JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1343166
J Contemp Med 2023;13(5):809-813

Original Article / Orijinal Araştırma

Evaluation of HBV Reactivation and Antiviral Prophylaxis in Patients Receiving Immunosuppressive Therapy

İmmünsupresif Tedavi Alan Hastalarda HBV Reaktivasyonu ve Antiviral Profilaksinin Değerlendirilmesi

Ahmet Şahin, Selda Aslan

Dr. Ersin Arslan Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Gaziantep, Turkey

Abstract

Aim: Patients with chronic hepatitis B and people with a history of hepatitis B (HBV) infection are at risk of HBV reactivation (HBVr) when they receive immunosuppressive therapy. In this study, we aimed to evaluate the hepatitis B serology, risk groups and antiviral prophylaxis of patients receiving various immunosuppressive therapies due to rheumatological diseases.

Material and Method: The study included 375 patients over 18 years of age who received tumor necrosis factor-α (TNF-α) inhibitor, tyrosine kinase inhibitor, steroids, methotrexate or anti-CD20 antibodies due to rheumatic diseases in a training and research hospital between May 2022 and May 2023. Hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (anti-Hbs), hepatitis B core protein antibody (anti-Hbc IgG) serologies, immunosuppressive therapies and oral antivirals were retrospectively analyzed.

Results: The average age of the 375 patients included in the study was 43.77±13.07 years. 193 (51.5%) of the patients were male. 11 (2.9%) patients were HbsAg positive, 150 (40%) patients were anti-Hbs positive, 19 (5.1%) patients were isolated anti-Hbc IgG positive, and 79 (21.1%) patients were both anti-Hbs and anti-Hbc IgG positive. According to serological findings, 109 (29%) patients had HBV exposure. All three test results of 194 (51.7%) patients were negative. A total of 85 (22.7%) patients received oral antiviral prophylaxis due to the use of immunosuppressive agents. In terms of HBVr, 16.5% were evaluated as high risk, 75.3% as moderate risk, and 8.2% as low risk. Out of 85 patients 79 received entecavir, 5 reveived tenofovir disoproxil fumarate (TDF) and 1 received tenofovir alafenamide fumarate (TAF). The mean duration for the immunosuppressive therapy was 6.41±4.20 years. HBVr was not observed in any of our patients.

Conclusion: Before patients receive immunosuppressive therapy, hepatitis B serologies and prophylaxis indication should be evaluated firstly. In addition, as a preventive medicine activity, hepatitis B vaccinations of unvaccinated patients should be completed as quickly as possible.

Keywords: Immunosuppression, hepatitis B, reactivation

Öz

Amaç: Kronik hepatit B'li hastalar ve geçirilmiş hepatit B virüs enfeksiyonu olan kişiler immünsupresif tedavi aldıkları zaman HBV reaktivasyonu riskine maruz kalırlar. Bu çalışmada romatolojik hastalıklar nedeni ile çeşitli immünsupresif tedavileri alan hastaların hepatit B serolojilerini, risk gruplarını ve antiviral profilaksi alma durumlarını sunmayı amaçladık.

Gereç ve Yöntem: Çalışmaya Mayıs 2022 ile Mayıs 2023 tarihleri arasında bir eğitim ve araştırma hastanesinde romatolojik hastalıklar nedeni ile tümör nekroz faktör-α inhibitörü, tirozin kinaz inhibitörü, steroid, metotreksat veya anti-CD20 antikoru alan 18 yaş üstü 375 hasta dahil edildi. Hastaların HbsAg, anti-Hbs ve anti-Hbc IgG serolojileri, immünsupresif tedavileri ve süresi ile almış oldukları oral antiviraller retrospektif olarak incelendi.

