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Hepatitis B Immunity in Pediatric Rheumatology Patients: Serological Evaluation Before Biologic Therapy

Pediatrik Romatoloji Hastalarında Hepatit B Bağışıklığı: Biyolojik Tedavi Öncesi Serolojik Değerlendirme

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Abstract: Hepatitis B virus (HBV) infection remains a major global public health concern, particularly for children with chronic inflammatory diseases who require immunosuppressive or biologic therapy. Despite high childhood vaccination coverage in Türkiye, declining antibody levels over time may lead to insufficient protective immunity against HBV in some patients. This study aimed to evaluate hepatitis B immune status, vaccination history, and vaccine refusal among pediatric rheumatology patients scheduled to initiate biologic therapy, using real-world clinical data. This single-center, retrospective observational study included pediatric patients aged 2–18 years who were evaluated prior to biologic therapy initiation between August 2023 and December 2025. Demographic and clinical data, hepatitis B serological markers, vaccination history, and family-reported vaccine refusal were extracted from medical records. Protective immunity was defined as anti-HBs ≥10 mIU/mL. Statistical analyses were performed using SPSS version 25.0. A total of 58 patients were included, the majority diagnosed with juvenile idiopathic arthritis (94.8%). None of the patients were positive for HBsAg, HCV, or HIV. Protective anti-HBs levels were observed in 37 patients (63.8%), while 21 patients (36.2%) had non-protective anti-HBs levels (<10 mIU/mL) and were recommended for booster vaccination prior to biologic therapy. Only one patient (1.7%) had a documented history of vaccine refusal. Among the planned biologic therapies, adalimumab was the most commonly selected agent (65.5%). Exploratory analyses suggested potential associations between insufficient immunity and clinical variables, supporting the value of risk-based screening. A substantial proportion of pediatric rheumatology patients scheduled to receive biologic therapy were found to have insufficient hepatitis B immunity, even in a region where childhood vaccination coverage is relatively high. Routine HBV serological screening and timely booster vaccination should be integral components of pre-biologic assessment. Although vaccine refusal was infrequent, its presence highlights an additional preventable risk in this vulnerable population. Prospective studies evaluating immunity across different vaccination eras and strategies to address vaccine hesitancy are warranted.
Keywords: Hepatitis B immunity, Anti-HBs; Biologic therapy, Pediatric rheumatology; Vaccine hesitancy; Vaccine refusal

Özet: Hepatit B virüsü (HBV) enfeksiyonu, özellikle immünsupresif veya biyolojik tedavi gerektiren kronik inflamatuvar hastalığı olan çocuklar için önemli bir küresel halk sağlığı sorunu olmaya devam etmektedir. Türkiye'de çocukluk çağı aşılama oranlarının yüksek olmasına rağmen, zamanla azalan antikor düzeyleri bazı hastalarda HBV'ye karşı koruyucu bağışıklığın yetersiz olmasına yol açabilmektedir. Bu tek merkezli, retrospektif gözlemsel çalışmaya, Ağustos 2023 ile Aralık 2025 tarihleri arasında biyolojik tedavi başlanması planlanan ve tedavi öncesi değerlendirme yapılan 2–18 yaş arası pediatrik hastalar dahil edilmiştir. Demografik ve klinik veriler, hepatit B serolojik belirteçleri, aşılama öyküsü ve aile tarafından bildirilen aşı reddi bilgileri hasta dosyalarından elde edilmiştir. Koruyucu bağışıklık, anti-HBs ≥10 mIU/mL olarak tanımlanmıştır. İstatistiksel analizler SPSS sürüm 25.0 kullanılarak gerçekleştirilmiştir. Çalışmaya toplam 58 hasta dahil edilmiş olup, hastaların büyük çoğunluğu juvenil idiyopatik artrit tanısı almıştır (%94,8). Hastaların hiçbirinde HBsAg, HCV veya HIV pozitifliği saptanmamıştır. Otuz yedi hastada (%63,8) koruyucu düzeyde anti-HBs saptanırken, 21 hastada (%36,2) anti-HBs düzeyleri koruyucu eşik değerin altında (<10 mIU/mL) bulunmuş ve biyolojik tedavi öncesinde rapel aşı önerilmiştir. Yalnızca bir hastada (%1,7) belgelenmiş aşı reddi öyküsü mevcuttur. Planlanan biyolojik tedaviler arasında en sık tercih edilen ajan adalimumab olmuştur (%65,5). Keşifsel analizler, yetersiz bağışıklık ile bazı klinik değişkenler arasında olası ilişkiler bulunduğunu göstermiş olup, risk temelli taramanın değerini desteklemektedir. Biyolojik tedavi planlanan pediatrik romatoloji hastalarının önemli bir bölümünde, çocukluk çağı aşılama oranlarının görece yüksek olduğu bir bölgede dahi, hepatit B bağışıklığının yetersiz olduğu saptanmıştır. Bu bulgular, rutin HBV serolojik taramasının ve zamanında rapel aşılamanın biyolojik tedavi öncesi değerlendirmenin ayrılmaz bir parçası olması gerektiğini göstermektedir. Aşı reddi sıklığı düşük olmakla birlikte, varlığı bu kırılgan hasta grubunda önlenebilir ek bir risk faktörüne işaret etmektedir. Farklı aşılama dönemlerine göre bağışıklık durumunu değerlendiren ve aşı tereddüdü ile başa çıkmaya yönelik stratejileri inceleyen ileriye dönük çalışmalar gereklidir.
Anahtar Kelimeler: Hepatit B bağışıklığı, Anti-HBs; Biyolojik tedavi, Pediatrik romatoloji, Aşı tereddüdü, Aşı reddi

