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Mini-Review

Denosumab

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Denosumab is an anti-receptor activator of nuclear factor (NF)-kappaB (RANK) ligand human monoclonal antibody studied as a treatment for postmenopausal osteoporosis (PMO) and bone destruction due to rheumatoid arthritis (RA) or metastatic cancers. As of February 2009, the candidate was undergoing US Food and Drug Administration review, and might be approved by October 2009. Late phase clinical trials demonstrated that denosumab possesses a similar safety profile to bisphosphonates and that it can be either equally or more effective than bisphosphonates at preventing bone loss due to PMO, RA or cancer treatment and metastases.

Introduction

Denosumab (AMG-162) is a fully human monoclonal antibody (mAb) selected for its high affinity for the receptor activator of NF-kappaB (RANK) ligand. The molecule directly inhibits the RANK/RANKL signaling pathway, which is known to be vital for osteoclast activation, function, and survival.[1-3] To date, six published Phase 2 and 3 clinical studies have shown denosumab to be a safe and highly effective antiresorptive agent when used for the treatment of postmenopausal osteoporosis (PMO) and bone destruction due to rheumatoid arthritis (RA) or metastatic cancers. In February 2009, the United States Food and Drug Administration (FDA) accepted Amgen's Biologic License Application (BLA) for denosumab for the treatment of PMO and bone loss due to hormone ablation therapy for prostate and breast cancer. The BLA was given a standard review rating and has an action date of October 19, 2009. Similar applications have been filed in Canada, Australia, Switzerland and the European Union.

Denosumab, an inhibitor of the RANK/RANKL signaling pathway, was developed using XenoMouse transgenic mouse technology. By sequestering RANK ligand and preventing binding of the ligand to its receptor on the surface of osteoclasts, denosumab acts as a highly effective inhibitor of bone resorption both in vitro and in vivo.[4,5] Preclinical studies in cynomolgus monkeys showed a consistent effect. Intravenous administration (IV) of 0.1 and 10 mg/kg denosumab reduced levels of the bone collagen breakdown marker, N-telopeptide (NTx), by 81 and 94%, respectively, and subcutaneous (SC) administration of 1.0 mg/kg reduced NTx by 93%.

In 2004, Bekker et al. reported results from a human dose escalation study aimed at assessing the safety and tolerability of denosumab in healthy postmenopausal women.[6] A total of 49 subjects were enrolled in this study and given a single SC abdominal injection of denosumab (0.01–3.0 mg/kg) or placebo. The participants were assessed throughout a six or nine month period for adverse effects and markers of bone turnover. Additionally, denosumab serum concentrations were measured and the pharmacokinetics were found to be nonlinear with dose. The triphasic serum profiles were characterized by: a protracted absorption phase in which maximum serum concentrations increased 2.6-fold more than the given dose between 5–21 days post-administration; a similarly protracted β-phase in which the drug half-lives increased proportionally with dose, with the maximum at day 32; and a rapid terminal phase at concentrations <1 mg/ml, with an increase in half-life at doses 0.01–3.0 mg/kg. The mean serum residence time (MRT) was found to increase with dose from day 12–46. Denosumab had a dose-dependent effect on bone turnover markers (BTM), with a maximum reduction in urinary NTx/creatinine (uNTx/Cr) levels observed at two weeks in the ≤1.0 mg/kg treatment arms, one month in the 0.1 mg/kg arm, and three months in the 3.0 mg/kg arm. This effect was reversible, with uNTx/Cr levels nearing baseline by two months in the lowest administered doses (0.01 and 0.03 mg/kg) and nine months in the highest (1.0 and 3.0 mg/kg). No adverse effects were reported, and all administered doses were well-tolerated by the research subjects. These results confirmed that denosumab could be safely administered for the treatment of diseases associated with bone loss, and that a single administration could have a lasting effect on the reduction of BTM.

Clinical Studies in Primary Indication

In 2007, Lewiecki et al. reported results from a Phase 2, randomized, placebo-controlled, dose-ranging clinical study aimed at assessing the long-term (24 month) efficacy and safety of denosumab treatment for postmenopausal bone loss compared with alendronate therapy (Table 1).[7] This study (clinical trial

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Table 1 **Clinical studies in postmenopausal osteoporosis**

