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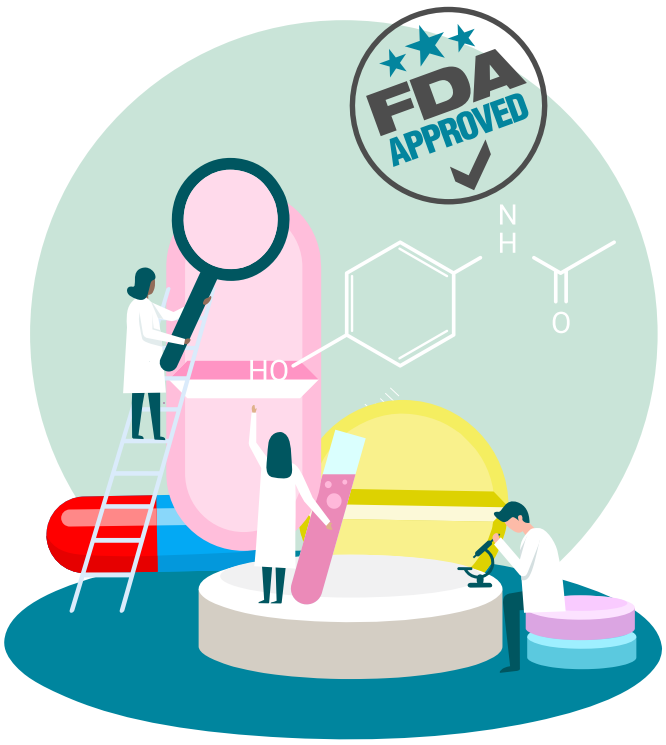
FDA Gives Full Approval to First IgA Nephropathy Drug

Tarpeyo to Target Underlying Mechanism of Action

By Eric Seaborg



Several glomerular disease specialists used the word "excited" to describe their reaction to the US Food and Drug Administration (FDA) granting full approval to a drug for treatment of immunoglobulin A (IgA) nephropathy. After giving Tarpeyo (budesonide) accelerated approval in December 2021, the FDA followed it up with full approval on December 21, 2023, based on clinical trial results for treatment of adults with primary IgA nephropathy.

"This approval is an incredibly big thing because in the world of primary kidney [diseases] we have had too few breakthroughs with medications designed to treat the mechanism of action," said Richard Lafayette, MD, professor of medicine at Stanford University, Stanford, CA, and principal investigator in the clinical trial underpinning the approval.

Lafayette said the disease is an autoimmune disorder in which the patient makes too much of an aberrant form of IgA: "The patients develop auto-antibodies to those elevated levels of circulating IgA. The kidneys both specifically and nonspecifically try to remove the immune complexes, which get caught in the glomerular mesangium, leading to inflammation. Patients who are predisposed develop hematuria, proteinuria, and progressive loss of kidney structure and function. Roughly half of them will be approaching dialysis within just 10 years."

In the past, treatment relied on "supportive care," according to Shikha Wadhwani, MD, MS, FASN, assistant professor of medicine in the Division of Nephrology and Hypertension at the Northwestern University Feinberg School of Medicine, Chicago, IL. "All we really had for decades were medications to lower protein in the urine—which also happen to be blood pressure medications—as well as steroids we use in a variety of different auto-immune diseases. Steroids come with their own problems—a lot of potential side effects."

In contrast, Tarpeyo is a B cell immunomodulator designed to target a source of the disease by reducing the production of pathogenic galactose-deficient IgA1 antibodies. The manufacturer describes it as an oral, delayed-release formulation of the corticosteroid budesonide. It is

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CMSS Grant Will Help Educate Clinicians about Race-Free Kidney Function Estimation

By Bridget M. Kuehn

The Council of Medical Specialty Societies (CMSS) has awarded $100,000 to ASN, advancing its ongoing work to promote equity in kidney care by teaching nephrologists and other clinicians how to use race-free algorithms for assessing kidney function (1).

The ASN-National Kidney Foundation (NKF) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases in 2021 recommended widespread adoption of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) algorithm with creatinine or creatinine and cystatin C instead of a previous race-corrected algorithm (2). The goal was to provide a more accurate assessment of kidney function for all patients and to help eliminate persistent delays in referral and transplant care for Black patients. The CMSS grant will support a multipronged educational campaign to help ASN's 21,000 members learn about the algorithm and how to apply it in practice and to help teach their fellow clinicians and patients about its use in medical decision-making.

"The CMSS grant will help accelerate our efforts to provide nephrologists and other kidney health professionals with the latest information about eGFR [estimated

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Inside

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.

A non-binder approach is now here

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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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FDA Gives Full Approval to Tarpeyo

Continued from cover

designed to remain intact until it reaches the ileum, where it targets mucosal B cells, including in the Peyer's patches, which are responsible for the production of the galactose-deficient IgA1 believed to underlie IgA nephropathy.

Successful clinical trials

The approval was based on the results of the phase 3 Efficacy and Safety of Nefecon in Patients with Primary IgA (Immunoglobulin A) Nephropathy (NeflgArd) clinical trial, a randomized, double-blind, multicenter, international study published in *The Lancet* (1). Approximately 360 participants were randomly assigned to receive daily oral Tarpeyo (referred to in the trial as Nefecon, its investigational drug name) or matching placebo for 9 months, followed by a 15-month follow-up period. All of the patients also received a renin-angiotensin-aldosterone system (RAAS) inhibitor throughout.

The study authors reported that the drug provided "a clinically relevant reduction in eGFR [estimated glomerular filtration rate] decline and a durable reduction in proteinuria versus placebo. [Tarpeyo] was also well-tolerated, with a safety profile as expected for a locally acting oral budesonide product." In the treatment group, the decline in eGFR was one-half that of patients who received placebo.

Kidney International published an analysis of another clinical trial aimed at exploring how Tarpeyo exerts its effects (2). The trial found that Nefecon led to significant reductions in serum levels of galactose-deficient IgA1 and pathogenic IgA-containing immune complexes, which the authors said was "supportive of Nefecon having a disease-modifying action in IgA nephropathy."

"For many years we have been primarily treating IgA nephropathy with drugs that target intra-renal injury, [such as] RAAS inhibitors," according to Brad H. Rovin, MD, FASN, director of the Division of Nephrology at The Ohio State University, Columbus, and a co-author of the study in *The Lancet*. "However, I have always been concerned that in the background, galactose-deficient IgA was still being made in abundance and still depositing in the kidney, so we were not stopping the root cause of IgA nephropathy. With Tarpeyo, based on its presumptive mechanism of action, we may, for the first time, be targeting a very early step in the pathogenesis of IgA nephropathy, potentially allowing us to control the disease and decrease further risk to the kidneys. While this remains to be proven, data so far are encouraging," said Rovin.

An underdiagnosed disease?

IgA nephropathy affects 130,000 to 150,000 people in United States, and the FDA has granted Tarpeyo orphan drug status. Wadhwani noted, however, that epidemiological data indicate that there may be more patients at risk for the disease than previously believed. "We are probably missing cases because a primary care doctor, internist, or family practice doctor has to check the urine, which a lot of people don't do, and then think it is worth making a referral if they find blood or protein," she said.

She hopes that increased education about the availability of a more effective and safer drug will give doctors more incentive to screen for it. "We are going to be biopsying people with blood in the urine much more often now that we have something to treat them with," Wadhwani shared.

She said that the disease is much more prevalent in the Asia Pacific region, and in Japan, children are routinely screened by testing urine. Lafayette agrees: "Too many of our patients, particularly in North America and Europe, are diagnosed very, very late. There is a lot of advocacy going around for better screening and for encouraging primary care doctors to do more blood pressure checks and more laboratory testing of the urine, at least with dipsticks, during routine primary care visits to try to find patients earlier. These things are done in China and Japan. It results in earlier diagnosis, and all of our therapies work much better if they are deployed early."

Encouraging early results

In the 2 years since Tarpeyo's accelerated approval, many specialists have been using it and have been pleased with the results. Wadhwani had two patients in the clinical trial that led to the drug's approval. When the trial was unblinded, she learned that both had been receiving the drug. "Both of my patients did remarkably well. One is in complete remission," she said.

Rovin has treated five or six patients and found it to be "well-tolerated with declines in proteinuria. Judging the stability of eGFR will take longer, but so far I have not had anyone progress to end stage kidney disease." Lafayette also expressed that the several patients he has treated have tolerated the drug well.

Wadhwani noted that, because the clinical trial compared Tarpeyo with placebo, "we don't know how it compares directly to corticosteroids—traditionally prednisone or prednisolone—that were given to people deemed at high risk of progression. But anecdotally, what I have seen in terms of side effects and what other nephrologists are seeing are that people are tolerating this medication better. To have a new drug that potentially mitigates some of the adverse reactions to steroids and is effective is really exciting."

Although it seems to be tolerated better than prednisone, Tarpeyo is still an immunosuppressive steroid that was tested in a 9-month course. "While a single, 9-month treatment course is not curative, the tolerability and toxicity profiles of Tarpeyo are such that it [Tarpeyo] is suitable for use as a cyclical treatment to chronically suppress pathogenic IgA production," according to Jonathan Barratt, PhD, professor of renal medicine at the University of Leicester in the United Kingdom and a co-author of both *The Lancet* and *Kidney International* articles.

"Tarpeyo is currently the only available treatment that has been shown to suppress the production of pathogenic IgA in IgA nephropathy. The now full approval opens up the opportunity for far more patients with IgA nephropathy to access this disease-modifying therapy and start treatment while they have good kidney function and will gain the maximum benefit from suppressing this disease early and preserving kidney function over the long term," he said.

Wadhwani has already begun fielding questions about its use from nephrologists who are not glomerular disease specialists. "[This drug] is safe and efficacious and is certainly something that any nephrologist can use in their [patients with IgA nephropathy] with monitoring as they would with any immune-modulatory drugs. So I think it is going to be used not just by academic institutions. It is already being used in community nephrology practices."

Another IgA nephropathy drug

The full approval of Tarpeyo came less than 1 year after the February 2023 accelerated FDA approval of another IgA nephropathy drug, Filspari (sparsentan).

Rovin said he is also excited about using Filspari, which he considers complementary to Tarpeyo. "While Tarpeyo is likely modulating the immune system and affecting IgA at an early step in its pathogenesis, Filspari is working, presumably, at the level of the kidney parenchyma to attenuate the kidney injury caused by the deposition of IgA immune complexes in the mesangium. We know that it does this better than our current standard of care (RAAS inhibitors). Because each drug works on a different part of the IgA nephropathy disease pathway, I believe that the combination may provide additive benefits for patients."

Wadhwani agrees that the drugs can be layered on top of each other: "One of my patients got Tarpeyo first, and after the 9 months had a partial remission. Then I started him on Filspari, which is nonimmunosuppressive, so he can stay on it long term."

Both drugs are expensive, with Reuters (3) reporting that Tarpeyo costs over $15,000 per month, and Filspari costs almost $10,000 per month, but the specialists interviewed reported no problems with getting insurance coverage approval.

Patients are also excited about the approval of Tarpeyo, according to Bonnie Schneider, director and co-founder of the IgA Nephropathy Foundation (https://igan.org/). "This first-ever IgA nephropathy treatment to get a full approval based on kidney function represents a beacon of hope for the entire IgA nephropathy community and signifies a critical step forward in the battle against IgA nephropathy," Schneider reflected.

Wadhwani does not expect the drug to be a panacea, but its development makes her optimistic for the future. "We refer to IgA nephropathy as though it is one disease, but it is actually very heterogeneous. Every patient's kidney biopsy looks a little bit different, and everyone is different in how they respond to treatment. It is naïve for us to think that one drug is going to be the answer to every single [problem for a patient with IgA nephrology], but it is really exciting that there are two drugs that have now gotten accelerated approval.

"There is a ton of interest by pharmaceutical companies in investing money and resources in drug development, which was not there 10 or 15 years ago. So I think what we are going to be able to offer patients is going to change dramatically in the course of even just the next 5 years because there are so many ongoing trials right now," Wadhwani concluded. ■

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Correction

The Fellows First article "Nephrology Match 2023: Fellows' Perspectives" published in January 2024 *Kidney News* listed an incorrect affiliation for one of the contributors. Farhana Begum, MD, is chief resident with the Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.

