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

3 **Short title:** Teriparatide in the management of MRONJ

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22 **Key Words:** Teriparatide; recombinant human parathyroid hormone; medication-related

23 osteonecrosis; MRONJ; bisphosphonate-related osteonecrosis; BRONJ; review; treatment

24 outcomes; efficacy measures.

25 **ABSTRACT**

26 Medication related osteonecrosis of the jaw (MRONJ) is a complex disease which can be
27 associated with multiple morbidities and is challenging to treat. This review evaluates the
28 literature on the role and efficacy of Teriparatide (TPTD) as a treatment for MRONJ. The
29 clinical, radiological, histopathological and serological parameters used to assess treatment
30 response have been described. Electronic databases were searched to retrieve articles (April
31 2005 and April 2020) based on a strict inclusion criterion. 17 articles were included in this
32 review. Of the 91 patients treated; only 6 received TPTD as a standalone treatment. There
33 were significant variations in defining treatment outcomes and measuring treatment
34 response. The longest follow-up period was 26 months, and twelve studies failed to report
35 follow up. The overall quality of evidence is weak with potential for a high risk of bias, making
36 it difficult to determine the efficacy of TPTD and its long-term effects. However, TPTD may
37 play a role for treatment of intractable MRONJ in osteoporotic patients or those unfit for
38 surgery. Therefore, randomised clinical trials on larger patient cohorts with long term follow
39 up is required to confirm efficacy, safety and inform treatment indications for TPTD in the
40 treatment of MRONJ.

41

42 **INTRODUCTION**

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

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

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

49 MRONJ was first documented in 2003². Initially, it was known as bisphosphonate related
50 osteonecrosis of the jaw (BRONJ) because it was exclusively associated with patients taking
51 bisphosphonates. Bisphosphonates are used in various conditions including the treatment of
52 osteoporosis, hypercalcaemia in metastatic breast cancer and multiple myeloma. However,
53 other antiresorptive medications such as denosumab and angiogenesis inhibitors have since
54 been identified as causing osteonecrosis of the jaw, hence the term MRONJ was coined¹.

55 MRONJ can occur as a result of an insult such as dental treatment (e.g. extractions) or
56 spontaneously. Despite it being relatively uncommon, it can affect up to 0.01% of patients
57 receiving oral bisphosphonates, 12% of patients receiving intravenous bisphosphonates, and
58 16% in patients receiving a combination of bisphosphonates and antiangiogenics¹.

59 Interventions used to treat this complication are diverse, controversial and largely empirical
60 hence the drive for preventative measures. In aggressive cases, MRONJ does not always
61 respond to routine treatments and may persist or progress to an advanced stage making it
62 challenging to treat. AAOMS outlines treatment strategies based on the stage of MRONJ¹. The
63 failure of conventional treatment strategies has led to research into more novel ways of treating
64 MRONJ, including hyperbaric oxygen therapy, platelet rich plasma, low-level laser irradiation,
65 bone morphogenic protein and the use of recombinant parathyroid hormone (PTH)¹.

66 Harper *et al.*³ (2007) reported the first case in which Teriparatide (TPTD) was successfully used
67 to treat BRONJ. Since then, there have been multiple publications on the use of TPTD for the
68 treatment of MRONJ, and the International Task Force on Osteonecrosis of the Jaw currently
69 considers TPTD as an option for treatment of MRONJ in osteoporotic patients⁴. TPTD is a
70 molecule that makes up the first 34 amino acids (recombinant 1-34 N-terminal sequence) of the

71 intact PTH⁵. It is involved in the stimulation of osteoblasts to promote bone formation, and
72 subsequently osteoclasts for bone resorption, thereby regulating bone remodelling ⁶ .
73 Depending on the duration and dose administered, TPTD can have both anabolic and catabolic
74 effects on bone, by either stimulating new bone formation or dissolving calcium from bone.
75 TPTD is able to reverse the anti-resorptive effects of bisphosphonates by promoting the activity
76 of osteoblasts and enhancing the metabolic function of osteoclasts. In the UK, it is the second-
77 line treatment for osteoporosis and the only licensed anabolic treatment for osteoporosis in
78 many other countries⁵.

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

83

84 **MATERIALS AND METHODS**

85 Electronic databases search in Pubmed, Embase via OVID and Scopus was conducted to retrieve
86 articles published in the English language between April 2005 and April 2020. The time period
87 was chosen as the first reported case of TPTD use for MRONJ management was described in
88 2007³.

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

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

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

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

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

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

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

127

128 **RESULTS**

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

134 A narrative synthesis of the main study findings is presented in Table 1. The 17 selected articles
135 consisted of nine case reports^{3,7,8,9,10,11,12,13,14}, two case series^{15,16}, two comparative pilot
136 studies^{17,18}, a retrospective longitudinal study¹⁹, a retrospective multicentre study²⁰, a
137 prospective preliminary study²¹ and a prospective interventional study²².

