Hypophosphatemic rickets: new treatments

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Disclosures

- Lectures and educational activities sponsored by Kyowa Kirin
- Advisory meetings for Kyowa Kirin
# Primary Hypophosphatemic rickets: a group of diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Abbreviation</th>
<th>Gene</th>
<th>FGF23 levels</th>
<th>Hypophosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Linked Hypophosphatemia</td>
<td>XLH</td>
<td>PHEX</td>
<td>↑</td>
<td>Y</td>
</tr>
<tr>
<td>Autosomal dominant hypophosphatemic rickets</td>
<td>ADHR</td>
<td>FGF23</td>
<td>↑</td>
<td>Y</td>
</tr>
<tr>
<td>Autosomal recessive hypophosphatemic rickets 1</td>
<td>ARHR1</td>
<td>DMP1</td>
<td>↑</td>
<td>Y</td>
</tr>
<tr>
<td>Autosomal recessive hypophosphatemic rickets 2</td>
<td>ARHR2</td>
<td>ENPP1</td>
<td>↑</td>
<td>Y</td>
</tr>
<tr>
<td>Autosomal recessive hypophosphatemic rickets 3 (Raine Syndrome)</td>
<td>ARHR3</td>
<td>FAM20C</td>
<td>↑</td>
<td>Y</td>
</tr>
<tr>
<td>Hypophosphatemic rickets with hypercalciuria</td>
<td>HHRH</td>
<td>SLC34A3 (NPT2C)</td>
<td>-</td>
<td>Y</td>
</tr>
</tbody>
</table>
FGF23

- FGF23 is a 32-D protein mainly produced by osteocytes in bone, (and less by osteoblasts and chondrocytes, and other organs (thymus, brain, spleen)
- FGF23 promotes phosphate excretion in the urine by suppressing the expression of sodium-phosphate co-transporters, NaPi-2a and NaPi-2c, in the proximal tubule
- FGF23 acts as a counter-regulatory hormone for vitamin D through inhibition of the renal 1α-hydroxylase, and stimulation of the 24-hydroxylase
- FGF23 also regulates PTH production by the parathyroid gland

X-Linked Hypophosphatemia

- It is the most common inherited form of rickets / osteomalacia
- Incidence 3.9/100,000 live newborns, prevalence 4.8/100,000

- It is caused by loss of function mutations in the \textit{PHEX} gene that encodes for an endopeptidase which is expressed predominantly in bones and teeth, in osteoblasts, osteocytes, and odontoblasts.

- Loss of function pathogenic variants in \textit{PHEX} lead to increased serum levels of FGF23 which results in:
  - high serum levels of FGF23
  - Renal phosphate wasting
  - Hypophosphatemia
  - Decreased 1-\(\alpha\) hydroxylation of 25(OH) vit D
### “Traditional” treatment of XLH rickets

#### Children: from diagnosis until the end of longitudinal growth (at least)

- **Oral phosphate supplements**
  
  20-40 mg/kg/day (≤ 100 mg/Kg/d in infants) divided in 3-5 daily doses

- **Oral Calcitriol (1α vit D)** different recommendations
  
  20-30 ng/Kg/day (in 2-3 daily doses)
  50-70 ng/kg/day (≤ 3 ug per day)

#### Adults: indications not well defined (bone pain, fractures, trauma surgery)

- **Oral phosphate supplements**: 750-1000 mg/day divided in 3 daily doses

- **Oral Calcitriol**: 0.5-0.75 ug/day

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*A. Linglart, endocrine connections, 2014; Ruppe MD, GeneReviews, 2017*
# XLH rickets treatment aims and limitations

<table>
<thead>
<tr>
<th>Aims</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing rickets</td>
<td>Hypophosphatemia persists</td>
</tr>
<tr>
<td>Leg deformities correction</td>
<td>Systemic manifestations</td>
</tr>
<tr>
<td>(± orthopedic surgery)</td>
<td>Side effects: GI disturbances and risk of nephrocalcinosis</td>
</tr>
<tr>
<td>Growth improvement</td>
<td>It is not focused on disease pathogenesis, and even increases FGF23 levels!</td>
</tr>
</tbody>
</table>
Growth hormone in XLHR

