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"Highlights in Pediatric Endocrinology"

New Insights in X-linked Hypophosphatemic Rickets

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Case of X-linked hypophosphatemic rickets (XLH)

A 7-month-old boy presented with lower limb bowing. He was born at 39 weeks of gestation and had normal development. His length was 64.5 cm (10th - 25th centile) and his weight was 7.5 kg (25th - 50th centile). He had no family history of bone or growth disorders. Physical examination revealed frontal bossing, rachitic rosary, flaring wrists, and systemic examination otherwise was unremarkable. X-ray showed the evidence of rickets with cupping and flaring of g owth plate.

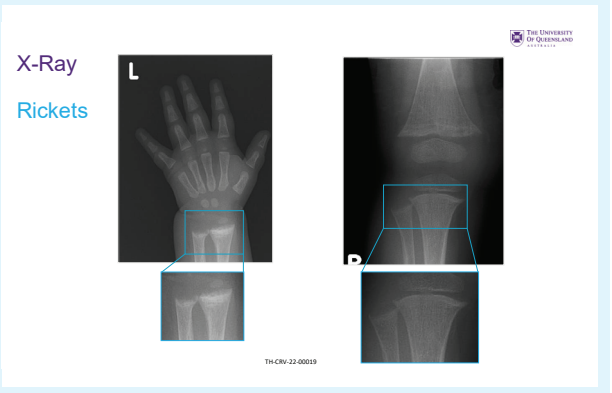

Figure 1

Blood tests showed normocalcemia (2.3 mmol/L, 9.2 mg/dL), hypophosphatemia (0.7 mmol/L, 2.2 mg/dL), elevated serum alkaline phosphatase (ALP, 586 IU/L), and normal para-thyroid hormone (PTH) level (6.2 pmol/L, 58 pg/mL), which was typical for XLH. Genetic study showed patho-genic variant in the *PHEX* gene (c.151C > T). He was started on standard therapy with phosphate and calcitriol the dose was increased gradually. At 10 years of age, he still had evidence of rickets despite good compliance with therapy. He had genu varum, aches and pains, short stature, and recurrent tooth abscess. He had low serum phosphate, elevated serum ALP without nephrocalcinosis. After 18 months of burosumab treatment (0.8 mg/kg every 2 weeks), his genu varum was improved. His X-ray showed no rickets. He had

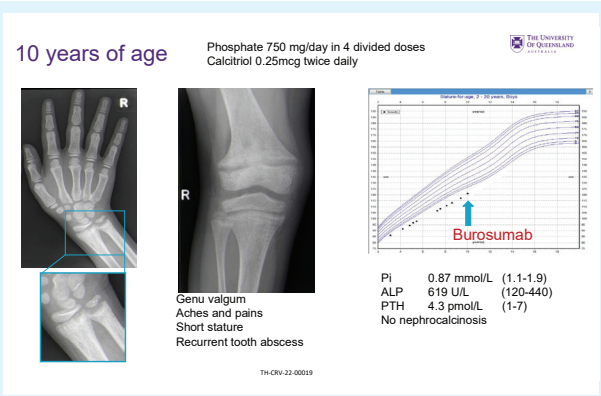

Figure 2

no limb pain nor tooth abscess and his serum phosphate and ALP levels were in the normal range.

Phosphate metabolism and regulation

All rickets is due to low serum phosphate. Most of filte ed phosphate is resorbed in renal proximal convoluted tubules by NaPi-IIa and NaPi-IIc. In total, 90 - 95% of filte ed phosphate is resorbed by the kidney, which is predominantly under the control of fib oblast growth factor 23 (FGF23), PTH, and other minor hormones including insulin-like growth factor 1 (IGF-1), insulin, and thyroxine. Intestinal phosphate absorption is either paracellular or via active mechanism of NaPi-IIb. Around 30% is under control of $1,25(OH)_2$ vitamin D.[1]

The main regulator of phosphate metabolism is FGF23, a 251-amino-acid molecule with its gene located in chromosome 12p13. It was first described in 2000 as a phosphatonin which lowers serum phosphate level. The production of FGF23 is stimulated by dietary phosphate and $1,25(OH)_2$ vitamin D. It is secreted from bone cells (osteoblasts and osteocytes) and requires Klotho as co-receptor to be active. FGF23 increases phosphate excretion by decreasing renal expression of NaPi-IIa and NaPi-IIc, and decreases phosphate absorption from gut by decreasing 1alpha hydroxylation of 25OH vitamin D. Thus, excessive FGF23 leads to decreased renal tubular phosphate reabsorption, decreased serum phosphate, and decreased activation of $1,25(OH)_2$ vitamin D. FGF23 overexpression leads to decreased serum phosphate level and osteomalacia (demineralized skeleton).

