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High-Impact Clinical Trials Show Promising Results Across the Spectrum of Kidney Diseases:

Studies on GLP-1 Agonists, SGLT2 Inhibitors, and Dialysis Pain and Itching Therapies Highlighted at Kidney Week 2024

By Bridget M. Kuehn

Studies presented during the High-Impact Clinical Trials session at Kidney Week 2024 in San Diego, CA, provided additional insights on which patients may benefit from glucagon-like peptide-1 (GLP-1) agonists or sodium-glucose cotransporter-2 (SGLT2) inhibitors, helping expand the number of patients who might benefit from these breakthrough drugs to include patients without diabetes and patients with advanced kidney diseases.

"The data are nicely lining up, suggesting that both SGLT2 inhibitors and GLP-1 agonists are kidney-protective drugs and preserve kidney function independently of the diabetes status of the patient," said David Wheeler, MD, professor of kidney medicine at University College London, United Kingdom, who was not involved in the studies.

Other studies presented during the session focused on two common dialysis side effects—persistent pain and itching—as well as therapies for rare kidney diseases and care for patients with kidney diseases who are critically ill.

Growing GLP-1 indications

Clinical trials have demonstrated the safety and efficacy of GLP-1 agonists, which have beneficial effects on kidney and heart health for patients with diabetes and obesity. However, questions remained about the use of the drugs in specific patient populations. For example, would patients with later stages of kidney diseases or without diabetes benefit? Studies presented during the Kidney Week High-Impact Clinical Trials sessions help to answer those questions.

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Kidney Care Community Comes Together in Aftermath of Historic Hurricane

By Lisa Schwartz

When historic hurricanes swept through the southern United States in late September and early October, no one could fathom the enduring impact they would have on the health care system, specifically patients with chronic kidney disease (CKD) relying on lifesaving dialysis.

Florida was struck by back-to-back storms, Hurricanes Helene and Milton, which caused devastating flooding, storm surge, and wind damage to dialysis centers around the state, displacing patients who relied on in-center treatment. Florida's experience with severe weather, such as category 5 Hurricane Michael in 2018 that destroyed parts of the Panhandle and left thousands of patients on dialysis without treatment, helped shape the state's preparedness and response systems during natural disasters (1). With contingency plans in place, Florida's dialysis community was able to get back online and expeditiously serve the needs of its patients despite continued power outages.

When Hurricane Helene's torrential rains hit North Carolina's mountainous regions—areas not often struck by catastrophic storms—in late September, the impact was a stark reminder of nature's unpredictability. The devastation experienced in North Carolina not only affected thousands of people with CKD and those undergoing dialysis in the region, but the downstream effects of a shortage of peritoneal dialysis (PD) fluids were also felt around the country. The crisis prompted a local and nationwide response and

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Inside

Hemodiafiltration launching in the US
What could this mean for dialysis delivery and standard of care?

Journey through the nephron
A case-based physiologic exploration of each unique segment

Call for transplant reform
Data presented at Kidney Week 2024 show growing numbers of discarded organs and out-of-sequence placements.

FABHALTA®
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FABHALTA IS NOW FDA APPROVED

for the reduction of proteinuria in adults with *primary IgAN* at risk of rapid disease progression, generally a UPCR ≥1.5 g/g[1]

This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FABHALTA® slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.[1]

Scan to learn more or visit fabhalta-hcp.com/igan

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

FABHALTA, a complement inhibitor, increases the risk of serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b. Life-threatening and fatal infections with encapsulated bacteria have occurred in patients treated with complement inhibitors. These infections may become rapidly life threatening or fatal if not recognized and treated early.

- **Complete or update vaccinations for encapsulated bacteria at least 2 weeks prior to the first dose of FABHALTA, unless the risks of delaying therapy with FABHALTA outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients receiving a complement inhibitor.**
- **Patients receiving FABHALTA are at increased risk for invasive disease caused by encapsulated bacteria, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious infections and evaluate immediately if infection is suspected.**

Because of the risk of serious infections caused by encapsulated bacteria, FABHALTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FABHALTA REMS.

CONTRAINDICATIONS

- In patients with serious hypersensitivity to FABHALTA or any of the excipients.
- For initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae* type b.

WARNINGS AND PRECAUTIONS

Serious Infections Caused by Encapsulated Bacteria

- FABHALTA, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis* (caused by any serogroup, including nongroupable strains), and *Haemophilus influenzae* type b. Life-threatening and fatal infections with encapsulated bacteria have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors. The initiation of FABHALTA is contraindicated in patients with unresolved serious infections caused by encapsulated bacteria.
- Complete or update vaccination against encapsulated bacteria at least 2 weeks prior to the start of FABHALTA, according to the current ACIP recommendations for patients receiving a complement inhibitor. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with FABHALTA. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent FABHALTA therapy is indicated in a patient who is not up to date with vaccines against encapsulated bacteria according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible. The benefits and risks of treatment with FABHALTA, as well as the benefits and risks of antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by encapsulated bacteria.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information, including Boxed WARNING on the following pages.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Serious Infections Caused by Encapsulated Bacteria (continued)

- Vaccination does not eliminate the risk of serious encapsulated bacterial infections, despite development of antibodies following vaccination. Closely monitor patients for early signs and symptoms of serious infection and evaluate patients immediately if an infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if they occur. Promptly treat known infections. Serious infection may become rapidly life threatening or fatal if not recognized and treated early. Consider interruption of FABHALTA in patients who are undergoing treatment for serious infections, depending on the risks of interrupting treatment in the disease being treated.

FABHALTA REMS

- FABHALTA is available only through a restricted program under a REMS called FABHALTA REMS, because of the risk of serious infections caused by encapsulated bacteria.
- Under the FABHALTA REMS, prescribers must enroll in the program; counsel patients about the risks, signs, and symptoms of serious infections caused by encapsulated bacteria; provide patients with the REMS educational materials; ensure patients are vaccinated against encapsulated bacteria; prescribe antibacterial drug prophylaxis if patients' vaccine status is not up to date and treatment must be started urgently; and provide instructions to always carry the Patient Safety Card during treatment and for 2 weeks following the last dose of FABHALTA.
- Further information is available by telephone: 1-833-993-2242 or online at **www.FABHALTA-REMS.com**.

Hyperlipidemia

- FABHALTA may increase total cholesterol, LDL cholesterol, and serum triglycerides. Some patients required cholesterol-lowering medications.
- Monitor serum lipid parameters periodically during treatment with FABHALTA and initiate cholesterol-lowering medications, if indicated.

ADVERSE REACTIONS

- The most common adverse reactions (≥5%) in adults with IgAN receiving FABHALTA were upper respiratory tract infection, lipid disorder, and abdominal pain.

DRUG INTERACTIONS

- Concomitant use of CYP2C8 inducers (eg, rifampin) may decrease iptacopan exposure, which may result in loss of or reduced efficacy of FABHALTA. Monitor the clinical response and discontinue use of the CYP2C8 inducer if loss of efficacy of FABHALTA is evident.
- Concomitant use of strong CYP2C8 inhibitors (eg, gemfibrozil) may increase iptacopan exposure, which may result in an increased risk for adverse reactions with FABHALTA. Coadministration with a strong CYP2C8 inhibitor is not recommended.

USE IN SPECIFIC POPULATIONS

- Because of the potential for serious adverse reactions in a breastfed child, breastfeeding should be discontinued during treatment and for 5 days after the final dose.
- FABHALTA is not recommended in patients with severe hepatic impairment (Child-Pugh class C). No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.

INDICATION

FABHALTA is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FABHALTA slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

Please see additional Important Safety Information on previous page and Brief Summary of full Prescribing Information, including Boxed WARNING on the following pages.

IgAN, immunoglobulin A nephropathy; UPCR, urine protein-to-creatinine ratio.

Reference: 1. Fabhalta. Prescribing information. Novartis Pharmaceuticals Corp.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Printed in USA 9/24 424579

FABHALTA® (iptacopan) capsules, for oral use
Initial U.S. Approval: 2023

BRIEF SUMMARY: Please see package insert for full prescribing information.

WARNING: SERIOUS INFECTIONS CAUSED BY ENCAPSULATED BACTERIA

FABHALTA, a complement inhibitor, increases the risk of serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae, Neisseria meningitidis*, and *Haemophilus influenzae* type b *[see Warnings and Precautions (5.1)]*. Life-threatening and fatal infections with encapsulated bacteria have occurred in patients treated with complement inhibitors. These infections may become rapidly life-threatening or fatal if not recognized and treated early.

- **Complete or update vaccination for encapsulated bacteria at least 2 weeks prior to the first dose of FABHALTA, unless the risks of delaying therapy with FABHALTA outweigh the risk of developing a serious infection. Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria in patients receiving a complement inhibitor. See *Warnings and Precautions (5.1)* for additional guidance on the management of the risk of serious infections caused by encapsulated bacteria.**
- **Patients receiving FABHALTA are at increased risk for invasive disease caused by encapsulated bacteria, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious infections and evaluate immediately if infection is suspected.**

Because of the risk of serious infections caused by encapsulated bacteria, FABHALTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the FABHALTA REMS *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Paroxysmal Nocturnal Hemoglobinuria

FABHALTA is indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH).

1.2 Immunoglobulin A Nephropathy

FABHALTA is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g.

This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether FABHALTA slows kidney function decline in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

4 CONTRAINDICATIONS

FABHALTA is contraindicated:

- in patients with serious hypersensitivity to iptacopan or any of the excipients.
- for initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, or *Haemophilus influenzae* type b.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections Caused by Encapsulated Bacteria

FABHALTA, a complement inhibitor, increases a patient's susceptibility to serious, life-threatening, or fatal infections caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis* (caused by any serogroup, including non-groupable strains), and *Haemophilus influenzae* type b. Life-threatening and fatal infections with encapsulated bacteria have occurred in both vaccinated and unvaccinated patients treated with complement inhibitors. The initiation of FABHALTA treatment is contraindicated in patients with unresolved serious infections caused by encapsulated bacteria.

Complete or update vaccination against encapsulated bacteria at least 2 weeks prior to administration of the first dose of FABHALTA, according to the current ACIP recommendations for patients receiving a complement inhibitor. Revaccinate patients in accordance with ACIP recommendations considering the duration of therapy with FABHALTA. Note that ACIP recommends an administration schedule in patients receiving complement inhibitors that differs from the administration schedule in the vaccine prescribing information. If urgent FABHALTA therapy is indicated in a patient who is not up to date with vaccines against encapsulated bacteria according to ACIP recommendations, provide the patient with antibacterial drug prophylaxis and administer these vaccines as soon as possible. Various durations and regimens of antibacterial drug prophylaxis have been considered, but the optimal durations and drug regimens for prophylaxis and their efficacy have not been studied in unvaccinated or vaccinated patients receiving complement inhibitors, including FABHALTA. The benefits and risks of treatment with FABHALTA, as well as the benefits and risks of antibacterial drug prophylaxis in unvaccinated or vaccinated patients, must be considered against the known risks for serious infections caused by encapsulated bacteria.

Vaccination does not eliminate the risk of serious encapsulated bacterial infections, despite development of antibodies following vaccination. Closely monitor patients for early signs and symptoms of serious infection and evaluate patients immediately if an infection is suspected. Inform patients of these signs and symptoms and instruct patients to seek immediate medical care if these signs and symptoms occur. Promptly treat known infections. Serious infection may become rapidly life-threatening or fatal if not recognized and treated early. Consider interruption of FABHALTA in patients who are undergoing treatment for serious infections, depending on the risks of interrupting treatment in the disease being treated.

FABHALTA is available only through a restricted program under a REMS *[see Warnings and Precautions (5.2)]*.

5.2 FABHALTA REMS

FABHALTA is available only through a restricted program under a REMS called FABHALTA REMS, because of the risk of serious infections caused by encapsulated bacteria *[see Warnings and Precautions (5.1)]*.

Notable requirements of the FABHALTA REMS include the following:

- Prescribers must enroll in the REMS.
- Prescribers must counsel patients about the risk of serious infections caused by encapsulated bacteria.
- Prescribers must provide patients with the REMS educational materials.
- Prescribers must assess patient vaccination status for vaccines against encapsulated bacteria and vaccinate if needed according to current ACIP recommendations two weeks prior to the first dose of FABHALTA.
- Prescribers must provide a prescription for antibacterial drug prophylaxis if treatment must be started urgently, and the patient is not up to date with vaccines against encapsulated bacteria according to current ACIP recommendations at least two weeks prior to the first dose of FABHALTA.
- Pharmacies that dispense FABHALTA must be certified in the FABHALTA REMS and must verify prescribers are certified.
- Patients must receive counseling from the prescriber about the need to receive vaccinations against encapsulated bacteria per ACIP recommendations, the need to take antibiotics as directed by the prescriber, and the early signs and symptoms of serious infections.
- Patients must be instructed to carry the Patient Safety Card with them at all times during treatment and for 2 weeks following the last dose of FABHALTA.

Further information is available by telephone: 1-833-99FABHA (1-833-993-2242) or online at www.FABHALTA-REMS.com.

5.3 Monitoring of PNH Manifestations After FABHALTA Discontinuation

In PNH patients, after discontinuing treatment with FABHALTA, closely monitor patients for at least 2 weeks after the last dose for signs and symptoms of hemolysis. These signs include elevated lactate dehydrogenase (LDH) levels along with a sudden decrease in hemoglobin or PNH clone size, fatigue, hemoglobinuria, abdominal pain, dyspnea, major adverse vascular events (such as thrombosis, stroke and myocardial infarction), dysphagia, or erectile dysfunction. If discontinuation of FABHALTA is necessary, consider alternative therapy.

If hemolysis occurs after discontinuation of FABHALTA, consider restarting treatment with FABHALTA, if appropriate, or initiating another treatment for PNH.

5.4 Hyperlipidemia

FABHALTA may increase total cholesterol, LDL-cholesterol, and serum triglycerides *[see Adverse Reactions (6.1)]*.

Of the 54 FABHALTA-treated patients who had a normal total cholesterol level at baseline in APPLY-PNH, 43% developed Grade 1 hypercholesterolemia during the randomized treatment period. One FABHALTA-treated patient in APPLY-PNH experienced increased total cholesterol that worsened to Grade 2 from Grade 1 at baseline.

Of the 34 FABHALTA-treated patients who had a normal cholesterol level at baseline in APPOINT-PNH, 24% developed Grade 1 hypercholesterolemia during the core treatment period.

Of the 60 FABHALTA-treated patients who had LDL-cholesterol ≤ 130 mg/dL at baseline in APPLY-PNH, 17% developed LDL-cholesterol > 130-160 mg/dL, 8% developed LDL-cholesterol > 160-190 mg/dL, and 7% developed LDL-cholesterol > 190 mg/dL during the randomized treatment period. Of the 36 FABHALTA-treated patients who had LDL-cholesterol ≤ 130 mg/dL at baseline in APPOINT-PNH, 11% developed LDL-cholesterol > 130-160 mg/dL and 3% developed LDL-cholesterol > 160-190 mg/dL.

Of the 52 patients with normal triglyceride levels at baseline in APPLY-PNH, 23% developed Grade 1 elevated triglycerides during the randomized treatment period. Three FABHALTA-treated patients in APPLY-PNH experienced an increase in triglycerides from Grade 1 to Grade 2.

Of the 37 FABHALTA-treated patients who had a normal triglyceride level at baseline in APPOINT-PNH, 27% developed Grade 1 elevated triglycerides in the core treatment period.

Of the 102 FABHALTA-treated patients in APPLY-PNH and APPOINT-PNH, two patients required cholesterol-lowering medications.

Monitor serum lipid parameters periodically during treatment with FABHALTA and initiate cholesterol-lowering medication, if indicated.

6 ADVERSE REACTIONS

The following clinically significant adverse reaction is discussed in greater detail in other sections of the labeling:

- Serious Infections Caused by Encapsulated Bacteria *[see Warnings and Precautions (5.1)]*.
- Hyperlipidemia *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trials 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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

The data described below reflects the exposure in adults with PNH who received FABHALTA (n = 62) or anti-C5 treatment (US-approved and non-US-approved eculizumab product or US-approved and non-US-approved ravulizumab product, n = 35) in APPLY-PNH [NCT04558918] and adults who received FABHALTA (n = 40) in APPOINT-PNH

[NCT04820530] at the recommended dosing regimen for 24 weeks. In APPLY-PNH, serious adverse reactions were reported in 2 (3%) patients with PNH receiving FABHALTA. Serious adverse reactions included pyelonephritis, urinary tract infection and COVID-19. In APPOINT-PNH, serious adverse reactions were reported in 2 (5%) patients with PNH receiving FABHALTA. Serious adverse reactions included COVID-19 and bacterial pneumonia. The most common adverse reactions (≥ 10%) with FABHALTA were headache, nasopharyngitis, diarrhea, abdominal pain, bacterial infection, viral infection, nausea, and rash.

Table 1 describes the adverse reactions that occurred in > 5% of patients treated with FABHALTA in the APPLY-PNH or APPOINT-PNH studies.

Table 1: Adverse Reactions Reported in > 5% of Patients Treated with FABHALTA in APPLY-PNH or APPOINT-PNH Studies (24-Week Treatment Period)

Adverse reactions	APPLY-PNH		APPOINT-PNH
	FABHALTA (N = 62) n (%)	Anti-C5 (Eculizumab or Ravulizumab) (N = 35) n (%)	FABHALTA (N = 40) n (%)
Headache[a]	12 (19)	1 (3)	11 (28)
Nasopharyngitis[b]	10 (16)	6 (17)	6 (15)
Diarrhea	9 (15)	2 (6)	3 (8)
Abdominal pain[a]	9 (15)	1 (3)	3 (8)
Bacterial infection[c]	7 (11)	4 (11)	2 (5)
Nausea	6 (10)	1 (3)	2 (5)
Viral infection[d]	6 (10)	11 (31)	7 (18)
Arthralgia	5 (8)	1 (3)	0
Thrombocytopenia[a]	4 (6)	0	0
Dizziness	4 (6)	0	1 (3)
Systemic hypertension[a]	4 (6)	0	0
Lipid disorder[e]	4 (6)	0	3 (8)
Rash[f]	2 (3)	0	4 (10)

[a]Includes similar terms.
[b]Nasopharyngitis contains: rhinitis allergic, upper respiratory tract infection, pharyngitis, rhinitis.
[c]Bacterial infection contains: pyelonephritis, urinary tract infection, bronchitis bacterial, bronchitis haemophilus, cholecystitis, folliculitis, cellulitis, arthritis bacterial, sepsis, klebsiella infection, staphylococcal infection, *Pseudomonas* infection, hordeolum, pneumonia bacterial.
[d]Viral infection contains: COVID-19, herpes zoster, oral herpes, nasal herpes, influenza A virus test positive, influenza.
[e]Lipid disorder contains: dyslipidemia, blood cholesterol increased, low density lipoprotein increased, hypercholesterolemia, blood triglycerides increased, hyperlipidemia.
[f]Rash contains: dermatitis allergic, acne, erythema multiforme, rash maculo-papular, rash erythematous.

Clinically relevant adverse reactions reported in less than or equal to 5% of patients includes urticaria in one patient (3%) in APPOINT-PNH.

Description of Select Adverse Reactions (graded per NCI CTCAE Version 4.03 unless noted otherwise)

Platelet Count Decreased
Of the 37 FABHALTA-treated patients who had normal platelet counts at baseline in APPLY-PNH, 43% experienced any Grade thrombocytopenia during the randomized treatment period. Three FABHALTA-treated patients in APPLY-PNH experienced decreased platelets that worsened to Grade ≥ 3 from baseline (one patient with normal platelets that worsened to Grade 4, one patient with baseline Grade 1 that worsened to Grade 4, and one patient with baseline Grade 3 that worsened to Grade 4).

Immunoglobulin A Nephropathy (IgAN)
The safety of FABHALTA was evaluated in APPLAUSE-IgAN, a randomized double-blind clinical study in adults with IgAN (eGFR ≥ 20 mL/min/1.73 m^2 at baseline).

The data below reflect FABHALTA exposure in 235 patients with IgAN (eGFR ≥ 20 mL/min/1.73 m^2 at baseline) with a median duration of 43 weeks (up to 104 weeks) in APPLAUSE-IgAN. Table 2 describes the adverse reactions that occurred in ≥ 3% of patients treated with FABHALTA and were ≥ 2% higher in frequency than placebo. All of these adverse reactions were mild or moderate in severity.

Table 2: Adverse Reactions Reported in ≥ 3% of Adult Patients with IgAN (eGFR ≥ 20 mL/min/1.73 m^2) Treated with FABHALTA and ≥ 2% Higher in Frequency Than Placebo in APPLAUSE-IgAN

Adverse reaction	FABHALTA (N = 235) n (%)	Placebo (N = 235) n (%)
Upper respiratory tract infection	20 (9)	16 (7)
Lipid disorder[1]	15 (6)	10 (4)
Abdominal pain[1]	15 (6)	5 (2)
Nausea	8 (3)	2 (1)
Dizziness	7 (3)	2 (1)

[1] Includes similar terms.

7 DRUG INTERACTIONS

7.1 CYP2C8 Inducers
Concomitant use of CYP2C8 inducers (e.g., rifampin) may decrease iptacopan exposure, which may result in loss of or reduced efficacy of FABHALTA. Monitor the clinical response and discontinue use of the CYP2C8 inducer if loss of efficacy of FABHALTA is evident.

7.2 Strong CYP2C8 Inhibitors
Concomitant use of strong CYP2C8 inhibitors (e.g., gemfibrozil) may increase iptacopan exposure, which may result in an increased risk for adverse reactions with FABHALTA. Coadministration with a strong CYP2C8 inhibitor is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Available data from clinical trials with FABHALTA use in pregnant women are insufficient to identify a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with untreated PNH and IgAN in pregnancy *(see Clinical Considerations)*. The use of FABHALTA in pregnant women or women planning to become pregnant may be considered following an assessment of the risks and benefits.

In animal reproduction studies, oral administration of iptacopan to pregnant rats and rabbits during organogenesis at exposures 4- to 6-times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 200 mg twice daily did not induce embryo or fetal toxicity *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of major birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
PNH in pregnancy is associated with adverse maternal outcomes, including worsening cytopenias, thrombosis, infections, bleeding, miscarriages, increased maternal mortality, and adverse fetal outcomes, including fetal death and premature delivery.

IgAN in pregnancy is associated with adverse maternal outcomes, including increased rates of cesarean section, pregnancy-induced hypertension, pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including stillbirth and low birth weight.

Data
Animal Data
In an embryo-fetal development study in rats, oral administration of iptacopan during organogenesis did not cause embryo-fetal toxicity when given up to the highest dose of 1,000 mg/kg/day, which corresponds to 4-times the MRHD based on AUC.

In an embryo-fetal development study in rabbits, oral administration of iptacopan during organogenesis did not cause embryo-fetal toxicity when given up to the highest dose of 450 mg/kg/day, which corresponds to 6-times the MRHD based on AUC.

In a pre- and postnatal development study in rats, oral administration of iptacopan during gestation, parturition, and lactation did not cause adverse effects in offspring when given up to the highest dose of 1,000 mg/kg/day, which corresponds to 4-times the MRHD based on AUC.

8.2 Lactation
Risk Summary
There are no data on the presence of iptacopan or its metabolites in either human or animal milk, the effects on the breastfed child or on milk production. Since many medicinal products are secreted into human milk, and because of the potential for serious adverse reactions in a breastfed child, breastfeeding should be discontinued during treatment and for 5 days after the final dose.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients with PNH or IgAN have not been established.

8.5 Geriatric Use
There were 29 PNH patients 65 years of age and older in APPLY-PNH and APPOINT-PNH *[see Clinical Studies (14) in the full prescribing information]*. Of the total number of FABHALTA-treated patients during the 24-week treatment period in these studies, 21 (20.6%) were 65 years of age and older, while 7 (6.9%) were 75 years of age and older. There were 8 IgAN patients 65 years of age and older in APPLAUSE-IgAN *[see Clinical Studies (14) in the full prescribing information]*. Of the total number of FABHALTA-treated patients, 3 (2.4%) were 65 years of age and older. Clinical studies of FABHALTA did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients.

8.7 Hepatic Impairment
The use of FABHALTA is not recommended in patients with severe hepatic impairment (Child-Pugh class C). No dose adjustment is required for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

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For more information, visit www.FABHALTA.com or call 1-888-669-6682.

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High-Impact Clinical Trials

Continued from cover

Hiddo J.L. Heerspink, PhD, PharmD, professor of clinical trials and personalized medicine in the Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen in the Netherlands, presented data from the SMART (Semaglutide and Albuminuria Reduction Trial in Obese Individuals Without Diabetes) trial showing the benefits of the GLP-1 agonist semaglutide in patients with chronic kidney disease (CKD) who were overweight or with obesity (1). Previously, the FLOW (A Research Study to See How Semaglutide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease) trial had demonstrated the benefits of the drugs for patients with diabetes who were overweight or with obesity. Heerspink and his colleagues randomized 101 patients with CKD who were overweight or with obesity, but were without diabetes, from 13 hospitals in 4 countries, to semaglutide or placebo and followed them for 24 weeks. Patients who received semaglutide had a 52% lower albumin-to-creatinine ratio than those who received placebo at the end of the trial. Patients in the semaglutide group also lost about 20 pounds and experienced an average 6.3 mm Hg reduction in their systolic blood pressure. "Future studies are needed to assess the long-term efficacy and safety of semaglutide in reducing the risk of kidney failure in these patients," Heerspink stated.

Wheeler said that although the trial assessed surrogate kidney outcomes, the results are encouraging and suggest that the drug's benefits could extend beyond patients with CKD who have diabetes. He said he would like to see a larger trial that includes clinical outcomes, such as patients developing kidney failure or starting dialysis.

Katherine Tuttle, MD, FASN, clinical professor of medicine at the University of Washington and executive director for research at Providence Health Care in Spokane, presented a subanalysis from the FLOW trial, which examined the effect of semaglutide treatment on patients with different stages of CKD (2). The original FLOW trial randomized more than 3500 patients with type 2 diabetes and CKD to receive semaglutide or placebo and found a 24% reduction in the risk of major kidney disease outcomes, cardiovascular events, and all-cause mortality. In the latest analysis, Tuttle and her colleagues found those benefits to be consistent across different stages of kidney diseases. The patients were all on standard-of-care therapy, and a previously published analysis (3) found benefits of semaglutide both in patients taking SGLT2 inhibitors and those who did not, suggesting that the drugs have independent and likely additive effects due to their distinct mechanisms of action, Tuttle explained.

