The Effect of Treatment with Teriparatide and Zoledronic acid in Patients with Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is an autosomal dominant inherited disease characterized by varying degrees of fragile bones and bone deformities, as well as other signs of defect connective tissue. These characteristics originates from mutations in one of the two genes encoding the collagen type 1 molecules (*COL1A1* on chromosome 17q21.31-q22 and *COL1A2* on chromosome 7q22.1). Mutations can be found in more than 90 % of the patients in different regions of the two genes. OI is a rare disease with a prevalence around 11/100.000 [1] and it has traditionally been divided into four subtypes based on clinical and paraclinical parameters [1; 2].

Several studies investigating the treatment of OI with bisphosphonates in children has demonstrated a positive effect on bone mineral density (BMD) and a reduction in fractures [1]. Only a few studies have investigated the effect of treatment of adult patients with OI with bisphosphonates [3]. These studies have demonstrated a positive effect on BMD, but no effect on fracture risk, probably because of insufficient statistical power [4].

Teriparatide (human PTH1-34) is a bone anabolic treatment, approved for the treatment of severe osteoporosis in postmenopausal women and men with glucocorticoid induced osteoporosis [5]. PTH is in clinical trials used in 36 months treating adults above the age of 22 years and has in one trial been investigated for the treatment of OI [6]. In patients with severe osteoporosis, treatment with PTH demonstrated larger increases in BMD compared with treatment with bisphosphonates. It would therefore be interesting to investigate the effects of PTH in patients with OI.

Adults with OI are routinely treated with bisphosphonates, despite this lack of evidence on fracture prevention. OI patients are generally treated in the same way as age related osteoporosis, despite significant differences in symptomatology, pathogenesis, and expected length of treatment in the two conditions.

The current study was initiated to investigate the effect of treatment of a well characterized cohort of adult OI patients with bisphosphonate (zoledronic acid), parathyroid hormone (PTH) or placebo on bone mass, fracture risk and quality of life with the aim to gain knowledge on the fracture preventive treatment of OI.

The study was designed as a double blind, placebo-controlled trial with an aim to include 80 adults with mild or moderate OI.

Participants received either zoledronic acid yearly for three years, daily teriparatide injections for two years followed by one year of zoledronic acid or placebo for three years. All participants were supplemented with 800 mg calcium and 1600 IU vitamin D daily for three years.

Following the inclusion of the first nine patients Eli Lilly withdrew their support to the study of teriparatide and placebo pens. After thorough consideration sponsor and investigators supported by the Danish Medicines Agency decided to stop further inclusion and unblind the participating patients. All participants were followed for the remaining study period. Eli Lilly agreed to provide teriparatide pens to the patients who were randomized to this treatment for the remaining time of the study. One patient withdrew consent because of this event, one patient was lost to follow up due to non-compliance. Seven patients completed the study.

Nine patients were randomized, six male and three female patients with a mean age of 44 years. Six had OI type I, and three were classified as OI type IV. Seven patients completed the study, five male and two females, mean age 46 years. Five had OI type one, two had OI type IV.

Of the three patients who received teriparatide, two had OI type I, one had OI type IV. The two patients with OI type I had an increase in lumbar spine bone mineral density (BMDls) of 8% over the three years whereas the patient with OI type IV had an insignificant loss in BMDls over the three years.

Of the three patient who received zoledronic acid, two had OI type I, one had OI type IV. Two patients (one OI type I, one OI type IV) had significant increases in BMDls, whereas one (OI type I) showed an insignificant gain in BMDls.

In total hip bone mineral density (BMDth) all patients remained unchanged over the three years expect from one patient with OI type I who had received teriparatide, in this patient BMDth decreased with 5%.

The treatments were in general well tolerated, there was no difference between the different treatment modalities and the occurrence of serious adverse events. None of the serious adverse events were considered related to the study drug.

References

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