flora

RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2020;25(1):91-97 • doi: 10.5578/flora.69260

The Association Between Vaccine Response and sCD30 Level in Patients Using Immunomodulator Drugs and Having Received Hepatitis B Vaccination

İmmünmodülatör İlaç Kullanan ve Hepatit B Aşısı Yapılan Hastalarda sCD30 Düzeyinin Aşı Yanıtı ile İlişkisi

Aslı HAYKIR SOLAY[1](İD), Selcan GÜLTUNA[2](İD), Rıdvan TAYŞİ[1](İD)

[1] Clinic of Infectious Diseases and Clinical Microbiology, Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey
[2] Clinic of Immunology and Allergy, Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey

Cite this article as: *Haykır Solay A, Gültuna S, Tayşi R. The association between vaccine response and sCD30 level in patients using immunomodulator drugs and having received hepatitis B vaccination. FLORA 2020;25(1):91-7.*

ABSTRACT

Introduction: *Biologic agents like adalimumab, infliximab, etanercept, ustekunimab and golimumab used for autoimmune diseases suppress T cell-mediated immune response. The defects of cytokines related to T helper 1 and 2 cells have been detected in non-responder subjects to hepatitis B virus (HBV) vaccine. Soluble Cluster of Differentiation 30 (sCD30) is related to the balance of T helper 1/2. Therefore, we investigated the impact of sCD30 on vaccine response. To our knowledge, this is the first study to evaluate the role of sCD30 as a potential serological marker of HBV vaccine response.*

Materials and Methods: *Seventy-five patients using biologic drugs were vaccinated with hepatitis B vaccine at a dosage of 20 or 40 µg. The serum titer of anti-HBs and sCD30 were measured four weeks after the last vaccine dose.*

Results: *Thirty-nine (52%) of the participants were male. Mean age was 43.4 ± 11.5 years. Forty-one (54.7%) patients received standard dose HBV vaccine. Thirty-eight (50.7%) patients responded. Serum sCD30 level was similar in responders and non-responders to HBV vaccine in the whole group. However, we found an inverse relation between antibody response to HBV vaccine and sCD30 level in patients with psoriasis who received high dose vaccine regime [69.5 (28.5-131.7) pg/mL and 47.1 (32.0-80.6) pg/mL respectively, p= 0.037].*

Conclusion: *This study pointed out that sCD30 may play a role in hepatitis B vaccine response.*

Key Words: *Hepatitis B vaccine; Response; sCD30; T cell*

Received/Geliş Tarihi: 25/11/2019 - Accepted/Kabul Ediliş Tarihi: 27/01/2020

ÖZ

İmmünmodülatör İlaç Kullanan ve Hepatit B Aşısı Yapılan Hastalarda sCD30 Düzeyinin Aşı Yanıtı ile İlişkisi

Aslı HAYKIR SOLAY[1], Selcan GÜLTUNA[2], Rıdvan TAYŞİ[1]

[1] Ankara Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, Ankara, Türkiye
[2] Ankara Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, İmmünoloji ve Allerji Kliniği, Ankara, Türkiye

Giriş: *Otoimmün hastalıklarda kullanılan adalimumab, infliksimab, etanersept, ustekunimab ve golimumab gibi biyolojik ajanlar T hücre aracılı immün yanıtı baskılar. T helper 1 ve 2 ile ilişkili sitokin salınımında gelişen sorun, hepatit B virüsü (HBV) aşısına yanıtsızlıkla sonuçlanmaktadır. sCD30 T helper ½ dengesi ile ilişkilidir. Bu nedenle bu çalışmada, sCD30'un aşı yanıtı üzerindeki etkisini incelemek amaçlanmıştır. Bu çalışma bildiğimiz kadarıyla, sCD30'un HBV aşı yanıtındaki rolünü değerlendiren ilk çalışmadır.*

