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Lupus Nephritis Guideline Updated to Advance Care, Reflect New Therapies

By Bridget M. Kuehn

Fewer than one-quarter of patients with lupus nephritis receiving standard-of-care treatment with drugs like mycophenolate achieved a complete response after 1 year of therapy at leading academic centers, according to recent data from the Accelerating Medicines Partnership (AMP) Lupus Network (1).

"Considering these were patients seen in expert centers and followed very carefully, to have that low level of complete response further underscores the real need we have for new therapies in lupus nephritis," said Jill Buyon, MD, director of the Division of Rheumatology and the Lupus Center in the Department of Medicine at New York University's Grossman School of Medicine. The AMP is analyzing biopsies from patients to understand how molecular differences affect clinical outcomes and to identify potential new treatment targets or biomarkers to guide therapy.

The data highlight the impetus behind a growing push to advance lupus nephritis care through new and more targeted therapeutic approaches. Since the AMP clinical data were collected, the US Food and Drug Administration (FDA) has approved two new drugs for treating lupus nephritis—belimumab and voclosporin—as add-on therapies to standard-of-care treatment (2, 3). The approvals prompted a faster-than-usual update to the Kidney Disease: Improving Global Outcomes (KDIGO) guideline for lupus nephritis to help incorporate the new therapies into care regimens (4). Peter Izmirly, MD, professor of medicine in the Department of Rheumatology at New York University's Grossman School of Medicine, said neither drug is a "game-changer." He explained that while both drugs appear safe, the response rate in their pivotal trials was about 50%, still lower than optimal. "We have got to get better," Izmirly said. "We are inching forward, and belimumab and voclosporin are positive steps in the right direction."

New therapeutic options

With growing numbers of nephrology drugs receiving approval and many more in the pipeline, KDIGO decided to adopt a more rapid approach to updating its recommendations based on emerging evidence. The KDIGO 2021

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ASN and Home Dialysis University Extend Partnership in 2024

By Karen Blum

Home dialysis has been associated with lower cost and equal or better clinical outcomes than facility-based dialysis (1). However, in 2021, only 14.1% of Medicare patients receiving dialysis underwent home dialysis, according to data from the National Institute of Diabetes and Digestive and Kidney Diseases (2). Additionally, despite a higher incidence and prevalence of kidney diseases among Black and Hispanic individuals, they are less likely to be treated with home dialysis when compared with non-Hispanic White individuals (3).

In July 2021, ASN formed a Home Dialysis Steering Committee to identify and prioritize gaps in training, education, and advocacy in home dialysis. Recommendations from the Steering Committee led to a collaboration between ASN and the Home Dialysis University (HDU) to boost nephrology trainees' knowledge and familiarity with home dialysis therapies. The agreement provided 30 nephrology fellows scholarships to attend a 2-day HDU training course plus participate in a virtual education series over the past year. It has proven so successful that ASN is extending the program, offering scholarships to 45 fellows in 2024.

"It's going great—the fellows are really engaged," said Jeffrey Perl, MD, FRCP, a co-chair of ASN's Home Dialysis Task Force and a staff nephrologist at St. Michael's Hospital in Toronto. "What we really want is for fellows who complete the program to feel that they're part of a home dialysis community and can continue to rely on the faculty and

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Inside

What percent of your patients on phosphate binders have serum phosphorus levels above target?

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INDICATION

XPHOZAH (tenapanor) 30 mg BID is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XPHOZAH is contraindicated in:

- Pediatric patients under 6 years of age
- Patients with known or suspected mechanical gastrointestinal obstruction

WARNINGS AND PRECAUTIONS

Diarrhea

Patients may experience severe diarrhea. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

MOST COMMON ADVERSE REACTIONS

Diarrhea, which occurred in 43-53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in XPHOZAH-treated patients were reported to be mild-to-moderate in severity and resolved over time, or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials.

Please see Brief Summary of full Prescribing Information on the following page.

Reference: XPHOZAH® (tenapanor) full Prescribing Information. Waltham, MA: Ardelyx, Inc.; 2023.

ardelyx®

XPHOZAH (tenapanor) tablets, for oral use
Brief Summary of Prescribing Information

1 INDICATIONS AND USAGE

XPHOZAH is indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

4 CONTRAINDICATIONS

XPHOZAH is contraindicated in patients under 6 years of age because of the risk of diarrhea and serious dehydration *[see Warnings and Precautions (5.1), Use in Specific Populations (8.5)]*.

XPHOZAH is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea

Diarrhea was the most common adverse reaction in XPHOZAH-treated patients with CKD on dialysis *[see Dosage and Administration (2) in the full Prescribing Information, Contraindications (4) and Adverse Reactions (6.1)]*. In clinical trials, diarrhea was reported in up to 53% of patients, reported as severe in 5%, and associated with dehydration and hyponatremia in less than 1% of patients. Treatment with XPHOZAH should be discontinued in patients who develop severe diarrhea.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described below reflect data from 754 adults with CKD on dialysis taking XPHOZAH in clinical trials as monotherapy and in combination with phosphate binders. Among the 754 patients, 258 patients were exposed to tenapanor for at least 26 weeks and 75 were exposed to tenapanor for at least one year. *[see Clinical Studies (14) in the full Prescribing Information]*.

Most Common Adverse Reaction

Diarrhea, which occurred in 43-53% of patients, was the only adverse reaction reported in at least 5% of XPHOZAH-treated patients with CKD on dialysis across trials. The majority of diarrhea events in the XPHOZAH-treated patients were reported to be mild-to-moderate in severity and resolved over time, or with dose reduction. Diarrhea was typically reported soon after initiation but could occur at any time during treatment with XPHOZAH. Severe diarrhea was reported in 5% of XPHOZAH-treated patients in these trials *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 OATP2B1 Substrates

Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1 *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with XPHOZAH. Monitor for signs related to loss of efficacy and adjust the dose of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was coadministered with XPHOZAH (30 mg twice daily for five days), the peak exposure (Cmax) of enalapril and its active metabolite, enalaprilat, decreased by approximately 70% and total systemic exposures (AUC) decreased by 50 to 65% compared to when enalapril was administered alone *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. However, the decrease in enalaprilat's exposure with XPHOZAH may be offset by the inherently higher exposures observed in patients with CKD on dialysis due to its reduced renal clearance. Therefore, a lower starting dose of enalapril, which is otherwise recommended in patients with CKD on dialysis is not required when enalapril is coadministered with XPHOZAH.

7.2 Sodium Polystyrene Sulfonate

Separate administration XPHOZAH and sodium polystyrene sulfonate (SPS) by at least 3 hours. SPS binds to many commonly prescribed oral medicines.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Tenapanor is essentially non-absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Therefore, maternal use is not expected to result in fetal exposure to the drug.

The available data on XPHOZAH exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. In reproduction studies with tenapanor in pregnant rats and rabbits, no adverse fetal effects were observed in rats at 0.2 times the maximum recommended human dose and in rabbits at doses up to 15 times the maximum recommended human dose (based on body surface area) *[see Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

The estimated background risk of major birth defects and miscarriage for women with CKD on dialysis with hyperphosphatemia is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal Data

In an embryofetal development study in rats, tenapanor was administered orally to pregnant rats during the period of organogenesis at dose levels of 1, 10 and 30 mg/kg/day. Tenapanor doses of 10 and 30 mg/kg/day were not tolerated by the pregnant rats and was associated with mortality and moribundity with body weight loss. The 10 and 30 mg/kg dose group animals were sacrificed early, and the fetuses were not examined for intrauterine parameters and fetal morphology. No adverse fetal effects were observed in rats at 1 mg/kg/day (approximately 0.2 times the maximum recommended human dose) and in rabbits at doses up to 45 mg/kg/day (approximately 15 times the maximum recommended human dose, based on body surface area). In a pre- and post-natal developmental study in mice, tenapanor at doses up to 200 mg/kg/day (approximately 16.5 times the maximum recommended human dose, based on body surface area) had no effect on pre- and post-natal development.

8.2 Lactation

Risk Summary

There are no data available on the presence of tenapanor in either human or animal milk, its effects on milk production or its effects on the breastfed infant. Tenapanor is essentially non-absorbed systemically, with plasma concentrations below the limit of quantification (less than 0.5 ng/mL) following oral administration *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. The minimal systemic absorption of tenapanor will not result in a clinically relevant exposure to breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XPHOZAH and any potential adverse effects on the breastfed infant from XPHOZAH or from the underlying maternal condition.

8.4 Pediatric Use

Risk Summary

XPHOZAH is contraindicated in patients less than 6 years of age. In nonclinical studies, deaths occurred in young juvenile rats (less than 1-week old rats; approximate human age-equivalent of less than 2 years of age) and in older juvenile rats (approximate human age-equivalent of 2 years of age) following oral administration of tenapanor, as described below in Juvenile Animal Toxicity Data.

The safety and effectiveness of XPHOZAH in pediatric patients have not been established.

Juvenile Animal Toxicity Data

In a 21-day oral dose range finding toxicity study in juvenile rats, tenapanor was administered to neonatal rats (post-natal day (PND) 5) at doses of 5 and 10 mg/kg/day. Tenapanor was not tolerated in male and female pups and the study was terminated on PND 16 due to mortalities and decreased body weight (24% to 29% reduction in females at the respective dose groups and 33% reduction in males in the 10 mg/kg/day group, compared to control).

In a second dose range finding study, tenapanor doses of 0.1, 0.5, 2.5, or 5 mg/kg/day were administered to neonatal rats from PND 5 through PND 24. Treatment-related mortalities were observed at 0.5, 2.5, and 5 mg/kg/day doses. These premature deaths were observed as early as PND 8, with majority of deaths occurring between PND 15 and 25. In the 5 mg/kg/day group, mean body weights were 47% lower for males on PND 23 and 35% lower for females on PND 22 when compared to the controls. Slightly lower mean tibial lengths (5% to 11%) were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups on PND 25 and correlated with the decrements in body weight noted in these groups. Lower spleen, thymus, and/or ovarian weights were noted at the 0.5, 2.5, and 5 mg/kg/day doses. Tenapanor-related gastrointestinal distension and microscopic bone findings of increased osteoclasts, eroded bone, and/or decreased bone in sternum and/or femorotibial joint were noted in males and females in the 0.5, 2.5, and 5 mg/kg/day dose groups.

In juvenile rats administered tenapanor at 0.03, 0.1, or 0.3 mg/kg/day on PND 5 through PND 61, treatment-related mortalities were observed at 0.3 mg/kg/day. Lower mean body weight gains were noted in the 0.3 mg/kg/day group males and females compared to the control group primarily during PND 12–24 but continuing sporadically during the remainder of the dosing period; corresponding lower mean food consumption was noted in this group during PND 21–33. As a result, mean body weights were up to 15.8% and 16.8% lower in males and females, respectively, compared to the control group; the greatest difference was on PND 24 for males and PND 21 for females. Mean body weight in the 0.3 mg/kg/day group males was only 3.9% lower than the control group on PND 61. There were no tenapanor-related effects on mean body weights, body weight gains, or food consumption in the 0.03 and 0.1 mg/kg/day group males and females. A dosage level of 0.1 mg/kg/day was considered to be the no-observed-adverse-effect level (NOAEL) for juvenile toxicity of tenapanor *[see Contraindications (4), Warnings and Precautions (5.1)]*.

In a 21-day oral dose range finding study in older (weaned) juvenile rats administered tenapanor at 0.1, 1, or 5 mg/kg/day on PND 21 through PND 41 (approximate human age-equivalent of 2 to 12 years of age), treatment-related mortalities or moribundities were observed during the first two days of the study in the 1 mg/kg/day males and the 5 mg/kg/day males and females. Watery feces, decreased food consumption, and lower mean body weight were also observed in the 1 and 5 mg/kg/day groups.

In weaned juvenile rats administered tenapanor at 0.1, 0.3, and 0.7 (males) or 1 (females) mg/kg/day on PND 21 through PND 80, no mortalities were observed. Significant decreases in mean body weights were observed in the 0.3 and 0.7 mg/kg/day males throughout the dosing period (up to 20.3% lower than control) and in the 1 mg/kg/day females between PND 23 to 35 (up to 16.7% lower than control), with food consumption notably decreased on PND 21 to 29. There were also reductions in tibia length between PND 76 and 80 in the 0.3 and 0.7 mg/kg/day males, and between PND 36 and 64 in the 0.7 mg/kg/day males, which were not observed during the 14-day recovery period. The NOAEL was considered to be 0.1 mg/kg/day for juvenile toxicity of tenapanor.

8.5 Geriatric Use

Of 1010 adult patients with CKD on dialysis randomized and treated in two randomized, double-blind, placebo-controlled randomized withdrawal clinical trials for XPHOZAH (TEN-02-201 and TEN-02-301) as well as a third randomized, double-blind, placebo-controlled trial (TEN-02-202) for XPHOZAH in combination with phosphate binders, 282 (28%) were 65 years of age and older. Clinical studies of XPHOZAH did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently than younger patients.

10 OVERDOSAGE

No data are available regarding overdosage of XPHOZAH in patients. Based on nonclinical data, overdose of XPHOZAH may result in gastrointestinal adverse effects such as diarrhea, as a result of exaggerated pharmacology with a risk for dehydration if diarrhea is severe or prolonged *[see Warnings and Precautions (5.1)]*.

17 PATIENT COUNSELING INFORMATION

Advise Patients:

Diarrhea

Instruct patients to contact their healthcare provider if they experience severe diarrhea *[see Warnings and Precautions (5.1)]*.

- Instruct patients not to use stool softeners or laxatives with XPHOZAH.

Administration and Handling Instructions

Instruct Patients:

- To take XPHOZAH just prior to the first and last meals of the day *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
- Patients should be counseled not to take XPHOZAH right before a hemodialysis session, and to take XPHOZAH right before the next meal, as some patients may experience diarrhea after taking XPHOZAH.
- If a dose is missed, take the dose just before the next meal. Do not take 2 doses at the same time *[see Dosage and Administration (2.2) in the full Prescribing Information]*.
- To keep XPHOZAH in a dry place. Protect from moisture. Keep in the original bottle. Do not remove desiccant from the bottle. Keep bottles tightly closed *[see How Supplied/Storage and Handling (16) in the full Prescribing Information]*.

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Lupus Nephritis Guideline Updated to Advance Care

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Clinical Practice Guideline for the Management of Glomerular Diseases, which included a chapter on lupus, was completed shortly before belimumab and voclosporin became the first two FDA-approved therapies for adults with lupus nephritis (5). In response, KDIGO released a focused update solely on lupus nephritis.

"Lupus nephritis was the obvious first choice for this living document [approach]," said Brad Rovin, MD, FASN, co-chair of KDIGO's lupus nephritis guideline work group and director of the Division of Nephrology at The Ohio State University Wexner Medical Center in Columbus.

National Kidney Foundation President-Elect Kirk Campbell, MD, FASN, called the updated lupus nephritis guideline "a welcome development." Campbell, a professor of medicine and pharmacological sciences at the Icahn School of Medicine at Mount Sinai, New York, explained, "It is important to put approved therapies in the proper context for practicing clinicians and to better inform patients about those treatment options that might be available."

With data from the pivotal clinical trials, Rovin and his colleagues crafted new recommendations on which patients might be appropriate candidates for the novel therapies. Rovin said that post hoc analyses that provided additional nuance are discussed in the guideline, although the evidence was not strong enough for specific recommendations. For example, he noted a nonsignificant trend toward less decline in estimated glomerular filtration rate among patients who received belimumab than among those who did not in the trial. This might suggest a potential benefit for patients already experiencing kidney impairment. Additionally, voclosporin was beneficial among patients with all levels of proteinuria, whereas belimumab had better outcomes among patients with proteinuria below 3 g/day, he noted. "We are getting closer to that idea of personalized or precision medicine," Rovin said.

Campbell agreed about the importance of matching therapies with patient characteristics. "A patient who is at higher risk of kidney disease progression or lupus nephritis flares may benefit from more aggressive treatment regimens from the outset," he explained. "That will ensure that they are not going to have repeated cycles of additional medications to treat flares and associated hospitalizations down the line."

Rovin said that it is also essential to consider the drugs' high price tags. Benlysta, the name brand of belimumab, has a list price of $1,210.63 per weekly subcutaneous injection, according to the patient assistance program of GlaxoSmithKline (GSK), the drug's manufacturer (6). Lupkynis, the name brand of voclosporin, costs $15,482 for 180 oral capsules, according to Drugs.com (7).

A cost-effectiveness analysis by the Institute for Clinical and Economic Review found that both drugs fall within the thresholds for cost-effective interventions (8). Rovin noted that the costs of poorly controlled lupus nephritis or progression to kidney failure are also substantial for both the health system and patients. However, in some cases, he noted, insurance companies will not approve the use of the drug unless a patient has failed another therapy. Alternatively, insurance companies may approve therapy use with a very high co-pay.

"We see patients from across the socioeconomic spectrum with lupus and lupus-related kidney disease, and many cannot afford the co-payments," he said. For patients without insurance, the costs of paying the full price are even farther out of reach, he noted. "Cost is a big consideration for the patient."

Campbell noted that there is also a public health need to ensure access to patients who would benefit. "We also need to ensure that the newly approved therapies are available and accessible to patients who need them the most," he said.

Rovin stated that another important consideration is whether patients are struggling with adherence to their current treatment regimens. "Patients who are having problems adhering to their medications may not enjoy the fact that the full dose of voclosporin used in the clinical trial is six additional pills a day," he said. He noted that some patients may already be taking 20 to 30 pills a day. "Belimumab can be given intravenously once a month or subcutaneously, so that might be necessary for patients having challenges with adherence." He noted that belimumab has long been FDA approved for systemic lupus erythematosus and may also be a better choice as an add-on for patients with many systemic lupus symptoms.

Buyon said the guideline was not overly prescriptive, and she would have liked to see more specific guidance on when to select the new drugs. Overall, she said, the guideline reinforced what many clinicians caring for patients with lupus nephritis already do. "Even with these [new] drugs, we still have a long way to go," she said.

Taking the long view

The new recommendations also highlight the importance of kidney preservation and balancing patients' quality of life with therapeutic considerations.

The guideline recommends pulsed doses of intravenous methylprednisolone at the start of therapy to enable lower dosing later and a more rapid taper even on a standard treatment regimen. Rovin noted that adding belimumab may enable clinicians to start with a modest dose of glucocorticoids, and voclosporin may enable patients to start with a very low dose. He asserted that lower glucocorticoid doses are vital to mitigate side effects that can lower patients' adherence, particularly at the start of therapy. "If you could start out with a lower steroid dose, and patients do not have as many side effects, and you are bolstering the immunotherapy because you have two different drugs on board," he said, "[patients] are going to be more likely to take the regimen and not be turned off immediately." Buyon agreed with the more conservative approach to using glucocorticoids, which she said reflected, in part, confidence in the potential of the new drugs.

Campbell noted that about half of patients with lupus will eventually develop kidney diseases, and approximately 1 in 10 patients advances to kidney failure. He said that makes controlling the symptoms of lupus to protect the kidneys and slowing the progression of kidney diseases when they occur essential. "Almost everyone after the first episode of lupus nephritis has chronic kidney disease," Rovin said. "We have to think about how we can preserve as much kidney function as possible so they can keep their kidneys their whole life expectancy."

Rovin noted that renin-angiotensin system inhibition is beneficial for preserving kidney function. He explained that there is evidence that belimumab may provide some kidney protection, and calcineurin inhibitors, like cyclosporine, may help protect podocyte integrity, vital to safeguarding nephrons. Campbell noted that sodium-glucose cotransporter-2 inhibitors and other therapies, like endothelin receptor antagonists, may also eventually help further customize patient care. "One could foresee in the future more options to optimize what we traditionally consider the supportive foundational regimens versus targeted disease-modifying

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immunosuppressive agents that we may not want to keep patients on indefinitely or may want to be more cautious about administering to the right patients," he reflected.

Izmirly recommended that rheumatologists and nephrologists rethink their reliance on proteinuria to diagnose and monitor lupus nephritis. Earlier work from AMP shows aggressive lupus nephritis in biopsies done with protein levels between 0.5 g/g and 1 g/g (9), and AMP is working on identifying potential urinary biomarkers to diagnose and track lupus nephritis (10–12). Buyon said that she was concerned that the KDIGO guideline which considers the threshold for kidney involvement and biopsy as 0.5 g/g for the urine protein-to-creatinine ratio (UPCR) is too conservative. She noted that in the continued new AMP, which is studying early nephritis, patients with a UPCR between 0.25 g/g and 0.49 g/g often have actionable lupus nephritis. "We see people rapidly progress from 0.4 to higher levels of proteinuria," she said. "If that is a window of opportunity, [this guideline] may be missing it."

