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Research Article

Prevalence of Hepatitis B Serology and Reactivation in Rheumatology Patients Receiving Biologic or Targeted Synthetic Disease-Modifying Antirheumatic Drugs

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Abstract

Aim: This study sought to assess hepatitis B virus (HBV) serology and the incidence of HBV reactivation (HBVr) in rheumatology patients with resolved hepatitis B infection (HBsAg negative and HBcAb positive) who were undergoing treatment with biologic or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs).
Material and Method: Data from rheumatology patients treated with b/tsDMARDs were retrospectively reviewed from the electronic records. The demographic data, the anti-rheumatic drugs used, and the hepatitis serologies (HBsAg, anti-HBc IgG, anti-HBs, and anti-HCV) of the patients were analyzed.
Results: The study included a total of 316 patients, of whom 217 (68.7%) were diagnosed with ankylosing spondylitis, 74 (23.4%) with rheumatoid arthritis, and 25 (7.9%) with psoriatic arthritis. Evaluation of the patients' viral serologies revealed that four (1.2%) were HBsAg positive, and 18 (5.7%) were HBsAg negative and HBcAb positive. Anti-HCV positivity was observed in one (0.3%) patient. All serologies were negative in 153 (48.4%) patients. No HBVr was detected during the follow-up of the patients.
Conclusion: The rate of resolved hepatitis B infection is relatively high in patients under rheumatologic follow-up. However, the use of biologics in these patients poses a low risk of HBVr.

Keywords: Biologic therapy, b/tsDMARD, hepatitis B virus reactivation, rheumatologic diseases

INTRODUCTION

Both rheumatic inflammatory diseases and viral hepatitis are serious health issues. It is known that approximately one in three people in the world is infected with hepatitis B virus (HBV) (1). In Türkiye, it is estimated that around 3.3 million people are HBV carriers, with an overall prevalence rate of 4.57% (2).

The pathogenesis of rheumatologic diseases is based on autoimmunity, necessitating the use of immunosuppressive agents in their treatment. Immunosuppressive therapy encompasses corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic disease-modifying antirheumatic drugs (bDMARDs), and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) (3). CsDMARDs include drugs like azathioprine, sulfasalazine, leflunomide, hydroxychloroquine, minocycline and methotrexate. bDMARDs consist of interleukin (IL)-1 inhibitors (canakinumab and anakinra), tumor necrosis factor (TNF) inhibitors (adalimumab, infliximab, etanercept, certolizumab and golimumab), IL-17 inhibitors (ixekizumab and secukinumab), IL-6 inhibitors (tocilizumab), and IL-23 inhibitors (guselkumab and ustekinumab). TsDMARDs include JAK kinase inhibitors such as tofacitinib, filgotinib, peficitinib, upadacitinib, and baricitinib (4). In recent years, b/tsDMARDs used in the treatment of rheumatic diseases have revolutionized rheumatology. However, these treatments have strong immunosuppressive effects (5). Extended use of b/tsDMARDs has been linked to a higher frequency of activation of opportunistic infections, tuberculosis, herpes zoster and infections caused by HBV or Hepatitis C virus (HCV) (6). Recent guidelines recommend hepatitis screening before starting biologic therapy (5,7). For

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patients who are HBsAg positive, prophylactic antiviral treatment is advised before initiating b/tsDMARD therapy. However, recommendations for HBsAg negative and HBcAb positive patients differ, and there is no agreed-upon guideline for prophylactic treatment (1). However, although the risk of HBVr in HBsAg negative and HBcAb positive patients is lower compared to HBsAg positive patients, the prevalence of HBcAb positive patients is higher than that of HBsAg positive patients (8). The general strategy is to handle HBsAg negative and HBcAb positive patients with detectable HBV DNA in a manner similar to HBsAg positive patients. For those with negative HBV DNA, regular monitoring of aminotransferase and HBV DNA levels is recommended, or they may be given prophylactic antivirals like lamivudine (9).

In this study, our goal was to evaluate the seroprevalence of HBV in patients diagnosed with ankylosing spondylitis (AS), rheumatoid arthritis (RA), and psoriatic arthritis (PsA) who were treated with various b/tsDMARDs at our center, and to assess the risk of HBV reactivation in patients with HBsAg negative and HBcAb positive serology.

