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Patient Experience Is Driving the Development of New Outcomes for Fluid Overload Treatment

By Bridget M. Kuehn

A decade ago, Christine Gwinn started noticing her clothes suddenly and inexplicably became tight during a fly-fishing trip in Colorado. Over the next 6 weeks, fluid buildup caused her weight to skyrocket from 120 to 200 pounds. Her physicians diagnosed her with focal segmental glomerulosclerosis (FSGS). Initial treatment with diuretics and fluid restriction were not effective, so Gwinn was started on emergent dialysis to alleviate the fluid buildup and protect her kidneys.

"When it's that kind of dramatic change, finding something that works is critical," Gwinn said. Eventually, she started taking prednisone. It worked well but had many side effects.

Now, Gwinn is part of a team effort to spur the development of new treatments for fluid buildup associated with nephrotic disease that better meet patients' needs. Gwinn is a member of the Stakeholder Engagement Committee for Prepare-NS (1), a US Food and Drug Administration (FDA)-funded study recruiting patients with nephrotic disease to share their experiences.

"The goal of the project is to create a set of outcome measures to capture the clinical benefit of new nephrotic syndrome treatments," said Co-Principal Investigator John Devin Peipert, PhD, assistant professor of medical social sciences at Northwestern University's Feinberg School of Medicine (Chicago, IL). "Patients are in the best position to tell you about their experience of that symptom, the severity of the symptom, the frequency, and how it impacts their life."

What's the catch?

Current treatments for fluid overload associated with nephrotic disease focus on either treating the underlying condition causing kidney dysfunction or using diuretics to help the kidneys remove the salt and water causing the buildup, said

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Team-Based Care Is Essential for Diabetic Kidney Disease

By Bridget M. Kuehn

The emergence of a new generation of kidney-protecting therapies for diabetes, including sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide 1 receptor agonists, and finerenone, will require better use of team-based care, according to a flurry of recent recommendations.

In recent months, Kidney Disease: Improving Global Outcomes (KDIGO) updated its diabetic kidney disease guidelines (1), and the American Diabetes Association (ADA) and KDIGO released a consensus report (2) on diabetic kidney disease management. According to the guidelines, making the most of the new practice-changing therapies along with lifestyle modifications and more traditional therapies will require new multidisciplinary, comprehensive models of care. The recommendations echo those of the ASN Diabetic Kidney Disease Collaborative Task Force (3) calling for the transformation of the care of patients with diabetic kidney disease.

"With the breakthrough therapies we now have, nephrology is poised to be completely transformed as a specialty," Katherine Tuttle, MD, chair of the ASN Diabetic Kidney Disease Collaborative Task Force and professor of medicine at the University of Washington in Spokane, said in an interview. "Instead of focusing on end stage and kidney failure, we now have the opportunity to focus on early diagnosis and treatment that [preserve] kidney function for a lifetime."

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Fluid Overload Treatment

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Eloise Salmon, MD, a Prepare-NS co-investigator and clinical assistant professor in the Division of Pediatric Nephrology at the University of Michigan (Ann Arbor). The effectiveness of these approaches varies from patient to patient, she noted. For patients like Gwinn, the questions are often, "What's the catch?" with a given treatment, and "How will it affect day-to-day life?"

"I've gone through a number of different treatments in the past 10 years," Gwinn said. "Some have worked; some haven't, and everything comes with a side effect. The more information you have, the better you can assess your options."

It is also important for children with nephrotic disease and their caregivers to have as much information as possible and have medications that meet their needs. "Children are especially resilient, but often under that tough exterior, they are suffering from edema and are impacted in ways health care professionals don't see or understand," said Kelly Helm, a parent of a patient with nephrotic disease, co-chair of the Stakeholder Engagement Committee for Prepare-NS, and executive director of patient engagement at NephCure Kidney International (King of Prussia, PA). "The effects of edema are often painful and exhausting, which limits kids' physical capabilities and ability to carry out their normal daily lives. Additionally, edema impacts the way they look and for some, impacts their interactions with peers."

The FDA has funded the Prepare-NS study with a pilot grant (2) as part of its Patient-Focused Drug Development efforts. In addition to patient perspectives, the study team has gathered input from various stakeholders, including nephrologists, industry representatives, payors, and regulators. The shared goal is to create patient-reported clinical trial outcome measures that investigators and the FDA can use to evaluate whether a new drug provides meaningful patient benefits.

"There is an unmet need for safe and effective treatments for rare kidney diseases that cause the nephrotic syndrome," said Kirtida Mistry, MBBCh, DCH, MRCPCH, senior physician in the Division of Cardiology and Nephrology at the FDA's Center for Drug Evaluation and Research (CDER), in an e-mailed comment.

The Prepare-NS team will work closely with the FDA staff to create a clinical outcome assessment over the course of about 5 years, according to Robyn Bent, RN, MS, director of Patient-Focused Drug Development at CDER. At the end of the process, they will have a core set of clinical outcome assessments that are publicly available for free or at a low cost, she said.