The guideline also highlighted the robust pipeline of new lupus nephritis drugs, which may lead to additional updates to the guideline. Rovin noted that the drugs may also enable more personalized approaches to patient care. Buyon agreed that future therapies may focus on more personalized approaches. She noted that emerging transcriptome data from AMP reveal that some patients may have more B cell activity. In contrast, others may have more T cell activation, which may help clinicians choose the best drugs for patients. She and Izmirly hope that the AMP study will help identify new drug targets, biomarkers, and other ways to enhance care.

Campbell also emphasized the importance of more research to help clinicians understand lupus nephritis' genetic and molecular basis. He indicated a need for biomarkers that can predict patients' response to therapy, provide even more targeted therapies, and allow clinicians to monitor their patients' treatment responses. "We need to develop and validate biomarkers that we can use to follow the tissue response to treatment in real-time to help manage immunosuppression and identify an impending lupus nephritis flare that can help us decide if we need preemptive immunosuppression," he said.

In the meantime, Rovin said that the approvals help create a pathway for future therapies. "We know we can get approval," Rovin said. "That is the most exciting part. These two drugs have kicked off a flurry of investment from smart scientists to develop drugs for lupus nephritis."

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ASN and Home Dialysis University Extend Partnership in 2024

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moderators for ongoing support around any home dialysis issues that they encounter in the future."

The program highlights ASN's commitment to improving education of home dialysis so that all patients in need of dialysis can have home dialysis as a possible treatment option, Perl explained. It will continue to evolve, he said, and seeks applicants from across the United States.

Fatima Ayub, MD, who will soon start as a faculty member with the University of Arkansas for Medical Sciences and the Central Arkansas Veterans Healthcare System in Little Rock, said that attending the HDU had been on her radar since a colleague recommended it, but receiving a scholarship last year was "the cherry on top."

As a busy mother of 2-year-old twins, Ayub said she does not have a lot of time for reading and studying at home. Preparing for the virtual sessions by reading about interesting cases and participating in them has helped reinforce information about home dialysis that she has taken with her into the clinic setting. "It's fabulous—I don't have enough words to describe it," Ayub said of the program, noting that it has helped clear up a lot of concepts for her regarding home dialysis and enabled her to feel more confident while managing patients. She is now routinely seeing patients in home therapy clinics and implementing the knowledge that she received from HDU faculty.

"Faculty members are extremely knowledgeable and easily accessible," she added. "They would answer and reply to even very basic questions and explain things in a way that would inspire the fellows and make difficult topics really interesting."

Ayub highly recommended that other fellows apply for the program. "It's a great opportunity—there are some topics that are covered in this fellowship program that you will never get the chance to read about again," she said. "Nephrology is a vast field, and in 2 years [of fellowship], there's only so much that you can do, especially when you're busy with inpatient and outpatient rotations and in dialysis units."

The scholarship covers attendance at an HDU course (September 8–10, 2024, in Chicago, IL), and participation in a virtual case-based education series to be held between August 2024 and June 2025. Virtual series sessions have covered a wide range of topics in home hemodialysis and home peritoneal dialysis, including dialysis access, complications' management, writing prescriptions, as well as day-to-day troubleshooting, described Christopher Chan, MD, FRCPC, a clinician investigator with the Toronto General Hospital Research Institute, who is a moderator of the virtual series.

"The intent of the virtual curriculum is to create a wealth of knowledge for people practicing home dialysis, much like a mini fellowship," Chan said. "There has been a really consistent and favorable uptake by all the fellows. People are quite open to asking questions and verifying and clarifying the content," he added. "There are lots of resources available, and I hope that this also will be an important resource for physicians who are dedicating their career to home dialysis."

"Funding for the scholarship opportunity stemmed from a cooperative agreement between ASN and the Centers for Disease Control and Prevention (CDC) to enable nephrology fellows to receive training in home hemodialysis and home peritoneal dialysis from respected leaders," Perl said. "As such, an important focus of the program is understanding best practices for prevention and management of infections for patients undergoing peritoneal dialysis. Infection is the leading cause behind why patients undergoing peritoneal dialysis have to transfer to hemodialysis," he said.

Eligible applicants for the scholarship must be second- or third-year nephrology fellows in an Accreditation Council for Graduate Medical Education-accredited training program, never have attended an HDU course, and have support from their training program director to attend the course and participate in the longitudinal virtual education program. They can have any level of prior experience with home dialysis.

Fellows selected for the program receive meeting costs of up to $1500 to cover HDU registration, two hotel nights, meals during the meeting, and reimbursed travel costs of up to $300. For more information, or to apply, visit the Home Dialysis Scholarship Program webpage: https://epc.asn-online.org/projects/hdp/home-dialysis-scholarship-program/#gsc.tab=0. The application is open through May 31, 2024, and notification of decisions will be sent in June. Fellows who are not awarded a scholarship for the virtual curriculum are still welcome to attend an in-person HDU training course, Perl said.

Visit the HDU website for more information on the program: https://3eaglesinc.com/hduforfellows/.

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Newer Options for SGLT2 Inhibitors in the United States

By Katherine Kwon

Millions of patients living with cardiovascular, kidney, and metabolic syndrome would benefit from treatment with sodium-glucose cotransporter-2 inhibitors (SGLT2i), yet their uptake in eligible populations remains poor. One study from 2022 showed that only 8% of patients with kidney diseases and diabetes received an SGLT2i (1); the combination of chronic kidney disease (CKD) and diabetes is a class 1A indication for SGLT2i therapy in the 2023 KDIGO guidelines draft (2). Drug cost is one barrier to patient access to this lifesaving class of medications. Three new entries in the SGLT2i market offer additional options for patients and their nephrologists.

The US Food and Drug Administration approved sotagliflozin in May 2023. Sotagliflozin is an inhibitor of SGLT1 and -2 combined. While SGLT2 is present in the nephron, SGLT1 receptors are in the gut. Sotagliflozin was approved for the treatment of patients with heart failure, CKD, and/or diabetes with the indication of preventing and reducing heart failure hospitalizations and cardiovascular death. The approval was based on data from the SOLOIST-WHF (NCT03521934) and SCORED (NCT03315143) trials, and it covers heart failure with both reduced and preserved ejection fractions (3). Sotagliflozin will be sold under the brand name Inpefa and is expected to be available mid-2024.

The SGLT2i bexagliflozin was approved in January 2023 as adjunctive therapy to lower blood glucose in patients with type 2 diabetes. Patients with an estimated glomerular filtration rate less than 30 are excluded on the label (4). Bexagliflozin (brand name Brenzavvy) was not expected to have much success as a late entrant into the field, especially since established SGLT2i, including dapagliflozin (Farxiga), canagliflozin (Invokana), and empagliflozin (Jardiance), have additional cardiovascular and kidney-labeled indications. However, in a novel marketing approach, bexagliflozin is available exclusively through Cost Plus Drugs at a cash price of approximately $50 per month (5). There are no required patient assistance programs or other qualifying steps to access the medication (Table 1). Prescribing physicians should exercise their best clinical judgment to determine if the evidence for a class effect of the SGLT2i is enough to warrant off-label use of bexagliflozin to provide benefit among patients with cardiovascular and kidney diseases.

AstraZeneca's Farxiga (dapagliflozin) does not go off patent until 2025, and in 2021, AstraZeneca successfully defended its patent against a challenge from a manufacturer of generic medications (6). However, generic dapagliflozin is now available in the United States. In a marketing strategy familiar to Costco shoppers, who purchase brand name products sold under the Kirkland label at a significant discount, AstraZeneca has licensed Prasco to sell dapagliflozin as an authorized generic. The medication is manufactured in the same facility as the branded product and is identical other than the packaging (7). There is the potential for savings to be passed on to the consumer, although the savings may also be captured by pharmacy benefit managers and the pharmacies.

These three new options in this important drug class may allow more patients to benefit. With such low prescribing rates for eligible patients, however, it seems likely that the larger barrier is doctors' inertia in updating their practice patterns. More education is needed to encourage the use of SGLT2i in accordance with the new standard of care. ■

Katherine Kwon, MD, FASN, is a regional medical director for Panoramic Health, a value-based care company, as well as a private practice nephrologist at Lake Michigan Nephrology, St. Joseph, MI.

Dr. Kwon reports being a speaker for and participating in research with AstraZeneca, the makers of Farxiga. Opinions expressed in this article are solely her own.

Acknowledgment: The author acknowledges the assistance of Priscilla Roberts, prior authorization specialist at Lake Michigan Nephrology, in creating the table.

These three new options in this important drug class may allow more patients to benefit.

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Table 1. Manufacturer savings available for various SGLT2 inhibitors

Drug name (brand)	Manufacturer	Manufacturer savings programs
Dapagliflozin (Farxiga)	AstraZeneca	Savings card is available for those with commercial insurance. Authorized generic is available. Patient assistance program is available; qualification is based on household income. Patients with Medicare can participate.
Empagliflozin (Jardiance)	Boehringer Ingelheim	Savings card is available for those with commercial insurance. Patient assistance program is available; qualification is based on household income. Patients with Medicare can participate.
Canagliflozin (Invokana)	Janssen	Savings card is available for those with commercial insurance. Patient assistance program is available; qualification is based on household income. Patients with Medicare can participate.
Bexagliflozin (Brenzavvy)	TheracosBio	Cash price for everyone is $52.85 for a 30-day supply; available only through Cost Plus Drugs.
Ertugliflozin (Steglatro)	Merck	Drug is not included in manufacturer's patient assistance program.
Sotagliflozin (Inpefa)	Lexicon	Drug is not yet on market.

ASN Executive Vice President's Update

How ASN Engages People Living with Kidney Diseases

By Tod Ibrahim

During the past decade, ASN has engaged people living with kidney diseases in the United States. By involving patients directly—as well as by partnering with patient organizations like the American Association of Kidney Patients (AAKP), the American Kidney Fund (AKF), and the National Kidney Foundation (NKF)—ASN has amplified the patient's voice in helping to realize the society's vision, mission, and goals (1).

ASN is a medical specialty society incorporated as a not-for-profit (or more precisely, tax-exempt) organization to advance kidney health through high-quality patient care, research, education, and administration. Whereas most of ASN's 21,655 members are nephrologists and PhD scientists in the United States, an increasing number of members live abroad (in 140 countries) or represent other members of the kidney care team, such as nurses, pharmacists, and advanced practice practitioners (APPs).

At their inception in the 18th century, medical societies did not include patients as members. This exclusion reflects the evolution of medicine, particularly in the United States. As Paul Starr explains in *The Social Transformation of American Medicine*, "Eventually, the boundaries would be drawn so that education and licensure coincided: Only graduates could be licensed and only the licensed could practice" (2). This approach meant that "all licensed physicians, therefore, would have strong inducements to join their local medical society."

From the 1700s through ASN's establishment in 1966 (and later for a few more specialties like emergency and hospital medicine in 1968 and 1997, respectively), the focus of US medical societies evolved from distinguishing between those who "are duly educated, and properly qualified for the duties of their profession, and those who may ignorantly and wickedly administer medicine" to defining specific specialties in medicine (2). After the American Gastroenterological Association was founded in 1897, societies were established in other internal medicine specialties, such as pulmonary diseases (1905), endocrinology (1916), rheumatology (1934), cardiology (1949), and hematology (1958).

To define their fields, specialty societies like ASN:

- hold annual meetings to showcase cutting-edge science and clinical excellence;
- publish peer-reviewed journals to define the field and codify advances;
- help regulators (like the Accreditation Council for Graduate Medical Education and the American Board of Medical Specialties) define graduate medical education, certification, and recertification;
- offer accredited continuing medical education;
- determine standards for high-quality care—often through clinical practice guidelines—which ASN will start producing later this year as kidney health guidance (3);
- advocate on behalf of their members in the legislative and regulatory arenas; and
- create networks of like-minded professionals.

Around the same time as physicians were joining US medical specialty societies to define their respective fields, voluntary health organizations were forming. During the 20th century, patients, their families and caregivers, and other advocates were establishing patient-centered organizations, such as the American Lung Association (1904), the American Cancer Society (1913), the American Heart Association (AHA; 1924), the American Diabetes Association (ADA; 1939), the Arthritis Foundation (1948), and the NKF (1964). Today, voluntary health organizations are called patient organizations, are also not for profit or are tax exempt, and "engage in an array of direct-service programs, which can include membership, support, advocacy, education, and research" (4).

Complementary to medical specialty societies, patient organizations:

- educate patients, their families and caregivers, and other advocates about the disease;
- connect patients with physicians, scientists, nurses, physician assistants, pharmacists, and APPs, as well as social workers, dieticians, and other allied health professionals;
- raise awareness about the disease among the public, the media, politicians, policymakers, patients, health professionals, researchers, and others;
- advocate for more government and private funding for disease-specific research, as well as communicate with government regulators, such as the US Food and Drug Administration;
- fund scientists, researchers, and other investigators to conduct disease-specific research, as well as invest in companies trying to bring new therapies to market;
- help patients access clinical care or participate in research studies; and
- create networks of patients, families, and caregivers to provide emotional, informational, and financial support.

The differing histories and contrasting (if complementary) purposes are also reflected in how medical specialty societies and patient organizations generate revenue. Traditionally, specialty societies rely on member dues, registration fees for meetings and educational activities, and publishing income, as well as corporate support through promotion at annual meetings and advertising in journals. Patient organizations depend on contributions from the public (including patients, their families and caregivers, and physicians and health professionals); funds raised at local events, such as community walks, which also raise awareness; financial support to establish coalitions mostly directed at politicians and policymakers; and sponsorship from commercial entities, foundations, and government.

The governance of medical specialty societies and patient organizations further highlights their differing purposes. For example, the ASN Council, the society's governing body, includes nine members who are nephrology clinicians or scientists elected by their colleagues, whereas the governing bodies for patient organizations are usually appointed. With 28 members, the NKF Board of Directors "consists of nephrologists, transplant surgeons and other kidney healthcare team members, civic leaders with diverse business expertise, volunteers, and people affected by kidney disease" (5).

Despite these differences in history, purpose, financing, and governance, medical specialty societies and patient organizations have started to become more alike during the past 2 decades. Much of this similarity results from efforts—particularly by specialty societies—to become more patient centered or directed. Additionally, external entities, such as regulators, have engaged patients as never before. For example, the American Board of Internal Medicine includes at least one person living with kidney diseases on its nephrology specialty board (currently, AAKP Chair of Policy and Global Affairs Paul T. Conway) and invites the NKF to join ASN and the Renal Physicians Association to participate in nephrology board meetings, comment on proposals related to certification and recertification for nephrologists, and define the "boundaries" of nephrology as a specialty.

Every tax-exempt organization is also trying to survive unprecedented pressures in 2024. Navigating technological innovations, the COVID-19 pandemic, tumultuous economic times, the acceleration of private equity into health care (which began in earnest following passage of the Affordable Care Act), a proliferation of not-for-profit and for-profit competitors, direct-to-consumer advertising, changing demographics and preferences, workforce shortages, and other challenges make medical specialty societies and patient organizations increasingly more difficult to differentiate. By working more closely together, however, specialty societies and patient organizations could strengthen the medical profession and clarify the roles that each can uniquely play.

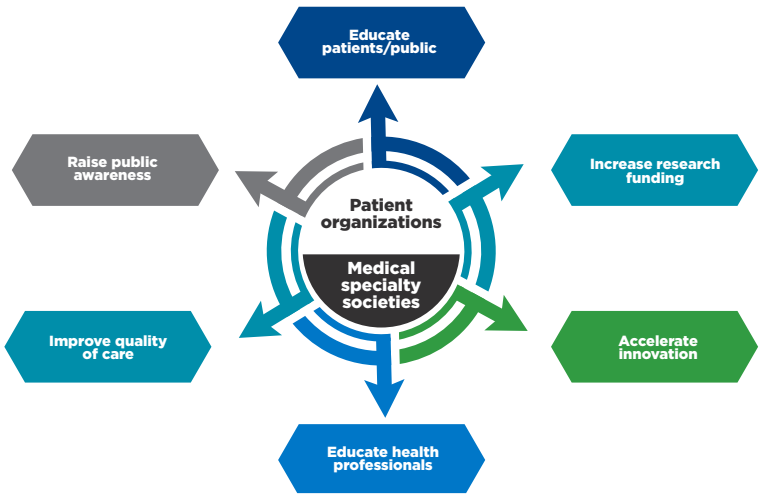
Recognizing the need for greater patient engagement and an increased focus on patient directedness, the ASN Council has developed a decision-making mantra that starts with the question: "What is in the best interests of people living with kidney diseases and their families?" (Table 1). This first question is especially important in guiding the society's efforts to influence legislative and regulatory policy. If patient organizations like the AAKP, the AKF, and the NKF succeed in raising awareness and increasing federal funding for medical research, then medical specialty societies like ASN are well positioned to advocate for innovative research, a strong educational continuum, and—most important—high-quality care.

Table 1. ASN's decision-making mantra

1	What is in the best interests of people living with kidney diseases and their families?
2	What is best for strengthening the relationship between the patients and their health care professional(s)?
3	What is best for the specialty of kidney medicine?
4	What is best for the kidney community?
5	What is best for ASN and the ASN Alliance for Kidney Health?

Greater alignment between medical specialty societies and patient organizations strengthens this "efficacious cycle" from awareness to research funding to innovation to education to care (Figure 1). For example, the cancer community has benefited from Mary Lasker's efforts to raise awareness in the 1950s and 1960s, former US President Richard Nixon's "war on cancer" in the 1970s (which was supposed to cure cancer in 5 years in time for the US Bicentennial), myriad innovations in the field, the popularity of oncology as a career choice, the advancements of current care options, and the Biden Administration's Cancer Moonshot to prevent "more than 4 million cancer deaths by 2047" (6, 7). This pattern repeats itself in cardiovascular diseases, diabetes, HIV/AIDS, and other diseases/specialties.

Figure 1. The efficacious cycle of medical specialty societies and patient organizations



In addition to aligning more closely with patient organizations and helping the kidney community benefit from the efficacious cycle, ASN benefits in at least seven ways from engaging people living with kidney diseases and becoming more patient directed.

1. **Enriches ASN's public-private partnerships.** Currently chaired by Patrick O. Gee, Sr., PhD, the Kidney Health Initiative (KHI) Patient and Family Partnership Council guarantees that KHI workgroups include patients or care partners, the KHI Board of Directors has patient representatives, and the KHI Annual Meeting spotlights real-life experiences of people living with kidney diseases. Included on the Kidney Innovation Accelerator (KidneyX) Steering Committee, patients review all submissions for KidneyX prize competitions. To date, KidneyX has awarded 25 prizes to people with kidney diseases who developed "ideas and fixes" through "their own everyday experiences and ingenuity" (8).

2. **Ensures ASN excellence in patient care.** Through 13 projects (10 current and 3 starting this year), ASN aims to improve clinical nephrology by ensuring "all people with kidney diseases receive the best evidence-based care possible" (9). To accomplish this goal—and "champion patient experiences, preferences, and values by actively engaging people with kidney diseases"—ASN includes patients in its activities to promote excellence in patient care. Patients serve on an advisory board that oversees all projects, are members of the steering committees for the initiatives, have prominent roles as speakers during webinars and other educational events, and help identify opportunities for improving clinical nephrology.

3. **Improves the quality of ASN Kidney Week and publications.** People living with kidney diseases serve as editors and authors for ASN's peer-reviewed journals: *JASN*, *CJASN*, and *Kidney360* (as well as contributors to *Kidney News*). They also participate in the planning process and as faculty for Kidney Week. Cele's Champions: Cele Fogarty Travel Support Program for Patients helps people with kidney diseases attend Kidney Week as active participants. For more than 30 years, Cele was responsible for the logistical aspects of ASN Kidney Week as it evolved from the ASN Annual Meeting into the premier nephrology meeting in the world. During this time, she lived with kidney diseases and kidney failure.

4. **Supports more effective ASN committees, task forces, and panels.** Beyond the public-private partnerships like the KHI, activities to promote excellence in patient care, kidney health guidance, publications, and Kidney Week, ASN is inviting people living with kidney diseases to serve on its panels. For example, Nichole M. Jefferson is helping the ASN Health Care Justice Committee identify "opportunities to promote justice in health care and society and influencing social determinants of health, particularly in populations at risk for and overburdened with kidney diseases" (10). Her personal experience with vascular access, peritoneal dialysis, and transplantation helps shape the committee's efforts for all kidney health professionals "to seek just and equitable social conditions for their patients, their colleagues, and their community."

