Denosumab: recent update in postmenopausal osteoporosis

Inês Silva[1], Jaime C Branco[1,2]

ACTA REUMATOL PORT. 2012;37:302-313

ABSTRACT

Postmenopausal osteoporosis is a major concern to public health. Fractures are the major clinical consequence of osteoporosis and are associated with substantial morbidity, mortality and health care costs. Bone strength determinants such as bone mineral density and bone quality parameters are determined by lifelong remodeling of skeletal tissue. Receptor activator of nuclear factor-kB ligand (RANKL) is a cytokine essential for osteoclast differentiation, activation and survival. Denosumab (Prolia®) is a fully human monoclonal antibody for RANKL, which selectively inhibits osteoclastogenesis, being recently approved for the treatment of postmenopausal osteoporosis in women at a high or increased risk of fracture by the FDA in the United Sates and by the European Medicines Agency in Europe since June 2010. FREEDOM, DECIDE and STAND are the phase 3 trials comparing denosumab with placebo and alendronate in postmenopausal osteoporosis. The authors aim to update denosumab role in postmenopausal osteoporosis with a physiopathological review.

Keywords: RANK; RANKL; Osteoprotegerin; Denosumab; Postmenopausal osteoporosis.

INTRODUCTION

Osteoporosis (OP) is a skeletal disease associated with an imbalance in bone resorption and formation, which turns to a loss of bone mass and deterioration of bone microarchitecture[1]. This results in low bone mineral density (BMD) and poor bone quality, reduced bone strength and increased risk of fractures[2]. Is a worldwide public health problem with serious consequences in personal suffering and economical costs[3,4]. Clinical tools to diagnose OP and predict fracture risk are available but patients who are at risk for fracture or with a previous fracture are very often not identified or treated[3,5-8]. The bone remodeling unit (BRU) includes a sequence of events, during which osteoclasts (OC) resorb bone over a period of 3 weeks, creating cavities that are termed as remodeling space. The resorption is followed by osteoblast (OB) activation and osteoid formation, filling the cavities over a period of 3 months. When the matrix synthesis is finished OB become embedded in the matrix as osteocytes (that will function as mechanoreceptors)[3,9]. Bone remodeling permits the repair of microdamage, maintains normal skeletal mass and participates in regulation of systemic calcium homeostasis[9,10-13]. As bone resorption/formation is tightly coupled, inhibition of resorption eventually results in inhibition of formation[9] (Figure 1). OP therapy may be classified as antiresorptive (estrogens, bisphosphonates, calcitonin and raloxifene) or anabolic [teriparatide (recombinant human parathyroid hormone PTH1-34) or PTH1-84)]. Strontium ranelate appears to have both functions[3,9]. Research is focusing on drugs that target the remodeling cycle acting in OC, OB and osteocytes or molecules that control the signaling pathway for cell functioning and gene transcription[9]. Examples of studies on way include Glucagon-like peptide 214, cathepsin K inhibitors[15], PTH1-28[16], calcium-sensing receptors[17], Wingless (Wnt)/ -catenin pathway[18], sclerostin and Dickkopf-1[19], activin (fusion protein ACE-011)[20]. However, the discovery of the receptor activator of nuclear factor KB ligand (RANK ligand, RANKL) osteoprotegerin (OPG) and RANK as a RANKL/OPG/RANK signaling pathway for the bone balance brought advances to the understanding of healthy bone turnover, and to osteolytic and destructive bone diseases like OP, rheumatoid arthritis (RA), Paget's disease of bone and metastatic bone diseases[10,11]. RANKL was identi-

1. Serviço de Reumatologia do Centro Hospitalar de Lisboa Ocidental, Hospital de Egas Moniz, EPE
2. CEDOC - Faculdade de Ciências Médicas, Universidade Nova de Lisboa

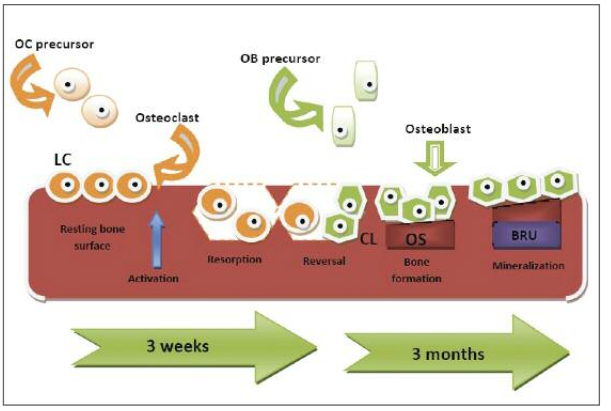

FIGURE 1. Bone remodeling sequences in healthy individuals. The bone remodeling unit (BRU) includes a sequence of events, during which osteoclasts (OC) resorb bone over a period of 3 weeks, creating cavities that are known as remodeling space. The resorption is followed by osteoblast (OB) activation and osteoid formation, filling the cavities over a period of 3 months. When the matrix synthesis is finished OB become embedded in the matrix as osteocytes (that will function as mechanoreceptors)[3,9]. Legend: BRU – bone remodeling unit; CL – cement line; LC – lining cells; OB – osteoblast; OC – osteoclast; OS – osteoid

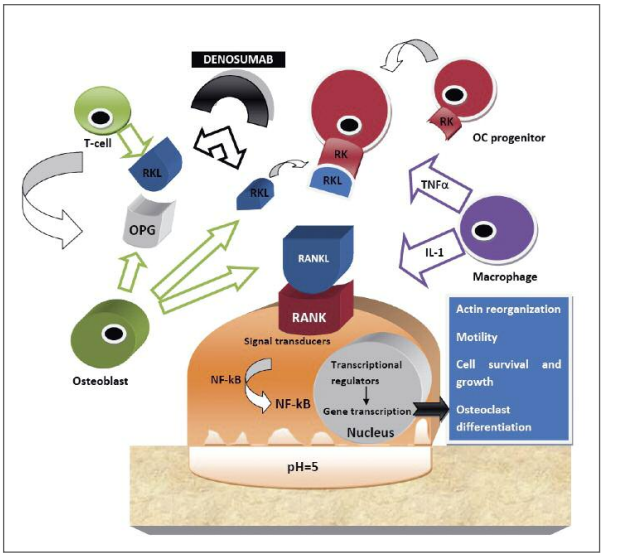

FIGURE 2. Control of osteoclastogenesis. Osteoclast (OC) differentiation is a contact-mediated process controlled by osteoblasts (OB). Membrane-bound receptor activator of nuclear factor kB (RANK or RK in the figure) ligand (RANKL or RKL in the figure) derived from OB and is necessary for OC differentiation. OB expression of RANKL is induced by hormones [e.g. parathyroid hormone (PTH) or cytokines (IL-6; PTH related protein)] and reduced by estrogen whereas osteoprotegerin (OPG) is suppressed by glucocorticoids or PTH. Soluble RANKL is also produced by activated T cells. Tumor necrosis factor-α (TNFα) stimulate RANKL release from OB and act on progenitors primed by RANKL to amplify osteoclastogenesis (with a gene transcription NF-kB mediated) in inflammatory conditions. RANKL and interleukine-1 (IL-1) act on OC to prevent their apoptosis. The postmenopausal decline in estrogen levels leads to overproduction of RANKL and increased OC-mediated bone resorption. The critical RANKL/RANK interaction is therapeutically disrupted by RANKL-specific monoclonal antibodies (denosumab)