Defective *PHEX* gene leads to increased plasma FGF23. XLH is caused by inactivating mutations of *PHEX* gene.[2], [3] It is the most common genetic hypophosphatemia with the incidence of 1:20,000 to 1:50,000. Despite X-linked dominant inheritance, XLH occurrence is frequently sporadic. Blood tests show low serum phosphate, elevated ALP, normal or mildly elevated PTH, normal serum calcium and 25OH vitamin D, low to normal $1,25(OH)_2$ vitamin D and elevated FGF23 (sometimes inappropriately normal related to low serum phosphate), and urine tests reveal reduced tubular threshold maximum for phosphate/glomerular filt ation rate (TMP/GFR) indicating loss of phosphate in urine. XLH is a multi-system disorder. Children may have incomplete healing of rickets with cholecalciferol, osteomalacia, long bone deformity, short stature, craniosynostosis, Chiari malformation, poor fracture healing, muscle weakness, pain of muscle and bones, dental abscess, and periodontal disease. Enthesopathy (ligament, tendon, or joint capsule calcification), osteophytes, arthritis, pseudofractures, insufficienc fractures and poor healing of fractures, hearing impairments, optic atrophy, and spinal stenosis can be found in adults. All patients may have consequences from phosphate and calcitriol treatment, including secondary and tertiary hyperparathyroidism, nephrocalcinosis, renal failure, hypertension, and ectopic calcification

The goals of treatment of XLH in children are optimizing growth and development, improving osteomalacia and rickets, straightening legs, improving bone pain, improving serum ALP, decreasing tooth abscess, and avoiding complication from the treatment.[3], [4], [5] Conventional treatment of XLH includes phosphate salts at a dose of 20 - 60 mg/kg/day and active vitamin D in the form of calcitriol 20 - 30 ng/kg/day to avoid hyperparathyroidism and improve phosphate resorption. (No phosphate given alone as hyperparathyroidism may occur.) Phosphate salt should be started at one third of maintenance dose and increased slowly to avoid gastrointestinal tract side effect . Typical maintenance

dose of phosphate salts is 750 mg/day in 4 - 5 divided doses and calcitriol 250 ng twice a day. Clinical outcomes of XLH are variable depending on compliance and complications of therapy. Growth, serum biochemistries, urine biochemistries, bone age X-ray and renal ultrasonography should be followed. A study showed that starting therapy before 12 months of the age leads to better final adult height than after 12 months of age.[6] It should be noted that variable outcomes may occur due to genetic expressions and compliance. Despite adequate phosphate and calcitriol therapy, every patient does have short stature. Nephrocalcinosis is an inevitable adverse effect in patients with XLH (50 - 80%). If it gets worsened, phosphate and calcitriol doses should be decreased, and thiazide diuretic should be considered. Phosphate and calcitriol therapy increases the risk of gastrointestinal side effects (dyspepsia, laxative effect of phosphate), hyperparathyroidism, hypercalcemia, hypercalciuria, nephrocalcinosis , chronic kidney disease, hypertension, and ectopic calcification

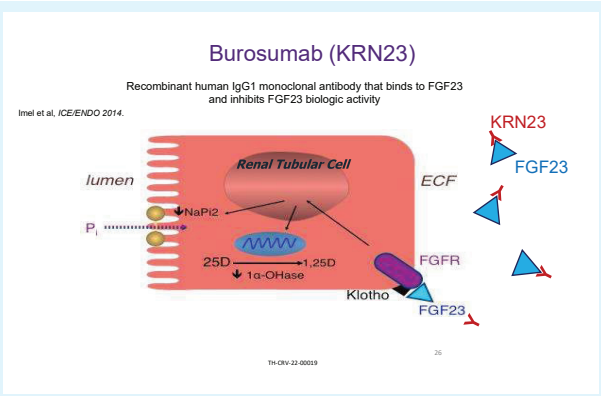

Figure 3

Because of the difficultie in the treatment of XLH, burosumab (KRN23), recombinant human IgG1 monoclonal antibody, is introduced for the treatment of XLH. By binding to FGF23 and inhibiting FGF23 biologic activity, burosumab inhibits urinary phosphate loss, maintains normal serum phosphate and normal mineralization.

