End Points for Clinical Trials in Primary Hyperoxaluria

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Abstract
Patients with primary hyperoxaluria experience kidney stones from a young age and can develop progressive oxalate nephropathy. Progression to kidney failure often develops over a number of years, and is associated with systemic oxalosis, intensive dialysis, and often combined kidney and liver transplantation. There are no therapies approved by the Food and Drug Association. Thus, the Kidney Health Initiative, in partnership with the Oxalosis and Hyperoxaluria Foundation, initiated a project to identify end points for clinical trials. A workgroup of physicians, scientists, patients with primary hyperoxaluria, industry, and United States regulators critically examined the published literature for clinical outcomes and potential surrogate end points that could be used to evaluate new treatments. Kidney stones, change in eGFR, urine oxalate, and plasma oxalate were the strongest candidate end points. Kidney stones affect how patients with primary hyperoxaluria feel and function, but standards for measurement and monitoring are lacking. Primary hyperoxaluria registry data suggest that eGFR decline in most patients is gradual, but can be unpredictable. Epidemiologic data show a strong relationship between urine oxalate and long-term kidney function loss. Urine oxalate is reasonably likely to predict clinical benefit, due to its causal role in stone formation and kidney damage in CKD stages 1–3a, and plasma oxalate is likely associated with risk of systemic oxalosis in CKD 3b–5. Change in slope of eGFR could be considered the equivalent of a clinically meaningful end point in support of traditional approval. A substantial change in urine oxalate as a surrogate end point could support traditional approval in patients with primary hyperoxaluria type 1 and CKD stages 1–3a. A substantial change in markedly elevated plasma oxalate could support accelerated approval in patients with primary hyperoxaluria and CKD stages 3b–5. Primary hyperoxaluria type 1 accounts for the preponderance of available data, thus heavily influences the conclusions. Addressing gaps in data will further facilitate testing of promising new treatments, accelerating improved outcomes for patients with primary hyperoxaluria.


Introduction
Primary hyperoxaluria is a rare disease, with <1000 individuals affected in the United States. There are three types of primary hyperoxaluria that differ in their severity and genetic cause. Each of the three known primary hyperoxaluria types is caused by a defect in a gene that governs the production of a different hepatic enzyme, and each result in the overproduction of oxalate by the liver. Because humans have no enzyme capable of degrading oxalate, it must be eliminated primarily by the kidneys, with a small amount by the gastrointestinal tract. Hyperoxaluria results in calcium oxalate kidney stones, progressive oxalate nephropathy, and kidney failure. To address the pressing need to evaluate new treatments for primary hyperoxaluria, the Kidney Health Initiative (KHI) (1), in partnership with the Oxalosis and Hyperoxaluria Foundation (OHF), initiated a project to identify end points that could be used in clinical trials. Published literature was examined to identify candidate end points. Workgroup members with expertise in oxalate biology and pathophysiology, clinical nephrology and urology, and drug development provided a critical analysis of each candidate. Patients with primary hyperoxaluria, their family members, and leadership of the OHF patient advocacy organization provided input throughout. This article discusses the pathophysiology of primary hyperoxaluria, current treatment strategies, approval pathways and end points in the United States, and the workgroup’s assessment of potential end points that could be used to evaluate the efficacy of new drugs for the treatment of primary hyperoxaluria. Because primary hyperoxaluria type 1 accounts for 70%–80% of all diagnosed patients with primary hyperoxaluria to date and appears to have the most severe clinical phenotype (2,3), knowledge is most extensive for this primary hyperoxaluria type. Thus, data relevant to primary hyperoxaluria type 1 influenced recommendations in this article more than other primary hyperoxaluria types.

Pathophysiology of Primary Hyperoxaluria
Primary hyperoxaluria is caused by deficiencies in enzymes involved in the metabolism of glycolate, glycine, and hydroxyproline within the liver. The resulting excess of glyoxylate leads to the synthesis and release of oxalate into the bloodstream. In the early stages of the disease, the increase in plasma oxalate is mitigated and compensated for by increased kidney excretion. Oxalate in the urine combines with calcium to form stones, as well as crystals that cause
that liver function is otherwise normal, and one that carries significant risks (9–11). Therefore, new treatments are urgently needed.

