Osteoporos Int (2011) 22:2329–2336
DOI 10.1007/s00198-010-1473-1

ORIGINAL ARTICLE

Association between timing of zoledronic acid infusion and hip fracture healing

C. Colón-Emeric · L. Nordsletten · S. Olson · N. Major · S. Boonen · P. Haentjens · P. Mesenbrink · J. Magaziner · J. Adachi · K. W. Lyles · L. Hyldstrup · C. Bucci-Rechtweg · C. Recknor · for the HORIZON Recurrent Fracture Trial

Received: 8 July 2010 / Accepted: 5 October 2010 / Published online: 9 December 2010

Abstract
Summary Patients in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Recurrent Fracture Trial were assessed for evidence of delayed hip fracture healing. No association was observed between zoledronic acid (ZOL) and delayed healing. We conclude that ZOL has no clinically evident effect on fracture healing, even when the drug is infused in the immediate postoperative period.
Introduction Intravenous zoledronic acid 5 mg (ZOL) given after a hip fracture reduces secondary fracture rates and mortality. It has been postulated that bisphosphonates may affect healing if given soon after a fracture. We sought to determine whether the timing of ZOL infusion affected the risk of delayed hip fracture healing.
Methods In the HORIZON Recurrent Fracture Trial, patients were randomized within 90 days of a low-trauma hip fracture to receive either once-yearly ZOL (n=1,065) or placebo (n=1,062). Clinical symptoms of delayed hip fracture healing were sought at randomization, 6 months and 12 months after fracture; if present, a central adjudication committee blinded to treatment assignment reviewed

This study is supported by Novartis Pharma AG.

C. Colón-Emeric · S. Olson · K. W. Lyles
Duke University Medical Center and the Geriatrics Research Education and Clinical Center, Veterans Affairs Medical Center, Durham, NC, USA

L. Nordsletten
Ullevål University Hospital,
Oslo, Norway

N. Major
Hospital of the University of Pennsylvania,
Philadelphia, PA, USA

S. Boonen
Division of Gerontology and Geriatrics, Leuven University,
Leuven, Belgium

P. Haentjens
Centre for Outcomes Research and Laboratory for Experimental Surgery, Universitair Ziekenhuis Brussel, Vrije Universiteit Brussel,
Brussels, Belgium

P. Mesenbrink · C. Bucci-Rechtweg
Novartis Pharmaceuticals,
East Hanover, NJ, USA

J. Magaziner
The University of Maryland,
Baltimore, MD, USA

J. Adachi
McMaster University,
Hamilton, ON, Canada

L. Hyldstrup
Hvidovre Hospital,
Hvidovre, Denmark

C. Recknor
United Osteoporosis Centers,
Gainesville, GA, USA

C. Colón-Emeric (✉)
Duke University Medical Center and the Durham VA GRECC,
508 Fulton St. GRECC 182,
Durham, NC 27705, USA
e-mail: colon001@mc.duke.edu

radiographs and clinical records. Median follow-up was 1.9 years.
Results The overall incidence of delayed healing was 3.2% (ZOL) and 2.7% (placebo; odds ratio [OR], 1.17; 95% confidence interval [CI], 0.72–1.90; p=0.61). Logistic regression models revealed no association between ZOL and delayed healing even after adjusting for other risk factors (OR, 1.21; 95% CI, 0.74–1.99; p=0.44). There was no interaction by timing of infusion, and nonunion rates were similar even when ZOL was given within 2 weeks of hip fracture repair. NSAID use was significantly associated with delayed fracture healing (OR, 2.55; 95% CI, 1.49–4.39; p<0.001).
Conclusions ZOL has no clinically evident effect on fracture healing, even when the drug is infused in the immediate postoperative period.

Keywords Bisphosphonates · Fracture healing · Hip fracture · Timing of infusion · Zoledronic acid

Introduction

Hip fractures are a major source of morbidity and mortality in older adults [1, 2]. Approximately 24% of hip fracture patients die within 1 year of the event, and 20% will suffer an additional osteoporotic fracture in the 2 years following the event [2, 3]. In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Recurrent Fracture Trial (HORIZON-RFT), intravenous zoledronic acid 5 mg (ZOL) given within 90 days of a hip fracture has been shown to reduce the risk of subsequent clinical fractures by 35% and the risk of death by 28% [4].

