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A retrospective analysis of nonresponse to denosumab after hip fractures

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Denosumab is an effective antiresorptive drug commonly prescribed for the treatment of osteoporosis. However, some patients do not respond well to denosumab treatment. The aim of this study was to evaluate the factors underlying treatment nonresponses to denosumab in elderly patients following hip fracture. This retrospective study included 130 patients treated with denosumab after osteoporotic hip fracture between March 2017 and March 2020. The patients were categorized as denosumab nonresponders if they had a T-score <−3 that persisted between dual-energy X-ray absorptiometry scans, a >3% decrease in bone mineral density (BMD), or an incident fracture on denosumab therapy. We examined the baseline characteristics associated with blunted BMD responses and compared the groups following denosumab treatment for 12 months. Of 130 patients with baseline data, 105 patients (80.8%) were considered responders. No difference in baseline vitamin D, calcium, BMI, age, gender, prior fracture history, or bisphosphonate use was observed between responders and nonresponders. A longer interval between denosumab injections was associated with suboptimal BMD response at both spine and total hip (p<0.001 and p=0.04, respectively). The overall L-BMD and H-BMD were significantly increased compared with pretreatment levels after denosumab treatment (5.7% and 2.5%, respectively). This study revealed that nonresponse was not strongly associated with certain baseline variables and it appears that the reponders and nonresponders were reasonably comparable in this study population. The results of our study highlight the importance of timely denosumab administration when using this drug for osteoporosis management. Physicians should keep these results in mind in clinical practice so that they can improve utilization of 6-month denosumab.

Keywords: Osteoporosis, denosumab, hip, fractures.

INTRODUCTION

The incidence of hip fracture has been increasing over time in global populations. While most traumatological presentations decreased in frequency over the course of the COVID-19 pandemic, the number of osteoporotic hip fractures remained stable[1]. As hip fracture patients are at high risk of subsequent osteoporotic fractures[2], anti-osteoporosis medication after hip fracture is widely recommended by clinical practice guidelines[3].

Denosumab, a human monoclonal antibody, is administered subcutaneously every 6 months for the treatment of postmenopausal osteoporosis. Preference and efficacy of denosumab treatment were assessed in various clinical trials. Available data suggest that denosumab is preferred to bisphosphonates, produces greater satisfaction than bisphosphonates, and would be preferentially chosen for long-term treatment for osteoporosis[4]. The majority of articles showed that denosumab was cost-effective, and even cost-saving in patients older than 75 years of age and those who have lower bone mineral density (BMD) T-scores, a history of previous fractures, and more risk factors[5]. However, in real-world clinical settings, some patients with osteoporosis do not respond to denosumab treatment for unknown reasons. Several clinical trials have suggested that response to treatment with antiresorptive agents may depend on the subjects' characteristics, such as baseline BMD and prevalent fractures[6]. However, to the best of our knowledge, there are no studies that have assessed the causes of nonresponse to denosumab in elderly patients after hip fracture.

The objectives of this study were to better understand the factors underlying treatment nonresponses to denosumab treatment following hip fracture and to compare nonresponders' and responders' characteristics in these elderly patients. After observing the problem of poor response to denosumab after hip fracture in some patients, we wished to test the hypotheses that nonresponse was associated with certain baseline variables.

MATERIALS AND METHODS

We performed a retrospective analysis of our institutional hip fracture database between March 2017 and March 2020, and identified all patients aged 65 years or older who had a hospitalization for hip fracture based on a diagnosis code as well as a procedure code for surgical treatment of the fracture. The institutional review board of the ethics committee of our institution approved this single-center retrospective comparative study (approval number: HGH-2021-OTH-006). Written informed consent was waived as this was purely retrospective review without intervention.

Patients who met the diagnostic criteria of a femoral neck or intertrochanteric fractures based on the International Classification of Diseases, 10th revision (ICD-10; S720, S721) were enrolled. The inclusion criteria were: (1) patients aged 65 years and older who received operative treatment for a hip fracture, (2) patients who had data available from two dual-energy X-ray absorptiometry (DXA) scans conducted on the same machine, (3) patients with osteoporosis (T-score of -2.5 or lower), and (4) patients who were prescribed denosumab after surgery at least for ≥ 12 months. The exclusion criteria were: (1) patients who had a prior diagnosis of metabolic bone disease other than osteoporosis, (2) pyogenic infections, (3) chronic renal failure, and (3) fractures caused by more than minimal trauma.

