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Recent Clinical Advancement of the Effects of Parathyroid Analogues on Fracture Healing in Humans: A Review of Literature

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Abstract: Problem statement: Numerous animal studies have shown that administration of Parathyroid Hormone (PTH) or a related analogue promotes callus formation and bone union. However, there has yet to be sufficient evidence in human subjects to justify the use of PTH or related analogues in promoting fracture healing. The purpose of this paper is to (1) review all literature involving the use of PTH analogues in humans (2) compare the clinical efficacy of PTH analogues to conventional management of fracture healing and (3) evaluate the safety profile and potential side-effects of PTH analogues administered in humans. **Approach:** We conducted a systematic review of multiple databases analysing papers within the last 10 years. All studies involving the use of PTH analogues in humans were included. All animal studies were excluded. Appropriate statistics regarding patient's age, gender, site of fracture, teriparatide treatment regime, clinical outcomes and imaging outcomes were extracted, analysed and summarized. **Results:** A total of 10 observational studies and 2 randomized controlled trials were evaluated in this study. With administration of teriparatide (PTH1-34), the mean time to 100% disappearance of fracture site pain was 3.1 months ±0.7 months. Delayed or non-union fractures achieved bony bridging in 4.3 months. For new fractures treated non-surgically, there have been reports of shorter time to cortical bridging in the treatment group (7.4 weeks, n = 34, p = 0.006) as compared to the control group (9.1 weeks, n = 34). Lastly, a total of 8 out of 254 patients (3.1%) experienced mild side effect from teriparatide administration. **Conclusion:** Teriparatide shows promise to be a viable option for the treatment of fractures. Although initial studies do prove encouraging, greater evidence is needed to evaluate the optimal dosing regimen and the patient and fracture types that would achieve the best response.

Key words: Parathyroid Hormone (PTH), Magnetic Resonance Imaging (MRI), analogues administered, optimal dosing regimen, imaging outcomes, Computed Tomography (CT)

INTRODUCTION

The use of teriparatide (PTH 1-34) is approved for use in patients who are at high risk for osteoporotic fractures. Its anabolic effects, via intermittent daily administration has been shown to increase bone mass by 10-15% per year and decrease risk of vertebrae fracture by 66% in osteoporotic individuals (Etoh and Yamaguchi, 2010; Ryder *et al*., 2010; Heaney, 2003). In addition, numerous animal studies have shown that teriparatide anabolic effects promote callus formation and bony union in various long bones (Bukata and Puzas, 2010). Its potential in augmenting fracture healing has sparked multiple off-labelled use of teriparatide in fracture healing in humans. Current literature provides anecdotal evidences that teriparatide

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shows promise as a viable pharmacological therapy in assisting with fracture healing (Whyte *et al*., 2007; Oteo-Alvaro and Moreno, 2010; Gagnon *et al*., 2010; Chintamaneni *et al*., 2010; Paul *et al*., 2010; Brunnemann *et al*., 2010; Aspenberg *et al*., 2010).

Teriparatide (PTH 1-34) is a synthetic polypeptide hormone manufactured via recombinant DNA technology. It contains the first 34 amino acid segment of the full length Parathyroid Hormone (PTH 1-84). The anabolic effects of teriparatide on bones are associated with enhanced trabecular connectivity, increased cortical thickness and stronger micro-architectural mechanical strength (Canalis *et al*., 2007; Lindsaym *et al*., 2007). The mechanism by which it achieves this is postulated to involve all stages of fracture healing. Nakajima *et al*. (2002) suggests that the increased proliferation of chondrocyte, osteoblastic progenitor cells, bone matrix protein and osteoclastogenesis explains the favourable response of teriparatide towards bone formation (Nakajima *et al*., 2002). Additionally, its effects are not limited by different bone surfaces with enhanced bone formation observed among endosteal, periosteal and trabecular bones (Dempster *et al*., 2001).