Ethics Committee Approval: The study was approved by the Ethics Committee of Eskisehir Sehir City Hospital (decision date:11.09.2025:, number: ESK/BAEK 2025/205.

Informed Consent: The study was designed retrospectively, and all data were analyzed in an anonymized manner.

Authorship, contributions: S.N.T. contributed to the conception and design of the study, conducted data collection, performed data analysis and interpretation, and drafted the manuscript.
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1. Introduction

Hepatitis B virus (HBV) infection remains an important global public health problem, and Türkiye is classified among countries with an intermediate level of endemicity (1). Despite the success of national immunization programs, incomplete vaccination in certain segments of the population or the gradual decline of antibody levels over time may result in insufficient protective immunity. This poses a clinically significant risk, particularly for children with chronic inflammatory diseases who require immunosuppressive therapy.

Biologic agents have provided a major advancement in the treatment of childhood autoimmune and autoinflammatory diseases. However, by suppressing the immune system, these medications increase susceptibility to infections; accordingly, there is a risk of HBV reactivation in individuals with prior exposure and a risk of de novo HBV infection in those who are non-immune. Current international guidelines recommend assessing patients' HBV serological status before initiating biologic therapy and, when indicated, implementing antiviral prophylaxis/monitoring or administering a booster vaccination (2-4).

In recent years, a notable increase in vaccine hesitancy and vaccine refusal has been observed both globally and in Türkiye (5,6). This trend undermines herd immunity and facilitates the re-emergence of preventable infections, particularly among children who require immunosuppressive therapy. Therefore, assessing the frequency of vaccine refusal and determining the level of immunity against hepatitis B in pediatric patients for whom biologic therapy is planned is of critical importance for both individual patient safety and public health.

This study aimed to evaluate the hepatitis B immune status of pediatric rheumatology patients scheduled to initiate biologic therapy using real-world clinical data. In addition, vaccination history and the presence of vaccine refusal were assessed alongside serological findings. By providing real-world data from a pediatric rheumatology cohort, this study aims to highlight the importance of routine HBV serological screening prior to biologic therapy and contribute to improved preventive strategies in this high-risk patient population.

2. Materials and Methods

Study Design and Ethical Approval

This study was conducted as a single-center, retrospective, descriptive observational investigation in the Pediatric Rheumatology Clinic of Eskişehir City Hospital. Ethical approval for retrospective analysis of patient data was obtained from the Institutional Review Board of Eskişehir City Hospital (Decision Date: 11/09/2025, Decision No: ESH/BAEK 2025/205). The study was carried out in accordance with the principles of the Declaration of Helsinki, and all data were analyzed in an anonymized manner.

