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Transition of Thyroid Autoantibodies by Rituximab Treatment in Women with Rheumatoid Arthritis

Romatoid Artritli Kadınlarda Rituksimab Tedavisiyle Tiroid Otoantikorlarının Geçişi

Hüseyin Demirci[1], Ebru Aydoğan[2], Bilge Ceydilek[3]

[1]Clinic of Endocrinology and Metabolism, Ankara Etlik City Hospital, Ankara, Türkiye
[2]Department of Occupational Medicine, Hacettepe University Hospitals, Ankara, Türkiye
[3]Clinic of Endocrinology and Metabolism, Acıbadem International Hospital, Ankara, Türkiye

ABSTRACT

Rituximab was first used as a treatment for B-cell malign lymphoma, and it is currently used in the treatment of rheumatoid arthritis. On the other hand, an association between rheumatoid arthritis with another autoimmune disease Hashimoto's thyroiditis is a condition that can be expected. Thirty-four-year-old female patient with rheumatoid arthritis received disease-modifying agents in various combinations for 9 years. Due to unresponsiveness to treatment, the biological agent rituximab was initiated. The patient also had euthyroided Hashimoto's thyroiditis and nodular goiter for 15 years. At the time of the diagnosis of Hashimoto thyroiditis, anti-thyroid peroxidase (anti-TPO): 45 IU/mL (0-35), anti-thyroglobulin (anti-Tg) >3000 IU/mL (0-115) but after 4 cycles of treatment with rituximab anti-TPO: 7.38 U/mL (0-35), anti-Tg <10 U/mL (0-115). According to the literature; in patients treated with rituximab for thyroid MALT lymphoma, rheumatoid arthritis, and Grave's disease, few have been reported to have declined levels of thyroid autoantibodies. The levothyroxine replacement dose decreased in some of these patients. The decline in thyroid antibodies with the treatment of rituximab reveals the hope that Hashimoto's thyroiditis may be treatable. To understand the effect of rituximab treatment on the pathogenesis of Hashimoto's disease further studies involving a large series is required.

Keywords: Hashimoto's thyroiditis, autoimmune thyroiditis, rituximab

ÖZ

İlk olarak B-hücreli malign lenfoma tedavisi için kullanılan rituksimab, günümüzde romatoid artrit tedavisinde de kullanılmaktadır. Öte yandan, romatoid artritin bir başka otoimmün hastalık olan Hashimoto tiroiditi ile birlikteliği de beklenen bir durumdur. Otuz dört yaşında romatoid artritli kadın hasta, 9 yıl boyunca hastalık modifiye edici ajanlar çeşitli kombinasyonlarda kullanıldı. Tedaviye yanıtsızlık nedeniyle biyolojik ajan rituksimab başlandı. Hastada ayrıca 15 yıldır ötiroid Hashimoto tiroiditi ve nodüler guatr vardı. Hashimoto tiroiditi tanısı konulduğunda anti-tiroid peroksidaz (anti-TPO): 45 IU/mL (0-35), anti-tiroglobulin (anti-Tg) >3000 IU/mL (0-115) iken rituksimab ile 4 kür tedavi sonrası anti-TPO: 7,38 U/mL (0-35), anti-Tg<10 U/mL (0-115) idi. Literatüre göre; tiroid MALT lenfoma, romatoid artrit ve Graves hastalığı için rituksimab ile tedavi edilen hastaların çok azında tiroid otoantikor seviyelerinde düşüş bildirilmiştir. Bu hastaların bazılarında levotiroksin replasman dozu azalmıştır. Rituksimab tedavisi ile tiroid antikorlarının azalması, Hashimoto tiroiditinin tedavi edilebilir olabileceği umudunu ortaya koymaktadır. Rituksimab tedavisinin Hashimoto hastalığının patogenezi üzerindeki etkisini anlamak için geniş serileri içeren daha ileri çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Hashimoto tiroiditi, otoimmün tiroidit, rituksimab

Address for Correspondence/Yazışma Adresi: Hüseyin Demirci, MD, Clinic of Endocrinology and Metabolism, Ankara Etlik City Hospital, Ankara, Turkey
E-mail / E-posta: drhdemirci@gmail.com
ORCID ID: orcid.org/0000-0003-0737-2360

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INTRODUCTION

Rituximab, a monoclonal antibody specific for CD20 positive B-lymphocytes, was first used to treat malign B-cell lymphomas (1). Nowadays, it is effective in the treatment of rheumatoid arthritis and is used in patients who are resistant to disease-modifying agents (2,3). On the other hand, an association of rheumatoid arthritis with another autoimmune disease Hashimoto's thyroiditis is a condition that can be expected. Thyroid autoantibody positivity was significantly higher in patients with rheumatoid arthritis than in those without autoimmune rheumatic disease (4,5). Lymphocytic infiltration is seen in the thyroid in Hashimoto's thyroiditis and can be seen in the synovium in rheumatoid arthritis. Here, we present a case of change in thyroid autoantibodies after rituximab use for the treatment of rheumatoid arthritis in patients with Hashimoto thyroiditis.

