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Infections in postmenopausal women with osteoporosis treated with denosumab or placebo: coincidence or causal association?

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Abstract

Summary Serious adverse events of infections that occurred in subjects receiving denosumab or placebo in the Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) study were examined in detail. Serious adverse events of infections in denosumab subjects had heterogeneous etiology, with no clear clinical pattern to suggest a relationship to time or duration of exposure to denosumab.

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Introduction Denosumab reduces the risk for new vertebral, hip, and nonvertebral fractures compared with placebo. In the pivotal phase 3 fracture trial (FREEDOM), the overall safety profile and incidence of adverse events including adverse events of infections were similar between groups. Serious adverse events of erysipelas and cellulitis were more frequent in denosumab-treated subjects. In this report, we further evaluate the details of infectious events in FREEDOM to better understand if RANKL inhibition with denosumab influences infection risk.

Methods FREEDOM was an international multicenter, randomized, double-blind, placebo-controlled study in postmenopausal women with osteoporosis randomly assigned to receive placebo ($n=3,906$) or denosumab 60 mg every 6 months ($n=3,902$). The incidence of adverse events and serious adverse events categorized within the Medical Dictionary for Regulatory Activities system organ class, "Infections and Infestations," was compared between the placebo and denosumab groups by body systems and preferred terms. The temporal relationship between occurrence of serious adverse events of infections of interest and administration of denosumab was explored.

Results Serious adverse events of infections involving the gastrointestinal system, renal and urinary system, ear, and endocarditis were numerically higher in the denosumab group compared with placebo, but the number of events was small. No relationship was observed between serious adverse events of infections and timing of administration or duration of exposure to denosumab.

Conclusions Serious adverse events of infections that occurred with denosumab treatment had heterogeneous etiology, with no clear clinical pattern to suggest a relationship to time or duration of exposure to denosumab.

Introduction

RANKL is recognized as an essential factor in the regulation of bone resorption. By signaling through its receptor RANK, RANKL increases osteoclast formation, differentiation, and activity and prolongs osteoclast survival [1–6]. In clinical trials, denosumab, a RANKL inhibitor, has demonstrated efficacy to reduce bone resorption, increase bone mineral density (BMD) and strength in both cortical and trabecular bone, and reduce the risk of vertebral, hip, and nonvertebral fractures [7–11].

In addition to expression in bone, RANKL and RANK are expressed by cells of the immune system including activated T lymphocytes, B cells, and dendritic cells [3, 12, 13], suggesting that immune cells might affect bone homeostasis or that RANKL inhibition might alter immune function. Gene deletion studies in rodents show that complete absence of RANKL or its receptor RANK during embryogenesis leads to absence of lymph nodes and changes in thymus architecture [3, 14]. However, in both RANKL and RANK deletion, dendritic cell and macrophage components were normal. In humans with osteoclast-poor osteopetrosis due to absence of RANKL and complete loss of function, there appears to be minimal, if any, effect on immune system development and function [15].

In studies of genetically modified rodents and in pharmacologic experiments in cynomolgus monkeys, inhibition of RANKL, rather than complete RANKL or RANK ablation, increased BMD but did not appear to have significant consequences on basal immune parameters, generation of T or B cell immune responses, or responses to immunization or other immune challenges [16–18]. In five distinct preclinical models of inflammatory arthritis and in a T cell-driven model of inflammatory bowel disease, RANKL inhibition decreased bone resorption while having no effect on parameters of inflammation including local edema, pannus formation, and cytokine and chemokine profiles or histopathologically evaluated gut inflammation [19–28].

Some in vitro and in vivo effects of RANKL inhibition on immune function have been noted in rodents with major defects in immune system stimulation mechanisms, such as IL-2 or CD40 depletion [12, 29, 30], which suggests that there may be redundancy within the immune system, with the RANKL pathway having a secondary role [29]. Additionally, it has been postulated that the RANKL–RANK interaction may modify immune responses in specific tissues such as the skin, potentially through an effect on the intensity of the inflammatory response, rather than through an immunosuppressive effect [31, 32].

