X-linked hypophosphatemia (XLH) is the most common heritable cause of hypophosphatemic rickets, and it is characterized by hypophosphatemia due to kidney phosphate wasting, deficiency of 1,25-dihydroxyvitamin D \([1,25(OH)_2D]\), rickets, and osteomalacia (1). Clinical features manifest as early as 6 months of age; children develop deformities of the lower extremities, including coxa vara, genu varus and valgus, and tibial bowing, and they often have short stature. Characteristic laboratory findings are serum phosphorus levels below normal for age, increased fractional excretion of phosphorus, and low or inappropriately normal serum 1,25(OH)2D. Radiographs in children demonstrate classic findings of rickets with metaphysical cupping and fraying, increased radiolucency, and lower limb deformities. In adults, joint pain and osteoarthritis can result from childhood skeletal deformities, and fractures and pseudofractures develop due to chronic hypophosphatemia and osteomalacia. Over time, individuals with XLH develop enthesopathy, spinal stenosis, dental caries and abscesses, and hearing loss. Thus, XLH is a lifelong, debilitating disease with significant morbidity; patients have diminished quality of life, and the psychosocial effect of the disease is largely underestimated.

XLH is caused by mutations in the gene Phosphate Regulating Endopeptidase Homolog X-Linked (PHEX), which encodes an osteocytic protein (1). Loss of function of PHEX results in excess production of fibroblast growth factor 23 (FGF23), a bone-derived hormone that regulates phosphorus and vitamin D metabolism. FGF23 principally targets the kidney, inhibiting reabsorption of phosphate and synthesis of 1,25(OH)2D in the proximal tubule. Together, hypophosphatemia and 1,25(OH)2D deficiency lead to rickets, osteomalacia, and impaired skeletal growth. In animal studies, blockade of FGF23 activity leads to reversal of biochemical abnormalities and improved skeletal mineralization, providing evidence that excess FGF23 is critical to the pathogenesis of XLH (2). These preclinical studies prompted research and development of novel therapeutic agents to treat XLH.

For the past 40 years, patients with XLH have been treated with multiple daily doses of oral phosphate salts and active vitamin D \([1,25(OH)_2D]\) or alphacalcidiol (1). The goals of such therapy were to heal rickets, improve growth in children, and improve osteomalacia in adults. Despite therapy, most patients have residual leg deformities, short stature, and significant morbidity, including chronic pain, stiffness, and decreased mobility. Additionally, adherence to therapy is made difficult due to need for frequent dosing and adverse effects of phosphate supplements, which can cause hyperparathyroidism and gastrointestinal symptoms (bloating, nausea, and diarrhea), and active vitamin D, which can result in hypercalcemia, hypercalciuria, and nephrocalcinosis. Furthermore, treatment with phosphate and calcitriol can itself increase serum FGF23, thus exacerbating the primary pathogenic defect in XLH. Thus, safer and more efficacious therapies were needed.

Burosumab is a fully human monoclonal IgG1 antibody against FGF23 recently approved by the US Food and Drug Administration and Health Canada as well as conditionally approved by the European Medicines Agency for treatment of adults and children with XLH. Burosumab binds circulating intact FGF23 and thereby, blocks its biologic effects in target tissues. The efficacy and safety of burosumab were examined in a series of recently concluded clinical trials in children and adults with XLH. In an open label, phase 2 trial, 52 children ages 5–12 years old with XLH were randomized to receive subcutaneous burosumab either every 2 or 4 weeks; the dose of burosumab was adjusted to achieve a serum phosphorus above the lower limit of normal (3). Burosumab administered every 2 weeks resulted in a sustained increase in serum phosphorus concentration to normal or near-normal levels, whereas dosing every 4 weeks was associated with lower levels of phosphorus at the end of the dose interval and larger fluctuations over time. The primary outcome, rickets severity assessed radiographically, improved significantly after 40 and 64 weeks of treatment, with greater improvement in the every 2-weeks dosing group. These findings indicate that burosumab administered every 2 weeks is an appropriate dosing regimen for children with XLH. In a subsequent phase 3 trial, 61 children ages 1–12 years old were randomized to receive either subcutaneous burosumab every 2 weeks or oral phosphate supplements and active vitamin D (4). After 40 weeks, the improvements in hypophosphatemia and rickets severity were significantly greater with burosumab than with conventional therapy. In both pediatric trials, standing height and mobility increased,
and in the latter trial, the improvements in both were greater with burosumab.

