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Osteogenesis imperfecta – a pilot trial on treatment with the RANKL-antibody denosumab

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Conclusions

- Denosumab increases vertebral areal bone mineral density and avoids new vertebral compression fractures in OI children.
- Denosumab leads to severe and repetitive alterations of the calcium homeostasis.
- Denosumab supresses bone resorption over 10-12 weeks.
- Denosumab seems to be safe in a one-year treatment course if a sufficient calcium and vitamin D substitution is guaranteed.
- Limitations: only short term data in 10 children are available yet; phase 3 trials are needed to assess risk benefit ratio detailed.

Background and Objective

Osteogenesis imperfecta (OI) is a rare disease leading to bone fragility. Many genes are known to perturb formation and processing of collagen leading to a disturbed function of osteoblasts and osteoclasts. Denosumab as a RANK ligand antibody inhibiting osteoclast maturation has been approved for osteoporosis treatment in adults. Almost no data about its use in children or in OI are available. We investigated efficacy and safety aspects after a 48 week treatment course in a phase-II-trial.

Primary objective of the study: Change of lumbar areal bone mineral density (aBMD) using dual energy x-ray absorptiometry after 48 weeks and four denosumab injections in children with OI.

Patients and Methods

- Single center trial included 10 patients in the age of 5-11 years with OI (confirmed mutations in COL1A1/A2) after at least 2 years of bisphosphonate treatment.
- Denosumab treatment s.c. (Prolia®, Amgen Inc., Thousand Oaks, CA) 1mg per kg body weight four times in an interval of 12 weeks (+/-7days).
- Measurement of aBMD at baseline and after 48 weeks
- Frequent serum calcium and urinary desoxypiridinoline measurements for safety and efficacy analyses
- Measurement of motor function at baseline, week 24, week 48

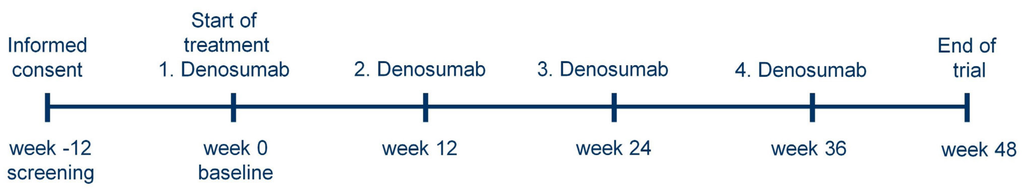

Fig. 1. Study design

Results I

Participants n	10
Male n (%)	7 (70)
Age Mean [years] (range)	7.00 (5.02 – 10.96)
Height Mean [cm] (range) Height Z-Scores ± SD	105.0 (66.0 – 134.0) -4.64 ± 3.72
Weight Mean [kg] (range)	19.27 (7.8 – 27.3)
BMI Mean [kg/m2] (SEM)	17.6 (13.1 – 33.0)
OI Type 1/4 n (%) Able to walk (GMFM item 69) n (%)	8 (80) 7 (70)
OI Type 3 n (%) Able to walk (GMFM item 69) n (%)	2 (20) 0 (0)

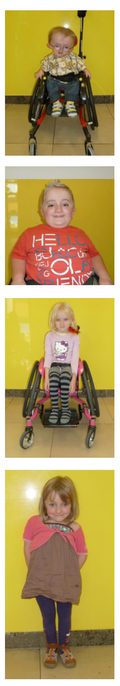

Table 1. Characteristics of study population at baseline

Results II

- Denosumab increases lumbar aBMD in the mean by 19%
- Short term side effects: hypocalcemia after application, rebound hypercalcemia after 10-12 weeks; general joint pain in 2 children
- Mean Height (±SD) z-scores increased from -4.64±3.71 to -4.62±3.58; p=0.6953) -> No growth arrest!
- Motor function assessment showed no further deterioration

