THE EFFECTS OF BISPHOSPONATES THERAPY IN PATIENTS WITH POSTMENAPOUSAL RHEUMATOID ARTHRITIS

POSTMENOPOZAL ROMATOİD ARTRİTLİ HASTALARDA BİFOSFONAT TEDAVİSİNİN HASTALIK AKTİVİTESİ ÜZERİNE ETKİSİ

Sühan TAŞKIN[1], Mehmet Onat ÇAKIT[2], Secil Pervane VURAL[1], Müyesser OKUMUŞ[3], Barış NACIR[1], Burcu Duyur ÇAKIT[1], Hakan GENÇ[1]

[1]S.B.U Ankara Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Ankara-TURKEY
[2]S.B.U Ankara Training and Research Hospital, Department of Family Medicine, Ankara-TURKEY
[3]Kırıkkale University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Ankara-TURKEY

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ABSTRACT

INTRODUCTION: Bisphosphonates therapy may be potential adjunctive therapy agents of synthetic disease modifying antirheumatic drugs in rheumatoid arthitis patients who have contraindications and who are intolerant to biologics. The aim of this retrospective study was to evaluate the effects of adjunctive Bisphosphonates on disease activity of our patients with rheumatoid arthitis who underwent the synthetic disease modifying antirheumatic drugs therapy.

MATERIAL AND METHOD: Retrospective data were collected from patient records of our Rheumatology department outpatient clinic. Files of 207 patients who are over 45 years old and whose bone mineral density were evaluated in the previous year were screened for the study. Patients demographics, medications, disease duration, the age of disease onset, anti-Cyclic Citrullinated Peptid, Rheumatoid factor positivily, Disease activity scores positivity were recorded. Bone mineral densitometry analyses were performed in patients by Dual Energy X-ray Absorptiometry. 106 patients (89 women, 17 men) who received bisphosponates therapy for 1 year constituted group1 and 101 patients (81 women 20 men) who did not receive bisphosponates constituted group 2.

RESULTS: The mean age of group 1 was 65.02 ± 11.14 years and group 2 was 63.64±9.1 years ($p > 0.05$). There was no statistically significant difference between groups in terms of age, gender and disease duration parameters. There were no statistically significant difference according to disease modifying antirheumatic drugs type and dosages between groups ($p > 0.05$) but in group 1, prednisolone users were more than group 2 ($p < 0.001$). The mean tender joint count changes were -0.64±0.63 in group 1 and 0.42±0.62 in group 2 ($p<0.001$). There were no significant difference according to bone mass density values of prednisolone users and nonusers at baseline and after 1 year.

DISCUSSION: For patients who cannot be treated with biological agents, effective prevention of focal bone damage and generalized bone loss will require new treatment strategies, like concomitant administration of drugs with specific effects on bone metabolism. Bisphosponates can prevent generalized bone loss and therapies may yield both medical and economic benefits in patients with rheumatoid arthritis.
CONCLUSION :We think that adjunctive bisphosponates may provide additional benefits in older rheumatoid arthritis patients with systemic and regional bone loss. However, further studies are needed to determine whether bisphosphonate therapies must be administered routinely with the disease modifying antirheumatic drugs and biologics.

Keywords: *rheumatoid arthritis, bisphosphonates, disease activity*

ÖZET

GİRİŞ: Bifosfonat tedavileri, biyolojik ajanlara intoleransı veya kontreendike durumu olan romatoid artrit hastaları için sentetik hastalık modifiye edici ajanların etkisini tamamlayan ajanlar olabilir. Bu retrospektif çalışmanın amacı bifosfonat tedavisinin sentetik modifiye edici ajan kullanan romatoid artrit hastalarındaki hastalık aktivitesi üzerine etkisini incelemektir.

