Review Article

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Osteosarcoma occurrence in pre-clinical and clinical experiments with teriparatide: A qualitative review

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ABSTRACT

Teriparatide (TPTD) is one of the medications commonly prescribed for the treatment of osteoporosis since its approval in November 2002 by the U.S. Food and Drug Administration. While some preclinical toxicological studies have linked the drug to a dose-dependent increase in the occurrence of osteosarcoma, clinical trials showed the benefits outweighing the risk for TPTD-induced human osteosarcoma. The objective of this qualitative review was to qualitatively assess the literature for the association of osteosarcoma and the usage of TPTD in animal and human subjects. Studies were selected from all available records in the electronic databases covering the period from January 1, 2002, to September 30, 2020. While using rats as the study specimen showed some risks to osteosarcoma dependent on dose and duration of administration, clinical trials proved TPTD to be a safe treatment in humans. It is worthwhile investigating longer treatment periods than the 2 years labeled period for TPTD for safety purposes.

Keywords: Osteosarcoma, safety studies, teriparatide, toxicological studies

INTRODUCTION

Osteoporosis, literally meaning porous bone, is a major and growing chronic skeletal disease characterized by decreased bone density and microarchitectural deterioration of bone tissue.[1-3] It was found that approximately 200 million women around the world suffer from osteoporosis.[2] Estimates show that this disease affects almost 10.2 million US citizens aged 50 years or older.[1] At a local scale in the United Arab Emirates, it was found that 24% and 2.5% (average age 42 years) of the population suffer from osteopenia and osteoporosis, respectively.[4] In 2007, it was revealed that almost half of women aged 50 or older and around one out of five men of the same age suffer from fractures caused by osteoporosis.[5]

Teriparatide (TPTD) is a recombinant form of parathyroid hormone (PTH) analog that is composed of the first 34 amino acids of the endogenous hormone.[6] PTH and PTH-related protein (PTHrP) employ their effects through binding to the PTH/PTHrP receptor, which is conveyed in many tissues including on the surface of osteoblasts, osteocytes, and renal tubule cells.[7,8] TPTD has direct effects on bone formation through a process of stimulation of osteoblast activity and combined with the inhibition of their apoptosis,[9] causes a rapid increase in bone formation because of the Tashjian effect.[10] This effective anabolic bone formation promoting agent is used sometimes off-label to speed fracture healing.[11] TPTD is the only anabolic agent prescribed to postmenopausal women at high risk for bone fracture or with a family history of osteoporotic fractures, subjects with multiple risk factors for bone fracture, and for patients who have not responded adequately to other osteoporosis treatments.[12] The medicine is marketed by Eli Lilly Company with brand name called Forteo® and received approval from the Food and Drug Administration in November 2002 for the treatment of osteoporosis in men and postmenopausal women who are at high risk for having a bone fracture.[13]

The safety aspect of TPTD has been a concern[14] because there is some theoretical basis for osteosarcoma supported by several preclinical toxicology studies on rats showing a

dose-dependent increase in the occurrence of osteosarcoma.[15] Osteosarcoma, also known as osteaogenic sarcoma, is a primary malignant bone tumor. It is a sarcoma in which the neoplastic cells produce osseous matrix.[16] The cancer cells look like an early form of bone responsible for new bone tissues in the human body. However, these bone tissue forms in osteosarcoma cases are not as strong as the normal bones.

Most osteosarcoma cases occur mainly in adolescents and the elderly ages and slightly higher incidence in males than females. Affected areas in individuals are where bones are growing quickly, such as the ends of leg and arm bones. A letter to the editor published in 2006 showed that the occurrence of osteosarcomas in women 60 years old or older is almost one in 250,000/year.[17] Because of this low incidence of osteosarcoma, Tashjian and Chabner called for careful post-marketing surveillance for the use of TPTD and any accompanied bone tumor.[18]

Since there has been a long time (more than 17 years) since the approval and marketing of TPTD, it is likely that the risk for osteosarcoma would be established. Therefore, this qualitative review of the possible association of osteosarcoma with the use of TPTD in humans and animals would be warranted for the future therapy options and additional research.

