Clinical Rheumatology (2019) 38:1237–1241
https://doi.org/10.1007/s10067-019-04448-x

ORIGINAL ARTICLE

Chronic hepatitis B viral infection among RA patients—a cross-sectional control study

Naim Mahroum[1,2] · Abdulla Watad[1,2] · Shmuel Tiosano[1,2] · Ashraf Hejly[1] · Hussein Mahagna[1] · Roy Waknin[2] · Doron Comaneshter[3] · Arnon D. Cohen[3,4] · Howard Amital[1,2]

Received: 17 January 2019 / Accepted: 21 January 2019 / Published online: 8 February 2019

Abstract

Background and objectives Rheumatoid arthritis (RA) is the most common inflammatory joint disorder presenting also with extra-articular manifestations. As many other autoimmune diseases, it has been suggested that infectious diseases might contribute to its emergence. Hepatitis viruses were suggested by several reports as a trigger of RA onset. We aimed to assess the association between RA and chronic hepatitis B viral infection (HBV).

Methods Patients with RA were compared with age- and sex-matched controls regarding the proportion of chronic HBV infection in a case-control study. The chi-square and *t* tests were used for univariate analysis, whereas a logistic regression model was used for multivariate analysis. The study was performed utilizing the medical database of Clalit Health Services.

Results There was a significantly higher proportion of chronic HBV infection in RA patients compared with controls (1.19% vs 0.63%, respectively; $p < 0.001$). In a multivariate logistic regression analysis, RA was significantly associated with chronic HBV infection (OR = 1.89, 95%CI 1.55–2.29, $p < 0.001$).

Conclusions Patients with RA have a greater proportion of chronic HBV infection than matched controls. Screening for HBV infection among RA patients may be warranted.

Keywords Autoimmune disease · Autoimmunity · Hepatitis B virus · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory joint disease associated with extra-articular and systemic effects [1, 2]. The extra-articular manifestations of RA can occur at any age after onset and more common in seropositive RA patients [3, 4]. Many studies have indicated that infections may contribute to the pathogenesis of the disease [5–9]. In addition, the coexistence of RA and various infections is speculated to facilitate the production of a wide range of autoantibodies as well [10–12].

In a series of studies, we described the coexistence of rheumatologic and autoimmune diseases with several infectious diseases [13, 14]. Patients with rheumatic diseases are at a higher risk of infection due to several factors including dysregulated immune-pathways in the host, and immunosuppressant therapy [15]. We previously showed that hepatitis C virus (HCV) infection is more common among systemic lupus erythematosus (SLE) patients compared with a large group of age- and sex-matched controls [16]. This was similarly illustrated regarding hepatitis B virus (HBV) among SLE patients [13]. Viruses, such as HBV and HCV as mentioned above, seem to be associated with many systemic rheumatic diseases [14, 17, 18]. A nationwide study from Taiwan based on extracted data between the years 1999 and 2009 showed a higher prevalence and risk for HBV infection in RA patients compared with non-RA cohort [19]. Hsu et al. [20] took this further and showed, in a recent study, HBV core antigen is present in the synovium of 64% of patients with RA and chronic

✉ Howard Amital
howard.amital@sheba.health.gov.il

1 Department of Medicine 'B', Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, 52621 Tel-Hashomer, Israel

2 Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

3 Chief Physician's Office, Clalit Health Services Tel Aviv, Tel-Aviv, Israel

4 Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel

HBV infection demonstrating an important role of HBV in the pathogenesis and progression of RA. HBV and hepatitis D virus (HDV) are DNA viruses and the former represents the leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). According to the WHO, HBV infection is prevalent in the Western Pacific and African regions where around 6–6.5% of the population are affected [21]. Serologic testing for HBV is mandatory in RA patients especially those planned to receive potentially hepatotoxic medications such as methotrexate or immunosuppressant therapy, namely biologic agents [22]. Vaccination to nonimmune patients is warranted and treatment should be offered to those chronically ill. Though considered safe, Kanduc and Shoenfeld suggested a safer approach to HBV vaccine production [23].

In the current study, we aimed to assess whether RA and chronic HBV infection coexist more commonly, by conducting a cross-sectional study utilizing an extensive database of Clalit Health Services (CHS).

