

Review Article

Revealing the therapeutic potential of teriparatide: a review

Sushant Srivastava^{1*}, Arvind Kumar¹, Vishal Kundnani^{2,3}, Amit Ajgaonkar^{4,5}

¹Department of Orthopaedics, MGM Medical College, Mata Gujri University, Kishanganj, Bihar, India

²Department of Orthopaedics, Lilavati Hospital, Mumbai, Maharashtra, India

³Department of Orthopaedics, Bombay Hospital, Mumbai, Maharashtra, India

⁴Department of Orthopaedics, BDBA Hospital, Kandivali, Mumbai, Maharashtra, India

⁵Zenith Hospital, Malad, Mumbai, Maharashtra, India

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*Correspondence:

Dr. Sushant Srivastava,

E-mail: sushant391992@yahoo.co.in

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ABSTRACT

Teriparatide is an FDA-approved medication for osteoporosis that presents promising results in treating various musculoskeletal conditions. It helps in improving the bone mineral density and preventing fractures in individuals with osteoporosis. Its effectiveness in treating non-union and delayed union fractures, atypical femoral fractures, and spinal fusion procedures makes it valuable in improving bone healing and reducing complications. Teriparatide also improves bone density and strength in individuals with osteogenesis imperfecta, helps prevent and treat hypocalcaemia post-thyroidectomy, and helps in the management of hypoparathyroidism. In MRONJ, teriparatide improves lesion resolution and reduces bony defects. Furthermore, it potentially prevents bone metastasis in cancer patients without stimulating tumour growth. Nevertheless, teriparatide may cause short-term side effects like nausea and long-term concerns pertaining to the risk of osteosarcoma. Recent European alliance of associations for rheumatology guidelines have highlighted teriparatide's superior effectiveness in achieving bone mineral density thresholds and reducing fracture risks. Further clinical trials are necessary to determine optimal dosages and treatment durations of teriparatide. The off-label use of teriparatide should be considered only under the guidance of a healthcare professional when standard options are unavailable or inadequate.

Keywords: Teriparatide off-label treatment, Fractures, Cancer, Medication-related osteonecrosis

INTRODUCTION

Teriparatide, approved by FDA, EMA and CDSCO as second- or third-line treatment after first-line therapy with Bisphosphonates, is an osteoanabolic drug indicated for treating osteoporosis in patients at high risk of fracture, including postmenopausal women, men with primary or hypogonadal osteoporosis, as well as both men and women with osteoporosis linked with persistent systemic glucocorticoid therapy.¹⁻⁴ It stimulates the function, differentiation, and survival of osteoblasts and osteoclasts, as well as helps improve the BMD and prevent fractures in individuals with osteoporosis.^{5,6} Its ability to enhance

various processes in forming endochondral bone and constructing the primary callus can aid in healing fractures.⁷ The pharmacology of teriparatide has been illustrated below in (Figure 1).

A growing body of evidence supports the use of teriparatide for off-label indications such as osteonecrosis of jaws and chronic periodontitis, improving fracture healing rates and treating osteogenesis imperfect in men and women.⁸⁻¹⁰ As the efficacy of teriparatide for these indications has yet to be fully established, it is apparent that for these indications, teriparatide should only be

considered when other treatment options have been exhausted, and the potential benefits outweigh the risks.

We aimed to present a review of the use of teriparatide to explore its potential as a treatment option for musculoskeletal conditions beyond osteoporosis and the potential for expanding the understanding of its mechanism of action and therapeutic applications. We believe that a review of the available literature can provide insights into the safety and efficacy of teriparatide for off-label use, guide clinical decision-making, and identify potential avenues for future research.

