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Risk of HBV Reactivation During Immunosuppressive Therapy in Psoriasis: A Retrospective Analysis

Psoriasis Hastalarında İmmünosüpresif Tedavi Süresince HBV Reaktivasyonu Riski: Retrospektif Bir Değerlendirme

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ABSTRACT

Objectives: This study aimed to evaluate the risk of hepatitis B virus (HBV) reactivation in patients with a history of resolved HBV infection or isolated anti-HB core immunoglobulin G positivity who received systemic immunosuppressive therapy for psoriasis.

Materials and Methods: A retrospective analysis was conducted on patients ≥18 years old with psoriasis who received systemic immunosuppressive therapy (≥3 months), including methotrexate (MTX), apremilast, cyclosporine, and various biologic agents [tumor necrosis factor-alpha, interleukin (IL)-17, IL-23, IL-12/23 inhibitors] between January 2018 and March 2025. Patients with baseline HBV-DNA positivity, human immunodeficiency virus/hepatitis C virus co-infection, or incomplete data were excluded. HBV reactivation was defined as either HB surface antigen (HBsAg) seroconversion or detectable HBV-DNA. Patients were classified into three risk groups based on serological status and immunosuppressive regimen. Anti-HBs levels were categorized (<10 IU/L, 10-99 IU/L, and ≥100 IU/L), and risk factors were analyzed using Fisher's exact test and logistic regression.

Results: Among 1200 patients screened, 138 eligible individuals were included (63.0% male; mean age 56.9±11.8 years). Seven patients (5.0%) experienced HBV reactivation during immunosuppressive therapy, with no cases of acute hepatitis. Reactivation occurred significantly more often in HBsAg-positive and anti-HBs-negative individuals (p=0.008 and p=0.018, respectively). No reactivation was observed in patients with anti-HBs ≥10 IU/L (p<0.001). Logistic regression showed a trend toward higher reactivation risk with HBsAg positivity (odds ratio:

ÖZ

Amaç: Bu çalışmada, geçirilmiş hepatit B virüsü (HBV) veya izole HB çekirdek antijenine karşı gelişmiş immünoglobulin G antikor pozitifliği olan ve sedef hastalığı nedeniyle sistemik immünosüpresif tedavi alan hastalarda HBV reaktivasyon riski değerlendirildi.

Gereç ve Yöntemler: Ocak 2018-Mart 2025 tarihleri arasında, 18 yaş ve üzerindeki psoriazis hastaları retrospektif olarak incelendi. En az üç aydır sistemik immünosüpresif tedavi metotreksat (MTX), apremilast, siklosporin veya biyolojik ajanlar [tümör nekroz faktörü (TNF)-alfa, interlökin (IL)-17, IL-23, IL-12/23 inhibitörü] alan hastalar dahil edildi. Başlangıçta HBV-DNA pozitif olanlar, insan bağışıklık yetmezlik virüsü/hepatit C virüsü ko-enfeksiyonu bulunanlar ve eksik kayıtlı hastalar çalışma dışı bırakıldı. HBV reaktivasyonu, hepatit B yüzey antijeni (HBsAg) serokonversiyonu veya ölçülebilir düzeyde HBV-DNA tespiti olarak tanımlandı. Hastalar serolojik profilleri ve tedavi rejimlerine göre üç risk grubuna ayrıldı. Anti-HBs düzeyleri (<10 IU/L, 10-99 IU/L ve ≥100 IU/L), ayrı ayrı değerlendirildi. Risk faktörleri Fisher'ın kesin testi ve lojistik regresyon analizi ile incelendi.

Bulgular: Taramaya alınan 1200 hastadan 138'i çalışmaya dahil edildi (%63,0 erkek; ortalama yaş 56,9±11,8 yıl). Yedi hastada (%5,0) HBV reaktivasyonu saptandı; hiçbirinde aktif hepatit gelişmedi. Reaktivasyon, HBsAg pozitif ve anti-HBs negatif hastalarda anlamlı olarak daha yüksekti (p=0,008 ve p=0,018). Anti-HBs ≥10 IU/L olan hiçbir hastada reaktivasyon izlenmedi (p<0,001). Lojistik regresyonda HBsAg pozitifliği anlamlılığa yakın risk faktörü olarak izlendi (olasılık oranı: 8,60; p=0,062). Düşük

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8.60; p=0.062). MTX, despite being classified as low risk, was associated with reactivation in HBsAg-positive patients.