However, there have been concerns that bisphosphonates might affect fracture healing [5, 6]. The primary action of bisphosphonates is suppression of bone resorption by inhibiting osteoclast formation, which may impact remodeling, bone mineral content, and tensile strength of healing bone [7–10]. Moreover, oral and intravenous bisphosphonates including ZOL appear to be preferentially deposited at the site of an acute fracture, thus increasing the possibility of a clinically significant impact on fracture healing [11, 12]. Delayed hip fracture healing or nonunion occurs in approximately 5% of intertrochanteric and subtrochanteric fractures and up to 36% of femoral neck fractures treated by osteosynthesis, with the incidence increasing with advancing age [13, 14]. Delayed hip fracture union results in substantial excess morbidity and cost. As more hip fracture patients are treated with ZOL or other bisphosphonates, it is important to identify any potential adverse affects on hip fracture healing, especially if the drug is administered soon after the event.

Due to these concerns, a secondary analysis of the HORIZON-RFT trial was planned a priori to examine the risk of delayed fracture healing in patients treated with ZOL compared with placebo. Other preplanned analyses demonstrated that the timing of the infusion was significantly associated with total hip and femoral neck bone mineral density (BMD) change and anti-fracture efficacy [15]. Therefore, we also chose to study the association between timing of ZOL infusion and delayed hip fracture healing in HORIZON-RFT subjects as a post hoc analysis.

Methods

Study design

This was an international, multicenter (148 clinical centers in 23 countries), event-driven, randomized, double-blind, placebo-controlled, parallel-group trial involving subjects with recent hip fractures. Randomization was blocked by center and accomplished through a central interactive voice-response system. The study was registered in ClinicalTrials.gov with the registry identifier NCT00046254. The study was approved by the appropriate Institutional Review Board and was performed according to Good Clinical Practice guidelines.

Study population

Men and women (N=2,127) aged≥50 years were randomized up to 90 days following surgical procedure of a low-trauma hip fracture to receive either once-yearly intravenous ZOL (n=1,065) or placebo (n=1,062). All patients were ambulatory with or without an assistive device prior to the hip fracture, and were unwilling or unable to take an oral bisphosphonate. Patients with previous use of bisphosphonates or teriparatide were enrolled after a washout period that was determined based on their pre-existing usage. Patients were excluded if they were taking oral corticosteroids, had active malignancies, or had a prior lower extremity amputation. For the safety analysis, only the 2,111 patients who received at least one dose of study drug were included.

Treatment

The type of surgical repair and rehabilitation were at the discretion of the treating physician. All patients were given a loading dose of 75,000–125,000 U of vitamin D2 or 50,000–75,000 U of vitamin D3 (intramuscular or oral) and daily oral supplementation of 800–1,200 IU of vitamin D and 1,000–1,500 mg elemental calcium. Concomitant osteoporosis therapy with calcitonin, raloxifene, or hormone replacement therapy was allowed.

Study drug

ZOL 5 mg or placebo infusion was administered within 90 days of the hip fracture repair and every 12 months for a maximum of 3 years. Follow-up visits were conducted at months 6, 12, 24, 36, and study closeout, and telephone interviews were conducted every 3 months starting at month 9.

Fracture healing assessment

All cases of delayed hip fracture healing were confirmed by a central adjudication committee consisting of an orthopedic surgeon, a geriatrician, and a bone radiologist who were blinded to treatment assignment. Potential cases were identified in two ways. First, all subjects were asked if they had continued pain or inability to bear weight on their index hip beginning at randomization and at every study contact throughout the first year. Second, the adverse events and concomitant medication databases were examined quarterly for adverse events and surgical procedures on the index hip using Medical Dictionary for Regulatory Activities and World Health Organization Drug Reference List search terms related to nonunion. After any of these triggers, pre- and postoperative radiographs and clinical notes were examined by the adjudication committee.

Subjects who had a total hip arthroplasty as their primary repair were excluded. Delayed hip fracture union was defined as one or more clinical symptoms (pain, inability to ambulate, and gait disorder) at least 6 weeks after surgical repair plus any one of the following radiographic findings (Fig. 1):

- Persistence of fracture line without change from initial radiograph
- Appearance of a fracture line not initially seen on radiograph in a fracture identified by magnetic resonance imaging, computerized tomography, or bone scan
- Displacement of a fracture not consistent with type of internal fixation
- Lack of callus formation or consolidation of the fracture over at least two cortices.