CASE REPORT

Informed consent was obtained from the patient. Thirty-four-year-old female patient diagnosed with seropositive rheumatoid arthritis is being followed for 11 years. At the time of diagnosis, there was bilateral arthritis in wrist joints and first and 3rd metacarpophalangeal joints, morning stiffness lasting about 4 hours, rheumatoid factor and anti-cyclic citrullinated peptide positivity, increase in sedimentation and C-reactive protein, and periarticular osteopenia on hand radiographs. Disease-modifying agents (DMARDs), methylprednisolone, hydroxychloroquine, sulfasalazine, leflunomide, and methotrexate were used in various combinations for 9 years. Two years ago, the patient was considered DMARD-resistant, and biological agents were considered suitable for treatment.

Because the patient had bilateral axillary lymphadenopathy 2 cm in size, to rule out the diagnosis of tuberculosis and lymphoma, lymph node biopsy was recommended, but the patient refused. Whereupon of biological agents, anti-tumor necrosis factor therapy was canceled, and rituximab was started to be given. Intravenous rituximab regimen of 1000 mg given twice at an interval of two weeks was repeated every 6 months. Four cycles of rituximab have been given to the patient so far. No side effects were observed during treatment. The DAS-28, which is used to assess disease activity score significantly decreased with rituximab treatment. Hydroxychloroquine 200 mg/day, methylprednisolone 2 mg/day, and methotrexate 15 mg/week were continued with rituximab therapy. There was nodular goiter and euthyroid Hashimoto's thyroiditis for nearly 15 years in the patient's medical history. Fifteen years ago, anti-thyroid peroxidase (anti-TPO): 45 IU/mL (0-35), anti-thyroglobulin (anti-Tg) >3000 IU/mL (0-115), thyroid-stimulating hormone (TSH): 0.9 mIU/L (0.4 to 4.6) (Table 1). In thyroid ultrasonography, the right lobe was 15x20x53 mm, the left lobe was 17x18x51 mm, and the parenchyma was minimally heterogeneous. There was a 20x18x8 mm solid nodule in the left lobe and fine needle aspiration biopsy was performed. There was no cytological atypia, which was consistent with Hashimoto thyroiditis. During the intervening 13 years, patients didn't go thyroid controls but rarely checked TSH levels were within the normal range, and patients didn't have levothyroxine replacement

Before starting treatment with rituximab anti-TPO: 42 U/mL (0-35), anti-Tg >2000 U/mL (0-115), TSH: 1.4 UI/mL (0.35-4.5), respectively (Table 1). In thyroid ultrasonography, the right lobe was 19x18x73 mm and the left lobe was 20x19x62 mm parenchyma was slightly heterogeneous, and there was a 12 mm solid nodule in the left lobe. After 4 cycles of rituximab treatment, anti-TPO: 7.38 U/mL (0-35), anti-TG <10 U/mL (0-115), TSH: 1.24 UI/mL (0.27 to 4.2) was detected (Table 1). Thyroid antibody levels at the last follow-up were rechecked and confirmed by the same laboratory.

When we compared thyroid ultrasonography just before the initiation of rituximab treatment and 4 cycles post-treatment, there were no changes in thyroid gland size, structure, parenchymal changes, or nodule size.

DISCUSSION

"May rituximab help to treat Hashimoto's thyroiditis due to the drop in the levels of thyroid autoantibodies?" questions come to mind. Hashimoto's thyroiditis is an autoimmune disease associated with lymphocytic infiltration of the thyroid gland and elevated thyroid autoantibody levels (6). Rheumatoid arthritis is an autoimmune disease associated with lymphocyte infiltration in the synovium of the joint space (7). Rituximab exerts its effect by binding to the CD20 antigen in B-cells and depleting B-lymphocytes. B-cell damage via direct apoptosis, complement-mediated cell lysis stimulation of Fc gamma receptor-mediated antibody-dependent cytotoxicity, and stopping the cell proliferation (8). Which of these mechanisms is more dominant is not yet known.