Conclusion: HBV reactivation is strongly associated with HBsAg positivity and low or absent anti-HBs levels. Pre-treatment serological screening and close monitoring, especially in anti-HBs-negative individuals, are essential for safe immunosuppressive therapy in psoriasis.

Keywords: Hepatitis B reactivation, psoriasis, immunosuppressive therapy

riskli kabul edilen MTX, HBsAg pozitif bireylerde reaktivasyonla ilişkiliydi.

Sonuç: HBV reaktivasyonu, HBsAg pozitifliği ve düşük/negatif anti-HBs düzeyleriyle güçlü şekilde ilişkilidir. Tedavi öncesi serolojik tarama ve özellikle anti-HBs negatif hastalarda yakın izlem, psoriazis tedavisinde güvenli immünosüpresyon için gereklidir.

Anahtar Kelimeler: Hepatit B reaktivasyonu, psoriazis, immünosüpresif tedavi

Introduction

Psoriasis vulgaris is a chronic inflammatory skin disease characterized by erythematous and scaly plaques. Treatment options for psoriasis vulgaris include conventional therapies such as methotrexate (MTX), cyclosporine, acitretin, and apremilast, as well as biologic agents targeting specific cytokines, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-12/23, IL-17, and IL-23 (1). These agents exert their effects by modulating distinct pathways within the immune system. However, their use in patients infected with hepatitis B virus (HBV) may trigger viral reactivation (2). HBV reactivation can result in serious hepatic complications and may compromise the safety of systemic treatment in affected individuals.

Anti-HB core (anti-HBc) positivity indicates prior exposure to HBV and represents a potential risk for reactivation. In HBsAg-negative individuals, occult HBV infection is characterized by the presence of low-level HBV-DNA in the liver, and occasionally in serum ($<10^3$ copies/mL), despite the absence of detectable surface antigen (3). Approximately 20% of patients with natural immunity exhibit isolated anti-HBc immunoglobulin G (IgG) positivity, a serologic profile that may mask ongoing viral persistence, thereby complicating recognition of reactivation risk (4). Thus, comprehensive serological and virological evaluation is critical prior to initiating immunosuppressive therapy.

This study aimed to assess the frequency of HBV reactivation and the contributing risk factors among psoriasis patients receiving immunosuppressive therapy.

Although the risk of HBV reactivation with certain high-risk immunosuppressive therapies is well known, limited data are available on HBV reactivation risk in psoriasis patients receiving a broader spectrum of systemic treatments, particularly those considered low risk, such as MTX or apremilast. Therefore, this study aimed to fill this gap by systematically evaluating reactivation rates across commonly used agents.

Materials and Methods

Patients aged 18 years or older who were diagnosed with psoriasis vulgaris and followed at the Department of Dermatology, University of Health Sciences Türkiye, Ankara Etlik City Hospital, between January 2018 and March 2025 were retrospectively evaluated. Although HBV reactivation is most commonly observed following the discontinuation of immunosuppressive therapy, cases of reactivation as early as the third month after initiation of treatment have been reported in the literature, characterized by rising HBV-DNA levels. (5,6,7). Therefore, patients who had been receiving systemic immunosuppressive agents for at least three months, including MTX, apremilast, cyclosporine, or biologics such as TNF-α inhibitors, IL-17 receptor blockers, IL-17A inhibitors, anti-IL-12/23, and anti-IL-23 agents, were included. Demographic, clinical, and laboratory data were obtained from the hospital information system.

Eligible patients had negative HBV-DNA at baseline and either isolated anti-HBc IgG positivity or a natural immunity profile (anti-HBc IgG and anti-HBs positive). Accordingly, all 138 patients included in the study had undetectable HBV-DNA at baseline. HBV reactivation risk was classified as high (≥10%), moderate (1-10%), or low (<1%) depending on serologic status and the immunosuppressive agent used (5,8,9). Patients were grouped accordingly into three risk categories. Their immunologic profiles and therapeutic regimens are detailed in Table 1.

