

## Primary Hyperoxaluria: A Need for New Perspectives in an Era of New Therapies

Michael J.G. Somers

**P**Primary hyperoxaluria (PH) is a rare metabolic anomaly inherited in an autosomal recessive fashion that manifests devastating clinical consequences. Its most common form, PH type 1 (PH1), stems from variants in the AGXT

---

### Related Article, p. \*\*\*

---

gene that lead to reduced enzymatic activity of alanine glyoxylate aminotransferase (AGT) in the hepatocyte peroxisome.<sup>1</sup> Consequently, large amounts of oxalate are generated, which often causes recurrent episodes of nephrolithiasis. Eventually, hyperoxaluria causes more profound kidney injury that progresses to kidney failure and deposition of oxalate systemically, most notably in the skeleton, heart, skin, and retina.

Over the last decade, there has been increasing focus on the use of small interfering ribonucleic acid (siRNA) to prevent the expression of specific genes in PH1 and thereby prevent the pathologic accumulation of oxalate.<sup>2</sup> In this issue of *AJKD*, Michael et al<sup>3</sup> report the results of a trial of lumasiran, the first commercially available siRNA therapy for PH1, in a cohort of 21 adults and children with advanced chronic kidney disease (CKD) from PH1. All trial participants had plasma oxalate levels  $\geq 20$   $\mu\text{mol/L}$  and an estimated glomerular filtration rate (GFR)  $\leq 45$   $\text{mL/min/1.73 m}^2$  if at least 12 months of age or elevated serum creatinine levels if younger. Of the 21 participants, 15 were on dialysis at study enrollment, and their results were analyzed separately from the other 6 with advancing CKD. All received lumasiran monthly for 3 initial doses and then monthly or quarterly following weight-based dosing. After 6 months, plasma oxalate levels fell by 33.3% in the group not receiving dialysis and 42.4% in the dialysis group. Therapy did not convey higher risk of significant siRNA-related adverse sequelae, although the study was small. This report is the first evidence of the efficacy of lumasiran in treating PH1 patients with limited kidney function or already on dialysis and joins earlier data demonstrating its efficacy in children and adults with preserved kidney function. The advent of such promising new agents to treat hyperoxaluria calls for reconsideration of contemporary standard clinical management approaches for PH1 patients across the spectrum of kidney function while also underscoring a new urgency to the timely diagnosis of this condition.

Historically, mainstays of treatment in PH1 have included hyperhydration and use of citrate, phosphate, or magnesium to help prevent crystallization of oxalate in the urine and subsequent kidney injury.<sup>4</sup> In select PH1 patients with specific variants that preserve AGT production but mistarget its delivery within the hepatocyte, pyridoxine

has been found to ameliorate pathologic oxalate production. Unfortunately, approximately 70% of PH1 patients are not responsive to pyridoxine and have ongoing hyperoxaluria with a tendency for recurrent nephrolithiasis and eventual kidney failure despite this supportive care.<sup>5</sup> In some cohorts, a PH1 diagnosis has not even been made until kidney failure was diagnosed in more than 40% of patients.<sup>6</sup>

Systemic deposition of oxalate accelerates with loss of glomerular filtration owing to decreased urinary oxalate excretion. For this reason, when the diagnosis is recognized, dialysis initiation has been recommended as plasma oxalate levels exceed 30  $\mu\text{mol/L}$ , a level that often occurs when a patient's residual GFR may not yet have declined to levels that normally require dialysis.<sup>7</sup> Moreover, PH1 patients may also require more intensive dialysis doses and restriction to hemodialysis as a modality to achieve the best oxalate clearance. Even with these burdensome regimens, PH1 patients who remain long-term on dialysis face significant oxalate-mediated toxicities.

In pyridoxine-sensitive patients with kidney failure, kidney transplantation can be considered with low risk of recurrence of oxalate-related nephropathy, since oxalate production is successfully blunted with ongoing pyridoxine treatment. In most PH1 patients, however, liver-kidney transplant is needed to provide hepatocytes with sufficient AGT activity for normal oxalate metabolism and prevent recurrent oxalate-mediated kidney failure in the allograft.<sup>8</sup>

