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Teriparatide: A Review For The Management Of Osteoporosis

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ABSTRACT:

Teriparatide is a medication used for treating osteoporosis. A metabolic bone disease characterised by low bone density and deterioration of bone structure that increases the risk of fractures. Osteoporosis-related fractures can increase pain, disability, nursing home placement, total health care costs, and mineral density (BMD) using non-invasive dual-energy x-ray absorptiometry. This is the first anabolic agent with a unique mechanism that increases bone formation. Osteoporosis is likely to rise with the increase in life expectancy of an ageing population first-line therapies for the treatment of osteoporosis are predominantly anti–resorptive. Daily subcutaneous injection for 6-24 months was effective in reducing vertebral and non-vertebral fracture, improving bone mineral density (BMD) and increasing bone formation rates in postmenopausal with osteoporosis similar benefits on bone mass and bone formation were seen in men with osteoporosis and glucocorticoid-induced osteoporosis. Teriparatide is generally well tolerated. The high treatment cost and inconvenient administration mode have limited its use to patients. Teriparatide treatment is currently restricted to a total lifetime treatment dose of 18 months of daily subcutaneous therapy due to concerns from animal studies suggesting an increased risk of osteosarcoma more safety data may permit a longer duration of treatment in future but will necessitate prolonged human studies.

Furthermore, the beneficial effects of teriparatide on vertebral fracture prevention and BMD appear to persist following treatment cessation. Teriparatide is generally well tolerated and treatment compliance rates are favorable. However, current limitations on the length of treatment and the high acquisition cost mean that teriparatide is best reserved for the treatment of patients with osteoporosis at high risk of fracture or for patients with osteoporosis who have unsatisfactory responses to or intolerance of other osteoporosis therapies.

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Keywords: Teriparatide, osteoporosis, bone mineral density. (BMD)

Introduction:

Osteoporosis is characterised by the loss of bone mass or the presence of a fragility fracture. [1] The pathogenesis of osteoporosis focuses on an imbalance between osteoclastic bone removal and osteoblastic bone formation activity. Although fragility fracture is the hallmark of osteoporosis, diagnosing osteoporosis also involves the assessment of bone mineral density with dual-energy x-ray absorptiometry[1] However, many individuals with osteoporosis are not diagnosed until fragility fractures occur. Fragility fractures are associated with significant disability, mortality and cost. Osteoporosis is an insidious, largely asymptomatic, widespread disease that affects more than 75 million people throughout Europe, the US and Japan, and its incidence is likely to increase as life expectancy increases. Osteoporosis is characterised by

low bone mineral density (BMD), leading to decreased bone strength and an increased risk of fracture. [2] Many individuals with osteoporosis are not diagnosed with the disease until a fracture occurs; after such an event, there is a considerable impact on health-related quality of life and related health costs. [3] osteoporosis is usually diagnosed by assessing BMD using defined as a BMD T-score of 2.5 standard derivations (SD) or more below the average for young, healthy, premenopausal women (equating to a T-score of less than or equal to 2.5 [a normal T-score is greater than -1]).[4,5]

Osteoporosis is more prevalent in women than men due to smaller bone size and the decrease in estrogen levels at menopause, which reduces estrogen-mediated prevention of bone mass. [4] In men, larger bones and thicker cortical bones are thought to delay the onset of osteoporosis and reduce fracture risk. [3] Other risk factors for osteoporosis include a family history of the disease, low body mass index, smoking, a sedentary lifestyle and long-term glucocorticoid therapy. [26, 3] Importantly, glucocorticoid-induced osteoporosis is the second most common form of osteoporosis after postmenopausal osteoporosis. [6] current pharmacological action for the treatment of osteoporosis includes antiresorptive (anticatabolic) mechanistic strategies to inhibit resorption of osteoclast (e.g.bisphosphonates, calcitonin and raloxifene), strontium ranelate, an antiresorptive agent that may also have anabolic activity (the letter agent is not approved for use in the US), [4,7,8] and recombinant form of parathyroid hormone (PTH). [9, 10] Two forms of human PTH are available; full-length PTH (PTH 1-84; Preotact (1)), which is approved in the EU only, [9] and teriparatide is, the 1-34 N- terminal active fragment (Forteo[TM], Forsteo[TM] is a recombinant form of teriparatide). [10]

Teriparatide is approved in several countries including the EU [11] and the US [12] for the treatment of postmenopausal women or men with idiopathic or hypogonadal osteoporosis with a high risk of fracture and, more latterly, in the EU [11] in patients with glucocorticoid-induced osteoporosis who are at increased risk of fracture.