Surrogate End Points and Approval Pathways in the United States

In the United States, the efficacy of a product (drug or biologic) in treating, mitigating, or preventing a disease can be established by demonstrating an effect on a clinical outcome, which reflects how a patient feels, functions, or survives. Alternatively, product approval or licensure may be based on a surrogate end point. Surrogate end points, which are often biomarkers such as a laboratory measurement, radiographic image, or physical sign, are not direct measures of clinical benefit, but instead are expected to predict the effect of a product on the clinical benefit of interest. Surrogate end points can be categorized as validated, reasonably likely, or candidate, based on the strength of evidence supporting their use. A validated surrogate end point is supported by strong scientific evidence that a treatment effect on the surrogate end point predicts the treatment effect on the clinical outcome of primary interest. A reasonably likely surrogate end point is also supported by strong scientific evidence, but lacks sufficient evidence to serve as a validated surrogate end point. Reasonably likely surrogate end points can be used as a basis for accelerated approval of products intended to treat a serious or life-threatening condition and that provide a meaningful advantage over available therapies. For products granted accelerated approval, adequate and well controlled postmarketing confirmatory studies have generally been required to verify and describe the anticipated clinical benefit (12–14).

Available Therapies and Unmet Need

Current strategies to prevent stones and kidney damage target reduction of calcium oxalate crystal formation in the urinary tract through high urine volume and medications such as citrate and magnesium. Pyridoxine is a cofactor for the alanine-glyoxylate aminotransferase (AGT) enzyme that is deficient in primary hyperoxaluria type 1. In certain primary hyperoxaluria type 1 genotypes characterized by mislocalization of AGT within hepatocytes, pharmacologic doses of pyridoxine increase enzyme activity and thus reduce oxalate production (3,4,6). Large daily fluid intake (e.g., 3.5–4 L/day in adults, with fluid prescription in children proportionate to body size) and a large pill burden compromise quality of life. Further, although these treatments may moderate the effects of hyperoxaluria, in many patients they do not prevent stone formation nor do they eliminate kidney failure in primary hyperoxaluria types 1 and 2 (3,7). The burden of frequent symptomatic kidney stones with associated hospitalizations and stone removal procedures, intensive dialysis if kidney failure ensues, systemic oxalate deposition, and transplantation are enormous. The companion paper to this article, written by patients with primary hyperoxaluria and their family members, provides insights into the experience of living with this disease (8). At this time, there are no FDA-approved pharmacologic therapies for primary hyperoxaluria. Liver transplantation can correct the metabolic deficiency in patients with primary hyperoxaluria types 1 and 2; this is an effective but extreme intervention, given that liver function is otherwise normal, and one that carries
Kidney Stones as a Clinical End Point

Stone burden is of particular interest in primary hyperoxaluria because stones are caused by high urine oxalate and often lead to pain, hospitalizations, and stone removal procedures. Although kidney stone disease directly affects the lives of patients with primary hyperoxaluria, work remains to develop reliable and safe methods for the assessment and quantification of stone events, and to more fully define the natural history of stone burden at all CKD stages. Assessment of stone number and size is influenced by the type of imaging modality used. Computerized tomography is recognized as the gold standard for stone detection (15,16), but longitudinal studies require technique standardization and entail recurring radiation exposure. Ultrasonography for stone measurement yields varying results depending upon the specific equipment used and sonographer technique (17). Longitudinal data documenting changes in kidney stone number or size have not been reported in a primary hyperoxaluria cohort. Kidney stones are often asymptomatic for long periods of time; thus, variability of stone symptoms must be considered when used as an end point for clinical trials. Further, neither definitions of symptomatic stone events nor standards for radiographic assessment of stone burden are commonly agreed upon. The effects of reduced GFR on stone burden are difficult to assess and have not been systematically described, and reduced calcium and oxalate excretion in advanced CKD could reduce stone activity. In sum, although stone burden is clinically meaningful, at the present time there are challenges related to its use as an end point in primary hyperoxaluria. As the natural history of stone disease in primary hyperoxaluria becomes informed by more robust data, its role as a feasible clinical end point should be reconsidered.

