FR0388

Findings from Denosumab (Prolia®) Post-marketing Safety Surveillance for Atypical Femoral Fracture, Osteonecrosis of the Jaw, Severe Symptomatic Hypocalcemia, and Anaphylaxis. M Geller[1], RB Wagman*[1], PR Ho[1], S Siddhanti[1], C Stehman-Breen[1], NB Watts[2], S Papapoulos[3]. [1]Amgen Inc., USA, [2]Mercy Health Osteoporosis & Bone Health Services, USA, [3]Leiden University Medical Center, Netherlands

Purpose: We characterize the Prolia post-marketing experience for 4 adverse drug reactions (ADRs): atypical femoral fracture (AFF), osteonecrosis of the jaw (ONJ), severe symptomatic hypocalcemia (SSH), and anaphylaxis.

Methods: The Amgen post-marketing database undergoes continual assessment of adverse events reported by health care providers, patients, and other sources. AFF and ONJ cases were assessed and adjudicated by independent committees. SSH and anaphylaxis prompted further review by Amgen Global Safety because causality due to Prolia could not be excluded.

Results: As of September 2013, estimated Prolia exposure was 1,252,566 patient-years. Four post-marketing reports were adjudicated as consistent with the AFF ASBMR definition (Shane *JBMR* 2010). All patients had used bisphosphonate (BP); 2 subjects healed and 2 had no follow-up information. For ONJ, 32 post-marketing reports were adjudicated as consistent with the AAOMS definition (Position Paper *AAOMS* 2009). Risk factors included ⩾ 1: glucocorticoids, chemotherapy, prior BP use, older age, and invasive dental procedures. One-third of reports indicated resolution, 1/3 were ongoing, and the remainder were unknown. Routine pharmacovigilance in 2011 showed 8 reports of medically confirmed SSH that included symptoms of seizures and/or tetany; 7 of 8 patients had chronic kidney disease, a risk factor for hypocalcemia; most events occurred within 30 days of Prolia administration and responded to IV/PO calcium/vitamin D. Routine pharmacovigilance in 2012 showed 5 reports of medically confirmed anaphylaxis that included hypotension, dyspnea, throat tightness, facial and upper airway edema, pruritus, and/or urticaria. Most events occurred within 1 day of the first Prolia dose; emergency room treatments included antihistamines and IV/PO steroids with no fatal outcomes. Amgen assessment of SSH and anaphylaxis as possibly related to Prolia led to product labeling updates.

Conclusion: These Prolia post-marketing events have not shown any unexpected findings; the benefit/risk profile remains favorable. Ongoing safety surveillance continues through clinical studies and pharmacovigilance activities.

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FR0391

Percentage of Women Achieving Non-osteoporotic BMD T-scores at the Spine and Hip Over 8 Years of Denosumab Treatment. S Ferrari*[1], C Libanati[2], CJF Lin[2], S Adami[3], JP Brown[4], F Cosman[5], C Czerwiński[6], LH de Gregório[7], J Malouf[8], J-Y Reginster[9], NS Daizadeh[2], A Wang[10], RB Wagman[10], EM Lewiecki[11], S Cummings[12]. [1]Geneva University Hospital, Switzerland, [2]Amgen Inc., USA, [3]University of Verona, Italy, [4]Laval University & CHU de Québec Research Centre, Canada, [5]Helen Hayes Hospital, USA, [6]Krakow Medical Center, Poland, [7]CCBR, Brazil, [8]Universitat Autònoma de Barcelona, Spain, [9]University of Liège, Belgium, [10]Amgen Inc., USA, [11]New Mexico Clinical Research & Osteoporosis Center, USA, [12]San Francisco Coordinating Center, CPMC Research Institute, & UCSF, USA

Purpose: Guidelines for the treatment of chronic conditions such as hypertension and diabetes include specific biomarker targets. This differs from osteoporosis treatment guidelines, which currently do not define treatment targets or goals. In general, absence of BMD loss and fracture are considered treatment successes. This is far from ideal because success defined by the lack of a negative outcome does not set a real goal for therapy. Potential goals for osteoporosis treatment might include reaching a BMD T-score value somewhere above –2.5 that represents an acceptable level of fracture risk. To provide insight into T-score values achieved over time with denosumab (DMAb), we report on the percentage of women who achieved a range of possible target BMD T-scores at both the lumbar spine and total hip over 8 years of treatment.

Methods: For these analyses, women received 3 years of DMAb (60 mg SC Q6M) during FREEDOM and 5 years of DMAb during the Extension for a total of 8 years of continued treatment. The percentage of women with T-scores >−2.5, >−2.2, >−2.0, and >−1.8 at both the lumbar spine and total hip, and T-scores >−2.5 at either the lumbar spine or total hip at baseline and over 8 years of DMAb treatment were determined. The influence of baseline T-score on subsequent T-score improvement was also explored.