Phases of study	Indications and doses studied	Endpoints and results
Phase 2[7]	Long-term (24 mo) efficacy and safety of denosumab in patients experiencing postmenopausal bone loss compared with alendronate Study arms: (1) oral 70 mg alendronate weekly (2) SC 6 mg denosumab every 3 mo (3) SC 14 mg denosumab every 3 mo (4) SC 30 mg denosumab every 3 mo (5) SC 14 mg denosumab every 6 mo (6) SC 60 mg denosumab every 6 mo (7) SC 100 mg denosumab every 6 mo (8) SC 210 mg denosumab every 6 mo (9) SC placebo	Endpoint(s): (1) Changes in BMD at the lumbar spine, total hip, one-third radius, and total body at 24 mo (2) Changes in BTM at 24 mo (3) Safety Results: (1) BMD increases were greater than placebo at all skeletal locations, at all doses studied. In addition, BMD was equal to or greater than alendronate at all skeletal locations, at doses equal to or greater than SC 30 mg (2) Denosumab suppressed BTM at all doses studied (3) Both drugs displayed similar safety profiles
Phase 2[8]	Long-term (48 mo) efficacy and safety of denosumab, as well as discontinuing and restarting treatment, in patients experiencing postmenopausal bone loss compared with alendronate Study arms: (initial treatment) (1) oral alendronate weekly (2) SC 6 mg denosumab every 3 mo (3) SC 14 mg denosumab every 3 mo (4) SC 40 mg denosumab every 3 mo (5) SC 14 mg denosumab every 6 mo (6) SC 60 mg denosumab every 6 mo (7) SC 100 mg denosumab every 6 mo (8) SC 210 mg denosumab every 6 mo (9) placebo (after 24 mo) (1) alendronate arm discontinued treatment (2) denosumab treated arms either discontinued therapy, received SC 60 mg denosumab for additional 24 mo, or discontinued therapy for 12 mo, then received SC 60 mg denosumab for an additional 12 mo (3) placebo arm continued treatments for an additional 24 mo	Endpoint(s): (1) Changes in BMD (2) Changes in BTM at 48 mo (3) Safety Results: (1) Continuous, long-term denosumab treatment increased BMD: 9.4 – 11.8%, lumbar spine; 4 – 6.1%, total hip. Discontinuation of denosumab decreased BMD: 6.6%, lumbar spine; 5.3% total hip. Denosumab retreatment increased BMD 9.0% above original baseline values. (2) Continuous, long-term denosumab treatment suppressed BTM. Discontinuation of denosumab increased BTM. Denosumab retreatment decreased BTM (3) Both drugs displayed similar safety profiles
Phase 3[9]	Efficacy and safety of denosumab for the treatment of postmenopausal bone loss (PLO) compared with alendronate Study arms: (1) SC 60 mg denosumab every 6 mo plus oral placebo weekly (2) oral 70 mg alendronate weekly plus SC placebo	Endpoint(s): (1) Changes in BMD at total hip, femoral neck, trochanter, lumbar spine, and one-third radius at 12 mo, compared with alendronate (2) Changes BTM at 12 mo (3) Safety Results: (1) Denosumab treatment resulted in BMD increases of: 0.9%, total hip; 0.6% femoral neck; 1.0%, trochanter; 1.1% lumbar spine; 0.6% one-third radius ($P \leq 0.0002$), vs. alendronate (2) BTM were lower at all time points for denosumab treatment arm. (3) Both drugs displayed similar safety profiles

identifier NCT00043186) enrolled 412 postmenopausal women with low bone mineral density (BMD), as measured by dual energy X-ray absorptiometry (DXA). Women with lumbar spine T-scores of -1.8– -4.0 or femoral neck/total hip (proximal femur) T-scores of -1.8– -3.5 were randomly assigned to be given double-blind, SC injections of: placebo; denosumab 6, 14 or 30 mg every three months; denosumab 14, 60, 100 or 210 mg every six months; or open-label oral alendronate 70 mg once weekly. Endpoint measurements included: BMD at the lumbar spine, total hip, distal one-third radius and total body; bone turnover markers (serum C-telopeptide, urine N-telopeptide and bone-specific alkaline phosphatase); and safety.