Bulgular: Çalışmaya alınan 375 hastanın yaş ortalaması 43.77±13.07 idi. Hastaların 193' ü (%51.5) erkek idi. Hastaların 11' inde (%2.9) HbsAg pozitif, 150' sinde (%40) anti Hbs pozitif, 19' unda (%5.1) izole anti-Hbc IgG pozitif ve 79 (%21.1) hastada ise anti-Hbs ile anti-Hbc IgG beraber pozitif idi. Serolojik bulgulara göre 109 (%29) hastada HBV ile karşılaşma durumu mevcuttu. Hastaların 194' ünde (%51.7) ise her üç tetkik sonucu da negatif idi. Toplamda 85 (%22.7) hasta immünsupresif ajan kullanımı nedeni ile oral antiviral profilaksi almaktaydı. HBV reaktivasyon riski profilaksi başlanan hastaların 14' ünde (%16.5) yüksek, 64' ünde (%75.3) orta, 7' sinde (%8.2) düşük riskliydi. Toplam 79 hasta entekavir, 5 hasta tenofovir disoproksil fumarat ve 1 hasta ise tenofovir alafenamid fumarat almakta idi. Ortalama immünsüpresif tedavi alma süresi 6.41±4.20 yıl idi. HBV reaktivasyonu görülen hasta olmadı.

Sonuç: Hastalar immünsupresif tedavi almadan önce hepatit B serolojileri ve profilaksi durumları öncelikle değerlendirilmelidir. Ayrıca koruyucu hekimlik faaliyeti olarak aşısız hastaların en kısa sürede hepatit B aşıları tamamlanmalıdır.

Anahtar Kelimeler: İmmünsupresyon, hepatit B, reaktivasyon

Corresponding *(İletişim)*: Ahmet ŞAHİN, Dr. Ersin Arslan Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, Gaziantep, Turkey
E-mail *(E-posta)*: ahmet27sahin@hotmail.com
Received *(Geliş Tarihi)*: 14.08.2023 **Accepted *(Kabul Tarihi)*:** 29.09.2023

INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem and is among the main causes of chronic hepatitis, liver failure and hepatocellular carcinoma in our country. It is estimated that approximately 296 million people worldwide suffer from chronic hepatitis B and there are approximately 1.5 million new infection cases each year.[1] Our country is located in a region with intermediate endemic hepatitis B seroprevalence. In the TURHEP study, hepatitis B surface antigen (HbsAg) positivity rate in our country was found to be 4% and hepatitis B core protein antibody (anti-Hbc Ig total) positivity rate was found to be 30.6%.[2]

Reactivation of HBV infection is an important cause of mortality and morbidity in rheumatology patients receiving immunosuppressive therapy. HBV reactivation (HBVr) provides insight into the disturbance of the balance between the host's immune system and viral replication.[3] Reactivation can occur spontaneously or after therapeutic agents adversely affect the host's immune system. Cytotoxic chemotherapies, steroid therapy, monoclonal antibody therapy and many other immunosuppressive agents used in the treatment of solid and hematological malignancies are potential risk factors for reactivation.[4] Patients should be closely monitored to prevent reactivation. Some studies have shown that screening for HBV infection in rheumatology patients receiving immunosuppressive therapy reduces the risk of reactivation.[5,6]

In our study, we aimed to present the hepatitis B virus serology data, prophylaxis receiving status and activities to prevent reactivation of patients who were referred to the infectious diseases outpatient clinic before immunosuppressive treatment due to rheumatological diseases.

MATERIAL AND METHOD

The study was carried out with the permission of Gaziantep Islamic Science and Technology University Noninvasive Clinical Researches Ethics Committee (Date: 16.06.2023, Decision No: 265.26.21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 375 patients over 18 years of age who received tumor necrosis factor-α (TNF-α) inhibitor (adalimumab, infliximab, golimumab, etanercept, secukinumab, certolizumab, risankizumab, ixekizumab...), tyrosine kinase inhibitors (baricitinib, tofacitinib...), steroid, methotrexate or anti-CD20 antibodies (rituximab) due to rheumatological diseases in a training and research hospital between May 2022 and May 2023. Age, gender, type of rheumatological diseases of the patients, their HbsAg, hepatitis B surface antibody (anti-Hbs), anti-Hbc IgG serologies, immunosuppressive treatments / durations and type of oral antivirals were retrospectively analyzed. Those who received prior oral antiviral therapy for chronic hepatitis B disease, those who received immunosuppressive therapy for anything other than rheumatological diseases, and patients under 18 years of age were excluded from the study. Patients who received oral antiviral prophylaxis were followed for at least six months for reactivation. In the analyzes, continuous variables that fit the normal distribution, mean and standard deviation, continuous variables that do not fit the normal distribution, median value and minimum-maximum categorical variables were presented as numbers and percentages. Patients receiving immunosuppressive therapy were evaluated in terms of HBVr risk by dividing them into three categories according to the American Gastroenterological Association (AGA) risk classification. These are: high risk (>10%), moderate risk (1-10%) and low risk (<1%) categories.[4]

Statistical Analysis

Statistical analysis was performed using IBM SPSS 22.0 version (IBM SPSS, Chicago, IL). Of the patients quantitative values, mean (standard deviation), number of patients, serological/virological distribution characteristics, and antiviral prophylaxis were shown as frequency and ratio (n and %).

