

Use of teriparatide off-label: our experience and review of literature

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Summary

The aim of this paper is to report our experience and to present a review of literature about the use of teriparatide off-label in the therapy of non-unions. Teriparatide is used exclusively in treatment of osteoporosis and to prevent bone fracture because it has a positive effect on bone strength and architecture. The use of teriparatide in non-unions is described as effective in numerous case report.

KEY WORDS: teriparatide; osteoporosis; non-union; bone remodeling.

Introduction

Fracture healing usually occurs spontaneously, by a primary way, if fracture fragments are very close and stable, or more often by a secondary healing through the production of abundant repairing tissue, the callus, if a gap or micro-movements between the fracture fragments are present (1).

There are several conditions affecting the rate of fracture healing: they are divided in general and local factors.

In the first group there are the age, the type of bone involved, nutritional status, drug therapy and bone pathology: speed of union of the fracture decreases with skeletal maturity and also if the patient is not in good nutritional status, many drugs and pre-existing bone pathology adversely affect fracture healing such as corticosteroids, NSAIDs or *osteogenesis imperfecta* and others metabolic disease of bone.

Local factors are the separation of bone ends, the disturbance of blood supply, infections, the property of bone involved and the type of fracture: bone ends must not be separated or with soft tissue interposition, blood supply is fundamental and its interruption may lead to necrosis, pathogens interact with reparative cellular activity resulting in a prolonged inflammatory phase and finally, any type and localization of fracture heal according to their intrinsic characteristics.

Movement of the fracture site interferes with vascularization of haematoma, disrupts bridging callus and endosteal bone growth. On the other side, an optimal balance between stability and micro-motion encourages callus formation and produces electrical local currents which improve bone healing by stimulating an inflammatory-type response and promoting calcification of fibrocartilage. Low-intensity pulsed ultrasound plays a relevant role in biomechanical environment, it accelerates fracture healing perhaps by acting directly to proliferation and differentiation of multipotent human bone marrow-derived mesenchymal stromal cells (2). Actually, the use of Platelet-Rich Plasma (PRP) seems to play an important role in the fracture healing and to favor fusion processes in spinal arthrodesis (3). Due to their osteoconduction activity, bone substitutes too such as hydroxyapatite and tricalcium phosphate represent an important resource to be used in delayed bone healing and in atrophic non-union with large bone gap (4).

The definition of non-union in fracture healing is a disturbance of normal repairing process with the expectation that no consolidation will be achieved without focused and accurate treatment (5).

Non-union are defined according to the American Food and drug Administration (FDA 1988) as “established when a minimum of 9 months has elapsed since injury and the fracture shows no visible progressive signs of healing for 3 months” (6). This definition is not always true because the healing time of a fracture depends from the bone concerned, for example a diaphyseal fracture of the femur needs for at least 4-6 months to heal. In some cases, it needs more time, especially if the fracture is open or comminuted. On the other hand, a femoral neck fracture can be considered as a non-union after only 3 months.

Here we want to focus on some of the aspects shown in non-unions that seem to be potential biomechanical and biochemical environment targets for teriparatide.

Non-union classifications

The non-union of fractures remains a challenging and clinically important problem in orthopaedic surgery.

There are many classifications on non-union, but the one that best classifies them according to different vitality and healing potential is the work of Weber and Čech in 1976. He described three type of non-union: hypertrophic, oligotrophic, and atrophic.

Hypertrophic non-union is characterized by hypervascular and/or hypertrophic ends of the fragment, high inflammatory reaction with rich blood supply visible in bone scintigraphy. The amount of the external callus is variable in response to motion at the fracture site. Bone scans in this type of non-union show increased activity at the fracture site, implying vascularity and osteogenesis (7).

In atrophic non-union, fragments have no biological reaction.

Contrary to what happens in hypertrophic non-unions, here we do not find an adequate blood supply at the ends of the fragment, the inflammatory reaction is abolished, there is not a callus visible and the fracture line persists.

In oligotrophic non-unions, there is minimal callus formation, but some biologic activity is maintained. This happens when the fracture fragments are not correctly apposed.

It is the oligotrophic and atrophic non-unions, which have impaired biologic potential to unite, that require a treatment directed toward improving the osteogenic ability and biology of fracture-healing.

The role of PTH in bone remodeling

PTH has a predominant role in regulating calcium-phosphate metabolism and it is secreted by parathyroid when serum calcium levels decrease.

Parathyroid hormone (PTH) secretion is characterized by an ultradian rhythm with tonic and pulsatile components. In healthy subjects, the majority of PTH is secreted in tonic fashion, whereas approximately 30% is secreted in low-amplitude and high-frequency bursts occurring every 10-20 min, superimposed on tonic secretion (8).