This review focuses on the pharmacological and clinical profile of teriparatide in these indications.[13]

Objectives:

- Identify the mechanism of action of teriparatide.
- Describe the potential adverse effect of teriparatide.
- Review the appropriate monitoring for patients using teriparatide.
- Summarize the importance of collaboration and communication amongst the inter-professional team to ensure appropriate osteoporosis management.

Background:

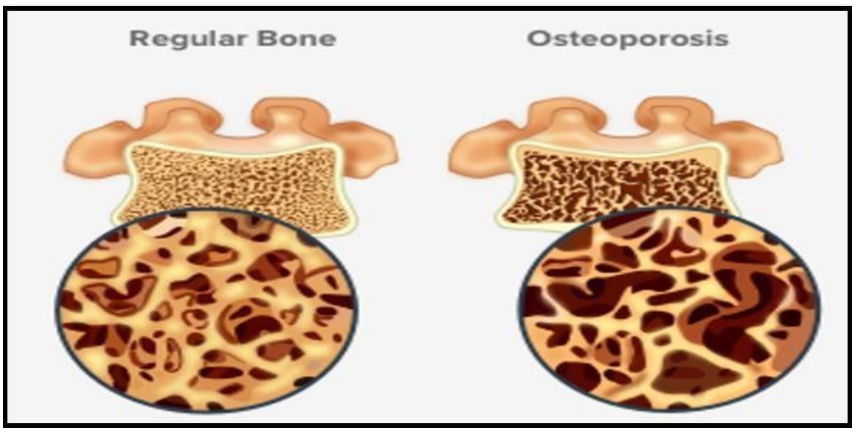
In osteoporosis, fractures are an increasing problem and cause of morbidity and mortality in the population. Teriparatide was approved by the European Medicine Agency in 2002 as the first anabolic agent for established osteoporosis. Teriparatide has been shown to reduce the risk for new vertebral compression by up to 65% and increase bone mineral density (BMD) by 9% lumber spin. [14] It was the first approved drug in the United States in November 2002. [15] A clinical trial studying the effect of growth hormone treatment in women with postmenopausal osteoporosis was also published in 2002. It showed improved BMD with a similar magnitude as the teriparatide study. [16] Both are anabolic agents and are administered subcutaneously once a day. Teriparatide is a recombinant PTH it comprises the first amino (N)-Terminal 34 amino acid.

With the ageing population and the resultant expected rise in fracture prevalence expanding shortly, there is growing interest in expanding therapies for osteoporosis (OP). Although op occurs in men and younger women, postmenopausal women remain the most affected, with a lifetime risk of fracture of 50%. The past 2 decades have seen incredible innovation in the bone field. The 1990s brought bisphosphonates (BPS), a class of bone-specific agents with versatile dosing options, impressive efficacy, and relative safety. Other advances in op treatment came when estrogen was proven to prevent hip fractures in the Women's Health Initiative. Still, enthusiasm was limited by the discovery of potential adverse effects likely associated with the timing of initiation that limits its more widespread use. The selective estrogen receptor modulator class was discovered and expanded but has limitations due to side effects, gender restrictions, and the lack of hip fracture reduction. Although multiple drugs are available to treetop, they had all previously belonged to the

anti-catabolic group, acting by inhibiting bone turnover. An entirely new class of therapeutic agents for op was announced in 2002 with the Food and Drug Administration (FDA) approval of teriparatide, the first medication available with an anabolic mechanism.

What is osteoporosis?

It is a medical condition that causes thinning and weakening of bones.