CMSS Grant Will Help Educate Clinicians

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glomerular filtration rate] and equip them to discuss the new metric with their patients with kidney diseases," said ASN's Executive Vice President Tod Ibrahim in a statement about the grant (3).

Diagnostic excellence

ASN was one of 11 medical specialty societies that received a grant from CMSS's 2023–2024 Promoting Diagnostic Excellence Across Medicine program (1), funded by the Gordon and Betty Moore Foundation and the John A. Hartford Foundation. Several of this year's grantees, including ASN, are focusing their projects on improving diagnostic equity, reflecting a growing push within CMSS and its 51 specialty society members to reduce health disparities. "Equity is among the top priorities of all our societies right now," said Helen Burstin, MD, MPH, FACP, executive vice president and chief executive officer of CMSS.

Many medical specialty societies are currently reconsidering the use of race in clinical decision-making tools, according to a recent CMSS report (4). This reflects growing recognition in medicine that race is a social construct and not a proxy for biology and that inappropriate use of race as a biological proxy may contribute to or exacerbate health disparities. The ASN-NKF task force's 2021 recommendation to adopt new race-free equations placed it at the head of the curve. Work by the two organizations has advanced well into the implementation phase, with approximately two-thirds of US laboratories reporting that they have implemented the race-free eGFR equation (5).

"ASN and NKF were early adopters in this space and, in many ways, are helping lead the way for other specialty societies," Burstin said. She noted that the speed of race-free eGFR implementation has been remarkable for medicine, which can often take a decade or more to implement new recommendations.

Cynthia Delgado, MD, FASN, co-chair of the ASN-NKF task force and a professor of medicine at the University of California, San Francisco, credited ASN's leadership for recognizing the importance of moving quickly to address the use of race in kidney function assessment, an issue about which members were increasingly expressing concerns. Delgado, then chair of ASN's Diversity, Equity, and Inclusion (DEI) Committee, said Ibrahim worked with the DEI Committee and NKF to assemble a task force that included 15 independent thinkers who represented a broad spectrum of the kidney care community.

"It was an all-hands-on-deck moment," she said. NKF took the lead on the initial implementation phase, providing guidance (6) and outreach to laboratories to expedite the implementation of the race-free eGFR. Implementation has had widespread downstream effects. For example, the United Network for Organ Sharing (UNOS) has since required transplant centers to use the race-free eGFR equations for transplant evaluations and to recalculate waitlist times for Black patients whose care may have been delayed by the race-adjusted algorithm (7). Burstin said she hoped the grant would help expand the adoption of the race-free eGFR even further, reaching the remaining clinicians who still need to make the switch.

Other 2023–2024 grantees working to address racial and ethnic disparities in diagnoses include the American Academy of Dermatology, which will use its grant to improve dermatologists' ability to diagnose skin conditions across skin tones, and the American Urological Association, which is developing a campaign to educate urologists and primary care specialists about the importance of early screening for prostate cancer for those at increased risk associated with Black ancestry, germline mutations, or a family history of prostate cancer, to help reduce disparities in outcomes in these groups. "We hope our efforts will inspire other medical societies to [review] long-established standards of care to identify and eliminate race-based disparities," Ibrahim said in the ASN statement (3).

Multipronged campaign

The CMSS grant will fund a multipronged outreach campaign to clinicians about race-free eGFR and its use in patient care. Delgado noted that clinicians use eGFR across specialties, including primary care, radiology, oncology, and pharmacy. She said ASN wants to ensure that the campaign's reach matches this clinical tool's reach. "We are going to work on further educating our nephrology colleagues and trainees," she stated. "I hope we create ambassadors who can educate non-kidney specialist [clinicians] on how to use the equation."

Burstin, a primary care general internist, said it is essential for clinicians across specialties to understand the new eGFR results and how to use them in clinical decision-making. She noted, for example, how to use the estimations in prescribing medications, such as the new classes of cardiometabolic drugs, or the implications for patients who may be candidates for transplant.

While the details of the educational materials are just beginning to be determined, Delgado said, one key point she hopes to include is that eGFRs are just estimates and are only one piece of kidney function assessment. She noted that the same is true for kidney transplant evaluation and that the new UNOS recommendation (7) reflects one small change in the complex algorithm that involves many other factors beyond eGFR. "We want to err on the side of being more ethical, fair, and equitable," she said.

Delgado shared that she and her ASN colleagues also hope to prepare nephrologists to discuss the eGFR algorithm comfortably with their patients in easy-to-understand terms. "It's very important for [patients] to understand how we think so they can also be advocates for themselves and their own health care," she said.

ASN will convene a group of kidney care specialists over the coming months to develop the educational tools and begin their rollout. The society will also likely collaborate with other partners such as NKF. "We will approach this work as we always do with collaboration from others," she said.

Delgado expressed that she is proud that ASN and NKF are leading the charge to eliminate the inappropriate use of race in clinical algorithms across specialties, which will ultimately change how medicine is practiced. "The kidney community at large should be very proud that we are on the cutting edge of this work and that we are making changes that will be lasting," Delgado said. ■

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Major Update to Guidelines for Managing Kidney Injury during Anticancer Drug Therapy in Japan

By Takehiko Wada

Cancer encompasses a critical group of diseases with a profound impact on life prognoses and affects half of the Japanese population during their lifetime. Over the past decade, the oncology field has witnessed continuous progress in developing new anticancer drugs and treatment protocols, marking significant advances in cancer therapy. At the same time, the incidence of kidney diseases associated with cancer treatment has increased, leading to a growing demand for consultation with nephrologists in such cases.

In response to this situation, the "Clinical Practice Guidelines for Management of Kidney Injury during Anticancer Drug Therapy 2022" have been extensively revised after 6 years to support clinical decision-making by evaluating published evidence based on systematic reviews (1). Similar to the previous edition, these guidelines were jointly developed by the Japanese Society of Nephrology, the Japan Society of Clinical Oncology, the Japanese Society of Medical Oncology, and the Japanese Society of Nephrology and Pharmacotherapy, with the participation of experts from each society, and have undergone significant revisions to adapt to the rapid advances in cancer pharmacotherapy. In particular, the addition of clinical questions (CQs) related to molecularly targeted agents, especially immune checkpoint inhibitors (ICIs), is a prominent feature (Table 1).

The updated version is organized along the timeline of cancer care. Beginning with pretreatment assessment of renal function, chapter 2 addresses the appropriate selection and administration of anticancer drugs in patients with renal impairment. It then discusses measures to manage renal impairment caused by anticancer pharmacotherapy. In addition, this edition includes information on managing chronic kidney disease (CKD) in cancer survivors, a topic not covered in the previous version, demonstrating careful consideration to provide valuable insight at each stage. Furthermore, the committee compiled the background knowledge for each chapter and published four review articles (2–5).

The new guidelines also provide background information as a comprehensive review to support a wide range of health care practitioners. Additionally, good practice statements (GPSs) have been introduced, highlighting CQs from the first edition that have gained widespread acceptance since publication and those with uncertain prospects for future clinical trials.

Although this revised set of guidelines has already found validity in clinical practice, more publications are needed to assess the certainty of evidence for CQs that address clinically significant questions. In anticipation of continued advances in cancer care, it is hoped that research in this area will keep pace with these trends. ■

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Table 1. CQs and GPSs in the Clinical Practice Guidelines for Management of Kidney Injury during Anticancer Drug Therapy 2022

Chapter 1	**Evaluation of Kidney Function in Patients Undergoing Anticancer Drug Therapy (2)**
CQ1	Is the use of an estimation formula recommended for assessing kidney function (glomerular filtration rate [GFR]) in patients with cancer?
CQ2	Is it recommended to use novel acute kidney injury (AKI) biomarkers for early diagnosis of AKI due to anticancer drugs such as cisplatin?
CQ3	If hydronephrosis is present before cancer treatments, is it recommended to perform a ureteral stent placement or nephrostomy?
Chapter 2	**Indications and Dosing of Anticancer Drug Therapy in Patients with Impaired Kidney Function (3)**
GPS1	Should carboplatin dosing be based on kidney function?
GPS2	Should dialysis be performed to remove the drug after administering cisplatin to patients on maintenance hemodialysis?
CQ4	Is the use of ICIs recommended in hemodialysis patients?
CQ5	Is the use of ICIs recommended in patients who have undergone kidney transplantation?
Chapter 3	**Management of Kidney Injury Caused by Cancer Drug Therapy (4)**
CQ6	What is the recommended method of hydration to alleviate kidney dysfunction during cisplatin administration in adults?
CQ7	Is the use of antiangiogenic agents recommended for patients with proteinuria or a history of proteinuria?
CQ8	Is additional magnesium supplementation recommended if a patient receiving anti-epidermal growth factor receptor antibody develops hypomagnesemia?
CQ9	Is it recommended to discontinue steroids being used to treat kidney injuries caused by ICIs after normalization of kidney function?
CQ10	Is the resumption of ICIs recommended after a patient has recovered from kidney injuries associated with ICIs?
Chapter 4	**CKD Treatment in Cancer Survivors (5)**
GPS3	Is growth hormone therapy recommended for childhood cancer survivors (CCSs) with CKD?
GPS4	What is the appropriate kidney replacement therapy for CCSs?
CQ11	Is the administration of erythropoiesis-stimulating agents recommended for renal anemia in cancer survivors?

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ASN Executive Vice President's Update

Supporting PhD Scientists to Help Drive Breakthroughs, Improve Care

By Tod Ibrahim

Accelerating innovation depends on a strong foundation of basic science. Any progress at the bedside builds on discoveries in the lab, and these breakthroughs require supporting PhD scientists, securing funding, and strengthening the infrastructure. Even with its increased focus on clinical nephrology during the last decade, ASN has never wavered in its 60-year commitment to researchers and scientists, especially those focused on basic investigation like many PhD scientists.

Before highlighting ASN's efforts to support PhD scientists, it is important to note that the greater focus on clinical nephrology has produced extraordinary results. If ASN Excellence in Patient Care were a separate organization, it would be one of the largest medical specialty societies representing US nephrologists (1). Despite "a dramatic productivity decline relative to previous years" of legislation being passed in Congress (2), this emphasis on clinical nephrology also helped produce incredible wins last year—especially related to transplant policy (3).

In 2024, ASN will continue to advocate for:

- Intervening earlier to prevent, diagnose, coordinate care, and educate
- Transforming transplant and increasing access to donor kidneys
- Accelerating innovation and expanding patient choice (including more access to home dialysis)
- Achieving equity and eliminating disparities
- Bolstering the kidney health professional workforce

To help guide these efforts, ASN welcomed three newly elected members to its nine-member governing board on Monday, January 1, 2024. Jeffrey H. Miner, PhD, FASN, will serve a 4-year term on the ASN Council as treasurer; Samir M. Parikh, MD, FASN, joined the council as secretary (and will serve as the society's president in 2026); and Daniel E. Weiner, MD, MS, FASN, will serve as one of the society's four at-large councilors through 2027.

As an elected member of both The American Society for Clinical Investigation and the Association of American Physicians, Parikh has demonstrated a career-long commitment to research. Weiner—the founding editor-in-chief of *Kidney Medicine* and ASN's representative to Kidney Care Partners (a community-wide advocacy coalition that supports increased federal funding for kidney research)—is an expert in the many policy processes needed to advance discovery and improve care.

Miner is the first PhD scientist to serve on the ASN Council since Diana Marver, PhD (1993–1995), who followed James A. Schafer, PhD (1990–1992), and Ruth Bulger, PhD (1985–1987). Four MD-PhDs have served or are currently on the council: George E. Schreiner, MD, PhD (1968–1972); Juha P. Kokko, MD, PhD (1979–1986); Joseph V. Bonventre, MD, PhD, FASN (2006–2012); and Prabir Roy-Chaudhury, MD, PhD, FASN (2019–2026), who will serve as ASN president in 2025.

In June 2013, Miner chaired ASN's first-ever PhD Summit (4) to identify ways for the society to generate more interest among current and future PhD scientists regarding the study of the normal and diseased kidney and to ensure that ASN is meeting the needs of its PhD members. Approximately 7% of ASN members are PhD scientists, and they conduct basic, translational, clinical, and epidemiological research, contributing across the continuum.

