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TITLE: The role, efficacy and outcome measures for Teriparatide use in the management of MRONJ - review of the literature

Short title: Teriparatide in the management of MRONJ

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ABSTRACT

Medication related osteonecrosis of the jaw (MRONJ) is a complex disease which can be associated with multiple morbidities and is challenging to treat. This review evaluates the literature on the role and efficacy of Teriparatide (TPTD) as a treatment for MRONJ. The clinical, radiological, histopathological and serological parameters used to assess treatment response have been described. Electronic databases were searched to retrieve articles (April 2005 and April 2020) based on a strict inclusion criterion. 17 articles were included in this review. Of the 91 patients treated; only 6 received TPTD as a standalone treatment. There were significant variations in defining treatment outcomes and measuring treatment response. The longest follow-up period was 26 months, and twelve studies failed to report follow up. The overall quality of evidence is weak with potential for a high risk of bias, making it difficult to determine the efficacy of TPTD and its long-term effects. However, TPTD may play a role for treatment of intractable MRONJ in osteoporotic patients or those unfit for surgery. Therefore, randomised clinical trials on larger patient cohorts with long term follow up is required to confirm efficacy, safety and inform treatment indications for TPTD in the treatment of MRONJ.

INTRODUCTION

The American Association for Oral and Maxillofacial Surgeons (AAOMS)[1] defines medication-related osteonecrosis of the jaw (MRONJ) if all the following criteria are met:

1) Current or previous treatment with antiresorptive or antiangiogenic agents.
2) Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than eight weeks.

3) No history of radiation therapy to the jaws or obvious metastatic disease to the jaws.

MRONJ was first documented in 2003[2]. Initially, it was known as bisphosphonate related osteonecrosis of the jaw (BRONJ) because it was exclusively associated with patients taking bisphosphonates. Bisphosphonates are used in various conditions including the treatment of osteoporosis, hypercalcaemia in metastatic breast cancer and multiple myeloma. However, other antiresorptive medications such as denosumab and angiogenesis inhibitors have since been identified as causing osteonecrosis of the jaw, hence the term MRONJ was coined[1].

MRONJ can occur as a result of an insult such as dental treatment (e.g. extractions) or spontaneously. Despite it being relatively uncommon, it can affect up to 0.01% of patients receiving oral bisphosphonates, 12% of patients receiving intravenous bisphosphonates, and 16% in patients receiving a combination of bisphosphonates and antiangiogenics[1].

Interventions used to treat this complication are diverse, controversial and largely empirical hence the drive for preventative measures. In aggressive cases, MRONJ does not always respond to routine treatments and may persist or progress to an advanced stage making it challenging to treat. AAOMS outlines treatment strategies based on the stage of MRONJ [1]. The failure of conventional treatment strategies has led to research into more novel ways of treating MRONJ, including hyperbaric oxygen therapy, platelet rich plasma, low-level laser irradiation, bone morphogenic protein and the use of recombinant parathyroid hormone (PTH)[1].

Harper *et al.*[3] (2007) reported the first case in which Teriparatide (TPTD) was successfully used to treat BRONJ. Since then, there have been multiple publications on the use of TPTD for the treatment of MRONJ, and the International Task Force on Osteonecrosis of the Jaw currently considers TPTD as an option for treatment of MRONJ in osteoporotic patients[4]. TPTD is a molecule that makes up the first 34 amino acids (recombinant 1-34 N-terminal sequence) of the

intact PTH[5]. It is involved in the stimulation of osteoblasts to promote bone formation, and subsequently osteoclasts for bone resorption, thereby regulating bone remodelling [6]. Depending on the duration and dose administered, TPTD can have both anabolic and catabolic effects on bone, by either stimulating new bone formation or dissolving calcium from bone. TPTD is able to reverse the anti-resorptive effects of bisphosphonates by promoting the activity of osteoblasts and enhancing the metabolic function of osteoclasts. In the UK, it is the second-line treatment for osteoporosis and the only licensed anabolic treatment for osteoporosis in many other countries[5].