In non-osteoporotic individuals, off-label use of teriparatide encompass its use for (1) delayed or non-union fractures that failed surgical intervention, (2) delayed or non-union fracture that failed conservative management, (3) new fractures treated with surgical intervention and (4) new fractures managed conservatively. The efficacy of teriparatide is yet to be fully studied as there is a lack of larger well designed studies to evaluate its efficacy and current literature contains papers mostly with level IV evidence.

This review paper aims to review all literature published within the last decade, where PTH analogues was used to aid new fractures or delayed or non-union fractures in humans. Also, we seek to compare the clinical efficacy of PTH analogues in particular teriparatide in contrast to conventional management for fracture healing. Lastly, we aim to evaluate the safety profile and potential side-effects of teriparatide administration in humans.

MATERIALS AND METHODS

A PubMed search was performed to identify all literature on the effect of PTH analogues on fracture healing or delayed or non-union in human subjects. The following key words were used: 'teriparatide', 'Parathyroid Hormone (PTH) analogues', 'fracture healing', 'human', 'non-union' and 'delayed union.' Detailed extraction of the data was carried out according to the search criteria. Further papers were identified through manual searches of the bibliography of the papers identified electronically. The inclusion criteria were all human studies published within the last 10 years involving only adults (age 18 and above). We analysed all clinical outcomes, clinical examination findings, radiological signs of fracture healing and functional assessment scores. All animal studies were excluded.

Appropriate statistics regarding patient's age and gender, site of fracture, dosage and length of treatment with teriparatide and clinical and imaging outcomes were extracted. To reduce bias, papers that did not include any new clinical trials but merely referenced another human trial, while focusing mainly on animal models, were not included. Of 356 papers identified initially, 12 papers met our criteria for eligibility. A total of 10 observational studies and 2 randomized controlled trials, 1 of which involving PTH (1-84) were included in this study. All data extracted from the papers were summarized into Table 1 and 2. Some data such as patients co-morbid could not be compared owing to much variation in presentation of data among the 12 journals.

RESULTS

Demographics: A total of 288 patients with 292 fractures treated were evaluated in this study (Table 1). The mean age of the patients were 62.0 years and ranged from 18-93 years. A total of 43 males (14.9%) and 245 females (85.1%) were involved. Fractures involving various anatomical sites were evaluated. Fracture sites include the sternum (1, 0.3%), ribs (3, 1.0%), humerus (14, 4.8%), radius (107, 36.6%), wrist (4, 1.4%), vertebrae (54, 18.5%), pelvis (26, 8.9%), femur (40, 13.7%), tibial (15, 5.1%), foot (18, 6.2%) and ankle (4, 1.4%). 6 fracture sites were not indicated. 3 fractures (1.0%) were delayed or non-union fractures that had failed surgical intervention, 153 fractures (52.4%) were delayed or non-union fractures that had failed conservative management. 34 new fractures (11.6%) were treated primarily with surgery and 102 new fractures (34.9%) were managed conservatively.

A total of 254 out of 288 patients had daily injection of subcutaneous teriparatide. The remaining 34 patients were administered a placebo drug. Majority of the patients (218, 75.7%) were administered 20μg day^{-1} dosing of teriparatide. 2 patients (0.7%) were administered 60 μg day^{-1}, 34 patients (11.8%) were administered 40 μg day^{-1} and 34 patients (11.8%) were administered placebo. Of those administered teriparatide, mean dosage time was 4.4 months ±4.0 months. The minimum duration was 1 month and the maximum duration was 18 months.

Table 1: Summary of Studies of Teriparatide on Fracture Healing (Patient and Feature Characteristics)