RESULTS

Of the 375 patients included in the study, 349 were receiving TNF-α inhibitor/steroid/methotrexate, 19 were taking tyrosine kinase inhibitors, and 7 were taking anti-CD20 antibodies. The average age of the patients was 43.77±13.07 years. 193 (51.5%) patients were male and 182 (48.5%) were female. The average duration of immunosuppressive therapy was 6.23±4.14 years. The results of HBsAg, anti-Hbs and anti-Hbc IgG were evaluated. 11 patients were HbsAg positive, 150 patients were anti-Hbs positive, 19 patients were isolated anti-Hbc IgG positive and 79 patients were both anti-Hbs and anti-Hbc IgG positive.

According to serological findings, 109 (29%) patients were exposed to HBV and 64 (17%) patients were found to be immune to HBV by vaccination. All three serology results of 194 (51.7%) patients were negative. A total of 85 (22.7%) patients reveived oral antiviral prophylaxis due to the use of immunosuppressive agents (**Table 1**). When the patients were evaluated in terms of HBVr, 14 (16.5%) patients were high risk, 64 (75.3%) moderate risk and 7 (8.2%) low risk. According to the distribution of prophylaxis, 79 patients were using entecavir, 5 patients were using tenofovir disoproxil fumarate (TDF) and 1 patient was using tenofovir alafenamide fumarate (TAF). Of the 85 patients receiving antiviral prophylaxis, 44 were men and 41 were women. The mean duration for the immunosuppressive therapy was 6.41±4.20 years. According to the distribution of patients who received antiviral prophylaxis for immunosuppressive therapy, 34 patients (40%) had rheumatoid arthritis, 29 patients (34.1%) had ankylosing spondylitis, 10 patients (11.7%) had psoriatic arthritis, 6 patients (7.1%) had Behcet's disease, and 6 (7.1%) patients had systemic lupus erythematosus (**Figure 1**). HBVr was not observed in any of our patients.

Table 1. Demographic and laboratory data of the patients

	All patients, n(%) or (min-max)	Patients receiving antiviral prophylaxis n(%) or (min-max)
Number of patients	375 (100)	85 (22.7)
Mean age ± SD	43.77±13.07	48.3±11.8
Male	193 (51.5)	44 (51.8)
ALT	23.7 (5-108)	25.8 (8-108)
HBsAg positive	11 (2.9)	11 (12.9)
Isolated anti-HBc positive	19 (5.1)	17 (20)
Both anti-HBs and anti-HBc Ig G positive	79 (21.1)	57 (67.1)

SD: Standart deviation, ALT: Alanine transaminase, HbsAg: Hepatitis B surface antigen, Anti-Hbs: Hepatitis B surface antibody, Anti-Hbc IgG: Hepatitis B core protein antibody