LITERATURE REVIEW

This is a systematic review that qualitatively describes the relationship between TPTD and osteosarcoma using relevant publications available in indexing databases. This process, as shown in Figure 1, was based on pre-determined inclusion and exclusion criteria following PRISMA guidelines. PubMed and Google Scholar databases were used in the study to conduct and filter search outcomes. These databases are used by many researchers as they provide access to peer-reviewed literature and information in animal and human subjects.[19,20]

SELECTION CRITERIA

The screened publications from the search results were selected based on five inclusion and four exclusion criteria. The inclusion criteria used in this study restrict the selected publications to be a clinical trial, case–control, cohort, case report, case series, and pre-clinical animal studies. Exclusion limits included studies published before 2002, the safety assessment that does not include osteosarcoma associated with the use of TPTD, studies assessing osteosarcoma using other osteoporosis medications, and the studies that cover Paget's disease, a history of irradiation, or hyperparathyroidism.

PRE-CLINICAL STUDIES

All the studies done on rodents linked TPTD intake and osteosarcoma cases. These studies thoroughly investigated the effect of TPTD treatment on different rodent genders, different dose levels, and different treatment durations on the incidents of osteosarcoma. Jolette *et al.* conducted a study to define a non-carcinogenic dose of recombinant human PTH 1–84, on Fischer-344 rats for 2 years injected subcutaneously daily (0, 10, 50, and 150 μg/kg/day).[21] The study used 720 male and female rats (9–11 weeks old) segregated into six groups and found at the end of the study that high doses of PTH were associated with a significant increase of osteosarcoma. Their study was supported later by other authors[15] who studied Sprague-Dawley rats (SD rats) to assess osteosarcoma after long-term therapy with TPTD. At the end of this study, results showed osteosarcoma incidents in all treated groups and suggested that osteosarcoma in SD rats depends on both dose level and treatment duration. The rats' model was studied also by other authors and was found to develop osteosarcoma in association with bone formation when using TPTD.[22,23]

Chen *et al.* used different animal species involving 60 adult cynomolgus ovariectomized monkeys treated with TPTD, aging around 9 years old.[24] Treatment was scheduled for 18 months and at the end of the experiment histological samples and radiographs were interestingly confirming that no proliferative bone lesions were detected. In the same year, Fox *et al.* published a study designed to assess the safety and pharmacodynamic effects on bone, by studying 28 mature ovariectomized rhesus female monkeys with PTH (1–84).[25] At the end of the experiment, results compared with the control animals showed an increase in BMC in treated monkeys and no bone tumors were found at necropsy confirming the previous results. The next year Vahle *et al.* published research in which they also used the monkeys and confirmed the previous findings.[26]

One study used 44 male white rabbits to study the effect of TPTD on subjects' bone mass volume compared to control groups.[27] Histological studies were performed at the end of this study, and the results did not show any evidence of osteosarcoma in the tested animals. However, the study was not designed to assess the safety of TPTD, so the results cannot be generalized, but has been presented here for reference. Table 1 summarizes pre-clinical studies of the use of TPTD and the development of osteosarcoma if any.

Among the three animal species reviewed (i.e., rats, rabbits, and monkeys), only the rat animal model developed osteosarcoma. However, the fact that the drug was administered to rat species at doses and duration many folds relative to the human administration may not allow the carcinogenic effect to be extrapolated to human subjects. For example, in the Jolette *et al.* work, the duration of daily subcutaneous dose is equivalent to almost the whole average lifespan Fischer-344 rats. In addition, the low dose of 10 μg/kg/day was comparable to the control, but this dose is 4.6-fold higher than the maximum human dose of 100 μg/day.[28] On the other hand, the similarity of skeletal biology between monkeys and humans suggested that TPTD would be safe in humans, even though there is non-similarity in the life span (20 years for monkeys compared to 76 for humans) and keeping in mind the 18 months of treatment for monkeys imply about 8-fold that recommended for humans. The monkeys' and rabbits' studies provided some assurance regarding the safety of the treatment in human subjects. However, they also indicated that the efficacy of the treatment can be gradually lost after the treatment period.