MATERYAL VE METHOD: Veriler kliniğimizin romatoloji departmanındaki hasta kayıtlarının retrospektif olarak incelenmesi ile elde edilmiştir. Çalışma için, 45 yaş üstü ve ardışık yıllarda kemik mineral yoğunluğu değerlendirilen 207 hasta dosyası tarandı. Hastaların demografik bilgileri, ilaçları, hastalık süreleri, hastalığa yakalandıkları yaş, anti-siklik sitrullin peptit, romatoid faktör pozitifliği, hastalık aktivite skorları gibi bilgiler kayıt edildi. Kemik mineral dansitesi analizleri dual enerji x-ray absorptiometri ile yapıldı. Bir yıldır bifosfonat tedavisi alan 106 hasta (89 kadın, 17 erkek) grup1, bifosfonat tedavisi almayan 101 hasta (81 kadın, 20 erkek) ise grup 2 olarak ayrıldı.

BULGULAR: Grup 1 hastaların yaş ortalaması 65.02 ± 11.14 yıl iken, grup 2 hastalarınki 63.64±9.1 yıl idi ($p>0.05$). Gruplar arasında yaş, cinsiyet, hastalık süresi açısından istatistiksel olarak anlamlı fark yoktu. Gruplar arasında kullanılan hastalık modifiye edici ilaç tipleri ve dozajları arasında istatistiksel olarak anlamlı fark yoktu ($p>0.05$), fakat grup 1'de prednizolon kullanımı grup 2'den daha fazlaydı ($p<0.001$). Ortalama hassas nokta sayısındaki değişimler grup 1'de -0.64±0.63, grup 2 ise 0.42±0.62 idi ($p<0,001$). Bir yıl sonunda prednizolon kullanan ve kullanmayan hastalar arasında kemik mineral dansitesi değerleri açısından istatistiksel olarak anlamlı fark yoktu.

TARTIŞMA: Biyolojik ajanlarla tedavi edilemeyen hastalar için, fokal kemik hasarının ve genel kemik kaybının etkili bir şekilde önlenmesi, kemik metabolizması üzerinde belirli etkilere sahip ilaçların eşzamanlı uygulanması gibi yeni tedavi stratejileri gerekmektedir. Bisfosfonatlar, jeneralize kemik kaybını önleyebilir ve romatoid artritli hastalarda hem tıbbi hem de ekonomik yararlar sağlayabilir.
SONUÇ: Bifosfonatların, sistemik ve bölgesel kemik kaybı olan daha yaşlı romatoid artritli hastalarda ek yararlar sağlayabileceğini düşünüyoruz. Bununla birlikte, bifosfonat tedavilerinin, rutin olarak antiromatizmal ilaçlar ve biyolojik maddeleri modifiye eden hastalıklarla birlikte uygulanmasının gerekip gerekmediğini belirlemek için daha ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: *romatoid artrit, bifosfonatlar, hastalık aktivitesi*

Sorumlu Yazar / Corresponding Author:
Secil Pervane VURAL
Ankara Training and Research Hospital, Department of Physical Medicine and Rehabilitation, 06230 Ankara-TURKEY
Tel: +90 312 595 34 05 **e-posta:** secilvural@hotmail.com

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease associated with progressive disability and serious comorbidities [1]. RA is characterized by multifaceted bone pathology, specifically generalized and juxtaarticular osteoporosis, as well as focal bone erosions at the joint [2]. Osteoclasts, the cell type responsible for bone resorption and the main target of the potent antiresorptive effect of bisphosponates (BPs), is responsible not only for the generalized bone loss, but also for the focal bone damage seen in RA [2,3,4].

Osteoporosis is common in both women and men with RA. The prevalence of osteoporosis in studies of RA has ranged from 20% to 30% [5,6]. The many factors that contribute to cause osteoporosis in patients with RA include glucocorticoid therapy, which is often given without prophylactic BP therapy, and disability related immobility [5]. Current treatment strategies in RA primarily target suppression of the inflammatory cascade with varying success in limiting the progression of focal bone des truction and generalized bone loss. Thus, therapies targeting osteoclasts need to be used in combination with effective anti-inflammatory agents [6]. Osteoimmunology, one of the leading new concepts, emerged from the fact that both the immune system and bone metabolism are regulated by the same cytokines (i.e.TNF-α, IL-1 and RANKL). Studies showing a central role for TNF-α in the inflammation and focal bone damage seen in RA led to development of TNF-α antagonists. However, intolerance or contraindications inhibit the usage of TNF-α antagonist therapy in a number of patients with severe RA. These limitations, together with the high cost of TNF-α antagonists, encourage an active search for treatment alternatives [5].

