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# Frequency of Hepatitis B Virus Screening in Patients with Systemic Lupus Erythematosus

## Sistemik Lupus Eritematozuslu Olgularda Hepatit B Virüs Tarama Sıklığı

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## Abstract

**Introduction:** Immunosuppressive drug use is common in the treatment of systemic lupus erythematosus (SLE). In cases receiving immunosuppressive therapy, screening for hepatitis B reactivation risk is also recommended. In this study, we aimed to investigate the frequency of hepatitis B screening in cases diagnosed as having SLE, who were followed up in the Rheumatology Clinic of Hatay Mustafa Kemal University.
**Materials and Methods:** We included 93 patients who were followed-up in the Rheumatology Clinic of Hatay Mustafa Kemal University with the diagnosis of SLE between July 2017-December 2019 in our study. The screening rates of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core protein antibody (anti-HBc IgG) of the cases and the immunosuppressive drugs used by them were analyzed retrospectively.
**Results:** The mean age of the cases was 38 years (minimum-maximum: 18-79), and 91.4% were women. Of the cases, 43 (46.2%) were determined to be never screened for hepatitis B, 34 (36.6%) screened inadequately, and only 16 (17.2%) screened fully. In 22 cases receiving high-risk immunosuppressive therapy, the rate of full screening of hepatitis B was 27.3%.
**Conclusion:** In patients with SLE, even those who used high-risk immunosuppressive therapy, screening rates were found low. We think that awareness should be increased in this regard by performing joint training with clinics that start immunosuppressive therapy, a periodic repetition of these trainings should be done, and also multi-center studies should be conducted.
**Keywords:** Systemic lupus erythematosus, hepatitis B screening, immunosuppressive therapy

## Öz

**Giriş:** Sistemik lupus eritematozus (SLE) tedavisinde immünosüpresif ilaç kullanımı sıktır. İmmünosüpresif tedavi alan olgularda hepatit B reaktivasyon riskine yönelik tarama yapılması da önerilmektedir. Bu çalışmada Hatay Mustafa Kemal Üniversitesi Romatoloji Kliniği'nde SLE tanısı konulan olgularda hepatit B tarama sıklığını araştırmayı amaçladık.
**Gereç ve Yöntem:** Çalışmamıza Temmuz 2017-Aralık 2019 tarihleri arasında SLE tanısıyla, Hatay Mustafa Kemal Üniversitesi Romatoloji Kliniği'nde takip edilen 93 olguyu dahil ettik. Olguların hepatit B yüzey antijeni (HBsAg), hepatit B yüzey antikoru (anti-HBs) ve hepatit B core protein antikoru (anti-HBc IgG) taranma oranları ve kullandıkları immünosüpresif ilaçlar retrospektif olarak incelendi.
**Bulgular:** Olguların yaş ortalaması 38 yıl (minimum-maksimum: 18-79) idi ve olguların %91,4'ü kadındı. Olguların 43'ünün (%46,2) hepatit B açısından hiç taranmadığı, 34'ünün (%36,6) eksik tarandığı ve sadece 16'sının (%17,2) tam olarak tarandığı tespit edildi. Yüksek riskli immünosüpresif tedavi alan 22 olguda hepatit B'nin tam olarak taranma oranı %27,3 idi.
**Sonuç:** Sistemik lupus eritematozuslu olgularda, yüksek riskli immünosüpresif tedavi kullananlarda dahi taranma oranları düşük bulundu. İmmünosüpresif tedavi başlayan klinikler ile ortak eğitimler yapılması, bu eğitimlerin periyodik olarak tekrarlanması, ayrıca çok merkezli çalışmalar yapılarak bu konuda farkındalığın artırılması gerektiğini düşünmekteyiz.
**Anahtar Kelimeler:** Sistemik lupus eritematozus, hepatit B taranması, immünosüpresif tedavi

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## Introduction

Systemic lupus erythematosus (SLE) is a systemic, autoimmune disease that is seen nine times more often in women of childbearing age than men. In SLE, which has a very heterogeneous clinic, arthritis, serositis, nephropathy, hemolytic anemia, skin findings such as malar rash, and central nervous system involvement can be seen[1]. Morbidity and mortality in SLE may be associated with different conditions such as the age of onset of the disease, gender, autoantibody profile, and major organ involvement such as nephropathy. In SLE, which has a wide clinical spectrum, the treatment decision should be individualized and made according to the prevalence and severity of the disease[2]. When major organ involvement in SLE occurs, intensive immunosuppressive therapy is required. After the symptoms of the disease are controlled, the treatment doses are reduced. Corticosteroids, hydroxychloroquine and immunosuppressive agents such as azathioprine and mycophenolat mofetil are generally used in the treatment[3]. In addition, biological agents such as rituximab, which is an anti-CD20 antibody, are used in the treatment of SLE[4].

