NHS England

Evidence Review:

Teriparatide for the treatment of osteogenesis imperfecta (Adults)

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Prepared by	Turnkey Clinical Evidence Review Team on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

Osteogenesis imperfecta (OI) is a group of genetic disorders that mainly affect the bones causing weakness of the skeleton leading to easy fractures.

Teriparatide stimulates bone formation, and has been shown to reduce fracture risk in osteoporosis. All the other established treatments for osteogenesis imperfecta work by inhibition of bone resorption. Teriparatide has been proposed as a treatment to improve bone density and reduce the risk of fracture in patients with increased bone turnover, as an alternative to conventional treatments (such as bisphosphonates).

2. Summary of results

Summary

Osteogenesis Imperfecta (OI) is a rare genetic disease characterised by increased bone fragility resulting in frequent fractures and deformities. OI has been classified into eight types (I, II, III, IV, V, VI, VII, and VIII) based on clinical presentation and radiographic findings. This classification system can be helpful in providing information about prognosis and management for a given individual. Type I is the mildest, accounting for around 50% of the total OI population. It is characterised by mild bone fragility, relatively few fractures, and minimal limb deformities. Type II and III are the most severe forms of the disease whilst Type IV varies between mild to severe presentation.

Bisphosphonates (BPs) are antiresorptive compounds widely used to treat patients with OI and are considered the prevailing standard of care for moderate to severe forms of the disease. Teriparatide (synthetic form of human parathyroid hormone) is a bone anabolic therapy that is used selectively in management of osteoporosis.

The review of current evidence for teriparatide was undertaken to:
• Determine whether it is a clinically effective treatment in adults with osteogenesis imperfecta (OI) compared to conventional therapies
• Assess whether the drug is more effective than conventional therapies in achieving critical and important patient outcomes
• Establish whether the drug is more effective as a first line treatment than as a second line treatment
• Determine the drug's cost effectiveness and safety in treating adults with OI

The literature on this topic was sparse with systematic search identifying only three relevant studies. These include one randomised control trial funded by Eli Lilly, one case series and a single case report. None of the studies directly compared the clinical or cost effectiveness of teriparatide with other conventional therapies for OI. The randomised control trial evaluated the clinical effectiveness of teriparatide compared to a placebo group. The prospective case series described the effects of teriparatide on bone turnover markers in thirteen postmenopausal women with Type I OI. The case report was not included in this summary as it reports on changes in bone turnover markers and bone fracture healing in a single patient on teriparatide.

In summary, the current limited evidence from one RCT and one small retrospective study indicates that teriparatide increases bone density and bone strength in adults with mild forms of OI (Type I). It is associated with good response in P1NP and other markers of bone turnover, particularly for Type I OI only. There is inconclusive and very low level evidence on reduction in fracture rates by teriparatide. No serious side-effects have been reported in the patient population subset included in the studies. There is currently no evidence on comparative clinical or cost effectiveness of teriparatide with other conventional therapies for OI. Due to lack of comparative data, this review is unable to establish whether teriparatide is more effective as first or second line treatment.

Summary of the evidence

A double-blind, randomised, placebo control trial to determine the clinical effectiveness of teriparatide in adults over 18 months of treatment was undertaken to determine the baseline change in the lumbar spinal areal bone mineral density (aBMD) between the treatment group and placebo group (Orwoll et al., 2014). The study concluded that at 18 months, change in aBMD in the teriparatide group was higher than the placebo group by:

- 5% at the total hip ($p < 0.001$)
- 3.3% at the lumbar spine ($p < 0.05$)
- 3.7% at the femoral neck (no statistical difference - p value not specifically stated)

A test of 3-way interaction (treatment group, time and OI type) showed that the trend in treatment response in aBMD over the course of the study was significantly different in patients with Type I OI compared to Type III/IV patients. Type I patients had significant treatment effects at 12 and 18 months ($p=0.04$ and $p=0.002$, respectively) while those with Type III/IV had no response at any time point. There were a total of 26 Type III/IV patients (14 type III and 12 type IV) in this sub group compared to 51 in Type 1 subgroup. This unequal distribution of subjects within subgroups could potentially impact adequate assessment of treatment effect.