Slope of the Glomerular Filtration Rate as a Surrogate End Point

For rare causes of CKD, the efficacy of products intended to reduce the risk of progression to kidney failure may be established by showing a treatment effect on the rate of decline in kidney function (GFR slope) or a sustained 30% decline in GFR (12,18). In primary hyperoxaluria, loss of kidney function can begin in infancy and early childhood. Among those with the most severe form, primary hyperoxaluria type 1, 50% will progress to kidney failure by 33 years of age, and nearly all by 60 years of age (2). In most patients, kidney function is not typically lost at a rapid rate. In a study by Tang et al. (7), the rate of loss of kidney function in a mixed group of patients with primary hyperoxaluria type 1, primary hyperoxaluria type 2, and primary hyperoxaluria type 3 ranged from −0.4 ml/min per 1.73 m² per year in those with no or prevalent nephrocalcinosis to −1.2 ml/min per 1.73 m² per year in those with incident nephrocalcinosis. A small study (19) reported a change of −1.7 ml/min per 1.73 m² per year in primary hyperoxaluria type 1 and −1.04 ml/min per 1.73 m² per year in primary hyperoxaluria type 2. Fargue et al. (20) reported a median decrease of −1.0 ml/min per 1.73 m² per year in 19 children with primary hyperoxaluria type 1 who were >2 years of age at diagnosis. Clinical experience suggests higher rates of GFR decline in those patients with primary hyperoxaluria who have more advanced CKD, particularly CKD stages 3b-4. Further, rapid declines in kidney function leading to kidney failure over weeks to months occasionally occur in patients with primary hyperoxaluria, sometimes precipitated by...
acute events such as dehydration or an obstructive kidney stone (3,21).

Additional research is needed to better define populations at greatest risk for progression and delineate the course of disease in children and adults (Table 2). Given the limited ability to identify patients at high risk of experiencing a significant loss of kidney function over the course of a trial and the size of the affected population, it is unclear whether GFR-based end points are, at present, feasible trial end points for primary hyperoxaluria.

**Table 1. Potential end points for clinical trials in primary hyperoxaluria**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Pros</th>
<th>Cons</th>
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<tbody>
<tr>
<td><strong>Clinical end points</strong></td>
<td></td>
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<tr>
<td>Stone events</td>
<td>Affects how most patients with primary hyperoxaluria feel and function</td>
<td>Standards for measurement and longitudinal monitoring lacking Accurate methods of measurement that do not rely on ionizing radiation are needed Reliability in CKD stages 3b–5 unknown</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>Important to patients, easy to measure</td>
<td>May not have many events in a trial, particularly if trial is conducted in the available number of patients with a reasonable length of follow-up</td>
</tr>
<tr>
<td>Oxalosis</td>
<td>Important to patients, severe morbidity</td>
<td>May not have many events in a trial, particularly if trial is conducted in the available number of patients with a reasonable length of follow-up</td>
</tr>
<tr>
<td><strong>Surrogate end points</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsening kidney function (GFR slope)</td>
<td>Accepted as surrogate end point for other conditions Easy to measure Rapid decline would be highly supportive of clinically meaningful benefit</td>
<td>May not detect change in patients with slow progression</td>
</tr>
<tr>
<td>Urine oxalate</td>
<td>Causal role in stone formation and kidney damage in CKD 1–3a and relationship between baseline urine oxalate and kidney failure Available data support use of substantial change as surrogate end point for traditional approval in patients with primary hyperoxaluria type 1 with CKD 1–3a Lesser treatment effects or effects in patients with primary hyperoxaluria without very high baseline levels reasonably likely to predict clinical benefit</td>
<td>Magnitude of change needed to predict clinical benefit across primary hyperoxaluria types warrants further study May not be useful in CKD 3b–5 due to reduced kidney function to excrete oxalate</td>
</tr>
<tr>
<td>Plasma oxalate</td>
<td>Reasonably likely to predict clinical benefit due to causal role in systemic oxalosis in CKD stages 3b–5 Causal role in stone formation and kidney damage (CKD stages 1–3a)</td>
<td>Magnitude of change in plasma oxalate in CKD stages 3b–5 likely to predict clinical benefit requires further study Value in CKD 1–3a for prediction of clinical outcome remains to be established Limited availability of laboratory measurement. Results vary by method</td>
</tr>
</tbody>
</table>

Data supporting these conclusions are heavily influenced by primary hyperoxaluria type 1, which accounts for the majority of patients with primary hyperoxaluria. Small numbers of patients with primary hyperoxaluria type 2 and primary hyperoxaluria type 3 in primary hyperoxaluria registries do not yet provide a similar strength of evidence for these biomarkers in other forms of primary hyperoxaluria.

