



Prevalence of Hepatitis B Virus Serological Groups in Rheumatoid Arthritis and Association of Previous Hepatitis B Virus Infection with Demographic Data and Parenteral Therapies

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ABSTRACT

Background: The aim of this study is to determine the frequency of Hepatitis B virus (HBV) serological groups in Rheumatoid arthritis (RA) and to compare the demographic characteristics and frequency of parenteral therapies between patient groups with and without previous HBV infection.

Material and Methods: Charts of RA patients were examined retrospectively. HBsAg, anti-HBc IgG, and anti-HBs test results were screened. All participants were divided into 3 serological groups (patients naive to HBV infection, previous HBV infection, vaccinated). Those with previous HBV infection were further divided into 3 serological subgroups (naturally immune, anti-HBc IgG positive only, chronic HBV infection). Findings were compared between RA patients with and without previous HBV infection.

Results: Four hundred and fifty-one patients (female/male: 343/108) were included. The prevalence of patients naive to HBV infection, with previous HBV infection and vaccinated were 59.4%, 33.7%, and 6.9%, respectively. The prevalence of patients with naturally immune, anti-HBc IgG positive only, and chronic HBV infection were 25.7%, 4.4%, and 3.5%, respectively. Age in RA patients with and without previous HBV infection was 60.8 ± 12.4 and 56.7 ± 14.2 years, respectively ($p < 0.001$). The frequency of previously administered joint injection, subcutaneous and intravenous therapies in RA patients was not different between the groups ($p = 0.644$, $p = 0.796$, and $p = 0.686$, respectively).

Conclusions: Chronic HBV infection in RA patients is close to the prevalence in the Turkish population. Previous HBV infection is common in RA and this group is older than those without previous HBV infection. Parenteral therapies in RA treatment options do not change the frequency of HBV exposure.

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Introduction

Hepatitis B virus (HBV) continues to be an important public health problem due to the mortality and morbidity it causes worldwide. Although HBV seroprevalence varies between regions, approximately 3% of the world population has chronic HBV disease.^{1,2} The rate of chronic HBV infection and the frequency of being infected with the HBV in Turkey is high. In a multi-center study conducted in Turkey, HBsAg positivity was found to be 4.0% and anti-Hepatitis B core antigen (HBc) IgG positivity was found to be 30.6%.³ Rheumatoid arthritis (RA) is a systemic inflammatory disease of unknown etiology, mainly involving the synovial membranes. Biological drugs such as rituximab and tumor necrosis factor (TNF) α inhibitors, disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, leflunomide, sulfasalazine and bridging drugs such as corticosteroids are frequently and continuously used in the treatment course of RA patients. These immunosuppressive (IS) drugs may cause reactivation in those with previous HBV infection, and the frequency of reactivation varies according to the serological group of HBV occurring in the host following HBV infection.⁴⁻⁷ While reactivation is most common in HBsAg (+) individuals following IS therapy, the frequency of reactivation varies significantly in HBsAg (-)/anti-HBc IgG (+) individuals according to the positive and negative status of antibodies against hepatitis B surface antigen (anti-HBs).^{6,7} Therefore, it is important for clinicians to have information about the frequency of HBV serological groups in RA patients. HBV can be transmitted sexually and parenterally. Parenteral treatments such as subcutaneous treatments and intravenous drugs, as well as interventional procedures such as intra-articular injections are among the treatment options for RA patients. According to the limited data in the literature HBsAg positivity in RA patients in Turkey is close to the frequency in the general population, but we have no information about the prevalence of HBV serological groups of RA patients in Turkey.^{3,8} In addition, we do not have any information on whether these parenteral treatments and interventional procedures, which are frequently used in RA patients, increase transmission.

The aim of this study is to determine the

frequency of HBV serological groups by investigating the seroprevalence of HbsAg, anti-HBc IgG and anti-HBs in RA patients followed up in a single center, and to compare demographic characteristics and frequency of parenteral therapies between patient groups with and without previous HBV infection.

Material and Methods

Study Design

Ethics committee approval of the study was obtained from Bursa Yuksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee (2011-KAEK-25 2018/11-12). The study was designed as a retrospective study and the charts of 1053 patients who were followed up with the diagnosis of RA in the Rheumatology department were examined. In the preliminary examination, the information recorded in the patients' charts was examined first, and when the investigated data were not found in the charts, the electronic archive records were examined.