5. **Prioritizes ASN's legislative and regulatory goals.** Whenever considering legislation, evaluating proposed rules and regulations, or determining how best to advocate for kidney health, ASN relies on its mantra (Table 1). Starting with the question, "What is in the best interests of people living with kidney diseases and their families?" helps guide ASN to make the right decisions for the right reasons in the legislative and regulatory arena. In turn, the society's positions are easy to communicate, understand, and defend—helping these perspectives endure in an environment that rewards "the long game." To support shared goals, ASN also prioritizes collaboration with patient organizations in advocacy efforts, such as during regular meetings with members of Congress and their staff.

6. **Reinforces ASN's messaging related to kidney health.** Inspired by the KHI's approach to patient engagement, ASN has moved from acronym-filled, confusing lexicons to language that raises awareness and promotes an understanding of kidney diseases by the public, the media, politicians, and policymakers. Kidney patients are referred to as people living with kidney diseases. Chronic kidney disease is discussed as kidney diseases. End stage renal disease and end stage kidney disease are called what they are: kidney failure (11). ASN is devoted to screening for, protecting, and championing kidney health, instead of waiting to start treatment when an individual experiences kidney failure.

7. **Strengthens relationships between ASN and patient organizations.** In addition to working closely with the three patient organizations that represent the entire spectrum of people living with kidney diseases (AAKP, AKF, and NKF), ASN values its relationships with the many patient organizations that represent specific aspects of this experience. These organizations include (but are not limited to) NephCure (rare kidney diseases), the PKD Foundation (polycystic kidney disease), the Oxalosis & Hyperoxaluria Foundation (hyperoxaluria), Dialysis Patient Citizens (dialysis), and TRIO (Transplant Recipients International Organization).

The recent AHA "Presidential Advisory" on "cardiovascular-kidney-metabolic health" provides an exciting opportunity for collaboration among medical specialty societies and patient organizations, such as ASN, the AHA, and the ADA, in these three fields (12). Since their inception in 1924 and 1939, respectively, the AHA and the ADA have awarded more than $6 billion in combined research grants to investigators (13, 14). How might the lives of people living with kidney diseases improve when more of this funding supports researchers focused on enhancing cardiovascular-kidney-metabolic health?

By building on the benefits already realized from meaningfully engaging people living with kidney diseases, ASN is ready to work with the AHA and the ADA—as well as their respective medical specialty societies, such as the American College of Cardiology and the Endocrine Society—and the rest of the kidney community. If aligned, medical specialty societies and patient organizations committed to cardiovascular-kidney-metabolic health can come together to raise awareness, increase research funding, accelerate innovation, strengthen education, and improve the quality of care. ■

Tod Ibrahim, MLA, is executive vice president, American Society of Nephrology, Washington, DC. You can reach him at tibrahim@asn-online.org.

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INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

TAVNEOS (avacopan) is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

CONTRAINDICATIONS

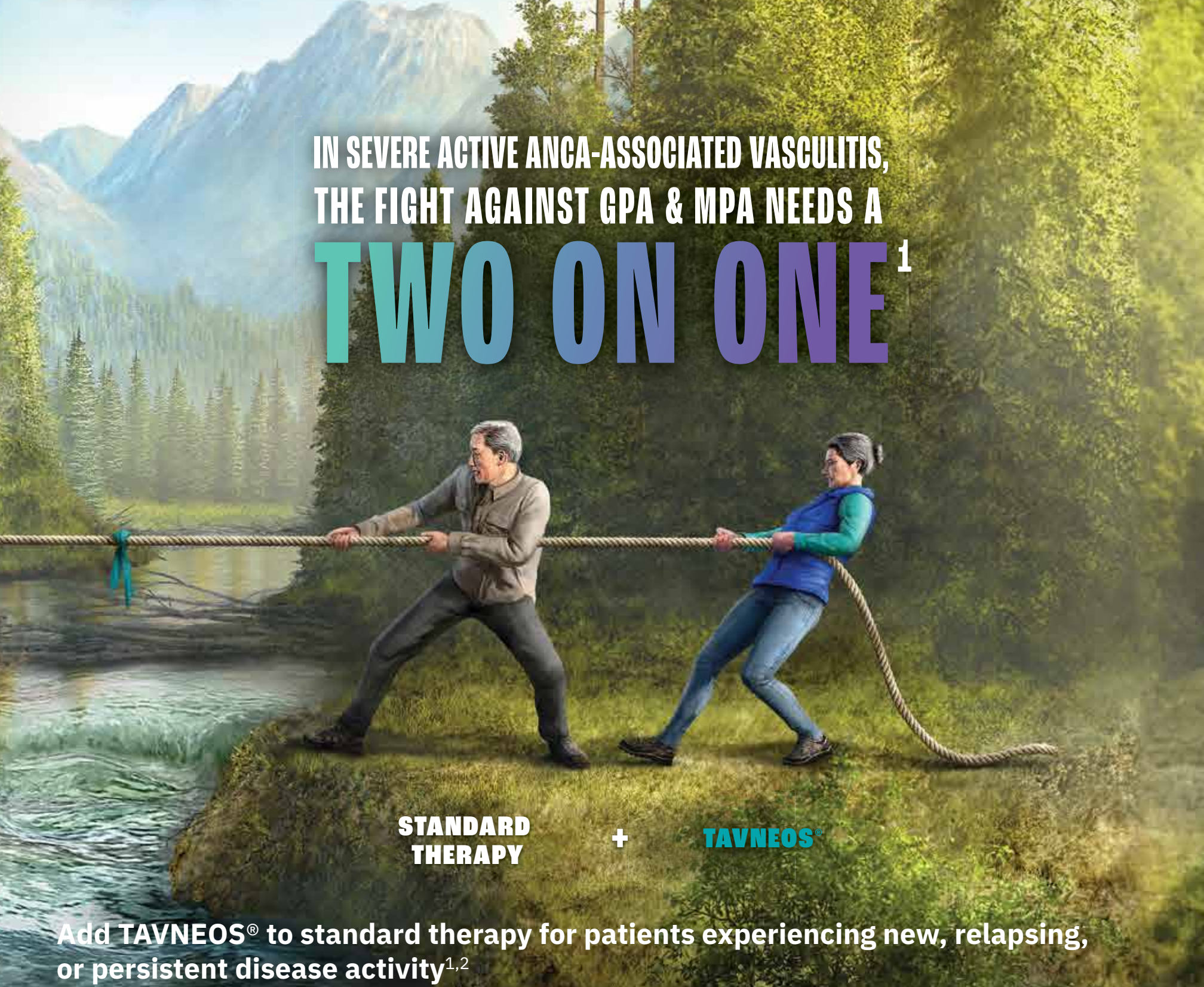
Serious hypersensitivity to avacopan or to any of the excipients.

WARNINGS AND PRECAUTIONS

Hepatotoxicity: Serious cases of hepatic injury have been observed in patients taking TAVNEOS, including life-threatening events. Obtain liver test panel before initiating TAVNEOS, every 4 weeks after start of therapy for 6 months and as clinically indicated thereafter. Monitor patients closely for hepatic adverse reactions, and consider pausing or discontinuing treatment as clinically indicated (refer to section 5.1 of the Prescribing Information). TAVNEOS is not recommended for patients with active, untreated, and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risks and benefits before administering this drug to a patient with liver disease.

Serious Hypersensitivity Reactions: Cases of angioedema occurred in a clinical trial, including 1 serious event requiring hospitalization. Discontinue immediately if angioedema occurs and manage accordingly. TAVNEOS must not be readministered unless another cause has been established.

Hepatitis B Virus (HBV) Reactivation: Hepatitis B reactivation, including life-threatening hepatitis B, was observed in the clinical program. Screen patients for HBV. For patients with evidence of prior infection, consult with physicians with expertise in HBV and monitor during TAVNEOS therapy and for 6 months following. If patients develop HBV reactivation, immediately discontinue TAVNEOS and concomitant therapies associated with HBV reactivation, and consult with experts before resuming.



Add TAVNEOS® to standard therapy for patients experiencing new, relapsing, or persistent disease activity[1,2]

Serious Infections: Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia and urinary tract infections. Avoid use of TAVNEOS in patients with active, serious infection, including localized infections. Consider the risks and benefits before initiating TAVNEOS in patients with chronic infection, at increased risk of infection, or who have been to places where certain infections are common.

ADVERSE REACTIONS

The most common adverse reactions (≥5% of patients and higher in the TAVNEOS group vs. prednisone group) were nausea, headache, hypertension, diarrhea, vomiting, rash, fatigue, upper abdominal pain, dizziness, blood creatinine increased, and paresthesia.

DRUG INTERACTIONS

Avoid coadministration of TAVNEOS with strong and moderate CYP3A4 enzyme inducers. Reduce TAVNEOS dose when coadministered with strong CYP3A4 enzyme inhibitors to 30 mg once daily. Monitor for adverse reactions and consider dose reduction of certain sensitive CYP3A4 substrates.

TAVNEOS is available as a 10 mg capsule.

To report a suspected adverse event, call 1-833-828-6367. You may report to the FDA directly by visiting **www.fda.gov/medwatch** or calling 1-800-332-1088.

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Please see Brief Summary of Prescribing Information for TAVNEOS® on the following pages.

12/23 USA-569-80504

AMGEN®

BRIEF SUMMARY OF PRESCRIBING INFORMATION
TAVNEOS® (avacopan) capsules, for oral use
Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

TAVNEOS is indicated as an adjunctive treatment of adult patients with severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]) in combination with standard therapy including glucocorticoids. TAVNEOS does not eliminate glucocorticoid use.

CONTRAINDICATIONS

TAVNEOS is contraindicated in patients with serious hypersensitivity reactions to avacopan or to any of the excipients *[see Warnings and Precautions (5.2)]*.

WARNINGS AND PRECAUTIONS

Hepatotoxicity

Serious cases of hepatic injury have been observed in patients taking TAVNEOS. During controlled trials, the TAVNEOS treatment group had a higher incidence of transaminase elevations and hepatobiliary events, including serious and life-threatening events *[see Adverse Reactions (6.1)]*.

Obtain liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating TAVNEOS, every 4 weeks after start of therapy for the first 6 months of treatment and as clinically indicated thereafter.

If a patient receiving treatment with TAVNEOS presents with an elevation in ALT or AST to >3 times the upper limit of normal, evaluate promptly and consider pausing treatment as clinically indicated.

If AST or ALT is >5 times the upper limit of normal, or if a patient develops transaminases >3 times the upper limit of normal with elevation of bilirubin to >2 times the upper limit of normal, discontinue TAVNEOS until TAVNEOS-induced liver injury is ruled out *[see Adverse Reactions (6.1)]*.

TAVNEOS is not recommended for patients with active, untreated and/or uncontrolled chronic liver disease (e.g., chronic active hepatitis B, untreated hepatitis C, uncontrolled autoimmune hepatitis) and cirrhosis. Consider the risk and benefit before administering TAVNEOS to a patient with liver disease. Monitor patients closely for hepatic adverse reactions *[see Use in Specific Populations (8.7)]*.

Hypersensitivity Reactions

TAVNEOS may cause angioedema *[see Adverse Reactions (6.1)]*. In clinical trials, two cases of angioedema occurred, including one serious event requiring hospitalization. If angioedema occurs, discontinue TAVNEOS immediately, provide appropriate therapy, and monitor for airway compromise. TAVNEOS must not be re-administered unless another cause has been established. Educate patients on recognizing the signs and symptoms of a hypersensitivity reaction and to seek immediate medical care should they develop.

Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, including life threatening hepatitis B, was observed in the clinical program.

HBV reactivation is defined as an abrupt increase in HBV replication, manifesting as a rapid increase in serum HBV DNA levels or detection of HBsAg, in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases, increase in bilirubin levels, liver failure, and death can occur.

Screen patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with TAVNEOS. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during TAVNEOS treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis, or HBV reactivation during and for six months following TAVNEOS therapy.

In patients who develop reactivation of HBV while on TAVNEOS, immediately discontinue TAVNEOS and any concomitant therapy associated with HBV reactivation, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming TAVNEOS treatment in patients who develop HBV reactivation. Resumption of TAVNEOS treatment in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing HBV.

Serious Infections

Serious infections, including fatal infections, have been reported in patients receiving TAVNEOS. The most common serious infections reported in the TAVNEOS group were pneumonia and urinary tract infections.

Avoid use of TAVNEOS in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating TAVNEOS in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with TAVNEOS. Interrupt TAVNEOS if a patient develops a serious or opportunistic infection. A patient who develops a new infection during treatment with TAVNEOS should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, the patient should be closely monitored, and TAVNEOS should be interrupted if the patient is not responding to antimicrobial therapy. TAVNEOS may be resumed once the infection is controlled.

ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Hepatitis B Virus (HBV) Reactivation *[see Warnings and Precautions (5.3)]*
- Serious Infections *[see Warnings and Precautions (5.4)]*

Clinical Trials Experience

Because the clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The identification of potential adverse drug reactions was based on safety data from the phase 3 clinical trial in which 330 patients with ANCA-associated vasculitis were randomized 1:1 to either TAVNEOS or prednisone *[see Clinical Studies (14)]*. The mean age of patients was 60.9 years (range of 13 to 88 years), with a predominance of men (56.4%) and Caucasians (84.2%). The cumulative exposure to TAVNEOS was 138.7 patient-years. Additionally, two phase 2 trials were conducted in ANCA-associated vasculitis. The cumulative clinical trial exposure from the phase 2 and 3 trials equals 212.3 patient-years.

The most frequent serious adverse reactions reported more frequently in patients treated with TAVNEOS than with prednisone were pneumonia (4.8% TAVNEOS vs. 3.7% prednisone), GPA (3.0% TAVNEOS vs. 0.6% prednisone), acute kidney injury (1.8% TAVNEOS vs. 0.6% prednisone), and urinary tract infection (1.8% TAVNEOS vs. 1.2% prednisone). Within 52 weeks, 4 patients in the prednisone treatment group (2.4%) and 2 patients in the TAVNEOS group (1.2%) died. There were no deaths in the phase 2 trials.

In the phase 3 trial, seven patients (4.2%) in the TAVNEOS treatment group and 2 patients (1.2%) in the prednisone treatment group discontinued treatment due to hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzymes abnormalities. The most frequent adverse reaction that led to drug discontinuation reported by > 1 patient and more frequently reported in patients treated with TAVNEOS was hepatic function abnormal (1.8%).

The most common adverse reactions that occurred in ≥5% of patients and higher in the TAVNEOS group as compared with the prednisone group are listed in Table 1.

Table 1: Adverse Reactions Reported in ≥5% of Patients and Higher in TAVNEOS Group vs. Prednisone Group in Phase 3 Trial

Adverse Reaction	Prednisone (N=164) n (%)	TAVNEOS (N=166) n (%)
Nausea	34 (20.7)	39 (23.5)
Headache	23 (14.0)	34 (20.5)
Hypertension	29 (17.7)	30 (18.1)
Diarrhea	24 (14.6)	25 (15.1)
Vomiting	21 (12.8)	25 (15.1)
Rash	13 (7.9)	19 (11.4)
Fatigue	15 (9.1)	17 (10.2)
Upper abdominal pain	10 (6.1)	11 (6.6)
Dizziness	10 (6.1)	11 (6.6)
Blood creatinine increased	8 (4.9)	10 (6.0)
Paresthesia	7 (4.3)	9 (5.4)

N=number of patients randomized to treatment group in the Safety Population; n=number of patients in specified category.

Hepatotoxicity and Elevated Liver Function Tests

In the phase 3 trial, a total of 19 patients (11.6%) in the prednisone group and 22 patients (13.3%) in the TAVNEOS group had hepatic-related adverse reactions, including hepatobiliary adverse reactions and liver enzyme abnormalities. Study medication was paused or discontinued permanently due to hepatic-related adverse reactions in 5 patients (3.0%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. Serious hepatic-related adverse reactions were reported in 6 patients (3.7%) in the prednisone group and 9 patients (5.4%) in the TAVNEOS group. A serious hepatic-related adverse reaction was reported in 1 patient in the TAVNEOS group in the phase 2 studies.

Angioedema

In the phase 3 trial, 2 patients (1.2%) in the TAVNEOS group had angioedema; one event was a serious adverse reaction requiring hospitalization.

Elevated Creatine Phosphokinase

In the phase 3 trial, 1 patient (0.6%) in the prednisone group and 6 patients (3.6%) in the TAVNEOS group had increased creatine phosphokinase. One TAVNEOS-treated patient discontinued treatment due to increased creatine phosphokinase.

DRUG INTERACTIONS

CYP3A4 Inducers

Avacopan exposure is decreased when co-administered with strong CYP3A4 enzyme inducers such as rifampin *[see Clinical Pharmacology (12.3)]*. Avoid coadministration of strong and moderate CYP3A4 inducers with TAVNEOS.

CYP3A4 Inhibitors

Avacopan exposure is increased when co-administered with strong CYP3A4 enzyme inhibitors such as itraconazole *[see Clinical Pharmacology (12.3)]*. Administer TAVNEOS 30 mg once daily when coadministered with strong CYP3A4 inhibitors.

CYP3A4 Substrates

Avacopan is a CYP3A4 inhibitor. Closely monitor patients for adverse reactions and consider dose reduction of sensitive CYP3A4 substrates with a narrow therapeutic window when coadministered with TAVNEOS *[see Clinical Pharmacology (12.3)]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies with TAVNEOS in pregnant women to inform a drug-associated risk. In animal reproduction studies, oral administration of avacopan to pregnant hamsters and rabbits during the period of organogenesis produced no evidence of fetal harm with exposures up to approximately 5 and 0.6 times, respectively, the exposure at the maximum recommended human dose (MRHD) of 30 mg twice daily (on an area under the curve [AUC] basis). Avacopan caused an increase in the number of abortions in rabbits at an exposure 0.6 times the MRHD *(see Animal Data)*.

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study with pregnant hamsters dosed by the oral route during the period of organogenesis from gestation days 6 to 12, avacopan produced an increase in the incidence of a skeletal variation, described as supernumerary ribs, at an exposure that was 5 times the MRHD (on an AUC basis with a maternal oral dose of 1000 mg/kg/day). No structural abnormalities were noted with exposures up to 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

In an embryo-fetal development study with pregnant rabbits dosed by the oral route during the period of organogenesis from gestation days 6 to 18, avacopan caused an increase in the number of abortions at an exposure 0.6 times the MRHD (on an AUC basis with a maternal oral dose of 200 mg/kg/day), however, no evidence of fetal harm was observed with such exposures. Maternal toxicity, as evidenced by decreased body weight gains, was observed at exposures 0.6 times and higher than the MRHD (on an AUC basis with maternal oral doses of 30 mg/kg/day and higher).

In a prenatal and postnatal development study with pregnant hamsters dosed by the oral route during the periods of gestation and lactation from gestation day 6 to lactation day 20, avacopan had no effects on the growth and development of offspring with exposures up to approximately 5 times the MRHD (on an AUC basis with maternal oral doses up to 1000 mg/kg/day).

Lactation

Risk Summary

There are no available data on the effects of avacopan on the breastfed child or on milk production. It is unknown whether avacopan is secreted in human milk. Avacopan was detected in the plasma of undosed hamster pups nursing from drug-treated dams *(see Animal Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TAVNEOS and any potential adverse effects on the breast-fed infant from TAVNEOS or from the underlying maternal condition.

Animal Data

Avacopan has not been measured in the milk of lactating animals; however, it was detected in the plasma of nursing offspring in a pre- and post-natal development study with hamsters at a pup to maternal plasma ratio of 0.37. This finding suggests that avacopan is secreted into the milk of lactating hamsters *[see Nonclinical Pharmacology (13.1)]*.

Pediatric Use

The safety and effectiveness of TAVNEOS in pediatric patients have not been established.

Geriatric Use

Of the 86 geriatric patients who received TAVNEOS in the phase 3 randomized clinical trial for ANCA-associated vasculitis *[see Clinical Studies (14)]*, 62 patients were between 65-74 years and 24 were 75 years or older. No overall differences in safety or effectiveness were observed between geriatric patients and younger patients.

Patients With Renal Impairment

No dose adjustment is required for patients with mild, moderate, or severe renal impairment *[see Clinical Pharmacology (12.3)]*. TAVNEOS has not been studied in patients with ANCA-associated vasculitis who are on dialysis.

