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Role of Teriparatide in Delayed Union and Non-Union of Fractures

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ABSTRACT

Delayed union or non-union remains a devastating complication of fracture in 10-15% of patients. It contributes towards prolonging patient morbidity, need of a revision surgery, time lost from work leading to a high financial burden on patients. Till date no drug is approved for enhancing fracture healing in India, despite many agents are under investigational use.

Teriparatide, a parathormone analogue has been approved for the postmenopausal women and men with osteoporosis for prevention of fractures as it has a positive effect on bone metabolism and bone architecture. Studies in animal models in both normal and delayed healing have shown efficacy of teriparatide in enhancing fracture healing by improvement in callus volume, mineralisation, bone mineral content and strength at fracture sites. However majority of clinical studies on teriparatide for fracture healing consist of low level of evidence with numerous case reports and very few randomized controlled trials which have reported controversial results offering poor guidance for clinical decision making. This review presents a critical appraisal of the current evidence that summarizes various studies including experimental studies, case reports and clinical studies on the use of teriparatide in enhancing human fracture healing.

Unclear mechanism of teriparatide for fracture healing, negative results from most of the randomized controlled trials contrary to results of the case reports, lack of high quality RCTs, crude method of assessment of radiographic fracture healing, highly variable duration of teriparatide therapy in clinical studies raising a doubt on causality between teriparatide use and fracture healing are the possible reasons teriparatide is yet to get regulatory approval for enhancing fracture healing.

Keywords: Fracture healing, Teriparatide, Non-union, Delayed union, Osteoporosis, Fractures

INTRODUCTION

Fracture healing is a process which requires the involvement of multiple tissue mechanisms for a successful outcome. Bony tissue is highly efficacious in its ability to regenerate completely under normal conditions. Despite this ability, delayed union or non-union remains a devastating complication of fracture in 10-15% of the patients [1]. It represents a critical management issue, despite the advancements in understanding the physiology of fracture healing and technologies available to treat fractures.

Delayed union is defined as a condition in which bone union is not achieved even after an adequate period of time has elapsed since the initial injury. While non-union is a consequence of delayed union, differentiation between the two often becomes difficult [2]. According to American Food and Drug Administration, a non-union is established when minimum of 9 months have elapsed since injury and the fracture shows no visible progressive signs of healing for 3 months [3]. Though it is practically difficult to apply this definition in every patient, the clinician may set clinical, radiological or biomechanical criteria to define delayed union or non-union of fractures.

There are a number of treatment strategies available for augmenting fracture healing in delayed or non-union. Amongst these, the role of parathormone and its analogues such as teriparatide have been studied extensively.

Various experimental studies have shown that teriparatide potentially enhances fracture healing by stimulating the proliferation and differentiation of osteoprogenitor cells, improvement in callous volume, mineralization and bone mineral density. Though the findings in animal studies strongly suggest efficacy of teriparatide in enhancing fracture healing, clinical studies whilst supporting teriparatide for fracture healing in delayed or non-union of fracture are mainly comprised of a low level of evidence such as case reports and small prospective studies which

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have a potential of publication bias. Based on the favourable results of teriparatide, this drug is being used off-license by clinicians for accelerating fracture healing in cases of delayed union or non-union. On the other hand, very few randomized well controlled studies have been conducted majority of which have reported controversial results.

The scope of this literature review is to retrieve and summarize various studies including experimental studies, case reports and clinical studies on the use of teriparatide in human fracture healing. The objectives of this review article are:

- To review the epidemiology and impact of delayed or non-union of fractures.
- To review existing therapies for delayed union or non-union of fractures and their pitfalls.
- To discuss the safety and efficacy of teriparatide from various preclinical and clinical studies for fracture healing.
- To opine on the challenges for approval of teriparatide for fracture healing based on current evidence.

EPIDEMIOLOGY OF DELAYED FRACTURE HEALING AND NON-UNION OF FRACTURES

The reported incidence of delayed union or non-union of fracture varies considerably depending upon the site of fracture and the criteria used for defining the same. It has been estimated that 100,000 fractures go on to non-union each year in the USA [4]. A retrospective analysis in a five year epidemiological study reported an overall incidence of non-union to be 18.4/100,000 per annum with non-union most commonly occurring in males of 30-40 years of age [5]. Another study conducted by the same author in 2013, stated that the overall rate of non-union was 1.9% per fracture with higher rates of non-union observed in tibial and clavicular fractures with younger and middle age adults involved more than elderly population [6].