The pulsatile secretion of PTH may have a role in physiological regulation of bone metabolism and structure. Although there are no animal models investigating specifically the skeletal effects of pulsatile PTH secretion, there is experimental evidence that intermittent administration of pharmacological doses of PTH has a bone anabolic effect, while continuous PTH administration is detrimental for the skeleton due to stimulation of bone resorption (9).

In hyperparathyroidism is well-known the catabolic effect on skeleton by continuous exposure to PTH, bone loss can be appreciated in both cortical and trabecular compartments of the skeleton (10).

Conversely, the foreshortened amino terminal peptide of PTH, teriparatide [PTH (1-34)] and the full length molecule [PTH (1-84)] are osteoanabolic when administered once daily in low doses for the treatment of osteoporosis (11-15).

It has been shown that teriparatide also accelerates fracture healing by improving the biomechanical properties of the fracture callus, increasing endochondral ossification and bone remodeling in animal models. This effect has been observed in several case reports (16).

The increase in the PTH-mediated bone resorption is due to an increased activity of the osteoclasts, but *in vivo* and *in vitro* studies show that the PTH action on osteoclast is indirect and mediated by osteoblasts and osteocytes (17, 18).

The OPG-RANKL-RANK pathway plays a critical role in bone resorption induced by PTH. In fact, continuous and high PTH levels increase RANKL and decrease OPG expression; the final result is an increased RANKL/OPG ratio that leads osteoclastogenesis and bone resorption (19-21).

The cells involved in bone formation process are many and they have all the PTH receptors. They are preosteoblasts, osteoblasts, lining cells, T-cells and osteocytes (22).

The stimulatory effects of PTH on bone formation have been explained by the so-called 'anabolic window', which means that during PTH treatment, bone formation is in excess over bone resorption during the first 6-18 months. This is due to the following: 1) PTH(1-34) seems to induce the proto-oncogene c-fos levels in osteoblastic cells *in vitro* via the activation of cyclic adenosine mono phosphate (cAMP) (23), 2)

PTH induces an increase in IGF-I expression in osteoblasts, 3) bone lining cells are driven to differentiate into osteoblasts and mesenchymal stem cells residing in the bone marrow increase c-fos expression (24), 4) mesenchymal stem cells adhesion to bone surface is enhanced, 5) PTH has a direct antiapoptotic effect on osteoblasts through a pathway involving cAMP-mediated PKA signaling, and subsequent phosphorylation and inactivation of the apoptotic protein Bad, 6) when PTH interferes with remodeling, the osteoblasts over-compensate (25), and 7) PTH also decreases sclerostin levels, thereby removing inhibition of Wnt signaling which is required for PTH's anabolic actions (26, 27).

Clinical data on use of teriparatide off-label

So far only a few studies have been conducted on the use of teriparatide in fracture healing.

In 2012 a prospective study was conducted involving 14 consecutive patients presenting during 2 years with atypical femoral fracture. Administration of 20 µg of teriparatide subcutaneously daily for 6 months to 5 of the 14 patients was associated with 2-3 fold increase in bone remodeling markers and fracture healing (28).

In 2011, a prospective randomized controlled study was published where PTH (1-84) administration determined in 21 patients, within a sample of 65 postmenopausal osteoporotic women suffering from pelvis fracture, a faster repair with an improvement in functional outcome (29).

In 2009, a prospective double blinded randomized controlled study on the effect of teriparatide therapy on the fracture healing, in 102 postmenopausal women with Colles fracture, demonstrated that 20 µg of teriparatide significantly reduce healing time, compared with placebo, but also with the 40 µg higher dose therapy. The study failed to prove the initial hypothesis of a dose related positive effect of teriparatide on bone healing. The effect was also seen through an increase in the resistance to load (30).

In the last years many case reports about the efficacy of use of teriparatide off-labels have been presented to the scientific community.

In 2009, Angel Otero-Alvaro reported of a 32-year-old Caucasian male with right diaphyseal humeral fracture fixed with elastic nail that after 6 months shown an atrophic non-union. The patient was treated with 20 µg/days of teriparatide and after 5 months of treatment healing was complete (31).

In 2015, was performed a retrospective chart review of patients with fracture non-union, aged 10 to 99, treated with teriparatide between 2002 and 2013. Six patients aged 19 to 64 years with tibial or femoral fractures that had not healed for 3 to 36 months were treated with teriparatide 20 µg/day. Accelerated healing of fracture non-union was confirmed in 5 of 6 patients with time to complete union of 3 to 9 months. The shortest time to recovery was observed in younger patients without comorbidities (32).