Open randomized controlled clinical trial in children 10y old
(16 treated with P + calcitriol + rhGH vs. 66 treated with P + calcitriol)

Limited effect of rhGH on growth impairment in children with XHR

Therapeutic management of hypophosphatemic rickets from infancy to adulthood


Endocrine Connections (2014) 3, R13-R30
Limitations for measuring treatment efficacy in XLHR

• Phenotype variability even within same family affected members
• Impact of the age of diagnosis and treatment initiation on outcome
• Gender effect: affected females and carries vs affected males
• Adherence
• Adverse effects: GI intolerance
• Evaluation of bone mineral pattern
New treatments for Hypophosphatemic rickets

• Calcimimetics

• anti-FGF23 ab (KRN23)
Cinacalcet in XLHR: case reports

5 y. old boy with XLH treated since 4 months age

Active rickets and 2nd. hyperparathyroidism due P intolerance

Good outcome and rickets healing treated with calcitriol + cinacalcet combination

JS VanSickle, et al. Pediatric Nephrology, 2018
Cinacalcet in XLHR: own data

6 XLHR patients with \textit{PHEX} mutations treated with reduced P dose and cinacalcet
Cinacalcet in XLHR: own data

6 XLHR patients with *PHEX* mutations treated with reduced P dose and cinacalcet

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>3 months</th>
<th>12 months</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum P (mg/dL)</td>
<td>2.48</td>
<td>2.5</td>
<td>2.35</td>
<td>no change</td>
</tr>
<tr>
<td>(p)</td>
<td>(0.46)</td>
<td>(0.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>78.71</td>
<td>51.23</td>
<td>40</td>
<td>decrease</td>
</tr>
<tr>
<td>(p)</td>
<td>(0.067)</td>
<td>(0.039)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGF23 (RU/ml)</td>
<td>255</td>
<td>165.91</td>
<td>156.8</td>
<td>decrease</td>
</tr>
<tr>
<td>(p)</td>
<td>(0.034)</td>
<td>(0.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRP (%)</td>
<td>55.66</td>
<td>72.39</td>
<td>77.4</td>
<td>increase</td>
</tr>
<tr>
<td>(p)</td>
<td>(0.023)</td>
<td>(0.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TmP/GFR (mg/dL)</td>
<td>1.37</td>
<td>1.76</td>
<td>1.67</td>
<td>increase</td>
</tr>
<tr>
<td>(p)</td>
<td>(0.014)</td>
<td>(0.03)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
anti-FGF23 ab (KRN23)

Effects of IV and sc KRN23 vs placebo on TmP/GFR, serum P and 1,25OH2D levels

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Effect of repeated doses of anti-FGF23 ab (KRN23) in adults

Anti-FGF23 ab (KRN23) in adults with XLH

A randomised, double-blind, placebo controlled, Phase III study (UX023-CL303) with open-label extension to assess the efficacy and safety of KRN23

UX023-CL303 study design

- Primary endpoint: Proportion achieving mean serum phosphorus levels above LLN by Week 24
- Key secondary endpoints:
  - Change in BPI Q3 (worst pain) at Week 24
  - WOMAC physical function (change from BL to Week 24)
  - WOMAC stiffness (change from BL to Week 24)

Study sites: United States, France, Ireland, Italy, UK, Japan and South Korea

ClinicalTrials.gov Identifier: NCT02528160

Courtesy of Kyowa Kirin
anti-FGF23 ab (KRN23) in adults with XLH

A randomised, double-blind, placebo controlled, Phase III study (UX023-CL303) with open-label extension to assess the efficacy and safety of KRN23

