ORIGINAL ARTICLE

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Subgroup Variations in Bone Mineral Density Response to Zoledronic Acid After Hip Fracture

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ABSTRACT

Minimizing post-fracture bone loss is an important aspect of recovery from hip fracture, and determination of factors that affect bone mineral density (BMD) response to treatment after hip fracture may assist in the development of targeted therapeutic interventions. A post hoc analysis of the HORIZON Recurrent Fracture Trial was done to determine the effect of zoledronic acid (ZOL) on total hip (TH) and femoral neck (FN) BMD in subgroups with low-trauma hip fracture. A total of 2127 patients were randomized (1:1) to yearly infusions of ZOL 5 mg ($n = 1065$) or placebo ($n = 1062$) within 90 days of operation for low-trauma hip fracture. The 1486 patients with a baseline and at least one post-baseline BMD assessment at TH or FN (ZOL = 745, placebo = 741) were included in the analyses. Percentage change from baseline in TH and FN BMD was assessed at months 12 and 24 and compared across subgroups of hip fracture patients. Percentage change from baseline in TH and FN BMD at months 12 and 24 was greater ($p < 0.05$) in ZOL-treated patients compared with placebo in most subgroups. Treatment-by-subgroup interactions ($p < 0.05$) indicated that a greater effect on BMD was observed for TH BMD at month 12 in females, in patients in the lower tertile body mass index at baseline ($\leq$22.6 kg/m^2), and in patients with baseline FN BMD *T*-score of ≤ -2.5; for FN BMD in patients who received ZOL for >6 weeks post-surgery; and for TH and FN BMD in patients with a history of one or more prior fractures. All interactions were limited to the first 12 months after treatment with none observed for the 24-month comparisons. (Clinical trial registration number NCT00046254.) © 2014 American Society for Bone and Mineral Research.

KEY WORDS: CLINICAL TRIALS; OSTEOPOROSIS; INJURY/FRACTURE HEALING; FRACTURE PREVENTION; ANTIRESORPTIVES

Introduction

Hip fractures are associated with increased mortality and morbidity, as well as costly hospitalization and lengthy rehabilitation.[1,2] In a previous investigation, the rate of subsequent fracture in hip fracture survivors was found to be 10.4 fractures/100 persons per year, which was 2.5 times higher than the age-matched subjects without previous hip fracture.[3] This high fracture rate may be attributable in part to rapid decreases in bone mineral density (BMD) and muscle mass occurring during the first year after fracture.[4–8] In another prospective study, a mean decrease of 5.4% in the contralateral femoral neck (FN) BMD and 2.9% in the lumbar spine BMD was reported during the first year after a hip fracture.[5] Several other studies have also reported a precipitous loss of BMD during the year after a fracture and lower BMD in hip fracture patients compared with age-matched controls.[4,9–14] Thus, minimizing post-fracture bone loss is an important aspect of comprehensive post-hip fracture care, and determination of factors that prevent loss or produce increases in BMD after fracture may assist in the development of therapeutic interventions, particularly among those at greatest risk.

Clinical practice guidelines recommend osteoporosis evaluation and treatment of adults with minimal-trauma hip fracture in an effort to prevent subsequent fractures; however, studies suggest that adults with hip fractures rarely receive bone-protective therapies.[15,16] Bisphosphonates, which inhibit osteoclast activity, are the most commonly used medications for the treatment of osteoporosis.[17,18] Zoledronic acid (ZOL), a bisphosphonate that can be administered as a 15-minute annual

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infusion, has demonstrated suppression of bone turnover markers and increases in BMD in postmenopausal women comparable to those achieved with daily oral bisphosphonates.[19] Authorities in both the US (Food and Drug Administration [FDA]) and the EU (European Medicines Agency [EMA]) have approved ZOL for use in both men and women with osteoporosis. EU approval for use of ZOL in men was based on findings from the HORIZON Recurrent Fracture Trial (RFT), a study involving more than 2100 men and women aged ≥50 years with a recent low-trauma hip fracture that had been surgically repaired.[20] Here, single yearly infusion of ZOL 5 mg was associated with a 35% risk reduction in all clinical fractures ($p = 0.001$) along with significant increases in total hip (TH) and FN BMD compared with placebo.[20]

