Effect of Denosumab on Fracture Healing in Postmenopausal Women With Osteoporosis: Results From the FREEDOM Trial

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INTRODUCTION

- Fractures are the hallmark of osteoporosis. The occurrence of a fracture provides a unique opportunity to evaluate and initiate therapy for osteoporosis. This opportunity is commonly missed and patients who have suffered an osteoporotic fracture may not receive appropriate therapy despite the obvious risk for subsequent fractures.
- Denosumab, a fully human monoclonal antibody to RANKL, significantly reduces the risk of new vertebral, hip and non-vertebral fractures[1]; and is approved in Europe and the USA for the treatment of osteoporosis in women at increased risk for fracture.
- Denosumab, a simple subcutaneous (sc) therapy, given every 6 months allows for a convenient approach to initiate therapy in those women at the time of a fracture. Therefore, data on the safety of administration of denosumab for osteoporosis at the time or immediately following the fracture is important.

OBJECTIVE

- In a prespecified analysis from the FREEDOM trial, complications related to fracture healing were evaluated for all nonvertebral fractures, including hip fractures
- In a separate distal radius fracture healing sub-study, post-fracture healing was also assessed using serial radiographs

METHODS

Study Design and Patients

- FREEDOM was a 3-year, randomized, double-blind, placebo-controlled trial[2] in 7868 postmenopausal women aged 60–90 years with spine or total hip bone mineral density (BMD) T-scores < –2.5, but not < –4.0 at either site
- Participants were randomized to receive denosumab 60 mg or placebo subcutaneously (sc) every 6 months, and all received daily elemental calcium and vitamin D
  - For those subjects who fractured on study, denosumab was administered according to the scheduled 6-monthly visits, regardless of timing of fracture

Assessments

- Fracture healing complications, including delayed healing and non-union, were documented by the investigator at 6 months post-fracture
- In the distal radius fracture healing sub-study, women who had a distal radius fracture were enrolled and were expected to remain in the study for at least another 3 months
  - Two independent reviewers evaluated antero-posterior and lateral radial X-rays for cortical bridging at 6 weeks, and 3 and 6 months post fracture
  - Delayed healing was defined as lack of complete bridging in any of the visualized cortex surfaces (dorsal, volar, radial or ulnar) at 3 months
  - Non-union status was defined as lack of complete bridging at 6 months

RESULTS

Nonvertebral Fractures in Overall Study

- In total, 667 subjects (placebo, 364; denosumab, 303) experienced at least one nonvertebral fracture in FREEDOM. The total number of fractures was 851 (placebo, 465; denosumab, 386) (Table 1)
- There were 6 subjects with delayed healing: 4 in the placebo arm (foot fracture, clavicle fracture and pelvic fractures [x2]), 2 in the denosumab arm (radius and ulna fracture and foot fracture), and 1 report of non-union in the placebo arm (humerus fracture)

Table 1. Fracture Healing Complications of Nonvertebral Fractures in the Overall Study