This clinical and radiographic definition was developed by the adjudication committee in the absence of any established, validated gold standard for the diagnosis of hip fracture delayed union and was based on prior studies [9, 14] and current clinical practice in the United States. Because the radiographic appearance during fracture healing differs by the type of hip fracture, radiographic criteria were chosen to include findings common in each of the major subtypes of hip fractures; impacted femoral neck fractures frequently do not initially have fracture lines visible, and therefore, the second and third criteria were included, while lack of callus formation and persistence of fracture line are more common in intertrochanteric fractures. Because many cases lacked immediate postoperative films, it was not possible to determine loss of fixation except in cases of gross failure; thus, cases were adjudicated either as healed or delayed healing regardless of cause. Two adjudication committee members independently examined the source documents; differences were resolved in committee meetings by consensus. The initial reviewer agreement in a subset of adjudicated cases was 76.5%, with kappa 0.65 (95% confidence interval, 0.26–0.94) indicating "good" level of agreement. Although to our knowledge there is no gold standard with which to formally validate our definition, all patients adjudicated as having a delayed union underwent additional surgical procedures, suggesting agreement with the clinicians caring for the patients.

Statistical analysis

All patients were categorized according to the time between their hip fracture repair and the receipt of their first study drug infusion: within 2 weeks (days 1–14), >2–4 weeks (days 15–28), >4–6 weeks (days 29–42), and >6 weeks (after day 42). Missing values were imputed using the mean of non-missing values in the safety population.

Logistic regression analysis was performed adjusting the treatment effect for the time of first study drug infusion. Within-subgroup comparisons for delayed fracture healing were also performed by timing of first study drug infusion interval. Additional covariates known to be risk factors for delayed fracture healing [16] were evaluated to adjust for baseline imbalances; these included age, sex, race, body mass index (BMI), fracture type (femoral neck versus all others), geographic location (as a surrogate for potential differences in perioperative treatment and rehabilitation), rheumatoid arthritis, diabetes, and nonsteroidal anti-inflammatory drug (NSAID) use.

Source of funding

The study was sponsored by Novartis Pharmaceuticals and was designed in collaboration with faculty at Duke University Medical Center and members of the HORIZON-RFT steering committee. An independent data and safety monitoring board met semi-annually to oversee study conduct and safety. Primary study data analysis was performed by the sponsor and independently confirmed by the coordinating center at the University of California, San Francisco. The present data analysis was performed by the sponsor and analyzed in collaboration with the Steering Committee members.

