Low Positive Rates for HBeAg and HBV DNA in Rheumatoid Arthritis Patients—A Case-Control Study

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Abstract

Background

The rates of hepatitis B virus (HBV) infection in rheumatoid arthritis (RA) patients were controversial when considering the reported outcomes. It was speculated that HBV infection status altered after suffering from RA, and variations over HBV infection rates became apparent.

Methods

To compare the positive proportions of hepatitis B e antigen (HBeAg) and HBV DNA, a case-control study was performed between the 27 chronic hepatitis B (CHB) patients with RA and the 108 age- and gender-matched CHB patients. In addition, the positive rates of hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) were surveyed among the 892 RA patients.

Results

Compared to the CHB patients, the CHB patients with RA exhibited lower rates of HBeAg positivity (11.1% vs. 35.2%, $P = 0.003$), HBV DNA positivity (37.0% vs. 63.9%, $P = 0.007$) and ALT elevation (11.1% vs. 35.2%, $P = 0.024$). In the 892 RA patients, the prevalence of HBsAg (3.0%) was lower than that of China national data (7.2%), whereas the anti-HBc positive rate of 44.6% was higher than that of 34.1%.

Conclusion

HBV infection status altered after suffering from RA. Compared to the matched CHB patients, low positive proportions of HBeAg and HBV DNA were observed for CHB patients with RA.

Introduction

It was observed that the HBV infection affected rheumatoid arthritis (RA), where HBV was considered as the suspected trigger for arthritis in the genetically susceptible individuals[1]. The rates of positivity for RF and ACPA were as high as 14.4% and 4.1%, respectively, in patients with chronic hepatitis B (CHB)[2]. Hepatitis B core antigen (HBcAg) was found in the synovium of RA patients with CHB, indicating that HBV may involve in the pathogenesis of local lesions[3]. In RA patients, immune dysregulation and the immunosuppressive therapies also influenced HBV infection[4, 5].

HBV infection with a high endemicity was reported in various regions of the Asia-Pacific and Sub-Saharan Africa[6, 7]. It also affects approximately 10 million people in China[8]. Unfortunately, the HBV infection rates were reported differently for RA patients in the previous studies. Yilmaz et al. reported a lower HBV infection prevalence in RA patients according to Turkish national data in comparison with the

general population[9]. Mahroum et al. performed a case-control study and showed the RA patients had a greater proportion of chronic HBV infection than the age- and sex-matched controls[10]. Hsu et al. observed that RA patients were characterized with an increased risk of HBV infection when comparing with that of the aged ≥ 18 years non-RA cohort[11]. The reasons for these differences were complicated, especially when these were no studies assessing the HBV infection status in the RA patients, including HBeAg-positive, HBV DNA load and ALT level.

Herein, a case-control study was performed to clarify the effect of RA on the HBV infection status. The positive rates of hepatitis B e antigen (HBeAg) were compared between the RA patients with CHB and the age-and gender-matched general CHB patients, in addition to positive rates of HBV DNA.

Methods

Study design

This was a case-control study. A total of 27 CHB patients with RA were enrolled from the department of Rheumatology and Immunology, First Affiliated Hospital of Xi'an Jiaotong University, from January 1st 2016 to December 31st 2019. Inclusion criteria: (i) HBsAg was positive for more than 6 months, (ii) patients fulfilled ACR/EULAR 2010 rheumatoid arthritis classification criteria. Exclusion criteria were if patients were serologic human immunodeficiency virus (HIV) or hepatitis C (HCV) or Hepatitis D virus (HDV) positive, had cirrhosis, liver cancer or fatty liver disease. To exclude the effect of antiviral therapy on the HBV infection status, the RA patients who accepted antiviral treatment were not included in the matched case-control study. During the corresponding period, the age- and gender- matched CHB outpatients were enrolled as 1:4 ratio from the department of Infectious Disease. In addition, the positive rates of HBsAg and anti-HBc were surveyed among the 892 RA patients over the corresponding period. This study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Ethics Committee of First Affiliated Hospital of Xi'an Jiaotong University (No. 2017.120), and the patients gave their written informed consent.

