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ARAŞTIRMA / RESEARCH

Comparison of antiresorptive agents in the treatment of osteoporosis in older adults

Yaşlı yetişkinlerde osteoporoz tedavisinde antirezorptif ajanların karşılaştırılması

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Abstract

Purpose: There are few studies comparing the effectiveness of anti-osteoporotic drugs among elderly population. In this study, we aimed to compare the effectiveness of alendronate, zoledronic acid, and denosumab in older adults.

Materials and Methods: A total of 350 older adults with osteoporosis, aged 65 and over were included in this retrospective study. The number of patients receiving alendronate, zoledronic acid, and denosumab was 111, 121, and 118, respectively. Bone mineral density (BMD) was measured at baseline and 24th month by performing dual-energy x-ray absorptiometry (DXA) scans.

Results: The age, comorbidities, and laboratory analysis results of the patients were similar. While there was no statistically significant difference in BMD response at the femoral neck between the treatment groups (Baseline BMDs for alendronate, zoledronic acid, and denosumab were 0.61, 0.59, and 0.58, respectively, while 24th month BMDs were 0.62, 0.60, and 0.59, respectively), alendronate and zoledronic acid improved lumbar spine BMD more than denosumab (Baseline BMDs for alendronate, zoledronic acid, and denosumab were 0.74, 0.74, and 0.71, respectively, while 24th month BMDs were 0.77, 0.78, and 0.73).

Conclusion: This study has shown that, like parenteral antiresorptive agents, alendronate can elicit a desirable BMD response in older osteoporotic adults. The results of our study may guide osteoporosis treatment in older individuals.

Keywords:. Older adults, osteoporosis, alendronate, zoledronic acid, denosumab

Öz

Amaç: Yaşlı popülasyonda anti-osteoporotik ilaçların etkinliğini karşılaştıran az sayıda çalışma bulunmaktadır. Bu çalışmada yaşlı yetişkinlerde alendronat, zoledronik asit ve denosumabın etkinliğini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Bu retrospektif çalışmaya 65 yaş ve üzeri osteoporozlu toplam 350 yaşlı dahil edildi. Alendronat, zoledronik asit ve denosumab alan hasta sayısı sırasıyla 111, 121 ve 118 idi. Kemik mineral yoğunluğu (KMY) başlangıçta ve 24. ayda çift enerjili x-ışını absorpsiyometri (DXA) taramaları yapılarak ölçüldü.

Bulgular: Hastaların yaşı, komorbiditeleri ve laboratuvar analiz sonuçları benzerdi. Tedavi grupları arasında femur boynunda KMY yanıtında istatistiksel olarak anlamlı bir fark bulunmazken (alendronat, zoledronik asit ve denosumab için başlangıç KMY'leri sırasıyla 0,61, 0,59 ve 0,58 iken 24. ay KMY'leri sırasıyla 0,62, 0,60 ve 0,59 idi), alendronat ve zoledronik asitin lomber omurga KMY'sini denosumab'dan daha fazla iyileştirdiğini bulduk (alendronat, zoledronik asit ve denosumab için başlangıç KMY'leri sırasıyla 0,74, 0,74 ve 0,71 iken, 24. ay KMY'leri sırasıyla 0,77, 0,78 ve 0,73 idi).

Sonuç: Bu çalışma, parenteral antirezorptif ajanlar gibi, alendronatın da yaşlı osteoporotik yetişkinlerde istenilen KMY yanıtını ortaya çıkarabildiğini göstermiştir. Çalışmamızın sonuçları yaşlı bireylerde osteoporoz tedavisine rehberlik edebilir.

Anahtar kelimeler: Yaşlı yetişkinler, osteoporoz, alendronat, zoledronik asit, denosumab

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INTRODUCTION

Osteoporosis, the most common bone disease in elderly, is characterized by bone micro-architectural deterioration, low bone density, and increased fracture risk[1]. It is estimated that more than 200 million people have osteoporosis worldwide. The incidence increases with age and is about 20% at the age of 70 and about 40% at the age of 80 years in women[2,3].