Although prior analysis of HORIZON-RFT data showed no clinically significant differences in the fracture reduction benefit across important subgroups, the study was not powered nor was it prespecified to examine efficacy for fracture reduction in patient subgroups. It was expected based on the increases in BMD observed in other studies[20,21] that there would be large differences in the effect on BMD between the treatment groups; thus, a post hoc analysis of HORIZON-RFT was performed to evaluate the effect of ZOL on TH and FN BMD in different subgroups of patients (age, sex, race, region, baseline body mass index [BMI], hip fracture location, baseline *T*-score at FN, fracture history, time to first infusion after hip surgery, baseline serum calcium, prior osteoporotic medications, cognitive status, and mobility problems prefracture) to determine if ZOL is equally beneficial in subgroups of hip fracture patients more than 2 years after hip fracture.

Materials and Methods

In this multicenter, randomized, double-blind, placebo-controlled trial, men and women aged ≥50 years were eligible for inclusion within 90 days after operation for a minimal-trauma hip fracture (ie, a fall from standing height or lower). Additional enrollment criteria included being ambulatory before the hip fracture and having both legs. Patients were enrolled from 24 countries across North America, South America, and Europe and were from a variety of cultural, ethnic, and racial groups. Exclusion criteria included previous hypersensitivity to a bisphosphonate, a calculated creatinine clearance of <30 mL/min, a serum calcium level of >11.0 mg/dL (2.8 mmol/L), or a corrected serum calcium level of <8 mg/dL (2 mmol/L) at screening and/or randomization, active cancer, metabolic bone disease other than osteoporosis, and a life expectancy of less than 6 months.[20,22]

Eligible patients were randomized (1:1) to receive either ZOL or placebo intravenously over 15 minutes within 90 days after operation for a hip fracture and every 12 months thereafter for up to 3 years. Patients also received a loading dose of vitamin D_3 or D_2 (50,000 to 125,000 IU orally or intramuscularly) 14 days before the first infusion of the study drug, and thereafter received daily oral calcium (1000 to 1500 mg) and vitamin D (400 to 800 IU) supplements during the study period.

Patients were followed up every 3 months for up to 3 years. The study was considered completed when 211 patients had reached the adjudicated primary endpoint of a new clinical fracture or until the last patient had made a month 36 visit, whichever occurred first. The study was conducted in compliance with the ethical principles of the Declaration of Helsinki (1989) and local applicable laws and regulations. Approval was obtained from an Institutional Review Board or Independent Ethics Committee for each participating study center. All patients provided a written informed consent before participating in the study.

BMD measurements

BMD of the TH and FN was measured using dual-energy X-ray absorptiometry (DXA) of the contralateral nonfractured hip in all patients at randomization, and at months 12, 24, and 36. DXA measurements were performed within 4 weeks of the scheduled visit date. Additional measurements were performed if the decrease from baseline in TH BMD was >8% at month 12 and >10% at month 24. BMD measurements were performed on the same machine at the same center for each patient over time, and they were entered into the clinical report forms by the investigators. Sites completed standard quality-assurance procedures on their machines every 12 months. BMD was adjusted to correct for brand variations of the imaging equipment, and *T*-scores were further adjusted for the difference in sex, using female and male reference data, respectively.[23,24]

