Literature Review

The Role of Denosumab in Osteoporosis Treatment

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ABSTRACT

Osteoporosis is one of the most common chronic diseases. This condition makes bones in a person to become more porous and fragile, therefore greatly increase their risk of suffering a fracture. In Asia, the mortality rate that are associated with these fractures occurred between 10–20% of cases within a year. Osteoporosis is a condition in which there is an imbalanced activity between osteoblast and osteoclast. Osteoblast and osteoclast are two types of bone cells that majorly involve in bone remodelling process. Osteoclasts adhere to the bone surface once it mature, after that osteoclast both produce and secrete chloride acid (HCl), which will acidify bones and dissolve the bone mineral. Receptor Activator of Nuclear Factor kappa B Ligand (RANKL) is one of the necessary factors in bone remodelling process. It will activate and mature the osteoclast. Denosumab is a monoclonal antibody that will inhibit the binding of RANKL to its receptor, decreasing osteoclastogenesis and bone-resorbing activity. This inhibiting activity will theoretically increase the bone mass density in ones' body, ergo will treat and prevent osteoporosis. Denosumab showed favourable effect on bone metabolism without having serious adverse events compared to control group. This paper reviews the clinical pharmacology, pharmacokinetic and pharmacodynamic properties, and tolerability in the denosumab in the management of osteoporosis.

ABSTRAK

Osteoporosis adalah salah satu jenis dari penyakit kronis yang sering terjadi. Penyakit ini menyebabkan tulang seseorang menjadi lebih berongga dan rapuh, kondisi ini meningkatkan risiko patah tulang pada orang-orang tersebut. Di Asia, mortality rate yang berhubungan dengan kejadian patah tulang ini berkisar antara 10 – 20% dalam satu tahun. Osteoporosis adalah suatu kondisi dimana terjadi ketidakseimbangan antara osteoblast dan osteoklas. Osteoblas dan osteoklas adalah dua tipe dari sel tulang yang berperan pada proses bone remodelling. Setelah matang, osteoklas akan menempel pada tulang untuk menghasilkan dan menyekresi HCl, yang dimana zat ini akan mengasamkan tulang dan meluruhkan mineral di tulang. Receptor Activator of Nuclear Factor kappa B Ligand (RANKL) adalah salah satu faktor yang dibutuhkan dalam proses remodelling tulang. RANKL akan mematangkan dan mengaktifkan osteoklas. Denosumab adalah antibody monoclonal yang menghambat ikatan dari RANKL kepada reseptor dari RANKL, menurunkan proses osteoklasogenesis dan aktivitas penyerapan tulang. Secara teori proses ini akan meningkatkan massa dari tulang dan mencegah osteoporosis. Denosumab menunjukan efek yang sbaik pada metabolisme tulang tanpa menunjukkan efek samping yang serius. Makalah ini akan meninjau tentang farmakologi klinis, farmakodinamik , dan farmakokinetik, serta tolerabilitas dari denosumab dalam terapi osteoporosis.

Kata kunci   : Denosumab, RANKL, osteoporosis, treatment

INTRODUCTION

Osteoporosis is one of the most common chronic diseases. This condition makes bones in a person to become more porous and fragile, therefore greatly increase their risk of suffering a fracture. Patients of these injuries often experience severe pain, long-term disability and even death. Due to the growing population in the world the burden to health systems and social economy sector is in great and increasing number.The gold standard for diagnosing osteoporosis is DXA scan. This scan is used to measured to bone density in the patients' body.(Mithal & Kaur. 2012) When the body mass density has the value between 1 SD and 2.5SD, these patients will be considered having low BMD, while those who have BMD value of < -2.5 SD, the person will be diagnosed with osteoporosis.

There are several therapies that can be used to treat this condition. Bisphosphonates are the primary treatment modalities for osteoporosis and metastatic bone disease. Although this drug class has limitations. Recent advanced studies about bone degradation have uncovered another options to treat osteoporosis and other metabolic bone disorders. (Burkiewicz, Scarpace &Bruce 2009).