Patients With Hepatic Impairment

No dosage adjustment is recommended for patients with mild or moderate (as indicated by the Child-Pugh method) hepatic impairment *[see Clinical Pharmacology (12.3)]*. TAVNEOS has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

The risk information provided here is not comprehensive. The FDA-approved product labeling can be found at www.tavneospro.com or contact Amgen Medical Information at 1-800-772-6436

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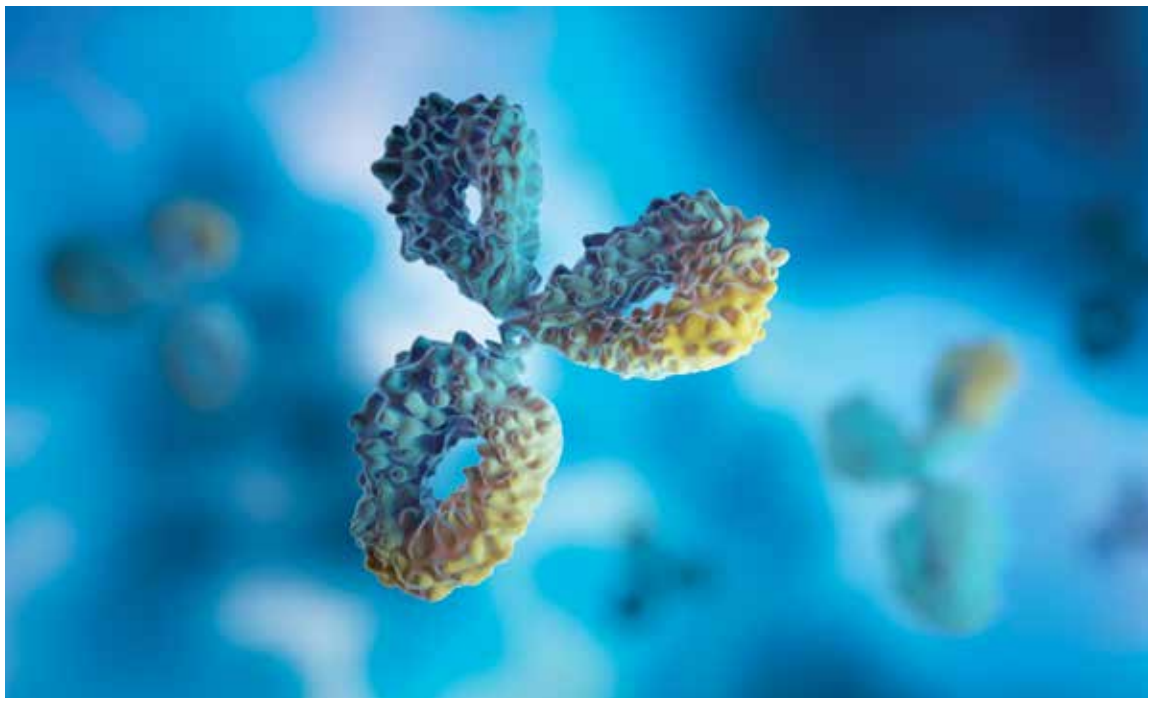
USA-569-80226

The Role of Complement Blockade in the Management of IgA Nephropathy

By Vinay Srinivasan and Nasim Wiegley



There has recently been a significant increase in available therapeutics and ongoing clinical trials that directly target the pathogenic mechanisms implicated in immunoglobulin A nephropathy (IgAN). Although systemic immunosuppression can be considered for patients at high risk of disease progression, it is associated with a wide degree of toxicities (1). Similar concerns remain present with the use of targeted-release enteric budesonide, although to a lesser extent (2). A growing body of evidence suggests that activation of the complement pathway plays an important role in IgAN pathogenesis, and numerous therapies targeting specific steps in the complement cascade are under development (3).

Galactose-deficient IgA1 deposition in tissues triggers local complement activation, and the alternative pathway is the primary cascade in IgAN. Activation of this cascade results in glomerular complement component 3 (C3) deposition, which has been observed in a significant majority of patients and correlates with disease progression. More intense complement deposition correlates with a worse prognosis and underscores the need for targeted complement inhibition in IgAN (4).

One such therapy is cemdisiran, a subcutaneously administered RNA interference therapeutic. Cemdisiran is designed to reduce hepatic production of C5 and thereby reduce formation of the membrane attack complex and anaphylatoxin C5a, which drive kidney injury. In a recent phase 2 study by Barratt et al. (5), adults with biopsy-proven IgAN were randomized in a 2:1 ratio to receive either cemdisiran (600 mg subcutaneously) or placebo every 4 weeks for 36 weeks.

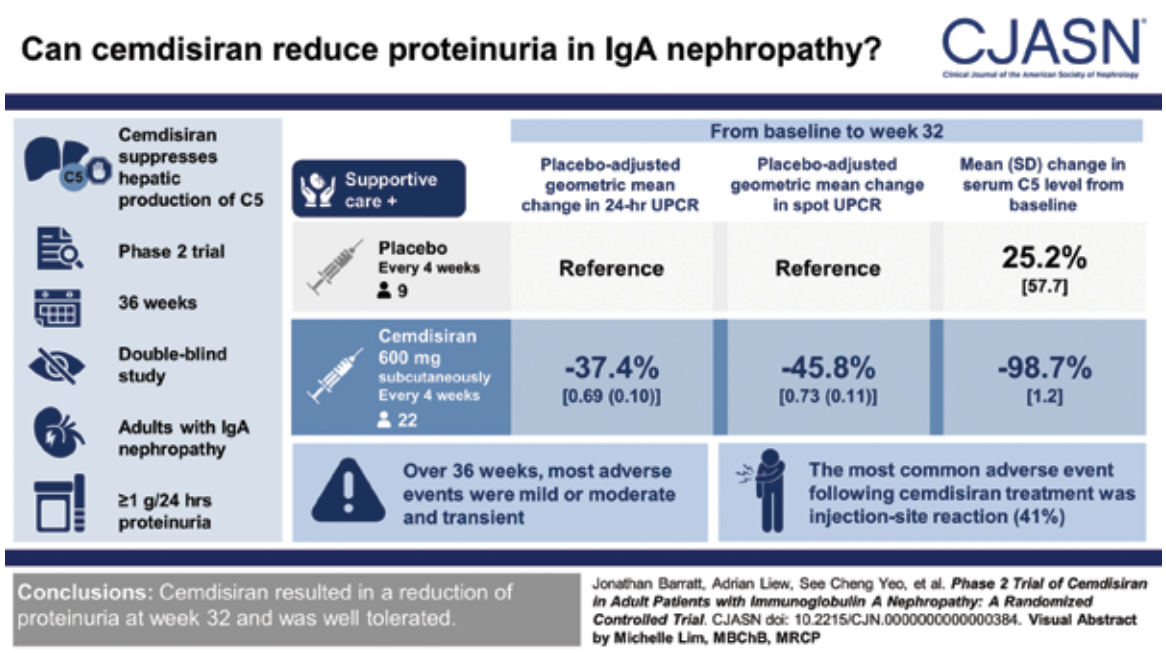
All participants were on maximally tolerated renin-angiotensin system blockade for at least 3 months and had >1 g/day of proteinuria. The primary endpoint of the study was the percentage change from baseline of the urine protein-to-creatinine ratio (UPCR) at week 32. Patients with other significant concurrent kidney diseases and an estimated glomerular filtration rate <30 mL/min/1.73 m^2 and those who had received systemic immunosuppression within the past 6 months were excluded (5).

The 24-hour mean UPCR decreased from 1.55 to 1.27 g/g at week 32 for patients treated with cemdisiran with a placebo-adjusted geometric mean change from baseline in a 24-hour UPCR of –37.4%. Mean serum C5 levels were also noted to decrease for patients treated with cemdisiran compared with placebo. The most common adverse effect was injection-site reactions in the cemdisiran group; one death occurred in the therapy group due to post-operative complications of elective cardiac surgery that was considered unrelated to the study drug. No other patients discontinued the study drug (5).

Although the results will need to be confirmed in a larger phase 3 trial, this study supports the hypothesis that targeting the complement pathway is another useful method to treat patients with IgAN at high risk of disease progression. However, as the authors acknowledge, the trial was conducted prior to the widespread adoption of sodium-glucose cotransporter-2 inhibitors, which have been shown to have a beneficial role in proteinuria reduction for patients with IgAN (6). Regardless, having another potential therapeutic for IgAN is a welcome development for both nephrologists and patients alike. ■

Vinay Srinivasan, MD, MBA, is an assistant professor of medicine and the director of onconephrology at Cooper Medical School of Rowan University and Cooper University Hospital, Camden, NJ. Nasim Wiegley, MD, FASN, is an associate professor of medicine and the director of the Glomerular Diseases Clinic at the University of California Davis Medical Center, Sacramento.

The authors report no conflicts of interest.



Reprinted with permission from *CJASN*. See Barratt et al. (5).

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This special section of *Kidney News* focuses on nephrology care in the face of global crises. *Kidney News* thanks Editorial Fellows Paul Hanna, MD, MSc, and Rasha Raslan, MD, for thoughtfully selecting and co-editing these articles.

NAVIGATING NEPHROLOGY
CARE DURING CRISES

By Paul Hanna

In the world of nephrology, in which the delicate balance of health and disease defines the lives of millions worldwide, the impact of crises—whether natural disasters, wars, or the ongoing challenges of climate change—can be profound and far-reaching. In this special issue of *Kidney News*, we take a deep dive into the multifaceted challenges faced by patients, health care professionals, and nephrology communities when navigating nephrological care in times of emergencies. From the devastation brought on by hurricanes and tornadoes to the enduring hardships of warfare, the articles presented here offer a comprehensive exploration of the intersection between nephrology and crisis management. Through insightful commentary, expert analyses, and firsthand accounts, we shed light on myriad complexities that are inherent in providing and receiving nephrology care amid adversity.

We begin by delving into the challenges posed by climate change, exploring how extreme weather events and environmental factors exacerbate the vulnerabilities of patients dependent on dialysis and managing transplantation. From heatwaves and wildfires to disruptions in dialysis services caused by natural disasters, the articles underscore the pressing need for proactive measures and preparedness within the nephrology community to ensure the continuity of care in the face of climate-related crises. Next, we examine the impact of war on patients undergoing hemodialysis, highlighting the dire consequences faced by those disconnected from life-sustaining treatments in war-torn regions. As health care infrastructure crumbles and resources become scarce, patients are left vulnerable, underscoring the urgent need for international collaboration and humanitarian aid to mitigate the devastating effects of conflict on kidney health.

Lastly, in a deeply personal reflection, we hear from a young Syrian refugee living with lupus nephritis, whose journey from war-torn Syria to resettlement in the United States offers a poignant reminder of the resilience and determination of patients navigating nephrology care amidst adversity. Through their lived experiences, we gain valuable insights into the unique challenges faced by individuals and families grappling with chronic kidney disease in the midst of crises.

In addition to insightful content, this special section features powerful images by Ed Kashi, renowned photojournalist, filmmaker, speaker, educator, and recipient of the 2023 ASN President's Medal. His photography and films have documented how climate change and chronic kidney disease have become a global health crisis. The photos featured in this issue capture the experiences of individuals living with chronic kidney disease in regions with extreme heat, including India and Nicaragua.

I hope that by the end of this special section, you realize the importance of perseverance, patient-centered care, and patient advocacy. As we confront the aforementioned trials, we must remain committed to supporting our patients and communities, ensuring access to life-saving treatments, and advocating for policies that prioritize kidney health in times of exigencies. Together, we can successfully navigate the complexities of nephrology care in crises, drawing strength from the resilience of patients, the expertise of health care practitioners, and the collective resolve of the nephrology community to address the challenges ahead. ■

Paul Hanna, MD, MSc, is the director of onconephrology in the Division of Nephrology, Department of Medicine, Medical College of Wisconsin, Milwaukee. Rasha Raslan, MD, is with the Division of Nephrology, Department of Medicine, Duke University Hospital, Durham, NC.

The author and section co-editors report no conflicts of interest.

Photo by Ed Kashi. Laborers prepare the Marakkanam salt pan fields for salt harvest near Pondicherry, India, on January 21, 2016.

Photo by Ed Kashi. A father and son pose in the cane fields of Chichigalpa, Nicaragua, on January 6, 2013. Both men experience chronic kidney disease.

The Kidney Community's Role in Natural Disasters and Climate Change

By Matthew F. Blum

Despite recent advances in efforts to mitigate climate change, greenhouse gas emissions continue to rise (1). Climate change has led to the increased frequency and severity of extreme weather events, which pose a major challenge for patients who are dependent on dialysis. Dialysis requires stable electricity, water, and transportation systems. When natural disasters disrupt these systems, access to dialysis—our patients' lifeline—is threatened. Therefore, the kidney health care community must address climate change and natural disaster management.

Hurricane Katrina, which struck the Gulf Coast in 2005, was a pivotal event for dialysis disaster mitigation efforts. Hurricane Katrina resulted in the closure of nearly 100 dialysis units and laid bare many challenges in dialyzing evacuees (2). In response, the Kidney Community Emergency Response was established to help dialysis facilities and patients treated with dialysis to respond to natural disasters with tools such as dialysis hotlines, emergency kidney diets, and disaster response guidance (3). In the face of further natural disasters, we have continued to learn how to best support our patients, such as identifying survival benefits of early dialysis during Hurricane Sandy (4) and navigating insurance challenges amidst patient displacement during Hurricane Maria (5).

Hurricanes are not the only climate change-related risk that our patients who are dependent on dialysis face. Extreme heat events and air pollution from wildfires, both of which we encountered on an unprecedented scale last year, are associated with increased mortality among patients receiving dialysis (6, 7). Even beyond catastrophic events, adverse weather such as snow, rain, and wind have been linked to missed dialysis sessions (8).

The kidney community must address climate change and its associated natural disasters, but implementing impactful solutions is challenging. I suggest three approaches:

1. Apply evidence-based, guideline-directed care to prevent or delay the need for kidney replacement therapies. This will reduce the number of patients who require dialysis amidst natural disasters and cut dialysis-related climate emissions (9).
2. Prepare our patients for dialysis disruptions with tools such as the 3-day emergency kidney diet and evacuation planning (3).
3. Advocate for the broadscale transition to carbon-free energy sources to slow climate change.

ASN has been a leader in this effort. In April 2022, the society released its "Statement on Climate Change," urging professionals in the nephrology sector to address climate change with specific, actionable steps to support patients with kidney diseases in the face of climate change, reduce the environmental impact of kidney care, and advocate for climate change mitigation policies (10). ASN has also launched the Emergency Partnership Initiative to work with people with kidney diseases, dialysis companies, hospital systems, and disaster relief agencies in North America and the Caribbean to prepare for natural disasters and to locate needed resources during and after major events. Likewise, nephrology organizations around the world are leading efforts to mitigate the discipline's environmental damage with programs such as the International Society of Nephrology's Global Environmental Evolution in Nephrology and Kidney Care (GREEN-K) initiative (11) and the European Renal Association's Sustainable Nephrology Task Force (12).

While we are fortunate to have professional organizations that prioritize addressing climate change and kidney diseases, it is in our hands to take up their call and ensure that plans lead to action. Natural disasters are occurring with increased ferocity in the era of climate change and threaten the lives of our most vulnerable patients. For their sake, we must continue to push for climate action. ■

Matthew F. Blum, MD, MHS, is an assistant professor of medicine in the Division of Nephrology, University of Wisconsin School of Medicine and Public Health, Madison.

The author reports no conflicts of interest.

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Challenges and Strategies in Managing Kidney Transplantation During Natural Disasters

By Aisha Batool, Cristina Popa, Badi Rawashdeh, and Beje Thomas

The past 3 decades have seen a significant global impact of natural disasters, affecting approximately 5 billion people. In 2021, 432 natural disasters impacted 101.8 million individuals (1). Current practices are often difficult to uphold when significant threats emerge and become challenging to follow during disasters. Despite these challenges, health care remains a fundamental human right. Looking through a chronic illness lens, and more specifically from a kidney transplant perspective, the stakes are even higher. Below are some of the key aspects of transplantation that are frequently affected.

Photo by Ed Kashi. A sugar cane cutter takes a hydration break from work in the fields at Ingenio San Antonio, or the San Antonio Sugar Mill, in Chichigalpa, Nicaragua, on February 29, 2020.

Patient and graft survival

During natural disasters, the continuity of transplant centers is severely affected due to the destruction of public services and the transplant infrastructure, financial instability, potential repurposing of medical workers, and limited medical supplies. The first wave of the COVID-19 pandemic underscored the vulnerability of kidney transplant recipients, with high mortality rates attributed to factors such as immunosuppression, comorbidities, and possible suboptimal health care (2). Insights from the pandemic and other natural disasters advocate for the continuation of transplantation programs during mass disasters under favorable conditions (3, 4). For displaced individuals, financial and language barriers, referral systems, and limited health care pose significant challenges. This necessitates local and international assistance to mitigate risks such as higher acute kidney injury incidence, infection risk, malnutrition, and lack of proper care in cases of kidney function deterioration (5, 6).

Immunosuppression management, outpatient follow-up, and the role of telemedicine

Medications can be in short supply in times of disasters, and access to them may be hindered. Establishing communication lines through non-governmental organizations and local groups can assist patients in obtaining medications. In cases in which usual drugs are unavailable, switching between immunosuppressive medications or adjusting the dosage of available drugs may be a viable option (4, 5). In some instances, patients can remain without optimal immunosuppression and be treated instead with high doses of steroids for months (5).

One of the proposed solutions to circumventing these issues is immunosuppression stocking, which might be limited by local regulations (5, 6). Since donations from humanitarian organizations might be unreliable for a longer duration due to unpredictable conditions, the creation of local registries containing information about medical institutions and contacts of medical suppliers would prove beneficial. These registries would calculate required medical supplies, relocate them to safer zones, help formulate plans for patient relocation, ensure the presence of medical personnel and supplies, and provide suggestions to medication adjustments based on their availability (7).

Communication between patients and physicians may also prove difficult. Telemedicine is valuable for non-transplant physicians managing patients undergoing transplant, especially for any modifications in immunosuppressants (7). Studies reported equivocal clinical endpoints for patients receiving video-based transplant care in disasters (7). Significant challenges for telemedicine encompass issues such as low literacy, limited computer technology familiarity, and the inability to connect to the internet.

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Table 1. Approaches to managing kidney transplantation during natural disasters

Domain of care	Challenges	Possible solutions
Immunosuppressant Medications	• Lack of access to pharmacy • Lack of supply/distribution • Lack of laboratory testing for therapeutic-level monitoring	• Stockpiling medications • Clear instructions to follow during disaster • Disaster emergency program should be discussed at least once a year with your patients. • Establish contact post-disaster to ensure patients have clear instructions.
Physical Displacement of Patients/ Health Care Workers	• Loss of infrastructures such as telephone and facsimile and possible loss of ways/means of travel.	• Carrying a week's supply with them • Patients should remember exact names/dose frequency of their IS regimen. • Channel inpatient supply to outpatient distribution.
Kidney Transplant Center and Health Care Personnel	• Damage to building, power failure, water shortage, shortage of medical supplies, communication difficulties, and transportation problem for health care personnel	• Establish institutional emergency preparedness bulletin/guidelines. • Health care workers' and staff's drills/training on disaster management • Identify coordinators, and define their tasks. • Assign back-up for every person and function. • Consider drawbacks toward infrastructure and medical supplies. • Check the addresses of patients and staff; consider alternate possibilities. • Back-up power generators • Identify contact information of manufacturers' distribution companies.
Patients' Emergency Preparedness	• Lack of stockpile of IS medications • Unhygienic environment • Unexpected natural disasters • Non-medical issues	• Clear communication on institutional emergency tool, national hotline number in case patients are physically displaced, readiness of emergency bag/kit, and education on emergent clinical signs and symptoms

IS, immunosuppression.

Challenges and Strategies in Managing Kidney Transplantation During Natural Disasters

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The pre-transplantation evaluation and new kidney transplants

The pre-transplantation evaluation during disasters necessitates adherence to existing principles. The transplant program should continue to operate if strategically possible. Following Hurricane Katrina, there was a 21% decrease in kidney transplantations in Louisiana. This decline can be attributed primarily to the widespread chaos and panic, the closure of two out of three major transplant centers in New Orleans, a shortage of medical supplies, inefficiency, and burnout among medical personnel. Additionally, the reduction in the number of deceased donors was influenced by limited availability of intensive care unit (ICU) beds and restrictions on organ transport (8).