With siRNA therapy in PH1, the ability to reverse extreme hyperoxaluria and protect against ongoing oxalate-mediated kidney injury is now achievable. If diagnosed and treated early in the disease course, this may potentially prevent loss of GFR and progression to kidney failure. In patients with pre-existing advanced CKD at initiation of siRNA therapy, progression to kidney failure may nonetheless occur, but the tempo of residual GFR decline may be altered by reducing ongoing oxalate-mediated injury. It may also be possible to now consider less intensive hemodialysis regimens or kidney transplant alone under ongoing siRNA therapy rather than the need for dual liver-kidney transplantation.<sup>9</sup>

These new management options require a new appreciation of the urgency of PH1 diagnosis among clinicians. In the former management era treatment was largely supportive until kidney failure and there were few effective approaches to stave off the most serious disease sequelae. In this setting, the ramifications of delayed diagnosis were less serious. Now, with effective therapy that can reduce plasma oxalate levels and ostensibly prevent relentless kidney injury, prompt diagnosis is critical.

Despite this increased need for prompt diagnosis, PH1 remains problematic for many clinicians to recognize. The disease spectrum is broad, with all age groups potentially affected and both indolent and acute presentations. Clinical clues to diagnosis are frequently underappreciated or ignored because the disease is rare, and most clinicians have limited appreciation of its manifestations. It becomes critical, as a result, for there to be better clinician education as to sentinel signs or symptoms of PH1, such as nephrolithiasis or nephrocalcinosis in childhood, nephrocalcinosis or recurrent calcium oxalate kidney stones as an adult, loss of GFR in the setting of nephrolithiasis or nephrocalcinosis, or the onset of kidney failure without a clear etiology.<sup>10</sup> Patients with these findings need to have targeted laboratories to diagnose and monitor PH1, since available siRNA therapy may now prevent significant patient morbidity and mortality.

Contemporary gold-standard confirmation of a suspected PH1 diagnosis is genetic testing to look for mutations in AGXT.<sup>11</sup> Urinary and plasma oxalate studies may confirm elevated levels of oxalate, yielding results that are typically available more quickly than genetic analysis, but genetic testing allows for specific delineation of a variant and an understanding of its pathogenicity.<sup>12</sup> In patients with pyridoxine-sensitive variants, these diagnostic tests allow clinical confidence in treatment with long-term pyridoxine provision, a therapy that is known to be safe and cost-effective. In others, siRNA therapy can now be considered, and the significant medical complications of unrelenting hyperoxaluria now rendered less problematic.

Given the importance of this confirmatory testing, it also becomes more pressing for clinicians to readily identify available and reliable laboratory resources for PH testing and to gain confidence in interpreting these laboratory tests or access expert consultation. Again, ongoing clinician education and the ready availability of testing information in searchable electronic formats will facilitate its dissemination to key resources and ultimately also help with more timely diagnosis. For key stakeholders such as PH advocacy groups, emphasizing educational opportunities and resources, especially for community-based nephrologists and urologists who may most likely first encounter undiagnosed patients, takes on added importance as a mission.

With the availability of new therapeutics for PH1 also comes new questions of health care access and equity. In most health care systems, patient access to many medications is restricted, and barriers to drug use in the form of approved formularies, prior authorization requirements, or co-payments complicate their provision. In the context of a drug that is rarely prescribed and costly, these administrative hurdles can significantly delay drug initiation and ongoing use. In the setting of a drug that is needed for a lifetime to prevent irreversible kidney failure and kidney-liver transplantation, long-term drug access becomes even more vital. Patients, clinicians, drug manufacturers, and health care administrators all need to be attuned to this issue.

Hand in hand with access difficulties are equity concerns. Medications that are difficult to access even for those with resources may become impossible to access in those facing significant health care disparities. Social and economic inequities underlie many adverse health outcomes in chronic disease and have complicated PH1 care even prior to new therapies such as siRNA. Addressing these disparities effectively takes great effort and many resources, but as therapies with the potential to change disease outcomes in profound ways are developed, health equity concerns related to these therapies also need to be carefully considered by all stakeholders.

As PH1 patients across the spectrum of chronic kidney disease are treated with siRNA, it will also be paramount to study its use and learn from its provision outside of the setting of a controlled clinical trial. Optimization of clinical management in a rare disease such as PH1 requires broad collaboration among clinicians, ready sharing of pertinent data, and a focus on key patient outcomes. Accordingly, the development of new therapies underscores the need for existing PH1 patient registries to develop close working relationships to study the clinical impact of changes in PH1 management so that therapeutic advances come to be applied in the most efficacious, beneficial, and equitable fashion.

