Bone Reports 7 (2017) 164–171

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Effects of 3-year denosumab treatment on hip structure in Japanese postmenopausal women and men with osteoporosis

Teruki Sone[a,1], Naohiro Kon[b,*,1], Kenneth W. Gaither[c,1], Naoki Okubo[d], Taisuke Osakabe[e], Yutaka Nakayama[f], Masao Fukunaga[g], Masako Ito[h], Toshitaka Nakamura[i]

[a] Department of Nuclear Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan
[b] Medical Science Department, Daiichi Sankyo Co. Ltd., Tokyo, Japan
[c] Bioclinica, Inc., 11731 Northeast Glenn Widing Drive Portland, Oregon 97220, United States
[d] Biostatistics and Data Management Department, Daiichi Sankyo Co. Ltd., Tokyo, Japan
[e] Clinical Development Department, Daiichi Sankyo Co. Ltd., Tokyo, Japan
[f] Post-Marketing Regulatory Affairs Department, Daiichi Sankyo Co. Ltd., Tokyo, Japan
[g] Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan
[h] Center for Diversity and Inclusion, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan
[i] Touto Sangenjaya Rehabilitation Hospital, 1-24-3 Sangenjaya, Setagaya-ku, Tokyo 154-0024, Japan

ARTICLE INFO

Keywords:
Osteoporosis
Denosumab
RANK ligand
Hip structural analysis
Japanese
Bone quality

ABSTRACT

Denosumab, a human monoclonal antibody against RANK ligand, is shown to have strong anti-fracture effects in Japanese osteoporosis patients. However, there have been no data showing actions on Japanese bone architecture. Here we show that denosumab continuously improves several geometrical parameters calculated by hip structural analysis for 3 years. Compared to placebo, denosumab significantly increased bone mineral density, cortical thickness and cross sectional area in all of the three analyzed areas: the narrow neck, intertrochanter and femoral shaft. The subsequent derived mechanical parameters, cross-sectional moment of inertia, section modulus and buckling ratio, were also improved by denosumab. In addition, the improvement of these parameters was also observed in the patients that had switched from placebo to denosumab treatment. The present study suggests the structural evidence explaining the strong anti-fracture efficacy of denosumab and its significant effects on cortical bone in Japanese.

1. Introduction

Osteoporosis is a systemic skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture (Black and Rosen, 2016). Typical traits of the disease are cortical thinning and a deterioration of trabecular microstructure. Osteoporotic fractures lead to severe consequences, such as hospitalization, immobility for long periods, surgical treatment or significant increase of mortality risk (Bolland et al., 2010; Tarantino et al., 2016a).

The risk of fractures is estimated by bone strength, which is considered to be primarily due to bone mineral density (BMD) and bone quality (Lorentzon and Cummings, 2015). Bone strength is improved by treatment with several pharmacologic agents, which are classified as anabolic or antiresorptive agents (Black and Rosen, 2016; Russell, 2015; Appelman-Dijkstra and Papapoulos, 2015). The anabolic agent parathyroid hormone (PTH) stimulates osteoblasts to form new bone by activating its receptors. On the other hand, antiresorptives including bisphosphonates and denosumab, target osteoclast-mediated bone resorption. Bisphosphonates have been used in clinical medicine for > 40 years. After binding to bone matrix, bisphosphonates are internalized into osteoclasts. Bisphosphonates act as analogs of pyrophosphate enzyme substrates and interfere with several biochemical processes, which results in suppression of osteoclast activities. Denosumab is the first biologic therapy approved to treat osteoporosis. Denosumab inhibits bone resorption by binding to and inactivating RANK ligand (RANKL), a key mediator of osteoclast formation, maturation and

Abbreviations: RANK, receptor activator of nuclear factor kappa-B; HSA, hip structural analysis; BMD, bone mineral density; FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months; DIRECT, Denosumab fracture Intervention Randomized placebo Controlled Trial; DXA, dual-energy X-ray absorptiometry; PBO/DMAb, placebo/denosumab; DMAb/DMAb, denosumab/denosumab; ED, endocortical diameter; OD, outer diameter; CoTh, cortical thickness; CSA, cross sectional area; CSMI, cross sectional moment of inertia; SM, section modulus; BR, buckling ratio

* Corresponding author at: Medical Science Department, Daiichi Sankyo Co., Ltd., 3-5-1, Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japan.
E-mail address: konntgf@gmail.com (N. Kon).

[1] These authors equally contributed to this work.

https://doi.org/10.1016/j.bonr.2017.11.002
Received 4 April 2017; Received in revised form 7 November 2017; Accepted 13 November 2017
Available online 14 November 2017

activation.

In the pivotal phase 3 trial FREEDOM, subcutaneous administration of 60 mg denosumab every 6 months significantly reduced the risk of new vertebral, nonvertebral and hip fractures compared to placebo in predominantly postmenopausal Caucasian women with osteoporosis (Cummings et al., 2009). The study was extended to a total of 10 years of treatment, and the results showed continuous BMD increase, low fracture incidence and good safety profile (Bone et al., 2017). The continuous BMD increase by denosumab is clinically important, because the effects of bisphosphonate treatment appear to plateau earlier, after about 3 years (Russell, 2015). In addition, several studies revealed advantages of denosumab compared to bisphosphonates (Scott, 2014; Zebaze et al., 2014; Benjamin et al., 2016). For example, denosumab increases BMD and reduces markers of bone turnover to a significantly greater extent than bisphosphonates (Brown et al., 2009). The strong effects of denosumab are also observed in those who had switched from alendronate to denosumab treatment (Kendler et al., 2010).