138 Across all studies, there were a total of 94 MRONJ patients initially treated with TPTD (mean
139 age 76 years). However, as three patients dropped out of TPTD treatment early, treatment
140 outcomes were only reported in 91 patients. More than 50% of patients were female, although
141 it was not possible to provide an exact breakdown as gender was not uniformly reported across
142 all studies. Most patients (n=88) were taking oral bisphosphonates which included alendronate,
143 risedronate, ibandronate, pamidronate or minodronate, and in some cases, more than one of
144 these medications was being taken. The remaining patients (n=6) were taking intravenous (IV)
145 antiresorptive medications including zoledronate (n=2) and Denosumab (n=2). The IV
146 medication name was not specified in two patients^{19,20}. The antiresorptive medications were
147 mostly taken for treatment of primary or secondary osteoporosis. In three articles the reason
148 for taking bisphosphonates had not been stated^{15,15166,20}. The shortest duration a patient had
149 been taking an oral bisphosphonate before developing MRONJ was six months²¹; this
150 information had not been reported for patients taking IV antiresorptives.

151 Some studies reported spontaneous development of MRONJ, but in most cases a surgical,
152 traumatic or infective aetiology was reported. These included extractions, endodontic
153 treatment, implant surgery, traumatic prosthesis and periodontitis. In four studies the cause of
154 MRONJ was not documented^{8,15,1516,21} MRONJ predominantly occurred in the mandible (n=68)
155 followed by the maxilla (n=15) which included the unusual site of the palatal torus¹³ and in a
156 few patients both jaws were affected (n=5)²². In some patients the clinical site had not been
157 specified (n=6). The osteonecrosis defect size had not been reported in any studies, but the
158 clinical staging had been documented in most cases. The AAOMS¹ classification was most
159 frequently used except Pelaz *et al.*¹⁷ used the Ruggiero classification (2006)²³ and Morishita *et*
160 *al.*²⁰ staged according to the classification outlined in the Position Paper (2017) of the Japanese
161 Allied Committee on Osteonecrosis of the Jaw²⁴ (Table 1). Harper *et al.*³ did not provide any
162 information on clinical staging and Kwon *et al.*¹⁵ did not mention the staging system used. Doh

163 *et al.*⁹ used AAOMS treatment recommendations although the actual clinical staging was not
164 stated. Most patients were diagnosed with either stage 2 or 3 MRONJ, except for one patient
165 who was diagnosed with stage 1²⁰. In the case of studies where the clinical staging was not
166 mentioned, based on the reported clinical descriptions they were classified according to the
167 AAOMS guidelines. Where specified, the time from MRONJ diagnosis to the time of starting TPTD
168 treatment ranged between 2 to 26 months^{3,7,9,10,11,12,13,14,15}.

169 The dose and frequencies of TPTD treatment varied, as some were taken daily and others at
170 weekly or monthly intervals. As documented in table 1, in eleven studies TPTD was administered
171 daily at a dose of 20µg subcutaneously. In four studies TPDP was administered weekly at a dose
172 of 56.5µg. Yoshiga *et al.* (2013)¹⁶ prescribed daily TPDP for one patient and weekly for the other.
173 There are only three studies^{16,15,17,19,17} in which TPTD can be strictly described as a stand-alone
174 treatment, since they were not receiving any other intervention at the time of taking TPTD. One
175 study compared the efficacy of daily versus weekly TPTD injections⁸. A further study compared
176 MRONJ treatment using TPTD and plasma rich growth factors, producing better results with the
177 latter treatment¹⁷. The longest duration of treatment with TPTD was a period of 26 months^{20,22}
178 It was highlighted that TPTD treatment should not be taken for longer than two years duration
179 due to the risk of osteosarcoma⁵.

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

187 details regarding this are not clearly specified. Follow up on completion of TPTD ranged from 6-
188 24 months^{7,8,9,17,19,17}. The majority of studies do not document any follow up on completion of
189 TPTD treatment.

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

193

194 ***Clinical treatment measures***

195 Across the studies, clinical improvement was seen in 32 patients (35%), complete resolution in
196 50 patients (55%), no improvement in 2 patients (2%)^{17,22}, stable disease in 6 patients (7%)²⁰
197 and worsening of disease in 1 patient²⁰ (1%).

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

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

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

216

217 ***Radiographic treatment measures***

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

228 In addition to clinical and serological outcome modalities Ohbayashi *et al.* (2020)¹⁸ utilised
229 various imaging techniques (Table 4) to assess the response of treatment. Bone metabolism
230 was measured by bone scintigraphy which was performed using a dual-head single-photon
231 emission computerised tomography (SPECT)/CT system. Unlike previous studies using SPECT in
232 MRONJ^{25,26}, the bone scintigraphy images were quantified using the bone uptake value (BUV),
233 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

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

269
270 Doh *et al.* (2015)⁹ was the only study to document histological features in assessing the
271 response to TPTD. Irregular reversal lines and active osteoblasts were noted adjacent to the
272 lesion of necrotic bone indicating active bone remodelling.