Gatti et al. (2013) evaluated the clinical effectiveness of teriparatide treatment in 13 adult patients with Type I OI over an 18-month period. The study found BMD at the lumbar spine increased significantly throughout treatment by up to 3.5% ($p=0.001$). However, unlike Orwoll et al (2014), Gatti et al. (2013) did not find any significant changes in hip BMD (no p value specifically stated).

Eleven patients in the teriparatide treatment group (29%) and 14 in the placebo group (36%) reported fractures (odds ratio, 0.73; 95% CI, 0.28-1.90) during the randomised control trial (Orwoll et al., 2014). During the Gatti et al. (2013) study, none of the patients reported new fractures during the treatment. However, the duration of follow-up in this study. However, both studies had limited follow-up period (18 months) and were not powered to adequately assess the effect of teriparatide on fracture risk. Given the small number of patients, the extent to which these studies represents the actual patient population, remains a concern which was not adequately addressed in either of the trial methodologies.

Bone turnover markers, such as N-propeptide of type I collagen (P1NP), bone alkaline phosphatase (bAP), are associated with bone formation whilst C-terminal telopeptide of type I collagen (serum CTX) is associated with bone resorption. The randomised trial found that P1NP levels increased rapidly with a maximum at month 12 (134.6%) in intervention group which was significantly higher than the placebo group ($p < 0.001$). Patients with Type I OI had more significant increases in serum P1NP ($p < 0.001$) than those with Types III and IV (Orwoll et al., 2014). Gatti et al. (2013) reported significant ($p < 0.005$) increase in P1NP, bAP and serum CTX in response to teriparatide treatment. The study also found positive correlation ($p < 0.01$) between elevation of bone formation markers (P1NP and bAP) with percentage changes in DKK1 which is an inhibitor of the wnt/B-cantenin pathway for bone formation.

Orwoll et al. (2014) found that teriparatide was well-tolerated and there were no differences in adverse events observed between the treatment and placebo groups. Gatti et al. 2013 reported over half (N = 7) reported mild nausea after injection, however this did not lead to treatment discontinuation.

In conclusion, at biochemical level, teriparatide is associated with good response in P1NP and other bone turnover markers, particularly for patients with less severe Type I OI. This response is reflected in the radiological effectiveness where teriparatide appears to increase lumbar bone density and bone strength in adults with the mild form of OI (Type I) and not in patients with Type III/IV OI. In the absence of well-designed studies to assess the actual clinically meaningful impact of this treatment such as reduction in fracture risk in target population, the clinical effectiveness of teriparatide remains inconclusive. There is currently no evidence regarding clinical or cost effectiveness of teriparatide in comparison to other conventional therapies for OI. Due to lack of comparative data, this review is also unable to establish whether teriparatide is more effective as first or second line treatment. The drug appears to be well tolerated, in the small subset of patients included in the studies.

3. Research questions

1. Is teriparatide a clinically effective treatment in adults with osteogenesis imperfecta who remain inadequately controlled with, or have contraindications to, conventional therapy of antiresorptive therapies (including bisphosphonate and denosumab)?

2. Is teriparatide more effective in treating osteogenesis imperfecta than the comparison therapies (including bisphosphonate and denosumab) in achieving the critical and important patient outcomes (including bone density, bone formation, bone resorption, fracture reduction including atypical fractures, and quality of life)?

3. To improve bone density, improve bone formation and reduce fractures when treating osteogenesis imperfecta, is teriparatide as a first line treatment more effective than teriparatide as a second line treatment?