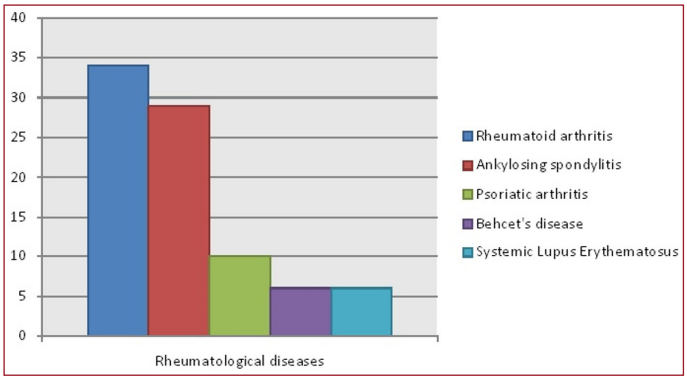

Figure 1. Distribution of patients receiving antiviral prophylaxis

DISCUSSION

HBVr remains an important cause of morbidity and mortality in patients with chronic hepatitis B or resolved HBV infection receiving immunosuppressive therapy. However, according to the risk status of the patients, it is a preventable condition with various options such as close follow-up, preemptive treatment or antiviral prophylaxis.[7,8] HBVr is seen at a rate of 12% in HbsAg-positive and 3-5% in HbsAg-negative / anti-Hbc Ig G-positive patients with rheumatological disease who do not receive antiviral prophylaxis.[9] In a study in which 278 patients receiving TNF-α inhibitor were evaluated in the study of Karadağ et al., 29 patients had a history of HBV infection or isolated anti-HBc total positivity, HBV reactivation was found in 5 (17.2%) patients.[10] In the study of Çabalak et al. Hbs Ag positivity was 4.1%, but no reactivation was observed.[11] We think that the absence of HBVr in our study is due to the low number of high risk patients.

Patients at risk of HBVr were divided into three groups according to AGA risk classification, depending on HBV serology (HbsAg and/or anti-Hbc IgG positivity) and the type of immunosuppressive agent used. These are high risk (>10%), moderate risk (1-10%) and low risk (<1%) patients.[4] Although there are some differences between the guidelines for the follow-up of these patients, the common feature of these guidelines is that it is definitely recommended to start antiviral prophylaxis in high risk patients. On the other hand, in low and moderate risk patients, it varies according to the type of immunosuppressive agent received and HBV serology status, initiation of antiviral prophylaxis with follow-up is left to the physician's decision for these group.[4,12-14] In our study, the majority of patients who received HBVr preventive prophylaxis were in the moderate risk group (75.3%). In the study of Ceylan et al., 35% of the patients were in the high risk group, 49% in the moderate risk group, and 16% in the low risk group.[15] In the study of Durak and Coşar 24.5% were at high risk, 42.6% were at moderate risk and 33% of patients were at low risk.[16]

Entecavir, TDF and TAF used in the treatment of chronic hepatitis B are effective and safe drugs. Guidelines recommend entecavir, TDF or TAF for prophylactic antiviral treatment because of their high genetic barriers and efficacy.[17] However drug interaction, renal dysfunction, osteoporosis are factors that should be considered in the selection of antiviral drugs.[18,19] In one meta-analysis study, initiation of any of these antivirals was shown to inhibit reactivation.[20] In comparative studies with lamivudine, Picardi et al. and Yang et al. showed that the risk of HBVr were lower in patients using TDF and entecavir, respectively.[21,22] In our study, entecavir was the most commonly used antiviral for prophylaxis purposes (92.9%). It was observed that different antivirals were used in different proportions in the literature. The initiation rate of entecavir was 67% in Ceylan et al. study for prophylaxis.[15] Starting entecavir, TDF or TAF varies on the clinician's decision, the patient's condition, and the underlying disease.

It is recommended that antiviral prophylaxis be started 1-3 weeks before or at least concomitantly with immunosuppressive therapy.[12,14] In our study, 27 (31.8%) patients were started concomitantly, while the remaining patients were started later on. No reactivation was observed in these patients. In their study of 2334 rheumatoid arthritis patients, Chen et al. followed up 123 HbsAg positive/high-risk patients without antiviral prophylaxis and reactivation was observed among 30 of them (24.4%).[23] In a multicenter and retrospective study, reactivation was not detected after initiation of prophylaxis in the moderate risk patient group.[24] In another prospective study, among 234 high risk patients, there had been 3 (two chronic HBV, one resolved HBV) reactivation cases.[25] In the study by Harigai et al., reactivation was observed in 14.8% after immunosuppressive treatment.[26] HBVr was 12.3% in the study of Lee et al.[27] which included HbsAg positive patients, and 5% in Urata's study of HBsAg-negative/anti-HBc-positive patients.[28] Studies in the literature also show that strict follow-up is required in terms of HBVr, especially in the high risk group.