In a dose-ranging study of denosumab in healthy postmenopausal women, no clinically meaningful differences in overall lymphocyte counts, T cells, or B cells were observed in subjects treated with denosumab [33]. In the phase 3 international, double-blind pivotal trial demonstrating fracture reduction efficacy of denosumab in postmenopausal women with osteoporosis (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM)], the overall incidence of adverse events and serious adverse events was similar between denosumab- and placebo-treated subjects; however, some numeric imbalances in specific events were reported, including serious adverse events of infections involving the skin [8]. To better understand the potential influence of RANKL inhibition on infections, we examined the incidence and types of infections as well as details of individual cases among participants in the pivotal phase 3 denosumab fracture trial, which represents 10,826 patient-years of exposure to denosumab.

Materials and methods

Subjects and database

Adverse events and serious adverse events of infections as reported in the denosumab pivotal phase 3 fracture trial were examined. The study design and primary results of the study have been previously reported [8]. Briefly, it was a 3-year multicenter, international, randomized, double-blind, placebo-controlled study in 7,808 postmenopausal women with osteoporosis. Subjects received placebo or denosumab subcutaneously 60 mg every 6 months (Q6M). The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by an institutional review board or ethics committee for each study site. All subjects provided written informed consent.

Safety was assessed through adverse event reporting for all women who received at least one dose of investigational product (3,876 placebo and 3,886 denosumab). Information about adverse events was collected by investigators at each study visit. The investigator's verbatim description of an adverse event was converted into standardized terminology based on the Medical Dictionary for Regulatory Activities (MedDRA) version 11 and entered in the safety database as preferred terms. Adverse events and serious adverse events were defined according to regulatory criteria: an adverse event was defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. A serious adverse event was defined as any adverse event that resulted in any of the following outcomes: death, life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. In addition, any event that did not meet the regulatory definition of a serious adverse event, but in the opinion of the investigator

or sponsor represented a significant medical hazard, was also considered a serious adverse event.

Adverse events and serious adverse events of infections—those adverse events categorized in the MedDRA system organ class "Infections and Infestations"—were evaluated for this report. This category is broad and includes contagious as well as noncontagious (e.g., appendicitis, cholecystitis, diverticulitis) events.

Information about antibiotic treatments was obtained from case narratives and/or concomitant medication listings. Microbial classification (bacterial, viral, or fungal) could only be determined if cultures were collected at the time of event and culture results were reported by the investigators. Microbial classification was listed as unknown if cultures were not collected at the time of event, no organisms were isolated upon culture, or no culture results were reported.

Serious adverse events of opportunistic infections were identified by a search of the clinical trial safety database using predefined MedDRA terms that included fungal and mycobacterial infections. The presence of an organism by itself was not sufficient to qualify an adverse event as a serious opportunistic infection; events needed to meet the regulatory definition of serious (described above) and were verified by medical review. Colonization or localized infections were distinguished from invasive or disseminated infections. For example, shingles confined to a single dermatome would not be considered opportunistic, but herpes zoster infection that was disseminated or involved multiple dermatomes would be included. Queries were generated by the sponsor to obtain additional information from investigators if important case-level detail was missing.

Statistical analysis

Demographic data for all randomized subjects were summarized by treatment group. Safety data were summarized by actual treatment received. Thus, seven subjects assigned to placebo who received a single dose of denosumab at some point during the study were included in the denosumab group for purposes of safety assessments. Yearly incidence rates of serious adverse events of infection were calculated. The temporal relationship between occurrence and resolution of serious adverse events of infections of interest and administration of investigational product was explored. P values were

based on the log-rank test. The analyses did not include any adjustments for multiplicity and should be considered exploratory.

Results

Baseline characteristics of subjects enrolled in the pivotal phase 3 fracture trial have been previously reported [8]. Subjects were primarily Caucasian (93%); the mean (SD) age was 72.3 (5.2) years and 74% were 70 years of age or older. As previously reported, the overall incidence of adverse events of infections was similar between the placebo and denosumab groups (54.4% vs 52.9%, respectively; $P=0.17$), and serious adverse events of infections were reported in 3.4% of placebo subjects and 4.1% of denosumab subjects ($P=0.14$) [8].

