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.

REFERENCES

1. Haas NP (2000) Callus modulation-fiction or reality? Chirurg 71: 987-988.
2. Heppenstall RB (1980) Fracture treatment and healing. Philadelphia, WB Saunders.
3. Nandra R, Grover L, Porter K (2016) Fracture non-union epidemiology and treatment. Trauma 18: 3-11.
4. Hak DJ, Fitzpatrick D, Bishop JA, Marsh JL, Tilp S, et al. (2014) Delayed union and non-unions: Epidemiology, clinical issues and financial aspects. Injury 45: S3-S7.
5. Mills LA, Simpson AH (2013) The relative incidence of fracture non-union in the Scottish population (5.17 million): A 5-year epidemiological study. BMJ Open 3: e002276.
6. Mills LA, Aitken SA, Simpson AHRW (2017) The risk of non-union per fracture: Current myths and revised figures from a population of over 4 million adults. Acta Orthop 88: 434-439.
7. Calori GM, Albisetti W, Agus A, Iori S, Tagliabue L (2007) Risk factors contributing to fracture non-unions. Injury 38: S11-S18.
8. Mehmood M, Deshpande S, Khan SM, Singh PK, Patil B, et al. (2017) Epidemiology of delayed union of long bones. J Trauma Treat 6: 370.
9. Ekegren CL, Edwards ER, de Steiger R, Gabbe BJ (2016) Incidence, costs and outcomes of non-union, delayed union and mal-union following long bone fracture. Int J Environ Res Public Health 22: A283.
10. Schlundt C, Bucher CH, Tsitsilonis S, Schell H, Duda GN, et al. (2018) Clinical and research approaches to treat non-union fracture. Curr Osteoporos Rep 16: 155.
11. Emara KM, Diab RA, Emara AK (2015). Recent biological trends in management of fracture non-union. World J Orthop 6: 623-628.
12. Zimmermann G, Muller U, Loffler C, Wentzensen A, Moghaddam A (2007) Therapeutic outcome in tibial pseudarthrosis: Bone morphogenetic protein 7 (BMP-7) versus autologous bone grafting for tibial fractures. Unfallchirurg 110: 931-938.
13. Bhargava R, Sankhla S, Gupta A, Changani R, Gagal K (2007) Percutaneous autologous bone marrow injection in the treatment of delayed or nonunion. Indian J Orthop 41: 67-71.

14. Giordano A, Galderisi U, Marino IR (2007) From the laboratory bench to the patient's bedside: An update on clinical trials with mesenchymal stem cells. J Cell Physiol 211: 27-35.

15. Kettunen J, Mäkelä EA, Turunen V, Suomalainen O, Partanen K (2002) Percutaneous bone grafting in the treatment of the delayed union and non-union of tibial fractures. Injury 33: 239-245.

16. Sanchez AR, Sheridan PJ, Kupp LI (2003) Is platelet-rich plasma the perfect enhancement factor? A current review. Int J Oral Maxillofac Implants 18: 93-103.

17. Sanchez M, Anitua E, Azofra J, Andía I, Padilla S, et al. (2007) Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. Am J Sports Med 35: 245-251.

18. Calori GM, Donati D, Di Bella C, Tagliabue L (2009) Bone morphogenetic proteins and tissue engineering: Future directions. Injury 40: S67-S76.

19. Dempster DW, Cosman F, Parisien M, Shen V, Lindsay R (1993) Anabolic actions of parathyroid hormone on bone. Endocr Rev 14: 690-709.

20. Martin TJ, Quinn JMW, Gillespie MT, Ng KW, Karsdal MA, et al. (2006) Mechanisms involved in skeletal anabolic therapies. Ann N Y Acad Sci 1068: 458-470.

21. Pharmacodia (2016) Teriparatide. Accessed on July 19 2018. Available online at: https://www.pharmacodia.com/yaodu/html/v1/biologics/b252e54edce965ac4408effd7ce41fb7.html.

22. Central Drugs Standard Control Organization (2003) List of drugs approved during 2003. Available online at:http://www.cdsco.nic.in/writereaddata/list_of_drugs_approved_during_2003.html.

23. Berg C, Neumeyer K, Kirkpatrick P (2003) Fresh from the pipeline: Teriparatide. Nat Rev Drug Discov 2: 257-258.

24. File E, Deal C (2009) Clinical update on teriparatide. Curr Rheumatol Rep 11: 169-176.

25. Ciurlia E, Leali PT, Doria C (2017) Use of teriparatide off-label: Our experience and review of literature. Clin Cases Miner Bone Metab 14: 28-34.

26. Compston JE (2007) Skeletal actions of intermittent parathyroid hormone: Effects on bone remodelling and structure. Bone 40: 1447-1452.

27. Li YF, Zhou CC, Li JH, Luo E, Zhu SS, et al. (2012) The effects of combined human parathyroid hormone (1-34) and zoledronic acid treatment on fracture healing in osteoporotic rats. Osteoporos Int 23: 1463-1474.

28. Andreassen TT, Ejersted C, Oxlund H (1999) Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. J Bone Miner Res 14: 960-968.

29. Nakajima A, Shimoji N, Shiomi K, Shimizu S, Moriya H, et al. (2002) Mechanisms for the enhancement of fracture healing in rats treated with intermittent low-dose human parathyroid hormone (1-34). J Bone Miner Res 17: 2038-2047.

30. Alkhiary YM, Gerstenfeld LC, Krall E, Westmore M, Sato M, et al. (2005) Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). J Bone Joint Surg Am 87: 731-741.

31. Kaback LA, Soung do Y, Naik A, Geneau G, Schwarz EM, et al. (2008) Teriparatide (1-34 human PTH) regulation of osterix during fracture repair. J Cell Biochem 105: 219-226.