Risk factors for delayed or non-union include the location of the fracture, extent of soft tissue injury and bone loss, inadequate reduction and immobilization, fracture distraction, insufficient blood supply and infection while the patient risk factors include advanced age, cigarette smoking, diabetes, infections, nutritional deficiencies, hyperparathyroidism etc **(Table 1)** [7]. Early recognition of delayed or non-union of fracture improves outcome of the patient and prevents further disability.

Table 1. Risk factors for delayed union and non-union of fractures [7,8].

Patient related factors	Fracture-specific factors
Advanced age	High energy trauma or injury
Cigarette smoking	Severe bone loss
Poorly controlled diabetes	Inadequate reduction and immobilization, fracture
Infection	Distraction
Nutritional deficiencies (calcium, vitamin D)	Insufficient blood supply
Hyperparathyroidism	Biomechanical instability
Osteoporosis	Large hematoma
Menopause in females	Prolonged NSAIDs use

IMPACT OF DELAYED UNION AND NON-UNION OF FRACTURES

Delayed union or non-union of the fractures contributes for prolonging patient morbidity, need of a revision surgery, time lost from work and high financial burden on patients. It has a direct cost implication to the health services and an indirect cost to patients through lost days at work. The management of non-union has reported to impose a direct cost of £7000 to £79,000 per patient. [5] A study conducted by Ekegren CL et al. on the incidence, costs and outcome of delayed or non-union of fractures reported that approximately 10% patient readmissions occurred for fracture complications, 77% of which were due to non-union of fractures. Readmissions due to complications of fractures incurred an extra three days in hospital and costs of around AUD $25,000 per patient (AUD $5.4 M in total). Patients with delayed or non-union of fractures also reported worse function, poor quality of life with return to work rates of 12 months post-injury [9].

CURRENT LINE OF MANAGEMENT FOR FRACTURE HEALING

Currently there is a plethora of various treatment strategies available for delayed or non-union fractures to augment the bone regeneration. These include autologous bone graft,

distraction osteogenesis, allograft implantation, gene therapy, of which autologous bone graft is the gold standard. Autologous bone graft besides a successful treatment outcome has its own limitations: Major limitation is the high cost as second surgery is required for harvesting the bone material and material is highly limited [10].

An improved understanding of the pathophysiology of bone repair and remodelling has led to the development of various pharmacological therapies which include orthobiologics such as stem cells, growth factors such as BMPs (Bone mrphogenetic proteins), VEGF (Vascular endothelial growth factor), osteoprogenitor cells, osteoinductive growth factors and anabolic agents **(Table 2)**. These newer therapies have the potential to accelerate fracture repair in case of delayed or non-union of fractures [11].

Table 2. Treatment strategies for enhancing bone repair in delayed or non-union of fractures.

Treatment strategies	Comments
Bone grafting and bone substitutes Autologous Bone Graft	Gold standard with success rate 50-80% [12] Drawbacks: Harvesting complications and need of a revision surgery [13]
Allogeneic bone graft	No issues with harvesting or graft quantity Drawbacks: High cost, risk of rejection, immunogenicity, infection [14]
Bone graft substitutes	Consists of collagen, hydroxyapatite, which enhance bone cell proliferation for bone regeneration [15]
Percutaneous bone marrow grafting	Minimally invasive technique with no harvesting complications Disadvantage: May not be effective for large bone complex fractures [16]
BMPs (Bone marrow proteins) Enhance maturation and function of chondrocytes and osteoblasts	Limitations [11] Multiple doses needed for complete healing (short half-life) • Ideal carrier matrix for BMPs not yet identified Need of supraphysiological doses with doubtful long term safety • Not approved in children, pregnant women Complications such as paraplegia, osteopenia, neuritis, heterotopic ossification
Platelet rich plasma Platelets contain granules with multiple growth factors and cytokines which help bone repair	Procedure Drawing of blood into a tube containing anticoagulant followed by centrifugation and then treated with CaCl2 and bovine thrombin to form a gel like substance for direct application [17] Advantage: No risk of rejection, immunogenic reactions