About 40% of the serious adverse events of infection (41.3% with placebo and 44.7% with denosumab) were of mild or moderate severity, although they met the regulatory definition of "serious adverse events." Usually, the "serious" definition was applied due to hospitalization of the subject. The number of subjects discontinuing the study as a result of adverse events of infection was low and similar between treatment groups (four placebo, three denosumab; Table 1). No increased risk for fatal infections was observed with denosumab (six placebo, six denosumab; Table 1).

Serious adverse events of infections over time

The incidence of serious adverse events of infection across the 3 years of study was examined. The rate of infection did not change with increasing duration of denosumab exposure (Table 2). The rates of known bacterial, viral, and fungal infections also did not increase with duration of denosumab exposure (Table 2).

Opportunistic infections

Serious adverse events of opportunistic infections were prospectively identified as events of interest. The incidence of serious adverse events of opportunistic infections was low and similar in the placebo (three [<0.1%]) and denosumab

Table 1 Summary of adverse events and serious adverse events of infection

	Placebo ($N=3,876$), n (%)	Denosumab ($N=3,886$), n (%)	P value
Adverse events of infections	2,108 (54.4)	2,055 (52.9)	0.1721
Serious adverse events of infection	133 (3.4)	159 (4.1)	0.1399
Serious opportunistic infection	3 (<0.1)	4 (0.1)	0.7130
AEs of infection leading to study discontinuation	4 (0.1)	3 (<0.1)	0.6979
Fatal infections	6 (0.2)	6 (0.2)	0.9787

Table 2 Incidence of serious adverse events of infections by year of study and microbial classification

	Year 1	Year 2	Year 3
Incidence of serious adverse events of infection by year			
Placebo	42 (1.1%)	49 (1.3%)	47 (1.4%)
Denosumab	55 (1.4%)	58 (1.6%)	54 (1.5%)
Positively identified bacterial infections			
Placebo	10 (0.3%)	12 (0.3%)	10 (0.3%)
Denosumab	13 (0.3%)	15 (0.4%)	19 (0.5%)
Positively identified viral infections			
Placebo	0 (0.0%)	1 (<0.1%)	5 (0.1%)
Denosumab	2 (0.1%)	4 (0.1%)	2 (0.1%)
Positively identified fungal infections			
Placebo	1 (<0.1%)	0 (0.0%)	0 (0.0%)
Denosumab	1 (<0.1%)	0 (0.0%)	1 (<0.1%)

(four [0.1%]) groups [8]. No clear pattern in the type of infections was observed. In the placebo group, all three subjects had tuberculosis (preferred terms of tuberculosis or pulmonary tuberculosis) and one event was fatal. In the denosumab group, the opportunistic infections were tuberculosis (two subjects), aspergillosis of the face, and disseminated herpes zoster. No risk factors for the opportunistic infections were identified in these subjects. No temporal relationship was observed between the occurrence of these opportunistic infections and administration of the investigational product (Fig. 1a). Nonserious adverse events of opportunistic infections were not specifically identified and categorized as such, but individual terms included tuberculosis, which was reported as a nonserious adverse event in four subjects receiving placebo and no subjects receiving denosumab.

Skin infections

Serious adverse events of infections involving the skin occurred in 3 (<0.1%) placebo subjects and 15 (0.4%) denosumab subjects (P<0.05; Table 3). These were not injection-site reactions. In the denosumab group, most of these skin infections were cellulitis or clinically diagnosed erysipelas involving the lower extremities that resolved with administration of common antibiotics. The overall incidence of adverse events of cellulitis and erysipelas (i.e., both serious and nonserious adverse events) was not significantly different between treatment groups (0.9% placebo, 1.2% denosumab) [8]. There was no temporal association between the onset of serious adverse events of cellulitis and erysipelas and duration of treatment or time since last dose of investigational product (Fig. 1b).

Cellulitis and erysipelas are usually caused by *Streptococcus pyogenes*, *Staphylococcus aureus*, and other gram-positive bacterial infections. In this study, serious adverse events of cellulitis and erysipelas were diagnosed clinically and not usually confirmed by culture. A positive *S. pyogenes* culture was obtained for 1 of the 12 subjects experiencing a serious adverse event of cellulitis or erysipelas in the denosumab group.