Subgroups compared

The subgroups evaluated for change in TH and FN BMD in response to ZOL treatment were age (<65 years, 65 to 74 years, ≥75 years), sex (men, women), race (white, other), region (North America/Oceania, Latin America, Western Europe, and Eastern Europe), BMI (lower tertile [≤22.6 kg/m^2], middle tertile [>22.6 to 26.3 kg/m^2], upper tertile [>26.3 kg/m^2]), baseline *T*-score at contralateral FN (≤ −2.5, > −2.5 to ≤ −1.0 and > −1.0), entry hip fracture location (intertrochanteric, FN), fracture history (hip fracture only, hip fracture + one or more other nonvertebral and vertebral fractures), time to receiving first infusion of the study drug after hip fracture surgery (≤6 weeks, >6 weeks), baseline calcium levels (<8.5 mg/dL, ≥8.5 mg/dL), prior use of osteoporosis medications (yes/no), Charlson comorbidity index (≤2, 3, ≥4), the mobility item from the EQ-5D profile (none versus some or extreme problem),[25,26] and mental status determined by "The Short Portable Mental Status Questionnaire" (SPMSQ) (0 to 2, >2).[27]

Statistical analysis

The Data and Safety Monitoring Committee recommended study close-out because it was determined that the requisite 211 clinical fracture endpoints would be met within the 90-day close-out time frame. At the end of study close-out, a total of 231 patients had confirmed clinical fractures and the total duration of the study was 60 months with a median follow-up time of 1.9 years. Because of the event-driven design of the trial, only about 15% of patients had available data at month 36; consequently, month 36 data was excluded from the subgroup analyses. The present analysis was restricted to patients who had a baseline and at least one post-baseline BMD assessment. For the percentage change in TH and FN standardized BMD relative to baseline at months 12 and 24, the effect of ZOL in each subgroup was evaluated using the analysis of variance (ANOVA) models, with treatment and geographic region as the explanatory variables. The robust effect of ZOL across different subgroups (treatment-by-subgroup interaction) was evaluated using ANOVA model with treatment, geographic region, subgroup, and treatment-by-subgroup interaction. In addition, as a sensitivity analysis, the effect of ZOL in each subgroup and the consistent effect of ZOL across different subgroups were evaluated using a random-effects model with treatment, baseline BMD, age, sex, time (in days), BMD dropout status before month 24, treatment