CLINICAL STUDIES

Clinical studies gave a better view of the relationship between TPTD and the possibility of developing osteosarcoma. Many

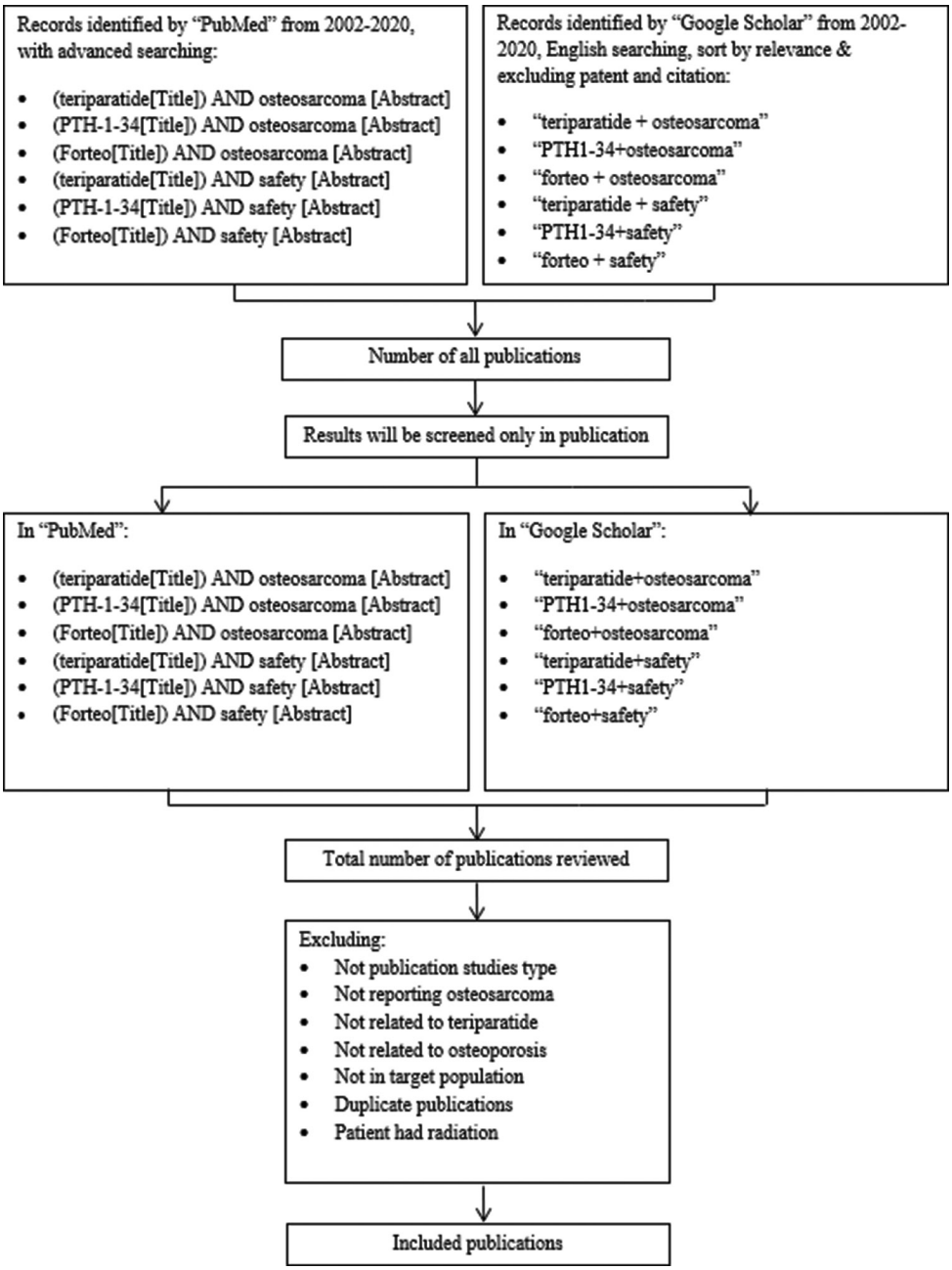

Figure 1: Flowchart of literature review methodology for the collection of publications for teriparatide and osteosarcoma in human and animal subjects for the year 2002–2020

clinical studies have been conducted to monitor patients undergoing TPTD therapy, some of these studies focused on female individuals, others on males and some were on mixed genders. All came to the same conclusion proving the safety of TPTD treatment regarding the risk of developing osteosarcoma when taken within the limits already defined for the therapy. These limitations of TPTD therapy requested that patients did not undergo radiation therapy before treatment, did not suffer from Paget's disease of bone, and are not children or young adults with open epiphyses and that the therapy period does not extend beyond 2 years.[29]

Prince *et al.* studied a total of 1637 postmenopausal women with osteoporosis.[30] They were randomly divided into three groups; placebo, TPTD 20 μg/day, and TPTD 40 μg/day. They demonstrated the positive effects of TPTD therapy in reducing non-vertebral fractures in the combined treatment groups, which were sustained during the 50 months involving both treatment and follow-up. In the safety aspect of this study, none of the women had any bone malignancy or osteosarcoma resulting from the treatment.

Later on, another study designed as an open-label, multicenter trial was conducted on 198 postmenopausal women treated with TPTD (20 μg/day) in the United States. Female patients from 11 different centers who were at least 50 years old, had a previous clinical diagnosis of osteoporosis, and had been previously treated for 18 months minimum with

Table 1: Summary of the pre-clinical research studies reporting on osteosarcoma incidents with the use of teriparatide

Reference	**Watanabe** *et al.*[15]	**Vahle** *et al.*[22]	**Vahle** *et al.*[23]	**Vahle** *et al.*[26]	**Jolette** *et al.*[28]	**O'Loughlin** *et al.*[27]	**Chen** *et al.*[24]
