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POSITION PAPER

Clinical practice guidelines for paediatric X-linked hypophosphataemia in the era of burosumab

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X-linked hypophosphataemia (XLH), the most common inherited form of rickets, is caused by a PHEX gene mutation that leads to excessive serum levels of fibroblast growth factor 23 (FGF23). This leads to clinical manifestations such as rickets, osteomalacia, pain, lower limb deformity and overall diminished quality of life. The overarching aims in the management of children with XLH are to improve quality of life by reducing overall burden of disease, optimise an individual's participation in daily activities and promote normal physical and psychological development. Burosumab, a monoclonal antibody targeting FGF23, has been shown to improve biochemistry, pain, function and radiological features of rickets in children with XLH and has transformed management of XLH around the world. Burosumab has been recently approved for clinical use in children with XLH in Australia. This manuscript outlines a clinical practice guideline for the use of burosumab in children with XLH to assist local clinicians, encourage consistency of management across Australia and suggest future directions for management and research. This guideline also strongly advocates for all patients with XLH to have multidisciplinary team involvement to ensure optimal care outcomes and highlights the need to consider other aspects of care for XLH in the era of burosumab, including transition to adult care and the effective coordination of care between local health-care providers and specialist services.

Key words: bone health; monoclonal antibody; rickets.

X-linked hypophosphataemia (XLH), the most common inherited form of rickets,[1] is caused by an inactivating mutation in the Phosphate Regulating Endopeptidase Homologue, X-linked (*PHEX)* gene, leading to elevated levels of fibroblast growth factor 23(FGF23).[2] Elevated FGF23 leads to hypophosphataemia by increasing phosphaturia, as well as suppressing 1,25-dihydroxyvitamin D synthesis.[2] Clinical features include impaired growth, rickets and osteomalacia, long-bone deformities, hearing loss, dental abscesses, joint stiffness, bone and joint pain, enthesopathy (pain/inflammation at site of bony insertion of tendons/ligaments), osteoarthritis, delayed bone healing, spinal stenosis, osteophytes, Chiari 1 malformation and syringomyelia. Overall this leads to diminished quality of life and psychosocial impacts.[2,3]

Conventional medical therapy involves multiple daily doses of oral phosphate and calcitriol and has been shown to improve lower limb deformities, growth and dental health.[4] However, there is incomplete correction of biochemistry and rickets with this therapy and persistent elevation of FGF23.[5] In addition, without careful titration of phosphate and calcitriol, nephrocalcinosis, renal failure and secondary hyperparathyroidism may result.[4,6–8] Conventional treatment is onerous; frequent monitoring is required to prevent complications; phosphate is taken multiple times per day, has an unpleasant taste and can cause gastrointestinal side effects. These factors contribute to the burden of disease in XLH and poor adherence.[9,10]

Burosumab, a monoclonal antibody targeting FGF23, is now approved for clinical use in children with XLH in Australia. While the FGF23 levels remain high, its biochemical effects are blunted. Clinical trials in adults and children assessing burosumab therapy in XLH have shown improvements in biochemistry, function, pain, radiological features of rickets and limb bowing.[10–16] Real-world data show promising clinical translation of these trials[17,18] but as with any new therapy, there are challenges in adapting trial protocols into clinical practice.

There are 62 children in Australia currently receiving burosumab through the Early Access Program, most of whom are managed using a protocol based on the paediatric phase 3 clinical trial.[10] The aim of this paper is to outline a clinical practice guideline for burosumab use in children with XLH to assist local clinicians, encourage consistency of management across Australasia and suggest some future directions for management and research.

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Methods

Recommendations were evaluated using the Grading of Recommendations, Assessment, Development and Evaluation system (GRADE) as recommended by the National Health and Medical Research Council (NHMRC).[19,20] Further details are outlined in Tables 1 and 2.

Guideline and Recommendations for the Use of Burosumab Therapy

Patient selection

Criteria for the Early Access Program were adapted from the clinical trial (Table 3). However, moving forward, access will be dependent on local authorities and approvals. Due to the clear benefits seen in clinical trials, we suggest consideration of burosumab therapy in all children with XLH who are eligible (B,1+++).