When compared with nephrology, PhD scientists in most other specialties receive greater funding from the National Institutes of Health (NIH) because they submit more grant applications than do MDs (or other physicians with equivalent degrees) or MD-PhDs (5). The NIH and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) are pay-line driven; that is, more applications typically result in more funding. As such, specialties with more PhD scientists submitting applications have an advantage over specialties with fewer PhD submissions—like nephrology.

Across the NIH, PhD scientists submit approximately 70% of applications, whereas MDs submit approximately 15% of applications (5). In contrast, PhD scientists typically submit just 50% of applications for kidney research funding from the NIDDK (Table 1) (6). The kidney community is fortunate to have so many physicians engaged in research. ASN must do everything possible to support them, especially as interest in nephrology fellowship training declines, and other challenges discourage nephrologists from research careers.

Table 1. Unique applicant summary for NIDDK's Division of Kidney, Urologic, and Hematologic (KUH) Diseases in fiscal year 2023

Academic degree	Application specialty, %			
	NIDDK (total)	Kidney	Urology	Hematology[a]
MD	23	33	28	14
MD-PhD	12	14	9	24
PhD	65	53	63	62

Adapted from Ketchum (6).
[a]It is important to note that the National Heart, Lung, and Blood Institute funds most clinical benign hematology research, which may help explain why so few physicians apply to the NIDDK for hematology funding.

However, these trends also suggest an opportunity to recruit more PhD scientists into kidney research. If successful, such recruitment should lead to more grant submissions—and, therefore, funding—for kidney research.

The ASN PhD Summit resulted in several recommendations to address these and other concerns for advancing PhD interest in kidney research and improving the environment for PhD members of the society. Resulting in at least 10 improvements to ASN, the summit has served to change the society's culture. Since 2013, ASN's leadership and staff have attempted to include current and future PhD scientists in every aspect of the society and the broader ASN Alliance for Kidney Health (7).

As a result of the ASN PhD Summit, the approved improvements:

1. **Expanded ASN's travel support opportunities for trainees to include future PhD scientists.** These opportunities for medical students, residents, fellows, and PhD candidates include ASN Kidney STARS (Students and Residents); the Karen L. Campbell, PhD, Travel Support Program for Fellows; and the William E. Mitch, III, MD, FASN, International Scholars Travel Support Program. In 2023, ASN supported 66 current and future PhD scientists to attend Kidney Week.

2. **Invited future PhD scientists and first-year postdoctoral fellows to participate in the ASN Kidney TREKS (Tutored Research and Education for Kidney Scholars) Program.** Last year, 14 future PhD scientists and first-year postdoctoral fellows participated in Kidney TREKS, a program that fosters interest in careers in nephrology and research through a week-long research course retreat and long-term mentorship program. Kidney TREKS includes two locations: the MDI Biological Laboratory in Bar Harbor, ME, and The University of Chicago in Chicago, IL.

3. **Established the KidneyCure (the ASN Foundation for Kidney Research) Pre-Doctoral Fellowship Program.** Since 2018, KidneyCure has funded 22 PhD students to conduct original research projects. This program fosters graduate students on a PhD track who are highly motivated to make contributions to the understanding of kidney biology and diseases under the direction of a sponsor. Kurt Amsler, PhD, and Ambra Pozzi, PhD, DrPH, are to be commended for their efforts in establishing this important program.

4. **Ensured that PhD scientists can compete for KidneyCure funding.** Each year, KidneyCure supports the Ben J. Lipps Research Fellowship Program and the Transition to Independence Grants Program to fund nephrology fellows and early-career investigators, respectively. Together, these two programs support approximately 20 new and 20 continuing grants each year. Since 2013, 59 PhD scientists have received these grants from KidneyCure (21 Ben J. Lipps Research Fellows and 38 Transition to Independence Grants Recipients).

5. **Applied efforts to promote diversity, equity, and inclusion for PhD scientists.** KidneyCure partners with the Robert Wood Johnson Foundation to support the Harold Amos Medical Faculty Development Program Award. This award aims to increase diversity among future leaders in nephrology by supporting the research and career development

of a kidney scholar and future health care leader from a historically disadvantaged background. Additionally, ASN provides travel support for its members to participate in the Network of Minority Health Research Investigators (NMRI) Annual Workshop, which is supported by the NIDDK. On average, 35% of the NMRI Annual Workshop participants funded by ASN are PhD scientists.

6. **Created a more welcoming environment for PhD scientists at ASN Kidney Week.** As the world's premier nephrology meeting, Kidney Week tries to balance three priorities: showcasing cutting-edge science in nephrology and beyond, inspiring high-quality kidney care for the more than 850 million people worldwide living with kidney diseases, and offering a convivial environment for the kidney community and everyone committed to a world without kidney diseases. PhD scientists are interested in all three facets, and ASN works to increase the relevance of Kidney Week by supporting the Advances in Research Conference (ARC) as an early program, providing travel support for future PhD scientists to attend ARC, and providing numerous educational sessions during the meeting.

7. **Reorganized ASN to create a focus on research, discovery, and innovation that includes KidneyCure, the Kidney Health Initiative (KHI), and the Kidney Innovation Accelerator (KidneyX).** As a result of this focus, ASN now offers a home for PhD scientists, much like what is available to clinically focused nephrologists through ASN Excellence in Patient Care. In addition to KidneyCure funding available to PhDs, ASN Research, Discovery, and Innovation engages researchers and scientists through KHI's many projects to "catalyze innovation and the development of safe and effective patient-centered therapies for people living with kidney diseases" (8) and KidneyX's efforts to "support innovation," "advance solutions" (including an artificial kidney), and "build community" (9).

8. **Revised ASN's bylaws to create distinct paths for serving on the ASN Council.** As recommended by the PhD Summit in 2013—and to make the ASN Council more diverse, equitable, and inclusive—the society revised its bylaws in 2016. This revision resulted in expanding the number of pathways to the council from two (being elected to serve a 7-year term that included 1 year as president or being elected to serve a renewable 3-year term as treasurer) to three (establishing non-renewable, 4-year terms for executive councilors, treasurers, and at-large councilors).

9. **Collaborated with other entities that focus on basic science.** ASN supported the American Physiological Society Control of Renal Function in Health and Disease Conferences in 2019 and 2022. ASN will partner this year with The University of Alabama at Birmingham (UAB) for the CRRT (Continuous Renal Replacement Therapy) Academy as well as with UAB and Children's of Alabama for the inaugural International Neonatal Nephrology Symposium. In 2025, ASN will administer the Acute Kidney Injury: From Bench to Bedside Conference. The society is currently negotiating to hold a joint international conference in 2026 for early career investigators.

10. **Advocated for more federal research funding to improve kidney health.** In addition to individual efforts to advocate for more federal funding—particularly for the NIDDK—ASN actively participates in at least 11 advocacy coalitions (in alphabetical order): The Ad Hoc Group for Medical Research; Coalition for Health Funding; Coalition for Kidney Health; Friends of the Agency for Healthcare Research and Quality; Friends of (the Department of Veterans Affairs) VA Medical Care and Health Research; Friends of the NIDDK; Friends of the National Institute on Aging; Kidney Care Partners; National Heart, Lung, and Blood Institute Constituency Group; National Institute of Arthritis and Musculoskeletal and Skin Diseases Coalition; and Research!America.

Despite all this progress, ASN failed to accomplish at least two recommendations from the PhD Summit. First, ASN has not managed to collaborate with the biotechnology, medical device, and pharmaceutical industries to establish an industry PhD fellowship, in conjunction with academia or government programs (4, 10). Because one of the goals in ASN's current strategic plan is to build "research readiness, inclusiveness, and translation in kidney medicine, which requires championing clinical trials" (7), perhaps an opportunity exists to combine this goal with the summit recommendation.

Second, ASN has not managed to institute an ASN-designated research center recognition program (similar to the National Cancer Institute's Comprehensive Cancer Center) (4, 10). In 2017, the Infectious Diseases Society of America (IDSA) launched the Antimicrobial Stewardship Centers of Excellence Program to promote "excellence in antimicrobial use and combating antimicrobial resistance by recognizing hospitals that effectively demonstrate excellence in this work" (11). To date, 177 programs have received the "Centers of Excellence" designation from IDSA. Even though this program is more clinically focused, it could serve as a potential model for ASN.

ASN's effectiveness comes from balancing all components of its mission to "elevate care by educating and informing, driving breakthroughs and innovation, and advocating for policies that create transformative changes in kidney medicine throughout the world" (7). For the past decade, ASN deepened its commitment to PhD scientists to help drive breakthroughs and innovation. This focus has produced remarkable results for ASN, researchers and scientists, and—most importantly—the more than 850 million people worldwide living with kidney diseases. ■

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Treating Patients with C3G or aHUS: ACE Inhibitors, AT1 Blockers, or Aliskiren?

By Hassan Izzedine

The renin-angiotensin system (RAS) is a vital, modifiable target in treating renal and cardiovascular diseases. Therapy targeting the angiotensin-converting enzyme (ACE) or the angiotensin II type 1 (AT1) receptor is an important strategy not only for treating hypertension but also for reducing proteinuria and slowing the progression of mild-to-moderate chronic kidney disease. Other therapies targeting the RAS include mineralocorticoid receptor blockers and renin inhibitors. Several renin inhibitors have been synthesized, but aliskiren is the only US Food and Drug Administration-approved renin inhibitor used clinically to treat essential hypertension. However, a specific contraindication concerning its combination with an ACE inhibitor or AT1 blocker in patients who are diabetic limits its use due to risk of hyperkalemia, declining renal function, low blood pressure, and non-fatal stroke (1). In addition, the potential reno-protective effects of aliskiren have not been widely studied in clinical trials (2).

An hypothesis suggests that by suppressing the RAS, increased renin production may activate the alternative complement pathway, leading to the cleavage of C3 into C3b and the formation of a functional C3 convertase. This mechanism implies that aliskiren, due to its specific inhibition of renin, might be a more suitable treatment than ACE inhibitors or AT1 receptor blockers for patients with C3 glomerulopathy (C3G) or primary atypical hemolytic uremic syndrome (aHUS). In their 2018 article in *Kidney International*, Békássy and colleagues (3) reported that aliskiren use was associated with decreased systemic and renal complement activation, in addition to glomerular basement membrane thickness in three patients with dense depot disease over a follow-up period of 4 to 6 years. In 2019, Plasse et al. (4) reported a favorable evolution of aHUS, initially resistant to the combination of conventional-dose aliskiren and eculizumab, with aliskiren at a supratherapeutic dose. Thus, aliskiren may be preferable to other renin-angiotensin-aldosterone system inhibitors for the treatment of the rare complement-mediated kidney diseases caused by dysregulation of the alternate fluid-phase (C3G) and/or cell-surface (aHUS) complement pathways (5, 6). Based on these studies and the possibility of an interaction between renin and the complement system, a phase 2 clinical trial evaluating the efficacy of aliskiren in patients with C3G is currently underway (7).

A study by Zhang et al. (8), recently published in *Kidney International*, questions the use of aliskiren in complement-associated kidney diseases. The authors provide seven lines of evidence showing that renin does not cleave C3, suggesting that the use of aliskiren as a renin inhibitor to reduce C3 convertase formation in patients with C3G and aHUS is misguided (Figure 1).