I will present the data from phase 3 studies of burosumab in children conducted as multicentric international randomized controlled trial between phosphate and calcitriol and burosumab in children aged 1 - 12 years.[7], [8] There were 61

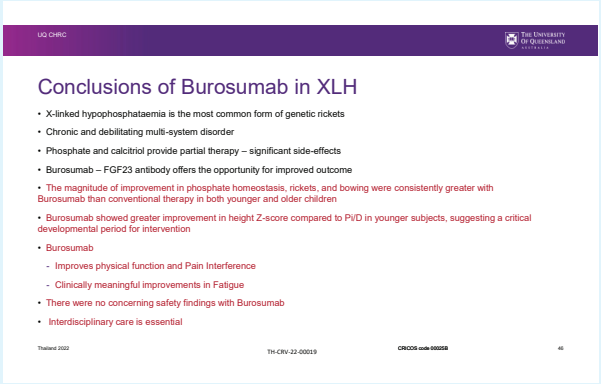

Figure 4

children included, stratified by age (< 5 and ≥ 5) and rickets severity. After 64 weeks of the treatment, fasting serum phosphate, TMP/GFR, serum ALP in burosumab group were better than conventional group in both age groups. Iliac bone biopsy in a 24-year-old female with XLH also showed reduction of osteoid (unmineralized bone) at 48 weeks after burosumab treatment. There were improvements of rickets in terms of radiographic criteria. Regarding the height Z-score, in children < 5 years, height Z-score in burosumab group was 0.2 more than conventional group, while in children ≥ 5 years, height Z-score in burosumab group was 0.09 more than conventional group. Annualized growth rate at 64 weeks after treatment was 6.65 cm in burosumab group and 5.94 cm in conventional group. There was significant better improvement in function, pain, quality of life in burosumab group at 40 weeks after the treatment. No statistical diffe ences in physical function and fatigue were found. Quality of life reported by caregiver was improved in physical health but no significant change in psychological health. The incidence of pyrexia in burosumab group was significantly higher, but in my real practice, I have never seen any patients got pyrexia. Longer term follow-up for 160 weeks in 26 children showed persistent beneficial effect on serum phosphate, urine phosphate, serum $1,25(OH)_2$ vitamin D, and rickets.[9] Serum phosphate level was less fluctuating if burosumab was administered every 2 weeks in place of every 4 weeks.

Q & A

Q : Are serum FGF23 level measurement and genetic testing of PHEX mutation required before burosumab treatment?

A : Yes. They should be performed to make sure the diagnosis of XLH before starting the treatment.

Q : Is burosumab effective in other hypophosphatemic rickets?

A : Burosumab should be effecti e in any types of hypophosphatemic rickets due to FGF23 excess. There was evidence showing that it was effecti e in tumor-induced osteomalacia.

Q : Arrange the sequence of improvement after burosumab treatment.

A : Improvement in TMP/GFR > Improvement in serum phosphate > Decreased serum ALP (couple of months) > Improved rickets (6 - 12 months) > Growth improvement

Pain may subside as quickly as 3 months after treatment, or 6 - 12 months in some patients.

Q : What is youngest age for burosumab treatment?

A : 12 months.

Q : At what level of serum phosphate should be kept during burosumab treatment? Is low normal / mid normal of serum phosphate better?

A : No data, just keep normal serum phosphate.

Q : Is there any data regarding burosumab antibody?

A : There has not been established data, but it has been observed that some patients require higher dose of burosumab.

Q : Is phosphate and calcitriol dose titration required before commencing burosumab treatment?

A : Phosphate and calcitriol cessation should be done 2 weeks prior to the treatment and make sure that the patients have low serum phosphate level before starting burosumab.

Q : Regarding burosumab in adult, should it be continued?

A : Treatment in adults may have benefit in the improvement of pain, function fracture healing, and osteomalacia. The recommended interval is every 4 weeks. There has been no data for therapy cessation. If the symptoms get better, the interval may be lengthened to every 8 weeks.

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