Denosumab is the firstThe approval of denosumab has further expanded treatment options. Denosumab is a monoclonal antibody that inhibit the binding of RANKL to its osteoclast-derived receptor (RANK), an interaction that is required for osteoclast formation, activation, and survival. (Tsai et al.2013) Denosumab is a subcutaneously administered drug for the treatment of osteoporosis. This drug is mainly used in postmenopausal women who have one of these following conditions; a high risk for fracture , who refractory decrease in BMD, cannot tolerate other therapies for osteoporosis (Bridgeman & Pathak 2011).

The objectives of this article are to review the clinical pharmacology, pharmacokinetic and

pharmacodynamic properties, and tolerability in the denosumab in the management of osteoporosis.

LITERATURE REVIEW

Pathophysiology of Osteoporosis

The cellular structures of bone are composed of several types of cell. There are osteoblasts and osteocytes as bone-forming cells, osteoclasts as bone-reabsorbing cells and osteoid as the bone matrix. The balance between these cells will properly keep the bone minerals and minerals in body amounts within the normal range. When the balance between bone resorption and deposition disrupt and tips toward excessive resorption, bone loss occurs and lead to osteoporosis. (Tabatabaei-Malazy,2017)

The osteoclast (OC) is a bone tissue-specific multinucleated cell that differentiates from hematopoietic stem cells similar to those giving rise to monocyte/macrophage. Osteoclasts will mature. After maturing, osteoclast will adhere to the bone surface and both produce HCl. HCl is used to acidify and dissolve the bone mineral. Osteoclastogenesis is activated by a number of pro-inflammatory cytokines. However, the only two factors that are both necessary and sufficient for osteoclast differentiation are colony-stimulating factor-1 (CSF-1 or M-CSF) and receptor activator of nuclear factor kappa b (RANK) ligand (RANKL). The mature, multinucleated OC is further activated by RANKL binding to its receptor RANK. To countervail the differentiation and activation of osteoclasts, osteoblasts will also produce osteoprotegerin (OPG), a decoy receptor which will binds RANKL and prevent the binding between RANKL and RANK. Thereby, OPG counteract osteoclastogenesis, promotes apoptosis of mature osteoclasts, and ultimately inhibits bone resorption . Postmenopausal women will have an increase of RANKL/OPG ratio Because the production of RANKL as well as other cytokines is downregulated by estrogen. This explain their accelerated bone turnover and bone loss. (Tabatabaei-Malazy,2017)

Clinical Description of Burden of Osteoporosis

A growing elderly population will potentially increase the incidence of osteoporosis, as well as the increasing burden of disease. Fractures of the hip is one of the burden of this disease. This will lead to great social and economic burden for government and society. In Asia, these fractures are associated with a mortality rate of 10–20% within a year of occurrence, while almost one third of these people remain disabled. The cost of hip fracture treatment in Singapore is US$17 million in 1998, while it will be expected to reach US$145 million in 2050.(Tahir, 2017)

Diagnostics of Osteoporosis

Current Modalities of Treatment

Managing lifestyle is one of treatment that can be recommended for this disease. Lifestyle modifications through receiving adequate nutritional supplements weight bearing activity at least 30 minutes daily, avoiding or stopping smoking, avoiding heavy alcohol consumption to ≤2 servings daily, limiting caffeine intake. Those are modifications suggested to those who are in risk to suffer osteoporosis (Tabatabaei-Malazy,2017)

Pharmacological agents are used as the typical treatment of osteoporosis, besides lifestyle modifications. There are two kinds of drugs for treating osteoporosis in general. Those are antiresorptive agents and anabolic agents. The main mechanism of action of antiresorptive agents is reducing the resorption of bones by inhibiting the activity of osteoclasts. Calcitonin, bisphosphonates, selective estrogen-receptor modulators(SERMs), and denosumab are a few that belong to this class of drugs.