Given the current evidence and awaiting further clinical research, physicians may prefer ACE inhibitors and AT1 blockers over aliskiren due to a more established safety profile across various renal pathologies. This preference will likely persist until larger studies can definitively compare the efficacy and safety of aliskiren with these more traditional therapies. ■

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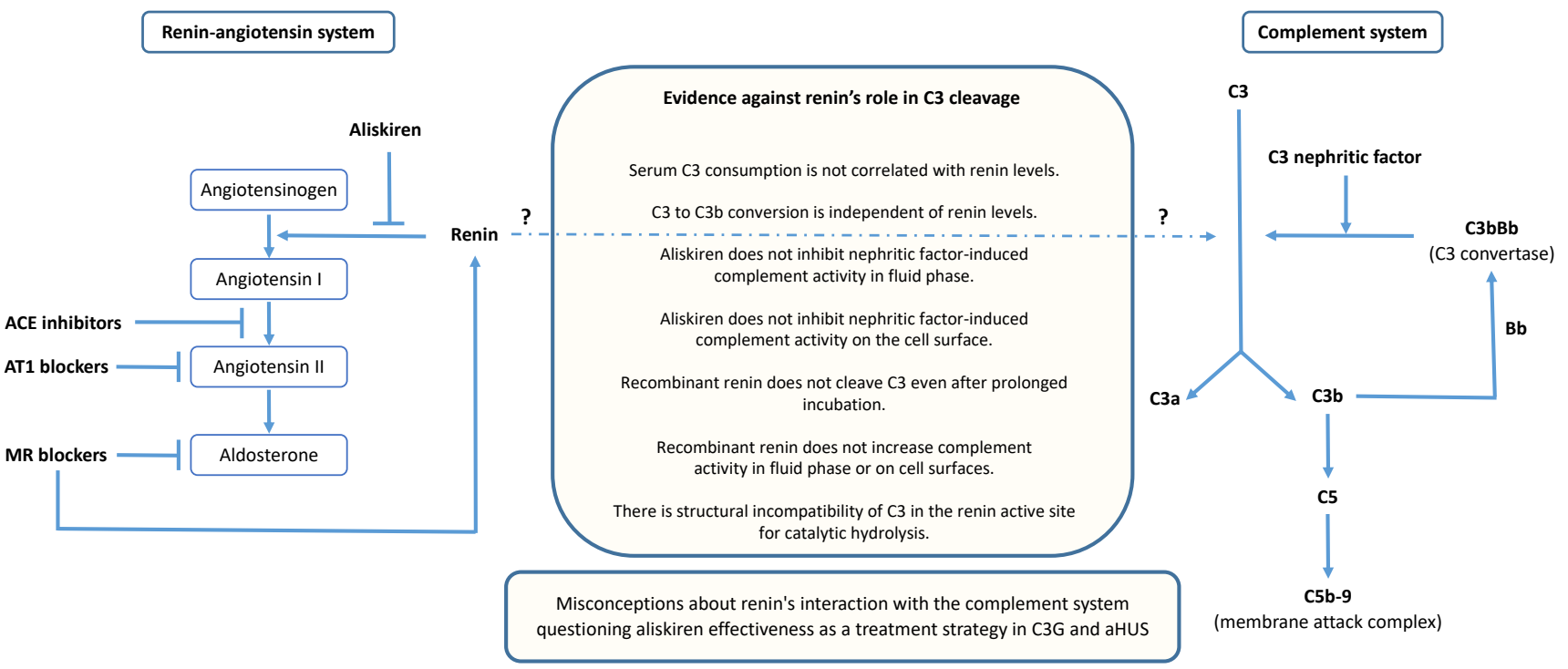
Figure 1. Renin and renin blockade have no role in complement activity



MR, mineralocorticoid receptor. Based on Zhang et al. (8).

Fellows First

In Search of the "White Whale": Is Urine Sodium Effective at Guiding Decongestion?

By Mohamed Ibrahim and Nayan Arora

Despite significant advances in both medical and device-based management, acute heart failure persists as a predominant cause of hospitalization in the Unites States, contributing significantly to health care expenditure and imposing a large burden of morbidity and mortality on affected individuals. Treatment of acute decompensated heart failure is primarily focused on relieving congestion, although studies have indicated that a significant proportion of patients are inadequately decongested at the time of discharge, leading to high rates of rehospitalization and mortality. Although loop diuretics remain a cornerstone of therapy, the ability to assess an adequate therapeutic response remains elusive. Traditional metrics such as changes in weight and cumulative fluid balance are often difficult to assess with accuracy, are unreliable, and often lead to delays in care while data are obtained.

More recently, evaluation of natriuresis via a spot or timed urine sample has garnered interest after several studies have demonstrated benefit in monitoring urine sodium (UNa) to gauge a natriuretic response to decongestive therapy (1–4). This has culminated in the European Society of Cardiology Heart Failure Guidelines (5), which adopts UNa assessment in a spot urine sample 2 hours after diuretic therapy as a recommendation. Various thresholds have been suggested to indicate an insufficient diuretic response, necessitating escalation of therapy.

Recently, two pragmatic trials, Efficacy of a Standardized Diuretic Protocol in Acute Heart Failure (ENACT-HF) (6) and Pragmatic Urinary Sodium-Based Treatment Algorithm in Acute Heart Failure (PUSH-AHF) (7), demonstrated efficacy using a natriuresis-guided therapy utilizing spot UNa levels compared with standard of care (SOC). Although prior studies primarily assessed the impact of initial doses of loop diuretics on spot UNa values, the pragmatic nature of these studies allowed for assessment of protocolized natriuresis-guided decongestion in a diverse group of patients. The PUSH-AHF study (7) randomized 310 adult patients with decompensated heart failure (mean age, 74 years; 45% female; mean left ventricular ejection fraction, 35%; and creatinine, 1.2) to natriuresis-guided therapy versus SOC. The trial design allowed for broad inclusion criteria with main exclusions including severe renal impairment requiring dialysis and dyspnea due to other causes. In the intervention group, spot UNa was assessed at various time points, and treatment intensified if values were less than 70 mmol/L. For the SOC group, diuretic management was not mandated and was left to the discretion of the treating physician. The dual primary outcomes were mean total 24-hour natriuresis and a combined endpoint of time to all-cause mortality or adjudicated heart failure rehospitalization at 180 days. The natriuresis endpoint was met, with natriuresis in the intervention group reported as 409 ± 178 mmol compared with 345 ± 202 mmol in the SOC group. The natriuresis-guided group received a greater cumulative diuretic dose, and a minority of participants received adjunctive agents in response to suboptimal UNa levels. There were no observed differences in all-cause mortality or rehospitalization rates between groups.

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In the *Journal of the American Heart Association*, Olivia-Damaso et al. (8) recognized a need for a validated metric to assess the diuretic response and acknowledge the promise of UNa to tailor diuretic therapy, although they additionally raised valid concerns and limitations with this approach. They expressed concern of the usefulness of UNa as a biomarker beyond day 1 due to the urine becoming more hypotonic in subsequent days in response to hemodynamic, as well as adaptive, changes in the nephron after repeated exposure to loop diuretics. It should be acknowledged that the single center study (9), cited in their article, suffered from a significant degree of missing urinary data after day 2 and was performed in the absence of a diuretic protocol, with treating physicians unblinded to results; therefore, therapy may have been modified.

Olivia-Damaso et al. (8) additionally raised concerns regarding the validity of a UNa-guided approach to therapy in the setting of acute kidney injury (AKI), citing changes to urinary composition due to impact on sodium handling with acute tubular injury, which is the most common cause of AKI in hospitalized patients. A natriuresis-guided approach has not been validated in patients with a reduced estimated glomerular filtration rate (eGFR) in etiologies other than presumed cardiorenal syndrome, although it is worth noting that both aforementioned pragmatic trials (6, 7) enrolled patients with a wide range of eGFRs, including as low as 35 mL/min/1.73 m^2. Finally, the authors queried the ability to monitor UNa in response to alternative decongestive agents, specifically aquaretics (such as vasopressin 2 receptor antagonists), which dilute urine by increasing water excretion and hence lower UNa measurements. Although this is mechanistically correct, the overall role for aquaretics as part of decongestive therapy is questionable with trials failing to demonstrate the benefit of vasopressin antagonists compared with placebo in acute decompensated heart failure (10).

The impact of sodium-glucose cotransporter-2 (SGLT2) inhibitors is of greater importance. Although their role in acute decompensated heart failure has not been established, with improvement in filling pressures correlating better with

metabolic effects rather than reductions in plasma volume, a high prevalence of patients are expected to be treated with these medications due to their role as part of guideline-directed medical therapy. These agents appear to increase urine output primarily using glycosuria, resulting in an osmotic diuresis, which could confound UNa assessments. Importantly, the study by Ter Maaten et al. (7) included additional agents, such as hydrochlorothiazide, acetazolamide, and SGLT2 inhibitors, in their diuretic protocol to address suboptimal UNa levels. A multicenter randomized trial is underway to assess the utility of a UNa-guided approach with combination diuretic therapy (11).

In summary, despite these concerns, UNa is an easily obtainable, inexpensive marker that may provide a tailored approach to decongestion in patients with acute decompensated heart failure. The use of spot UNa analysis to guide diuretic therapy has demonstrable success in both observational and pragmatic randomized trials. Like many protocols in medicine, UNa should not be used in isolation from other markers of decongestion but viewed as a tool to gauge an appropriate threshold response to decongestive therapy with a primary benefit of escalating care more rapidly, potentially leading to decreased length of hospitalization. Future trials to further define the optimal threshold for UNa values as well as the impact of adjunctive diuretics and other interventions to intensify decongestion will further strengthen its utility as a biomarker. ■

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Community Collaborates to Address Clinical Trial Endpoints for FSGS

By Melissa West

"Living with FSGS [focal segmental glomerulosclerosis] impacts every aspect of my life…physically, mentally, financially. It's hard to keep hope sometimes. It's not just the medical bills…it's the travel [to see a specialist out of state]; it's the time spent talking to insurance companies and pharmacies. There is physical fatigue and emotional exhaustion that impact the day to day. My body has changed so many times because of the disease and treatments that I've had to buy a whole new wardrobe multiple times…. Every aspect of your life is totally flipped around," shared Becky Bunker, a person living with FSGS for 2.5 years.

In recent years, there has been an increasing interest in developing new therapies for people with FSGS. This rare glomerular disease affects children and adults and has a high likelihood of progression to kidney failure. There are no approved treatments, and the available options are far from perfect, with limited efficacy and significant side effects. Although we now have a much better understanding of the cause(s) of FSGS and its natural history, much more work remains to be done to understand the disease pathobiology and accelerate the development of effective treatments for various causes of FSGS.

Over the past 5 years, the kidney community has done important work to identify endpoints and outline regulatory pathways for new therapies with the patient experience at the center. The Kidney Health Initiative (KHI) convened a group of experts—including patients, clinicians, representatives from the US Food and Drug Administration (FDA), industry, and trialists—to identify potential clinical trial endpoints for FSGS. Under the leadership of Keisha L. Gibson, MD, FASN, MPH (University of North Carolina, Chapel Hill), and Laura H. Mariani, MD, MS, FASN (University of Michigan), three manuscripts, outlining strengthens and limitations of proteinuria and estimated glomerular filtration rate (eGFR) as trial endpoints and novel biomarkers as drug development tools, are in the final stages of development for publication. "What we learned through the KHI project is that there must be strong evidence to support a surrogate endpoint for clinical trials. The KHI project highlighted the urgent need to come together as a community and share existing patient-level data, in a manner that adequately protects patient privacy and that honors informed consent, to address the current gaps in the evidence," said Mariani. "We hope that with the continued work through a new data-sharing effort, we will provide the needed guidance for [the] FDA, industry, clinicians, and patients," she continued.

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Although the FDA currently accepts a complete remission or near normalization of proteinuria as a surrogate endpoint and basis for traditional approval of new treatments for FSGS, further work is needed to support the use of lesser changes in proteinuria as a basis for accelerated or traditional approval. Proteinuria and GFR as Clinical Trial Endpoints in Focal Segmental Glomerulosclerosis (PARASOL) is a collaborative, international effort that aims to define the quantitative relationships between short-term changes in biomarkers (e.g., proteinuria and GFR) and long-term outcomes to support the use of alternative proteinuria-based endpoints as a basis for accelerated or traditional approval (1). The project is sponsored by NephCure (lead), the International Society of Glomerular Disease (ISGD), the KHI, and the National Kidney Foundation (NKF). The project is led by primary investigators Matthias Kretzler, MD, and Mariani; biostatistical support by Margaret Helmuth, MS; Abigail Smith, PhD; and Alex Mercer, PhD; and project management support by Howard Trachtman, MD, FASN, and ISGD staff including Executive Director Laurel Damashek, MA. (See Table 1 for a complete listing of the Organizing Committee.)