First Author	Sample Size (n)	Age of Patient, (Gender)	Fracture (n)	Fracture(#) Characteristic/Bone	Modality to assess fracture	Treatment done before initiation of PTH (1-34)
M P. Whyte	1	56y / (F)	3	Spontaneous Right 4th Metatarsal (MT) stress # Spontaneous Left 5th MT stress # Spontaneous Right Proximal Femur #	X-Ray	Nil
A O. Alvaro	1	32y / (M)	1	Atrophic Non-union Right diaphyseal Humerus # (sustained after trauma)	X-Ray	Intramedullary Osteosynthesis with Hackethal technique with 2 elastic nails
C. Gagnon	1	53y / (F)	2	Non-union Left Femoral # (sustained after minimal trauma) Pseudo-fracture of the Right Femur	X-Ray	Gamma Nail Surgery Nil
S. Chintamaneni	1	67y / (M)	1	Atrophic Non-union Body of Sternum # (oblique #, sustained after trauma)	CT / MRI	Nil
P T. Rubery	3	91y / (F)	3	Delayed Union type 3 Odontoid # (sustained after trauma)	CT	Rigid Cervical Collar (8 weeks)
		84y / (F)		Delayed Union type 3 Odontoid # (sustained after trauma)	X-Ray / CT	Halo Vest (9 weeks) thereafter rigid cervical collar (5 weeks)
		82y / (F)		Delayed Union type 3 Odontoid # (sustained after trauma)	CT	Halo Vest (13 weeks) thereafter soft cervical collar
P. Aspenberg	34 34 34	61.4y ± 8.6 / (F) (45–85y)	102	Acutely Acquired (<10 days) Unilateral Dorsally Angulated Distal Radius #	X-Ray / CT	Conservative Treatment (close reduction and immobilization)
S V. Bukata	143	Not stated 29 (M) 114 (F)	143	Unhealed Fracture (> 6 mth) at a wide variety of anatomical sites - Spine (48), Ribs (3), Pelvis (26), Femur (19), Tibial (11), Foot (16), Humerus (10), Wrist (4)	X-Ray / CT	Not stated
	1	58y / (M)	1	Delayed union of tibia and fibula #		Casting (4 months) thereafter partial weight bearing (2 months)
	1	93y / (F)	1	Non-union of a Odontoid #		Cervical Collar (9 months)
C E Brunnemann	1	71y / (F)	1	Periprosthetic femoral fracture (type 3) (sustained after trauma)	X-Ray	External mono-lateral fixator applied followed with administration of PTH (1-34) 2 months later
	1	53y / (F)	1	Periprosthetic Left distal femoral # (sustained after trauma)		Reduction of # with fixed angle distal condylar buttress plate and autologous cancellous bone together with PTH (1-34)
	1	18y / (M)	1	Left Radial Shaft # (sustained after trauma)		Osteosynthesis with bone grafting (failed) followed with autologous tri-cortical iliac crest bone graft with PTH (1-34)
G. Resmini	1	79y / (F)	1	Acutely Acquired Left Proximal Humerus # (sustained after trauma)	X-Ray	Conservative Treatment with soft bandage as patient is already on PTH (1-34) for past 10 months owing to spontaneous vertebral compression # at T8 and T11
T P. Knecht	1	47y / (M)	1	Acutely Acquired Right Tibial and Fibula # (sustained after trauma)	X-Ray	Intramedullary Rod in Right Tibial followed with administration of PTH (1-34) starting 7 weeks later
U. Tarantino	29[a]	65.2y ± 18.4/ (9M|20F) (25–93y)	30	Fracture at a wide variety of anatomical sites – Femur (16), Vertebrae (2), Tibial (2), Ankle (4), Humerus (2), Radius (4)	X-Ray	Surgical Intervention followed with administration of PTH (1-34)
Total	288	62.0y / (43M 245F)	292	Sternum (1), Ribs (3), Humerus (14), Radius (107), Wrist (4), Vertebrae (54), Hip (26), Femur (40), Tibial (15), Foot (18), Ankle (4), unknown (6)		Delayed/non-union fractures that had failed surgical intervention (3), delayed/non-union fractures that had failed conservative management (153), acutely acquired fractures treated surgically (34) and acutely acquired fractures managed conservatively (102).

a: Tarantino *et al*. (2007) presented on 34 surgical patients who received teriparatide, however, only 29 out of the 34 patients were diagnosed and treated for fractures.