fied as a potential target for therapeutic intervention in the treatment of these diseases. Possible strategies to down-regulate RANKL include inhibition of RANKL production, stimulation of endogenous OPG, and administration of exogenous OPG, soluble RANK or antibody to RANKL[2] (Figure 2). Denosumab (Prolia®, AMG 162; Amgen Inc., Thousand Oaks, California, USA) is a fully human monoclonal antibody (IgG2 immunoglobulin isotype) with a high affinity and specificity for RANKL[2,3,11], currently approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) for clinical use in postmenopausal women OP with high risk of fracture and for the treatment of bone loss associated with hormone ablation in men with prostate cancer[11,21].

This manuscript reviews Denosumab pharmacological and clinical data in postmenopausal osteoporosis, with a previous physiopathology overview.

ADULT SKELETON

PHYSIOLOGY

The adult human skeleton is a metabolically organ with a coupled bone turnover that maintains the equilibrium in the trabecular and cortical bone. The total amount of bone loss is proportional to the number of BRUs activated at the bone surface at a given time[10]. In the healthy adult, more than 1 million BRUs are active and up to 5-10% of existing bone is replenished annually. Full skeletal regeneration is accomplished once every decade[21]. High bone turnover diminishes bone strength independently of BMD, because excessive number of resorption cavities act as areas of stress that may be a source of microcracks[2,3,11]. This high turnover can eventually result in osteopenia or osteoporosis[3].

RANKL/OPG/RANK SIGNALING PATHWAY

OB are mononuclear cells responsible for the deposition of bone matrix and for OC regulation. They originate from mesenchymal stem cells (MSC) by the ac-

tion of transcription factors like core binding factor α1 (Cbfa-1) also known as Runx2, osterix (Osx), activating transcription factor 4 (ATF4), and bone morphogenic proteins (BMP) as BMP4[22]. OC are derived from mononuclear precursors in the myeloid lineage of hematopoietic cells that also originate macrophages. Macrophage-colony stimulating factor (M-CSF) expression by osteoblastic stromal cells is required for progenitor cells to differentiate into OC, but is unable to complete this process by its own[23]. The principal final mediator of osteoclastic bone resorption is RANKL, highly expressed by OB and T cells (mainly T helper cells 17)[3]. RANK is located on the cell membrane of OC and pre-OC and is a receptor for RANKL. RANKL/RANK binding stimulates OC differentiation and survival, resulting in increased bone resorption[3,11,21]. OPG is a "decoy receptor" for RANKL, preventing its interaction with RANK, OC differentiation, activation of mature OC and permits OC apoptosis[3,21] (Figure 2). RANKL/OPG ratio represents an important determinant of bone resorption. This ratio is decreased by estrogens, interleukin-4 (IL-4), IL-13, interferon-γ (IFN-γ), transforming growth factor- (TGF-), and increased by glucocorticoids, PTH, PTH-related protein, prostaglandins, IL-1, IL-17, tumor necrosing factor-α (TNF-α), 1,25-dihydroxyvitamin D (1,25vitD) and BMP[23,11,21]. The precise role of the RANKL/OPG/RANK signaling pathway in regulating bone remodeling and mass was validated by gene studies in mice, with genetic RANKL or its receptor deficiency and OPG overexpression resulting in osteopetrosis, and genetic OPG ablation resulting in osteoporosis[24-27]. The Wnt signaling in OB is also a source of OPG regulation. This pathway integrated with RANKL/OPG/RANK enabled to understand the normal and diseased bone[11]. Many familiar bone diseases are mediated by RANKL/OPG/ /RANK pathway[21] (Table I). Evidence is accumulating that bone remodeling is modulated through the interaction of OC and OB with immune cells, cytokines and circulating hormones[28]. It was demonstrated that activated T cells directly stimulate osteoclastogenesis through RANKL, and RANKL prolongs the survival of dendritic cells and thereby increases T cells activity[29]. Infection and malignancy concerns have been raised by inhibiting RANKL, however it seems that RANKL/ /OPG/RANK system does not have an essential role in immune function of adults, who already have a fully developed immune system[30].

POSTMENOPAUSAL OSTEOPOROSIS

Estrogen is a positive regulator of OPG expression and its decrease in postmenopausal women are associated with increased RANKL expression, which shifts the bone remodeling balance toward the bone resorption[31]. The incidence of postmenopausal OP is growing due to changing demographics and increasing life expectancy, which will also increase its economic and social burden fracture-related[31,32]. OP fractures occur more frequently in women, its frequency increases with age, and spine, hip and wrist are the skeletal sites typically associated to OP[31]. Vertebral fractures may result from relatively mild trauma in osteroporosis and

TABLE I[21]. REVIEW OF THE DISEASES MEDIATED BY DISRUPTIONS IN RANKL/OPG/RANK SIGNALING PATHWAY

RANKL/OPG/RANK-mediated diseases	Mechanism(s)
Postmenopausal osteoporosis	↑ bone marrow stromal cell expression of RANKL
Primary hyperparathyroidism	↑ RANKL, ¯ OPG expression by osteoblasts
Bone Paget's disease	↑ stromal cell expression of RANKL
Rheumatoid Arthritis	↑ RANKL expression by synoviocytes and T cells
Periodontal bone loss	↑ RANKL expression by activated T cells
Myeloma bone disease	↑ RANKL expression by myeloma cells
Osteolytic bone metastases	↑ RANKL expression by tumour cells
Humoral hypercalcaemia of malignancy	Parathyroid hormone related protein (PTHrP) mediated: ↑ RANKL, ↓ OPG by osteoblasts
Familiar expansile osteolysis	Activating mutations of the RANK gene
Idiopathic hyperphosphatasia (Juvenil Paget's disease)	Inactivating mutations of the OPG gene

Legend: OPG – osteoprotegerin; RANK – receptor activator of nuclear factor kappa B; RANKL – receptor activator of nuclear factor kappa B ligand.

are associated to an increased risk for subsequent fracture. Hip fractures are associated with worst outcomes and secondary complications, and their risk increases in women from the age of 70 years[31-33]. Healthcare costs due to OP are difficult to calculate as they include the costs of acute hospital care, loss of working days for family carers, longterm care and medication[31-33]. The International Osteoporosis Foundation (IOF) estimated that the number of osteoporotic fractures in 2000 was 3.79 million and the total direct costs resulting from these fractures was estimated at €31.7 billion, which is expected to increase to €76.7 billion by 2050[34]. Prevention of osteoporosis-related fractures appears to be essential to the quality of life and independence of postmenopausal women and prevent the economic burden[32-34].