Critical to the success of this effort will be data sharing from various registries and other data sources (Table 2). The community's efforts to develop these registries are a tribute to the many primary investigators and also to the patients who graciously agree to enroll in the registry and share their data. The data sets are unique and will require harmonization to use their different strengths. "With every call or invitation to join us, we have received a warm welcome and agreement to participate. We all recognize that the investment in FSGS clinical trials is important to our clinical care and appreciate the interest in this effort, which will use data to definitively answer the relationship between short-term changes in biomarkers and long-term outcomes," said Kretzler.

PARASOL has defined an aggressive timeline with a milestone to submit the results for presentation at Kidney Week 2024 in San Diego, CA. The project deliverables include:

- **A series of internationally supported cross-stakeholder workshops** with community discussion and review of the analyses, including the FDA and European Medicines Agency, as well as professional and patient non-profit advocacy organizations, culminating in a public scientific consensus workshop
- **Suggested endpoint models** derived from analysis of data sets, to inform feasible trial designs and future regulatory pathways for FSGS
- **Relevant peer-reviewed published paper(s) and communications**

Over 60 people are participating in the collaborative effort led by the team at the University of Michigan and partnering organizations. The drive and passion to prioritize this work come from interacting with people living with FSGS who are willing to contribute their data or participate in a clinical trial. "Data sharing can transform a drug development landscape. I'm very excited about this effort to bring together the available data to identify alternative proteinuria-based endpoints that could potentially be used to establish the efficacy of new therapies for FSGS," said Aliza Thompson, MD, MS, deputy director of the Division

of Cardiology and Nephrology at the Center for Drug Evaluation and Research at the FDA. Josh Tarnoff, NephCure chief executive officer, reflected, "Being in the room, I was struck by the sense of community, with all the world's key FSGS databases coming together for the first time to address this critical issue. The collaboration among and between the various organizations—patient and professional—is unprecedented. We are thrilled and enthusiastically anticipate a positive outcome by year end."

"Industry has shown a strong commitment to developing new therapies for patients with FSGS," said Uptal Patel, MD, chair of the KHI. "KHI is pleased to join NephCure, ISGD, and NKF and greatly appreciates the willingness of the community to share data. The community has had some recent successes in defining clinical trial endpoints that [have] transformed therapeutic options for patients with some kidney diseases. Similarly, we hope to advance pathways to develop therapies in collaboration with all the FSGS stakeholders involved in clinical trials including primary investigators, clinicians, [the] FDA, patients, and researchers," Patel added. Kerry Willis, PhD, chief scientific officer at the NKF, shared: "The NKF is pleased to participate in this effort and plans to offer our knowledge and experience from NKF's previous clinical trial endpoint-related work throughout the process. We look forward with anticipation to seeing where these analyses can take us making better use of biomarkers and designing successful trials."

To learn more about PARASOL, please visit https://www.is-gd.org/parasol, or contact Laura H. Mariani, MD, MS, FASN, at lmariani@med.umich.edu or Laurel Damashek, MA, at ldamashek@is-gd.org.

Melissa West is the senior director for Strategic Relations and Patient Engagement at ASN.

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Table 1. PARASOL Organizing Committee

Member	Affiliation
Matthias Kretzler, MD Co-Chair	University of Michigan
Laura H. Mariani, MD, MS, FASN Co-Chair	University of Michigan
Laurel Damashek, MA	International Society of Glomerular Disease
Hailey Desmond, MS	University of Michigan
Lauren Eva	NephCure
Barbara S. Gillespie, MD, FASN	Fortrea University of North Carolina, Chapel Hill
Tobias B. Huber, MD	University Medical Center Hamburg-Eppendorf International Society of Glomerular Disease
Alex Mercer, PhD	JAMCO Pharma Consulting
Glory Onwuka, MS	International Society of Glomerular Disease
Abigail Smith, PhD	Northwestern University
Josh Tarnoff	NephCure
Aliza Thompson, MD, MS	US Food and Drug Administration
Howard Trachtman, MD, FASN	University of Michigan
Melissa West	American Society of Nephrology/ Kidney Health Initiative
Kerry Willis, PhD	National Kidney Foundation

Table 2. Pending registries and data sets to support PARASOL

CKiD (Chronic Kidney Disease in Children Study)
CureGN (Cure Glomerulonephropathy Network)
DAPA-CKD (Dapagliflozin in Patients with Chronic Kidney Disease)
FONT I and FONT II (Novel Therapies for Resistant FSGS)
FSGS-CT (FSGS Clinical Trial)
GLEAN (Glomerular Disease Learning Network)
Hamburg GN Registry (The Hamburg Glomerulonephritis Registry)
Kaiser Permanente Southern California
KRN (Kidney Research Network)
NEPTUNE (Nephrotic Syndrome Study Network)
RaDaR (National Registry of Rare Kidney Diseases, UK)
Toronto Glomerulonephritis Registry
University of North Carolina GDCN (Glomerular Disease Collaborative Network)

Representatives from these organizations and trials presented at the December 2023 kickoff meeting. The PARASOL leadership team greatly appreciates the interest in the project to date. Please contact PARASOL if you have data and would like to participate.

Pregnancy-Related ESKD Linked to Disparities in Care

Black women have disproportionately high rates of pregnancy-related end stage kidney disease (ESKD), associated with disparities in access to nephrology care and kidney transplantation, reports a study in *JAMA Network Open*.

The researchers analyzed data from 183,640 women of reproductive age with incident ESKD between 2000 and 2020, drawn the from the US Renal Data System and the US Centers for Disease Control and Prevention. From this cohort, 341 patients with pregnancy-related ESKD were identified. Patient characteristics and outcomes were analyzed, including the impact of pre-ESKD nephrology care.

A pregnancy-related primary cause of ESKD was identified in 0.19% of patients. Black women accounted for 31.9% of women with pregnancy-related ESKD compared with 16.2% of the general birthing population.

On multivariable analysis, patients with pregnancy-related ESKD had mortality similar to that of patients with glomerulonephritis or cystic kidney disease and lower than those with diabetes or hypertension (hazard ratio [HR], 0.49) or other/unknown primary causes of ESKD (HR, 0.60).

Despite its high mortality risks, patients with pregnancy-related ESKD had lower access to kidney transplantation compared with those with glomerulonephritis or cystic kidney disease (HR, 0.51), diabetes or hypertension (HR, 0.81), and unknown/other causes (HR, 0.82). Pregnancy-related ESKD was also associated with a lower likelihood of nephrology care (adjusted relative risk [RR], 0.47) or placement of a graft or arteriovenous fistula before ESKD onset (RR, 0.31).

Pregnancy-related acute kidney injury (AKI) is rising in incidence, with a substantial risk of maternal morbidity including ESKD. The study provides new evidence on the characteristics and outcomes of pregnancy-related ESKD, including racial disparities, in the incidence and care for this condition.

"Despite having equivalent or better survival with ESKD, access to transplant among those with pregnancy-related ESKD was surprisingly low, and appeared to be at least partly related to a lack of pre-ESKD nephrology care," the researchers conclude. They add, "[O]ur findings may serve as a foundation to guide clinical care and future research within the much larger population of patients with pregnancy-related AKI who are at significant risk for mortality and severe morbidity" [Kucirka LM, et al. Characteristics and outcomes of patients with pregnancy-related end-stage kidney disease. *JAMA Netw Open* 2023; 6:e2346314. doi: 10.1001/jamanetworkopen.2023.46314]. ■

Higher Hyperkalemia Risk with DPP-4i Compared with Alternatives

In patients with chronic kidney disease (CKD) and type 2 diabetes, treatment with dipeptidyl peptidase-4 inhibitors (DPP-4is) is associated with a greater risk of hyperkalemia compared with sodium-glucose cotransporter-2 inhibitors (SGLT2is) or glucagon-like peptide-1 receptor agonists (GLP-1RAs), reports a recent paper in *Kidney International*.

The study used large datasets of patients with stages 3 to 4 CKD and type 2 diabetes, drawn from Medicare and commercial insurance claims data. The analysis included three cohorts of patients initiating treatment with differing classes of diabetes medications: 141,671 patients receiving SGLT2i versus DPP-4i therapy, 159,545 receiving GLP-1RA versus DPP-4i, and 93,033 receiving SGLT2i versus GLP-1RA.

Diagnosis of hyperkalemia in an outpatient or inpatient setting was compared among groups, along with secondary outcomes. Analyses included adjustment for

more than 140 potential confounders by propensity score matching.

Patients initiating SGLT2i therapy were less likely to develop hyperkalemia compared with those receiving DPP-4i (hazard ratio [HR], 0.74) or GLP-1RA (HR, 0.92). Hyperkalemia risk was lower with GLP-1RA compared with DPP-4i (HR, 0.80). Absolute rate differences per 1000 person-years were –24.8 for SGLT2i versus DPP-4i, –5.0 for SGLT2i versus GLP-1RA, and –17.7 for GLP-1RA versus DPP-4i. Two-year absolute risk differences were –4.3%, –1.8%, and –2.3%, respectively.

Similar patterns were noted for secondary outcomes, including inpatient or emergency department diagnoses of hyperkalemia and serum potassium levels of 5.5 mmol/L or higher. Findings were also similar across demographic and clinical subgroups and on analysis of individual SGLT2i and GLP-1RA agents.

In patients with type 2 diabetes and CKD, hyperkalemia may limit the use of guideline-recommended renin-angiotensin system inhibitors. There are limited data comparing the effects of SGLT2i, GLP-1RA, and DPP-4i in this clinical situation. Reports have suggested that SGLT2i may have a protective effect against hyperkalemia.

The authors discuss the study implications for antihyperglycemic medication choices in patients with type 2 diabetes and CKD. Treatment with SGLT2i or GLP-1RA "may enable the use of other guideline-recommended medications that improve clinical outcomes but increase serum potassium, such as renin-angiotensin system inhibitors" [Fu EL, et al. A population-based cohort defined risk of hyperkalemia after initiating SGLT-2 inhibitors, GLP1 receptor agonists or DPP-4 inhibitors to patients with chronic kidney disease and type 2 diabetes. *Kidney Int*, published online December 13, 2023. doi: 10.1016/j.kint.2023.11.025]. ■

Increased Risks of Urinary Tract Cancers in Advanced CKD

Patients with moderate to severe chronic kidney disease (CKD) are at elevated risk of kidney cancer and urothelial carcinoma, according to a paper in *Nephrology Dialysis Transplantation*.

The researchers performed a systematic review of the literature to identify studies of incident urinary tract

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malignancies associated with CKD. The review identified six studies including more than 8.6 million individuals with moderate to severe CKD, excluding those receiving dialysis or kidney transplant. Associations with kidney cancer and urothelial carcinoma were analyzed, including the effects of CKD severity.

In general, risk of urinary tract cancers increased along with CKD severity. The presence of CKD was associated with a threefold increase in kidney cancer (incidence rate ratio [IRR], 3.36) and a fourfold increase in urothelial malignancy (IRR, 3.96).

After adjustment for confounding factors known to affect kidney or urothelial cancer risk, CKD-associated hazard ratios (HRs) were 3.36 for kidney cancer and 1.40 for urothelial malignancy. The increases were significant for stage 3 CKD (kidney cancer: HR, 1.89 and urothelial malignancy: HR, 1.40) and stages 4/5 CKD (kidney cancer: HR, 2.30 and urothelial malignancy: HR, 1.24).

End stage kidney disease is associated with increased risk of kidney or urothelial cancer. However, less is known about cancer risks associated with non-end stage CKD. Some studies have reported increased malignancy risks even after adjustment for shared risk factors, such as diabetes and hypertension.

Based on the new meta-analysis, "Even moderate CKD is associated with elevated risk of kidney cancer and UC [urothelial carcinoma]," the researchers write. They discuss the implications for assessment and monitoring of patients with CKD, especially those with persistent or worsening hematuria [Brooks ER, et al. Chronic kidney disease and risk of kidney or urothelial malignancy: Systematic review and meta-analysis. *Nephrol Dial Transpl*, published online November 30, 2023. doi: 10.1093/ndt/gfad249].

NT-proBNP Predicts Kidney Function Changes on Anti-Hypertensive Therapy

Patients who have decreased levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) during hypertension treatment are at lower risk of subsequent decline in kidney function, according to the *American Journal of Kidney Diseases*.

