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Retrospective Comparison of the Effect of IL-17 Blocker Therapy and Anti-TNF Agent Therapy on Bone Mineral Density in Axial Spondyloartropathy Patients

Aksiyel Spondiloartropatili Hastalarda IL-17 Bloker Tedavisi ve Anti-TNF Ajan Tedavisinin Kemik Mineral Yoğunluğu Üzerine Etkisinin Retrospektif Karşılaştırılması

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Abstract

Objective: Our aim was to compare the bone mineral density (BMD) levels in axial spondyloarthropathy (AxSpA) patients treated with tumor necrosis factor-α (TNFα) agents and interleukin-17 (IL-17) blockers.

Materials and Methods: This retrospective study was approved by the local ethics committee (07/01/2020, 7). We evaluated the medical records of AxSpA patients treated with either anti-TNFα or IL-17 blocker. Sixty-six patients with two consecutive dual energy X-ray absorptionmetry measurements (baseline and year one) were included. Twenty-seven patients were receiving anti-TNFα and 39 patients were receiving IL-17 blocker treatment. Outcome measures were compared between the IL-17 blocker and anti-TNFα agent treatment groups.

Results: Sixty-two percent of the patients were male and 38% were female. The mean lumbar region (L1-L4) BMD value of the patients was 1.19±0.15 gr/cm^2 and the mean femoral neck BMD value was 0.95±0.13 gr/cm^2 at baseline (p>0.05). A statistically significant increase in BMD values in the lumbar region (L1-L4, L2-L4), femoral neck and femur total was detected at the end of one year observation in patients using both anti-TNF and IL-17 blockers (p<0.05). The rate of increase in femoral total BMD was higher in patients receiving IL-17 blockers than in those receiving anti-TNF (p=0.013).

Conclusion: BMD is decreased in AxSpA patients due to inflammation. Our results showed that biological agents in AxSpA increase BMD values in addition to preventing bone loss. Femoral total BMD increase was found to be higher in patients using the IL-17 blocker.

Keywords: Axial spondyloarthropathy, ankylosing spondylitis, IL-17 blockers, bone mineral density, osteoporosis, TNF inhibitors

Öz

Amaç: Amacımız, tümör nekroz faktörü-α (TNFα) ajanları ve interleukin-17 (IL-17) blokerleri ile tedavi edilen aksiyal spondiloartropati (AxSpA) hastalarında kemik mineral yoğunluğu (KMY) düzeylerini karşılaştırmaktır.

Gereç ve Yöntem: Bu retrospektif çalışma yerel etik kurul tarafından onaylanmıştır (07/01/2020, 7). Anti-TNFα veya IL-17 bloker ile tedavi edilen AxSpA hastalarının tıbbi kayıtlarını değerlendirdik. İki ardışık dual enerjili X-ışını absorpsiyometri ölçümü (başlangıç ve yıl 1) olan 66 hasta dahil edildi. Yirmi yedi hasta anti-TNFα ve 39 hasta IL-17 bloker tedavisi alıyordu. Sonuç ölçümleri, IL-17 bloker ve anti-TNFα ajan tedavi grupları arasında karşılaştırıldı.

Bulgular: Hastaların %62'si erkek, %38'i kadındı. Hastaların ortalama lomber bölge (L1-L4) KMY değeri 1,19±0,15 gr/cm^2 ve ortalama femur boyun KMY değeri 0,95±0,13 gr/cm^2 olarak saptandı (p>0,05). Hem anti-TNF hem de IL-17 bloker kullanan hastalarda 1 yıllık gözlem sonunda lomber bölge (L1-L4, L2-L4), femur boynu ve femur total KMY değerlerinde istatistiksel olarak anlamlı artış saptandı (p<0,05). IL-17 blokerleri alan hastalarda femoral total KMY'deki artış oranı, anti-TNF alanlara göre daha yüksekti (p=0,013).

Sonuç: AxSpA hastalarında enflamasyon nedeniyle KMY azalmaktadır. Sonuçlarımız, AxSpA'daki biyolojik ajanların kemik kaybını önlemenin yanı sıra KMY değerlerini artırdığını gösterdi. IL-17 bloker kullanan hastalarda femoral total KMY artışı daha yüksek bulundu.