Study Population and Data Collection

Pediatric patients aged 2–18 years who were scheduled to initiate biologic therapy in the Pediatric Rheumatology Outpatient Clinic of Eskişehir City Hospital between August 1, 2023, and December 1, 2025, were included in this study. The inclusion criteria comprised having a diagnosis of a chronic inflammatory disease (such as juvenile idiopathic arthritis or familial Mediterranean fever), being a candidate for biologic therapy, and having hepatitis B serology assessed prior to treatment initiation. Patients with missing laboratory data, a known history of previous HBV infection, or documented immunodeficiency were excluded from the analysis.

Data were obtained retrospectively from the hospital information management system (HIMS) and patient medical records. The collected variables included age, sex, clinical diagnosis, the type of biologic agent planned, hepatitis B serological markers, vaccination history, and family-reported vaccine refusal status. Vaccination history was obtained from hospital medical records and parental reports and was additionally reviewed, when available, through the national electronic health record system (e-Nabız), which integrates primary care vaccination records in Türkiye. In our clinic, hepatitis B serological screening is routinely performed at the time of initial evaluation before the initiation of conventional immunosuppressive therapy or biologic agents. Therefore, most patients included in this cohort had not yet received disease-modifying antirheumatic drugs or systemic corticosteroids at the time of serological assessment.

Hepatitis B serological status was classified according to anti-HBs levels. In line with commonly

used serological definitions, anti-HBs levels ≥10 mIU/mL were accepted as the conventional seroprotective threshold, whereas levels <10 mIU/mL were considered below this threshold (4,7). All serological analyses were performed in the institutional laboratory using a chemiluminescent immunoassay (CLIA) method.

Statistical Analysis

All data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation or median (minimum–maximum), while categorical variables were presented as counts and percentages. Between-group differences were assessed using the Chi-square test or Fisher's exact test for categorical variables, the Student's t-test for normally distributed continuous variables, and the Mann–Whitney U test for non-normally distributed variables. A p-value < 0.05 was considered statistically significant. Because of the limited sample size, the findings of this study should be interpreted with caution and considered hypothesis-generating rather than confirmatory.

3. Results

Demographic and clinical characteristics of the study population are summarized in Table 1. A total of 58 pediatric patients scheduled to receive biologic therapy were included in the study. The cohort predominantly consisted of patients with juvenile idiopathic arthritis, with a smaller number of patients diagnosed with familial Mediterranean fever and idiopathic inflammatory pericarditis.

Table 1. Demographic and Clinical Characteristics of the Patients

Characteristic	Value
Total number of patients	58
Sex (Female/Male)	32 / 26
Age (years)	Median 16
Age range	2–17 years
Diagnoses	
• Juvenile Idiopathic Arthritis (JIA)	55 (94.8%)
• Familial Mediterranean Fever (FMF)	2 (3.4%)
• Idiopathic inflammatory pericarditis	1 (1.7%)

When HBV serology was examined, no patient tested positive for HBsAg, and all patients were negative for HCV and HIV. Evaluation of anti-HBs levels showed that 37 patients (63.8%) had sufficient immunity (≥10 mIU/mL), whereas 21 patients (36.2%) had insufficient immunity (<10 mIU/mL). Accordingly, HBV booster vaccination/re-immunization was recommended for these 21 patients (36.2%) prior to initiating biologic therapy (Table 2).

When vaccination history was evaluated, only one patient (1.7%) was found to have an incomplete childhood immunization schedule due to family-reported vaccine refusal. In this patient, the vaccination program was resumed after the decision to initiate biologic therapy, and re-immunization was completed before treatment was started. All other patients had no documented history of vaccine refusal and were found to be vaccinated in accordance with the national immunization schedule.

