A retrospective study of the clinical, biochemical and radiological profile of children with genetic hypophosphataemic rickets: Response to conventional treatment

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Background. In South Africa, there is a paucity of data on the profile of hypophosphataemic rickets and response to conventional treatment like oral phosphate and alfacalcidol

Objectives. To assess the clinical, biochemical and radiological profile of children with genetic hypophosphataemic rickets and their response to conventional treatment.

Methods. Retrospective descriptive study of children under the age of 18 years with hypophosphataemic rickets. Height, calcium, phosphorus, alkaline phosphatase (ALP), and parathyroid hormone (PTH) levels were assessed at 3, 6, 9 and 12 months of age and annually thereafter. The Thacher radiological score at baseline and at regular intervals was determined after commencing treatment.

Results. Seventy patients met the inclusion criteria. A positive family history was obtained in 32 (46%) patients. Thirty-three (47%) patients were poorly compliant with treatment. The patients were short-statured with a mean height-for-age *Z*-score (HAZ) of –3.4 (1.79). The mean (standard deviation) calcium, phosphate, ALP and PTH levels and median (range) Thacher score were 2.3 (0.16) mmol/L, 0.84 (0.19) mmol/L, 776.6 (531) U/L, 7.15 (4.8) pmol/L and 8 (4 - 8), respectively, at baseline. At 5-year follow-up, improvements were seen in ALP (525 (232) v. 776 (531); $p<0.001$) and Thacher scores (2 (1-3.5) v. 8 (4 - 8); $p=0.01$) with treatment, however, there were no changes in phosphate levels or HAZ.

Conclusion. Conventional therapy for treatment of hypophosphataemic rickets is not associated with an improvement in HAZ despite an improvement of the Thacher score and ALP. Compliance is a major challenge for majority of patients.

Keywords. X-linked hypophosphataemic rickets, rickets, treatment response, children, serum alkaline phosphatase.

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Rickets is a bone disorder characterised by decreased mineralisation of cartilage matrix at the growth plate, resulting from disrupted calcium or phosphate homeostasis. X-linked hypophosphataemic (XLH) rickets is the most common inheritable form of hypophosphataemic rickets caused by a loss-of-function mutation in the phosphate regulating endopeptidase homologous on the X chromosome *(PHEX)* gene, leading to excess circulating fibroblast growth factor 23 (FGF23), impairing phosphate reabsorption in the kidneys and reducing the synthesis of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), thus resulting in renal phosphate wasting and hypophosphatemia.[1] Other less common inheritable forms of hypophosphataemic rickets (excluding various inherited forms of Fanconi syndrome) include autosomal dominant and recessive forms affecting FGF23 homeostasis or hereditary hypophosphataemic rickets with hypercalciuria (HHRH).

Phosphate is essential for bone formation. Phosphate deficiency results from poor absorption in the gut or excessive loss through the kidneys. The main regulators of phosphate homeostasis are parathyroid hormone (PTH), FGF23, αKlotho, PHEX and $1,25(OH)_2D$. PTH mobilises phosphate from skeletal bones into the blood stream by enhancing osteoclastic bone resorption[2] and decreases reabsorption of filtered phosphate along the proximal tubule. FGF23 is a glycoprotein that decreases renal phosphate reabsorption. FGF23 also decreases $1,25(OH)_2D$ leading to decreased calcium and phosphate absorption in the gut and in the kidneys.[3,4] PHEX regulates and restricts FGF23 expression. Inactivating mutations in PHEX increase circulating levels of FGF23 that result in phosphaturia, hypophosphataemia and suppressed conversion of 25-hydroxyvitamin D (25(OH)D) to $1,25(OH)_2D$ in the kidney.[5] $1,25(OH)_2D$ also stimulates phosphate absorption from the gut. Lower $1,25(OH)_2D$ levels result in decreased intestinal phosphate absorption and non-suppression of PTH synthesis and FGF23 production.[6]

Diagnosis of genetic hypophosphataemic rickets (mainly XLH) involves three main possibilities:

