Denosumab Administration is Not Associated With Fracture Healing Complications in Postmenopausal Women With Osteoporosis: Results From the FREEDOM Trial

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INTRODUCTION

- A fracture provides a sensible opportunity to educate postmenopausal women with osteoporosis about their disease, and to initiate therapy to reduce the risk of further fractures. Unfortunately, despite available therapies, most of these women still do not receive treatment to reduce their proven increased fracture risk.
- Theoretical concerns about potential complications of fracture healing if therapy were initiated at the time or near the time of fracture may put off initiation of osteoporosis treatment with agents otherwise known to reduce fracture risk.
- In the FREEDOM trial, denosumab, a fully human monoclonal antibody to RANKL, significantly reduced the risk of new vertebral, hip and nonvertebral fractures[1] and was recently approved in Europe, USA, Canada and Australia for the treatment of osteoporosis in women at increased risk for fracture.
- Denosumab, administered subcutaneously (sc) every 6 months, provides a simple and convenient approach to treat postmenopausal women at the time of their fracture. Therefore, it is important to understand the complications, if any, associated with the management or healing of fractures in postmenopausal women who receive denosumab.

OBJECTIVE

- In a prespecified analysis from the FREEDOM trial, complications related to fracture healing were evaluated for all nonvertebral fractures, including hip fractures, regardless of location and trauma severity.
- Complications associated with the fracture or the surgical management of those fractures are also described, including for those women who were administered denosumab near the time of fracture.

METHODS

Study Design and Patients

FREEDOM was a 3-year, randomized, double-blind, placebo-controlled trial[1] in 7808 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:

- Subjects were randomized to receive denosumab 60 mg or placebo sc every 6 months, and all received daily elemental calcium and vitamin D.
- For subjects who fractured on study, denosumab was administered according to the scheduled 6-monthly visits, regardless of timing of fracture.

Assessments

- Nonvertebral fractures, excluding skull, facial, mandible, metacarpus, finger phalanges, and toe phalanges, were radiographically confirmed for efficacy evaluation.
- Fracture healing complications, including delayed healing and non-union, were reported by the investigator for all nonvertebral fractures, regardless of location and trauma severity. Data on fracture healing complications were collected on a specific case report form at 6 months post-fracture.
- Fracture occurrences as a function of time from denosumab administration were evaluated in this analysis.

RESULTS

Nonvertebral Fractures in Overall Study

- In total, 851 nonvertebral fractures (placebo, 465; denosumab, 386) were documented in 667 subjects (placebo 364, denosumab 303).

Timing of Nonvertebral Fractures Relative to Denosumab Administration

- Nonverterbal fracture occurrences were evenly spread across the 6-monthly dosing intervals (Figure 1)
- Approximately, 38% of all nonvertebral fractures in the denosumab group occurred within 6 weeks preceding or following denosumab injection, allowing the evaluation of complications for those women who suffered a fracture in close proximity to denosumab administration. In those women densoumab was administered as close as the day after or the day before the fracture.

Subjects With Delayed Healing or Non-Union

- There were 6 subjects with delayed fracture healing: 4 in the placebo arm, 2 in the denosumab arm and 1 subject with a fracture non-union in the placebo arm:
  - In the placebo group, delayed fracture healing was reported for fractures that occurred 13 (foot fracture), 15 (clavicle fracture), 18 (pelvic fracture) and 19 (pelvic fracture) weeks following placebo administration; the one case of non-union (humerus fracture) had received placebo 15 weeks earlier.
  - In the denosumab group, delayed fracture healing was reported for a wrist fracture (radius and ulna) on a subject who had received denosumab 7 weeks earlier and a foot fracture on a subject who had received denosumab 16 weeks earlier.
- There were no occurrences of delayed healing or non-union in fractures occurring in those subjects who received denosumab within the 6 weeks preceding or following the fracture.