According to the available medical records, patients had undergone liver function testing (alanine aminotransferase and aspartate aminotransferase) approximately every three months to monitor for signs of active hepatitis. In cases where elevated liver enzymes were noted, HBsAg and HBV-DNA levels were subsequently assessed (5). HBV reactivation was defined as HBsAg seroconversion or detectable HBV-DNA in serum (10).

Table 1. HBV reactivation risk groups

Group	HBsAg status	Anti-HBc status	Agents used	Risk level	Explanation
Group 1	Negative or positive	Positive	Methotrexate, apremilast, cyclosporine	Low risk	Considered low risk for HBV reactivation.
Group 2	Negative	Positive	TNF-α inhibitors, IL-17R blockers, IL-17A inhibitors, anti-IL-12/23, anti-IL-23	Moderate risk	Considered moderate risk for HBV reactivation.
Group 3	Positive	Positive	TNF-α inhibitors, IL-17R blockers, IL-17A inhibitors, anti-IL-12/23, anti-IL-23	High risk	Received HBV prophylaxis according to current guidelines.

HBsAG: Hepatitis B surface antigen, Anti-HBc: Anti-hepatitis B core, HBV: Hepatitis B virus, TNF: Tumor necrosis factor, IL: Interleukin

Anti-HBs titers were stratified as <10 IU/L, 10-99 IU/L, and ≥100 IU/L, and their association with HBV reactivation was analyzed. Potential effects of age and sex were also evaluated. Patients with HBV-DNA positivity at baseline, human immunodeficiency virus/hepatitis C virus co-infection, liver failure, other significant liver disease, use of non-immunosuppressive systemic agents (e.g., acitretin), combination immunosuppressive therapy, or incomplete records were excluded.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics v15.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to assess the distribution of continuous variables. The Mann-Whitney U test was used for non-normally distributed variables, and associations between categorical variables were analyzed using Fisher's exact test. A multivariate logistic regression analysis was conducted to evaluate independent predictors of HBV reactivation, including age, sex, HBsAg status, anti-HBs titer, immunosuppressive drug type, and treatment duration. A p-value of <0.05 was considered statistically significant.

The study was approved by the Scientific Research Evaluation and Ethics Committee of the University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2025-0290, date: 26.03.2025) and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Results

Among 1,200 psoriasis patients retrospectively reviewed, 200 had serological evidence of past HBV infection (anti-HBc IgG positive). After excluding 62 patients due to detectable HBV-DNA or lack of immunosuppressive therapy, 138 patients were included in the final analysis (Figure 1). Baseline HBV-DNA levels were undetectable in all included patients. Detailed information regarding patients' HBsAg and anti-HBs status, as well as prior systemic immunosuppressive therapies—including those administered to patients who developed HBV reactivation—is summarized in Table 2.

Of the 138 patients included in the study, 87 (63.0%) were male and 51 (37.0%) were female, with a mean age of 56.9±11.8 years (range: 28-80 years). The mean duration of treatment

