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Impact of tumor necrosis factor alpha antagonist treatment on antibody titer of hepatitis B surface antigen

Tümör nekroz faktörü alfa antagonisti tedavisinin hepatit B yüzey antijeninin antikor düzeyine etkisi

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Abstract

Aim: Tumor necrosis factor alpha antagonists (anti-TNF-α) have recently been used successfully in various diseases. On the other hand, due to their potential immunogenic effects, they cause hepatitis B virus (HBV) reactivation. The objective of this study is to examine the change in the levels of hepatitis B surface antigen (HBsAg) and antibody (anti-HBs) in patients with negative HBsAg who were administered different anti-TNF-α drugs as well as the factors that influence this change.

Methods: This research was designed as a retrospective cohort study. Patients with autoimmune diseases who were followed up at General Internal Medicine outpatient clinics between 2012 and 2019, screened for hepatitis B virus (HBV) infection prior to treatment, checked for serological markers (HBsAg, anti-HBs, hepatitis B core antigen antibody (anti-HBc)), and treated with anti-TNF for at least a year were included. The inclusion criteria were as follows: Patients with negative HBsAg and whose liver function tests were within normal limits, and the exclusion criteria included patients with positive HBsAg and whose liver function tests were above the normal upper limit.

Results: A total of 221 adult patients who were treated with anti-TNF-α were included in the study. The pretreatment anti-HBs levels of the patients were significantly higher than the posttreatment levels (P<0.001). Of the 211 patients with positive pretreatment anti-HBs levels, 17 patients had posttreatment anti-HBs levels below 10 IU/L. The anti-HBs levels of five patients with positive anti-HBc dropped below 10 IU/L.

Conclusions: The anti-HBs levels of the patients who were administered anti-TNF-α agent decreased significantly, whereas there was no reactivation of HBV or de novo HBV infection in HBsAg-negative patients. It was observed in a small group of patients (8.0%) that the levels of anti-HBs decreased to a risky level.

Keywords: Tumor necrosis factor antagonist, Hepatitis B surface antigen antibody, Autoimmune diseases

Öz

Amaç: Tümör nekroz faktör alfa antagonisleri (anti-TNF-α) bir çok hastalıkta başarıyla kullanılmaktadır. Öte yandan, potansiyel immünojenik etkileri nedeniyle, hepatit B virüsü (HBV) yeniden aktivasyonuna neden olurlar. Bu çalışmanın amacı, farklı anti-TNF- α ilaçları ile uygulanan hepatit B yüzey antijeni (HBsAg) negatif hastalarda, HBsAg antikoru (anti-HBs) düzeylerindeki değişimi ve etkileyen faktörleri incelemektir.

Yöntemler: Bu araştırma, retrospektif kohort çalışma olarak tasarlanmıştır. Otoimmün hastalıkları nedeniyle 2012-2019 yılları arasında Genel Dahiliye polikliniğine başvuran ve anti-TNF-α tedavi ile tedavi edilen ve en az 1 yıl bu tedaviyi alan ve Hepatit B virusu için tarama amaçlı serolojik belirteçleri (HBsAg, anti-HBs, hepatit B kor antijen antikoru (anti-HBc)) değerlendirilen hastalar çalışmaya alındı. Dahil edilme kriterleri; HBsAg negatif olan ve karaciğer fonksiyon testleri normal sınırlar içinde olan hastalar ve dışlama kriterleri ise; HBsAg pozitif ve karaciğer fonksiyon testleri yüksek olan hastalar.

Bulgular: Anti-TNF-α ile tedavi edilen toplam 221 erişkin hasta çalışmaya dahil edildi. Hastaların tedavi öncesi anti-HBs düzeyleri, tedavi sonrası düzeyler ile karşılaştırıldığında, anlamlı derecede yüksekti (P<0,001). Tedavi öncesi anti-HBs düzeyleri pozitif (titre ve aşılı veya virusla karşılaşmış) 211 hastanın 17'sinde tedavi sonrası anti-HBs düzeyleri 10 IU / L'nin altındaydı. Anti-HBc pozitif beş hastanın anti-HBs seviyeleri 10 IU / L'nin altına düştü.