A detailed description of the cases of serious adverse events of cellulitis and erysipelas is provided in Table 4. The median duration of hospitalization for denosumab subjects was 5.5 days (range, 1–17 days), and most subjects responded well to treatment with common antibiotics (Table 4). Preexisting risk factors including venous ulcers and skin wounds were reported in 5 of 12 denosumab subjects reporting serious adverse events of cellulitis and erysipelas.

No subjects in either group discontinued treatment due to skin infection, and in only one subject was a recurrent serious adverse event of skin infection observed (denosumab subject 7; Table 4). This subject had a history of varicose ulceration of a lower extremity before starting the study and experienced serious adverse events of lower left limb erysipelas, lower right limb skin ulcer, and lower right limb cellulitis over the course of the study, with the first event occurring on study day 39. One subject with a confirmed neuroendocrine carcinoma of pancreas experienced a fatal event associated with cellulitis of the right leg; the case was complicated by sepsis, shock, and multiple organ failure (denosumab subject 5; Table 4).

Gastrointestinal infections

Serious adverse events of infections were also examined in more detail according to body system. Serious adverse events of infections involving the gastrointestinal system occurred in 28 (0.7%) placebo subjects and 36 (0.9%) denosumab subjects (Table 5). The preferred terms categorized under the gastrointestinal body system correspond to infections with heterogeneous etiology, and no consistent pattern was observed in the type of infections. For individual preferred
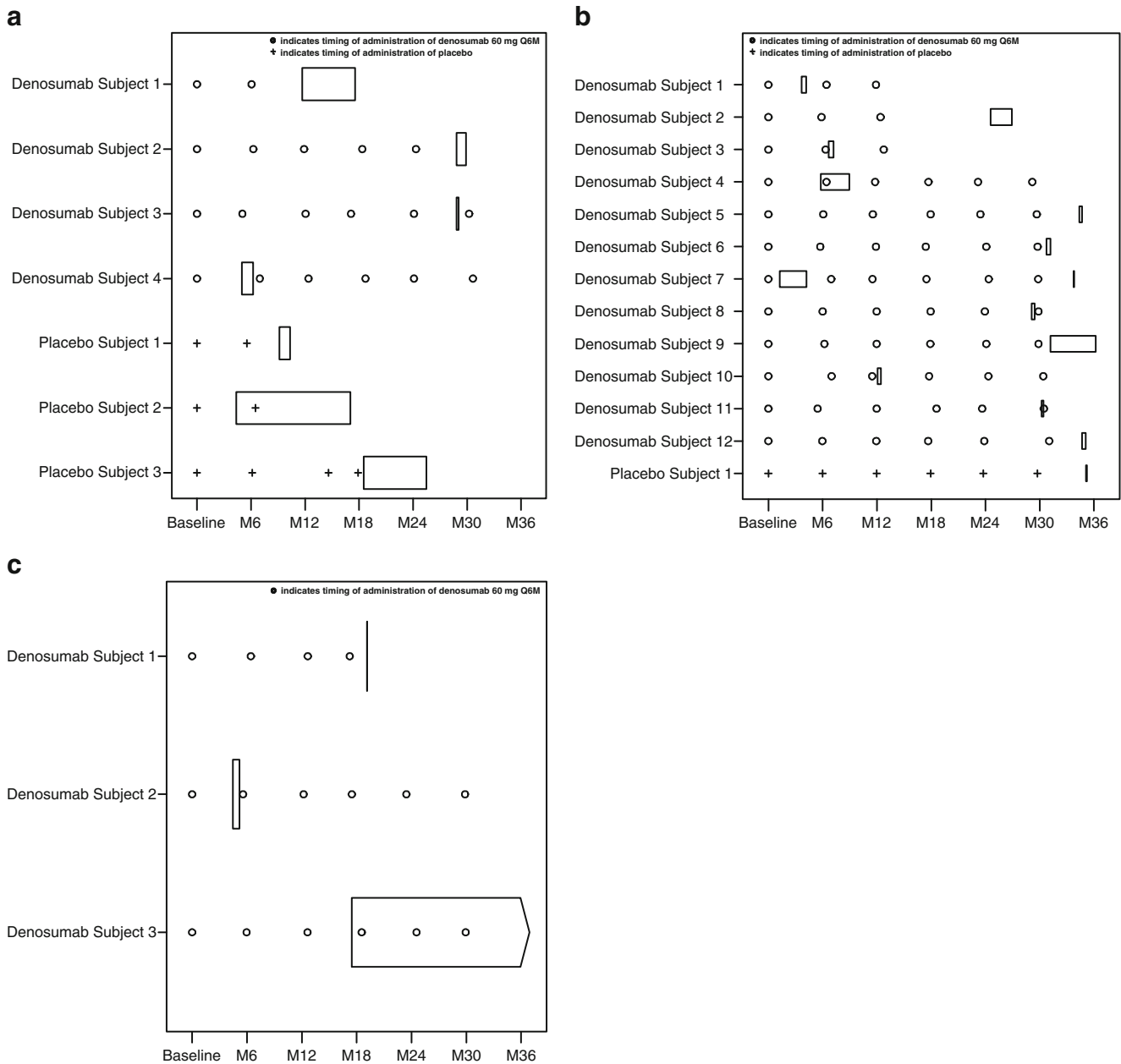
a