Agents currently approved for the treatment of osteoporosis can be classified as antiresorptive and osteoanabolic. Bisphosphonates (BPs) are commonly used antiresorptive agents and have oral and parenteral formulations. They increase BMD and reduce the hip and spine fracture risk[4]. Among the oral BPs, alendronate is the most commonly used agent[5]. Zoledronic acid is a strong BP administered annually by intravenous infusion[5].

Denosumab, another antiresorptive agent, is a monoclonal antibody and blocks the proliferation and differentiation of osteoclasts by neutralizing the receptor activator of nuclear factor kappa-B ligand[6]. Denosumab (60 mg) is administered by subcutaneous injection every six months. Long-term therapy with denosumab progressively increases BMD at both hip and the lumbar spine and reduces the risk of fracture[7].

A meta-analysis comparing the efficacy and safety of denosumab and alendronate among postmenopausal women (with a mean age ranging between 60.3–68.2 years) showed that denosumab treatment was more effective at increasing BMD, but was unable to reduce fracture risk any more than alendronate treatment. In the meta-analysis, the authors stated that some of the studies included had a short follow-up period, some had a significant number of patients without follow-up, some had patients receiving different denosumab doses, and more importantly, they stated that all of the studies were sponsored by the pharmaceutical company related to denosumab[8].

A cohort study showed that denosumab and alendronate treatments were associated with similar risks of hip or any fracture, but the lack of data including comorbidities, BMD measurements, and laboratory analysis results of the participants stood out as important limitations of the study[9].

To address the lack of comparative effectiveness data for older adults, in this study, we aimed to evaluate whether there is a difference in response to osteoporosis treatment between treatment agents in older adults. We hypothesized that BPs would be as effective as denosumab in osteoporotic older adults.

MATERIALS AND METHODS

Study design and participants

In this retrospective study, 423 older adults (aged 65 and over) who were initiated osteoporosis treatment at geriatric outpatient clinic of Gaziantep University Medical Faculty Hospital between January 1, 2018, and March 1, 2019, were identified by physicians working at the clinic. Of these, patients with a baseline and repeat DXA at 24th month were eligible for this analysis. The sample size was calculated using the Epi Info software and the minimum sample size was 291 participants at the level of $\alpha = 0.05$ with 95% power. Vitamin D level above 30 nmol/L before initiating treatment was considered as an inclusion criterion. Exclusion criteria were primary bone disease other than osteoporosis, primary or metastatic bone tumor, parathyroid disease, and renal impairment (GFR<60 ml/min). Concomitant diseases, medications, and laboratory test results were recorded. Glucocorticoid medication was considered as the use of ≥5 mg/day prednisolone or equivalent over 3 months[10]. Vertebral fracture evaluation was performed for 402 of the patients (21 had missing data). Of these, 45 patients without 24th month DXA scans, 4 patients with vertebral fractures at baseline, and 3 patients with vertebral fractures during the treatment were excluded. Figure 1 shows the study profile.

DXA scan

DXA scans (using Hologic scanners) were performed at baseline and 24th month for the left proximal femur and lumbar spine. A T score of -2.5 or less at the femoral neck or lumbar spine was considered osteoporosis as stated by WHO. The same side was used for the proximal femur at baseline and month 24.

Fracture risk assessment

The 10-year probability of hip and major osteoporotic fractures was calculated using the FRAX®. A probability of ≥3% for hip and/or ≥20% for major osteoporotic fracture meets the criteria for anti-fracture therapy[1]. Risk scores between 10% and 20% probability for major osteoporotic fracture are

defined as moderate risk for future fractures[11]. The following parameters were entered into the FRAX online tool in order to generate the scores: sex, age, weight, height, previous fracture, glucocorticoid use, smoking, secondary osteoporosis, rheumatoid arthritis, alcohol consumption, parental hip fracture, and femoral neck BMD[12]. The presence of type 1 diabetes, untreated hyperthyroidism, chronic liver disease, malabsorption, osteogenesis imperfecta in adulthood was termed secondary osteoporosis for the FRAX calculation.