Sonuç: Anti-TNF-α tedavi uygulanan hastalarda anti-HBs düzeyleri önemli ölçüde azalırken, HBsAg-negatif hastalarda HBV veya de novo HBV enfeksiyonu için reaktivasyon yoktu. Küçük bir grup hastada (%8,0) anti-HBs düzeylerinin riskli bir seviyeye düştüğü gözlendi.

Anahtar kelimeler: Tümör nekroz faktör antagonisti, Hepatit B yüzey antijeni antikoru, Otoimmun hastalık

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Introduction

Tumor necrosis factor alpha antagonists (anti-TNF-α) have recently been used successfully in various areas, primarily in autoimmune-based dermatological, gastroenterological, and rheumatologic diseases [1,2]. Besides, anti-TNF-α drugs increase the risks of infection, latent tuberculosis, and hepatitis B virus (HBV) reactivation due to their potential immunogenic side effects [3]. Due to such risks, patients who are administered anti-TNF-α are advised to get screened for tuberculosis and HBV [4]. Data on HBV reactivation under anti-TNF-α treatment are quite limited and mostly include retrospective studies and case reports [5-7].

The serologic markers screened for HBV infection in patients receiving anti-TNF-α treatment include hepatitis B surface antigen (HBsAg), hepatitis B surface antigen antibody (anti-HBs), and hepatitis B core antigen antibody (anti-HBc) [4,8]. Theoretically, TNF-α assists the elimination of HBV in hepatocytes and synergistically prevents HBV replication through interferons [9]. In patients receiving anti-TNF treatment, the risk of HBV infection may increase, the existing HBV replication may escalate, and clinical hepatitis may occur [10,11]. Studies in the literature focus on the reactivation risk in patients with chronic HBV infection who receive anti-TNF-α treatment [12,13]. The infection risk in HBsAg-positive patients was defined as 12%–39% when anti-TNF-α agents such as infliximab, adalimumab, and certolizumab were used [14]. It is reported that anti-TNF-α agents with lower potency such as etanercept pose lower risk of reactivation (1%–5%) in HBsAg-positive patients [6]. In addition, this risk was lower in HBsAg-negative and anti-HBc-IgG-positive patients [15].

There is limited information about the relationship between anti-HBs levels and anti-TNF-α treatment. Tamori et al. [16] reported that anti-HBS levels of the patients who were administered anti-TNF-α decreased significantly. Similarly, Vassilopoulos et al. [12] reported that the anti-HBS levels in 19 patients inoculated with HBV decreased significantly following anti-TNF-α treatment. Preclinical studies showed that TNF-α is essential in host defense against external pathogens [10,17]. Additionally, TNF-α is thought to play a crucial role in anti-HBs acquisition after HBV inoculation [18].

The objective of this study is to examine the change in pretreatment and posttreatment anti-HBs levels in patients with negative HBsAg who were administered anti-TNF-α drugs as well as the factors that influence this change.

Materials and methods

Patients with autoimmune diseases who were followed up at General Internal Medicine outpatient clinics between 2012 and 2019 and who received anti-TNF-α treatment for at least 1 year were included in the study. The study was approved by the local ethics committee (OMU KAEK, 12/26/2019, 2019/842). This research was designed as a retrospective cohort study. The inclusion criteria were as follows: Patients with negative HBsAg (negative ≤0.9 COI, gray zone ≥0.9 but <1 COI, positive ≥1 COI), whose liver function tests were within normal limits, whose anti-HBs (negative ≤10 IU/L, positive ≥10 IU/L) titers were checked at least once before and during the treatment, and who had positive or negative anti-HBc antibody (negative ≥1 COI, positive ≤1 COI) levels. The exclusion criteria included patients with positive HBsAg and whose liver function tests were higher than the normal upper limit. Hepatitis markers were examined using the COBAS E 601 device. Patients with positive HBsAg and HBV-DNA, those with positive hepatitis C virus (HCV), and alcoholic liver disease, primary biliary cholangitis, or autoimmune hepatitis were excluded from the study. Genders and ages of the patients, their autoimmune diseases, immunosuppressive drugs used, drug exposure time, and HBV markers checked during and throughout the treatment were retrospectively examined and recorded.