Table 1. Demographics and Baseline Characteristics of the Patient Subgroups

Characteristic	Treatment	
	Zoledronic acid ($n = 745$)	Placebo ($n = 741$)
Age (years), mean (SD)	73.1 (9.19)	73.3 (9.63)
Age groups, *n* (%)		
<65 years	140 (18.8)	149 (20.1)
65–74 years	238 (31.9)	214 (28.9)
≥75 years	367 (49.3)	378 (51.0)
Sex, *n* (%)		
Men	171 (23.0)	176 (23.8)
Women	574 (77.0)	565 (76.2)
Race, *n* (%)		
White	679 (91.1)	670 (90.4)
Hispanic	50 (6.7)	51 (6.9)
Black	3 (0.4)	5 (0.7)
Other	13 (1.7)	15 (2.0)
Region, *n* (%)		
North America	154 (20.7)	179 (24.2)
Latin America	98 (13.2)	93 (12.6)
Western Europe	287 (38.5)	265 (35.8)
Eastern Europe	206 (27.7)	204 (27.5)
Baseline BMI (kg/m^2), mean (SD)	24.9 (4.19) ($n = 731$)	25.2 (4.22) ($n = 729$)
Baseline *T*-score at femoral neck, *n* (%)		
<−2.5	336 (45.1)	330 (44.5)
−2.5 to −1.0	371 (49.8)	369 (49.8)
>−1.0	36 (4.8.)	36 (4.9)
Missing	2 (0.3)	6 (0.8)
Entry hip fracture location, *n* (%)		
Femoral neck	428 (57.4)	439 (59.2.5)
Intertrochanteric	232 (31.1)	211 (28.5)
Subtrochanteric	32 (4.3)	401 (5.4)
Other	53 (7.1)	51 (6.9)
Fracture history, *n* (%)		
Hip fracture only	425 (57.0)	471 (63.6)
Hip + other nonvertebral fractures	261 (35.0)	228 (30.8)
Hip + 1 vertebral fractures	23 (3.1)	23 (3.1)
Hip + nonvertebral + vertebral fractures	36 (4.8)	19 (2.6)
Time-to-first-infusion from hip surgery (days), *n* (%)		
≤6 weeks	307 (41.2)	328 (44.3)
>6 weeks	437 (58.7)	413 (55.7)
Baseline serum calcium level, *n* (%)		
<8.5 mg/dL	47 (6.3)	56 (7.6)
≥8.5 mg/dL	693 (93.0)	682 (92.0)
Prior use of osteoporosis medications, *n* (%)		
No	713 (95.7)	707 (95.4)
Yes	32 (4.3)	34 (4.6)
Bone mineral density (g/cm^2), mean (SD)		
Total hip	0.7 ± 0.15 ($n = 707$)	0.7 ± 0.15 ($n = 701$)
Femoral neck	0.7 ± 0.11 ($n = 743$)	0.7 ± 0.12 ($n = 735$)
EQ-5D$_{profile}$-mobility, *n* (%)		
Walking	156 (20.9)	178 (24.0)
Some walking	559 (75.0)	532 (71.8)
Mental status (baseline SPMSQ scores), *n* (%)		
0–2	611 (82.1)	600 (81.0)
>2	89 (11.9)	104 (14.0)
Charlson comobility score, *n* (%)		
≤2	209 (28.1)	202 (27.3)
3	263 (35.3)	242 (32.7)
≥4	272 (36.5)	297 (40.1)