1. Diagnosis of familial cases: About 85 - 90% of familial cases follow an X-linked dominant inheritance pattern. Babies born to an affected parent should undergo biochemical screening, including measuring serum calcium, PTH, phosphate and ALP levels as well as measuring urinary tubular reabsorption of phosphate. In hypophosphataemic rickets, the serum phosphate level is typically below the normal range for age, while ALP is above the upper level of normal.[1]
2. Diagnosis of *de novo* cases of XLH rickets: Children with XLH rickets due to PHEX mutations without a family history but with clinical, radiological and biochemical abnormalities should be evaluated. Clinical features include leg bowing, widening of the metaphyses at the ankles and wrists, and dental abnormalities.[6]

Radiological signs include long bone deformities, abnormal growth plates with splayed and frayed metaphyses and dense-appearing cortices.[7] Biochemically, serum phosphate levels are below normal for age, while ALP levels are above the upper limit of normal. PTH levels are usually in the normal or upper normal range and serum calcium is normal. Other disorders causing phosphate wasting and vitamin D or dietary calcium deficiencies must be ruled out.[8]

3. Genetic confirmation of XLH: Definitive confirmation of XLH is achieved through identification of mutations in the PHEX gene.[8]

Treatment should be initiated early to prevent rachitic changes, leg bowing and short stature. Conventional therapy includes oral phosphate supplements and active vitamin D (calcitriol or alfacalcidol (1- hydroxycholecalciferol)).[9] Since serum phosphate returns to baseline concentrations within 1.5 hours of phosphate intake, medication must be given frequently 4 - 6 times daily. Active vitamin D is given in addition to oral phosphate supplements to counteract calcitriol deficiency, prevent secondary hyperparathyroidism and to increase phosphate absorption from the gut.[10]

In SA, there is a paucity of published data on the management of genetic hypophosphataemic rickets and the response to conventional treatment. Burosumab is a human monoclonal IgG1 antibody that neutralises FGF23. In February 2018, burosumab was approved for the treatment of XLH by The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).[9] Although long-term follow-up is only now becoming available, data suggest that burosumab has a number of advantages compared with conventional therapy.[11] Burosumab is an expensive drug, with an average annual drug cost of USD129 780 to S1 168 196 (https://www.formulary.health.gov.on.ca/formulary/) recorded in September 2019).[11] Burosumab is neither approved for use nor available in SA and conventional treatment is offered to patients. We hypothesise that conventional therapy for the treatment of genetic hypophosphataemic rickets (mainly XLH rickets) and other genetic causes of hypophosphataemic rickets is not adequate. If this hypothesis is proven true, burosumab should be made available to all patients with genetic hypophosphataemic rickets in SA, provided funding is possible.

Methods

Aim

To report the biochemical profile of presumed genetic hypophosphataemic rickets, including XLH at presentation and to monitor the biochemical and radiological response to conventional therapy.

Primary objectives

1. To assess the biochemical profile of genetic forms of hypophosphataemic rickets at baseline.
2. To evaluate the effectiveness of conventional therapy in treating genetic hypophosphataemic rickets by assessing improvements in biochemical and serum bone markers (calcium, phosphate, ALP and PTH) at 3, 6, 9 and 12 months after the start of treatment and annually thereafter.
3. To assess changes in the Thacher radiological score from baseline to 12 months after commencing treatment and intermittently thereafter at follow-up.

Secondary objectives

1. To review medical records for documentation of compliance issues at 3, 6, 9 and 12 months and annually thereafter.
2. To assess improvement or changes in height for age z (HAZ) scores at 6, 12 and 24 months and annually thereafter.
3. To assess the presence of a family history of genetic hypophosphataemic rickets.

Study population and sample size

Children under the age of 18 years who commenced treatment for hypophosphataemic rickets at the Metabolic Bone Clinic at Chris Hani Baragwanath Academic Hospital from 1 January 2006 until 30 April 2020, and who were following up at the clinic thereafter, were included.