Materyal ve Metod: *Biyolojik ilaç kullanan ve 20 veya 40 µg dozda hepatit B aşısı yapılan 75 hasta çalışmaya dahil edildi. Son aşıdan dört hafta sonra anti-HBs ve sCD30'un serum titresi ölçüldü.*

Bulgular: *Hastaların 39 (%52)'u erkektir ve ortalama yaşları 43.4 ± 11.5 yıl olarak bulunmuştur. Kırk bir (%54.7) hastaya standart doz HBV aşısı yapılmıştır. Otuz sekiz (%50.7) hastanın aşı yanıtı vardı. Serum sCD30 düzeyi, HBV aşı yanıtı olan ve olmayan gruplarda benzerdi. Fakat, yüksek doz aşı yapılan psöriyazisli hastalarda HBV aşısına karşı antikor yanıtı ile sCD30 düzeyi arasında ters ilişki [sırasıyla 69.5 (28.5-131.7) pg/mL ve 47.1 (32.0-80.6) pg/mL, p= 0.037] bulunmuştur.*

Sonuç: *Bu çalışma sCD30'un hepatit B aşı yanıtında rol oynayabileceğini işaret etmektedir.*

Anahtar Kelimeler: *Hepatit B aşısı; sCD30; T hücre; Yanıt*

INTRODUCTION

Hepatitis B virus (HBV) vaccination is considered the main effective method to reduce the incidence of HBV worldwide. The rate of non-responders of HBV vaccine has been observed in 4-10% of healthy people[1]. This rate has been demonstrated to be higher in some immune-mediated inflammatory diseases such as celiac disease, rheumatoid arthritis (RA), and systemic lupus erythematosus and immunocompromised patients with human immunodeficiency virus (HIV) infection[2,3]. Various factors have been supposed as potentially influencing the response to HBV such as vaccine type, vaccine dosage, obesity, smoking, age of host, immunological and genetic factors, and primary and secondary immunodeficiency[4,5]. Defect of T lymphocytes which recognize hepatitis B surface antigen (HBsAg) with its receptors plays an essential role in poor or non-response to HBV vaccine[5,6]. Anti-tumor necrosis factor (TNF) drugs (etanercept, adalimumab, golimumab, and infliximab) modulate T-cell response in autoimmune diseases[7]. Anti-TNF drugs and ustekinumab both named as biologic drugs suppress T cell-mediated immune response by blocking TNF-α directly and indirectly respectively[8-10]. It has been observed that the response of HBV vaccine in patients using biologic drugs is lower[11,12].

Soluble Cluster of Differentiation 30 (sCD30) is a soluble form of CD30. Indeed, CD30 is a transmembrane molecule which is a member of TNF receptor superfamily. It was originally defined as a cell surface antigen on Reed-Sternberg cells in Hodgkin's disease[13]. It is also expressed in various cell types such as T cells, B cells and natural killer[14]. sCD30 has been described as a marker of Th2 cells and promotes the development of Th2[14]. Also, it has been suggested as a costimulatory molecule in the regulation of the balance between Th1/Th2 pathways[14,15]. HBV vaccine induces humoral immunity through Th2 cell stimulation and the production of interleukin (IL)-4[16]. One of the immunologic mechanisms to non-response to HBV vaccine is inadequate Th1 and Th2 cytokine[1]. To our knowledge, there is not any study about the probable role of sCD30 in response or nonresponse to HBV vaccine of

the patients using biologic drugs. In light of these findings, we aimed to determine the relationship between sCD30 and HBV vaccine in patients using biologic drugs.