SD = standard deviation; BMI = body mass index; BMD = bone mineral density; SPMSQ = short portable mental status questionnaire.

by time, dropout by treatment, dropout by time, and dropout by time by treatment interactions as fixed effects, random time effect with unstructured covariance. Because these ad hoc analyses were conducted after the database lock, all confidence intervals for the treatment difference were nominal at the 95% level without adjustment for multiple comparisons.

Results

Baseline characteristics

Of the 508 men and 1619 women aged 50 years and older who were included in the main study, 347 (68%) men and 1139 (70%) women qualified for this analysis. At baseline, the average age of participants was 73 years with a mean BMI of 25 kg/m^2; approximately 90% of the patients were white. Forty-five percent of participants had a baseline FN BMD *T*-score of ≤ −2.5 and 40% had a history of prior fractures. The Charlson comorbidity score is greater than two in 72% of patients, indicative of a population with multiple medical conditions other than their hip fracture.

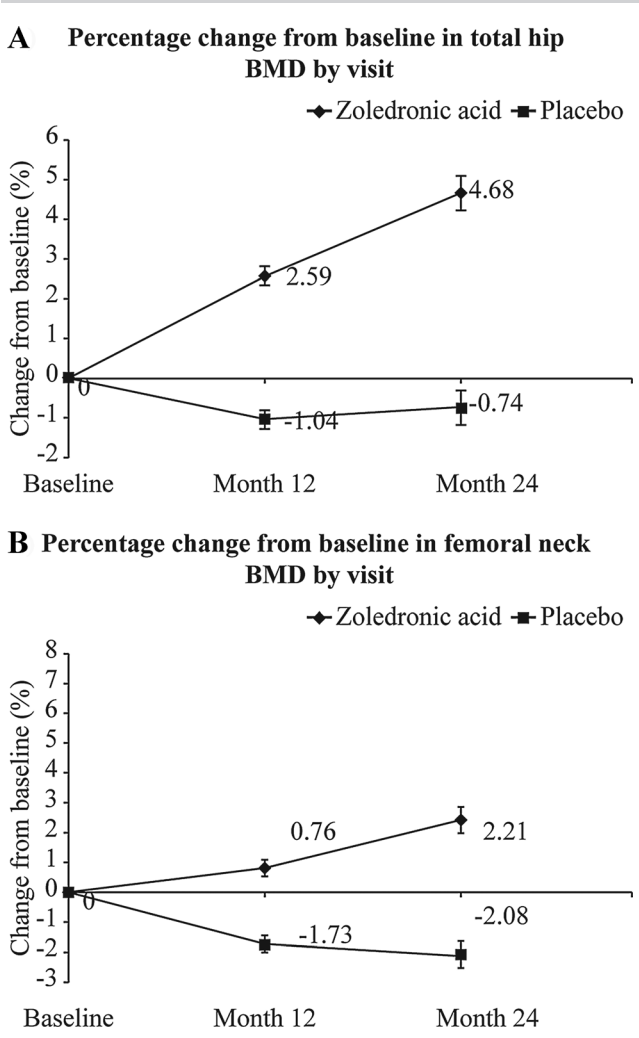

Fig. 1. Percentage change from baseline in total hip and femoral neck BMD over 2 years. Percentage change from baseline in total hip (*A*) and femoral neck BMD (*B*) by visit. The data represent percentage change in least square mean (± SE) at months 12 and 24 for ZOL and placebo. BMD = bone mineral density; ZOL = zoledronic acid.

Demographic and baseline characteristics of various subgroups were comparable between the two treatment groups (Table 1).

TH and FN BMD

As reported previously for the full 36-month follow-up,[20] the ZOL treatment group showed a significant gain in TH and FN BMD over 2 years compared with placebo (Fig. 1). The treatment differences in TH BMD were 3.6% and 5.4% at months 12 and 24, respectively, and 2.5% and 4.3%, respectively, for FN BMD, with greater increases in the ZOL group compared with placebo.

Subgroup analysis

In this post hoc analysis, greater improvements in TH and FN BMD were noted at months 12 and 24 in all the subgroups treated with ZOL compared with placebo (Fig. 2 and Fig. 3). The improvement was statistically significant at the nominal 5% level without multiplicity adjustment for the majority of subgroups. Regarding TH BMD, at month 12, significant variability was found in the treatment difference for subgroups by sex, baseline BMI, baseline *T*-score at FN, fracture history, and time to first infusion after hip surgery, as indicated by the subgroup by treatment interaction p values ($p < 0.05$). However, the difference in subgroup levels was not more than 2.7 percentage points in any of the subgroups with treatment-by-factor interactions with nominal p values < 0.05. No treatment-by-factor interactions with nominal p value < 0.05 were observed at month 24 in any subgroup.

Regarding FN BMD, at month 12, treatment-by-factor interactions with nominal p value < 0.05 were observed for the fracture history and time-to-first-infusion subgroups. The maximum between-treatment difference for fracture history was only 1.8 percentage points. For the time-to-infusion subgroup, the treatment-by-factor interaction was driven by the more than sixfold greater effect observed when the first infusion was administered more than 6 weeks after hip fracture repair (3.9%) versus when the first infusion was administered, 6 weeks or sooner, after hip fracture repair (0.6%). No treatment-by-factor interactions were observed at month 24.