Through the same mechanism mentioned in osteoimmunology concept, therapies targeting bone metabolism may affect the cytokines of immune system and may act as an anti-inflammatory agents. Thus, BPs may be potential adjunctive therapy agents of synthetic disease modifying antirheumatic drugs (DMARDs) in RA patients who have contraindications and who are intolerant to biologics. The aim of this retrospective study was to evaluate the effects of adjunctive BPs on disease activity of our patients with RA who underwent the synthetic DMARD therapy.

MATERIAL AND METHODS

Retrospective data were collected from patient records of our Rheumatology department outpatient clinic. The study was approved by the research ethics committee of the Ministry of Health, Ankara Training and Research Hospital. From the archives of Rheumatology department, files of 350 RA patients who are over 45 years old and whose bone mineral density (BMD) were evaluated in the previous year were screened for the study. Inclusion criteria were as follows: using synthetic DMARDs on a stable dose for a year, having clinical synovitis in at least the hand and wrist or hand joints and being monitored for at least two years with a diagnosis of RA. Patients in whom baseline creatinine clearance was <30 ml/minute, and who had a disease known to affect bone metabolism, such as hyperparathyroidism, hyperthroidism, osteomalacia and hepatic dysfunction were excluded. Other exclusion criteria were use of anabolic steroids, growth hormone, raloxifene, or calcitonin within the previous 6 months. Sixty-five patients who did not meet the inclusion criteria and 78 patients with exclusion criteria were excluded from the study. As a result, the study group comprised 207 patients fulfilling the 2010 ACR/EULAR RA classification criteria [7].

Patients demographics, medications, disease duration, the age of disease onset, anti-Cyclic Citrullinated Peptid (anti-CCP) and Rheumatoid factor (RF) positivity were recorded. Disease activity scores in 28 joints (DAS28) within 1 year before the study began were recorded from the patients' files. DAS28 values were re-calculated in patients who completed one year of treatment with bisphosphonates. Swollen and tender joint counts, erythrocyte sedimentation rate and C-reactive protein levels which are calculation parameters of DAS28 were recorded also separately. Patients subjective assessments of pain was recorded on a 0-10 visual analogue scale (VAS) (in a range from 0 (no pain) to 10 (worst pain one could encounter)) at both baseline and after one year of BP treatment.

Bone mineral densitometry analyses were performed in all RA patients by Dual Energy X-ray Absorptiometry (DEXA; Hologic QDR 4500 SL, Bedford.MA). BMDs of the lumbar spine (L1-L4 total) and left femoral neck were recorded from the patient files before starting the BP therapies. The results were expressed as T scores and patients were classified as osteopenic for a T score between -1 and -2,5 and osteoporotic for a T score ≤-2,5 according to World Health Organization Guidelines. After BMD analysis, BP therapies were prescribed to the 106 patients with osteoporosis and osteopenia including annual zoledronate (5mg/100 ml intravenous infusion), monthly ibandronate (150 mg oral tablet) and risedronate (one 75 mg tablet orally, taken on two consecutive days for a total of two tablets each month) or weekly alendronate (70 mg oral tablets). 106 patients (89 women, 17 men) who received BP therapy for 1 year constituted group1 and 101 patients (81 women 20 men) who did not receive BPs constituted group 2.

All patients used stable doses of methotrexate (MTX), sulphasalazine (SZN) and/or hydroksichloroquine (HQ) and were allowed to use corticosteroids (<15mg/day) if stable at least one month before inclusion.

Statistical analysis

Statistical analysis was performed using SPSS 11 (SPSS, Chicago, IL, USA). The results were expressed as mean ± SD. Significance was set at a $p < 0,05$.