Inclusion criteria: Those whose current disease age is over 18, those who were diagnosed with RA by a specialist rheumatologist and had a rheumatology follow-up chart were included.

Exclusion criteria: Patients for whom all HBV serological test results (HBsAg, anti-HBc IgG and anti-HBs) could not be reached from the follow-up charts or electronic archive were excluded.

Examining the Data of the Patients Included in the Study

Demographic information (age and gender), disease duration, auto-antibody tests [Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP)] were obtained from records of patients whose HBV serological test results were available. In addition, it was investigated whether intra-articular injection, subcutaneous treatments [subcutaneously administered methotrexate and/or insulin and/or biological therapy (etanercept, adalimumab, golimumab, serralizumab)] or intravenous therapy (infliximab, rituximab, tocilizumab or abatasept) were applied before the date of HBV serological tests.

Hepatitis B Serological Subgroups

All participants were divided into 3 serological groups according to their HBV serological test results;

- Patients naive to HBV infection: HBsAg (-), anti-HBc IgG (-), anti-HBs (-)
 - Previous HBV infection: HBsAg (-/+), anti-HBc IgG (+), anti-HBs (-/+)
 - Vaccinated: HBsAg (-), anti-HBc IgG (-), anti-HBs (+)
- Those with previous HBV infection were further divided into 3 subgroups;
- Naturally immune: HBsAg (-), anti-HBc IgG (+), anti-HBs (+)
 - Anti-HBc IgG positive only: HBsAg (-), anti-HBc IgG (+), anti-HBs (-)
 - Chronic HBV infection: HBsAg (+), anti-HBc IgG (+), anti-HBs (-)

Comparisons Between Serological Groups

Demographic data, disease duration, presence of RF and anti-CCP autoantibodies were compared between serological groups of RA patients with and without previous HBV infection. Medical history including intra-articular injection, subcutaneous therapy and intravenous therapy was compared between the groups of patients with and without previous HBV infection.

Statistical Analysis

Descriptive statistical data were given together with mean, standard deviation, median, minimum, maximum values and frequencies. Shapiro-Wilks or Kolmogorov-Smirnov test

was used to determine whether the continuous variables had normal distribution or not. In the comparison of quantitative data between the groups, the Student's t-test was used when there was normal distribution, and the Mann-Whitney-U test was used when there wasn't normal distribution. Fisher's exact test or Chi-square (χ^2) test was used for the comparison of qualitative data between the groups.

Results

HBV Test Results and HBV Serological Groups in the Study Population

Among 1053 patients, 451 patients (343 females and 108 males, mean age 57.7 ± 13.8 years) whose all HBV serological test results could be reached were included in the study. Demographic data, HBV serological test results and HBV serological groups of RA patients included in the study are shown in Table 1. HBsAg positivity was 3.5% and anti-HBc IgG positivity was 33.7%. The frequency of those naive to HBV infection was 59.4%, while the frequency of those vaccinated was 6.9%. Out of 152 patients with previous HBV infection, 116 were positive for anti-HBs antibodies (naturally immune), while 20 were found to be negative for anti-HBs antibodies (Anti-HBc IgG positive only).

Table 1. Demographic data, HBV serological test results and HBV serological subgroups of rheumatoid arthritis patients included in the study.

	(n=451)
Age, mean \pm SD,	57.7 \pm 13.8
Female, n (%)	343 (76.1)
<i>HBV serological test results, n (%)</i>	
HBsAg	16 (3.5)
Anti-HBs	148 (32.8)
Anti-HBc IgG	152 (33.7)
<i>HBV serological groups, n (%)</i>	
Patients naive to HBV infection	268 (59.4)
Previous HBV infection	152 (33.7)
Naturally immune	116 (25.7)
Anti-HBc IgG positive only	20 (4.4)
Chronic HBV infection	16 (3.5)
Vaccinated	31 (6.9)

SD: standard deviation, HBsAg: Hepatitis B surface antigen, HBc: Hepatitis B core antigen, HBV: Hepatitis B virus.

Table 2. Comparison of demographic data, duration of disease, autoantibodies and parenteral treatments between those with and without previous HBV infection among RA patients.