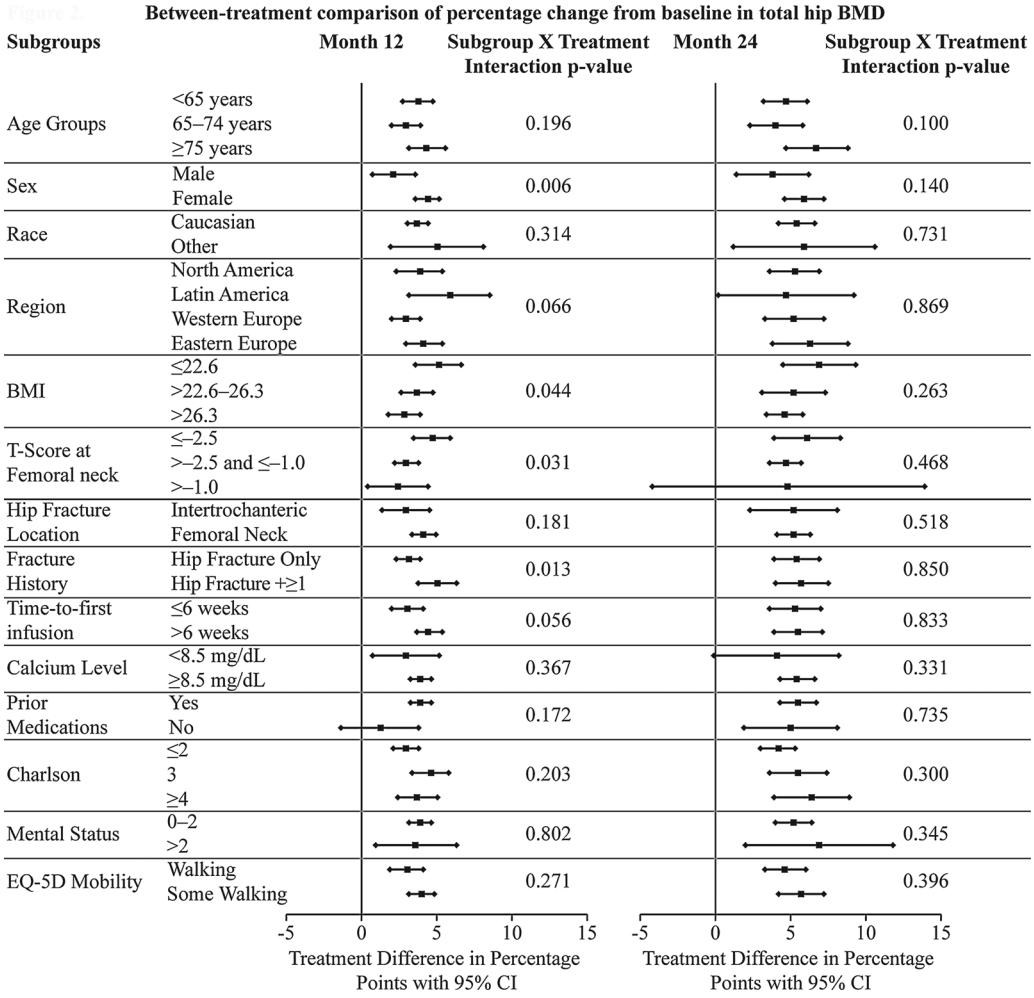

Fig. 2. Between-treatment comparison of percentage change from baseline in total hip BMD. The square data point represents treatment difference and the endpoints represent the 95% CI values. Each subgroup has a corresponding subgroup X treatment interaction *p*-value. BMD = Bone mineral density; BMI = Body mass index