The patients received 6-month denosumab at a dose of 60 mg (Prolia®; Amgen, Thousand Oaks, CA, USA), which was administered subcutaneously, and their compliance with the medication was assessed during each clinic visit. Appropriate adherence was defined as less than 7 months between 2 consecutive denosumab injections[7,8], which corresponds to a delay of <1 month for the subsequent dose.

Lumbar spine (L1-4) BMD (L-BMD), and total hip BMD (H-BMD) were was measured by DXA at admission and at 12 months of therapy (The measurement of BMD using DXA is covered by insurance one year after previous measurement in South Korea). Values and percentage changes in BMD were determined for each time point, and comparisons were made between the groups by statistical analysis. Fracture sites were avoided during the evaluation of BMD. For each patient we collected data at two time points: baseline (at time of the hip fracture), one year after the hip fracture event. Based on previously reported values[9,10], nonresponse included any of the following: (1) T-score of<-3.0 at the lumbar spine, femoral neck, total hip, or trochanter despite >12 months of denosumab therapy (2) Decrease of >3.0% in BMD at the lumbar spine, femoral neck, total hip, or trochanter between the baseline and follow-up DXA scans (3) Incident low-trauma fracture despite >12 months of therapy (Only fractures that occurred after a minimum of 12 months treatment were included). No change (-3.0% to 3.0% based on the measurement error of DXA scans) or an increase in BMD at all of the above sites was considered an adequate response[11].

The level of co-morbidities before the hip fracture was assessed by means of the Charlson Comorbidity Index (CCI)[12]. The CCI was developed and validated as a measure of comorbidities and their overall impact on survival, allowing prediction of the risk of mortality over 1 year. The average age of the patients at the time of surgery was 80.5 years (range, 65-99 years). Minimum follow-up was 12 months (average, 1.9 years; range, 1.0-4.0 years). All surgical procedures were performed by a single surgeon and all patients underwent surgery under general anesthesia and. Patients were seen for follow-up at 4, 8, and 12 weeks and then every 3 month thereafter. Patients were asked to report any side effects after medications and new fractures occurring since the baseline visit, and fracture site information was collected. Data were obtained from medical records and radiographs.

The following possible determinants of response to denosumab treatment were considered: age, gender, body mass index (BMI), CCI, length of stay in hospital, smoking, alcohol, prior bisphosphonate treatment, prior osteoporotic fractures, baseline L-BMD, baseline serum calcium concentration, baseline serum vitamin D concentration, and interval between denosumab injections.

All data were recorded into an Excel spreadsheet (Microsoft Corp, Redmond, WA) and subsequently copied to a statistical analysis software SPSS version 13.0 (SPSS Inc, Chicago, IL, USA). Continuous data were summarized by mean and standard deviation (SD) and categorical data by percentage. The longitudinal BMD changes in each group were analyzed using a paired t test. Differences between groups in the continuous data were assessed by the Mann-Whitney U test and categorical data by the Fisher exact test. The data were further analyzed using multiple regression analysis to estimate the effect of selected factors on BMD response to denosumab. Statistical analysis was performed by an independent statistician blinded to group allocations. Significance was reported at the 95% confidence level ($p < 0.05$).

RESULTS

We identified 130 patients who received at least 2 doses of denosumab, amounting to a total of 528 denosumab injections (Fig 1). The mean follow-up was 22.8 (range 12 to 48) months. These patients received an average of 4 doses of denosumab (4.1 for responders and 4.0 for nonresponder); 32% received 2 to 3 doses, 40% received 4 to 6 doses, and 28% received more than 6 doses. In the present study, the effect of denosumab was evaluated at 12 months after treatment initiation, with BMD measurements at 0 and 12 months. Overall, 20.7% of denosumab injections (27 patients) were delayed by more than 1 month between first 2 doses (poor adherence), 79.3% patients received injections within the preferred interval for the second injection (Table I).

Baseline and follow-up characteristics were summarized and compared between responders and nonresponders (Table 1). One hundred five patients (80.8%) were considered responders. A total of 59.2% had a history of fragility fracture (other than the index hip fracture), 35.3% had a history of bisphosphonate use, and 9% had a history of prior teriparatide treatment. The nonresponder and the responder groups did not differ significantly in relation to age, the proportion of females, the CCI, the BMI, prior bisphosphonate treatment, the fracture history, the serum calcium concentration, the serum vitamin D level, and the serum uric acid concentration (Table II). The proportion of patients with poor adherence was significantly different between groups after 12 months treatment (p=0.004).