Methods

Measures

A cross-sectional population study has been conducted utilizing the CHS database. The latter is the largest healthcare maintenance organization in Israel, providing public and semi-private health services for approximately 4,400,000 members representing half of the Israeli population. The CHS chronic disease registry receives input data from a variety of sources, namely pharmaceutical, medical, and administrative computerized operating systems.

RA diagnosis was defined as such when there was a documented diagnosis of this entity at least twice in the medical records registered by a physician in the community or when they were listed in the diagnoses of discharge letters from hospitals (specialist). All RA patients detected in the CHS database were considered eligible and, as such, enrolled in this study. Controls were randomly selected from the CHS database, with the exclusion of RA patients.

Similar to RA, HBV infection was determined according to the subjects' medical records. These diagnoses were validated by a systematic methodology, performing regular checks of these diagnoses logistically by comparing different sources of information and directly by physician-patient individual level. The validity of the diagnoses in the registry has been shown to be high and was used for research purposes in the past [24–27].

Statistical analyses

Using a χ^2 test for gender and socioeconomic status and a t test for age; the distribution of sociodemographic and clinical factors was compared between patients with and without RA. Crude ORs and 95% confidence intervals (CIs) are presented. Logistic regression models were used to estimate the association between RA and chronic hepatitis B in a multivariate analysis. Statistical analysis was performed using R Statistical Software (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria).

Results

The study included 11,782 RA patients and 57,973 age- and sex-matched controls. In both study groups, the median age was around 61 years old, with a predominance of the female gender (77%). Pertinent to SES, no significant difference was noted between RA patients and controls. The smoking rate was significantly higher in RA patients than in controls (32.8% vs 28.8%, respectively, < 0.001). Regarding alcohol abuse habit, no significant difference was found among the two study groups ($p = 0.474$). Interestingly, there was a significantly higher proportion of chronic HBV infection in RA patients as compared with controls (1.19% and 0.63%, respectively; $p < 0.001$). Further details regarding the basic characteristics of both study groups are reported in Table 1.

The interaction between RA and various factors in terms of association with chronic HBV infection reported the highest OR of 2.32 (95%CI 1.33–3.90) among those of high SES (Table 2). The association was consistent in both sexes although it was more prominent in females. Moreover, the association was significant through all SES and age groups.

In a multivariate logistic regression analysis and after adjusting for confounders including age, socioeconomic class, alcohol abuse habit, and smoking, RA was significantly associated with chronic HBV infection (OR = 1.89, 95%CI 1.46–2.90). Moreover, alcohol abuse habit (OR 4.13, 95%CI 2.211–7.072) and smoking (OR 1.25, 95%CI 1.029–1.514) were significantly associated with chronic HBV infection (Table 3). By contrast, high SES was inversely associated with chronic HBV infection (OR 0.44, 95%CI 0.334–0.580) (Table 3).

Discussion

In this large cross-sectional study, a higher proportion of chronic HBV infection in RA patients compared with controls was found.

The association between rheumatic/autoimmune diseases and infection has long been described in medical

Table 1 RA patients and matched controls basic characteristics

Variable	Controls $N = 57,973$	RA $N = 11,782$	OR	p value
Gender, female	44,589 (76.9%)	9103 (77.3%)	1.02 [0.97; 1.07]	0.413
Age	60.8 ± 17.0	61.1 ± 17.0	1.00 [1.00; 1.00]	0.174
SES				
Low	22,657 (39.2%)	4505 (38.3%)	Ref.	Ref.
Medium	22,831 (39.5%)	4816 (41.0%)	1.06 [1.01; 1.11]	0.009
High	12,334 (21.3%)	2438 (20.7%)	0.99 [0.94; 1.05]	0.831
Smoking	16,671 (28.8%)	3865 (32.8%)	1.21 [1.16; 1.26]	0.000
Alcohol abuse habit	275 (0.47%)	50 (0.42%)	0.90 [0.66; 1.20]	0.474
Chronic HBV infection	365 (0.63%)	140 (1.19%)	1.90 [1.56; 2.30]	< 0.001