Anahtar kelimeler: Aksiyal spondiloartropati, ankilozan spondilit, IL-17 blokerleri, kemik mineral yoğunluğu, osteoporoz, TNF inhibitörleri

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Introduction

Axial spondyloarthropathy (AxSpA) is a chronic inflammatory disease mainly affects axial skeleton. Despite new bone formation, which is the characteristic finding of AxSpA, an important condition that occurs even in early mild forms and causes an increase in fractures is osteoporosis (1). Decreased bone mineral density (BMD) is a common clinical finding in patients with AxSpA (2). The prevalence of low BMD in patients with ankylosing spondyitis (AS) with a disease duration less than 10 years has been reported to be as high as 54% at the spine and 51% at the femoral neck (3). In the early period at the disease, the inflammatory process is mainly responsible for the decrease in BMD. In addition, increase in bone turnover, immobilization and drugs are also responsible for osteopenia and osteoporosis in patients (4).

Tumor necrosis factor-α (TNFα) which plays an essential role in inflammation, is also a well-known osteoclast activator. In addition to the proven effect of TNFα inhibitors in the treatment of AxSpA on disease activity and progression, many studies have shown that these drugs also positively affect BMD values (5-7). Interleukin-17 (IL-17) blockers have been shown to improve symptoms and significantly reduce inflammation in AxSpA (8). IL-17 is also involved in the inflammatory process that causes BMD loss in AxSpA patients (9,10). Studies showed that anti-TNF treatment increases BMD in AxSpA patients although evidence is limited. However effects of IL-17 blockers on BMD are limited. In this study, we aimed to evaluate and compare the effects of TNFα inhibitors and IL-17 blockers on BMD in AxSpA with dual energy X-ray absorptiometry (DXA) measurements.

Materials and Methods

Ethics Committee

This retrospective study was approved by Okmeydanı Training and Research Hospital's Local Ethics Committee (decision no: 7, date: 07.01.2020). The study protocol was prepared in accordance with the Declaration of Helsinki. Informed written consent was obtained from the participants in the study.

Patient Selection and Data Collection

Medical records of the files of 170 patients aged 18-65 years, who were diagnosed with AxSpA according to the The Assessment of SpondyloArthritis International Society criteria, who applied to the Rheumatology Outpatient Clinic between 01/01/2018 and 30/09/2020 were recruited (Figure 1). Patients with a history of malignancy, pregnancy, patients under corticosteroid and osteoporosis medication, inflammatory rheumatic disease other than AxSpA or metabolic bone disease, and patients with insufficient medical records were excluded from the study. Since non-radiographic AxSpA (nr-AxSpA) patients had more inflammatory load we excluded nr-AxSpA patients that were receiving either IL-17 blockers or anti-TNF agents.

Sociodemographic data of all patients, (gender, age, height, body weight, smoking and alcohol use), erythrocyte sedimentation rate, C-reactive protein (CRP), 25-hydroxyvitamin D values were recorded. Anteroposterior lumbar, femoral neck and femoral total BMD taken by DXA at baseline (T0) and at year one (T1) were evaluated. During the T0 DXA evaluation, a total of 18 patients were using biological therapy of which 10 were using anti-TNF and 8 patients were using IL-17 blockers. Bath Ankylosing Spondylitis Disease Activity index and Bath Ankylosing Spondylitis Functional index evaluation scales, which are disease activity and function indices, were also recorded at baseline and at year one.

Outcomes were compared between those who received IL-17 blocker (secukinumab) therapy and those who received anti-TNF agent therapy.

Materials

Anteroposterior DXA imaging was performed from L1-L4, L2-L4, femur neck and femur total regions of the patients included in the study, and BMD was determined in g/cm^2. Measurements of each patient were made with the same DXA device (Osteosys Primus) by the same DXA technician.

