

Giampiero I. Baroncelli*, Silvano Bertelloni, Mirna Cosci o Di Coscio, Nina Tyutyusheva, Sofia D'Elia and Diego Peroni

Management of patients with X-linked hypophosphatemic rickets during Covid-19 pandemic lockdown

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Abstract

Objectives: To identify a safe pathway for management and treatment of patients with X-linked hypophosphatemic rickets (XLH) during Covid-19 pandemic lockdown.

Methods: Twenty-six patients with XLH (age 3.1–25.7 years) were enrolled in Pediatric Endocrine Unit; nine of them were receiving human monoclonal anti-fibroblast growth factor 23 antibody (burosumab) and 17 (pediatric patients, age 9.5–17.9 years, n=7; young-adult patients, age 20.1–25.7 years, n=10) received conventional treatment with inorganic oral phosphate salts and active vitamin D metabolites. A Covid-19 free pathway was addressed for XLH patients receiving burosumab treatment in hospital. XLH patients receiving conventional treatment were followed by phone calls, e-mails, or telemedicine.

Results: All XLH patients receiving burosumab continued the scheduled follow-up and treatment; none of them was infected by Covid-19. Seven XLH patients out of 17 (41%) receiving conventional treatment showed some complication related to the disease itself or its treatment: periapical abscess with gingival fistula was diagnosed in five patients (three children and two young-adults) and treated with antibiotics with complete resolution; one child showed abdominal pain due to the administration of high doses of inorganic oral phosphate salts solved by reducing the dosage, and one child had severe legs pain during deambulation after orthopedic surgery solved with common analgesics.

Conclusions: Covid-19 free pathway was safe and effective to manage XLH patients receiving burosumab. E-health

technologies were useful methods to follow XLH patients receiving conventional treatment during Covid-19 pandemic lockdown.

Keywords: burosumab; conventional treatment; Covid-19; telemedicine; Womac questionnaire; X-linked hypophosphatemic rickets.

Introduction

X-linked hypophosphatemic rickets (XLH, MIM 307800) is the most common inherited form of rickets. Prevalence is 1:20,000–60,000 [1, 2]. XLH is due to loss-of-function mutations in the gene encoding phosphate-regulating endopeptidase homolog X-linked, which results in excess circulating fibroblast growth factor 23 (FGF23). High FGF23 levels impair renal reabsorption of phosphate and 1 α -hydroxylase activity, and stimulate renal 24-hydroxylase activity which lead to hypophosphatemia and low or inappropriately normal circulating levels of 1,25-dihydroxyvitamin D in the setting of hypophosphatemia [3, 4]. XLH patients show rickets and osteomalacia, which result in stunted growth, lower limb deformity, bone pain, and physical dysfunction with limited daily activities [4]. XLH patients may also develop dental and periodontal lesions as spontaneous periapical abscesses with fistulae occurring without any history of trauma or dental decay [5].

Osteomalacia with pseudofractures, early osteoarthritis and enthesopathies, musculoskeletal pain, dental and periodontal issues, and severe deformities at lower limbs requiring orthopedic surgery are main complications in most adults with XLH [4].

Conventional treatment of XLH patients is based on the administration of inorganic oral phosphate salts associated with active vitamin D metabolites; however, clinical and biochemical effects of this treatment are poor in the majority of XLH patients, and it may be associated with considerable toxicity [4, 6].

Recently, a human monoclonal IgG1 anti-FGF23 antibody (burosumab) has shown very promising results in patients with XLH. Preliminary data clearly demonstrated

*Corresponding author: Giampiero I. Baroncelli, MD, Division of Pediatrics, Department of Obstetrics, Gynecology and Pediatrics, University-Hospital, Via Roma 67, 56126 Pisa, Italy, Phone: +39 050 993168, Fax: +39 050 992641, E-mail: g.baroncelli@med.unipi.it
Silvano Bertelloni, Mirna Cosci o Di Coscio, Nina Tyutyusheva, Sofia D'Elia and Diego Peroni, Division of Pediatrics, Department of Obstetrics, Gynecology and Pediatrics, University-Hospital, Pisa, Italy

that burosumab treatment rapidly improved phosphate metabolism, severity of rickets, and quality of life [7–9], suggesting that likely it will be the main treatment in patients with XLH.