Denosumab Subject 1
Denosumab Subject 2
Denosumab Subject 3
Denosumab Subject 4
Placebo Subject 1
Placebo Subject 2
Placebo Subject 3

Baseline M6 M12 M18 M24 M30 M36

b

Denosumab Subject 1
Denosumab Subject 2
Denosumab Subject 3
Denosumab Subject 4
Denosumab Subject 5
Denosumab Subject 6
Denosumab Subject 7
Denosumab Subject 8
Denosumab Subject 9
Denosumab Subject 10
Denosumab Subject 11
Denosumab Subject 12
Placebo Subject 1

Baseline M6 M12 M18 M24 M30 M36

c

Denosumab Subject 1
Denosumab Subject 2
Denosumab Subject 3

Baseline M6 M12 M18 M24 M30 M36

Fig. 1 **a** Serious adverse events of opportunistic infections and relationship to timing of administration of investigational product. **b** Serious adverse events of cellulitis and erysipelas and relationship to timing of administration of investigational product. Denosumab subject 5 experienced a fatal adverse event associated with cellulitis. **c** Events of endocarditis and relationship to timing of administration of investigational product. Denosumab subjects 1 and 2 experienced serious adverse events of endocarditis; denosumab subject 3 experienced a nonserious adverse event of endocarditis. *Circles* indicate denosumab injections; *plus signs* indicate placebo injections; *rectangles* indicate onset and duration of the adverse event

terms, the difference between treatment groups was 0.1% or less. The most common events were gastroenteritis, diverticulitis, and appendicitis.

For subjects with serious adverse events of diverticulitis (six placebo, eight denosumab), the median hospital stay was similar between groups, 6 days (range, 1–8 days) for placebo subjects and 4 days (range, 1–15 days) for denosumab subjects. No subject in the placebo group and three subjects in the denosumab group had a history of diverticulitis before entering the study. One denosumab subject experienced two serious adverse events of diverticulitis on study.

Renal and urinary infections

Serious adverse events of infections involving the urinary tract were experienced by 20 (0.5%) placebo subjects and

Table 3 Incidence of serious adverse events of skin infection

	Placebo (N=3,876)[a], n (%)	Denosumab (N=3,886)[a], n (%)
Serious adverse events of infection involving the skin	3 (<0.1)	15 (0.4)*
Cellulitis and erysipelas	1 (<0.1)	12 (0.3)[b]
Skin bacterial infection	0 (0)	2 (<0.1)
Staphylococcal infection	1 (<0.1)	1 (<0.1)
Infected skin ulcer	0 (0)	1 (<0.1)[b]
Subcutaneous abscess	1 (<0.1)	0 (0)

*P<0.05 vs placebo

[a] Number of subjects who received ≥1 dose of investigational product

[b] One subject in the denosumab group experienced events of cellulitis and erysipelas and infected skin ulcer

29 (0.7%) denosumab subjects (Table 5). The most common serious adverse events included urinary tract infection, cystitis, and pyelonephritis. Culture results indicated these were typically due to *Escherichia coli* and other common gram-negative bacteria. The difference in incidence between treatment groups for individual preferred terms was 0.1% or less.