MATERIALS and METHODS

Participants

Seventy-five patients using biologic drugs with negative serology of HBV admitted to the outpatient clinic of Infection Disease and Clinical Microbiology between January and December 2018 were included into this study. Negative serology for HBV was defined as the absence of all three of HBsAg, hepatitis B surface antibody (anti-HBs) and hepatitis B core antibody immunoglobulin G (anti-HBc IgG). Being younger than eighteen years old, having a concomitant disease other than primary disease which is the reason for using biologic dugs, using more than one immunosuppressive drug, pregnancy, the presence of HBsAg and HBcAb, and patients who have received hepatitis B vaccine were the exclusion criteria. The study was conducted in accordance with the Helsinki Declaration and ethical permission was obtained from the ethical review board of University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital. Written informed consent was obtained from all participants prior to the initiation of the study. Demographic data and medical history of all patients were recorded.

Hepatitis B Vaccination

After the first evaluation, the patients were randomly (in deltoid muscle) injected with 20 µg as standard dose or 40 µg as high dose of HBV vaccine intramuscularly (Engerix-B 20 µg/mL, GlaxoSmithKline) in a three dose schedule (of 0, 4 and 24 weeks). All vaccines which we used were stored according to vaccine cold chain procedure. The serum titer of anti-HBs was measured four weeks after the last vaccine dose for the assessment of seroprotection by enzyme-linked immunosorbent assay (ELISA). The patient with anti-HBs serum titer cutoff is over 10 IU/L was recorded as responder and anti-HBs titer below 10 IU/mL was recorded as nonresponder.

Serum sCD30 Level

Serum samples for sCD30 measurement were obtained from all subjects when taking a sample to measure anti-HBs by centrifugation of venous blood and stored at -80°C until analysis. The serum level of sCD30 (eBioscience, Austria) were measured by ELISA. Absorbance readings were carried out on the Raytomicroplate reader. Concentrations were determined from the curve obtained with the standards.

Statistical Analysis

Statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) software program version 11.5. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not normally distributed. Descriptive analyses were presented using medians and minimum-maximum (min-max) for the non-normally distributed. Nominal values were expressed as number (n) and percentage (%). As sCD30 levels were not normally distributed, Mann-Whitney U test was conducted to compare the parameters. The correlation coefficients and their significance were calculated using the Spearman test. A p value of less than 0.05 was considered to show a statistically significant result and all significant levels were two-tailed.

RESULTS

The Demographics

Thirty-six (48%) of the participants were females and 39 (52%) were males. Mean age was 43.4 ± 11.5 years (40.7 ± 11.1 years for males, 46.3 ± 11.4 years for females). Fifty-seven (76%) patients had psoriasis, 9 (12%) patients had Crohn disease, 3 (4%) patients had rheumatoid arthritis, 3 (4%) patients had ulcerative colitis, 2 (2.7%) patients had hidradenitis suppurativa and, 1 (1.3%) patient had Behçet disease. Forty-one (54.7%) patients were using adalimumab, 18 (24%) patients were using ustekunimab, 9 (12%) patients were using infliximab, 6 (8%) patients were using etanecept and, 1 (1.3%) patient was using golimumab.

Response Rate of Hepatitis B Vaccination

Forty-one (54.7%) patients received standard dose HBV vaccine, and 34 (45.3%) patients received high dose HBV vaccine. In all participants, 38 (50.7%) patients were "responders" and 37

(49.3%) were "non-responders". Twenty-three (60.5%) of the patients who received standard dose HBV vaccine were "responders" and 15 (39.5%) of the patients who received high dose HBV vaccine were "non-responders".

Serum sCD30 Level

Median sCD30 level in the responders and non-responders group was statistically similar (Table 1). There was not any correlation between serum sCD30 level and the titer of HBsAb (r= -0.123, p= 0.292). Serum sCD30 level was similar both in patients who received standard dose and high dose vaccine median 60.6 (27.3-121.7) pg/mL and 52.1 (28.5-213.0) pg/mL respectively, p= 0.569). sCD30 levels in standard and high dose vaccines were examined. There was no statistically significant difference between responders and non-responders (Table 1).