In order to compare the baseline values between patients,

we used Student's paired 2-tailed t-test for continuous variables, Mann Whitney U test for ordinal data and Chi-square test for categorical variables. To compare baseline and 1 year-after values, Student's unpaired 2-tailed t-test for continuous variables and Wilcoxon signed rank test for categorical variables were used.

RESULTS

The mean age of group 1 was 65,02 ± 11,14 years and group 2 was 63,64±9,1 years (p > 0,05). There was no statistically significant difference between groups in terms of age, gender and disease duration parameters. Initial DAS 28 levels (3,66 ± 1,16) of the group 1 was slightly higher than group 2 (3,07 ± 1,08) (p = 0,035). Late onset RA ratio of the group 1 was 36,8% and group 2 was 37,2% (p >0 .05) **(Table 1).**

Baseline mean lumbar spine BMD of group 1 was 0,644±0,106 g/cm2 and group 2 was 0,687±0,05 g/cm2 (p<0,001). Baseline mean femoral neck BMD in group 1 was 0,682±0,112 g/cm2 and group 2 was 0,783±0,071 g/cm2 (p<0,001). In group 1, 51 patients (48,1%) had osteoporosis and 55 patients (51,9%) had osteopenia while in group 2, 4 patients (4%) had osteoporosis and 95 patients (94,1%) had osteopenia in femur neck and/or spine at baseline **(Table 1).**

Of the 106 patients who were prescribed BPs, 6 of them (5.7%) used zoledronate, 65 (61.3%) used alendronate, 17(16,0%) used ibandronate and 18(17,0%) used risedronate. The characteristics, including dose and type of DMARD of the two groups at baseline were similar (Table 2). There were no statistically significant difference according to DMARD type and dosages between groups (p > 0,05) but in group 1, prednisolone users were more than group 2 (p < 0,001).

The mean MTX dose of group 1 was 13,43 ± 3,4 mg/week, group 2 was 12,88 ± 2,98 mg/week (p = 0,062). A total of 77 (72,6%) patients from group 1 used prednisolone at a mean dose of 5,71 ± 2,55 mg/day, and 49 (48,5%) patients from group 2 used prednisolone at a mean dose of 4,8±1,57 mg/day (p>0,05 for mean dosages). The mean doses of other DMARDs were shown in **Table 2.**

The mean DAS28 score decreased from 3,66±1,16 at baseline to 2,89±1,1 at month 12 (p<0.001) in group 1 and from 3,07±1,08 at baseline to 2,92±0,96 in group 2. At month 12 there were 2(1,9%) good, 56 (52,8%) moderate and 48 non-responders in group 1 and 3 (3%) good, 22 (21,8%) moderate and 76 non-responders in group 2 according to the EULAR response criteria (p<0,001) **(Table 3).**

Table 1: Baseline Characteristics of Patients

	Group 1 (n=106)	Group 2 (n=101)	p
Age (years)	65,02±11,14 (45-90)	63,64±9,1 (45-90)	>0,05
Gender (Female/Male)	89/17	81/20	>0,05
Disease duration (years)	11,73±8,97 (2-44)	8,73±4,98 (2-25)	>0,05
Late Onset RA n(%)	39(36,8)	38(37,2)	>0,05
RF positivity n(%)	66(62,3)	62(61,4)	>0,05
CCP positivity n(%)	54(50,9)	31(30,7)	>0,05
Tender joint count	3,08±5,09 (0-22)	1,3±2,84 (0-22)	<0,001*
Swollen Joint Count	0,55±1,06 (0-4)	0,2±0,53 (0-4)	0,009*
Visual Analogue Scale	42,84±18,89 (10-90)	30,58±14,34 (10-80)	0.04**
DAS28	3,66±1,16 (1,15-6,53)	3,07±1,08 (0,68-6,94)	0,01**
Lumbar Spine BMD (g/cm2)	0,644±0,106 (0,32-0,89)	0,687±0,05(0,53-0,87)	0,046*
Lumbar Spine T Score	-2,21±0,88 (-4,5- -0,02)	-1,73±0,49 (-3,3-0,5)	<0,001*
Femur Neck BMD (g/cm2)	0,682±0,112 (0,30-0,89)	0,783±0,071 (0,64-0,9)	<0,001**
Femur Neck T Score	-1,84±0,86 (-4,7- -0,1)	-1,09±0,43 (-2,3-0,0)	<0,001**