Holm J. reported a case of a successfully healed atypical femoral fracture (AFF) following treatment with teriparatide in a patient with *osteogenesis imperfecta* (OI). The patient was treated with hormone replacement therapy for 18 years and bisphosphonates for 9 years before suffering a spontaneous AFF in the form of a dislocated non-comminuted transverse fracture of the right femoral shaft, and an open reduction and internal fixation (ORIF) with a T2 femoral nail was done. Due to non-union and another fracture distal to the nail, the pa-

tient was re-operated on with exchange ORIF and off-label treatment with teriparatide 20 µg/day was started. An X-ray 1 month later showed early signs of fracture healing. A subsequent X-ray 6 months after the last operation showed a solid healing of both right femoral fractures (33).

Etzebarria-Fononda I. reported of a young male patient diagnosed with *osteogenesis imperfecta* and who received treatment with bisphosphonates for several years, developing over time an atypical diaphyseal femoral fracture which was treated surgically by means of an intramedullary nailing and with later pharmacological treatment with teriparatide, with a satisfactory outcome at one-year follow-up (34).

Mouyis M. reported a case of a 76-years-old-woman with rheumatoid arthritis, osteoporosis, multiple comorbidities and septic left elbow prosthesis. Treatment included combination antibiotic therapy and removal of the prosthesis. Week later she was started on teriparatide. Her elbow symptoms resolved (35).

Lee YK. reported 3 cases of femur non-union after initial surgical intervention. Teriparatide was administered for 3-9 months after a diagnosis of non-union. A successful union was obtained in all 3 patients without further surgical intervention, and no adverse events related to the use of teriparatide were observed (36).

Hiroyuki T. presented two cases of incomplete atypical femoral fractures showing a favorable course after being treated by locking plate surgery and prescribed teriparatide (37).

Caffarelli C. described a successful novel therapeutic intervention with teriparatide with one patient with Rett syndrome, after suffering from recurrent low-trauma fractures at intervals of several years. Treatment consists with teriparatide and subsequently with intravenous bisphosphonate. Since the initiation of the treatment, there was an evident improvement at densitometric and QUS parameters. Until the present, no new fractures have appeared (38).

Corrigan R.A. reported a case of a 21-year-old female with extended oligoarticular juvenile idiopathic arthritis diagnosed at the age of 8 years who sustained a low-impact short oblique closed fracture of her right lower tibia. The fracture failed to unite over 2 years. Bone healing following prolonged non-union was induced by combined treatment with teriparatide and a single zoledronic acid infusion; while calcification of the callus could have occurred in the absence of zoledronic acid, the callus should have started to calcify within 12 weeks of teriparatide therapy (39).

Chintamaneni S. reported a case of a 67-year-old white male who was involved in a motor vehicle accident in December 2007. He sustained a fracture of the body of the sternum which subsequently failed to heal, and an atrophic non-union was demonstrated by repeated CT. The patient consented to an empiric trial of teriparatide (20 µg sq injection daily) in an attempt to treat the atrophic non-union. Follow-up imaging studies revealed significant healing of the sternal non-union within 3 months and complete healing after 9 months (40).

Mitani Y. described a case of 88-year-old female with rheumatoid arthritis and a Garden type II displaced femoral neck fracture who underwent surgery with a Hansson hook-pin system. At 11 months, the patient still complained of mild groin pain on ambulation. A diagnosis of non-union was given. The patient accepted treatment with a once-weekly injection of 56.5 µg chemically synthesized teriparatide. At 18 months post-operatively, CT imaging after 20 consecutive

weekly administrations of teriparatide revealed signs of healing and the patient reported a gradual decrease in groin pain on ambulation. Complete union of the fracture was obtained at 23 months (41).

Nozaka K. reported a case of a 56-year-old Japanese male with a femoral shaft fracture who underwent intramedullary osteosynthesis nailing initially. He had no radiologic or clinical sign of healing 3 months later and low-intensity pulsed ultrasound was initiated at that time. He was reassessed in another 3 months, with evidence of mild bone consolidation but the fracture gap persisted. Subsequent treatment with human parathyroid hormone was initiated in combination with low-intensity pulsed ultrasound. Full fracture healing was present 6 months after beginning the combination low-intensity pulsed ultrasound and teriparatide (42).

Giannotti S. reported a case of a Caucasian 80-year-old white woman who had an accident in October 2011. She was diagnosed with right distal metaphyseal femoral fracture on total knee arthroplasty. She underwent surgery at our center consisting of ORIF with lateral femoral locking plate. Radiological controls at 5 and 7 months show signs of atrophic non-union. After 2 months of treatment with 20 µg/day of teriparatide, X-ray showed the presence of bone bridges and a decreased gap. After 3 months of treatment healing was complete (43).