Further, we evaluated the relation between serum sCD30 level and HBV vaccine response in patients with psoriasis. Median sCD30 level was not statistically significant between responders and non-responders (Table 2). There was a nearly significant inverse correlation between serum sCD30 level and the titer of anti-HBs (r= -0.259, p= 0.052). In the patients vaccinated with standard dose, there was not a statistically significant association between serum sCD30 level and the response rate of HBV vaccine. Median sCD30 level was significantly higher in non-responder patients with psoriasis who received high dose HBV vaccine compared to responders (Table 2).

DISCUSSION

In the present study, we evaluated the relationship between serum sCD30 level and HBV vaccine response in patients using biologic drugs. Serum sCD30 level was similar in responders and non-responders to HBV vaccine. Any significant difference could not be found regarding sCD30 level between the groups vaccinated with standard dose and high dose HBV vaccine. We found an inverse relation between antibody response to HBV vaccine and sCD30 level in the patients with psoriasis who received high dose vaccine regime. To our knowledge, this is the first study to evaluate the role of sCD30 as a potential serological marker of HBV vaccine response in patients using biologic drugs.

The therapeutic use of biologic agents is increasing day by day to achieve efficient management of autoimmune diseases. There is a potential risk for reactivation of HBV infection

Table 1. sCD30 levels after hepatitis B vaccine

	Responders	Non-responders	p
sCD30 level at all patients (pg/mL) (n= 75)	51.3 (32.0-213.0) (n= 38)	61.5 (27.3-131.7) (n= 37)	0.484
sCD30 level at patients vaccinated with 20 µg (pg/mL) (n= 41)	60.6 (38.5-86.8) (n= 19)	59.9 (27.3-121.7) (n= 22)	0.882
sCD30 level at patients vaccinated with 40 µg (pg/mL) (n= 34)	48.3 (32.0-213) (n= 19)	66.1 (28.5-131.7) (n= 15)	0.222

* sCD30: Soluble cluster of differentiation 30.

Table 2. sCD30 levels after hepatitis B vaccine in psoriasis patients

	Responders	Non-responders	p
sCD30 level at all psoriasis patients (pg/mL) (n= 57)	50.3 (32.0-97.5) (n= 30)	63. 6 (28.5-131.7) (n= 27)	0.155
sCD30 level at psoriasis patients vaccinated with 20 µg (pg/mL) (n= 31)	55.7 (38.5-97.5) (n= 14)	60.9 (29.2-113.1) (n= 17)	0.784
sCD30 level at psoriasis patients vaccinted with 40 µg (pg/mL) (n= 26)	69.5 (28.5-131.7) (n= 16)	47.1 (32.0-80.6) (n= 10)	0.037

* sCD30: Soluble cluster of differentiation 30.

in patients using biologic drugs[17,18]. Besides, the prevalence of HBV infection in patients with chronic autoimmune diseases is higher than in the general population[19]. So, it has been suggested that vaccinating patients using biological drugs with negative screening tests, especially in HBV endemic regions is crucial[17,20]. However, as mentioned before, biologic drugs are one of the risk factors for an impaired response to HBV vaccine[21]. Poor or non-response to HBV vaccine is an undesirable consequence to lead uncontrollable infections in the risk groups. Various factors affecting response to HBV vaccine, other than immunologic factors have been investigated to understand the ethiogenesis of non-responsiveness so far for enhancing the HBV vaccine efficacy[5]. Since esponse to HBV vaccine is related to antibody level, Th cells presenting HBsAg have been the most emphasized subjects[22]. Th cells are divided into Th1 and Th2 cells based on the types of secreted cytokine. Some studies have been designed to investigate the role of Th1 and Th2 functions in the immune response to HBV vaccine[6,22]. In non-responders, low levels of Th1 and Th2 cytokines has been detected[6]. So, it is critical to put forth the role of sCD30 in vaccine response. Since it was thought that sCD30 is not only marker of Th2 cells but also related to the balance of Th1/Th2 pathways[15].