Inclusion criteria

Children diagnosed with presumed genetic hypophosphataemic rickets with typical clinical and radiological features, and with the characteristic biochemical profile at baseline or prior to treating (normal calcium, normal PTH or <2.5 times the upper limit of normal) and low phosphate levels (below the normal reference limits for age[12]), with or without a positive family history of hypophosphataemic rickets and who commenced on conventional treatment of phosphate and alfacalcidol.

Exclusion criteria were:

- Calciopaenic rickets
- Hypophosphataemic rickets secondary to Fanconi syndrome or renal tubular acidosis
- Hypophosphataemic rickets secondary to tumour-induced osteomalacia or fibrous dysplasia.
- Patients already commenced on conventional therapy (> 3 months duration) at referral.
- Hypocalcaemia or hypercalcaemia, defined as serum calcium levels outside age-adjusted normal limits.
- Evidence of hyperparathyroidism (PTH levels >2.5 times the upper limit of normal)

Study design and methods

This was a retrospective descriptive study. Patient medical records were reviewed for clinic attendance, clinical findings (including anthropometric measurements), laboratory tests (serum phosphate, ALP, PTH and calcium) and prescribed treatment. The biochemical profile at the first visit was compared with the profiles at 3, 6, 9, 12 months and annually until the last recorded follow-up visit after starting treatment.

The Thacher score is a 10-point scoring system of radiographic rachitic changes, where a score of 10 is extreme changes and 0 is absence of radiological rachitic changes. This score was utilised to measure severity and to assess radiographic response following treatment.[13] The Thacher severity score was performed by the researcher (NI) and confirmed by the supervisor (KT) on wrist and knee x-rays done at baseline and repeated for x-rays performed at 12-monthly intervals until the last available radiological assessment.

Compliance was recorded in the patients' files by the attending doctor. This was based on missed appointments or if the patient reported non-compliance with therapy or missed collecting medication from the pharmacy on a monthly basis between check-ups.

Statistical analysis

Statistical analyses were descriptive. Data were captured in a Microsoft Excel spreadsheet (Microsoft Corp. USA) and analysed using Statistica version 13.5 (TIBCO Software Inc., USA). Categorical variables are reported as numbers and percentages. Continuous variables are reported as means and standard deviations (SDs) or

medians and interquartile ranges (IQRs) where applicable. Mann-Whitney *U*-test and student's *t*-test were performed to compare the variables within the different time periods of follow-up visits. For mean changes in biochemical markers, radiological scores and HAZ scores from baseline until the 5-year follow-up, the Wilcoxon matched paired tests was performed to generate box-whisker plots with means (SD) and $p<0.05$ was regarded as significant.

Ethics

The protocol was approved by the Human Research Ethics Committee of the University of the Witwatersrand and permission was obtained from the CEO of CHBAH (HREC ref. no.: M191123). To maintain anonymity, patients were assigned study numbers.

Results

A total of 70 patients (n/*N*=70/83) met the inclusion criteria and majority of patients were black South Africans (*n*=54;77%). The male to female ratio was 1:1.7. The mean (SD) age of the patients at presentation was 59.1 (44.6) months; range was 2 -193 months. There was a positive family history for hypophosphataemic rickets in 32 (46%) patients, of whom 23 had first-degree relatives (parent or siblings) affected and the remainder were second-degree (uncles, aunts or grandparents). The areas of referral were from within Gauteng Province for 55 (79%) patients, while 7 (10%) patients were from North West, 5 (7%) from Limpopo Province and 3 (4%) patients were from neighbouring countries.

Most of the patients (*n*=55 (80%)) were short-statured (HAZ <–2) with a mean (SD) HAZ of –3.4 (1.79), and 40 patients (58%) were of normal weight with a mean (SD) weight-for-age *Z*-score (WAZ) of –1.7 (1.7).

Clinical characteristics at presentation

The main reason for referral in most patients was long-bone deformities. Most patients presented with genu varus deformities (*n*=57; 81%), widened wrists (*n*=51; 73%), frontal bossing (*n*=44; 63%) and rachitic rosary (*n*=42; 60%).