RA: Rheumatoid Arthritis
RF: Rheumatoid Factor
CCP: Cyclic Citrullinated Peptid
*Student T Test statistics
**Mann Whitney U Test statistics
Values are expressed as mean±SD (range)

Table 2: The Bisphosphonates and DMARDs using by patients.

	Group 1 (n=106)	Group 2 (n=101)	p
Zoledronate n(%)	6 (5,7)	-	
İbandronate n(%)	17 (16,0)	-	
Risedronate n(%)	18 (17)		
Alendronate n(%)	65 (61,3)	-	
Methotrexate n (%) Dosage (mg) (range)	 72(67,9) 13,43±3,4 (7,5-20)	 57(57,4) 12,88±2,98 (7,5-20)	 0,062 >0,05*
Leflunomide n (%) Dosage (mg)	 16 (15,1) 20	 8 (7,9) 20	 0,081
Hydroxychloroquine n (%) Dosage (mg)	 46 (43,4) 400	 59 (58,4) 400	 0,021***
Prednisolone n (%) Dosage (mg) (range)	 77 (72,6) 5,71±2,55 (2,5-15)	 49 (48,5) 4,8±1,57 (2,5-10)	 0,008*** >0,05**
Sulfasalazine n (%) Dosage (gr)	 8 (7,5) 2	 6 (5,9) 2	 0,428

*Mann Whitney U
**Student T
***Chi-Square

The mean values of tender joint count decreased from 3,8±5,09 at baseline to 3,16±4.77 at month 12 (p<0.001) in group 1 and increased from 1,3±2,84 to 1,73±3,29 in group 2 (p<0.001). The mean tender joint count changes were -0,64±0,63 in group 1 and 0,42±0,62 in group 2 (p<0,001) **(Table 3).**

The mean values of swollen joint count decreased from 0,55±1,06 at baseline to 0,25±0,74 at month 12 (p<0.001) in group 1 and increased from 0,20±0,53 to 0,23±0,69 in group 2 (p>0,05). The mean swollen joint count changes were -0,3±0,48 in group 1 and 0,02±0,35 in group 2 (p>0,05) **(Table 3).**

The mean values of VAS decreased from 54.16±14.98 at baseline to 42.84±18.89 at month 12 (p<0.001) in group 1 and increased from 30.58±14.34 to 35.98±16.85 in group 2 (p<0.001). The mean VAS changes were -11,31±6,91 in group 1 and 5,39±6,84 in group 2 (p<0,001) **(Table 3).**

There were no significant difference according to BMD values of prednisolone users and nonusers at baseline and after 1 year **(Table 4).**

There were no significant differences among BP types with respect to suppression of disease activity. There were no correlations between disease activity parameters and BMD values.

DISCUSSION

This retrospective analysis showed that disease activity and pain could be controlled with BPs as an adjunctive therapy of synthetic DMARD in RA patients older than 45 years.

Interactions between activated T cells and macrophages drive the process of bone destruction that occurs in RA by releasing proinflammatory cytokines, especially tumor necrosis factor α (TNF α), interleukin-1 and IL-17, which transform myeloid precursor cells and synovial fibroblasts into tissue destructive effector cells. TNF α from activated macrophages, in the presence of permissive levels of RANKL stimulates production of osteoclasts. The BPs inhibit osteoclast formation, function, and survival at least in part by inhibiting the mevalonate pathway enzyme, farnesyl diphosphate synthase and might be effective in preventing structural damage in arthritis [8,9]. BPs may also induce osteoclast apoptosis [10] and suppress osteoclast function via accessory cells, such as osteoblasts [11]. Besides these physicochemical and antiosteoclastic effects, BPs have anti-inflammatory activities. These potent anti-inflammatory activities were first suggested by their use as adjuvant treatment in RA. Indeed, clodronate, pamidronate and etidronate were shown to ameliorate the clinical activity of patients or some clinical and laboratory parameters of RA [12,13,14].