Ear infections

Serious adverse events of infections involving the ear occurred in no placebo subjects and five denosumab subjects (Table 5). These infections were primarily labyrinthitis (four cases), of which two cases were moderate and two were severe; the other serious adverse event was otitis media. Resolution of labyrinthitis occurred within 2 and 13 days in cases of moderate severity and in 6 weeks in a severe case. In one subject with a history of recurrent labyrinthitis, the event was ongoing. No apparent relationship was observed between onset of the events and time since initiation of denosumab (range, 6–31 months).

Most subjects with serious adverse events of ear infections had preexisting complicating factors. For example, three of the four subjects with labyrinthitis had a prior history of labyrinthitis. The subject with otitis media had a previous stapedectomy and tympanoplasty in the same ear approximately 3 years prior. She was hospitalized for an exploratory tympanoplasty.

Endocarditis

Three events of endocarditis (one adverse event and two serious adverse events) were reported in the denosumab group and none in the placebo group. No relationship was observed between the onset of endocarditis and the duration of treatment or time since last dose of denosumab (Fig. 1c), and a causative pathogen was not identified in any case. Two of the subjects underwent echocardiography and the diagnosis was reported to be confirmed. One of these

subjects was hospitalized for treatment with antibiotics and the other was treated as an outpatient. In the third subject, acute bacterial endocarditis was suspected as a probable contributor to a fatal event of multiorgan failure; no treatment details from the case were available, including echocardiography, and an autopsy was not performed.

Respiratory, mediastinal, and other thoracic infections

Serious adverse events of infections involving the respiratory tract occurred in 68 (1.8%) placebo subjects and 69 (1.8%) denosumab subjects (Supplementary Table 1). Incidence of individual preferred terms was similar between groups.

Osteomyelitis

One subject in each treatment group experienced a nonserious adverse event of osteomyelitis of the jaw. Both cases were adjudicated negative for osteonecrosis of the jaw. The denosumab subject received only one dose of denosumab on study; the event occurred 2 years after denosumab administration.

Peripheral white blood cell counts

Neutrophil, lymphocyte, and monocyte counts were similar between the placebo and denosumab groups throughout the study (Supplementary Fig. 1). Cell counts did not change with increased duration of denosumab exposure.

Discussion

This study examined the incidence, types, and details in individual subjects of adverse events of infections observed in postmenopausal women treated with the RANKL inhibitor denosumab or placebo in the phase 3 pivotal fracture trial, which represents more than 10,000 patient-years of denosumab exposure. The overall incidence of infections was similar

Table 4 Case descriptions for subjects with serious adverse events of cellulitis and erysipelas

Subject	Age (years)	Study day	Number of days hospitalized	Culture	Event description	Treatment
Denosumab subject 1	82	113	15	No cultures	Erysipelas of the left leg	IV benzylpenicillin, IM amikacin, oral roxithromycin
Denosumab subject 2	84	750	15	No cultures	Bilateral leg cellulitis. History of atrial fibrillation, asthma	IV and oral antibiotics (unspecified)
Denosumab subject 3	79	204	17	No cultures	Severe erysipelas of the left lower extremity. History of venous ulcer, chronic cardiac failure	IV cefotaxime
Denosumab subject 4	71	177	5	No cultures	Cellulitis. Subject cut her left foot on thorns while gardening.	Oral flucloxacillin, metronidazole, and phenoxymethylpenicillin
Denosumab subject 5	65	~180 days	<1 day as subject died on day of hospitalization	*Streptococcus pyogenes*	The subject had a confirmed neuroendocrine carcinoma of pancreas with penetration to spleen and ventricle and presented with a painful, bluish and swollen right leg. Cellulitis was confirmed by culture. At admission, the subject experienced atrial fibrillation and low blood pressure with same-day deterioration to multiorgan failure, severe shock, and death.	IV oxacillin
Denosumab subject 6	66	939	2	No cultures	Cellulitis of the face following possible insect bite. History of scleroderma and hypothyroidism	IV vancomycin and cefazolin, oral cephalexin
Denosumab subject 7	73	39	6	No cultures	Moderate erysipelas of left lower limb. Bilateral phlebitis in both legs, and edema	IV cefalotin, IM penicillin
	75	861	6	No cultures	Worsening of infection of right lower limb varicose ulcer.	IV penicillin
	76	1,030	3	No cultures	Lower extremity cellulitis. History of bilateral varicose ulceration of lower extremity, stasis dermatitis, thrombophlebitis of the leg, and obesity.	Oral cephalexin
Denosumab subject 8	81	889	10	*Klebsiella pneumonia*	Erysipelas of right leg	Unspecified antibiotics
Denosumab subject 9	87	952	7	No cultures	Right leg erysipelas	Oral penicillin
Denosumab subject 10	85	369	5	Negative blood cultures	Right lower limb erysipelas. History of lower extremity varicose veins and left first toe cellulitis	IV cefalotin and oral amoxicillin
Denosumab subject 11	87	922	2	Culture results not reported	Erysipelas. Ulcer on the left leg with formation of a progressive swollen red patch associated with local edema and heat although the subject was afebrile.	IV cefalotin and oral cefaclor
Denosumab subject 12	73	1,059	4	Negative cultures	Cellulitis of the left foot	IV cefazolin and ceftriaxone
Placebo subject 1	80	1,072	2		Cellulitis of left foot	Oral ciprofloxacin