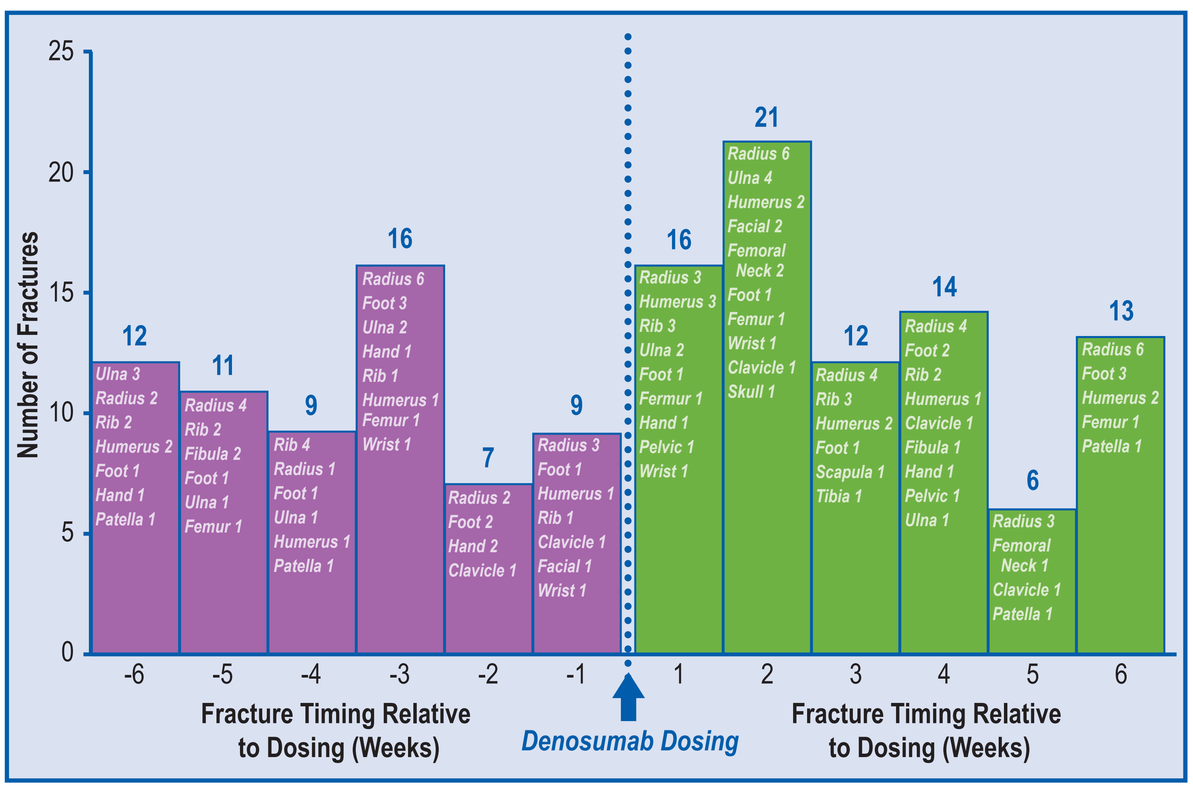
	Placebo (N = 3876)	Denosumab 60 mg Q6M (N = 3886)	*P*-value
Number of nonvertebral fractures	465	386	
Number of subjects with a nonvertebral fracture on study	364 (9.4%)	303 (7.8%)	0.01*
Number of delayed unions	4 (1.1%)	2 (0.7%)	0.38**
Number of non-unions	1 (0.3%)	0 (0%)	1.00**

N = Number of subjects who received ≥ 1 dose of investigational product. *Chi-squared test; **Fisher's exact test

Timing of Nonvertebral Fractures Relative to Denosumab Administration

- Approximately, 38% of all nonverebral fractures in the denosumab group occurred up to 6 weeks prior to or 6 weeks after denosumab injection
  - Fracture occurrences in the densoumab group were evenly distributed within 6 weeks before and after the denosumab administration (Figure 1)
  - There were no occurrences of delayed healing or non-union in fractures occurring in the densoumab group within this 12-week period

Figure 1. Location and Distribution of Fractures Occurring Within 6 Weeks Before and After Denosumab Administration



Fracture Healing Sub-study

- The fracture healing sub-study enrolled 25 subjects (Table 2)
- Three subjects in each of the placebo and denosumab arms, respectively, were healed by 6 weeks (Table 2)
- At 3 months, 2 subjects in the placebo arm and one in the denosumab arm had delayed radiographic healing
  - All three subjects had documented complete healing by month 6

Table 2. Fracture Healing Complications In The Distal Radius Fracture Healing Sub-Study

	Total (N = 25)	Placebo (N = 17)	Denosumab 60 mg Q6M (N = 8)
Number of subjects with X-rays evaluable per protocol	22	15	7
Healed by 6 weeks*	6 (29%)	3 (21%)	3 (43%)
Healed by 3 months*	18 (86%)	12 (86%)	6 (86%)
Healed by 6 months	22 (100%)	15 (100%)	7 (100%)

N = number of subjects enrolled.
One subject in the placebo arm was enrolled by error. No actual radius fracture had occurred.
One subject in each treatment group had non-evaluable X-rays at all 3 time points.
*There were 14 subjects (placebo group) and 21 subjects (total) with evaluable X-rays at 6 weeks and 3 months, because 1 subject in the placebo arm had an X-ray only at 6 months.

CONCLUSIONS

- Denosumab, a new therapy for osteoporosis, administered sc every 6 months significantly reduced the risk of nonvertebral and hip fractures
- Denosumab was not associated with delayed fracture healing, even when given 6 weeks before or after a fracture occurrence
- Fracture healing progressed without increased risk of delayed healing or non-union even when bone resorption was significantly reduced by denosumab
- These data suggest that denosumab could provide a convenient and simple approach to initiate therapy in postmenopausal women at risk of fracture when they are being evaluated and treated for an acute fracture event.

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