Commencing burosumab therapy: Aims and prior work-up

The overarching aims in managing paediatric XLH are to improve quality of life by reducing burden of disease, optimising participation in daily activities and promoting normal physical and psychological development. Specific aims of therapy include improving growth, correcting or preventing lower limb deformity and rickets, normalising biochemistry and prevention of complications of the disease and treatments. Burosumab should not be co-administered with conventional therapy (phosphate and active vitamin D analogues); conventional therapy should be discontinued 1 week prior to commencing burosumab with a fasting serum phosphate performed to confirm that the child is hypophosphataemic (A, 1+++). Patients should have a dental review prior to commencing therapy and maintain good oral hygiene and dental reviews throughout therapy (A,1+++).

Administration and dose

The starting dose is 0.8 mg/kg of body weight, rounded to nearest 10 mg (maximum dose 90 mg), administered subcutaneously every 2 weeks (A, 1+++). Burosumab is administered by a health-care provider. At present, the first two doses are given at the child's treating hospital with the child observed for 30-min post-injection to ensure that there are no adverse events, although no severe acute reactions have been reported. Subsequent injections are given at either the hospital, home-visiting services or the child's local doctor's rooms. It may be possible in the future for the agent to be administered outside of a health-care setting by parent/carer or the patient themselves.

Table 1 Grading of Recommendations, Assessment, Development and Evaluation system (GRADE)

Recommendation	Level of evidence
1 *Strong recommendation* Applies to most patients, benefits clearly outweigh risk 2 *Weak recommendation* Recommendations should be considered depending on individual circumstance, benefit/risks are balanced or uncertain, further research may change recommendation	High-quality evidence (++++) • RCTs, unbiased observational studies Moderate-quality evidence (+++) • RCTs or observational studies with minor flaws Low-quality evidence (++) • Indirect evidence or from RCTs/observational studies with major flaws Very-low-quality evidence (+) Very indirect evidence or clinical observations

Table 2 NHMRC grades of recommendation

A – Body of evidence can be trusted to guide practice
B – Body of evidence can be trusted to guide practice in most situations
C – Body of evidence provides some support for recommendation(s) but care should be taken in its application
D – Body of evidence is weak and recommendation must be applied with caution

Table 3 Early Access Program eligibility requirements

Indications and requirements	Relative or absolute contraindications
Children 1 year of age up to closure of growth plates confirmed on bone age X-ray	Concomitant use of phosphate and/or calcitriol
X-linked hypophosphataemic Rickets (XLH) supported by ONE of the following: • Family history which supports X-linked inheritance • Confirmed PHEX mutation in the patient • Elevated serum FGF23 level	Pregnancy History of hypersensitivity to Burosumab likely to lead to adverse reaction Nephrocalcinosis on renal USS ≥ Stage 3 (uniform intense echoes throughout the pyramid) Hypocalcaemia or hypercalcaemia (fasting bloods)
Fasting serum phosphorus ≤0.90 mmol/L	Tertiary hyperparathyroidism
Fasting serum creatinine within normal range	25 hydroxyvitamin D < 50 nmol/L
Height < 50th centile (length for children <2 years old)	Immunodeficiency (congenital or acquired)
Radiographic evidence of rickets	Use of other monoclonal antibody within 90 days of starting Burosumab
At least 6 months of phosphate and calcitriol therapy	

Clinical approach

Clinical assessment of a child with XLH should include monitoring of height and height velocity, weight and assessment of rickets and lower limb deformity, including visual evaluation, measurement of intercondylar or intermalleolar distances (ICD/IMD) and assessment of limb length discrepancy. Radiographic assessment is important in monitoring rickets and deformity and helps guide referral for orthopaedic intervention. Evaluation for symptoms such as pain, fatigue and psychosocial impacts may be measured using patient reported outcomes or questionnaire tools. Functional assessments (such as 6-min walk test) can assist in understanding the burden and impact of disease. Signs of craniosynostosis (head shape, size and neurological complaints), kyphoscoliosis, and dental issues should be assessed and may prompt specialist referrals. Neurological symptoms such as neck or back pain, lower limb parasthesias or weakness may indicate a rarer neurological complication such as spinal stenosis, syringomyelia or Chiari malformation, while vomiting or headache may reflect raised intracranial pressure.[5,21,22] Regular monitoring of biochemistry (ensuring use of age appropriate reference ranges) assists with adjustment of medication dosing of burosumab or conventional therapy. Table 4 shows the screening and follow-up used at the authors' centres and suggested in the protocol (B,1++). Post-menarchal femlaes should be counselled on the need for contraception where appropriate as this agent is not currently approved for use in pregnancy.

