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DENOSUMAB- A REVIEW OF ITS USE IN THE TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

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Abstract: *Denosumab is a human recombinant monoclonal antibody that is approved for the treatment of postmenopausal osteoporosis in women at high or increased risk of fracture in the US, the EU and several other countries. Denosumab binds to receptor activator of nuclear factor κB ligand and inhibits bone resorption by inhibiting osteoclast formation, function and survival. In postmenopausal women with low bone mineral density (BMD) or osteoporosis, treatment with denosumab increased BMD and decreased markers of bone turnover more than alendronate in those who were switched from alendronate to denosumab or continued alendronate treatment. In this review article the guidelines for pharmacologic properties, clinical efficacy, and safety profile of the injectable agent denosumab for the treatment of postmenopausal women with osteoporosis are discussed.*

Keywords: *Denosumab, Post menopause, Osteoporosis, Fractures.*

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INTRODUCTION

Osteoporosis is defined as impairment in bone strength due to an abnormal quantity and/or quality of bone. Quantity is evaluated by measuring BMD. Quality is affected by many factors, including the degree of mineralization, the rate of bone remodelling, the connectivity of the bony trabeculae, the quality of the collagen fibres, and the health of the bone cells[1]. The 3 types of bone cells are osteoblasts, osteoclasts, and osteocytes. The osteocytes function as "mechanostats", sensing the degree of microdamage and triggering remodelling in areas of stress and strain, thus allowing continual renewal, repair, and replacement of bone. This process of remodelling maintains bone strength [2].

Bone Remodeling: Bone is made of collagen, calcium and phosphate salts, and bone cells (e.g., osteoclasts and osteoblasts). Collagen is the flexible framework for bony structures. Calcium and phosphate salts, particularly hydroxyapatite, deposit into the collagen matrix and mineralize bone [3]. These minerals are responsible for the strength of bone, as well as regulation of calcium and phosphorous blood levels. Osteoclasts and osteoblasts are responsible for bone remodeling.

Bone Loss in Osteoporosis: Bone loss associated with osteoporosis is generally due to an increase in osteoclastic action. Most people possess 85 to 90% of their adult bone mass by the age of 18 years in females and 20 years in males [4]. Once adult bone mass is obtained, it is maintained with minimal bone loss for a period of time. However, once this plateau is reached, bone loss accelerates, causing osteoporosis.

Incidence and risks:

Approximately 10 million Americans have osteoporosis and an additional 34 million have low bone mass. Gender, age, and race are important risk factors for osteoporotic fractures [5]. Of the 10 million people with osteoporosis, 8 million are women. At least 55% of American postmenopausal woman have decreased bone density at the hip.

Certain medications (particularly glucocorticoids) and various medical conditions (e.g., renal failure, hypogonadism, and alcoholism) are important secondary causes of osteoporosis [6].

Etiology and Pathophysiology:

Normal bone loss- Bone remodeling is an ongoing, cyclic process of bone formation and resorption at the cellular level. Osteoclasts adhere to bone and remove it, while osteoblasts secrete osteoid and help build bone [7]. Any imbalance in these two processes produces net bone loss or gain.

Glucocorticoid related bone loss-

The etiology of glucocorticoid-induced osteoporosis and associated fractures is not fully understood, but is multifactorial and different from postmenopausal osteoporosis. Bone resorption is increased, possibly due to stimulation of osteoclast differentiation [8,9].

Clinical Risk Factors:

BMD, by itself, is an excellent predictor of fracture risk, at least as good as cholesterol as a predictor of heart disease, and blood pressure as a predictor of stroke.[9] However, multiple clinical factors, including family history, medical conditions, and medications, are also important in the assessment of patients at risk for low bone density and osteoporotic fractures.

Age-

Skeletal mass is maximal in the third decade of life and depends primarily on diet (especially calcium and vitamin D), physical activity, and genetics [10].

Gender-

During the first few years after menopause, women typically have a rapid loss of bone, as much as 5% per year in trabecular bone and 2-3% per year in cortical bone. This early postmenopausal loss is primarily due to increased osteoclast activity [11]. Later, a decline in osteoblast activity predominates and the rate of loss slows to 1-2% or less per year.

Ethnicity- Bone strength and risk factors for fracture differ by race. In community-dwelling white women age 65 years and older, osteoporotic fracture is significantly correlated with: previous fracture of any type after age 50; maternal history of hip fracture [12], long-acting benzodiazepine or anticonvulsant drug use; previous hyperthyroidism etc.

Organ failure and transplantation-

Patients with organ failure, particularly liver and kidney, are at significant risk for osteoporosis and fracture [13].