Bisphosphonates (BPs) are recommended as the first-line medications for treatment of osteoporosis. Bisphosphonates shows its effects on bone cells, through inactivating osteoclastic bone resorption. Bisphosphonates induce and accelerate the process of apoptosis of osteoclasts as well. BMD of a person is likely to increase, due to this effect, thus be able to decrase the risk of fracture. BP that are world widely used are alendronate and risendronate. (Tabatabaei-Malazy,2017)

Selective estrogen-receptor modulators (SERMs) is a drug that contain nonsteroidal synthetic compounds with similar effects of estrogen on bone and cardiovascular system. Raloxifene is one of drugs that belong to this group. (Tabatabaei-Malazy,2017)

Denosumab is a human monoclonal RANKL antibody that show its effect in inactivating osteoclast, Denosumab has high affinity and specificity with RANKL. This action promoting apoptosis process, and reducing osteoclasts' differentiation are another effect of denosumab. Denosumab blocks the binding of RANKL to RANK in order to do this process. Denosumab show its effect in decreasing the serum level of CTX-1. Denosumab can be choice for treatment of osteoporosis in certain patients who are intolerant to oral BPs or have renal breakdown.(Tabatabaei-Malazy,2017)

Recombinant human parathyroid 1-34 is an anabolic agents that show its effects on bone mass and skeletal structure. Teriparatide is one of anabolic agents for osteoporosis treatment that was approved by FDA. This class of drug promotes bone formation through activating osteoblasts' function by binding to PTH/PTHrP type 1 receptor. This drug stimulate the Wnt signalling pathway after binding to its receptor, which result in increasing BMD and reducing fracture risk. This drug is not currently recommended for first-line treatment of osteoporosis. (Tabatabaei-Malazy,2017)

Mechanism of Action

Skeletal bone remodelling is a dynamic process mediated by 2 distinct bone cell types. They are osteoblasts and osteoclasts. Osteoclast mediate the production of acids and enzymes to dissolve bone minerals and proteins, which is a process known as bone resorption. Osteoblasts can be differentiated from mesenchymal stem cell or bone line cell(Kenkre & Bassett. 2018) is a type of bone cell that stimulate bone formation and collagen production. An imbalance between osteoclastic and osteoblastic cell functions is thought to contribute to changes in Bone Mineral Density(BMD) . When the imbalance tips toward the bone resorption process, the structure of the bone become more porous and fragile. If this condition keep being untreated, it will lead to osteoporosis. (Bridgeman & Pathak 2011). Denosumab shows its function by binding receptor activator of nucleus factor kappa B ligand (RANKL), a cytokine that is essential for the formation, function, and survival of osteoclast. (Cumming et al. 2009)

RANKL, a member of tumour necrosis family, is a transmembrane-bound protein expressed by osteoblast, T cells, and tumour cells.(Lewiecki, et al. 2018) RANK will be activated by RANKL, after its release. Binding between RANK and its RANKL will result in the proliferation of osteoclast and destruction of bone is subsequently occur. (Burkiewicz, Scarpace & Bruce 2009). Denosumab will bind RANKL, this mechanism will prevent the interaction of RANKL with its receptor, RANK. This binding will inhibit the maturation and activation of osteoclasts and inhibits osteoclast-mediated bone resorption. (Cumming et al. 2009)

Pharmacology, Pharmacokinetics & Pharmacodynamics

From earlier studies, the pharmacokinetic of denosumab is believed to be nonlinear and dose dependent. After administration, the C max would be reached at 5-21 days. Half-life

of denosumab would be reached in 32 days. (Bekker et al.2004) Nowadays, It was found that a 60mg fixed dose of denosumab given every six months provided similar RANKL inhibition as using weight-based dosing. (Zaheer, LeBoff, & Lewiecki, 2015)

The metabolism and elimination of denosumab is not clearly known, but this process seems to be via through immunoglobulin clearance pathway. (Scott & Muir. 2011) Antibodies are eliminated by either catabolism or excretion. The large molecules of antibodies does not allow itself to be excreted by kidney, because they are filtered and reabsorbed by nephrons of kidney. Immunoglobulins are mostly eliminated by intracellular catabolism. This elimination process due to the degradation process by lysosomes into amino acids

