2nd Edition of the Contest of Clinical Cases related to the non-surgical clinical management of kidney stones

Title: New horizon in the treatment of primary hyperoxaluria type I

Keywords: primary hyperoxaluria, lumasiran, oxalate, glycolate oxidase, interfering RNA.

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1. Summary

Objective: To introduce a new drug approved for the treatment of primary hyperoxaluria (PH) type I.

Method: We present the case of a paediatric patient with type I PH diagnosed by genetic study. On her debut she presented with right kidney stone and left coralliform stone that required surgical treatment by percutaneous nephrolithotomy together with medical treatment, potassium citrate and pyridoxine, with a good initial response. In view of the elevated levels of oxalate in urine, treatment was started with a new drug approved for type I PH, Lumasiran, which inhibits the production of the enzyme that synthesises oxalate in the liver.

Result: After one month of treatment, the patient showed a reduction in oxalate levels, good tolerance to the drug and no adverse effects were reported.

Conclusion: Lumasiran is the recently approved treatment for type I PH that acts by inhibiting oxalate synthesis, preventing its visceral deposition, representing a better prognosis for affected patients.

2. Introduction

PH is an autosomal recessively inherited genetic disorder that involves excessive production of oxalate in the liver. The most common and severe form is PH type I. Deficiency in the liver enzyme alanine-glycolate aminotransferase (AGT) leads to the formation and deposition of calcium oxalate crystals in the urinary tract. It can present as recurrent nephrolithiasis, nephrocalcinosis and progress to end-stage renal failure and systemic oxalosis with a poor prognosis and greatly reduced life expectancy (1).

Medical treatment is aimed at preventing mineralisation of oxalate crystals in the kidney as well as symptomatic treatment of kidney stones and pyridoxine. Peritoneal dialysis and haemodialysis are necessary in cases of end-stage renal failure, but hepatorenal transplantation is the only known curative treatment to date (1,2). A new drug, Lumasiran, which targets the mRNA of the AGT enzyme has recently been approved, providing for the first time an approach to the cause and possible cure (8).

The case of a patient with type I PH who meets criteria for initiation of treatment with Lumasiran is presented.

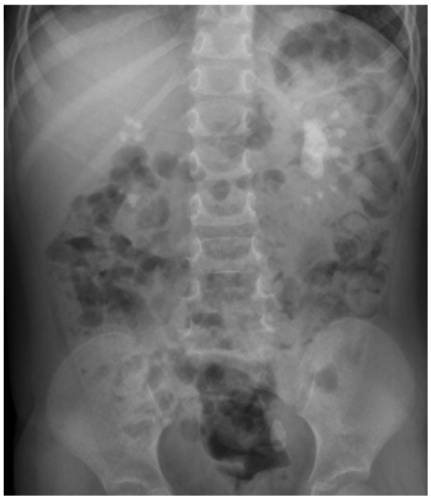
3. Description of the clinical case

a) Important background information

A female patient of 3 years and 6 months who has 3 episodes of macroscopic hematuria in the last 6 months. The mother reports expulsion of lithiasis and sandy sediment in urine, especially in relation to physical exercise. She has not presented with colicky pain or urinary tract infection. She denies other associated micturition symptoms. History of controlled pregnancy, at term, with normal intrauterine ultrasound scans. Regarding family history, both maternal grandparents suffer from episodes of kidney stones with chronic renal failure undergoing haemodialysis treatment and the paternal great-uncle has a history of calculi.

b) Diagnostic support studies and results

Initially, a renal ultrasound was requested, showing hyperechogenic images compatible with kidney stones occupying all the right renal calyces, larger than 7mm, and left coralliform stone. The abdominal X-ray showed the stone described above.



For treatment planning, an unconstraste computed tomography (CT) scan is requested that reports multiple right calicial lithiasis, left coraliform lithiasis and 8mm left ureteral lithiasis.

The metabolic study objective hyperoxaluria with 130 mg/dL of oxalate in urine and hypocitraturia with 33 mg/dL of citrus in urine and an oxalate/creatinine ratio of 0.312 mg/mg (reference normal values 0.008-0.095 mg/mg).

The blood test has a creatinine value of 0.45 mg/dL and a glomerular filtration rate (Schwartz, BUN/cis/cre,2012) of 85 ml/min/1.73 m2.