Biochemistry, HAZ and radiological findings at presentation and follow-ups

The mean (SD) serum total calcium at presentation was 2.3 (0.16) mmol/L (reference range 2.12 - 2.54). The mean (SD) phosphate was low (0.84 (0.19) mmol/L (reference range 1.38 - 2.19)) at presentation and it did not improve (0.91 (0.24); $p=0.50$) at the 5-year follow-up visit (Fig. 1). The mean ALP was elevated at presentation (776.6 (531)U/L (reference range 75 - 341)) and improved at the 5-year follow-up (525 (231); $p<0.001$) (Fig. 2). Mean PTH at presentation was 7.15 (4.8) pmol/L (reference range 1.6 - 6.9) and at the last follow-up visit it was 6.61 (3.81) pmol/L ($p=0.62$). The mean (SD) HAZ did not improve over the follow-up period (–3.74 (1.59); $p=0.21$) (Fig. 3). There was improvement in the median (IQR) Thacher scores from baseline to the 5-year follow up (8 (4 - 8) v. 2 (1 - 3.5); $p=0.01$), but radiological evidence of mild rickets was still evident in the majority of patients at the end of 5 years of treatment.

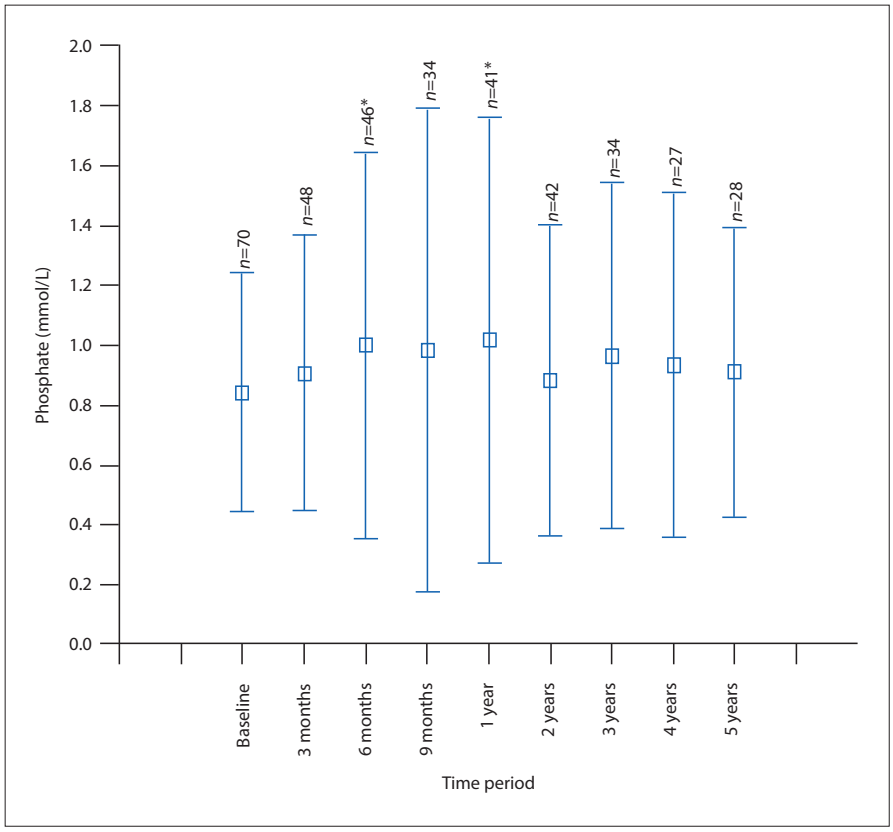

*Fig. 1. Phosphate from baseline until 5-year follow-up. (*p<0.05; †p<0.01: ‡p<0.001)*

Nearly half of the patients (*n*=33; 47%) were noted to have poor compliance with treatment. In patients with good compliance (51%), the mean ALP improved from 858 (646) U/L to 477 (211) U/l; $p=0.04$, while in the poor compliance group, the mean ALP remained high; 678 (333) U/L at the beginning of treatment and 574 (248) U/L ($p=0.30$) at their last recorded follow-up visit.

