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An inconvenient status in anti-osteoporotic treatment process: corticosteroid use

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SUMMARY

OBJECTIVE: There are limited studies investigating the comparison of the efficacy of anti-osteoporotic drugs in different conditions resulting in osteoporosis in older adults. This study aimed to compare the effectiveness of anti-osteoporotic agents in older adults with or without glucocorticoid-induced osteoporosis.

METHODS: This retrospective study included 364 patients with osteoporosis, aged 65 years and older. Bone mineral density measurement was performed, and the percent change from baseline was calculated at month 24.

RESULTS: Of the 364 patients, 80 were glucocorticoid users. Similar changes in the bone mineral density of the lumbar spine and femoral neck and fracture risk were found in patients with or without glucocorticoid-induced osteoporosis. There was no significant difference in bone mineral density changes between the groups in terms of anti-osteoporotic agents used.

CONCLUSIONS: This study demonstrated that the response to anti-osteoporotic agents was similar in older adults with glucocorticoid-induced osteoporosis and those without glucocorticoid-induced osteoporosis. The results of our study may guide osteoporosis treatment in older individuals with glucocorticoid-induced osteoporosis.

KEYWORDS: Elderly. Osteoporosis. Glucorticoid effects. Alendronate. Zoledronic acid. Denosumab. Teriparatide.

INTRODUCTION

Osteoporosis is a skeletal disorder characterized by low bone mass, microarchitectural disruption, and bone fragility, resulting in increased fracture risk. The social and economic burden of osteoporosis is increasing constantly due to the aging of the world population[1] Glucocorticoid-induced osteoporosis (GIOP) is the most common type of secondary osteoporosis[2]. An important characteristic of GIOP is rapid bone loss immediately after initiation of glucocorticoid (GC) therapy[3]. Fracture is the most common serious and preventable adverse event associated with GCs. The use of approximately 5 mg of prednisone or its equivalent for 3 months has been shown to result in a measurable increase in fracture risk[4].

Bisphosphonates are recommended as an initial anti-osteoporotic therapy because of their efficacy, favorable cost, and long-term safety[5]. Alendronate, risedronate, ibandronate, and zoledronic acid have been shown to improve bone mineral density (BMD) in postmenopausal women with osteoporosis[6]. Denosumab can be preferred as initial therapy in certain patients who are at high risk for fracture and intolerant or unresponsive to other therapies like intravenous bisphosphonates, or who have markedly impaired renal function. Denosumab improves BMD and reduces fracture risk in postmenopausal women with low BMD[7]. Denosumab may be an alternative in some patients with GIOP, especially those who are at high risk due to advanced age. Both the features of superiority to the bisphosphonates and the similarity of the adverse events make denosumab an appropriate alternative for these patients[8].

Teriparatide is recommended for patients who have severe osteoporosis (low BMD [T-score <-2.5] and at least one fragility fracture) or who do not have improvements with the previous therapy[9]. Teriparatide directly stimulates osteoblastogenesis and inhibits osteoblast apoptosis; therefore, it could be another alternative as anabolic therapy in patients who are receiving long-term GCs and are at high risk for fracture[10]. Teriparatide is also superior to bisphosphonates in increasing BMD of the lumbar spine, total hip, and femoral neck in patients with GIOP[11].

In this study, we aimed to compare the efficacy of anti-osteoporotic medications in osteoporotic older adults with or without GIOP.

METHODS

Participants

This retrospective study included 412 patients, aged 65 years or older and diagnosed with osteoporosis, who visited our geriatric medicine outpatient clinic between January 1, 2018, and March 1, 2019. Notably, 29 patients with insufficient data and

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19 patients without dual-energy x-ray absorptiometry (DXA) scan at month 24 were excluded. The study was completed with 364 participants. The sample size was calculated using the Epi Info software, and the minimum sample size was 120 participants, with 80% power at the level of α=0.05. Exclusion criteria were renal impairment, primary or metastatic bone tumor, and bone diseases other than osteoporosis. BMD measurement of the lumbar spine and proximal femur was performed by DXA method (using Hologic scanners) before treatment and at month 24. The percentage change from the baseline BMD was calculated at month 24. Drugs administered included the following: alendronate 70 mg/week orally, zoledronic acid 5 mg/year intravenously, denosumab 60 mg/every 6 months subcutaneously, and teriparatide 20 µg/day subcutaneously. All patients were prescribed 1000 mg of calcium and 800 IU of vitamin D per day. GC use was considered the use of ≥5 mg/day prednisolone or equivalent for ≥3 months.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 22.0 (IBM SPSS Statistics, Armonk, NY, USA). The distribution of normality was checked using the Shapiro-Wilk test. We used the Mann-Whitney U test and independent samples t-test to compare two independent groups of variables, the chi-square test to assess the relationship between categorical variables, and Spearman's rank correlation coefficients between numerical variables. Logistic regression analysis was used to determine the independent predictors of low BMD. A p<0.05 was accepted as statistically significant.