	Limitation: Risk of life-threatening coagulopathies [16]
Fibroblast growth factor (FGF) Promotes multiple gene expression involved in osteogenesis	Limitation No clinical study demonstrated efficacy in enhancing bone repair over control [11].
Mesenchymal stem cells	Limitations [11] • Costly • Risk of contamination during harvesting • Time consuming as need two stage surgery • Lack of studies demonstrating efficacy.
Bone tissue engineering	Limitation Still in the stage of infancy and concerns of efficacy, safety and costs need to be addressed before clinical application [11]
Gene therapy Involves transfer of genetic material into the target cell genome	Experimental studies involving delivery of BMPs for enhancing bone healing showed promising results, but clinical studies are lacking and issues of safety, efficacy and costs are major concerns [18]
Systemic anabolic agents such as parathormone and analogues	Advantages Non-invasive technique Stimulation of healing for a prolonged period of time Extensive experimental studies which have shown promising results

THE MECHANISM OF TERIPARATIDE IN BONE REMODELLING AND CURRENT STATUS

Parathormone is a naturally occurring 84 amino acid polypeptide secreted by the parathyroid gland. Its predominant function is to increase serum calcium levels in response to hypocalcaemia. In addition to this function, it has also been shown to physiologically regulate the bone metabolism and structure. Studies also indicate that parathormone assists in fracture healing so as to increase the bone mass and bone strength [19].

Teriparatide (PT 1-34) is a recombinant drug which is a biologically active component of parathormone. The drug is an osteoanabolic agent approved in various countries for postmenopausal women and men with osteoporosis for prevention of fractures [20] **(Table 3)**.

Table 3. Approval status of teriparatide in various countries [21,22].

Countries with approval for Teriparatide	**Approval year**	**Approved indication**
USFDA	November 2002	Post-menopausal women and men with
European Medicine Agency (EMA) , Europe	June 2003	

CDCSO, India	September 2003	osteoporosis at high risk of fractures, Patients with glucocorticoid-induced osteoporosis
Pharmaceuticals and Medicals Devices Agency, Japan (PMDA)	July 2010	
China Food and Drug Administration (CFDA)	March 2011	

Teriparatide is manufactured by using a genetically modified strain of E. coli and is given as a solution for subcutaneous injection [23].

Apart from this approved indication in osteoporosis, there is a growing body of evidence to suggest the use of teriparatide for accelerating fracture healing in case of delayed union and non-union of fractures. Teriparatide increases cortical as well as trabecular bone density by increasing bone formation and also promotes resorption of the bone by osteoclasts [24].

Teriparatide has been shown to accelerate fracture healing by increasing the endochondral ossification and improving the biomechanical properties of the fracture callus. The stimulatory effects of teriparatide on fracture healing have also been explained by 'anabolic window' which means that during teriparatide treatment, bone formation is in excess over bone resorption up to first 18 months [25].

The biochemical action of teriparatide is via stimulation of PTH-1 receptors which are present on the osteoblasts and bone marrow stromal cells to induce osteoblastic bone formation and increased mineralization [26]. As a result of this increased mineralization, there is a reduction in the fragility fractures which is equal to or more than, that observed with the use of antiresorptive agents [27].

PRECLINICAL STUDIES: TERIPARATIDE FOR NORMAL FRACTURE HEALING

Preclinical studies in animals have demonstrated the potential of teriparatide on fracture healing. In 1999, Andreassen et al. showed that teriparatide injections increased callus formation and ultimate load to failure for tibial fractures in rats [28]. Another study in rats has shown that a daily subcutaneous injection of 10 µg/kg of teriparatide administered during the entire healing period of femoral fractures significantly increased the bone mineral content (BMC), bone mineral density (BMD) and increased bone markers in calluses as compared to the controls [29].

A study in 270 rats with femoral fractures in which rats were divided in 3 groups and were administered 5µg/kg or 30 µg/kg of teriparatide and vehicle (control) for 35 days. A group which was administered 30µg/kg of teriparatide showed significant increase in BMC, BMD, bone strength and callous formation compared to other groups, suggesting enhanced fracture healing [30].

A study in rats with tibial fractures showed that administration of teriparatide in a high dose of 200 µg/kg/day as well as 60 µg/kg/day enhanced callous volume and mechanical strength of fractures after 40 days of healing [28].

