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EVALUATION OF ANTIBODY RESPONSE TO PNEUMOCOCCAL VACCINATION IN PATIENTS WITH INFLAMMATORY ARTHRITIS UNDER ANTI-TNF (ADALIMUMAB) TREATMENT

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ABSTRACT

Inflammatory arthritis increases the risk of pneumococcal infections. This study is aimed to investigate the immunoglobulin response to pneumococcal vaccine in patients with inflammatory arthritis receiving anti-TNF treatment.

In this prospective observational study, a 0.5 ml 13-valent pneumococcal conjugate vaccine was injected to patients receiving 40 mg subcutaneous anti-TNF-α injection once every 15 days for inflammatory arthritis. Levels of anti-pneumococcal IgG were measured using the Enzyme-Linked ImmunoSorbent Assay (ZenTech) method in serum from patients pre- and 4 weeks post-vaccination.

The study included 36 patients, 16 diagnosed with rheumatoid arthritis, 2 with psoriatic arthritis, and 18 with ankylosing spondylitis. Patients with rheumatoid arthritis had used corticosteroids during their follow-up. Patients that received pneumococcal vaccination were not included in the study.

Anti-pneumococcal IgG titers in patients receiving anti-TNF treatment before pneumococcal vaccination varied: 4 patients had antibody titers below while 32 patientshad antibody titers above the protective levels (lower than 250 mU/ml according to kit instructions). Four weeks after the pneumococcal vaccine, the antibody titers of 4 patients, who had pre-vaccination levels below the protective threshold, increased above 250 mU/ml. Among the other 32 patients, the antibody titers doubled in 8 patients and tripled in 24 patients.

While it is thought that the pneumococcal vaccine should preferably be injected before initiating the anti-TNF treatment in rheumatologic patients, we observed that sufficient protection was provided when it was done during the treatment, and we emphasized the significance of vaccination in these patients.

Keyword: *Infection, vaccine, rheumatoid arthritis, anti-TNF*

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ANTİ-TNF (ADALİMUMAB) TEDAVİSİ ALAN İNFLAMATUAR ARTRİTLİ HASTALARIN PNÖMOKOK AŞISINA VERDİKLERİ ANTİKOR CEVABININ ARAŞTIRILMASI

ÖZET

İnflamatuar artritlerde pnömokok enfeksiyonları riski artmaktadır. Bu çalışmada anti-TNF tedavisi alan inflamatuar artritli hastaların pnömokok aşısına verdikleri immunoglobulin yanıtını araştırmayı amaçladık.

Bu prospektif çalışmada, onbeş günde bir subkutan 40 mg anti TNF alfa(adalimumab) tedavisi alan inflamatuar artritli hastalara 0,5 ml 13-valan pnömokok aşısı uygulanmıştır. Aşılamadan önce ve aşıdan 4 hafta sonra enzim immune assay (ZenTech ELISA) yöntemiyle anti-pnömokokal IgG düzeyleri ölçülmüştür.

Çalışmaya 16'sı romatoidartrit, 2'si psoriatik artrit, 18'i ankilozan spondilitli olmak üzere 36 hasta alınmıştır. Romatoid artritli hastalar takipleri sırasında kortikosteroid kullanmışlardı. Daha önce pnömokok aşısı yapılmış olan hastalar çalışmaya alınmadı.

Anti-TNF tedavisi alan hastalarda aşılamadan önce anti pnömokok IgG titreleri: 4 hastada kit prospektüsünde belirtilen koruyucu değerin (250 mU/ml) altında iken 32 hastada üzerinde saptanmıştır. Aşılamadan dört hafta sonra ise aşılamadan önce antikor düzeyi koruyucu değerin altında olan dört hastada 250mU/ml'nin üzerine çıkmıştır. Diğer 32 hastanın 8'inde antikor düzeyi iki kat, 24'ünde ise üç kat artmıştır.

Romatolojik hastalık nedeniyle anti-TNF tedavisi alan hastalarda tedaviye başlamadan önce pnömokok aşısı önerilmesine rağmen tedavi sırasında aşılama yapıldığında da yeterli koruma sağlandığını gözlenmiştir.