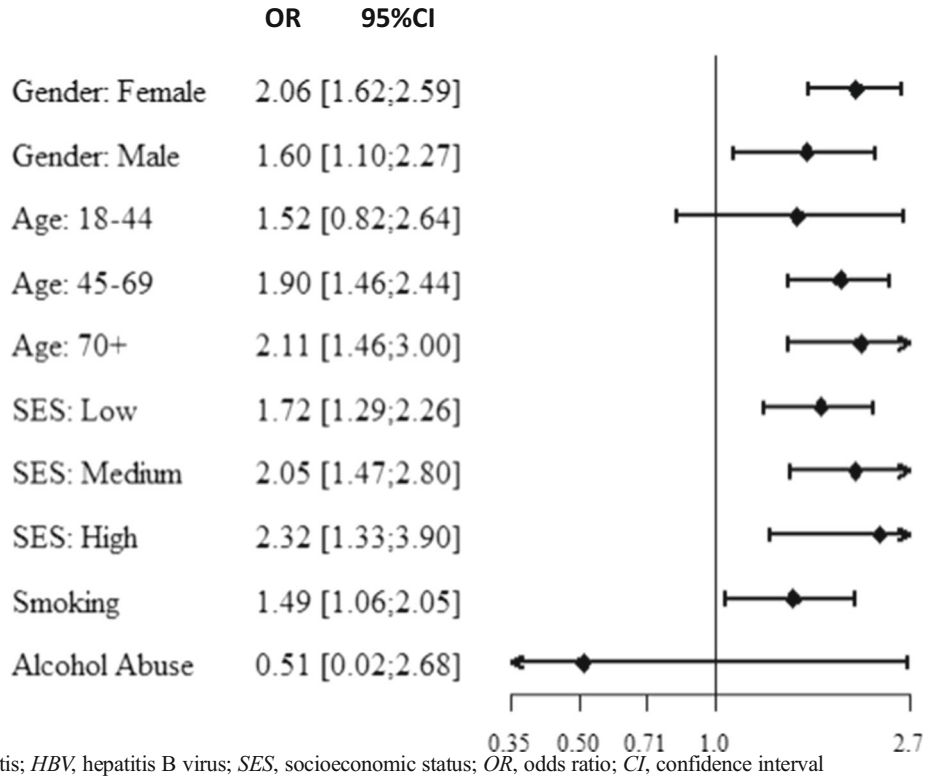
RA, rheumatoid arthritis; *SES*, socioeconomic status; *OR*, odds ratio; *CI*, confidence interval; *HBV*, hepatitis B virus

literature [13, 28, 29]. The link between infection and RA is bidirectional. On the one hand, several infections such as EBV, parvoviruses, and retroviruses have been reported to trigger RA disease although establishing a causal relationship between the two conditions is extremely difficult [30, 31]. On the other hand, RA patients are at a higher risk of infection and this can be attributed to various factors such as a dysregulated immunity related to the disease itself or anti-disease medications [32, 33].

HBV infection can manifest with an array of rheumatic manifestations and autoimmune laboratory findings. These manifestations seem to occur in around 20% of patients infected with HBV whether acute or chronic and thought to be mediated mainly by circulating immune complexes [34, 35]. These include, among others, arthralgias, arthritis, myalgia, fatigue, and fibromyalgia [36].

Regarding HBV and RA, Lin et al. [37] compared HBV testing in the USA and Taiwan and showed low testing rates in both countries, though this rate is increasing in the last decade. In fact, the association between RA and HBV is described in the medical literature mainly in

Table 2 Interaction between RA and various factors in terms of association with chronic HBV infection



RA, rheumatoid arthritis; *HBV*, hepatitis B virus; *SES*, socioeconomic status; *OR*, odds ratio; *CI*, confidence interval

Table 3 Logistic regression—covariates associated with chronic HBV infection

	OR	95%CI	*p* value
(Intercept)	0.01	0.004–0.008	< 0.001
Gender (male)	1.41	1.155–1.724	< 0.001
Age	1.00	0.998–1.009	0.22
SES	NA	NA	NA
Medium vs low	0.66	0.543–0.799	< 0.001
High vs low	0.44	0.334–0.580	< 0.001
Alcohol abuse	4.13	2.211–7.072	< 0.001
Smoking	1.25	1.029–1.514	0.02
RA	1.89	1.551–2.297	< 0.001

