	Biologic therapies (mostly used)	Prophylaxis, *n*	Reactivation, *n* (%)*
Charpin *et al*., 2009[18]	PsA, 5	0	5	ETA	0	0
Prestinari *et al*., 2010[19]	PsO, 1	0	1	ETA	0	0
Nosotti *et al*., 2010[20]	PsO, 4; PsA, 3	1	6	ETA	1	0
Caporali *et al*., 2010[21]	PsA, 4	0	4	INF	0	0
Kim *et al*., 2010[3]	PsA, 2	0	2	ETA	0	0
Fotiadou *et al*., 2011[22]	PsO, 7	7	0	ADA, ETA	7	0
Prignano *et al*., 2011[23]	PsO, 12	0	12	ETA	0	0
Cassano *et al*., 2011[24]	PsO, 28; PsA, 34	0	62	ETA	0	0
Cho *et al*., 2012[25]	PsO, 7	7	0	ETA	1	0
Koskinas *et al*., 2013[26]	PsO, 1	0	1	UST	0	1
Laurenti *et al*., 2013[27]	PsA, 8	1	7	ADA	1	0
Navarro *et al*., 2013[28]	PsO, 5	5	0	ETA	5	0
Notarnicola *et al*., 2014[29]	PsA, 1	0	1	INF	0	1
Navarro *et al*., 2014[30]	PsO, 13	0	13	ETA	0	0
Sanz-Bueno *et al*., 2015[31]	PsO, 20	0	20	ETA, ADA	0	0
Snast *et al*., 2017[15]	PsO, 26	1	25	ETA	2	0
Solay *et al*., 2018[17]	PsO, 23	0	23	ADA	3	4 (17.3%)
Ting *et al*., 2018[13]	PsO, 54	10	44	UST	2	3 (5.6%)
Chiu *et al*., 2018[32]	PsO, 49	25	24	SEC	3	7 (14.2%)
This study	PsO, 16	0	16	INF	3	1 (6.2%)

*Percentage values are for studies only. ADA: Adalimumab, ETA: Etanercept, INF: Infliximab, SEC: Secukinumab, UST: Ustekinumab, PsO: Psoriasis, PsA: Psoriatic arthritis, HBV: Hepatitis B virüs, HBcAb: HBV core antibody, HBsAb: HBV surface antibody, HBsAg: HBV surface antigen

positive receiving biologic drugs is entirely clear. Besides the physician's discretion, comorbidity status of patients, and the resources made available by the healthcare system may also impact this decision.[9]

Out of the 16 patients, 13 had HBsAb positive and 3 had HBsAb negative (isolated HbcAb positive) in this study. HBV reactivation occurred in the patient who had both HBcAb and HBsAb positive. While some evidence concerning the risk for HBV reactivation suggests that patients who are HBsAb negative are at slightly higher risk compared with those who are HBsAb positive, several studies suggest that there are limited data on this issue.[33] Therefore, it is not clear whether the risk of HBV reactivation in patients with HBcAb positive receiving biologic drugs varies depending on the HBsAb status.

Most cases of HBV reactivation in patients treated with biologic drugs reported in the literature, occurred in those using infliximab for rheumatological and dermatological diseases.[9] Infliximab ($n = 13$) was the most common biologic agent used, and also found the responsible drug for the reactivation in the patient with past HBV infection in this study. However, there are also various studies reporting that etanercept or adalimumab also were reported as responsible drugs for the reactivation in patients [Table 3]. As a class, TNF-alpha inhibitors have been considered to be associated with a relatively high incidence of HBV reactivation compared to other biologics. There may be two possible explanations for this. The first is that reactivation of HBV in patients receiving TNF inhibitors may be related to a suppressive effect of endogenous TNF-alpha on the replication of HBV. The second is that TNF inhibitors are one of the first biologic drugs that enter the pharmaceutical market. For the second reason, more experience and reports on side effects of TNF inhibitors are expected than interleukin (IL) inhibitors. Although the risk of HBV infection reactivation appears to be low for IL inhibitors (ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab), there are several studies reporting that HBV reactivation occurred in patients with HBV using ustekinumab and secukinumab for psoriasis published in the literature.[13,32] However, it can be said that there is not an increase in HBV reactivation rates based on long-term data on ustekinumab.[15] Clinical data on the effect of IL-17 inhibitors (secukinumab, ixekizumab, brodalumab) on HBV reactivation are limited to case reports. A recent study investigating the risk of reactivation of HBV or HCV in psoriasis patients receiving secukinumab reported that seven of all patients (7/49) developed HBV reactivation.[32] The effects of IL-23 inhibitors (guselkumab, tildrakizumab, risankizumab) on psoriasis patients with HBV are unclear because of excluding patients with HBV from phase trials. However, based on their mechanism of action, IL-17 and IL-23 inhibitors theoretically may not significantly increase the risk of HBV reactivation. Since the risk for reactivation of HBV infection appears to be low for IL-17 and IL-23 inhibitors, these drugs seem to be the preferred biologic agents for psoriasis patients with HBV infection for now.

This study has several limitations. The first one is its retrospective nature. The second one is that the study includes low number of cases. Another one is that the patients who were consulted to the gastroenterologists for the requirement of antiviral prophylaxis, were examined by different gastroenterologists.

Conclusion

On the basis of the available evidence, it remains unclear how exactly the biologic drugs for psoriasis impact viral reactivation. Therefore, it is very important to define the safety profile of biologic drugs in psoriasis patients with positive HBV serology. Although patients who are HBsAg positive are at higher risk for HBV reactivation, patients who are HBsAg negative and HbcAb positive are also at low risk. Therefore, triple serology testing with HBsAg, HBsAb, and HBcAb must be done to identify HBV status before treatment with biologic drugs. The patients who have positive HBV serology must be monitored closely and receive antiviral prophylaxis if they are at moderate to high risk of HBV reactivation. In conclusion, because each patient and its disease have their own characteristics, every patient should be carefully evaluated for the risk: benefit ratio of biologic therapy.

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Conflicts of interest

There are no conflicts of interest.

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