Anahtar kelimeler: Enfeksiyon, aşı, romatoid artrit, anti-TNF

INTRODUCTION

Patients with inflammatory diseases, particularly rheumatoid arthritis, have a higher risk of infection than healthy individuals.[1-3] Macrophages and dendritic, B, and T cells are involved in the etiology of autoimmune diseases. Macrophages release the proinflammatory cytokine TNF-α that triggers T cell-dependent B lymphocyte response.[4] Thus, TNF blockers are efficient in the treatment of inflammatory diseases, including rheumatoid arthritis. However, long-term use of these agents increases the risk of clinical bacterial, viral, and fungal infections. One of the most common of these is the pneumococcal infection, which can cause pneumonia, necrotizing fasciitis, or fatal septicemia.[1]

Vaccination can prevent some of these infectious diseases.[2] The Center for Disease Control and Prevention, World Health Organization, and Advisory Committee on Immunization Practices recommend pneumococcal vaccination PCV13, and a 23-valent pneumococcal polysaccharide vaccine, for all adults aged 65 years or older and for patients undergoing immunosuppressive treatment.[2,5-8] These vaccines include 13 serotypes of Streptococcus pneumoniae (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 18C, and 23F) and provide seroimmunity against types causing invasive pneumococcal infection.[9,10] Vaccination rates remain low in patients with rheumatoid arthritis (25-30%) due to little awareness among health practitioners and patients' lack of trust in vaccine effectiveness.[6] Nonetheless, influenza vaccination is more frequent than pneumococcal in patients with rheumatological diseases.[6,9] Various studies, however, reported a decreased response against influenza and pneumococcal vaccination in patients under anti-TNF-α treatment.[1,2] Thus, this study aims to investigate the immunoglobulin response to conjugate pneumococcal vaccine in patients with inflammatory arthritis receiving anti-TNF treatment.

MATERIAL AND METHOD

The study was designed as a prospective, evaluated as a retrospective study, and included 36 patients (50-50% males-females, respectively) aged between 18-62 years, all under anti-TNF-α treatment. Of these, 16 were diagnosed with rheumatoid arthritis, 2 with psoriatic arthritis, and 18 with ankylosing spondylitis. Patients with rheumatoid arthritis had used corticosteroids during their follow-up. Patients who had received pneumococcal vaccination previously were excluded. The study was conducted in a tertiary referral hospital.

Ethical consideration: Oral and written information was provided to all subjects who were invited to participate and written informed consent was obtained from each participant before enrollment. (Ethical number; 2019/0029,02.06.2019 Göztepe EAH)

Patients receiving 40 mg subcutaneous anti-TNF-α (Adalimumab) injection once every 15 days for inflammatory arthritis were injected intramuscularly with 0.5 ml PCV13 over the course of 6 months.

ELISA

Serum levels of anti-pneumococcal IgG were measured before and 4 weeks after vaccination using ELISA (ZenTech). Serum samples were stored at -20°C until the study completion and were analyzed all together. The samples were diluted and added to wells coated with 23 pneumococcal polysaccharides. After washing, peroxidase-conjugated anti-human IgG was added. The chromogenic solution was added after washing again, and the reaction was stopped with H_2SO_4. Anti-pneumococcal antibody levels were measured with a spectrophotometer at 405 and 450 nm.

RESULTS

Analysis of the anti-pneumococcal IgG titers before vaccination in patients treated with adalimumab shows that 4 patients had antibody titers below the protective level (250 mU/ml) while remaining 32 patients had titers below the protective level. However, in the same 4 patients with pre-vaccination antibody levels below the protective threshold, we found that 4 weeks after vaccination, the titers increased above 250 mU/ml. Of these 4 patients, 3 were diagnosed with ankylosing spondylitis and 1 with Rheumatoid arthritis. In the 32 patients whose levels were already above the protective threshold, the antibody titers were doubled in 24 and tripled in 8 patients. Antibody titers were doubled in 14 patients with rheumatoid arthritis, 8 patients with ankylosing spondylitis, and 2 patients with psoriatic arthritis patients. These titers tripled in 1 patient with rheumatoid arthritis and 7 patients with rheumatoid (Table 1). Pre- and post-vaccination IgG levels are shown in Table 2.