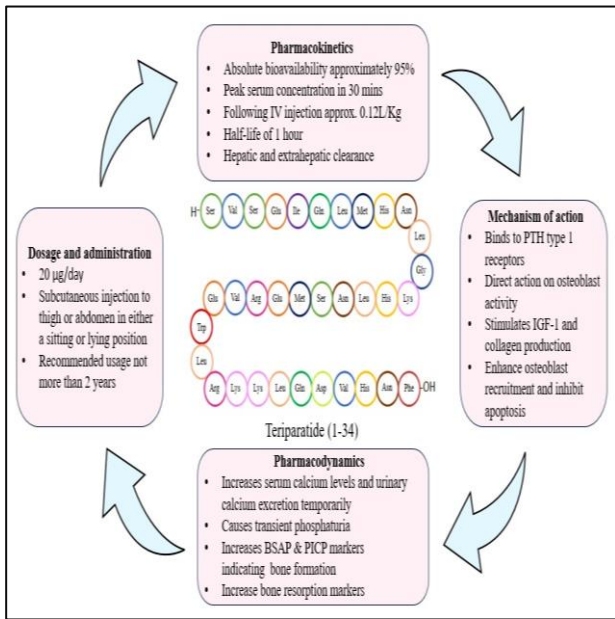


Figure 1: Pharmacology of teriparatide.¹

TERIPARATIDE: BEYOND OSTEOPOROSIS

The utilization of teriparatide for a medical condition or purpose that has not received approval from the local regulatory bodies is termed as its off-label indication.^{2,11} The (Figure 2) depicts the potential uses of teriparatide.

Faster fracture healing

Teriparatide is a potential option for accelerating fracture healing, showing promising results in clinical studies. One such randomized controlled study compared the effects of bisphosphonate and weekly teriparatide therapy on 43 patients with fresh spinal vertebral compression fractures in osteoporotic patients, where the teriparatide group (N=19) showed a significantly higher fracture-healing rate (73%) than the bisphosphonate group (N=24) (45%) at week 12 (p<0.05), with a significantly reduced mean time of fracture-healing of 2.8 months in the teriparatide group and 3.9 months for the bisphosphonate group (p<0.05).¹² Similarly, in a retrospective cohort study that compared three groups of patients with intertrochanteric fractures, i.e. patients who had not received any osteoporosis medication prior to fracture and postoperatively received

only calcium and vitamin D (Group 1) (N=83), patients not on any osteoporosis medication prior to fracture, but received teriparatide and calcium and vitamin D postoperatively (Group 2) (N=47), patients on alendronate prior to fracture and post fracture received teriparatide, calcium and Vitamin D (Group 3) (N=59).

A significantly shorter time-to-union; mean, 13.6, 12.3, and 10.6 weeks, respectively (p=0.002) was noted in the teriparatide-treated group.⁹ This action of teriparatide can be attributed to its ability to induce osteoblastic and chondroblastic progenitor cells, promoting callus formation and remodeling. Improved bone matrix protein synthesis and stimulation of the Wnt/β-catenin signalling pathway resulting in increased formation of types II and X collagen, contribute to fracture healing.^{13,14}

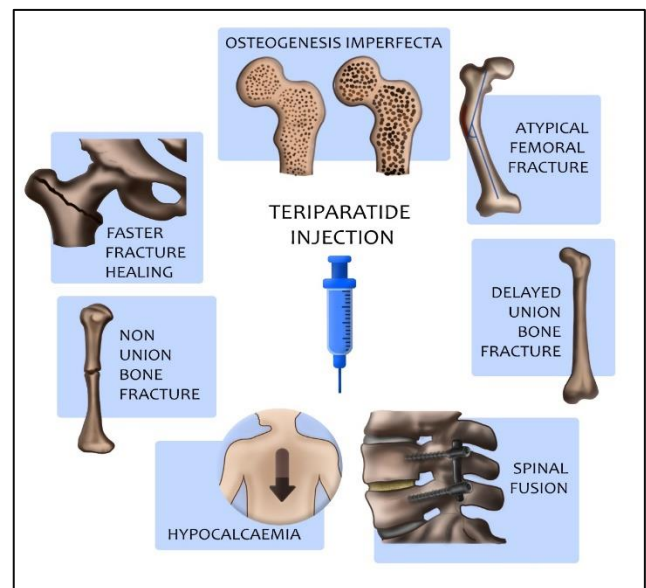


Figure 2: The potential uses of teriparatide.

Nonunion fracture

According to the US FDA, nonunion of fracture is defined as “a fracture that persists for a minimum of 9 months without signs of healing for three months”.¹⁵ But some studies consider any disturbance of routine healing as a nonunion. Nonunion fractures may require surgical intervention to promote bone healing and restore function.¹⁶ Chintamaneni et al reported a case of a 67-year-old male who sustained a fracture of the body of the sternum which subsequently failed to heal, resulting in a painful atrophic nonunion.

