# COMPARISON OF DENOSUMAB TO ZOLEDRONIC ACID EFFECTS UPON OSTEOPOROSIS OF CHILDREN WITH AUTOSOMAL RECESSIVE TYPES OF OSTEOGENESIS IMPERFECTA

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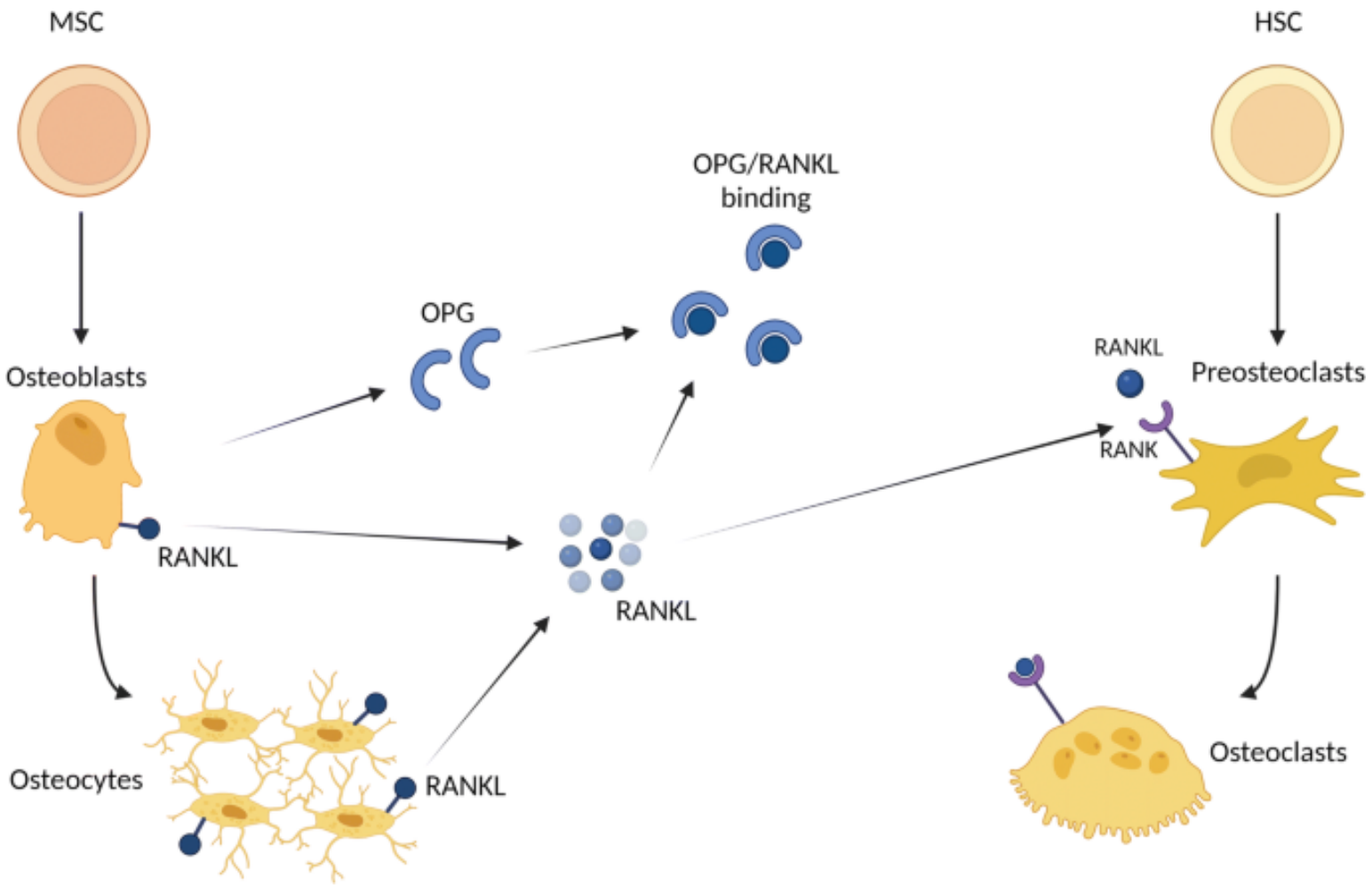
Denosumab as a RANK ligand antibody inhibiting osteoclast maturation has been approved for osteoporosis treatment in adults.

In fact not enough data about its efficacy and safety in children or in OI are available.