"From earlier to later stages of CKD, people benefit similarly [from semaglutide]," Tuttle said. "We can say with certainty that semaglutide saves kidneys, and it safely reduced the risk of major kidney outcomes, irrespective of CKD severity, whether defined by baseline GFR [glomerular filtration rate] or urine albumin in participants with type 2 diabetes and CKD."

Wheeler noted that many diabetes medications are stopped in patients with diabetes and stages 4–5 CKD because of the risk of adverse events. As an alternative, many patients with diabetes and CKD are prescribed GLP-1 agonists to control their blood sugar levels. The findings of the FLOW trial provide confidence that using GLP-1 agonists has broader clinical benefits. "Seeing that GLP-1 agonists have kidney benefits in these patients is exciting and provides [a] stronger rationale for using these drugs in patients with type 2 diabetes and advanced CKD when we have to stop metformin and sulfonylureas," he said.

SGLT2 inhibitor staying power

Clinical trials over the past several years have also demonstrated the beneficial effects of SGLT2 inhibitors for patients with diabetes and kidney diseases, as well as individuals with heart disease. But, similar to GLP-1 agonists, questions remained about their use. Studies presented at Kidney Week answered some of the most pressing questions, including how long patients need to take these drugs and whether they are safe and effective for patients with later stages of CKD.

Will Herrington, MBBS, MA, MD, professor of clinical trials and epidemiology of kidney disease at the University of Oxford in the United Kingdom, presented long-term results from the EMPA-Kidney (The Study of Heart and Kidney Protection With Empagliflozin) trial of the SGLT2 inhibitor empagliflozin, which enrolled more than 6600 patients with CKD (4). The trial was stopped early, after 2 years, because it demonstrated a 28% reduction of the primary outcome of kidney disease progression or cardiovascular death during an interim analysis. Herrington presented data on an additional 2 years of post-trial follow-up. Patients who stopped taking the drug after the trial still had a 13% lower risk of these outcomes 2 years later, showing some carryover effect after drug discontinuation but not as large of a benefit as seen while taking the drug.

"Maximizing the benefits of SGLT2 inhibitors in people with CKD requires you to carry on with the treatment," Herrington said. "We know the drug is safe, we know that it works, and now we need to keep people [treated] to make sure we maximize the benefits."

Wheeler explained that the early stopping of the trial had limited the ability to look at certain endpoints and smaller patient subgroups. He said the results of the trial extension are reassuring. "We are more confident that the SGLT2 inhibitors' kidney-protective effects are class-wide," he stated.

Chi-Chih Hung, MD, professor in the Division of Nephrology at Kaohsiung Medical University in Taiwan, presented results of the DAPA-advKD (Dapagliflozin and Renal Surrogate Outcomes in Advanced Chronic Kidney Disease) trial and found that the SGLT2 inhibitor dapagliflozin is also beneficial for patients with stages 4–5 CKD (5). In the trial, 180 patients were randomized two to one to dapagliflozin or integrated CKD care to slow progression. Patients receiving dapagliflozin were started slowly on 5 mg/day, increasing up to 10 mg/day. The authors found an improved estimated GFR slope and improved kidney outcomes in the dapagliflozin group. "[We] found a similar effect of dapagliflozin in patients between stage[s] 4 and 5 CKD and many other prespecified subgroups," Hong said.

Wheeler expressed that the trial fills an essential knowledge gap regarding the use of dapagliflozin. He noted that investigators of previous clinical trials of SGLT2 inhibitors had excluded patients with advanced stages of CKD because the drugs may not have been safe or beneficial for them. Yet, the newer trial found a similar safety profile of dapagliflozin in patients with later-stage kidney diseases as compared with previous dapagliflozin trials. Additionally, Wheeler highlighted that fewer patients who received dapagliflozin at later CKD stages showed progression of their kidney diseases, suggesting that dapagliflozin protected kidney function even in these later stages of disease. "We may be able to start dapagliflozin in patients with CKD and estimated GFRs lower than 20 and may still preserve kidney function and delay the start of renal replacement therapy," he stated.

Wheeler said that he would like to see additional studies assessing the use of GLP-1 agonists and SGLT2 inhibitors in patients without albuminuria and patients with stage 5 CKD, including those undergoing dialysis and kidney transplant recipients. He also expressed that studies on using these drugs in combination will also be helpful to guide care.

Dampening dialysis symptoms

Dialysis can be grueling for people living with kidney diseases and is often associated with symptoms that can greatly impact patients' quality of life. Effective interventions for prevalent symptoms like chronic pain or itching in this population have been elusive. But results presented at Kidney Week offer promising new approaches.

The HOPE Consortium Trial to Reduce Pain and Opioid Use in Hemodialysis (HOPE) randomized 643 participants at 16 centers and 103 outpatient dialysis facilities to a cognitive behavioral intervention called pain-coping skills training, designed for the dialysis setting, or to usual care (6). Patients received the pain intervention for 24 weeks but were followed for 36 weeks. During the first 12 weeks, patients in the intervention group received weekly, 45-minute video coaching while they were receiving dialysis or at home. Coaches used cognitive behavioral techniques and motivational interviewing to teach patients self-efficacy and pain-coping skills.

During the second 12 weeks, patients engaged in 5-minute automated interactive phone sessions daily to help them maintain their coping skills. Patients in the intervention reported significant reductions in how much their pain interfered with their lives after 12 weeks compared with patients in the usual care group who continued through week 24. However, the difference disappeared at week 36. The investigators are exploring ways to continue refreshing patients' pain-coping skills through low-intensity interventions over the longer term, said Laura Dember, MD, FASN, professor of medicine at the University of Pennsylvania Perelman School of Medicine, Philadelphia, who presented the results.

"The intervention resulted in a clinically meaningful improvement for a substantial proportion of participants; the benefits were also apparent for the secondary outcomes of pain, severity, catastrophizing, depression, anxiety, and quality of life," Dember explained. "In our view, the efficacy, acceptability, and safety of the intervention support future work to develop strategies for adopting pain-coping skills and training in dialysis clinical care."

As many as 50%–80% of patients undergoing dialysis experience persistent itching that negatively impacts their quality of life, and for 40%, the condition is moderate to severe. Although the exact causes of this distressing condition are unknown, an imbalance between mu and kappa opioid receptors (KORs) has been identified as a potential contributor, said Bi-Cheng Liu, MD, PhD, professor at the Institute of Nephrology at Zhongda Hospital and Southeast University in Nanjing, China. KOR is a promising target because it controls the transmission of itch signals to the brain and may lessen associated inflammation, Liu said.

He presented the results of a clinical trial that randomized 545 patients to receive intravenous HSK21542, a peripheral selective agonist of KORs, compared with placebo (7). Of the patients who received HSK21542, 51% had at least a 3-point reduction in their itching score at week 12 compared with only 24% of the placebo group. Patients receiving the drug continued seeing improvements during the 40-week trial extension. Safety was similar between the groups, although the group receiving HSK21542 had slightly higher rates of dizziness and hypotension. "The newly developed high selective KOR agonist HSK21542 had a remarkable therapeutic efficacy on CKD-associated pruritis, and it could be a new solution for this troubling clinical issue," Liu said.

Other studies highlighted

Additional studies presented during the High-Impact Clinical Trials session examined interventions for patients who are critically ill, transplant recipients, and patients with rare kidney diseases. Their findings demonstrate that:

- Finerenone reduces proteinuria in patients with heart failure with a mildly reduced or preserved ejection fraction (8).
- Rapid personalized electronic recommendations for acute kidney injury care from a multidisciplinary team improve clinician behavior but not patient outcomes of worsening kidney injury, needing dialysis, or death (9).
- Tacrolimus reduced risk of relapse in pediatric patients with frequently relapsing or steroid-dependent nephrotic syndrome by 65% compared with mycophenolate mofetil (10).
- Hyponatremia correction did not improve outcomes for hospitalized patients, suggesting that it may be a marker of poor outcomes rather than a cause (11).
- Pegcetacoplan reduced proteinuria by 68.3% compared with placebo in patients with complement 3 glomerulonephritis before or after transplant (12).
- Humacyte's acellular tissue-engineered vessel maintained patency better than traditional arteriovenous fistulas, especially for patients with a higher risk of failure, such as female patients or patients with diabetes or obesity (13). ■

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Hemodiafiltration's US Launch: A New Chapter in Kidney Care

Technology and Evidence Featured at Kidney Week

By Katherine Kwon

Hemodiafiltration (HDF) increases convective clearance by injecting large volumes of sterile replacement fluid into the bloodstream and removing an equivalent volume via ultrafiltration across the dialysis membrane. Earlier this year, Fresenius announced plans for a broad commercial launch of HDF in US markets in 2025 (1).

HDF technology was highlighted in multiple presentations and abstracts during Kidney Week 2024, where Fresenius also held a satellite reception to debut its 5008X dialysis machine. This device is capable of online generation of replacement fluid and allows the delivery of HDF in outpatient dialysis centers without significant retrofitting of the water system. Additionally, Fresenius promoted a new medical education website about HDF, and its latest annual report emphasizes its focus on this technology (2).

Yan Zhang, PhD, of Fresenius Medical Care Deutschland GmbH, Germany, presented an oral abstract of an observational study of over 78,000 patients undergoing dialysis in Fresenius clinics across 23 countries (the United States was not included) (3). Compared with patients receiving standard thrice-weekly, high-flux intermittent hemodialysis (IHD), patients who were treated with HDF had fewer hospitalizations and shorter lengths of stays. Patients undergoing HDF in the higher tertiles of replacement fluid volume had better results.

A large-scale shift to HDF would represent one of the first significant changes in dialysis delivery in the past few decades.

Peter Blankestjin, PhD, professor at Utrecht University, the Netherlands, presented a new study, simultaneously released in *The Lancet*, during Kidney Week's late-breaking clinical trials session (4). This was a meta-analysis incorporating data from five randomized trials of HDF versus IHD. The studies are unblinded, as the machines used to deliver the treatments are different. The meta-analysis shows that HDF improves all-cause and cardiovascular mortality. From their summary, "When updated evidence on cost-effectiveness and on patient-reported outcomes is added to this information, it then proves a solid basis for recommendations for a change in clinical practice."

Immediately after the conclusion of Kidney Week, Fresenius released its 2024 Annual Medical Report (2) including a chapter, entitled "Strategy to Expand High-Volume Hemodiafiltration Worldwide." The authors note that HDF has been a standard therapy in Fresenius clinics in Europe, North Africa, the Middle East, and Asia since 2004. They cite studies showing multiple benefits of HDF, including improved nutritional status, anemia, and quality of life. The report mentions barriers to more widespread adoption of HDF. Sustainability is an important factor, but the increased water used to generate the replacement fluid may be offset by decreased use of dialysate. While there are upfront costs of the new machines, the authors postulate that long-term use of HDF will generate savings, including avoidance of hospitalizations (with more treatments occurring in centers as a result) and decreased medication expenses. Payment policies differ across countries, but HDF has already been introduced in some countries that do not provide any additional reimbursement for HDF compared with IHD.

The timeline by which Fresenius units will introduce HDF into their US units has not been released, but the company has built significant infrastructure to support the transition. Medical directors and joint venture owners should anticipate discussions about the capital expenditures associated with new machines, as well as training costs for staff. A large-scale shift to HDF would represent one of the first significant changes in dialysis delivery in the past few decades. It remains to be seen if the observed clinical benefits from other countries will be replicated here, and how other dialysis companies choose to respond. ■

Katherine Kwon, MD, FASN, is a private practice nephrologist in St. Joseph, MI, and Vice President of Clinical Affairs at Panoramic Health.

Dr. Kwon is a joint venture partner in two dialysis units with Fresenius.

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Kidney Care Community Comes Together

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coordinated effort among kidney care professionals who came together in an extraordinary show of teamwork.

North Carolina's uphill battle

No one knows better than those in the midst of the crisis in North Carolina about what it was like in the aftermath of the hurricane. William Durham, MD, and Matthew Volk, MD, of Mountain Kidney and Hypertension Associates, which operates across the western part of the state, found themselves in the thick of the region's health care emergency in the wake of the storm. The practice runs multiple CKD outpatient sites and in-center dialysis units, and when Hurricane Helene hit, access became nearly impossible. Western North Carolina and the populous city of Asheville were battered and buried by mudslides and floods that washed out highways and homes. Transportation was halted, communications went dark, and water access was cut off, putting the lives of hundreds of patients on dialysis at risk.

"I spent days chainsawing my way out of my home, which was blockaded by downed trees," Durham recalled. He and the team spent hours during the days after the hurricane locating their patients on dialysis. "Within the first week, 100% of our patients [on dialysis] were accounted for," he said. Durham noted that Henderson County's dialysis center suffered such extensive damage that over 100 patients have had to be bused to other dialysis centers—a daunting reality that could last until the spring of 2025. "There was enough water in this dialysis center to float a refrigerator," he recalled.

Complicating matters further, the hurricane disrupted Asheville's main water reservoir. This has left the city relying on tanker deliveries for potable water to operate its dialysis centers and inpatient dialysis unit at Mission Hospital—a reality that may continue through the end of the year.

Volk's arrival at Asheville's Mission Hospital in the storm's immediate aftermath was also eye-opening. "The hospital was running on generators, there was no water, and cell service was out. I didn't know how to reach anyone on my team. I remember thinking, 'What do we do now?'"

Thanks to lessons learned from a major freeze 2 years prior, Mission Hospital had a plan in place to address water outages. Engineering teams set up an emergency water supply using fire hoses that fit into a sleeve in the building to pipe in water from tankers, allowing the dialysis unit to resume operations quickly. Foreseeing the hurricane's track through Asheville, the hospital had water tankers stationed and prepared before the storm hit on Friday, September 27th.

"We only missed about four patients on Friday for dialysis when the water ran out. By Saturday, the dialysis unit was back up and running," Volk said, noting that the 10-station inpatient dialysis unit operated 24-7 from Sunday through Tuesday following the storm to accommodate the influx of displaced patients in need of treatment. "It was phenomenal that we were able to get all that together in less than 1 day."

The collaboration of regional and national kidney care specialists helped avert what could have been a large-scale health care disaster for patients on dialysis in North Carolina. Both physicians credited HCA Healthcare and dialysis companies providing services in the area, including DaVita, for being instrumental in keeping hemodialysis operations going and for sending in water tankers, fuel, and even extra nursing staff from other areas. "The response was nothing short of incredible," Volk said.

Heading off a second crisis

Hurricane Helene, which also wreaked havoc on Baxter's North Cove plant in Marion, NC, presented a national problem, as the manufacturing company produces approximately half of the country's PD fluids. The closure of the Baxter plant and the resulting disruption of the supply chain for both dialysate and intravenous (iv) fluids posed a serious threat to the more than 550,000 people living with kidney failure who require both solutions to live.

Heeding the call for assistance, the national kidney community stepped up to help manage the looming crisis. ASN's Excellence in Patient Care (EPC) team and Emergency Partnership Initiative (EPI), under the guidance of Susie Stark, vice president of EPC, and Liz McNamara, MS, RN, former chief nursing officer at Northwest Kidney Centers and current nursing consultant to EPC, set forth a collaborative relief plan to connect people with resources and organizations that could help restore dialysis services and supplies.

The team brought in colleagues Suzanne Watnick, MD, FASN, ASN's Health Policy Scholar in Residence and member of the ASN Quality and Policy and Advocacy Committees; Jeffrey Silberzweig, MD, FASN, chair of EPI and cochair alongside McNamara of EPC's Current and Emerging Threats Steering Committee; and David White, regulatory and quality officer on ASN's Policy team. Their strong ties within the kidney community quickly brought together key stakeholders.

"When we got word that Baxter's North Cove plant in North Carolina was shut down without knowledge of when it was going to be reopened, we knew it was going to be an extreme challenge for patients on dialysis," said Watnick. Silberzweig mobilized the chief medical officers (CMOs) from dialysis organizations around the United States—who represent about 97% of all patients undergoing dialysis nationwide—to devise a plan.

Stepping into action

Within days of the crisis, the collective committee rolled out a plan to conserve PD fluids and advocated for emergency imports from Baxter's international facilities. The efforts focused on creating resource documentation and strategies for medical units managing low supplies of PD fluids.

ASN's interim strategies document was distributed in early October and highlighted patient-level changes including conservation approaches related to bag-sparing and medications that could extend PD fluid supply (2). The workgroup immediately posted the document on the websites of ASN, major dialysis companies, and the Centers for Disease Control and Prevention. A similar document was posted for pediatric patients on dialysis. Because the CMOs of the dialysis companies had been engaged from the start, communication about bag-sparing protocols was seamless.

"The work we did as a group during [the COVID-19 pandemic] for emergency preparedness allowed us to form close relationships that we might not have had before," added Silberzweig, organizer of the weekly CMO meetings. "We were able to quickly ramp back up to discuss ways to conserve PD fluids to ensure [that] every patient was able to maintain their lifesaving treatment."

In the wake of Hurricane Helene, ASN's Policy, EPC, EPI, and Current and Emerging Threats teams also collaborated with dialysis CMOs to draft two letters to the White House urging President Biden to declare a shortage of PD fluids and sterile iv solutions and to declare a national Public Health Emergency. "We had a letter signed by ASN President Deidra Crews, MD, ScM, FASN (3), and a letter signed by every CMO of a major dialysis, which were sent directly to the White House, urging the need for immediate action to ensure PD fluids could be acquired," explained McNamara. "These letters were critical pieces in getting federal support."

White noted that the Biden administration invoked the Defense Production Act, securing emergency imports of PD fluids from Baxter's international facilities by mid-October, while the US Army Corps of Engineers was deployed to assist in securing and restoring access to the plant. ASN's advocacy at the highest levels helped safeguard PD and iv fluid supplies. Watnick explained, "We adopted mechanisms to allow things to move forward expeditiously, both from a policy perspective, administration perspective, and direct patient care perspective."

Lessons learned

The challenging months this fall have underscored the critical need for preparation. Durham reflected on this reality, saying, "Preparedness is the number one takeaway. No one expects a crisis of this magnitude or length." Volk highlighted the challenges of lost communication: "We need clear protocols for when there's no way to contact anyone. That's essential."

On a larger scale, the efforts revealed how far collaboration goes when a crisis strikes. McNamara added, "ASN had a perfect foundation in place for these relief efforts to happen just as quickly as they did, and that was due in large part to the COVID-19 pandemic and the CMO group that was created back in 2020. Having this group already in place allowed us to mobilize quickly to respond to the needs of the affected patients."

Although this natural disaster tested the kidney care community, the response showed that through strong partnerships, planning, and collaboration, even the most difficult challenges could be met. "We're all stronger when we work together to share information, strategies, and resources during times of adversity," Silberzweig said.

Stark summed up the relief efforts, saying, "It was like going back to COVID-19 mode with the kidney care community coming together to support our vulnerable patients on dialysis. The CMOs put aside the fact that they were competitors to ensure [that] all patients in the affected areas could get the supplies and treatment needed to survive. It's been extraordinary to see how altruistic this group has been throughout the crisis, and we are now successfully coming out the other side." ■

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ASN President's Update

Learning All the Time

By Deidra C. Crews

Even as 2024 comes to a close, I am still basking in all of the excitement of Kidney Week. It is difficult to choose, but most of my favorite moments during the meeting were those in which I had an opportunity to reconnect with colleagues or newly meet many of the people that make the global kidney community so vibrant. The energy was palpable, and I enjoyed every conversation I had and every selfie I took.

ASN Kidney Week is the world's premier nephrology conference, and this year's meeting was a tremendous opportunity to learn and be inspired by the contributions of the hundreds of people who delivered lectures, presented posters, or shared ideas through discussions with other attendees. For me, Kidney Week was a powerful reminder of the many things that I have learned this past year while having the privilege of serving as ASN president. I would like to share five of these observations with you.

1) **Nephrology has a deep "bench" of talent.** A highlight for me each year at Kidney Week is seeing the videos that honor each of the recipients of ASN Lifetime Achievement Awards. I find learning about their remarkable contributions awe-inspiring to the point of it giving me chills. What I have come to learn, though, is that there are many kidney professionals well on their way to a lifetime of trailblazing work in our field, and they have an increasingly diverse range of expertise including in clinical practice, research, medical education, health system leadership, and public policy. As evidence of this amazing talent, 10 more individuals received ASN Midcareer Awards at Kidney Week (1). I was also delighted to meet a number of the early career investigators funded through KidneyCure (the ASN Foundation for Kidney Research) at the Kidney Innovation Conference in June (2). These scholars are creating the future of discovery and innovation in nephrology.

2) **ASN takes on challenges with courage and through collaboration.** This year brought its fair share of challenges to be overcome, but I learned that our community courageously endeavors to always be doing—as the ASN mantra states—"what is in the best interests of people living with kidney diseases and their families." With this mantra as a north star and in collaboration with numerous partners in the kidney community and in other disciplines, ASN addressed challenges such as the impacts of severe weather events on patients' access to dialysate (3), the lack of accreditation of US transplant nephrology fellowships (4), and the need for greater investment in kidney health research across the US federal government (5). This month, I will travel to Parma, Italy, for the annual joint leadership meeting of ASN, the European Renal Association, and the International Society of Nephrology. Among other topics, we will discuss our collaborative efforts to urge the World Health Organization to recognize kidney disease as a major noncommunicable disease responsible for premature death.

3) **People with kidney diseases are the strongest advocates for kidney health.** One of the most compelling experiences during Kidney Week was Alonzo Mourning's remarks via video as he accepted the ASN President's Medal. His contributions as an advocate, awareness-builder, and philanthropist reminded me of the importance of kidney professionals' work, not just being *for* the benefit of people living with kidney diseases, but it should also be conducted *with* these individuals as our partners. This lesson was reinforced by time that I and other ASN councilors were able to spend with the Cele's Champions (of the Cele Fogarty Travel Support Program for Patients) during Kidney Week. Inspired by their ingenuity and tenacity, I look forward to partnering in our advocacy efforts.

4) **The future of nephrology is blindingly bright.** Among the people that I have learned a lot from this year are the scores of students, residents, fellows, and other trainees just launching their careers in nephrology who I have had the pleasure of meeting while representing ASN at conferences, such as the Nephrology Business Leadership University (6) and the Network of Minority Health Research Investigators annual meeting (7). These trainees, as well as those who I met at Kidney Week who were participating in the ASN Kidney STARS (Students and Residents) program (8), have a view of the future of nephrology that is expansive and far ranging. They are not bound by memories of prior barriers to progress imposed on our field—and therefore, they also give me a lot of hope.

5) **ASN volunteer members, leaders, and staff are extraordinary.** ASN has over 21,000 members in 141 countries, and approximately 1000 members serve as volunteers on ASN's various panels. Nine of these volunteers serve on the ASN Council. I learned this year, over and over again, how truly extraordinary these volunteers are, along with the incomparable ASN staff members who drive the society's mission forward through their work day to day. I am grateful for their service and commitment.

When the clock strikes midnight, and December 31, 2024, becomes January 1, 2025, ASN will mark several leadership transitions, with two ASN councilors completing their terms. Since January 2021, Patrick H. Nachman, MD, FASN, has served as an ASN councilor-at-large, offering his invaluable guidance and principled approach as the council confronted one challenging issue after another. Patrick has been particularly instrumental in helping advance ASN's efforts to ensure excellence in patient care.

And after 4 years, including service as ASN president, Michelle A. Josephson, MD, FASN, will also rotate off the council. Michelle was the first ASN president to be elected under the new bylaws. She also started her term on the council in 2021 when we were still navigating the COVID-19 pandemic. Michelle had a remarkable tenure on ASN Council and was pivotal in transforming transplant policy in the United States. Beyond these contributions, she has been a constant source of support for me this year while I attempted to step into her shoes.

Looking forward to 2025, Prabir Roy-Chaudhury, MD, PhD, FASN, will become ASN president on January 1st. A transplant nephrologist and translational researcher, Prabir has served on ASN Council since 2019 (initially as a councilor-at-large). He will share his priorities for next year in an upcoming issue of *Kidney News*. We will also welcome two new councilors: Crystal A. Gadegbeku, MD, FASN, and Alessia Fornoni, MD, PhD, FASN. In 2025, as past president, my service will include chairing the ASN Awards Selection Committee and Nominating Committee. I hope you will nominate your deserving colleagues for the society's awards and to the society's leadership.

At the end of my address during the opening plenary at Kidney Week, I highlighted that we have the authority and the mandate to #RedefineTheStandard for kidney health—because, in fact, we are the standard bearers. And I invited everyone (myself included), upon returning home from Kidney Week, to spend some time asking:

- What am I going to do today, as the standard bearer, with my knowledge, my platform, and my influence?
- How will I promote fairness and justice in kidney health?
- What is the next discovery I will make?
- How will I engage and prepare the next generation of kidney professionals?
- What will I do to advocate for policy change?
- And finally, how will I deliver high-quality care that improves both the quantity of years and the quality of moments for people living with kidney diseases?

There is a lot of work to be done. But we have been doing it. You have been doing it. I have learned from so many of you this year while watching you #RedefineTheStandard, and I am more optimistic than ever that a world without kidney diseases is within our reach. ■

Deidra C. Crews, MD, ScM, FASN, is professor of medicine at Johns Hopkins University School of Medicine, deputy director of the Johns Hopkins Center for Health Equity, and ASN president.

To comment on Dr. Crews' editorial, please contact email@asn-online.org.

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Diagnosing Acute Tubulointerstitial Nephritis: Where Does F_{18}-FDG PET-CT Stand?

By Mark A. Perazella

Acute tubulointerstitial nephritis (ATIN) occurs in approximately 15% of patients who are hospitalized with acute kidney injury (AKI). Medications are the most common cause with antimicrobial agents, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, and immune-checkpoint inhibitors (ICPIs) as notable offenders (1). An early ATIN diagnosis is paramount to promoting kidney function recovery; however, the lack of suitably diagnostic clinical, laboratory, and imaging tests is a major impediment (2). The dearth of reliable tests makes kidney biopsy the best option despite its limitations and invasive nature.