OSTEOPOROSIS TREATMENT: DENOSUMAB AS A NEW OPTION

The ideal anti-osteoporotic agent would have to meet the following favorable biological properties: a rapid onset action, long duration effect, patient's compliance and persistence, documented cost-effectiveness and excellent safe profile[10,11]. Denosumab is a fully human monoclonal immunoglobulin G2 antibody that binds with high affinity and targets the activity of human RANK ligand , preventing it to interact with RANK on the OC surface, which turns into the disruption of cellular signaling of bone resorption OC-mediated[3,10,11,31]. Denosumab inhibits numerous aspects of OC differentiation and function (fusion, differentiation, attachment to bone, activation and survival), by inhibiting the intracellular signal pathways that are activated by the RANKL /RANK binding[10]. Denosumab does not bind to murine RANKL1, and does not cross-react with other human proteins of similar structure to RANKL, such as TNF-α, TNF- , TNF-related apoptosis-inducing ligand (TRAIL) or CD40 ligand[11,31].

PHARMACOKINETICS AND METABOLISM

The pharmacokinetics of denosumab is nonlinear with dose. Although the absorption, bioavailability, distribution, and elimination are not well defined, studies with similar IgG antibodies showed that subcutaneous denosumab is absorbed by the lymphatic system with subsequent drainage into the vascular system[2,3]. The bioavailability is probably 50-100% with a distribution that is about the same as the plasma volume, the clearance is probably by the reticuloendothelial system and no significant amount of denosumab seems to be filtered and excreted by the kidneys[35]. Subcutaneous administration is characterized by 3 stages: a prolonged absorption phase with the maximum serum concentration (at 5-21 days post-dose) increasing disproportionately than the increase in dose; a long duration phase with half-life of a maximum of 32 days; a rapid terminal phase when serum concentration is lower than 1000ng/ml[36]. The long duration of denosumab activity is probably due to a combination of a long half-life and a very potent antiresorptive effect at early stages of OC differentiation[2,10]. A feature that distinguishes denosumab from biphosphonates is the rapid reversibility of its antiresorptive effect once it has been eliminated and OC regeneration has occurred, since it is not incorporated in the bone matrix as the biphosphonates[3]. Its capacity to reduce bone resorption was measured by serum C-telopeptide (CTX-1), by 82% within 72 hours post-dose, with a sustained effect during the 6-month dosing interval[37].

PRE-CLINICAL STUDIES

The preclinical studies evaluating the RANKL/OPG/ /RANK role in bone showed: RANKL induces OC-like cells formation in cell cultures[38], recombinant OPG inhibits OC differentiation in a dose-dependent manner[39], osteotropic hormones and cytokines regulate RANKL and OPG expression in human-derived OB cell lines[40], OPG knockout mice develop OP and fragility fractures[41], RANKL and RANK knockout mices have osteopetrosis with the total absence of OC[24,25,42,43]. Human monoclonal antibodies (mAbs) are the fastest--growing category of mAb therapeutics entering clinical studies[44]. Murine antibodies are easier to produce, but are limited by safety issues and diminished efficacy owing to the immunogenicity of the mouse-derived protein sequences[44,45]. One path started to develop mAbs containing a combination of rodent-derived and human-derived sequences, resulting in chimeric and humanized mAbs. During the 2000s, human mAbs stand for 45% of the mAb candidates in the clinic and 88 are now in clinical development. Denosumab is one of the 7 mAbs currently approved for marketing in the United States[44-46]. Denosumab was generated by immunizing the XenoMouse with full-length human RANKL protein, producing a fully human IgG1 mAb known as AMG 161. Because human IgG1 can direct complement-dependent cytotoxicity or antibody-dependent cell cytotoxicity to target cells, appeared the

concern that AMG 161 could have a toxic profile caused by death of RANKL-producing cells. It was converted to noncytotoxic IgG2 mAb, AMG 162, with high affinity for human RANKL[45,48]. The difficulty of AMG 162 to recognize rodent RANKL has complicated pre-clinical studies and the relevant data were obtained from cynomolgus monkeys[45]. The majority of the preclinical studies in RANKL inhibition in mice and rats used other agents than denosumab. The most commonly used were fusion molecules of recombinant OPG or RANK and the Fc fragment of IgG, called OPG-Fc or RANK-Fc, respectively[3]. These studies demonstrated that recombinant OPG prevents bone loss in ovariectomized (OVX) rats[39], recombinant OPG decreases OC differentiation in normal mice, resulting in non-lethal osteopetrosis[39], recombinant OPG prevents bone loss in mice with low BMD that over-express TNF-α[49], RANKL inhibition increases bone mineralization and improves mechanical strength in the femur of young male rats[50], in aged OVX rats a combination of rat OPG and PTH increased BMD more than either agent alone[51].

In the cynomolgus monkeys the preclinical studies showed: 5-year-old male monkeys treated with denosumab had an increased bone mass and improved bone strength in femur and lumbar vertebral bodies[52], skeletal benefits were demonstrated with the RANKL inhibition in RA models[53], ovariectomy models[54], multiple myeloma models[55] and inflammatory bowel disease models[56]. Knocking technology has been recently used to create a genetically engineered mouse expressing a chimeric form of RANKL (human/murine) that is bound and neutralized by denosumab, which has been studied for evaluating the skeletal effects of denosumab in different circunstances[57,58].

