Experience of burosumab therapy for 6 months in four children with X-linked hypophosphataemic rickets in Saudi Arabia

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BACKGROUND

- X-linked hypophosphataemia (XLH) is the most common form of inherited hypophosphataemic rickets, caused by loss-of-function mutations in the gene encoding phosphate-regulating endopeptidase homologue X-linked (*PHEX*), resulting in excess circulating fibroblast growth factor 23 (FGF-23)[1,2]
- In children, clinical features include delayed walking, waddling gait, leg bowing, pain, spontaneous dental abscesses and growth failure. Current therapies do not treat the underlying cause of the disease,[2] resulting in persistence of rickets, growth impairment, and gastrointestinal side effects[3]
- Burosumab is a novel, fully human anti-FGF-23 immunoglobulin G1 monoclonal antibody that binds and inhibits FGF-23 activity[4,5]
- Here, we describe the clinical and biochemical features of XLH in four paediatric patients treated with burosumab

CASE PRESENTATION

Patient characteristics

- Patients (one male, three females) were aged 2–11.5 years at diagnosis
- Classical radiological signs of rickets were seen in all 4 patients
- Patient family histories are shown in (**Table 1**)
- Baseline patient characteristics are shown in (**Table 1**)

Table 1. Baseline patient characteristics

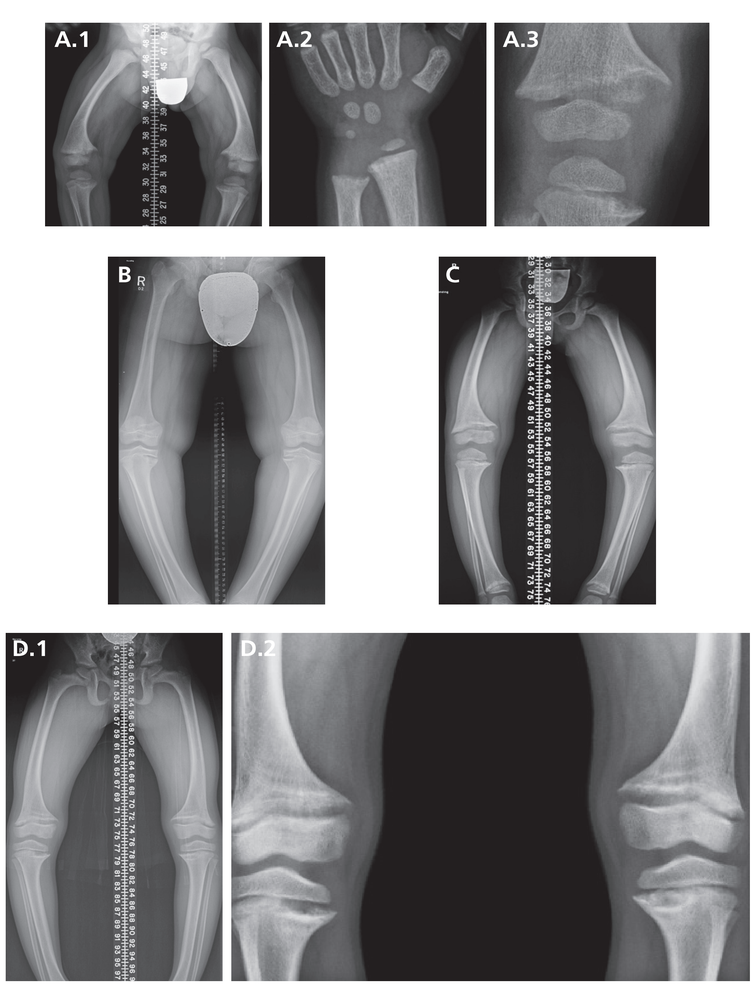
	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	2	11.5	4	8
Gender	Male	Female	Female	Female
Weight, kg	12.0	61.8	13.9	17.9
Height, cm	83.7	138.2	90.7	110
Median duration of conventional treatment, years	2.4	9	1.6	1.6
Serum phosphate, mmol/L (1–1.95)	0.90	0.90	0.90	0.85
PTH, pmol/L (1.60–7.20)	16.06	9.7	6.34	3.07
25-OH Vit D, nmol/L (50–125)	52.3	33.6	79.3	60.5
$1,25[OH]_2D$, pmol/L (62.2–228)	183.9	72.1	450.8	450.4
ALP, U/L (reference)	937 (156–369)	376 (141–460)	391 (156–369)	472 (156–369)
TmP/GFR mmol/L (1.15–2.44)	0.61	0.81	0.65	0.65
Intact FGF-23 levels RU/mL (26–110)	139	77	137	129
PHEX mutation	Positive Hemizygous *PHEX* mutation c1077del, heterozygous CYP2R1 mutation	Positive Heterozygous *PHEX* mutation c2070+5 G>A	Positive Heterozygous *PHEX* mutation c1682 G>A	Positive Heterozygous *PHEX* mutation c1682 G>A
Family history	No family history	Father has the same mutation and is severely affected by his symptoms	Father has the same mutation but is asymptomatic	Father has the same mutation but is asymptomatic

