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Original Investigation

Prevalence of hepatitis B and C infections in rheumatoid arthritis and ankylosing spondylitis: A multicenter countrywide study

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Abstract

Objective: Immunosuppressive therapies, especially tumor necrosis factor-α inhibitors, are frequently used in treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS). These therapies can induce viral reactivation in concurrent hepatitis B virus (HBV)- or hepatitis C virus (HCV)-positive patients. On the other hand, the prevalence of HBV and HCV infections is not exactly known in RA and AS patients. The aim of this study was to investigate the prevalence of HBV and HCV infections in RA and AS patients.

Material and Methods: A group of 1517 RA and 886 AS consecutive patients followed by six different rheumatology outpatient clinics of Turkey were recruited in this study. The prevalence of HBV surface antigen (HBsAg) and HCV antibody (anti-HCV) were retrospectively investigated.

Results: The mean age was 49.0±13.2 years in RA and 37.3±10.5 years in AS patients. HBsAg prevalence was 35 (2.3%) in RA and 27 (3%) in AS patients. Anti-HCV prevalence was 17 (1.1%) and 10 (1.1%), respectively. In the RA group, both HBsAg and anti-HCV positive patients were older than negative ones ($p<0.05$), and the highest prevalence was found in those 60-69 years ($p<0.05$).

Conclusion: In previous national data, the prevalence of HBsAg has been reported as 3.99% and shown to increase with age. In this study we have found a lower HBV infection prevalence in both RA and AS patients according to Turkish national data. This result may explain by being younger age of our patients. In another conclusion, lower prevalence could be related to, joint complaints may less consulted to Rheumatologist in HBV positive.

Key words: Hepatitis, rheumatoid arthritis, ankylosing spondylitis

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Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are systemic inflammatory rheumatic diseases with a complex and partially understood etiology. Several pathogens have been debated to trigger the initial immune response necessary for development of RA or AS in a genetically susceptible host (1-4). Numerous viruses have been associated with the development of inflammatory arthritis, including the hepatitis viruses [hepatitis B virus (HBV) and hepatitis C virus (HCV)], human immunodeficiency virus, parvovirus B19, human T-cell lymphotropic virus-I, and alpha viruses (5).

Hepatitis infections are widespread diseases in the world, and an estimated 2 billion people have been infected with HBV (6) and 170 million people have been infected with HCV (7). Immunosuppressive therapy, especially tumor necrosis factor-α (TNF-α) inhibitors and anti-B cell therapy, can induce viral reactivation in patients with concurrent HBV infection (8-10). Therefore, screening for HBV and HCV infection is recommended for patients who receive immunosuppressive therapy (11).

The prevalence of HBV and HCV infections in the general population may differ according to geographic regions. In Turkey, HBV and HCV prevalence was reported to be 3.99% and 0.95%, respectively (12). Although the frequency of HBV and HCV infections is not expected to be different in RA (13) and AS patients from the general population, multicenter countrywide studies are required to support this idea. The aim of this study was to investigate the prevalence of HBV and HCV infections in RA and AS patients.

Material and Methods

Study Population and Design

A total of 1517 (female/male: 1185/332) RA and 886 (female/male: 394/492) AS consecutive patients regularly being followed in rheumatology outpatient clinics from six different countrywide geographic areas of Turkey were recruited in this study. Inclusion criteria were fulfilling American College Rheumatology (ACR) 1987 RA (14) or 1984 New York AS criteria (15) and being ≥18 years old. The prevalence of HBV surface antigen (HBsAg) and HCV antibody (anti-HCV) was retrospectively investigated and compared with results of

a nationwide prevalence study of "Turkish association for the study of liver," which included 5465 subjects (12).

Clinical and laboratory data [serum aminotransferase (aspartate aminotransferase- AST, alanine aminotransferase- ALT), HBsAg, anti-HCV, HBV DNA, and HCV RNA] were evaluated according to patient medical records. ALT and AST levels >40 IU/mL were considered high transaminase levels.