Table 5 Incidence of serious adverse events of infections related to the gastrointestinal, renal and urinary, and ear and labyrinth body systems

	Placebo (N=3,876)[a], n (%)	Denosumab (N=3,886)[a], n (%)	P value
Serious adverse events of infections related to the gastrointestinal system	28 (0.7)	36 (0.9)	0.3322
Gastroenteritis	7 (0.2)	9 (0.2)	
Diverticulitis	6 (0.2)	8 (0.2)	
Appendicitis	7 (0.2)	7 (0.2)	
Abdominal abscess	0 (0)	2 (0.1)	
Helicobacter infection	0 (0)	2 (0.1)	
Clostridium difficile colitis	2 (0.1)	1 (<0.1)	
Anal abscess	0 (0)	1 (<0.1)	
Biliary tract infection fungal	0 (0)	1 (<0.1)	
Gastric infection	0 (0)	1 (<0.1)	
Gastroenteritis *Escherichia coli*	0 (0)	1 (<0.1)	
Gastroenteritis bacterial	0 (0)	1 (<0.1)	
Gastroenteritis rotavirus	0 (0)	1 (<0.1)	
Gastroenteritis viral	0 (0)	1 (<0.1)	
Post procedural infection	0 (0)	1 (<0.1)	
Salmonellosis	2 (0.1)	0 (0)	
Abscess intestinal	1 (<0.1)	0 (0)	
Gastrointestinal infection	1 (<0.1)	0 (0)	
Infected cyst	1 (<0.1)	0 (0)	
Peridiverticular abscess	1 (<0.1)	0 (0)	
Peritoneal abscess	1 (<0.1)	0 (0)	
Typhus	1 (<0.1)	0 (0)	
Serious adverse events of infections related to the renal and urinary systems	20 (0.5)	29 (0.7)	0.2105
Urinary tract infection	10 (0.3)	16 (0.4)	
Cystitis	2 (0.1)	6 (0.2)	
Pyelonephritis	2 (0.1)	5 (0.1)	
Urosepsis	2 (0.1)	1 (<0.1)	
Pyelonephritis acute	1 (<0.1)	1 (<0.1)	
Pyelonephritis chronic	0 (0)	1 (<0.1)	
Escherichia infection	2 (0.1)	0 (0)	
Bacterial pyelonephritis	1 (<0.1)	0 (0)	
Kidney infection	1 (<0.1)	0 (0)	
Renal abscess	1 (<0.1)	0 (0)	
Serious adverse events of infections related to the ear and labyrinth systems	0 (0)	5 (0.1)	0.0260
Labyrinthitis	0 (0)	4 (0.1)	
Otitis media	0 (0)	1 (<0.1)	

[a] Number of subjects who received ≥1 dose of investigational product

between treatment groups. No increased risk of opportunistic infection was seen with denosumab.