Analysis of spontaneously expelled stones showed a composition of calcium oxalate monohydrate (whewellite) at 100%.

c) Diagnosis

It was decided to request a genetic study, confirming the diagnosis of type I PH with the presence of two mutations in the AGXT gene. The Lys12Glnfs*156 mutation is pathogenic for PH and has a poor prognosis, and the Phe152Ile variant mutation is associated with a good response to treatment with pyridoxine.

d) Treatment

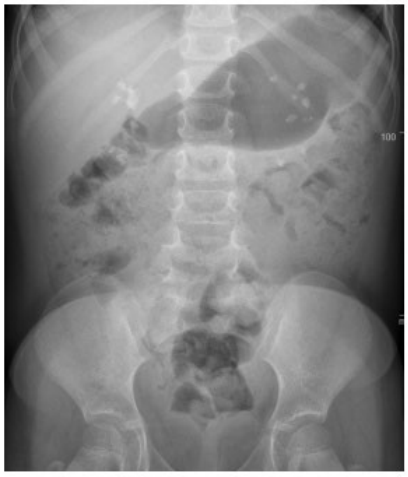
Surgical treatment of the left kidney was decided by means of left percutaneous mini-nephrolithotomy and ipsilateral ureterorenoscopy, leaving calyceal stone and ureter free of calculi. As for medical treatment, firstly, an increase in water intake to 2L/day was indicated together with potassium citrate 2mMol/kg/day in 10.75% potassium citrate solution, supplemented with magnesium in doses of 2g (5 ml)/day and cotrimoxazole in a prophylactic nocturnal dose. Pyridoxine was prescribed, starting at 5 mg/kg/day and progressively increasing the dose, reaching a dose of 16 mg/kg/day after ten months. After initiation of pyridoxine treatment, oxaluria levels decreased from an initial oxalate/creatinine ratio of 0.36 mg/mg to 0.19 mg/mg after three months of treatment. Subsequently, after six months, the oxalate/creatinine ratio increased again to 0.28 mg/mg and treatment with the recently approved Lumasiran was considered. The induction dose via subcutaneous injection is 6 mg/kg monthly for three months, followed by a maintenance dose of 6/kg quarterly, which is administered as a day hospital treatment.

e) Evolution

After three months of treatment with Lumasiran the oxalate/creatinine ratio has decreased, the patient has had good tolerance and no adverse effects have been reported.

f) Clinical results

After the left percutaneous mini-nephrolithotomy, both the residual stone of the left kidney and the untreated calculus of the right kidney have remained stable and no related complications have appeared, presenting normal renal function at all times.



After two months of treatment with Lumasirán, after completing three induction doses, the patient presents a reduction in the oxalate/creatinine ratio evident, presenting a current value of 0.09 mg/mg (within the normal reference values).

4. Discussion

PH is a pathology of **autosomal recessive pathology** that is characterized by the excessive production of oxalate by the liver with an infamous prognosis and until now treated only symptomatically. In the case presented, the patient has type I PH with two mutations in the AGXT gene. One of them, Lys12Glnfs*156, is reported to be one of the most frequent pathogenic variants, with a more severe phenotype and early onset, worsening her prognosis (1).

According to the literature, the **average age** of diagnosis is 5.5 years of life, although it can appear at any age. It may present asymptomatically or with isolated episodes of kisdey stones or start with nephrocalcinosis in childhood or childhood end-stage renal disease (1). In the case presented, the patient presented with isolated episodes of haematuria without alterations in renal function.

The most common place of **deposit of oxalate crystals** is the kidney, although it can also affect joints, skin, spinal cord, heart or nervous system (2). In the case of our patient, she did not present extrarenal manifestations.

The **excretion of oxalate** via the urinary tract is variable, especially in the first year of life. However, persistently elevated excretion requires further studies to confirm the diagnosis. In the case of paediatric patients, the oxalate/creatinine ratio in an isolated urine sample is used to assess urinary oxalate levels. Normal age-adjusted values range from 0.008 to 0.095 mg/mg (3).

Measures to avoid urinary oversaturation of calcium oxalate are essential to try to prevent crystal formation. Increased water intake is paramount in preventing stone formation. Administration of potassium citrate is necessary to maintain pH around 6.2 and 6.8 to alkalinise urine and inhibit crystallisation. Magnesium-rich supplements also help inhibit mineralisation and administered with meals help reduce oxalate absorption (2).