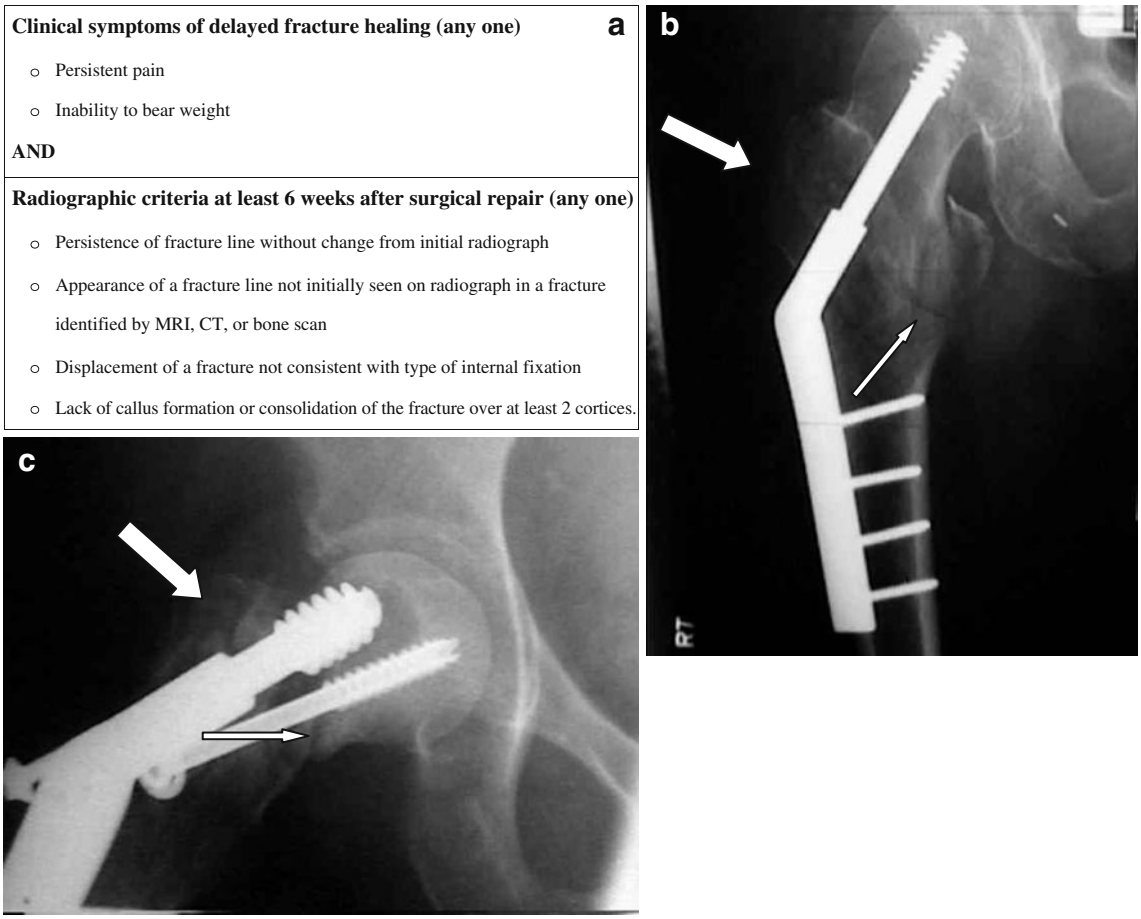


Fig. 1 **a** (*Box*) Adjudication criteria for delayed fracture healing. **b** AP radiograph of delayed union of intertrochanteric fracture demonstrating persistent fracture line (*thin arrow*) and lack of bridging callus (*thick arrow*). From Wheeless'textbook of Orthopedics, http://www.wheelessonline.com/ortho/intertrochanteric_fractures, permission granted. **c** Frog leg lateral radiograph of delayed union of femoral neck fracture demonstrating persistent fracture line (*thin arrow*) and distraction (*thick arrow*). From Wheeless' textbook of Orthopedics, http://www.wheelessonline.com/ortho/femoral_neck_non_union, permission granted

Results

Baseline characteristics were similar between the ZOL and placebo groups (Table 1). The overall incidence of delayed union of hip fracture in the study population was 34 (3.2%) in the ZOL group and 29 (2.7%) in the placebo group (odds ratio [OR], 1.17; 95% confidence interval [CI], 0.72–1.90; p=0.61). In the ZOL group, 62.2% of the cases of delayed healing occurred in femoral neck fractures compared with 54.8% for the placebo group.

In logistic regression models, only NSAID use (defined as use of any NSAID excluding cyclooxygenase-2 inhibitors after randomization) was significantly associated with delayed fracture healing (OR, 2.55; 95% CI, 1.49–4.39; p< 0.001), and the risk associated with ZOL remained nonsignificant (OR, 1.21; 95% CI, 0.74–1.99; p=0.44; Table 2). The number of patients with concomitant NSAID use was similar between the ZOL and placebo groups (Table 1). Additionally, there was no difference in the rate of delayed fracture healing between the ZOL and placebo groups in either NSAID users (4.66% vs 4.87%; OR, 0.95; 95% CI, 0.53–1.72; p=0.88) or non-NSAID users (2.50% vs 1.24%; OR, 2.04; 95% CI, 0.84–5.42; p=0.12).

Previous analyses demonstrated a numerically smaller improvement in total hip BMD over 12 months when ZOL was administered within 2 weeks of the initial fracture repair and decreased anti-fracture efficacy when ZOL was administered within 2 weeks [15]. Examining the incidence of delayed healing by the time between hip fracture repair and infusion, ZOL had a similar incidence of delayed hip fracture healing compared with placebo when the drug was administered early (within 2 weeks; ZOL, 1.8%; placebo, 8.7%; OR, 0.19; 95% CI, 0.01–1.35; p=0.10), between 2 and 4 weeks (ZOL, 3.1%; placebo, 4.0%; OR, 0.78; 95% CI, 0.25–2.40; p=0.67), between 4 and 6 weeks (ZOL, 5.2%; placebo, 3.0%; OR, 1.80; 95% CI, 0.73–4.67; p> 0.20) and after 6 weeks (ZOL, 3.1%; placebo, 2.1%; OR, 1.48; 95% CI, 0.72–3.20; p>0.20) from the surgical repair

Table 1 Baseline characteristics for zoledronic acid- and placebo-treated subjects