HBV, hepatitis B virus; *SES*, socioeconomic status; *OR*, odds ratio; *CI*, confidence interval; *RA*, rheumatoid arthritis

the context of the reactivation of HBV infection in RA patients receiving immunosuppressive therapy including glucocorticoids as well as biologic agents [38, 39]. This phenomenon is known since the introduction of biologic agents in RA [40]. For this reason, antiviral therapy is recommended for such patients while on biological drugs [22]. Our report supports this recommendation, given the excessive cooccurrence of RA and the diagnosis of chronic HBV infection.

Jeong et al. [41] in a study from South Korea compared RA population with matched non-RA population and illustrated a higher prevalence of comorbidities in RA patients. Significant associations were found between RA and myocardial infection, angina pectoris, thyroid disease, and depression, but only a nonsignificant trend was observed concerning HBV infection in RA patients. Although there are some similarities between the Korean and our study, our study was designed to primarily investigate the prevalence of chronic HBV infection in RA, demonstrating a statistically significant association between the two conditions. It is pertinent to mention that HBV incidence and prevalence differ worldwide; this seems to be one of the main reasons for the difference between the findings of the two studies.

Our study has several strengths, mainly being based on a very large database. However, there are several limitations that should be acknowledged. The main limitation is the lack of data concerning the medical treatment of RA patients, serology, and their disease activity.

In conclusion, we found a higher proportion of chronic HBV infection among RA patients in a large control case study. Physicians in general and those dealing with RA patients in particular should be aware of these findings and probably consider HBV infection screening in all RA patients regardless of their planned or current medical therapy.

Compliance with ethical standards The study was approved by the ethical committee of CHS, located at the Soroka Medical Center, Beer-Sheva, Israel.

Conflict of interest Naim Mahroum- no conflict of interests.
Abdulla Watad - no conflict of interests.
Shmuel Tiosano - no conflict of interests.
Ashraf Hejly - no conflict of interests.
Hussein Mahagna - no conflict of interests.
Roy Waknin - no conflict of interests.
Doron Comaneshter - no conflict of interests.
Arnon Cohen received research grants from Janssen, Novartis, AbbVie, and Sanofi. Other relationships: In the last 3 years, Prof. Arnon Cohen served as a consultant, advisor, or speaker to AbbVie; Amgen; Boehringer Ingelheim; Dexcel pharma; Janssen; Kamedis; Lilly; Neopharm; Novartis; Perrigo; Pfizer, Rafa, Sanofi, Sirbal; Taro.
Howard Amital- received research grants from Janssen, Novartis, AbbVie and Pfizer. Other relationships: In the last 3 years Howard Amital served as a consultant, advisor or speaker to AbbVie; Boehringer Ingelheim; Janssen; Neopharm; Novartis; Perrigo; Pfizer, Rafa, Sanofi, Sanofi, Taro, Roche.

References

1. McInnes IB, Schett G (2011) The pathogenesis of rheumatoid arthritis. N Engl J Med 365(23):2205–2219. https://doi.org/10.1056/NEJMra1004965
2. Firestein GS (2003) Evolving concepts of rheumatoid arthritis. Nature 423(6937):356–361. https://doi.org/10.1038/nature01661
3. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL (2003) Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis 62(8):722–727
4. Myasoedova E, Crowson CS, Turesson C, Gabriel SE, Matteson EL (2011) Incidence of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, in 1995–2007 versus 1985–1994: a population-based study. J Rheumatol 38(6):983–989
5. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, Spitz PW, Haga M, Kleinheksel SM, Cathey MA (1994) The mortality of rheumatoid arthritis. Arthritis Rheum 37(4):481–494
6. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, Stampfer MJ, Curhan GC (2003) Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 107(9):1303–1307
7. Guler-Yuksel M, Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Groenendael JH, Mallee C, de Bois MH, Breedveld FC, Dijkmans BA, Lems WF (2009) Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis 68(3):330–336. https://doi.org/10.1136/ard.2007.086348
8. Choy E, Sattar N (2009) Interpreting lipid levels in the context of high-grade inflammatory states with a focus on rheumatoid arthritis: a challenge to conventional cardiovascular risk actions. Ann Rheum Dis 68(4):460–469. https://doi.org/10.1136/ard.2008.101964
9. Smitten AL, Simon TA, Hochberg MC, Suissa S (2008) A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther 10(2):R45. https://doi.org/10.1186/ar2404

