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

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

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.
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). 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. 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. 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. Using ultrasound (US), 20–76% of women had at least one thyroid nodule. The cancer rate under the nodules was about 5–6.5%. 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. The participants first provided written informed consent. 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 sacroilitis was determined according to the Modified New York criteria (bilateral grade 2 or unilateral grade 3–4). 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 sacroilitis on MRI was considered positive, along with bone marrow edema and osteitis, as indicated in the ASAS guideline.

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.
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% 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
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 Registry (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 spondyloarthritis, 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.

**Table 3. Predictors for thyroid nodules in all axSpA patients**

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

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

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.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.


**References**