Numbers in brackets denote reference values unless otherwise stated. ALP, alkaline phosphatase; FGF-23 fibroblast growth factor 23; PTH, parathyroid hormone; *PHEX*, phosphate-regulating endopeptidase homologue X-linked; TmP/GFR, renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate; 25-OH Vit D, 25-hydroxyvitamin D.

Patient symptoms

- Physical symptoms included leg bowing in all patients (**Figure 1**); three patients had dental caries, two patients presented with a larger head circumference (≥95th percentile) and one patient had craniosynostosis. Other physical symptoms included short stature and wide wrists

Figure 1. X-rays showing skeletal abnormalities in four paediatric patients with XLH



Classical radiological signs of rickets can be seen in all patients. A. X-rays of patient 1 (at age 2 years) showing genu varum deformity. There is mild widening of growth plate, cupping and fraying of the distal metaphysis of the ulna, the radius, the femur and the proximal metaphysis of the tibia. Mild fraying is seen involving the proximal metaphysis of the fibula; B. Genu varum deformity in patient 2 (at age 10 years); C. Genu varum deformity in patient 3 (at age 4 years) and D. Genu varum deformity in patient 4 (at age 8.25 years). XLH, X-linked hypophosphataemia.

Conventional treatment course

- All patients received conventional treatment for their symptoms, including PO_4 supplementation and a vitamin D analogue (alfacalcidiol) (**Table 1**)
- Following renal ultrasound, nephrocalcinosis was not observed in any of the patients
- Despite conventional treatment in all four patients, clinical signs of rickets did not improve and due to the persistence of unpleasant side effects as a result of conventional therapy, burosumab was considered