The chance of developing osteoporosis increases with age, after menopause or by taking corticosteroid medication (such as prednisolone) for a long period. Although fragility fracture is the hallmark of osteoporosis, diagnosing osteoporosis also involves the assessment of bone mineral density with dual-energy x-ray absorptiometry. If proper treatment is not provided then it can even result in a broken bone. In the starting days, osteoporosis does not show any symptoms However if proper treatment is not provided then it can even lead to broken bones. In minor activities. Fractures usually occur at the hip, spine or wrist which can even lead to a stooped posture (dowagers hump) and loss of movement.

Stages of osteoporosis:
Osteoporosis is a progressive bone disease that weakens the bone structure and increases fracture risk. There are four stages of osteoporosis:

Stages 1: Normal bone density.

In this stage, the bone density is considered normal, and there is no visible sign of osteoporosis.

Stage 2:

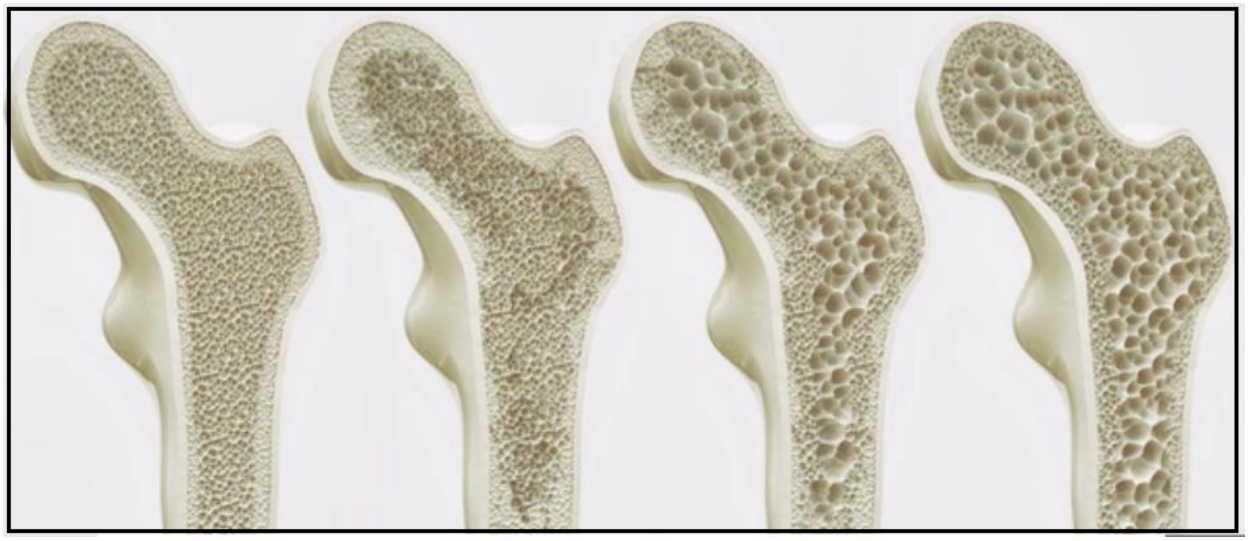
This stage is characterised by a loss of bone mass and density, but the bone loss is not yet severe enough to be diagnosed as osteoporosis. Osteopenia is warming sign that the bone is starting to weaken, and it is often reversible with appropriate lifestyle changes and medical treatment.

Stage 3: Osteoporosis.

In this stage, there is a significant loss of bone density, and the bones become weaker, making them more susceptible to fractures.AT this stage, bone loss is typically irreversible, and medical intervention is necessary to manage the condition.

Stage 4: severe osteoporosis.

This is the most advanced stage of osteoporosis, characterised by a substantial loss of bone density and a high risk of fracture. The bones fragile and may fracture it minor trauma, leading to chronic pain, disability, and loss of independence. [17]



1. 2. 3. 4.