CLINICAL STUDIES ON POSTMENOPAUSAL OSTEOPOROSIS

The first study of RANKL inhibition in humans was conducted with OPG-Fc, a phase 1 randomized, double-blind, placebo-controlled, sequential dose escalation study in healthy postmenopausal women. Each of the 52 subjects received a single subcutaneous dose of OPG-Fc 0.1, 0.3, 1.0, 3.0 mg/kg or placebo. It was shown that a single dose of OPG-Fc caused a rapid, reversible and dose-dependent suppression of bone resorption, with no adverse events (AEs) or neutralizing antibodies[59]. This provided support for further clinical studies.

Phase 1: a phase 1 study was conducted in 49 healthy postmenopausal women who received a single subcutaneous dose of denosumab 0.01, 0.03, 0.1, 0.3 and 3.0 mg/kg or placebo. All the cohorts had a follow-up of 6 months, except the highest doses (0.1, 0.3 and 3.0 mg/kg) that were followed 9 months. Pharmacological effect was assessed by urinary N-telopeptide (NTX) and seric serum bone-specific alkaline phosphatase (BSAP) levels. Rapid and reversible NTX reduction was sustained for 6 months. Later BSAP reduction occurred with a lesser magnitude. Denosumab was well tolerated with no drug-related serious adverse events (SAEs) reported or study discontinuation due to AEs. Infectious events were similar in both groups (33% in placebo versus 38% in denosumab). Two hospitalizations: severe undetermined abdominal pain (in the 0.01mg/kg group) and a cholecystitis (in the 0.1 mg/kg group). Mild transient dose-dependent decrease in albumin-adjusted serum calcium and dose-dependent early increase in PTH levels[36] (Table II).

Phase 2: a randomized phase 2 study was performed to evaluate the efficacy and safety of denosumab compared with alendronate or placebo, in postmenopausal women with low bone mass (lumbar vertebra T-score:-1.8 to -4 or total hip or femoral neck T-score: -1.8 to -3.5). The 412 patients enrolled in this study were randomized to receive subcutaneous denosumab 6, 14, or 30 mg every 3 months; 14, 60, 100, or 210 mg every 6 months; open-label alendronate 70 mg/week; or placebo for 24 months. Primary endpoint was the percent change in BMD at the lumbar spine at 12 months compared to baseline. At 12 months denosumab group achieved an increase of 3.0 to 6.7% in lumbar spine BMD compared to baseline, with a dose-dependent rapid and sustained decrease in the bone turnover markers (BTMs). At 24 months the patients continued the study with a 60mg subcutaneous denosumab dose each 6 months and were randomized to continue treatment for 24 months, discontinue, or switch to placebo for 12 months and resume denosumab treatment for 12 months. The 48 months denosumab group treatment showed an increase in BMD at the lumbar spine (9.4% to 11.8%) and total hip (4.0 to 6.1%) with the BTMs remaining suppressed, while the placebo group showed a loss of 2.4% and 3.5% at the spine and hip, respectively. Within the first 12 months of denosumab discontinuation BMD decreased 6.6% in the lumbar spine and 5.3% in total hip. Retreatment with denosumab at month 36 increased

TABLE II. RESUME OF THE PHASE I AND II TRIALS OF DENOSUMAB IN POSTMENOPAUSAL WOMEN

Authors	Study phase	Number and mean age of patients/subjects	Study characteristics	Study duration	Primary endpoints	Key efficacy results	Key safety profile
Bekker et al[36]	I	49 healthy PMW; 59.6 years	RT, DB, SD, DE	6 or 9 months	Bone antiresorptive depending on dosing	Dose-dependent, activity and safety rapid (within 12h), profound (up to 84%) and and sustained (up to 6 months) decrease in bone turnover	No related SAEs, no clinical significantly laboratory changes
McClung et al[37]	II	412 PMW with low BMD; 63 years	RT, PC, dose-ranging, also included an open-label ALN group (70mg orally, once weekly)	12 months	Percent change from baseline in BMD at LS, changes in BTMs	Increased BMD (LS: 3.0 to 6.7% compared with a decrease of 0.8% in placebo) and decreased BTMs (within 72h) compared to placebo	No significant differences between the ALN, denosumab and placebo profiles
Lewiecki et al[61]	II	412 PMW with low BMD; 63 years	Extension study of McClung et al; same design	24 months	Percent change from baseline in BMD at LS, changes in BTMs	Continuing increases in BMD (4.13% to 8.89% compared with – 1.18% with placebo) and maintained suppression of BTMs	6 cases of infections associated to hospitalization in the denosumab group; similar AEs
Miller and et al[62]	II	412 PMW with low BMD; 63 years	Extension study of McClung et al; study design reviewed, modification of the denosumab regimens; in the ALN group no additional ALN for the 24 months period extension	48 months	Percent change from baseline in BMD at LS, changes in BTMs New endpoints: effects of discontinuing and reinitiating denosumab on bone density and remodeling	Significant increases in BMD (LS: 9.4% to 11.8% and TH: 4.0% to 6.1%) and sustained suppression of BTMs; discontinuing therapy for 24 months decreased BMD to baseline levels; retreatment for 12 months increased LS BMD by 9% from original baseline values.	Similar AEs, more infections as SAEs in the denosumab group
Seeman et al[68]	II	247 osteopenic, osteoporotic PMW; 60.6 years	DB; patients randomized to denosumab, ALN or placebo	12 months	Evaluation of the denosumab and ALN effects on cortical and trabecular microarchi-tecture with pQCT	Better effects with denosumab than ALN	Incidence of AEs similar in both groups

Legend: AEs – adverse events; ALN- alendronate; BMD – bone mineral density; BTMs – bone turnover markers; DB – double-blinded; DE – dose-escalation; LS – lumbar spine; PC- placebo-controlled; PMW – postmenopausal women; pQCT – peripheral quantitative computed tomography; RT – randomized trial; SAEs – serious adverse events; SD – single-dose

TABLE III. RESUME OF THE PHASE III TRIALS OF DENOSUMAB IN POSTMENOPAUSAL OSTEOPOROSIS TREATMENT

Study	Number and mean age of patients	Baseline T-score	Study characteristics	Study duration	Primary endpoints	Key efficacy results	Key safety profile
FREEDOM[63]	7868 osteoporotic PMW; 72.3 years	< -2.5 at LS or TH and ≥-4.0 at both sites	RT, pivotal, international; largest phase III trial; denosumab vs placebo; treatment of PMO	36 months	Reduction in incident morphometric new vertebral fracture	Denosumab reduced the risk of vertebral (68%), hip (40%) and nonvertebral (20%) fractures	Similar AEs and SAEs compared to placebo
DECIDE[65]	1189 PMW naive with low BMD; 64.4 years	≤-2.0 at LS or TH	Multi-center, DB, non--inferiority; head-to-head comparison denosumab vs ALN	12 months	Changes in BMD at the TH, FN, LS and DR from baseline	Greater increases in BMD at all measured skeletal sites in denosumab group	Similar overall rates of AEs and SAEs in both groups
STAND[66]	504 osteopenic--osteoporotic PMW pretreated with ALN; 67.6 years	<-2.0 to ≥ -4.0 at LS or TH	Multi-center, DB, non--inferiority; head-to-head comparison denosumab vs ALN	12 months	TH BMD, bone remodeling and safety at 12 months	Transition to denosumab increased BMD (1.9% denosumab vs 1.05% ALN) and reduced BTMs to a greater extent than continued ALN	Similar overall rates of AEs and SAEs in both groups