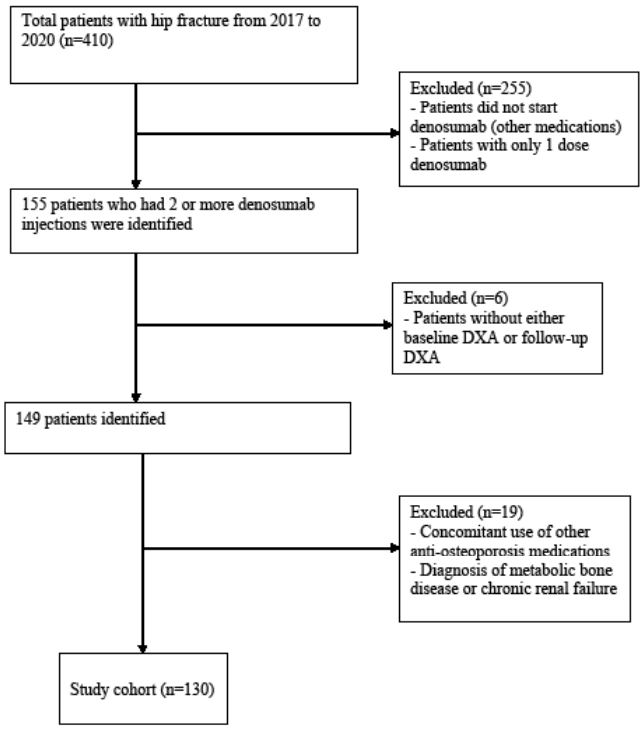

Fig. 1. — Patient flow chart of the study.

In the multiple regression models, which included age, the baseline BMD, the baseline calcium concentration, and the baseline vitamin D concentration, none of the determinants showed significant correlations with the BMD increase. However, a longer interval between denosumab injections was associated with suboptimal

Table I. — The demographic data for each group

	Nonresponder	Responder	P value
Number of patients (%)	25 (19.2)	105 (80.8)	
Age in years	80.4 ± 10.8	81.2 ± 10.5	0.844
Follow-up (months)	22.6 (range, 12-40)	24.2 (range, 12-48)	0.261
Female sex (%)	23 (92.0)	102 (97.1)	0.245
BMI (kg/m^2)	21 ± 4.6	22 ± 6.0	0.432
Prior bisphosphonate therapy (%)	13 (52.0)	33 (31.4)	0.065
Previous osteoporotic fractures (%)	17 (68)	60 (58.1)	0.496
Charlson Comorbidity Index	2.71 ± 1.38	2.86 ± 1.68	0.304
Baseline L-BMD (T-score)	0.820 ± 0.164 (-3.2 ± 0.90)	0.805 ± 0.162 (-3.4 ± 1.21)	0.812
Hospital stay (day)	17.8 ± 5.1	16.2 ± 4.2	0.522
Mean serum calcium (mg/dL)	9.3 ± 0.5	9.5 ± 0.6	0.144
Mean serum vitamin D (ng/ml)	40.0 ± 12.6	32.7 ± 15.1	0.061
Number of poor Adherence (%)	10 (40.0)	15 (14.2)	0.009
Smoking (pack-years)	2.8 ± 4.5	1.8 ± 4.2	0.312
Alcohol (g/week)	24.5 ± 34.9	18.8 ± 39.9	0.164

Table II. — Summary of bone mineral density (BMD) changes after osteoporosis medication

	Nonresponder (n=25)	Responder (n=105)	P-value
At admission			
L-BMD	0.820 ± 0.164	0.805 ± 0.162	0.812
H-BMD	0.632 ± 0.085	0.621 ± 0.128	0.533
At 12 months			
L-BMD	0.822 ± 0.085	0.855 ± 0.125	<0.001
H-BMD	0.628 ± 0.095	0.639 ± 0.118	0.01
% change in L-BMD	0.243 ± 3.51	6.250 ± 11.58	<0.001
% change in H-BMD	-0.632 ± 4.33	2.816 ± 8.42	0.02

BMD response at both spine and total hip (p<0.001 and p=0.04, respectively). In addition, patients with good adherence had an annualized BMD increase of 5.9% at the lumbar spine, compared with poor adherence (1.6%, p<0.001) (Figure 2). Patients with good adherence had an annualized BMD increase of 2.1% at the total hip, compared with patients with poor adherence (0.5%, p=0.02).