Pharmacokinetic profile:

Data has been derived from Phase I and Phase III trials in men and women with osteoporosis receiving subcutaneous Teriparatide 20 or 40 micrograms daily. [18] When teriparatide is administered as a daily subcutaneous injection it is quickly and almost completely absorbed with apeak serum concentration at 30 minutes after administration to healthy volunteers. Teriparatide has a half-life of approximately 1 hour. After approximately 3 hours, the concentration of teriparatide declines significantly and is no longer readily measurable whilstteriparatide is detectable in the circulation, endogenous PTH is undetectable and as the level of teriparatide declines, the level of endogenous PTH Increases[19]

Following teriparatide 20 micrograms subcutaneous dose administration, serum calcium levels increase approximately 2 hours after dosing, reaching a modest Median increases of 0.2 mol/L and start to decline 6 hours after administration. Serum calcium reaches a nadir at approximately 16 to 24 hours after subcutaneous administration. [15]

The pharmacokinetics of single-dostherapy were similar in patients with mild or moderate chronic kidney diseases (creatinine clearance ≥30 Ml/min) compared to healthy volunteers (creatinine clearance90 mL/min). within the age group of 31 years to 85 years, similar pharmacokinetics were identifiable so no dose adjustment is probably needed based on age alone.[20] no dose adjustments are suggested according to gender but circulating levels of teriparatide are 20%-30% lower in men compared with women.[21]

Mechanism of action:

Teriparatide is the synthetic form of parathyroid hormone (PTH). It is an endogenous hormone that regulates calcium and phosphate in the kidney and bone. It regulates bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. [22] In disease states associated with the asses PTH in blood, such as primary hyperthyroidism, increased osteoclast activity, and then accelerated bone reabsorption occurs. [23] Teriparatide is the first approved anabolic or bone-building drug in it bone formation is stimulated more than reabsorption. Clinicians this seems counterintuitive because the elevated levels of PTH found in reduced BMD and increased the fracture risk. [24]

Teriparatide mediates its osteoanabolic action by binding to the N-terminal moiety to PTH type-1 receptors, which are G-protein coupled receptors expressed on various cells, including osteoblast, osteocytes and renal tubular cells. [25] Adenylate cyclase catalyzes the generation of secondary messenger CAMP, which ultimately activates protein kinase A (PKA) although PTH activates both PKA and PKC dependant signalling pathways, the PKA dependant pathway is primarily used for its anabolic and catabolic effect on bone. [26] The anabolic effects of PTH are mediated by upregulated transcriptional expression of pro osteoblastogenic growth factor 2(FGF2). [27] Modulation of the Wnt/beta-catenin osteoanabolic signalling pathway by down-regulating the synthesis of the Wnt antagonist sclerostin. [28]

Metabolism:

Whilst no metabolism or excretion studies have been conducted in humans, peripheral metabolism of teriparatide is believed to be initiated in the river. PTH fragments are then excreted via the kidney. It is not anticipated that teriparatide should be accumulated within bone tissue, providing further differentiation from bisphosphate metabolism.

Teriparatide: (use, storage, handling)

Teriparatide belongs to the class of medication called anabolic (promoting bone formation) agents indicated for the prevention and treatment of osteoporosis in adults and helps to strengthen the bone. This medication also helps to reduce the risk of spine and hip fractures. Osteoporosis is a medical condition in which bone becomes thin or weak. The chance of developing osteoporosis increases with age

.

Use:
A nurse or other trained health professional will give you this medicine. It is given as a shot under your skin, usually in the stomach or thigh.

This medicine comes with a medication guide and a user manual. Read and follow the instructions carefully. Ask your doctor if you have any questions.

Teriparatide may sometimes be given at home to patients who do not need to be in a hospital or clinic. If you are using this medicine at home, your doctor or nurse will teach you how to prepare and inject the medicine. Be sure that you understand how to use the medicine.

You should receive the first several injections of this medicine while sitting or lying down if needed, until you know how this medicine affects you.

If you use teriparatide at home, you will be shown body areas where this shot can be given. Use a different body area each time you give yourself a shot. Keep track of where you give each shot to make sure you rotate body areas. This will help prevent skin problems.

Use a new needle each time you inject your medicine. Do not store the prefilled pen with the needle attached.

If the medicine in the prefilled syringe has changed color, or if you see particles in it, do not use it.

You may take calcium and vitamin D supplements while you are using this medicine if needed. Follow your doctor's instructions about how to take these supplements.