4. Is teriparatide as cost effective as comparison therapies (including bisphosphonate and denosumab)?

5. Is teriparatide a safe treatment for adults with osteogenesis imperfecta?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and			Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complicat-ions noted	Benefits noted	Comments
1+	RCT	79	1) Subcutaneous 20 ug/d recombinant human parathyroid hormone (teriparatide)	Clinical effectiveness of the intervention	1) % change in lumbar spine areal bone mineral density (aBMD)	1) At 18 months, change in aBMD in the teriparatide group was higher than in the placebo group by: i) 5% at the total hip (P < 0.001) ii) 3.3% at the lumbar spine (P < 0.05) iii) 3.7% at the femoral neck (no statistical difference - P value not specifically stated) 2) A test of 3-way interaction (treatment group, time and OI type) showed that the trend in treatment response in lumbar spine aBMD over the course of the study was significantly different in patients with Type I vs Type III/IV patients (P = 0.98) 3) Interaction analysis demonstrated that Type I patients had significant treatment effects at 12 and 18 months (P = 0.04 and P = 0.002 respectively) while those with Type III/IV had no response at any time point	1) % change in bone remodelling markers 2) % change in vertebral volumetric BMD (vBMD) 3) Mineral metabolism 5) Fractures 4) Safety	1) % change in bone remodelling markers a) In a placebo-treated group, levels of all bone remodelling markers remained essentially stable. With teriparatide treatment, P1NP levels increased rapidly with a maximum at month 12 (134.6%) and declined somewhat afterwards but remained significantly higher than the placebo (P < 0.001) b) Patients with Type I OI had more significant increases in serum P1NP (P < 0.001) than those with Types III and IV (P = 0.87) 2) % change in volumetric BMD (vBMD) a) vBMD increased considerably in the teriparatide-treated patients (18.3%) and decreased in placebo group (-4.7%) (p < 0.05) 3) Mineral metabolism a) Parathyroid hormone concentrations declined by 30% at 1 and 3 months in the teriparatide-treated group but returned to levels similar to placebo group. No P values specifically stated b) Serum calcium levels were stable and no episodes of hypercalcemia were observed. Mean 24-hour urine calcium excretion remained stable with placebo but increased with teriparatide-treated patients 4) Fractures a) 11 patients in the teriparatide treatment group (29%) and 14 in the placebo group (36%) reported fractures during the study (odds ratio, 0.73; 95% CI, 0.28-1.90) 5) Safety a) Teriparatide was well-tolerated. No differences in adverse events observed between treatment groups	Orwoll, Eric S.; Shapiro, Jay; Veith, Sandra; Wang, Ying; Lapidus, Jodi; Vanek, Chaim; Reeder, Jan L.; Keaveny, Tony M.; Lee, David C.; Mullins, Mary A.; Nagamani, Sandesh C. S.; Lee, Brendan. Evaluation of teriparatide treatment in adults with osteogenesis imperfecta. J. Clin. Invest.. 2014.	Not stated	Teriparatide might be of more clinical utility in patients with less severe OI (Type I)	At the time this study was undertaken, it was a randomised, double-blind placebo-controlled treatment trial in adults with OI. There were a total of 26 Type III/IV patients (14 type III and 12 type IV) in this sub group compared to 51 in Type 1 subgroup. This could impact the treatment effect between the two groups. The trial was not powered to adequately assess the effect of teriparatide on fracture risk. Overall, this was deemed to be a good quality study as it was both randomised and double-blinded and 18-month follow-up. While there were sufficient number of patients with Type I OI to confidently detect a meaningful change in BMD, the number of patients with Type III/IV was limited. The trial was not powered to adequately assess the effect of teriparatide on fracture risk.