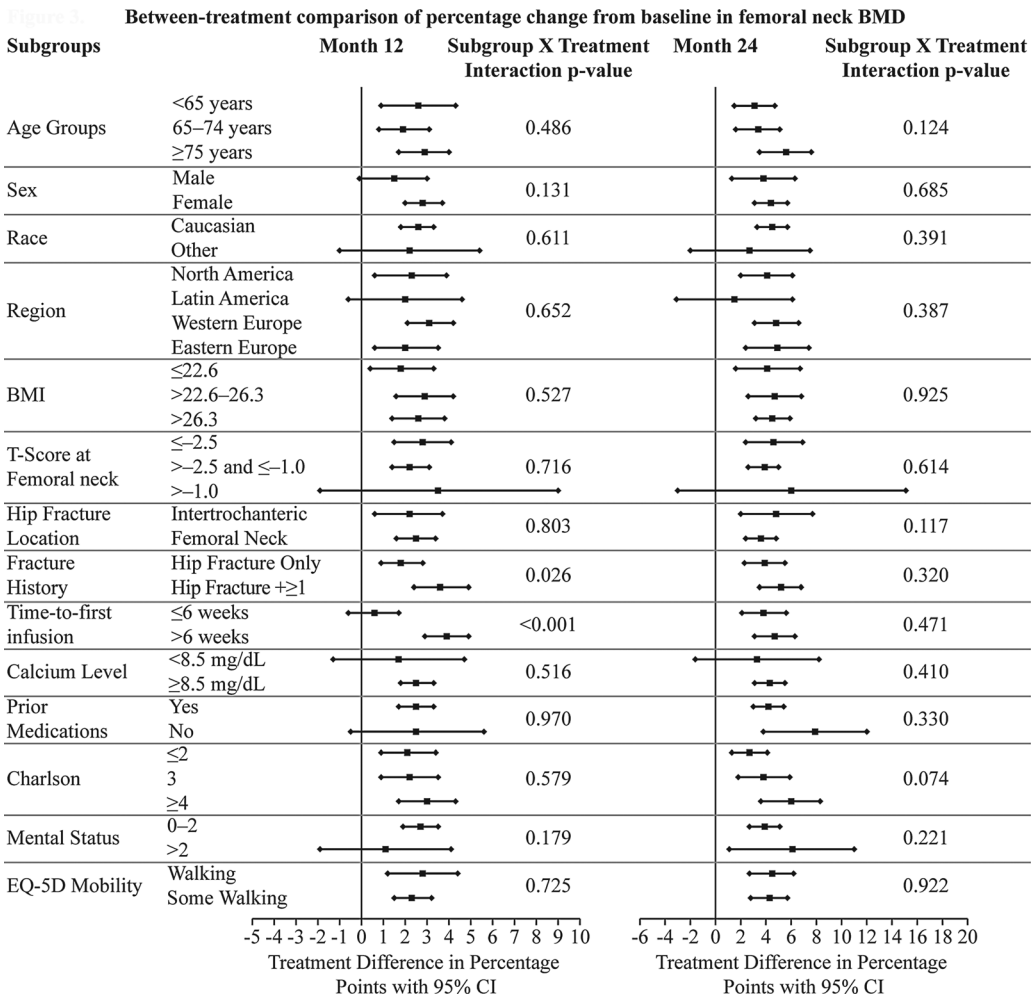

Fig. 3. Between-treatment comparison of percentage change from baseline in femoral neck BMD. The square data point represents treatment difference and the endpoints represent 95% CI values. Each subgroup has a corresponding subgroup X treatment interaction *p* value. BMD = bone mineral density; BMI = body mass index.

Sensitivity analyses

Analyses using random-effect models showed results that were in general consistent with Figs. 2 and 3 and indicate that the findings were robust to different statistical methods.

Safety results

Adverse events were not analyzed separately for the subgroups reported here. The incidence of adverse events in the overall population has been previously reported to be comparable between ZOL and placebo, except for a higher incidence of deaths in the placebo group (ZOL 9.6% versus placebo 13.3%).[20]

Discussion

Hip fracture is a major public health problem, and the absolute number of hip fractures is anticipated to increase over the next several decades in light of the fact that there will be more older persons at risk of fracture worldwide,[28,29] despite a reduced incidence or proportion who have had fractures in many countries over the past one to two decades.[30–33] Substantial loss of BMD and muscle mass of the affected and contralateral hip is common within 1 year after hip fracture.[4] However, increase in BMD with pharmacological interventions given after hip fracture is associated with a major reduction in the risk of subsequent fractures.[34] HORIZON-RFT, the study on which this post hoc analysis was based, demonstrated a 35% risk reduction of subsequent clinical fractures, 28% reduction in deaths, and a significant improvement in TH BMD and FN BMD in patients administered ZOL up to 90 days after operation for hip fracture compared with placebo.[20] Despite known benefits of pharmacological interventions in reducing risk of subsequent clinical fractures, only a small percentage of patients who experienced a prior hip fracture (45% of whom had a *T*-score < -2.5 when tested before randomization) had a history of prior osteoporotic treatment (4% to 5%) (Table 1). Reasons for lack of treatment vary, and future efforts need to be directed at understanding and addressing possible patient-, provider-, and health system-level factors responsible for not treating these osteoporotic patients.[35–38]