Major results: Majority of the studies analysed the efficacy of teriparatide via clinical and radiological outcomes. Clinical outcomes measured mostly involved pain scores with some journals measuring ability to mobilise, range of motion and function. Radiological findings involved the use of X-Rays, Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI) to assess for callus formation, bony bridging, reduction of fracture line and complete bony union. As not all studies were written with similar outcome measures, the following results were taken from a distinct subset of the 12 journals involved.

Table 2: Summary of Studies of Teriparatide on Fracture Healing (Clinical and Radiological Outcomes

First Author	Bone	Dose of PTH (1-34)/day	Time to bony bridging after starting PTH (1-34)	Duration of Treatment of PTH (1-34)	Clinical Outcome	Imaging Outcomes
M P. Whyte	Metatarsal	20µg	4 months	16 months	(6 weeks) -90% reduction in foot pain and 50% reduction in right thigh pain	(2months) – bony bridging and reduction of fracture line
		Metatarsal		10 months	(4 months)-disappearance of all # pain	(2months) – calcification with callus, (10months) – 50% further of fracture line gone with bony bridging
		Femur		4 months	8 months off PTH (1-34), patient remains pain free of all fracture site pain	(4 months) – significant improvement with reduction of fracture line and bony union
A O. Alvaro	Humerus	20µg	3 months	5 months	(5 months) – 100% reduction in # pain with complete ROM of shoulder and elbow joint 1 month off PTH (1-34), patient returned to work	(3 months) – bony bridging with decreased fracture gap (5 months) –complete healing (6 month) – complete healing
C. Gagnon	Femur	20µg	N/A	13 months	(7 months) – 100% reduction in # pain with increased mobility 2 months off PTH (1-34), patient reported pain in right thigh	(8 months) – complete healing of right pseudo# and appearance of bony callus on the left 2 months off PTH (1-34), pseudo# of right femur re-appeared
S. Chintamaneni	Sternum	20µg	3 months	> 9mth	(9 months) – 100% reduction in # pain, able to return to exercise regime of weight lifting	(3 months) – bony bridging with decreased fracture gap and callus formation (9 months) – complete fracture healing
P T. Rubery	C2 Vertebrae	20µg	2 months	> 2 mth	(2 months) – 100% reduction in neck pain	(2 months) – bony bridging with mature cancellous bone formation
			3 months	> 3mth	(2.3 months / 10 weeks) – 100% reduction in neck pain	(3 months) – bony union
			4 months	> 4mth	(4 months) – 100% reduction in neck pain	(4 months) – bony union
P. Aspenberg	Radius	Placebo	9.1 weeks	1.8 months	Patient-Rated Wrist Evaluation (PRWE) questionnaire (assess pain and function scores) and grip strength showed significant improvement compared to baseline. Not statistically significance between placebo and PTH (1-34) treatment groups.	(9.1 weeks) – bony bridging in at least 3 of four cortices (11.3 weeks) – 4 out of 4 cortical bridging (7.4 weeks) – bony bridging in at least 3 of four cortices (10.9 weeks) – 4 out of 4 cortical bridging
			20µg	7.4 weeks		(8.8 weeks) – bony bridging in at least 3 of four cortices (11.0 weeks) – 4 out of 4 cortical bridging
			40µg	8.8 weeks		
S V. Bukata	Range of # Tibia & Fibula C2 Vertebrae	20µg	Varied, average not stated	Until orthopaedic provider deems # to be healed	(7 weeks) – 100% pain reduction at fracture site (6 weeks) – 100% pain reduction at fracture site	(12 weeks) – 97.2% (141/145) of patients had 100% reduction of pain at the fusion or fracture site	12 weeks) – 93.0% had radiological (and clinical union of fractures. 4% (6/145) demonstrated partial radiographic union of fracture but clinically functioned as a healed fracture. 3% (4/145) failed to observe radiographic or clinical improvements
C E Brunnemann	Femur	60µg	Not stated	1.4 months	(2 months) – patient able to mobilize	(10months) – stable consolidation of fracture	Note that PTH 1-34 used in conjunction with other intervention (see Table 1)
	Femur	20µg		2.3 months	Not stated	(10 weeks) – fracture healing	(6 months) – pseduoarthrosis fully stabilized
	Radius	60µg		1.4 months	Not state		(25 days) after # – bony bridging and reduction of fracture line
G. Resmini	Humerus	20µg	25 days (on PTH (1-34) for 10 mth prior to #)	18 months	(4 weeks) after # – complete range of motion of shoulder The speed of clinical and radiological improvements attributed to treatment with PTH (1-34)	
T P. Knecht	Tibial Fibula	20µg	not stated	6 months	(1.4 months) after PTH (1-34) introduced – patient resumed running The speed of clinical and radiological improvements attributed to treatment with PTH (1-34)	Radiological findings showed fracture union
U. Tarantino	Range of #	20µg	Not stated	9.7mth ± 7.57 / (1mth to 18mth)	26/29 (89.6%) showed decrease in pain perception based on visual analogue scale (VAS) before and after treatment	24/29 patients (82.7%) achieved complete fracture healing (duration of treatment 10.5 mths ± 7.7 mths), 5/29 patients (17.3%) fracture healing still on-going (current duration of treatment 2.2 mths ± 0.8 mths)
Total		34 patients = placebo 218 patients = 20µg/day 34 patients = 40µg/day 2 patients = 60µg/day		4.4mths ± 4.0 (1mth to 18 mths)		