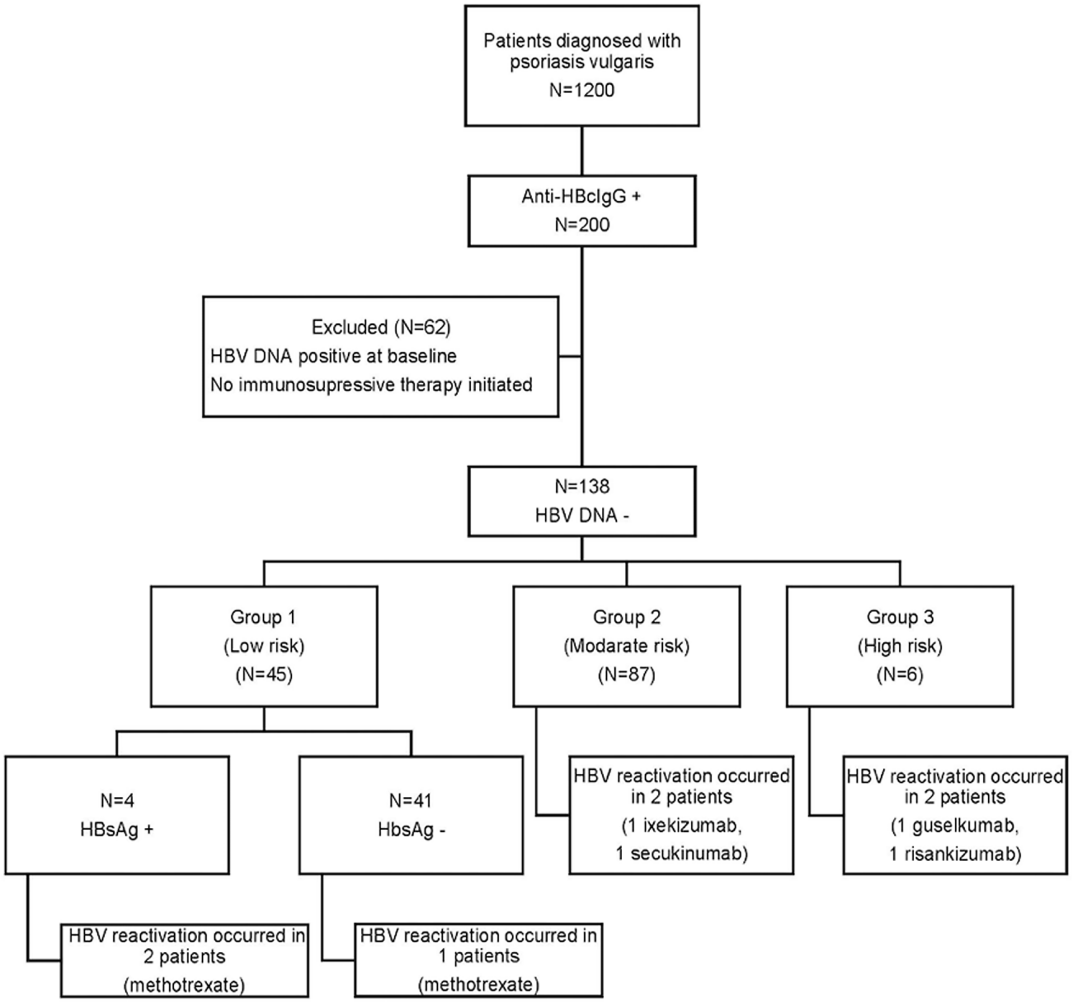

Figure 1. Flow diagram illustrating the characteristics and distribution of the study population
HBV: Hepatitis B virus, HBsAG: Hepatitis B surface antigen

was 21.3±18.9 months (range: 3-108 months). Details regarding treatment agents and durations are provided in Table 3.

Group 1 consisted of 45 patients: 42 on MTX, one on cyclosporine, and two on apremilast. Group 2 included 87 patients, with the most commonly used agent being ixekizumab (n=22), followed by secukinumab (n=18), risankizumab (n=16), ustekinumab (n=12), guselkumab (n=11), adalimumab (n=5), certolizumab (n=2), and bimekizumab (n=1). In group 3, there were six patients who received concurrent antiviral prophylaxis alongside immunosuppressive therapy: two were treated with secukinumab, two with guselkumab, one with risankizumab, and one with ixekizumab.

HBV reactivation occurred in two of the four HBsAg-positive patients in group 1 and in one of the 41 HBsAg-negative patients. In group 2, reactivation was observed in two patients (one on ixekizumab and one on secukinumab), both of whom were HBsAg-negative. In group 3, reactivation developed in two patients (33.3%; 95% confidence interval: 4.3-77.7), both of whom were receiving IL-23 inhibitors (one guselkumab, one risankizumab).