Kaback LA et al. investigated the mechanisms underlying teriparatide accelerated fracture repair. Osx (osterix) and osteoblast phenotypic gene expression in cultured bone marrow cells of mice from both the groups was assessed by real-time RT-PCR. Significant up regulation of Osx and Runx2 was observed in marrow-derived MSCs of mice systemically treated with teriparatide compared to controls. This study suggested that teriparatide enhances fracture healing by inducing Osx expression in MSCs [31].

PRECLINICAL STUDIES: TERIPARATIDE FOR DELAYED FRACTURE HEALING

In order to study the beneficial effect of teriparatide in cases of delayed healing, Nozoka K et al. performed a study in normal and ovariectomized rats that had undergone cancellous bone osteoctomy. Weekly injections of teriparatide 100 µg/kg for four weeks increased the cancellous bone volume in normal as well as ovariectomized rats by increasing osteoblastogenesis. This suggested that teriparatide enhances healing in cases of delayed fractures [32].

Another study was conducted in rabbits with delayed fracture healing model produced by administering daily injections of prednisolone started two weeks before surgery and continued until killing. Surgery consisted of creation of 1 mm defect bilaterally in ulnae of rabbits. Daily subcutaneous injections of parathormone analog RS-66271 and injections of normal saline were given to the respective groups. Nine of ten ulnae from parathormone treated rabbits showed radiographic union, which was significant compared to control group ($p<0.01$). Ulnae in the parathormone-analog-treated rabbits showed greater radiographic intensity (20%-40%), larger callus area (209% anteroposterior view, 417% lateral view) and greater stiffness (64%) and torque (87%) when compared with controls [33].

CASE REPORTS ON FRACTURE HEALING BY TERIPARATIDE

Various case reports of fracture healing with teriparatide use (Table 4) as well as a number of case series [34,35] have

been published. A summary of fracture healing by teriparatide is as follows.

Fracture intra capsular neck of femur

Fracture intra capsular neck of femur with non-union and signs of avascular necrosis wherein two doses of teriparatide administered at monthly interval demonstrated 90% union at the end of two months with no need for surgical intervention and no adverse events. Author suggested teriparatide as an effective alternative to surgical intervention [36].

Radial neck fracture

Radial neck fracture with non-union in which a 60 year old female with severe osteoporosis and persistent pain at elbow joint was given daily teriparatide injections reported full range of motion with no pain at the same joint and complete union at two years follow up [37].

Vertebral fracture in ankylosing spondylitis

Vertebral fracture in ankylosing spondylitis wherein patient declined surgery for fracture at T2 and C5 vertebral body and was then given daily injections of teriparatide for six months. The case was unique in that complete union of vertebral fracture was achieved at six months without any adverse events or complications with no requirement for preceding surgical intervention [38].

Distal humeurs fracture

Distal humeurs fracture with non-union requires an open reduction and internal fixation. An 87 year old woman with risk of general anesthesia being elderly, associated osteoporosis and difficult operative procedure due to involvement of small bones in distal humeurs fracture non-union was given conservative treatment in the form of injection teriparatide daily for 12 months. Complete union was observed three months after discontinuation of teriparatide with good range of motion at elbow joint and so good quality of life [39].

Sternal fractures

Sternal fractures with non-union, though very rare, are onerous for the patient. A patient of sternal fracture which demonstrated atrophic non-union on CT scan of the chest consented for the trial of teriparatide injection daily. Imaging studies revealed significant healing of the sternal non-union within three months and complete healing after nine months. Patient reported dramatic improvement in his quality of life [40].

Odontoid fractures

Odontoid fractures with non-union wherein the author reported three cases of type III odontoid fractures which failed to unite even after external immobilization causing persistent pain. Teriparatide daily injections were given to these patients for between six weeks to two years. All the patients reported marked improvement in neck pain and complete healing of fracture was observed on CT scan at between four months to seven months of starting the treatment [35].

Emanuele C et al. [41] and Xiofeng LI et al. [42] also reported similar case study results of improved fracture healing with teriparatide use in non-union of fracture **(Table 4)**.

Table 4. Evidence for use of teriparatide in human fracture healing: Case reports.