In the literature, HbsAg or anti-Hbc Ig G positivity shows regional differences. In our study, HbsAg positivity was 2.9% and HBV exposure was 29% in the rheumatologic patient group. In a study conducted in Italy in which 292 rheumatology patients were included, HbsAg was found to be 2% and HBV exposure was 24%.[29] In another study in

Iran in which 93 systemic lupus erythematosus patients were included, HbsAg positivity was 3.2% and HBV exposure was 8.7%.[30] There was no HBsAg positivity in the study in Turkey, but HBV exposure screening was insufficient.[31]

In our study, our negative patient rate was 51.7% in all three HbsAg, anti-Hbc IgG and anti-Hbs tests. About half of our patients were susceptible to HBV infection. HBV infection is a vaccine-preventable viral infection. The increase of comorbid diseases among immunosuppressive patients negatively affects their quality of life. In addition to the 0-1-6 calendar, which is the most commonly used in HBV vaccination, there are also different hepatitis B vaccination schedules such as 0-1-2-6, 0-1-12, 0-1-2-12.[32] However, in a study comparing a single dose of the vaccine and a double dose among immunosuppressive patients, a higher anti-Hbs titer was detected in those who received a double dose of hepatitis B vaccine.[33] In our study, we recommended a double dose of hepatitis B vaccine on a 0-1-6 schedule, for HBV-susceptible patients to prevent chronic hepatitis B.

There are some limitations of our study. First, this was a single-center, retrospective design study with a sample size. Second, our patients were receiving immunosuppressive therapy only for rheumatological diseases. Cytotoxic chemotherapies and other immunosuppressive agents may also be included. Third, while it is recommended to start oral antiviral therapy in patients according to the risk classification, in our study, the AGA 2015 guideline was used instead of APASL 2021 in terms of HBV reactivation risk and the content of immunosuppressive agents was not specified. These issues should be considered in future studies.

CONCLUSION

The available data suggest that due to the increasing use of TNF-α inhibitor and other biologic immunosuppressive agents, patients should be screened for hepatitis before treatment and regular follow-up should be performed afterwards. The risk of HBVr associated with the ever increasing new immunosuppressive agents is not clear. More comprehensive studies are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziantep Islamic Science and Technology University Noninvasive Clinical Researches Ethics Committee (Date: 16.06.2023, Decision No: 265.26.21).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Sono S, Sae-Chan J, Kaewdech A, Chamroonkul N, Sripongpun P. HBV seroprevalence and liver fibrosis status among population born before national immunization in Southern Thailand: Findings from a health check-up program. PLoS One. 2022;17(6):e0270458.
2. Tozun N, Ozdogan O, Cakaloglu Y, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect. 2015;21(11):1020-6.
3. Wu T, Li J, Shao L, et al. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. Gut. 2018;67(12):2181-91.
4. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148(1):215-9; quiz e16-7.
5. Fukuda W, Hanyu T, Katayama M, et al. Risk stratification and clinical course of hepatitis B virus reactivation in rheumatoid arthritis patients with resolved infection: final report of a multicenter prospective observational study at Japanese Red Cross Hospital. Arthritis Research & Therapy. 2019;21(1):255.
6. Mahroum N, Watad A, Tiosano S, et al. Chronic hepatitis B viral infection among RA patients-a cross-sectional control study. Clin Rheumatol. 2019;38(5):1237-41.
7. Etienne S, Vosbeck J, Bernsmeier C, Osthoff M. Prevention of Hepatitis B Reactivation in Patients Receiving Immunosuppressive Therapy: a Case Series and Appraisal of Society Guidelines. J Gen Intern Med. 2023;38(2):490-501.
8. Aygen B, Demir AM, Gümüş M, et al. Immunosuppressive therapy and the risk of hepatitis B reactivation: Consensus report. Turk J Gastroenterol. 2018;29(3):259-69.
9. Pattullo V. Prevention of Hepatitis B reactivation in the setting of immunosuppression. Clin Mol Hepatol. 2016;22(2):219-37.
10. Karadağ Ö, Kaşifoğlu T, Özer B, et al. Viral hepatitis screening guideline before biological drug use in rheumatic patients. Eur J Rheumatol. 2016;3(1):25-8.
11. Cabalak M, Bal T, Ocak S. İmmünsüpresif Tedavi Alacak Hastalarda Hepatit Serolojisi. Harran Üniversitesi Tıp Fakültesi Derg. 2020;17.
12. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-98.
13. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560-99.
14. Lau G, Yu ML, Wong G, et al. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. Hepatol Int. 2021;15(5):1031-48.
15. Ceylan M, Turken M, Singil S, Pelin A, Şükran K. İmmunsupresif Tedavi Alan Hastalarda Hepatit B Reaktivasyonu Riskinin Değerlendirilmesi. İzmir Tıp Fakültesi Derg. 2022;1(3):112-6.
16. Durak S, Coşar AM. Evaluation of the safety and antiviral efficacy of the tenofovir alafenamide fumarate molecule in immunosuppressed patients. J Health Sci Med. 2022;5(6):1688-92.
17. Jeong S, Shin HP, Kim HI. Real-World Single-Center Comparison of the Safety and Efficacy of Entecavir, Tenofovir Disoproxil Fumarate, and Tenofovir Alafenamide in Patients with Chronic Hepatitis B. Intervirology. 2022;65(2):94-103.
18. Baranek B, Wang S, Cheung AM, Mishra S, Tan DH. The effect of tenofovir disoproxil fumarate on bone mineral density: a systematic review and meta-analysis. Antivir Ther. 2020;25(1):21-32.
19. Ha NB, Ku K, Ha NB, Chaung KT, Trinh HN, Nguyen MH. Renal Function in Chronic Hepatitis B Patients Treated With Tenofovir Disoproxil Fumarate or Entecavir Monotherapy: A Matched Case-Cohort Study. J Clin Gastroenterol. 2015;49(10):873-7.