Monitoring, follow-up and adjustment of burosumab dose

After commencing burosumab, fasting serum phosphate should be measured every 4 weeks for the first 3 months then 3-monthly thereafter. The dose is increased if fasting serum phosphate is below the normal range for age on two consecutive occasions 4 weeks apart, and the dose withheld if the level is above normal range, then recommenced at a decreased dose once the level is below the normal range (see Fig. 1). Fasting serum phosphate level should be reassessed 4 weeks after any dose adjustment. Burosumab should not be adjusted more frequently than every 4 weeks as a shorter interval does not allow for the outcome of the new dose to be assessed (A,1+++). Some centres additionally measure phosphate to calculate Tmp/GFR to assess degree of renal phosphate wasting, but this is not part of routine care at most centres, and the authors are unaware of this being used to adjust burosumab dose.

Side-effects of burosumab

The most commonly reported adverse effect of burosumab in children is injection site reaction, including injection site pain, erythema, swelling and rash. Most require no treatment and self-resolve in 1–3 days. It is the experience of the authors that injection site reactions reduce with time. If the reactions are troublesome, a dose of oral non-sedating antihistamine can be given 30 min before burosumab injection – this appears to lessen the skin reaction. The most common hypersensitivity reactions seen

Table 4 Recommended schedule of assessments in children with XLH treated with Burosumab

		Initial 12 weeks				3 monthly follow-up †						
Stage	Screening	Day of first injection	W4	W8	W 12	M6	M9	M12	M15	M18	M21	M24
Written consent	X											
Auxology	X				X	X	X	X	X	X	X	X
DXA/pQCT (if available)	X							X				X
Renal USS	X							X				X
Dental review	X (with OPG)					X		X		X		X
AP X-ray knees and wrist	X							X				X
Serum calcium, P04, Mg, ALP, albumin,	X	X	X	X	X	X	X	X	X	X	X	X
UEC	X				X	X		X		X		X
PTH	X				X	X		X		X		X
25 OH Vit D	X					X		X		X		X
1,25 dihydrox Vit D	X					X		X		X		X
Urine Ca:Cr ratio	X				X	X		X		X		X
Pregnancy test‡	X											
6MWT	X							X				X

† After 24 months remain on 3 monthly follow up protocol. ‡ Post-menarchial females. PO4 and ALP levels need to considered alongside appropriate age and gender matched reference ranges. 6MWT, 6 min walk test; ALP, alkaline phosphatase; AP, anterior–posterior; DXA, dual-energy X-ray absorptiometry; Mg, magnesium; PO4, phosphate; pQCT, peripheral quantitative computed tomography; PTH, parathyroid hormone; UEC, urea and electrolytes.