The first wave of the COVID-19 pandemic significantly impacted deceased and live-donor kidney transplantation, with global centers temporarily halting procedures. Living donor kidney transplantation was suspended in 67% of North American centers and 91% of European centers. In France, there was a significant reduction of up to 90.6% in deceased donor transplantation during the same period (2, 9). Subsequent waves had a milder impact, suggesting improved handling of medical and logistical challenges. A phased approach—prioritizing urgent cases and ensuring safe living donation—has been suggested to resume transplantation activities (2–4). Simulator models suggest a potential advantage of kidney transplantation in certain scenarios, and urgent indications may override concerns, allowing transplantation even in disasters (9–11).

Ethical issues

Mass disasters raise ethical dilemmas. These include performing kidney transplantation despite high morbidity and mortality risks, using ICU beds for potential deceased donors, and applying the same allocation rules as before the disaster. Classic ethical principles like non-maleficence, beneficence, distributive justice, and respect for autonomy should guide transplantation practices during disasters. Health care workers may face a higher risk of malpractice stemming from insufficient resources and by making medical decisions in unique scenarios not addressed by guidelines.

Clinical research

The absence of experimental models underscores the critical role of disaster-related clinical research. Despite methodological drawbacks, the pandemic emphasized the importance of cost-effective and high-quality research for future guidance, setting a path for the role of ongoing research. Continuing, ongoing clinical trials during disasters are desirable, with necessary protocol modifications to prevent study patients from facing additional risks (12).

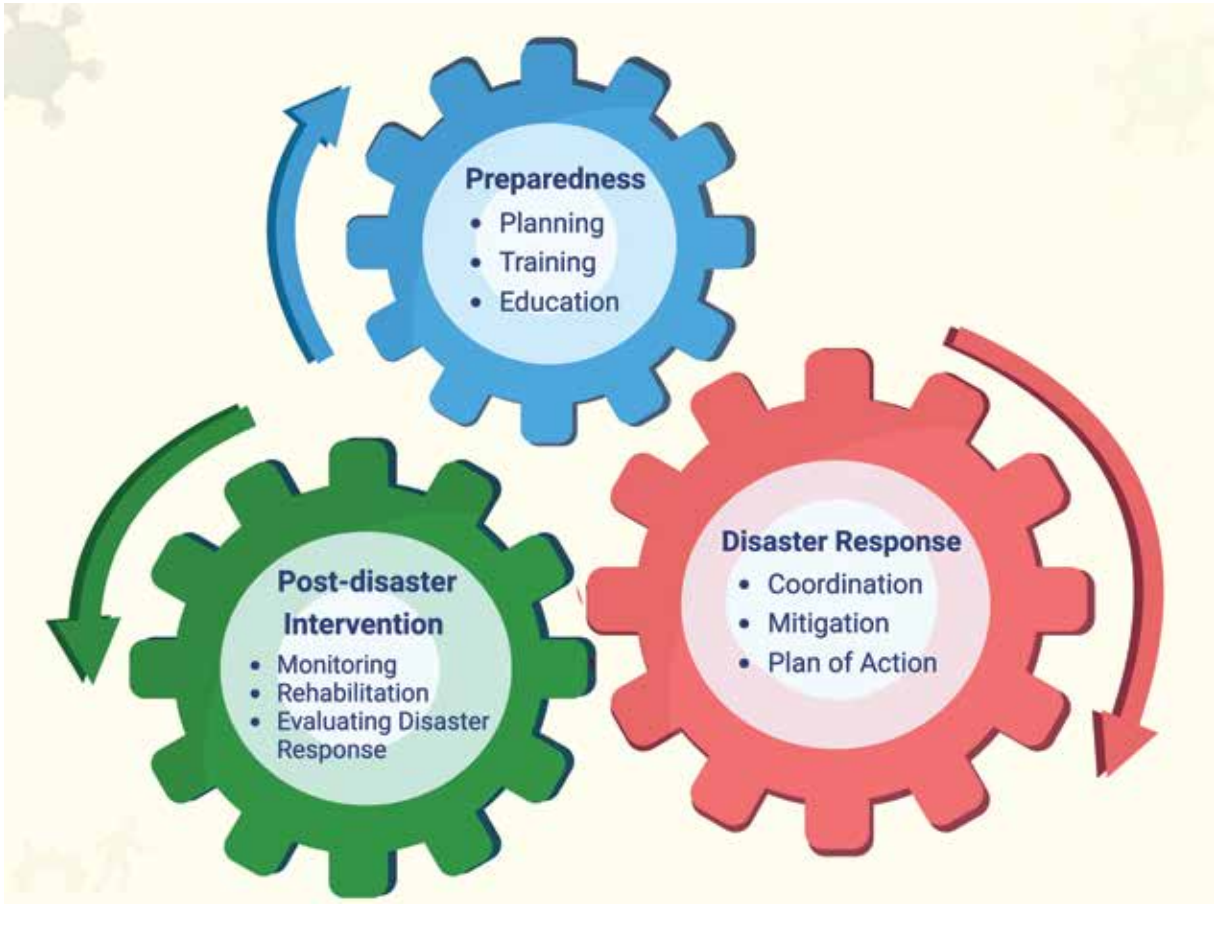
Resuming care after disaster

Effective disaster response requires thorough preparation and ongoing evaluation of post-disaster interventions and rehabilitation. A phased approach is suggested for resuming transplantation activity, prioritizing urgent cases, and ensuring safe living donations (13–15).

In conclusion, managing kidney transplantation during disasters demands a multifaceted approach addressing logistical, ethical, and clinical challenges (Table 1 and Figure 1). Strategic planning, international collaboration, and ongoing research are key elements to ensure the survival and well-being of transplant recipients in the face of unforeseen crises. ■

Aisha Batool, MD, and Beje Thomas, MD, are with the Division of Nephrology, and Badi Rawashdeh, MBBS, is with the Division of Transplant Surgery at the Medical College of Wisconsin, Milwaukee. Cristina Popa, MD, is with the Nephrology, Dialysis, and Transplantation Department at Dr. C.I. Parhon Hospital, Iasi, Romania.

Figure 1. Coordination of natural disaster response



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CKDu: Heat, Health, and Harm

By Anna Strasma

Chronic kidney disease of unknown etiology (CKDu) has been called "the black lung of climate change" (1). CKDu was first reported in the early 2000s to describe localized regions of high prevalence of CKD among young people without diabetes or hypertension in Central America and Southeast Asia (2, 3). The cause of this chronic tubulointerstitial nephritis is likely multifactorial (Table 1). Lead suspects include heat stress and toxic environmental exposures such as agrichemicals or heavy metals. Although there is disagreement among researchers over the exact combination of factors leading to the disease, most agree that heat plays some role in its development. CKDu is endemic in regions with high ambient temperatures, and it is strongly associated with occupational heat exposure in agriculture and other sectors. CKD could develop secondary to daily subclinical acute kidney injury from heat exposure, volume depletion, and exercise-induced hyperuricemia (4, 5). Heat may also exacerbate kidney injury from environmental exposures (such as contaminated water) and/or alter the body's response to xenobiotic elements (3). CKDu is often diagnosed at advanced stages of disease, and patients commonly progress to kidney failure within several years (2).

Since this disease has emerged relatively recently and people have been laboring in hot environments for millennia, one of the main scientific questions is "Why now?" A plausible answer is "climate change." There has been an increase in average temperature of 0.18° C per decade globally and an increase in frequency and severity of heat waves over the past 50 years (4, 6). However, all parts of the globe are not affected uniformly, and certain CKDu localities, such as a CKDu endemic area of Nicaragua, had an increase in 0.7° C per decade between 1970 and 1990 (7). Workers in endemic areas with strenuous occupations, such as harvesting sugarcane, are frequently exposed to temperatures high enough that the Occupational Safety and Health Administration recommends extensive rest, shade, and rehydration interventions. Unfortunately, these interventions are inconsistently performed (4, 8).

Occupational health policies and interventions are extremely important to protect workers; however, these measures alone are insufficient in addressing a likely key driver of the disease—climate change. CKDu is a result of environmental injustice, in which low-income communities with limited political power and health care access are harmed by entities from which they do not benefit. Children and women, two especially vulnerable populations within communities, are severely impacted by the societal impacts of CKDu, and there is growing evidence that they too experience CKDu-related kidney injury (3, 9). Current CKDu-focused efforts include the CKDu in Agricultural Communities (CURE) Research Consortium, the International Society of Nephrology's (ISN's) CKDu Network (i3C), and the Consortium on the Epidemic of Nephropathy in Central America and Mexico (CENCAM). Through interdisciplinary, interinstitutional, and international collaboration, all CKDu underlying factors, including heat stress, can be identified and addressed.

The nephrology community must take environmentally protective actions, as described in the ASN's Statement on Climate Change (10), to curb the CKDu epidemic. We need more population-level research on climate change health effects, climate change-related disaster relief preparedness for patients with kidney diseases, and advocacy for public policies that protect the environment. The nephrology community should also promote environmentally sustainable kidney care, as outlined by the ISN's Global Environmental Evolution in Nephrology and Kidney Care (GREEN-K) initiative, with a focus on limiting the environmental impact of dialysis treatments (11). CKDu is a wake-up call to the immediate necessity of protecting the environment, our patients, and vulnerable populations around the globe. ■

Photo by Ed Kashi. Sugar cane workers cutting in burned fields, with dust monitors on their chests, as part of the Adelante Initiative at the Ingenio San Antonio, or San Antonio Sugar Mill, in Chichigalpa, Nicaragua, on February 24, 2020.

Table 1. Proposed CKDu contributing factors of a multifactorial disease

Factors	Rationale
Heat stress and recurrent volume depletion	Endemic areas have hot climates with disproportionate effects from climate change. CKDu is more common in agricultural or other strenuous labor occupations that have unhealthy working conditions (including inadequate access to water, shade, and rest) that are a known risk factor for acute kidney injury and possibly CKD.
Agrichemical exposure	Agricultural workers and residents of agricultural communities are at increased risk for CKDu, and many agrichemicals have established nephrotoxic effects.
Environmental exposures (i.e., heavy metals in well-water, smoke inhalation from burning crops)	Localized epidemics occur in communities with similar water-source and air pollution exposures. Cases of CKDu exist in those without a history of strenuous labor occupation. Some heavy metals have established nephrotoxic effects.
Genetic/developmental	Localized epidemics exist in small communities. Cases of CKDu appear in those without a history of strenuous labor occupation. There is growing evidence that kidney dysfunction in endemic areas starts in childhood.
Infections	Many tropical infections, including leptospirosis and hantavirus, have known deleterious kidney effects and are common in many CKDu-endemic areas.
Nephrotoxin ingestions	Non-steroidal anti-inflammatory drugs, unregulated alcohol use, and fructose-rich beverages are reportedly common in endemic regions.

See Johnson et al. (2) and Jayasumana et al. (3).

Anna Strasma, MD, is a nephrologist in the Duke University Division of Nephrology and an affiliate of the Duke Global Health Institute in Durham, NC.

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Green Kidney Care in Australia: Looking Backward and Forward

By Anoushka Krishnan and Katherine Barraclough

It was over 2 decades ago that pioneering Australian nephrologist John Agar, MBBS, first alerted the kidney care community to the extraordinarily high resource consumption profile of hemodialysis. He documented that each 4-hour treatment used in excess of 500 L of water, with two-thirds discarded to drain as reverse osmosis (RO) reject water (1). Per-treatment power usage was similarly high (more than one-quarter of the total daily power consumed by an average Australian home), and hemodialysis' annual per-patient carbon footprint was more than one-half of the mean Australian per capita estimate (2).

His group then implemented a range of strategies to minimize their service's resource impact. These included capturing RO reject water for reuse elsewhere—for the first time globally—and installing solar panels to power dialysis equipment (1, 3). Agar called loudly for others to follow his lead. But he was a lone voice, and at the time, few, aside from some in the United Kingdom, heard his rallying call.

Broader action

It took over 10 years for the broader Australian kidney care community to spur to action. In 2017, with a new generation of nephrologists pressuring leadership, mentored by Agar, the Australian and New Zealand Society of Nephrology (ANZSN) established an Environmental Sustainability Committee (ESC). The group's aim was to foster, promote, and support environmentally sustainable kidney care in Australia and New Zealand. The range of initiatives it has undertaken over the years since is outlined in Table 1.

Collectively, this work has led to significant increases in awareness of both the need for and ways to achieve "green kidney care." Yet, despite these efforts, a 2020 survey of Australian and New Zealand dialysis services found that environmental sustainability remained a low priority in clinical practice, building design and infrastructure, and management systems (6).

Accordingly, the ESC has since turned its attention to initiatives aimed at stimulating "on-ground" change. In 2022, it published best practice guidelines for the design, construction, and operation of dialysis facilities (7). These outline objectives and minimum requirements across the areas of energy, water, waste, and resource recovery (Figure 1). They have been incorporated into the Australasian Health Facility Guidelines for Dialysis Units, which should aid broad implementation. The ESC has also developed guides for optimizing RO plant settings, hemodialysis machine disinfection schedules, and acid concentrate use. Work is now underway to identify "green champions" in each kidney care service to apply the guidance.

Where to go from here?

The global situation is markedly different today compared with Agar's day. Rather than being a future threat, climate change is currently exerting an escalating toll on nature and people. Simultaneously, there is now widespread acceptance of the need for deep, rapid, and sustained action, including from within the kidney care community.

Green kidney care committees and initiatives now exist in multiple world regions, including the United Kingdom, Europe, and Canada. UK efforts are particularly notable and provide a model for us all to follow (8). We believe the establishment of similar committees in other world regions, including in the United States, is critical for driving change. These might begin by looking at strategies and guides developed in other world regions and adapting them to suit local circumstances.

More recently, the International Society of Nephrology established GREEN-K (Global Environmental Evolution in Nephrology and Kidney Care) (9), an initiative designed to be "inclusive and global, focusing on collaborative action to develop a coordinated plan to achieve low carbon kidney services across our spectrum of care" (10). Regional societies worldwide have also been invited to participate, providing a ready opportunity for them to learn from and work with others.

Is this enough? Not nearly, given what is at stake. Yet it is progress, and from its humble beginnings in Australia, it is fair to say that an increasingly global green kidney care movement is now underway.

In Australia, the ESC's plans for the coming year include:

- broad kidney community engagement through establishment of a green champions network;
- increased industry engagement, given that the supply chain is where the bulk of kidney care carbon emissions reside; and
- concerted international collaboration because we are stronger together, and so we may learn from each other.

We aim to dig deep and give it our all. Because in the words of Agar, we can, and simply must, do better. In this, we sincerely hope others will join us. ■

Anoushka Krishnan, FRACP, is with the Department of Nephrology, Royal Perth Hospital, Western Australia. Katherine Barraclough, MBBS (Hons), PhD, is with the Department of Nephrology at The Royal Melbourne Hospital and the School of Medicine at The University of Melbourne, Parkville, Victoria, Australia.

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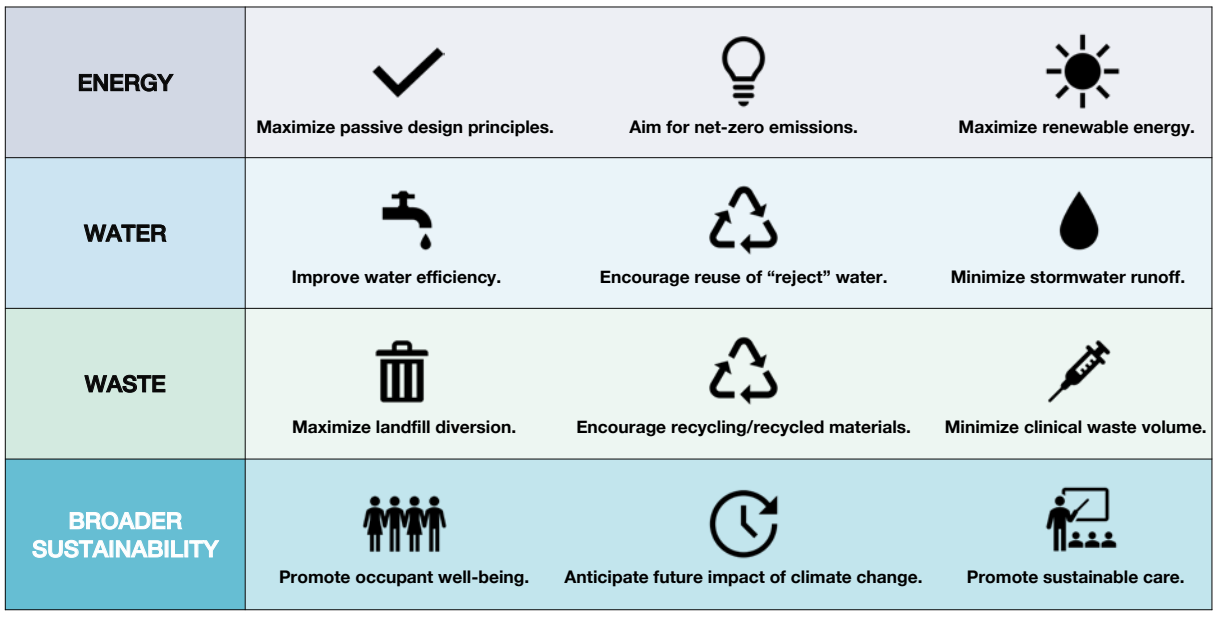
Table 1. Environmental Sustainability Committee initiatives

Educational symposiums held annually at meetings of the ANZSN and the Renal Society of Australasia (the region's peak renal nursing body)
Regular online teaching seminars to nephrology trainees and fellows
Development of an Environmental Research Prize, awarded annually
Development of a Sustainable Event Guide to facilitate eco-conscious kidney care community meetings and conferences (4)
Development of an ANZSN position statement on environmentally sustainability kidney care, which includes a commitment from the ANZSN to achieve net-zero emissions from its activities by 2030 (5)
Support provided to the ANZSN to divest from fossil fuels
Development of a dedicated web portal on "Green Nephrology" on the ANZSN website to house educational material, guidelines, and the ESC's position statement

Figure 1. Examples of objectives for opportunity areas identified in dialysis units



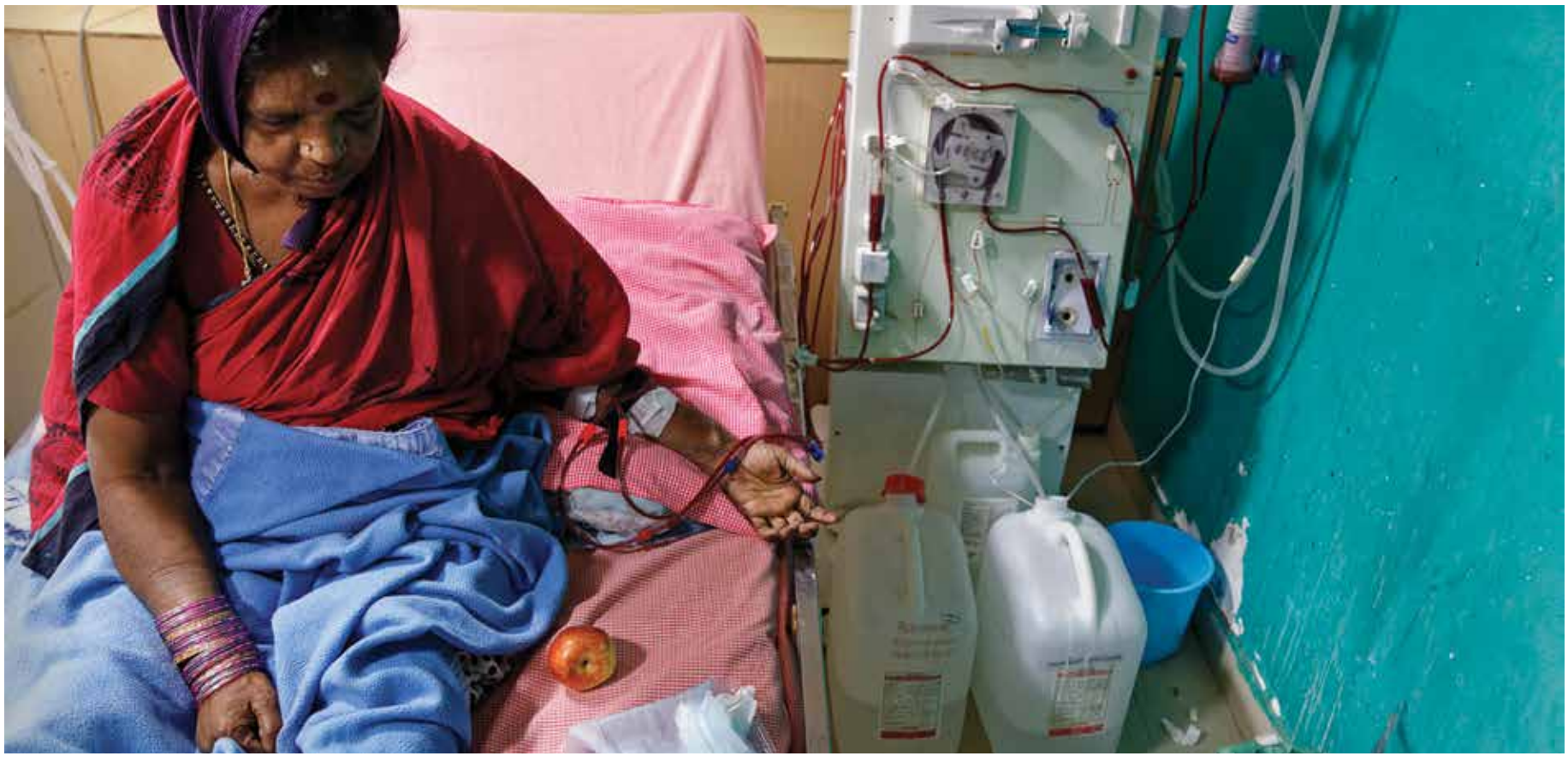


Photo by Ed Kashi. A woman enduring CKD receives dialysis at the Rajiv Gandhi Medical Institute of Sciences in Srikakulam, India, on January 30, 2016.

