End Points for Clinical Trials in Hyperoxaluria: Case Study of Patient-Focused Drug Development in a Rare Disease

John C. Lieske, Meaghan A. Malley, Melissa West, Kim Hollander, and Dawn S. Milliner

Over the last decade, many exciting developments and treatment approaches for kidney disease have emerged.1 There are many underlying reasons for this, including rapid advances in understanding the pathogenesis for specific kidney diseases. The increased availability of high-throughput genetic sequencing, single-cell gene expression analysis, and ever more powerful bioinformatic techniques are just a few of the contributing factors. Equally important are efficient yet rigorous methods to conduct clinical trials to assure the safety and efficacy of new treatments in a cost-efficient and timely manner. Clinical trial design has been particularly important in kidney disease, given the relatively long time it takes to progress to clinically meaningful end points such as kidney failure. Clinical trials in rare diseases pose additional challenges in identification of end points that are achievable in small patient populations. It is equally important to consider the views of the target patient population for any given treatment, since for many diseases with potentially serious and painful outcomes, patients may be willing to assume greater uncertainty about the ultimate safety and efficacy of new treatment approaches.2

The US Food and Drug Administration (FDA) recognizes the importance of balancing rigorous evaluation of novel therapeutics and the impact that delay of any effective treatments will have on families and patients, many of whom are children, and thus the role of patient-focused drug development (PFDD) has evolved.3 For kidney diseases overall, there have been careful considerations of what changes—ie, estimated glomerular filtration rate, slope of estimated glomerular filtration rate decline, or change in albuminuria—would be acceptable for traditional or accelerated drug approval.4

Oxalate is a small 2-carbon molecule found in certain plants in the form of calcium oxalate crystals. Oxalate is also produced in the human liver as a product of metabolism. Since humans have no enzyme to degrade oxalate, whatever oxalate is absorbed from dietary sources or produced by the liver must be excreted, primarily by the kidneys.5 Within the urinary tract, oxalate can combine with calcium to form calcium oxalate crystals and kidney stones. Extreme hyperoxaluria can result from 2 major causes: primary hyperoxaluria due to hepatic overproduction of oxalate because of a defect in 1 of 3 known genes,6 and enteric hyperoxaluria due to gastrointestinal fat malabsorption that causes increased intestinal absorption of dietary oxalate.7 In both cases the excess oxalate markedly increases the risk of kidney stones and chronic kidney disease.6-11 In primary hyperoxaluria, the more extreme and persistent hyperoxaluria is frequently associated with kidney failure, and if kidney failure ensues systemic oxalosis can occur.12 Continued hyperoxaluria following kidney transplantation can lead to transplant failure in both primary and enteric forms of the disease.

Fortunately, novel therapies are in the pipeline for both primary and enteric hyperoxaluria; however, clinical trials in rare diseases such as these are challenging. The number of affected individuals is small for trial recruitment. In genetic diseases there is added complexity for conducting studies in a pediatric population. In enteric and primary hyperoxaluria kidney stone events are a key clinical end point, but since stone events generally occur every 2-3 years in an active patient, the number of patients necessary for traditional placebo-controlled trials is quite large and trial duration long. Kidney failure is an important clinically significant outcome, but even for primary hyperoxaluria the number of patients and time they would need to be followed using this end point in a trial is daunting. Regulatory authorities recognize these obstacles. Thus, although patient-centered clinical outcomes are always most important, surrogate end points can often support efficacy of a given therapy. In general, for a surrogate end point to be acceptable for approval of a therapy, even as a contingent

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Policy Forum Editorial

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Policy Forum highlights aspects of nephrology relating to payment and social policy, legislation, regulation, demographics, politics, and ethics, contextualizing these issues as they relate to the lives and practices of members of the kidney community, including providers, payers, and patients.
approval, evidence linking that surrogate to patient outcome must be available.\(^6\)

The Oxalosis and Hyperoxaluria Foundation (OHF; www.ohf.org/) is a donor-funded, 501(c)(3) not-for-profit dedicated to finding treatments and a cure for all forms of hyperoxaluria that supports research and spreads awareness about the disease among patients, medical professionals, government officials, the general public, and industry. This passionate and forward-looking patient advocacy group recognized imminent opportunities for novel treatments, as well as the potential barriers to confirming their efficacy and getting these therapies to hyperoxaluria patients as soon as possible. Thus a group of scientists, clinicians, industry representatives, patients, and their families were brought together 5 years ago to examine barriers to rapid implementation of novel treatments. This group worked to develop a shared understanding of patient experiences with hyperoxaluria, the current treatment options, gaps in those approaches, and patient willingness to adopt novel approaches. Definition of clinically meaningful and potential surrogate end points for clinical trials and identification of data gaps were identified as critical needs in order to approach regulatory agencies. Thus, the OHF work group approached the Kidney Health Initiative (KHI), a public-private partnership between the American Society of Nephrology (ASN), the FDA, and over 100 member companies and organizations including those that represent industry and kidney patients. KHI fosters a precompetitive collaborative environment to address regulatory issues that can ultimately expedite the development and approval of promising therapies. The KHI endorsed a project in 2017 and charged a workgroup with identifying surrogate end points for trials in enteric and primary hyperoxaluria.