As a whole, all 12 studies have shown radiological evidence of fracture union following PTH analogue administration. This has been associated with marked improvements in clinical parameters and functional outcomes in patients treated. The mean time to 100% disappearance of fracture site pain after starting teriparatide (PTH1-34) was 3.1 months ± 0.7 months. This was evaluated from 151 fracture sites. For the remaining fracture sites, majority of the authors documented a decrease in pain perception.

The mean time to bony bridging after starting PTH (1-34) varied widely across different fracture sites. For delayed or non-union fractures that failed conservative treatment, administration of teriparatide was associated with a mean time to bony bridging of 4.3 months. Bukata *et al*. (2009) who presented an observational cohort of 145 patients with delayed fracture healing (> 6 months) noted that 135 patients (93%) achieved radiological union of fracture with teriparatide administration within 2.8 months (Bukata *et al*., 2009).

For new fractures that were treated conservatively, administration of teriparatide was associated with decreased time for bony bridging. This was demonstrated in a study by Aspenberg *et al*. (2010) who showed that osteoporotic distal radius fractures that were treated with teriparatide 20 µg day^{-1} resulted in cortical bridging within 7.4 weeks as compared to a placebo group which took 9.1 weeks (p = 0.006) (Aspenberg *et al*., 2010). Similarly an isolated case report of a proximal humeral fracture achieved bony bridging within 3.6 weeks with teriparatide (Resmini and Iolascon, 2007).

A total of 8 patients out of 254 patients (3.1%) experienced mild side effect from teriparatide administration. 2 patients (Tarantino *et al*., 2007) complained of dizziness and rash while 6 patients[11] reported mild side effects such as nausea, vomiting and headache. These 6 patients were being administered teriparatide at a dosage of 40 µg day^{-1}. No other side effects were noted from the studies involving teriparatide administration.

DISCUSSION

Teriparatide has been shown to be beneficial in promoting fracture healing. Studies on the use of teriparatide in primary union, delayed and non-union have resulted in improvement in the time to clinical and radiological union. Chintamaneni *et al*. (2010) noted that the dramatic radiographic healing of a non-union sternal fracture was achieved only after intervention with teriparatide (Chintamaneni *et al*., 2010). Also Rubery and Bukata (2010) attributed the rapid pain relief and bony bringing experienced by 3 patients with delayed type 3 odontoid fractures solely to the initiation of teriparatide (Paul *et al*., 2010). Similar results have been illustrated in patients with varying ages, gender and fracture sites.