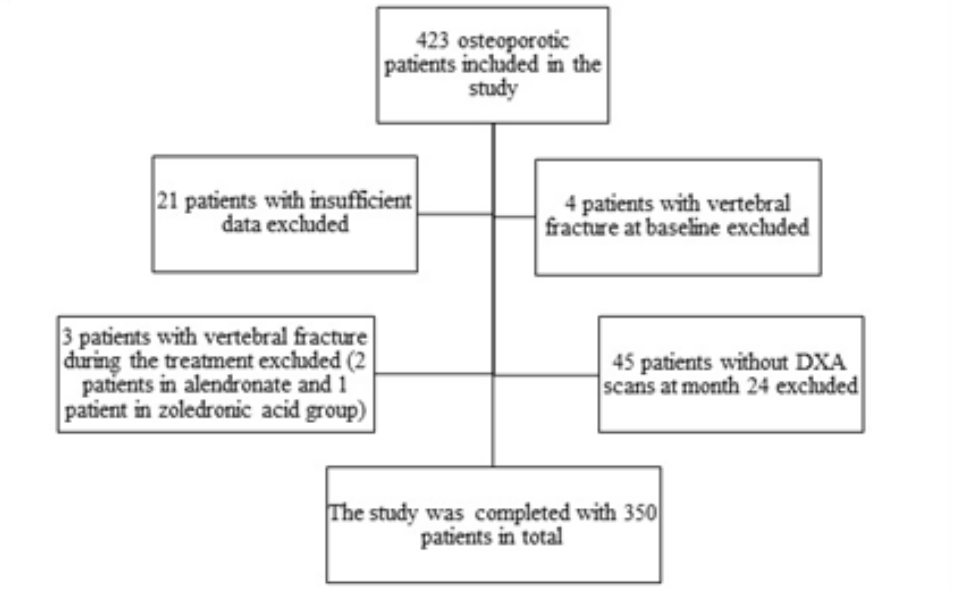

Figure 1. Flow chart of study participants

Drugs

Alendronate (orally 70 mg per week), denosumab (subcutaneously 60 mg every 6 months), and zoledronic acid (intravenously 5 mg per year) were used for the treatment. All patients had been prescribed calcium carbonate (1000 mg) and vitamin D (800 IU) for daily use.

Statistical analysis

The independent samples t-test and Kruskal–Wallis H test were used to compare the numeric variables between the treatment groups. The relationship between categorical variables was evaluated using the $\chi 2$ test. Mixed effects model was applied to investigate the impact of treatment, time, and their interactions on femoral neck and lumbar spine BMD values. SPSS for Windows version 22.0 was used and a *p*-value of < 0.05 was accepted as statistically significant.

RESULTS

The mean age of the 350 patients was 69.7±5.5 years and the proportion of female patients was 90.6%. Most of them were in the 65-74 years age group. Thirty-two of the participants were smokers and none of them had alcohol consumption. There was no significant difference in comorbidities, age, inflammatory markers, and other laboratory measurements between treatment groups. Table 1 provides the demographic information about the participants.

Denosumab group had a lower mean lumbar spine BMD at baseline than the zoledronic acid and alendronate groups (p=0.001), as well as a lower mean femoral neck BMD (p=0.037) than the alendronate group. Also, there was a statistically significant difference between the baseline major osteoporotic fracture risk between the denosumab

and alendronate groups (11.68% vs 9.34%, respectively) (Table 2). There was no correlation between the number of comorbidities, number of medications, age, and the BMD change.