Table 3: Absolute changes in VAS, DAS28, tender and swollen joint counts values after 1 year.

	Group 1 (n=106)		Group 2 (n=101)		p
	After 1 year	Changes	After 1 year	Changes	
Tender joint count	3,16±4,77	-0,64±0,63	1,73±3,29	0,42±0,62	<0,001*
Swollen Joint Count	0,25±0,74	-0,3±0,48	0,23±0,69	0,02±0,35	<0,001**
Visual Analogue Scale	42,84±18,89	-11,31±6,91	35,98±16,85	5,39±6,84	<0,001*
DAS28	2,89±1,1	-0,76±1,08	2,92±0,92	-0,15±1,09	<0,001*
EULAR Response n(%) Good response Moderate response Non-responder	2 (1,9) 56 (52,8) 48 (45,3)		3 (3) 22 (21,8) 76 (75,2)		

*Mann Whitney U
**Student T
***Chi-Square

Table 4: Comparisons of BMD values of prednisolone users and nonusers at baseline and after 1 year.

	Group 1 (n=106)				Group 2 (n=101)			
	Prednisolone Users	p	Prednisolone non-users	p	Prednisolone Users	p	Prednisolone non-users	p
Lumbar Spine BMD (g/cm2)	0,636±0,112	>0,05	0,659±0,094	>0,05	0,682±0,045	0,024*	0,691±0,05	>0,05
Lumbar Spine BMD (g/cm2) After 1 year	0,612±0,175		0,662±0,099		0,676±0,039		0,70±0,08	
Lumbar Spine T Score	-2,27±0,92	>0,05	-2,09±0,8	>0,05	-1,79±0,42	0,014*	-1,68±0,54	>0,05
Lumbar Spine T Score After 1 year	-2,32±0,81		-2,06±0,83		-1,85±0,4		-1,66±0,66	
Femur Neck BMD (g/cm2)	0,686±0,116	>0,05	0,673±0,104	>0,05	0,795±0,071	0,049*	0,773±0,071	>0,05
Femur Neck BMD (g/cm2) After 1 year	0,697±0,118		0,682±0,140		0,784±0,065		0,764±0,082	
Femur Neck T Score	-1,82±0,87	>0,05	-1,88±0,84	>0,05	-1,02±0,45	0,047*	-1,15±0,41	>0,05
Femur Neck T Score After 1 year	-1,84±0,88		-1,90±0,85		-1,04±0,33		-1,16±0,42	

* Wilcoxon Signed Rank Test

These results were not confirmed by all the studies and thus, the therapeutic use of BPs in RA is not established. However, these trials were not designed for detecting a therapeutic effect of the tested drug [15]. In our group 1 patients who underwent BP therapy, DAS28 score, number of swollen and tender joints and acute phase reactants were decreased significantly after one year of treatment. Thus, our findings suggested that the disease activity might be controlled with BPs as an adjunctive therapy of synthetic DMARD.

The effects of BPs on disease activity of RA patients have been evaluated in several clinical trials [16]. Alendronate

was shown to selectively act on antigen presenting cells, but not on T cells. This drug also had the ability to inhibit cytokine production (IL-1α, IL-6 and TNF-α) by activated macrophages in a dose dependent fashion [15]. The use of Zoledronate in RA showed that this BP had an effect on radiological progression. In a placebo controlled trial involving 39 patients with early RA being treated with methotrexate, the reduction of wrist and hand bone erosions was higher in the zoledronate group compared with the placebo group after 26 weeks. This study suggested that zoledronate may provide structural benefit in RA patients [3]. We prescribed 4 different aminobisphosphonates to our group 1 patients including zoledronate, alendronate, ibandronate and risedronate and found that aminobisphosphonate usage was associated with reduced disease activity. We didn't observe any differences between BP types with respect to suppression of disease activity.