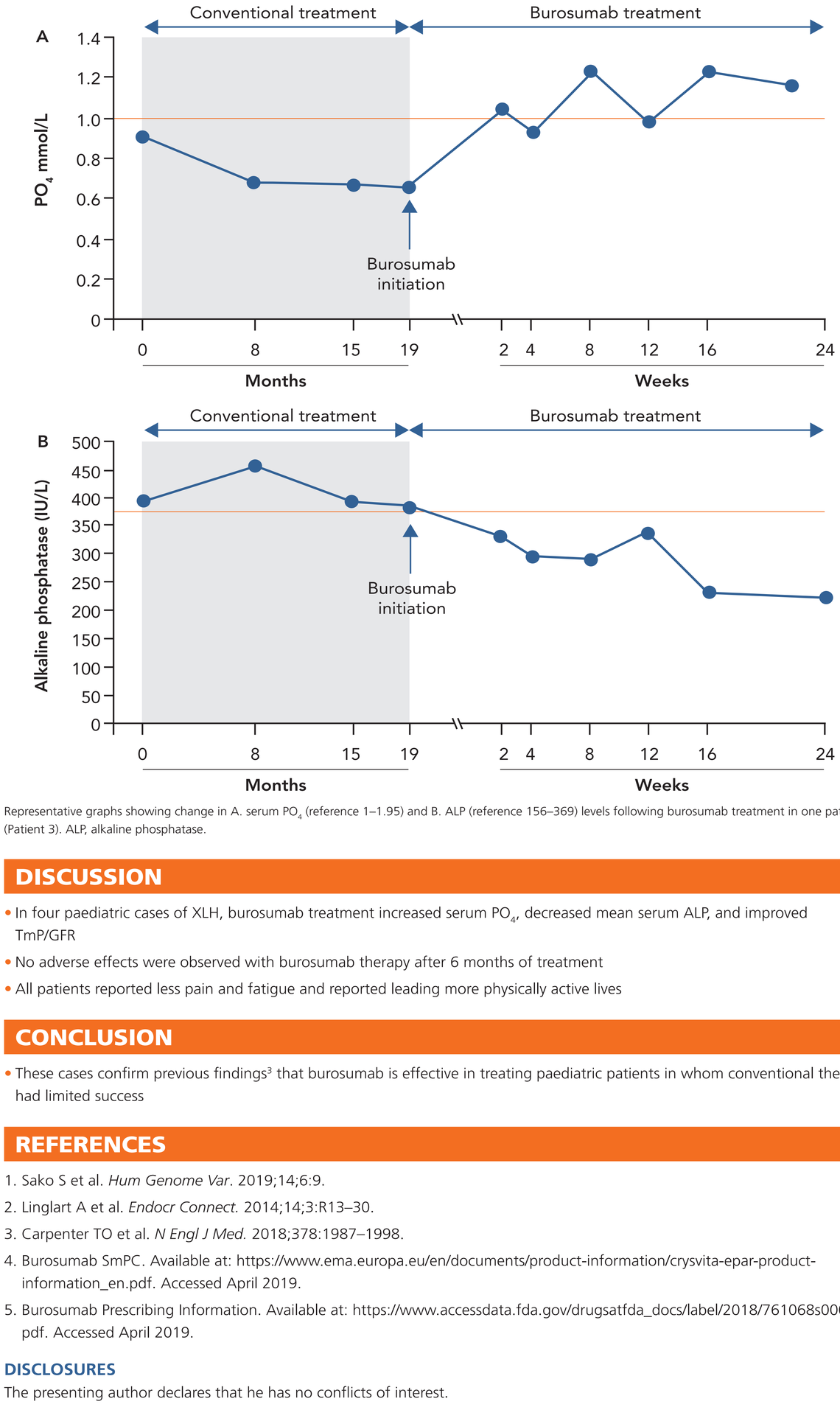
Burosumab treatment

- Prior therapies were stopped 1 week before burosumab treatment initiation
- Fasting biochemical investigations were carried out for alkaline phosphatase (ALP), parathyroid hormone (PTH), 25-hydroxyvitamin D (25 OH vit D), $1,25[OH]_2D$, and urine PO_4. Renal tubular maximum reabsorption rate of phosphate to glomerular filtration rate (TmP/GFR) was also measured
- Burosumab (subcutaneous) was administered at the FDA-recommended starting dose of 0.8 mg/kg of body weight,[4,5] rounded to the nearest 10 mg and administered every 2 weeks
- Serum PO_4 was measured every 2 weeks for the first month, monthly for 2 months and then every 3 months as appropriate after injection
- Burosumab dose was adjusted every 4 weeks if serum PO_4 was not maintained within the reference range (1–1.6 mmol/L)
- Patients' weight was measured every 2 weeks and height was measured every 3 months. Urine samples were taken every 4 weeks and a fasting blood test was taken at week 0, 2, 4, 8 and 12

Burosumab treatment outcome

- Burosumab increased serum PO_4 and decreased mean serum ALP (**Figure 2**)
- There was also an improvement in TmP/GFR in all four patients

Figure 2. A. Serum PO_4 and B. ALP levels in a paediatric patient treated with burosumab



Representative graphs showing change in A. serum PO_4 (reference 1–1.95) and B. ALP (reference 156–369) levels following burosumab treatment in one patient (Patient 3). ALP, alkaline phosphatase.

DISCUSSION

- In four paediatric cases of XLH, burosumab treatment increased serum PO_4, decreased mean serum ALP, and improved TmP/GFR
- No adverse effects were observed with burosumab therapy after 6 months of treatment
- All patients reported less pain and fatigue and reported leading more physically active lives

CONCLUSION

- These cases confirm previous findings[3] that burosumab is effective in treating paediatric patients in whom conventional therapy had limited success

REFERENCES

1. Sako S et al. *Hum Genome Var*. 2019;14;6:9.
2. Linglart A et al. *Endocr Connect.* 2014;14;3:R13–30.
3. Carpenter TO et al. *N Engl J Med.* 2018;378:1987–1998.
4. Burosumab SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/crysvita-epar-product-information_en.pdf. Accessed April 2019.
5. Burosumab Prescribing Information. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761068s000lbl.pdf. Accessed April 2019.

DISCLOSURES

The presenting author declares that he has no conflicts of interest.

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