We investigated efficacy and safety aspects after a 24-month treatment course in a phase-II-trial

- Denosumab is a fully human monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (RANKL), the principal regulator of osteoclastic bone resorption. By binding and neutralizing RANKL, it is a potent inhibitor of osteoclast differentiation, activity, and survival.
- Denosumab reduces the risk of vertebral fractures, nonvertebral fractures, and hip fractures with a generally favorable safety profile. Larger increases in total hip BMD are associated with greater reductions in the risk of new or worsening vertebral fractures.
- Atypical femur fractures and osteonecrosis of the jaw have been reported in patients treated with denosumab.
- There is no evidence that denosumab impairs fracture healing.
- BMD increases with denosumab are greater than with bisphosphonates.
- Discontinuation of denosumab is followed by a rapid decrease in BMD, a rise in bone turnover marker levels to above baseline, and a return of vertebral fracture risk to baseline with an apparent increase in the risk of multiple vertebral fractures.
- Patients who stop denosumab should be continued on treatment with another antiresorptive agent (bisphosphonates, anabolic steroids, GH, etc.)




ANKL/RANK/OPG pathway. RANKL is produced by cells of the osteoblast lineage, including matrix-embedded osteocytes. Membrane bound RANKL is cleaved by proteases to form soluble RANKL. OPG is predominantly secreted by osteoblasts to bind to RANKL to suppress its activity and regulate osteoclastic bone resorption. RANKL binding to its receptor RANK promotes the differentiation of mature osteoclasts which are capable of attaching to and resorbing bone. Abbreviations: RANKL, receptor activator of nuclear factor kappa beta ligand, OPG, osteoprotegerin, MSC, mesenchymal stem cells, HSC, hematopoietic stem cells

**Objective:** The aim of this study was to compare the effect of subcutaneous denosumab with that of IV zoledronic acid upon osteoporosis of children with autosomal recessive type of osteogenesis imperfecta. Secondarily, to compare their safety and effects on their agility.

**Design:** This was a prospective, blinded-randomized controlled clinical trial.

**Setting:** The study was performed at the outpatient pediatric endocrine clinic of Genomic Research Center of Shahid Beheshti University of medical Sciences and pediatric ward of Loghman Hakim General Hospital in Tehran for 4 years.

**Patients:** 26 children (3.4-7.6 years old) with autosomal recessive types of OI, divided in two equal member-groups were studied for two years.

**Intervention:** They were treated with denosumab s.c. (Prolia®) 1mg/kg/dose  or zoledronic acid i.v. (Zometa®) 0.025mg/kg/dose for 2-5y/o and 0.025 - 0.05mg/kg/dose for >5y/o in an interval of 16 weeks for 2 years.

- Single center 4 year trial included 26 patients in the age of 3.4-7.6 years with OI (confirmed mutations by WES/NGS, Sanger and segregation studies divided in two equal member-groups, studies either with denosumab or zoledronic acid for two years.
- denosumab s.c. (Prolia® 60 mg vial) 1mg/kg/dose or zoledronic acid i.v. (Zometa® 4mg/5ml vial) 0.025mg/kg/dose for 2-5y/o and 0.025 - 0.05mg/kg/dose
- Measurement of aBMD at baseline and after 12 and 24 months in each case
- Frequent serum calcium, phosphate, vitamin D3, creatinine, urinary calcium, bone turn-over markers, and *urinary desoxypiridinoline* measurements for safety and efficacy analyses
- Measurement of motor function at baseline, month 12, month 24

