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TERIPARATIDE IN POST-MENOPAUSAL OSTEOPOROSIS - A NEW REVOLUTION FOR OSTEOPOROSIS

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ABSTRACT

Osteoporosis is a clinical condition resulting in bone resorption and weakening of bones leading to fractures and brittle bones. Even the slightest cough, mild stress or fall can lead to fracturing of bones. Various factors play a vital role in the development of osteoporosis and it is slowly emerging as a common problem in post menopausal women. There are no symptoms in the early stages of bone loss. But once the bones have been weakened by osteoporosis, signs and symptoms like back pain, loss of height or a stooped posture starts appearing. The current treatment protocol includes medications that slow down the bone resorption. Teriparatide is an anabolic drug that promotes bone formation and has been approved by the Food And Drug Administration and Central Drugs Standard Control Organisation for the treatment of osteoporosis in post menopausal women who are at high risk of fracture.

KEYWORDS: Teriparatide, Osteoporosis, post menopausal, fracture, anabolic agents.

INTRODUCTION

Osteoporosis can be defined as a progressive, systemic, skeletal disease characterized by low bone mass and damage of bone tissues with resultant increase in bone fragility and susceptibility to fracture.[1] Osteoporosis mainly is influenced by various factors such as age, race, sex and it is more common in women and is slowly emerging as a ‘silent killer’ among post menopausal women. In India, osteoporosis in postmenopausal women is as common as 25% to 62% as evidenced in various studies.[2],[3],[4]. Postmenopausal osteoporosis is due to the decrease in the protective effect of estrogen at menopause and increase in follicle-

stimulating hormone, all contributing to increased bone resorption, leading to easy bone brittling and fracture.[5]

Current treatment options of osteoporosis include antiresorptive agents (e.g. bisphosphonates, calcitonin, and raloxifene), antiresorptive agent with anabolic activity, and osteoanabolic agents (teriparatide). Teriparatide acts by directly stimulating bone formation, thereby improving bone mass and quality. It is the only anabolic agent approved for the treatment of post-menopausal osteoporosis, idiopathic or hypogonadal osteoporosis in men, and glucocorticoid-induced osteoporosis,[6] and has opened new therapeutic avenues. It is an anabolic bone forming drug that has been approved by the Food And Drug Administration, FDA (in 2002) and Central Drugs Standard Control Organisation, CDSCO (in 2010) for the treatment of osteoporosis in post menopausal women who are at high risk of fracture. Recently the Drug Controller General of India (DCGI) has also approved the marketing of teriparatide on 4th February, 2021 for the treatment of the same. It will be available as prefilled injectable form and will be cost effective as well as easy to use.

Here we will discuss the role of injectable teriparatide in prevention of fractures in a postmenopausal women and hypogonadal osteoporosis in men.

PHARMACOLOGICAL BASIS OF TERIPARATIDE IN OSTEOPOROSIS

Teriparatide is the first approved anabolic, or bone building drug, where bone formation is stimulated more than resorption[7]. It is a recombinant parathyroid hormone (PTH) consisting of the first 34 amino acids, which is the bioactive portion of the hormone. It is identical to a portion of human parathyroid hormone (PTH) and intermittent use activates osteoblasts more than osteoclasts, which leads to an overall increase in bone.(Fig.1)

Effects on Bone Metabolism

Increased PTH in the blood resulting from any diseased state, such as primary hyperparathyroidism leads to bone resorption due to increase in osteoclast activity. This however occurs when bone is continuously exposed to PTH. On the other hand, intermittent exposure to low dose PTH or its analogues like teriparatide induce bone formation instead. The main mechanism behind this is still under investigation, though molecular signaling has been proposed as the reason. This effect of teriparatide makes it a suitable candidate for treatment of osteoporosis.[9,10,11]

Teriparatide is an analogue of PTH that binds through the N-terminal to PTH type 1 receptors (Fig 2). These are G-protein coupled receptors (GPCRs) expressed on surfaces of various cells, the most important of which are osteoblasts, osteocytes, and renal tubular cells. Following ligand binding to the receptor, both Gs–mediated activation of adenylate cyclase and Gq-mediated activation of protein kinase C (PKC) occur[11,12]. Activation of adenylate cyclase results in the generation of the secondary messenger cAMP, which ultimately activates protein kinase A (PKA), which in turn activates the PKA dependant pathway for its anabolic effects on bone.[12]

The anabolic effects of intermittent PTH are mediated by (1) upregulation of pro-osteoblastogenic growth factors like insulin-like growth factor 1 (IGF1), fibroblast growth factor 2 (FGF2); (2) modulation of the osteoanabolic signalling pathway by down-regulating the synthesis of the sclerostin, and (3) increased expression and activity of Runx2 - a transcription factor essential for differentiation of osteoblasts.[9,11,12] This leads to the new growth of trabecular and cortical bones due to an increased osteoblast number.