The prospective observational study included data on 8005 patients with hypertension from the Systolic Blood Pressure Intervention Trial (SPRINT). In that study, patients were randomly assigned to "intensive" (120 mm Hg) or "standard" (140 mm Hg) systolic blood pressure targets.

Patients with diabetes and proteinuria greater than 1 g/day were excluded from the trial. In the main SPRINT results, the intensive treatment target was associated with lower risk of major cardiovascular events and death but increased rates of certain adverse events.

In the new analysis, patients were classified as having a 1-year increase or decrease in NT-proBNP (≥25%) or stable NT-proBNP (<25% in either direction). Associations with change in kidney function were compared between groups, with stratification by chronic kidney disease (CKD) status.

Patients with a 25% or greater decrease in NT-proBNP had a slower decline in kidney function. An adjusted difference in estimated glomerular filtration rate (eGFR) was 1.09% per year among patients with CKD versus 0.51% per year in those without CKD. In contrast, patients with baseline CKD receiving treatment who had an increase in NT-proBNP showed a faster decline in eGFR: adjusted difference, 1.04% per year. Patients with CKD with increased NT-proBNP were also more likely to have a 30% or greater decline in eGFR: adjusted odds ratio, 1.44. The impact was similar in patients assigned to intensive versus standard blood pressure targets.

"Changes in NT-proBNP during blood pressure treatment are independently associated with subsequent kidney function decline, particularly in people with CKD," the investigators conclude. They discuss the potential implications for dynamic monitoring of NT-proBNP for assessing kidney risk during anti-hypertensive therapy [Ascher SB, et al. Changes in natriuretic peptide levels and subsequent kidney function decline in the SPRINT trial. *Am J Kidney Dis*, published online November 20, 2023. doi: 10.1053/j.ajkd.2023.09.018].

Clinician Perspectives on Barriers to Use of Palliative Care among Patients with Failing Kidney Allografts

By Nicola Feldman and Staci Leisman

Patients who have undergone kidney transplant and have failing grafts experience significant medical, social, and psychological distress (1, 2). Distress caused by serious illness is often targeted by palliative care specialists, whose interventions improve quality of life and symptom burden during a life-limiting illness (3). Although clinician attitudes toward palliative care in lung, heart, and liver transplant settings have been explored (4–6), kidney transplant is unique in multiple ways that may affect perspectives on the use of palliative care. For one example, graft failure does not necessarily correspond to end of life given the availability of hemodialysis; for another example, patients with minimal graft function may be relatively asymptomatic for a long period of time.

An article recently published in the *American Journal of Kidney Diseases* (7) examined clinicians' perspectives on palliative care for patients with failing kidney allografts to elucidate patterns of use and barriers to use of palliative care. The mixed-methods study included a survey plus semi-structured interviews and targeted all members of the transplant team, providing helpful, multidisciplinary insight.

Overall, clinicians acknowledged under-use of palliative care services. Although the vast majority appreciated the benefit of palliative care and trusted colleagues in that field, 61% would only consult palliative care near the end of life, and only 19% referred patients to outpatient palliative care. Clinicians' comments revealed barriers to palliative care involvement at multiple levels (Figure 1).

Perceived barriers to palliative care at the patient level included the belief that patients would not want to have serious illness conversations; clinicians believed that patients would feel scared or anxious, like they were giving up, or depressed if palliative care was discussed. Importantly, these were clinicians' perceptions of patient preferences, not patients' own concerns, and in other settings, patients have been shown to value the information revealed by difficult conversations (8). Clinicians also worried that referral to palliative care would cause patients to think that their transplant clinician was abandoning or "giving up on" them. It would be interesting to explore whether re-initiation of dialysis with transfer to a dialysis care team would elicit the same concerns.

At the clinician level, barriers included clinicians' beliefs about the role of transplant as life-prolonging: 41% thought the goals of transplant and palliative care were contradictory, given that palliative care focuses on quality rather than length of life. This also suggests persistence of a common misconception: that involvement of palliative care requires cessation of curative or life-prolonging therapies. Another barrier was clinician discomfort with communicating the purposes of palliative care to patients with diverse language and cultural backgrounds. This obstacle requires urgent attention. Although clinicians appropriately recognized the distinct needs of diverse populations, inadequate training about how to meet those needs exacerbates the inequities that clinicians intended to address.

At the systems level, transplant clinicians also found challenging the lack of standardization in criteria for palliative care referral, which led to uncertainty about whether and when to refer patients. In addition, limited care coordination between transplant and palliative care services was a barrier, as it required patients to be referred separately for palliative care and to establish relationships with new clinicians. Clinicians also felt that external pressures related to 1-year post-transplant survival metrics, which affect transplant centers' funding and certification (9), created a disincentive to refer some patients to palliative care.

These findings highlight a need for patient and clinician education on the roles of palliative care beyond end-of-life care as well as a need for expansion and integration of palliative care into transplant services. Given the unique elements of kidney graft failure, the most useful roles for palliative care teams may include counseling on prognoses, goals-of-care discussions, and management of psychosocial distress rather than end-of-life care or symptom management. The next steps should include solicitation of patient perspectives, which may help dismantle the patient-level barriers that clinicians perceived. Nephrology transplant training programs and their accrediting bodies may also consider incorporation of existing palliative care training initiatives (10, 11), creation of palliative care-related clinical competencies, and addition of relevant questions to certifying exams. This may improve transplant clinicians' familiarity with the wide range of possible roles for palliative care among patients with failing allografts. ■

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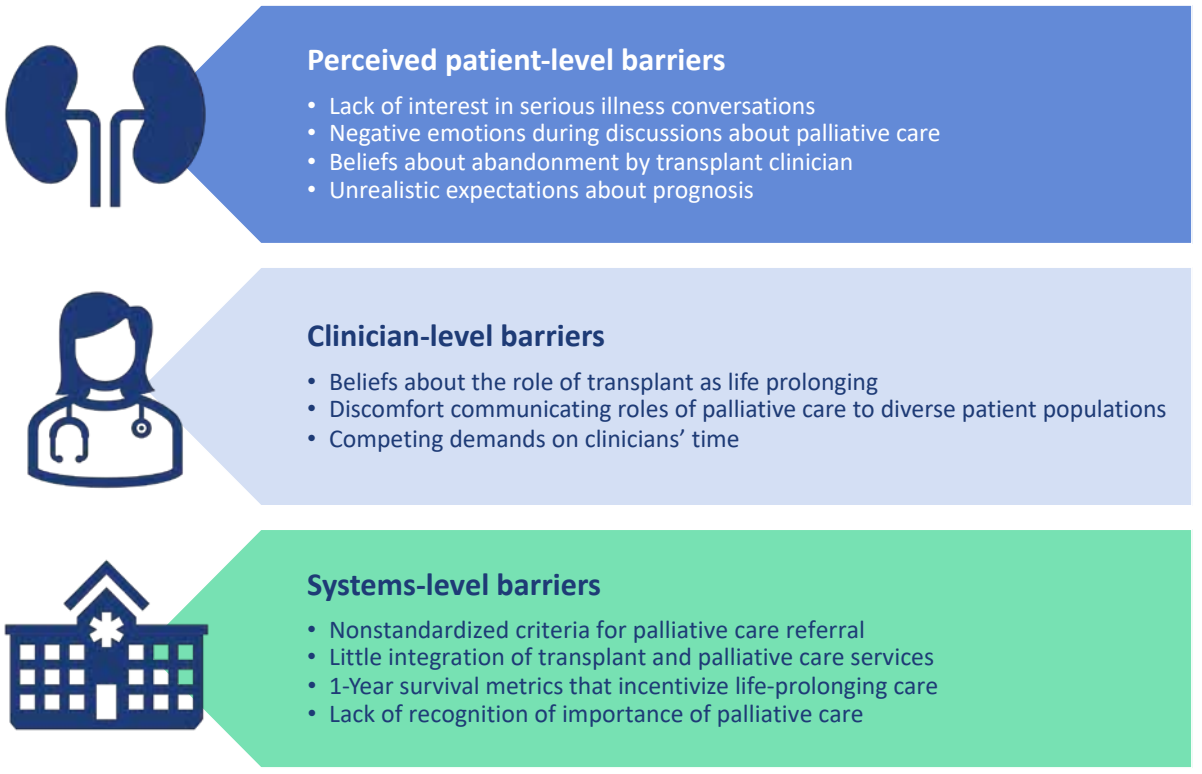
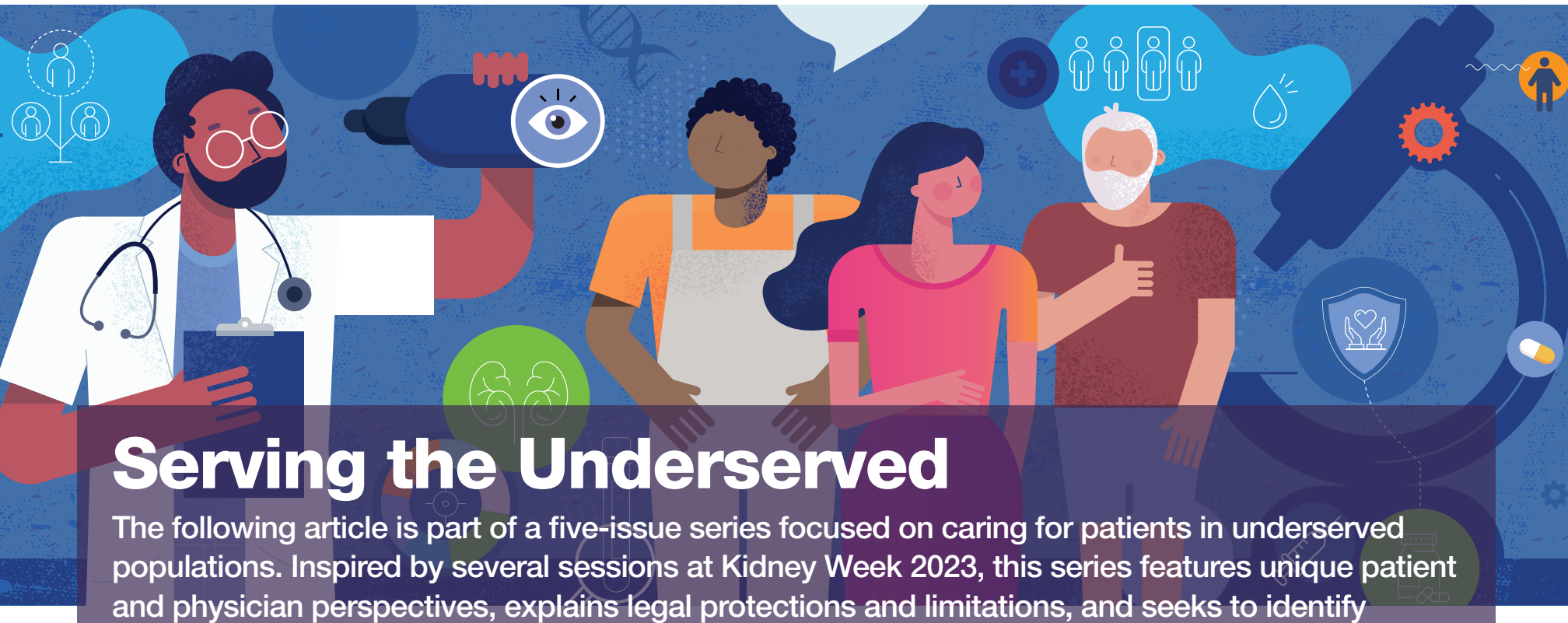
Figure 1. Clinician perceptions of barriers to use of palliative care among patients with failing kidney allografts





Serving the Underserved

The following article is part 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.

Transforming Kidney Care for Fast-Growing Asian American, American Indian, and Alaska Native Populations

By Bridget M. Kuehn

Asian American, American Indian, and Alaska Native communities are three of the fastest-growing populations in the United States. Yet their kidney care needs often go unrecognized or are inadequately met, according to speakers at the "Serving the Underserved: Improving Kidney Health in Underserved Populations" session at Kidney Week 2023 in Philadelphia, PA. Individuals from these communities and clinicians partnering with them are working to change that. Leslie Wong, MD, MBA, FACP, FASN, chief kidney health officer and senior medical director of medical specialties at Intermountain Health in Salt Lake City, UT, shared his perspective on the multitude of cultures that make up the Asian American population, their kidney needs, and the recently launched Coalition of Asian Americans Transforming Opportunities in Nephrology (CATION+). He noted that currently used metrics may not accurately estimate kidney function in Asian Americans or assess their body mass index (BMI) and that they remain woefully underrepresented in nephrology and other health research.