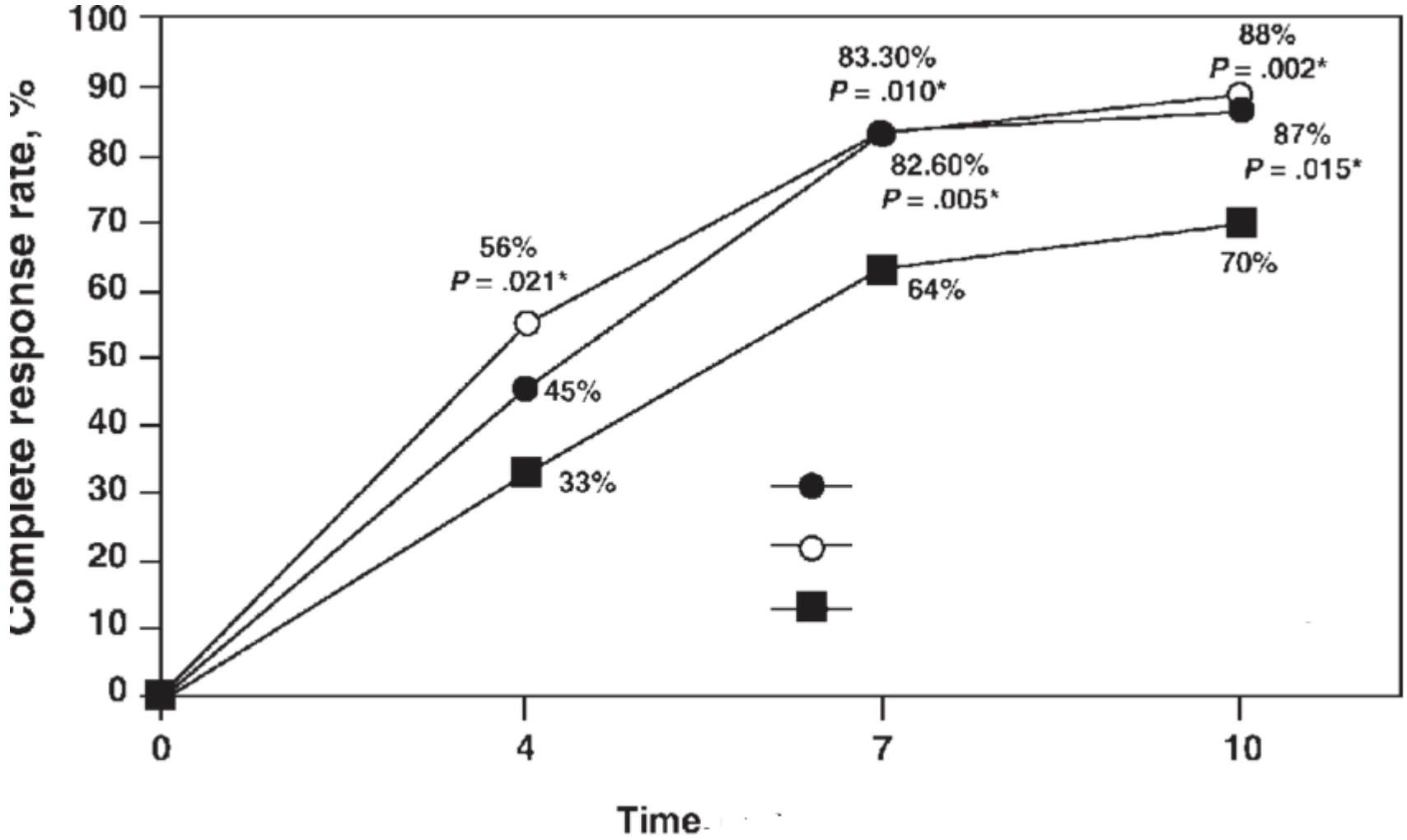
**Main outcome majors:** The main outcome measures was change of lumbar areal bone mineral density (aBMD) using dual energy x-ray absorptiometry after 24 months with four- month intervals of denosumab injections in children with OI.

**Results:**

- Denosumab is effective to reduce bone resorption and increase bone mineral density in children with autosomal recessive OI.
- Denosumab increases vertebral areal bone mineral density and avoids new vertebral compression fractures in OI children.
- Instant Vertebral Assessment (IVA), a rapid (10-second), low-dose x-ray scan of the spine, taken in combination with standard aBMD showed better improvement in denosumab group.

- Denosumab suppresses bone resorption over 3-6 months, much faster than that of the zoledronate group.
- Denosumab seems to be safe in the short-term application at least if a close monitoring and substitution of calcium and vitamin D3 are guaranteed.
- Longer observation and higher sample size studies are needed to compare the cost-effectiveness of these two treatment strategies.

- After two years treatment with denosumab, no severe side effects were observed.
- A slight hypocalcemia with no clinical significance was seen in most children of denosumab group.
- DXA assessment showed a mean increase of lumbar spine Z-scores of and total body less head Z-scores significantly.
- Mobility and agility improved in both groups equally.


Complete response rate, %
100
90
80
70
60
50
40
30
20
10
0
0
4
7
10
Time
83.30%
P = .010*
88%
P = .002*
87%
P = .015*
82.60%
P = .005*
56%
P = .021*
45%
33%
64%
70%