Statistical analysis

Statistical analysis was performed using the Wilcoxon rank test for comparison of quantitative variables between the different patient subgroups. For repeated measurements, the Wilcoxon signed ranks test for paired samples was used. The results were expressed as mean (standard deviation). Statistical significance was set at *P*-value <0.05 in a two-tailed test.

Results

A total of 221 adult patients were included in the study. The mean age of the patients was 47.3 (15.1) years, and 46.1% of them were female. The disease age was 2.54 (1.23) years, and most patients received anti-TNF-α treatment due to ankylosing spondylitis (32.1%). Total anti-HBc was positive in 52.3% of the patients. Table 1 summarizes the sociodemographic and clinical data of the patients.

The pretreatment anti-HBs levels (316.39 (356.57), mean rank: 102.99) in the anti-HBs–positive patient group were significantly higher than the posttreatment levels (251.62 (312.059), mean rank: 92.60) (Z:-6.839, *P*<0.001). The anti-HBs levels in the adalimumab, infliximab, and etanercept drug groups decreased significantly. The comparison of pre- and posttreatment anti-HBs levels in anti-TNF drug groups is presented in Table 2.

Of the 221 patients, 10 had no HBV exposure and their pre- and posttreatment anti-HBc / anti-HBs levels were negative. It was observed that the anti-HBs levels of 17 patients out of 221 patients with positive anti-HBs levels before the treatment fell below 10 IU/L posttreatment. Anti-HBs levels in five patients with positive anti-HBc dropped below 10 IU/L. Table 3 shows the change in anti-HBs levels throughout the treatment.

Table 1: Clinical and sociodemographic data of the patients

Age (year)	47.3 (15.1)	
Gender (female)	46.4%	
Disease age (years)	2.54 (1.23)	
Primary Diagnosis	Ankylosing Spondylitis	32.1% (n: 71)
	Psoriasis	27.6% (n: 61)
	Rheumatoid arthritis	13.1% (n: 29)
	Ulcerative colitis	11.8% (n: 26)
	Crohn's disease	9.0% (n: 20)
	Behçet's disease	6.3% (n: 14)
Anti-TNF drugs	Adalimumab	47.5% (n:105)
	Infliximab	32.6% (n: 72)
	Etanercept	14.5% (n: 32)
	Golimumab	3.1% (n: 7)
	Certolizumab	2.3% (n: 5)
HBV antibodies	No HBV exposure: HBsAg (-), Anti HBc total (-), Anti HBs (-)	10
	HBV vaccinated: HBsAg (-), Anti HBc total (-), Anti HBs (+)	91
	Previous HBV: HBsAg (-), Anti HBc total (+), Anti HBs (+)	110

Anti-TNF: Anti-Tumor Necrosis Factor, HBV: Hepatitis B Virus, HBsAg: Hepatitis B Surface Antigen, Anti HBc: Hepatitis B Core Antigen Antibody, Anti HBs: Hepatitis B Surface Antigen Antibody

Table 2: Comparison of anti-HBs levels before and after treatment in anti-TNF drug groups

Anti-TNF drug	Anti-HBs level before the treatment (mIU/mL)	Anti-HBs level after the treatment (mIU/mL)	*P*-value*
Adalimumab (n:105)	329.00 (348.15)	281.63 (318.09)	0.002
Infliximab (n: 72)	289.96 (365.72)	217.69 (306.70)	<0.001
Etanercept (n:32)	330.28 (382.25)	235.96 (326.12)	0.008
Golimumab (n:7)	422.63 (396.81)	328.25 (294.12)	0.068
Certolizumab (n:5)	169.80 (150.43)	93.20 (110.15)	0.052

Anti-TNFα: Anti-Tumor Necrosis Factor α, Anti-HBs: Hepatitis B Surface Antigen Antibody, *Wilcoxon Signed-Ranks was used.