Serological Tests

HBsAg and anti-HCV were detected using enzyme-linked immunosorbent assay (ELISA). Patients with positive HBsAg or anti-HCV results were additionally tested for HBV DNA or HCV RNA in serum. HBV DNA and HCV RNA were tested by a real-time polymerase chain reaction (real-time PCR)-based method. Positive tests were defined as >50 IU for HBV DNA.

Statistical Analysis

Variables are labeled as mean±standart deviation (SD). Comparisons between medians were made by using Mann-Whitney U-tests, due to the abnormal distribution of continuous variables; differences were considered significant when $p<0.05$. Chi-square test was used in quantitative variables.

Results

HBsAg and anti-HCV prevalence of the general population and RA and AS patients is summarized in Table 1.

RA patients

The mean age was 49.0±13.2 years, and the mean disease duration was 6.6±6.2 years in the RA group. HBsAg seropositivity was found in 35 (2.3%) patients, and anti-HCV was in 17 (1.1%) patients. Both HBsAg- and anti-HCV-positive patients were older than negative ones [mean age; (HBsAg(+): 55.1±11.1 vs. HBsAg(-): 48.8±13.2 years, p=0.002) and (anti-HCV (+): 57.7±9.6 vs. anti-HCV (-): 48.9±13.2 years, p=0.005)]. HBsAg was more prevalent in male patients (male: 4.2% vs. female: 1.8%, p=0.009) and subjects aged 60-69 years (p=0.005) (Table 2).

In the HBsAg(+) group, 17/30 (56.6%) patients had positive HBV DNA results and 7 patients had high AST and/or ALT levels. In patients with anti-HCV(+), 4/14 (28.5%) had positive HCV RNA results and 2 had high AST and/or ALT levels.

AS Patients

The mean age was 37.3±10.5 years, and the mean disease duration was 6.6±6.0 years in AS group. HBsAg seropositivity was found in 27 (3%) and anti-HCV was in 10 (1.1%) patients. According to age, there was no difference between the HBsAg- and anti-HCV-positive and -negative patients [(HBsAg(+): 39.9±11.4 vs. HBsAg(-): 37.2±10.5 years, p=0.16) and (anti-HCV(+): 46.7±12.6 vs. anti-HCV(-): 37.2±10.4 years, p=0.08)]. In addition, no difference was observed in HBsAg and anti-HCV results between gender in the AS group (HBsAg; 3.9% vs. 2% and anti-HCV; 1.2% vs. 1%, respectively, p>0.05).

In the HBsAg(+) group, 8/20 (40%) patients had positive HBV DNA results and 4 patients had high AST and/or ALT levels. In anti-HCV(+) patients, only one patient had positive HCV RNA results and 2 had high AST and/or ALT levels.

Table 1. HBsAg and anti-HCV prevalence in RA and AS patients and general population

	HBsAg n (%)	Anti HCV n (%)
General population (n:5465)	218 (3.99)*	52 (0.95)
RA (n:1517)	35 (2.3)	17 (1.1)
AS (n:886)	27 (3)	10 (1.1)

*p<0.01; * vs. RA and AS patients.
HBsAg: hepatitis B virus surface antigen; anti-HCV: hepatitis C virus antibody; RA: rheumatoid arthritis; AS: ankylosing spondylitis

Table 2. Seropositivity rate of HBsAg according to age groups

Age (years)	RA		AS	
	n	%	n	%
18-29	140	0.7	208	1.4
30-39	225	1.3	346	3.5
40-49	392	1	214	3.3
50-59	422	2.8	85	3.5
60-69	255	5.1*	33	6.1
70-79	83	2.4	--	--
Overall	1517	2.3	886	3

*p=0.009, 60-69 years vs. other ages, in RA group.
HBsAg: hepatitis B virus surface antigen; RA: rheumatoid arthritis; AS: ankylosing spondylitis