This post hoc analysis is the first of its kind to analyze the TH and FN BMD responses to ZOL treatment versus placebo in a wide range of hip fracture patient subgroups. The results of this analysis demonstrate that in a population of patients after an

incident hip fracture, ZOL improves TH and FN BMD in nearly all the subgroups compared with placebo. Although slightly higher improvements in BMD at 12 months with ZOL treatment were noted in some subgroups (females, lower tertile BMI, BMD *T*-score ≤ -2.5, history of hip fracture $+\geq 1$ fractures, ZOL infusion >6 weeks), the interactions between subgroup characteristics and treatment were nonsignificant at 24 months and not clinically relevant for percentage changes in TH and FN BMD. With the exception of time until infusion ≤ 6 weeks for FN BMD, where those receiving infusion earlier did not demonstrate a positive effect, the smaller differential effects by subgroup were always themselves significantly different from zero in a positive direction. Therefore, although the response of BMD to ZOL attributable to timing of infusion or membership in a specific subgroup may have differed modestly after the first dose, the differential effect was negligible after the second dose. It also is notable that in a previous post hoc analysis of these data we found a suggestion of a reduced effect on BMD and efficacy (with respect to survival and fracture reduction) in those infused within 2 weeks of their fracture repair, with relative benefit to all others.[39] Whether the subgroup receiving ZOL earlier than 6 weeks should have had a second dose sooner than a year later or whether all doses should be delayed until at least 6 weeks have not been adequately studied; however, it appears that delaying the administration of ZOL for 2 or more weeks after fracture is effective in reducing subsequent fracture.[39]

In conclusion, a yearly ZOL 5-mg infusion demonstrated similar effects in terms of greater improvements in TH and FN BMD versus placebo over 2 years in the patient subgroups who sustained hip fracture. Our findings in this comparatively older and less healthy subpopulation who have already sustained a hip fracture offer further evidence of the beneficial effects of ZOL in improving BMD regardless of patient demographics and baseline characteristics.

Disclosures

JSM received consulting fees from Amgen, Ammonett, Merck, Eli Lilly, OrgaNext, Regeneron, GTx, Sanofi, and Novartis and grant support through the University of Maryland from Novartis, Eli Lilly, and Merck. He received support for travel to steering committee meetings from Novartis and payment for lectures from Novartis, Pfizer, and Merck. He served on the advisory board for Ammonett, Glaxo SmithKline, American Orthopedic Association, and Amgen. DLO received consulting fees from Eli Lilly and Ammonett and grant support from Novartis. KWL received grant support from Novartis, Amgen, and Kirin pharmaceuticals and consulting fees from Novartis, Amgen, and University of California, Berkeley. He is listed as an inventor on a U.S. patent application (20050272707) covering methods for preventing or reducing secondary fractures after hip fracture and on another provisional patent application for medication kits and formulations for preventing, treating, or reducing secondary fractures after a previous fracture. LN received grants from the Norwegian health authority South-East, travel grant from Novartis steering committee, consulting fee from Novartis, advisory board fees from Eli Lilly, Biomet and DePuy, and lecture fees from Novartis. SB received consulting fees and research support from Novartis. JDA received consulting fees from Amgen, Eli Lilly, Merck, Novartis, and Warner Chilcott and grant support from Amgen, Eli Lilly, Merck, and Novartis. CR received support for travel from United Osteoporosis Centers. CSC-E received consulting fees from Novartis and Amgen, and research grants from Novartis. She is the inventor on two provisional U.S. patent applications related to the use of bisphosphonates for cardiovascular indications and the co-owner of Biscardia, Inc. PM, CB-R, and GS are employees of and own stock in Novartis. CFP and RJ state that they have no conflicts of interest.

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Authors' roles: Conception and design: JSM, KWL, PM. Analysis and interpretation of the data: PM, GS, CBR. Drafting of the article: JSM. Critical revision of the article for important intellectual content: JSM, DLO, KWL, LN, SB, JDA, CR, CSC-E, PM, CR, GS, RJ, and CFP. Final approval of the article: JSM, DLO, KWL, LN, JDA, CR, CSC-E, PM, CB-R, GS, RJ, and CFP. Provision of study materials or patients: JSM, DLO, KWL, LN, SB, JDA, CR, CSC-E, and CFP. Obtaining of funding: KWL. Collection and assembly of data: JSM, PM, CB-R, and GS.

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