Statistical Analysis

Statistical analysis were made with SPSS version 25.0 program. The conformity of the variables to the normal distribution was examined with the Kolmogorov-Smirnov test. Mean, standard deviation and median values were used for descriptive analyses. Categorical variables were compared with the Pearson chi-square test. Mann-Whitney U test was used for non-normally distributed variables and Student t-test was used for normally distributed variables. Cases with a p-value below 0.05 were considered statistically significant.

Results

The study included 66 patients, 41 men and 25 women. The mean age of the patients in the study was 45.02±8.21 years. The mean disease duration was 5.39±2.77 years. The demographic, clinical characteristics and baseline DXA values of the patients are given in Table 1.

BMI and CRP values were significantly higher and the duration of disease was shorter in the patient group using IL-17 blockers. In the initial BMD values, the femoral total initial BMD value was significantly lower in the IL-17 blocker group than in the anti-TNF group.

There was a significant increase in both lumbar region and femoral region BMD at the end of one year in all patients participating in the study (Table 2).

BMD increase rates at year 1 were compared between the patient groups receiving anti-TNFα and IL-17 blocker treatment (Table 3). The rate of increase in femoral total BMD values was significantly higher in the IL-17 blocker group.

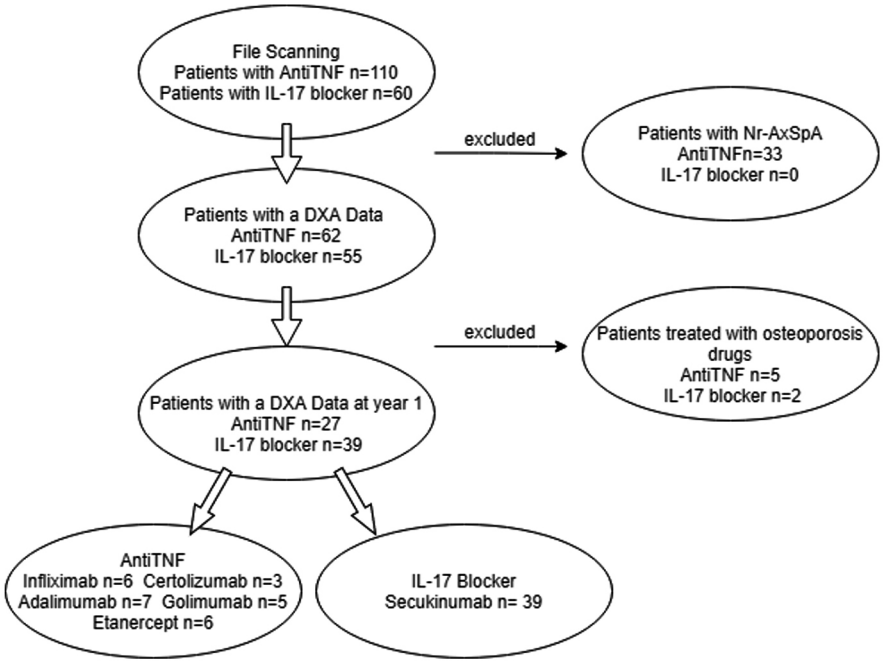

Figure 1. Patient selection flowchart
IL-17: Interleukin-17, AntiTNF: Anti-tumor necrosis factor, Nr-AxSpA: Non-radiographic AxSpA, DXA: Dual energy X-ray absorptiometry