During Covid-19 pandemic lockdown in Italy (from March 3 to May 18, 2020) in order to continue burosumab administration in hospital a priority pathway for XLH patients was addressed. Moreover, the scheduled hospital admissions in XLH patients receiving conventional treatment were replaced by phone calls, e-mails, and telemedicine.

In this study we reported our experience in XLH patients receiving burosumab or conventional treatment followed in our Pediatric Endocrine Unit during Covid-19 pandemic lockdown.

Subjects and methods

Twenty-six patients with XLH (range 3.1–25.7 years) were followed at the Pediatric Endocrine Unit, University-Hospital, Pisa, Italy. Seventeen of them (pediatric patients, age 9.5–17.9 years, $n=7$, one male and six females; young-adult patients, age 20.1–25.7 years, $n=10$, one male and nine females) received conventional treatment by inorganic oral phosphate salts (pediatric patients: 20–60 mg/kg/daily, 4–6 doses per day, as elemental phosphorus; young-adult

patients: 100 mg, 4 times per day, as elemental phosphorus) associated with active vitamin D metabolites (pediatric patients: calcitriol 20–40 ng/kg/daily, 2–3 doses per day, or alfacalcidol 20–60 ng/kg/daily, once a day; young-adult patients: calcitriol 0.25 µg, 2–3 times per day). Nine pediatric patients affected by a severe form of the disease (age 3.1–15.5 years, five males and four females) were selected to receive burosumab (Crysvita®, Kyowa-Kirin, Japan; 0.8–1.2 mg/kg, subcutaneously, every 2 weeks); range of treatment was 4–18 months. Burosumab was made available by special national funds (Italian Medicines Agency act n. 326/2003) ($n=7$) or by reimbursement when appropriate ($n=2$). The administration of burosumab was performed in hospital as at time of Covid-19 pandemic lockdown home therapy was not yet available. Both pediatric and young-adult XLH patients receiving conventional treatment continued to take their therapy at home.

In order to continue the hospital admissions during Covid-19 pandemic lockdown a priority pathway for patients with XLH receiving burosumab treatment was addressed according to the Regional Health Service guidelines to prevent Covid-19 infection in patients with rare or chronic diseases [10] (Figure 1).

Pediatric XLH patients receiving conventional treatment were addressed to assess some clinical parameters at home, including height (standing back to the wall) and weight measurements (if weight scale was available) following