	Previous Hepatitis B infection + n= 152	Previous Hepatitis B infection - n=299	p
Age, mean±SD	60,8±12.4	56.7±14.2	<0.001
Age distribution, n (%)			
Under 30	2 (1.3)	9 (3.0)	
30-40	4 (2.6)	31 (10.4)	
40-50	22 (14.5)	53 (17.7)	
50-60	35 (23.0)	79 (26.4)	
60-70	57 (37.5)	74 (24.7)	
70-80	23 (15.1)	40 (13.4)	
80-90	6 (3.9)	12 (4.0)	
Over 90	3 (2.0)	1 (0.3)	
Gender, n (%)			0.076
Female	108 (71.5)	235 (78.3)	
Male	43 (28.5)	65 (21.7)	
Disease duration, years	5.0 (1-40)	5.0 (1-40)	0.597
Autoantibodies, positive, n (%)			
RF	107 (70.4)	181 (60.7)	0.044
Anti-CCP	90 (59.2)	161 (54.0)	0.295
Parenteral therapies, n (%)			
Subcutaneous treatment	102 (67.1)	197 (65.9)	0.796
IV treatment	9 (5.9)	15 (5.0)	0.686
Intraarticular injection	3 (2.0)	8 (2.7)	0.644

RA: rheumatoid arthritis, SD: standard deviation, min: minimum, max: maximum, RF: rheumatoid factor, Anti-CCP: Antibodies against cyclic citrullinated peptide, IV: intravenous.

Comparison of Data Between the Groups

Comparison of demographic data, duration of disease, autoantibodies and parenteral treatments between those with and without previous HBV infection among RA patients is shown in Table 2. Mean age in RA patients with and without previous HBV infection was 60.8±12.4 and 56.7±14.2 years, respectively ($p<0.001$). While RA patients with previous HBV infection mostly cluster in the age range of 60-70 years (37.5%), RA patients without previous HBV infection mostly cluster between the ages of 50-60 years (26.4%). RA disease duration and gender distribution were not different between the groups. RF positivity was found in 70.4% and 60.7% of RA patients with and without HBV infection, respectively ($p=0.044$). Anti-CCP positivity was not different between the groups ($p=0.295$). The frequency of previously administered parenteral therapies (joint injection, subcutaneous and intravenous therapies) in RA patients was not

different between the groups ($p=0.644$, $p=0.796$ and $p=0.686$, respectively).

Discussion

In this study, HBV seroprevalence was investigated in a cohort of RA patients from a single center in the eastern region of one of the largest cities in Turkey. The prevalence of chronic HBV infection in our RA cohort, was found to be close to the normal population prevalence of chronic HBV in Turkey. It was also found that one third of the RA patients in our cohort had previous HBV infection, most of whom developed anti-HBs. When demographic data were compared between those with and without previous HBV infection, it was found that gender distribution was not different between the groups, but those with previous HBV infection were older. In addition, it was observed that parenteral treatment and interventions were

not different between those with and without previous HBV infection. Although no research has been conducted in our country according to HBV serological groups in RA patients, in the study of Yılmaz et al.⁸ HBsAg seroprevalence was found to be 2.3% in RA patients, and it was found that HBV seroprevalence was most common in the age range of 60-69 years in these patients. Similarly, in the present study, the most common age range in which RA patients with previous HBV infection cluster was found between the ages of 60-70 years, and the HBsAg seroprevalence was found to be close to the frequency of HbsAg positivity in the study conducted by Yılmaz et al.³ In a multicenter study HBsAg positivity was found in 4.0% of the normal population in Turkey. Therefore, we can say that chronic HBV infection in RA patients in our country is at least not higher than the normal population. The fact that the duration of RA disease was not different between those with and without previous HBV infection in the present study is another proof that the presence of RA does not change the risk of HBV infection in our country. However, in order to make a definite comment on this issue, it is necessary to conduct studies comparing the HBsAg seroprevalence between healthy population and RA patients in our country. Already, the data of studies in some other countries contradict our findings. In a study conducted in Israel, by Mahroum et al.⁹ the prevalence of chronic HBV in RA patients was found higher than the control group (1.19% vs 0.63%, $p < 0.001$). And in another study conducted in Belgium, Permin et al. found that 3 of 74 RA patients (4%) were HBsAg positive (10). Although no comparison with the control group was made, the rate they found is much higher than the general chronic HBV prevalence in Belgians (0.67%).¹¹