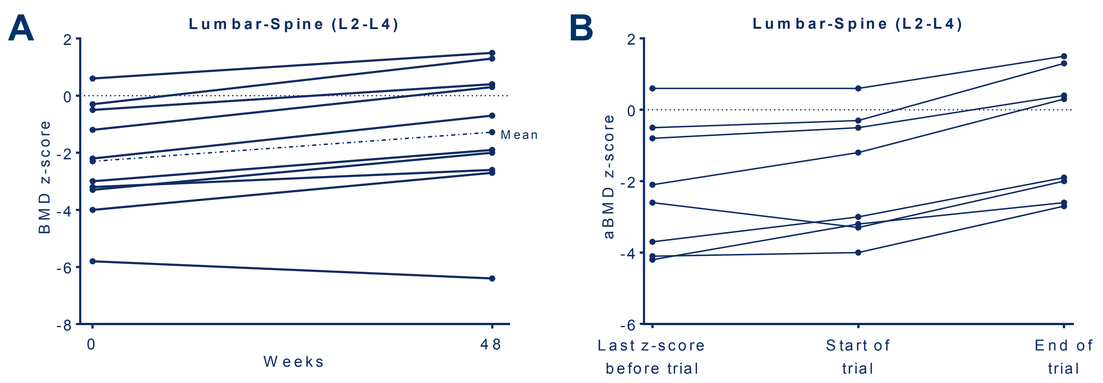

Fig. 2A/B individual courses of lumbar aBMD z-scores: (A) Mean relative change from baseline to week 48: + 19 % (95%-CI: 7-31%); 2.23±2.03 to-1.27±2.37 (p=0.0006) ; (B) mean z-score difference±SD before trial period= +0.3125±0.512 vs. +1.15±0.316 within the trial period; p= 0.0156; n=8

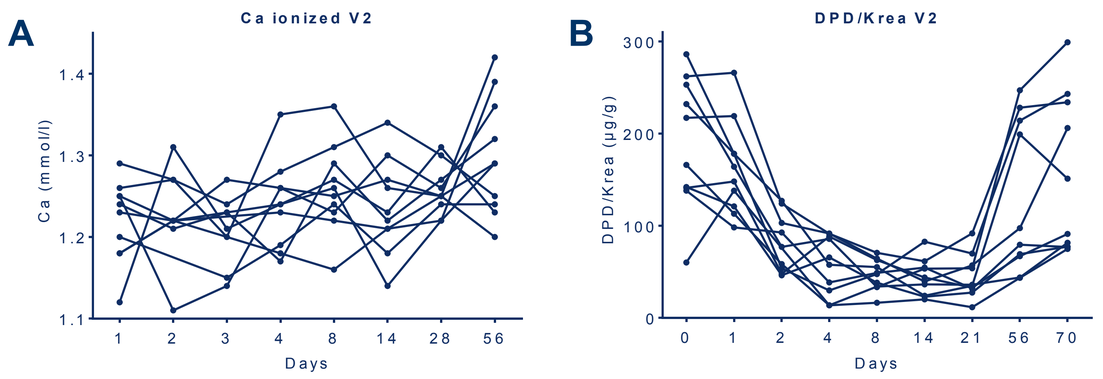

Fig. 3A/B individual courses of ionized calcium levels (A) and urinary DPD excretion as osteoclastic activity marker (B) after the first denosumab injection

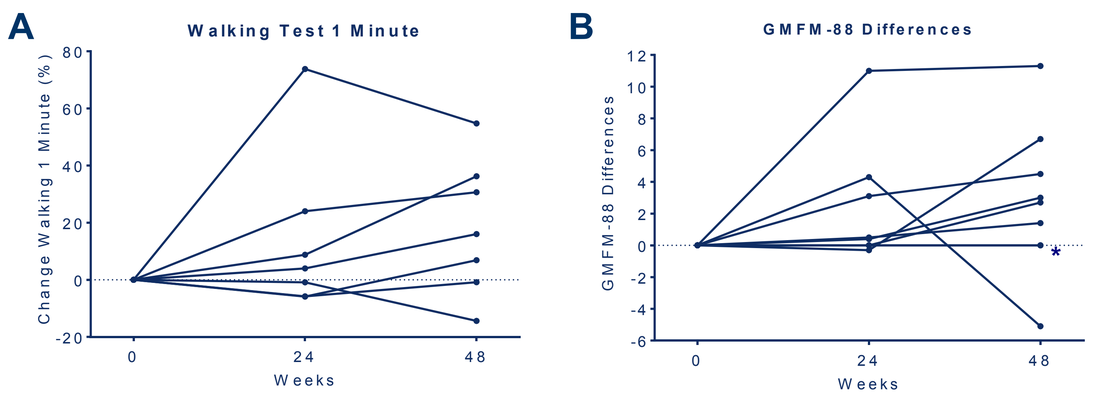

Fig. 4A/B individual relative percentual changes of 1-min-walking distances (A) mean increase of 18.47 % (absolute change from 86.6 m±26.83 to 97.6±18.0 m; n= 7; p=0.141) and absolute percentual change of GMFM-88 (B) 77.58±31.64% to 80.30±31.06 %; p=0.156)

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