The primary aim of this study is to review the existing scientific literature to evaluate the role and efficacy of TPTD as a treatment modality for MRONJ. We will describe the clinical, radiological, histopathological and serological parameters used to assess the treatment response of TPTD as either a stand-alone treatment or as part of multi-therapy regime.

MATERIALS AND METHODS

Electronic databases search in Pubmed, Embase via OVID and Scopus was conducted to retrieve articles published in the English language between April 2005 and April 2020. The time period was chosen as the first reported case of TPTD use for MRONJ management was described in 2007[3].

The search strategy was jointly developed by the authorship team in collaboration with a medical information specialist (Librarian from University of Sheffield, UK). Tailored search strings containing keywords and database-specific medical subject headings (MeSH) for the two major topics (MRONJ treatment and TPTD) were developed. Multiple variations of search terms were combined to produce different sets of results and the final search strategy was pilot-tested

and modified accordingly. The final search including the following terms: “MRONJ” OR “medication related osteonecrosis” OR “BRONJ” OR “bisphosphonate related osteonecrosis” AND “teriparatide” OR “recombinant parathyroid hormone” AND “management” OR “treatment”. In addition to the electronic searches, grey literature and reference lists of selected articles were screened for relevant studies that may not have been identified through the electronic search.

Article citations were exported to EndNote® reference manager software (Clarivate Analytics, Philadelphia, USA) and duplicates were removed. The first screen based on analysis of title and abstract was conducted by the two independent reviewers and any articles deemed not relevant were removed. The second screen involved detailed examination of full-text articles against the eligibility criteria by the same two reviewers. The shortlists were compared, and differences discussed, obtaining a final selection of studies.

The inclusion criteria were studies which looked at the use of TPTD for management/treatment of MRONJ/BRONJ in human subjects. Only articles published in the English language in indexed peer-reviewed journals were included. Abstracts, letters to the editor, commentaries, animal studies and those which focussed on the treatment of osteoradionecrosis with TPTD were excluded.

Relevant data from selected articles were extracted, processed and tabulated into a pre-developed data collection form in Microsoft Excel® (Microsoft Corporation, Washington, USA) by three reviewers. The following information was recorded:

- Study details (authors, year and country of publication, aims)
- Study methods (design, sample size and selection)

- Patient details (demographics, cause of MRONJ including details of relevant medications, whether MRONJ-related medication was continued whilst being treated with TPTD)
- MRONJ diagnosis (site and size, clinical staging, duration of osteonecrosis prior to TPTD treatment)
- TPTD (dose, route, stand-alone or multi-therapy, duration of treatment, side-effects, follow-up period)
- Treatment response (clinical, radiological, histopathological and serological outcome measures)
- Description of outcome variables (no improvement, partial healing, complete resolution or worsened disease)

RESULTS

The electronic search identified 103 records. In addition, one article was identified through citation searching. Fifty-nine duplicates were removed. After the first screen based on analysis of titles and abstracts, 20 articles did not satisfy the inclusion criteria and were excluded. A full text examination of the remaining 24 articles excluded a further 7 articles, resulting in 17 articles for inclusion in this review paper.

A narrative synthesis of the main study findings is presented in Table 1. The 17 selected articles consisted of nine case reports[3,7,8,9,10,11,12,13,14], two case series[15,16], two comparative pilot studies[17,18], a retrospective longitudinal study[19], a retrospective multicentre study[20], a prospective preliminary study[21] and a prospective interventional study[22].

Across all studies, there were a total of 94 MRONJ patients initially treated with TPTD (mean age 76 years). However, as three patients dropped out of TPTD treatment early, treatment outcomes were only reported in 91 patients. More than 50% of patients were female, although it was not possible to provide an exact breakdown as gender was not uniformly reported across all studies. Most patients (n=88) were taking oral bisphosphonates which included alendronate, risedronate, ibandronate, pamidronate or minodronate, and in some cases, more than one of these medications was being taken. The remaining patients (n=6) were taking intravenous (IV) antiresorptive medications including zoledronate (n=2) and Denosumab (n=2). The IV medication name was not specified in two patients[19,20]. The antiresorptive medications were mostly taken for treatment of primary or secondary osteoporosis. In three articles the reason for taking bisphosphonates had not been stated[15,15166,20]. The shortest duration a patient had been taking an oral bisphosphonate before developing MRONJ was six months[21]; this information had not been reported for patients taking IV antiresorptives.