"Patient-reported outcomes are a relatively new concept," said Patrick Nachman, MD, co-chair of the Stakeholder Engagement Committee and director of the Division of Nephrology and Hypertension at the University of Minnesota in Minneapolis. "The FDA is encouraging all stakeholders, physicians, investigators, patients, patient advocates, [and] pharmaceutical companies to think about clinical trial development outside of the traditional metrics or end points used in clinical trials."

Traditional clinical outcome assessments might focus on changes in patient weight or a clinician assessment of fluid overload, noted Salmon. But those assessments only capture one point in time and may differ from the measures most important to patients, she said. Nachman said that other common traditional end points in nephrology studies are kidney diseases' progression, needing dialysis or a transplant, and patient survival. But he said those end points take a long time to happen.

"As nephrologists, we obsess over the proteinuria levels, creatinine, and glomerular filtration rate," said Barbara Gillespie, MD, vice president and therapeutic head of nephrology at LabCorp Drug Development and adjunct professor in the Division of Nephrology and Hypertension at the University of North Carolina (Chapel Hill). "But patients, when they come to the clinic, they are ready to talk about their leg swelling, not their lab value."

Meaningful measures

To find out what is important to patients with fluid overload, Salmon and her co-investigators are starting with a qualitative study. The team is recruiting patients or caregivers of individuals with FSGS, minimal change disease, membranous nephropathy, or unbiopsied childhood with nephrotic syndrome to participate in the first phase. Prospective participants will complete a screening questionnaire on the https://www.prepare-ns.org/ website. Patients selected to participate will complete a 30- to 60-minute interview by telephone or Zoom with one of the study coordinators. Patients who do not qualify for the study's first phase are still encouraged to register and may be selected to participate in later stages of the study.

"Hopefully, we'll get a global sense of how edema affects the patient and [his or her] daily activities," Salmon said. For example, Peipert noted that swelling could lead to fatigue or limit patients' daily activities. The team will use the information to design and validate patient-centered outcome measures.

Gillespie said that patient-centered outcomes are critical because they can help new therapies win FDA approval. For example, she noted that the FDA approved difelikefalin, a drug used to treat pruritis in dialysis patients, based on a patient-reported outcome—itch-related quality of life measured on a rating scale (3, 4). She noted that there is a misperception that patient-reported outcomes can only be used as a secondary outcome or only in the FDA's accelerated approval pathways. But the difelikefalin approval provides a clear precedent in the field of nephrology that a patient-reported outcome can be a primary end point, Gillespie said.

"In clinical trials, we want to be confident we are asking the questions that matter to patients," Gillespie said. She noted that other efforts are underway in nephrology to develop patient-centered outcomes, including the Standardised Outcomes in Nephrology initiative (5). That initiative is developing standardized outcomes for hemodialysis, transplantation, peritoneal dialysis, children and adolescents with kidney diseases, glomerular disease, and polycystic kidney disease.

Nachman noted that quality-of-life measures have long been used as secondary end points in studies but that the shift to using well-tested and validated patient-reported outcomes as a primary end point is an exciting development. It is also a shift that patients, their caregivers, physicians, researchers, and pharmaceutical companies all welcome, he said.

"You can go to the FDA and say we have a validated tool; we have demonstrated that our new treatment is improving how the patients are functioning and feeling," he said.

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>
> **—Barbara Gillespie**

The Prepare-NS team encourages patients with nephrotic disease to register and has flyers available that nephrologists can post in their practices to help patients learn more. Ultimately, the Prepare-NS team hopes the study will result in new and better treatment options for patients with fluid overload.

"Patient-reported outcomes from both caregivers and the pediatric patients themselves are essential in providing not only optimal treatments but also implementing holistic patient-centered care," Helm said. ■

References

1. Prepare-NS. Welcome to Prepare-NS. https://www.prepare-ns.org/
2. US Food and Drug Administration. CDER pilot grant program: Standard core clinical outcome assessments (COAs) and their related endpoints. January 18, 2022. https://www.fda.gov/drugs/development-approval-process-drugs/cder-pilot-grant-program-standard-core-clinical-outcome-assessments-coas-and-their-related-endpoints
3. Cara Therapeutics. GlobeNewswire. Cara Therapeutics and Vifor Pharma announce U.S. FDA approval of KORSUVA™ (difelikefalin) injection for the treatment of moderate-to-severe pruritus in hemodialysis patients. August 23, 2021. https://www.globenewswire.com/news-release/2021/08/23/2285085/0/en/Cara-Therapeutics-and-Vifor-Pharma-announce-U-S-FDA-approval-of-KORSUVA-difelikefalin-injection-for-the-treatment-of-moderate-to-severe-pruritus-in-hemodialysis-patients.html
4. Fishbane S, et al.; KALM-1 Trial Investigators. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med* 2020; 382:222–232. doi: 10.1056/NEJMoa1912770
5. Standardised Outcomes in Nephrology (SONG). The SONG Initiative. https://songinitiative.org/