The mean serum phosphate remained unchanged in response to treatment irrespective of compliance ($p=0.44$) (Fig. 1). The patients' mean HAZ remained low (Fig. 3), even in the complaint group after being on treatment (–3.54 (1.78) v. –3.37 (–1.82); $p=0.76$).

Discussion

XLH is the most common form of inherited hypophosphataemic rickets and therapy should be aimed at counteracting consequences of FGF23 excess. As XLH is an X-linked dominant condition, females are disproportionately affected.[14] A positive family history was noted in 32 (46%) patients, indicating that sporadic cases were more common than the hereditary type. Sporadic cases tend to be more prevalent in the black population (64%) compared with the white population (41%) in SA.[14] The current conventional treatment available in SA is multiple daily dosing of oral phosphate supplementation to compensate for renal phosphate wasting, together with active vitamin D analogues to counteract decreased $1,25(OH)_2D$ levels. The primary end-point for treatment shows improvement in rickets as evidenced by a reduction in ALP levels and improved radiological features.[15] Our study shows that, although conventional treatment improves some aspects of XLH, the renal wasting of phosphate and final height do not improve. Burosumab is a monoclonal antibody that targets FGF23 and is shown to be more effective in treating hypophosphataemic rickets by normalising

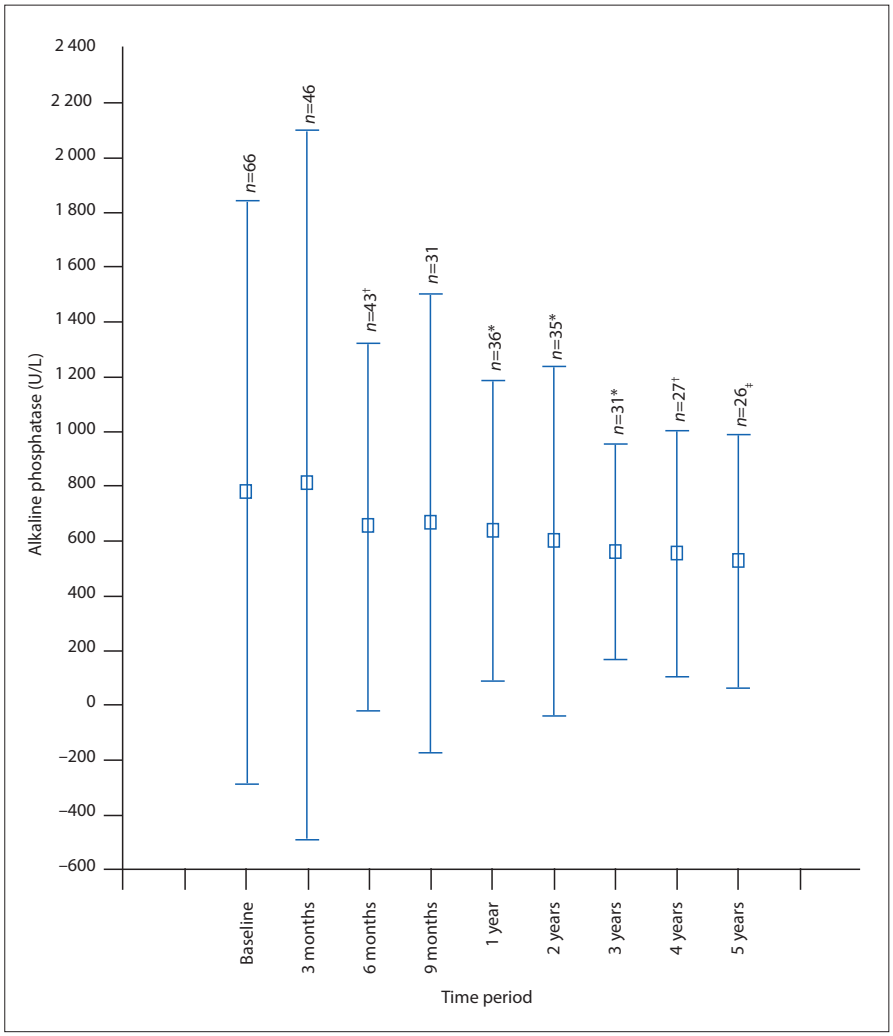

*Fig 2. Alkaline phosphatase (ALP) from baseline until 5-year follow-up. (*p<0.05;†p<0.01;‡p<0.001)*