According to mixed effects model results, there was no significant difference in femoral neck BMD change and time-treatment interactions among treatment groups (p=0.062 and p=0.291, respectively). There was an increase in femoral neck BMD scores in all treatment groups at 24th month (p=0,001) (Table 2, Figure 2). However, there was a statistically significant difference in lumbar spine BMD change and and time points among treatment groups (p=0.001 and p=0.001, respectively). There was no time-treatment interaction among treatment agents in lumbar spine BMD (p=0.538). Post-hoc analysis was applied to compare the lumbar spine BMD response among treatment agents. Denosumab group had lower treatment response in lumbar spine BMD than zoledronic acid and alendronate groups (p=0.001 and p=0.001, respectively), while there was no significant difference between alendronate and zoledronic acid groups (p=0.567) (Table 2, Figure 3).

Table 1. Socio-demographic characteristics and laboratory analysis results of the participants

	Treatment Subgroups			**Total(n=350)**	***p***
	Alendronate (n=111)	Zoledronate (n=121)	Denosumab (n=118)		
Gender					
Female	98 (88.3%)	101 (83.5%)	118 (100%)	317 (90.6%)	<0.001*
Male	13 (11.7%)	20 (16.5%)	0 (0.0%)	33 (9.4%)	
Age(years)#	68.6±4.6*	69.7±5.5	70.6±5.9*	69.7±5.5	0.025*
Age group					
65-74 years	101 (91.0%)	98 (81.0%)	90 (76.3%)	289 (82.6%)	0.032*
75-84 years	10 (9.0%)	18 (14.9%)	23 (19.5%)	51 (14.6%)	
≥85 years	0 (0.0%)	5 (4.1%)	5 (4.2%)	10 (2.9%)	
Medical disorders requiring glucocorticoid use					
Rheumatoid arthritis	15 (14.9%)	7 (5.8%)	9 (7.6%)	31 (8.9%)	0.099
Other	7 (6.3%)	7 (5.8%)	3 (2.5%)	17 (4.9%)	0.562
Other Comorbidities					
Hypertension	49 (44.1%)	44 (36.4%)	54 (45.8%)	147 (42.0%)	0.290
Diabetes mellitus	26 (23.4%)	20 (16.5%)	25 (21.2%)	71 (20.3%)	0.408
Coronary artery disease	14 (12.6%)	15 (12.4%)	14 (11.9%)	43 (12.3%)	0.983
Asthma/COPD†	9 (8.2%)	10 (8.3%)	9 (7.6%)	28 (8.0%)	0.982
Cancer	4 (3.6%)	8 (6.6%)	7 (5.9%)	19 (5.4%)	0.575
Serum 25-OH vitamin D (nmol/L) #	36.1±5.8	36.8±6.2	35.9±5.0	34.2±9.9	0.854
Parathyroide hormone (pg/ml) #	58.3±27.6	61.4±48.8	63.4±47.2	62.7±51.6	0.601
Serum calcium (mg/dl) #‡	9.7±0.6	9.7±0.5	9.7±0.6	9.7±0.6	0.894
Serum phosphorus (mg/dl) #	3.6±0.4	3.7±0.6	3.7±0.5	3.7±0.5	0.855
C-reactive protein (mg/dl)	2.78	2.50	3.00	2.90	0.517
Erythrocyte sedimentation rate (mm/hr)	17	18	17	17	0.465
Serum creatinine (mg/dl) #	0.71±0.18	0.71±0.20	0.72±0.22	0.71±0.20	0.912

* p<0.05; #Data are presented as mean±SD; Data are presented as median; †COPD, chronic obstructive pulmonary disease; ‡ Albumin-adjusted calcium.

Table 2. Comparison of the DXA scan assessments of the treatment subgroups

	Treatment Subgroups				Mixed effect model		
	Alendronate	Zoledronate	Denosumab	$P_{univariate}$	P_{Time}	$P_{treatment}$	$P_{Interaction}$
Lumbar spine					0.001*	0.001*	0.538
Baseline BMD (g/cm²)	0.74±0.08	0.74±0.08	0.71±0.09*	0.001*			
24th month BMD (g/cm²)	0.77±0.08	0.78±0.09	0.73±0.09				
Femoral neck					0.001*	0.062	0.291
Baseline BMD (g/cm²)	0.61±0.09*	0.59±0.07	0.58±0.09*	0.037*			
24th month BMD (g/cm²)	0.62±0.08	0.60±0.07	0.59±0.09				
Baseline major osteoporotic fracture risk (%)	9.34±5.45*	9.75±6.84	11.68±7.16*	0.015*			
Baseline hip fracture risk (%)	3.49±2.20	4.07±2.61	5.07±3.15	0.059			