"Asian Americans are a rapidly growing segment of the US population and are at risk for CKD [chronic kidney disease]," Wong said. "Attention is desperately needed to ensure kidney health equity is appropriately addressed for Asian Americans."

Vallabh "Raj" Shah, PhD, distinguished and regents' professor at The University of New Mexico School of Medicine, Albuquerque, shared how community health workers providing culture-centered care may help to address persistent health disparities among Native Americans, including American Indian and Alaska Native people in the United States. He also emphasized the importance of greater support for health systems serving Native American communities and for public health approaches to tackling social determinants of health.

"To begin to put Native Americans on a path to health equity, adequate funding that supports evidence-based, outcome-based, and community-based approaches is essential," Shah said.

Not a monolith

By 2060, the US Asian American population is projected to more than double from 17.8 million to 46 million people (1), making it one of the largest racial or ethnic groups in the country, Wong said. Fifteen in 100 Asian Americans 65 years and older live with CKD. Nearly one-half the Asian American population is concentrated on the West Coast, about one in four live in the South, and substantial populations exist across the country, he added. People of Chinese, Filipino, Indian, Japanese, Korean, and Vietnamese origins make up the largest Asian American subgroups in the United States, according to the Pew Research Center (2). "It is a rich mosaic of ethnicities, culture, and heritage," he said.

Social determinants of health, such as income levels, may also vary widely across Asian American ethnic groups. Wong noted that a common stereotype is that Asian Americans are well-educated and wealthy, but educational and income levels vary across or within subgroups. Language barriers, levels of health literacy, and ability to navigate the health care system may also vary across subgroups, he said. Other demographics can also have a substantial influence on health behaviors. For example, high-risk health behaviors like smoking were higher among Asian American males born in the United States compared with Asian individuals born elsewhere. Additionally, Asian Americans who were married and college educated and earned a higher income had lower risks of diabetes or hypertension than Asian Americans from groups with fewer social supports. "We know [that] different cultures, different beliefs, all influence important health behaviors," he said.

While their ancestry may vary, Wong noted that many Asian Americans feel a sense of shared identity and noted examples, such as the central role of rice in many Asian cuisines and shared difficulties with assimilation and anti-Asian racism. Asian Americans are also increasingly involved in advocating for their communities, he said. "Asian Americans have a stereotype of being silent, not wanting to be heard, but it is clear that the majority of Asian Americans want a voice, they want a leader, they want leaders to speak up and represent their interests," Wong said.

Underrecognized diseases

Overall, Asian American adults have approximately 50% higher proportional kidney disease mortality than non-Hispanic White adults, and Filipino American adults have the highest proportional mortality, more than twice that of White adults and approximately 10% higher than Black adults (3).

The presentation of kidney diseases in Asian Americans may also differ. Wong noted that Asian American patients often have higher albuminuria but are at a lower risk of having reduced estimated glomerular filtration rates (eGFRs) compared with White patients. For example, one study found 1.35 higher adjusted odds of elevated albuminuria among Asian patients and 2.77 higher adjusted odds of severe albuminuria (4). "There seems to be a clear signal for increased albuminuria in this population," he said.

Additionally, Wong cited studies that indicate country-specific differences in eGFRs across those in South Asia, suggesting that developing country-level ethnic adjustments may be necessary to achieve accurate kidney function assessments (5). He proposed that using the creatinine–cystatin C equation may provide more accurate kidney function estimations than equations based on either biomarker alone (5). "If you use creatinine–cystatin C, it is a little better, but it is still not as accurate as developing and using that country-specific eGFR," he said.

Using the race-free CKD-Epidemiology Collaboration, however, may reclassify many Asian patients to a lower (better) CKD stage (6). "You have to wonder and ask what systematic bias might be created by the equations if they are not adjusted for these specific American populations," he said.

Wong noted that Asian Americans have lower rates of diabetes than Black or Hispanic people but much higher than White people. Furthermore, the American Diabetes Association recommends a lower BMI threshold for Asian individuals because what may be a healthy BMI in other racial or ethnic groups may be, in fact, overweight in Asian populations (7), and failing to correct for that may skew risk stratification or management.

Despite some of the unique needs of Asian Americans, little research has been dedicated to understanding how to best care for them. A National Institutes of Health (NIH) consensus report published in the *Annals of Internal Medicine* found that just 0.17% of its budget is spent on research on Asian Americans, Native Hawaiians, or Other Pacific Islander populations, and only 2% of NIH trial participants are representative of these groups (8). With such low representation, uncovering data on the diverse subgroups is near impossible. A recent analysis also found that Asian Americans are underrepresented in kidney disease research as well (9). "Underrepresentation of Asian American populations in health research both undermines health equity and limits important scientific discoveries that would advance prevention in disease clinical care," Wong said.

Inadequate population samples may also contribute to disparities in kidney care. For example, Asian American people make up 8.5% of candidates on the US organ transplant list but only receive 5.7% of the allografts compared with White candidates who make up 40% of the transplant waitlist but receive 55% of the allografts (10).

To help better address these disparities and improve kidney care for Asian American patients, Wong partnered with other Asian American colleagues to create CATION+. Informal conversations among Asian American colleagues during the COVID-19 pandemic about their experiences with anti-Asian hate or workplace discrimination led to the group's formation. The group hopes to raise awareness, fill data gaps, and create resources for addressing kidney diseases in the Asian American population. It also hopes to address the underrepresentation of Asian American nephrologists in faculty and leadership positions, provide mentors and role models for students and trainees, and help reduce workplace bias. "If we can energize, align, and empower Asian American nephrologists nationally, it would be such a great addition to overall efforts to improve health equity for all minority patient populations and ensure we are adequately represented in our health care institutions," Wong said.

Disproportionate burdens

Between 2000 and 2017, the population of American Indian or Alaska Native people in the United States grew by 26%, from 2.6 million to 5.6 million, according to US Census Bureau data (11). Shah said this growth rate is twice as fast as the US population. Some American Indian and Alaska Native communities face extraordinarily high rates of kidney diseases. For example, 18% of people in the Zuni communities in New Mexico, where Shah works, experience kidney failure compared with 1.2% in the US population and 3.1% of American Indian and Alaska Native people nationwide.

Efforts to curb high rates of kidney failure in this population have had some success. For example, between 1996 and 2013, ESKD rates dropped by about half from 57.3 to 26.5, according to data from the US Centers for Disease Control and Prevention (12). "The impact [kidney failure] on communities is really widespread," Shah said. "[Despite] pockets of good news, well-documented challenges and underfunding remain."

Shah noted that individuals from 573 federally recognized tribes are eligible for care through the Indian Health Service (IHS). However, approximately one-half of American Indian and Alaska Native people with low incomes are uninsured. As a result of colonialism and resulting economic adversity, these communities face a disproportionate disease burden, lower life expectancies, inadequate education, and other hardships. He noted that 12% of households in these communities lack safe water and waste-disposal services.

Chronic underfunding of the IHS and its clinics, which may serve individuals across 100 or 200 miles, contributes to care gaps and fragmented care, he said. Often, individuals do not receive guideline-directed care, and the nation's first people often receive "second-class care," according to Shah. He also said it could be challenging to work as a health care professional in these communities that include individuals who may distrust them because of historical wrongs against their community and may blame, as Shah articulates, "white flour, white sugar, and White people" for the health disparities they face.

Shah emphasized the need for cultural sensitivity among practitioners and for engaging patients in their care. He said this should include understanding community values, beliefs, and ways of life. It may also include considering health care access, age, gender, abilities, sexual orientation, religion, socioeconomic factors, community resiliency, and community trauma. "You have to think about cultural considerations," he said. "You have to treat the person first."

He cited a review highlighting the need to incorporate translators, traditional practices, respect for elders, support for caregivers, storytelling and Indigenous art, and culturally consistent and community-based health care resources and personnel (13). The review also cited the need for clinicians to address the harmful legacy of colonialism, address adverse assumptions or stereotypes, listen intensively to convey respect, work with Indigenous clinicians, pay community members for cultural training of health care workers, and respect a role for traditional practices like "smudging," a practice that involves burning plants for purification or cleansing, in dialysis or other patient care.

Culture-centered care

Shah and his colleagues launched a culturally congruent care program using community health workers as frontline agents for change. He said the initial cohort of local community health workers began as high school graduates and continued with the program, and now a few have nursing degrees. The team has improved access to health care, increased health screening, promoted better understanding between the community and the health team, bolstered guideline-directed care, and reduced the need for emergency and specialty services. The team also provides a bridge between the health system and the community. "They are familiar with the culture and language," he said. "They can leverage the influence of peer and social support in health care decision-making."

Shah said it is vital for programs using community health workers to recognize their dual roles as community members and clinicians and help integrate them into local health care systems. Health systems, he said, should implement concomitant, systems-level improvements and provide continuous development opportunities for community health workers and other clinicians. He emphasized the importance of storytelling, such as survivor stories, and providing opportunities for community health workers to "teach back" in their communities.

According to Shah, it is also essential to go beyond focusing on a single disease. He conducted a randomized clinical trial of community health care workers in the Zuni community, in which 48 patients were randomized to usual, clinic-based care and 50 to home-based care, including lifestyle coaching and later, reinforcement of self-monitoring, medication adherence, diet and exercise changes, and use of stress-coping strategies (14). The study monitored patients for 12 months and found that the home-based care group had higher patient-activation scores, lower BMI and reduced hemoglobin A1c levels, threefold reductions in C-reactive protein, and improved mental health screening scores.

Shah shared a toolkit for clinicians and researchers working with rural and health disparity communities (15). He also highlighted the need for more programs aimed at reducing chronic disease in American Indian and Alaska Native populations, increasing access to specialists for these communities, and building a more robust pipeline of Indigenous health professionals. "A strong investment in public health and illness prevention is essential to turning the tide on severe chronic illness in these populations," he concluded. ■

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Visit TAVNEOSPRO.com to explore the data

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

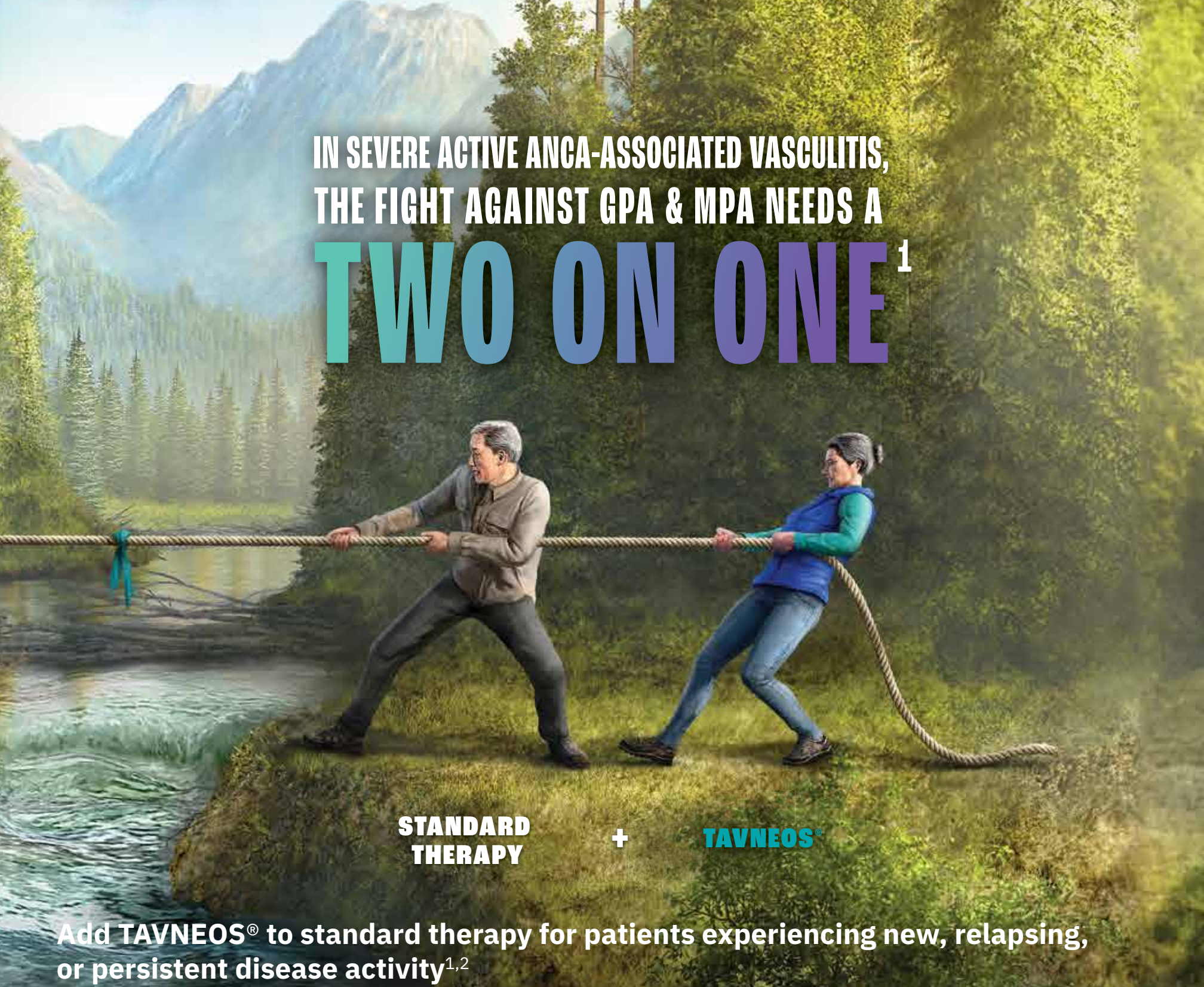
Serious hypersensitivity to avacopan or to any of the excipients.