MATERIAL AND METHOD

This retrospective study involved the electronic review of the data from a total of 316 patients diagnosed with AS, RA, and PsA who visited the physical therapy and rehabilitation outpatient clinic and the pulmonary diseases outpatient clinic for drug safety monitoring between January 1, 2018, and December 31, 2023, and were treated with b/tsDMARDs. The recorded data included patients' age, gender, diagnosis, b/tsDMARD therapy, hepatitis serology (HBsAg, HBsAb, HBcAb, and anti-HCV), and serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. An anti-HBs value above 10 mIU/mL was considered positive.

Inclusion and Exclusion Criteria

The inclusion criteria were being aged 18 or over, being diagnosed with AS, RA, or PsA, undergoing b/tsDMARD therapy, having hepatitis serology (HBsAg, HBsAb, HBcAb and anti-HCV) tests annually, and having AST and ALT levels measured every three months. Patients who did not meet these criteria and those with incomplete data were excluded. The study received approval from the local ethics committee at Ordu University Faculty of Medicine (decision number: 2024/56).

Statistical Analysis

All statistical analyses were conducted using the SPSS software (version 22.0, Inc., Chicago, Illinois, USA). Comparative statistical tests were not used. Simple descriptive statistics, such as percentages and means, were utilized.

RESULTS

A total of 316 patients diagnosed with AS, RA, and PsA who were being followed up at our hospital under any of the b/tsDMARD therapies were retrospectively evaluated. The mean age of the patients was 47.87±12.59 years, with 160 (50.6%) males and 156 (49.4%) females. Among the patients, 217 (68.7%) had AS, 74 (23.4%) had RA, and 25 (7.9%) had PsA. Regarding the b/tsDMARDs used, 100 patients were on adalimumab, 89 on etanercept, 35 on secukinumab, 34 on certolizumab, 27 on golimumab, 16 on infliximab, nine on tofacitinib, three on tocilizumab, and three on baricitinib. Concerning the viral serologies, four (1.2%) patients were HBsAg positive, 18 (5.7%) were HBsAg negative and anti-HBc IgG positive, and 52 (16.5%) were HBsAg positive and anti-HBc IgG positive. Anti-HCV positivity was found in one (0.3%) patient. The number of patients with negative serologies for all markers was relatively high, at 153 (48.4%). Tenofovir was used prophylactically in 4 HBsAg positive patients. None of the other patients were receiving antiviral treatment. No reactivation was detected in any of the patients (Table 1).

Table 1. Clinical characteristics of the patients

Clinical characteristics	n (%)
Age, mean±SD	47.87±12.59 (19-77)
Gender	
Male	160 (50.6%)
Female	156 (49.4%)
Disease diagnosis	
Ankylosing spondylitis	217 (68.7%)
Rheumatoid arthritis	74 (23.4%)
Psoriatic arthritis	25 (7.9%)
B/tsDMARD	
Adalimumab	100 (31.6%)
Etanercept	89 (28.2%)
Secukinumab	35 (11.1%)
Certolizumab	34 (10.8%)
Golimumab	27 (8.5%)
Infliximab	16 (5.1%)
Tofacitinib	9 (2.8%)
Tocilizumab	3 (0.9%)
Baricitinib	2(0.6%)
Abatacept	1 (0.3%)
Viral serology	
HBsAg positive	4 (1.2%)
HBsAg negative and anti-HBc IgG positive	18 (5.7%)
HBsAg positive and anti-HBc IgG positive	52 (16.5%)
Anti-HCV positive	1 (0.3%)
All serologies negative	153 (48.4%)
HBV reactivation	0

DISCUSSION

Globally, more than 2 billion individuals are estimated to have been exposed to HBV, with approximately 292 million suffering from chronic infections (10). It is known that

immunosuppressive therapies increase the risk of HBV. These treatments can cause reactivation in patients with HBsAg negative and HBcAb positive, causing various liver problems that can result in death (11). The risk of HBVr is affected by host factors, HBV viral status, as well as the type and duration of immunosuppressive therapy (12). A systematic review showed that 6.5% of HBsAg negative and HBcAb positive patients receiving immunosuppressive therapy had HBVr. In the same study, when patients were grouped, the HBVr rate was reported as 10.9% in those with hematological disease, while this rate was reported as 3.6% in those without hematological disease. The findings also indicated that the risk of HBVr was lower in patients with non-hematologic conditions and those not on rituximab-containing regimens. As a result, it was concluded in the study that anti-HBV prophylaxis may not be necessary for patients who are HBsAb positive and HBV DNA negative (8).