Promising serum and urine biomarkers have the potential to fill the gap in diagnostic tests for ATIN (3). The imaging modality 2-deoxy-2-[18F]fluoro-D-glucose (F_{18}-FDG) positron emission tomography-computed tomography (PET-CT) scan has shown potential in the diagnosis of ATIN (4). It is widely used in the diagnosis, staging, and restaging of many cancers, as well as in diagnosing various nononcologic disorders (5, 6). The test is based on F_{18}-FDG uptake in glucose-using cells with high rates of anaerobic glycolysis, such as metabolically active tumor cells, and infected and inflamed tissues (Figure). Renewed interest in this diagnostic test, especially for ICPI-associated ATIN, is based on case reports and a study that reported increased renal parenchymal F_{18}-FDG activity in 14 patients with ATIN who were treated with ICPIs (7).

A recent publication by Gupta et al. in *The Journal of Clinical Investigation* demonstrates utility for F_{18}-FDG PET-CT in diagnosing ICPI-AKI (8). The authors used data from a previously published study of 429 patients with ICPI-AKI, many with biopsy-proven ATIN (9). Patients with non-ICPI-AKI and ICPI treated without AKI were included as controls. Inclusion required F_{18}-FDG PET-CT scans at baseline and within 14 days of AKI onset or at follow-up for patients without AKI. After appropriate exclusion, 53 patients were included (9 with ICPI-AKI, 24 with non-ICPI-AKI, and 20 treated with ICPI without AKI). Of the nine patients with ICPI-AKI, three had biopsy-proven ATIN, and six had clinically adjudicated ATIN. The patients with non-ICPI-AKIs had prerenal AKI (n = 10), ischemic or septic acute tubular necrosis (n = 10), or other AKI etiologies (n = 4).

Patients with ICPI-AKI had a significantly increased F_{18}-FDG uptake compared with controls. The mean standardized uptake value (SUV_{mean}) from baseline to follow-up was 57.4%, whereas the SUV_{mean} increased by only 8.5% in patients with non-ICPI-AKI and decreased by 0.8% in patients treated with ICPI without AKI. The area under the curve was 0.97 (95% confidence interval, 0.93–1.00) for the differentiation of the SUV_{mean} percent change for ICPI-AKI versus the two control groups. These results suggest that this scan has diagnostic utility in noninvasively differentiating ICPI-AKI from non-ICPI-AKI.

However, there are drawbacks to acknowledge. Notably, six of nine patients with ICPI-AKI in this study did not have definitive (biopsy-proven) ATIN. Additionally, patients require a baseline F_{18}-FDG PET-CT scan to allow comparison. This could be quite limiting in the setting of routine clinical care.

What should we take away from this study? I believe we should be optimistic that this test may be helpful in our quest to noninvasively diagnose ATIN—including both ICPI-associated ATIN and other causes of ATIN. There is no reason to think that the F_{18}-FDG PET-CT scan will not light up positively in most types of ATIN since the inflammatory interstitial infiltrate is quite similar across all forms of ATIN. Since differentiating ATIN from acute tubular necrosis as the cause for hospital-acquired AKI is a common dilemma for clinicians, a positive F_{18}-FDG PET-CT may be sufficiently diagnostic to avert kidney biopsy for many patients. Perhaps combining F_{18}-FDG PET-CT with serum or urine biomarkers will be the answer. Ultimately, this modality requires prospective study to validate these findings. ■

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The author reports no conflicts of interest.

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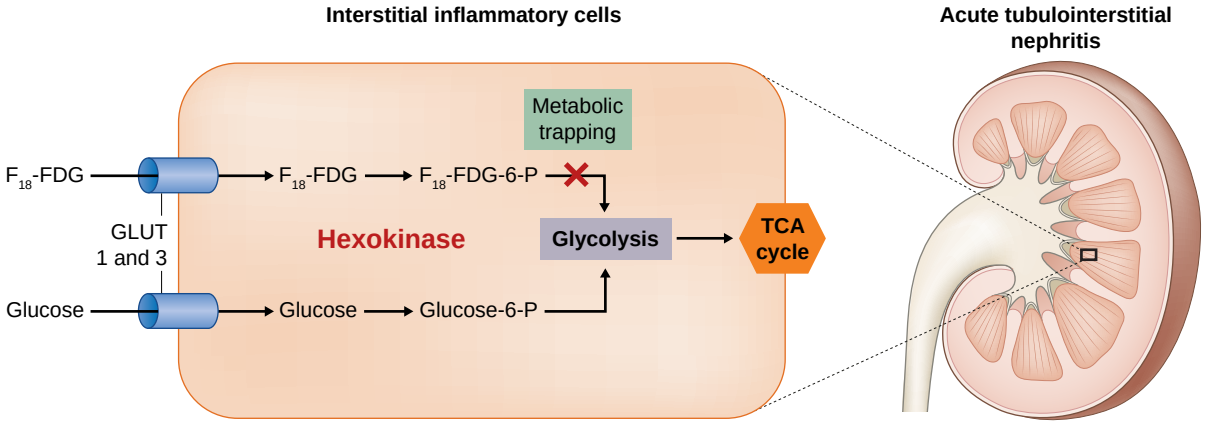
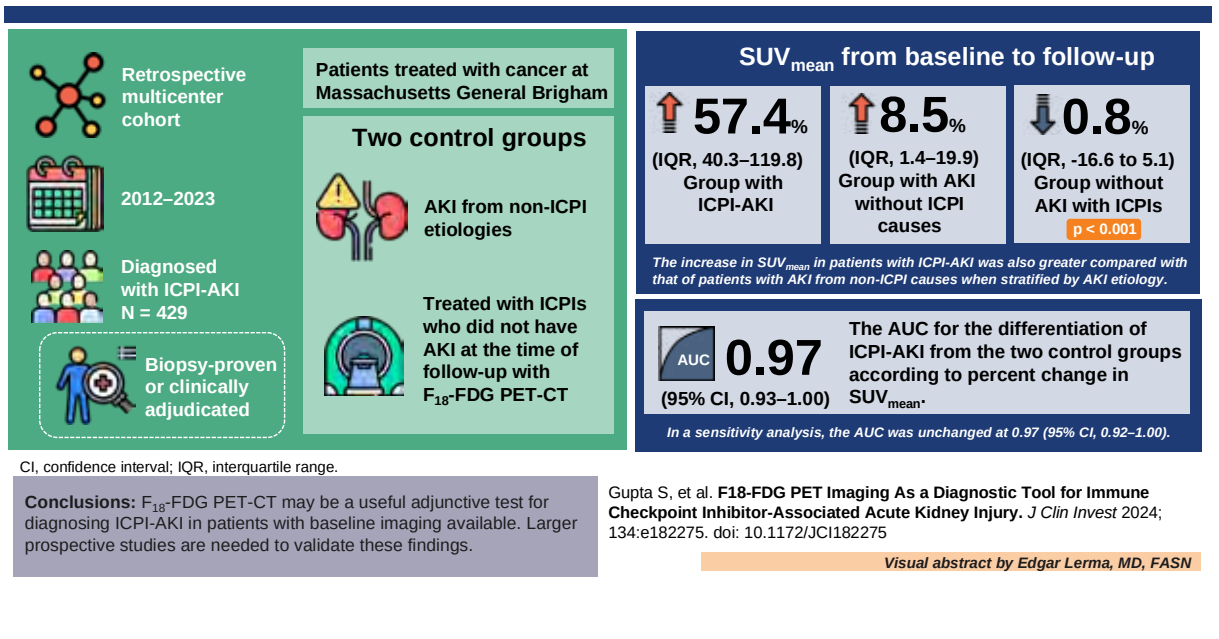
Figure. Uptake of F_{18}-FDG by renal interstitial inflammatory cells



Glucose and F_{18}-FDG uptake by inflammatory cells is shown with a high rate of anaerobic glycolysis using glucose as a major energy source. Glucose and F_{18}-FDG are phosphorylated by hexokinase. Phosphorylated F_{18}-FDG, which is metabolically trapped and blocked from entering the tricyclic acid (TCA) cycle (by the F_{18} atom), accumulates within the cells. The accumulated F_{18}-FDG is then visualized on a PET-CT scan. 6-P, glucose-6-phosphate; GLUT, facilitated diffusion glucose transporter.



Leveraging Technology to Improve Care and Workflows: Challenges in Tools, Funding, and Time

By Bridget M. Kuehn

It took Gaurav Jain, MD, FASN, a professor in the Division of Nephrology at The University of Alabama at Birmingham, and his colleagues about 1½ years to get up and running with the CKD [Chronic Kidney Disease] Insights program. However, once they did, data from their patients' electronic health records (EHRs) started automatically flowing into a dashboard that stratified their patients by disease stage and risk profile, helping them proactively identify patients in need of interventions, such as patient education, mental health care, or transitional care.

The team implemented the CKD Insights program to help them meet their metrics in the Centers for Medicare & Medicaid's Kidney Care First program. "[We were] finding ways to make the data easily accessible and then using that data and technology to try to make our lives easier, hopefully improve the quality of care, and keep the cost down as much as possible," Jain explained. He pulled off the implementation with a small team that included himself and a nurse coordinator, who led the program's patient education, mental health components, and patient survey administration. They also worked to leverage existing resources to avoid adding unnecessary costs. But despite the ease of using the dashboard, many team members did not want to log into another program, and the program could not send information or action alerts back to the EHR system. "The only people using it were myself and our care coordinator," he explained. "We had a really tough time trying to engage other physicians to use it."

There were also challenges with determining how to pay for the program, and Jain's institution ultimately decided to sunset the program several months ago. He shared his perspective at ASN's Nephro-Economics in 2024: From the Big Picture to Advances in Transplant Policy symposium hosted by ASN and the Division of Nephrology, Columbia University Irving School of Medicine, on September 6, 2024 (1). Although Jain was disappointed in the project's outcome, he is still optimistic about the potential of such technology to help support value-based care initiatives and help ease the burden on an overstretched nephrology workforce. His optimism was shared by fellow speaker Navdeep Tangri, MD, PhD, professor in the Department of Community Health Sciences at the University of Manitoba, Canada. Tangri highlighted the potential of technologies like artificial intelligence (AI) to support nephrology care.

Jain and Tangri shared perspectives on the appropriate use of different technologies. They highlighted cases of both successful and unsuccessful use and offered tips on navigating these emerging tools and avoiding pitfalls. "The truth about these things is that we need to find sustainable models that work," Jain said.

Finding partners

Despite the setback with CKD Insights, Jain and his colleagues persisted in their efforts to find a way to identify patients who are high-risk for kidney diseases. They found an approach by partnering with the dialysis company DaVita, which serves many of these patients. A consultant working with DaVita was able to share insights with Jain and his team from DaVita's Shared Patient Care Coordination program on 100 patients living with kidney failure who produce the highest costs.

DaVita's nurses and social workers risk-stratified shared patients and regularly met with Jain and his colleagues. They worked as a team to identify which patients may be at very high risk of hospitalization or an emergency department visit, may have run out of insulin, or need a wheelchair or other interventions to address their growing fall risk, and they developed plans to address the patients' needs in collaboration. "The big win of this program is that we were all sitting together frequently talking about these patients and trying to solve problems," Jain said. In fact, he noted that the annual cost of care for patients in the cohort decreased from $83,000 in 2021 to $73,000 in 2024.

Jain and colleagues are also collaborating with a program called REACH Kidney Care and Blue Cross Blue Shield to improve patient management. REACH's educators and navigators work with patients to check their blood pressure, manage diabetes, and share what they learn with the nephrologists. Although the program is small, it has helped ensure that 83% of participating patients who develop kidney failure receive a preemptive transplant or home dialysis. Jain's team also uses a program called IllumiCare, allowing them to create alerts in their health record system for patients whose proteinuria or potassium levels are concerning. For patients identified this way, the team has a contract with Blue Cross Blue Shield's Medicare Advantage plan that will pay for an annual nephrology wellness visit.

As a mandatory part of the Centers for Medicare & Medicaid's Kidney Care First program, Jain and his team also regularly survey roughly 180 patients to assess their engagement with their care. The 13-item questionnaire includes whether the patients know what each medication does and whether they are confident about contacting a physician or handling health problems independently. The survey helps Jain and colleagues identify patients who may need extra support or education. It also helps them connect patients who have mental health needs with a psychologist, who runs their clinic specializing in neurologic and psychiatric care for patients with kidney diseases, and patients who need medication support with a pharmacist. Over the past 2 years, they have improved their patient scores on the surveys with the help of multidisciplinary partnerships. "If you have the data, and you have targeted interventions, without a lot of resources, you are able to make a difference in a patient population of this size," Jain said.

Telehealth and remote monitoring

Telehealth and remote monitoring have also proven valuable for Jain's team. He noted that they increase access to patient education and mental health care and reduce the burden for patients on home dialysis who live far from the clinic. "It is clearly beneficial," he said. "It improves compliance, increases access to nephrologists and transplant nephrologists, and increases access to education."

However, he emphasized that it is essential to have systems and support in place to deliver telehealth care successfully. Jain said that his health system is working to integrate telemedicine into its EHR system to streamline the process further. He also noted a need to ensure that EHR systems at health systems, dialysis facilities, and other specialist offices can effectively communicate. Additionally, Jain's organization hired patient navigators to facilitate telehealth visits between nephrologists and patients during dialysis sessions. "It's been very beneficial in decreasing the burden of disease for patients," he shared.

They also use remote monitoring integrated into their home dialysis machines to flag potential problems. Jain called it an "eye-opener," enabling the team to learn that many patients who had good laboratory results and who were thought to be adherent were not undergoing even half of their recommended treatments. This indicated that many patients may have undergone treatments before the laboratory tests to produce acceptable results. He said that creating workflows and assigning responsibility for such monitoring tasks are critical. He also suggested being mindful to ensure that the use of technology does not disproportionately benefit those who are more technology literate or have more resources, which could reinforce socioeconomic disparities.

Jain recommended that nephrologists, particularly those participating in value-based care programs, look at all of the programs and resources available in their area. He said that it has helped his team be successful in the Kidney Care First program. "We've actually been able to pay for all the resources, and we are still left with some money to reinvest in the program to make care better," he shared.

AI applications

Tangri highlighted several ways that AI may help improve kidney care. It can detect cases of acute kidney injury, analyze kidney biopsies, predict adverse events like intradialytic hypotension during dialysis, or help streamline physician note-taking. For example, Tangri said the Cleveland Clinic created an AI tool to predict acute kidney injury in patients undergoing cardiac surgery using six variables from the patient's first postoperative metabolic panel (2).

"You've got to have high accuracy, good calibration, and external validation," Tangri said. He also emphasized the importance of optimizing AI-driven diagnostic or predictive tools for specificity to ensure that they do not generate too many false alarms for clinicians, causing alarm fatigue.

Deep learning models are also being used to analyze imaging data. Tangri noted that 87% of US Food and Drug Administration-approved AI medical devices are for imaging. For example, AI can be trained to detect changes in pathology slides or predict graft failure. It may also be used to help automate the process of biopsy analysis or help assess fibrosis via ultrasound or magnetic resonance imaging.

Tangri and his colleagues developed and externally validated a tool to predict CKD progression risk that generates a report directly in the patient's EHR. "To get people to take action on [patients who are high risk], you need to integrate it into the workflow," he said.

The report includes a set of physician orders appropriate for a patient's risk level to help nudge their physicians to take appropriate action. Tangri noted that these recommendations can also be built into an EHR smart order set and best practices alerts.

Clinicians are also using generative AI tools to help alleviate administrative burdens. Many are using AI medical scribes to record the entire patient encounter and generate notes that the clinician reviews and edits as necessary. A study in two academic centers showed that AI scribes save, on average, between about 5 and 8 minutes of time (3). Tangri said that could free up additional time for more important patient care tasks or help reduce the after-hours work burden on physicians. "They decrease your note time and your pajama time," he said. "That's quite meaningful."

Tangri cautioned that not all studies of AI generative-based interventions have found benefits, and he said there is a need for more rigorous tool studies moving forward.

Jain noted that leveraging new technology to further value-based care will require local commitment and national policy changes. "It takes a lot of innovation, and it takes policy," he said. "We are seeing results both at an organizational and national level." ■

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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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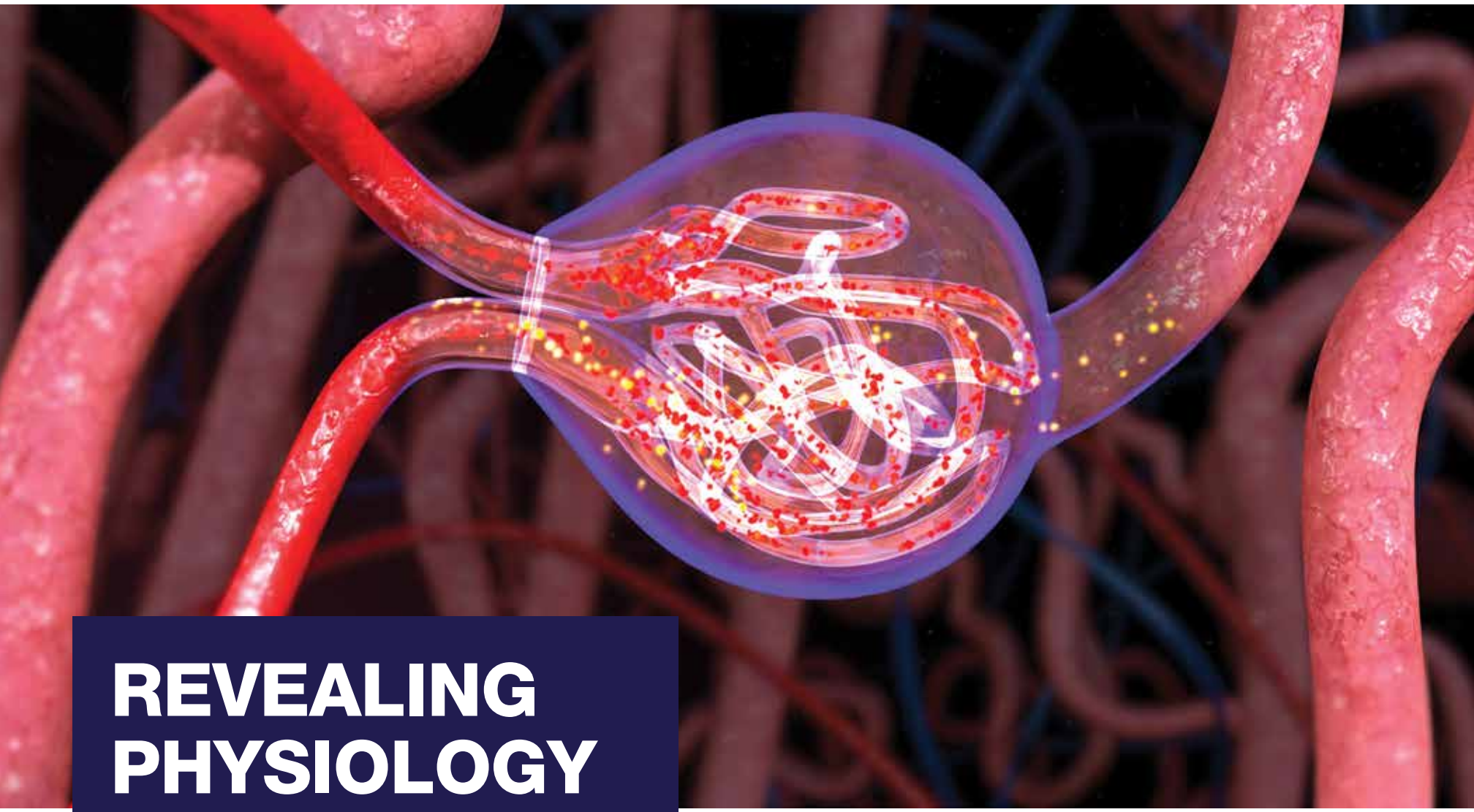

REVEALING PHYSIOLOGY THROUGH PATHOPHYSIOLOGY

By Paul Hanna and Rasha Raslan

In this physiology-focused section, we explore seven unique segments of the nephron, each introduced through a clinical case to reveal its physiology through pathophysiology. From filtration to fine-tuning electrolytes and regulating acid-base balance, as well as hormonal signals, each segment of the nephron plays an essential role in maintaining homeostasis.

You will meet different patients at each nephron "station"—starting from the glomerulus; winding through the proximal tubule, loop of Henle, distal tubule, collecting duct, and macula densa; and finishing in the renal interstitium—gaining insights into the crucial job that each segment provides. By way of this case-based journey through the nephron, we hope that you will gain a better understanding of the nephron's physiology in a clinical context. ■

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The section coeditors report no conflicts of interest.

The Glomerulus Chronicles: Diabetic Nephropathy Unveiled

By Niloufar Ebrahimi, Saloni Gupta, and Sayna Norouzi

Introduction

The glomerulus is a specialized network of capillaries designed for blood filtration and the regulation of body homeostasis (Figure 1). Podocytes are distinct epithelial cells, both morphologically and functionally characterized by foot processes that envelop the glomerular capillaries (1). Together with the fenestrated endothelium and basement membrane, the foot processes of the podocytes form the glomerular filtration barrier (2). The disruption of the glomerular filtration barrier leads to protein leakage from the plasma into the urine (proteinuria), which is linked to the loss of normal kidney function and is a significant risk factor for disease progression toward organ failure (3). Glomerular diseases encompass a broad range of etiologies and clinical manifestations, yet they nearly always result from disruptions in the glomerular filtration barrier (4).

Case

A 45-year-old male with a history of uncontrolled diabetes and biopsy-proven diabetic nephropathy diagnosed 3 years ago presents with worsening kidney function and proteinuria (Table). Vital signs are normal, except for a blood pressure measurement of 153/92 mm Hg. His physical examination is significant for decreased sensation and 2+ pitting edema in lower extremities. The patient inquires why his kidney function is worsening. He is currently being treated with empagliflozin, finerenone, and losartan.

Discussion

Each kidney comprises approximately 500,000 glomeruli, which are multicellular structures composed of capillaries designed for blood filtration and the regulation of body homeostasis found in the outer rim of the kidney (cortex) (4). The kidneys receive about 20%–25% of cardiac output, which equals 1–1.2 L/min. The calculated plasma renal flow rate using renal

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The Glomerulus Chronicles

Continued from page 15

blood flow (RBF)×1-HCT (hematocrit) is approximately 600–720 mL/min, and a glomerular filtration rate (GFR) is approximately 120 mL/min (180 L/day) (5).

In the diabetic kidney, the initial phase consists of a supraphysiologic increase in the whole-kidney GFR (sum of all functional nephrons), known as glomerular hyperfiltration secondary to diabetes-induced structural changes (6). This is followed by subsequent nephron damage due to increased glomerular hydraulic pressure and transcapillary convective flux of the ultrafiltrate. Furthermore, single nephrons increase filtration to compensate for reduced functional nephrons, leading to more damaged glomeruli (6). This phenomenon is thought to precede albuminuria and the decline in kidney function. Therefore, whole-kidney GFR may be normal despite significant loss of nephrons (Figure 2) (6).

Teaching points

- Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers reduce proteinuria by promoting efferent arteriolar vasodilation, which lowers intraglomerular pressure and mitigates hyperfiltration. They also reduce cytokine-induced glomerulosclerosis and fibrosis, preserving kidney function (6).
- Sodium-glucose cotransporter-2 inhibitors reduce proteinuria by enhancing tubuloglomerular feedback with increased sodium passing along the nephron, leading to afferent arteriolar constriction and reduced intraglomerular pressure and hyperfiltration (7). Additionally, improving tubular oxygenation and metabolism reduces kidney inflammation and fibrosis, offering further protection against kidney damage. In combination with these medications, strict glycemic control is critical to preventing further kidney damage and disease progression (8).
- Finerenone, a nonsteroidal, selective mineralocorticoid receptor antagonist, is used due to its anti-inflammatory and antifibrotic effects on the kidney; studies show a reduction in the urinary albumin-to-creatinine ratio with use, leading to a delay in kidney disease progression and cardiovascular dysfunction (9). ■

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The authors report no conflicts of interest.