4	Case report	1	Potential fracture healing of teriparatide	Clinical effectiveness of the intervention	1) Fracture healing effect through change in bone mineral density (BMD)	1) BMD a) One year after starting treatment with teriparatide, a 3.2% improvement in the lumbar spine BMD was observed b) After 2 years of treatment, BMD in the lumbar region increased by 16.8% (BMD of 0.717 g/cm^2 and T-score of -3.3) c) Afterwards, zoledronic acid 5 mg/year was reinstated and no further fractures occurred in patient as it was thought that the risk of new fractures due to OI and osteoporosis was very high Authors concluded that teriparatide was an important factor in successful healing of the patient	None	None	Holm, Jakob; Eiken, Pia; Hyldstrup, Lars; Jensen, Jens-Erik Beck. Atypical femoral fracture in an osteogenesis imperfecta patient successfully treated with teriparatide. Endocr Pract. 2014.	None	None	This case report on one patient and therefore not likely to be representative of the patient population and other limitations of observational case reports apply. This study was not independent as the authors are affiliated with Eli Lilly, the developer and manufacturer of the drug.

3	Case series	13	Teriparatide (pens administered bi-monthly, but dosage not stated); patients were treated for 18 months	Clinical effectiveness of the intervention	1) Bone mineral density (BMD)	1) Changes in BMD a) BMD at the lumbar spine increased significantly throughout the treatment; up 3.5% (P = 0.001) b) No significant changes noted in the hip BMD (no P value specifically stated)	1) Biochemical parameters - markers used to measure bone formation and resorption 2) Fractures 3) Side effects	1) Biochemical parameters - bone turnover markers were measured by the IDS-ISYS multi-discipline automated analyser a) Values for all biochemical parameters were detectable i) N-propeptide of type I collagen (P1NP), bone alkaline phosphatase (bAP) and C-terminal telopeptide of type I collagen (serum CTX) rose significantly (p < 0.005 versus baseline) (P1NP and bAP are associated with bone formation whilst CTX is associated with bone resorption) ii) Two- and four-fold increases bAP and P1NP respectively suggest an excellent response to teriparatide b) Wnt/B-catenin pathways - measured by ELISA Wnt pathway is a major promoter of bone formation and opposed by various intracellular and secreted factors such as serum clerostin and DKK1 i) Non-significant changes observed for serum clerostin levels (p value not specifically stated) whilst DKK1 rose gradually and significantly compared to the baseline ii) Elevation of bone formation markers (P1NP and bAP) was positively correlated with percentage changes in DKK1 (P < 0.01) 2) Fractures a) None of the patients reported new fractures during the treatment 3) Side Effects a) Over half (7 patients) reported mild nausea after injection - did not lead to treatment discontinuation *Overall, study concluded that treatment of Type I OI with teriparatide is associated with a remarkable response in P1NP and other markers of bone turnover	Gatti, Davide; Rossini, Maurizio; Viapiana, Ombretta; Povino, Maria Rosaria; Liuzza, Saverio; Fracassi, Elena; Idolazzi, Luca; Adami, Silvano. Teriparatide treatment in adult patients with osteogenesis imperfecta type I. Calcif. Tissue Int.. 2013.	Not Stated	Results of this study open a new option in patients with Type I OI in whom positive effects of bisphosphonate treatment appear to be clinically optimal	The study illustrated that postmenopausal women with type I OI respond to teriparatide in terms of bone turnover markers. The major limitation of this study is the lack of control group and the small size of the study (only 13).

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	None
Updated search terms - Population	Osteogenesis imperfecta OR OI
Updated search terms - Intervention	Teriparatide OR Bisphosphonates OR Bisphosphonate OR Denosumab OR rhPTH 1-84
Updated search terms - Comparator	Antiresorptive OR Anti-resorptive OR Placebo
Updated search terms - Outcome	Bone density OR Bone mineral density OR Bone formation OR Bone resorption OR Fracture reduction OR Atypical fracture reduction OR Quality of life OR Cost effectiveness OR Adverse effects OR Safe

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	None
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist) 7. Narrative / non-systematic reviews (relevant referenced studies to be included)
	Specific exclusion criteria
	None