The effect of sCD30 on vaccine response has been evaluated in a few studies in the literature. Ausiello et al. have reported the correlation between induction of T cell proliferation by sCD30 level and antibody response to pertussis toxin[23]. Iyer et al. have investigated the effect of inflammatory markers, including sCD30 as a potential marker in response to pneumococcal vaccination in HIV positive and negative adults. They have reported that sCD30 did not adversely affect vaccine response[24]. To our knowledge, the relation between sCD30 level and HBV vaccine response has not been investigated before in any group. Our study draws attention in this aspect. One of the important aspects of our study is that we also evaluated the relationship between sCD30 and vaccine dose regime. Although the difference did not reach statistical significance, sCD30 level was higher in non-responders in the whole group. But, in psoriasis which has a maximum number among the diseases in our study group, sCD30 level was significantly higher in non-responder patients receiving high dose vaccine. We thought that through this significance, sCD30 was related to vaccine response considering that high dose of HBV vaccine has been recommended in immunosuppressive patients by some authors[25]. Unexpectedly, there was an inverse correlation between sCD30 level and vaccine response based on the knowledge of HBV vaccine induces Th2 pathway. It can be speculated that sCD30 may be more related to nonresponsiveness rather than responsiveness. Although some studies have reported inadequacy of Th1 and Th2 cytokines in non-responders, Larsen et al. have reported that poor responders produce primarily Th2 cytokines similar to our results[22,26]. These different results may depend on different technical methods (in vivo and in vitro cytokine measurement) and the demographics of the study groups, but may also be interpreted as sCD30 plays an essential role in the balance of Th1/Th2 response rather than being a marker of Th2 considering all of the mentioned studies. Besides, high level of sCD30 in non-responders may have arisen from the defect in signal transduction through pathway of this cytokine. Our study group composed of different diseases and biologic drugs. Disease-related factors and the effect of biologic drugs must be considered in the assessment of the results. The impact of biologic drugs on T cell repertoire has been reported by Dulic et al[27]. Anti-TNF drugs increases cytokines of Th2 pathways by blocking Th1 pathway[28]. The relatively high level of sCD30, whether statistically significant or not, in non-responders in our study may be related to this effect of biologic drugs. Disease-related factors could affect the level of sCD30; Gao et al. reported that sCD30 level was significantly higher in AS[29]. Duzgun et al. have reported the correlation between sCD30 and Behçet disease[30]. Also, in rheumatoid arthritis, Fölster-Holst et al. did not find a difference between psoriasis and control group in terms of sCD30 level[31]. Considering the results of Föls-

ter-Holst et al., there was a direct relation between SCD30 and vaccine response rather than the effect of disease-related factors due to psoriasis was the central disease of the study group[32].

There are some limitations in our study. We could not examine the serum level of sCD30 before vaccination. Evaluation of changes in sCD30 levels before and after vaccination could indicate the definitive relationship between sCD30 and vaccine response. Heterogenous distribution of our study group was the other limitation. It would be more plausible that our study could be designed based on one disease and biologic drug. But we investigated the impact of one disease as psoriasis with further analysis. The impact of biologic drugs may be ignored because one study reported that immunosuppressive therapy did not influence the vaccine response[33].

In conclusion, we did not demonstrate an association between sCD30 level and HBV vaccine. However, we showed that sCD30 level significantly was elevated in patients with psoriasis who received high dose vaccine. This study points out sCD30 may play a role in the HBV vaccine response. Our study would shed light to further studies to develop vaccine adjuvants for improving the effectiveness of HBV vaccine.