An empiric trial of 20 µg/day of teriparatide showed significant healing of the nonunion within three months and complete healing and symptomatic resolution after nine months.¹⁷ In another similar case, a 78-year-old woman with osteoporosis and a sternal nonunion after a blunt chest trauma was treated with teriparatide, resulting in complete nonunion healing within six months. The follow-up imaging showed improved BMD and complete

fracture healing.¹⁸ Thus, these case reports provide evidence for the beneficial effect of teriparatide on nonunion. However, more extensive studies are required to prove this effect conclusively.

Delayed union fracture

Delayed unions generally refer to fractures that exhibit a lack of healing progress within a reasonable time frame (no radiographic evidence of healing after 3-6 months following the initial injury) for the specific fracture type and patient characteristics.¹⁹

However, to overcome the delayed union, teriparatide is a promising intervention to enhance fracture healing, as is evident from the following retrospective study of 20 patients with unconsolidated fractures treated with teriparatide for 6 months showing positive radiographic indications of bone callus improvement in 15% of cases after 1 month of therapy, with 80% displaying healing progression at 3 months, and 10% achieving complete healing. By the 6-month mark, 85% of patients with delayed or nonunion fractures had experienced healing with no significant side effects.²⁰

Similarly, in a 64-year-old woman with a periprosthetic humeral fracture who underwent surgical plating and cerclage reported persistent pain after six months and was diagnosed as a delayed union. Administration of teriparatide along with vitamin D and calcium resulted in callus formation and healing in the next six months.¹¹ Thus, teriparatide could be a promising treatment for delayed union fractures by promoting bone induction and accelerating the healing process.

Atypical femoral fracture

Atypical femoral fracture (AFF) is a rare type of femur fracture that occurs spontaneously, without significant trauma, in patients taking certain medications for osteoporosis, such as bisphosphonates, for an extended period.²¹ The Fracture Improvement with Teriparatide (Fix-IT) study compared the effectiveness of immediate therapy with teriparatide to delayed therapy for six months in promoting fracture healing after an AFF.

The immediate therapy group had a trend for superior healing with the composite score and lesser declines in BMD at the 1/3 distal radius after 12 months.²² According to a report of a task force of the ASBMR, teriparatide may be considered as a potential treatment option for patients with stress fractures or subtrochanteric/femoral shaft fractures when conventional therapies are ineffective, though the evidence supporting its efficacy remains limited due to the rarity of these fractures and ethical constraints on controlled trials. It is suggested particularly for cases showing slow healing progress after surgical intervention.²³ reports suggest teriparatide may effectively promote bone healing and bone-forming ability in patients with AFF.

Spinal fusion

Spinal fusion is defined as a surgical procedure used to rectify problems with small bones of the spine (vertebrae).²⁴ A meta-analysis of 771 patients across 12 studies found that teriparatide significantly increased lumbar spinal fusion rates by 2.15-fold (OR 2.15, 95%CI 1.56–2.97, $p < 0.00001$) compared to non-teriparatide treatment. The treatment effect of teriparatide had significantly reduced subsequent vertebral fractures (OR 0.16, 95%CI 0.06-0.41, $p = 0.0002$), sagittal malalignment (MD -3.85, 95%CI: 6.49 to 1.21, $p = 0.004$), limb visual analogue score (VAS) (MD 0.36, 95%CI 0.64 to 0.09, $p = 0.008$), and spinal VAS (MD 0.24, 95%CI 0.44 to 0.04, $p = 0.02$) compared to the non-teriparatide group.²⁵ This suggests teriparatide may be an effective treatment option for promoting bone union and reducing complications in patients with osteoporosis undergoing spinal fusion procedures.

Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a rare hereditary condition that makes bones brittle and prone to breaking even under light stress or damage. The classical type of OI is caused by gene mutations that produce type 1 collagen, reducing bone density and strength.²⁶ In an interventional study, thirteen postmenopausal women with OI (type I) who experienced new vertebral fractures during neridronate treatment were treated with teriparatide for 18 months.

Teriparatide therapy significantly increased lumbar spine BMD ($p = 0.001$), bone formation and resorption marker along with the Wnt inhibitors serum dickkopf-1 (DKK-1) levels, indicating a normal osteoblastic response.²⁷ Teriparatide, as demonstrated above, has a significant anabolic response, increases BMD and strength, aiding in the treatment of this rare genetic condition.