The medical records of patients were reviewed, and the data of the following variables were collected: age, gender, diagnosis, duration of disease, HBsAg, HBeAg, anti-HBc, ALT, HBV DNA load. All the test data of RA patients were collected at the first visit time and the data of CHB patients were collected before their antiviral treatment.

The primary outcome was the comparison of the positive rates of HBeAg and HBV DNA between the CHB patients with RA and the age- and gender- matched CHB patients. The secondary outcomes were the followings: (i) the comparison of the elevated ALT rates between the CHB patients with RA and the CHB patients, (ii) the comparison of the HBeAg titer, HBV DNA load and ALT levels between CHB patients with RA and the CHB patients, (iii) the comparison of HBsAg-positive rates between the RA patients and Chinese general population (CGP), (iv) the comparison of anti-HBc-positive rates between the RA patients and CGP.

Laboratory methods

The titers of HBsAg, HBeAg and anti-HBc were quantified by The Abbott ARCHITECT assays (Abbott Laboratories, Chicago, IL, USA). The lower limit of detection for HBsAg was 0.05 IU/mL, HBeAg was 1 s/co and anti-HBc was 1 s/co. The HBV DNA load was measured by the Roche COBAS AmpliPrep/COBAS TaqMan HBV test (Roche Molecular Systems, California, IL, USA), and the lower limit of detection was 12 IU/mL. Liver function tests were performed with an automated bioanalyzer (Olympus AU5400, Japan).

Statistical analysis

The analyses were performed by SPSS software 13.0 (SPSS Inc. Chicago, IL, USA). Conditional logistic regression was used to compare the proportions between 2 groups. Quantitative data were analyzed with Shapiro-Wilk test and Levene statistic for normality and homogeneity of variance, respectively. According to situation, Paired-Samples t test or Signed rank Wilcoxon test was used to evaluate differences between two groups. *P* value < 0.05 was considered statistically significant.

Results

Basic characteristics of the CHB patients with RA

27 (3.0%) RA patients were HBsAg-positive and enrolled in this study. Among these, seven patients (25.9%) had HBV family history, seventeen patients (63.0%) had the HBV infection duration more than 10 years, and one patient (3.7%) had the RA duration more than 10 years (Table 1).

Table 1
Basic characteristics of the RA patients with HBV infection

Variable	Value
Age, years*	52.0 (28.0 – 74.0)
Gender, female (%)	19 (70.4)
Duration of RA, years*	3.0 (0.2 – 18.0)
> 10	1 (3.7)
1 ~ 10	19 (70.4)
< 1	7 (25.9)
HBV family history (%)	7 (25.9)
Duration of HBV infection, years	
> 20	11 (40.7)
10 ~ 20	6 (22.2)
1 ~ 10	2 (7.4)
Unknow	8 (29.6)
ALT, U/L*	15.0(7.0 – 476.0)
HBV DNA > 10 ² IU/mL (%)	10 (37.0)
HBeAg-positive (%)	3 (11.1)
* The values were expressed as the median (range). Abbreviations: ALT, alanine transaminase; HBeAg, hepatitis B e antigen; HBV, Hepatitis B virus; RA, rheumatoid arthritis.	

Low proportions of HBeAg-positive and HBV DNA-positive in the CHB patients with RA

As shown in the methods, 108 age-and gender-matched CHB outpatients were enrolled from the department of infectious disease over the same period in this case-control study. In the CHB patients with RA, the proportion of HBeAg(+) was 11.1% (3/27), which was much lower than that of the matched CHB patients (11.1% vs. 35.2%; *OR* = 0.128; 95% CI, 0.033 to 0.493; *P* = 0.003; Figure 1A). The titers of HBeAg were lower in the RA patients compared with those of the CHB patients [-0.5 (-0.6 – 3.2) vs. -0.4 (-0.6 – 3.2), *Z* = -4.517, *P* < 0.001]. For three HBeAg(+) patients, the titers of HBeAg were 0.2, 1.4 and 3.2 Log₁₀ s/co, respectively. The corresponding value for the 38 CHB patients were 1.6 (0.02 – 3.2) Log₁₀ s/co (Figure 1B).