Legend: AEs – adverse events; ALN- alendronate; BMD – bone mineral density; BTMs – bone turnover markers; DB – double-blinded; DR – distal radius; FN - femoral neck; LS – lumbar spine; NA – not available; PC- placebo-controlled; PMI – polar moment of inertia; PMO – postmenopausal osteoporosis; PMW – postmenopausal women; pQCT – peripheral quantitative computed tomography; RT – randomized trial; SAEs – serious adverse events; SD – single-dose; TH – total hip; vBMD – volumetric BMD; vBMC – volumetric bone mineral content.

BMD to an extend similar to that observed with denosumab initial treatment. By month 48, BMD increased 9% at the lumbar spine and 3,9% at the total hip from baseline and the BTM values were similar to those of the continuous treatment group. In 3.2% of denosumab patients occurred infections, all were common community-acquired (no opportunistic infections), with required hospitalization solved with standard antibiotics. This original study was extended 4 additional years with all patients switched to denosumab 60 mg/6 months subcutaneous and a further analysis 2 years after (6 years of denosumab treatment) reported an BMD increase of 13.3% at the lumbar spine with sustained suppression of BTMs[37,60-62] (Table II).

PHASE 3:

TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

"Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months" (FREEDOM)[63], randomized 7668 postmenopausal women with osteoporosis into 2 groups: placebo or subcutaneous denosumab 60mg/6 months. Primary endpoint was a reduction in the incidence of new radiographic vertebral fractures in a 3-years period. Secondary endpoints were reduction in hip and other nonvertebral fractures and changes in BMD and BTMs. Denosumab group presented a 68% reduction in new vertebral fracture risk compared to placebo (2.3% vs. 7.2%; p<0.0001), 40% reduction in the hip fracture (0.7% denosumab vs. 1.2% placebo; p=0.036), and 20% reduction in the nonvertebral fractures risk (6.5% denosumab vs. 8.0% placebo; p=0.011). Denosumab group showed a significantly increase in BMD at all skeleton, mainly in the

forearm. No differences of total incidence of AEs or SAEs were reported in both groups. The incidence of serious infections was similar in both groups. Infections resulting in death were 0.2% in both groups. Few denosumab patients were diagnosed endocarditis (n=3), pancreatitis (n=8), eczema was reported in 3% of denosumab group versus 1.7% in placebo group (p<0.001). Cellulitis as an SAE occurred in 0.3% (12/3886) in the denosumab group versus less than 0.1% (1/3876) in the placebo group (p=0.002). This study was extended for 2 years with all patients switched to open-label denosumab 60 mg/6 months (with a significantly CTX-1 reduction and BMD increase[64]), and then it was extended 5 more years to complete a total of 10 years of denosumab exposition. Authors concluded that denosumab given subcutaneously twice yearly for 36 months reduced the risk of new vertebral, nonvertebral and hip fractures in women with OP.

Head-to-head comparison with Alendronate

"Determining Efficacy: Comparison of Initiating Denosumab Versus Alendronate" (DECIDE)[65], a double-blind, double-dummy noninferiority 1-year study to compare the effects of denosumab and alendronate on BMD and BTM in naïve postmenopausal women (n=1189) with T-score of lumbar spine or total hip <-2. Patients were randomized to receive subcutaneous denosumab 60mg/6months plus oral placebo/week or oral alendronate 70mg/week plus subcutaneous placebo/6months. The primary endpoint was percent change from baseline in total hip BMD at month 12 and the secondary endpoints were percent change in femoral neck, trochanter, lumbar spine and one-third distal radius BMD, and changes in BTM. Denosumab group showed a greater BMD increase at the total hip versus placebo (3.5% vs. 2.6%; p<0.0001) and a greater reduction in BTMs compared to alendronate. The overall incidence of AEs, SAEs, infections or neoplasms was similar between both groups. Authors concluded that denosumab was associated with both significantly more reduction in bone resorption and greater gains in BMD at all measured skeletal sites compared to alendronate.

Transitioning from Alendronate to Denosumab

"Study of Transitioning from Alendronate to Denosumab" (STAND)[66], a randomized, double-blind, double-dummy, parallel-group, 1-year study in postmenopausal women (n=504) previously treated with alendronate at least 6 months, and with a lumbar spine or total hip T-score of -2.0 to -4.0. The primary endpoint was percent change in BMD at the total hip at 12 months for denosumab compared to alendronate. The study design allowed testing the primary endpoint for superiority if noninferiority was demonstrated. At 12 months denosumab group presented a significantly greater increase in BMD at the total hip (denosumab 1.9% vs. alendronate 1.05%; p<0.0001), lumbar spine, and distal one-third radius, compared with continuing of alendronate. AEs and SAEs were similar in both groups. Authors concluded that postmenopausal women with low BMD can be safely transitioned from weekly oral alendronate to 6-monthly subcutaneous denosumab to achieve an incremental increase in bone mass.

FURTHER CLINICAL STUDIES

Histology and Histomorphometry with Denosumab

Reid et al[67], collected iliac crest biopsies from FREEDOM and STAND populations, after 12, 24 and 36 months of denosumab exposition. In the FREEDOM study median eroded surface was reduced by greater than 80% and OC were absent from greater than 50% of biopsies in the denosumab group. It was shown a reduction in fractures in the same cohort of patients in whom there was such a clear histological evidence of reduced turnover. In STAND study, the histomorphometry indicates that denosumab 60mg/6months produces greater inhibition of turnover than occurs with alendronate 70mg/week, but without evidence of any untoward interaction after the transition from alendronate to denosumab.