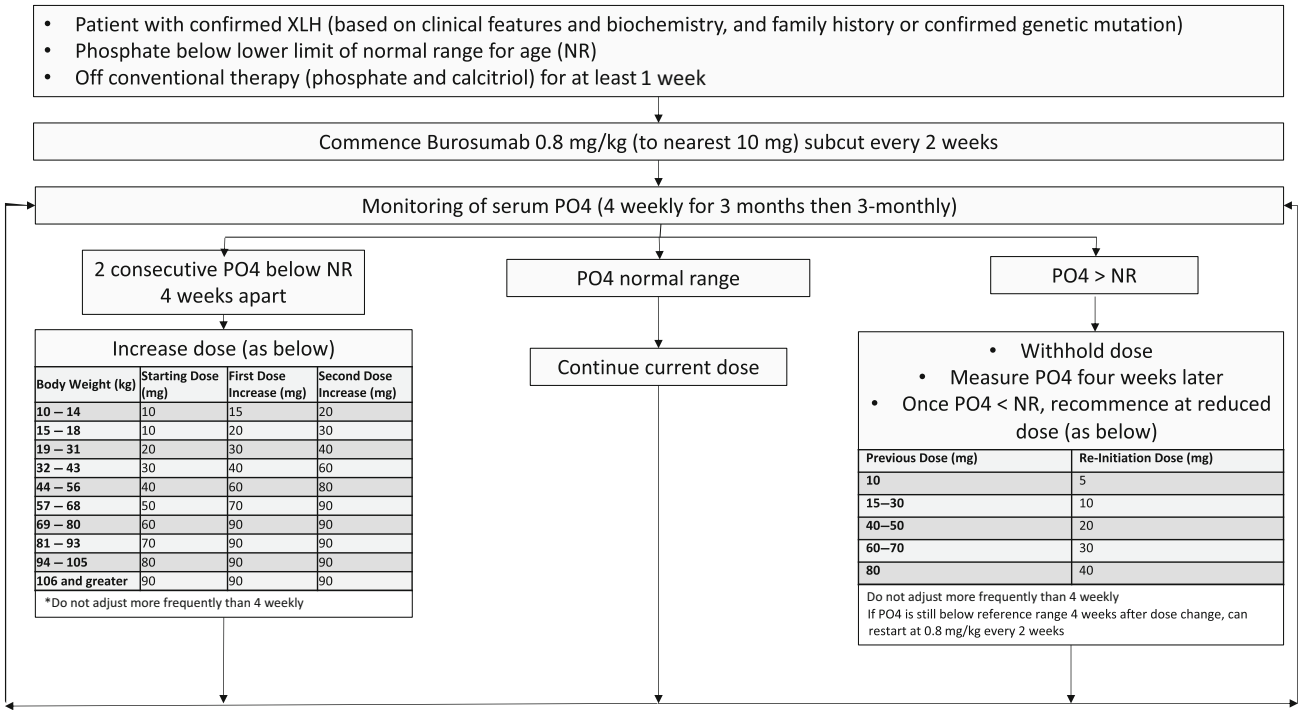

Fig. 1 A guide to dose adjustment for patients on burosumab.

are rashes and have been reported as mild or moderate in severity. Other adverse events noted in clinical trials included an increase in frequency of tooth abscess and dental caries in the burosumab group as compared to the control group, gastrointestinal (vomiting, diarrhoea and constipation), and reduction in serum 25-hydroxy vitamin D, although the latter is unlikely to be related to the agent.[10] Fever in children and restless leg syndrome or bone pain in adults have also been reported. The authors have not seen these side-effects in their clinical experience; however, the dental effects of burosumab require further investigation.

Current and Future Considerations in Management of XLH

Multidisciplinary team management

A coordinated multidisciplinary team is integral to the management of all individuals with rare bone diseases, yet there is variable access to this across Australasia and the world. The authors' recommendations for multidisciplinary team members are outlined below. Care can be coordinated by a paediatrician, general practitioner or a specialist paediatric endocrinologist or nephrologist.

Endocrinologist/nephrologist

We recommend that the management of all children with XLH be supervised by a paediatric endocrinologist or nephrologist, preferably with experience in bone disorders. Following the start of burosumab, we recommend that patients are reviewed by their endocrinologist or nephrologist fortnightly for the first month, then 3 monthly. With time, these reviews may be able to become less frequent, particularly if patients are seen by a local general practitioner or general paediatrician. During these visits, the treating clinician should assess for complications and comorbidities as outlined above.

Physiotherapist and occupational therapist

Optimisation of physical function and participation in school are key goals in the management of paediatric XLH. Regular reviews by physiotherapists and occupational therapists are essential to achieving these aims. There is evidence that physiotherapy programs improve motor function in patients with XLH.[23] Collaboration with schools and local therapy services are other important roles of treating therapists (B,1++).

Psychologist and social worker

In addition to (and because of) the significant physical burden of disease, XLH often impacts on the psychological wellbeing of patients with XLH, especially during adolescence.[24,25] Qualitative research has found that the lives of those with XLH are negatively impacted in many aspects, including quality of life, physical activity, psychological distress, family and social life, and that the life-long burden of disease can manifest as depression, anxiety and isolation.[24] Studies have also demonstrated an increased rate of mental health issues such as depression and low self-esteem in individuals with XLH.[24–27] Despite this, most Australian centres do not have a dedicated or specialised social worker or

psychologist for paediatric bone disorders. The authors recommend that all children with XLH have access to psychological services. The treating team also need to be aware of the psychological impact of XLH, be proactive in holistic assessments and refer early if concerns are noted (B, 1++).

General practitioner (and/or general paediatrician)

Engagement with a patient's local doctor is an essential aspect of care for all chronic diseases, especially for patients living remotely.[28] As burosumab injections are administered by healthcare professionals, engaging the child's general practitioner is essential to ensure access to therapy. Utilising a secure online database, such as REDCap, which allows GPs to record and share information with specialists (e.g. doses given, side effects, and investigations) can support shared GP/specialty care. Such a database has the potential to be developed into a national database to assist in quality assurance and research.

