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Do TNF Inhibitors Increase the Frequency of Thyroid Nodules in Axial-spondyloarthritis Patients? A Case–control Study

TNF İnhibitörleri Aksiyel Spondilartrit Hastalarında Tiroid Nodüllerinin Sıklığını Artırır mı? Bir Olgu Kontrol Çalışması

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ABSTRACT

Objectives: Tumor necrosis factor (TNF) inhibitors have made great progress in the management of axial spondyloarthritis (axSpA). An increase in malignancies associated with TNF inhibitors has always raised suspicions but is unproven. The aim of this study is to investigate whether there is an increase in the frequency of thyroid nodules in axSpA patients treated with TNF inhibitors and to determine the predictive factors.

Methods: In this retrospective case–control study, axSpA patients who received and did not receive TNF inhibitor treatment were divided into two groups. Patients were enrolled by age, gender, symptom duration, duration of anti-TNF therapy, human leukocyte antigen B27 (HLA-B27) status, smoking history (current smokers), and family history of thyroid malignancy. Thyroid ultrasound was performed in all patients, and thyroid nodule positivity, number, and nodule characteristics were recorded.

Results: A total of 75 patients with axSpA (37 patients were in the TNF inhibitor group and 38 patients were in the control group) were included in the study. Nodule positivity was similar in both groups (p=0.571), and no malignancy was detected in patients with thyroid nodules. No difference was found between nodule positivity and gender, HLA B27, smoking, or family history (p=0.10, p=0.10, p=0.726, and p=0.843, respectively). Age was the only predictor for thyroid nodule positivity in all axSpA patients (p:0.009, 95% of CI: 0.004–0.02).

Conclusion: TNF inhibitors do not increase thyroid nodules or malignancies in axSpA patients.

Keywords: Axial spondyloarthritis; Thyroid nodule; Tumor necrosis factor inhibitor.

ÖZET

Amaç: Tümör nekroz faktörü (TNF) inhibitörleri, aksiyel spondiloartropatinin (axSpA) tedavisinde büyük ilerleme kaydetti. TNF inhibitörleri ile ilişkili malignitelerdeki artış her zaman şüphe uyandırmıştır, ancak kanıtlanmamıştır. Bu çalışmanın amacı, TNF inhibitörleri ile tedavi edilen aksiyel spondiloartropati hastalarında tiroid nodül sıklığında artış olup olmadığını araştırmak ve prediktif faktörleri belirlemektir.

Yöntem: Bu retrospektif olgu kontrol çalışmasında aksiyel spondiloartropati hastaları TNF inhibitörü kullananlar ve kullanmayanlar olarak iki gruba ayrıldı. Hastalar yaş, cinsiyet, semptom süresi, anti-TNF tedavi süresi, HLA-B27 durumu, sigara içme öyküsü (halen sigara içenler) ve ailede tiroid malignite öyküsüne göre kaydedildi. Tüm hastalara tiroid ultrasonu yapıldı ve tiroid nodülü pozitifliği, sayısı ve nodül özellikleri kaydedildi.

Bulgular: Aksiyel spondiloartropatili toplam 75 hasta (37 hasta TNF inhibitörü ve 38 hasta kontrol grubundaydı) çalışmaya dahil edildi. Nodül pozitifliği her iki grupta benzerdi (p=0,571) ve tiroid nodülü olan hastalarda malig-

nite saptanmadı. Nodül pozitifliği ile cinsiyet, HLA B27, sigara ve aile öyküsü arasında fark bulunmadı (sırasıyla p=0,10, p=0,10, p=0,726 ve p=0,843). Tüm aksiyel spondiloartropati hastalarında tiroid nodül pozitifliği için tek prediktif faktör yaştı (p=0,009, %95 GA 0,004-0,02).

Sonuç: TNF inhibitörleri aksiyel spondiloartropati hastalarında tiroid nodül ve malignite sıklığını artırmaz.

Anahtar sözcükler: Aksiyel spondiloartropati; Tiroid nodülü; Tümör nekroz faktörü.