Year of publication	2012	2004	2002	2008	2006	2009	2007
Journal	The Journal of Toxicological Sciences	Toxicologic Pathology	Toxicologic Pathology	JBMR	Toxicologic Pathology	SPINE	JBMR
Subjects	A total of 1265 rats divided into five studies to assess carcinogenicity, reproducibility of study, the relation between age of rat at the initiation of the treatment and induction of the osteosarcoma, the relation between duration of the treatment term and the risk of osteosarcoma, and toxicokinetic study	A total of 480 rats divided into eight groups (60/group), to assess the effect of level dose and duration of action in the induction of the osteosarcoma	A total of 480 Fischer rats divided into four groups (60/sex/group) to assess the skeletal changes in rats when given daily doses of rPTH (1–34) for 2 years	A total of 60 monkeys, 9-year-old cynomolgus macaques, ovariectomized and divided into two groups, vehicle control and treatment groups	A total of 720 male and female Fischer rats (9–11 weeks old), divided into six groups to assess the effect of the dose level at the induction of osteosarcoma	A total of 44 male white rabbits divided into two groups	A total of 60 monkeys, cynomolgus (*Macaca fascicularis*) of 9 years of age, given TPTD 1.0 μg/kg/day, TPTD 5.0 μg/kg/day for 18 months
Main Outcome	31 total cases of osteosarcoma in the five studies	20 cases are the total number of osteosarcoma cases among the eight groups	66 in male and 42 in female cases of osteosarcoma	No bone proliferation lesions or microscopic osteosarcoma seen	Total numbers of osteosarcoma were 54, 40 in male and female, respectively. Total numbers of metastatic osteosarcoma were 26 and 16 in male and female, respectively	Histological studies did not show any evidence of osteosarcoma	No bone proliferation lesions or microscopic osteosarcoma were seen

either antiresorptive treatments: Alendronate 70 mg/week or raloxifene 60 mg/day were recruited.[31] The study results indicated that none of the patients developed osteosarcoma.