Aminobisphosphonates also inhibit angiogenesis in tumor models. RA is a chronic inflammatory disease associated with increased synovial vascularity. Angiogenesis is involved in RA and also in spondyloarthropathies (SpA). It was reported that both RA and SpA patients elevated serum vascular endothelial growth factor (VEGF) correlated with disease activity [17,18]. A number of bisphosphonates, such as zoledronate, inhibit angiogenesis in tumor models. Angiogenesis is a key factor in the inflammatory response [5]. BP therapy may be a new strategy for inhibiting angiogenic factors in disease models of RA [19]. The reduction of disease activity as well as tender and swollen joint count in our study may also be explained with inhibition of angiogenesis of BPs therapy.

Another property of BPs which could explain their therapeutic use in RA is the reduction of bone pain in malignancy. BPs are used in skeletal metastasis and multiple myeloma in order to reduce the occurrence of skeletal events, such as bone pain, fractures and hypercalcemia. BPs (clodronate, pamidronate and zoledronate) demonstrated their efficacy in such conditions by diminishing bone pain and improving the quality of life of cancer patients [15]. Another important finding in our study was significant reduction of VAS values in patients who underwent BPs therapy. This may be explained with reduced bone pain due to the BP therapy.

The main perturbation of bone metabolism in RA is increased osteoclastic bone resorption which is correlated with high inflammatory disease activity [2]. Forsblad et al. stated that there is a strong relationship between radiographic joint destruction and generalized osteoporosis. [21]. But in our study we could not find any relationship between disease activity and generalized osteoporosis. This may be due to low mean DAS28 levels of our patients whose mean ages were over 45 years.
Soejima et al. reported that alendronate monotherapy was effective against active arthritis and inflammation associated bone damage in a patient with RA and hepatitis C. They concluded that alendronate might be an effective therapy in patients with early RA who cannot be treated with DMARD [22]. Sims et al. showed that, single doses of zoledronic acid effectively suppressed focal bone erosions and juxtaarticular bone loss in collagen induced arthritis model. They concluded that targeting osteoclasts with zoledronate may be an effective adjunctive strategy for preventing structural joint damage and generalized osteoporosis in RA [2]. Another inflammatory disease of bone and joints is ankylosing spondylitis and several studies show that BPs are also effective on disease activity and pain of this disease. As a potent BP, Pamidronate has been shown to have a symptom-modifying effect in ankylosing spondylitis in one randomized controlled trial [23], but being less effective than TNF-α inhibitors, it is used mainly in patients who cannot use anti-TNF-α treatments [24]. In a case report, a patient with ankylosing spondylitis, after demonstrating incomplete clinical response to adalimumab, received three monthly infusions of pamidronate along with continuing TNF-α blockade. Complete disappearance of the back pain was reported after the second pamidronate infusion. This report suggested that the addition of pamidronate may be administered in some AS patients with incomplete clinical response to TNF-α blockade [25]. In the light of the findings of these reports and according to our findings, BP therapy may be used as an adjunct therapy with synthetic DMARD and biologic agent.

We couldn't include patients with severe disease activity. This may be a drawback of our study. Another drawback may be that we also couldn't evaluate the radiographic joint destruction.

CONCLUSION

For patients who cannot be treated with biological agents, effective prevention of focal bone damage and generalized bone loss will require new treatment strategies, like concomitant administration of drugs with specific effects on bone metabolism. BPs might prove useful in patients who have severe RA and have contraindications or intolerance to TNF-α antagonist therapy. BPs can prevent generalized bone loss and BP therapies may yield both medical and economic benefits in patients with RA. We think that adjunctive BPs may provide additional benefits in older RA patients with systemic and regional bone loss. However, further studies are needed to determine whether bisphosphonate therapies must be administered routinely with the DMARDs and biologics.

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