Axial spondyloarthritis (axSpA) is an inflammatory arthritis of the spine that usually presents as chronic back pain, typically before the age of 45. The pathologic processes seen in axial spondyloarthritis include inflammation, bone erosion, and new bone formation, each associated with the pro-inflammatory cytokine tumor necrosis factor (TNF).[1] Therefore, anti-TNF therapy is an effective therapy option for this patient group. TNF triggers the apoptosis of tumor endothelial cells and has antitumor effects.[2,3] However, as a pro-inflammatory cytokine, TNF is secreted by inflammatory cells that may be involved in inflammation-associated carcinogenesis. It is well known that inflammation is closely related to cancer and is a major contributor to the development and progression of malignant diseases. It has been reported that chronic inflammation triggered by immune cells and molecular signaling pathways leads to the susceptibility of the human body to various types of cancer.[4] Putting all these results together, it is difficult to say whether TNF inhibitors can cause malignancy or not.

Before starting anti-TNF treatment, patients are recommended to have an age-appropriate cancer screening test. Although thyroid cancer is the most common form of endocrine malignancy, there is no recommendation for routine screening for thyroid cancer. Most thyroid nodules cannot be detected clinically. In a large population study, clinically visible thyroid nodules were present in 6.4% of women and 1.5% of men.[5] Using ultrasound (US), 20–76% of women had at least one thyroid nodule.[6,7] The cancer rate under the nodules was about 5–6.5%.[8]

In this study, we aimed to investigate whether there is an increase in the frequency of thyroid nodules in axSpA patients receiving TNF inhibitors and to determine the predictive factors.

Methods

In this single-center retrospective study, a total of 75 axial spondyloarthritis (axSpA) patients who applied to the outpatient clinic between December 01, 2018, and January 01, 2019 were included. The diagnosis of axSpA was made based on the ASAS classification criteria.[9] The participants first provided written informed concent. Patients with a diagnosis of psoriatic arthritis, IBD-related arthritis, or reactive arthritis were excluded. Patients who have a history of thyroid or any other type of cancer or a history of head and neck irradiation were excluded from the study. All patients were in euthyroid status.

Patients were selected and divided into 2 groups: patients receiving anti-TNF treatment (TNF inhibitors include adalimumab, etanercept, infliximab, and golimumab) and control axSpA patients. Each patient was registered for age, sex, symptom duration, duration of anti-TNF therapy, smoking history (current smokers), and family history of thyroid malignancy. The results of human leukocyte antigen B27 (HLA B27) were recorded. HLA B27 antigen expressions were studied in total genomic DNA isolated from peripheral blood samples and investigated using the polymerase chain reaction method.

Radiographs of the sacroiliac joints and the lateral cervical and lumbar spines were performed. Radiographic sacroiliitis was determined according to the Modified New York criteria (bilateral grade 2 or unilateral grade 3–4).[10] Magnetic resonance imaging (MRI) was performed on 1.5-T systems. 12 slices of coronal oblique T1-weighted and short tau inversion recovery sequences of the SI joints were included. The slice thickness was 4 mm. The presence of sacroiliitis on MRI was considered positive, along with bone marrow edema and osteitis, as indicated in the ASAS guideline.[11]

A thyroid US was performed in all patients by the same radiologist. Nodule positivity, number, and features of nodules were recorded. Larger than 1 cm, solid, hypoechoic nodule on US with one or more of the following features: irregular margins, microcalcifications taller than wide, rim calcifications with extrusive soft tissue, or extrathyroidal extension are suspected for malignancy. Patients with suspicions of malignancy were referred to the endocrinology specialist. A thyroid fine needle biopsy was performed on patients who were considered necessary, and pathology results were recorded.

The University of Health Sciences Istanbul Fatih Sultan Mehmet Training and Research Hospital Ethics Committee approved the study (protocol number: 2019/7). During the study, the guidelines of the World Medical Association Helsinki Declaration and Good Clinical Practice Guidelines were followed.

Table 1. Baseline characteristics of axSpA patients

Variable	Anti-TNF treatment group (n=37)		Control axSpA group (n=38)		p
	n	%	n	%	
Age (mean)	43.38±10.558		43.82±13.504		0.953
Gender					
Female	17	45.9	24	63.2	0.134
Male	20	54.1	14	36.8	
Disease duration (years)	7.78±5.702		5.13±3.685		0.16
HLA B27					
Positive	10	27	15	39.5	0.853
Negative	27	72	23	60.5	
Family history					
Positive	9	24.3	13	34.2	0.347
Negative	28	75.7	25	65.8	
Smoking					
Positive	11	29.7	4	10.5	0.38
Negative	26	70.3	34	89.5	
Nodule positivity	17	46	15	40	0.571

axSpA: Axial spondyloarthritis; TNF: Tumor necrosis factor; HLA B27: Human leukocyte antigen B27.