In all doses studies, denosumab treatment for 24 months significantly increased BMD at all skeletal sites compared to placebo. At the lumbar spine, BMD increases ranged from 4.13–8.89% compared with a -1.18% change from baseline in the placebo group ($p < 0.001$ for all doses of denosumab vs placebo). With the exception of the SC 14 mg denosumab six month treatment arm, BMD changes in patients treated with denosumab were similar to, or greater than, BMD changes in those treated with alendronate at 24 months. All treatment groups reported similar frequencies of adverse events. In both the denosumab and alendronate treatment arms, BTM were lower at all doses and time points, and both drugs were deemed safe based on the frequency and type of

Table 2 **Clinical studies in cancer treatment related bone loss**

Phases of study	Indications and doses studied	Endpoints and results
Phase 2[16]	Bone metastases and elevated uNTx levels in breast cancer patients not receiving IV BP therapy Study arms: (1) IV BP every 4 wk (2) SC 30 mg denosumab every 4 wk (3) SC 120 mg denosumab every 4 wk (4) SC 180 mg denosumab every 4 wk (5) SC 60 mg denosumab every 12 wk (6) SC 180 mg denosumab every 12 wk	Endpoint(s): (1) Median % change in uNTx/CR from baseline values at wk 13 (2) The percentage of patients > 65% reduction in uNTx/CR at wk 13 (3) Percentage of patients with SREs (4) Safety Results: (1) 71% denosumab (pooled) vs.79% BP (2) 74% denosumab (pooled) vs. 63% BP (3) 9% denosumab vs. 16% BP (4) Both denosumab and BPs displayed similar safety profiles
Phase 2[17]	Bone metastases and elevated uNTx levels in patients receiving IV BP therapy Study arms: (1) IV BPs every 4 wk (2) SC 180 mg denosumab every 4 wk (3) SC 180 mg denosumab every 12 wk	Endpoint(s): (1) Proportion of patients with uNTx < 50 at wk 13 (2) Proportion of patients with uNTx < 50 at wk 25 (3) Time to uNTx < 50 (4) Duration of uNTx < 50 (5) Change in other BTMs (6) Proportion of patients experiencing SREs (7) Safety Results: (1) 71% denosumab vs. 29% BP ($p < 0.001$) (2) 64% denosumab vs.37% BP ($p < 0.01$) at wk 25 (3) 9 days denosumab vs. 65 days BP (4) Not reached (5) All BTMs measured were suppressed by denosumab (6) 8% denosumab vs. 17% BP (7) Both denosumab and BPs displayed similar safety profiles

adverse occurrences. This study concluded that, in postmenopausal women with low BMD, treatment with denosumab for 24 months was associated with prolonged increases in BMD and reductions in BTM compared to placebo.

Following this report, the same group published results from a Phase 2 study aimed at determining the effects of discontinuing and restarting denosumab treatment in postmenopausal women with low bone mass (Table 1).[8] Postmenopausal women with a lumbar spine T-score of -1.8–-4.0 or proximal femur T-score of -1.8–-3.5 were recruited and randomized into the following treatment groups: SC 6, 14 or 30 mg denosumab every three months; SC 14, 60, 100, or 210 mg every six months; placebo; or open-label oral alendronate weekly. After 24 months, patients receiving denosumab either continued treatment with SC 60 mg for an additional 24 months, discontinued therapy, or discontinued treatment for 12 months and then re-initiated SC 60 mg denosumab for 12 months. The placebo cohort was maintained. Alendronate-treated patients discontinued alendronate and were monitored. Changes in BMD and BTM as well as safety outcomes were evaluated.

Continuous, long-term denosumab treatment increased BMD at the lumbar spine (9.4–11.8%) and total hip (4.0–6.1%). BTM were consistently suppressed over 48 months. Discontinuation of denosumab was associated with a BMD decrease of 6.6% at the lumbar spine and 5.3% at the total hip within the first 12 months of treatment discontinuation. Retreatment with denosumab increased lumbar spine BMD by 9.0% from original baseline values. Levels of BTM increased upon discontinuation and decreased with retreatment. Adverse event rates were similar among treatment groups. The studies concluded that for postmenopausal women with low BMD, long-term denosumab treatment led to gains in BMD and reduction of BTM throughout the course of the study. The effects on bone turnover were fully reversible with discontinuation and restored with subsequent retreatment.

In 2009, Brown et al. published the results of a Phase 3, international, multicenter, double-blind, 12 month study aimed at comparing the efficacy and safety of denosumab with alendronate in women with PMO (Table 1).[9] For this study (clinical trial identifier NCT00330460), the investigators recruited 1,189 postmenopausal women with a T-score ≤2.0 at the lumbar spine or total hip. The subjects were randomized equally into two research arms that either received SC denosumab injections (60 mg every six months) along with an oral placebo weekly, or oral alendronate (Fosamax®, 70 mg) weekly along with SC placebo injections. The primary endpoint measurement was the percent change in BMD at the total hip at month 12. Secondary endpoint measurements included percent change in BMD at the femoral neck, trochanter, lumbar spine, and one-third radius at month 12. Finally, BTM were measured at months 1, 3, 6, 9 and 12. Safety was assessed based on reported adverse events and changes in clinical laboratory values that could be attributed to treatment with denosumab.