Author	Age/sex of patient	Type of fracture	Site of fractures	Time of initiation of teriparatide	Duration of teriparatide	Outcome of therapy
Dr Sujoy Kundu 2018 [36]	39/M	Non-union fracture	Fracture ICNF	Immediately after diagnosis of non-union	Two doses for 2 months at monthly interval	90% union of fracture achieved after 2 doses at monthly interval and patient improved symptomatically.
Garg B et al. 2017 [37]	60/F	Non-union fracture along with	Radial neck fracture	After the diagnosis of osteoporosis	3 months daily injections of	3 months daily injections of teriparatide 20

		osteoporosis		on DEXA scan to rule out the cause of non-union	teriparatide 20 µg	µg.
Biro Izolda et al. 2017 [38]	56/M	-	Vertebral body C5 and T2 fracture	Started after the patient refused for surgical treatment	6 months daily injections of teriparatide 20 µg	Patient mobilised and was pain free within 2 months of teriparatide and complete healing in 6 months
Yonezu hiroshi et al. 2017 [39]	87/F	Non-union (3 months after cast fixation)	Distal humeurs	Started after diagnosis of non-union	12 months weekly injections of teriparatide 20 µg	Complete union 3 months after discontinuation of teriparatide with good range of motion
Chintamaneni S et al. 2010 [40]	67/M	Non-union fracture	Sternal fracture	After recognition of an atrophic non-union	9 months daily injections of teriparatide 20 µg	Significant healing of non-union within 3 months and complete healing after 9 months
Emanuele C et al. 2017 [35,41]	64/F	Non-union of periprosthetic fracture	Distal humeurs	Started post operatively	3 months daily injections of teriparatide 20 µg	Complete fracture healing at one year postoperatively
Xiofeng LI et al. 2017 [42]	44/F	Non-union fracture	Tibia and femur	Immediately after recognition of non-union	8 months daily injections of teriparatide 20 µg	Bony bridging at 4 months of treatment Complete fracture reunion 12 months after start of teriparatide

CLINICAL STUDIES ON FRACTURE HEALING BY TERIPARATIDE

Various clinical studies have been conducted in patients reporting the results of teriparatide use for fracture healing **(Table 4)** however; only randomized controlled trials are discussed here.

A randomized, placebo controlled, double blind trial was conducted by Bhandari M et al. to evaluate the effect of teriparatide versus placebo injections on fracture healing in patients of unilateral femoral neck fracture. Injections were given daily for six months and the effect on fracture healing was assessed. The study hypothesized that the adjuvant therapy to surgical internal fixation with teriparatide could offer a biological advantage compared to internal fixation alone. Study parameters were need for revision surgery, radiographic fracture healing, pain control and safety. There were no significant differences between the two groups in the proportion of patients requiring a revision surgery at 12 months (p=0.743), in proportion of patients achieving radiographic fracture healing at 12 months (p=0.692), in pain control measures (p=0.681) or incidence of adverse events (p=0.634) [43].

Although preclinical studies in animal models and case reports in patients show an anecdotal benefit of teriparatide in fracture healing, this study, which was one of the very few well controlled trials, reported no such benefit of the study drug. However, study had several limitations which include; smaller cohort size than planned, which made the study underpowered to detect the treatment effect included in the original study protocol. Other limitations were too small sample size to detect the difference in revision surgery and assessment of radiographic healing at 10 weeks, 6 months, 12 months intervals which may be too crude for evaluation of femoral neck fracture healing.

Johanssen et al. [44] randomized 40 postmenopausal women with proximal humeurs fractures into two groups; injection teriparatide daily for four weeks vs. control group (no placebo). The teriparatide group did not show any significant radiographic signs of enhanced healing, improved pain score measures or functionality of patients when compared with control group. As far as the side effects, teriparatide was tolerated well with only mild side effects such as nausea and headache. The study had major limitations such as too small sample size and the length of time for which teriparatide was administered was very short compared to the various case reports or studies in which drug was given for between two months to 24 months [44].

In another randomized, double-blind, placebo-controlled study of teriparatide in fracture healing, postmenopausal women with a dorsally angulated distal radial fracture (colles fracture) were randomized to eight weeks therapy of daily injections of teriparatide 20 µg, 40 µg, or placebo (n=34 in each group). The study demonstrated that 20 µg as well as 40 µg teriparatide significantly improved healing time compared to placebo. A significant difference was observed in median time to cortical bridging in teriparatide 20µg group (7.4weeks) compared with placebo (9.1weeks) (p=0.006) but not with teriparatide 40 µg (8.8 weeks) vs. placebo (p=0.523). Based on the study results, the initial hypotheses of a dose related positive effect of teriparatide on bone healing was rejected. The results of the study suggested caution while interpretation and warranted further research [45].