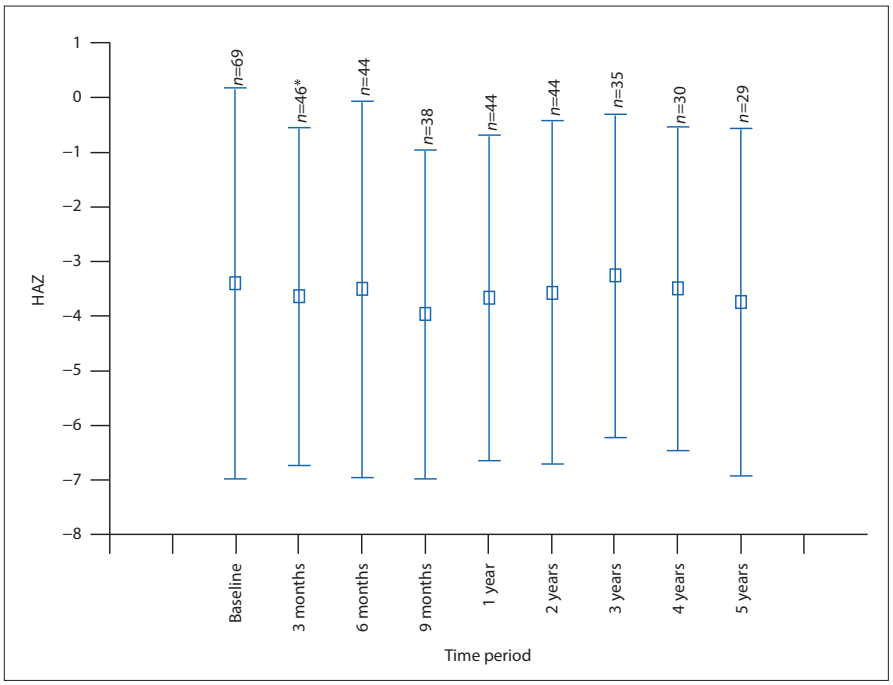

*Fig. 3. Height-for-age Z-score (HAZ) from baseline until 5-year follow-up. (*p<0.05; †p<0.01; ‡p<0.001).*

serum phosphate and ALP levels and height in patients with XLH.[10] Burosumab is also known to be well tolerated and the two weekly dosing regimens may make it more convenient to administer thus improving compliance.[10]

It has been shown that commencing treatment earlier in infancy within 3 months of age with conventional therapy yielded better results compared with commencing later.[16] Active rickets presents with bone deformities and disproportionate growth retardation which are major manifestations of XLH in the paediatric age. Dental mineralisation defects are also common problems.[6] The majority of patients included in this study presented with bone deformities and short stature, with only a few (2.9%) presenting with dental problems.

Conventional treatment did not improve height and the patients remained short for their age throughout the follow-up. A study has shown that after a year on burosumab, the height of patients increased from −3.56 to −0.46 SD,[10] suggesting that burosumab is a better modality of treatment in improving final height compared to conventional treatment.

At presentation the mean serum phosphate level was below the normal range for age, as expected with renal phosphate wasting. At the 5-year follow-up, while still on conventional treatment, the mean phosphate levels remained low, showing persistent renal phosphate wasting.

In keeping with the changes in the Thacher rickets score, the mean (SD) ALP level had improved over 5 years of follow-up (from 776 (531) U/L to 525 (232) U/L; $p<0.001$) indicating that rickets activity was improving on conventional treatment.