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by Project Coordination Unit of University of Health Sciences, Diskapi Yildirim Beyazit Training and Research Hospital.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: AHS, SG

Analysis/Interpretation: SG

Data Acquisition: AHS, RT

Writting: AHS, SG

Critical Revision: SG

Final Approval: AHS, SG

REFERENCES

1. *Goncalves L, Albarran B, Salmen S, Borges L, Fields H, Montes H, et al. The nonresponse to hepatitis B vaccination is associated with impaired lymhpocyte activation. Virology 2004;326(1):20-8.*
2. *Mormile R. Hepatitis B vaccine non response: a predictor of latent autoimmunity. Med Hypotheses 2017;104:45-7.*
3. *Chatkittikunwong G, Khawcharoenporn T. Hepatitis B revaccination in HIV-infected vaccine non-responders: are double dosing always necessary? Int J STD AIDS 2016;10:850-5.*
4. *Qiu S, He P, Fang X, Tong H, Lv J, Liu J, et al. Significant transcriptome and cytokine changes in hepatitis B vaccine non-responders revealed by genome-wide comparative analysis. Hum Vaccin Immunother 2018;7:1763-72.*
5. *Madalinski K, Kolakowska A, Godzik P. Current views on the persistence of immunity following hepatitis B vaccination. Przegl Epidemiol 2015;69:47-51.*
6. *Jafarzadeh A, Shokri F. The antibody response to HBs antigen is regulated by coordinated Th1 and Th2 cytokine production in healthy neonates. Clin Exp Immunol 2003;131:451-6.*
7. *Davignon JL, Rauwel B, Degboe Y, Constantin A, Boyer JF, Kruglov A, et al. Modulation of T-cell responses by anti-tumur necrosis factor treatments in rheumatoid arthritis: a review. Arthritis Res Ther 2018;20:229.*
8. *Kalfa M, Aksu K. Treatment with tumor necrosis factor-alpha antagonists and infections. RAED Journal 2011;3:49-56.*
9. *Tak PP, Taylor PC, Breedveld FC, Smeets TJM, Daha MR, Kluin PM, et al. Decrease in cellularity and expression of adhesion molecules by anti-tumor necrosis factor alpha monoclonal antibody treatment in patients with rheumatoid arthritis. Arthritis Rheum 1996;39:1077-81.*
10. *Benson JM, Peritt D, Scallon BJ, Heavner GA, Shealy DJ, Giles-Komar JM, et al. Discovery and mechanism of ustekinumab: a human monoclonal antibody targeting interleukin-12 and interleukin-23 for treatment of immune-mediated disorders. MAbs 2011;3:535-45.*
11. *Andrade P, Santos-Antunes J, Rodrigues S, Lopes S, Macedo G. Treatment with infliximab or azathioprine negatively impact the efficacy of hepatitis B vaccine in inflammatory bowel disease patients. J Gastroenterol Hepatol 2015;30:1591-5.*
12. *Haykir Solay A, Eser F. High dose hepatitis B vaccine is not effective in patients using immunomodulatory drugs: apilot study. Hum Vaccin Immunother 2019;15:1177-82.*
13. *Fattovich G, Vinante F, Giustina G, Morosato L, Alberti A, Ruol A, et al. Serum levels of soluble CD30 in chronic hepatitis B virus infection. Clin Exp Immunol 1996;103:105-10.*
14. *Fernandez-Ruiz M, Parra P, Lopez-Medrano F, Ruiz-Merlo T, Gonzalez E, Polanco N, et al. Serum sCD30: A promising biomarker for predicting the risk of bacterial infection after kidney transplantation. Transplant infect Dis 2017;19:e12668.*

15. *Pellegrini P, Berghella AM, Contasta I, Adorno D. CD30 antigen: not a physiological marker for Th cells but an important costimulator molecule in the regulation of the balance between Th1/Th2 response. Transpl Immunol 2003;12:49-61.*

16. *Saco TV, Alexandra TS, Ledford DK. Hepatitis B vaccine non-responders: possible mechanisms and solutions. Ann Allergy Asthma Immunol 2018;121(3):320-7.*