The **formation of renal stones** is a very frequent finding in this pathology. They are usually large stones composed of calcium oxalate monohydrate (whewelite), which makes them very hard. Due to their size and composition, these stones usually require more than one invasive treatment to be resolved. In the case described, it was decided to initially treat the left kidney due to the presence of ureteral stones and complete coraliform calculus. In the case of the right kidney, observation is decided for the time being, given that it remains asymptomatic and has poor percutaneous access, which would require multiple endoscopic procedures to eliminate the stones.

Pyridoxine or vitamin B6 has been shown to be effective in reducing oxalate levels in type I PH, with a starting dose of 5 mg/kg/day and a progressive increase up to 20mg/kg/day (4). Responders are patients who achieve a reduction in urinary oxalate levels of more than 30% of baseline values. The presence of Gly170Arg and Phe152Ile genotypes are associated with good response to pyridoxine treatment. In the absence of a decrease in urinary oxalate levels, treatment can be discontinued after three months from the start of treatment. In the case of our patient with the Phe152Ile variant in her genetic study, there was a decrease in the initial oxalate/creatinine ratio of more than 30% from the start of treatment to three months. However, the oxalate/creatinine ratio increased again after six months of treatment and therefore completely lost its efficacy. In case of **severe renal failure**, in addition to the above measures, replacement therapy by haemodialysis or peritoneal dialysis should be considered, although they have not been shown to be effective in the clearance of oxalate generated in type I PH (5).

The curative treatment until now has been **hepatorenal transplantation**, because although the main problem is at the hepatic level, renal functionality is altered in a secondary way and both transplants are necessary. This entails a high surgical aggressiveness as well as a state of chronic immunosuppression triggering important comorbidities and a high mortality rate.(6)

Currently there are **several lines of research** to obtain molecules by different routes of action with the common objective of avoiding the accumulation of oxalate and the progression of kidney disease. First, the possibility of increasing the elimination of oxalate via the intestine through its degradation thanks to oxylobacter formigenes, an anaerobic bacterium, is being investigated. Other avenues of research include decreasing endogenous oxalate synthesis by inhibiting the enzyme that produces it. The possibility of acting on the inflammatory pathway produced by calcium oxalate to prevent renal fibrosis is also being investigated. Finally, gene therapy is being investigated, with the aim of replacing the defective gene in type I PH by means of viral vectors (7).

In addition, one of the most successful preclinical treatments studied to date, **Lumasiran**, was approved for all age groups in the European Union and the United States in November 2020. It is an interfering RNA molecule that targets the messenger RNA for the hydroxyacid oxidase 1 (HAO1) gene encoding glycolate oxidase. By silencing the coding of this enzyme, it inhibits oxalate synthesis, thus preventing its formation and visceral deposition (8).

This drug is indicated for all paediatric or adult patients with type I HP. It is administered subcutaneously and treatment consists of three monthly induction doses followed by a quarterly maintenance dose (8). The dose is adjusted according to weight, so in our patient a loading dose of 6 mg/kg per month and a maintenance dose of 6mg/kg every three months is indicated. No adjustment is required in patients with a glomerular filtration rate between 90-30 ml/min/1.73 m2. No studies are available on the dose in patients with a glomerular filtration rate of less than 30 ml/min/1.73m2 or on dialysis. According to the studies, adverse effects are few and mild, which confers a great advantage in terms of tolerability as well as adherence to treatment. Among the most reported are skin reactions at the injection site, headache, rhinitis and upper respiratory tract infection (8).

Some results have been published on treatment with Lumasiran. Graffels et al. (9) conducted a clinical trial involving 39 patients with type I PH randomised so that 26 started treatment with Lumasiran and 13 with placebo. The Lumasiran-treated group reduced the 24-hour urine oxaluria level by 65.4% and the effects were seen within the first month of treatment. At 6 months after treatment, 84% of Lumasiran-treated patients had urine oxalate values at or near normal range.

Due to the recent start of treatment in our case, long-term clinical and analytical results are currently lacking. Currently, after three months of treatment and three induction doses, the patient has a 67.86% reduction in the oxalate/creatinine ratio and good initial tolerance to the drug and has not reported any possible adverse effects.

5. Conclusions and recommendations

Lumasiran is currently indicated for patients of any age with type I PH. The reduction in urinary oxalate excretion as well as good tolerability and its low spectrum of adverse effects, make it a hope for halting the progression of the pathology, improving the long-term prognosis and being able to avoid its definitive treatment so far known, hepatorenal transplantation.

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