Denosumab does not require dose adjustment when used in patients with renal impairment. however, if the creatinine clearance rate is < 30 mL/min or the patient is on dialysis, serum calcium concentrations should be carefully monitored. (Bridgeman & Pathak, 2011)

Pharmacodynamic response of denosumab may be measured by several biomarkers of bone turnover, some of them are the serum N- and C- telopeptides of the crosslinks of type 1 collagen (NTX and CTX) which are the markers of bone resorption. Serum procollagen type 1 N-terminal peptide (P1NP) and Serum procollagen type 1 NC-terminal peptide (P1CP) which are the markers of bone formations may be used as well. (Burkiewicz,Scarpace, & Bruce 2009). In clinical studies using subcutaneous administration of 60 mg of denosumab, CTX marker value was reduced by 85% by three days. CTX levels were found to be below the limit of the assay in 39% of the patients in one month and 69% of the patients in three months. At the end of each dosing interval, CTX reductions were partially attenuated from maximal reduction of $\geq 87\%$ to $\geq 45\%$ (range: 45% to 80%), reflecting the reversibility of the effects of denosumab bone remodelling. (Zaheer, LeBoff, & Lewiecki 2015)

Indication and Contraindication

Denosumab is approved by FDA in 2010 for the treatment of osteoporosis in postmenopausal women and men at increased risk of fractures and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. Denosumab is contraindicated in women with hypocalcaemia or with hypersensitivity to any of the constituents of the formulation. Its use is not recommended in pregnancy or in the paediatric population (age ≤ 18 years). (Compston, et al.2017)

Dosage and Administration

Denosumab is a type of drug that is administered through subcutaneous injection. Denosumab is recommended to administered in a single dose injection of 60mg every 6 months for the treatment of osteoporosis. This drug should be administered in one of these following areas, which are upper arm, thigh, or abdomen. (AMGEN, 2010) Calcium and vitamin D supplementation shoukd be given while receiving denosumab treatment. (Moen & Kean 2011)

Clinical Trial of Denosumab
Phase I Study

In a randomized, single-dose, placebo-controlled study of denosumab in 49 healthy postmenopausal women, subjects were divided into groups in which each of the group that administered with single subcutaneous dose of 0.01, 0.03, 0.1, 0.3, 1.0, 3.0 mg/kg or placebo. After administration of single-dose injection, the pharmacokinetics properties, effects on biochemical markers of bone turnover, and tolerability of denosumab were monitored. Bone turnover which reflected by the changes observed in urinary NTX/creatinine, was found

to be decreased with a mean decrease from baseline in urinary NTX/creatinine of 73% in group that administered the 3.0mg/kg. There was an early increase in serum iPTH levels with maximum mean increase up to threefold in the 3.0 mg/kg group 4 days after dosing. There was no serious adverse events related to this drug were reported (Bekker et al.2004).

Phase II Study

A randomized, blinded, dose-ranging study was conducted in 304 postmenopausal women up to 80 years old with BMD T-score of -1.8 to -4.0 at the lumbar spine or -1.8 to -3.5 at the femoral neck or total hip. For the first 24 months, patients were randomized to one of nine treatment cohorts (8 blinded, and 1 open-label alendronate) which are denosumab 6 and 14 mg every 3 months (Q3 M) and 14,60, and 100 mg Q6 M cohorts received denosumab 60mg Q6 M for phase 3 trials. Patients randomized to the 210 mg Q6 M cohort received placebo for the remainder of the study. Patients randomized to 30mg Q3 M, received placebo for 12 months and re-treated with denosumab 60 mg Q6M for 12 months. Alendronate patients stopped continuing therapy after 24 months and were followed. The placebo group was maintained for 48 months. All patients received calcium of 1000mg/day and vitamin D of 400 IU/day supplementation. BMD and BTM the were measured at month 36 and 48.(Miller et al. 2008)