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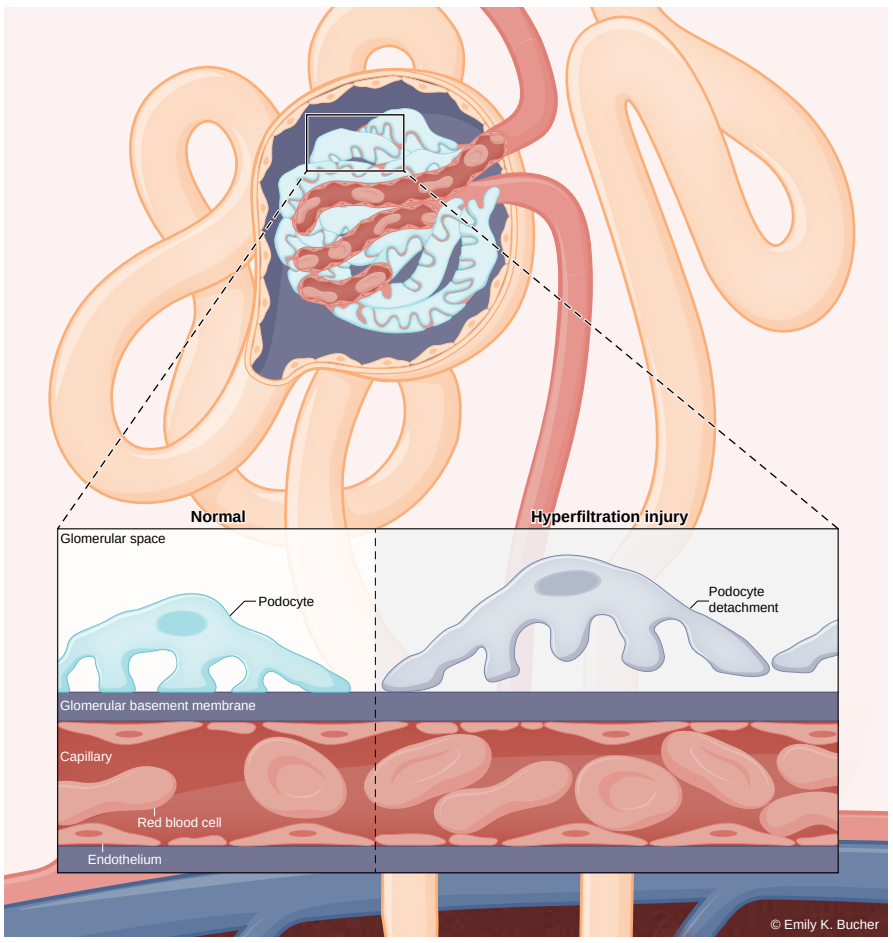
Table. Laboratory results from the initial diagnosis 3 years prior and 3 years later before current treatment initiation

Laboratory test	3 Years prior	3 Years later
Serum creatinine, mg/dL	1.8	2.4
eGFR, mL/min/1.73 m²	45	28
Blood urea nitrogen, mg/dL	32	45
Urine albumin/creatinine ratio, mg/g	600	1500
Hemoglobin A1c, %	8.2	9.0
Serum potassium, mmol/L	4.3	5.2
Hemoglobin, g/dL	12.5	10.8
Serum albumin, g/dL	3.5	3.0
LDL cholesterol, mg/dL	110	130

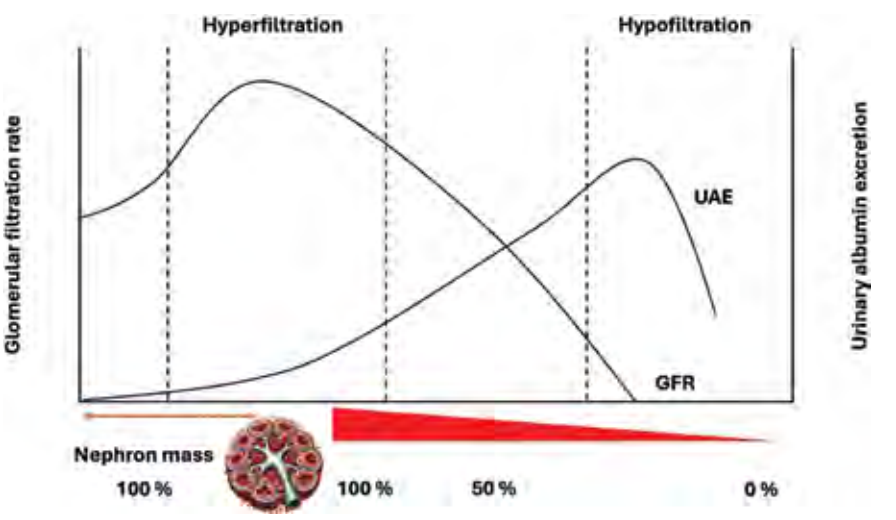
eGFR, estimated GFR; LDL, low density lipoprotein.

Figure 1. Glomerulus



Left panel: Normal podocyte with intact glomerular basement membrane. Right panel: Hyperfiltration injury showing podocyte detachment, foot process effacement, and increased blood flow through the glomerulus.

Figure 2. Classic progression of GFR and UAE in the proteinuric course of diabetic nephropathy



Adapted from Tonneijck et al. (6). Peak GFR often occurs in the prediabetic stage or shortly after a diabetes diagnosis, whereas urinary albumin excretion (UAE) can indicate subclinical loss of functional nephron mass.

Proximal Tubule: The Unsung Powerhouse

By Emmanuel A. Adomako

Introduction

The proximal tubule (PT) is the segment of the nephron intermediate between the glomerulus and the thin descending limb of the loop of Henle (Figure). It is recognized for its resorptive prowess, which is fundamental to the maintenance of a stable internal environment (1). PT cells have high energy needs, which are required to satisfy the demands of reabsorbing 99% of the glomerular filtrate. PT senses changes in the internal environment, adapts to these changes, and communicates with distant organs like the bone and the heart using intricate metabolic processes (2). In disease states, these processes may be maladaptive, further perpetuating the underlying disease and/or resulting in proximal tubular dysfunction.

Case

A 40-year-old man presented with a 1-year history of low back pain and progressively worsening muscle weakness. His vital signs were unremarkable. The rest of his examination was significant for reduced power in all extremities. The patient's serum and urine chemistries are outlined in the Table. An x-ray showed compression fractures of L2, L4, and L5. A bone marrow biopsy reported 70%–80% monoclonal kappa plasma cells, involving a variably cellular marrow with decreased trilineage hematopoiesis. He was diagnosed with multiple myeloma with Fanconi syndrome and acute kidney injury. He received lenalidomide, bortezomib, and dexamethasone and required electrolyte replacement with sodium-potassium phosphate and potassium chloride. One year later, he underwent an autologous stem cell transplant and remained in remission without additional requirements for electrolyte replacement.

Discussion

In steady state, free light chains (FLCs) are filtered, and most of them are reabsorbed by PT (3). Losing FLCs in the urine would lead to the loss of valuable amino acids. This response, however, becomes maladaptive when paraproteinemia occurs. The prodigious generation of FLCs by B cells/plasma cells overwhelms the endocytic and degradation pathways. The accumulation of FLCs in PT mediates injury through diverse mechanisms including inflammation, mitochondrial dysfunction, lysosomal dysfunction, and activation of oxidative injury (4). The characteristic pathologic lesion is a monotypic proximal tubular light chain inclusion (5). The clinical phenotype, De Toni Debré Fanconi syndrome (FS), presents with varied degrees of normoglycemic glycosuria, phosphaturia, aminoaciduria, hyperuricosuria, and proximal renal tubular acidosis. Disordered phosphate balance may manifest with pathologic fractures (4–6). Although both crystalline and noncrystalline light chain inclusions are associated with FS, the former has characteristic biochemical features and is more commonly associated with FS than the latter (3). There are variable rates of resolution of FS even when a hematologic response is achieved (5, 6).

This paradigm is pertinent to the maladaptive response of PT in diabetes mellitus, in which an attempt to reabsorb all of the filtered glucose and an increase in PT gluconeogenesis further perpetuates hyperglycemia. An increased rate of PT gluconeogenesis is counterintuitive regarding glucose control but valuable to the kidney's response to the challenge of acidosis (7). In handling these macromolecules, PT is altruistic; neither glucose nor amino acids are its preferred energy sources. In health, PT metabolizes very little glucose, and even this does not appear to serve a primary need for energy. Glucose metabolism in PT may be the signal to the bone to control the release of fibroblast growth factor 23 (8).

Inhibiting these maladaptive changes is the target of medications like sodium-glucose cotransporter-2 inhibitors (9). Considering the central role of PT in homeostasis, it is not surprising that interference of maladaptive processes by sodium-glucose cotransporter-2 inhibitors has been shown to have dramatic effects on and beyond kidney health.

Teaching points

- PT is the workhorse of kidney reabsorption, rendering the tubular filtrate free of important nutrients including glucose and amino acids.
- PT is crucial to homeostasis; as a result, PT dysfunction may present with kidney and distant organ dysfunction.
- Targeting PT transport offers therapeutic opportunities for disease processes including chronic kidney disease and cardiovascular and bone diseases. ■

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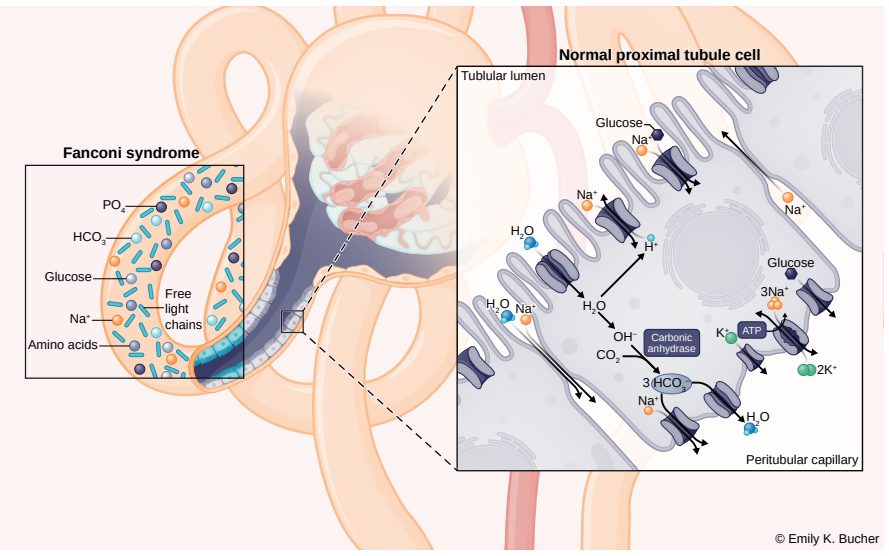
The author reports no conflicts of interest.

Figure. Proximal tubule



Right panel: Magnified cell showing normal proximal tubule reabsorption processes through numerous channels. Left panel: Fanconi syndrome with urinary wasting of solutes including phosphate, bicarbonate, amino acids, and glucose.

Table. Serum and urine chemistries

Variable	Value	Reference value
Creatinine, mg/dL	1.31	0.4–1.0
Urea nitrogen, mg/dL	2	7–25
Sodium, mmol/L	139	137–147
Potassium, mmol/L	3.7	3.5–5.1
Chloride, mmol/L	117	98–110
Bicarbonate, mmol/L	17	21–30
Glucose, mg/dL	92	70–100
Calcium, mg/dL	9.8	8.5–10.6
Phosphorus, mg/dL	1.5	2.0–4.5
Uric acid, mg/dL	<1.5	2.0–7.0
Alkaline phosphatase, U/L	217	25–110
Free light chain ratio, kappa/lambda	727.20	0.26–1.65
Urinary glucose, mg/dL	1272	Negative
Urinary pH	7.0	5.0–8.0
Urinary phosphorus, 24 h, mg	646.2	400–1300
Urinary protein/creatinine, g/g	11.5	<0.15
Urinary paraprotein and amino acid screen	Positive	Negative

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Loop of Henle: Architect of Ionic Balance

By Fiona Splaine and Susan L. Murray

Introduction

The loop of Henle plays a major role in urine concentration and ion reabsorption (Figure). It is the second component of the renal tubule, following the proximal convoluted tubule. It lies in the renal cortex or medulla and consists of three sections: the descending limb, the thin ascending limb, and the thick ascending limb (TAL).

Case

A 62-year-old female with newly diagnosed non-small cell lung cancer is initiated on pemetrexed and cisplatin. Six weeks later, she presents to the emergency department with progressive weakness, muscle cramps, and an inability to walk. She endorses nausea but denies diarrhea. Her initial exam is remarkable for Trousseau and Chvostek signs. Her laboratory results are notable for sodium 128 mEq/L, potassium 3.0 mEq/L, blood urea nitrogen 18 mg/dL, creatinine 1.1 mg/dL, calcium 6.0 mg/dL, phosphate 4.2 mg/dL, albumin 3.9 gm/dL, ionized calcium 0.68 mmol/L, magnesium 1.1 mg/dL, urine random creatinine 372 mg/dL, and urine random magnesium 11 mg/dL. Computed tomography of the abdomen and pelvis demonstrates no acute changes.

Discussion

The structure of the loop of Henle was first described by Jacob Henle in 1862, but it was not until 1942 that Werner Kuhn proposed that the shape of the loop could function as a countercurrent multiplication system (1).

Countercurrent refers to the phenomena that solute equilibration is more efficient when the two solutions are in parallel with opposing velocity, such as the filtrate and blood in the nephron (2). The multiplication component refers to a concentration gradient that further drives solute exchange (2). The kidneys have a lower concentration in the outer cortex and a higher concentration in the renal medulla; the U-shaped loop is positioned so that the hairpin is at the point of highest concentration.

As filtrate travels down the thin descending limb, water diffuses into the interstitium via aquaporins and then into the bloodstream via vasa recta. As the filtrate moves up the loop into the TAL, which is impermeable to water, there is active transport of the ions sodium, potassium, and chloride out of the tubules via the Na-K-2Cl (sodium-potassium-2 chloride) cotransporter (3).

Loop diuretics block the active reabsorption of ions in the TAL. This causes the filtrate to have a higher concentration of ions, which overwhelms the active transport pumps in the distal convoluted tubule and collecting duct. The increased ion concentration pulls more water into the urine from the blood, causing an increased volume of urine to be excreted (4).

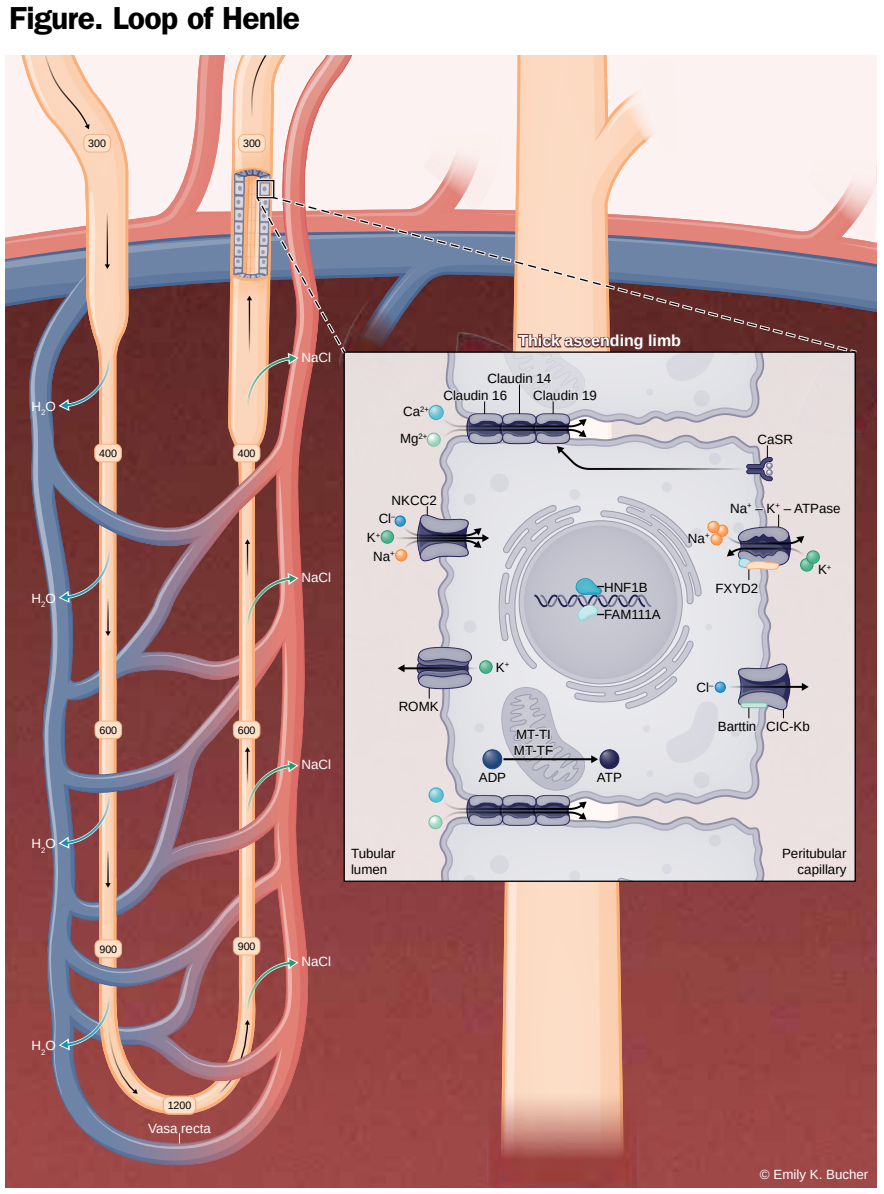
Within the TAL, there are channels that allow for potassium to "leak" from the blood back into the filtrate. This creates a positive charge in the tubular lumen that drives the paracellular reabsorption of magnesium and calcium (5). The loop of Henle is responsible for 50%–70% of total magnesium reabsorption in the kidneys (5).

In our patient's case, the primary electrolyte abnormality is hypomagnesemia, which is a well-known, dose-dependent side effect of cisplatin (6). Although not completely understood, it is thought that cisplatin causes direct damage to the nephron including the TAL (disrupting the paracellular mechanism), as well as interferes with active magnesium transport in the distal part of the nephron (6, 7).

Hypomagnesemia can cause a secondary hypokalemia by impairing the back leak of potassium through the renal outer medullary potassium channel, as well as secondary hypocalcemia by impairing parathyroid hormone secretion (5).

In patients with severe and symptomatic hypomagnesemia, it is recommended that intravenous repletion should be given. This should be given slowly over 12–24 hours, as high magnesium serum levels will overwhelm the renal reabsorption mechanisms and lead to large amounts of magnesium in the urine (up to 50% of the dose) (7, 8). For patients who are asymptomatic, oral magnesium supplements are preferred, in particular, sustained-release preparations because of their slower absorption (9). Potassium-sparing diuretics such as amiloride have been used as an adjunctive therapy in hypomagnesemia, but studies have called their effectiveness into question (10). Certain case reports suggest that sodium-glucose cotransporter-2 inhibitors may be useful in treating refractory hypomagnesemia (11).

Figure. Loop of Henle



Countercurrent multiplication system in the nephron, highlighting the thick ascending limb and its role in water reabsorption. Note magnesium reabsorption through paracellular pathways. NKCC2, Na-K-2Cl cotransporter; ROMK, renal outer medullary potassium.

Teaching points

- The loop of Henle achieves efficient solute exchange and water reabsorption through a countercurrent multiplication system.
- The loop of Henle is also responsible for ion exchange and reabsorption, most notably magnesium.
- Magnesium repletion is more effective if given over 12–24 hours intravenously or in a sustained-release oral form. ■

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The authors report no conflicts of interest.

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Hyperkaliuresis: Turbo-Charging the Distal Nephron

By Shyam Raja and Graham Gipson

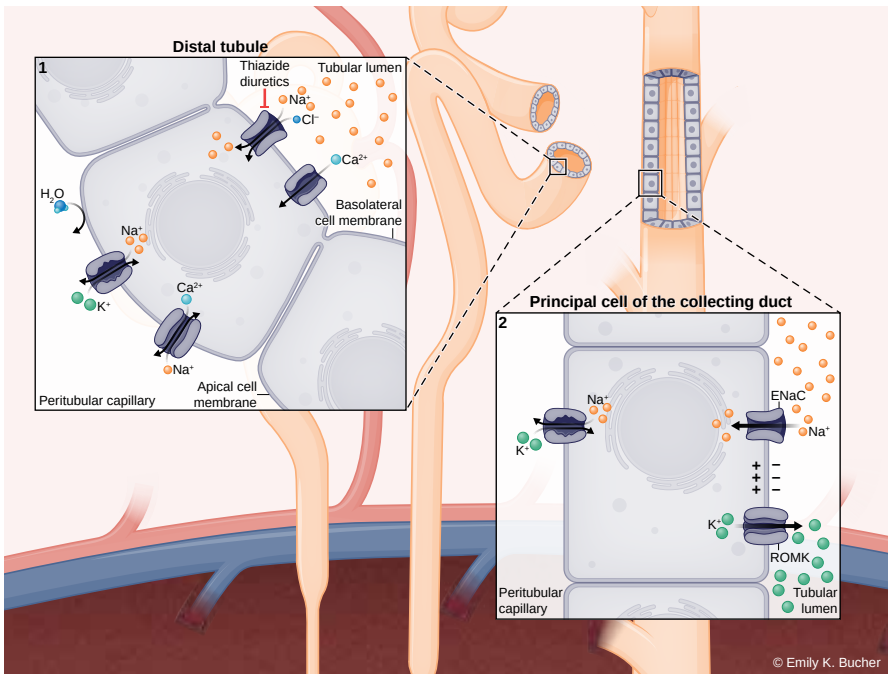
Introduction

Severe hyperkalemia and acute hemodialysis (HD) typically go hand in hand, but do they have to? Full pharmacologic exploitation of the distal tubule's capacity for potassium excretion could save a patient from HD or at least reduce the time exposed to this potentially life-threatening electrolyte derangement.

Case

A 52-year-old male with hypertension and noninsulin-dependent diabetes mellitus presents to the emergency department with fatigue, weakness, and headaches. He reports having these symptoms for the past week, but they were progressively worsening, prompting him to seek evaluation. His medications include lisinopril metoprolol, metformin, and glipizide. His vital signs show a blood pressure of 140/92 mm Hg but no other abnormalities. His physical examination is unremarkable. Laboratory results show a serum potassium of 7.0 mmol/L (not hemolyzed; normal: 3.5–5.2 mmol/L), a blood glucose of 174 mg/dL (normal: 60–90 mg/dL), and a mildly elevated serum creatinine of 1.4 mg/dL (normal: 0.6–1.2 mg/dL). He denies any problem with urination. His electrocardiogram discloses a slightly widened QRS and sharply peaked T waves. He is given calcium gluconate, insulin, and dextrose, as well as intravenous (iv) furosemide. Transfer to a tertiary-care center for possible acute HD is initiated. The emergency department physician is advised to continue aggressive medical management until transfer is possible. His potassium is rechecked after a few hours and improves modestly to 6.5 mmol/L. He is then given a higher dose of iv furosemide along with 1000 mg iv chlorothiazide. The next repeat potassium analysis several hours—and several liters of urine—later is 5.3 mmol/L. The patient's weakness is improved, and his electrocardiogram looks more normal. The transfer process is canceled. He is then discharged with instructions to stop lisinopril and to follow up with his primary care physician.

Figure. Distal tubule



Increased sodium delivery to ENaC in the collecting duct due to thiazide blockage at the distal tubule, leading to potassium wasting in the urine through the ROMK channel.

Discussion

Hyperkalemia can lead to life-threatening electrocardiac and neuromuscular complications. Management of hyperkalemia ultimately aspires to a reduction in total-body potassium content (1). The three canonical therapeutic interventions to accomplish this are urinary excretion (via diuretics), gut excretion (via enterocolonic-binding resins), and HD (1, 2). We focus here on diuretics and their mechanism of action for lowering serum potassium. Several classes of diuretics are available for clinical use. The kaliuretic effect of these diuretics differs between the classes and is explained by their sites of action, meaning that kaliuretic effectiveness is closely tied to the anatomy and physiology of the nephron, particularly the distal segments (3).

The distal nephron comprises the thick ascending loop of Henle, macula densa, distal convoluted tubule, connecting tubule, and collecting duct (Figure). As glomerular filtrate flows through the tubules, many processes take place for electrolyte and water balance. Sodium is (quantitatively) the main electrolyte in the filtrate, which parallels its primacy in the extracellular space. While the proximal tubule absorbs the majority of sodium, the loop of Henle absorbs approximately 25% of sodium via the sodium-potassium-chloride (Na-K-Cl) cotransporter (NKCC) (4). More distally, the Na-Cl cotransporter in the distal convoluted tubule and the epithelial Na channel (ENaC) in the collecting duct absorb another 5%–10% and are the last chances for reabsorption (4).

Loop diuretics are used to promote sodium and water excretion in edematous disorders and potentially kaliuresis in the setting of hyperkalemia. When the loop diuretic blocks the reabsorption of the sodium at NKCC, sodium remains in the lumen and flows onto the distal nephron. Nonreabsorbed sodium will next face the Na-Cl cotransporter in the distal tubule (4). This cotransporter is sensitive to thiazide diuretics, which block its function, thereby maintaining a large sodium presence in the tubular lumen. After further flow, sodium will encounter the principal cells, which express ENaC and the renal outer medullary potassium (ROMK) channel. The generous load of nonreabsorbed sodium drives ENaC transport, which then drives ROMK-mediated potassium excretion through an electrogenetic phenomenon. The larger the sodium flow delivered to ENaC, the larger the potassium secretion via the ROMK channel.

With loop diuretics alone, nonreabsorbed sodium escapes NKCC-mediated reabsorption only to be reabsorbed in the distal nephron. In real-world clinical practice, the redundancy of sodium reabsorption mechanisms along the nephron finds relevance as the mechanism behind loop diuretic braking and resistance. Loop diuretic braking and resistance are often overcome with the addition of thiazide diuretics or potassium-sparing diuretics (ENaC inhibitors and mineralocorticoid receptor antagonists) as adjuncts to the loop diuretic. Such sequential nephron blockade effectively provides sodium a free pass to flow distally with minimal reabsorption (5).

So how does all of this apply to hyperkalemia? The same adaptive responses to loop diuretic-induced sodium inflow to the distal nephron undermine the ability of loop diuretics to promote potassium excretion. Both established nephron physiology and decades of clinical experience with thiazide diuretics (and their prevalent complication of hypokalemia) offer us an upgraded strategy to combat hyperkalemia: Coadminister a thiazide diuretic alongside a loop diuretic. Prompt administration of an iv thiazide diuretic like chlorothiazide, if available, could exert a sufficient kaliuretic force to lower blood potassium rapidly and hopefully avoid a more aggressive intervention like HD.

Teaching points

- The distal nephron enjoys a large capacity to excrete potassium.
- Definitive hyperkalemia management is founded on reduction in total-body potassium content, conventionally with loop diuretics.
- Addition of a high-dose iv thiazide may sufficiently augment kaliuresis sufficiently to avoid acute HD or at least to reduce the time exposed to this potentially life-threatening electrolyte derangement. ■

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The authors report no conflicts of interest.