Some studies reported spontaneous development of MRONJ, but in most cases a surgical, traumatic or infective aetiology was reported. These included extractions, endodontic treatment, implant surgery, traumatic prosthesis and periodontitis. In four studies the cause of MRONJ was not documented[8,15,1516,21] MRONJ predominantly occurred in the mandible (n=68) followed by the maxilla (n=15) which included the unusual site of the palatal torus[13] and in a few patients both jaws were affected (n=5)[22]. In some patients the clinical site had not been specified (n=6). The osteonecrosis defect size had not been reported in any studies, but the clinical staging had been documented in most cases. The AAOMS[1] classification was most frequently used except Pelaz *et al.*[17] used the Ruggiero classification (2006)[23] and Morishita *et al.*[20] staged according to the classification outlined in the Position Paper (2017) of the Japanese Allied Committee on Osteonecrosis of the Jaw[24] (Table 1). Harper *et al.*[3] did not provide any information on clinical staging and Kwon *et al.*[15] did not mention the staging system used. Doh

et al.[9] used AAOMS treatment recommendations although the actual clinical staging was not stated. Most patients were diagnosed with either stage 2 or 3 MRONJ, except for one patient who was diagnosed with stage 1[20]. In the case of studies where the clinical staging was not mentioned, based on the reported clinical descriptions they were classified according to the AAOMS guidelines. Where specified ,the time from MRONJ diagnosis to the time of staring TPTD treatment ranged between 2 to 26 months[3,7,9,10,11,12,13,14,15].

The dose and frequencies of TPTD treatment varied, as some were taken daily and others at weekly or monthly intervals. As documented in table 1, in eleven studies TPTD was administered daily at a dose of 20µg subcutaneously. In four studies TPDP was administered weekly at a dose of 56.5µg. Yoshiga *et al*. (2013)[16] prescribed daily TPDP for one patient and weekly for the other. There are only three studies[1615,17,1917] in which TPTD can be strictly described as a stand-alone treatment, since they were not receiving any other intervention at the time of taking TPTD. One study compared the efficacy of daily versus weekly TPTD injections[8]. A further study compared MRONJ treatment using TPTD and plasma rich growth factors, producing better results with the latter treatment[17]. The longest duration of treatment with TPTD was a period of 26 months[,20,22] It was highlighted that TPTD treatment should not be taken for longer than two years duration due to the risk of osteosarcoma[5].

In twelve studies the antiresorptive treatment was stopped prior to starting TPTD, although five studies do not specify whether antiresorptive treatment had been stopped or not[10,11,17,18,19]. Amongst the studies where antiresorptive medications were stopped, six studies did not specify the cessation period before starting TPTD, three studies reported a cessation period between three and twelve months [3,14,16] and the other three studies indicated that TPTD was started immediately after cessation of the antiresorptive treatment [8,12,13] In one study, for patients to be included in the study they needed to "continue osteoporosis treatment"[18], although the

details regarding this are not clearly specified. Follow up on completion of TPTD ranged from 6-24 months[7,8,9,17,19,17]. The majority of studies do not document any follow up on completion of TPTD treatment.

The treatment response to TPTD was assessed using clinical, radiological, histological and biochemical markers (BCM) including bone turnover markers (BTM). Details of these methods are provided in Tables 2,3, and 4 and the results of each will be presented.

Clinical treatment measures

Across the studies, clinical improvement was seen in 32 patients (35%), complete resolution in 50 patients (55%), no improvement in 2 patients (2%)[17,22], stable disease in 6 patients (7%)[20] and worsening of disease in 1 patient[20] (1%).

Clinical outcomes measures included: improvements in pain, neurosensory disturbance, absence of pus, discharge or infection, healing of fistula, reducing area of bone exposure and movement of associated pathological fracture. In some cases, spontaneous exfoliation of the sequestrum has been reported as a favourable clinical outcome.