Using eligible male patients (n = 437) from 37 centers in 11 countries aging between 30 and 85 years, they were randomly assigned to three groups; placebo group, TPTD 20 μg/day, and TPTD 40 μg/day.[32] The results showed three cancer incidents occurring in the placebo group as well in the 20 μg TPTD group, while none in the 40 μg TPTD group. However, none of these cases was of osteosarcoma. In 2013, Koski *et al.* studied the effectiveness of TPTD in clinical practice, which comprised 119 osteoporotic patients receiving 20 μg/day TPTD for about 539 days as a median duration.[33] The follow-up period varied from a few months to 2 years. It was found that BMD has increased by a mean of 0.9% in the total hip, 2.1% in the femoral neck, and 8.5% in the lumbar spine. Adverse events were limited to leg pain, nausea, and dizziness with no cases of osteosarcoma reported in support of previous studies.

In a large case–control study, concerning the Danish population and the impact of recombinant PTH (rPTH) on malignancy and mortality compared to 4104 patients receiving rPTH with 40,953 patients not receiving the treatment.[34] The period covered was 1995 through 2010 and the participants in the case group comprised 80.3% of female patients. No excessive risk of cancer was reported other than lung cancer in the group receiving rPTH. The authors described that their study does not support the claim of the possible link between rPTH treatment and the development of osteosarcoma with no cases reported in the Danish population since the introduction of rPTH to the Danish market. On the other hand, nine osteosarcoma patients were found among controls. It is worth mentioning that the authors of the study used broad ICD-10 codes C40-C41 which can obscure a real relationship between primary osteosarcoma and rPTH. This means that the study could have captured many types of bone-related tumors. This gives additional assurance to the safety of rPTH. On the other hand, evidence from retrospective studies is generally regarded as weaker compared to controlled clinical trials involving large groups.

In a recent publication evaluating the safety and effectiveness of daily TPTD in Japanese patients with osteoporosis and at high risk of fracture, a 24-month post-marketing surveillance study was conducted.[35] Individuals (n = 1847) from 238 sites across Japan were selected, of which 92% were female and 90.8% of them were postmenopausal. Through the safety profile of this study, the author reported that there were no cases of osteosarcoma.

An interim 7 years surveillance study 2003–2009 was published as part of ongoing US 15 years post-marketing surveillance for adult osteosarcoma associated with TPTD. The study reported one case of osteosarcoma in the TPTD-treated group, which was the single reported case from 430,000.[36] However, the incident reported that the patient previously

Table 2: Summary of the clinical and observational research studies reporting on osteosarcoma incidents with the use of teriparatide