Results: At FREEDOM baseline, mean (SD) lumbar spine and total hip T-scores were −2.83 (0.67) and −1.85 (0.79), respectively, for the DMAb Extension participants (N=2343). The percentage of women with T-scores >−2.5, >−2.2, >−2.0, and >−1.8 at both the lumbar spine and total hip progressively increased from baseline over 8 years of DMAb treatment as follows: 11% to 82% (>−2.5), 4% to 65% (>−2.2), 2% to 53% (>−2.0), and 1% to 39% (>−1.8) (Fig. 1). At individual sites, the percentage of women with a T-score >–2.5 increased from baseline over 8 years of DMAb treatment from 19% to 86% (lumbar spine) and from 75% to 94% (total hip). Baseline T-scores by quartile remained largely consistent throughout the 8 years of DMAb treatment, which showed similar trajectory in BMD across subjects regardless of initial BMD (not shown).

Conclusion: DMAb enables a substantial proportion of women with osteoporosis to achieve non-osteoporotic T-scores. The data reported here contribute insightful information to discussions on the topic of treatment goals for osteoporosis.

Fig. 1. Percentage of Women Achieving a Particular T-score at Both the Lumbar Spine and Total Hip

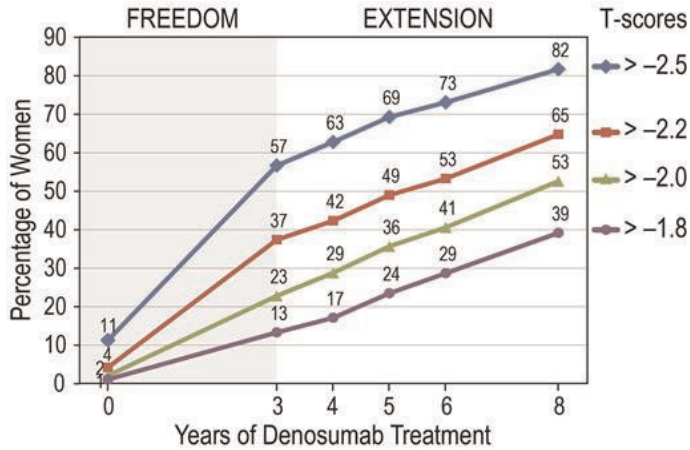

Fig. 1

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FR0396

The Extent of Symmetry on Images of Bilateral Atypical Femoral Fractures. Linda Probyn*[1], Angela M. Cheung[2], Jonathan Adachi[3], Leon Lenchik[4], Aliya Khan[5], Earl Bogoch[6], Robert Josse[7], Catherine Lang[8], R Bleakney[9]. [1]University of Toronto, Sunnybrook Health SC, Dept. Medical Imaging, Canada, [2]University Health Network-University of Toronto, Canada, [3]St. Joseph's Hospital, Canada, [4]Wake Forest University, USA, [5]McMaster University, Canada, [6]St. Michael's Hospital, Canada, [7]St. Michael's Hospital, University of Toronto, Canada, [8]University of Toronto, Canada, [9]Mount Sinai Hospital, Canada

Purpose: Atypical Femoral Fractures (AFFs) are commonly bilateral. The purpose of this study is to evaluate bilateral AFFs and to determine if the imaging features of both fractures are similar.

Materials and Methods: Imaging studies of 76 patients with bilateral AFFs from the Ontario AFF cohort were retrospectively reviewed (3 men, 73 women, age range 31.1 to 91 years, mean age 67.3 years). The time interval between fracture diagnoses was determined. For each fracture, the following imaging features were evaluated: location of fracture, femoral angle, length of cortical thickening, comminution, medial spike (proximal or distal fragment) and fracture orientation (superior/inferior). Associations between imaging findings on pairs of bilateral fractures were assessed with Spearman's correlation (r_s) and the Kappa (κ) statistic.

Results: Bilateral fractures (62 incomplete and 14 complete) are diagnosed within 12 months of each other in 59/76 cases (77.6%). Average time between fracture diagnoses was 10.2 months. 90% of bilateral fractures was diagnosed within 2.9 years of each other (range 0 to 120 months). There was a strong correlation between fracture location (r_s =0.68) with 58/76 cases (76.3%) of bilateral fractures occurring within a distance of less than 5 cm. 41/76 cases (53.9%) had a distance of less than 2.5 cm between bilateral fractures. There was moderate correlation between femoral angles (r_s=0.4) and weak correlation between length of cortical thickening (r_s=0.28). There was substantial agreement for medial spike location (κ=0.67) and fracture orientation (κ=0.62) and moderate agreement for lack of comminution (κ=0.42). These findings were independent of time between fractures.

Conclusion: Patients with bilateral AFFs are likely to be diagnosed with the second one within the first year of presentation of the first one. Bilateral fractures are likely to have similar imaging findings and location along the femur, regardless of the time interval between fractures.