Among 130 patients who had been prescribed osteoporosis medication, six patients (4.6%) suffered a new osteoporotic fracture, comprised of 3 vertebral fractures (1 multiple) and 3 nonvertebral fractures (1 contralateral hip, 1 proximal humerus, and 1 distal radius) as a result of a fall. There were no cases of atypical femoral fracture or osteonecrosis of the jaw, or serious adverse events of fracture healing complications, myalgia, eczema, or hypersensitivity.

At the final follow-up, the overall L-BMD and H-BMD were significantly increased compared with pretreatment levels after 12 months of denosumab treatment (5.7% and 2.5%, respectively). Nonresponders (19.2%) had mean BMD change = 0.2% after 12 months of denosumab treatment. The percent change in L-BMD between non-responders and responders was highly significant (p < 0.001) (Fig 2). The percent change in H-BMD between non-responders and responders was also significant (p = 0.02) (Table 2).

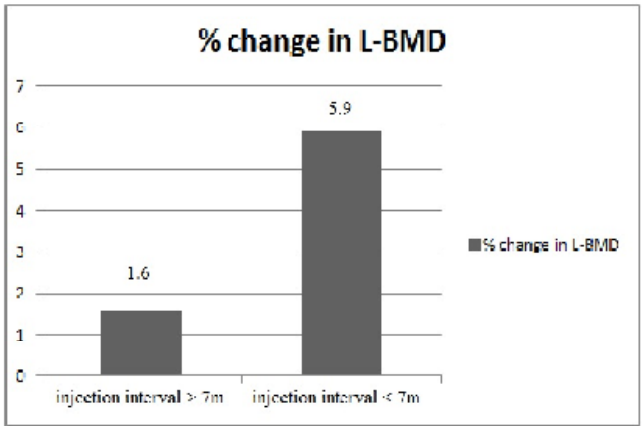

Fig. 2. — BMD increase at the lumbar spine according to the adherence (injection interval) after denosumab treatment.

DISCUSSION

Currently, treatment with osteoporosis medication is strongly recommended in patients with hip fracture to prevent subsequent fractures[13]. Denosumab is an effective antiresorptive drug commonly prescribed for the treatment of osteoporosis. However, our clinical experience suggests that many patients may be non-responders, raising questions as to the true efficacy of denosumab in improving BMD in osteoporotic patients. The main finding of our study is that a longer interval between denosumab injections was associated with suboptimal BMD response in elderly patients with hip fractures.

Denosumab, a human monoclonal antibody, is administered subcutaneously every 6 months for the treatment of postmenopausal osteoporosis and it is an effective antiresorptive drug commonly prescribed. Preference and adherence to Denosumab treatment were assessed in various clinical trials. A large phase 3 randomized, placebo-controlled trial showed that denosumab 60 mg every 6 months significantly increased BMD over 24 months[8]. However, in real-world clinical settings, not every patient receiving denosumab shows a significant increase in BMD. Several factors associated with BMD increase have been previously reported with osteoporosis treatment. With respect to age, there may be a tendency that nonrespondents are somewhat older than respondents, although the literature is inconsistent on the role of age[14,15]. Obermayer-Pietsch et al showed that the effects of daily teriparatide treatment on BMD were greater in older patients[10]. Marcus et al[16] reported that the skeletal response to teriparatide is largely independent of age and initial BMD in postmenopausal women with osteoporosis. Bisphosphonate has also been shown to reduce vertebral fractures to a similar degree in osteoporotic patients in diverse age groups (i.e., <65 years of age and ≥65 years of age)[17]. Similarly, in the current study, age had no effect on the degree to which denosumab enhanced BMD.