RESULTS

In this study, the mean age of 364 older adults was 69.9±5.4 years, and 90.4% were women. Most of the participants (82.1%) were in the age group 65–74. Twenty-eight were smokers and none of them consumed alcohol. The proportion of those with diabetes mellitus and coronary artery disease was significantly higher in the non-GC-user group. C-reactive protein level was higher in GC-users; however, there was no difference between the groups in terms of age, gender, anti-osteoporotic agents used, and other laboratory tests (Table 1).

Baseline BMD of the lumbar spine and femoral neck, as well as BMD changes were similar between the groups (Table 2). There was no significant difference in BMD changes between the GC-users and the non-GC-users in terms of anti-osteoporotic agents used (Table 3). In addition, it was observed that parenteral anti-osteoporotic agents were more effective in BMD improvement compared with alendronate, although there was no statistically significant difference.

Age, the number of comorbidities, and medications were not correlated with the BMD change and fracture risk reduction. A statistically significant strong positive correlation was found between femur neck BMD change and major osteoporotic and hip fracture risk reduction percentage (p=<0.001, r=0.961 and p=<0.001, r=0.962, respectively). In addition, there was a statistically significant negative correlation between the baseline femur neck and the BMD changes (p£0.001, r=–0.292), between major osteoporotic and hip fracture risk reductions (p£0.001, r=–0.335, and p£0.001, r=–0.274, respectively), and between the baseline BMD and BMD change in the lumbar spine (p£0.001, r=–0.232).

According to the multivariate logistic regression analysis, BMD change of the femoral neck was an independent variable for both major osteoporotic (p=0.000, OR=4.11) and hip fracture risk reductions (p=0.000, OR=4.01).

DISCUSSION

In our study, it was noticeable that BMD changes of the lumbar spine and femur neck showed similar responses to treatment agents in both the groups who received and who did not receive GC medication. Major osteoporotic and hip fracture risk reductions were also similar in both the groups. Parenteral anti-osteoporotic agents were found to be more effective in BMD improvement, although there was no statistically significant difference.

Glucocorticoid-induced osteoporosis is characterized by a greater reduction in osteoblastic activity at different levels of the bone, leading to reduced bone formation dramatically when compared with postmenopausal osteoporosis[12]. "Similar responses to the treatment" is a rather remarkable result, especially when we consider expectations for better responses to the treatment in patients with GIOP. Another cause of these similar responses may be ongoing GC treatment of the GC-receiving group. While a dramatic improvement in BMD is expected with anti-osteoporotic therapy after cessation of GC drugs, ongoing GC therapy may cause a slowdown in anti-osteoporotic treatment response. With this point of view, especially for those who have to continue their GC treatment, we can conclude that depending on GC doses and the condition of the underlying disease, one of the second-line anti-osteoporotic agents may be preferred as a first-line option or earlier than bisphosphonates therapy in GIOP treatment[13]. Oral bisphosphonates are generally the first-line

Table 1. Sociodemographic characteristics and laboratory analysis results of the participants.

	GC-user (n=80)	Non-GC-user (n=284)	p	Total (n=364)
Gender				
Female	73 (91.3%)	256 (90.1%)	0.480	329 (90.4%)
Male	7 (8.8%)	28 (9.9%)		35 (9.6%)
Age (years) #	69.0±4.5	70.1±5.6	0.092	69.9±5.4
65–74	74 (92.5%)	225 (79.2%)	0.016*	299 (82.1%)
75–84	4 (5.0%)	51 (18.0%)		55 (15.1%)
≥85	2 (2.5%)	8 (2.8%)		10 (2.7%)
Treatment agent				
Alendronate	32 (40.0%)	79 (27.8%)	0.130	111 (30.5%)
Zoledronic acid	23 (28.7%)	98 (34.5%)		121 (33.2%)
Denosumab	24 (30.0%)	94 (33.1%)		118 (32.4%)
Teriparatide	1 (1.3%)	13 (4.6%)		14 (3.8%)
Other comorbidities				
Hypertension	30 (37.5%)	119 (41.9%)	0.521	149 (40.9%)
Diabetes mellitus	8 (10.0%)	65 (22.9%)	0.011*	73 (20.1%)
Coronary artery disease	4 (5.0%)	39 (13.8%)	0.031*	43 (11.8%)
Asthma/COPD	10 (12.5%)	19 (6.7%)	0.103	29 (8.0%)
Cancer	2 (2.5%)	17 (6.0%)	0.268	19 (5.2%)
Smoker	4 (5.0%)	24 (8.5%)	0.306	28 (7.7%)
Serum 25-OH vitamin D (nmol/L) #	35.9±6.4	34.0±5.7	0.158	34.4±6.2
Parathyroid hormone (pg/ml) †	56	48	0.167	49
Serum calcium (mg/dl) # ‡	9.7±0.6	9.7±0.5	0.579	9.7±0.6
Serum phosphorus (mg/dl) #	3.7±0.6	3.6±0.4	0.601	3.6±0.5
C-reactive protein (mg/dl) †	3.0	2.6	0.017*	2.8
Erythrocyte sedimentation rate (mm/h) †	18	17	0.461	17
Serum creatinine (mg/dl) #	0.73±0.24	0.70±0.18	0.201	0.71±0.20

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

Table 2. Comparison of the dual-energy x-ray absorptiometry scan assessments, bone mineral density changes, and fracture risk reduction.