The load of HBV DNA represents the degree of HBV replication. The positive rate of HBV DNA in the RA patients was less than the matched CHB patients (37.0% vs. 63.9%; *OR* = 0.244; 95% CI, 0.089 to 0.674; *P*

= 0.007; Figure 1C). In addition, HBV DNA load in the RA patients was lower than the CHB patients (1.5 ± 2.4 vs. 4.4 ± 3.3 Log₁₀ IU/ml, $t = -3.859$, $P = 0.001$, Figure 1D).

The elevated ALT showed the hepatitis activity. Compared to the matched CHB patients, the proportion of elevated ALT (>40U/L) was significantly lower in the RA patients (11.1% vs. 35.2%; $OR = 0.233$; 95% CI, 0.066 to 0.824; $P = 0.024$; Figure 1E), together with the level of ALT (15.0 (7.0 – 97.0) vs. 22.0 (10.0 – 476.0), $Z = -2.066$, $P = 0.039$, Figure 1F).

Low prevalence of HBsAg and high prevalence of anti-HBc in RA patients

With respect to the rate of HBsAg-positive, the second Chinese National Hepatitis Seroepidemiological Survey demonstrated that the rate was 7.2% in 2006 (Figure1A)[8]. Then, the Polaris Observatory Collaborators developed models for 120 countries, and estimated that the China prevalence of HBsAg in 2016 was 6.1% (5.5% – 6.9%)[12]. Based on the included 27 studies, Wang et al. estimated prevalence of 6.89%(5.84 – 7.95%) for HBV infection in the general population of China from 2013 to 2017 [13]. In the present work, 3.0% of RA patients (27/892) were HBsAg-positive. This is lower than the above reported data (Figure 2A).

Anti-HBc positivity most occurs in chronic HBV infection or resolved infection[14]. The anti-HBc(+) rate was 44.6% (398/892) in RA patients, higher than the data of Chinese National Hepatitis Seroepidemiological Survey (44.6% vs. 34.1%, Figure 2B).

Discussion

For RA patients, the reported difference of the HBV infection rates may associate with the alteration of HBV infection status after suffering from RA. To elucidate this issue, the current case-control study was performed. Compared to the age-and gender-matched general CHB patients, low proportions of positivity for HBeAg and HBV DNA were observed for the CHB patients with RA.

The HBeAg positivity often represents a high replicative phase of the chronic HBV infection, and HBeAg loss is considered as a partial immune control of the chronic HBV infection[15]. In this study, the CHB patients with RA exhibited lower positive rates of HBeAg and titers of HBeAg when comparing with the matched CHB patients. HBV DNA directly indicates HBV replication. The positive rate of HBV DNA in the CHB patients with RA was less than that of the matched CHB patients, as well the HBV DNA load. It demonstrated that CHB patients with RA had more probability of HBeAg seroconversion and HBV DNA load decline, which may associate with immune control after suffering from RA.

Immune dysregulation is the characteristics of RA. It plays a complicated role in HBV infection for abnormal innate and adaptive immune activation of RA patients. First, the type I interferons (IFNs) play a critical role in defending against HBV, and the type I interferon signature is detectable in the peripheral blood of RA patients[16]. Second, CD8⁺ T cells are capable to control HBV infection and eliminate HBV infected cells[17]. For RA patients, CD8⁺ T cells are abundant and associated with disease activity, due to

pro-inflammatory cytokines production[18] and self-antigens response upon cross-presentation[19]. Third, the humoral immune response has protective role against pathogens[20]. Abnormalities in B cells not only participates in pathogenesis of RA[21] (including production of autoantibody, presentation of autoantigens and secretion of proinflammatory cytokines)[22], but also affects HBV elimination.