10. van Boekel MA, Vossenaar ER, van den Hoogen FH, van Venrooij WJ (2002) Autoantibody systems in rheumatoid arthritis: specificity, sensitivity and diagnostic value. Arthritis Res 4(2):87–93. https://doi.org/10.1186/ar395
11. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE (2002) Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheumatol 46(9):2287–2293
12. Baum J (1971) Infection in rheumatoid arthritis. Arthritis Rheumatol 14(1):135–137
13. Gendelman O, Mahroum N, Comaneshter D, Rotman-Pikielny P, Cohen AD, Amital H, Sherf M (2017) Hepatitis B carrier state among SLE patients: case-control study. Immunol Res 65(1):257–261. https://doi.org/10.1007/s12026-016-8834-6
14. Maya R, Gershwin ME, Shoenfeld Y (2008) Hepatitis B virus (HBV) and autoimmune disease. Clin Rev Allergy Immunol 34(1):85–102
15. Watad A, Azrielant S, Bragazzi NL, Sharif K, David P, Katz I, Aljadeff G, Quaresma M, Tanay G, Adawi M, Amital H, Shoenfeld Y (2017) Seasonality and autoimmune diseases: the contribution of the four seasons to the mosaic of autoimmunity. J Autoimmun 82:13–30. https://doi.org/10.1016/j.jaut.2017.06.001
16. Mahroum N, Hejly A, Tiosano S, Gendelman O, Comaneshter D, Cohen AD, Amital H (2017) Chronic hepatitis C viral infection among SLE patients: the significance of coexistence. Immunol Res 65(2):477–481. https://doi.org/10.1007/s12026-016-8886-7
17. Ramos-Casals M, Muñoz S, Medina F, Jara L-J, Rosas J, Calvo-Alen J, Brito-Zerón P, Forns X, Sánchez-Tapias J-M (2009) Systemic autoimmune diseases in patients with hepatitis C virus infection: characterization of 1020 cases (The HISPAMEC Registry). J Rheumatol 36(7):1442–1448
18. De Virgilio A, Greco A, Magliulo G, Gallo A, Ruoppolo G, Conte M, Martellucci S, de Vincentiis M (2016) Polyarteritis nodosa: a contemporary overview. Autoimmun Rev 15(6):564–570
19. Chen YL, Jing J, Mo YQ, Ma JD, Yang LJ, Chen LF, Zhang X, Yan T, Zheng DH, Pessler F, Dai L (2018) Presence of hepatitis B virus in synovium and its clinical significance in rheumatoid arthritis. Arthritis Res Ther 20(1):130. https://doi.org/10.1186/s13075-018-1623-y
20. Hsu CS, Lang HC, Huang KY, Lin HH, Chen CL (2016) Association of rheumatoid arthritis and hepatitis B infection: a nationwide nested case-control study from 1999 to 2009 in Taiwan. Medicine (Baltimore) 95(18):e3551
21. World Health Organization (2017) Global Hepatitis Programme. Global hepatitis report, 2017
22. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, Moreland LW, O'Dell J, Winthrop KL, Beukelman T, Bridges SL, Chatham WW, Paulus HE, Suarez-almazor M, Bombardier C, Dougados M, Khanna D, King CM, Leong AL, Matteson EL, Schousboe JT, Moynihan E, Kolba KS, Jain A, Volkmann ER, Agrawal H, Bae S, Mudano AS, Patkar NM, Saag KG (2012) 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 64(5):625–639
23. Kanduc D, Shoenfeld Y (2016) From HBV to HPV: designing vaccines for extensive and intensive vaccination campaigns worldwide. Autoimmun Rev 15(11):1054–1061. https://doi.org/10.1016/j.autrev.2016.07.030
24. Watad A, Bragazzi NL, Adawi M, Aljadeff G, Amital H, Comaneshter D, Cohen AD, Amital D (2017) Anxiety disorder among rheumatoid arthritis patients: insights from real-life data. J Affect Disord 213:30–34. https://doi.org/10.1016/j.jad.2017.02.007