Use of telehealth medicine has increased due to the global COVID-19 pandemic, with studies indicating their ongoing use post-pandemic is likely.[29,30] Benefits of telehealth in paediatric XLH may include reduced travel for families, better engagement within the MDT, as well as allowing specialist clinicians or therapists to guide local GPs or therapists in clinical assessment of patients. Despite potential benefits, the authors do not recommend exclusive use of telehealth given limitations in clinical examination that are important in the assessment of children with XLH.

Orthopaedic surgeon

Children with lower limb or spinal deformities should be referred to an orthopaedic surgeon with experience in metabolic bone disease for consideration of operative management. In the absence of significant deformity, the degree of lower limb deformity should be noted (intercondylar and/or intermalleolar distance depending on deformity) at each visit, and if increasing or not improving, a referral should be made for orthopaedic review. Children presenting later with significant lower extremity bowing may demonstrate gradual improvement in deformity with optimal medical treatment, but growing children may benefit from guided growth (hemiepiphysiodesis) or more extensive surgery to improve residual bowing after optimisation of medical therapy. Post-surgical optimisation of medical therapy is critical to ensure that the benefits of surgical intervention are maintained[5] (B, 1++).

Dentist

Abnormal tooth development in XLH results in increased risk of periodontal disease, dental caries and abscess, so dental hygiene and frequent dental reviews are important, with 6 monthly review recommended in childhood.[2,5] The effect of burosumab on dental manifestations in XLH is unclear. The phase 3 RCT of burosumab versus conventional therapy in children with XLH noted a numerical increase in frequency of dental complications in the burosumab group,[10] but the clinical relevance of this has not been determined. This has not been seen in other studies and further research is needed (A,1+++).

Genetics counsellor/clinical geneticist

XLH is an X-linked dominant genetic disease that can be sporadic or inherited. Genetic testing for *PHEX* mutations can be helpful in diagnosis and to counsel the family on inheritance risk for family members. This includes antenatal genetic counselling for future siblings of the proband and the risk of the patient's own child inheriting XLH. Involvement of a clinical geneticist or genetic counsellor is important in this process, as well as social work or psychology as needed.[5] The impact on the family of an inherited disease can include guilt surrounding inheritance, sibling issues, and anxiety regarding implications for a child's future family (B,1++).

Radiologist

Involvement of a radiologist, ideally with experience in paediatrics and/or bone disorders, is important in managing XLH. Radiographical scoring systems for rickets (Thacher Rickets Severity Score and Radiographical Global Impression of Change) are validated in XLH, shown to correlate with clinical parameters, and are useful in tracking clinical improvements.[31,32] In the absence of significant lower limb bowing, a bone age X-ray is sufficient to monitor rickets. Monitoring for spinal cord stenosis is also important, and needs to be considered in the presence of back pain.

Plain X-rays of upper and lower limbs are used to identify and score rickets and assess for leg length discrepancy or lower limb deformity.[31,32] Spinal X-rays are indicated when there is clinical evidence of scoliosis, and cranial imaging (X-rays, CT, or MRI) is indicated in those with suspected craniosynostosis or neurological symptoms.[33] Renal ultrasound is the modality of choice for monitoring for nephrocalcinosis and allows for grading and tracking of severity of nephrocalcinosis[34] (B,1++).

Transition

As with all chronic health conditions, transition of care from paediatric to adult services is an important consideration. Although systematic data on management of adults with XLH in Australia are lacking, anecdotal data suggest that many adults with XLH are not on specific medical therapy and do not have regular review. With burosumab approved for both adults and children, guidelines and systems are needed to facilitate effective transition to adult care. Furthermore, there are very limited data guiding appropriate dosing of burosumab for adults who started burosumab in childhood. While the long-term outcomes of burosumab therapy are not yet clear, those who have been treated with burosumab from an early age are likely to have a reduced burden of disease compared to those who have not, and therefore a reduced health-care requirement throughout adulthood.