Hemodialysis in Times of War

By Sahar H. Koubar

Author's Note: This article is dedicated to all patients on hemodialysis who have been disconnected from their lifelines during agonizing periods of war.

The pairing of "human" and "war" is a distressing combination yet still a confirmed reality of the 21st century. Ironically, many major medical advances have historically occurred during times of war. For example, the rotating drum dialyzer was deployed during the Korean War in 1952. This breakthrough invention, developed by Dr. Willem Kolff, who is considered to be one of the founding fathers of artificial organs, reduced mortality from crush injuries from 90% to 53% (1).

The population undergoing hemodialysis requires a sophisticated infrastructure to survive. During times of war, health priorities shift toward the wounded and injured, leaving such a population particularly vulnerable and adversely affected. Furthermore, contemporary wars predominantly occur in transitional countries that are already burdened by poor infrastructure and limited resources. This creates a greater need for international rescue and non-governmental organizations to provide the much-needed assistance and support to those patients. (2).

Medical facilities also bear the brunt of armed conflicts. Medical personnel are killed, health care facilities become targets of attacks, and there is a massive exodus of health workers (3, 4). In non-government-besieged northwest Syria, it is estimated that 1 nephrologist serves a population of 1 million, and only 6 out of 20 dialysis units have a supervising nephrologist (5). This scarcity of health care personnel has given rise to the concept of the "super technician." In this role, the dialysis technician takes on the responsibilities of a nephrologist, dialysis nurse, dietitian, water-treatment specialist, machine maintenance personnel, and social worker.

Medical care can also be criminalized in opposition areas, supplies besieged, and international laws violated (3, 4). Wars can also lead to the destruction of infrastructure, resulting in the disconnection of patients on hemodialysis from their life-sustaining treatments. It is not uncommon for these patients to go without dialysis for 1 week or, tragically, succumb to their disease due to lack of treatment. Furthermore, those experiencing acute kidney injury, due to rhabdomyolysis resulting from crush injuries, may also have dialysis needs that go unmet.

Even in cases in which dialysis is being performed, the scarcity of resources results in poor-quality dialysis and unfavorable outcomes. For example, in Syria, the mortality rate is 2.5 times higher for patients receiving hemodialysis within the besieged areas compared with the non-affected areas (6). In the Iraq-Kuwait war, the mortality rate of patients who underwent hemodialysis and remained in the country was almost four times higher than those who fled Kuwait (7). Among Syrian refugees in Jordan, approximately 45% of individuals with a hemoglobin level below 8 g/dL have no access to erythropoietin-stimulating agents, and 14% were positive for hepatitis C virus (8).

Unexpected opportunities

The scarcity of available resources has led to some unexpected innovations. In one example, a rudimentary continuous renal replacement therapy (CRRT) machine, made of an extracted pump from a conventional dialysis machine and powered with a car battery (in the absence of electricity), using homemade dialysate, saved the life of three patients (9). Another CRRT machine, using ultrafiltration with intravenous saline as replacement fluid, set up in a school basement, stabilized the lives of 12 patients on chronic hemodialysis. Some of the measures implemented for patients on hemodialysis during armed conflicts are summarized in Table 1. Unfortunately, scarcity of resources often persist for patients on hemodialysis who are forcefully displaced into other, safer countries, as most neighboring countries also suffer from a fragile and crippled health system (10).

Perhaps the collateral beauty of physician exodus is their unwavering dedication and commitment to their fellow citizens. Expat physicians facilitated and advanced much of the work needed by volunteering their service and efforts to guide on-the-ground medical personnel. They developed educational curriculum in areas with protracted conflicts, advocated for these vulnerable populations at international societies, and helped secure donations from supply companies (11). Their steadfast work is only second to the heroic efforts by the local doctors on the ground.

Overcoming the chaos of war highlights the importance of preparedness, organization, collaboration, and solidarity. The nature of war can politicize humanitarian aid; however, humanitarian efforts should be unhindered, as any disruption in providing care equates to a disruption in life itself. There should be zero tolerance to violate the Geneva Conventions and International Humanitarian Law Rule 25 (12). Thus, I call on international societies to take a more significant and proactive role globally in such cases without any limitations. It is only through concerted and unwavering international collaboration that we can mitigate the distressful impact of conflicts on the vulnerable population undergoing hemodialysis and ensure the provision of essential health care services, regardless of geographical boundaries or political constraints. ■

Sahar H. Koubar, MBBS, is an assistant professor of medicine in the Division of Kidney Diseases and Hypertension, University of Minnesota, Minneapolis.

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Table 1. Measures used to mitigate lack of dialysis in armed conflict zones

Measures	Implementation/Rationale
Dialysis rationing	▸ Reducing frequency of dialysis, especially among patients with residual kidney function ▸ Reducing duration of sessions ▸ Reducing dialysate flow
Extreme dietary restrictions	▸ Low potassium diet ▸ Low animal protein
Manual reuse of dialyzers	▸ Using the dialyzer multiple times for a single patient ▸ Currently practiced in several developing regions of the world to save on cost
Emergency kits for patients	▸ Evacuation plan ▸ Medical history and dialysis prescription ▸ Medications list ▸ Potassium binders ▸ Diuretics
Probiotics/gum arabic (acacia gum)	▸ Some studies showed a reduction in serum urea (13).
Conservative kidney management (choice restricted)	▸ Can be considered in protracted conflicts in which dialysis availability is limited

Nephrology Care in Challenging Circumstances: A Patient's Perspective

By Rasha Raslan

In this special section of *Kidney News*, you will read about the intersection of nephrology and a spectrum of disasters, ranging from hurricanes and tornadoes to modern-day warfare. We hope you gain insight into the mounting challenges that the nephrology workforce faces all around the world. We will share countless statistics and ongoing efforts that are being made to address these hurdles. But amidst all of these challenges, we must not lose sight of our primary focus: our patients. True progress can only be made with them at the forefront, and it is imperative that we remain their unwavering advocates and provide them with platforms to voice their concerns and aspirations.

Below is an excerpt of an interview I conducted with one of my clinic patients, a young Syrian refugee with lupus nephritis who recently relocated to the United States from Türkiye (formerly Turkey).

This interview was originally conducted in Arabic and has been translated to English. Permission to publish this interview was obtained.

Q: How old were you when you were diagnosed with lupus?

A: I was 9 years old. My younger sister was diagnosed at an even younger age, and my older brother was diagnosed after I [was]. Unfortunately, he passed away from complications of lupus as a teenager.

Q: Describe the start of the war in Syria and how that impacted your life.

A: The war broke out in 2011, when I was 12 years old. In the first few months, it did not affect my family, as the war was mostly concentrated around the city of Homs. Eventually, the war reached my village. We then had to leave home and move to the city of Aleppo (the biggest city near us), where we were homeless and sheltered in abandoned schools. We had no electricity or clean water. We then eventually moved back to our village around 6 months later, although it was not very safe there.

Q: Describe your access to medical care before and after the war.

A: I used to see a nephrologist, but he left soon after the war broke out; I think he moved to the United States. Prior to the war, I had no issues [in] obtaining my medications. These included prednisone, methotrexate, and hydroxychloroquine. After the war broke out, it became much harder. The cost became much higher as well. Since we lived in the rebel-controlled areas, medications were scarce. My father used to make routine trips to Aleppo, which was under government control at the time, to buy them. It was during one of those trips that he was arrested and later killed. When I ran out of medications, my symptoms, such as rash and hematuria, flared again.

Q: You eventually left Syria and moved to Türkiye. How was your medical care there?

A: My family and I moved to Kilis, Türkiye, as refugees in 2013. I was not able to see a nephrologist there due to long wait times, but I was able to see a dermatologist who prescribed my lupus medications. By then, [the physician] started me on monthly rituximab infusions, which I kept receiving until moving to the United States. Medications were expensive there, but the local pharmacist understood our situation and allowed us to pay in installments. We did not receive much aid from NGOs [non-governmental organizations] but could rely on the local Red Crescent Society [International Federation of Red Cross and Red Crescent Societies] for occasional financial help and assistance in obtaining identification, which would allow us to work.

Q: Is there anything else you would like our readers to know about your experience?

A: Life was very difficult during our time in Türkiye, although we were safer there than in Syria. It's been an adjustment living in the United States, but we are slowly getting used to it. We have no problem obtaining our medications here. But in my opinion, the best thing about living in North Carolina has been the weather and our ability to have access to air conditioning during the summer and heating during the winter.

Updates on Public Policy for Nephrology 2024: From the Hill and Medicare to Nephrology Practice

By Keith A. Bellovich and Robert E. Blaser

Much like any other year, the first quarter of 2024 has experienced a kaleidoscope of public policy issues impacting nephrology (Table 1). Beginning with legislative priorities, in early March, Congress passed fiscal year (FY) 2024 appropriations legislation that included a partial payment fix in the Medicare conversion factor (CF), providing an additional 1.68% offset in the CF for the balance of 2024. (The CF was originally scheduled for a 3.37% cut.) Also included was an extension of the bonus for participating in Medicare alternative payment models (APMs) for 2024, albeit at a reduced rate of 1.88%. (For 2023, it was 3.5%.) These issues were legislative priorities for the Renal Physicians Association (RPA) for 2024, and these changes represent victories for nephrology and organized medicine broadly. However, the work is not complete, as medicine has still sustained an approximate 2% cut relative to 2023.

Congress is also deliberating on numerous bills pertaining to organ donation, including the Living Donor Protection Act of 2023 (HR 2923/S 1384) (1, 2), which has great co-sponsor numbers but has been bogged down procedurally. Other significant kidney-specific legislative initiatives this year include an effort to reverse the Supreme Court decision from 2022 and restore Medicare Secondary Payer (MSP) protections for patients with kidney failure (3) as well as the advancement of legislation to delay inclusion of oral-only drugs in the End Stage Renal Disease (ESRD) Prospective Payment System (PPS) bundle (4). Note that this year's high level of Congressional dysfunction hampers clear expectations for all legislation.

On the regulatory side, a new complexity add-on code, G2211, has been implemented in the Medicare Physician Fee Schedule. This code can be added to most outpatient evaluation and management (E&M) services for complex patients with whom the nephrologist has an ongoing, longitudinal relationship and thus should be compliantly billable with most E&M services provided to patients with chronic kidney disease covered by Medicare. The RPA has issued guidance for the use of this code in nephrology practice (5). Another recent development with a potential impact on nephrology is the 2025 Medicare Advantage Advance Notice, which has rate-setting implications for Kidney Care Choices (KCC) voluntary kidney models. There was negative news for kidney care in last year's Advance Notice (for 2024), in which the rate setting resulted in an approximate 8% decrease overall in the kidney model payment rates. A repeat of this level of reduction is not expected for the next performance year but is projected to be approximately 3%–4%, which would result in a cumulative 2-year reduction of 11%–12%. Finally, the RPA will soon be leading an effort to revise a family of dialysis access codes as part of the Current Procedural Terminology (CPT) Editorial Panel process, after which the American Medical Association's Relative Value Scale Update Committee (RUC) would value the codes. The RPA has represented the nephrology specialty with both the CPT and RUC for the last 30 years.

As has been the case throughout its 50-year history, the RPA will continue to monitor these socioeconomic concerns on behalf of all nephrologists and seek to collaborate with kidney community leaders, such as ASN and others, as it strives for optimal kidney care for all. ■

Keith A. Bellovich, DO, FASN, is president of the Renal Physicians Association, Rockville, MD, and he serves as chief medical officer at Ascension St. John Hospital, Detroit, MI. Robert E. Blaser is director of public policy at the Renal Physicians Association.

The authors report no conflicts of interest.

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Table 1. Public policy updates impacting nephrology practice

Update	Explanation
FY 2024 government funding delay	Congress passed the first half of FY 2024 appropriations in early March, and it included partial payment relief from the 3.37% payment cut affecting all Medicare Part B providers.
Medicare APMs bonus extension	The FY 2024 appropriations bill also included an extension of the bonus for participating in Medicare APMs.
Organ donation legislation	Deliberation on bills like the Living Donor Protection Act of 2023 is facing procedural delays.
MSP protections for patients with kidney failure	Efforts are underway to reverse a Supreme Court decision and restore MSP protections for patients with kidney failure.
Delayed inclusion of oral-only drugs in the ESRD PPS bundle	Legislation advancement is to delay inclusion of oral-only drugs in the ESRD PPS bundle.
Implementation of the G2211 code	A new complexity add-on code (G2211) for outpatient E&M services for complex patients, aimed at nephrology practice, has been implemented.
2025 Medicare Advantage Advance Notice	There are rate-setting implications for KCC models, with a potentially negative impact on nephrology payment rates.
Dialysis acces codes revision	The RPA is leading an effort to revise dialysis access codes, with valuation by the AMA's RUC.

Urine Cotinine Improves Assessment of CKD Risk

Compared with patient-reported smoking history, a urine cotinine measurement may provide a more reliable indicator of the risk for developing chronic kidney disease (CKD), according to a study in *Nephrology Dialysis Transplantation*.

The analysis included data on 4333 individuals from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) trial, a population cohort study examining the progression of urinary albumin excretion (UAE) and its impact on kidney diseases and cardiometabolic conditions. The participants (mean age, 52 years) had no history of CKD at baseline. Self-reported smoking status was 31% in participants who never smoked; 41.5%, former smokers; 10%, light and current smokers; and 17%, heavy and current smokers. Smoking status was also assessed by measurement of urine cotinine.

Self-reported smoking status was strongly correlated with urine cotinine level. However, the two measures showed only weak agreement in classification of smoking status. Of 3140 self-reported never or former smokers, 1.8% were classified as active smokers on cotinine measurement, with an overall misclassification rate of 4.6%.

At 7 years' follow-up, CKD developed in 593 participants. After adjustment for established risk factors, the likelihood of CKD was elevated for light and heavy current smokers: hazard ratio (HR), 1.48 for each compared with never smokers. On further adjustment for UAE, the HRs associated with self-reported smoking were no longer significant. In contrast, HRs associated with cotinine-assessed light and heavy smoking were 1.23 and 1.32, respectively, with "minimal" effect of adjustment for UAE.

Previous reports of the association between smoking and CKD risk have been based mainly on patient–patient-reported smoking status. The new study examines CKD risks associated with urine cotinine, an objective measure of nicotine exposure.

The results suggest that urine cotinine measurement provides a more reliable indicator of CKD risk compared with self-reported smoking. Associations between patient-reported current smoking and CKD appear to be dependent on UAE.

The findings indicate a "considerable rate of misclassification" of smoking status based on patient report, whether associated with underreporting or lack of awareness of exposure to tobacco smoke. Citing the effects of adjustment for UAE, smoking-related kidney damage may be "partly mediated through its effects on or biological mechanisms related to increasing albumin excretion," the researchers write [Kunutsor SK, et al. Urine cotinine versus self-reported smoking and the risk of chronic kidney disease. *Nephrol Dial Transpl*, published online February 24, 2024. doi: 10.1093/ndt/gfae054]. ■

Study Looks at Human Factors Affecting Infection Prevention in Dialysis Care

A wide range of organizational and sociotechnical factors affects infection prevention practices at outpatient hemodialysis centers, reports a study in the *American Journal of Kidney Diseases*.

The researchers used structured macroergonomic observations at a convenience sample of six US dialysis facilities. Observations were made by a multidisciplinary team following the Systems Engineering Initiative for Patient Safety model 1.0. Observations addressed system components, including human factors, work system factors, and extrinsic factors. The study focused on four infection processes: environmental disinfection, hand hygiene, injection safety, and vascular access care. The researchers underwent a total of 157.5 hours of observations over approximately 2.5 days per facility, from early morning to evening shifts.

Qualitative and quantitative data analyses identified a range of work system barriers to and facilitators of infection prevention. Human factors included interruptions, which occurred in 19% of encounters. Alarms occurred in just over one-half of encounters and were described by staff as "prevalent and disruptive." Other issues included task stacking or simultaneously performing multiple tasks and inconsistent understanding of the terms "clean" and "dirty."

Analysis of factors in the physical environment showed wide variation in work practices and design. Several physical design factors were identified as barriers or fa-

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Human Factors Affecting Infection Prevention

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cilitators of infection prevention, along with workflow scheduling and variation in policies and procedures. Staff at several facilities cited factors associated with a supportive culture, including the presence and engagement of facility leadership during work hours. Staff also identified extrinsic patient factors leading to disruptions in the flow of care, including hygiene, transportation, vascular assess, and hemostasis.

This small, exploratory study identifies macroergonomic factors potentially affecting infection prevention practices during dialysis care. "[T]he complex constellation of human skills required for the optimal completion of infection prevention tasks within dialysis may be significantly affected (both positively and negatively) by the design of our systems of care," the researchers write. Further studies are needed to incorporate the observations into strategies to reduce infection risks [Parker SH, et al. Human factors contributing to infection prevention in outpatient hemodialysis centers: A mixed methods study. *Am J Kidney Dis*, published online March 4, 2024. doi: 10.1053/j.ajkd.2023.12.024].

Cefepime-Taniborbactam Is Superior to Meropenem for Complicated UTI

The β-lactam and β-lactamase inhibitor combination cefepime-taniborbactam offers a higher treatment success rate in the treatment of complicated urinary tract infection (UTI) compared with meropenem, reports a clinical trial in *The New England Journal of Medicine*.

The phase 3 "Safety and Efficacy Study of Cefepime/VNRX-5133 in Patients with Complicated Urinary Tract Infections" (CERTAIN-1) trial enrolled 661 patients with complicated UTI. Patients were randomly assigned in a 2:1 ratio to treatment with cefepime-taniborbactam (2.5 g intravenously [IV]) or meropenem (1 g IV), every 8 hours for 7 days. In patients with bacteremia, treatment could be extended to 14 days.

Microbiologic and clinical success rates were assessed at 19 to 23 days in a microbiologic intention-to-treat population of 436 patients with positive urine culture for a qualifying gram-negative pathogen, most

commonly Enterobacterales species. In this group, the mean age was approximately 56 years, and 53% of patients were women. The diagnosis was complicated UTI in 57.8% of patients and acute pyelonephritis in 42.2%.

Composite microbiologic and clinical success rates were 70.6% with cefepime-taniborbactam versus 58.0% with meropenem. A prespecified superiority analysis showed a significant 12.6 percentage-point difference between groups. At late follow-up (28 to 35 days), composite and clinical success rates remained higher with cefepime-taniborbactam. Among patients with bacteremia, composite success rates at test of cure were 81.6% with cefepime-taniborbactam versus 68.4% with meropenem.

Headache, gastrointestinal events, and hypertension were the most common adverse events with cefepime-taniborbactam. Serious adverse events occurred in approximately 2% of both groups.

Emerging resistance to β-lactam antibiotics poses a challenge to treatment of complicated UTI, as for other serious infections. The cefepime-taniborbactam combination has shown promise for treatment of serious gram-negative infections.