Prior osteoporosis therapies may affect the skeletal response to denosumab. It has been reported that prior bisphosphonate treatment, especially alendronate, is significantly associated with LS BMD absolute response to daily teriparatide treatment in patients with osteoporosis[10]. Carmel et al[9] also found prolonged duration of bisphosphonate therapy was associated

with significantly increased odds of non-response. To confirm whether nonresponse to denosumab was associated with prior osteoporosis therapies, we included patients with prior anti-osteoporosis medications which means that there were patients with severe osteoporosis in the present study. Interestingly, prior bisphosphonate use lost its correlation with subsequent BMD increase in the multiple regression models in our study. There are a few reports about the effectiveness of denosumab in patients who were treated previously with bisphosphonates[18,19]. Mok et al[20] observed that compared to the continuation of the bisphosphonates, switching to denosumab was associated with a greater increase in the lumbar spine BMD. In contrast, Suzuki et al[21] reported that switching bisphosphonates to denosumab did not significantly improve the lumbar spine BMD suggesting that the therapeutic effect of denosumab might be limited by prior bisphosphonate treatment. There has been no systematic analysis to investigate the clinical determinants associated with nonresponse to 6-month denosumab treatment, especially in elderly patients with hip fractures. It the present study, prior bisphosphonate therapy had only a modest effect on increases in BMD (p=0.065).

In most of the clinical trials of osteoporosis treatment, it has been suggested that an adequate calcium, with or without vitamin D, is necessary to enable the optimal increase in bone density to occur[22]. Vitamin D insufficiency is also an important potential cause of a failure to respond to osteoporosis treatment. Carmel et al[9] reported that patients with a mean 25(OH)D ≥33 ng/ml had a substantially greater likelihood of maintaining bisphosphonate response. In addition, significantly greater increases in lumbar spine and femoral neck BMD were observed in the vitamin D replete group after 12 months' treatment with cyclical etidronate[23]. These studies suggest that calcium and vitamin D supplementation may be useful in patients who fail to respond to bisphosphonates. This is also likely to be the case for denosumab, but there is no definite evidence to confirm this. In the current study, we could not prove that clinical response to denosumab could in part be dependent on circulating vitamin D. Overall, the role and importance of vitamin D in osteoporosis outcomes may be considered controversial.

It has been already demonstrated that appropriate adherence (timely denosumab injection) was associated with greater annualized BMD response at both the lumbar spine and the total hip[7]. Discontinuation of denosumab or unintended delay may lead to a rapid reversal of its therapeutic effect[24]. The reasons for non-adherence have been demonstrated to be multifactorial and differ between various medications[25]. In case of denosumab, because its administration requires an appointment with the health care system, delays may be unavoidable in routine clinical practice. In addition, during the COVID-19 pandemic, another possible reason for this could be that the patients and their families did not want to go to the hospital for second injection because they were afraid that they would probably be exposed to COVID 19 infection. Physicians should keep these results in mind in clinical practice so that they can improve the effect of 6-month denosumab therapy to treat osteoporosis especially in elderly patients after hip fracture.

One thing should be noted that occasional apparent failures of BMD response in patients receiving anti-osteoporosis medication are probably not due to failure of response at the level of the bone remodeling apparatus, but instead reflect a combination of measurement imprecision and variable bone remodeling balance[26].

There are several limitations to the current study. First, this was a retrospective study with all the inherent weaknesses and our sample size was small, which could limit its statistical power. There were differences in total injections given and duration of follow-up between two groups. Even though the statistics in our study revealed significant differences in BMD increase according to denosumab adherence, our analyses might have been underpowered. Due to a higher level of dependence, the presence of comorbidities, and a low follow-up rate, there are as yet very few specific data from a 1-year follow-up in frail, elderly subjects with a hip fracture. A randomized controlled trial is the gold standard for evaluating the efficacy of interventions. However, a randomized controlled trial is not feasible in the case of denosumab dosing delay. Second, in routine medical practice, the background of patients may vary more widely than that in the patients of this study. For instance, there are a number of potential causes of unknown secondary osteoporosis. Future prospective, multicenter research with long term follow-up is required to identify the reasons behind nonresponse and to improve response to anti-osteoporosis medications.

CONCLUSION

In conclusion, in the present study, 19.8 % of the patients did not achieve an adequate response in the BMD after 12 months of denosumab treatment. As a longer interval between denosumab injections was associated with suboptimal BMD response at both spine and total hip in the current study, we believe that timely

administration of denosumab is imperative in real-world settings. However, because patient compliance, preference, and adherence are complex, methods to increase adherence beyond dosing schedules should be further investigated.

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