The current HBV serological group and the immunosuppressive drug to be used are the most important factors affecting whether reactivation occurs after immunosuppressive drugs in patients who have previously had HBV infection. Rituximab and high doses of corticosteroids are the most common causes of reactivation, followed by anti-TNF drugs.¹² The serological group at greatest risk is the group that is HBsAg positive. In the study of Chiu et al.⁵

while the frequency of detecting ALT elevation increased 3 times in HBsAg positive patients compared to non-infected patients in the use of anti-TNF drugs, there was no difference in HBsAg (-)/anti-HBc IgG (+) patients compared to those who were not infected. In the study of Tamori et al.⁶ reactivation was observed in 2 of 5 patients with HBsAg (+), while reactivation was detected in only one of 45 patients with HBsAg (-)/anti-HBc IgG (+) after anti-TNF drug use. In the HBsAg (-)/anti-HBc IgG (+) serological group, the most important factor affecting whether reactivation occurs is the presence of anti-HBs antibody. Chen et al.⁷ investigated the frequency of reactivation in 103 patients with HBsAg (-)/ anti-HBc IgG (+) following rituximab treatment and found the reactivation frequency to be 20% in those with anti-HBs (-) and 4% in those with anti-HBs (+). In the study of Fukuda et al.¹³ as a result of a 4-year follow-up of patients with previous HBV infection and using corticosteroids and synthetic DMARDs, they found that being over 70 years of age and having anti-HBs (-) in this group of patients were independent risk factors for reactivation. In our cohort, 3/4 of those with previous HBV infection were found to have anti-HBs antibodies, and only 1/5 of them were over 70 years old. According to these results we can conclude that many of the patients receiving IS drugs with previous HBV infection in our cohort were not in the risk group for HBV reactivation.

Although HBV has not been found to be an etiological factor in the occurrence of RA in the studies conducted so far, a relationship has been found between HBV infection and autoantibodies especially with RF. When Su et al. evaluated the risk of hepatitis C virus (HCV) and HBV infections to develop RA, they found that while HCV increased the risk of RA, HBV did not (14). Shim et al.¹⁵ found RF positivity as 3.7% in healthy population in Korea, while they found RF positivity as 11.8% in HBsAg positive patients. When Generalli et al.¹⁶ examined a 15-year database, among HBsAg positive patients, they found a relative risk of 5.7 (CI: 1.2-26.3) indicating RA development in those with RF (+), compared to 13.2 (CI: 3.8-46.3) in those with anti-CCP (+). All these results suggest that RF positivity in chronic HBV patients can be seen

independent of the presence of RA. As a matter of fact, in our study, in accordance with the literature data, RF positivity was found with a higher frequency in RA patients with previous HBV infection compared to those who did not have HBV before. The reason why RF was more common in RA patients with previous HBV infection in our study may be related to the increase in the formation of RF autoantibodies induced by HBV.

In our study, the percentage of patients who received neither subcutaneous nor IV treatment was found to be different between RA patients with and without previous HBV infection. In addition, the frequency of intra-articular injection was not different between the groups. These results suggest that parenteral treatment and procedures in RA patients do not affect HBV transmission. Besides, HBsAg seroprevalence was not found to be higher than the country average in the RA cohort in our study. Today, the use of subcutaneous treatments mostly with disposable injectors and the increasing hygiene conditions in our country may be the reasons for the seroprevalence of HBV, which is not seems to be different from the normal population, in RA patients with intensive parenteral treatments.

The data of this study were obtained retrospectively from a single center, which reduces the reliability of the data. Our findings need to be confirmed by multi-center prospective studies. A larger sample size is needed to assess the effects of interventional procedures across the groups. In addition, since the drugs used by the patients were obtained from the records in our study, we may have made insufficient evaluation due to the lack of information such as whether the patients actually used these drugs and how often they used them.

In conclusion, the prevalence of chronic HBV in RA patients in our region is close to the prevalence in normal population. HBV infection has been experienced in a significant part of the RA patients and immunity has occurred in most of them. The percentage of those vaccinated is low and more than half of RA patients are naive to HBV. Because of the majority of patients naive to HBV infection in our RA cohort, more attention should be paid to routine HBV vaccination of these patients. Those with previous HBV infection

are older than those who do not. Interventional applications in RA treatment options do not change the frequency of HBV exposure.

Conflict of Interest

Authors have no conflict of interest to declare.

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Authors' Contribution

Study Conception: KA; Study Design: KA, AA, OO; Supervision: KA, AA; Data Collection and/or Processing: OO, MT, TDH, KA; Statistical Analysis and/or Data Interpretation: KA, MT; Literature Review: KA, TDH; Manuscript Preparation and Critical Review: KA, OO, MT, TDH, AA

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