Table 2. Hepatitis B Serological Findings

Variable	n (Number of Patients)	% (out of 58)
HBsAg positivity	0	0%
Anti-HBs ≥10 mIU/mL (Protective immunity)	37	63.8%
Anti-HBs <10 mIU/mL (Non-protective immunity)	21	36.2%
Patients recommended for re-immunization	21	36.2%
History of active vaccine refusal	1	1.7%
HCV positivity	0	0%
HIV positivity	0	0%

When the distribution of biologic agents was examined, adalimumab was identified as the most frequently prescribed medication, used in 38 patients (65.5%). This was followed by etanercept (n = 14; 24.1%) and anakinra (n = 3; 5.2%). Less commonly, canakinumab (n = 1), tocilizumab (n = 1), and tofacitinib (a targeted synthetic DMARD, n = 1) were utilized as treatment options. These findings indicate that anti-TNF agents (adalimumab and etanercept)—particularly adalimumab—predominate in biologic therapy use in our clinic (Table 3).

Table 3. Distribution of Biologic Agents

Biologic Agent	n (Number of Patients)	% of Total (n = 58)
Adalimumab	38	65.5%
Etanercept	14	24.1%
Anakinra	3	5.2%
Canakinumab	1	1.7%
Tocilizumab	1	1.7%
Tofacitinib	1	1.7%
TOTAL	**58**	**100%**

4. Discussion

One of the most notable findings of this study is that approximately one-third (36.2%) of pediatric rheumatology patients had anti-HBs levels <10 mIU/mL, indicating antibody levels below the conventional seroprotective threshold. However, these findings should be interpreted cautiously, as the present study did not include a healthy control group and may be subject to potential selection bias due to its retrospective single-center design.

The number of studies evaluating HBV immunity based on real-world data in pediatric rheumatology populations is limited. Most existing evidence derives from adult rheumatology cohorts, in which immunosuppressive therapies have been associated with declining HBV antibody titers over time (8,9). However, in our study, serological evaluation was performed prior to the initiation of biologic therapy; therefore, the present findings do not allow conclusions regarding the potential effect of immunosuppressive treatment on HBV immunity. Nevertheless, the identification of patients with anti-HBs levels below the protective threshold highlights the importance of evaluating HBV serological status before initiating biologic therapy.

One possible explanation for the insufficient hepatitis B immunity observed is the gradual decline of anti-HBs antibody titers over time following the primary vaccination series administered during childhood (10). In the literature, it has been reported that antibody levels may decline more rapidly in individuals with chronic diseases requiring immunosuppressive therapy; however, what is particularly noteworthy is that a strong anamnestic response can be elicited in most patients when a booster dose is administered (8,9,11). Therefore, reassessing immune status before initiating biologic therapy and administering a booster vaccination when necessary should be considered an essential component of safe treatment planning. Although an anti-HBs level ≥10 mIU/mL is widely used as the conventional seroprotective threshold after hepatitis B vaccination, this cutoff represents a serological marker rather than an absolute indicator of protective immunity. Studies have shown that vaccinated individuals with anti-HBs levels below 10 mIU/mL may still retain immune memory and can mount a rapid anamnestic response after booster vaccination (7). Therefore, antibody titers alone may not fully reflect the overall immune status of the patient, particularly in previously vaccinated individuals.

Data regarding hepatitis B immunity in pediatric rheumatology populations remain limited, and most of the available evidence derives from adult rheumatology cohorts. However, several studies evaluating vaccine-related immunity in children with rheumatic diseases have been published in recent years. Kasapçopur et al. evaluated hepatitis B vaccine responsiveness in children with juvenile idiopathic arthritis and reported that although most patients developed an adequate antibody response, anti-HBs titers were lower compared with healthy controls (12). Similarly, Çakmak et al. assessed

hepatitis B immunity in treatment-naïve JIA patients and found that the seroprotection rate was 59.1%, which was significantly lower than that observed in healthy peers (13). In a more recent study, Nepesov et al. evaluated newly diagnosed JIA patients and reported lower mean anti-HBs levels compared with healthy children, although overall seroprotection rates were comparable (14). Furthermore, Demirbuğa et al. reported protective hepatitis B antibody levels in 68.8% of pediatric rheumatology patients receiving biologic therapy and emphasized the importance of monitoring vaccine-related antibody levels before and during biologic treatment (15). Consistent with these findings, a considerable proportion of patients in our cohort had anti-HBs levels below the protective threshold, supporting the clinical importance of assessing hepatitis B immunity in pediatric rheumatology patients prior to immunosuppressive or biologic therapy.