Post-thyroidectomy hypocalcemia

Hypocalcemia is a commonly observed electrolyte imbalance in clinical practice, often stemming from a diverse array of underlying medical conditions frequently encountered in both surgical and medical services.²⁸ After thyroidectomy, hypocalcemia can be temporary (6-12 months) or permanent (>12 months). Studies have reported incidence rates of temporary hypocalcemia from 43% to 68%. While the risk of persistent hypocalcemia ranged from 1.6% to as high as 5%.²⁹⁻³¹

Teriparatide acetate has shown promise in rapidly increasing calcium levels in these patients.³² The Primary prevention of post thyroidectomy hypocalcemia (TYPHOS) trial randomized 26 patients with low intact parathyroid hormone levels after thyroidectomy to receive either 20 µg of teriparatide subcutaneously every 12 hours or standard care.

The treatment group had a significantly lower incidence of hypocalcemia (3/13) compared to the control group (11/13) and a shorter median hospital stay (2 days vs. 3 days). After 1-month of follow-up, more patients in the treatment group had discontinued calcium carbonate supplements.³³ These findings suggest that teriparatide may prevent postoperative hypocalcemia, shorten hospitalization, and reduce the need for calcium and vitamin D supplementation in high-risk patients undergoing thyroid surgery.

Hypoparathyroidism

A deficiency of parathyroid hormone, known as hypoparathyroidism, leads to the development of hypocalcemia, hyperphosphatemia, and increased neuromuscular irritability.³⁴ Hypoparathyroidism lacks standard hormone replacement therapy, and conventional treatments may not fully address complications like hyperphosphatemia, peripheral calcification, kidney stones, and bone disease.³⁵ Therefore, teriparatide has been considered as a potential treatment option to treat the same. In a 3-year randomized trial involving 27 patients with hypoparathyroidism, twice-daily teriparatide was found to effectively maintain normal serum calcium levels without hypercalciuria, providing a safe alternative to calcitriol therapy.³⁶

In cases of chronic hypoparathyroidism, ASBMR panel recommended conventional therapy using calcium and active vitamin D metabolites as the first-line treatment. This is considered a weak recommendation supported by low-quality evidence. However, the panel suggested considering the use of parathyroid hormone as an alternative treatment option in patients whose chronic hypoparathyroidism is inadequately controlled by conventional treatment, defined by symptomatic hypocalcemia, hyperphosphatemia, renal insufficiency, hypercalciuria, or reduced quality of life.

Parathyroid hormone therapy may also benefit individuals with compliance issues, malabsorption, intolerance to high calcium and active vitamin D doses, or those requiring substantial conventional therapy (e.g., calcium >2 g/day or active vitamin D >2 µg/day).³⁷

Medication-related osteonecrosis of the jaw

American association of oral and maxillofacial surgeons (AAOMS) states that MRONJ is a rare but severe adverse drug reaction associated with bisphosphonates,

denosumab and romosozumab.³⁸ Medication-related osteonecrosis of the jaw (MRONJ) is most frequently observed while treating osteoporosis, malignancy-associated metabolic bone lesions, and Paget’s disease, with an estimated incidence of 0.001% to 0.01% in the osteoporosis patient population.^{38,39} Santos Ferreira et al. analyzed the teriparatide therapy in combination with antibiotic therapy being effective in treating MRONJ based on a comprehensive analysis of 111 cases from 26 publications.

According to Poisson regression analysis, those with MRONJ stage 1 had a 1.21-fold higher chance than those with stage 3 (CI=1.02-1.43 p<0.023), and those who received teriparatide in conjunction with another therapeutic modality had a 1.21-fold higher chance of having fully resolved osteonecrosis than those who received teriparatide alone (CI=1.40-1.39 p<0.010).⁴⁰

In a double-blind, randomized trial, 34 participants with MRONJ were given either teriparatide or placebo along with the standard of care for eight weeks. Teriparatide group had a higher rate of MRONJ lesion resolution; odds ratio (OR) 0.15 vs. 0.40, p=0.013 and reduced bony defects at 52 weeks (OR 8.1, p=0.017) compared to the placebo.⁴¹ This evidence suggests teriparatide may be a beneficial treatment for MRONJ compared to standard conservative management.