B-cells are important for the development of most of the autoimmune diseases. The activation of CD4 T-lymphocytes makes the beginning of the autoimmune pathways of Hashimoto's thyroiditis, then both CD4 lymphocytes and CD8 T-lymphocytes stimulate B-cells (9). It has been shown that B-cell depletion inhibits spontaneous autoimmune thyroiditis in NOD.H-2h4 mice (10).

Similarly, in the case of Raterman et al. (11), the patient with Hashimoto's thyroiditis using levothyroxine replacement after 1 cycle of rituximab treatment for rheumatoid arthritis developed thyrotoxicosis with immeasurably low thyroid autoantibody titers.

Levothyroxine replacement itself may cause a drop in anti-TPO levels (12). Kahara et al. (13) reported a case of 3 patients who developed thyroid MALT lymphoma on the basis that Hashimoto's thyroiditis

Table 1. Thyroid autoantibodies and thyroid-stimulating hormone levels

	At the time of diagnosis	Before starting rituximab	After four cycles of rituximab
TSH (mU/mL)	0.9 (0.4-4.6)	1.4 (0.35-4.5)	1.24 (0.27-4.2)
Anti-Tg (U/mL)	>3000 (0-115)	>2000 (0-115)	<10 (0-115)
Anti-TPO (U/mL)	45 (0-35)	42 (0-35)	7.38 (0-35)

Anti-TPO: Anti-thyroid peroxidase, TSH: Thyroid-stimulating hormone, Anti-Tg: Anti-thyroglobulin.

showed a significant decrease in the levels of both TSH and anti-TPO after rituximab treatment.

The first of these patients had rituximab treatment in association with high-dose chemotherapy, and the second one had rituximab treatment in association with high-dose steroids, and these agents have been shown to reduce the levels of thyroid autoantibodies (14). The third patient in this case had radiotherapy due to nasopharynx carcinoma 1 year before rituximab treatment. Just before initiating rituximab therapy, the third patient was subclinical hypothyroid and then became euthyroid after treatment. In our case, the patient did not have levothyroxine replacement, and her medical history, there were no high-dose steroids, chemotherapy, or radiotherapy. During low-dose steroid treatment before starting rituximab, thyroid autoantibodies remained high.

In the prospective cohort study of Kaklamanos et al. (15), the first group with autoimmune rheumatic diseases was treated with rituximab, the second group with autoimmune rheumatic disease without treatment, and 3rd healthy group was compared for TSH, fT4, fT3, anti-Tg, and anti-TPO levels three times during 24 months. At the end of the study, for any period in which all groups had all evaluated parameters, no change indicates statistical significance. There was also no change in thyroid morphology in patients (15).

When the rituximab group was analyzed, at the beginning of the study, only 3 of 18 patients had anti-TPO positivity and 2 of them had anti-Tg positivity. If there were a greater number of patients with high thyroid autoantibody titers in the study would have been more informative regarding the mechanism of action of rituximab.

In recent years, rituximab has been used for the treatment of Graves' ophthalmopathies. Salvi et al. (16) reported in a review that 43 patients had received rituximab for ophthalmopathy so far. 91% of these patients had become inactive, 1/3rd had side effects that were recorded in the form of an infusion reaction (16).

Vannucchi et al. (17) conducted a study to understand the mechanism of action of rituximab in patients with Graves' ophthalmopathies. They found no changes in thyroid autoantibodies before and after treatment with rituximab, but they found increase in chemokine ligand -10 level which is a marker of B-cell lysis.

Researchers have defended the notion that rituximab exerts its effect not by reducing antibody levels but by increasing the lysis of B-cells, which interferes with antigen presentation to B-cells (17).

Due to the unavailability of follow-up data in our case, we were unable to determine the duration of the effect. To clarify the effect of rituximab on thyroid autoantibodies, more prospective controlled studies that involve more patients with positive thyroid autoantibodies are needed. However, on the basis of this case and data from previous studies, we can say that thyroid function tests and thyroid autoantibodies should be checked before and during rituximab treatment.

Ethics

Informed Consent: It was obtained.

Authorship Contributions

Concept: H.D., Design: H.D., Supervision: H.D., Materials: H.D., Data Collection or Processing: B.C., Analysis or Interpretation: H.D., Literature Search: E.A., Writing: H.D., Critical Review: H.D.

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