Urine Oxalate as a Surrogate End Point

Urine Oxalate as a Causal Factor in Stone Formation and Loss of Kidney Function. Persistently elevated urine oxalate levels cause kidney stone formation and also contribute to progressive kidney damage and loss of kidney function (2,3,7,21–23). In all primary hyperoxaluria types, the urine becomes supersaturated, resulting in formation of calcium oxalate crystals that aggregate within the tubular lumen. The crystals can attach to the surface of kidney tubular cells and become internalized, they then migrate into the kidney interstitium (nephrocalcinosis) where they induce inflammation, ultimately resulting in progressive damage and CKD (3). In animal models of crystal nephropathy, prolonged activation of the intrarenal inflammasome by calcium oxalate crystals appears to be one mechanism that promotes the loss of kidney function (24,25). Nephrocalcinosis is also associated with risk of kidney failure in patients with primary hyperoxaluria (7,26,27).

In all types of primary hyperoxaluria, calcium and oxalate can also crystallize upon an anchored nidus in the kidney papillum to form a stone (urolithiasis). Although higher
urine oxalate correlated with a greater number of stones on radiographic images in one study (7), the relationship of urine oxalate to clinical stone events or stone burden has not been otherwise reported. Obstructing stones or stone removal procedures can contribute to the loss of kidney function in individual patients. However, in contrast to nephrocalcinosis, the number of stones and symptomatic stone events do not appear associated with kidney survival in primary hyperoxaluria at a population level (7).

**Epidemiologic Data.** Epidemiologic data on the relationship between urine oxalate and loss of kidney function is derived from primary hyperoxaluria registries, observations in secondary causes of hyperoxaluria, and in a large cohort of patients with CKD with other forms of kidney disease. Analyses of primary hyperoxaluria registry data show a strong relationship between urine oxalate and loss of kidney function (21). Primary hyperoxaluria type 1 accounts for a majority of subjects. Data in primary hyperoxaluria type 2 and primary hyperoxaluria type 3 are more limited but show urine oxalate, risk of nephrocalcinosis, and risk of kidney failure to be less in primary hyperoxaluria type 2 compared with primary hyperoxaluria type 1, and even lower in primary hyperoxaluria type 3 (2,3,5,7). Nonetheless, an analysis of the OxalEurope primary hyperoxaluria type 2 registry data clearly indicates that this patient population has significant disease burden and morbidity (5).

Evidence supporting the association of potential end points with disease progression differs by CKD stage. Urine oxalate is a more useful biomarker when kidney function is preserved but is expected to decrease as GFR falls to low levels. Plasma oxalate becomes the biomarker of choice when the failing kidney is no longer able to adequately excrete oxalate into the urine (CDK stages 3b–5). Additional study is needed to determine whether plasma or urine oxalate performs better as a biomarker in CKD stage 3.

### Table 2. Gaps in data requiring additional research

<table>
<thead>
<tr>
<th>End Point</th>
<th>CKD Population (Stage)</th>
<th>Gaps in Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney stones</td>
<td>1–3b</td>
<td>Standards for definition of clinical stone event do not exist</td>
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<tr>
<td></td>
<td></td>
<td>Standards for radiographic assessment of stone burden are not available</td>
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<tr>
<td></td>
<td></td>
<td>Quantitative methods for stone assessments which avoid ionizing radiation not available</td>
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<tr>
<td></td>
<td>4–5a</td>
<td>No reported studies</td>
</tr>
<tr>
<td>Slope of GFR</td>
<td>1–4</td>
<td>Changes in rate of decline by CKD stage are not well defined</td>
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<td></td>
<td></td>
<td>Patient-patient variability is not well understood</td>
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<tr>
<td></td>
<td></td>
<td>Discontinuity in eGFR formula performance as children transition to adulthood</td>
</tr>
<tr>
<td>Urine oxalate excretion</td>
<td>1–3a</td>
<td>Correlation between spot urine oxalate/creatinine and 24-h urine oxalate excretion not established</td>
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<tr>
<td></td>
<td></td>
<td>Confirmation of the relationship of urine oxalate excretion and incident ESKD in a validation cohort</td>
</tr>
<tr>
<td></td>
<td>3b–5a</td>
<td>Relationship of urine oxalate and plasma oxalate over the range of GFR not well described</td>
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<tr>
<td></td>
<td></td>
<td>Interplay between urine oxalate and plasma oxalate and the development of intrarenal calcium oxalate crystals and kidney damage are poorly understood</td>
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<tr>
<td></td>
<td></td>
<td>Quantitative effect of reduction of urine oxalate on GFR and stone burden is not known</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Effect of low GFR on urine oxalate has not been described; urine oxalate expected to decrease at low GFR due to declining kidney function.</td>
</tr>
<tr>
<td>Plasma oxalate concentration</td>
<td>1–3a*</td>
<td>Not widely used in clinical practice; minimal data available</td>
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<tr>
<td></td>
<td></td>
<td>Biologic variation not characterized</td>
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<tr>
<td></td>
<td>3b–5</td>
<td>Biologic variation not well characterized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Standards for sample collection, processing, and measurement are lacking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interpretation requires correction for GFR due to kidney clearance</td>
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<tr>
<td></td>
<td></td>
<td>Dynamic equilibrium between plasma oxalate and tissue oxalate stores is poorly understood</td>
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<tr>
<td></td>
<td></td>
<td>Predictive value of elevated plasma oxalate on clinical end points including risk for ESKD not defined</td>
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<tr>
<td></td>
<td></td>
<td>Magnitude of decrease in plasma oxalate needed to achieve a meaningful clinical benefit not known</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quantitative effect of plasma oxalate on systemic oxalosis is not known</td>
</tr>
</tbody>
</table>