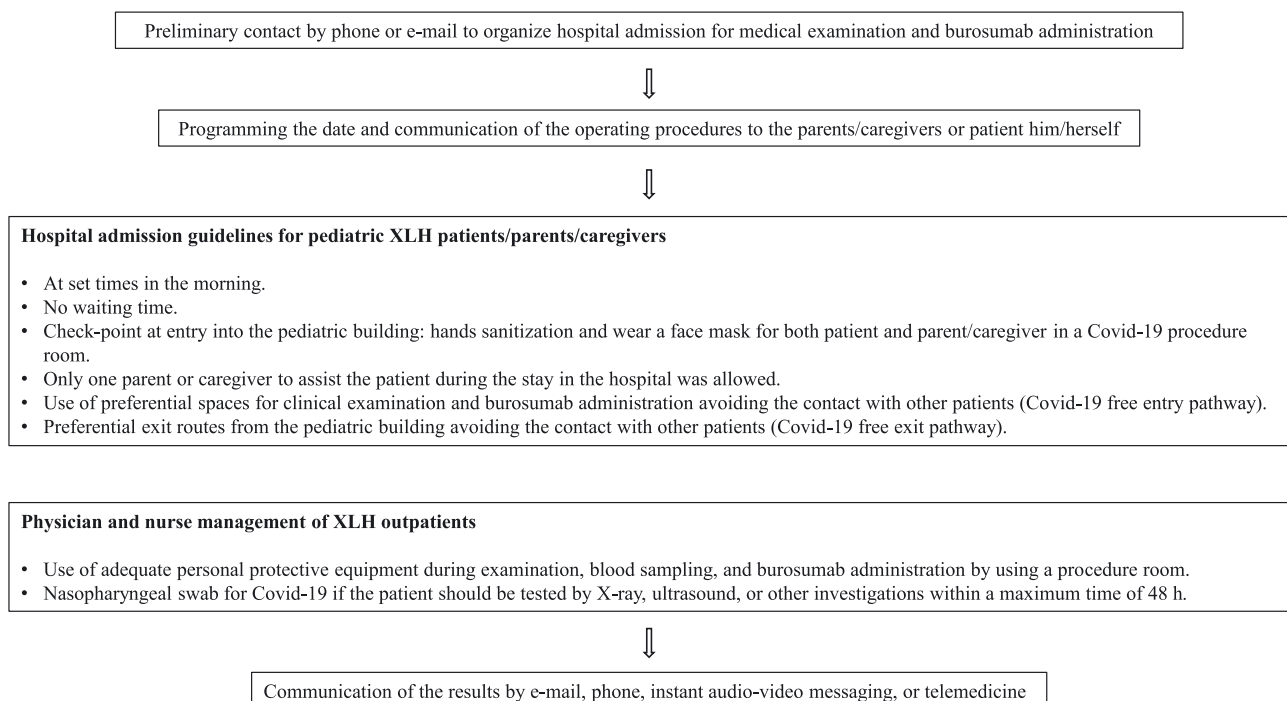


Figure 1: Approach and priority pathway in pediatric XLH patients receiving burosumab treatment during Covid-19 pandemic lockdown.

accurate instructions by the physician. Furthermore, a picture of the lower limbs to estimate the deformation of the legs, mainly in patients undergo to surgery, as well as a picture of the teeth in which an abscess with gingival fistula was suspected, were taken with a smartphone.

Young-adults XLH patients receiving conventional treatment were addressed to use a self-administered weekly questionnaire to assess their quality of life by using Western Ontario and the McMaster Universities Osteoarthritis Index (Womac) which focused on patient perception of joint pain, stiffness, and physical function at hip and knee [11]. Data were compared with the Womac questionnaire assessed in pre-pandemic period.

Communications between physicians and parents/caregivers or patients themselves were performed by e-mail, phone calls, social networks, or telemedicine. All the patients were contacted at least once a week during Covid-19 pandemic lockdown.

The study protocol was approved by the Ethics Committee for human investigation of our Department. All parents or patients themselves, when appropriate, provided informed consent to perform the study. The study was conducted according to the Declaration of Helsinki II and the Good Clinical Practice guidelines.

Results

All XLH patients receiving burosumab were able to continue the treatment and to carry out all clinical, biochemical, and other scheduled investigations. No XLH patient was infected by Covid-19 during follow-up based on clinical data and repeated nasopharyngeal swabs performed at the hospital admission. Deliverables in XLH patients receiving burosumab treatment following Covid-19 hospital guidelines are summarized in Table 1. The main results were improved parents/caregivers and patient his/herself awareness of the disease and strengthening “physician-patient” relationship. Deliverables in XLH patients receiving conventional treatment during lockdown

Table 1: Deliverables in XLH patients receiving burosumab treatment following Covid-19 pandemic hospital guidelines.

- Improved parents/caregivers and patient his/herself (if appropriate for age) awareness of the disease.
- Improved “physician-patient” relationship.
- Low risk of Covid-19 infection during hospital admissions.
- Improved supervision of potential side effects related to treatment.
- On-demand options.