#Data are presented as mean±SD.. *Significant at 0.05 level; $P_{univariate}$: Kruskal Wallis test. BMD, bone mineral density

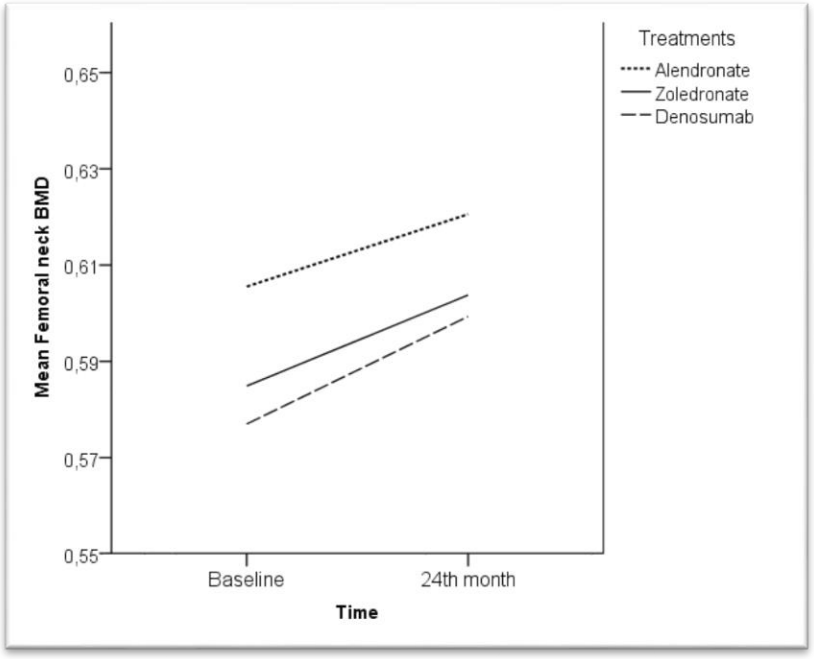

Figure 2. Line graph of the treatment response in femoral neck BMD.

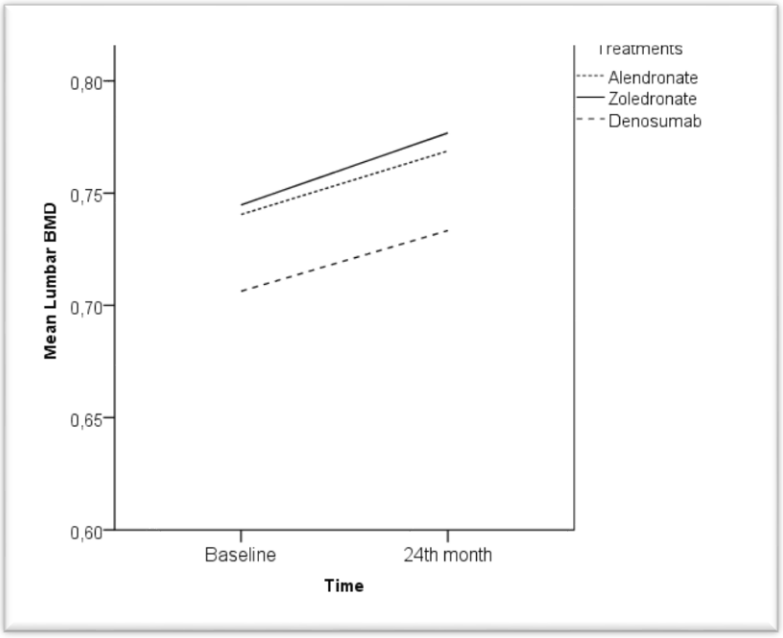

Figure 3. Line graph of the treatment response in lumbar BMD.