The CERTAIN-1 findings suggest that cefepime-taniborbactam is superior to meropenem for treatment of complicated UTI including acute pyelonephritis. Safety profiles are similar between the two treatments. Cefepime-taniborbactam is "a potential treatment option for patients with complicated UTI and acute pyelonephritis caused by Enterobacterales species and *Pseudomonas aeruginosa*, including antimicrobial-resistant strains," the investigators conclude [Wagenlehner FM, et al.; CERTAIN-1 Study Team. Cefepime-taniborbactam in complicated urinary tract infection. *N Engl J Med* 2024; 390:611–622. doi: 10.1056/NEJMoa2304748].

Racial Differences in ADPKD Mortality for Older Adults

A large analysis of patients with autosomal-dominant polycystic kidney disease (ADPKD) finds differences in mortality risk for Black versus White patients aged 65 years or older, reports a study in *BMC Nephrology*.

The researchers analyzed US Renal Data System data for patients with ADPKD from 2014 through 2016. The analysis included a cohort of 1936 patients with non-end stage renal disease (ESRD) chronic kidney disease (CKD) and a cohort of 37,461 patients with ESRD. The mean age was 71.4 years in the cohort with non-ESRD CKD and age 59.2 years in the cohort with ESRD. Race was classified as White in 79.6% and 73.8%, respectively.

After adjustment for age, mortality was 18.4 per 1000 patient-years in patients with ADPKD with non-ESRD CKD and 37.4 per 1000 patient-years for those with ADPKD and ESRD. On Cox regression modeling in the cohort with non-ESRD CKD, risk of death was higher for patients with more advanced disease: hazard ratio (HR), 1.59 for stage 4 and 2.71 for stage 5 CKD compared with stage 3. In the cohort with ESRD, risk of death was more than twice as high among patients undergoing dialysis: HR, 2.36.

Among patients with non-ESRD CKD aged 65 years or older, age-adjusted mortality was highest for Black patients: 82.7 deaths per 1000 patient-years. In contrast, among older adults in the cohort with ESRD, mortality was highest for White patients: 136.1 deaths per 1000 patient-years.

The study revealed findings regarding mortality specific to patients with ADPKD, the leading inherited cause of ESRD. For patients aged 65 or older with ADPKD and ESRD, the data show a "numerically lower" mortality compared with previous reports, possibly reflecting "more effective treatment and disease management."

In the same age group, the findings suggest racial differences in both cohorts of non-ESRD CKD and ESRD of patients with ADPKD, with a possible survivorship effect among Black patients. "Black patients may be less likely than other racial groups to survive long enough to reach ESRD, perhaps because of inequities in care," the researchers write. "ADPKD also may be underdiagnosed in Black patients with a hypertension comorbidity" [Mladsi D, et al. Mortality risk in patients with autosomal dominant polycystic kidney disease. *BMC Nephrol* 2024; 25:56. doi: 10.1186/s12882-024-03484-3].

Serving the Underserved

The following article is the fourth of a five-issue series focused on caring for patients in underserved populations. Inspired by several sessions at Kidney Week 2023, this series features unique patient and physician perspectives, explains legal protections and limitations, and seeks to identify opportunities to improve kidney care for these communities.

Improving Care Access and Research Are Key to Boosting LGBTQ+ Kidney Care

By Bridget M. Kuehn

After being turned away by a physician because she was a transgender woman, a 56-year-old Black patient had not seen a physician in a decade but was seeking chronic kidney disease (CKD) care. The patient had elevated blood pressure, an estimated glomerular filtration rate (eGFR) of 20, and growing fatigue, according to a case presented by Dinushika Mohottige, MD, MPH, assistant professor at the Institute for Health Equity Research at the Icahn School of Medicine at Mount Sinai and the Barbara T. Murphy Division of Nephrology, New York, NY, at Kidney Week 2023.

"We are left with many questions in this case," Mohottige said during the "We Are Never over the Rainbow: Nephrology Care for the LGBTQ+ Community" session at Kidney Week. "What is the impact of prior and current discrimination and structural inequities on the experience of seeking kidney care?"

The case reflects a common hurdle to care for transgender patients, 29% of whom report having been refused care by a clinician (1). These concerns often extend to other members of the lesbian, gay, bisexual, transgender, queer or questioning, plus (LGBTQ+) community as well, with 8% reporting they had been denied health care due to their actual or perceived gender identity. Presenter Yuvaram Reddy, MBBS, MPH, FASN, assistant professor and Director of Diversity, Equity, and Inclusion for the Renal-Electrolyte and Hypertension Division at the Perelman School of Medicine, University of Pennsylvania, Philadelphia, and other speakers at the symposium highlighted the importance of creating welcoming clinical environments, understanding the clinical implications of gender-affirming care, and engaging in robust, shared decision-making as ways to improve kidney care for LGBTQ+ patients. They also emphasized the importance of engaging this community in research to help close knowledge gaps.

"Your LGBTQ patients have faced discrimination," explained Reddy, who identified himself as the second "out" gay person in his department. Addressing session attendees and speaking as part of the LGBTQ+ community, Reddy said, "We are still facing discrimination, and [members of the LGBTQ+ community] may fear it. Don't make their fears come true. Help them feel like you are allies rather than accomplices in the system."

Intersectional challenges

LGBTQ+ patients face many of the same barriers to health care as other marginalized groups, Reddy stated. Social determinants of health such as poverty, inadequate housing, economic and food insecurities, discrimination, and lack of insurance may all create barriers to access, he noted. For example, he said that one in three transgender adults has a household income below $25,000, and the same proportion has experienced homelessness in their lifetime (2). "Remember that being a sexual or gender minority is not the risk factor," Mohottige said. "It is actually a domain through which other key social determinants of health are allocated."

Social determinants of health may drive higher rates of risk factors for kidney diseases, such as smoking (3) and obesity, among LGBTQ+ individuals (4). Stress caused by marginalization also increases cortisol and causes other physiologic changes that can affect overall health or kidney health, Reddy noted. "Increased smoking and obesity run the cascade of exacerbating CKD," he said. "Because social supports may be lacking, home dialysis and transplant may be more challenging."

For individuals who have multiple marginalized identities, these challenges are often compounded, Mohottige explained. For example, she noted that gender and sexual minority individuals who are also from racially minoritized groups face much higher rates of violence. Additionally, gender and sexual minority individuals who have disabilities are more likely to face employment discrimination or health care access challenges. "Discrete categories like race and gender don't account for the multidimensional experiences of people experiencing simultaneous forms of marginalization," she said. She noted that it is important to acknowledge individuals' experiences and recognize how policies and social structures may affect them.

Despite recent progress in the United States, such as securing the right to same-sex marriage in 2015, equality for LGBTQ+ people have come under attack with discriminatory laws passed in 25 states that are home to 40% of the LGBTQ+ population, Reddy said (5). The same number of states has laws specifically targeting the rights of transgender individuals. "With every step forward that you take with communities, there are sometimes steps taken back," he said.

Reddy stated that such laws make people feel unsafe. For example, a 2022 survey by The Trevor Project, a nonprofit organization, found that nearly half of LGBTQ youth had considered self-harm in the past year (6). The survey also found youth with support from their family had half the rate of suicidal ideation as individuals without such support, but fewer than one in three transgender or nonbinary youth reported they had such support. Supportive schools and communities were also protective. "Having affirming folks in your life helps substantially," Reddy said.

Cultural humility

Too often, when LGBTQ+ individuals seek health care, they may find their clinicians are unprepared to provide safe and affirming care, which affects their ability to trust the medical system, Reddy noted. Two-thirds of transgender adults report worrying that their health evaluations will be affected by their sexuality or gender identity (2). Half of transgender adults report negative or discriminatory experiences with the health care system. "There is a large sense of mistrust, and that mistrust is not misplaced," Reddy said. "We should be more supportive and inclusive."

Reddy noted failure to inquire about sexual orientation or gender identity may make patients feel like they cannot share information about their lives or partners. Instead, they may report living alone and not having someone who could help with home dialysis or be a living donor. Creating a welcoming environment can help patients feel psychologically safe. He suggested examples such as routinely collecting sexual orientation and gender identity

information in a non-judgmental way; learning and respecting pronouns and proper language when referring to patients and/or their partners; providing all-gender, single-user bathrooms; and displaying Pride (a celebration of LGBTQ+) flags or pins. He acknowledged that physicians may not always feel prepared for conversations about gender or sexuality, but training and cultural humility can help.

"Cultural humility is really important and being okay with not having all the answers, being okay with making mistakes and learning through the process," Reddy explained. "With the right training, we could create a welcoming environment to invite the opportunity to talk about it, and if people don't want to, that's okay. But many people are willing to talk about it and don't feel like we are creating space for them."

Because sexual orientation and gender identity data are not routinely collected in many clinical and research settings, there are significant gaps in data on this population. Reddy noted that fewer than 1% of National Institutes of Health-funded projects focus on LGBTQ+ individuals. Mohottige recommended engaging LGBTQ+ individuals at every point in the research process and designing better health care systems. "We need to center the expertise of marginalized voices as a starting point because that is where so much knowledge is inherently embodied," she said.

Reddy also emphasized the importance of collective and individual advocacy. He noted ASN's decision to hold Kidney Week in Florida in 2022 and "bring ASN's [supportive] values" to the state, which had recently enacted a bill prohibiting the discussion of sexual orientation or gender identity in schools. During the meeting, ASN and its members donated approximately $35,000 to the onePulse Foundation, a local LGBTQ+ charity, he said.

Reddy noted that until 1973, the *Diagnostic and Statistical Manual of Mental Disorders* listed homosexuality as a mental disorder. However, advocacy by LGBTQ+ individuals and psychiatrists, such as John Fryer, MD, who had been removed from his residency at the University of Pennsylvania for being gay and was fired by another hospital for his advocacy, helped change that (7). "Individual advocacy has a strong place here, and there's good trouble to get into," Reddy explained. "Sometimes it is with consequences, but it can leave a long-term impact for generations."

Clinical considerations

Sex is frequently a variable used in clinical decision-making tools. However, clinicians may face questions about using these tools in the care of gender-diverse or gender-nonbinary individuals. Reddy explained that individuals who identify with their sex assigned at birth are *cisgender*, whereas individuals who identify as a different gender than their sex assigned at birth are *transgender*. Some individuals also identify as *nonbinary* (outside the gender binary categories of man and woman) or *gender fluid* (shifting between genders), he noted.

"There is a spectrum of gender identities," said David Collister, MD, PhD, FRCPC, assistant professor, Department of Medicine, at the University of Alberta, Canada. Approximately 0.5% of the US population, or about 1 million people, identify as transgender (8). Based on data from the Centers for Disease Control and Prevention and the US Renal Data System, Samira Farouk, MD, MS, FASN, a transplant nephrologist and professor of medicine and medical education at the Icahn School of Medicine at Mount Sinai, estimated that these data translate into approximately 176,000 transgender individuals with CKD and 4000 with end stage kidney disease.

Some transgender individuals receive gender-affirming hormone therapy or surgery to help their physical appearance match their gender identity. Gender-affirming care improves quality of life, mental health, and sexual function, Collister noted. The Endocrine Society's 2017 guideline (9) for gender-affirming hormone therapy highlights myriad treatment choices, which may include oral, sublingual, transdermal, or injectable options, Collister noted. However, there is no mention of a need for kidney-function monitoring or kidney risks in either the Endocrine Society guidelines or the World Professional Association for Transgender Health's standards of care (10), Collister said.

There are limited data on the kidney-related considerations of gender-affirming care, but Collister and other researchers hope to have more information in the coming years. In the meantime, he highlighted a few potential kidney-related considerations to gender-affirming hormone therapies (11). Typically, transgender women receive an estrogen and an anti-androgen, such as spironolactone, he said. "With spironolactone, you have to be careful with side effects of hyperkalemia, so it is generally not advised if the patient's eGFR is less than 30," he warned. European clinicians typically use cyproterone acetate, which does not have to be renally dosed, he said.

Testosterone may be given to transgender men in several formulations, including patches and gels, to reach the normal reference ranges of testosterone of cisgender men, Collister said. Farouk noted that taking testosterone may increase a patient's creatinine to a level close to the threshold for acute kidney injury, whereas taking estrogen may lower creatinine levels and has been shown to have kidney-protective effects (12).

Collister recommended using both male and female inputs to calculate transgender patients' eGFRs and engage in shared decision-making with patients, acknowledging the potential uncertainty due to limited data. Additionally, he noted that a sex-free and gender-free version of the CKD-Epidemiology Collaboration (CKD-EPI) 2021 was also presented at Kidney Week 2023 (13), and the European Kidney Function Consortium also has a new gender-free and race-free formula (14). "The bottom line is if you've got to know a patient's GFR precisely for clinical decision making, do a measured GFR, and measure proteinuria," he said.

Farouk agreed that it was essential to look at eGFR estimates with both male and female coefficients for transgender individuals and assess which estimate is likely to be most accurate based on the patient's circumstances. She said that this is particularly important when a patient's eGFR on one of the calculations crosses a clinically important threshold. "We put a lot of weight on this number, even though we recognize how much uncertainty there is," she said.

For example, she highlighted the case of a 55-year-old transgender woman who presented to a transplant center for evaluation with well-controlled diabetes and hypertension. In addition to metformin and nifedipine, she was taking estradiol and spironolactone. Using the CKD-EPI equation with creatinine alone with a male coefficient, the patient had an eGFR of 26, but with a female coefficient, she had an eGFR of 19. However, with the CKD-EPI with cystatin C alone, the patient's eGFR was below 20 with either gender coefficient.

Farouk noted that a patient taking exogenous estrogen may potentially be at increased risk of pulmonary embolism or deep vein thrombosis (DVT) when immobilized after surgery (15). "Transdermal preparations may be better [than oral ones] in this context [transplant surgery], not only for those with CKD but also perhaps for those preparing to undergo any surgery," she said.

Collister cited research in cisgender women that showed that taking estrogen-containing oral contraceptives activates the renin-angiotensin-aldosterone (RAS) system because it must be first metabolized by the liver (16). Transdermal application of estrogen-containing contraceptives, however, circumvents the liver and is not associated with as much RAS activation, which may be better for patients with CKD.

"There [are] no data to support routine perioperative discontinuation of gender-affirming hormone therapy, and this decision needs to be the result of shared decision-making, and the risks and benefits need to be discussed, including the impact of discontinuation on [a] patient's mental health," Farouk added. "Perhaps for this particular patient, stopping hormone therapy [would have been] more harmful than this theoretical risk of developing DVT."

Farouk also recommended shared decision-making with transplant patients who may be considering the risks of future gender-affirming surgeries and their potential impact on the allograft or discussing the optimal timing of surgeries. She said clinicians use the same process for transplant patients considering any future surgeries. Farouk emphasized the importance of clinicians learning about gender-affirming therapies and connecting with experts on transgender care.

"It is our role to become comfortable and familiar with [gender-affirming therapy and its effects] so we know what the right questions are to ask and know where to go when we need help," Farouk said. ■

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CMS Seeks Input on Medicare Advantage Data, Implements Changes to Data Access and Use

By Lauren Ahearn

There are two major issues before the Centers for Medicare & Medicaid Services (CMS) involving Medicare Advantage (MA) data and research requests involving CMS data. Both issues are policy priorities for ASN. Updates for both follow.

CMS seeks public input on MA data collection and transparency

On January 30, 2024, CMS issued a request for information (RFI) seeking public input on data needed for Medicare Part C, known as the MA program (1). According to CMS, the goal of this RFI is to provide the agency with feedback on both the format and types of data that will allow CMS to have better insight into MA organizations and their operations (2).

This RFI follows a previous RFI released by CMS in August 2022 in which CMS sought feedback from the public on ways to strengthen the MA program and align it more closely with Medicare's vision and strategic pillars. CMS received more than 4000 responses to this RFI from a variety of stakeholders. A few key themes identified by CMS in these responses included the need for stronger beneficiary protections, payment issues, and programmatic data.

The follow-up RFI released this past January is notably broad; CMS states that it is seeking stakeholder input on "all aspects of data related to the MA program—both data not currently collected as well as data currently collected" (1). CMS's eventual goal is to align MA data with the data collected and available for Medicare Parts A and B. CMS believes stakeholder input gained from this RFI will help in the development of future rulemaking to address perceived shortcomings and to ensure transparency into MA organizations.

As MA enrollment continues to climb, policymakers are increasingly interested in aligning it with original Medicare. As of 2023, 30.8 million people are enrolled in an MA plan, accounting for 51% of the population eligible for Medicare and $454 billion (or 54%) of total federal Medicare spending (3). In 2016, the 21st Century Cures Act was passed, which granted patients with kidney failure the ability to enroll in MA plans starting in 2021. Since that enrollment period opened, it is estimated that 37.7% of beneficiaries with kidney failure are enrolled in an MA plan (4), and closer to 50% of all patients with kidney failure are enrolled in Medicare. The number of MA enrollees with kidney failure is expected to continue to rise, and ASN remains committed to ensuring that MA plans are required to adhere to the same regulatory standards and quality of care as is the traditional Medicare program. ASN has noted in previous letters to CMS regarding MA data that as more patients eligible for Medicare enroll in MA plans, it is crucial that the kidney failure-related data that are available for patients with Medicare Fee-for-Service as their primary coverage include MA enrollees, as this issue impacts the integrity of the US Renal Data System. Also, ASN advocated for stricter regulatory action related to overuse of prior authorizations in MA. ASN will continue to advocate for these changes in its response to the RFI, which is due May 29, 2024.

Major changes coming to CMS Research Identifiable File (RIF) access

On February 12, 2024, CMS announced significant changes to the method in which researchers gain access to data through its research data request and access policy (5). Previously, CMS offered researchers two options for accessing CMS RIF data: 1) Researchers could request that physical data extracts be shipped to their institution, or 2) researchers could access the data needed in the Chronic Conditions Warehouse Virtual Research Data Center (CCW VRDC), which CMS describes as a "secure CMS research environment."

Beginning in the summer of 2024, all researchers requesting RIFs must access data within CMS's CCW VRDC environment and comply with CMS CCW VRDC policies. CMS is discontinuing the delivery of physical data extracts that support external research projects—only federal and state agencies may request an exception to this new policy. CMS has cited "growing data security concerns and an increase in data breaches across the healthcare ecosystem" as its reason for this change.

In addition to this policy change announcement, CMS also released a corresponding RFI on the proposed changes. The RFI asks numerous questions among five domains:

1. CCW VRDV process/access
2. CCW VRDC tools
3. Data/project
4. Data access fees
5. Transition timing

CMS has stated that it will not be responding to individual comments on the RFI. Instead, it will be sending out additional guidance later this year and final guidance prior to requiring researchers to transition their ongoing research studies to the CCW VRDC.

ASN is working with other members in the kidney community to address the challenges that this proposal presents, including an exhaustive research fee list that begins with a $20,000 initial project fee and a $10,000 project renewal fee. Those fees would apply to every member of the research team who would work directly with the data.

The use of CMS data in research has had a significant impact on health care policy. In a letter from researchers across the country to CMS, voicing strong objection to the proposal, Zack Cooper, PhD, and Alexia Witthaus, BS, of Yale University, New Haven, CT, developed a list of high-impact scholarship that were derived from Medicare claims data including:

- Formed the intellectual basis for the Affordable Care Act
- Helped motivate the Medicare Hospital Readmissions Reduction Program
- Informed and helped assess Medicare payment policy, including Accountable Care Organizations and bundled payments
- Analyzed the efficiency of the MA program
- Identified the causes of mortality differences across regions
- Identified the causes of the opioid epidemic
- Described the causes and consequences of variation in Medicare spending across the United States and identified strategies to address them
- Documented racial disparities in the Medicare program
- Identified the effect of private equity firms on the survival of Medicare beneficiaries
- Illustrated how hospital competition and mergers impact mortality
- Proposed strategies to identify and root out Medicare fraud
- Documented how to measure providers' quality and insurance plan quality
- Described the presence of low-value care delivered to Medicare beneficiaries

ASN is committed to improving the policies outlined to date to protect valuable kidney research and other health care research conducted by using CMS data and will provide updates in *Kidney News*. ■

Lauren Ahearn is a quality and regulatory affairs associate at ASN.

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ASN Raises Profile of Transplant Network Modernization as Congressional Funding Talks Begin

By Zachary Kribs

On March 11, 2024, the White House released the fiscal year (FY) 2025 president's budget, kickstarting congressional action to fund the government for the FY that spans October 1, 2024–September 30, 2025. Still operating under a series of temporary funding agreements, named continuing resolutions, for FY 24, Congress will spend the rest of April developing its funding proposal for FY 25.