.	GC-user (n=80)	Non-GC-user (n=284)	p	Total (n=364)
Lumbar spine				
Baseline T score#	-2.90±0.78	-2.98±0.84	0.460	-2.97±0.83
Baseline BMD (g/cm^2) #	0.73±0.09	0.72±0.09	0.658	0.72±0.09
24th month BMD (g/cm^2)#	0.76±0.09	0.75±0.09	0.508	0.75±0.09
BMD change (%)†	3.68	3.99	0.581	3.93
Femur neck				
Baseline T score#	-2.36±0.72	-2.39±0.75	0.355	-2.39±0.75
Baseline BMD (g/cm^2) #	0.59±0.08	0.58±0.09	0.394	0.59±0.08
24th month BMD (g/cm^2)#	0.61±0.08	0.60±0.08	0.734	0.60±0.08
BMD change (%)†	3.57	2.93	0.770	2.99
Major osteoporotic fracture risk reduction (%)†	6.67	9.09	0.642	8.33
Hip fracture risk reduction (%)†	10.31	14.28	0.399	13.72

#Data are presented as mean±SD; †Data are presented as median. BMD: bone mineral density.

Table 3. Comparison of the bone mineral density changes between treatment agents.

Treatment agent		Lumbar spine BMD change (%)	p	Femur neck BMD change (%)	p
Alendronate (n=111)	Non GC-user (n=79)	3.27	0.984	2.28	0.607
	GC-user (n=32)	3.38		2.31	
Zoledronic acid (n=121)	Non GC-user (n=98)	4.41	0.746	2.79	0.761
	GC-user (n=23)	3.55		5.57	
Denosumab (n=118)	Non GC-user (n=94)	3.61	0.784	3.79	0.721
	GC-user (n=24)	3.40		3.64	
Teriparatide (n=14)	Non GC-user (n=13)	8.19	0.143	3.16	0.429
	GC-user (n=1)	30.5		15.19	

BMD: bone mineral density; GC: glucocorticoid. Data are presented as median.

therapy for GIOP in most patients due to their proven efficacy, good safety, and low cost. However, the superiority of teriparatide to oral bisphosphonates especially in increasing BMD and reducing fracture risk may provide an advantage for GIOP patients who have ongoing GC treatment[14,15]. Giving high-dose teriparatide may be another way to provide a faster and greater BMD increase in GIOP patients. In a recent study, patients receiving high-dose teriparatide treatment achieved clinically meaningful and rapid gains in hip and spine BMD[16]. Moreover, some studies indicate that cyclic administration of teriparatide either alone or in combination with ongoing bisphosphonates may achieve the best outcomes for patients with severe osteoporosis[17,18]. The small number of patients receiving teriparatide in our study may be the reason for the lack of significant difference in BMD changes.

Most of our patients were using intravenous zoledronic acid, which is more effective than risedronate in increasing lumbar spine BMD and reducing serum bone turnover markers (BTM). Therefore, treatment of GIOP patients with intravenous zoledronic acid may be more reasonable than the oral forms of other bisphosphonates. Denosumab can be considered as one of the therapeutic options for GIOP patients, especially when the efficacy of bisphosphonate treatment is diminished or teriparatide treatment is discontinued[19].

This study has many limitations. First, there is a lack of BTM measurement at baseline and month 24 in both the groups. Second, a much longer follow-up may better show the differences in fracture incidence. Third, we need more teriparatide-receiving patients in both the groups in order to acquire more accurate comparisons and achieve a treatment approach. Despite these limitations, our study has some strength. First, our study includes only older patients. Second, we compared the effects of the anti-osteoporotic agents among themselves, while most previous studies compared the effects of the drugs with placebo. Similarities in laboratory test results and sociodemographic characteristics between groups were also important for a clearer comparison of treatment response.

CONCLUSIONS

This study showed that older adults with GIOP had a similar anti-osteoporotic treatment response compared to those without GIOP. Even though the second-line anti-osteoporotic agents have particular indications to use as anti-osteoporotic treatment, it can be considered to use these agents as the first-line treatment options in patients with GIOP in order to achieve more effective BMD responses. Furthermore, among osteoporotic patients, considering that GIOP is a more destructive process, alternative treatments like high-dose teriparatide can be given as an anti-osteoporotic treatment. However, further studies are needed to obtain more strong data to support our results.

ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval for the study was granted by the Local Ethics Committee.

AUTHORS' CONTRIBUTIONS

EÖ: Investigation, Project administration, Resources, Writing – original draft. **AÇ:** Data curation, Validation. **GÇ:** Methodology, Visualization. **ZAÖ:** Conceptualization, Supervision, Writing – review & editing.'

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