Hepatitis due to hepatitis B virus (HBV) reactivation can be severe and fatal, but this can be prevented[5]. Hepatitis B surface antigen (HBsAg) positivity in the adult population in Turkey was found to be 4%[6]. All current guidelines recommend that HBsAg, hepatitis B core protein antibody [anti-HBc immunoglobulin (IgG)] and hepatitis B surface antibody (anti-HBs) should be screened before immunosuppressive treatment in countries with HBsAg prevalence over 2%[7-9]. Seronegative patients for hepatitis B should be referred to pre-treatment vaccination[10]. HBV reactivation risk varies according to immunosuppressive drug classes. The reactivation risk is over 10% when high dose corticosteroids, drugs that suppress B cells, and anthracycline derivatives are used. The risk of reactivation with the use of tumor necrosis factor-α, cytokine, integrin and tyrosine kinase inhibitors and medium dose corticosteroids is between 1% and 10% depending on the hepatitis B serology of the patients. The reactivation risk is less than 1% with the use of low dose or intraarticular corticosteroids and traditional immunosuppressive drugs (azathioprine, methotrexate, 6-mercaptopurine)[11-13]. High dose and prolonged use of steroids have been identified as risk factors for reactivation[11]. Prednisolone is used in the treatment of many autoimmune diseases. However, the use of these drugs is associated with an increased risk of HBV reactivation, both in monotherapy and in combination[14]. Steroids suppress the specific T cell response and increase the replication of the virus. The risk of infection is directly proportional to the dose and duration of steroid taken[15].

In our study, we aimed to present real-life data on pre-treatment screening in patients who were followed up in the rheumatology clinic for SLE and received immunosuppressive therapy.

## Materials and Methods

Ninety-three patients with SLE who were followed up in the rheumatology clinic between July 2017 and December 2019 were included in the study. Tests performed for HBsAg, anti-HBs, anti-HBc IgG were retrospectively screened. The patients in whom all these three parameters were examined were accepted as fully screened. The patients in whom at least one of the three parameters were not examined were considered incompletely screened. The patients in whom all the three parameters were not examined were considered as not screened.

HBsAg positive patients were considered to have encountered HBV. HBsAg negative, anti-HBc IgG positive, anti-HBs positive patients were accepted as naturally immune. Patients with negative HBsAg, negative anti-HBc IgG and positive anti-HBs, and patients who were vaccinated but negative for all three parameters were considered as patients who had never encountered hepatitis B.

Patients who used ≥20 mg/day for more than four weeks were accepted as using high dose steroid. Patients who used <10 mg/day for less than four weeks were accepted as using low dose steroid.

The study was conducted with the approval of the Hatay Mustafa Kemal University Faculty of Medicine retrospective ethics committee (reference number: 05.12.2019-15).

### Statistical Analysis

IBM SPSS version 21.0 statistical package program (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The compliance of the variables to normal distribution was tested using the Kolmogrov-Smirnov test and histogram. The median (median) and interquartile range were used for variables that had normal distribution. Chi-square test was used to compare categorical variables that did not have normal distribution.

## Results

The mean age of 93 patients who were followed up with the diagnosis of SLE in the Rheumatology Clinic of Hatay Mustafa Kemal University Hospital was 38 (18-79). Of the patients 91.4% were female and 8.6% were male.

It was found that 43 (46.2%) of the patients were never screened for hepatitis B, 34 (36.6%) were incompletely screened and only 16 (17.2%) were fully screened.

It was found that HBsAg was screened in 52.7% of the patients and no positivity was detected. It was found that anti-HBs

antibody was not screened in 50.5% of the patients, 35.5% of those screened for anti-HBs antibody were found negative and 15% were found positive for anti-HBs antibody. Total anti-HBc IgG positivity was observed in 16.1% of the patients and total anti-HBc IgG was not screened in 83.9% of the patients. Isolated anti-HBc IgG positivity was detected in two patients (2.2%). Screening results of the patients in terms of hepatitis serology are summarized in Table 1.

In our study, 71 patients used drugs such as low-dose corticosteroid (<10 mg/day), quinine, azathioprine, methotrexate, 6-mercaptopurine, mycophenolate mofetil, cyclosporine, and cyclophosphomide alone or in combination. Twenty-two patients were identified who received immunosuppressive therapy with high-risk for hepatitis B reactivation. These were patients using rituximab and high-dose corticosteroids.

In our study, it was found that a patient using rituximab was fully screened, but two of the four patients using rituximab and high-dose corticosteroids were fully screened, one was incompletely screened, and one was not screened. It was found that three patients using high-dose corticosteroids were fully, nine patients were incompletely screened, and five patients were not screened. The screening rate of hepatitis B serology in patients using high-risk immunosuppressive therapy is summarized in Table 2.