Discussion

Hepatitis virus infections are an important issue for rheumatologists because of the difficulties in the diagnostic and therapeutic approach of rheumatic diseases. HBV and HCV infections may present with several rheumatic manifestations and may have a role in the etiopathogenesis of autoimmune diseases (5-6, 8-12). Otherwise, immunosuppressive drugs are commonly used in the management of rheumatic diseases and were shown to induce viral reactivation in HBV- and HCV-positive patients, and in most instances, flares are asymptomatic. Several case reports have documented HBV reactivation in inactive HBV carriers treated with methotrexate (16) and biologic agents, including infliximab (17-20), etanercept (21), adalimumab (22), and rituximab (23, 24). Therefore, ACR recommends screening for HBV and HCV before non-biologic or biologic immunosuppressive therapy (11).

Hepatitis B virus and HCV infections are widespread diseases in the world, and their prevalence in the general population differs according to geographic regions, ranging from over 10% in Asia to under 0.5% in the United States and Northern Europe (25). In another point, hepatitis infection may present with numerous extrahepatic manifestations, and patients often apply to different specialties according to the predominant clinical feature. Patients' joint symptoms (of the most common extraarticular findings) may be believed to be associated with HBV in certain times, and this situation may reduce referrals to rheumatologists in patients with joint complaints. So, the real prevalence of these infections is not exactly known in RA and AS patients. In the ESPOIR cohort, the seroprevalence of HBV and HCV infection was reported as 0.12% and 0.86% in early arthritis (13). In addition, HCV prevalence was reported as 0.65% in 309 RA patients in France (26, 27). These values were not greater than expected based on data from the general population in the same geographic area (28-31). In another study from China, the prevalence of HBsAg was shown as 12.8% in the general population, 9.6% in RA patients, and 23.9% in AS patients (32).

In our country, HBV and HCV prevalence was reported as 3.99% and 0.95% in the general population, and the prevalence was shown to differ according to age and geographic region. The highest HBV prevalence was found in the southeastern part (9.9%), and the lowest prevalence was found in the western part (0.7-2.5%) of Turkey (12). In our study, we found similar anti-HCV prevalence in RA and AS patients compared to the general population. On the

other hand, we showed a lower prevalence of HBsAg seropositivity in both RA (2.3%) and AS (3%) patients according to our national data. The highest HBV prevalence was found in Diyarbakir (RA: 4.3% and AS: 4.7%), and the lowest prevalence was determined in Adapazari (RA: 1.4% and AS: 1.9%); this distribution was similar to the nationwide data of Turkey.

According to age, HBV and HCV positivity was lowest in 18-30 years (2.9%) and tended to increase by age; the highest level was seen in 50-59 years (5.3%) for HBV and >70 years (2.4%) for HCV in the general population(12). However, in our study group, the mean age was 49 years in RA and 37.3 years in AS patients. In addition, a large amount of patients (in AS group; 96.2% and in RA group; 77.7%) were under 60 years. Based on the results of our study, lower prevalence of HBV infection in both groups may be related to be younger age of patients. In another point, treatment guidelines recommend HBV vaccination prior to immunosuppressive therapy in recent years. Although we do not have the exact history about patients' vaccinations, we recommend HBV vaccine to all patients before starting therapy with both biologic and nonbiologic drugs. HBV vaccination may be responsible for the low HBsAg prevalence in our patients.

Our retrospective observational study has a number of limitations. First, we did not screen our patients for anti-HBs (HBV surface antibody) and anti-HBc (HBV core antibody) antibodies. Therefore, we can not rule out that some of our patients had HBV infection with HBsAg levels below the detection threshold. Second, we have some missing data about HBV DNA and HCV RNA results and HBV vaccination history.

In conclusion, we have found a lower HBV prevalence in patients with RA and AS according to the general population. This result may be associated with being young age or vaccination of HBV in our groups. In another comment, HBV-positive patients with joint complaints may be less consulted to rheumatologist. This observational result must be replicated in further large-scale studies.

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