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When Antifungals Go Rogue: The Link to Mineralocorticoid Excess

By Caitlin Womack and Rasha Raslan

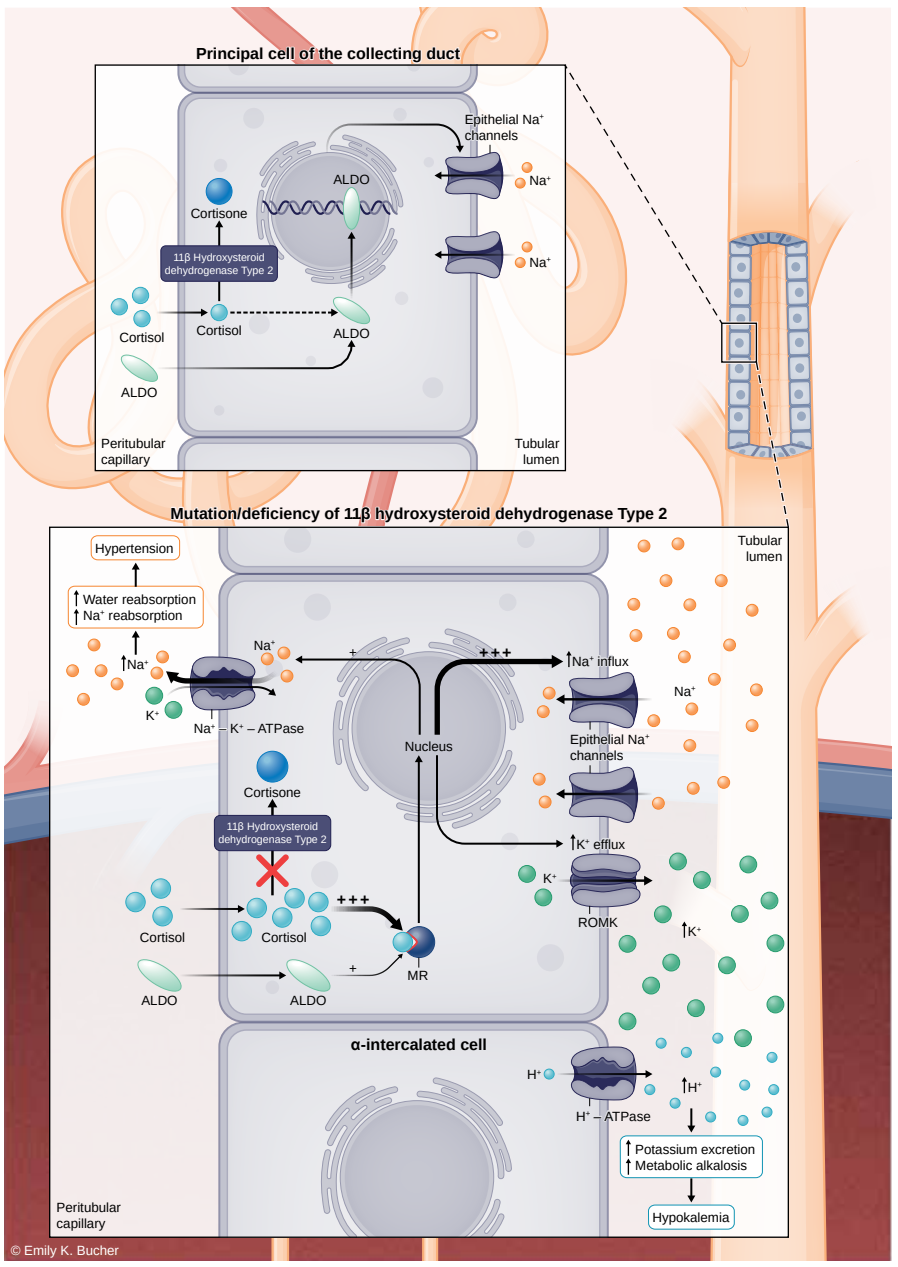
Introduction

The collecting duct consists of a series of tubules and ducts that interact with tubular fluid at the last step on its way to the ureter (Figure). It is composed of two distinct morphologic cell types: the principal cells (PCs) and the intercalated cells (ICs). PCs regulate water and sodium balance by expressing apical epithelial Na^+ channels (ENaC) and aquaporin channels regulated by aldosterone and antidiuretic hormone activation. ICs regulate acid-base balance independent of Na^+, aided by vacuolar-type H^+-ATPases and carbonic anhydrase II (1, 2). Ultimately, the complex interplay among hormones, receptors, transporters, and channels allows for fine-tuning of fluid, electrolyte, and acid-base homeostasis that can go awry if any one component is defective.

Case

A 62-year-old male, newly diagnosed with acute myeloid leukemia, was admitted for induction chemotherapy with curative intent. His medical history was notable only for hypertension, which was well-controlled on losartan 50 mg daily. He was initiated on cytarabine and daunorubicin, accompanied by antimicrobial prophylaxis, which included posaconazole 300 mg daily in anticipation of prolonged neutropenia. His initial vital signs were within normal limits with blood pressures of approximately 120/60 mm Hg; however, over the next week, blood pressures increased to 165/95 mm Hg despite stable antihypertensive therapy. His physical examination revealed pallor, mild mucositis, and bilateral lower-extremity edema.

Figure. Collecting duct



In apparent mineralocorticoid excess, a deficiency in the enzyme 11-βHSD2 prevents the conversion of cortisol to inactive cortisone, allowing cortisol to bind the mineralocorticoid receptor. This leads to increased sodium reabsorption via ENaC, potassium excretion, water retention (causing hypertension), and metabolic alkalosis. ALDO, aldosterone; ROMK, renal outer medullary potassium.

Table 1. Basic laboratory data on admission and hospital day 8

Laboratory data	Admission	Hospital day 8
Sodium, mEq/L (normal, 135–145)	138	137
Potassium, mEq/L (normal, 3.5–5.0)	3.6	2.7
Chloride, mEq/L (normal, 98–108)	103	94
Bicarbonate, mEq/L (normal, 21–30)	26	35
Blood urea nitrogen, mg/dL (normal, 7–20)	11	12
Creatinine, mg/dL (normal, 0.6–1.3)	0.9	0.9
Magnesium, mg/dL (normal, 1.6–2.2)	2.2	1.7

About 8 days into the hospitalization, he developed severe hypokalemia (Table 1); an additional workup was sent (Table 2). The 24-hour urine cortisone was low, and the ratio of urine-free cortisol to urine-free cortisone was elevated, concerning for apparent mineralocorticoid excess (AME) attributed to the posaconazole. The patient was started on spironolactone 50 mg daily with improvement in electrolyte abnormalities and hypertension. He remained on spironolactone until posaconazole was discontinued with resolution of neutropenia, after which he remained normotensive without recurrence of metabolic abnormalities.

Discussion

This case of posaconazole-induced AME highlights PCs as a critical physiologic powerhouse attuned to the adjacent hormonal milieu to regulate electrolyte and fluid balance. On binding aldosterone, the intracellular mineralocorticoid receptor (MR) in PC activates gene expression at the nucleus, leading to increased expression and translocation of ENaC and activity of basolateral Na-K ATPase channels. Cortisol has equivalent-binding affinity to MR as aldosterone at 100-fold the plasma concentration, but the local 11β-hydroxysteroid dehydrogenase isoform 2 (11-βHSD2), expressed by cortical-collecting cells, normally prevents constitutive activation of MR by converting cortisol to the poor agonist cortisone. Like black licorice, triazole antifungals, including posaconazole and itraconazole, have been shown to mimic the genetic syndrome of AME by inhibiting 11-βHSD2, leading to uninhibited MR activation by cortisol and resulting hypertension, hypokalemia, and metabolic alkalosis (3–5).

Another disease that can present with low renin and aldosterone is Liddle syndrome, which is an autosomal-dominant condition leading to constitutively active ENaC channels. Although the presentation may be similar to AME, the disease is quite rare and usually presents earlier in life. Additionally, Liddle syndrome will only respond to a diuretic that selectively inhibits ENaC, such as amiloride or triamterene. In this case, spironolactone will not be effective, as the increase in sodium channel activity is not aldosterone-mediated.

Spironolactone works in AME by competitively antagonizing MR at PC, thwarting the constitutive action at this receptor in this disease state. This has the advantage over ENaC blockers by also impeding ENaC-independent aldosterone effects. Thiazide diuretics may additionally be added for further blood pressure control and to reduce hypercalciuria and nephrocalcinosis, although hypokalemia may limit its use (6). Low-dose dexamethasone can be an effective adjunct by suppressing endogenous cortisol production, thereby diminishing cortisol's effects at MR (6, 7). Pharmacotherapy should be accompanied by a low-salt diet for optimal hypertension management (8). In cases of medication-induced AME, as in our case, the culprit medication should be discontinued if clinically feasible.

Teaching points

- The collecting tubule is composed of PCs and ICs. While PCs primarily contribute to net Na^+ absorption and K^+ secretion, ICs are primarily involved in Na^+-independent regulation of acid-base balance.
- The combination of hypertension, hypokalemia, and metabolic alkalosis should prompt investigation into either real or AME states. Low renin and aldosterone levels in this setting should prompt investigation for hypercortisolism and culprit medications, including azoles.
- MR antagonists, such as spironolactone, are the mainstay of management, combined with a low-salt diet and discontinuation of any culprit medication. Thiazide diuretics and/or dexamethasone may be useful adjuncts for refractory cases. ■

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Table 2. Additional workup on hospital days 8–12

Source	Laboratory data	Hospital days 8–12
Blood	Venous blood pH (normal, 7.32–7.42)	7.53
	Venous blood PCO2, mm Hg (normal, 39–55)	47
	Plasma aldosterone concentration, ng/dL (normal, 7–30)	1.5
	Plasma renin activity, ng/mL/h (normal, 0.7–3.3)	0.07
	Serum cortisol after an overnight 1-mg dexamethasone test, nmol/L (normal, <30)	<30
Urine	Random urine potassium, mEq/L	46
	Random urine creatinine, mg/dL	36
	24-h Urine volume, mL	1825
	24-h Urine-free cortisol, µg (normal, 4–50)	20
	24-h Urine-free cortisone, µg (normal 23–195)	16
	Urine-free cortisol to urine-free cortisone ratio (normal, 0.4–0.5)	1.25
	Computed tomography abdomen/pelvis	No adrenal masses

PCO2, partial pressure of carbon dioxide.

The authors report no conflicts of interest.

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Macula Densa: The Master Regulator

By Alexa J. O'Hara and Graham Gipson

Introduction

The macula densa (MD) is made up of 15–20 specialized cells located in the thick ascending limb of the loop of Henle (formally a part of the distal tubule), strategically placed adjacent to the glomerular arterioles (1, 2) (Figure). Its unique location within the juxtaglomerular apparatus allows it to communicate with granular cells of the afferent arteriole and extraglomerular mesangial cells of the efferent arteriole (3). This specific architecture has a crucial functional outcome: autoregulation of kidney blood flow (KBF) and glomerular filtration rate (GFR), as well as control of renin release.

Case

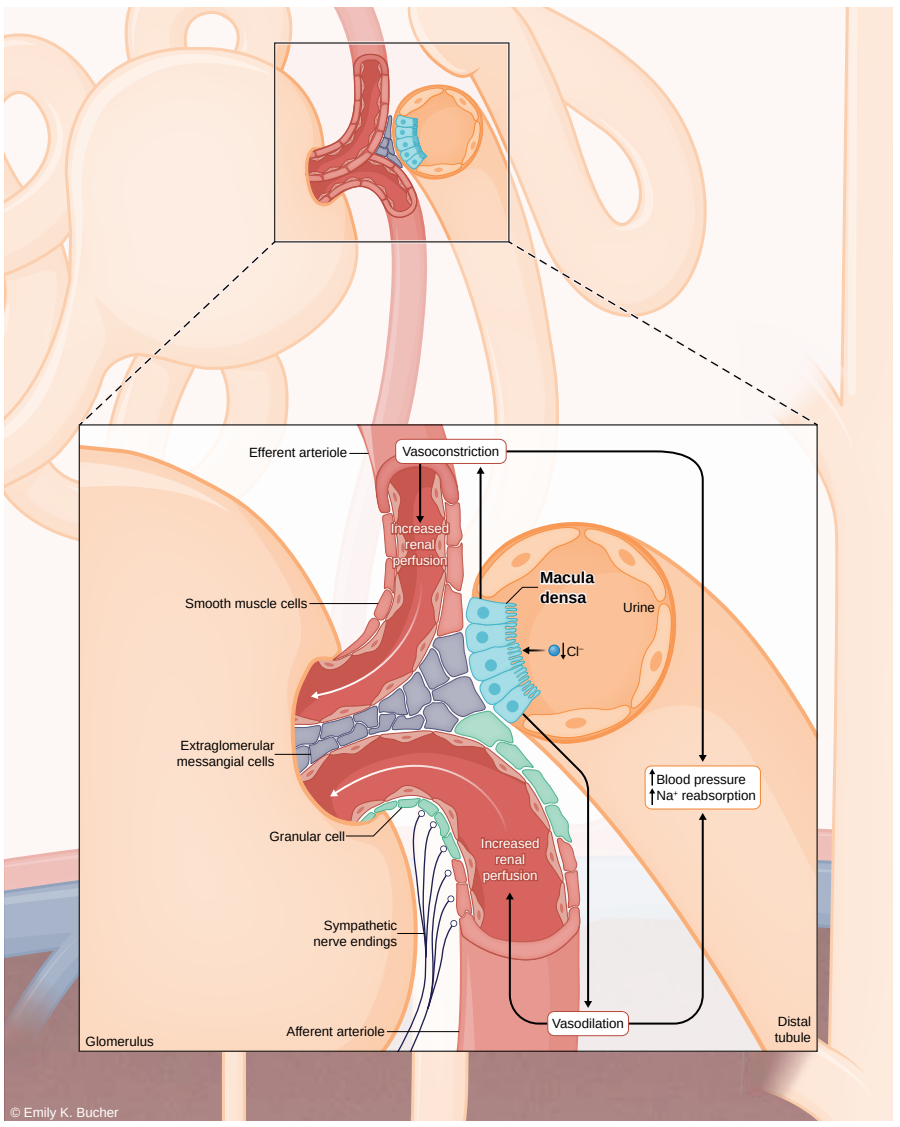
Real-world demonstration of MD physiology is found in the case of a 52-year-old female with a history of gastric bypass who presented to the emergency department with a 2-day history of vomiting, diarrhea, generalized weakness, fatigue, and decreased urine output. Her vital signs were notable for a blood pressure (BP) of 84/52 mm Hg and a heart rate of 106/min on arrival. Her physical examination revealed mild abdominal tenderness to palpation. Pertinent laboratory results included a serum creatinine level of 2.6 mg/dL (with a baseline serum creatinine of approximately 1.0 mg/dL; normal: 0.6–1.2 mg/dL) and a serum potassium level of 3.3 mmol/L (normal: 3.5–5.0 mmol/L). The patient was given 2 L of normal saline and 40 mmol of oral potassium in the emergency department, and her BP improved to 108/64 mm Hg. She was admitted for observation. Her gastrointestinal pathogen panel returned positive for *Campylobacter*, and she was treated with azithromycin. Serum creatinine trended down toward baseline over the next few days, her diarrhea resolved, and she was discharged home.

Discussion

This case of run-of-the-mill prerenal acute kidney injury (AKI) is packed with MD physiology. Mechanistically, we are dealing with this sequence of events: Extracellular fluid volume (ECFV) contraction from diarrhea led to a decrease in systemic BP and thus kidney perfusion pressure. Low kidney perfusion pressure translated into a drop in KBF. Prior to activation of any compensatory mechanisms, low KBF directly mediated a drop in GFR (4). This uncompensated GFR reduction was then transmitted down the nephron as a reduction in tubular fluid flow rate. Tubular fluid flow rate, which is "encoded" by a tubular fluid chloride ion (Cl^-) concentration, constitutes the signal monitored constantly by MD. At the molecular level, this Cl^- signal is "sensed" via the Na-K-2Cl (sodium-potassium-2 chloride) cotransporter, which sits on the apical side of the MD epithelium. Alteration of tubular fluid flow and consequently Cl^- concentration then leads to a signaling cascade of various mediators such as adenine derivatives

Continued on page 22

Figure. Macula densa



Decreased chloride delivery to the macula densa leads to increased blood pressure, renal perfusion (afferent vasodilation and efferent arteriole constriction), and sodium reabsorption.

Macula Densa

Continued from page 21

(adenosine triphosphate [ATP], adenosine), prostaglandins, intracellular calcium, and nitric oxide. Each component of the signaling cascade is responsible for a different feedback response (5, 6).

MD functions, which intertwine and work closely together, can be broken down into three parts: autoregulation of renal perfusion, regulation of GFR via tubuloglomerular feedback, and regulation of BP through renin release. Autoregulation of renal perfusion and regulation of GFR via tubuloglomerular feedback use the same cascade and occur through release of prostaglandins (mediated by extracellular-regulated protein kinase 1/2, p38, and cyclooxygenase-2) and ATP (mediated by an increase in the Cl^- concentration and cell volume change) (7). When the Cl^- concentration sensed by MD cells is low (implying that tubular flow is low), prostaglandins trigger afferent arteriole vasodilation, leading to increased KBF and improving GFR. In contrast, when the Cl^- concentration sensed by MD cells is high, ATP dominates. ATP reaches the extraglomerular mesangial cells of the afferent arteriole and affects vasoconstriction, leading to a decrease in KBF and subsequently GFR (7). Renin release signals occur inside and outside of MD, but within MD, a drop in BP or volume causes a decrease in renal perfusion and decreased Cl^- delivery to MD. A decrease in Cl^- delivery uses the same prostaglandin release pathway to release renin, which subsequently triggers the renin-angiotensin-aldosterone system. The downward effects of this system—namely an increase in sodium absorption and extracellular volume expansion via aldosterone and an increase in systemic BP via angiotensin II—help restore normal kidney perfusion (7).

Over the course of an untreated volume-losing process (like gastrointestinal illness), ECFV is continuously reduced. Continuous ECFV reduction leads to continuous reduction of KBF and GFR. Fortunately, these KBF and GFR reductions are transient: They are reversed once MD "senses" them and deploys their local corrective mechanisms. Ultimately, prostaglandin-driven vasodilation restores KBF and GFR to normal. However, the influence of these corrective, or autoregulatory, mechanisms only extends so far. Once ECFV falls past a critical point, systemic regulatory mechanisms are activated. The major mechanism is the neurohumoral system, which comprises the sympathetic nervous system and total-body renin-angiotensin system. Once neurohumorally driven vasoconstriction sets in, local vasodilatory autoregulation is overpowered (7). What started as "subclinical AKI" (KBF/GFR under threat but compensated) now manifests as "prerenal AKI." The volume responsiveness of prerenal AKI is thus founded on sufficient ECFV resuscitation to suppress systemic neurohumoral activation. Such suppression then allows for the intrarenal/local autoregulation of KBF and GFR to restore normalcy.

In summary, MD is a small but critical control point regulating a comparatively massive tubulovascular system. Positioned strategically at the nexus of the proximal and distal nephron divisions, MD transduces a relatively simple chemical signal (tubular fluid Cl^- concentration) that encodes the complex interplay of upstream biophysical processes (perfusion, filtration, and reabsorption). This transduction modulates the intricate balance of a multifaceted biochemical transmission network founded on purinergic and prostanoid effectors, as well as a local renin-angiotensin system. These effectors ultimately feed back on the source of their progenitor signal to (relatively) preserve perfusion and filtration in the face of perturbing systemic circumstances. Despite the banality of prerenal AKI, even an entry-level nephrology problem is an example of the sophisticated physiology embodied in MD, the master regulator of the nephron.

Teaching points

- MD ensures constant delivery of filtrate to the distal nephron through local regulation of KBF and GFR.
- Prerenal AKI represents the balance of *systemic* neurohumoral activation, charged with defense of total-body hemodynamics, and *local* MD-mediated regulation. The net effect is redistribution of cardiac output to the heart and brain with consequent *mild* reduction in GFR.
- Prompt remediation of total-body hemodynamic disturbances (e.g., with ECFV resuscitation) can extinguish systemic neurohumoral activation, thereby permitting MD-mediated regulation to restore GFR to normal. ■

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The authors report no conflicts of interest.

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Renal Interstitium: The Silent Guardian

By Namrata Krishnan

Introduction

The renal interstitium consists of the extracellular matrix, cells (dendrites, macrophages, lymphocytes, and fibroblasts), lymphatics, and fluid (Figure 1). The cortical interstitium is smaller (accounts for 8% of the total parenchymal volume) than the medullary interstitium (40%), and each has distinct functions.

Historically, the renal interstitium was considered a passive component of the renal parenchyma. Since the 1990s, evolving interest has revealed important physiologic and pathologic roles of the renal interstitium, which include its endocrine functions, fluid and electrolyte exchange and insulation, molecular switch promoting interstitial fibrosis, chronic kidney disease (CKD) progression, and role in the renal immune system in health and disease (1–3).

The activation of the interstitial immune system in response to endogenous and exogenous allergens forms the basis of acute interstitial nephritis (AIN) and chronic interstitial nephritis. The renal interstitial fibroblasts are a heterogenous group of cells that are responsible for production of erythropoietin (in response to hypoxia), renin, as well as collagen and the extracellular matrix (3). In chronic renal injury, collagen-producing fibroblasts increase whereas erythropoietin-producing fibroblasts decrease in number, resulting in CKD progression and anemia. Renin-producing perivascular cells accumulate in the interstitium, promoting salt-sensitive hypertension in CKD (1).

Case

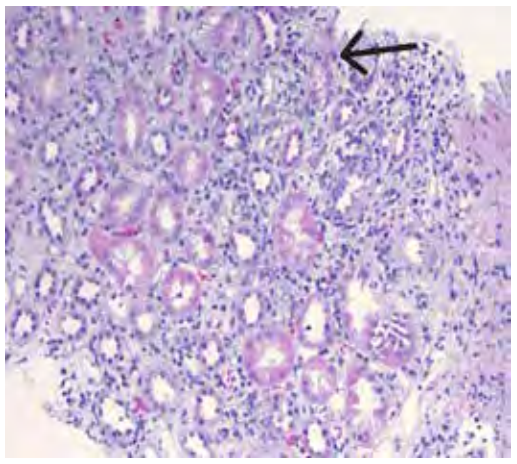
A 73-year-old male with poorly differentiated esophageal carcinoma—in remission while treated with pembrolizumab, a programmed cell death protein 1 inhibitor, for the past 15 months—Barrett's esophagus, and hypertension presented to the emergency department with several days of urinary urgency and difficulty urinating. He reported occasional ibuprofen use. His past medical history was significant for prior immune checkpoint inhibitor (ICI) complications of hepatitis and hypothyroidism. Outpatient medications included omeprazole, levothyroxine, sucralfate, venlafaxine, iron, and senna. His last dose of pembrolizumab was 1 month prior.

On examination, he was normotensive. There was no flank or suprapubic tenderness or skin rash. The rest of the examination was unremarkable. Laboratory data showed a serum creatinine of 1.8 mg/dL, elevated from a previous baseline of 1.2 mg/dL, 1 month prior. Urinalysis test results included the following: specific gravity, 1.009; white blood cell (WBC), 95/high power field; red blood cell (RBC), 4/high power field; trace protein/urine microscopy-monomorphic RBCs; numerous WBCs; no RBC or WBC casts; and urine protein-creatinine ratio, ~340 mg/g. A renal biopsy revealed robust tubulointerstitial lymphocytic and eosinophilic infiltrate with 30% tubulointerstitial fibrosis (Figure 2). The patient was treated with high-dose steroids, and ICI was discontinued with improvement in serum creatinine to 1.4 mg/dL over the next 2 weeks.

Discussion

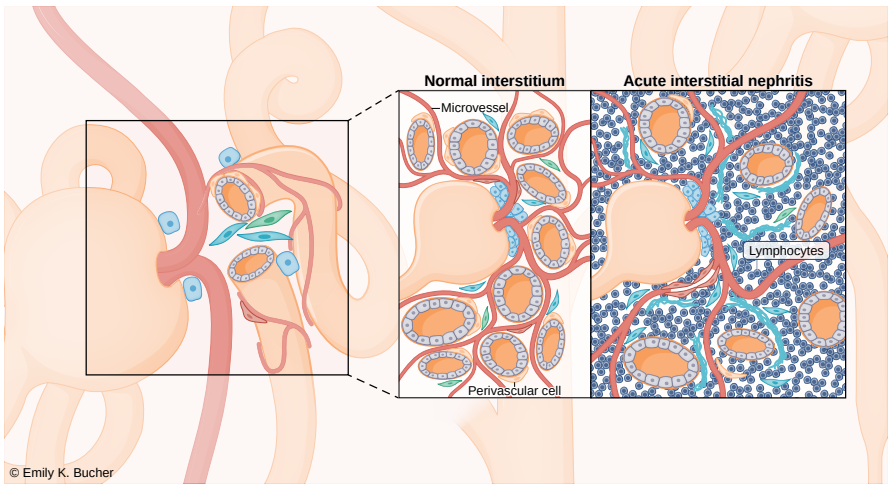
Based on clinical and biopsy data, the patient was diagnosed with ICI-related AIN, which is an immune T cell-mediated injury of the renal tubule interstitium caused by ICI therapy (as evidenced by the lymphocytic mononuclear infiltrate in Figure 2). Drugs are the most common cause of AIN; however, infections and autoimmune etiologies have also been implicated (4). ICIs are emerging as an important cause of AIN in patients with cancer; however, nonsteroidal anti-inflammatory drugs, antibiotics, and proton pump inhibitors remain the more common culprits in the general population. Concomitant use of an ICI and a proton pump inhibitor confers an even higher risk of AIN than each medication alone, as does the presence of baseline CKD (4, 5). Older individuals are at a higher risk of AIN due to polypharmacy and higher CKD prevalence. Anemia, hypertension, and an absence of high-grade proteinuria are important clinical features of tubulointerstitial disease. A definitive diagnosis requires a renal biopsy.

Figure 2. H&E stain of the renal tubulointerstitium



This hematoxylin and eosin (H&E) stain of the renal tubulointerstitium demonstrates a robust mononuclear infiltrate, interstitial edema, and areas of tubulointerstitial fibrosis. The arrow shows eosinophilic infiltration suggestive of drug-induced interstitial nephritis.

Figure 1. Interstitium



Hypercellularity due to aggregation of inflammatory cells within the interstitium.

Persistent tubulointerstitial injury can rapidly progress to interstitial fibrosis (within days to weeks) and result in incident CKD and its progression. Treatment of drug-induced AIN centers around immediate discontinuation of the offending drug. Steroid use may be beneficial in severe cases of AIN when initiated early (<7–10 days from the onset of injury) (6). Although re-exposure to the drug is typically not recommended, risk versus benefit may justify re-exposure to ICIs in patients with cancer who have limited alternative treatment options. Reported incidence of recurrent AIN with ICI rechallenge is small, at 16%–20% (7).

Teaching points

- The renal tubulointerstitium has several important functions, including endocrine functions (renin and erythropoietin release); fluid and electrolyte exchange and insulation; immune function in health and disease; and its role in CKD progression.
- Acute tubulointerstitial injury is often an immune (T cell)-mediated injury and is commonly caused by drugs. In the presence of continued exposure to the allergen and ongoing interstitial injury, there is rapid progression (within days) to irreversible interstitial fibrosis.
- ICIs are an emerging cause of drug-induced AIN and respond favorably to steroid treatment. Incidence of recurrent AIN with ICI rechallenge is low and may be considered if clinically necessary. ■

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Can your patients with lupus nephritis achieve renal remission (CRR) with BENLYSTA (belimumab)?