XLH, X-linked hypophosphatemic rickets.

Table 2: Deliverables in pediatric and young-adults XLH patients receiving conventional treatment during Covid-19 pandemic lockdown.

- No transportation time or costs.
- No need to take time off work.
- No hospital admissions.
- Improved parents/caregivers and patient his/herself (if appropriate for age) awareness of the disease.
- Improved “physician-patient” relationship.
- Good management and treatment of the disease.
- On-demand options.

XLH, X-linked hypophosphatemic rickets.

are summarized in Table 2; no transportation time or costs and no need to take time off work were the most appreciated advantages.

Adverse events related to XLH treatment regimen or to the disorder itself, and other diseases occurring during Covid-19 pandemic lockdown are summarized in Table 3. Pediatric XLH patients receiving burosumab treatment did not show adverse effects or suffered periapical abscesses; one patient showed a mild form of Rotavirus gastroenteritis. Five out of seven (71%) pediatric patients receiving conventional treatment showed some complication due to the disease itself or related to its medical and surgical treatment; three patients had a spontaneous periapical abscess with gingival fistula at incisor teeth that were treated with antibiotics up to complete resolution. One patient had abdominal pain with diarrhea due to the administration of high doses of inorganic oral phosphate salts; the therapy was suspended for some days and then reintroduced at lower dosage with a good clinical response. One patient who undergo orthopedic surgery in December 2019 for the correction of angular deformities by bilateral tibial and femoral hemiepiphysiodesis developed severe

Table 3: Adverse events reported in XLH patients during Covid-19 pandemic lockdown according to treatment regimen.

Treatment regimen	Pediatric XLH patients (n=16)	Young-adult XLH patients (n=10)
Burosumab (n=9)	– gastroenteritis (n=1)	–
Conventional therapy (n=17)	– spontaneous periapical abscess (n=3)	– spontaneous periapical abscess (n=2)
	– abdominal pain (n=1)	– worsening of pain at hip and/or knee (n=4)
	– severe pain to the legs after surgery (n=1)	

XLH, X-linked hypophosphatemic rickets.

pain to the legs during deambulation. A movie performed by parents with a smartphone and sent to physician by e-mail was accurately examined and analgesic treatment was started for some days with a complete pain relief. Follow-up of the patient by telemedicine examination confirmed the progressive normalization of the clinical picture. Three out of seven (43%) pediatric XLH patients showed some signs or symptoms not related to the disease itself: one had atopic dermatitis reactivation, one showed a mild gastroenteritis due to *Escherichia coli* infection, and one had sore throat with fever for 3 days. The cause of fever in this patient was not ascertained but he was negative for Covid-19 infection. Complication rates due to the disease itself or related to its medical treatment in the seven pediatric patients receiving conventional treatment during Covid-19 pandemic lockdown did not differ ($p = \text{NS}$) in comparison with the pre-pandemic period (data not shown). Five patients (two children and three young-adults) receiving conventional treatment developed nephrocalcinosis in pre-pandemic period that did not worsen during Covid-19 pandemic lockdown. No patient receiving burosumab treatment had nephrocalcinosis.

Four out of 10 (40%) young-adult patients receiving conventional treatment showed an increased Womac score during lockdown (pre-lockdown: 54.3 ± 7.1 ; during lockdown 70.1 ± 8.2 ; $p < 0.02$) (Table 3). The main cause was an increased functional limitation associated with severe pain at lower limbs due to reduced possibility to regularly perform walk outside the house during lockdown. Analgesic treatment and physical exercise at home had only a partial effect on symptoms. Moreover, two young-adult patients (20%) showed a spontaneous periapical abscess with gingival fistula at incisor teeth treated with antibiotics up to complete resolution.

No XLH patient receiving conventional treatment had hospital admissions during the period of Covid-19 pandemic lockdown.