32. Nozaka K, Miyakoshi N, Kasukawa Y, Maekawa S, Noguchi H, et al. (2008) Intermittent administration of human parathyroid hormone enhances bone formation and union at the site of cancellous bone osteotomy in normal and ovariectomized rats. Bone 42: 90-97.

33. Bostrom MP, Gamradt SC, Asnis P, Vickery BH, Hill E, et al. (2000) Parathyroid hormone-related protein analog RS-66271 is an effective therapy for impaired bone healing in rabbits on corticosteroid therapy. Bone 437-442.

34. Kundu S (2017) Teriparatide treatment in non-uniting fracture: A case report. Int J Res Orthop 3: 890-894.

35. Rubery PT, Bukata SV (2010) Teriparatide may accelerate healing in delayed unions of type III odontoid fractures: A report of 3 cases. J Spinal Disord Tech 23: 151-155.

36. Kundu S (2018) Successful treatment of nonuniting fracture ICNF with teriparatide in young adult osteopenic male. Int J Res Orthop 4: 326-329.

37. Garg B, Batra S, Dixit V (2018) An unexpected healing of an established non-union of the radial neck through teriparatide: A case report and review of literature. J Clin Orthop Trauma 9: S103-S105.

38. Biro I, Bubbear J, Donnelly S, Fattah Z, Sarkodieh J, et al. (2017) Teriparatide and vertebral fracture healing in Ankylosing Spondylitis. Trauma Case Rep 12: 34-39.

39. Yonezu H, Mikami H, Oba K, Miyatake K, Takai M, et al. (2017) Successful treatment with a weekly injection of teriparatide for the nonunion of a distal humerus fracture. Open J Orthop 7: 173-179.

40. Chintamaneni S, Finzel K, Gruber BL (2010) Successful treatment of sternal fracture non-union with teriparatide. Osteoporos Int 21: 1059-1063.

41. Ciurlia E, Leali PT, Doria C (2017) Use of teriparatide off-label: Our experience and review of literature. Clin Cases Miner Bone Metab 14: 28-34.

42. Xiaofeng L, Daxia X, Yunzhen C (2017) Teriparatide as a nonoperative treatment for tibial and femoral fracture nonunion: A case report. Medicine (Baltimore) 96: e6571.

43. Bhandari M, Jin L, See K, Burge R, Gilchrist N, et al. (2016) Does teriparatide improve femoral neck fracture healing: Results from a randomized placebo-controlled trial. Clin Orthop Relat Res 474: 1234-1244.

44. Johansson T (2016) PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures. A randomized, controlled study of 40 patients. Acta Orthop 87: 79-82.

45. Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, et al. (2010) Teriparatide for acceleration of fracture repair in humans: A prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res 25: 404-414.

46. Shi Z, Zhou H, Pan B, Lu L, Liu J, et al. (2016) Effectiveness of teriparatide on fracture healing: A systematic review and meta-analysis. PLoS One 11: e0168691.

47. Hodsman AB, Bauer DC, Dempster DW, Dian L, Hanley DA, et al. (2005) Parathyroid hormone and teriparatide for the treatment of osteoporosis: A review of the evidence and suggested guidelines for its use. Endocr Rev 26: 688-703.

48. Harper KD, Krege JH, Marcus R, Mitlak BH (2007) Osteosarcoma and teriparatide? J Bone Miner Res 22: 334.

49. Forteo (teriparatide [rDNA origin] injection) (2014) Kobe, Japan: Eli Lilly Japan K.K. Accessed on: 11 July 2018. Available online at: http://pi.lilly.com/us/forteo-pi.pdf

50. Nishikawa A, Ishida T, Taketsuna M, Yoshiki F, Enomoto H (2016) Safety and effectiveness of daily teriparatide in a prospective observational study in patients with osteoporosis at high risk of fracture in Japan: Final report. Clin Interv Aging 11: 913-925.

51. Caggiari G, Leali PT, Mosele GR, Puddu L, Badessi F, et al. (2016) Safety and effectiveness of teriparatide vs. alendronate in postmenopausal osteoporosis: A prospective non randomized clinical study. Clin Cases Miner Bone Metab 13: 200-203.

52. Yoshiki F, Nishikawa A, Taketsuna M, Kajimoto K, Enomoto H (2017) Efficacy and safety of teriparatide in bisphosphonate-pre-treated and treatment-naive patients with osteoporosis at high risk of fracture: Post hoc analysis of a prospective observational study. J Orthop Sci 22: 330-338.

53. Andrews EB, Gilsenan AW, Midkiff K, Sherrill B, Wu Y, et al. (2012) The US post marketing surveillance study of adult osteosarcoma and teriparatide: Study design and findings from the first 7 Years. J Bone Miner Res 27: 2429-2437.

54. Saraf HR, Munot S (2017) Role of teriparatide in fracture healing: A prospective study. Int J Orthop Sci 3: 445-452.

55. Iwata A, Kanayama M, Oha F, Hashimoto T, Iwasaki N (2017) Effect of teriparatide (rh-PTH 1–34) versus bisphosphonate on the healing of osteoporotic vertebral compression fracture: A retrospective comparative study. BMC Musculoskeletal Disord 18: 148.

56. Huang TW, Chuang PY, Lin SJ, Lee CY, Huang KC, et al. (2016) Teriparatide improves fracture healing and early functional recovery in treatment of osteoporotic intertrochanteric fractures. Medicine (Baltimore) 95: e3626.

57. Chiang CY1, Zebaze RM, Ghasem-Zadeh A, Iuliano-Burns S, Hardidge A, et al. (2013) Teriparatide improves bone quality and healing of atypical femoral fractures associated with bisphosphonate therapy. Bone 52: 360-365.