**Table 1. Screening results of hepatitis B serology of the patients**

| Hepatitis B serology | n (%) |
|---|---|
| **HBsAg** | |
| Positive | 0 (0) |
| Negative | 49 (52.7) |
| Not screened | 44 (47.3) |
| **Anti-HBs** | |
| Positive | 13 (14) |
| Negative | 33 (35.5) |
| Not screened | 47 (50.5) |
| **Isolated Anti-HBc IgG** | |
| Positive | 2 (2.2) |
| Negative | 13 (13.9) |
| Not screened | 78 (83.9) |

Data are presented as n (%).

HBsAg: Hepatitis B surface antigen, anti-HBs: Hepatitis B surface antibody, anti-HBc IgG: Hepatitis B core antibody

## Discussion

Hepatitis B virus is an important cause of morbidity and mortality in immunsupressed patients[5]. Although current guidelines recommend screening for hepatitis B reactivation in patients who will receive immunosuppressive therapy, the rate of hepatitis B screening was low in our study, and the most striking result of our study was that the full screening rate was 17.2%. The most important reason for this was thought to be the lack of awareness of the physicians performing the screening.

HBsAg prevalence in patients with rheumatoid arthritis in a multicenter study in Turkey was found as 2.3% and it was found as 3% in patients with ankylosing spondylitis[16]. In another study performed on patients with ankylosing spondylitis, the prevalence of HBsAg was found to be 4.5%[17]. The prevalence of HBsAg in normal population in Turkey has been identified as 4%[6]. In our study, seroprevalence could not be determined in patients with SLE. The reason for this result could be explained by the low number of patients, but the main reason for this was that the patients were not screened. We could not find any study performed in Turkey on hepatitis prevalence in patients with systemic lupus erythematosus in our literature search. When we looked at the international literature, we found the systemic review and meta-analysis by Wang et al.[18] examining the prevalence of HBV infection in patients with SLE. According to that study, hepatitis B prevalence was found to be lower in patients with SLE compared to the control group in 10 studies conducted in Asia. However, a study conducted in Israel did not support that result[19]. Therefore, we think that multi-center hepatitis B seroprevalence studies are needed in patients with SLE in our country.

In our study, it was found that there were deficiencies in the screening of hepatitis B serology in 22 patients who used high-dose corticosteroids and received B-cell suppressing drug (rituximab) treatment, especially in those who used high-dose

**Table 2. Hepatitis B serology screening rate in high-risk immunosuppressive therapy users**

| | Screening results (n,%) | | | |
|---|---|---|---|---|
| | **Full** | **Incomplete** | **Not screened** | **Total (n, %)** |
| R* | 1 (100) | - | - | 1 (100) |
| R + HDS$^{+}$ | 2 (50) | 1 (25) | 1 (25) | 4 (100) |
| HDS | 3 (17.6) | 9 (52.9) | 5 (29.4) | 17 (100) |
| Total | 6 (27.3) | 10 (45.4) | 6 (27.3) | 22 (100) |

Data are presented as n (%).

R*: Rituximab, HDS$^{+}$: High dose steroid

corticosteroids. Engin et al.[20] found the screening rates low in patients who received cytotoxic chemotherapy and steroid therapy, and found hepatitis B reactivation in two patients. Although no patient with hepatitis B reactivation was found in our study, it might be a result of the insufficient screenings.

In a study in which patients with lymphoma were reviewed retrospectively, it was observed that there were deficiencies in the screening and follow-up of hepatitis serology. They did not detect hepatitis B reactivation and HBsAg positivity during chemotherapy[21]. Another study found that most Australian medical oncologists did not adopt universal HBV screening prior to chemotherapy[22]. In our study, it was found that physicians in the rheumatology outpatient clinic were not aware of HBV screening and hepatitis B exacerbation when starting immunosuppressive therapy, and there were deficiencies in directing to vaccination.

The limitations of our study were that it was a retrospective study, the rates of referral to vaccination were unknown and the seroprevalence of hepatitis could not be determined. In addition, patients were not evaluated clinically in terms of hepatitis B exacerbation after using immunosuppressive drugs.

## Conclusion

It was found that hepatitis B was not screened or screened incompletely in patients with SLE in which immunosuppressive therapy was initiated. In order to raise awareness, we think it is important to provide trainings to clinics where immunosuppressive therapy is initiated, to repeat these trainings at certain intervals and to conduct multi-center studies. In addition, awareness can be increased and hepatitis B exacerbations can be prevented by giving information with pop-ups about hepatitis B in hospital automation systems for patients who will be started on immunosuppressive therapy.

### Ethics

**Ethics Committee Approval:** The study was conducted with the approval of the Hatay Mustafa Kemal University Faculty of Medicine retrospective ethics committee (reference number: 05.12.2019-15).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: M.Ç., G.K., T.B., Concept: M.Ç., G.K., Design: M.Ç., G.K., T.B., Data Collection or Processing: M.Ç., G.K., Analysis or Interpretation: M.Ç., G.K., T.B., Literature Search: M.Ç., G.K., Writing: M.Ç., G.K.

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