The best evidence to date involves a prospective randomized controlled study. The study analysed the effects of PTH (1-84) on fracture healing in 65 post-menopausal women with osteoporosis who had sustained a pelvic fracture. Although the PTH compound used was different (PTH 1-84 vs. PTH 1-34), the additional fifty amino acids in PTH 1-84 are inactive and the resulting bio-efficacy of the two compounds remain the same. Both are known to have similar anabolic effects although there is currently a paucity of comparative studies between the two (Verhaar and Lems, 2009). Peichl *et al*. (2011) found that administration of PTH 1-84 (100 µg day^{-1}) resulted in a shorter fracture union time in primary union compared to a control group (Peichl *et al*., 2011). Pubic bone fracture treated with PTH 1-84 achieved fracture union in 7.8 weeks compared to 12.6 weeks a control group (p<.001). By eight weeks all fractures in the treatment group (n = 21) had healed in contrast to 4 fractures in the control group (n = 44). (Healing rate, 100% [95% CI, 86.7-100.0%] compared with 9.1% [95% CI, 2.5-21.7%]). The treatment group also had statistically significant improved clinical and functional outcomes (p<0.001) as compared to the control group (assessed with both visual analogue scale for pain and a timed up and go test).

In another prospective randomized double-blind clinical study by Aspenberg *et al*. (2010) the use of teriparatide (PTH 1-34) resulted in shorten time to fracture healing in conservatively treated distal radial fractures (Aspenberg *et al*., 2010). Time to healing was significantly shorter in the treatment group (n = 34) that received teriparatide 20 µg day^{-1} (7.4 weeks, p = 0.006) as compared to the control group (9.1 weeks, n = 34). Surprisingly, the study acknowledges a lack of dose-response relationship with intermittent administration of PTH 1-34. The treatment group (n = 34) that received teriparatide 40 µg day^{-1} showed shorter healing time compared to the control group. This however was not statistically significant (8.8 weeks, p = 0.523). Clinical outcomes measuring pain and functional results (assessed using the Patient-Rated Wrist Evaluation questionnaire and grip strength via a Jamar dynamometer) also failed to achieve statistically significant differences between the treatment groups and the control group.

For the management of delayed or non-union fractures, we evaluated the efficacy of teriparatide

against bone grafting. Treatment with bone grafting is widely accepted as the gold standard in the management of delayed or non-union fractures. We analysed two studies where patients had similar fracture sites with the main difference being the administration of teriparatide. Brunnemann *et al*. (2010) presented a case of a 53 year old female who sustained a left distal femoral fracture who was treated with a buttress plate and autologous cancellous bone graft together with administration of PTH (1-34) (Brunnemann *et al*., 2010). Fracture union was achieved in 10 weeks. In comparison, a prospective study by Gardner *et al*. (2008) where 31 patients with a distal femoral fracture were treated similarly but without administration of teriparatide, achieved fracture healing with a mean of 16.1 weeks (range 10-32 weeks). Another study by Brunnemann *et al*. (2010) showed that bone grafting together with administration of teriparatide in a non-union radial shaft fracture (initially failed primary treatment with bone grafting) achieved union after 6 months (Brunnemann *et al*., 2010).

Teriparatide has also been shown to be effective as an isolated form of treatment in the management of fractures. Resmini and Iolascon (2007) presented a case of a 79 year old osteoporotic female who benefited from conservative management and intermittent teriparatide therapy following a displaced 2 part proximal humerus fracture (Resmini and Iolascon, 2007). Radiographic evidence showed bony union after 3.6 weeks while clinically, full range of motion was achieved in 7.6 weeks. In contrast, a recent study by Gupta *et al*. (2012) showed that displaced 2 part proximal humeral fracture treated with external fixation achieved fracture union in 6.5 weeks (range 6-8 week) (Gupta *et al*., 2012). Also, full range of motion was achieved in a mean duration of 16.5 weeks (range 8-32 weeks) (Gupta *et al*., 2012). It appears that the use of teriparatide may be a reasonable alternative with improved radiological and clinical benefits without the associated risks from external fixation such as wire and pin tract infections or loosening. Furthermore, in severely osteoporotic individuals where achieving rigid fixation in osteoporotic cancellous bone can be challenging, teriparatide would be a more viable option as compared to operative intervention.