Table 2. Baseline virologic status and treatment history of included patients

Variable	**n (%)**
Number of patients included	138
Baseline HBV-DNA level	Undetectable in all patients
HBsAg status	Positive: 10 (7.2%) Negative: 128 (92.8%)
Anti-HBs status	<10 IU/L: 37 (26.8%) 10-99 IU/L: 31 (22.5%) ≥100 IU/L: 70 (50.7%)
Anti-HBc IgG positivity	138 (100%)
Prior systemic immunosuppressive therapy • Methotrexate • Cyclosporine • Apremilast • Biologics • TNF-alpha inhibitors • IL-17 inhibitors • IL-23 nhibitors • IL-12/23 inhibitors	Yes: 92 (66.7%) No: 46 (33.3%) 88 (63.8%) 40 (29.0%) 5 (3.6%) 4 (2.9%) 3 (2.2%) 1 (0.7%) 0 (0%)
Prior systemic immunosuppressive therapies administered to patients exhibiting reactivation • None • Methotrexate • Adalimumab • Cyclosporine	7 3 (42.9%) 4 (57.1%) 1 (14.3%) 3 (42.9%)

HBV: Hepatitis B virus, TNF: Tumor necrosis factor, IL: Interleukin, HBsAG: Hepatitis B surface antigen, Anti-HBc: Anti-hepatitis B core, Anti-HBs: Anti-hepatitis B surface, IgG: Immunoglobulin G

Table 3. Immunosuppressive agents used in the study population and duration of use

Drug	**Total number (%) (n=138)**	**Mean duration (months) ± SD (min-max)**
Methotrexate	42 (30.4%)	15.95±15.98 (3-80)
Cyclosporine	1 (0.7%)	6.0±0.0 (6-6)
Apremilast	2 (1.4%)	4.5±1.5 (3-6)
Adalimumab	5 (3.6%)	52.2±20.2 (15-72)
Bimekizumab	1 (0.7%)	3.0±0.0 (3-3)
Guselkumab	13 (9.4%)	22.5±19.88 (3-82)
Ixekizumab	23 (16.7%)	20.9±12.34 (6-60)
Risankizumab	17 (12.3%)	14.5±7.31 (6-30)
Secukinumab	20 (14.5%)	24.1±14.6 (6-60)
Certolizumab	2 (1.4%)	30.00±6.00 (24-36)
Ustekinumab	12 (8.7%)	35.75±31.62 (3-108)

SD: Standard deviation, min: Minimum, max: Maximum

Table 4. Characteristics of patients with HBV reactivation and distribution by risk group

Patient no	Age	Sex	Immunosuppressive agent	Risk group	HBsAg status	Anti-HBs status	Time to reactivation (months)	Prophylactic agent used	Development of hepatitis
1	80	M	Methotrexate	Group 1	-	-	10	-	-
2	72	M	Methotrexate	Group 1	+	-	12	-	-
3	65	M	Methotrexate	Group 1	+	-	15	-	-
4	59	M	Secukinumab	Group 2	-	-	6	-	-
5	45	M	Ixekizumab	Group 2	-	-	30	-	-
6	72	F	Risankizumab	Group 3	+	-	6	Entecavir	-
7	39	M	Guselkumab	Group 3	+	-	12	Tenofovir	-

F: Famale, M: Male, HBsAG: Hepatitis B surface, Anti-HBs: Anti-hepatitis B surface, HBV: Hepatitis B virus

Statistical analysis revealed a significant association between reactivation and serological markers (HBsAg and anti-HBs). In group 1, Fisher's exact test showed that anti-HBs-negative individuals had a significantly higher reactivation rate than those who were positive (30% vs. 0%, p=0.008). Reactivation was also significantly more frequent in HBsAg-positive individuals (50% vs. 2.4%, p=0.018). Notably, all cases of reactivation occurred in anti-HBs-negative patients, especially among those who were both HBsAg-positive and anti-HBs-negative; this serological combination was associated with the highest risk.

In group 2, where all 87 patients were HBsAg-negative, reactivation was significantly more common among anti-HBs-negative individuals compared to anti-HBs-positive ones (10.5% vs. 0%, p=0.046). No reactivation was observed in the 68 anti-HBs-positive patients. In group 3, all six patients were both HBsAg-positive and anti-HBs-negative; two developed reactivation (33.3%). Since all patients had the same serological profile, statistical testing could not be performed; however, this profile again appeared to confer high risk.