The BMD gains reached similar levels for all cohorts that switched to 60 mg Q6M dose. At the lumbar spine, the mean percentage change in BMD ranged from 9.4% to 11.8%, compared with -2.4% for the placebo group at months 48. The BTM was reported to decrease over the entire 48 months of treatment. Discontinuing treatment resulted in decrease in BMD by 6.6% at the lumbar spine, 5.3% at the total hip, and 0.8 at the distal 1/3 radius at

month 36. After 24 months without treatment, BTM returned to value near baseline (Miller et al. 2008).
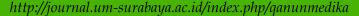
Phase III Study

FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 months) was a three-year Phase III clinical trial in 7868 postmenopausal women whose age are 60 - 90 years old. Inclusion criteria are BMD value of either lumbar spine or total hip T-score lesser than < -2.5 but greater than < -4.0. These subjects then were randomized to receive either 60 mg Q6M SC administration of denosumab (n = 3902) or placebo (n = 3906). The primary efficacy endpoint was new vertebral fractures at 36 months. The denosumab group had significant relative risk reduction for vertebral fractures with the value of 68%, 40% in hip fractures, and 20% in non-vertebral fractures compared with placebo. Denosumab decrease serum CTX by 72% by months 36. The levels of P1NP were less than placebo group at the same time points of evaluation. (Cumming et al. 2009)

FREEDOM extension trial was a seven years continuation evaluation after a prior three-years FREEDOM trial in 2626 postmenopausal women with similar inclusion criteria. They are a group of women between 60-90 years old with lumbar spine or total hip BMD T-score of less than -2.5 at either location but greater than -4.0 who were all received 60 mg denosumab administration and divided into two groups; long-term denosumab , and cross-over denosumab. A simulation method was used to estimate expected fracture rates because there was no placebo group. Based on the virtual twins model, the estimated virtual risk for new vertebral fractures was 0.62 (95% CI 0.47-0.80) and 0.54 for non-vertebral fractures (95% CI 0.43-0.48). After 5 years of denosumab treatment, the degree of bone mineralisation for total bone (median 1.132 g/cm3 [IQR

1.110 – 1.150]) was greater than that of 2 or 3 years of treatment in FREEDOM (1.081 g/cm3 [1.059 -1.107]); p<0.0001). In the crossover group, median concentration BALP, serum CTX and P1NP reduced rapidly after the initial administration of denosumab. These reductions were sustained throughout 7 years of treatment. Mean percentage changes from baseline in BMD at the lumbar spine, total hip, and femoral neck were greater at each timepoint than those observed at the previous timepoint for both groups. (Bone et al. 2017)

ADAMO trial was a 24 months phase III trial in 242 men (age 30 – 85 years old) with low BMD value. Men considered eligible if they had a T-score (based on male reference ranges) of $\leq$ -2.0 and $\geq$ -3.5 at the lumbar spine or femoral neck or a T-score of $\leq$-1.0 and $\geq$ -3.5 at the lumbar spine or femoral neck with a prior major osteoporotic fracture and had at least 2 lumbar vertebrae, 1 hip, and 1 forearm evaluable by dual-energy x-ray absorptiometry (DXA). The study comprised two 12-months phases. The first 12-months was a double-blind, randomized trial comparing 60 mg of denosumab SC every 6 months (Q6M) with placebo, followed by administration of 60 mg SC of denosumab for each group in month 12 and 18. The result of this study showed that during the 12-months open-label phase, there was an continued increase in BMD with long-term denosumab treatment at all skeletal sites. The cumulative gain from baseline to month 24 of 8.0% at lumbar spine, 3.4% at total hip. 3.4% at femoral neck, 4.6% at trochanter and 0.7% at 1/3 radius (all p<0.01). The crossover group showed significant gains in BMD with the value of 4.9% at the lumbar spine, 1.7% at total hip, 1.9% at femoral neck, 2.0% at the trochanter, and 1.0% at 1/3 radius in the open-label phase (all P < 0.0001) (Langdahl, et al. 2015)