In the BLISS-LN study, renal remission (CRR) was defined as[1,2]:

- **eGFR ≥90 mL/min/1.73 m²**
  or eGFR no worse than 10% below the preflare value
- **and**
  uPCR <0.5 g/g
- **and**
  not a treatment failure*

Renal remission is defined as complete renal response (CRR) and was a secondary endpoint in the 104-week BLISS-LN study.[1]

Primary endpoint: Renal response defined as eGFR ≥60 mL /min/1.73 m² or eGFR no worse than 20% below preflare value, uPCR ≤0.7, and not a treatment failure at Week 104. Significantly more BENLYSTA patients (n=223) achieved renal response vs placebo (n=223); 43% vs 32%, respectively (*P*=0.031).

* Treatment failures were defined in the BLISS-LN study as patients who received prohibited therapy due to inadequate control of their lupus nephritis symptoms or renal flare management.[1]

AZA = azathioprine; BLISS-LN = Belimumab International SLE Study in Lupus Nephritis; CI = confidence interval; CYC = cyclophosphamide; eGFR = estimated glomerular filtration rate; IV = intravenous; LN = lupus nephritis; MMF = mycophenolate mofetil; OR = odds ratio; ST = standard therapy; uPCR = urine protein:creatinine ratio.

INDICATION

BENLYSTA is indicated for patients aged ≥5 with active systemic lupus erythematosus (SLE) or active lupus nephritis who are receiving standard therapy. BENLYSTA is not recommended in patients with severe active central nervous system lupus.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATION

Previous anaphylaxis with BENLYSTA.

WARNINGS AND PRECAUTIONS

Serious Infections: Serious and sometimes fatal infections have been reported and occurred more frequently with BENLYSTA. Use caution in patients with severe or chronic infections, and consider interrupting therapy in patients with a new infection.

Progressive Multifocal Leukoencephalopathy (PML): Cases of JC virus-associated PML resulting in neurological deficits, including fatal cases, have been reported. If PML is suspected, immunosuppressant therapy, including BENLYSTA, must be suspended until PML is excluded. If confirmed, stop immunosuppressant therapy, including BENLYSTA.

Hypersensitivity Reactions (Including Anaphylaxis): Acute hypersensitivity reactions, including anaphylaxis and death, and infusion-related reactions have been reported. Generally, reactions occurred within hours of the infusion but may occur later, including in patients who have previously tolerated BENLYSTA. Non-acute hypersensitivity reactions (eg, rash, nausea, fatigue, myalgia, headache, and facial edema) typically occurred up to a week after infusion. Monitor patients during and after treatment and be prepared to manage anaphylaxis and infusion-related reactions. Be aware of the risk of hypersensitivity reactions, which may present as infusion-related reactions. Discontinue immediately in the event of a serious reaction. With intravenous administration, if an infusion reaction develops, slow or interrupt the infusion.

Depression and Suicidality: Depression and suicidality were reported in patients receiving BENLYSTA. Before adding BENLYSTA, assess patients' risk of depression and suicide and monitor them during treatment. Instruct patients/caregivers to contact their HCP if they experience new/worsening depression, suicidal thoughts/behavior, or other mood changes.

Malignancy: There is an increased risk of malignancies with the use of immunosuppressants. The impact of BENLYSTA on the development of malignancies is unknown.

Immunization: Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as clinical safety has not been established.

In the BLISS-LN study, patients on ST + MMF or ST + CYC were

74% more likely

to achieve complete renal response (renal remission) at Week 104 with BENLYSTA[1,3]

(30% vs. 20% for placebo + ST, OR=1.74; 95% CI: 1.11, 2.74; *P*=0.0167)

Study design: BLISS-LN was a Phase III study of 448 adult patients with active lupus nephritis (confirmed biopsy-proven Class III, IV, V, or V in combination with III or IV) who were randomized to BENLYSTA 10 mg/kg + ST or placebo. Therapy was administered by IV infusion on Days 0, 14, and 28, and at 4-week intervals thereafter through Week 104. ST was defined as: MMF + high- dose steroids, followed by MMF + low-dose steroids or CYC + high-dose steroids, followed by AZA + low-dose steroids.[1]

References: 1. Furie R, *et al*. *N Engl J Med*. 2020;383(12):1117-1128.
2. Furie R, *et al*. *N Engl J Med*. 2020;383(Suppl):1-15. **3.** Data on File, GSK.

Learn more about the renal remission (CRR) data for lupus nephritis

Use With Biologic Therapies: Available data do not support the safety and efficacy of concomitant use of BENLYSTA with rituximab in patients with SLE. An increased incidence of serious infections and post-injection systemic reactions in patients receiving BENLYSTA concomitantly with rituximab compared to patients receiving BENLYSTA alone has been observed. The safety and efficacy of BENLYSTA concomitantly with other biologic therapies, including B-cell-targeted therapies, have not been established. Caution should be exercised if BENLYSTA is administered in combination with other biologic therapies.

ADVERSE REACTIONS

The most common serious adverse reactions in adult SLE clinical trials were serious infections; some were fatal. The most common adverse reactions (≥5%) were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, pharyngitis, and injection site reactions (subcutaneous injection).

Adverse reactions reported in clinical trials with SLE pediatric patients (≥5 years) and adult patients with lupus nephritis were consistent with those observed in adult SLE trials.

USE IN SPECIFIC POPULATIONS

Pregnancy: There are insufficient data in pregnant women to establish whether there is drug-associated risk for major birth defects or miscarriage. After a risk/benefit assessment, if prevention is warranted, women of childbearing potential should use contraception during treatment and for ≥4 months after the final treatment.

Pregnancy Registry: HCPs are encouraged to refer patients and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/benlysta-belimumab/.

Please see Brief Summary of full Prescribing Information for BENLYSTA on the following pages.

To report SUSPECTED ADVERSE REACTIONS, contact GSK at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Benlysta (belimumab)
Intravenous Use 120 mg/vial
Subcutaneous Use 200 mg/mL

GSK

PMUS-BELJRNA240005 July 2024
Produced in USA.

BRIEF SUMMARY

BENLYSTA (belimumab) for injection, for intravenous use.
BENLYSTA (belimumab) injection, for subcutaneous use.

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

BENLYSTA (belimumab) is indicated for the treatment of:

- patients aged 5 years and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy, and
- patients aged 5 years and older with active lupus nephritis who are receiving standard therapy.

Limitations of Use
The efficacy of BENLYSTA has not been evaluated in patients with severe active central nervous system lupus. Use of BENLYSTA is not recommended in this situation.

4 CONTRAINDICATIONS

BENLYSTA is contraindicated in patients who have had anaphylaxis with belimumab.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections: Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA. Overall, the incidence of serious infections in controlled trials was similar in patients receiving BENLYSTA compared with placebo, whereas fatal infections occurred more frequently in patients receiving BENLYSTA *[see Adverse Reactions (6.1)]*.

Consider the risk and benefit before initiating treatment with BENLYSTA in patients with severe or chronic infections. Consider interrupting therapy with BENLYSTA in patients who develop a new infection while receiving it and monitor these patients closely.

Progressive Multifocal Leukoencephalopathy (PML): Cases of JC virus-associated PML resulting in neurological deficits, including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including BENLYSTA. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. Consider the diagnosis of PML in any patient presenting with new-onset or deteriorating neurological signs and symptoms and consult with a neurologist or other appropriate specialist as clinically indicated. In patients with suspected PML, immunosuppressant therapy, including BENLYSTA, must be suspended until PML has been excluded. If PML is confirmed, immunosuppressant therapy, including BENLYSTA, must be discontinued.

5.2 Hypersensitivity Reactions, including Anaphylaxis: Acute hypersensitivity reactions, including anaphylaxis and death, and infusion-related reactions have been reported in association with BENLYSTA *[see Adverse Reactions (6.1)]*. These events generally occurred within hours of the infusion; however, they may occur later. Non-acute hypersensitivity reactions including rash, nausea, fatigue, myalgia, headache, and facial edema, have been reported and typically occurred up to a week following the most recent infusion. Hypersensitivity, including serious reactions, has occurred in patients who have previously tolerated infusions of BENLYSTA. Limited data suggest that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk.

Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion-related reactions in all cases. In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, some patients (13%) received premedication, which may have mitigated or masked a hypersensitivity response or infusion-related reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of hypersensitivity reactions or infusion-related reaction.

BENLYSTA for intravenous use should be administered by healthcare providers prepared to manage anaphylaxis and infusion-related reactions. Healthcare providers should be aware of the risk of hypersensitivity reactions, which may present as infusion-related reactions. In the event of a serious reaction, discontinue BENLYSTA immediately and administer appropriate medical therapy. With intravenous administration, the infusion rate may be slowed or interrupted if the patient develops an infusion reaction. Monitor patients during infusion and for an appropriate period of time after intravenous administration of BENLYSTA. Consider administering premedication as prophylaxis prior to intravenous dosing *[see Dosage and Administration (2.2) of full prescribing information]*.

Inform patients receiving BENLYSTA of the signs and symptoms of hypersensitivity reactions and instruct them to seek immediate medical care should a reaction occur.

5.3 Depression and Suicidality: In controlled clinical trials, depression and suicidality were reported in patients receiving BENLYSTA *[see Adverse Reactions (6.1)]*. Assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with BENLYSTA and continue to monitor patients during treatment. Instruct patients receiving BENLYSTA (and caregivers, if applicable) to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or behavior, or other mood changes. Consider the risk and benefit of continued treatment with BENLYSTA for patients who develop such symptoms.

5.4 Malignancy: There is an increased risk of malignancies with the use of immunosuppressants. The impact of treatment with BENLYSTA on the development of malignancies is not known *[see Adverse Reactions (6.1)]*.

Consider the individual benefit-risk in patients with known risk factors for the development or reoccurrence of malignancy prior to prescribing BENLYSTA. In patients who develop malignancies, consider the risk and benefit of continued treatment with BENLYSTA.

5.5 Immunization: Because of its mechanism of action, BENLYSTA may interfere with the response to immunizations. Live vaccines should not be given for 30 days before or concurrently with BENLYSTA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving BENLYSTA or the effect of BENLYSTA on new immunizations.

5.6 Concomitant Use with Other Biologic Therapies: Available data do not support the safety and efficacy of concomitant use of BENLYSTA with rituximab in patients with SLE. An increased incidence of serious infections and post-injection systemic reactions in patients receiving BENLYSTA concomitantly with rituximab compared to patients receiving BENLYSTA alone has been observed *[see Adverse Reactions (6.1)]*. The safety and efficacy of BENLYSTA concomitantly with other biologic therapies, including B-cell-targeted therapies, have not been established. Caution should be exercised if BENLYSTA is administered in combination with other biologic therapies *[see Warnings and Precautions (5)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and in the Warnings and Precautions section:

- **Serious Infections** *[see Warnings and Precautions (5.1)]*
- **Hypersensitivity Reactions, including Anaphylaxis** *[see Warnings and Precautions (5.2)]*
- **Depression and Suicidality** *[see Warnings and Precautions (5.3)]*
- **Malignancy** *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience with Intravenous Administration

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.

Adult Patients with SLE: The data described in Table 1 reflect exposure to BENLYSTA administered intravenously plus standard therapy compared with placebo plus standard therapy in 2,133 adult patients with SLE in 3 controlled trials (Trials 1, 2, and 3). Patients received BENLYSTA plus standard therapy at doses of 1 mg/kg (n=673), 4 mg/kg (n=111; Trial 1 only), or 10 mg/kg (n=674), or placebo plus standard therapy (n=675) intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days. In 2 of the trials (Trial 1 and Trial 3), treatment was given for 48 weeks, while in the other trial (Trial 2) treatment was given for 72 weeks *[see Clinical Studies (14.1 in full prescribing information)]*. Because there was no apparent dose-related increase in the majority of adverse events observed with BENLYSTA, the safety data summarized below are presented for the 3 intravenous doses pooled, unless otherwise indicated; the adverse reaction table displays the results for the recommended intravenous dose of 10 mg/kg compared with placebo.

In these trials, 93% of patients treated with BENLYSTA plus standard therapy reported an adverse event compared with 92% treated with placebo plus standard therapy.

The most common serious adverse events were serious infections (6% and 5.2% in the groups receiving BENLYSTA and placebo plus standard therapy, respectively), some of which were fatal.

The most commonly reported adverse events, occurring in ≥5% of patients in clinical trials, were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis.

The proportion of patients who discontinued treatment due to any adverse reaction during the controlled clinical trials was 6.2% for patients receiving BENLYSTA plus standard therapy and 7.1% for patients receiving placebo plus standard therapy. The most common adverse reactions resulting in discontinuation of treatment (≥1% of patients receiving BENLYSTA or placebo) were infusion reactions (1.6% BENLYSTA and 0.9% placebo), lupus nephritis (0.7% BENLYSTA and 1.2% placebo), and infections (0.7% BENLYSTA and 1% placebo).

Adverse reactions, regardless of causality, occurring in at least 3% of patients with SLE who received BENLYSTA 10 mg/kg plus standard therapy and at an incidence at least 1% greater than that observed with placebo plus standard therapy in 3 controlled trials (Trials 1, 2, and 3) were: nausea 15% and 12%; diarrhea 12% and 9%; pyrexia 10% and 8%; nasopharyngitis 9% and 7%; bronchitis 9% and 5%; insomnia 7% and 5%; pain in extremity 6% and 4%; depression 5% and 4%; migraine 5% and 4%; pharyngitis 5% and 3%; cystitis 4% and 3%; leukopenia 4% and 2%; viral gastroenteritis 3% and 1%.

Infections: In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, the overall incidence of infections was 71% in patients receiving BENLYSTA compared with 67% in patients receiving placebo. The most frequent infections (>5% of patients receiving BENLYSTA) were upper respiratory tract infection, urinary tract infection, nasopharyngitis, sinusitis, bronchitis, and influenza. Infections leading to discontinuation of treatment occurred in 0.7% of patients receiving BENLYSTA and 1% of patients receiving placebo.

In a randomized, double-blind, placebo-controlled, 104-week trial of active lupus nephritis in adults receiving BENLYSTA administered intravenously (N=448), the overall incidence of infections was 82% in patients receiving BENLYSTA compared with 76% in patients receiving placebo.

Serious Infections: In controlled trials of BENLYSTA administered intravenously in adults with SLE, the incidence of serious infections was 6% in patients receiving BENLYSTA and 5.2% in patients receiving placebo. The most frequent serious infections included pneumonia, urinary tract infections, cellulitis, and bronchitis. Fatal infections occurred in 0.3% (4/1,458) of patients receiving BENLYSTA and in 0.1% (1/675) of patients receiving placebo.

In a randomized, double-blind, placebo-controlled, 52-week, postmarketing safety trial of BENLYSTA administered intravenously in adults with SLE (N=4,003), the incidence of serious infections was 3.7% in patients receiving BENLYSTA compared with 4.1% in patients receiving placebo. Serious infections leading to discontinuation of treatment occurred in 1% of patients receiving BENLYSTA and in 0.9% of patients receiving placebo. Fatal infections occurred in 0.45% (9/2,002) of patients receiving BENLYSTA and in 0.15% (3/2,001) of patients receiving placebo, where the incidence of all-cause mortality was 0.50% (10/2,002) in patients receiving BENLYSTA and 0.40% (8/2,001) in patients receiving placebo.

Hypersensitivity Reactions, including Anaphylaxis: In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, hypersensitivity reactions (occurring on the same day of infusion) were reported in 13% (191/1,458) of patients receiving BENLYSTA and 11% (76/675) of patients receiving placebo. Anaphylaxis was observed in 0.6% (9/1,458) of patients receiving BENLYSTA and 0.4% (3/675) of patients receiving placebo. Manifestations included hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea.

Infusion-Related Reactions: In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, adverse events associated with the infusion (occurring on the same day of the infusion) were reported in 17% (251/1,458) of patients receiving BENLYSTA and 15% (99/675) of patients receiving placebo. Serious infusion reactions (excluding hypersensitivity reactions) were reported in 0.5% of patients receiving BENLYSTA and 0.4% of patients receiving placebo and included bradycardia, myalgia, headache, rash, urticaria, and hypotension. The most common infusion reactions (≥3% of patients receiving BENLYSTA) were headache, nausea, and skin reactions.

Depression and Suicidality: In controlled clinical trials of BENLYSTA administered intravenously in adults with SLE (N=2,133), psychiatric events were reported more frequently with BENLYSTA (16%) than with placebo (12%), primarily related to depression-related events (6.3% BENLYSTA; 4.7% placebo), insomnia (6% BENLYSTA; 5.3% placebo), and anxiety (3.9% BENLYSTA; 2.8% placebo). Serious psychiatric events were reported in 0.8% (12/1,458) of patients receiving BENLYSTA and 0.4% (3/675) of patients receiving placebo. Serious depression was reported in 0.4% (6/1,458) of patients receiving BENLYSTA and 0.1% (1/675) of patients receiving placebo. Two suicides (0.1%) were reported in patients receiving BENLYSTA (one with 10 mg/kg and one with 1 mg/kg).

In a randomized, double-blind, placebo-controlled, 52-week, postmarketing safety trial of BENLYSTA administered intravenously in adults with SLE (N=4,003), serious psychiatric events were reported in 1% (20/2,002) of patients receiving BENLYSTA and 0.3% (6/2,001) of patients receiving placebo. Serious depression was reported in 0.3% (7/2,002) of patients receiving BENLYSTA and in <0.1% (1/2,001) receiving placebo. The overall incidence of serious suicidal ideation or behavior or self-injury without suicidal intent was 0.7% (15/2,002) of patients receiving BENLYSTA and 0.2% (5/2,001) of patients receiving placebo. On the Columbia-Suicide Severity Rating Scale (C-SSRS), 2.4% (48/1,974) of patients receiving BENLYSTA reported suicidal ideation or behavior compared with 2% (39/1,988) of patients receiving placebo. No suicide was reported in either group.

The intravenous trials above did not exclude patients with a history of psychiatric disorders.

Malignancy: In the controlled clinical trials of BENLYSTA administered intravenously in adults with SLE, malignancies (including non-melanoma skin cancers) were reported in 0.4% of patients receiving BENLYSTA and 0.4% of patients receiving placebo. In the intravenous controlled clinical trials, malignancies, excluding non-melanoma skin cancers, were observed in 0.2% (3/1,458) and 0.3% (2/675) of patients receiving BENLYSTA and placebo, respectively.

Black/African-American Patients: The safety of BENLYSTA 10 mg/kg administered intravenously plus standard therapy (n=331) compared with placebo plus standard therapy (n=165) in Black patients with SLE (Trial 4) was consistent with the known safety profile of BENLYSTA administered intravenously plus standard therapy in the overall population *[see Clinical Studies (14.1) of full prescribing information]*.

Adult Patients with Lupus Nephritis: The safety of BENLYSTA 10 mg/kg administered intravenously plus standard therapy (n=224) compared with placebo plus standard therapy (n=224) was evaluated in adults with lupus nephritis for up to 104 weeks (Trial 5) *[see Clinical Studies (14.2) of full prescribing information]*. The adverse reactions observed were consistent with the known safety profile of BENLYSTA administered intravenously plus standard therapy in patients with SLE. Cases of myelosuppression, including febrile neutropenia, leukopenia, and pancytopenia, were observed in subjects who received induction therapy with cyclophosphamide followed by maintenance therapy with azathioprine, or mycophenolate.

Pediatric Patients: The safety of BENLYSTA administered intravenously plus standard therapy (n=53) compared with placebo plus standard therapy (n=40) was evaluated in 93 pediatric patients with SLE (Trial 6). The adverse reactions observed were consistent with those observed in adults with SLE *[see Clinical Studies (14.3) of full prescribing information]*.

Clinical Trials with Subcutaneous Administration in Adults: The data described below reflect exposure to BENLYSTA administered subcutaneously plus standard therapy compared with placebo plus standard therapy in 836 patients with SLE in a controlled trial (Trial 7). In addition to standard therapy, patients received BENLYSTA 200 mg (n=556) or placebo (n=280) (2:1 randomization) once weekly for up to 52 weeks *[see Clinical Studies (14.4) of full prescribing information]*.

In the trial, 81% of patients treated with BENLYSTA plus standard therapy reported an adverse event compared with 84% treated with placebo plus standard therapy. The proportion of patients who discontinued treatment due to any adverse reaction during the controlled clinical trial was 7.2% of patients receiving BENLYSTA plus standard therapy and 8.9% of patients receiving placebo plus standard therapy.

The safety profile observed for BENLYSTA administered subcutaneously plus standard therapy was consistent with the known safety profile of BENLYSTA administered intravenously plus standard therapy, with the exception of local injection site reactions.

(continued on next page)

Benlysta (belimumab)

Infections: In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the overall incidence of infections was 55% in patients receiving BENLYSTA compared with 57% in patients receiving placebo. The most commonly reported infections with BENLYSTA administered subcutaneously were similar to those reported with BENLYSTA administered intravenously.

Serious Infections: In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the incidence of serious infections was 4.1% in patients receiving BENLYSTA and 5.4% in patients receiving placebo. Fatal infections occurred in 0.5% (3/556) of patients receiving BENLYSTA and in none of the patients receiving placebo (0/280).

Depression and Suicidality: In a controlled trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), which excluded patients with a history of psychiatric disorders, psychiatric events were reported in 6% of patients receiving BENLYSTA and 11% of patients receiving placebo. Depression-related events were reported in 2.7% (15/556) of patients receiving BENLYSTA and 3.6% (10/280) of patients receiving placebo. Serious psychiatric events were reported in 0.2% (1/556) of patients receiving BENLYSTA and in no patients receiving placebo. There were no serious depression-related events or suicides reported in either group. On the C-SSRS, 1.3% (7/554) of patients receiving BENLYSTA reported suicidal ideation or behavior compared with 0.7% (2/277) of patients receiving placebo.

Malignancy: In a controlled clinical trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the reports of malignancies were similar to those reported with BENLYSTA administered intravenously.

Injection Site Reactions: In a controlled clinical trial of BENLYSTA administered subcutaneously in adults with SLE (N=836), the frequency of injection site reactions was 6.1% (34/556) for patients receiving BENLYSTA plus standard therapy and 2.5% (7/280) for patients receiving placebo plus standard therapy. These injection site reactions (most commonly pain, erythema, hematoma, pruritus, and induration) were mild to moderate in severity. The majority (94%) did not necessitate discontinuation of treatment.

Concomitant Use of Rituximab in Adults: BENLYSTA administered subcutaneously in combination with rituximab was studied in a Phase III, randomized, double-blind, placebo-controlled, 104-week study in adult patients with SLE. Patients were randomized to 1 of the 3 treatment arms: BENLYSTA with a single cycle of rituximab (n=144); BENLYSTA with placebo (n=72); BENLYSTA plus standard therapy (n=76). In general, adverse reactions were consistent with the known safety profile of BENLYSTA and rituximab. When compared with BENLYSTA and placebo or BENLYSTA plus standard therapy, BENLYSTA in combination with rituximab was associated with higher frequency of serious adverse events (13.9%, 19.7%, 22.2%), serious infections (2.8%, 5.3%, 9%), and post-injection systemic reactions (9.7%, 5.3%, 13.2%).

6.2 Postmarketing Experience: The following adverse reactions have been identified during postapproval use of BENLYSTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

• Fatal anaphylaxis *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with BENLYSTA. In clinical trials BENLYSTA was administered concomitantly with other drugs, including corticosteroids, antimalarials, immunomodulatory and immunosuppressive agents (including azathioprine, cyclophosphamide, methotrexate, and mycophenolate), angiotensin pathway antihypertensives, HMG-CoA reductase inhibitors (statins), and/or non-steroidal anti-inflammatory drugs (NSAIDs) without evidence of a clinically meaningful effect of these concomitant medications on belimumab pharmacokinetics. The effect of belimumab on the pharmacokinetics of other drugs has not been evaluated *[see Clinical Pharmacology (12.3) of full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that evaluates pregnancy outcomes in women with lupus exposed to BENLYSTA during pregnancy. Healthcare professionals are encouraged to refer patients and pregnant women are encouraged to enroll themselves by calling 1-877-311-8972 or visiting https://mothertobaby.org/ongoing-study/benlysta-belimumab/.

Risk Summary: Available data on use of BENLYSTA in pregnant women, from observational studies, published case reports, and postmarketing surveillance, are insufficient to determine whether there is a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with SLE *(see Clinical Considerations)*. Monoclonal antibodies, such as belimumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the in utero-exposed infant *(see Clinical Considerations)*. In an animal combined embryo-fetal and pre- and post-natal development study with monkeys that received belimumab by intravenous administration, there was no evidence of fetal harm with exposures approximately 9 times (based on intravenous administration) and 20 times (based on subcutaneous administration) the exposure at the maximum recommended human dose (MRHD). Belimumab-related findings in monkey fetuses and/or infants included reductions of B-cell counts, reductions in the density of lymphoid tissue B-lymphocytes in the spleen and lymph nodes, and altered IgG and IgM titers. The no-adverse-effect-level (NOAEL) was not identified for these findings; however, they were reversible within 3 to 12 months after the drug was discontinued *(see Data)*. Based on animal data and the mechanism of action of belimumab, the immune system in infants of treated mothers may be adversely affected. It is unknown, based on available data, whether immune effects, if identified, are reversible *[see Clinical Pharmacology (12.1) of full prescribing information]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk: Pregnant women with SLE are at increased risk of adverse pregnancy outcomes, including worsening of the underlying disease, premature birth, miscarriage, and intrauterine growth restriction. Maternal lupus nephritis increases the risk of hypertension and preeclampsia/eclampsia. Passage of maternal autoantibodies across the placenta may result in adverse neonatal outcomes, including neonatal lupus and congenital heart block.

Fetal/Neonatal Adverse Reactions: Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to BENLYSTA in utero. Monitor an infant of a treated mother for B-cell reduction and other immune dysfunction *[see Warnings and Precautions (5.5)]*.

Data *[see Data (in 8.1) of full prescribing information]*.

8.2 Lactation

Risk Summary: No information is available on the presence of belimumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BENLYSTA, and any potential adverse effects on the breastfed child from BENLYSTA or from the underlying maternal condition. *[See Lactation (in 8.2) of full prescribing information]*.