Table 2. Comparison of the clinical characteristics of thyroid nodule-positive and -negative axSpA patients

	Nodule positive	Nodule negative	p
Gender			
Female	21	20	0.100
Male	11	23	
HLA B27			
Positive	4	17	0.100
Negative	28	26	
Family history			
Positive	9	13	0.843
Negative	23	30	
Smoking			
Positive	7	8	0.726
Negative	25	35	

HLA B27: Human leukocyte antigen B27.

Statistical Analysis

The baseline characteristics of axSpA patients were compared using a t-test or Mann–Whitney U-test for continuous variables, a chi-square test for categorical measures, or Fisher's exact test when the chi-square test was not suitable. The significant independent variables in the univariate analyses were tested in multivariate stepwise regression models. The 95% confidence interval (95% CI) was calculated, and a $p<0.05$ was considered significant.

SPSS version 20 was used for the data analysis.

Results

A total of 75 patients with axSpA were included in the study. 37 of these patients received anti-TNF treatment, and 38 were in the control group.

The mean age was 43.38±10.5 years in the anti-TNF treatment group and 43.82±13.5 years in the axSpA control group. Seventeen (45.9%) patients were female and 20 (54.1%) were male in the anti-TNF treatment group. In the axSpA control group, 24 (63.2%) patients were female and 14 (36.8%) patients were male. The mean disease duration was 7.78±5.7 years in the anti-TNF group and 5.13±3.6 years in the control group. In the anti-TNF treatment group, the mean treatment duration was 28.14±25.8 months. HLA B27 antigen was positive in 10 (27%) patients in the anti-TNF group and 15 (39.5%) patients in the control group. Gender, age, disease duration, and HLA B27 positivity rates were similar in both groups. Baseline characteristics of axSpA patients are shown in Table 1.

Nine (24.3%) patients in the anti-TNF group and 13 (34.2%) patients in the control group had a family history of thyroid malignancy. 11 (29.7%) patients in the anti-TNF treatment group were smokers. Seventeen (45.9%) patients in the anti-TNF treatment group and 15 (39.5%) patients in the control group had thyroid nodules. No difference was found between the groups in terms of nodule positivity. A total of 14 patients with thyroid nodules (6 patients in the anti-TNF treatment group, 8 patients in the control group) underwent fine needle biopsy, and all of them were reported as benign.

When all patients were examined, no difference was found between nodule positivity and gender, HLA B27, smoking, or family history. A comparison of the clinical characteristics of thyroid nodule positive and negative axSpA patients is shown in Table 2. There was no correlation between nodule positivity and anti-TNF treatment duration (p=0.890). Age was the only predictor for thyroid nodule positivity in all axSpA patients (p:0.009, 95% of CI: 0.004–0.025) (Table 3).

Discussion

In our study, gender, age, disease duration, and HLA-B27 positivity rates were similar in patients receiving TNF inhibitors and axSpA control patients. No difference was observed between groups in terms of nodule positivity, and no

Table 3. Predictors for thyroid nodules in all axSpA patients

Variable	Coefficient β	p	95% CI	
			Lower	Upper
Treatment group	0.049	0.680	−0.181	0.276
Age	0.363	0.009*	0.004	0.025
Gender	0.006	0.965	−0.263	0.275
Disease duration	−0.063	0.609	−0.030	0.018
HLA B27	−0.165	0.177	−0.445	0.083
Smoking	0.051	0.657	−0.216	0.340
Family history	0.038	0.740	−0.199	0.279

*Means statistical significance. axSpA: Axial spondyloarthritis; CI: Confidence ınterval; HLA B27: Human leukocyte antigen B27.

malignancy was observed in patients with thyroid nodules. There was no association between nodule positivity and gender, HLA B27, smoking, or family history. The only predictor factor for a thyroid nodule was advanced age.

TNF-α is linked to immune response, inflammation, and carcinogenesis, although in some studies, it has been shown to be associated with antitumor activity. So, TNF-α activity may be responsible for its anti- and pro-tumor activities depending on the cell, environment, dose, and other factors.[12] Although some meta-analyses of clinical trial data have found increased cancer risk with TNF inhibitor use, observational data, particularly from registries, have generally been unable to confirm these findings.[13-19] In the Swedish Rheumatoid Arthritis Registry (n=53,067) and the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (n=11,767), two registry-based studies found no overall increase in the risk of solid organ malignancies with TNF inhibitors.[20,21] The ARTIS and DANBIO registers also showed that in patients with spondyloarthropathies, treatment with TNF inhibitors was not associated with increased risks of cancer.[22] Also, these large registries have not shown an increased frequency of thyroid malignancy in particular. There are only a few cases of thyroid cancer reported as case reports. The data in our study also support the literature data that TNF inhibitors do not increase thyroid cancer risk.