Ochi K. described a case of a 74-year-old woman with a 26-year history of rheumatoid arthritis who sustained a peri-prosthetic femoral fracture secondary to a fall from the stairs that occurred 13 years after she underwent TKA. The fracture was internally fixed with a periarticular locking plate and hydroxyapatite graft and additionally treated with daily low-intensity pulsed ultrasound. Non-union became apparent when the locking plate broke 9 months after the internal fixation. Patient underwent to a second intervention. Nine months after, scan revealed signs of non-union. Thus, the patient was additionally treated with once-weekly teriparatide injections for 6 months so as to heal the fracture (44).

Tachiiri H. reported 2 cases of delayed union that were effectively treated with weekly teriparatide administration. The first case is a 72-year-old woman with delayed union after 4 months from treatment of hallux valgus. The second case is a 72-year-old woman with delayed union after 4 months from open reduction and internal fixation of an olecranon fracture (45).

Personal experience

We report of a case of a 38-year-old man who had a car accident in June of 2011 (the patient authorized his clinical data to be published in a scientific journal) with a left diaphyseal comminuted humeral fracture. He underwent surgery consisting of osteosynthesis with a bridge plate and 6 screws. Radiologic controls at 4 months did not show any signs of healing, a 1 cm gap between fracture fragments was present (Figure 1). The patient underwent revision surgery 8 months after the first surgery removing plate and screws and positioning anterograde intramedullary nailing and autologous iliac bone grafts (Figure 2). X-rays achieved 3 months after the revision surgery did not show any signs of healing (Figure 3). This was consistent with the clinical manifestations of pain, movements at the fracture site, and left arm weakness. The physical examination and laboratory tests, including white blood cell counts, C-reactive protein, and ery-



Figure 1 - Plain radiographs achieved 4 months post-op show atrophic non-union with a 1 cm gap of the fracture line.

throcyte sedimentation rate, were normal, which permitted to rule out underlying infection. The patient denied smoking, alcohol abuse, and had no history of metabolic disease or glucocorticoid intake.

The patient refused to be re-operated to perform a new osteosynthesis, and accepted an empiric, off-label therapy with teriparatide at approved doses for the treatment of osteoporosis (20 µg/day). After 3 months of treatment with teriparatide radiographs showed bone bridges and a reduction of the gap between fragments (Figure 4). After 6 months of treatment bone healing was complete (Figure 5) and clinical manifestations disappeared. No side effect due to the drug was observed during treatment.

Discussion

Scientific literature of last year seems to show a great efficacy of teriparatide to treat bone non-unions.

There is increasing evidence that treatment with PTH (1-34) enhances callus formation by stimulating the proliferation and differentiation of osteoprogenitor cells and increasing the production of bone matrix proteins (46, 47).

The basic science studies suggest at least two mechanisms for bone formation: 1) stimulation of endochondral ossification, perhaps by slowing hypertrophic chondrocyte differentiation and thus maintaining a pool of proliferative chondrocytes and 2) stimulation of mesenchymal cell differentiation into osteoblasts (48).

These mechanisms and the anabolic effect of PTH (1-34) on bone density and periosteal bone formation in osteoporotic patients suggest a role for this agent in accelerating fracture healing.



Figure 2 - Plain radiographs achieved after revision surgery using anterograde intramedullary nail.



Figure 3 - Plain radiographs achieved 3 months after the revision surgery did not show any signs of bone healing.



Figure 4 - Plain radiographs achieved after 3 months of treatment with teriparatide showed bone bridges and a reduction of the gap of the fracture line.



Figure 5 - Plain radiographs achieved after 6 months of treatment with teriparatide showed fracture healing and bone remodeling.

Conclusion

In different case reports teriparatide showed to have positive effect on fracture healing.

The evidence suggests that teriparatide may give a further boost in healing process when fracture environments do not permit its healing.

Especially in hypertrophic non-union where the biologic reaction is increased in response to an altered biomechanical environment we can find several cytokines that play an important regulatory role in the process of osteogenesis. Most importantly, the expression of many of these molecules has been shown to be influenced by mechanical load (49).

Mechanical stress can be considered the cause of hypertrophic non-union but many studies supports the notion that the microenvironment or niche is chiefly modulated by the mechanical forces applied to the area. The osteoblast-osteocyte network is reported to play an essential role by providing natural cues for osteocyte differentiation (50, 51).

It is not yet clear how teriparatide acts on fracture healing, but the presented evidences show a hypothetical common points in non-union biomechanical environment and action of teriparatide.

In conclusion, on the strength of available data, it is possible to affirm that the use of teriparatide off-label has a positive and additive effect when combined with primary treatment.

Ethical considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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