EFFECTS OF DENOSUMAB ON BONE MICROARCHITECTURE

Seeman et al[68], conducted a double-blind pilot study to compare the effect of denosumab and alendronate on cortical and trabecular microarchitecture at the radius and tibia in postmenopausal women using a quantitative computed tomography (QCT) and a high-resolution peripheral QCT (HR-pQCT). The women were randomized to receive subcutaneous denosumab 60mg/6months (n=83), oral alendronate 70mg/week (n=82) or placebo (n=82). Trabecular BMD and cortical thickness at the distal radius at month 12 decreased in the placebo group while was preserved in alendronate group. Denosumab prevented the decline or improved these variables. Similar results were achieved in the tibia.

DENOSUMAB IN PATIENTS WITH RENAL IMPAIRMENT

Block et al[69], conducted a phase 1 study to evaluate the pharmacokinetics, pharmacodynamics and safety of a single dose of 60mg subcutaneous denosumab in 55 patients with different degrees of renal function. Results showed that the renal impairment did not affect the denosumab pharmacokinetics and pharmacodynamics, and no dose adjustment is necessary in impairment renal function. About 30% of patients with severe renal function and hemodialysis showed symptomatic hypocalcaemia.

BESIDE POSTMENOPAUSAL OSTEOPOROSIS TREATMENT

Prevention of postmenopausal osteoporosis

"Denosumab Fortifies Bone Density" (DEFEND)[70], was a randomized, placebo-controlled, trial to evaluate efficacy and safety of denosumab in postmenopausal women with osteopenia.

Denosumab is currently being studied for other indications as RA bone erosions, bone loss associated with androgen deprivation therapy, bone loss associated with aromatase inhibitor therapy and for the treatment of bone metastases. However these studies are beyond the scope of this paper.

TABLE IV. REPORTED DIFFERENCES BETWEEN DENOSUMAB AND THE BIPHOSPHONATES

Denosumab compared to biphosphonates

- Denosumab blocks osteoclasts formation, function and survival while biphosphonates cause loss of resorptive function but "disabled" osteoclasts may persist[78]
- Exerts its effect from within the extracellular fluid[67] Rapid offset of action at about 6 months[11,57]
- Induces more rapid and greater reduction in bone remodeling[63]
- Superior pharmacokinetic properties (better distribution, no excretion of kidneys)[10]
- Greater increase in bone mineral density[64]
- Positive effect on both cancellous and cortical bone[3,72]
- Better strength indexes and geometrical bone variables[67,68]
- Completely reversible effect and no accumulation in bone[3]
- Possible non-blunting effect on subsequent anabolic therapy[10]
- Better patient's convenience and compliance[1]
- Denosumab was the first anti-bone resorbing agent that showed to halt bone erosions in Rheumatoid Arthritis[11]

SAFETY AND TOLERANCE

In the DEFEND, DECIDE, and STAND studies, AEs and SAEs, including infections and malignancies, were similar in both groups[33]. In DECIDE the most common types of infections were nasopharyngitis, influenza and upper respiratory tract infections. In STAND were nasopharyngitis and bronchitis[1]. In the FREEDOM study the only significant AE were cellulitis and eczema[71,72]. The longest exposure to denosumab reported to date is 6 years. No significant differences in infections, neoplasms were reported as SAEs for denosumab[11]. There were no denosumab-related cases of osteonecrosis of jaw, fracture repair problems, changes in white blood cells counts, T, B, or natural killer cell counts, immunoglobulins or antibodies to denosumab[1,11].

COST-EFFECTIVENESS PROFILE

Affordability of a drug therapy is a concern for healthcare system and patients[73]. Hiligsmann et al[74], assessed the potential cost effectiveness of denosumab in the treatment of postmenopausal osteoporotic women in an updated version of a validated Markov microsimulation model populated with cost and epidemiological data from Belgium and a base-case population defined from FREEDOM. It was concluded that denosumab is cost effective compared with no treatment[74] and oral bisphosphonates[75] for postmenopausal Belgian women similar to FREEDOM population. Additional published studies with data from England, Wales and Sweden concluded that denosumab has a higher probability of being cost-effective in some patients subgroups[76,77]. A cost-utility analysis of denosumab versus standard care (alendronate and colecalciferol) in the treatment of post-menopausal osteoporosis in Portugal concluded that denosumab is a cost-effective therapeutic strategy with an Incremental Cost-effectiveness Ratio (ICER) OF 14.887 € per Quality Adjusted Life Year (QALY) gained. The analysis was undertaken from a NHS perspective, efficacy data for denosumab was taken from FREEDOM and the comparator was taken from a meta-analysis conducted by National Institute for Health and Clinical Excellence (NICE). Epidemiological Portuguese data were complemented with Swedish data whenever the former were unavailable. The model pre-

dicts that relative to the comparator, denosumab would prevent 12 hip, 22 vertebral, 2 wrist and 1 other osteoporotic fractures, per 1000 patients, over a 10 years period, and the probability of cost-effectiveness was between 91% and 64%[78,79].

DIFFERENCES BETWEEN DENOSUMAB AND THE BIPHOSPHONATES

The effect of RANKL inhibition is quite unique among antiresorptive agents. Table IV shows how denosumab differs from the effects of byphosphonates on bone in several aspects[11,31,67,81].

CONCLUSION

In postmenopausal women with osteoporosis denosumab reduced the risk of vertebral and nonvertebral fractures versus placebo. In those with low BMD or OP it increased BMD and decreased BTMs more than alendronate, both in treatment-naïve and who switched from alendronate. Denosumab was safety and well tolerated, being cost-effective.

CORRESPONDENCE TO
Inês Maria Crispim Gomes da Silva
Alta do Lumiar, Rua Helena Vaz da Silva nº4 3ºD
1750-429 Lisboa
E-mail: inescrispin@hotmail.com