Conclusion

Burosumab has transformed management of XLH and been shown to result in significant improvements in burden of disease. While there are challenges in adapting new therapies to the "real-world" context, this guideline has been used successfully in managing patients around Australia and the world during the Early Access Program. Some areas of further research to improve

management of XLH in the era of burosumab include assessment of burosumab's dental effects in XLH, determining of optimal frequency of reviews and monitoring of those on long-term burosumab, optimising dose adjustment and the transition from paediatric to adult care. Although burosumab negates the detrimental effects of elevated FGF23 levels in children with XLH, it is unclear if the *PHEX* mutation itself has other non-FGF23 mediated bone or non-bone effects that will need ongoing management.

As with most chronic health conditions, multidisciplinary management is essential in ensuring quality, holistic care. The improvements seen with burosumab are promising and will likely lead to less morbidity for patients and reduce the overall burden on the health-care system, including reduced pain and functional impairment, frequency of specialist reviews, and orthopaedic or other surgical procedures. However, these potential improvements do not lessen the importance of collaboration within these health teams and the wider community to further optimise care for children and adults with XLH in order to enhance quality of life and further limit disease burden.

References

1 Carpenter TO, Shaw NJ, Portale AA, Ward LM, Abrams SA, Pettifor JM. Rickets. *Nat. Rev. Dis. Primers* 2017; **3**: 17101.
2 Beck-Nielsen SS, Mughal Z, Haffner D *et al*. FGF23 and its role in X-linked hypophosphatemia-related morbidity. *Orphanet J. Rare Dis.* 2019; **14**: 58.
3 Che H, Roux C, Etcheto A *et al*. Impaired quality of life in adults with X-linked hypophosphatemia and skeletal symptoms. *Eur. J. Endrocrinol* 2016; **174**: 325.
4 Linglart A, Biosse-Duplan M, Briot K *et al*. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr. Connect.* 2014; **3**: R13–30.
5 Haffner D, Emma F, Eastwood DM *et al*. Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. *Nat. Rev. Nephrol.* 2019; **15**: 435–55.
6 Imel EA, DiMeglio LA, Hui SL, Carpenter TO, Econs MJ. Treatment of X-linked hypophosphatemia with calcitriol and phosphate increases circulating fibroblast growth factor 23 concentrations. *J. Clin. Endocrinol. Metab.* 2010; **95**: 1846–50.
7 Antoniucci DM, Yamashita T, Portale AA. Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. *J. Clin. Endocrinol. Metab.* 2006; **91**: 3144–9.
8 Carpenter TO, Imel EA, Holm IA, Jan de Beur SM, Insogna KL. A clinician's guide to X-linked hypophosphatemia. *J Bone Mineral Res.* 2011; **26**: 1381–8.
9 Ferizović N, Marshall J, Williams AE *et al*. Exploring the burden of X-linked hypophosphataemia: An opportunistic qualitative study of patient statements generated during a technology appraisal. *Adv. Ther.* 2020; **37**: 770–84.
10 Imel EA, Glorieux FH, Whyte MP *et al*. Burosumab versus conventional therapy in children with X-linked hypophosphataemia: A randomised, active-controlled, open-label, phase 3 trial. *Lancet* 2019; **393**: 2416–27.
11 Schindeler A, Biggin A, Munns CF. Clinical evidence for the benefits of Burosumab therapy for X-linked hypophosphatemia (XLH) and other conditions in adults and children. *Front Endocrinol.* 2020; **11**: 338.
12 Imel EA, Biggin A, Schindeler A, Munns CF. FGF23, hypophosphatemia, and emerging treatments. *JBMR Plus.* 2019; **3**: e10190.
13 Portale AA, Carpenter TO, Brandi ML *et al*. Continued beneficial effects of burosumab in adults with X-linked hypophosphatemia: Results from a 24-week treatment continuation period after a 24-week double-blind placebo-controlled period. *Calcif. Tissue Int.* 2019; **105**: 271–84.
14 Insogna KL, Briot K, Imel EA *et al*. A randomized, double-blind, placebo-controlled, phase 3 trial evaluating the efficacy of burosumab, an anti-FGF23 antibody, in adults with X-linked hypophosphatemia: Week 24 primary analysis. *J. Bone Miner. Res.* 2018; **33**: 1383–93.