In three articles[17,1917,20], the authors have stated how they stratified the clinical treatment outcome. Kim *et al.* (2014)[19] measured treatment outcome based on the improvement of BRONJ stage and the evolution of the disease after 6 months of treatment which was stratified as: “No improvement” (no improvement or worsening of BRONJ status), “Moderate improvement” (one stage of improvement of BRONJ status), “Marked improvement” (improvement of two stages of BRONJ or complete healing). Pelaz *et al.* (2014)[17] defined treatment success if there was clinical evidence of healing or symptomatic/asymptomatic bone exposure. Morishita *et al.* (2020)[20] defined treatment outcomes according to the following

criteria: “complete resolution”(the disappearance of all objective symptoms for at least 3 months), “improvement” (the down-staging of MRONJ for at least 3 months), “stable disease” (no change in the stage of MRONJ during the observation) and “exacerbation” (up-staging of MRONJ during the observation). The treatment was defined as “effective” in the cases of “complete resolution” and “improvement”, and “no response” in the cases of “stable disease” and “exacerbation” based on above clinical findings on the last observation day.

Radiographic treatment measures

Ohbayashi *et al*. (2013)[8] demonstrated remarkable bone regeneration on the CT scan six months after starting TPTD treatment and bone scintigraphy showed regression of the uptake area. Kakehashi *et al.* (2015)[22] reported partial improvement in one patient from their study and assessment of dual-energy x-ray absorptiometry (DXA) scanning and BTM revealed that this patient did not show any improvement in the bone mineral quantity in either the spine or femoral areas. Jung *et al.* (2017)[21] used cone beam computed tomography (CBCT) scans to compare between treatment groups by measuring the bone regeneration ratio and comparing it by superimposition of CBCT scans, acquired immediately post-operation and after 6 months. For standardisation they considered bone tissue as having 350 to 3000 pixels of the Hounsfield unit.

In addition to clinical and serological outcome modalities Ohbayashi *et al.* (2020)[18] utilised various imaging techniques (Table 4) to assess the response of treatment. Bone metabolism was measured by bone scintigraphy which was performed using a dual-head single-photon emission computerised tomography (SPECT)/CT) system. Unlike previous studies using SPECT in MRONJ[25,26], the bone scintigraphy images were quantified using the bone uptake value (BUV), which was calculated as the bone accumulation of radiopharmaceuticals by correcting each

234 pixel value of the bone scintigraphy. They calculated the BUV at baseline and six months
235 following treatment for blinded assessment of the BUV.
236
237 ***Serum treatment measures***
238 In eleven studies, serum markers were used to evaluate the response to TPTD treatment (Table
239 2). Pelaz *et al.* (2014)[17] measured baseline levels of alkaline phosphatase and calcium to rule
240 out unexplained high levels prior to starting TPTD. These levels were monitored throughout
241 treatment, however no further details were provided. Five studies showed a significant increase
242 in BTM[19921,13,1419, 21] over a variable range of 4-42 weeks. Kim *et al.* (2014)[19] observed an obvious
243 anabolic window, with earlier changes in OCN values and later increases in CTX values due to
244 TPTD treatment. However, in other studies, there were variable results. For example, Kwon *et*
245 *al.* (2012)[15] reported a statistically significant increase ($p = 0.006$) in the s-OC values in all
246 patients between values at baseline, two and three months. The S-CTX values also increased in
247 four patients, whereas the remaining two patients showed minimal change, which was
248 marginally significant ($p = 0.018$) between the mean values at baseline and 3 months.
249
250 Ohbayashi *et al*. (2013)[8] found significantly increasing bone formation and resorption markers
251 except for uNTX at one month, but most markers except for BAP and TRACP-5b had decreased
252 at nine months. However, all markers remained at a high level when compared with the
253 baseline. While there was no significant difference in the percentage change between bone
254 formation and bone resorption markers, variation in percentage change of each marker over
255 time was statistically significant during TPTD administration. The authors recommended
256 monitoring uric acid levels during treatment for assessment of adverse events.
257