A systematic review and meta-analysis on safety and effectiveness of teriparatide on fracture healing was done in 380 patients randomly assigned in 5 randomized controlled trials. The study showed that teriparatide lacked the effectiveness for fracture healing. This was the first meta-analysis that also included non-osteoporotic fracture patients in addition to those with osteoporotic fractures and was the first one to include outcome parameters such as fracture healing rate and reduction in pain. This study had limitations like the small sample sizes of included studies and small number of studies, diversity in control groups, diversity in treatment initiation period as well as in duration of treatment leading to insufficient evidence [46].

SAFETY CONCERNS OF TERIPARATIDE

Teriparatide has been observed with both short and long term adverse effects. Hypercalcemia and hypercalciuria are the two most common side effects [47]. However, hypercalciuria is not significant and there were no cases of nephrocalcinosis with teriparatide [48]. Absolute contraindications of teriparatide include primary and tertiary hyperparathyroidism, elevated alkaline phosphatase of uncertain cause, Paget's disease, open epiphysis in children, osteosarcoma, pregnancy, lactation, end-organ failure, metastatic skeletal malignancy and prior skeletal irradiation [49].

In practice, teriparatide has been reported as a safe drug with no major serious adverse events. In a post marketing surveillance study involving 1847 patients who received teriparatide injections daily for 24 months, 140 patients reported adverse drug reactions; the most common ADRs were hyperuricemia, nausea and dizziness. Only six patients reported serious ADRs, most common being nausea implying that teriparatide has a favourable safety profile [50]. Similar results of no major safety concerns were reported by Caggiari G et al. [51] and Yoshiki F et al. [52]. In a post hoc analysis of post marketing observational study in osteoporotic patients with severe stages of CKD (chronic kidney disease), no serious ADRs were observed with no safety concerns after teriparatide use [50].

Very few long term side effects have been reported. However, osteosarcoma is a concern with the use of teriparatide. Preclinical studies have reported an occurrence of osteosarcoma with teriparatide use; however, no

conclusive results on the association of osteosarcoma with teriparatide have been reported in clinical studies. In 2008, Harper et al. reported the first case of osteosarcoma in a patient treated with teriparatide among more than 300000 cases worldwide, suggesting that the benefit of the drug outweighs the risk associated [48]. Findings from 7 years of US post marketing surveillance study of adult osteosarcoma and teriparatide reported no case of osteosarcoma with teriparatide use suggesting no causal relationship between osteosarcoma and teriparatide [53].

CONCLUSION

The use of teriparatide in fracture healing is of great interest in the field of orthopaedics. However, the effect of teriparatide in accelerating healing in delayed union or non-union of fractures remains uncertain. Animal studies as well as case reports yielded consistently positive results suggesting benefit of teriparatide for fracture healing. But case reports or case series offer poor guidance for clinical decision making.

The available evidence is insufficient to support regulatory approval on the use of teriparatide for an indication of enhanced fracture healing. In view of the limitations of the controlled trials, high quality randomized controlled trials are needed in order to confirm whether teriparatide improves fracture healing in delayed or non-union fracture with special emphasis on to address the optimum duration of teriparatide therapy for fracture healing.

The authors believe that following might be the reasons that teriparatide not yet approved in any country for enhancing fracture healing.

- The precise mechanism by which teriparatide orchestrates fracture healing is less clear.
- Low level of evidence comprising mainly of case reports or case series depicting positive results but amounts to high risk of publication bias.
- Very few randomized controlled trials most of which have reported negative results.
- No large scale randomized controlled trial so far.
- Duration of teriparatide therapy to achieve the desired effect on fracture healing vary considerably in all the clinical studies (from just two injections a month to 24 months daily) which raises doubt on causal association between teriparatide administration and improved fracture healing **(Table 3 and 4)**.
- Crude method of assessment of radiological fracture healing in most of the studies.

However, considering the safety profile of teriparatide, clinicians can opt for teriparatide as a reasonably safe choice to accelerate fracture healing, particularly in a setting of delayed union or non-union in patients who are not willing for revision surgeries. Both patients and clinicians should be aware that this would be an 'off-license' use taking into consideration the fact that clinical data supporting this indication is extremely limited.

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