Well-developed patient registries based in Europe and the United States and several relevant peer-reviewed publications already existed for primary hyperoxaluria.\(^8\)-10 Subgroups were immediately formed around potential primary hyperoxaluria clinical trial end points, including kidney stone events, and surrogate markers urine oxalate, kidney function, and plasma oxalate. After a systematic review of the literature and available data, the subgroups compiled a single document that was reviewed and further edited in collaboration with patients, clinicians, industry, and the FDA. The final product was subsequently published and serves as a roadmap for biotech companies interested in potential therapies for primary hyperoxaluria.\(^6\) In parallel with this work, patients and their caregivers, led by OHF, reported their experiences and perspectives on living with primary hyperoxaluria and their hopes for future treatments.\(^6\) Ongoing collaborations with the KHI culminated in a primary hyperoxaluria PFDD meeting on October 5, 2020. Altogether, more than 300 persons attended this virtual meeting held at the height of the COVID-19 pandemic, over half being patients and caregivers, with the remainder representing the FDA, academia, industry, and patient advocates. This forum allowed patients to openly share their life experience with primary hyperoxaluria and discuss their willingness to accept novel treatments and their risk tolerance for receiving them. Key patient messages are highlighted in Box 1, and a Voice of the Patient document summarizing this event is in preparation and will be published on the FDA’s PFDD website.\(^3\)

The KHI workgroup pursued the same general process for enteric hyperoxaluria. Unfortunately, a mature patient registry and robust publications regarding the natural history of enteric hyperoxaluria were lacking. Thus, completion of a systematic review was an essential first step.\(^7\) The next step will be evaluation of potential end points for clinical trials based upon this literature, expert opinion, and other background information, working in close concert with the FDA.

Developing novel therapies for rare diseases remains a challenge owing to the small number of patients and the

### Box 1. Patient and Caregiver Perspectives on Living With Primary Hyperoxaluria

<table>
<thead>
<tr>
<th>Common symptoms/manifestations</th>
<th>Kidney stones (80%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pain (57%)</td>
</tr>
<tr>
<td></td>
<td>UTI/dysuria (54%)</td>
</tr>
<tr>
<td></td>
<td>CKD/kidney failure (50%)</td>
</tr>
<tr>
<td></td>
<td>Nausea/vomiting (47%)</td>
</tr>
<tr>
<td></td>
<td>Anxiety/depression (44%)</td>
</tr>
<tr>
<td>Most troublesome symptoms/manifestations</td>
<td>Kidney stones (76%)</td>
</tr>
<tr>
<td></td>
<td>CKD/kidney failure (53%)</td>
</tr>
<tr>
<td></td>
<td>Pain (24%)</td>
</tr>
<tr>
<td></td>
<td>Anxiety/depression (23%)</td>
</tr>
<tr>
<td></td>
<td>UTI/dysuria (23%)</td>
</tr>
<tr>
<td>Current and recent major interventions</td>
<td>Ureteroscopy (37%)</td>
</tr>
<tr>
<td></td>
<td>Percutaneous nephrolithotomy (24%)</td>
</tr>
<tr>
<td></td>
<td>Shock wave lithotripsy (18%)</td>
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<td></td>
<td>Dialysis (18%)</td>
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<tr>
<td>Current medical treatments</td>
<td>Very high fluid intake (91%)</td>
</tr>
<tr>
<td></td>
<td>Prescription medications, including pyridoxine (80%)</td>
</tr>
<tr>
<td></td>
<td>Low-oxalate diet (67%)</td>
</tr>
<tr>
<td></td>
<td>CKD diet (low sodium, potassium, and protein) (55%)</td>
</tr>
<tr>
<td></td>
<td>Counseling (15%)</td>
</tr>
</tbody>
</table>

Therapeutic priorities:

- Prevent kidney stones (61%)
- Prevent CKD/kidney failure (47%)
- Decrease treatment burden (23%)
- Prevent organ transplantation\(^a\)
- Willing to participate in clinical trials and incur study burden and potential risks\(^a\)

Data based upon responses at FDA externally led Patient Focussed Drug Development meeting held October 5, 2020. Percentages based upon live polling at the meeting. Abbreviations: CKD, chronic kidney disease; UTI, urinary tract infection.

\(^a\)No polling data available, but frequently mentioned in the final discussion session.
limitations this imposes on clinical trials. Prerequisites include detailed knowledge of the natural history of the disease as well as input from patients to help gauge their willingness to participate in clinical trials and the level of risk they would be willing to take to embark upon novel therapies. The experience of OHF shepherding these processes over the course of the last 5 years provides a paradigm for other rare diseases. Development of a community of scientists, caregivers, patients, and industry partners with a common purpose is fundamental to success. This diverse working group brought complementary expertise and viewpoints as well as efficient collation of data and literature, which was followed by the development of rigorous scientific documents that incorporated the patient perspective. The partnership with KHI was an additional important feature that drove the work efficiently, including facilitating interactions with the FDA through the process. The effort was a good example of PFDD in a rare disease, including a well-attended and impactful meeting with the FDA that amplified the concerns of this patient community. Importantly, in large part owing to the hard work and collaboration of this group, in late 2020 a small inhibitory RNA against hepatic glycolate oxidase was approved by the FDA and the European Medicines Agency as a treatment of primary hyperoxaluria type based upon a significant reduction in urinary oxalate excretion. Parallel work is ongoing in enteric hyperoxaluria to facilitate cost-effective trials for emerging and novel therapies directed at this disorder. The important documents generated by this KHI-led effort are serving as road maps for other researchers and biotech companies looking at novel therapies for primary and enteric hyperoxaluria. 

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