Yoshiga *et al*. (2013)[16] found that the s-NTX level increased slightly in both patients they presented, but in the first patient serum P1NP level decreased after initiation of TPTD treatment whilst in the second patient serum P1NP level significantly increased 2 months after initiation of TPTD treatment . Kakehashi *et al.* (2015)[22] reported a tendency for BAP and CTX to increase, however there was no statistically significant difference observed from baseline values. They concluded that BAP and CTX can not be used as predictive markers for the clinical outcome of TPTD therapy. Out of the serum markers utilised by Ohbayashi *et al.* (2020)[18] (Table 4) only OC and P1NP were significantly different between both groups; OC and P1NP at 3 months of treatment, and P1NP at 6 months. Changes in BTM were noted less in the weekly TPTD group compared to the daily TPTD group, but the values were comparable at six months following the start of treatment.

Doh *et al.* (2015)[9] was the only study to document histological features in assessing the response to TPTD. Irregular reversal lines and active osteoblasts were noted adjacent to the lesion of necrotic bone indicating active bone remodelling.

Prognostic treatment parameters

Some studies looked at possible prognostic factors that can influence the result of TPTD treatment in MRONJ patients. Morishita *et al.* (2020)[20] identified no prognostic factors for TPTD therapy. However, the oral administration of bisphosphonates might have a possibility for successful treatment outcomes with TPTD (p= 0.062). Jung *et al.* (2017)[21] found that deep and narrow defects rapidly healed with regenerated new bone, rather than flat and shallow defects. Ohbayashi *et al*. (2013)[8] suggested that P1NP level might be a good predictor of a positive prognosis of TPTD treatment.

Kim *et al.* (2014)[19] compared baseline parameters (age, BMI, duration of bisphosphonates usage, BTM, Vitamin D) between patients that had shown either moderate or marked improvement with TPTD treatment. Amongst these parameters, only baseline Vitamin D levels revealed a significant influence on the effect of TPTD. A multivariate analysis of various baseline parameters (age, BMI, duration of bisphosphonate usage, CTX, OCN) showed the difference in baseline Vitamin D levels to have remained significant (p=0.021) between both groups. However, this difference was not significant following adjustment of baseline PTH concentration.

Complications and adverse side-effects

Only three studies have documented complications related to TPTD treatment. Morishita *et al.* (2020)[20] aimed for a 24 month course of TPTD treatment but five patients (17%) discontinued or interrupted treatment due to adverse side effects. They reported a patient who suffered from TPTD-induced arthritis which resulted in discontinuing treatment after 12 days. One patient experienced nausea and discontinued at 3 months and another patient experienced malaise and discontinued at 5 months. Treatment was interrupted due to inner stigma and renal dysfunction in two patients at one month and two months, respectively.

Two out of ten patients in the study conducted by Kakehashi *et al.* (2015)[22] dropped out due to adverse side effects. These included facial and lower limb oedema, nausea, and vomiting in one patient which starting three days after starting TPTD, in addition to knee arthralgia in one further patient one week after administration. Pelaz *et al.* (2014)[17] reported psychological problems in one out of four patients treated with TPTD.

DISCUSSION

With an increasing ageing population, Oral and Maxillofacial surgeons may see a greater proportion of patients exposed to antiresorptive medications[27]. These patients may present with multiple medical comorbidities and polypharmacy that may complicate the presentation and treatment options and render aggressive surgical treatment an unsuitable option.

MRONJ is a complex disease process that can adversely affect quality of life[28,29]. It has a poorly understood pathophysiology[1,2] with multiple hypothesises postulated to understand the mechanism of this disease affecting the jaw bones[30,31]. Theories include altered bone remodelling or over suppression of bone resorption[3029,32], angiogenesis inhibition[29,3130,32,33], constant microtrauma[34], suppression of innate or acquired immunity[34,35], vitamin D deficiency[36], soft tissue bisphosphonate toxicity[37], and inflammation or infection[38,39,40]. Most of this evidence based on animal models suggests the disease process to be multifactorial, contributing to the difficulty in developing effective targeted treatments.