273

274 ***Prognostic treatment parameters***

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

282

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

291

292 ***Complications and adverse side-effects***

293 Only three studies have documented complications related to TPTD treatment. Morishita *et al.*
294 (2020)²⁰ aimed for a 24 month course of TPTD treatment but five patients (17%) discontinued
295 or interrupted treatment due to adverse side effects. They reported a patient who suffered
296 from TPTD-induced arthritis which resulted in discontinuing treatment after 12 days. One
297 patient experienced nausea and discontinued at 3 months and another patient experienced
298 malaise and discontinued at 5 months. Treatment was interrupted due to inner stigma and renal
299 dysfunction in two patients at one month and two months, respectively.

300

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

306

307 **DISCUSSION**

308 With an increasing ageing population, Oral and Maxillofacial surgeons may see a greater
309 proportion of patients exposed to antiresorptive medications²⁷. These patients may present
310 with multiple medical comorbidities and polypharmacy that may complicate the presentation
311 and treatment options and render aggressive surgical treatment an unsuitable option.

312

313 MRONJ is a complex disease process that can adversely affect quality of life^{28,29}. It has a poorly
314 understood pathophysiology^{1,2} with multiple hypotheses postulated to understand the
315 mechanism of this disease affecting the jaw bones^{30,31}. Theories include altered bone
316 remodelling or over suppression of bone resorption^{30,32}, angiogenesis inhibition^{29,31,30,32,33},
317 constant microtrauma³⁴, suppression of innate or acquired immunity^{34,35}, vitamin D
318 deficiency³⁶, soft tissue bisphosphonate toxicity³⁷, and inflammation or infection^{38,39,40}. Most of
319 this evidence based on animal models suggests the disease process to be multifactorial,
320 contributing to the difficulty in developing effective targeted treatments.

321

322 Current treatment strategies based on AAOMS guidance¹ is stage-specific and ranges from
323 conservative to surgical management, which has shown varying degrees of success in treating
324 MRONJ. Conservative treatment including sequestrectomy and/or debridement has shown
325 partial success with mucosal closure in 50% of cases, whereas more complex surgical
326 treatments (i.e. resection) has shown healing success rate of 80%. However, the latter may not
327 be a feasible option in some patients, particularly those with complex medical status, due to
328 the associated surgical and anaesthetic risks of invasive surgery. This highlights the need for
329 non-invasive therapeutics as an alternative or adjunctive treatment option.

330

331 TPTD was approved by the US Food and Drug Administration agency in 2002 as the first
332 osteoporosis therapy to stimulate bone formation in patients at high risk of bone fracture⁴¹.
333 Abaloparatide, another PTH analogue, has since been approved by the FDA in 2017 also for
334 severe osteoporosis⁴².

335

336 This review highlights the lack of high-quality randomised evidence to assess the use of TPTD
337 for MRONJ treatment, as the literature comprises mostly of case reports and case series (11 out
338 of 17 studies). Whilst a clinical improvement has been demonstrated in a large proportion of
339 patients, the relatively high success rate should be treated with caution since only six out of the
340 91 patients received TPTD in isolation (Table 1). Amongst those receiving TPTD as part of a
341 multi-therapy regime, there were a range of adjunctive treatments provided with ranged. There
342 were also varying definitions and measurements of treatment outcomes, making it difficult to
343 ascertain the efficacy of TPTD and whether the reported clinical improvements in MRONJ were
344 related to TPTD alone or in combination with the other adjunctive treatments. Furthermore,
345 twelve studies failed to report follow-up and in those which did, the follow-up period varied
346 between 6 and 24 months. This makes it difficult to measure the long-term treatment outcomes
347 and extent of adverse drug effects or complications.

348

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

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

357

358 The FDA⁴³ have reported multiple adverse side-effects associated with TPTD use. This review
359 has shown effects including arthralgia, malaise, nausea, vomiting, renal impairment, and
360 psychological problems in 8.5% of patients, which resulted in either discontinuation or
361 interruption of treatment. The FDA⁴³ have highlighted certain groups of patients in which TPTD
362 is contraindicated:

363

- 364 • Bone metastases and skeletal malignancies
- 365 • Metabolic bone conditions
- 366 • Hypercalcemia and Hypercalcaemic Disorders
- 367 • Urolithiasis or Pre-existing Hypercalciuria
- 368 • Orthostatic Hypotension
- 369 • Drug Interactions (Digoxin)
- 370 • Hypersensitivity

371

372 In addition to the above, patients at risk of developing malignant bone tumours (Paget's disease
373 of bone, paediatric and young adult patients with open epiphyses, and patients with prior
374 external beam or implant radiation involving the skeleton) should be treated with extreme
375 caution due to the risk of developing osteosarcoma which has been associated with high
376 exposure to TPTD. As this risk is dose and duration dependent, the FDA do not recommend the
377 use of TPTD for longer than 24 months⁴³. The findings from studies in this review showed that
378 duration of TPTD treatment varied between 0.3 to 26 months due to certain factors including
379 differences in study design, financial implications, adverse side-effects and early resolution of

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

382

383 TPTD treatment is under strict prescribing regulations under the UK's NHS presumably due to
384 the side effect profile and concerns related to risk of malignancy. It is also associated with a
385 high financial cost⁴⁴ which should be take into consideration.

386

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

396

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400

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403

404

405

406

407

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