In rheumatic diseases like RA and AS, the risk of reactivating viral infections is heightened by immunosuppressive therapy. The frequency of HBV infection in these patients is thought to be the same as in the general population, with an estimated HBsAg positive prevalence ranging from 3% to 3.5% and a past infection rate of 13% to 50% (12). Therefore, it is recommended that patients with rheumatologic diseases receiving immunosuppressive therapy, such as DMARDs, undergo appropriate screening and treatment to mitigate the risk of HBVr (11). In a study conducted by Fidan et al. with 272 HBsAg negative and HBcAb positive patients, no HBVr was observed in the 31 patients receiving antiviral prophylaxis, while only one (0.4%) of the 241 patients not receiving prophylaxis experienced HBVr (13). Similarly, a multicenter study by Çapkın et al. found a reactivation rate of 11.4% in HBsAg positive rheumatology patients receiving biologics, compared to a reactivation rate of 0.82% in HBsAg negative and HBcAb positive patients (14). A recent study reported that HBV DNA development was at a very low rate of 0.9% for all biological agents in HBsAg negative and HBcAb positive patients using biological agents, thus posing a very low risk of reactivation (15). In another study, all HBsAg positive or HBsAg negative and HBcAb positive patients were given prophylactic antiviral treatment with entecavir or tenofovir before starting b/tsDMARD therapy, and no HBVr was observed during the study period. The absence of reactivation was attributed to the antiviral treatment administered (1). A recent meta-analysis included 26 studies involving a total of 2252 HBsAg negative and HBcAb positive patients with RA receiving b/tsDMARD therapy. IL-6, TNF-a and JAK inhibitors were found to have low HBVr rates of 0%, 0% and 1%, respectively. The study shows that each of these three agents is safe for patients with RA and prophylactic antiviral treatment may not be necessary due to low reactivation rates and cost-effectiveness (16). In our study, four patients were HBsAg positive and all were using tenofovir prophylactically. Additionally, 18 patients were HBsAg negative and HBcAb positive, and 52 were HBsAg positive and HBcAb positive. None of these patients were receiving prophylactic antiviral treatment, and no reactivation was detected during follow-up.

Studies have presented conflicting information on the HBVr risk in HBsAg negative and HBc Ab positive rheumatologic patients receiving biologic therapy, with the prevalence ranging from 0 to 5.5% (6). In our study, no HBVr was observed in AS, RA, and PsA patients receiving different b/tsDMARD therapies. The discrepancy in reactivation incidence among different studies may be due to variations in follow-up duration and/or the number of patients included. Studies indicate that the HBVr rate is very low, especially in patients with resolved HBV infection; thus, prophylactic antiviral treatment for these patients remains a topic of discussion.

In our study, we observed that 153 (48.4%) patients had negative serologies for all markers, highlighting gaps in patient management. Türkiye is considered an intermediate endemic region, and mandatory HBV vaccination at birth commenced in 1998, indicating that individuals born before this date are at risk (17). Ideally, hepatitis markers should be requested from all rheumatology patients after diagnosis, especially in areas with high HBV prevalence. HBV vaccination should be administered before starting anti-TNF therapy or within the first six months of treatment due to potential reductions in vaccine efficacy associated with these drugs (18).

The limitations of this study involve the relatively brief follow-up period and the retrospective nature of the design. However, the study's strength lies in the inclusion of patients receiving various b/tsDMARD therapies with regular three-month follow-ups.

CONCLUSION

Although HBc IgG positivity is highly prevalent in RA, AS, and PsA patients, the HBVr rate is very low. Additionally, a significant portion of rheumatology patients in Türkiye have not been vaccinated against HBV. Despite the low HBVr rate, it would be beneficial to screen and vaccinate these patients before initiating immunosuppressive therapy, given the potential need for lifelong immunosuppressive treatment.

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