Current treatment strategies based on AAOMS guidance[1] is stage-specific and ranges from conservative to surgical management, which has shown varying degrees of success in treating MRONJ. Conservative treatment including sequestrectomy and/or debridement has shown partial success with mucosal closure in 50% of cases, whereas more complex surgical treatments (i.e. resection) has shown healing success rate of 80%. However, the latter may not be a feasible option in some patients, particularly those with complex medical status, due to the associated surgical and anaesthetic risks of invasive surgery. This highlights the need for non-invasive therapeutics as an alternative or adjunctive treatment option.

TPTD was approved by the US Food and Drug Administration agency in 2002 as the first osteoporosis therapy to stimulate bone formation in patients at high risk of bone fracture[41]. Abaloparatide, another PTH analogue, has since been approved by the FDA in 2017 also for severe osteoporosis[42].

This review highlights the lack of high-quality randomised evidence to assess the use of TPTD for MRONJ treatment, as the literature comprises mostly of case reports and case series (11 out of 17 studies). Whilst a clinical improvement has been demonstrated in a large proportion of patients, the relatively high success rate should be treated with caution since only six out of the 91 patients received TPTD in isolation (Table 1). Amongst those receiving TPTD as part of a multi-therapy regime, there were a range of adjunctive treatments provided with ranged. There were also varying definitions and measurements of treatment outcomes, making it difficult to ascertain the efficacy of TPTD and whether the reported clinical improvements in MRONJ were related to TPTD alone or in combination with the other adjunctive treatments. Furthermore, twelve studies failed to report follow-up and in those which did, the follow-up period varied between 6 and 24 months. This makes it difficult to measure the long-term treatment outcomes and extent of adverse drug effects or complications.

Variable outcome measures were reported (Table 4) of which the most important is the improvement in clinical signs and symptoms. However, imaging and serum markers can be useful adjuncts for diagnosis and assessment of treatment response. This review highlighted four possible prognostic parameters to predict a positive response to TPTD treatment. These included baseline Vitamin D levels, P1NP levels, deep and narrow bone defects and patients with oral bisphosphonates exposure as opposed to intravenous antiresorptive treatment. Most

other reported serum markers have shown a significant change in response to TPTD treatment (Table 4).

The FDA[43] have reported multiple adverse side-effects associated with TPTD use. This review has shown effects including arthralgia, malaise, nausea, vomiting, renal impairment, and psychological problems in 8.5% of patients, which resulted in either discontinuation or interruption of treatment. The FDA[43] have highlighted certain groups of patients in which TPTD is contraindicated:

- Bone metastases and skeletal malignancies
- Metabolic bone conditions
- Hypercalcemia and Hypercalcaemic Disorders
- Urolithiasis or Pre-existing Hypercalciuria
- Orthostatic Hypotension
- Drug Interactions (Digoxin)
- Hypersensitivity

In addition to the above, patients at risk of developing malignant bone tumours (Paget's disease of bone, paediatric and young adult patients with open epiphyses, and patients with prior external beam or implant radiation involving the skeleton) should be treated with extreme caution due to the risk of developing osteosarcoma which has been associated with high exposure to TPTD. As this risk is dose and duration dependent, the FDA do not recommend the use of TPTD for longer than 24 months[43]. The findings from studies in this review showed that duration of TPTD treatment varied between 0.3 to 26 months due to certain factors including differences in study design, financial implications, adverse side-effects and early resolution of

MRONJ. This risk highlights the importance of long-term follow-up, which unfortunately most of the studies have failed to report.

TPTD treatment is under strict prescribing regulations under the UK's NHS presumably due to the side effect profile and concerns related to risk of malignancy. It is also associated with a high financial cost[44] which should be take into consideration.

The available literature does not provide sufficient evidence to address our aim of determining the efficacy of TPTD treatment, mainly due to the lack of high-quality studies, control groups and randomisation. The overall quality of evidence is low and largely comprising isolated case reports, case series and small studies (largest study population of 29 patients) which increases the risk of bias in data interpretation and reporting. This review serves to highlight the need for further research and multicentre randomised-control trials to evaluate the efficacy of TPTD and treatment response on a bigger patient cohort to help inform its role in the management of MRONJ and provide guidance for adjunctive radiological, serological and histopathological measures of tissue response.

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