8.3 Females and Males of Reproductive Potential

Contraception: Following an assessment of benefit versus risk, if prevention of pregnancy is warranted, females of reproductive potential should use effective contraception during treatment and for at least 4 months after the final treatment.

8.4 Pediatric Use: Safety and effectiveness of BENLYSTA have been established for the treatment of SLE and lupus nephritis in pediatric patients 5 to 17 years old.

Use of BENLYSTA in pediatric patients with SLE is supported by evidence from pharmacokinetic (PK) and efficacy results from a pediatric study (Trial 6), as well as PK exposure and extrapolation of the established efficacy of BENLYSTA plus standard therapy from the Phase 3 intravenous studies in adults with SLE. A randomized, double-blind, placebo-controlled, PK, efficacy, and safety study (Trial 6) to evaluate intravenously administered BENLYSTA 10 mg/kg plus standard therapy compared with placebo plus standard therapy over 52 weeks was conducted in 93 pediatric patients with SLE. The proportion of pediatric patients achieving an SRI-4 response was higher in patients receiving BENLYSTA plus standard therapy compared with placebo plus standard therapy. Pediatric patients receiving BENLYSTA plus standard therapy also had a lower risk of experiencing a severe flare

compared with placebo plus standard therapy *[see Clinical Studies (14.3)]*. Pharmacokinetics were evaluated in a total of 53 pediatric patients with SLE and were consistent with the adult population with SLE *[see Clinical Pharmacology (12.3)]*.

Use of BENLYSTA in pediatric patients with active lupus nephritis is based on the extrapolation of efficacy from the intravenous study in adults (n=224) with active lupus nephritis, and supported by pharmacokinetic data from intravenous studies in adults (n=224) with active lupus nephritis and from pediatric patients (n=53) with SLE. Estimated belimumab exposures for pediatric patients were comparable to adults with active lupus nephritis *[see Clinical Pharmacology (12.3)]*.

Use of BENLYSTA, administered subcutaneously in pediatric patients (5 to less than 18 years of age and weighing at least 15 kg) with SLE, is supported by evidence from an open-label pharmacokinetic trial (subcutaneous administration of BENLYSTA in pediatric patients with SLE) and Trial 6 (a pharmacokinetic, efficacy, and safety study of intravenous dosing in pediatric patients with SLE). The pharmacokinetics of belimumab, following subcutaneous administration in pediatric patients, are estimated to be similar to adults who receive BENLYSTA subcutaneously and pediatric patients who receive BENLYSTA intravenously *[see Clinical Pharmacology (12.3)]*.

The safety and effectiveness of the subcutaneous administration of BENLYSTA, in pediatric patients less than 18 years of age with active lupus nephritis, have not been established. The safety and effectiveness of BENLYSTA have not been established in pediatric patients less than 5 years of age.

8.5 Geriatric Use: Clinical studies of BENLYSTA did not include sufficient numbers of subjects aged 65 or older to determine whether they respond differently from younger subjects. Use with caution in geriatric patients.

8.6 Renal Impairment: No dosage adjustment is recommended in patients with renal impairment.

8.7 Hepatic Impairment: No dosage adjustment is recommended in patients with hepatic impairment.

8.8 Racial Groups: In Trial 2 and Trial 3 (intravenous dosing), SLE SRI-4 response rates were lower for Black patients receiving BENLYSTA plus standard therapy relative to Black patients receiving placebo plus standard therapy *[see Clinical Studies (14.1) of full prescribing information]*.

In Trial 4 (intravenous dosing), a 2:1 randomized, placebo-controlled trial in Black patients, SLE Responder Index (SRI-S2K) response rates were higher for Black patients receiving BENLYSTA plus standard therapy (49%) relative to Black patients receiving placebo plus standard therapy (42%). However, the treatment difference was not statistically significant *[see Clinical Studies (14.1) of full prescribing information]*.

In Trial 7 (subcutaneous dosing), SRI-4 response was 45% (26/58) in Black patients receiving BENLYSTA plus standard therapy compared with 39% (13/33) in Black patients receiving placebo plus standard therapy *[see Clinical Studies (14.4) of full prescribing information]*.

The safety profile of BENLYSTA in Black patients was consistent with the known safety profile of BENLYSTA administered in the overall population *[see Adverse Reactions (6.1)]*.

10 OVERDOSAGE

There is limited experience with overdosage of belimumab.

12 CLINICAL PHARMACOLOGY

12.6 Immunogenicity

In Trials 2 and 3 (intravenous dosing in adults with SLE), anti-belimumab antibodies were assessed during the respective 52-week and 76-week, placebo-controlled periods and detected in 4 of 563 (0.7%) patients receiving BENLYSTA 10 mg/kg and in 27 of 559 (4.8%) patients receiving BENLYSTA 1 mg/kg. The reported frequency for the group receiving 10 mg/kg may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentrations. Neutralizing antibodies were detected in 3 patients receiving BENLYSTA 1 mg/kg. Three patients with anti-belimumab antibodies experienced mild infusion reactions of nausea, erythematous rash, pruritus, eyelid edema, headache, and dyspnea; none of the reactions were life-threatening. In Trial 4 (intravenous dosing in adult Black patients), anti-belimumab antibodies were detected in 2 of 321 (0.6%) patients receiving BENLYSTA 10 mg/kg during the 52-week, placebo-controlled period. In Trial 5 (intravenous dosing in adults with lupus nephritis), there was no formation of anti-belimumab antibodies in 224 patients receiving BENLYSTA 10 mg/kg plus standard therapy during the 104-week, placebo-controlled period. In Trial 6 (intravenous dosing in pediatric patients with SLE), there was no formation of anti-belimumab antibodies in 53 patients receiving BENLYSTA 10 mg/kg plus standard therapy during the 52-week, placebo-controlled period. In Trial 7 (subcutaneous dosing in adults with SLE), there was no formation of anti-belimumab antibodies in 556 patients receiving BENLYSTA 200 mg during the 52-week, placebo-controlled period.

The clinical relevance of the presence of anti-belimumab antibodies is not known.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of belimumab. Effects on male and female fertility have not been directly evaluated in animal studies.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use) of full prescribing information.

Serious Infections: Inform patients that BENLYSTA may decrease their ability to fight infections, and that serious infections, including some fatal ones, occurred in patients receiving BENLYSTA in clinical trials. Instruct patients to tell their healthcare provider if they develop signs or symptoms of an infection *[see Warnings and Precautions (5.1)]*.

Progressive Multifocal Leukoencephalopathy: Advise patients to contact their healthcare professional if they experience new or worsening neurological symptoms such as memory loss, confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems *[see Warnings and Precautions (5.1)]*.

Hypersensitivity Reactions/Anaphylaxis: Educate patients on the signs and symptoms of hypersensitivity reactions and infusion-related reactions. Instruct patients to immediately tell their healthcare provider if they experience symptoms of an allergic reaction during or after the administration of BENLYSTA. Inform patients about possible delayed reactions that may include a combination of symptoms such as rash, nausea, fatigue, muscle aches, headache, and/or facial swelling that may occur after administration of BENLYSTA and advise them to contact their healthcare provider *[see Warnings and Precautions (5.2)]*.

Depression and Suicidality: Instruct patients/caregivers to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes *[see Warnings and Precautions (5.3)]*.

Immunizations: Inform patients that they should not receive live vaccines while taking BENLYSTA. Response to vaccinations could be impaired by BENLYSTA *[see Warnings and Precautions (5.5)]*.

Pregnancy Registry: Inform patients that there is a pregnancy registry to evaluate fetal outcomes of pregnant women with lupus exposed to BENLYSTA *[see Use in Specific Populations (8.1)]*.

Pregnancy: Inform female patients of reproductive potential that BENLYSTA may impact the immune system in infants of treated mothers and to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

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Greater Transparency, Policy Changes Needed to Drive More Kidney Transplants

By Bridget M. Kuehn

Nichole Jefferson, MBA, feels better than she has in decades living with her second kidney allograft, which she describes as an "ugly kidney." She explained that much went wrong with the allograft, which had been transported all the way from Washington state to Iowa, likely because other transplant centers had repeatedly declined it. But, after her first allograft deteriorated, she was willing to take the risk of an imperfect kidney to avoid having to undergo dialysis again.

Looking back, Jefferson is glad she took the risk. She said that transplant teams need to educate patients about the potential benefits of an imperfect kidney instead of waiting in vain for a "perfect kidney," which, she noted, does not always work out as hoped.

"Doctors need to stop telling people that [some] kidneys are perfect and also let them know of options that are available," she said during the Celeste Castillo Lee Endowed Lectureship, honoring the late patient-empowerment advocate. Instead, Jefferson and other speakers at Kidney Week 2024 called for greater transparency throughout the transplant process and shared decision-making with patients every step of the way.

"Transplantation is the optimum intervention for [kidney diseases]," said Matthew Cooper, MD, chief of transplantation and the Mark B. Adams Distinguished Professor of Surgery at the Medical College of Wisconsin in Milwaukee, during a Kidney Week session, entitled "Why Aren't We Sharing More Declined Kidney Offers With Waitlisted Patients?"

Cooper noted that there is a growing need for kidney transplants, with 800,000 individuals in the United States living with kidney failure, yet only 25,000 transplants are completed each year, according to the US Centers for Disease Control and Prevention. Many patients never make it through the process of getting on the list, and many more will die waiting while transplant centers decline multiple organ offers on their behalf.

Opening the "black box"

Many speakers at Kidney Week shared stories of patients who had undergone dialysis for years and thought that they were on the kidney transplant waiting list but were not. Rachel Patzer, PhD, MPH, president and chief executive officer of the Regenstrief Institute in Indianapolis, IN, noted that the proportion of patients on the waiting list has fallen 30% since 2013. As of 2020, only about 13% of patients living with kidney failure are on the waitlist. Patzer spoke during the Kidney Week session, "Kidney Transplantation in 2024: Change Isn't Coming, It's Here."

Existing data show large geographic variations in transplant referral and evaluation, Patzer noted. For example, New England transplant centers evaluated 62% of referred patients within 6 months (1). By contrast, Ohio Valley region transplant centers had evaluated only about 46% of those referred within 6 months. "This variation suggests that there are inconsistent practices that are leading to disparities in treatment and poor access for some patients," she said.

Patzer explained that the process of getting on the transplant waitlist is complicated for patients, and there are very little data about prewaitlisting practices, making it a black box for researchers. However, recent policy changes, including new Health Resources and Services Administration requirements for organ procurement transplant networks and mandatory Centers for Medicare & Medicaid Services data collection, may soon help fill these gaps.

There is also substantial variation in the way organs are procured and allocated throughout the country. Jesse Schold, PhD, MEd, MS, professor in the Department of Surgery and Epidemiology at the University of Colorado Anschutz Medical Campus in Aurora, presented the Christopher R. Blagg, MD, Endowed Lectureship in Kidney Diseases and Public Policy during the same session as Patzer. In the talk, Schold explained that donor service areas throughout the country resemble gerrymandered voting districts. For example, he noted that the 4000-square-mile donor service area covering New York has twice as many patients as a 184,000-mile service area covered by Colorado.

"[There have] been lots of data demonstrating [that] every time we predict that the next offer is going to be a better offer, [the] patient actually doesn't ever get that transplant, and they die waiting on the list."

Organ procurement organizations (OPOs) may also follow widely different practices across the country. Schold noted that new and controversial rules from the Centers for Medicare & Medicaid Services are going to change the way OPOs are regulated, including requiring more objective data of potential donors and setting targets that the organizations must meet to remain certified, including holding them accountable for how many allografts are transplanted. But, he noted that this has led to greater out-of-order placement of organs on the waitlist through "expedited placements." Additionally, he said that as many as 40% of OPOs could be reclassified under the rules, which will greatly impact the overall system.

Schold urged greater coordination of policies regarding all parts of the health care system, including value-based care initiatives. He said that getting the quality metrics right is critical because they greatly impact care. "They change the way we select patients; they change the way to select organs," he said. "They have a significant impact on our care, which also suggests [that] if we get them right, they have incredible potential benefits."

Declined organs

However, collecting more organs and enrolling patients on the transplant waitlist are not enough. There are currently about 100,000 people on the kidney transplant waiting list in the United States. Patients who do undergo a transplant may wait, on average, 6 years, and nearly one-third may die waiting on the list.

Spending time on the waiting list exacts a toll on patients psychologically, socioeconomically, and physically, noted Joyce Popoola, MBChB, MD, PhD, a consultant nephrologist and senior lecturer at St George's University of London, United Kingdom, during the Kidney Week session on declined kidney offers. She noted that patients' illness, disability, and risk of death grow over time while waiting. For example, an 18-year-old waiting for 5 years has morbidity similar to that of a 50- to 60-year-old, she said.

A growing number of deceased donor organs are collected, totaling about 26,000 each year. But more than one in four are discarded, Cooper said. Many of the organs are from higher-risk donors with a higher kidney donor profile index. Some may have anatomic abnormalities, some may have acute kidney injury, or the donor may have a history of hepatitis C or HIV. "It is easy, in the middle of the night, to say no to an imperfect organ," Cooper said. "[There have] been lots of data demonstrating [that] every time we predict that the next offer is going to be a better offer, [the] patient actually doesn't ever get that transplant, and they die waiting on the list."

In fact, Syed Ali Husain, MD, MPH, MA, FASN, assistant professor and transplant nephrologist at Columbia University in New York, NY, conducted an analysis of US data on transplant offers. During the Kidney Week session on declined kidneys, he revealed findings that over 6000 deceased patients remained on the list, having received an average of four organ offers after their deaths, often more than 1 month after their passing (2). Husain said that the data show how little patient engagement is happening and how frequently centers do not even contact potential recipients about offers. The same data show that 30% of patients die or are removed from the waiting list before receiving a transplant after a center declined an allograft that was transplanted into a patient who was farther down the waiting list. On average, the deceased patients had received 16 total offers while on the waitlist before being removed, he said. "People start to accumulate organ offers pretty quickly after waitlisting that are routinely declined on their behalf," Husain explained. "It's pretty consequential to have the patient's voice not heard in this process."

Cooper emphasized that many discarded organs may be usable. For example, he noted evidence that biopsy data may not be a good indicator or outcome, that kidneys with acute kidney injury can recover, that hepatitis C can be cured, and that organs from a donor with HIV can be given to a recipient who is HIV positive. Dual organ transplant, in which two kidneys are transplanted at once, is another option, but there are few surgeons experienced with dual organ transplant, he said. As a result, long cold ischemic times when dual transplant-ready organs have been turned down repeatedly often render them unusable. "If we could find a way to get more efficient and get these allocated to the proper patients, we could probably utilize more of these organs as well," Cooper noted. He and his colleagues have created a list of patients who might benefit from dual transplants and have developed a rapid transplant protocol for them.

Cooper said that new policies will require transplant centers to track and report data on their referral, evaluation, and transplant statistics. He also urged transplant surgeons

to review outcomes for their patients after turning down an organ and to review the outcome of the donor allograft, as well as to benchmark their center's statistics against others. Popoola and her colleagues conduct such a quarterly review, and they have found that most of the patients who have received a declined kidney allograft offer are still waiting 1 year later. They also work collaboratively as a single system. There is only one waiting list for the entire United Kingdom, and different centers work to facilitate successful transplants for recipients by sharing facilities when needed. "The waiting list is not a safe place for patients," Cooper said. "We have to educate our patients better about the data, the options, and outcomes."

Out-of-sequence transplants

A growing practice of out-of-sequence transplants is exacerbating inequities in the US organ allocation system, according to an oral abstract presentation by Sumit Mohan, MD, MPH, FASN, professor of medicine and epidemiology at Columbia University School of Medicine. During Kidney Week, Mohan presented data from an analysis of all of the deceased donor kidneys placed out of sequence between 2020 and 2023 (3). He found a 9-fold increase in out-of-sequence allocations during this period, with one in six kidneys allocated out of sequence. He noted that the organs offered out of sequence span the kidney quality spectrum, with only a small fraction being higher-risk kidneys. "What [OPOs] have chosen to do is basically call a friend," he said during a press briefing at Kidney Week. "They get to pick which friend, and the friend gets to pick which one of their patients they get to put a kidney in."

Mohan noted during the press briefing that OPOs are sending most of these out-of-sequence kidneys to a small number of transplant centers without a clear reason. At some transplant centers, 60% to 70% of their transplants may be out of sequence. In some cases, he said, organs are being flown thousands of miles to Florida from densely populated areas in the Northeast, where many nearby patients could benefit from them. He noted that although it is good that an organ is getting used, patients who were in line to receive an organ are getting passed over and are sometimes not offered another allograft.

Growing numbers of out-of-sequence transplants are just one of many policy-related challenges facing the field of transplants. Husain noted that at every stage in the process, from organ procurement to allocation and transplant, there can be misaligned incentives and efforts to game the system in ways that do not benefit patients. "We have had the privilege of self-regulation, but we are losing that," said Husain during the session Kidney Transplantation in 2024: Change Isn't Coming, It's Here.

Recognition of these problems is leading to greater outside regulation of the transplant process. Husain described his wishlist of changes that includes the realignment of incentives to promote good behavior, transparency about organ offers and placement, public records of Organ Procurement and Transplantation Network meetings and decision-making, expanded definitions of conflicts of interest, and new approaches to implementing policy changes.

A seat at the table

Jefferson advocated for greater patient involvement on the transplant center's patient-selection committees and in organ-offer decisions. "The care team actually gets together to discuss you, the patient, to see if you should be waitlisted, deferred, or just completely rejected," Jefferson said. "Everyone is talking about you, but you are not even there."

She said that engagement on the patient-selection committee would keep patients better informed of where they are in the process. It would also help them to understand and challenge potential reasons that they are not being listed. For example, it is inadequate when a committee concludes that a patient does not have a support system because the committee just does not accept the patient's support system.

Jefferson also advocated for greater transparency and education about the convoluted transplant process. The first time that she needed a transplant in 2003, she only joined the waitlist at one center because she did not know that she could join multiple centers' waitlists. When her first allograft began to fail, she joined the waitlist at multiple centers in several states. She explained that the waitlist time where she lived in Texas was 10 years, whereas other states had much shorter waitlist times.

The complicated process can also contribute to reduced waitlisting for individuals with lower socioeconomic status or individuals from racial and ethnic minority groups, Jefferson said. She explained that patients with limited funds or restrictive insurance may not be able to pursue waitlisting in multiple states. For example, she had to travel to Iowa from Texas repeatedly before receiving her second transplant, and she had to stay in Iowa for 1 month after the transplant, which many people may not be able to afford.

Jefferson emphasized that a concerted effort by all stakeholders is needed to improve the process for patients to make it more equitable. She argued that better patient engagement in decision-making would build patient and community trust in the transplant system and improve patient engagement.

Husain indicated that the transplant system can be paternalistic about making decisions on a patient's behalf, often with very little information about what patients want. At his center, for example, a transplant surgeon may have only seen a patient once before beginning to consider offers on their behalf. Because the surgical team consists of five to six surgeons who review offers, in some cases, the person reviewing the offer may have never met the patient. "If centers are going to make these life-or-death decisions on behalf of a patient, hopefully, they at least know what patients want," he said. "You hope they're making decisions that reflect what a patient would make if they were making it on their own."

However, preliminary results of a survey by Husain and colleagues found that one in five patients on the waiting list does not believe their centers understand their values and preferences, and one in four does not trust their center to make decisions on their behalf. To improve the situation, Popoola suggested that transplant center teams begin discussing and recording patient preferences regarding allograft offers at the first visit and explaining the pros and cons of different scenarios.

Husain recommended getting patients' pretransplant teams involved in the educational process, noting that they may have a deeper relationship with the patient. He also suggested that patients receive updates on how many organs were declined on their behalf to facilitate shared decision-making. He suggested that the Organ Procurement and Transplantation Network could develop a patient portal that would allow patients to check their status on the list and review any offers made to them, giving patients control over how much information and how often they choose to receive it.

"We need to be included every step of the way because this is our life," Jefferson said. "One of the things that I often say is [that] my lived experience with kidney disease is just as valuable, if not more valuable, than your learned experience with kidney disease." ■

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ASN Advances Key Policy Priorities in 2024

By Ryan Murray

ASN continued to champion the interests of kidney health professionals and people with kidney diseases by advocating for policies that enhance patient care, advance research, address systemic barriers to kidney care, and support the kidney health team. With the rising prevalence of kidney diseases globally, ASN's policy efforts championed by the ASN Council, the ASN Policy and Advocacy Committee, the ASN Quality Committee, the ASN Health Care Justice Committee, and the ASN Transplant Workgroup have become more crucial than ever. This article reviews ASN's major policy accomplishments from this past year on which to build its 2025 policy priorities.

1) Intervening earlier in kidney care

A cornerstone of ASN's 2024 policy efforts was the goal of intervening earlier to prevent, diagnose, and manage kidney diseases. With kidney diseases affecting 37 million Americans, and nearly 9 of 10 of those Americans not knowing they are affected, improving early detection and prevention is a top priority.

- **Increasing awareness and screening for kidney diseases**
  ASN worked tirelessly to increase congressional awareness about the importance of early kidney disease screening, particularly in high-risk populations. Through its efforts, the society pushed for expanded screening recommendations by the US Preventive Services Task Force. These recommendations aim to improve the early detection of chronic kidney disease, enabling patients to receive timely interventions, thus preventing disease progression to kidney failure.

- **Advocating for a national Office of Kidney Health and Transplantation**
  ASN called for the establishment of an Office of Kidney Health and Transplantation within the Department of Health and Human Services, a dedicated body to oversee and coordinate policies related to kidney health. This office would work to streamline care coordination, increase access to early diagnosis, and better allocate resources for kidney health at the federal level.

- **Supporting improvements in the Kidney Care Choices (KCC) Model**
  ASN engaged the Center for Medicare and Medicaid Innovation on topics related to the KCC Model, particularly concern regarding optimal starts. ASN will continue to monitor developments to the KCC Model and provide ongoing updates.

2) Transforming transplant processes and increasing access

Kidney transplantation remains the optimal therapy for most people living with kidney failure. In 2024, ASN focused more than ever on transforming the transplant system to improve access for those who could benefit by making the system more transparent, efficient, and accountable.

- **Increasing Organ Transplant Access through advocacy**
  ASN's advocacy played a pivotal role in the establishment of the proposed Increasing Organ Transplant Access Model by the Center for Medicare and Medicaid Innovation. If finalized, this model would incentivize transplant programs to expand access to transplantation by increasing transplant rates and encouraging more attention on populations that have historically been underserved by the transplant system. The model would also make the process more transparent and patient-centric by sharing critical information about patients' own care—such as the criteria for being waitlisted at each program and organ offers made on patients' behalf—and by promoting attention to longer-term outcomes.

- **Supporting living donors through legislative measures**
  ASN championed the introduction of the Honor Our Living Donors Act in Congress and helped secure its unanimous passage out of the House Energy and Commerce Committee, demonstrating strong bipartisan support for the bill. This legislation would support living donors by assessing the donors' eligibility to receive reimbursement for donation-related costs through the Living Organ Donor Reimbursement Program, ensuring that financial barriers do not prevent individuals from becoming living donors. (Currently, living donors' eligibility to receive donation-related costs is based on recipient income, not donor income, not only creating a complicated bureaucracy but also preventing donation for some due to lack of reimbursement.)

- **Implementing a historic funding increase for the Organ Procurement and Transplantation Network (OPTN) Modernization Initiative**
  During ASN's spring 2024 Capitol Hill Day, advocates focused on increasing funding for the Health Resources and Services Administration to modernize the transplant system, implementing the Securing the US OPTN Act—ASN's most significant legislative victory of 2023. Congress delivered in a big way, recommending the largest funding increase ever for the Health Resources and Services Administration for transplant system reforms.

- **Collecting data on transplant referrals and waitlisting**
  ASN gained federal commitment to collect data on kidney transplant referrals and waitlisting, providing a clearer picture of gaps in access to transplantation and enabling policymakers to address inequities in the system.

3) Advancing kidney research and innovation

ASN's commitment to advancing kidney research and fostering innovation saw several critical successes in 2024. The society continued to push for sustained federal funding and innovative research initiatives aimed at transforming kidney health to position the United States as a global leader in kidney health innovation.

- **Supporting federally funded kidney research**
  ASN, together with community partners—the American Association of Kidney Patients, the American Kidney Fund, the American Society of Pediatric Nephrology, and the National Kidney Foundation—established the Transforming Kidney Health Research panel, a group tasked with developing a bold and comprehensive research plan that identifies existing and emerging areas of opportunity for kidney health research across the entire federal government. The plan will emphasize advancing kidney disease research, exploring novel therapeutics, and promoting new treatment approaches, such as regenerative medicine and artificial kidney technologies.

- **Sustaining funding for the Kidney Innovation Accelerator (KidneyX) and research agencies**
  Through continued advocacy, ASN sustained funding for KidneyX (a public-private partnership between ASN and the Department of Health and Human Services driving innovation in kidney care) and federal agencies such as the Advanced Research Projects Agency for Health and the National Institute of Diabetes and Digestive and Kidney Diseases, ensuring robust support for critical research on kidney disease pathophysiology, novel therapeutics, and cutting-edge technologies such as artificial kidneys and xenotransplantation.

- **Advancing the Kidney PATIENT Act**
  ASN also advocated for the Kidney PATIENT Act, an effort aimed at retaining Medicare Part D coverage for essential oral medications, such as phosphate-lowering agents, used by patients with kidney diseases.

4) Achieving equity and eliminating disparities in kidney care

ASN's policy efforts in 2024 were also geared toward achieving equity and eliminating disparities in kidney care. This focus aimed to ensure that all patients, regardless of race, ethnicity, or socioeconomic status, have access to high-quality kidney care.

- **Removing race from the Kidney Donor Profile Index (KDPI)**
  ASN, working closely with the National Kidney Foundation and OPTN, secured the removal of race from KDPI, which grades the quality of donor kidneys, recognizing that race is a social construct and not a biological determinant. With the new approach, some kidneys that may have otherwise been considered unsuitable for transplantation, due to the inclusion of race in the KDPI formula, will now receive more favorable scores, including some that will now be classified with scores that make them more appropriate for transplant.