DISCUSSION

This study suggests that for older patients who are able to tolerate oral BPs, alendronate is an optimal treatment. The results of our study showed that a significant improvement was achieved in femoral neck BMD with alendronate, zoledronic acid, and denosumab treatments. Also, participants who received alendronate and zoledronic acid showed greater improvements in lumbar spine BMD than those who received denosumab.

A study including postmenopausal women reported a BMD improvement of 4.1% at the hip and 6.8% at the lumbar spine with alendronate administered 70 mg weekly for 24 months[13]. Zoledronic acid has also been found to be effective in increasing total hip and lumbar spine BMD and reducing the incidence of fractures[5,14].

A randomized study comparing oral BPs (risedronate or alendronate) with zoledronate reported that the total hip BMD change was similar in the patients, but the study did not have enough power to show any difference in fracture incidence[15]. On the other hand, Wu at al. demonstrated showed in their meta-analysis that denosumab was more effective than BPs at improving BMD at the lumbar spine, total hip, and femoral neck[16]. However, the authors reported that drug dealer sponsorship and patient heterogeneity were important limitations of the studies included in the meta-analysis.

A more recent network meta-analysis has also study reported that denosumab was more effective than zoledronic acid and alendronate in increasing both lumbar and hip BMD in postmenopausal osteoporotic patients[17]. However, the inclusion criterion in this meta-analysis, unlike in our study, was that the patients had received antiosteoporotic therapy for at least 12 months. Also, the authors have reported that some of the studies in the meta-analysis had heterogeneities in patient characteristics. On the other hand, another study found that zoledronic acid was more effective than alendronate in increasing lumbar spine BMD, while alendronate was more effective in increasing hip BMD[18].

Studies have shown that improvements in the lumbar spine and femoral neck BMD are associated with a reduced risk of hip and vertebral fractures[19,20,21]. Alendronate, zoledronic acid, and denosumab have all been found to be effective in reducing hip, vertebral, and nonvertebral fractures[22,23,24]. Recent

meta-analyses have shown that there was a fracture risk reduction of 42% with denosumab treatment and 45% with alendronate treatment compared with placebo[25,26]. Also, Coyle and colleagues found that alendronate was more cost-effective than zoledronic acid and denosumab[27].

Our study has some potential limitations. First, a longer follow-up of patients could better show the differences in fracture incidence. Second, a subgroup analysis of male osteoporosis could not be performed due to the insufficient number of male patients. Third, there was a lack of falls and previous fracture data of the patients. In spite of these limitations our study has also some strengths. First, unlike most studies, only elderly individuals were included in our study. Second, we compared the effects of alendronate, zoledronic acid, and denosumab among themselves, while most previous studies compared the effects of the drugs with placebo. Third, the similarity of age, comorbidities, inflammatory markers, and other laboratory measurements between treatment groups in our study was important to compare the treatment agents more transparently.

In conclusion, we have shown that like parenteral antiresorptive agents, alendronate can elicit a desirable BMD response in older osteoporotic adults. Given its low cost, alendronate may be considered primarily for the treatment of osteoporosis in eligible older adults. This study will help physicians make more accurate decisions in choosing osteoporosis treatment agents in older adults. Prospective and randomized controlled studies can better evaluate and compare the efficacy of antiresorptive agents.

Yazar Katkıları: Çalışma konsepti/Tasarımı: EME; Veri toplama: EME, AÇ, SG; Veri analizi ve yorumlama: AÇ, SG; Yazı taslağı: EME, AÇ, SG, ZAÖ; İçeriğin eleştirel incelenmesi: ZAÖ; Son onay ve sorumluluk: EME, AÇ, SG, ZEÖ; Teknik ve malzeme desteği: -; Süpervizyon: AÇ, SG; Fon sağlama (mevcut ise): yok.
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