Parents/caregivers of XLH patients expressed gratitude for the efforts of nurses and physicians to take care of their children during Covid-19 pandemic lockdown. Compliance with the proposed approaches was very good in both pediatric and young-adult XLH patients.

Discussion

The outbreak of Covid-19 pandemic has created a global health crisis with deep impact in the management of pediatric patients. During Covid-19 pandemic lockdown the number of patients admitted to Pediatric Intensive Care Unit was significantly reduced compared with the same

time period in 2019 and 2018 [12]. Furthermore, patients with rare diseases [13, 14], inherited metabolic disorders [15], or chronic diseases [16] experienced a feeling of abandon and fear to continue follow-up and treatment as outpatients. Indeed, in most hospitals routine outpatient clinics were suspended during Covid-19 pandemic lockdown [15]. No evidence of increased risk of Covid-19 in patients with disorders of bone and mineral metabolism has been reported, but the global lockdowns have significantly affected their care [17]. However, immunodeficiency associated with some chronic diseases could be worsened by Covid-19 infection by affecting the immune system [16].

In Italy, during Covid-19 pandemic lockdown pediatric hospital activity has been completely reorganized so that many pediatricians were redeployed to hold Covid-19 patients. This reorganization resulted in an almost total suspension of the Endocrine Pediatric Unit activity, even though urgent and non-deferrable activities were guaranteed by the pediatric endocrinologists in addition to their involvement in the Covid-19 pandemic activity.

During Covid-19 pandemic lockdown XLH patients receiving burosumab were at risk to discontinue the treatment for the lack of nurses and pediatric endocrinologists who were moved to other assignments due to Covid-19 pandemic, lack of safe spaces to examine them, and high risk of becoming infected with Covid-19 during the hospital admissions. However, nurses and pediatric endocrinologists were able to manage XLH patients by a Covid-19 free priority pathway accurately predisposed to clinical examination and burosumab administration avoiding compromising public health objectives. After the Covid-19 pandemic lockdown, a new care facility for in-home therapy in XLH patients receiving burosumab by qualified nurses and physicians has been activated. This will further reduce the number of hospital admissions for XLH patients receiving burosumab as well as the risk of Covid-19 infection.

In pediatric and young-adult XLH patients receiving conventional treatment the temporary suspension of the hospital admissions was replaced by phone calls, e-mails, instant audio-video messaging, or telemedicine with good parents/caregivers and patients themselves acceptance. Through these technological methods we were able to diagnose some minor illnesses as well as to adjust treatment regimen avoiding hospital admissions during Covid-19 pandemic lockdown. Therefore, in some circumstances telemedicine may be a useful way for the management of patients during Covid-19 pandemic, as also reported in China [18], Israel [19], and United States [20]. However, it should be considered that telemedicine cannot replace face-to-face care in XLH patients mainly if physical examination

and diagnostic imaging techniques are required. Indeed, telemedicine is not yet uniformly integrated into regular healthcare systems and it necessitates major adaptations to existing frameworks [21, 22].

Our experience confirm the ability and readiness of pediatric endocrinologists to support the National Health Service bringing competence, dedication and sense of responsibility, as the counterpart of adult endocrinologists has done [23]. Furthermore, in order to tackle the Covid-19 emergency, the European Reference Network on Rare Bone Diseases coordination team and Italian Rare Bone Disease healthcare professionals created the “Covid-19 Helpline for Rare Bone Diseases” to provide high quality-information and expertise on rare bone diseases remotely to patients and healthcare professionals [24]. It could serve as a primer of gold-standard remote care for patients with rare diseases, inherited metabolic disorders, and chronic diseases for the other European countries and globally.

Conclusion

The pathways we developed to manage and treat pediatric and young-adult patients with XLH during Covid-19 pandemic lockdown were safe and effective. Albeit with some limitation, telemedicine and other digital technologies may have a role to support the patients with XLH when hospital admissions are restricted.

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