## Article Information

**Author's Affiliation:** Division of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts.

**Address for Correspondence:** Michael J.G. Somers, MD, Division of Nephrology, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. Email: [michael.somers@childrens.harvard.edu](mailto:michael.somers@childrens.harvard.edu)

**Support:** None.

**Financial Disclosure:** Dr Somers has served on Advisory Boards for Alnylam Pharmaceuticals, Cantero Therapeutics, and Dicerna Pharmaceuticals. He also chairs a Data Safety Monitoring Board for a clinical trial for Dicerna. He is a member of the Scientific Advisory Board of the Oxalosis and Hyperoxaluria Foundation.

**Peer Review:** Received July 27, 2022, in response to an invitation from the journal. Direct editorial input from an Associate Editor and a Deputy Editor. Accepted in revised form August 18, 2022.

**Publication Information:** © 2022 by the National Kidney Foundation, Inc. Published online month xx, xxx with doi [10.1053/j.ajkd.2022.08.005](https://doi.org/10.1053/j.ajkd.2022.08.005)

## References

1. Cochat P, Rumsby G. Primary hyperoxaluria. *N Engl J Med*. 2013;369(7):649-658. doi:[10.1056/NEJMra1301564](https://doi.org/10.1056/NEJMra1301564)
2. Garrelfs SF, Frishberg Y, Hulton SA, et al. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N Engl J Med*. 2021;384(13):1216-1226. doi:[10.1056/NEJMoa2021712](https://doi.org/10.1056/NEJMoa2021712)
3. Michael M, Groothoff JW, Shasha-Lavsky H, et al. Lumasiran for advanced primary hyperoxaluria type 1: phase 3 Illuminate-C trial. *Am J Kidney Dis*. Published online July 13, 2022. doi:[10.1053/j.ajkd.2022.05.012](https://doi.org/10.1053/j.ajkd.2022.05.012)
4. Gupta A, Somers MJG, Baum MA. Treatment of primary hyperoxaluria type 1. *Clin Kidney J*. 2022;15(Suppl 1):i9-i13. doi:[10.1093/ckj/sfab232](https://doi.org/10.1093/ckj/sfab232)
5. van Woerden CS, Groothoff JW, Wijburg FA, Annink C, Wanders RJ, Waterham HR. Clinical implications of mutation

- analysis in primary hyperoxaluria type 1. *Kidney Int.* 2004;66(2):746-752. doi:10.1111/j.1523-1755.2004.00796.x
6. Mandrile G, van Woerden CS, Berchiolla P, et al; OxalEurope Consortium. Data from a large European study indicate that the outcome of primary hyperoxaluria type 1 correlates with the AGXT mutation type. *Kidney Int.* 2014;86(6):1197-1204. doi:10.1038/ki.2014.222
  7. Cochat P, Hulton SA, Acquaviva C, et al; OxalEurope. Primary hyperoxaluria type 1: indications for screening and guidance for diagnosis and treatment. *Nephrol Dial Transplant.* 2012;27(5):1729-1736. doi:10.1093/ndt/gfs078
  8. Harambat J, van Stralen KJ, Espinosa L, et al; European Society for Pediatric Nephrology/European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry. Characteristics and outcomes of children with primary oxalosis requiring renal replacement therapy. *Clin J Am Soc Nephrol.* 2012;7(3):458-465. doi:10.2215/CJN.07430711
  9. Stone HK, VandenHeuvel K, Bondoc A, Flores FX, Hooper DK, Varnell CD Jr. Primary hyperoxaluria diagnosed after kidney transplant: a review of the literature and case report of aggressive renal replacement therapy and lumasiran to prevent allograft loss. *Am J Transplant.* 2021;21(12):4061-4067. doi:10.1111/ajt.16762
  10. Milliner DS. The primary hyperoxalurias: an algorithm for diagnosis. *Am J Nephrol.* 2005;25(2):154-160. doi:10.1159/000085407
  11. Mandrile G, Beck B, Acquaviva C, et al; OxalEurope Consortium/Erknet Guideline Workgroup On Hyperoxaluria. Genetic assessment in primary hyperoxaluria: why it matters. *Pediatr Nephrol.* Published online June 13, 2022. doi:10.1007/s00467-022-05613-2
  12. Sas DJ, Harris PC, Milliner DS. Recent advances in the identification and management of inherited hyperoxalurias. *Urolithiasis.* 2019;47(1):79-89. doi:10.1007/s00240-018-1093-3