RISK ASSESSMENT AND MANAGEMENT

Risk factors for osteoporosis have been identified and the presence of risk factors in a postmenopausal woman justifies bone densitometry. Osteoporosis is diagnosed in a postmenopausal woman on the basis of a BMD T-score of less than −2.5 at the lumbar spine, hip (femoral neck or total hip), or radius (distal third) [14]. Clinically it is diagnosed in a postmenopausal woman in the presence of a low-trauma fracture. In a premenopausal woman osteoporosis is diagnosed only in the presence of fragility fractures; BMD alone cannot be used for diagnosis [15].

In premenopausal women a normal BMD is defined as being within 2 standard deviations of the age-matched reference mean. Comparison with the age-matched reference range is represented by the Z score, and in premenopausal women Z scores should be used instead of T scores [16]. Low bone density is defined as a BMD Z score 2 or more standard deviations below the mean age-matched reference value.

Pharmacologic therapy is considered in postmenopausal women after exclusion of secondary causes of low bone density. [17]. If the 10-year absolute fracture risk is greater than 20% (high), then drug therapy is advised. In those with a moderate risk (10% to 20%), management decisions are individualized [18].

Prevention of post menopausal Osteoporosis and Related Fractures:

General prevention- Encourage all patients to eat a balanced diet that includes adequate calcium and vitamin D (using supplements only when necessary), engage in regular physical activity, avoid heavy alcohol consumption, and refrain from smoking [19].

A Brief Review of FDA-Approved Medications for the Treatment of Post menopausal Osteoporosis

DRUG THERAPY	BRAND NAME	ROUTE	TREATMENT DOSING	ADVERSE EFFECTS
Alendronate [20]	Fosamax	Oral	10 mg daily, or 70 mg weekly [21]	Esophagitis Dysphagia Gastric ulcers [22]
Risedronate [23]	Actonel	Oral	5 mg daily, or 35 mg weekly, or 150 mg monthly	Myalgia Arthralgia Fever Headache [24]
Ibandronate [25]	Boniva	Oral	2.5 mg daily, or 150 mg monthly	Osteonecrosis of the jaw Bone pain Atrial fibrillation [26]
Calcitonin [27]	Miacalcin	IM, SC	100 units/every other day	Transient nausea/vomiting Injection site reaction Flushing [28]
Teriparatide [29]	Forteo	SC	20 mcg daily	Transient hypercalcemia Nausea Dizziness Headache Leg cramps [29]

Table 1: ***FREEDOM Trial: Effect Of Denosumab on Fracture Rates in Postmenopausal Osteoporosis [40]***

Outcome	Denosumab	Placebo	Relative risk or hazard (95% CI)*	NNT†
New radiographically detected vertebral fracture‡	2.3%	7.2%	0.32 (0.26 to 0.41)	21
Non-vertebral fracture	6.5%	8.0%	0.8 (0.67 to 0.95)	67
Hip fracture	0.7%	1.2%	0.6 (0.37 to 0.97)	200

**Non-vertebral and hip fractures reported as hazard ratios*

†Number who needed to be treated with denosumab 60 mg every 6 months instead of placebo to prevent one fracture over 3 years of treatment

‡Defined as an increase of at least one grade in a vertebral body that was normal at baseline by semi-quantitative grading scale [40].

DENOSUMAB:

DESCRIPTION: Denosumab (Prolia; Xgeva; AMG 162) is a fully human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to RANKL. It prevents RANKL from binding to its receptor, RANK, [30-32] on the surface of osteoclast precursors and osteoclasts, thereby inhibiting osteoclast differentiation, activation, and survival. Increased osteoclast activity is critical in the pathogenesis of diseases that result from excessive bone resorption such as osteoporosis [33]. In a phase III clinical trial of denosumab for glucocorticoid-induced osteoporosis, denosumab is administered by subcutaneous injection (SC) at 60mg every six months [34].

Mechanism of Action, Metabolism and Pharmacokinetics:

Denosumab is a fully human monoclonal antibody to RANKL that has been designed to imitate the inhibiting actions of OPG over RANKL [35]. Denosumab is an IgG2 with high affinity for RANKL. By binding RANKL denosumab prevents RANKL and RANK interaction, in a similar way to OPG, and thus inhibiting formation, activation and survival of osteoclasts, decreasing bone resorption [36]. Denosumab is highly specific to RANKL and does not bind to other members of the TNF family, including TNFα, TNFβ, TNF-related apoptosis-inducing ligand (TRAIL), or CD40 ligand.

Similar to other fully human monoclonal antibodies, the pharmacokinetics of denosumab are nonlinear with dose [37]. Healthy postmenopausal women were given a subcutaneous dose of denosumab ranging from 0.01 to 3.0 mg/kg and followed for up to nine months. Three phases were observed [38].