*aMinimal data available.
analyzed as a continuous time-dependent covariate, the risk of kidney failure was greater with increasing urine oxalate levels, yielding a hazard ratio of 1.8 (95% CI, 1.2 to 2.5) per 1 mmol/1.73 m² per 24-hour increase. In a separate primary hyperoxaluria registry analysis (7), urine oxalate excretion rates in patients with primary hyperoxaluria were higher among those with nephrocalcinosis (2.0 mmol/24 hours) versus those without nephrocalcinosis (1.3 mmol/24 hours), P<0.01, again demonstrating a relationship between urine oxalate and kidney damage. In a large population of patients who did not have primary hyperoxaluria with baseline CKD stages 2–4, higher 24-hour urinary oxalate excretion was an independent risk factor for CKD progression and kidney failure (23). In a review of 108 patients with secondary forms of hyperoxaluria, 55% required dialysis due to biopsy-proven oxalate nephropathy (28).

Importantly, although it is difficult to draw definitive conclusions from these cross-sectional analyses, the data support the principle that those patients with the highest levels of urine oxalate are at greatest risk for primary hyperoxaluria disease progression, an important consideration for use of urine oxalate as a surrogate end point. The workgroup acknowledges that this conclusion is driven by primary hyperoxaluria type 1 data, which represent the majority of primary hyperoxaluria cases, and that direct evidence of the relationship between urine oxalate and clinical outcome for primary hyperoxaluria type 2 and primary hyperoxaluria type 3 is not yet available.

Treatment Effects. Currently, the only treatment directly targeting urine oxalate reduction is pyridoxine, which appears to increase the enzyme activity of a subset of mutant AGT forms found in primary hyperoxaluria type 1 (29,30). Approximately 30% of patients with primary hyperoxaluria type 1 show some degree of responsiveness (31,32). A retrospective review demonstrated mean urine oxalate reduction on pyridoxine of 73% from a baseline of 1.5 mmol/1.73 m² per day among six patients with primary hyperoxaluria type 1 who were homozygous for the most common pyridoxine-responsive AGT mutation (G170R); four achieved normal urine oxalate excretion (33). In the same study, eight patients who were heterozygous achieved a 45% reduction from a baseline of 2.2 mmol/1.73 m² per day. Pyridoxine effect was sustained during 6.5 and 8.4 years of follow-up, respectively. Primary hyperoxaluria registry studies confirm that patients with primary hyperoxaluria type 1 who have the G170R mutation have better preservation of kidney function than those patients without this mutation (2,34). Similarly, in four of five patients with late diagnosis of primary hyperoxaluria but with urine oxalate excretions normal or near normal after initiation of pyridoxine (<0.5 mmol/1.73 m² per day), stable kidney function was maintained during a median of 8.5 years after a kidney-alone transplant (35). The only graft loss occurred at 13.9 years post-transplant. Normalization of oxalate excretion and stabilization of kidney function has also been observed after pre-emptive liver transplantation, and nephrocalcinosis has resolved after liver-alone transplant in a few reported cases (36–38).