Use of this medicine and parathyroid hormone analogues for more than 2 years during your lifetime is not recommended. Talk with your doctor if you have any concerns about this. [30]

Storage:

- Store in a refrigerator. Do not freeze.
- Keep out of the reach of children.
- Do not keep outdated medicine or medicine no longer needed.
- Ask your healthcare professional how you should dispose of any medicine you do not use.
- You might not use all of the medicine in each prefilled pen. Throw away any unused medicine after 28 days, even if there is still medicine in it.
- Throw away used needles in a hard, closed container that the needles cannot poke through keep this container away from children and pets. [30]

Handling:

This medication comes in a prefilled injection, which looks like a pen. To inject the medicine, the injector on thigh or abdomen pushes the button and the medication is automatically injected. The dose is 20 mcg a day, which is present by a pen. The needle is the same as the insulin needle. The injector has enough medicine for 28 days and should be kept refrigerated. [31]

Toxicity:

There is no specific antidote for a teriparatide overdosage. Treatment of suspect overdose should include discontinuation of teriparatide monitoring of serum calcium, and phosphate and implementation of supportivemeasures. Such as hydration. No deaths have been reported fromteriparatide overdose. [32]

Results reported from a long-term oncogeicity study in rats treated with daily teriparatide suggested a drug and dose-related incidence of osteosarcoma. [32] Consequently, two pivotal clinical trials, the fracture prevention trial [28] in postmenopausal women and the trial involving men with osteoporosis [33] were brought to early closure. However, findings from a subsequent oncogenicity study in rats and an expert histological review showed that the increased incidence of osteosarcoma and exaggerated bone formation was probably a mechanism of epigenesis and that the rat is hypersensitive to the anabolic effects of PTH relative to humans. [34] Also noted was that during the carcinogenicity study, the rats were treated with life-long high doses over the recommended human dose. [34] There were no reports of osteosarcoma in patients with osteoporosis in the clinical trials discussed in the sectionfurthermore, no evidence of bone tumours was shown in the preclinical study in over-the-customizedmonkeys administered teriparatide for 18 months. [35]

Side effects of teriparatide:

- Nausea.
- Vomiting.
- Joint pain.
- Leg cramps.
- Diarrhea.
- Cough.
- Runny nose.
- Feeling dizzy.
- Tired.
- Weak. [35]

Contradiction:

Teriparatide is contraindicated for those with open epiphyses, metabolic bone disease, Paget's disease of bone, metastases, history of skeletal malignancies, or prior external beam or implant radiation therapy involving the skeleton. In animal studies and one human case after over two years of use. [36]

Adverse effects:

Adverse effects of teriparatide include headache, nausea, dizziness, and limb pain [37]. Teriparatide has a heretical risk of osteosarcoma, which was found in rate studies but not confirmed in humans. [38] This may be because, unlike humans, rat bones grow for their entire life. [38] The tumours found in rat studies were located on the end of the bones which grew after the injection began. [39]After nine years on the market, there were only two cases of osteosarcoma reported. The FDA considered this risk as extremely rare (1 in 100,000 people). [36] Inside only slightly more than the incidence in the population over 60 years old (0.4 in 100,000) [36]

The most concerning adverse effect of teriparatidetherapy is the risk of skeletal carcinogenesis, most notably osteosarcoma. Researchers detected the carcinogenic effects in fisher rats subjected to the treatment of relatively high doses ranging from 5 to 75 mcg/kg/day for two years. It is considered to be minimal and nonsignificant in humans because of several lines of evidence: differences between rat and human skeletal physiologic, the fact that 2-years represent almost 90% of the rat'slifespanwhile representing only 2 to 3% of that of humans and the doses used are three to 58-fold the prescribed human dose, the detection of only 3 cases of osteosarcoma with unproven causality in over 1 million patients treated with teriparatide and an ongoing post-marketing surveillance study of striped use in human showing no incident risk of osteosarcoma at 8-years interim analysis. [40][41][42][43] It bears mentioning that the FDA limited approval to 2 years based on the Fisher rates toxicity study because of the uncertain relevance of rat osteosarcoma findings to, humans, as mentioned in the FDA drug label, and that much of the available evidence regarding teriparatide–related osteosarcoma risk in humans was not available at the time approval in 2002.

