NHS England

Clinical Commissioning Policy Proposition:

Teriparatide for the treatment of osteogenesis imperfecta (Adults)

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Clinical Commissioning Policy Proposition: Teriparatide for the treatment of osteogenesis imperfecta (Adults)

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Plain Language Summary

Osteogenesis imperfecta (OI) is a group of genetic disorders that mainly affect the bones causing weakness of the skeleton. This leads to bones breaking easily, which gives the disorder its alternative name of "brittle bone disease". The risk of fractures is high in childhood and although this declines following puberty, the risk of fracture still remains high compared to individuals with normal bones.

Teriparatide is a drug which stimulates bone formation, and has been shown to reduce fracture risk in osteoporosis (NICE Technology Appraisal Guidance TA161, 2008).

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of teriparatide for treatment of osteogenesis imperfecta in adults.

1. Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission teriparatide for adults with osteogenesis imperfecta.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether teriparatide as a treatment for adults with osteogenesis imperfecta will not be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

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).

3. Definitions

Osteogenesis imperfecta (OI) is a group of genetic disorders that mainly affect the bones. It is an inherited disorder in which there is an abnormality of production of type I collagen. This causes weakness of the skeleton, leading to easy fracture and the alternative name of "brittle bone disease". The majority of affected individuals will suffer from a significant fracture burden during infancy and childhood; the fracture risk declines following puberty but still remains significantly raised compared to individuals with normal bones.

Patients with osteogenesis imperfecta are at significantly increased risk of fracture, suffer skeletal pain and in some cases disability as a result of previous fractures. In addition to bone abnormalities, patients with osteogenesis imperfecta often experience hypermobility syndrome, cardiac abnormalities, dental problems, and deafness.

The characteristic features of OI vary greatly from person to person, even among people with the same type of OI, and even within the same family. Not all characteristics are evident in each case. The majority of cases of OI (possibly 85-90%) are caused by a dominant mutation in a gene coding for type I collagen (Types I, II, III, and IV). Types VII and VIII are newly identified forms that are inherited in a recessive manner. The genes causing these two types have been identified. Types V and VI do not have a type 1 collagen mutation, but the genes causing them have not yet been identified.

Although the types of OI are clearly defined, the treatment approach for Type I and Type IV are similar.

Teriparatide is a recombinant human version of the active portion of the parathyroid hormone molecule and, as an anabolic agent, it stimulates new formation of bone and increases resistance to fracture. Unlike any of the other treatments for osteogenesis imperfecta, teriparatide works by stimulation of bone formation. All the other established treatments work by inhibition of bone resorption.

4. Aim and objectives

This policy proposition aims to define NHS England's commissioning position on teriparatide as part of the treatment pathway for adult patients with osteogenesis imperfecta.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with osteogenesis imperfecta.

5. Epidemiology and needs assessment

It is estimated that osteogenesis imperfecta is present in one in every 15,000 people (Brittle Bone Society, 2015), with approximately two thirds of affected people having the mildest form of the condition (type I osteogenesis imperfecta).

In 2013/14, there were nine individual funding requests (IFR) for teriparatide for osteogenesis imperfecta.

6. Evidence base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of teriparatide for osteogenesis imperfecta (OI) in adult patients.

There is evidence that teriparatide stimulates bone formation, and has been shown to reduce fracture risk in osteoporosis (NICE Technology Appraisal Guidance TA161, 2008).

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.

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.

7. Documents which have informed this policy proposition

NICE Technology Appraisal Guidance: TA161 Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, 2008

8. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).