15 Whyte MP, Carpenter TO, Gottesman GS *et al*. Efficacy and safety of burosumab in children aged 1–4 years with X-linked hypophosphataemia: a multicentre, open-label, phase 2 trial. *Lancet Diab. Endocrinol.* 2019; **7**: 189–99.
16 Carpenter TO, Whyte MP, Imel EA *et al*. Burosumab therapy in children with X-linked hypophosphatemia. *N. Engl. J. Med.* 2018; **378**: 1987–98.
17 Sandy J, Cross R, Santos R, *et al*. Nine-month follow-up data on biochemical, clinical, radiological and functional parameters in a clinical cohort of children at Evelina London Children's Hospital with X-linked hypophosphataemia treated with Burosumab. Bone Abstracts. 2019.
18 Cheung M, Sakka S, Gilbey-Cross R, Harries M, Mathieson L. SUN-523 XLH outcome data from one centre experience with burosumab. *Journal of the endocrine Society* 2019; **3** (Supplement_1). https://doi.org/10.1210/js.2019-SUN-523
19 Swiglo BA, Murad MH, Schünemann HJ *et al*. A case for clarity, consistency, and helpfulness: State-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. *J. Clin. Endocrinol. Metab.* 2008; **93**: 666–73.
20 National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendation. December 2009. Canberra, ACT. 2009.
21 Chesher D, Oddy M, Darbar U *et al*. Outcome of adult patients with X-linked hypophosphatemia caused by PHEX gene mutations. *J. Inherit. Metab. Dis.* 2018; **41**: 865–76.
22 Watts L, Wordsworth P. Chiari malformation, syringomyelia and bulbar palsy in X linked hypophosphataemia. *BMJ Case Rep.* 2015; **2015**: bcr2015211961.
23 Hughes M, Macica C, Meriano C, Doyle M. Giving credence to the experience of X-linked hypophosphatemia in adulthood: An Interprofessional mixed-methods study. *J. Patient Cent. Res. Rev.* 2020; **7**: 176–88.
24 Cheung M, Rylands AJ, Williams A, Bailey K, Bubbear J. Patient-reported complications, symptoms, and experiences of living with X-linked hypophosphatemia across the life-course. *J. Endocr. Soc.* 2021; **5**: bvab070.
25 Lo SH, Lachmann R, Williams A, Piglowska N, Lloyd AJ. Exploring the burden of X-linked hypophosphatemia: A European multi-country qualitative study. *Qual. Life Res.* 2020; **29**: 1883–93.
26 Theodore-Oklota C, Bonner N, Spencer H, Arbuckle R, Chen CY, Skrinar A. Qualitative research to explore the patient experience of X-linked hypophosphatemia and evaluate the suitability of the BPI-SF and WOMAC® as clinical trial end points. *Value Health* 2018; **21**: 973–83.
27 Hawley S, Shaw NJ, Delmestri A *et al*. Higher prevalence of non-skeletal comorbidity related to X-linked hypophosphataemia: A UKparallel cohort study using CPRD. *Rheumatology (Oxford)* 2021; **60**: 4055–62.
28 Valentijn PP, Schepman SM, Opheij W, Bruijnzeels MA. Understanding integrated care: A comprehensive conceptual framework based on the integrative functions of primary care. *Int. J. Integr. Care* 2013; **13**: e010.
29 Bitar H, Alismail S. The role of eHealth, telehealth, and telemedicine for chronic disease patients during COVID-19 pandemic: A rapid systematic review. *Digit. Health* 2021; **7**: 20552076211009396.

30 Andrews E, Berghofer K, Long J, Prescott A, Caboral-Stevens M. Satisfaction with the use of telehealth during COVID-19: An integrative review. *Int. J. Nurs. Stud. Adv.* 2020; **2**: 100008.
31 Lim R, Shailam R, Hulett R *et al*. Validation of the radiographic global impression of change (RGI-C) score to assess healing of rickets in pediatric X-linked hypophosphatemia (XLH). *Bone* 2021; **148**: 115964.
32 Thacher TD, Pettifor JM, Tebben PJ *et al*. Rickets severity predicts clinical outcomes in children with X-linked hypophosphatemia: Utility of the radiographic rickets severity score. *Bone* 2019; **122**: 76–81.
33 Vega RA, Opalak C, Harshbarger RJ *et al*. Hypophosphatemic rickets and craniosynostosis: A multicenter case series. *J. Neurosurg. Pediatr.* 2016; **17**: 694–700.
34 Boyce AM, Shawker TH, Hill SC *et al*. Ultrasound is superior to computed tomography for assessment of medullary nephrocalcinosis in hypoparathyroidism. *J. Clin. Endocrinol. Metab.* 2013; **98**: 989–94.