20. Su J, Long L, Zou K. Antiviral prophylaxis for preventing reactivation of hepatitis B virus in rheumatic patients: a systematic review and meta-analysis. Clin Rheumatol. 2018;37(12):3201-14.
21. Picardi M, Della Pepa R, Giordano C, et al. Tenofovir vs lamivudine for the prevention of hepatitis B virus reactivation in advanced-stage DLBCL. Blood. 2019;133(5):498-501.
22. Yang C, Qin B, Yuan Z, Chen L, Zhou HY. Meta-analysis of prophylactic entecavir or lamivudine against hepatitis B virus reactivation. Ann Hepatol. 2016;15(4):501-11.
23. Chen M-H, Chen M-H, Liu C-Y, et al. Hepatitis B Virus Reactivation in Rheumatoid Arthritis Patients Undergoing Biologics Treatment. The Journal of Infectious Diseases. 2016;215(4):566-73.
24. Padovan M, Filippini M, Tincani A, et al. Safety of Abatacept in Rheumatoid Arthritis With Serologic Evidence of Past or Present Hepatitis B Virus Infection. Arthritis Care Res (Hoboken). 2016;68(6):738-43.
25. Vassilopoulos D, Delicha EM, Settas L, et al. Safety profile of repeated rituximab cycles in unselected rheumatoid arthritis patients: a long-term, prospective real-life study. Clin Exp Rheumatol. 2016;34(5):893-900.
26. Harigai M, Winthrop K, Takeuchi T, et al. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. RMD Open. 2020;6(1).
27. Lee YH, Bae SC, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. Int J Rheum Dis. 2013;16(5):527-31.
28. Urata Y, Uesato R, Tanaka D, et al. Prevalence of reactivation of hepatitis B virus replication in rheumatoid arthritis patients. Mod Rheumatol. 2011;21(1):16-23.
29. Canzoni M, Marignani M, Sorgi ML, et al. Prevalence of Hepatitis B Virus Markers in Patients with Autoimmune Inflammatory Rheumatic Diseases in Italy. Microorganisms. 2020;8(11).
30. Makvandi M, Noormandi Pour S, Teimoori A, et al. Frequency of Hepatitis B Markers in Systemic Lupus Erythematosus Patients in Iran. Asian Pac J Cancer Prev. 2022;23(6):1921-6.
31. Cabalak M, Kimyon G, Bal T. Frequency of Hepatitis B Virus Screening in Patients with Systemic Lupus Erythematosus. Mediterranean Journal of Infection Microbes and Antimicrobials. 2020;9.
32. Yang S, Tian G, Cui Y, Ding C, Deng M, Yu C, et al. Factors influencing immunologic response to hepatitis B vaccine in adults. Sci Rep. 2016;6:27251.
33. Öztürk S, Kaçar M, Toprak S, Çolak O, Öztürk D, Agalar C. Hepatit B Aşılama Verileri; İmmünsüpresif Hastalarda Tek Doz mu? Çift Doz mu? Namık Kemal Tıp Derg. 2020;8(3):499-506.