

## **LB1** IDENTIFICATION OF RANK MUTATIONS IN PATIENTS WITH OSTEOCLAST-POOR AUTOSOMAL RECESSIVE OSTEOPETROSIS

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### Background

Autosomal recessive osteopetrosis (ARO) is a heterogeneous genetic disorder characterized by bone sclerosis, fractures, pancytopenia and neurological defects. So far, five genes have been described as responsible for this rare bone defect. Most ARO patients have normal or elevated osteoclast number (osteoclast-rich ARO), although cases in which osteoclasts are absent (osteoclast-poor ARO) also exist. Recently our group has found that a subset of osteoclast-poor ARO is caused by mutations in RANKL, the master gene driving osteoclast differentiation along the RANKL-RANK axis. Here we have further dissected the molecular basis of osteoclast-poor ARO, focusing on the involvement of RANK.

### Methods

In a large series of ARO patients we selected for analysis a consanguineous family of Turkish descent with two siblings affected by ARO and hypogammaglobulinemia, with no defects in TCIRG1, CLCN7, OSTM1, PLEKHM1 and RANKL genes. Sequencing was performed on PCR amplified DNA segments.

### Results

By analysing genes involved in the RANKL pathway, we identified mutations in the RANK gene in the Turkish family as well as in four other patients from 4 unrelated families. In vitro cultures were carried out to assess osteoclast formation and activity, by culturing peripheral blood monocytes on dentine discs with RANKL + M-CSF. Cells from both Turkish siblings showed a severe impairment of their monocytes to differentiate into osteoclasts, and complete lack of resorptive activity. Furthermore, RANKL-induced activation of p38 in these cells was absent, although TNFalpha-induced p38 activation was normal, suggesting that this mutation severely affects RANK signalling. Immunological analysis revealed hypogammaglobulinemia associated with a low number of immunoglobulin-secreting B cells.

### Conclusion

In conclusion, we have identified a novel clinical entity resulting from RANK mutations, which is characterised by severe ARO associated with an immunoglobulin production defect. Our findings highlight the importance of identifying the genetic cause of osteoclast-poor ARO since these patients, unlike those with RANKL mutations, may benefit from bone marrow transplantation.

Conflict of interest: None declared

**LB2** COMPARISON OF THE EFFECTS OF DENOSUMAB VERSUS  
ALENDRONATE ON BONE MINERAL DENSITY: RESULTS FROM A  
RANDOMIZED BLINDED PHASE 3 TRIAL

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Denosumab is an investigational fully human monoclonal antibody that specifically targets RANKL, a key mediator of osteoclast formation, function, and survival. Results from previous phase 2 and 3 studies showed denosumab treatment consistently increased bone mineral density (BMD) and decreased bone turnover markers. We now report results from a completed phase 3 trial comparing the efficacy and safety of denosumab with alendronate over 12 months in postmenopausal women with low BMD.

Eligible ambulatory postmenopausal women with a T-score  $\leq -2.0$  at the lumbar spine or total hip were randomized 1:1 to receive subcutaneous denosumab injections (60 mg every 6 months [Q6M]) plus oral placebo weekly or oral alendronate weekly (70 mg) plus subcutaneous placebo injections Q6M. All subjects received supplemental calcium and vitamin D. The primary endpoint was the percentage change from baseline in total hip BMD at month 12. Secondary endpoints included percentage change from baseline in BMD at the trochanter, 1/3 radius, lumbar spine, and femoral neck. Safety was also evaluated.

Subjects (n=1189; 594 denosumab; 595 alendronate) had a mean age of 64.4 years and mean lumbar spine T-score of -2.57. At the total hip, denosumab significantly increased BMD compared with alendronate (3.5% vs 2.5%,  $p < 0.0001$ ). Denosumab also significantly increased BMD compared with alendronate at the trochanter (4.5% vs 3.5%), 1/3 radius (1.1% vs 0.6%), lumbar spine (5.3% vs 4.2%), and femoral neck (2.2% vs 1.6%;  $p \leq 0.0003$  at all sites). The safety profiles were similar between denosumab- and alendronate-treated subjects. The incidence and type of adverse events and serious adverse events were balanced. No patients developed neutralizing antibodies to denosumab.

Denosumab, a RANKL inhibitor, demonstrated greater gains in BMD compared with alendronate at all measured skeletal sites. The safety profiles were similar for the treatment groups. Ongoing clinical trials will assess the anti-fracture efficacy of denosumab.

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