17. *Francesca DN, Todoerti M, Grosso V, Monti S, Breda S, Rossi S, et al. Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologic treatment: extending perspective from old to newer drugs. World J Hepatol 2015;27:344-61.*

18. *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;148:215-9.*

19. *Ljungman P. Vaccination of immunocompromised patients. Clin Microbiol Infect 2012;18:93-9.*

20. *Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al. Centers for Disease Control and Prevention (CDC), recommendations for identification and public health management of persons withchronic hepatitis B virus infection. MMWR Recomm Rep 2008;19:1-20.*

21. *Pratt PK, David N, Weber HC, Little FF, Kourkoumpetis T, Patts GJ, et al. Antibody response to hepatitis B virus vaccine is impaired in pateints with inflammatory bowel disease on infliximab therapy. Inflamm Bowel Dis 2018;24:380-6.*

22. *Sabry R, Mohamed ZAZ, Abdalla AM. Relationship between Th1 and Th2 cytokine serum levels and immune response to hepatitis B vaccination among Egyptian health care workers. J Immunoassay Immunochem 2018;39:496-508.*

23. *Ausiello CM, Palazzo R, Spensieri F, Urbani F, Massari M, Triebel F, et al. Solble CD30 and lymphocyte activation gene-3 (CD223) as potential serological maerkers of T hepler-type cutokine response induced by a cellular pertussis vaccine. Int J Immunopathol Pharmacol 2006;19:97-104.*

24. *Iyer AS, Khaskhely NM, Leggat DJ, Ohtola JA, Saul-McBeth JL, Khuder SA, et al. Inflammatory markers and immune response to pneumococcal vaccination in HIV-positive and negative aduts. Phys Rev Lett 2016;11:e010261.*

25. *European Association for the Study of the liver, EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-98.*

26. *Larsen CE, Xu J, Lee S, Dubey DP, Uko G, Yunis EJ, et al. Complex cytokine responses to hepatitis B surface antigen anf tetanus toxoid in responders, nonresponders and subjects naive to hepatitis B surface antigen. Vaccine 2000;18:3021-30.*

27. *Dulic S, Vasarhelyi Z, Bajnok A, Szalay B, Toldi G, Kovacs L, et al. The impact of anti-TNF therapy on CD4+ and CD8+ cell subsets in ankylosing spondiitis. Pathobiology 2018;85(3):201-10.*

28. *Nakamura M, Lee K, Singh K, Zhu TH, Farahnik B, Abrouk M, et al. Eczema as an adverse effect of anti-TNFα therapy in psoriasis and other Th1-mediated diseases: a review. J Dermatolog Treat 2017;28:237-41.*

29. *Gao R, Sun W, Chen Y, Su Y, Wang C, Dong L. Elevated serum levels of soluble CD30 in ankylosing spondylitis patients and its association with disease severity-related parameters. Biomed Res Int 2015;e:617282.*

30. *Düzgün N, Ayaslioglu E, Tutkak H. Serum soluble CD30 levels in Behçet's disease. Clin Exp Rheumatol 2004;22:17-20.*

31. *Kadin ME. Regulation of CD30 antigen expression and its potential significance for human disease. Am J Pathol 2000;156:1479-84.*

32. *Fölster-Holst R, Henseler T, Wehde J, Lemke H, Weichental M, Christophers E, et al. Soluble CD30 plasma concentrations correlate with disease activity in patients with atopic dermatitis. Acta Derm Venereol 2002;82:245-8.*

33. *Belle A, Baumann C, Bigard M, Zallot C, Gizard E, Gueant J, et al. Impact of immunosuppessive therapy on hepatitis B vaccination in inflammatory bowel diseases. Eur J Gastroenterol Hepatol 2015;27(8):877-81.*

Address for Correspondence/Yazışma Adresi

Uzm. Dr. Aslı HAYKIR SOLAY

Ankara Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, İnfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, Ankara-Türkiye

E-mail: aahaykir@hotmail.com