Cancers

Teriparatide has been the subject of two experimental studies investigating its potential effects on tumour growth in a mouse lung cancer model with bone metastasis and in murine as well as human breast cancer models. In the first trial, teriparatide injections at intermittent intervals reduced the amount of bone around the metastatic lesions while preventing the formation of metastatic bone tumours in mice.⁴² Another study demonstrated that anabolic teriparatide treatment could modify the bone microenvironment and minimize the incidence of skeletal metastasis in patients with advanced breast cancer.⁴³ Here, both studies imply that teriparatide therapy may potentially prevent bone metastasis in cancer patients, particularly those with advanced breast cancer, without boosting tumour growth.

Side effects and safety considerations

Side effects and safety considerations of teriparatide are listed in (Table 1).

Table 1: Side effects and safety considerations of teriparatide.^{44,45}

Parameters	Observations
Recommended dose	20 µg/day
Treatment duration	Not more than 24 months

Continued.

Parameters	Observations
Contraindications	Primary and tertiary hyperparathyroidism, elevated alkaline phosphatase of uncertain cause, Paget's disease, open epiphysis in children, pregnancy, lactation, end-organ failure, metastatic skeletal malignancy, and prior skeletal irradiation
Side effects	Short-term side effects: nausea, headache, dizziness, and orthostatic hypotension. Alterations of calcium metabolism with hypercalcemia and hypercalciuria Long-term side effects: Osteosarcoma

EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY (EULAR) GUIDELINES 2023

In the recent recommendation of the EULAR guidelines, the “Proportion of patients reaching the bone mineral density (BMD) surrogate threshold effect (STE) with bisphosphonates, denosumab and teriparatide” study report was presented. Following were the key takeaways noted; Faster Achievement of BMD Thresholds: Patients on teriparatide achieved the BMD STE faster compared to bisphosphonates and denosumab.⁴⁶ This was particularly evident at the two-year mark. The study reported a statistically significant difference in reaching BMD STEs between teriparatide and bisphosphonates at two years (log-rank p<0.001). Risk Reduction: Teriparatide was associated with significant risk reduction for vertebral fractures, with a BMD increase of 4.6%, resulting in >50% risk reduction compared to other treatments. Long-term Success: While a smaller proportion of patients on teriparatide reached BMD STEs at two years compared to denosumab, teriparatide demonstrated comparable effectiveness at two years and surpassed bisphosphonates at this milestone. Additionally, nearly all subjects achieved STEs after six years of follow-up with teriparatide. These takeaways and the bar graph displayed in Figure 3 comparing bisphosphonates, denosumab, and teriparatide in terms of patient proportions reaching specific STEs over time highlight the superior effect of teriparatide in this study in terms of achieving BMD thresholds and reducing fracture risk, particularly in comparison to bisphosphonates and denosumab.

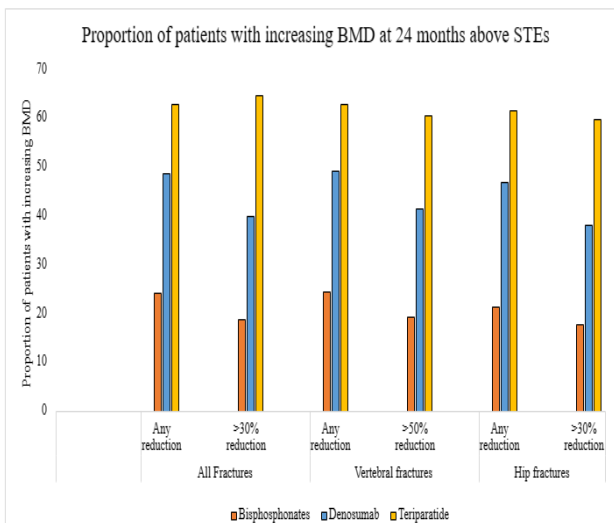


Figure 3: Bar graph indicating proportion of patients with increasing BMD at 24 months above STEs.⁴⁶

CONCLUSION

Numerous studies and case reports have examined the off-label use of teriparatide for treating conditions such as atypical femoral fractures, osteogenesis imperfecta, and nonunion fractures, indicating its potential effectiveness. However, further carefully planned clinical trials are required to validate these results and establish the optimum teriparatide dosage and duration of therapy for these patient groups. It should be emphasized that the off-label use of teriparatide is only appropriate when standard treatment options are inadequate or unavailable and must be administered under the close supervision of a competent healthcare professional.

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Conflict of interest: None declared

Ethical approval: Not required

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