The elevated ALT is an important characteristic of immune clearance[23], and inactive HBsAg carrying status can be obtained after immune clearance. Compared to the matched CHB patients, low proportion of ALT > 40U/L and low ALT levels were found for the CHB patients with RA. This suggested that CHB patients with RA were more prone to obtain immune control for HBV after immune clearance.

HBsAg positivity is a definite HBV infection marker. In the present work, low HBsAg(+) rate of 3.0% was found in the RA patients, which was consistent with the previous study[9]. Then, survey outcomes also indicated that RA patients exhibited low HBsAg(+) rate according to the second Chinese National Hepatitis Seroepidemiological Survey[8] and the estimated China prevalence of HBsAg[12, 13]. Hepatitis B core antigen (HBcAg) is an inner nucleocapsid component, the production of anti-HBc is induced by a cellular and humoral immune response to HBcAg during natural HBV infection. Anti-HBc positivity mostly occurs in chronic HBV infection or resolved infection[14]. We found that the positive rate of anti-HBc was 44.6% in the RA patients, higher than the rate of Chinese general population from the China national data[8]. Consistent with the previous studies[10, 11], the RA patients may have higher risk of HBV infection in comparison with the general population, due to receiving disease modifying antirheumatic drugs and complicated immunity related to the disease itself[4, 5]. During the natural history of HBV, HBsAg seroclearance can emerge in 0.5 – 1.0% patients per year after immune clearance phase[24]. It was expected that low positive rate of HBsAg suggested HBsAg seroclearance was more common in the RA patients. The susceptible ages were different for RA and CHB patients. The mother-to-infant transmission was the main route of HBV infection in China. HBV infected early in life, and conferred a high risk of chronicity[25]. In contrast, RA occurred much frequently in the elderly women. Hence, RA was supposed to be later than HBV infection for most patients. We speculated that HBV infection status altered after suffering from RA. Among the 27 patients in this study, 62.9% of them had the HBV duration more than 10 years, and 96.3% of them had the RA duration less than 10 years. This indicates that the majority suffered from RA after HBV infection. After suffering from RA, HBV DNA declines, HBeAg and even HBsAg lose as consequent.

Here, some limitations of the study were as follows: the numbers of patients were limited, a prospective cohort study with large sample size is necessary to evaluate the difference in the natural history of chronic HBV infection between RA and general CHB patients.

In conclusion, HBV infection status altered after suffering from RA. Compared to the matched CHB patients, variations were significant, including low positive proportions of HBeAg and HBV DNA, due to immune dysregulation of RA patients.

Declarations

Conflict of Interest Statements: All the authors declare that they have no competing interests, and all authors confirm its accuracy.

Ethics approval: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University (No. 2019.013), and patients gave their written informed.

Consent of publication: not applicable.

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Availability of data: The data in the current study are available from the corresponding author on reasonable request.

Authors' contributions: JW and LH conceived of the presented idea. YJ, JJZ, PW and JZ acquired data in the study. JZ, ML, NH and YW analyzed data. JW, YJ and JJZ drafted the paper, and all authors discussed the results and contributed to the final manuscript.

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Figures

Figure 1

The comparison of HBV infection status between the RA patients and the age-and sex-matched CHB patients: (A) The comparison of HBeAg(+) rates; (B) The comparison of HBeAg titers; (C) The comparison of different HBV DNA gradients rates; (D) The comparison of HBV DNA load; (E) The comparison of elevated ALT rates; (F) The comparison of ALT levels. Abbreviations: ALT, alanine transaminase; CHB, chronic Hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; RA, rheumatoid arthritis.

Figure 2

The comparison of HBsAg(+) rate and anti-HBc(+) rates between the RA patients and the Chinese general population: (A) The comparison of HBsAg(+) rates; (B) The comparison of anti-HBc(+) rates.

*The CGP data: CGP in 2006[8], CGP in 2016[12] and CGP from 2013 to 2017[13]. Abbreviations: anti-HBc, hepatitis B core antibody; CGP, Chinese general population; HBsAg, hepatitis B surface antigen; RA, rheumatoid arthritis.