Table 3 **Clinical studies in rheumatoid arthritis-related bone loss**

Phases of study	Indications and doses studied	Endpoints and results
Phase 2[18]	Bone loss in rheumatoid arthritis (RA) patients receiving methotrexate therapy Study arms: (1) SC placebo every 6 mo for 12 mo (2) SC 60 mg denosumab every 6 mo for 12 mo (3) SC 180 mg denosumab every 6 mo for 12 mo	End point(s): (1) Change in the mean MRI erosion score from baseline at 6 mo (2) Change in the total modified Sharp score at 12 mo (3) Change in the modified Sharp erosion score at 6 and 12 mo (4) Change in the modified Sharp joint space narrowing at 6 and 12 mo (5) Percent change in BTM at 3, 6, and 12 mo (6) Percent change in BMD at 12 mo (7) Safety Results: (1) Placebo, 1.75; SC 60 mg denosumab, 0.13 (p = 0.118); SC 180 mg denosumab, 0.06 (p = 0.007) (2) Placebo, 1.87; SC 60 mg denosumab, 0.85 (p = 0.032); SC 180 mg denosumab, 0.97 (p = 0.180) (3) (6 months) Placebo, 0.59; SC 60 mg denosumab, 0.25 (p = 0.277); 180 mg denosumab, 0.05 (p = 0.019); (12 months) Placebo, 1.34; SC 60 mg denosumab, 0.33 (p = 0.012); 180 mg denosumab, 0.19 (p = 0.007) (4) No effect (5) Decrease over placebo at all time points and doses (6) Positive effects over placebo at all time points and doses (7) No adverse safety concerns

At month 12, denosumab treatment significantly increased BMD from baseline measurements compared with alendronate (3.5% denosumab vs 2.6% alendronate; one sided $p < 0.0001$). A similar increase in BMD was observed at the femoral neck (2.4% vs 1.8%; $p = 0.0001$), trochanter (4.5% vs 3.4%; $p < 0.0001$), lumbar spine (5.3% vs 4.2%; $p < 0.0001$), and one-third radius (1.1% vs 0.6%; $p < 0.0001$). This study concluded that denosumab treatment led to a significantly greater increase in BMD and a reduction of BTM compared with alendronate therapy. The overall safety profile and the frequency of adverse events were similar for both treatments.

Clinical Studies in Cancer Treatment Related Bone Loss

Bone is a frequent site of metastasis in cancers of the prostate and breast.[10] While metastatic prostate cancers can be osteolytic or osteoblastic in nature, metastatic breast cancers are largely osteolytic, resulting in high morbidity due to pathologic fractures. Patients with bone metastases and elevated BTMs, such as uNTx, are at increased risk for skeletal-related events (SREs), cancer progression, and death.[11-13] IV bisphosphonates (BPs) have proven effective in reducing the frequency of pathologic fractures and pain associated with bone metasteses (Table 2).[14,15]

In 2007, Lipton et al. published a Phase 2, randomized, active-controlled, international, multicenter study (clinical trials identifier NCT00104650) designed to evaluate the efficacy and safety of five dosing regimens of denosumab in BP-naïve patients with breast cancer-related bone metastases.[16] This study enrolled 255 women who were randomly assigned to one of six treatment arms: SC 30, 120 or 180 mg denosumab every four weeks for 24 weeks; SC 60 or 180 mg denosumab every 12 weeks for 24 weeks; or IV BP every four weeks for 24 weeks. The primary end point was percentage of change in uNTx/Cr from baseline to study week 13. The percentage of patients achieving ≥65% uNTx/Cr reduction, the percentage of patients experiencing one or more on-study SRE, and safety were also evaluated.

At study week 13, the median percent reduction in uNTx/Cr was 71% for the pooled denosumab groups and 79% for the IV BP group. Overall, 74% of denosumab-treated patients achieved ≥65% reduction in uNTx/Cr compared with 63% of BP-treated patients. SREs were experienced by 9% of denosumab-treated patients versus 16% of BP-treated patients. No adverse events related to denosumab were reported, and it was concluded that denosumab may be similar to IV BPs in preventing bone loss and reducing the risk of pathologic bone fractures.