In Japanese osteoporosis patients, the efficacy of denosumab was evaluated by the study called DIRECT, a double-blind, placebo-controlled trial with an open-label weekly 35 mg alendronate arm. The DIRECT study showed that 2-year treatment of denosumab significantly reduced incidence of new vertebral fracture by 74.0% compared to placebo (Nakamura et al., 2014). The following 12-month extension study showed that 3-year treatment of denosumab was associated with low fracture rates, persistent bone turnover marker reductions and continuous BMD increase (Sugimoto et al., 2015).

In addition to the BMD change, analyses of effects on bone quality parameters, including bone geometry, are important for understanding the basis of the strong anti-fracture efficacy of denosumab (Beck et al., 2008; Austin et al., 2012). To this point, hip structural analysis using dual-energy X-ray absorptiometry (DXA) data is useful to evaluate hip geometry (Beck and Broy, 2015), as demonstrated to be a good predictor of hip fracture risk by prospective studies (Rivadeneira et al., 2007; Kaptoge et al., 2008). The previous HSA study showed denosumab improves structural parameters for 2 years in Caucasian osteoporosis patients (Beck et al., 2008), supporting the good results shown by the FREEDOM study. Because several reports have indicated significant differences in hip axis length between Asian and Caucasian (Broy et al., 2015; Cummings et al., 1994), it is important in clinical pharmacology to clarify effects of denosumab on hip structure in Japanese. Thus, we investigated denosumab effects on the HSA parameters using data of the DIRECT study. In addition, the present study shows 3-year effect of denosumab on the HSA parameters for the first time.

2. Materials and methods

2.1. Study participants

DIRECT study consisted of a 2-year randomized, double-blind, placebo-controlled phase and a 1-year open-label extension phase, in which all subjects received denosumab. The study participants were described previously (Nakamura et al., 2014). The present analysis used DXA data of the total hip obtained at baseline (before the administration), 6, 12, 24 and 36 months after the start of the treatment with denosumab or placebo. While images for 952 patients were obtained for placebo/denosumab (PBO/DMAb) group and denosumab/denosumab (DMAb/DMAb) group in DIRECT study, it is impossible to analyze the images for 265 patients because the scanners used were not applicable to HSA. Thus, the images for 687 patients were used for the present HSA study.

2.2. Analysis of hip geometry

Quality control and analysis of DXA scans were performed by trained DXA technicians from Bioclinica (Oregon, USA) in a blinded manner. Bioclinica DXA technicians are annually tested to within 1.5% rmsCV of a gold standard set of images. Hip geometry was analyzed using Hologic Apex DXA software version 13.5 (Madison, WI) in accordance with a standardized HSA analysis protocol (Beck, 2002). The DXA technologists defined a global region of interest around the proximal femur and placed three analysis regions in their defined positions on the femur image within the DXA analysis software. The narrow neck region was placed perpendicular to the neck axis and at the narrowest section of the neck (Supplementary Fig. 1). The intertrochanteric region was placed in order to bisect the neck shaft angle, defined as the intersection of the neck and shaft midlines, and should rest above the lesser trochanter. The shaft region was placed perpendicular to the shift midline and 2 cm below the distal edge of the lesser trochanter. All regions were adjusted to include at least 1 but optimally 5 pixels of soft tissue in either end of the region. At follow-up visits, the three analysis regions were placed in the same way in order to match the baseline analysis as closely as possible. If the follow-up scan positioning was dissimilar to such a degree that the analysis regions could not be placed similarly to baseline, the scan was excluded.

The HSA program derives the geometry from lines of pixel values (mass profiles) traversing the bone at each of the three regions. All cross-sectional geometries are calculated from mass profile distributions converted to linear thickness by dividing each pixel value by the effective mineral density of fully mineralized tissue. Measurements include: BMD as average pixel value in the profile, bone outer diameter (OD), endocortical diameter (ED), mineralized bone cross-sectional area (CSA), average cortical thickness (CoTh), cross-sectional moment of inertia (CSMI) as BMD times square of the distance from the center of mass, section modulus (SM) as CSMI divided by D_{max} (maximum distance between the center of the mass and the outer cortex), buckling ratio (BR) as the ratio of bone diameter to average cortical thickness, and D_{max}. Neck and shaft sections are modeled as circular annuli with 60% and 100% of the CSA in the cortex respectively. The intertrochanteric region is modeled as an elliptical annulus with an anteroposterior diameter as the measured shaft width and 70% of the CSA in the cortex. Models are used for cortex estimates and buckling ratio but not for OD, CSA, CSMI and SM.

2.3. Statistical analysis

Statistical analysis included all randomized subjects who received at least one dose of investigational product and had a baseline and at least one post-baseline scan. The images for 687 patients were evaluable for HSA in the present study. Percent change from baseline in HSA parameters at each time point were analyzed using one-sample *t*-test. Comparisons between the treatment groups for the percent changes in HSA parameters at each time point were performed using a two-sample t-test. Missing values were imputed using the last observation carried forward method. The mean values and 95% confidence intervals over time were graphically presented.

3. Results

In the images obtained in DIRECT study for 952 patients, the images for 687 patients applicable to HSA were used in the present study. Baseline characteristics (sex, age, proximal femoral BMD and femoral neck BMD) in the 687 patients were similar to those in the total 952 participants (Table 1) (Nakamura et al., 2014). Geometric parameters in hip structure are depicted in Table 2. These background parameters were well matched between PBO/DMAb and DMAb/DMAb. A summary of all HSA parameters analyzed in the present study, difference between PBO/DMAb and DMAb/DMAb in mean percent change from baseline at month 12 is depicted in Table 3. HSA parameters were analyzed in three ways: 1) change from baseline at each time point in PBO/DMAb, 2) change from baseline at each time point in DMAb/DMAb and 3) comparison of the changes at each time point between PBO/DMAb and