Risk factors for osteoporosis:

Various factors contribute to an individual’s risk of developing osteoporosis. These risk factors include age, genetics, hormonal changes, inadequate calcium or vitamin D intake, certain medications, smoking, excessive alcohol consumption, and a sedentary lifestyle. Advancing age is a significant risk factor, as bone density naturally declines as we age, making older adults more susceptible to osteoporosis. Women over the age of 50, in particular, face a higher risk, with statistics showing that one in three women will experience an osteoporotic fracture in their lifetime. Genetic factors also play a role, as individuals with a family history of osteoporosis are more likely to develop the condition. Hormonal changes such as those that occur during menopause, can accelerate bone loss in women. Additionally, lifestyle factors such as low calcium or vitamin D intake, smoking, excessive alcohol consumption, and a sedentary lifestyle contribute to increased osteoporosis risk. Recognizing these risk factors and taking appropriate preventive measures, including lifestyle modifications and Regular screening is crucial for reducing the likelihood of developing osteoporosis and preventing fractures. [39]

The future of osteoporosis management:

Research in the field of osteoporosis management is continuously uncovering new insights and advancements that hold promise for improved outcomes. Several notable research areas and advancements in osteoporosis management include:

1. Bone targeted therapies:

Researchers are exploring innovative medications targeting bone-regulatingmechanisms to enhance bone formation and reduce bone resorption. For example, studies are investigating the effectiveness of monoclonal antibodies that inhibit specific proteins involved in bone breakdown, such as sclerostin. These medications have shown potential in increasing bone density and reducing fracture risk.

2. Combination therapies:

Researchers are studying the potential benefits of combining different classes of medication to optimize treatment outcomes. For instance, clinical trials evaluate the efficacy and safety of combination antiresorptive medication (e.g., bisphosphonates) with anabolic agents (e.g., teriparatide) to achieve synergistic effects on bone health.

3. Advances in imaging techniques:

Imaging technologies, such as high-resolution peripheral quantitative computed tomography (HR-PQCT), are defined to provide more detailed information about bone structure and quality. These advertisements enable better assessment of bone health and help predict fracture risk with greater accuracy.

4. Personalized medicine:

Personalized medicine is gaining traction in osteoporosis management. Genetic testing and identifying specific genetic markers associated with osteoporosis susceptibility may help tailortreatment plans to individual patients, improving treatment effectiveness and reducing adverse effects.

5. Nutritional approaches:

Researchers are the role of various nutrients and dietary factors in bone health. For example, studies are exploring the potential benefits of specific dietary patterns, such as the Mediterranean diet, in promoting bone health and reducing the risk of fracture.

6. Exercise interventions:

Ongoing research focuses on optimizing exercise interventions for individuals with osteoporosis. Studies examine the adverse effects of different exercise modalities, Such as high-density resistance training, weight-bearing activities, and balance and coordination exercises, on bond density, strength, and fracture prevention.

It is important to note that while these advancements show promise, further research and clinical trials are necessary to establish their long-term effectiveness, safety, and applicability to different populations. Staying informed about ongoing research and discussing potential advancements with healthcare professionals can help individuals make informed decisions about their osteoporosis management and benefit from emerging therapies in future. [39]

Conclusion:

Osteoporosis is a disease in which teriparatide is used to reduce fracture teriparatide is recommended as the first-line treatment in the secondary prevention of osteoporosis. It is the disease in which managing osteoporosis requires a compressive approach encompassing medication, nutrition, exercise, and lifecycle modification. Remember to consult with the health care professional for proper use of osteoporosis evaluation, diagnosis and management. Educating yourself about the warning signs, risk factors and available strategies for managing osteoporosis is the first step toward taking control of your bone health. A diagnosis of osteoporosis doesn't have to limit your quality of life.

Stay protective, stay informed, and prioritise your bone health for the long future.

Abbreviations:

BMD: bone mineral density.

PTH: parathyroid hormone.

HR-PQCT: high-resolution peripheral quantitative computed tomography.

FDA: Food and Drug Administration.

PKC: protein kinase C.

PKA: protein kinase A.

CAMP: cyclic adenosine monophosphate.

DXA: Duel-energy x-ray absorptiometry.

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