(1) a prolonged absorption phase with maximum serum concentration obtained at 5–21 days after dose, increasing as dose increased;

(2) a prolonged beta phase, with a serum half-life up to 32 days for the maximum dose, and

(3) a rapid terminal phase occurring when serum concentration dropped below 1000 ng/ml.

Bioavailability is estimated to be in the range of 50%–100%, with a distribution about the same as the plasma volume, and clearance is most probably by the reticulo-endothelial system. Denosumab does not seem to be filtered or excreted by the kidneys [39].

Denosumab's effects on fracture risk reduction:

Fracture risk reduction is the most important end-point in all studies of medical agents used in the treatment of osteoporosis and the ultimate goal of anti-osteoporotic therapy 41-43].

Denosumab effects on BMD and bone metabolism markers:

These effects have been evaluated in several studies. Denosumab effects on BMD and bone turnover markers were evaluated in women with osteoporosis [44]. After two years of treatment with denosumab at a dose of 60 mg every six months, spinal BMD increased by 6.5% vs. the base values. A significant increase of BMD was also observed in the hip, the radial bone and the total body [45].

Denosumab in patients at high fracture risk:

In an analysis comparing various subpopulations at high fracture risk with other patients it was demonstrated that, in the majority of those subpopulations, denosumab was effective, both in the patients at lower, and those at higher, fracture risk [46].

PLACE OF DENOSUMAB IN POST MENOPAUSAL OSTEOPOROSIS:

For the treatment of osteoporosis, Denosumab 60 mg every 6 months is administered as a subcutaneous injection in the upper arm, upper thigh, or abdomen. All patients should take 1000 mg of calcium and at least 400 IU of vitamin D daily in conjunction with Denosumab [47]. If a dose of denosumab is missed, administer the injection as soon as convenient and then schedule injections every 6 months from the date of the last injection. Prior to administration, denosumab should be removed from the refrigerator and brought to room temperature [48].

The most common adverse effects identified in initial studies of postmenopausal women include arthralgia (25%), naso pharyngitis, back pain, headache, extremity pain, upper respiratory infection, constipation, urinary tract infection, and shoulder pain [49]. Sore throat, rash, and asymptomatic hypocalcemia have also been reported. Malignancy has also been a concern with Denosumab [50]. Denosumab is contraindicated in patients with severe hypocalcemia. Caution should be used in patients with impaired renal function as they are at an increased risk of hypocalcemia [51].

SAFETY:

Data on the long-term safety of denosumab are limited; the largest clinical trial enrolled approximately 7,800 women and followed them for three years [52]. The most serious safety issue is the risk of hypocalcemia, which occurs in about 2 percent of women who receive Denosumab [53]. The risk is higher in patients with renal impairment. Patients should seek prompt medical attention if they develop symptoms of infection [54].

TOLERABILITY:

Back pain, extremity pain, hypercholesterolemia, musculoskeletal pain, and cystitis occur in more than 5 percent of women receiving denosumab, and are more common than with placebo [55]. In clinical trials, dropout rates because of adverse effects were similar

between treated patients and those receiving placebo [56].

EFFECTIVENESS:

Compared with weekly administration of alendronate (Fosamax), denosumab significantly increases bone mineral density in postmenopausal women with low bone mass [57]. Among postmenopausal women who had received alendronate for at least six months, those switched to denosumab significantly increased bone mineral density at one year versus those who continued receiving alendronate [58].

Information for patients:

Provide patients and their carers with the following information.

- Denosumab is an injection to the top of the thigh, the abdomen or back of the arm. It is given once every 6 months [59].
- Stop taking bisphosphonates or other antiresorptive medicines before the first denosumab injection.
- Continue taking calcium and vitamin D if these have been prescribed [60].
- Maintain good oral hygiene and complete necessary dental work before starting denosumab. Consider providing patients with a referral letter stating that denosumab is indicated.
- Report fever, chills and hot or tender skin to their doctor immediately [61].
- Rash and itchy dry skin are common and not restricted to the injection site.
- Denosumab is a new medicine with a novel mechanism. Its long-term side effects are not yet known [62].

CONCLUSION:

Denosumab is a new option for the treatment of postmenopausal osteoporosis with a unique mechanism of action and dosing convenience. Denosumab reduces the risk of vertebral, hip and non-vertebral fractures and increases BMD at all skeletal sites, notably at predominantly cortical sites, an effect not seen with other treatments for osteoporosis. The rate of increase in BMD is sustained over time. Denosumab is well tolerated, with a favorable safety profile and good compliance. The main safety concerns are the effects of a prolonged suppression of bone turnover and the potential adverse effects on the immune system that might increase the risk of infection or malignancy.

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