In a randomized, blinded, phase 3 trial in 134 adults with XLH, burosumab administered every 4 weeks was compared with administration of placebo (5). Fractures and pseudo-fractures were detected in 52% of subjects at enrollment. At week 24, the percentage of fully healed fractures was greater in the burosumab group than in the placebo group (43.1% versus 7.7%, respectively), with the odds of full healing being 17-fold greater in the burosumab group. Serum phosphorus was normalized in 94% of those receiving burosumab compared with 8% receiving placebo. Burosumab also significantly reduced the Western Ontario and McMaster Universities Osteoarthritis Index stiffness subscale score at week 24 relative to placebo. Adverse effects of burosumab were mild to moderate in severity; the most common adverse effects in children were injection site reactions, headache, and cough, and in adults, they were back pain, nasopharyngitis, tooth abscess, and headache (3,5). No subject required withdrawal of medication. Hyperphosphatemia was reported in 6% of adult subjects and resolved with burosumab dose reduction. Urine calcium excretion was unchanged during treatment for all age groups. Thus, burosumab seems to be a novel, safe, and effective treatment for children and adults with XLH.

In CKD, plasma FGF23 increases early and progressively as GFR declines, reaching levels in patients with ESKD that are 100- to 1000-fold higher than in those with XLH (6). High plasma FGF23 is strongly and independently associated with left ventricular hypertrophy in children and adults with CKD as well as increased cardiovascular and all-cause mortality in adults (7). Although its primary physiologic target is the kidney, in the setting of advanced CKD, FGF23 can target the heart, directly inducing cardiac hypertrophy, an effect that can be attenuated by blockade of FGF receptor 4 (8). However, not all studies in CKD show a relationship between circulating FGF23 and cardiovascular outcomes (7), possibly due to differences in experimental design, study end points, and variations in FGF23 assays. Additionally, preclinical and clinical studies in XLH show either a significant relationship or no relationship with left ventricular hypertrophy (8). Taken together, these conflicting reports suggest that other coexisting factors (e.g., hyperphosphatemia, hypertension, inflammation, iron deficiency, and vitamin D status) may play a key role in the actions of FGF23 on the cardiovascular system. Nevertheless, these observations raise the question of whether reduction in circulating bioactive FGF23 would prevent cardiovascular complications in CKD.

Data from studies in experimental CKD offer insights into the potential risks versus benefits of anti-FGF23 antibody therapy in patients with CKD. In the two studies published to date, the experimental design, nature of antibody used, and duration of treatment differed significantly. In rats with antilamineral basement membrane nephritis and CKD stage 2–4, a single injection of monoclonal mouse anti-human FGF23 antibody was associated with a dose-dependent decrease in serum parathyroid hormone and increase in serum phosphorus and 1,25(OH)2D, when measured 72 hours after administration (9); however, effects on the heart were not examined. In 5/6 nephrectomized rats with CKD stage 3–4 fed a high-phosphorus diet, administration of anti-rat FGF23 antibody three times per week for 6 weeks led to sustained decreases in serum parathyroid hormone, increases in serum 1,25(OH)2D, and normalization of bone histomorphometric markers (10). However, FGF23 blockade induced hypercalcemia, marked hyperphosphatemia, and aortic calcification, and it increased mortality; furthermore, it failed to have an effect on ventricular hypertrophy or hemodynamic parameters. The authors speculated that the vascular calcification and early mortality in antibody-treated animals resulted, at least in part, from feeding of a high-phosphorus diet, which they chose to simulate the Western diet and accelerate CKD progression in the model studied. Furthermore, an increase in serum phosphorus is a predictable consequence of FGF23 blockade whether GFR is normal or reduced. Thus, it remains to be determined whether combining FGF23 blockade with dietary or pharmacologic control of phosphorus would lessen the risk of vascular calcification and early mortality in experimental CKD. If such an approach were successful, one could further examine the potential for FGF23 blockade to ameliorate or prevent the adverse effects of FGF23 excess in human CKD.

In early CKD, phosphorus homeostasis is maintained, in part, by the progressive increase in circulating FGF23, although 1,25(OH)2D deficiency and hyperparathyroidism are the tradeoffs. Given the observations in experimental CKD, blockade of FGF23 activity in human predialysis CKD currently would seem to pose an unacceptable risk of hyperphosphatemia and its associated complications, even if hyperparathyroidism was mitigated. However, FGF23 blockade in ESKD might pose a lower risk, because phosphorus homeostasis could be attained by other means (i.e., dietary and pharmacologic restriction and extracorporeal removal of phosphorus). Whether FGF23 blockade would increase 1,25(OH)2D production in the kidney or other tissues is unknown. Nevertheless, it now seems feasible to examine whether burosumab can mitigate or prevent left ventricular hypertrophy and decrease mortality in patients with ESKD. Additional preclinical and clinical studies are, therefore, required before administration of burosumab can be considered in patients with CKD and ESKD.

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