Complications Associated With Fracture or Surgical Management of the Fracture

- Complications associated with the fracture or surgical management of the fracture occurred in 5.5% of placebo subjects and 1.7% of denosumab subjects ($p < 0.01$) (Table 1 and Figure 2)

Figure 1. Distribution of Nonvertebral Fractures Across the 6-Monthly Dosing Intervals With Denosumab

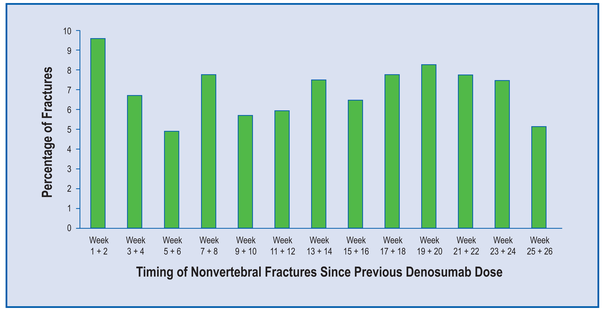
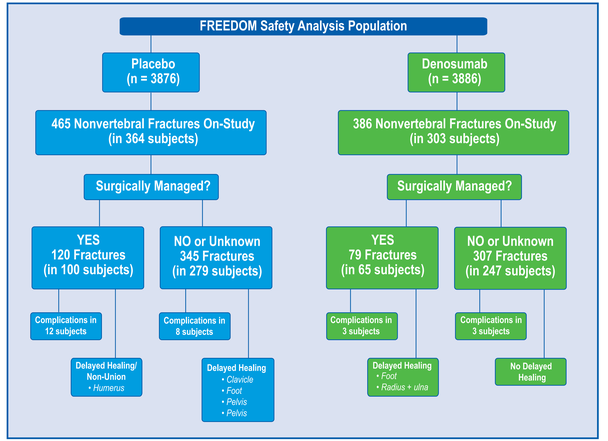


Table 1. Subject Incidence of Complications Associated With Fracture or Surgical Management of Fracture

	Placebo (N = 364)		Denosumab (N = 303)	
	n (%)	Site of Fracture	n (%)	Site of Fracture
Number of subjects with complications associated with fracture or surgical management	20 (5.5%)		5 (1.7%)	
Infection	3 (0.8%)	Radius + ulna radius, femur	1 (0.3%)	Radius + ulna
Avascular necrosis	2 (0.5%)	Radius, tibia	0 (0%)	
Thromboembolic events	0 (0%)		1 (0.3%)	Patella
Neurologic and vascular injury	1 (0.3%)	Femoral neck	0 (0%)	
Posttraumatic arthritis	1 (0.3%)	Foot	0 (0%)	
Other				
Pain	3 (0.8%)	Radius + ulna	1 (0.3%)	Radius + ulna
Carpal tunnel syndrome	1 (0.3%)	Ulna	0 (0%)	
Dislocation of bone	1 (0.3%)	Radius	0 (0%)	
Humeral nail moved in situ	1 (0.3%)	Humerus	0 (0%)	
Screw dislocation	1 (0.3%)	Tibia	0 (0%)	
Wrist mobility diminished	0 (0%)		1 (0.3%)	Radius + ulna
Foot ulcer	0 (0%)		1 (0.3%)	Foot
Bedsore	1 (0.3%)	Femur	0 (0%)	
Right knee cellulitis	0 (0%)		1 (0.3%)	Patella
No symptom improvement 2 months after fracture	1 (0.3%)	Foot	0 (0%)	
Anemia	2 (0.5%)	Femur	0 (0%)	
Chest pain	1 (0.3%)	Sternum	0 (0%)	
Tachycardia	1 (0.3%)	Femur	0 (0%)	
Pneumonia; pseudo-obstruction, colonic	1 (0.3%)	Femur	0 (0%)	

Figure 2. Complications Associated with the Fracture or Surgical Management of the Fracture



CONCLUSIONS

- Denosumab, a new therapy for osteoporosis, administered sc every 6 months significantly reduced the risk of nonvertebral and hip fractures.
- Fracture healing progressed normally in subjects receiving denosumab, even when denosumab was administered in the proximity of the fracture occurrence.
- Complications associated with fracture or surgical management of the fracture occurred in fewer denosumab than placebo subjects.
- These findings suggest that denosumab can be safely administered in the immediacy of a fracture, and because of its convenience may help address the significant problem of subjects not receiving therapy for their osteoporosis after a fracture.

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