Recommendation for Urine Oxalate. Available data support a substantial change in urine oxalate (e.g., near normalization) as a surrogate end point and basis for traditional approval for the treatment of primary hyperoxaluria type 1 in patients with CKD 1–3a. Lesser treatment effects or effects in patients without very high baseline levels could also translate into clinical benefit and possibly serve as a reasonably likely surrogate and basis for accelerated approval, but the magnitude of reduction needed is unclear at this time.

Urinary oxalate appears to be the preferred end point in CKD 1–3a because urine oxalate is a causal factor in kidney stones and nephrocalcinosis in these patients with higher GFR. Changes in urine oxalate over the disease course have not been well described in patients who have progressed to CKD stages 3b–5. Urine oxalate is expected to decrease as GFR falls to very low levels (GFR<15 ml/min per 1.73 m²); ultimately excretion will cease with oligoanuria. The effects of very low levels of kidney function on stone burden and nephrocalcinosis have not been systematically described. Timed 24-hour urine collections are needed for the most accurate measurement of urine oxalate excretion rate but are challenging, especially in children. Additional work to quantitate the relationship between spot urine oxalate/urine creatinine measurements (39) or shorter duration collection with 24-hour urine oxalate excretion is needed. In pediatric patients, urine oxalate measurements must account for changes in reference ranges due to maturation of kidney function and growth throughout infancy and childhood.

Plasma Oxalate as a Surrogate End Point

Plasma Oxalate as a Causal Factor in Loss of Kidney Function and Systemic Oxalosis. Plasma oxalate directly reflects hepatic synthesis of oxalate. When kidney function (GFR) is normal, the overproduction of oxalate is balanced by kidney excretion. Thus, plasma oxalate remains within the normal range, or mildly elevated, at the expense of markedly increased urine oxalate (40). As GFR declines, plasma oxalate increases due to dependence on the kidney for elimination. When plasma oxalate exceeds 35–50 μmol/L, physicochemical properties favor crystallization, leading to systemic calcium oxalate crystal deposition (41,42). Crystal injury to tissue (43) can cause bone fractures, impaired erythropoiesis, infiltrative cardiomyopathy, arrhythmias, peripheral neuropathy, retinopathy, and ischemic ulcers (4,44). Thus, in CKD stages 3b–5 (GFR<45 ml/min per 1.73 m²), elevated plasma oxalate is directly related to the pathophysiology of oxalosis. In contrast, although oxalate overproduction is a key causal factor in loss of kidney function, plasma oxalate in isolation may not track well with the loss of kidney function at higher eGFR levels (>45 ml/min per 1.73 m²) because of the ability of the kidney to excrete the excess load.

Epidemiologic Data. In patients with primary hyperoxaluria, plasma oxalate increases from normal/modestly increased (2–10 μmol/L; normal is 1–3 μmol/L with most assays) when GFR is well preserved (>60 ml/min per 1.73 m²) to markedly increased (>90–100 μmol/L) in patients with CKD stage 5 (3,4,40) (Figure 2). Plasma oxalate concentrations that exceed the supersaturation threshold for calcium oxalate are typically observed in patients with primary hyperoxaluria with GFR ≤30–40 ml/min per 1.73 m² (CKD 3b–5) (4,45). Only patients with primary hyperoxaluria who have advanced CKD and markedly increased plasma oxalate experience clinically overt systemic deposition of calcium oxalate.
in multiple body tissues, resulting in severe disease and ultimately death (3,4,45). Although the risk and manifestations of oxalosis are most severe in primary hyperoxaluria, lesser elevations in plasma oxalate in patients with kidney failure from any cause can be associated with a mild form of systemic calcium oxalate deposition (46,47). In patients with primary hyperoxaluria who have preserved GFR (CKD 1–3a), the role of plasma oxalate in disease progression has not been studied. This may, in part, be related to the small number of laboratories performing plasma oxalate measurements, differences in measurement methods, and infrequent measurement of plasma oxalate in earlier stages of CKD.

**Treatment Effects.** Evidence that reduction in plasma oxalate reduces the risk or severity of subsequent systemic oxalosis is limited to anecdotal experience with intensive dialysis regimens and the resolution of disease manifestations after transplantation. Plasma oxalate decreases rapidly after liver transplantation (48), with gradual resolution of oxalosis reported (37). Studies of treatment response to plasma oxalate reduction in patients with primary hyperoxaluria who have CKD stages 1–3a are lacking.