HBV reactivation occurred exclusively in patients with anti-HBs levels <10 IU/mL. No reactivation was observed among anti-HBs-positive patients (≥10 IU/mL), and this finding was statistically significant (p<0.001, Fisher's exact test).

Overall, seven patients (5.0%) developed HBV reactivation during immunosuppressive therapy, with a mean time to reactivation of 15 months. Antiviral treatment was initiated in these patients, and no cases of clinical hepatitis were observed (Table 4).

There was no statistically significant difference in reactivation rates among different treatment agents (p=0.435). In logistic regression analysis, age, treatment duration, and risk group were not independently associated with reactivation. Additionally, MTX was associated with a 1.33-fold higher odds of HBV reactivation compared to biologic agents, although this difference did not reach statistical significance (p=0.70).

However, HBsAg positivity approached statistical significance [odds ratio (OR): 8.60, p=0.062]. Pairwise comparison using Fisher's exact test showed that HBsAg-positive patients had an approximately 28-fold higher risk of reactivation compared to HBsAg-negative patients (OR: 27.78; p=0.00045), supporting HBsAg positivity as a strong and independent risk factor.

Discussion

HBV infection manifests across a broad clinical spectrum, ranging from acute infection to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. This course is determined by both viral characteristics and the host immune response (11). As of 2022, approximately 254 million individuals globally were living with chronic HBV infection, underscoring its status as a major public health concern (12). The reported prevalence of HBV infection in patients with psoriasis ranges from 0.45% to 5.6% (13,14), and the risk of HBV reactivation in this population varies according to the immunosuppressive regimen and individual serological profile (13).

Although MTX is generally regarded as low risk for HBV reactivation and may be used with close monitoring in the absence of antiviral prophylaxis (9,13), several studies have reported increased risk among HBsAg-positive individuals. One such study in patients with psoriasis identified a reactivation rate of 28.6% in HBsAg-positive MTX users (15). In our study, 2 of 4 HBsAg-positive patients on MTX experienced reactivation (50%), along with 1 of 41 HBsAg-negative patients (2.4%), confirming HBsAg positivity as a strong predictive factor. While current guidelines categorize MTX use as low risk irrespective of HBsAg status, our findings challenge this approach and suggest a need to re-evaluate the risk stratification, especially in the presence of HBsAg positivity. Notably, MTX showed a reactivation rate comparable to or even higher than certain biologics. Although the observed OR did not reach statistical significance, this trend suggests that MTX may not be inherently low risk, particularly in anti-HBs-negative individuals. These findings underscore the importance of nuanced risk assessment and support the need for larger, comparative studies to better guide clinical decision-making and future HBV management strategies.

TNF-α inhibitors are the most extensively studied biologics in terms of HBV reactivation risk (3). Guidelines recommend antiviral prophylaxis in HBsAg-positive patients, with reactivation rates reported between 14% and 63% in the absence of prophylaxis (6). For HBsAg-negative/anti-HBc-positive individuals, the risk is lower (3-5%), and regular monitoring is generally considered sufficient (16). In our cohort, no reactivation was observed among anti-TNF users who were HBsAg-negative.

Studies evaluating ustekinumab, an IL-12/23 inhibitor, report reactivation in 25% of HBsAg-positive and 2.6% of occult HBV-

infected individuals; however, none developed severe hepatitis or liver failure (17). In our study, all patients receiving ustekinumab were HBsAg-negative, and no reactivation occurred, supporting its relative safety in patients with resolved HBV infection.

IL-17 inhibitors (ixekizumab, secukinumab, bimekizumab) are considered low-risk agents (18,19,20). However, in our cohort, reactivation occurred in two patients (20%) with isolated anti-HBc IgG positivity, while no cases were observed among patients with natural immunity. This highlights the protective role of anti-HBs positivity against HBV reactivation.

Although data on IL-23 inhibitors are limited, current evidence suggests a low risk of reactivation (21). In our study, no reactivation was observed in HBsAg-negative patients receiving IL-23 inhibitors. However, among three HBsAg-positive patients on prophylaxis, two (one on guselkumab, one on risankizumab) developed reactivation. This suggests that IL-23 inhibitors cannot be considered inherently safe in HBsAg-positive patients, and warrant close monitoring even with prophylaxis.