25. Watad A, Bragazzi NL, Tiosano S, Yavne Y, Comaneshter D, Cohen AD, Amital H (2018) Alzheimer's disease in systemic sclerosis patients: a nationwide population-based cohort study. J Alzheimers Dis 65(1):117–124
26. Watad A, Tiosano S, Azrielant S, Whitby A, Comaneshter D, Cohen AD, Shoenfeld Y, Amital H (2017) Low levels of calcium or vitamin D - which is more important in systemic lupus erythematosus patients? An extensive data analysis. Clin Exp Rheumatol 35(1):108–112
27. Watad A, Tiosano S, Yahav D, Comaneshter D, Shoenfeld Y, Cohen AD, Amital H (2017) Behcet's disease and familial Mediterranean fever: two sides of the same coin or just an association? A cross-sectional study. Eur J Intern Med 39:75–78. https://doi.org/10.1016/j.ejim.2016.10.011
28. Dvir R, Sautto GA, Mancini N, Racca S, Diotti RA, Clementi M, Memoli M (2017) Autoimmune hepatitis and occult HCV infection: a prospective single-centre clinical study. Autoimmun Rev 16(3):323–325. https://doi.org/10.1016/j.autrev.2017.01.015
29. Tosato G, Steinberg AD, Blaese RM (1981) Defective EBV-specific suppressor T-cell function in rheumatoid arthritis. N Engl J Med 305(21):1238–1243
30. Wilder RL, Crofford LJ (1991) Do infectious agents cause rheumatoid arthritis? Clin Orthop Relat Res (265):36–41
31. Balandraud N, Roudier J (2018) Epstein-Barr virus and rheumatoid arthritis. Joint Bone Spine 85(2):165–170. https://doi.org/10.1016/j.jbspin.2017.04.011
32. Listing J, Gerhold K, Zink A (2013) The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology 52(1):53–61
33. Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, Ghogomu ET, Coyle D, Clifford T, Tugwell P, Wells GA (2015) Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet 386(9990):258–265. https://doi.org/10.1016/s0140-6736(14)61704-9
34. Alpert E, Isselbacher KJ, Schur PH (1971) The pathogenesis of arthritis associated with viral hepatitis: complement-component studies. N Engl J Med 285(4):185–189
35. Dienstag JL (1981) Hepatitis B as an immune complex disease. Semin Liver Dis 1(1):45–57. https://doi.org/10.1055/s-2008-1063929
36. Cacoub P, Saadoun D, Bourlière M, Khiri H, Martineau A, Benhamou Y, Varastet M, Pol S, Thibault V, Rotily M (2005) Hepatitis B virus genotypes and extrahepatic manifestations. J Hepatol 43(5):764–770
37. Lin TC, Hashemi N, Kim SC, Yang YK, Yoshida K, Tedeschi S, Desai R, Solomon DH (2018) Practice pattern of hepatitis B testing in rheumatoid arthritis patients: a cross-national comparison between the US and Taiwan. Arthritis Care Res (Hoboken) 70(1):30–38. https://doi.org/10.1002/acr.23241
38. Urata Y, Uesato R, Tanaka D, Kowatari K, Nitobe T, Nakamura Y, Motomura S (2011) Prevalence of reactivation of hepatitis B virus replication in rheumatoid arthritis patients. Mod Rheumatol 21(1):16–23
39. Tamori A, Koike T, Goto H, Wakitani S, Tada M, Morikawa H, Enomoto M, Inaba M, Nakatani T, Hino M (2011) Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. J Gastroenterol 46(4):556–564
40. Lahiri M, Dixon WG (2015) Risk of infection with biologic antirheumatic therapies in patients with rheumatoid arthritis. Best Pract Res Clin Rheumatol 29(2):290–305
41. Jeong H, Baek SY, Kim SW, Eun YH, Kim IY, Kim H, Lee J, Koh E-M, Cha H-S (2017) Comorbidities of rheumatoid arthritis: results from the Korean National Health and Nutrition Examination Survey. PLoS One 12(4):e0176260