REFERENCES

1. Moen AD, Kean SJ. Denosumab: a review of its use in the treatment of postmenopausal osteoporosis. Drugs Aging 2011;28:63-82.
2. Lewiecki EM. Denosumab update. Current Opinion in Rheumatology 2009;21:369-373.
3. Lewiecki EM. Denosumab: an investigational drug for the management of postmenopausal osteoporosis. Biologics: Targets and Therapy 2008;2:645-653.
4. Burge R, Dawson-Hughes B, Solomon DH. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005-2025. J Bone Miner Res 2007;22:465-475.
5. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int 2005;16:581-589.
6. Solomon DH, Morris C, Cheng H, et al. Medication use patterns for osteoporosis: an assessment of guidelines, treatment rates, and quality improvement interventions. Mayo Clin Proc 2005;80:194-202.
7. Johnell O, Kanis JA, Odén A, et al. Fracture Risk following an osteoporotic fracture. Osteoporos Int 2004;15:175-179.
8. Feldstein A, Elmer PJ, Orwoll E, Herson M, Hillier T. Bone mineral density measurement and treatment for osteoporosis in older individuals with fractures – a gap in evidence-based practice guideline implementation. Arch Intern Med 2003;163:2165-2172.
9. Deal C. Future therapeutic targets in osteoporosis. Current Opinion in Rheumatology 2009;21:380-385.
10. Charopoulos I, Orme S, Giannoudis P. The role and efficacy of denosumab in the treatment of osteoporosis: an update. Expert Opin Drug Saf;doi:10.1517/ard2010.
11. Geusens P. Emerging treatments for postmenopausal osteoporosis – focus on denosumab. Clinical Interventions in Aging 2009;4:241-250.
12. Anastasilakis AD, Toulis KA, Goulis DG, et al. Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis. Horm Metab Res 2009;41:721-729.
13. Bolland MJ, Grey AB, Gamble GD, Reid IR. Effect of osteoporosis treatment on mortality: a meta-analysis. J Clin Endocrinol Metab 2010;95:1174-1181.
14. Henriksen DB, Alexandersen P, Hartmann B, et al. GLP-2 significantly increases hip BMD in postmenopausal women: a 120-day study. J Bone Miner Res 2007;22(suppl1):S37.
15. Gauthier JY, Chauret N, Cromlish W, et al. The discovery of odanacatib (MK-0822), a selective inhibitor of cathepsin K. Bioorg Med Chem Lett 2008;18:923-928.
16. Okazaki M, Potts JT, Gardella TJ. Identification and optimization of residues in PTH and PTHrP that determine altered modes of binding to the PTH/PTHrP receptor. J Bone Miner Res 2008;23:S103.
17. Brown EM. The calcium-sensing receptor: physiology, pathophysiology and CaR-based therapeutics. Subcell Biochem 2007;45:139-167.
18. Baron R, Rawadi G. Targeting the Wnt/beta-catenin pathway to regulate bone formation in the adult skeleton. Endocrinology 2007;148:2635-2643.
19. Padhi D, Stouch B, Fang L. Antisclerostin antibody increases markers of bone formation in healthy postmenopausal women. J Bone Miner Metab 2007;22 (Suppl 1):S37.
20. Ruckle J, Jacobs M, Kramer W. A single dose of ACE-011 is associated with increases in bone formation and decreases in bone resorption markers in healthy postmenopausal women. J Bone Miner Res 2007;22 (Suppl 1):S38.
21. Romas E. Clinical applications of RANK-ligand inhibition. Internal Medicine Journal 2009;39:110-116.
22. Caetano-Lopes J, Canhão H, Fonseca JE. Osteoblasts and bone formation. Acta Reumatol Port 2007;32:103-110.
23. Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Archives of biochemistry and biophysics 2008;473:139-146.
24. Kong YY, Yoshida H, Sarosi I. OPG is a key regulator of osteoclastogenesis, lymphocyte development and lymph-node organogenesis. Nature 1999;397:315-323.
25. Li J, Sarosi I, Yan XQ. RANK is the intrinsic hematopoietic cell surface receptor that controls osteoclastogenesis and regulation of bone mass and calcium metabolism. Proc Natl Acad Sci U S A 2000; 97:1566-1571.
26. Bucay N, Sarosi, Dunstan CR. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev 1998;12:1260-1268.
27. Mizuno A, Amizuka N, Irie K. Severe osteoporosis in mice lacking osteoclastogenesis inhibitory factor/osteoprotegerin. Biochem Biophys Res Commun 1998;247:610-615.
28. Clowes JA, Riggs BL, Khosla S. The role of the immune system in the pathophysiology of osteoporosis. Immunol Rev 2005;208:207-227.