Effects on Calcium and Phosphate Homeostasis

Teriparatide acts similar to endogenous PTH on calcium and phosphate homeostasis i.e increases serum calcium and lowers serum phosphate. These effects are similar to the well-known effects of PTH on kidneys and bone. In bone, PTH moves calcium from the bone matrix into circulation. And in the kidney, PTH stimulates distal tubular reabsorption of calcium, inhibits proximal tubular reabsorption of phosphate, and activates the 1-alpha-hydroxylase enzyme, which converts the filtered 25-hydroxyvitamin D to 1,25-dihydroxy vitamin D, the most active metabolite of vitamin D.

These two modes of actions form the primary basis of the use of teriparatide in osteoporosis induced by menopause in women and hypogonadal status in men.

PHARMACOKINETICS

The pharmacokinetics of this drug includes rapid absorption and elimination with a decline in concentrations. It first reaches a maximum concentration in about 30 min after subcutaneous injection, and then declines with a half-life of one hour. This is the time required for absorption from the injection site. However the true half-life following intravenous administration is 5 min.[13]

Usual Adult Dose for Osteoporosis[7]

20 mcg subcutaneously once daily in the thigh or abdominal wall.

Teriparatide is available in the markets as a prefilled multi dose injection, to be administered daily for a duration of two years at the maximum. There are no studies to suggest its usage beyond two years.

Dose adjustment for children has not been established and no adjustment is required for renal or liver diseases.

ADVERSE EFFECTS[7,10,13]

Teriparatide has been found to result in some side effects including osteosarcoma, hypercalcemia, urolithiasis, orthostatic hypotension, arthralgia, dizziness and pain.

Osteosarcoma: incidence of osteosarcoma was found in male and female rats that were dependent on dose of Teriparatide and treatment duration.

Bone metastases and skeletal malignancies: Patients with a history of skeletal malignancies and bone metastases should avoid teriparatide.

Metabolic bone diseases: Metabolic bone diseases other than osteoporosis should not be treated with teriparatide.

Hypercalcemia and hypercalcemic disorders: This drug has not been studied in patients with pre-existing hypercalcemia. Patients with primary hyperparathyroidism, should not be treated with Teriparatide. Treatment in such patients is risky because of the possibility of exacerbating hypercalcemia.

Urolithiasis or pre-existing hypercalciuria: No studies have been done in patients with urolithiasis. Measurement of urinary calcium excretion should be considered if suspected patients are advised the drug.

Orthostatic hypotension: If symptoms of orthostatic hypotension occur, the patient should be asked to lie down or sit. It can happen within 4 hours of dosing and can be resolved by placing the person in a reclining position for a few minutes to a few hours.

DRUG INTERACTIONS

Teriparatide increases serum calcium. In patients receiving digoxin, caution is advised as hypercalcemia may predispose patients to digitalis toxicity.