In 2009, Fizazi et al. published a randomized, multicenter, international Phase 2 study (clinical trials identifier NCT00104650) aimed at comparing the efficacy and safety of denosumab treatment with BP therapy in patients with bone metastases from prostate, breast, multiple myeloma, or other cancers (Table 2).[17] Enrolled patients had confirmed bone metastases and elevated uNTx levels despite ongoing BP therapy. Patients were stratified by tumor type and screening uNTx levels (50–100 or >100 uNTx/Cr), and

randomly assigned to continue IV BPs every four weeks or receive SC 180 mg denosumab every four weeks or every 12 weeks. The primary endpoint was the proportion of patients with uNTx <50/Cr at week 13. Secondary efficacy end points included: uNTx/Cr <50 at week 25; time to reduction of uNTx/Cr <50; duration of uNTx/Cr <50; change in other BTMs from baseline to week 25; proportion of patients experiencing SREs, and the time to first on-study SRE. Safety end points included incidence of adverse events and changes from baseline in laboratory assessments.

The primary end point of uNTx/Cr <50 at week 13 was achieved by 71% of the patients in the denosumab arms versus 29% of the patients in the IV BP arm ($p < 0.001$). The proportion of patients with uNTx/Cr <50 was maintained at week 25 (64% denosumab arms vs 37% IV BP arm; $p = 0.01$). The median time to achieve uNTx/Cr <50 was nine days with denosumab treatment compared with 65 days with IV BPs. All measured BTMs were reduced in the denosumab-treated arms. The incidence of SREs was 8% and 17% in the denosumab group and IV BP group, respectively. This study concluded that denosumab was more effective at normalizing BMT levels than BP therapy in patients with elevated uNTx despite ongoing IV BP therapy. Rates of adverse events were similar between all treatment groups, but on-study SREs were less frequent in patients receiving denosumab versus those receiving IV BPs.

Clinical Studies in Cancer Rheumatoid Arthritis Related Bone Loss

Rheumatoid arthritis is a chronic inflammatory disorder characterized by bone loss due to excessive osteoclast activity. In 2008 Cohen et al. published results from a multicenter, randomized, double-blind, placebo-controlled, 12 month Phase 2 study designed to evaluate the effects of denosumab on structural bone damage in patients with RA receiving methotrexate treatment (Table 3). This study (clinical trial identifier NCT00095498) recruited patients diagnosed with RA for ≥24 week who had also been taking methotrexate for ≥8 weeks, and randomly assigned them to one of three treatment arms. At day one and six months, the patients received SC placebo, SC 60 mg denosumab, or SC 180 mg denosumab. Study end points were changes from baseline in the magnetic resonance imaging (MRI) erosion score at six months, the modified Sharp score at 12 months, the modified Sharp erosion score and the modified Sharp joint space narrowing score at six and 12 months, percentage change in BTM at three, six and 12 months, percentage change in BMD at 12 months, and mean change in laboratory outcomes at six and 12 months.

Compared to placebo, the increase in the MRI erosion score from baseline was less in the 60 mg denosumab arm (mean change 0.13 vs 1.75; $p = 0.118$), and significantly less in the 180 mg denosumab arm (mean change 0.06; $p = 0.007$) at six months. Differences in the modified Sharp erosion score became significant by six months in the 180 mg denosumab arm ($p = 0.019$) and by 12 months in both the 60 mg ($p = 0.012$) and the 180 mg ($p = 0.007$) denosumab arms. Though denosumab reduced BTM and increased BMD at all doses and time points, it did not have an effect on joint space narrowing. There were similar frequencies of adverse events in the denosumab and placebo arms. This study concluded that, compared to placebo, twice-yearly injections of denosumab in combination with methotrexate treatment inhibited RA-related bone damage for up to 12 months without an increased risk of adverse effects.

Future Prospects

Denosumab will potentially enter a market occupied by several antiresorptive drugs. In view of the fact that BPs are safe and effective, one may wonder whether denosumab can compete. Doctors and patients may ultimately prefer denosumab, since it can be SC administered every six months compared to the more frequent dosage schedule of BPs. Furthermore, denosumab was shown to be well-tolerated, whereas some patients do not tolerate BP therapy. Another possible deciding factor against BP therapy is that the products are contraindicated for patients with renal impairment and for patients undergoing certain dental procedures. The studies outlined in this review demonstrate that denosumab not only possesses a similar safety profile to BPs, but that it can be equally or more effective than BPs at preventing bone loss due to postmenopausal osteoporosis, rheumatoid arthritis, or cancer treatment and metastases. Given that many other diseases are associated with bone loss, including hyperparathyroidism, Paget disease, and periodontal disease, the potential for additional indications for denosumab therapy are promising.

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