	Zoledronic acid N=1,054	Placebo N=1,057	P value
Female (%)	810 (76.8)	796 (75.3)	0.41
Age in years (%)			
<65	172 (16.3)	191 (18.1)	0.25
65–74	305 (28.9)	268 (25.3)	
75–84	440 (41.7)	447 (42.3)	
≥85	137 (13.0)	151 (14.3)	
Race (%)			
Caucasian	962 (91.3)	960 (90.8)	0.76
Others	92 (8.7)	97 (9.2)	
Geographic region (%)			
North America	297 (28.2)	313 (29.6)	0.90
Latin America	132 (12.5)	131 (12.4)	
Western Europe	356 (33.8)	353 (33.4)	
Eastern Europe	269 (25.5)	260 (24.6)	
BMI (kg/m^2)			
<19	79 (7.5)	72 (6.8)	0.90
19–25	502 (47.6)	506 (47.9)	
>25	441 (41.8)	450 (42.6)	
SPMSQ score (%)			
0	524 (49.7)	523 (49.5)	0.78
>0–2	283 (26.9)	285 (27.0)	
>2	168 (15.9)	180 (17.0)	
Missing	79 (7.5)	69 (6.5)	
Femoral neck T-score			
≤−2.5	448 (42.5)	437 (41.3)	0.94
>−2.5 to −1.5	360 (34.2)	374 (35.4)	
>−1.5	122 (11.6)	121 (11.4)	
Missing	124 (11.8)	125 (11.8)	
Hip fracture type (%)			
Intertrochanteric	335 (31.8)	342 (32.4)	0.78
Subtrochanteric	48 (4.5)	57 (5.4)	
Femoral neck	575 (54.6)	584 (55.3)	
Others	76 (7.2)	74 (7.0)	
Prior residence (%)			
Private home	945 (89.7)	928 (87.8)	0.35
Assisted living	60 (5.7)	61 (5.8)	
Skilled nursing facility	31 (2.9)	44 (4.2)	
Others	18 (1.7)	24 (2.3)	
NSAID use	494 (46.87)	493 (46.64)	0.93
Hypertension (%)	543 (51.5)	567 (53.6)	0.34
Diabetes (%)	173 (16.4)	160 (15.1)	0.44
Stroke (%)	181 (17.2)	190 (18.0)	0.65
Coronary artery disease (%)	209 (19.8)	224 (21.2)	0.45
Tachyarrhythmia (%)	61 (5.8)	79 (7.5)	0.14

P value based on Fisher's exact test/chi-square test as applicable

(Fig. 2). Logistic regression models revealed no association between the timing of ZOL infusion and delay in fracture healing (OR, 1.20; 95% CI, 0.74–1.95; p=0.44), even after adjusting for other risk factors.

Discussion

It has long been debated whether bisphosphonates are helpful or harmful in acute fracture healing. Animal

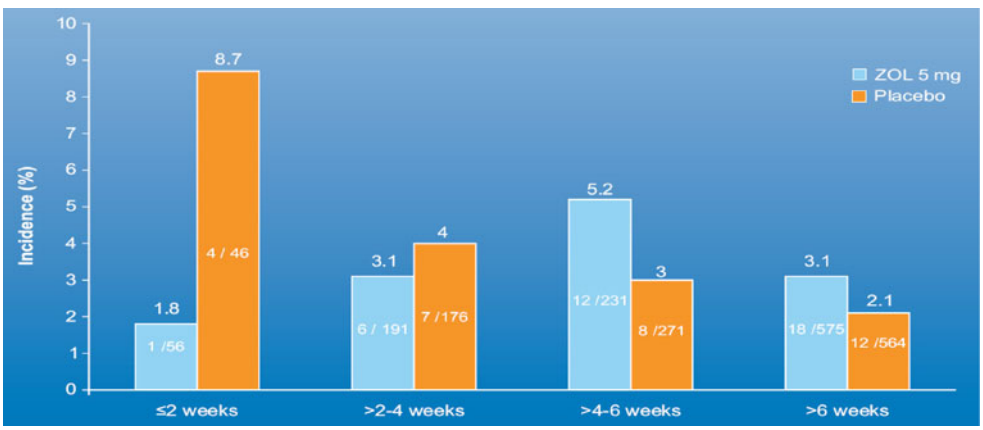
Table 2 Risk of delayed fracture healing from a multivariable logistic regression model.