Citation	Gilsenan *et al.*[45]	Orwoll *et al.*[32]	Andrews *et al.*[36]	Prince *et al.*[30]	Bang *et al.*[34]	Nishikawa *et al.*[35]	Wermers *et al.*[31]	Koski et al.[33]
Study design	Cohort	Case–control study	Cohort	Case–control study	Case–control study	Clinical	Cohort study	Clinical
Year of Publication	2020	2003	2012	2005	2014	2016	2008	2013
Journal	Pharmacoepidemiol Drug Saf.	JBMR	JBMR	JBMR	Osteoporosis International	Clinical Intervention in Aging	Osteoporosis International	Annals of Medicine
Subjects	153–316 elderly men and women with an average age of 76.9	437 elderly osteoporotic men, age 30–85 years	1448 osteosarcoma cases identified by 15 registers 2003–2009	1637 postmenopausal women with osteoporosis	4104 patients diagnosed with osteoporosis receiving TPTD (case group) compared with 40,953 patients not receiving the treatment (controls)	1847 Participants were patients with osteoporosis, older age injected 20 μg TPTD daily for 24 months	198 postmenopausal women with osteoporosis, who had previously treated with alendronate or raloxifene for 18 months	119 individuals (113 women and six men), who received TPTD at a dosage of 20 μg/day
Main Outcome	No cases of osteosarcoma were observed in the teriparatide cohort	No cases of osteosarcoma	No osteosarcoma patient who had a prior history of TPTD treatment	No occurrence of osteosarcoma	No patients in the rPTH group were registered with osteosarcoma compared with nine patients among the controls	No reports of osteosarcoma	There were no deaths or reports of osteosarcoma	No case of osteosarcoma was reported

went through radiation therapy for prostate cancer, a contraindication to the administration of TPTD. More recently, an entire 15 years of surveillance results were published, which indicated that the incidence of osteosarcoma associated with TPTD was not different from what would be expected based on the background incidence rate of osteosarcoma.[37] In one case report of a 22-year-old Persian man, the patient developed osteoblast hyperactivation state observed during treatment with TPTD for 7 months.[38] However, the authors did not preclude the patient's history as possible cause. Another case report suggested the acceleration of the growth of pre-existing bone tumor of the femur following 2 months TPTD treatment.[39] While TPTD is contraindicated in irradiated bones, two patients with tongue cancer and late emerging osteoradionecrosis were successfully treated with TPTD for 4–6 months.[40] This was indicated by the progress of osteoradionecrosis, and bone defect regenerating well. Therefore, such published cases cannot prove or refute the usefulness of TPTD in pre-existing bone tumor. For a summary of the clinical studies reporting on osteosarcoma incidents associated with the use of teriparatide, refer to Table 2.

Research indicated that when TPTD is discontinued, BMD starts to decrease necessitating the prompt administration of antiresorptive therapy.[41-43] Since TPTD therapy is supported by long post-marketing safety profile, it is worthwhile investigating longer treatment period and perhaps indefinitely considering the old age of the affected individuals as the case in the management of diabetes by SC insulin injections.[19,20] The 2-year limit set for TPTD therapy is based on the expert review that the osteosarcoma found in rats is unlikely to occur in humans with the treatment of up to 2 years.[30] Furthermore, controlled clinical trials did not cover the treatment period exceeding 2 years to uncloud the longer time safety of TPTD. A follow-up study in clinical practice settings showed after the discontinuation of TPTD, anti-fracture efficacy may persist for up to 18 months.[44]

CONCLUSION

Pre-clinical investigations are important in finding demonstrating drug safety and toxicity and are, therefore, essential before clinical trials begin. Unfortunately, these non-clinical studies are usually done using much larger doses and for a much longer duration (3–60 times) than would be required in human subjects. In several cases, the applicability of findings to humans is also questioned by the differences between animal species. For example, while studies done using rats revealed that TPTD can cause osteosarcoma, results from rabbits and monkey indicated a safe and effective therapy. The biology and structure of bone in human differs from the studied rats, as rodents lack osteonal remodeling and exhibit skeletal growth throughout life.

Clinical trials and post-marketing surveillance have undoubtedly proved the efficacy and safety of the TPTD. The efficacy of TPTD does not persist after its discontinuation and it was advocated to start an antiresorptive therapy immediately thereafter. Considering the therapy contraindications discussed earlier, that is, avoiding TPTD therapy with prior radiation therapy, having no history of Paget's disease of bone, and avoiding TPTD therapy for children or young adults with open epiphyses, it is worthwhile investigating the usefulness and safety of therapy over a period lasting more than 2 years.

DISCLOSURE STATEMENT

No potential competing interest was reported by the authors.

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