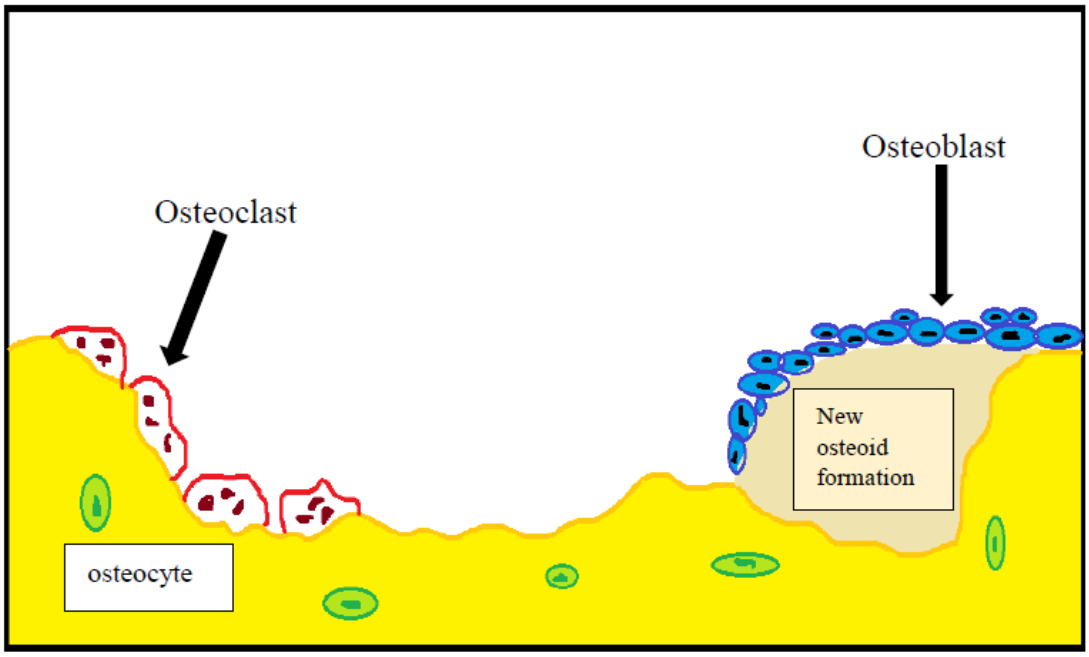

Fig.1: Normal bone construction- osteoclast removes dead and damaged bone while osteoblast forms new osteoid – this action is in balance in normal bones. In osteoporosis the bone resorption is more than the new bone formation, resulting in negative bone balance.

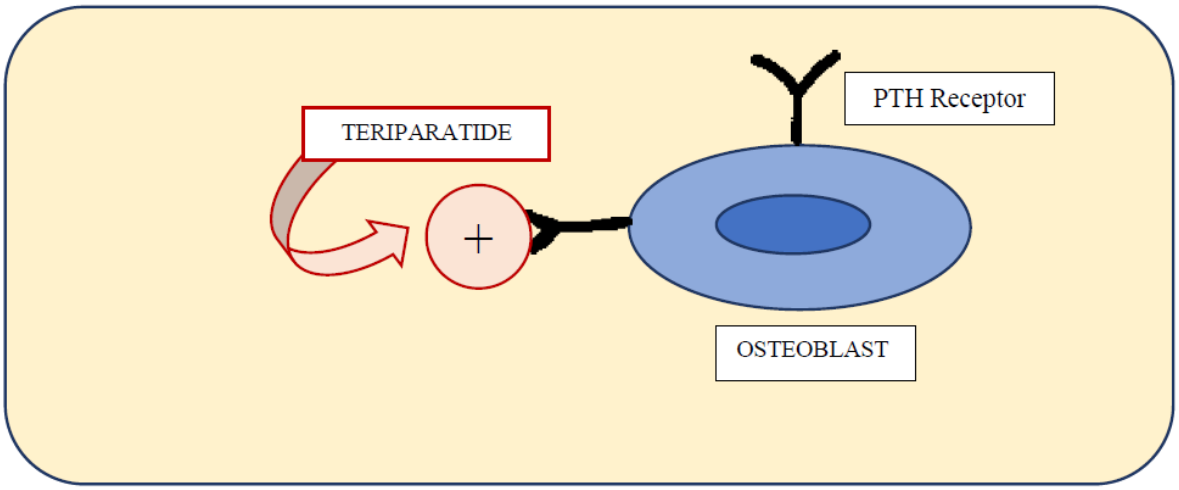

Fig 2: Action of Teriparatide on osteoblast:- Teriparatide binds to PTH receptor on osteoblast surface and promotes bone formation through new osteoid formation, thereby restoring normal bone balance.

CONCLUSION

Under proper guidance and monitoring, teriparatide can usher in a new dimension to the current treatment protocol of post menopausal osteoporosis in women and hypogonadal osteoporosis in men. It will provide relief as well better bone life to such patients and is also available in a easy to administer penfil form. Teriparatide is clinically approved for a dosage of 24 months, when taken daily, but this use can increase bone life significantly.[14]

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