	Odds ratio	95% confidence interval	*P* value[a]
Zoledronic acid treatment	1.21	(0.74, 1.99)	0.44
Female gender	1.65	(0.97, 2.81)	0.07
NSAID use	2.55	(1.49, 4.39)	<0.01
Diabetes	1.19	(0.63, 2.22)	0.60
Rheumatoid arthritis	1.33	(0.30, 5.64)	0.72
Race	1.42	(0.26, 7.79)	0.68
Femoral neck fracture	1.21	(0.73, 2.00)	0.47
Age	NA	NA	0.59
Geographic region	NA	NA	0.47
BMI	NA	NA	0.19

[a] *P* values derived from logistic regression model adjusting for zoledronic acid treatment, gender, NSAID use, active rheumatoid arthritis (yes/no), active diabetes (yes/no), race, age, geographic region (North America, South America, Western Europe, Eastern Europe), and baseline BMI (<19, 19–25, >25 kg/m^2)

experiments have shown that bisphosphonate treatment during acute fracture results in increased callus size, higher bone mineral content, no change in endochondral ossification, and retardation in callus remodeling [8, 17–19]. Although the suppression of osteoclast activity with supra-therapeutic doses of alendronate was shown to result in poor bone quality by histology in a rat model [10], most animal experiments have demonstrated either no change or improvement in the tensile strength of bisphosphonate-treated bone after experimental fracture [8, 11, 17, 20–22].

On the other hand, the few available studies in humans have reported conflicting results. While oral clodronate and i.v. pamidronate were found to be potentially beneficial in small studies of adults with Colles' fracture [23] and children with osteogenesis imperfecta [24], a recent case–control study of more than 19,000 patients with humerus fractures demonstrated a twofold increased risk of nonunion in those exposed to bisphosphonates postfracture [25]. However, it is likely that patients who are prescribed bisphosphonates differ in important ways from those who are not, and the observed risk increase may be related to these unmeasured confounders, such as BMD or corticosteroid use rather than the bisphosphonate itself. Additional concerns about a bisphosphonate effect on fracture healing have been raised by case series of atypical non-spine fractures seen in patients on long-term bisphosphonate therapy [6, 26–28]. Many of these patients exhibited delayed or absent fracture healing for 3 months to 2 years during therapy. Histomorphometric analysis of the cancellous bone showed markedly suppressed bone formation, with reduced or absent osteoblastic surface. Matrix synthesis was markedly diminished, with absence of double-tetracycline label and absent or reduced single-tetracycline label. The same trend was seen in the intracortical and endocortical surfaces. These cases suggest the possibility that severe suppression of bone turnover may develop during long-term bisphosphonate therapy, resulting in increased susceptibility to and delayed healing of non-spine fractures. However, these case series lack an appropriate comparison group and shed no light on the impact of bisphosphonates on fracture healing in patients without extensive prior use.



Odds ratio (95% CI)	**0.19 (0.01, 1.35)**	**0.78 (0.25, 2.40)**	**1.80 (0.73, 4.67)**	**1.48 (0.72, 3.20)**
P-value	**0.10**	**0.67**	**0.20**	**0.29**

Fig. 2 Delayed hip fracture healing by time between hip fracture surgery and first study drug infusion

In the HORIZON-RFT trial, 2,127 hip fracture patients were randomized to i.v. ZOL or placebo and therefore provided an opportunity to examine the impact of ZOL on the incidence of delayed hip fracture healing in a controlled setting. As subjects received their medication within a 90-day period after the fracture repair, we were also able to study the effect of the timing of infusion on fracture healing outcomes. Other study strengths include the prospective, blinded adjudication of fracture healing. We found no increased risk of delayed fracture healing with ZOL, even when the drug was infused within 2 weeks of the index hip fracture. While the upper 95% CI of our estimate includes the possibility of a clinically important increased risk of delayed healing with ZOL (OR, 1.17; 95% CI, 0.72–1.90), the large and significant benefit of ZOL in both secondary fracture reduction and mortality likely outweighs this smaller possibility of harm. On the other hand, the logistic regression model showed that delayed fracture healing is significantly increased in patients treated with non-selective NSAIDs, adding new information to this controversial issue.

Our study has several limitations. First, case report forms were not designed to capture the type of initial surgical repair performed on the index hip fracture, and thus, we were unable to exclude those who had a hip arthroplasty from the analysis. This likely explains the lower incidence of delayed healing we observed compared with previous reports [9, 14]. Second, there are no universally accepted criteria for diagnosing delayed hip fracture healing, and there is considerable variation in how fracture healing is assessed and managed by orthopedic surgeons [29–31]. Therefore, we used a combination of clinical symptoms and radiographic evidence to adjudicate delayed healing in an effort to standardize the diagnosis across the diverse investigational sites. Third, we did not grade the quality of the initial surgical repair because of the lack of a validated rating system [30]. However, differences in surgical repair are unlikely to have influenced our results since the study was block-randomized by site such that a single surgeon would have equal number of patients in the intervention and control arms, and we corrected for geographical region to mitigate any systematic differences in perioperative management. Similarly, the type of surgical repair was decided by the operating surgeon who was unaware of treatment assignment. Fourth, our data do not allow us to comment on the impact of previous, long-term bisphosphonate use on fracture healing since subjects had limited or no prior exposure to these agents.