**Recommendation for Plasma Oxalate.** Available data support the use of a substantial change in plasma oxalate in patients with CKD stages 3b–5 and markedly elevated plasma oxalate levels as a reasonably likely surrogate for a treatment’s effect on systemic manifestations of the disease. Among patients with CKD 1–3a, the major utility for plasma oxalate may be as a readily obtainable

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**Figure 2.** Plasma oxalate increases exponentially as eGFR declines below 60 ml/min per 1.73 m². Plasma oxalate values and eGFR taken from the latest visit of 128 patients with primary hyperoxaluria (PH) who were >2 years of age (PH type 1, n=96; PH2, n=14; PH3, n=18) were plotted. Plasma oxalate values are relatively stable in the eGFR range of >60 ml/min per 1.73 m², and then they increase exponentially as eGFR declines. Plasma oxalate concentration was measured by ion chromatography. The CKD Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR in adults, and the modified Schwartz equation at <18 years of age. The model was fit using a third degree polynomial regression (plotted as a black line). Both quadratic and cubic terms were statistically significant by the likelihood ratio test (P<0.001 for both). The 95% confidence interval of the regression model is indicated by the shaded region. Data shown is from the Rare Kidney Stone Consortium Primary Hyperoxaluria Registry.
biomarker that reflects the net effect of oxalate burden and urinary oxalate excretion (49). Limited data are available on the magnitude of change in plasma oxalate required to confer clinical benefit. Further, in advanced systemic oxalosis, the exchange of oxalate between tissue stores and plasma is poorly understood (41,42,47). Additional research is needed to address these gaps in the data.

Other Markers Considered as Potential Surrogate End Points

Nephrocalcinosis, urine calcium oxalate supersaturation (50), and primary hyperoxaluria metabolites (glycolate, glycerate, dihydroxyglutarate, and 4-hydroxy-2-oxoglutarate) (51) were also considered as potential surrogate end points. Progression of nephrocalcinosis and its relationship with kidney function has not been studied. Further, the absence of quantitative methods for nephrocalcinosis measurement is a current barrier for its use as a marker of disease progression. Measurements of primary hyperoxaluria metabolites and calculation of calcium oxalate supersaturation are currently performed by only a few laboratories and not widely used in clinical practice. Thus, there have been no studies in primary hyperoxaluria cohorts that demonstrate a correlation of these parameters with stone burden or with progression of disease.

Among patients with primary hyperoxaluria who have CKD stages 3b–5, severity of systemic oxalosis was considered. New imaging techniques show promise for assessment of systemic calcium oxalate burden (e.g., retinal imaging with spectral domain optical coherence tomography, speckle tracking echocardiography, cardiac elastography, and quantification of calcium oxalate deposits in bone through computed tomography or magnetic resonance imaging). There is limited experience in the use of these imaging techniques in patients with primary hyperoxaluria, and no systematic studies to define their usefulness in disease progression. Thus, in the absence of standardized and reproducible measures of severity, assessment of oxalosis requires additional research.

Conclusion

To address the pressing need to evaluate new treatments for primary hyperoxaluria, KHI, in partnership with OHF, initiated a project to identify end points that could be used in clinical trials. The workgroup, which included experts in primary hyperoxaluria, patients living with primary hyperoxaluria and their families, industry, and United States regulators, considered potential clinical outcomes, as well as possible surrogate end points that could be used to establish the efficacy of new treatments. The strengths and limitations of the end points considered by the group are summarized in Table 1, and important gaps in the data are discussed in Table 2. Available evidence supports urine oxalate in CKD stages 1–3a and plasma oxalate in CKD stages 3b–5 as end points for clinical trials in primary hyperoxaluria.

We are at a tipping point in the development of new treatments for patients with primary hyperoxaluria, made possible by decades of dedicated patient participation in registries and clinical studies, the OHF in their support of primary hyperoxaluria patient and research communities, basic and clinical investigators, and the more recent investment of the pharmaceutical industry. Although work remains, patients with primary hyperoxaluria and their physicians can face the future with optimism.