Summary and conclusions

- This study demonstrated that burosumab 1 mg/kg administered subcutaneously every 4 weeks for 24 weeks to adult subjects with XLH:
  - Led to an increased mean serum phosphorus above LLN in 94% of patients across midpoints of dose intervals through week 24
  - Significantly reduced subject stiffness and showed strong trends toward positive effects on subjects’ physical function and pain at its worst
  - Improved active fracture/pseudofracture healing and reduced fracture/pseudofracture worsening, demonstrating an overall positive effect on bone health over time
  - Demonstrated a similar safety profile to the placebo treatment group, with no difference in the overall incidence of TEAEs, treatment-related AEs or serious TEAEs between the two treatment groups

Courtesy of Kyowa Kirin
anti-FGF23 ab (KRN23) in children

A randomised, open-blind, Phase II study (UX023-CL201) in 52 children with XLH

UX023-CL201: study design

- Study population: Children with XLH, Ages 5–12 years, N=52, Tanner ≤2
- Screening:
  - 14-day wash-out
  - Vitamin D metabolites/analognes
  - 7-day wash-out oral phosphate
- Q2W dose group (SC):
  - Titration period 16 weeks
  - Treatment period 48 weeks
- Q4W dose group (SC):
  - Titration period 16 weeks
  - Treatment period 48 weeks
- Extension study

- Primary analysis: Week 40
- Extended analysis: Week 64
- Pre-specified subgroups based on baseline total RSS ≥ or <1.5
- Initial doses were 0.1, 0.2 or 0.3 mg/kg Q2W or 0.2, 0.4 or 0.6 mg/kg Q4W
anti-FGF23 ab (KRN23) in children

A randomised, open-blind, Phase II study (UX023-CL201) in 52 children with XLH

**UX023-CL201: summary and conclusions**

- Children aged 5–12 years old with XLH treated with burosumab for up to 64 weeks demonstrated improved clinical outcomes
  - Improved serum phosphorus, TmP/GFR, 1,25(OH)₂D, and ALP levels compared with baseline
  - Rickets improved substantially despite previous conventional treatment for a mean of ~7 years
  - Improvements in rickets scores were greater in patients with more severe baseline rickets, with the greatest improvements in patients receiving Q2W dosing
  - Improved growth velocity compared with baseline
  - Improved 6MWT compared with baseline, especially in those with significant walking impairment at baseline
  - Improved health-related quality of life in paediatric XLH, shifting the overall mean POSNA-PODCI score into the normal range
  - AEs were predominantly mild to moderate; no deaths or discontinuations were reported
  - No clinically meaningful changes were observed in serum PTH, serum or urine calcium, or renal ultrasounds. Hyperphosphatemia was not observed
anti-FGF23 ab (KRN23) in children

Study of the safety, pharmacodynamics and efficacy of KRN23 in children 1-4 y old (UX023-CL205) in 13 children with XLH

UX023-CL205: study design

- Study population
  - Children with XLH
  - A RSS at the knee of ≥1.5 is required in ≥5 patients
  - Ages 1–4 years
  - N=13

- Treatment period
  - 7-day wash-out
  - Vitamin D metabolites/analogue, oral phosphate
  - Open label SC burosumab
  - 0.8 mg/kg Q2W

- Extension study

- Interim analysis: Week 40
- Final analysis: Week 64
anti-FGF23 ab (KRN23) in children

Study of the safety, pharmacodynamics and efficacy of KRN23 in children 1-4 y old (UX023-CL205) in 13 children with XLH

UX023-CL205: summary and conclusions

- In children 1–4 years old with XLH, treatment with burosumab for up to 40 weeks:
  - Increased serum phosphorus compared with baseline
  - Increased serum 1,25(OH)₂D compared with baseline
  - Decreased serum ALP compared with baseline
- Radiographic assessment of rickets at Week 40 shows a decrease in RSS scores and substantial healing as assessed by RGI-C
- Burosumab had a similar safety profile to previous paediatric trials; AEs were predominately mild to moderate
  - There were no instances of hyperphosphatemia
anti-FGF23 ab (KRN23)

• Very promising results

• Questions
  • Long term outcome and safety
  • Indication and prescription
  • Treatment assessment: FGF23 monitoring, bone indicators?
  • Access and cost
Thank you for your attention