Table 1. Post vaccinationantibodytiters.

Patients	Above 250 mU/mL	Doubled	Tripled
With RA	1	14	1
With SA	3	8	7
With PA	none	2	none

RA: Rheumatoid arthritis. **SA:** Ankylosing spondylitis. **PA:** Psoriatic arthritis

Table 2. Pre- and post-vaccinationIgGtiters.

	405 nm n=36	450 nm n=36
Pre-vaccination median (IQR)	936,7 (413,3-2065,8)	1121,1 (462,4-2373,0)
Post-vaccination (4 weeks) median (IQR)	2413,3 (1295,0-3210,0)	2915,5 (1564,9-3803,6)

IQR: Interquartile rage

DISCUSSION

Anti-TNF therapy is associated with an increased risk of bacterial infections. Case reports published a relationship between adalimumab treatment and serious infections caused by Mycobacterium spp., Staphylococcus aureus, Streptococcus pyogenes, Legionella pneumophila, Francisellatularensis, Nocardiaspp., and Propionibacterium acnes.[10-14]

CDC and The European League Against Rheumatism recommend a sequential injection of PCV13 and PPS23, in respective order, in immunosuppressed individuals. For patients who had already received a PPS23 injection, a single PCV13 shot is recommended.[2,5-8,11,15-17]

In our study, we found that the antibody response is not affected by pneumococcal vaccination in patients using TNF-α blockers, confirming results from similar studies performed using other pneumococcal vaccines.[5]

A Swiss study revealed that methotrexate, TNF-α blocker, or prednisolone use has no significant effect on the response to pneumococcal vaccination in patients with rheumatoid arthritis. However, the authors detected a faster decrease in antibody titers after one and a half years.[1,2,4] In all our patients, the antibody titers increased, consistent with other studies that used different pneumococcal antigens.[1,2,6,16-18] In agreement with our results, a meta-analysis in patients undergoing TNF blocker, methotrexate or rituximab treatment also revealed no significant changes in humoral response against pneumococci and influenza.[6] Studies including control groups consisting of healthy individuals show no significant difference in antibody response between this and the patients' group; however, we were not able to establish a control group.[6,7] Nevertheless, the anti-TNF treatment causes a decrease in T cell-dependent and independent antibody response to pneumococcal vaccination, the latter due to altered B cell-function.[16]

Another study on 17 patients with rheumatoid arthritis and ankylosing spondylitis receiving anti-TNF treatment showed that the antibody response to pneumococcal vaccination is not impaired. However, in some patients with rheumatoid arthritis the response was not sufficient.[15,16,18,19]

The antibody titers necessary for protection from invasive pneumococcal infections in adults have not been defined with precision. A two-fold increase of pneumococcal IgG was considered an acceptable antibody response in several studies.[9,11] We too regarded pneumococcal IgG levels of higher than 250 mU/ml as protective according to the ELISA kit instructions. If we had defined the antibody response as a two-fold increase, we would have observed the antibody response in all our patients.

Owing to intensive training of rheumatologists in the effectiveness and trustworthiness of vaccination, the fatality rate from infection in rheumatologic patients is decreasing.[6] Notably, vaccination with the heptavalent pneumococcal conjugate vaccine in patients with inflammatory arthritis decreased the rate of serious pneumococcal infections by 45%.[13,15,17,19]

The fact that we were not able to establish a control group consisting of healthy individuals may be a limitation of our study. Nonetheless, studies containing control groups show no significant difference in the antibody response.

In conclusion, we demonstrate that vaccinating patients against pneumococcal infections prior to anti-TNF treatment is beneficial. However, our study reveals that sufficient antibody response is provided also in patients who are vaccinated after initiating the anti-TNF treatment.

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