Conclusion

Based on the results of the current study, TNF inhibitors do not increase the incidence of thyroid nodules or malignancies. Therefore, there is no need for routine screening for thyroid nodule malignancy before the administration of a TNF inhibitor. However, as in the normal healthy population, risk assessment may be required in patients of advanced age.

Disclosures

Ethics Committee Approval: The study was approved by Fatih Sultan Mehmet Training and Research Hospital Ethics Committee, Date: 25.06.2019, decision number: 2019/7.

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References

1. Magrey MN, Khan MA. The paradox of bone formation and bone loss in ankylosing spondylitis: Evolving new concepts of bone formation and future trends in management. Curr Rheumatol Rep 2017;19:7.
2. Robaye B, Mosselmans R, Fiers w, Dumont JE, Galand P. Tumor necrosis factor induces apoptosis (programmed cell death) in normal endothelial cells *in vitro*. Am J Pathol 1991;138:447–53.
3. Tartaglia LA, Ayres TM, Wong GH, Goeddel DV. A novel domain within the 55 kd TNF receptor signals cell death. Cell 1993;74:845–53
4. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell 2011;144:646–74.
5. Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. Ann Intern Med 1968;69:537–40.
6. Ezzat S, Sarti DA, Cain DR, Braunstein GD. Thyroid incidentalomas: Prevalence by palpation and ultrasonography. Arch Intern Med 1994;154:1838–40.
7. Brander A, Viikinkoski P, Nickels J, Kivisaari L. Thyroid gland: US screening in a random adult population. Radiology 1991;181:683–7.
8. Belfiore A, Giuffrida D, La Rosa GL, Ippolito O, Russo G, Fiumara A, et al. High frequency of cancer in cold thyroid nodules occurring at young age. Acta Endocrinol Copenh 1989;121:197–202.
9. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of assessment of spondyloarthritis international society classification criteria for axial spondyloarthritis (Part II): Validation and final selection. Ann Rheum Dis 2009;68:777–83.
10. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
11. Lambert RG, Bakker PA, van der Heijde D, Weber U, Rudwaleit M, Hermann KG et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: Update by the ASAS MRI working group. Ann Rheum Dis 2016;75:1958–63.
12. Younes A, Aggarwall BB. Clinical implications of the tumor necrosis factor family in benign and malignant hematologic disorders. Cancer 2003;98:458–67.

13. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum 2007;56:1433–9.
14. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: Systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275–85.
15. Askling J, Fored CM, Baecklund E, Brandt L, Backlin C, Ekbom A et al. Haematopoietic malignancies in rheumatoid arthritis: Lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1414–20.
16. Mariette X, Matucci-Cerinic M, Pavelka K, Taylor P, van Vollenhoven R, Heatley R et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: A systematic review and meta-analysis. Ann Rheum Dis 2011;70:1895–904.
17. Askling J, Fahrbach K, Nordstrom B, Ross S, Schmid CH, Symmons D. Cancer risk with tumor necrosis factor alpha (TNF) inhibitors: meta-analysis of randomized controlled trials of adalimumab, etanercept, and infliximab using patient level data. Pharmacoepidemiol Drug Saf 2011;20:119-30.
18. Dommasch ED, Abuabara K, Shin DB, Nguyen J, Troxel AB, Gelfand JM. The risk of infection and malignancy with tumor necrosis factor antagonists in adults with psoriatic disease: A systematic review and meta-analysis of randomized controlled trials. J Am Acad Dermatol 2011;64:1035–50.
19. Thompson AE, Rieder SW, Pope JE. Tumor necrosis factor therapy and the risk of serious infection and malignancy in patients with early rheumatoid arthritis: A meta-analysis of randomized controlled trials. Arthritis Rheum 2011;63:1479–85.
20. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis 2005;64:1421–6.
21. Mercer LK, Lunt M, Low AL, Dixon WG, Watson KD, Symmons DP et al. Risk of solid cancer in patients exposed to anti-tumour necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis 2015;74:1087–93.
22. Hellgren K, Dreyer L. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: A collaborative study from the ARTIS and DANBIO registers. Ann Rheum Dis 2017;76:105–11.