In our cohort, vaccine refusal was identified in one patient, defined as a parental decision to decline all recommended routine childhood vaccinations, including hepatitis B vaccination. This information was obtained from parental report and verified through the national electronic health record system (e-Nabız). Because the study had a retrospective design and the number of such cases was extremely limited, the possibility of incomplete reporting cannot be excluded, and no further analysis regarding vaccine refusal could be performed. Following the COVID-19 pandemic, several reports have indicated a decline in confidence in childhood vaccinations and disruptions in routine immunization programs in various countries (16). Similar concerns regarding vaccine hesitancy and exposure to misinformation have also been reported in Türkiye (17).

HBV screening prior to biologic therapy is strongly recommended in international guidelines. The European Association for the Study of the Liver (EASL), the American Association for the Study of Liver Diseases (AASLD), the Asian Pacific Association for the Study of the Liver (APASL), and current rheumatology guidelines all recommend evaluating a three-component serological panel—HBsAg, total anti-HBc, and anti-HBs—before initiating biologic agents or other immunosuppressive treatments (18-21). In particular, the risk of HBV reactivation is increased under anti-TNF and other similar immunosuppressive therapies, which may lead to serious consequences such as liver injury, fulminant hepatitis, and interruption of treatment (21). These recommendations are also consistent with pediatric rheumatology guidelines, which emphasize reviewing vaccination status and administering indicated vaccines prior to the initiation of immunosuppressive or biologic therapy whenever possible (2).

The national childhood immunization schedule in Türkiye has a dynamic structure and has been updated multiple times over the years, with the addition of new vaccines and revisions in dose timing. The hepatitis B vaccine was first incorporated into the routine national immunization program in 1998 and has subsequently undergone several modifications (23,24). More recently, in 2025, the introduction of the hexavalent vaccine led to further changes in the administration method and timing of the hepatitis B vaccine (25). Moreover, long-term data on the new-generation immunity profiles that will emerge following the widespread use of the hexavalent vaccine after 2025 are expected to constitute an important area of future research. These changes may contribute to differences in long-term antibody levels across different birth cohorts, and the present real-world data may serve as a useful reference for future comparisons evaluating the impact of these modifications in the national immunization program.

This study has several limitations that should be considered when interpreting the findings. First, the retrospective and single-center design may have introduced potential selection and information bias. Second, the relatively small sample size limits the statistical power of subgroup analyses and restricts the strength of the inferences that can be drawn from the findings. Third, the study population consisted predominantly of patients with juvenile idiopathic arthritis, which may limit the generalizability of the findings to the broader pediatric rheumatology population. Therefore, the results should be interpreted with caution, and larger multicenter prospective studies including more heterogeneous patient populations are needed to confirm these findings.

In addition, the exact timing of completion of the hepatitis B vaccination series could not be reliably determined for all patients due to the retrospective nature of the study and incomplete vaccination records. Therefore, the relationship between time since vaccination and anti-HBs levels could not be analyzed.

Finally, total anti-HBc testing was not routinely performed in all patients during the study period and was assessed only when clinically indicated; therefore, these data were not available for the entire cohort.

5. Conclusion

This study shows that a substantial proportion of pediatric rheumatology patients scheduled to receive biologic therapy have anti-HBs levels below the conventional protective threshold. The identification of insufficient immunity in a country with high childhood vaccination coverage underscores the importance of comprehensive HBV serological evaluation prior to initiating biologic treatment. Although vaccine refusal was identified in only one patient in our cohort, this finding highlights that vaccination attitudes may still represent a potential challenge in ensuring adequate protection against vaccine-preventable infections in children requiring immunosuppressive therapy.

Patients with anti-HBs levels below the protective threshold may benefit from reassessment of their vaccination status according to current immunization recommendations, particularly before initiating immunosuppressive or biologic therapy. In conclusion, careful assessment of hepatitis B immunity prior to initiating biologic therapy is critical for ensuring clinical safety, and prospective studies comparing immunity profiles across different vaccination schedule eras—as well as evaluating strategies to address vaccine refusal—are warranted.

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