Table 1. Baseline demographic and clinical characteristics of patients

	Total (n=66)	Anti-TNFα (n=27)	IL-17 blocker (n=39)	p-value
Gender[a]				
Female	41 (62.12)	11 (40.74)	14 (35.90)	0.690[1]
Male	25 (37.88)	16 (59.26)	25 (64.10)	
Postmenopause[a]	10 (40.0)	5 (45.5)	5 (35.71)	0.622[1]
Smoking[a]	24 (36.36)	12 (44.44)	12 (30.77)	0.256[1]
Drinking[a]	12 (18.18)	8 (29.63)	4 (10.26)	0.045[1]
Age[b] (year)	45.02±8.21	45.07±7.07	44.97±9.01	0.962[2]
BMI[b] (kg/cm^2)	27.39±5.02	25.71±4.86	28.54±4.86	0.023[2]
Disease duration[c] (year)	5.0 (1.00-12.00)	6.00 (2-10)	4.00 (1-12)	0.035[3]
BASDAI[c]	6.7 (5.40-8.60)	7.00 (5.4-8)	6.50 (5.5-8.6)	0.067[3]
BASFI[c]	6.7 (4.30-8.70)	7 (5-8.7)	6.7 (4.3- 8.2)	0.546[2]
ESR[b]	33.35±9.45	31.3±8.7	34.74±9.79	0.151[2]
CRP[c]	12.0 (2.00-90.00)	10.00 (4-33)	16.00 (2-90)	0.048[3]
L1-L4 BMD[c]	1.20 (0.89-1.44)	1.22 (0.89-1.44)	1.19 (0.91-1.44)	0.653[3]
L2-L4 BMD[c]	1.18 (0.88-1.88)	1.2 (0.89-1.40)	1.14 (0.88-1.88)	0.662[3]
Femur neck BMD[b]	0.95±0.13	0.95±0.14	0.94±0.12	0.930[2]
Femur total BMD[c]	0.90 (0.72-1.34)	0.92 (0.77-1.34)	0.89 (0.72-1.10)	0.047[3]

[1]Chi-square test, [2]Student t-test, [3]Mann-Whitney U test
[a] n (%), [b]Mean ± standard deviation, [c]Median (minimum-maximum)
BMD: Bone mineral density, BMI: Body mass index, BASDAI: Bath Ankylosing Spondylitis Disease Activity index, BASFI: Bath Ankylosing Spondylitis Functional index, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, IL-17: Interleukin-17, anti-TNF: Anti-tumor necrosis factor

Discussion

Decreased BMD is a common clinical finding in patients with AxSpA (11). During inflammation, immune cells secrete many cytokines, including TNF, and IL-17, which shift the balance between bone formation and resorption in favor of osteoclast function and bone resorption. Anti-TNFα and IL-17 blockers used in the treatment of AxSpA are expected to decrease osteoclast

Table 2. Changes in DXA for all patients at year 1 (n=66)				
	T0 DXA	**T1 DXA**	**Difference (%)**	**p-value**
L1-L4 BMD[c]	1.20 (0.89-1.44)	1.24 (0.90-1.49)	2.81 (0.07-9.01)	<0.001[4]
L2-L4 BMD[c]	1.18 (0.88-1.88)	1.21 (0.90-1.47)	5.29 (-52.07-21.22)	<0.001[4]
Femur neck BMD[c]	0.92 (0.71-1.32)	0.93 (0.71-1.36)	0.89 (-4.4-9.9)	<0.001[4]
Femur total BMD[c]	0.90 (0.72-1.34)	0.92 (0.74-1.37)	1.11 (-0.78-21.7)	<0.001[4]
BMD: Bone mineral density, DXA: Dual energy X-ray absorptiometry, T0: Baseline BMD, T1: BMD at year 1, [4]Wilcoxon test, [c]Median (minimum-maximum)				

Table 3. Comparison of DXA change in percentages between groups			
	Anti-TNFα (n=27)	**IL-17 blocker (n=39)**	**p-value**
L1-L4 BMD[c]	2.9 (0.7-9)	2.7 (0.1-8.4)	0.46[3]
L2-L4 BMD[c]	4.8 (0.8-16)	5.4 (-52-21.2)	0.74[3]
Femur neck BMD[c]	0.9 (-0.1-9.8)	0.8 (-4.4-4.4)	0.73[3]
Femur total BMD[c]	1.0 (-0.5-21.7)	1.5 (-0.7-15.5)	0.01[3]
[3]Mann-Whitney U test, [c]Median (minimum-maximum). BMD: Bone mineral density, DXA: Dual energy X-ray absorptiometry, IL-17: Interleukin-17, anti-TNF: Anti-tumor necrosis factor			

function and increase BMD (12). Briot et al. (4) investigated the role of inflammation in bone loss and showed that the main risk factor associated with low BMD is inflammation visualized by magnetic resonance imaging and systemic inflammation. Although mechanical stress changes due to immobility and spinal stiffness in advanced AS are a cause of osteoporosis, it has been revealed that the main cause is the inflammatory process related to the disease itself, which affects bone metabolism. Based on this, it is expected that anti-inflammatory drugs will affect bone loss. In another study, IL-17 blockers were also shown to reduce inflammation in the sacroiliac joint (13). Thus, it is expected that IL-17 blocker treatment will also cause an increase in BMD values.

