FGF23, thereby correcting the renal phosphate leak, improving mineral metabolism and reducing osteomalacia by 50-75% in adults [1]. Whether this results in measurable changes in skeletal mass and microarchitecture is unclear.
Objective: We examined the impact of burosumab on regional bone mineral density (BMD) and trabecular bone scores (TBS) in study subjects involved in two phase III clinical trials of burosumab.
Methods: In these trails subjects received burosumab 1 mg/kg every 4 weeks. Some patients received placebo for the first 6 months of one trial so we considered their month 6 data as their baseline. Most of the patients had been treated at some point in the past with calcitriol and phosphorus. DXA and TBS were obtained at baseline and then after 6, 12 and 18-24 months of drug treatment. Paired t-tests and ANOVA were performed to assess changes in L-spine BMD, Total Hip BMD and TBS.
Results: 25 subjects with XLH (mean age 38.9 years, 56% female) were enrolled in these studies. Paired data were available in 23 subjects at 6 months, 15 subjects at 12 months and 18 subjects at 18-24 months. Compared to baseline, there were significant increases in L-spine BMD at all time points by paired analysis: 6 months (+6.0%, p=<0.0001), 12 months (+6.95%, p=<0.0001), 18-24 months (+6.13%, p=0.0005). Although there was no significant difference in total hip BMD at 6 months when compared to baseline, there were significant increases at 12 months (+6.72%, p=0.0005) and a further increase at 18-24 months (+10.02%, p=0.0029). When all available subjects were analyzed by one-way ANOVA, there was a significant effect of time of treatment on these regional BMD measurements. There was no change in trabecular bone score over the course of treatment.
Conclusion: Treatment with burosumab is associated with a marked improvement in BMD, particularly in the hip. Since the hip is a frequent site of fracture in XLH, the effect of burosumab at this site is of considerable clinical relevance. The lack of an effect on TBS may relate to the fact that this measurement is much less sensitive to therapeutic interventions than BMD assessed by DXA.
References:
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Pediatric Endocrinology

PEDIATRIC SEXUAL DIFFERENTIATION, PUBERTY, AND BONE BIOLOGY

Novel Genetic and Biochemical Findings of DLK1 Deficiency in Children with Central Precocious Puberty - a Collaborative Brazilian-Spanish Study

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SUN-089

Background: Delta-like 1 homolog (DLK1), also known as pre-adipocyte factor 1 (Pref-1), is part of the Notch signaling pathway that controls many developmental processes. Loss-of-function mutations of *DLK1* have been identified in children with central precocious puberty (CPP), as well as in women who had precocious menarche (≤ 9 years) with an unfavorable metabolic profile. **Objective:** To investigate genetic and biochemical aspects of *DLK1* in a cohort of children with CPP. **Patients:** A large cohort of Spanish children with idiopathic CPP (Spanish PUBERE Registry) was studied. Genomic DNA was obtained from 444 individuals, including 168 index cases with CPP and their close relatives. Automatic sequencing of the coding region (5 exons) of *DLK1* was performed in all index cases. Serum DLK1 levels were measured by using a soluble DLK1 enzyme-linked immunosorbent assay (ELISA). **Results:** A rare allelic deletion (c.401_404 + 8del) of a splice site junction of *DLK1* was identified in a girl with sporadic CPP. Pubertal signs appeared at 5.7 years of age with progressive puberty (basal LH: 1.7 mIU/mL, peak LH: 32.77 mIU/mL; basal FSH: 6.32 mIU/mL, peak FSH: 19.89 mIU/mL), BA/CA 1.7 years; normal cranial MRI). She received LHRH analogues (6.3 - 10.1 years of CA) with no side effects. At 14.9 years of age height and BMI are 152.9 cms and 18 kg/m^2, respectively, presenting regular menses. Familial segregation analysis showed that the affected child was the only carrier of this deletion characterizing a *de novo* mutation (biological paternity and maternity were confirmed by microsatellite analysis). Serum DLK1 levels were undetectable (<0.4 ng/mL) in this girl, supporting that the deletion lead to complete lack of DLK1 production. Her father, mother and sister had normal serum DLK1 levels (ranged 6.36 ng/mL to 8.98 ng/mL). Two rare consecutive nucleotide changes in the promoter region of the *DLK1* gene (c.-222 C>A and c.-223 G>A) were also identified in an adopted child with CPP. They are located in a transcription factor binding site for SP1 (a zinc finger transcription factor). Pubertal signs appeared at 6.7 years of age with progressive puberty (Basal LH: 0.5 mIU/mL, peak LH: 15.9 mIU/mL, basal FSH: 1.52 mIU/mL, peak FSH: 6.56 mIU/mL, BA/CA 1.4 years; normal cranial MRI). She is under therapy with LHRH analogues with no side effects. **Conclusion:** Novel *DLK1* findings were identified in the Spanish cohort of children with CPP, reinforcing a significant role of this factor in human pubertal timing.