In summary, treatment with ZOL following hip fracture repair does not significantly delay fracture healing, even when the drug is infused in the immediate postoperative period. Patients can be treated for osteoporosis with an annual infusion of ZOL 5 mg following hip fracture repair without resulting in the additional morbidity and cost of delayed fracture healing.

Acknowledgements The authors thank Vikrant Pallapotu (MSCD-India, Novartis) and Holly Gilbert-Jones (BioScience Communications) for their editorial assistance.

Conflicts of interest Dr. Colón-Emeric serves as a consultant for Novartis and Amgen. Dr. Nordsletten has no conflicts of interest. Dr. Olson has no conflicts of interest. Dr. Major has no conflicts of interest. Dr. Boonen has received research funding and consulting fees from Novartis. Dr. Haentjens has no conflict of interest. Dr. Mesenbrink is an employee of Novartis and owns stock in the company. Dr. Magaziner serves as a consultant for Novartis, Eli Lilly and Amgen, and has research grants from Novartis and Merck. Dr. Adachi serves as a consultant/advisor for Amgen, Astra Zeneca, Eli Lilly, Glaxo Smith Kline (GSK), Merck, Novartis, Nycomed, Pfizer, Procter & Gamble, Roche, Sanofi-Aventis, Servier, Wyeth, Bristol-Myers Squibb. Dr. Lyles serves as a consultant for Novartis, Procter & Gamble, Merck, Amgen, Kirin Pharmaceutical, GTx, Lilly, GSK, Bone Medical Ltd., Wyeth and Osteologix, and receives research support from Novartis, Alliance for Better Bone Health and Amgen. Dr. Hyldstrup serves as a consultant for Novartis, Nycomed, Unilabs and Amgen.Dr. Bucci-Rechtweg is an employee of Novartis and owns stock in the company. Dr. Recknor serves as a consultant/advisor for Roche, GSK, Lilly, Procter & Gamble, Merck, Novartis, Amgen, NPS and Zelos.

References

1. Magaziner J, Lydick E, Hawkes W, Fox KM, Zimmerman SI, Epstein RS, Hebel JR (1997) Excess mortality attributable to hip fracture in white women aged 70 years and older. Am J Public Health 87:1630–1636
2. Melton LJ III (2003) Adverse outcomes of osteoporotic fractures in the general population. J Bone Miner Res 18:1139–1141
3. Colón-Emeric C, Kuchibhatla M, Pieper C, Hawkes W, Fredman L, Magaziner J, Zimmerman S, Lyles KW (2003) The contribution of hip fracture to risk of subsequent fractures: data from two longitudinal studies. Osteoporos Int 14:879–883
4. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S (2007) Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 357:1799–1809
5. Fleisch H (2001) Can bisphosphonates be given to patients with fractures? J Bone Miner Res 16:437–440
6. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY (2005) Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 90:1294–1301
7. Cao Y, Mori S, Mashiba T, Westmore MS, Ma L, Sato M, Akiyama T, Shi L, Komatsubara S, Miyamoto K, Norimatsu H (2002) Raloxifene, estrogen, and alendronate affect the processes of fracture repair differently in ovariectomized rats. J Bone Miner Res 17:2237–2246
8. Goodship AE, Walker PC, McNally D, Chambers T, Green JR (1994) Use of a bisphosphonate (pamidronate) to modulate fracture repair in ovine bone. Ann Oncol 5(Suppl 7):S53–S55
9. Marsh D (1998) Concepts of fracture union, delayed union, and nonunion. Clin Orthop Relat Res 355:S22–S30