Table 3: Effects of anti-TNF drugs on anti-HBs levels according to HBV exposure

HBV exposure	Anti-HBs level before treatment (mIU/mL)	Anti-HBs level after treatment (mIU/mL)	*P*-value*
HBV vaccinated (n: 91)	289.96 (365.72)	217.69 (306.70)	<0.001
Previous HBV (n: 110)	330.28 (382.25)	235.96 (326.12)	0.008

No HBV exposure: HBsAg (-), Anti HBc total (-), Anti HBs (-), HBV vaccinated: HBsAg (-), Anti HBc total (-), Anti HBs (+), Previous HBV: HBsAg (-), Anti HBc total (+), Anti HBs (+), *Wilcoxon Signed-Ranks was analyzed.

Discussion

This study evaluated 221 patients who were receiving anti-TNF-α drugs. Most of the patients were followed up for ankylosing spondylitis (32.1%) and psoriasis (27.6%). Biological therapies have improved disease management in many rheumatic diseases, and they will probably be used in various other fields in the coming years [19]. In many rheumatologic and dermatologic diseases, anti-TNF therapies in early phases are more successful than standard treatments and are recommended as primary therapy [20,21]. It is anticipated that the increased use of biological agents in the future may increase the concerns about the infection risk from anti-TNF agents as they inhibit mechanisms that play essential roles in host defense [22].

In the present study, reactivation was not observed in patients who received anti-TNF-α treatment, and the posttreatment anti-HBs levels of 17 patients (8.0%) out of 221 patents with positive pretreatment anti-HBs levels were observed to decrease below 10 IU/L posttreatment. In addition, anti-HBs levels in five anti-HBc–positive / anti-HBs–negative patients fell below 10 IU/L. In anti-HBc–positive patients, anti-HBs negativity is the only known risk factor for HBV reactivation. The low level of 10 mIU/mL in anti-HBs titer poses a significant risk [22]. Pauly et al. [23] reported that 178 patients out of 4.620 who received anti-TNF treatment were HBsAg-negative and anti-HBc-positive, and reactivation was observed in none of these patients. HBsAg-negative/anti-HBc–positive patient group is heterogeneous and anti-HBs test is advised for these patients [24]. In the present study, although there is no reactivation, the anti-HBs levels decreased to a risky level for HBV, which poses an apparent risk for our country where HBV is endemic [25].

A statistically significant decrease has been observed in the posttreatment anti-HBs levels in the adalimumab, infliximab, and etanercept groups. Charpin et al. [26] demonstrated that the anti-HBs levels in 21 HBsAg-negative / anti-HBs–positive patients who received adalimumab, infliximab, and etanercept decreased by >30%. It has been speculated that the decrease in anti-HBs may be related to the underlying chronic disease in addition to immunosuppressive treatment. Ballanti et al. [27] examined the effects of etanercept and adalimumab in 32 patients with rheumatoid arthritis and previous HBV or HCV infection and reported that there was no reactivation. However, there have been reports of occult HBV infection reactivation and de novo hepatitis B in patients with rheumatoid arthritis [28]. Moreover, fulminant, and fatal hepatitis have been reported in HBV carriers who were treated with immunosuppressants [29]. Mori et al. [30] have demonstrated an increase in HBV-DNA titers of only 1 patient out of 239 patients with rheumatoid arthritis who have been infected with HBV and reported that anti-TNF agents are safe and effective. Tamori et al. [16] have reported reactivation in only one (2.2%) patient throughout the 2-year period in patients who had undergone HBV infection and received anti-TNF treatment.

Limitations

As the present study is retrospective, the inability to examine HBV-DNA levels can be considered as a limitation regarding activation. However, no transaminase increase was observed in the patient population that may suggest activation. Moreover, anti-HBS levels were not compared as comparable numbers could not be attained among patient groups.

Conclusions

We observed that the anti-HBs levels of patients who received anti-TNF agents decreased significantly; however, there was no reactivation of HBV or de novo HBV infection in HBsAg-negative patients. It was observed that the anti-HBs levels of a small group of patients (8.0%) dropped to a risky level. Thus, intermittent booster doses of HBV vaccination can be useful after administering anti-TNF-α. Although anti-TNF agents are considered safe in anti-HBs positive patients, it would be appropriate to follow these patients in cooperation with a gastroenterologist or an infectious diseases specialist.

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