As Congress considers these proposals, ASN is leading efforts to secure a significant $67 million investment for the Organ Procurement and Transplantation Network (OPTN). In 2023, ASN and stakeholders in the kidney health community successfully advocated for passage of the Securing the US OPTN Act, legislation to increase transparency, accountability, and competition in the management of the nation's transplant system. These changes are now included as part of the Health Resources and Services Administration (HRSA) OPTN Modernization Initiative, a sweeping set of reforms to "better serve patients in need of transplants and their families" (1).

For these changes to be fully implemented, Congress must now increase the funding provided to the transplant network. According to the HRSA, funding will be used to launch the construction of a new information technology infrastructure to support the transplant system, support a new independent board of directors, and support the development of a transition plan to a modernized transplant system.

This month, advocates from ASN will travel to Washington, DC, to advocate with their members of Congress for investing in the transformation of the transplant system. The OPTN Modernization Initiative represents the first significant reform of the transplant system since its inception in 1984. ASN and stakeholders across the kidney and transplant communities are urging Congress to fully take advantage of the opportunity brought by these reforms to increase the number of transplants performed in the United States, generating better outcomes for patients.

In addition to requesting an increase in funding for modernizing the transplant system, ASN will continue to champion longstanding priorities such as increasing funding for kidney health research innovation and supporting the health workforce through graduate medical education funding.

On March 8, 2024, Congress passed partial Medicare physician payment relief as a component of a package to fund part of the government. Starting in calendar year 2024, physicians participating in Medicare had been experiencing a 3.37% cut to the conversion factor as well as facing the expiration of a 3.5% bonus for participation in an alternative payment model (APM). Responding to advocacy by ASN and stakeholders from across the field of medicine, Congress reduced the conversion factor cut by an additional 1.68% and extended the APM bonus for another year at 1.88%. ■

Zachary Kribs is the manager of congressional affairs at ASN.

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mTOR Inhibitors and Pulsed Steroid Regimen in Kidney Transplant Recipients Undergoing Immune Checkpoint Inhibitor Therapy for Advanced Cutaneous Malignancies: The Key Toward Maximizing Efficacy and Mitigating Rejection

By Rose Mary Attieh, Kenar D. Jhaveri, and Hani M. Wadei

Immune checkpoint inhibitors (ICIs) have revolutionized treatment of patients with advanced cutaneous malignancies (1). By stimulating T cell-mediated antitumor responses, ICIs offer new hope for a durable response and improved survival in these patients who previously had a poor prognosis. Kidney transplant recipients (KTRs) are particularly susceptible to cutaneous malignancies due to their immunocompromised state. In fact, the risk of non-melanoma skin cancer is 65- to 250-fold higher among KTRs compared with the general population, and this risk continues to increase with time following transplantation. Unfortunately, KTRs have traditionally been excluded from clinical trials involving ICIs due to concerns over lack of efficacy and fear of precipitating allograft rejection when graft-specific memory T cells are reactivated.

Various modifications to immunosuppression (IS) regimens have been proposed in an effort to enhance antitumor response and mitigate rejection risk among KTRs receiving ICIs. Although some experts have suggested maintaining baseline IS without modification (2), others have recommended converting the calcineurin inhibitor (CNI) to a mammalian target of rapamycin (mTOR) inhibitor along with a dynamic mini-steroid pulse (3). Unfortunately, robust evidence guiding the management of KTRs with advanced cutaneous malignancies treated with ICIs is still lacking.

To address this critical unmet need, two trials were recently conducted and published this year in the *Journal of Clinical Oncology* (4, 5). The study by Schenk et al. (4) explored the safety and efficacy of low-dose tacrolimus plus prednisone in patients receiving nivolumab (NIVO) ± ipilimumab (IPI) in 8 KTRs, whereas the study by Hanna et al. (5) investigated the use of an mTOR inhibitor along with pulsed dose corticosteroids and cemiplimab in 12 KTRs. Table 1 illustrates key differences in study design, participant characteristics, and outcomes among the three main prospective clinical trials conducted to date in KTRs receiving ICI therapy.

In summary, the trial conducted by Hanna et al. (5) demonstrated that the cancer response to cemiplimab among KTRs with cutaneous squamous cell carcinoma (SCC) maintained on an mTOR inhibitor with a pulsed prednisone regimen was satisfactory in both magnitude and duration. The tumor response was comparable to that observed among the general population with SCC treated with cemiplimab. In addition, there was no reported rejection among the patients. On the contrary, the study by Schenk et al. (4) showed that tacrolimus and prednisone not only proved ineffective in providing sufficient protection against rejection but also hindered the generation of an adequate antitumor response to NIVO and IPI. Elevated donor-derived cell-free DNA (dd-cfDNA) levels were proposed as an early marker of allograft rejection.

The investigators who conducted the two most recent trials are to be commended for their remarkable efforts. Despite their limitations, these trials mark one of the rare instances in which rigorously conducted prospective research has been undertaken in the field of transplant onconephrology. Nevertheless, caution is warranted when comparing these trials and generalizing their results to the broader KTR population undergoing ICI therapy. Patients in these trials had distinct types of cutaneous malignancies, were treated with different ICIs, and had failed previous lines of therapy (including immunotherapy with cetuximab). Moreover, the two trials had small sample sizes and lacked a control arm. Notably, neither of the two trials performed surveillance allograft biopsies. Although dd-cfDNA elevation preceded the rise in serum creatinine and treatment-related allograft loss, testing was not consistently performed in the trial by Hanna et al. (5), which reported no allograft rejection.

We eagerly anticipate the results of follow-up trials with larger numbers of KTRs to shed more light on the optimal IS regimen for these patients. We propose that future trials consider minimizing steroid exposure, for instance, by using the pulsed steroid regimen only with the initial dose of the ICI, when the risk of rejection is highest. This approach is likely to reduce the overall risk of hyperglycemia and infection and may also enhance the antitumor response. Further research is needed to determine the most effective IS regimen for KTRs with other malignancies and for recipients of non-renal allografts. ■

Rose Mary Attieh, MD, is the Galdi Fellow in Onco-Nephrology and Glomerular Diseases at Northwell Health, and Kenar D. Jhaveri, MD, FASN, is professor of medicine and an attending nephrologist at Northwell Health in New Hyde Park, NY, and is editor-in-chief of Kidney News. *Hani M. Wadei, MD, FASN, is a transplant nephrology specialist and professor of medicine at the Mayo Clinic, Jacksonville, FL.*

The authors report no conflicts of interest.

Is nivolumab (NIVO) + tacrolimus (TAC) + prednisone (PRED) ± ipilimumab (IPI) safe and effective in treating kidney transplant recipients with advanced skin cancers?

KidneyNews

METHODS

Study Design

Phase 1/2, single-arm, multi-center trial

Kidney transplant recipients with advanced cutaneous cancer

N = 8

Treatment Regimen

TAC + PRED → NIVO → IPI ± NIVO (if develops progressive disease)

RESULTS

Primary Endpoint
Disease control rate without graft loss = 0

Complete response = 2 (1 with allograft loss)

Progressive disease = 4 (1 with allograft loss)

Donor-derived cell-free DNA to monitor allograft rejection

Elevation occurred 10–15 days before rise in serum creatinine.

Conclusion: In most KTRs with advanced skin cancer, TAC and PRED provide insufficient allograft protection and compromise immune-mediated tumor regression after administration of NIVO ± IPI. Elevated dd-cfDNA levels can signal treatment-related allograft rejection earlier than rises in serum creatinine.

Schenk KM, et al. **Nivolumab + tacrolimus + prednisone ± ipilimumab for kidney transplant recipients with advanced cutaneous cancers.** *J Clin Oncol* 2024; 42:1011–1020. doi: 10.1200/JCO.23.01497

Visual Graphic by Jia H Ng, MD, MSCE

Cemiplimab for kidney transplant recipients with advanced cutaneous squamous cell carcinoma

KidneyNews

METHODS

Study Design

Phase 1, single-arm, single-center trial

Kidney transplant recipients with advanced squamous cell carcinoma

N = 12

Cross-Tapering Process

Existing immuno-suppressant → mTOR inhibitor + prednisone → IV cemiplimab

RESULTS

Endpoints

Kidney rejection or loss = 0

Response to cemiplimab = 5

Adverse events = 5

Death = 1

Conclusion: mTOR inhibitor and corticosteroids represent a favorable immunosuppressive regimen for KTRs with advanced cutaneous SCC receiving immunotherapy. This combination resulted in durable antitumor responses with no kidney-rejection events. IV, intravenous.

Hanna GJ, et al**. Cemiplimab for kidney transplant recipients with advanced cutaneous squamous cell carcinoma.** *J Clin Oncol* 2024; 42:1021–1030. doi: 10.1200/JCO.23.01498

Visual Graphic by Jia H Ng, MD, MSCE

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Table 1. Comparison of main prospective clinical trials of ICI therapy among KTRs

Study specifics	Carroll et al. (2)	Schenk et al. (4)	Hanna et al. (5)
Design	Prospective, multi-center, single-arm, phase 1 trial	Prospective, multi-center, single-arm, phase 1/2 trial	Prospective, single-center, single-arm, phase 1 trial
Number of KTRs enrolled	17	8	12
Median age of KTRs	67 years	66 years	62 years
Cancers included	Locally advanced incurable cancer or defined metastatic solid tumors (53% with cutaneous cancers)	Advanced melanoma (n = 1), cutaneous SCC (n = 5), or Merkel cell carcinoma (n = 2)	Advanced (incurable or metastatic) cutaneous SCC
Immunologic risk	KTRs with DSA allowed but not if MFI >4000 (mean MFI, 2500)	KTRs with DSA excluded	DSA not reported
ICI used	NIVO (3 mg/kg IV every 14 days, 5 times; then 480 mg IV every 28 days)	NIVO (480 mg IV every 4 weeks) in all patients initially; then in six of eight patients with PD: IPI (1 mg/kg IV) + NIVO (3 mg/kg IV every 3 weeks, four times), followed by NIVO alone	Cemiplimab (350 mg IV every 3 weeks) for up to 2 years
Maintenance IS regimen selected	No change in baseline IS	Low-dose tacrolimus (target through 2–5 ng/mL) + prednisone (5 mg once daily)	Cross-taper from CNI to mTOR inhibitor 7–10 days before start of cemiplimab (target through 4–6 ng/mL) + pulsed prednisone regimen (40 mg once daily starting the day before ICI and until days 1–3 of each cycle, followed by 20 mg once daily on days 4–6; then 10 mg once daily until the day before each subsequent cycle)
Median time from transplantation to start of ICI	15.6 years	13 years	7.2 years
Primary endpoint	Composite endpoint of irretrievable allograft rejection without evidence of tumor response	Composite endpoint of disease control rate (CR, PR, or SD) without allograft loss at 16 weeks	Rejection or allograft loss
Median follow-up	28 months	9.1 months	6.8 months
Efficacy outcomes	Median OS, 3.2 months; ORR, 53%: 4 CR and 5 PR; median duration of response, 27.7 months; in patients with PD: median PFS, 2.5 months	No patients met the primary endpoint (all had PD on NIVO); median OS, 9.1 months; on NIVO: ORR, 0%: median PFS, 1.8 months; on IPI + NIVO (n = 6): 2 CR and 4 PD; ORR, 33%: median PFS, 3 months; duration of response, 6 months.	Median OS, 22.5 months; ORR, 46%: 3 CR and 2 PR; median duration of response, 11.4 months; 2 patients had SD; 4 patients had PD (median time to progression, 1.4 months; median PFS, 22.5 months)
Safety outcomes	No patients had irretrievable rejection without tumor response; no treatment-related deaths or serious TRAE; rejection (with tumor response) occurred in two patients (12%), but only one (6%) had TRAL.	Three of eight patients experienced TRAL; excluding TRAL: no grade 3 or higher TRAE related to IPI + NIVO.	No patients had rejection or allograft loss; TRAE occurred in 83% (grade 3 or higher in 42%).
dd-cfDNA	Not performed	Performed every 2 weeks in all patients and weekly if rising; increased 10–15 days before rise in creatinine in two of three patients with TRAL	Performed in five patients at baseline and after cemiplimab; minor increase in only one patient with allograft pyelonephritis
Surveillance kidney biopsy	Not performed	Not performed	Not performed
Tumor biopsies	Not performed	Pre-NIVO: Seven of eight biopsies showed poor immune infiltration of tumor; post-NIVO: two of five biopsies had moderate immune-cell infiltrate (consistent with both patients who eventually achieved CR after IPI).	Higher TMB and CD8+ cytotoxic T lymphocytes were in responders; even patients with low PD-L1-expressing tumors had clinical benefit from cemiplimab.
Rejecting allograft biopsies	Severe TCMR (two of two) + arteritis (one of two)	Severe TCMR (three of three) + ABMR (two of three)	Not applicable; no rejection was noted.
Conclusions	Response to NIVO is similar to the general population, and allograft rejection rates are low when baseline IS is maintained.	Tacrolimus and prednisone do not protect against rejection and hinder an antitumor response.	Response to cemiplimab is similar to the general population, and safety profile and rejection rate are acceptable when using an mTOR inhibitor and a pulsed prednisone regimen.

ABMR, antibody-mediated rejection; CR, complete response; DSA, donor-specific antibody; IV, intravenous; MFI, mean fluorescence intensity; ORR, overall response rate; OS, overall survival; PD, progression of disease; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; TCMR, T cell-mediated rejection; TMB, tumor mutational burden; TRAE, treatment-related adverse event; TRAL, treatment-related allograft loss.

Fostering Early Interest in Nephrology: A Student's Unforgettable Experience

Kidney News editorial board member and visual abstract editor Edgar Lerma, MD, FASN, interviews Ms. Isabella Tabora, a first-year undergraduate student at Tufts University, Boston, MA. Tabora was invited to present a scientific poster at the National Kidney Foundation (NKF) Spring Clinical Meetings held in Austin, TX, in April 2023 when she was a senior in high school at Ed W. Clark High School, Las Vegas, NV. Lerma also served as a mentor to Tabora on the poster.

(From left) Michelle Estrella, MD (NKF Program Committee Co-Chair 2023); Isabella Tabora; Bernard Jaar, MD, MPH, FASN (NKF Program Committee Chair 2023); and Dr. Lerma during the poster session at the NKF Spring Clinical Meetings on April 12, 2023. Courtesy of Edgar Lerma.

Lerma: Tell us something about yourself.

Tabora: Currently, I attend Tufts University and plan on pursuing a major in biology and community health. I am also beginning to research the inter-organ crosstalk between the kidney and heart using extracellular vesicles and fluorescence microscopy, with the help of Tufts faculty. In my free time, I enjoy exploring Boston, hanging out with friends, and trying new foods!

Lerma: What was your experience attending the 2023 NKF Spring Clinical Meetings?

Tabora: Last year, I was both thrilled and nervous when I found out I had been invited to the 2023 NKF Spring Clinical Meetings. The idea of being able to present this project to experts in the field was quite captivating, and it made me feel like a real professional. At the same time, however, I was worried that the research would not be taken seriously if I did not present properly, which would not be a very favorable outcome considering the work put into this project by not just me but also others with the Advocate Christ Medical Center: Dr. Lerma, Section of Nephrology educational coordinator, and Angela Pauline Calimag, MD, and Tazeen Rizvi, DO, internal medicine residents.

Fortunately, my anxiety had transformed into relief during my time at the conference. Everyone who I encountered was welcoming and genuinely interested in what I had to offer. I was able to engage in conversations not only about my research but about other people's research as well. Observing and analyzing other posters at the conference enabled me to see nephrology from an entirely new perspective. In addition to this, I had the wonderful opportunity to meet and discuss my project with medical students, nephrologists, and even leaders of the NKF. This was truly an unforgettable experience, and I can confidently say that it is the first of many more research conferences to come.

Lerma: Tell us about your poster, how you developed the idea for doing the research, and what you learned.

Tabora: Before elaborating upon the contents of my poster, I want to express my immense gratitude to you, Dr. Lerma, for guiding me throughout the entire process. Prior to this project, I had never even heard about the underlying dangers of chronic kidney disease (CKD) in patients with type 2 diabetes, so I was shocked to learn that progression to diabetic kidney disease (DKD) remains rampant in 20% to 40% of [patients with diabetes]. I felt compelled to learn about ways to improve the pre-existent secondary prevention approaches and to mitigate these negative health outcomes. Assembling a quality improvement initiative to not only understand the root of the issue but to also find solutions on a local level was necessary.

My poster depicted the research I conducted on a primary care clinic in Las Vegas, with the goal of gaining more insight regarding the success rate at which primary care clinics in Nevada test their [patients with diabetes] for CKD. By using Practice Fusion to collect patient data, I was able to determine that a majority of patients diagnosed with diabetes and CKD did not obtain annual eGFR [estimated glomerular filtration rate] or UACR [urine albumin-creatinine ratio] tests, which are screenings recommended by the American Diabetes Association (ADA) intended to detect DKD early and prevent disease progression. The unfortunate reality of the situation was consistent with the fact that on a national level, less than 20% are tested annually for the screenings recommended by the ADA's 2021 guidelines.

Ultimately, it was determined that the clinic in this study was not at par with national ADA guidelines. Solutions to better the quality of patient treatment in this practice included flagging patient charts for the population at risk and enhancing education toward staff and patients. When looking at the social factors of the issue with approaches that are more preventative or upstream, more awareness could be spread about this issue on a community level through health advocacy, while individual health education could be improved through the development of informational brochures.

Lerma: Who or what influenced your decision to pursue a career in the field of medicine?

Tabora: My mother is a pediatrician, and my father is an internist, so I was exposed to the medical field at a very young age. As a young child, I would follow my mother around the clinic, observing everything she did and even pretending I was the one administering care to her patients. Being able to perceive my parents' unending thoughtfulness inside and outside the workplace caused me to mirror their kind-hearted actions in my everyday life. My parents are my idols, my inspiration, and most of all, my biggest supporters. They have spent their entire careers giving back to the community despite all the hardships they have undergone. The morals they have instilled and the example they have set for me have influenced me to pursue a career in health care, in which I can provide a place of safety for those suffering, listen to their problems with an open mind, and encourage them to take charge of their lives despite any health obstacles.

Lerma: Where do you envision yourself 10 years from now?

Tabora: In the next 10 years, I see myself having graduated from Tufts University with a degree in biology and community health. I hope to have made it through medical school

by then, pursuing a residency in a specialty that I am truly intrigued by. Additionally, I hope to have implemented public health interventions that have made lasting impacts in several communities, especially when it comes to alleviating the severity of the health outcomes of DKD. I also hope to have expanded my research on the mechanisms that influence kidney and heart damage. At the same time, I hope to have pursued some of my personal aspirations in 10 years, like seeing the northern lights and visiting my family in the Philippines. For the most part, I look forward to being more involved in the field of health care in the future and to having attended many more health conferences, including the NKF Spring Clinical Meetings.

Lerma: What advice would you give to others in your age group?

Tabora: A piece of advice I can give is to avoid comparing yourself to others and to start comparing yourself to your past self. Most people my age likely grew up using social media, and although it enhances our lives in many ways, it also makes it very easy to compare other people's possessions, achievements, and capabilities to our own. But each person has different goals, personalities, and experiences, which essentially make everyone's lives incomparable. In the end, I find that it is beneficial to be the best version of yourself every day and take note of how we can improve from the past.

In fact, think of yourself like a flower. When life is difficult, drink water, get some sunshine, and surround yourself with a warm, loving environment full of other lovely flowers. Remember that you don't need to compete with other flowers, and instead, focus on your own growth.

Lerma: How would you like to see nephrology organizations and leaders engage youths and cultivate interest in nephrology?

Tabora: I believe that nephrology organizations, such as the NKF or the ASN, should contemplate establishing a summer research program that is directed toward high school students with an interest in the field of nephrology. These programs could educate students about kidney function, spark engaging discussions about prevalent issues within the community, and encourage students to give presentations on a research topic at the end of the program.

Additionally, this program could advertise the NKF Spring Clinical Meetings to students who intend to continue their research for the rest of the year. Having students attend the Spring Clinical Meetings will have myriad benefits for not only the students but for the conference as a whole. Students will have the ability to share their own project, expand their knowledge regarding other research methods and topics, make connections with professionals in the field, and actively converse with individuals who share the same yearning to develop solutions to urgent health issues. Most importantly, having the youth be involved in these meetings will spur proactive behavior within the nephrology community and can ultimately benefit the kidney health of many more populations. If this is done, however, it may be helpful to connect these students to mentors who are able to guide students with the entire process of researching, applying to, and attending the meetings.

One of the first steps to allow this idea to come to fruition is to get nephrology organizations to expand their social media presence on platforms like Instagram or TikTok. By doing this, organizations can get the attention of the youth and motivate them to make a difference in the field of nephrology early on. ■

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