10. Sama AA, Khan SN, Myers ER, Huang RC, Cammisa FP Jr, Sandhu HS, Lane JM (2004) High-dose alendronate uncouples osteoclast and osteoblast function: a study in a rat spine pseudarthrosis model. Clin Orthop Relat Res 425:135–142
11. Amanat N, McDonald M, Godfrey C, Bilston L, Little D (2007) Optimal timing of a single dose of zoledronic acid to increase strength in rat fracture repair. J Bone Miner Res 22:867–876
12. Li J, Mori S, Kaji Y, Kawanishi J, Akiyama T, Norimatsu H (2000) Concentration of bisphosphonate (incadronate) in callus area and its effects on fracture healing in rats. J Bone Miner Res 15:2042–2051
13. Frihagen F, Nordsletten L, Madsen JE (2007) Hemiarthroplasty or internal fixation for intracapsular displaced femoral neck fractures: randomised controlled trial. BMJ 335:1251–1254
14. Rodriguez-Merchan EC, Forriol F (2004) Nonunion: general principles and experimental data. Clin Orthop Relat Res 419:4–12
15. Eriksen EF, Lyles KW, Colón-Emeric CS, Pieper CF, Magaziner JS, Adachi JD, Hyldstrup L, Recknor C, Nordsletten L, Lavecchia C, Hu H, Boonen S, Mesenbrink P (2009) Antifracture efficacy and reduction of mortality in relation to timing of first dose of zoledronic acid after hip fracture. J Bone Miner Res 24:1308–1313
16. Lynch JR, Taitsman LA, Barei DP, Nork SE (2008) Femoral nonunion: risk factors and treatment options. J Am Acad Orthop Surg 16:88–97
17. Boyce RW, Paddock CL, Gleason JR, Sletsema WK, Eriksen EF (1995) The effects of risedronate on canine cancellous bone remodeling: three-dimensional kinetic reconstruction of the remodeling site. J Bone Miner Res 10:211–221
18. Li C, Mori S, Li J, Kaji Y, Akiyama T, Kawanishi J, Norimatsu H (2001) Long-term effect of incadronate disodium (YM-175) on fracture healing of femoral shaft in growing rats. J Bone Miner Res 16:429–436
19. Li J, Mori S, Kaji Y, Mashiba T, Kawanishi J, Norimatsu H (1999) Effect of bisphosphonate (incadronate) on fracture healing of long bones in rats. J Bone Miner Res 14:969–979
20. Amanat N, Brown R, Bilston LE, Little DG (2005) A single systemic dose of pamidronate improves bone mineral content and accelerates restoration of strength in a rat model of fracture repair. J Orthop Res 23:1029–1034
21. Koivukangas A, Tuukkanen J, Kippo K, Jamsa T, Hannuniemi R, Pasanen I, Vaananen K, Jalovaara P (2003) Long-term administration of clodronate does not prevent fracture healing in rats. Clin Orthop Relat Res 408:268–278
22. Peter CP, Cook WO, Nunamaker DM, Provost MT, Seedor JG, Rodan GA (1996) Effect of alendronate on fracture healing and bone remodeling in dogs. J Orthop Res 14:74–79
23. Adolphson P, Abbaszadegan H, Boden H, Salemyr M, Henriques T (2000) Clodronate increases mineralization of callus after Colles' fracture: a randomized, double-blind, placebo-controlled, prospective trial in 32 patients. Acta Orthop Scand 71:195–200
24. Munns CF, Rauch F, Zeitlin L, Fassier F, Glorieux FH (2004) Delayed osteotomy but not fracture healing in pediatric osteogenesis imperfecta patients receiving pamidronate. J Bone Miner Res 19:1779–1786
25. Solomon DH, Hochberg MC, Mogun H, Schneeweiss S (2009) The relation between bisphosphonate use and non-union of fractures of the humerus in older adults. Osteoporos Int 20:895–901
26. Goh SK, Yang KY, Koh JS, Wong MK, Chua SY, Chua DT, Howe TS (2007) Subtrochanteric insufficiency fractures in patients on alendronate therapy: a caution. J Bone Joint Surg Br 89:349–353
27. Kwek EB, Goh SK, Koh JS, Png MA, Howe TS (2008) An emerging pattern of subtrochanteric stress fractures: a long-term complication of alendronate therapy? Injury 39:224–231
28. Lenart BA, Lorich DG, Lane JM (2008) Atypical fractures of the femoral diaphysis in postmenopausal women taking alendronate. N Engl J Med 358:1304–1306
29. Bhandari M, Guyatt GH, Swiontkowski MF, Tornetta P III, Sprague S, Schemitsch EH (2002) A lack of consensus in the assessment of fracture healing among orthopaedic surgeons. J Orthop Trauma 16:562–566
30. Einhorn TA (1998) Breakout session. 1: definitions of fracture repair. Clin Orthop Relat Res 355:S353
31. Hammer R, Hammerby S, Lindholm B (1985) Accuracy of radiologic assessment of tibial shaft fracture union in humans. Clin Orthop 199:233–238