Teriparatide can also be used as an adjunct to operative treatments. Operative management unlike isolated teriparatide administration have the benefit of ensuring adequate anatomical reduction. When used together, new fractures treated surgically with concomitant administration of teriparatide achieves significant radiological and clinical improvements. An isolated case study presented by Knecht (2004) demonstrated the benefits of teriparatide when used as an adjunct in the management of a tibial and fibula fracture (Knecht, 2004). The patient, a 47 year old man, was able to resume running 3 months after the fracture and achieved complete healing clinically and radiologically after 6 months. In a larger study, Tarantino *et al*. (2007) showed that in a group of 34 surgical patients (29 out of 34 were treated after sustaining a fracture) who received teriparatide immediate after intervention, majority benefited from shorter time to fracture healing (Tarantino *et al*., 2007). The Visual Analogue Scale (VAS) which measured patient's perception of pain before and after treatment was noted to have decreased (Table 2).

Teriparatide also appears to have a role in the management of hypophosphatemic patients. These patients have defective bone mineralization, are highly susceptible to bony fractures and currently have no established medical therapy available. In 2 isolated case studies, institution of daily subcutaneous teriparatide (20 μg day^{-1}) led to clinical improvements of pain alleviation, increased mobility and improved biochemical response (Whyte *et al*., 2007; Gagnon *et al*., 2010) (Table 2).

The short-term safety profile of teriparatide continues to be excellent with only 3.1% (8 out of 254) of patients experiencing mild side effects ranging from nausea, vomiting and headache. In the study by Peichl *et al*. (2011) no adverse events or death were recorded among the 21 patients who took PTH 1-84 for 24 months (Peichl *et al*., 2011). The long-term safety profile of teriparatide is however still unknown. The anabolic effects of teriparatide when given long-term and in supra-physiological doses were associated with increased risk of osteosarcomas in Fisher rats (Vahle *et al*., 2002). This risk is negated by the use of smaller doses in humans and is somewhat comparable to the general population risk, where only 1 case of osteosarcoma has been reported (Harper *et al*., 2007) among more than 250,000-300,000 patients treated with teriparatide worldwide (Solomon *et al*., 2009). However, in view of this theoretical adverse effect, use of teriparatide is cautioned in individuals with significant history of primary or metastatic bone tumours, Paget's disease, unexplained high levels of ALP, history of radiation therapy involving the bones or metabolic bone disease excluding osteoporosis, pregnancy and breast feeding (Guide *et al*., 2002). Of all the studies we analysed, there were no reports of any osteosarcomas developing as a result of teriparatide administration. Other side effects of teriparatide include dizziness, constipation, lethargy, muscle weakness and leg cramps secondary to raised serum calcium levels. Local side effects at injection site include erythema, swelling, itch and pain. Teriparatide usage also can

raise serum uric acid levels and has been cautioned in renal impaired patients (Miller *et al*., 2007).

We acknowledge several limitations in our study. Considering the relative recent application of teriparatide in treating fracture healing, our results were limited by the small number of studies. In addition, 10 out of 12 of our studies were made up of case reports or series showing anecdotal evidences of the beneficial effects of teriparatide. The small sample size and the limited number of studies with higher level evidence in the literatures were limiting factors for our study. Also, there were some difficulties in the collection of data as some studies were unclear regarding patient demographics, time to fracture union of individual bones and teriparatide dosing regimen.

CONCLUSION

Teriparatide with its relatively safe drug profile continues to be a viable option for the treatment of fractures. Larger, well designed clinical trials should be conducted to evaluate (1) the optimal dosing regimen of teriparatide, (2) the patient type who would best benefit from teriparatide and (3) the type of fractures (delayed or non-union or new) that would respond best to teriparatide therapy. A prospective randomized controlled to compare conventional treatment against teriparatide therapy and against teriparatide plus conventional treatment with proper inclusion and exclusion criteria to account for potential confounding variables would be ideal in better understanding the clinical efficacy of teriparatide.

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