A recent meta-analysis reported HBV reactivation rates of 25.3% in high-risk and 5% in moderate-risk patients not receiving prophylaxis (22). In our study, these rates were 33.3% and 2.3%, respectively. While the discrepancy may be due to sample size, the results underscore the importance of considering HBsAg and anti-HBs status when using biologics.

Factors such as advanced age, prolonged immunosuppression, and high-potency immunosuppressants may contribute to reactivation despite antiviral prophylaxis (23). In the present study, two of six HBsAg-positive patients receiving antiviral prophylaxis experienced reactivation (33.3%). The study's findings indicated that both subjects were anti-HBs negative and on IL-23 inhibitors, suggesting that the absence of anti-HBs may be an additional risk factor that warrants further consideration. The potential for antiviral resistance should be considered, although it should be noted that resistance testing was not performed in the present study.

Anti-HBs positivity has consistently been associated with a lower risk of reactivation in patients receiving biologics. Some studies suggest that only high titers (e.g., ≥100 IU/L) confer significant protection (24,25,26). Moreover, anti-HBs titers may decline over time in immunosuppressed individuals, increasing vulnerability to reactivation. High-dose vaccination strategies may also fail to elicit protective titers in this population (27). All reactivation cases in our study occurred in patients with anti-HBs levels <10 IU/L. The absence of reactivation among anti-HBs-positive patients supports the antibody's protective role. Therefore, both the presence and the quantitative level of anti-HBs should be considered when formulating prophylactic or monitoring strategies.

This study represents one of the few comprehensive investigations of HBV reactivation risk associated with various immunosuppressive therapies in psoriasis. Stratification by HBsAg, anti-HBc, and anti-HBs status, as well as separate analysis of patients receiving prophylaxis, enabled precise evaluation of serological risk profiles. Additionally, drug-specific reactivation rates offer clinically actionable insights for therapeutic decision-making.

Study Limitations

The retrospective design of the study limits the ability to establish causality. Small sample sizes in some subgroups may reduce the statistical power of the analyses. Moreover, the absence of antiviral resistance testing precluded clarification of the underlying mechanisms in patients who developed reactivation despite prophylaxis. Future prospective studies with larger cohorts and genotypic resistance assessments are warranted to validate our findings.

Conclusion

HBV reactivation was most frequently observed in HBsAg-positive and anti-HBs-negative patients, and less commonly in those with isolated anti-HBc positivity. No reactivation occurred in patients who were anti-HBs positive, underscoring the protective role of this antibody.

Reactivation despite antiviral prophylaxis suggests that additional risk factors—such as advanced age, prolonged immunosuppressive treatment, potent immunosuppression, and possible antiviral resistance—should be considered. Notably, MTX-induced reactivation in HBsAg-positive patients challenges its current classification as a universally low-risk agent.

Therefore, comprehensive pre-treatment HBV serological screening is essential before initiating immunosuppressive therapy in psoriasis. Prophylaxis should be implemented as indicated, and anti-HBs-negative patients require close monitoring during therapy. Importantly, even patients receiving antiviral prophylaxis must undergo regular HBV-DNA surveillance to ensure early detection of reactivation and prevention of serious complications. Furthermore, no reactivation events were observed among anti-HBs-positive patients treated with anti-TNF agents, supporting their continued classification as low-risk options. Nevertheless, even these agents should be used with caution in seronegative individuals until larger studies confirm their safety.

Ethics

Ethics Committee Approval: The study was approved by the Scientific Research Evaluation and Ethics Committee of the University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2025-0290, date: 26.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: G.T.A., O.K.Y., H.K., B.Ç.C., S.P.K., Design: G.T.A., A.H.S., O.K.Y., H.K., B.Ç.C., Data Collection or Processing: G.T.A., O.K.Y., H.K., Analysis or Interpretation: G.T.A., A.H.S., Literature Search: G.T.A., A.H.S., B.Ç.C., S.P.K., Writing: G.T.A., A.H.S., B.Ç.C., S.P.K.

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