Mean PTH levels were in the upper normal range on presentation. Active vitamin D analogue supplementation is important to help prevent secondary hyperparathyroidism which can further worsen hypophosphataemia. All the patients in the study were supplemented with active vitamin D analogues. PTH levels at presentation and last follow-up visits were not significantly different ($p=0.62$), which shows that the patients were adequately supplemented with active vitamin D analogues and that secondary hyperparathyroidism was not a cause of the hypophosphatemia. In a previous study,[10] the use of burosumab for one year led to a mean (SD) increase in serum phosphate levels from 0.68 (0.13) to 1.07 (0.08), while the mean (SD) ALP improved from 628 (267) to 525 (419) U/L.

Radiographical examinations confirmed features of rickets with long-bone deformities, widened and frayed metaphyses, and thickened bone cortices. In this study, the median (range) Thacher score at baseline was 8 (4 - 8), while the Thacher score at 5-year follow-up improved to 2 (1 - 3.5) on conventional treatment.

Due to the multiple daily dosing of phosphate, compliance was recorded to be poor (47%). After categorising patients into good and poor compliance groups, the mean ALP had significantly declined or improved (p=0.04) in the good compliance group compared with the poor compliance group (p=0.30) from the beginning of treatment to the last recorded follow-up visits, indicating that compliance played a role in improved outcomes. However, mean phosphate levels remained low in the good compliance group on treatment (p=0.44).

The HAZ also did not improve in the compliant group as patients were still noted to be short after being on treatment (p=0.76). It is also important to take into consideration that in the compliant group, although the patients claimed to be compliant it does not mean they necessarily were compliant.

Burosumab is known to be well tolerated and the two-weekly dosing regimen makes it more convenient than the daily dosing of conventional treatment, thus possibly improving compliance.[10]

Owing to the retrospective nature of the study, we were unable to investigate the reasons for poor compliance, such as poor accessibility to a hospital (with medication available monthly), transport problems and financial constraints. Conventional treatment is frequently not available at their base hospital or clinic and patients often reside far away from CHBAH, contributing to the low compliance.

Although burosumab might be alternative medication, the financial and related ethical considerations such as cost-to-benefit ratio needs to be taken into consideration when prescribing this therapy.[17] However, given the costs of long-term treatment of patients with XLH, who often require surgery and prolonged admissions,[14] it may be beneficial to advocate for the use of burosumab in low- and middle-income countries to reduce the burden of this chronic condition. The consequent physical disability and short stature has an impact on these patients' psychosocial well-being. They also have an impact on their ability to secure a job in the long term or to do daily activities such as long-distance walking or driving. These adverse effects of the disease could possibly be reduced by treating with burosumab. Genetic confirmation of the underlying genetic mutation for affected families would be helpful although an added cost. In addition, it would be important to be part of collaborative international patient registries for XLH so that treatment options can be readily sourced for all patients with XLH.

Study limitations

Not all data were available for all patients at every time point owing to the retrospective nature of the study. Patients may have claimed compliance, but this may not have been true. Since no DNA testing is performed to confirm XLH or other genetic causes of hypophosphataemia in SA, patients were included in the study based on their biochemical profile, radiological findings (with or without a positive family history of hypophosphataemia) and commenced on conventional treatment after diagnosis. Therefore, this study may have included patients with other forms of inherited hypophosphataemic rickets involving FGF23 homeostasis and metabolism.

Conclusion

Conventional therapy for treatment of genetic hypophosphataemic rickets is not associated with an improvement in HAZ despite improvements in the radiological signs of rickets and ALP levels. Compliance is a major challenge for most patients, with the multiple daily dosing of phosphate supplements being a major contributory factor to poor compliance and outcomes.

On the other hand, burosumab has been shown to markedly improve ALP activity, serum phosphate levels and growth trajectories. Expanding access to this therapy in SA could transform the standard of care for patients with genetic hypophosphataemic rickets.

Declaration. The study was submitted in partial fulfilment of the Master of Medicine (Paediatrics) degree requirements by NI at the University of the Witwatersrand.

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Conflicts of interest. None.

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