29. Xing L, Schawrz EM, Boyce BF. Osteoclast precursors, RANKL/RANK, and immunology. Immunol Rev 2005;208:19-29.
30. Stolina M, Dwyer D, Morony S. Rats and mice overexpressing soluble OPG have high bone mass but no alteration in immunological parameters or lymphocyte function. Arthritis Rheum 2005;52:S708.
31. Singer A, Grauer A. Denosumab for the management of postmenopausal osteoporosis. Postgraduate Medicine 2010;122: 176-187.
32. Reginster JY. Antifracture efficacy of currently available therapies for postmenopausal osteoporosis. Drugs 2011;71:65-78.
33. Lewiecki EM. Denosumab for joints and bones. Current Rheumatology Reports 2009;11:196-201.
34. Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. Bone 2006;38(2 Suppl 1):S4-9.
35. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci 2004;93:2645-2668.
36. Beckker PJ, Holloway DL, Rasmussen AS, et al. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res 2004;19:1059-1066.
37. McClung MR, Lewiecki EM, Cohen SB, et al. Denosumab in postmenopausal women with low bone mineral density. N Eng J Med 2006;354:821-831.
38. Matsuzaki K, Udagawa N, Takahashi N, et al. Osteoclast differentiation factor (ODF) induces osteoclast-like cell formation in human peripheral blood mononuclear cell cultures. Biochem Biophys Res Commun 1998;246:199-204.
39. Simonet WS, Lacey DL, Dunstan CR, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 1997;89:309-319.
40. Hofbauer LC, Khosla S, Dunstan CR, et al. Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. Endocrinology 1999;140:4367-4370.
41. Bucay N, Sarosi I, Dunstan CR, et al. Osteoprotegerin-deficient mice develop early onset osteoporosis and arterial calcification. Genes Dev 1998;12:1260-1268.
42. Lacey DL, Tan HL, Lu J, et al. Osteoprotegerin ligand modulates murine osteoclast survival in vitro and in vivo. Am J Pathol 2000;157:435-448.
43. O'Brien EA, Williams JH, Marshall MJ. Osteoprotegerin ligand regulates osteoclast adherence to the bone surface in mouse calvaria. Biochem Biophys Res Commun 2000;274:281-290.
44. Nelson AL, Dhimolea E, Reichert JM. Development trends for human monoclonal antibody therapeutics. Drug Discovery 2010;9:767-774.
45. Schwarz EM, Ritchlin CT. Clinical development of anti-RANKL therapy. Arthritis Research and Therapy 2007:9(Suppl 1):S7(doi:10.1186/ar2171).
46. Scallon Bj, Moore Ma, Trinh H, Knight DM, Ghrayeb J. Chimeric anti-TNF-alpha monoclonal antibody cA2 binds recombinant transmembrane TNF-alpha and activates immune effector functions. Cytokine 1995:7:251-259.
47. Kostenuik PJ. Osteoprotegerin and RANKL regulate bone resorption, density, geometry and strength. Curr Opin Pharmacol 2005;5:618-625.
48. Biot J, Fasano C, Santos CD. D'orthoclone au dénosumab – l'expansion des anticorps monoclonaux à des fins thérapeutiques. Medicine Sciences 2009;25:1177-1182.
49. Schett G, Redlich K, Hayer S, et al. Osteoprotegerin protects against generalized bone loss in tumor necrosis factor-transgenic mice. Arthritis Rheum 2003;48:2042-2051
50. Ross AB, Bateman TA, Kostenuik PJ, et al. The effects of osteoprotegerin on the mechanical properties of rat bone. J Mater Sci Mater Med 2011;12:583-588.
51. Kostenuik PJ, Capparelli C, Morony S, et al. OPG and PTH-(1--34) have additive effects on bone density and mechanical strength in osteopenic ovariectomized mice. Bone 2004;142: 4295-4304.
52. Atkinson JE, Cranmer P, Saunders T. Denosumab (AMG 162), a fully human RANKL antibody, increases bone mass and bone strength in cynomolgus monkeys. J Bone Miner Res 2005;20(Suppl 1):S294.
53. Redlich K, Hayer S, Maier A, et al. Tumor necrosis factor alpha-mediated joint destruction is inhibited by targeting osteoclasts with osteoprotegerin. Arthritis Rheum 2002;46:785-792.
54. Kostenuik PJ, Bolon B, Morony S, et al. Gene therapy with human recombinant osteoprotegerin reverses established osteopenia in ovariectomized mice. Bone 2004;34:656-664.
55. Vanderkerken K, De Leenheer E, Shipman C, et al. Recombinant osteoprotegerin decreases tumor burden and increases survival in a murine model of multiple myeloma. Cancer Res 2003;63:287-289.
56. Byrne FR, Morony S, Warmington K, et al. CD4+CD45RBHi T cell transfer induced colitis in mice is accompanied by osteopenia which is treatable with recombinant human osteoprotegerin. Gut 2005;54:78-86.
57. Kostenuik PJ, Warmington K, Grisanti M, et al. RANKL inhibition with (denosumab) AMG 162, a fully human MAb, causes sustained suppression of bone resorption and increased BMD in knockin mice expressing humanized RANKL. J Bone Miner Res 2005;20 (Suppl 1):S261.
58. Ferrari SL, Pierroz D, Bonnet N. A comparison of denosumab and alendronate in combination with PTH in ovariectomized knockin mice expressing humanized RANKL. J Bone Miner Res 2007;22(Suppl 1):S37.
59. Beckker PJ, Holloway D, Nakanishi A, et al. The effect of a single dose of osteoprotegerin in postmenopausal women. J Bone Miner Res 2001;16:348-360.
60. Bogado CE, Zanchetta MB, Boailchuk JA, Massari FE, Zanchetta JR. Denosumab: what's new?. Curr Osteoporos Rep 2011;9:12-19.
61. Lewiecki EM, Miller PD, McClung MR, et al. Two-years treatment with denosumab (AMG 162) in a randomized phase 2 study of postmenopausal women with low BMD. J Bone Miner Res 2007;22:1832-1841.
62. Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on the bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy. A randomized blinded phase 2 clinical trial. Bone 2008;43:222-229.
63. Cummings SR, Martin JS, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Eng J Med 2009;361:756-765.
64. Papapoulos S, Chapurlat R, Brandi ML, et al. Five-year denosumab treatment of postmenopausal women with osteoporosis: results from the first two years of the freedom trial extension. JBMR;2010; DOI-10.1002/jbmr.251.
65. Brown JP, Prince RL, Deal C, et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res

2009;24:153-161.
66. Kendler DL, Roux C, Benhamou CL, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res 2010;25:72-81.
67. Reid IR, Miller PD, Brown JP, et al. Effects of denosumab on bone histomorphometry: the FREEDOM and STAND studies. J Bone Miner Res 2010;25:2256-2265.
68. Seeman E, Delmas PD, Hanley DA, et al. Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. J Bone Miner Res 2010;25:1886--1894.
69. Block G, Bone HG, Fang L. A single dose study of deonsumab in patients with various degrees of renal impairment. Am J Kid Dis 2010;55:A46.
70. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab 2008;93:2149-2157.
71. Iqbal J, Sun L, Zaidi M. Denosumab for the treatment of osteoporosis. Curr Osteoporos Rep 2010;8:163-167.
72. Pageou SC. Denosumab. Landes Bioscience 2009;1:210-215.
73. Lewiecki EM. Clinical use of denosumab for the treatment for postmenopausal osteoporosis. Current Medical Research and Opinion 2010;26:2807-2812.
74. Hiligsmann M, Reginster JY. Potential cost-effectiveness of denosumab for the treatment of postmenopausal osteoporotic women. Bone 2010;47:34-40.
75. Hiligsmann M, Reginster JY. Cost Effectiveness of Denosumab Compared with Oral Bisphosphonates in the Treatment of Post-Menopausal Osteoporotic Women in Belgium. Pharmacoeconomics 2011;29:895-911.
76. Scotland G, Waugh N, Royle P, et al. Denosumab for the prevention of osteoporotic fractures in post-menopausal women: a NICE Single Technology Appraisal. Pharmacoeconomics 2011; Epub ahead of print Aug 20.
77. Jönsson B, Ström O, Eisman JA, et al. Cost-effectiveness of Denosumab for the treatment of postmenopausal osteoporosis. Osteoporos Int. 2011 Mar;22:967-982. Epub 2010 Oct 9.
78. Pereira JA, Cristino J, Perelmann J, et al. O uso de recursos e custos dos diferentes tipos de fracturas osteoporóticas em Portugal – estimativas na perspectiva do Serviço Nacional de Saúde e do Estado. Acta Reumatol Port 2011;36:31(sup).
79. Cristino J, Canhão H, Perelman J, Santos C, Pereira J. Cost-utility analysis of denosumab versus standard care in the treatment of post-menopausal osteoporosis in Portugal. The Journal of The International Society for Pharmacoeconomics and Outcomes Research 2011;14:A128.
80. Baron R, Ferrari S, Graham R, Russel G. Denosumab and biphosphonates: differents mechanisms of action and effects. Bone 2011;48:677-692.

10TH INTERNATIONAL CONGRESS ON SLE

Buenos Aires, Argentina
18 a 21 Abril 2013