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.

References: 1. TAVNEOS [package insert]. Cincinnati, OH: Amgen Inc. **2.** Chung SA, Langford CA, Maz M, et al. *Arthritis Rheumatol*. 2021;73(8):1366-1383.

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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Xenotransplantation: Bridging Organ Shortages with Pioneering Advances

By Shikha Jaiswal, Manish Anand, and Amit Govil

As of September 2023, a staggering 96,000 patients were awaiting kidney transplants (1), underscoring a significant demand-supply gap. Cross-species transplantation (xenotransplantation) has witnessed multiple attempts throughout the past century, encompassing organs like the skin, liver, heart, and kidney. In the 1960s, Keith Reemtsma, MD, and his team embarked on a groundbreaking journey, performing 13 chimpanzee-to-human kidney xenotransplants (2) with varying degrees of success, attributed to limited immunosuppression availability and infectious complications. In 2022, the promising pig-to-human heart transplant was unfortunately curtailed at 2 months, presumably due to antibody-mediated rejection and activation of latent porcine cytomegalovirus (PCMV) and porcine roseolovirus infections (3).

Previous experiments involving pig-to-non-human primate transplants unveiled the presence of the galactose (Gal) oligosaccharide antigen on pig vascular endothelium, which is not expressed in humans. Genetic alterations were subsequently introduced to eliminate this porcine antigen, thus averting hyperacute rejections. Further genetic modifications targeting complement-mediated cytotoxicity and thrombosis were introduced. These genetically engineered pigs—endowed with 10 genetic (10-GE) modifications, including the insertion of human complement inhibitor and anticoagulant genes, along with deletion of pig Gal antigen and pig growth hormone receptor genes—now serve as subjects for xenotransplantation studies. Importantly, these 10-GE pigs do not express red blood cell antigens and are universal donors with respect to blood types.

A significant milestone was marked by Locke and colleagues (4) in 2022, who reported the first clinical-grade porcine-to-human xenotransplantation involving a 10-GE pig. The induction immunosuppression regimen included antithymocyte globulin, methylprednisolone, and rituximab, followed by maintenance with tacrolimus and mycophenolate mofetil. Despite the xenografts exhibiting urine production, renal function and creatinine clearance remained suboptimal, and the study was terminated at 77 hours due to severe coagulopathy and recipient exsanguination. Protocol biopsies taken on the first day revealed thrombotic microangiopathy (TMA), whereas day 3 biopsies showcased extensive cortical necrosis, with C4d remaining negative.

Montgomery et al. (5) undertook a series of two porcine-to-human xenotransplants using Gal knockout pigs. They transplanted a thymic autograft from the pig beneath the kidney capsule (thymokidney) to mitigate host T cell-mediated immune responses. Both recipients, closely monitored for 54 hours, demonstrated improved creatinine levels and glomerular filtration rates alongside brisk diuresis. However, post-explant phenotypic analysis (6) revealed microvascular inflammation, increased expression of genes linked to antibody-mediated rejection, and serological evidence of circulating donor-specific antibodies in both recipients. The absence of C4d hinted at alternative biological rejection pathways apart from complement cascade activation.

In a groundbreaking development in late 2023, Locke et al. (7) performed another porcine-to-human kidney xenotransplant using 10-GE pigs. This time, the procedure was done 24 hours after eculizumab administration, combined with conventional induction and maintenance immunosuppression. The recipient was monitored for 7 days; the xenografts initially produced 37 L of urine on day 1, eventually concentrating to 5 L by day 3, accompanied by improved creatinine clearance. Serial biopsies during this period did not show any signs of rejection or TMA.

Xenotransplantation is not without challenges and limitations. Concerns over PCMV and endogenous retrovirus transmission to humans can be managed through stringent pig housing and regular donor and recipient testing. Ethical considerations, encompassing informed consent, animal rights, and religious beliefs, also loom over xenotransplants. Despite favorable short-term outcomes, antibody-mediated rejection remains a possibility, necessitating the exploration of therapies targeting humoral immunity. A comprehensive evaluation of adaptive immune responses will hinge on long-term studies involving deceased human recipients.

In conclusion, xenotransplantation holds promise as a solution to the organ-shortage crisis, but it requires ongoing research, technological advancements, and careful consideration of ethical and safety concerns to become a widely accepted and sustainable medical practice. ■

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Cefepime versus Piperacillin-Tazobactam in Adults Hospitalized with Acute Infection

The ACORN Randomized Clinical Trial

By Aiman Ajaz and Medha Airy

Gram-negative infections continue to be one of the main reasons for in-patient morbidity and mortality (1). An appropriate choice of an empiric antibiotic treatment has been associated with improved short-term outcomes with reduced risk of in-hospital mortality and death (2). The selection of empiric antibiotics is often determined by their efficacy and adverse effect profile. The Infectious Diseases Society of America recommends use of beta-lactam antibiotics for pseudomonas infection (3). Piperacillin-tazobactam and cefepime are the mainstay for empiric treatment for gram-negative coverage, specifically pseudomonas, and are often combined with vancomycin to provide gram-positive coverage as well (3). Numerous anecdotal and in vitro studies have indicated risk of acute kidney injury (AKI) with the use of piperacillin-tazobactam (4–7) and have reported neurological toxicity associated with the use of cefepime (8, 9).

Qian and colleagues (10, 11) recently published Antibiotic Choice on Renal Outcomes (ACORN), a pragmatic open-label randomized clinical trial that compares the use of piperacillin-tazobactam with cefepime in a real-life setting in patients diagnosed with infection and needing anti-pseudomonal coverage. It also compares risk of AKI and neurologic dysfunction (10, 11). This trial is another exemplary illustration of the role of pragmatic trials in the current era of lack of funding and industry-driven explanatory trials.

Pragmatic trials have been adopted in the last decade as a method of trial that provides evidence for adopting the intervention into real-world clinical practice (12). These trials emphasize external validity by adapting to the current practice patterns so that the outcomes can be generalized as they influence clinical or policy decision-making. Specific guidance and scoring systems were made available originally by using the Pragmatic Explanatory Continuum Indicator Summary (PRECIS) tool and were subsequently revised in PRECIS-2 to have parameters for assessing the degree of pragmatism while addressing ethical and regulatory issues (12).

PRECIS-2 has nine dimensions for assessing the level of pragmatism, and the study by Qian et al. (10, 11) meets most

of these requirements (Table 1). The study included recruiting patients with suspected infection, a condition commonly presented in numerous health care facilities, aligning with the PRECIS-2 framework. Despite this, the study's exclusive execution at a single tertiary care hospital in the United States could potentially skew the findings. While the procedures implemented could be mirrored in comparable settings, it is important to note that the same might not hold true for less-equipped institutions, a factor that should be considered separately from the core objectives of the study. The nature of follow-up is not entirely objective and may introduce a confirmation bias, as there might have been a tendency to look for neurological endpoints in the group receiving cefepime. The between-group difference of 0.3 days for being free of delirium and coma and being alive would likely not lead to a change in clinical practice. The outcome for these patients was censored at hospital discharge, which can lead to information bias. Lastly, PRECIS-2 focuses on the relevance of the primary outcome to the participants, and in this case, it affects them directly and meets this requirement. However, as the authors state, comparing two safety outcomes increases the chances of type 1 error, and this needs to be considered while interpreting the results.

It must be underscored that in the context of diminishing funding options and industry-driven research, this approach is the sole, viable means to assess an established treatment protocol and gather relevant data. The pragmatic trial design allowed them to obtain a waiver of informed consent and permit enrollment comparable to a real-world situation. This is of utmost importance, as it overcomes the biggest hurdle of enlisting patients in the trial process. Qian and colleagues (10, 11) concluded that the highest stage of AKI or death was not significantly different in the piperacillin-tazobactam and the cefepime group (odds ratio, 0.95 [95% CI, 0.80–1.13]; p = 0.56). However, patients in the cefepime group experienced fewer days alive and free of delirium and coma within the 14 days than did the piperacillin-tazobactam group (mean [SD], 11.9 [4.6] days [cefepime group] vs 12.2 [4.3] days [piperacillin-tazobactam group]; odds ratio, 0.79 [95% CI, 0.65–0.95]). These findings should help reduce hesitation among prescribers to use piperacillin-tazobactam due to concern of kidney injury, an apprehension that had grown significantly since its combined use with vancomycin that led to the warning for AKI among its users. This was based on a review and meta-analysis of the observational studies that concluded a higher incidence of AKI with the use of vancomycin and piperacillin-tazobactam compared with vancomycin monotherapy (odds ratio, 3.40 [95% CI, 2.57–4.50]) (13). With the ACORN study, prescribers should be reassured about the use of piperacillin-tazobactam. ■

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Table 1. ACORN trial strengths and limitations

Trial procedures	Strengths	Limitations
Recruitment	• Open-label randomized clinical trial • Waiver of informed consent	• Single-center study
Intervention	• Rapid infusion of cefepime in one arm and piperacillin-tazobactam infusion in another arm	• Rapid infusion of cefepime has been associated with neurologic side effects and could explain the results. • Low-dose piperacillin was used for this trial and may have affected the results. • There was significant crossover in the antibiotics administration that has not been fully explained, which may have affected the group assignment.
Follow-up	• Antibiotics for median duration of 3 days (interquartile range, 1–4 days) and followed up for 4 days	• Outcomes that happened during the latter part of the follow-up period may not have been attributable to the antibiotics received in the earlier half. • Outcome assessment was censored at hospital discharge, which may have led to information bias.
Determination and analysis of outcome	• Highest stage of AKI or death by day 14 • Days free of delirium and coma within 14 days	• Delirium management practices were not standardized and would be difficult to be replicated in the real world.

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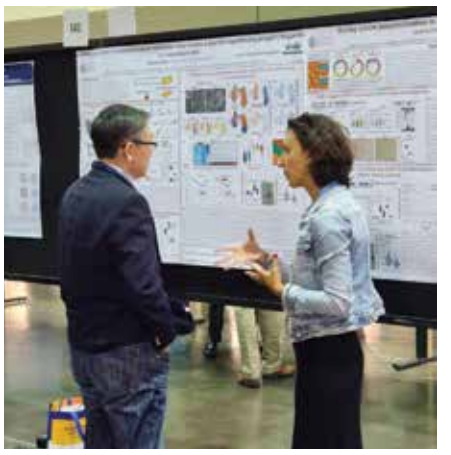

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