A positive effect of anti-TNFα therapy on bone loss has been demonstrated in AS (5-7). Moreover, even short-term anti-TNFα therapy can cause an increase in spinal BMD (4). Many clinical studies have shown that anti-TNFα therapy can not only prevent loss of BMD but also stimulate an increase in BMD in AxSpA patients (1,14,15).

In our study, we compared the BMD values of AxSpA patients receiving anti-TNFα and IL-17 blockers at the end of one year follow-up. We found an increase in both lumbar and femoral BMD values in both groups. In the measurements after one year, a 3.4% increase in L1-L4 BMD and a 0.92% increase in femoral neck BMD were found in patients receving anti-TNF treatment.

In a study conducted by Haroon et al. (16) on 568 AS patients, lumbar BMD was increased by 5.1% after one year of treatment with anti-TNFα agents and by 8.6% after two years. Femoral total BMD was increased by 1.8% after one year of treatment and by 2.5% after two years. Durnez et al. (7) found that the increase in BMD in patients with AS treated with anti-TNFα was 11.8% in the lumbar spine and 3.6% in the greater trochanter, at a mean follow-up of 6.5 years. In our study, an increase was found in lumbar and femoral BMD values in patients receiving anti-TNF.

In addition to playing a role in the pathogenesis of AxSpA, IL-17 also plays a role in osteoporosis. In a study by Tyagi et al. (17), it was found that oophorectomy in mouse osteopenia model, anti-IL-17 antibody protects against bone loss by suppressing osteoclast function and promoting osteoblast differentiation. Higher levels of IL-17 was found in women with low BMD compared to women with normal BMD (18,19). Serum IL-17 levels were also found to be higher in AS patients (20). This explains the low BMD seen in AS.

There are limited data on the effects of IL-17 blockage on bone density, and the effects on markers of bone turnover and fracture risk are still unknown (12).

In a study 104 AS patients who were treated with 150 mg subcutan secukinumab for two years, it was reported that lumbar spinal BMD was increased by 2.6% and 4.7% from baseline at week 52 and 104, respectively; femur total 0.9% and 0.5%, respectively; and femur neck 0.8% and 0.2% respectively (2018 annual meeting) (21).

Although our follow up time was short, we also found an increase in BMD in patients receving IL-17 blocker treatment, there was an increase of 2.7% in L1-L4 BMD and 0.8% in BMD of the femoral neck at one year follow up. Compared to patients using anti-TNF, the rate of increase in total femoral BMD was greater in patients using IL-17 blockers (1.01%, 1.5%, respectively).

Study Limitations

The limitations of our study was a retrospective study. The follow-up time was short, patient number was low, and measurement error caused by the DXA machine. Patients were evaluated with anteroposterior DXA measurements. This may cause false high values due to syndesmophytes, ligament calcification, etc. in the lumbar region.

Conclusion

Biological treatments in patients with AxSpA caused a significant increase in BMD at one year follow-up. Femoral total BMD increase was found to be higher in patients using IL-17 blocker. There is a need for further studies on this subject with larger number of patients.

Ethics

Ethics Committee Approval: This retrospective study was approved by Okmeydanı Training and Research Hospital's Local Ethics Committee (decision no: 7, date: 07.01.2020). The study protocol was prepared in accordance with the Declaration of Helsinki.

Informed Consent: Informed written consent was obtained from the participants in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.F., S.A., Concept: N.F., E.D., S.K., Ö.K., Design: N.F., E.D., S.K., Ö.K., Data Collection or Processing: N.F., S.A., Analysis or Interpretation: N.F., E.D., S.K., Ö.K., Literature Search: N.F., E.D., Writing: N.F.

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