Acknowledgments

In February 2018, the OHF conducted a workshop for members of the hyperoxaluria community, including patients and care partners, scientists, and clinicians. Clarity regarding end points for clinical trials of new agents for primary hyperoxaluria was identified as a high priority. Participants and other volunteers from the primary hyperoxaluria community, selected by the OHF and KHI as members of the KHI Workgroup, collated literature for each potential end point and presented the findings. The workgroup then deliberated and worked to a consensus on the feasibility and utility of each end point.

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The authors of this paper had full review authority and are fully responsible for its content. KHI makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the members of the workgroup. More information on KHI, the workgroup, or the conflict of interest policy can be found at www.kidneyhealth-initiative.org.

The views and opinions expressed in this publication are those of the authors and do not necessarily reflect the official policies of any KHI member organization, the US Department of Veterans Affairs, or the US Department of Health and Human Services, nor does any mention of trade names, commercial practices, or organization imply endorsement by the US Government.

Disclosures

Dr. Lieske is currently employed by Mayo Clinic. Dr. Lieske reports receiving grants from Allena, Alnylam, Dicerna, OxThera, Retrophin, and Siemens; receiving honoraria from Alnylam, American Board of Internal Medicine (ABIM), Dicerna, Orfan, OxThera, and Retrophin; serving as a consultant for ABIM, Allena, Alnylam, Dicerna, Orfan, OxThera, Retrophin, and Siemens; and serving as a scientific advisor or member of ABIM, Kidney International, and the Oxalosis and Hyperoxaluria Foundation; all outside of the submitted work. Dr. Milliner is currently employed by Mayo Clinic. Dr. Milliner reports receiving grants from Allena, Alnylam, Dicerna, and OxThera; receiving honoraria from Alnylam; serving as a consultant for Allena, Alnylam, Dicerna, and OxThera; serving in an advisory committee for Alnylam, a monitoring committee for a clinical trial conducted by Dicerna, on a data safety
monitoring board for a clinical trial conducted by OxThera, and on the editorial board for *Urolithiasis*, all outside of the submitted work. Dr. Milliner also has ongoing work with OHF outside of the submitted work. Ms. Allain and Ms. West are currently employed by the American Society of Nephrology. Dr. Blank, Dr. Thompson, and Dr. Yang are currently employed by the FDA. Dr. Dehmel is currently employed by and reports ownership interest in OxThera outside of the submitted work. Dr. Groothoff is currently employed by the Academic Medical Center, Amsterdam, and reports serving as a consultant for Alnylam and Dicerna, outside of the submitted work. Dr. Groothoff is supported by presentation fees from Alnylam and grants from Alnylam, Dicerna, and UniQure. Ms. Hollander is currently employed by the OHF. Ms. Hollander reports receiving grants on behalf of the OHF from Allena, Alnylam, Bridge Biopharma, Captozyme, Dicerna, EveryLife Foundation, Intella Therapeutics, Invitae Corporation, Novome Biotechnologies, Orfan, and OxThera; personal fees from Allena, Alnylam, and Dicerna; and nonfinancial support from Allena, Alnylam, Dicerna, KHL, and OxThera; all outside of the submitted work. Dr. Knight is currently employed by the University of Alabama, Birmingham. Dr. Knight reports receiving grants from Alnylam, Chinox Therapeutics, Intella Therapeutics, and Synlogic Operating Company, Inc.; receiving personal fees from Chinox Therapeutics; and has a pending patent for treating primary or idiopathic hyperoxaluria with small molecule inhibitors of lactate dehydrogenase. Dr. Lowther is currently employed by Wake Forest School of Medicine. Dr. Lowther reports receiving grants from Chinox Therapeutics and Paredox Therapeutics, having ownership interest in Chinook Therapeutics, and serving on the editorial board of the *Journal of Biological Chemistry* and the scientific advisory boards for Chinox Therapeutics and the Oxalosis and Hyperoxaluria Foundation, all outside of the submitted work. Dr. McGregor is currently employed by, has received travel support from, and has ownership interest in Alnylam Pharmaceuticals outside of the submitted work. Dr. Rosskamp is currently employed by and has ownership interest in Dicerna outside of the submitted work. Dr. Rumsby serves as a consultant for OxThera outside of the submitted work.

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**References**

33. Monaco CG, Rossetti S, Olson JB, Milliner DS: Pyridoxine effect in type I primary hyperoxaluria is associated with the most common mutant allele. Kidney Int 67: 1704–1709, 2005

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