Serious adverse events of cellulitis and erysipelas resulting in hospitalization occurred more frequently with denosumab, although the number of events was low. Hospitalized subjects responded to treatment with common antibiotics. No significant increase in overall incidence (serious and nonserious adverse events) of cellulitis and erysipelas was observed with denosumab. With the small numbers of subjects, the finding of more hospitalizations in

the denosumab group might be due to chance or could indicate that skin infections were more severe with denosumab treatment. Preclinical data suggest another possibility: inhibition of RANKL in keratinocytes may decrease the number of regulatory T cells (cells that suppress immune responses), leading to an increased inflammatory response in the skin [31, 32]. Thus, it may be that the appearance of the skin lesions was suggestive of greater severity of the inflammatory process in subjects receiving denosumab, resulting in more frequent hospitalization.

When serious adverse events of infections were reviewed according to body systems, events involving the abdomen, urinary tract, and ear, as well as endocarditis, were numerically more frequent in denosumab than placebo subjects, while serious adverse events of infections of the respiratory tract were balanced between treatment groups. The body system groupings were broad and included contagious as well as noncontagious events. In general, when numerical imbalances were reported—for example, ear and labyrinthitis events—subjects had preexisting risk factors for the condition. Given the age of the study population, many had multiple comorbidities including preexisting conditions that may have predisposed to the type to infections observed. Although general medical histories were collected from all subjects at study start, information relating to such potentially predisposing comorbid conditions was not collected systematically. Therefore, we were unable to determine from the available data if the overall baseline level for certain risk factors was similar between groups. Similarly, we could not conclusively investigate whether patients with particular baseline characteristics might be at increased risk to develop certain infections with denosumab.

In denosumab-treated subjects, white blood cell counts remained stable over time and similar to placebo. Serious adverse events of infections that occurred with denosumab had heterogeneous etiology, with no clear clinical pattern to suggest a relationship to time or duration of exposure to denosumab. In aggregate, these findings are consistent with the evidence that suggests there is a redundancy of function in the adult immune system, with RANKL playing a minimal role [34] and inhibition of RANKL having little or no adverse effect in this regard.

Denosumab safety has been evaluated across the clinical development program. In a small phase 3 trial comparing denosumab and placebo in a younger population (mean age, 59 years) of 332 postmenopausal women with low bone mass, subjects treated with denosumab had significantly more serious adverse events of infections that were associated with hospitalization [7]. The serious adverse events of infections were common infections for the population studied and were treated successfully with standard antibiotics; no pattern was observed in the type of body systems affected. No significantly increased risk of serious adverse events of infections was observed in any other phase 2 and phase 3 clinical trials of denosumab compared with placebo or alendronate in postmenopausal women with low bone mass [7, 35–37].

Denosumab has also been studied in other disease populations. No increased risk of infection with denosumab (60 or 180 mg Q6M) was noted in clinical trials of patients with rheumatoid arthritis receiving methotrexate or in patients receiving hormone ablation therapy for breast or prostate cancer (denosumab 60 mg Q6M) [38–40]. Similarly, no increased risk of infection was observed for a higher dose of denosumab (120 mg every 4 weeks) compared with zoledronic acid in several large trials in patients with advanced cancer or multiple myeloma and bone metastases [41–43].

In this analysis, we endeavored to develop a better understanding of the effects of RANKL inhibition with denosumab by evaluating infectious events in postmenopausal women with osteoporosis participating in the phase 3 pivotal fracture trial. Although this study represents the largest placebo-controlled trial with denosumab, it was not designed for evaluating statistical differences between groups of subjects who experienced adverse events where the number of events within a preferred term was low. The analysis of adverse events reported in a clinical trial relies on the mapping of investigator-provided terms for diagnoses to standardized terminology using a coding dictionary (MedDRA). This process can introduce a categorization bias when verbatim terms are grouped together into preferred terms based upon the judgment of the coding personnel. When these data are evaluated in aggregate, diagnostic subtlety may be lost, thus, apparent differences in outcome may reflect the lumping of verbatim terms into MedDRA categories as well as actual differences in the data.

The benefit/risk profile of denosumab continues to be evaluated in ongoing clinical trials, including an open-label extension of the phase 3 pivotal fracture trial that is planned to follow up subjects for up to 10 years. Over the first 3 years (reported here), there is no indication that inhibition of RANKL has any effect on defense mechanisms against infection. A preliminary report indicates that the safety profile of denosumab remains consistent over 5 years of treatment, with no evidence of an increase in the rate of infectious events over time [44].

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