Comparison with Alendronates

The DECIDE study is a study that compare the efficacy between denosumab and bisphosphonate. Alendronate is the bisphosphonate that was used by the researchers. The subjects of this study were postmenopausal women. This study was done by studying 1189 subjects who were randomized into two groups of 594 who received denosumab injection and 595 who received alendronate. This study resulted in showing that denosumab gave better improvement in bone mass density in total hip, denosumab have an improvement in bone density in total hips with the value of 3.5%, whereas alendronate gave the value of improvement of 2.6%(p<0.0001). Denosumab showed better improvement in other areas besides the hips. In trochanter area with the value of 4.5% for denosumab and 3.4% for alendronate. (Brown, et al. 2009)

DECIDE study showed that there was no significant difference observed during the study. The adverse events were mostly mild or moderate. The adverse events were reported in similar values, with the value of 17.0% in denosumab group and 18.3% in alendronate group. There is a concern in the rate of infection and neoplasm in denosumab group with the value of 37.3% in denosumab group, while the alendronate group has the value of 35.3% (Brown et al,2009)

Wu *et al*. conducted a research in 2018 to compare the efficacy between denosumab and bisphosphonates to treat postmenopausal osteoporosis. This paper is a meta-analysis study which review 11 RCT studies which involve 5446 patients. The changes in BMD that reviewed in this paper show more favourable outcome in denosumab group. It showed that denosumab be able to further increase BMD in various skeletal site better than alendronate does. The changes that were found in total hip BMD has a value of MD

1.05% CI 95% (p=0.000).Changes in another sites showed better result, in femoral neck the changes have the value of WMD 1.06%, CI 95% (p=0.000). The BMD in lumbar spine has the value of WMD 1.55% CI 95%(p=0.000) They showed in their study that there is no significant difference in adverse affects between denosumab and bisphosphonate, although there is a concern that immune cells have RANKL receptors and this will have effect in immune system (Wu, et al. 2018)

Adverse Events

From FREEDOM trial, there were no significant differences between subjects who received denosumab and those who received placebo in the total incidence of adverse events (AE), serious adverse events or discontinuation of study treatment because of adverse events. Seventy subjects with 1.8% of cases died in the denosumab group and 2.3% in the placebo group (p=0.08). Flatulence was reported more frequently in denosumab group with the value of 2.2% than in placebo group with the value of 1.4%(p=0.008). Eczema was reported in 3.0% of subjects in the denosumab group and 1.7% in the placebo group. 0.3% of cases in denosumab group reported serious adverse event of cellulitis, compared with one subject in placebo group with the value of < 0.1%) There were no significant differences in overall incidence of adverse event in cellulitis 1.2% in denosumab and 0.9% in placebo group. (Cumming et al. 2009)

FREEDOM extension trial study reported that the year-by-year result show that the safety profile of denosumab remained consistent and favourable over 10 years of treatment, The incidence of adverse events remained low. There were two cases of atypical femoral fracture, but the cumulative incidence remained low (0.8 per 10,000) Throughout the extension trial, the cases of osteonecrosis of jaw in both group were adjusted to be 5.2

per 10,000 the pathophysiological mechanism of osteonecrosis of the jaw remains unclear, even though a relation between denosumab treatment and osteonecrosis of the jaw seems to exist. (Bone et al. 2017)

ADAMO trial show only several AEs that are high in severity in both groups. Serious AEs occurred in 8.1% of the long-term group and 4.3% of the crossover group. One death caused by bacterial endocarditis was reported in long-term group. Malignancy AEs were reported with the value of 4.5% in long-term group and 1.7% in crossover group. There were no reports of hypocalcaemia, osteonecrosis of jaw. Fracture healing complications or atypical femoral fracture were not reported as well. The incidence of cardiac disorders, eczema, infections, acute pancreatitis, and AEs potentially associated with hypersensitivity was low and did not appear to increase with prolonged exposure over time. (Langdahl, et al.2015)

CONCLUSION

Denosumab is the first and only RANKL inhibitor approved for osteoporosis treatment so far. It is proven to be effective to decrease bone turnover. It has shown sustained efficacy in increasing BMD and decreasing fracture risk. Though the mechanism of the adverse events remains unclear, the data appear to be favourable in this aspect.

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