- **Expanding access to home dialysis for patients with acute kidney injury**
  In 2024, ASN enabled patients with acute kidney injury to access home dialysis services, allowing for more flexible, patient-centered care that improves outcomes and reduces the strain on hospital resources.

- **Securing medically necessary oral health coverage for patients with kidney diseases**
  A significant victory for patients was ASN's success in securing Medicare coverage for medically necessary oral health services for individuals with kidney failure. This policy change addresses the critical link between oral health and overall well-being for patients living with kidney diseases.

- **Supporting ASN members conducting state-level advocacy for dialysis access**
  ASN supported state-level advocates in its efforts to expand access to kidney care for undocumented individuals. In at least 24 states, ASN members are working to ensure that no patient is left without life-saving kidney care. Two virtual community meetings have been held to share advocacy solutions and connect with more than 60 kidney care advocates.

- **Integrating the Health Care Justice Committee**
  ASN integrated its Health Care Justice Committee into broader policy efforts, reinforcing its commitment to addressing health disparities and promoting social justice in kidney care.

5) Bolstering the kidney health workforce

Workforce challenges in nephrology, including shortages of trained professionals and underrepresentation of minority groups, have long been an issue. ASN's 2024 policy initiatives sought to strengthen the kidney health workforce to meet the growing demand for kidney care.

- **Stabilizing the physician workforce**
  ASN urged Congress to stabilize the physician workforce by implementing automatic payment adjustments, extending Medicare Access and CHIP Reauthorization Act alternative payment model incentive payments, and expanding Medicare-supported graduate medical

education (GME) positions. These efforts aim to ensure that the nephrology workforce remains strong and adequately compensated.

- **Collaborating with nephrology nursing organizations**
  ASN partnered with the American Nephrology Nurses Association to address the growing challenges faced by the nephrology workforce. Together, the organizations raised awareness in Congress about workforce shortages and the need for more comprehensive training and support.
- **Advocating for the Accreditation Council for Graduate Medical Education (ACGME) Accreditation**
  In collaboration with the American Society of Transplantation, ASN advocated for and achieved ACGME accreditation for transplant nephrology, a crucial step toward improving training and quality in kidney transplantation care, as well as enabling advancements such as dedicated relative value units for transplant nephrologists and Medicare GME funding for transplant nephrology training.

Conclusion

ASN's policy efforts in 2024 reflected the society's commitment to advancing kidney health, promoting equity, and supporting innovation. From securing key legislative victories to fostering groundbreaking research and addressing workforce challenges, ASN has made significant strides in improving the landscape of kidney care. As kidney diseases continue to be a major public health issue and as the White House changes hands once again, ASN's advocacy and leadership will remain vital in ensuring that patients receive the best possible care while supporting the kidney care workforce.

To keep track of ASN's policy efforts, follow coverage in *Kidney News* and the ASN podcast feed, and visit ASN's policy webpage (https://www.asn-online.org/policy/). For real-time updates from ASN Policy, follow @ASNAdvocacy on X.

Ryan Murray is the senior manager of Policy and Government Affairs at ASN.

2025 CMS ESRD PPS Final Rule Released

By Jacob Nysather and Gary Singer

In November, the Centers for Medicare & Medicaid Services (CMS) released its final rule for calendar year (CY) 2025 to update payment rates and policies under the End-Stage Renal Disease (ESRD) Prospective Payment System (PPS) for Medicare beneficiaries (CMS-1805-F) (1, 2).

Updates to ESRD PPS for CY 2025

Medicare plans to allocate $6.6 billion to approximately 7700 ESRD facilities with a base rate of $273.82, an increase of $2.80 from the current rate. This amount incorporates a wage index adjustment factor and a productivity-adjusted market basket increase. CMS expects a 2.7% payment increase for all ESRD facilities, with hospital-based facilities seeing a 4.5% increase and freestanding facilities a 2.6% increase.

A new wage index uses data from the Bureau of Labor Statistics and freestanding ESRD facility cost reports, replacing the current data derived from hospital cost reports. It will incorporate the latest area delineations from the Office of Management and Budget to more accurately reflect geographic wage differences. A wage index floor of 0.6000 and a 5% cap on wage index decreases from the previous year will be maintained.

Changes to the outlier policy include expanding the list of outlier services to cover certain drugs and biological products that were previously included in the composite rate. Technical adjustments to fixed-dollar loss (FDL) and Medicare allowable payment (MAP) calculations will also be made. For pediatric beneficiaries, FDL will increase from $11.32 to $234.26, and MAP will increase from $23.36 to $59.60. For adult beneficiaries, FDL will decrease from $71.76 to $45.41, and MAP will decrease from $36.28 to $31.02.

Oral-only dialysis drugs will be included in the ESRD PPS bundled payment. The rule outlines how these drugs and biological products will be integrated, including their budgetary impacts. To offset operational costs for facilities, there is an increase of $36.41 to the monthly Transitional Drug Add-On Payment Adjustment (TDAPA) for claims that use phosphate binders.

The rule also introduces a two-tiered Low-Volume Payment Adjustment (LVPA) system. Facilities providing fewer than 3000 treatments per year will receive a 28.9% increase to the ESRD PPS base rate, whereas those providing 3000–3999 treatments will receive an 18.3% increase. Eligibility for these adjustments would be based on the median treatment count over the past 3 years.

Changes to payment for dialysis services for individuals with AKI and ESRD Facilities Conditions for Coverage

The acute kidney injury (AKI) dialysis payment rate is set at $273.82, similar to ESRD. Additionally, at-home dialysis services for Medicare beneficiaries with AKI have been approved. This change aims to empower patients to make decisions about their care, reflect efforts to increase home dialysis access, and potentially aid in kidney recovery. ESRD facilities will be permitted to invoice for home and self-dialysis training for patients with AKI.

Changes to the ESRD Quality Incentive Program (QIP)

Starting with payment year 2027, the single Kt/V dialysis adequacy comprehensive clinical measure will be replaced with four separate measures: adult hemodialysis Kt/V, adult peritoneal dialysis Kt/V, pediatric hemodialysis Kt/V, and pediatric peritoneal dialysis Kt/V. Each measure will be scored individually for more accurate performance assessment based on the patient's age and the dialysis type. The combined weight of these measures remains at 11% of the total performance score. Additionally, the National Healthcare Safety Network (NHSN) Dialysis Event reporting measure will be removed from ESRD QIP. This change aims to streamline the measure set to focus on high-impact measures, although facilities would still need to comply with current NHSN protocols and report all event data.

Authors' opinion

Although the overall goal is improving access to care, there continue to be pitfalls and limitations in the ESRD bundle's current capacity (3, 4). There are positive steps in allowing access to home dialysis modalities for patients with AKI and mirroring the base payment rate to ESRD. The increase of the base payment continues to have shortcomings of accurately capturing changes in cost, which can impact physicians' ability to offer care and could limit patient access. Similarly, changes to the wage index and addition of LVPA could allow some sustainability for low-volume centers but potentially reduce the update in others. The impact of the addition of oral-only phosphate binders into the ESRD bundle has previously been well delineated (3, 4). The addition of TDAPA to help offset operational costs is appreciated but will still have a significant impact on patient care.

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The authors report no conflicts of interest.

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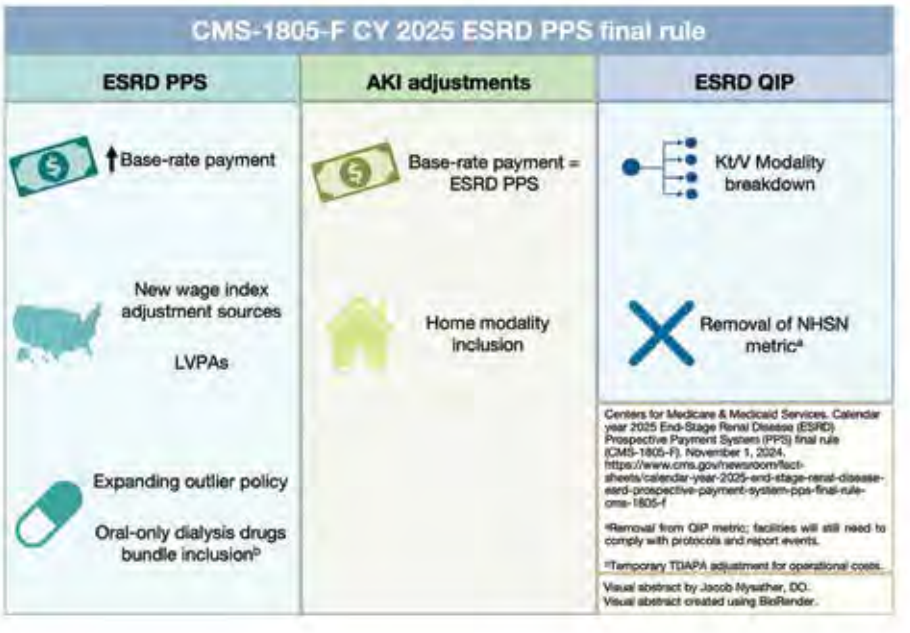

Calciphylaxis: Hexasodium Fytate as a Potential Treatment for a Devastating Disease

By Morgan Hedden and C. John Sperati

Calciphylaxis, or calcific uremic arteriolopathy (CUA), is a disorder of mineralization characterized by arterial calcification in the dermis and subcutaneous adipose tissue. It is predominately seen in patients with kidney failure at an incidence of 3.5 per 1000 person-years. Current evidence supports dysregulated mineralization in uremia leading to reduced synthesis of vitamin K-dependent inhibitors of mineralization, reduced concentration of pyrophosphate, and altered adipocyte signaling, precipitating deposition of calcium apatite in the walls of small- and medium-sized arteries. Thrombosis results in exquisite pain, retiform purpura, livedo reticularis, and ischemic ulceration, typically of the abdomen and proximal thighs, with a 1-year mortality rate of 45%–80%. There are currently no approved therapies for this disease (1).

At present, management focuses on excellent wound care, minimization of cutaneous trauma, maintenance of normal calcium and phosphorus concentrations, treatment of hyperparathyroidism, discontinuation of vitamin D analogues, and avoidance of vitamin K antagonists. Case reports suggest a potential role for bisphosphonates (pyrophosphate analogues) and hyperbaric oxygen therapy. The administration of intravenous or intralesional sodium thiosulfate has become a mainstay of therapy, although the efficacy remains uncertain (2). Randomized controlled trials researching this disease have been notoriously difficult to complete, and there is a critical unmet need for proven therapies (3, 4).

Hexasodium fytate is a manufactured hexasodium salt of myo-inositol hexaphosphate, a naturally occurring substance that binds hydroxyapatite. Hexasodium fytate binds to and slows the growth of hydroxyapatite crystals, thus potentially disrupting a proposed step in the pathogenesis of calciphylaxis. In the international, double-blind CALCIPHYX trial (Phase 3 Study of SNF472 for Calciphylaxis), Sinha and colleagues (5) randomized 71 patients undergoing hemodialysis to 12 weeks of intravenous hexasodium fytate or placebo, followed by 12 weeks of open-label treatment across 77 sites. The study was funded by Sanifit, a manufacturer of hexasodium fytate.

The two primary outcomes were a modified Bates-Jensen Wound Assessment Tool (BWAT-CUA) for the primary lesion and a Pain Visual Analogue Scale (Pain VAS) score. Randomization was stratified by baseline use of sodium thiosulfate, and the demographics of both groups were similar. Ninety-two percent of the hexasodium fytate-treated and 76% of placebo participants completed the 12-week randomized period. Both groups demonstrated improvements in wound assessment and reported pain without statistically significant between-group differences. At week 12, the mean (SD) changes for BWAT-CUA were −5.3 (5.2) in the hexasodium fytate group and −6.0 (6.2) in the placebo group, for a least-squares mean (SE) difference of 0.3 (1.3) (p = 0.88). The mean (SD) changes in Pain VAS were −19.5 (26.9) in the hexasodium fytate group and −32.2 (38.5) in the placebo group, for a least-squares mean (SE) difference of 11.5 (7.9) (p = 0.15). Calciphylaxis-related infections, hospitalizations, and death were lower in participants randomized to hexasodium fytate compared with placebo. No new calciphylaxis-related events led to hospitalization during the open-label or follow-up periods. Therapy was well tolerated.

To our knowledge, CALCIPHYX is the first randomized, double-blind clinical trial successfully completed for calciphylaxis. Although the primary outcomes were not met in this small study, the investigators acknowledged that there are currently no well-validated, patient-centered outcome metrics in the study of calciphylaxis. Patients with kidney failure and calciphylaxis are incredibly medically complex, highlighting difficulties in selecting appropriate clinical endpoints, conducting large trials, and ensuring complete data capture. The study was not powered for mortality, although post hoc endpoints from a small number of participants suggest a possible reduction. It remains to be determined if continued treatment with hexasodium fytate truly reduces calciphylaxis-related hospitalizations and mortality.

In summary, hexasodium fytate was a safe, well-tolerated intervention for calciphylaxis that failed to show superiority over placebo in wound healing or pain control. A post hoc analysis suggests that possible further study of this drug may be warranted, as the medical community continues to work toward development and demonstration of effective therapies for this devastating disease. ■

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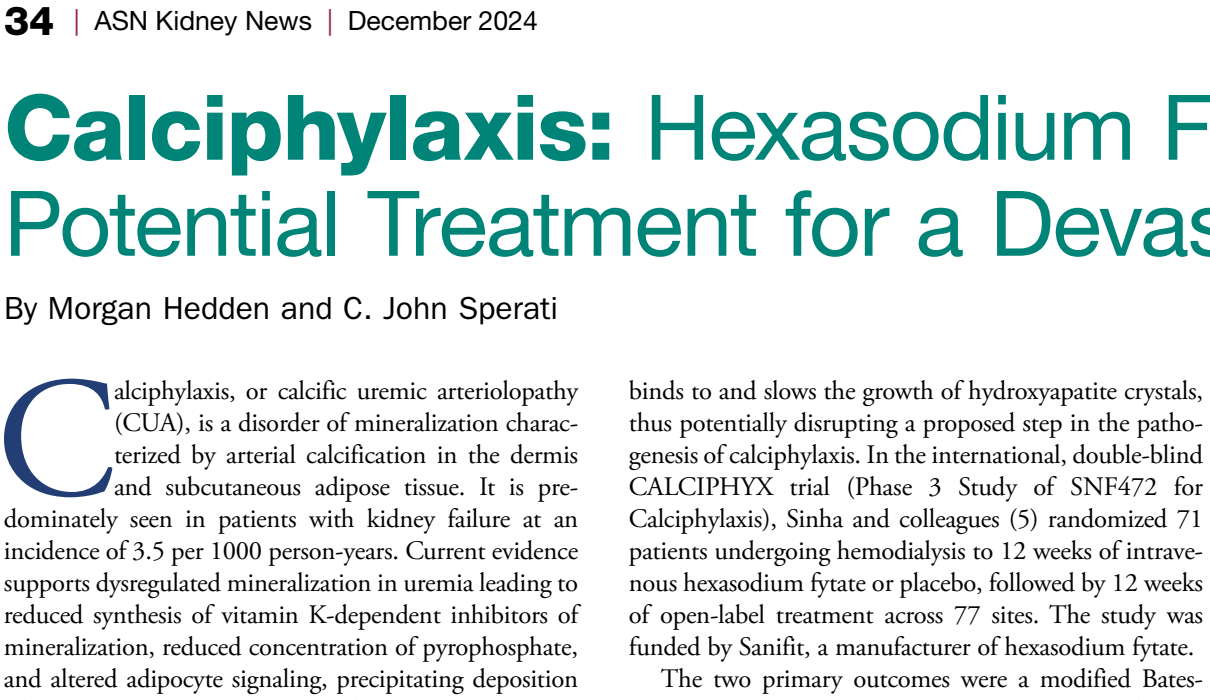
The authors report no conflicts of interest.



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Policy and Payment Changes on the Horizon for Kidney Care

By Bridget M. Kuehn

Shifts in health care coverage for patients with kidney diseases and growing use of value-based payment models are creating new opportunities and potential challenges for nephrologists and people living with kidney diseases.

Those changes were highlighted during ASN's Nephro-Economics in 2024 symposium in September. Speakers at the symposium highlighted the impact of a growing number of states embracing the Medicaid expansion and an increasing numbers of patients opting for Medicare Advantage plans offered by private insurers. They also discussed the efforts by the Centers for Medicare & Medicaid Services (CMS) to increase enrollment of clinicians in its value-based care payment models and the inadequate reimbursement rates for nephrologists.

Medicare Advantage growth

Medicare provides coverage for the majority of people living with kidney failure, yet a rapid shift toward coverage by private Medicare Advantage plans could have trade-offs for patients and nephrologists.

"Medicare provides crucial coverage to more than 90% of Americans with kidney failure, but there can be substantial out-of-pocket costs with traditional Medicare," explained Kevin Nguyen, PhD, assistant professor in the Department of Health Law, Policy, and Management at Boston University School of Public Health, MA.

These costs may arise from premiums, deductibles, or copays. Supplemental insurance may help to cover some of these costs or provide additional benefits like dental care or long-term care benefits, he noted. But people with kidney diseases may be denied supplemental insurance or charged a higher premium, except in the few states that require supplemental insurers to offer coverage to this patient population, he said.

Patients who meet certain income thresholds may also be eligible for Medicaid, depending on their state's rules and whether the state opted into the Medicaid expansion program. An analysis by Nguyen and his colleagues found that Medicaid expansion overall led to decreased hospital admissions during the high-risk period, 3 and 6 months after initiating dialysis (1). Patients in expansion states were also more likely to initiate dialysis with an arteriovenous fistula or graft. He noted that reductions in hospitalizations for complex patients in Medicaid expansion states could benefit from Medicare, which is the primary payor for kidney failure care. The potential cost reductions could also create an incentive for more states to expand Medicaid.

A growing number of people with kidney failure are embracing Medicare Advantage plans offered by private insurers. These plans offer trade-offs over traditional fee-for-service Medicare plans, which are accepted by almost any clinician, hospital, or dialysis facility in the country. Medicare Advantage plans may have low premiums and fewer out-of-pocket costs and offer additional services like dental coverage or food-delivery services, but they have more limited networks of clinicians and health facilities, Nguyen explained.

Medicare Advantage plans became available for people experiencing kidney failure in January 2021 as part of the 21st Century Cures Act. Overall, CMS anticipated that 30% of enrollees with kidney failure would opt for Medicare Advantage plans in 2021, yet only less than half had switched by 2022 (2). Enrollees who were White and those with other chronic conditions were least likely to leave traditional Medicare. By contrast, enrollees who were American Indian or Alaska Native, Black, or Hispanic made the switch in higher proportions. Individuals who were partially or fully dual eligible for Medicaid also were more likely to choose a Medicare Advantage plan over traditional Medicare.

Most participants who switched to Medicare Advantage stayed in the program, but about one-quarter of them switched to a different Medicare Advantage plan. Black patients were more likely than patients from other racial and ethnic groups to switch to a different Medicare Advantage plan. But the implications for kidney failure care are unknown.

"It will be crucial to monitor the adequacy of dialysis facility networks in Medicare Advantage contracts and assess health outcomes among individuals who switched," Nguyen said.

Rethinking 2008 health care

By 2030, CMS plans to have 100% of its beneficiaries being cared for through value-based care arrangements with clinicians and health systems. That shift is part of a growing effort to both improve care and curb the high costs of kidney care for CMS. Suzanne Watnick, MD, FASN, professor of medicine at the University of Washington, Seattle, and ASN's health policy scholar in residence, explained that patients receiving renal replacement therapy account for fewer than 1% of Medicare beneficiaries yet 6%–7% of all Medicare spending (3). That is more than 1% of the federal budget or more than $50 billion a year. "We have responsibility for using those hard-earned taxpayer dollars wisely," she said.

Value-based payment models may be one way to do that. Yet, Watnick noted that many payment models are still stuck in a 2008 time warp. At that time, the Medicare Improvements for Patients and Providers Act (MIPPA) was passed to help curb expenditures on overuse of drugs like erythropoietin-stimulating agents and to promote greater use of home dialysis. Watnick noted that MIPPA has helped reduce excessive use of drugs and that home dialysis is now used by about 15% of patients. Additionally, she noted that dialysis organizations learned how to use payments under the models to increase access, preserve quality, and not increase cost, which she said was a good lesson for the field of nephrology.

But Watnick said that more needs to be done to tie payments to quality measures and to continue improving care to meet today's and tomorrow's standards. "Our patients deserve better," she said. She noted that more can be done to increase the number of patients able to access home dialysis and incentivize continued improvements and innovations in kidney care.

"Anemic" payment growth

Some changes in payment models expected in 2025 may impede some of those goals. Watnick noted that current policy proposals could decrease reimbursement for home dialysis visits for patients with acute kidney injury by $8, in part, to offset the costs of training for these patients. She said that she and her colleagues at ASN have commented on the proposals to ensure equal access to home dialysis for patients with acute kidney injury.

Other notable changes include the bundling of payments for phosphate binders to dialysis facilities, which, she explained, will have dialysis facilities acting as a pharmacy. She noted that although this change may increase access to these medications for Medicare patients who do not have drug coverage through Medicare Part D, it is unclear how it will affect access to these medications for patients in skilled nursing facilities.

Woefully anemic updates to the physician fee schedule for nephrologists are another concern, Watnick said. She noted that nephrology faces rising costs and staffing shortages, yet there is no inflationary adjustment for nephrologists' payments. "How do you have a negative [profit] margin and maintain a viable business?" she questioned. "This is something that needs to be tackled in the future."

She said that the challenge with advocating for greater pay is that many policy changes must be budget neutral, so increased reimbursements in one area may mean decreased reimbursements in another. Additionally, she noted that the Medicare Payment Advisory Commission (MedPAC), which independently assesses physician payment advocacy, acknowledges that current payments provide negative margins but argues that there is still good access to outpatient dialysis. But Watnick suggested that advocacy by nephrologists can help shift the conversation. "We have a voice," she said. "Advocacy does help."

Watnick noted that one potential avenue for addressing these concerns is to more strongly tie quality metrics to reimbursement. She suggested that bundles could be expanded to promote better care coordination and a wider array of patient options beyond in-center dialysis, including more home dialysis and preemptive transplants. She also emphasized the need for more advanced care planning, for care to prevent emergency department visits and hospitalizations, and to provide palliative care. Leveraging technology may also help nephrologists proactively monitor patients and help prevent more expensive care episodes.

She argued that it may be time for an act of Congress to overhaul the current system for kidney care, which emphasizes in-center dialysis using technology that dates back decades. Instead, she said there needs to be a push to make dialysis obsolete, embrace new technology and innovation, and emphasize care that improves outcomes while reducing costs. She noted that steps like vaccinating patients against COVID-19 to prevent hospitalizations both improves patient outcomes and cuts costs. "We need to do better," Watnick emphasized. "There are all kinds of things we can do to improve the future direction of [kidney care]." ■

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Hemodiafiltration: A "Superior Alternative" to Hemodialysis?

Across subgroups of patients with kidney failure, hemodiafiltration reduces mortality compared with standard hemodialysis, concludes a meta-analysis in *The Lancet*.

The researchers analyzed patient-level data from five randomized controlled trials comparing online hemodiafiltration with low-flux and high-flux hemodialysis in adults with kidney failure. The meta-analysis included 2083 patients receiving hemodiafiltration and 2070 patients receiving hemodialysis.

The primary outcome of all-cause mortality was analyzed by intention to treat. Further analyses focused on subgroups defined by age, sex, diabetes, cardiovascular disease, duration of dialysis, vascular access, and achieved convection volume.

At a median 30 months' follow-up, all-cause mortality was 23.3% with hemodiafiltration versus 27.0% with hemodialysis: hazard ratio (HR), 0.84. The benefit of hemodiafiltration was similar across patient and treatment characteristics. Numbers needed to treat to prevent one event were 26 patients for all-cause mortality and 48 patients for cardiovascular mortality.

There was a graded association between convection volume and mortality risk: adjusted HR, 0.63 at achieved convection volumes >23 L. Within the hemodiafiltration group, the higher the convection volume, the greater the mortality benefit.

The CONVINCE (An Investigator Initiated International, Multi-Centre, Prospective, Randomised, Controlled Study Comparing High-Dose Haemodiafiltration [HDF] Versus Conventional High-Flux Haemodialysis [HD]) trial reported a 23% reduction in mortality with high-dose hemodiafiltration compared with conventional high-flux hemodialysis. The recent meta-analysis supports the reduction in all-cause and cardiovascular mortality with hemodiafiltration, with similar effects across patient subgroups.

"[T]his analysis strengthens the argument that haemodiafiltration is a superior alternative to standard haemodialysis, which constitutes the first time in decades that a change in the principles of the haemodialysis process has been found to be clinically meaningful," the researchers write. They discuss the implications for adopting hemodiafiltration into routine clinical practice [Vernooij RWM, et al.; CONVINCE Scientific Committee; HDF Pooling Project Investigators. Haemodiafiltration versus haemodialysis for kidney failure: An individual patient data meta-analysis of randomized controlled trials. *Lancet*, published online October 25, 2024. doi: 10.1016/S0140-6736(24)01859-2]. ■

Intensive BP Strategy Shows Safety in Advanced CKD

Intensive monitoring and titration to maintain a systolic blood pressure (SBP) of <120 mm Hg are safe and feasible for patients with advanced chronic kidney disease (CKD), reports a study in the *American Journal of Kidney Diseases*.

The pilot randomized clinical trial included 108 patients with advanced CKD, defined as an estimated glomerular filtration rate of ≤30 mL/min/1.73 m^2, associated with hypertension. Patients were randomly assigned to an intensive strategy, with antihypertensive medications titrated to an SBP target of <120 mm Hg or to a less-intensive target of 130–140 mm Hg.

BP readings were performed by the patients at home using a Bluetooth-enabled monitor. The main efficacy outcome of interest was achievement of clinic BP from 4 to 12 months. Safety outcomes included hyperkalemia, falls or syncope, and the need for dialysis or kidney transplantation.

The intensive therapy group had a lower SBP at 12 months: 124.7 mm Hg compared with 138.2 mm Hg in the less-intensive group. Intensive therapy reduced mean clinic SBP by 11.7 mm Hg, averaged over 4–12 months.

For all safety events considered, there was no significant difference between the two strategies. Risk of kidney failure onset was low but was higher in the more-intensive group: 5% versus 0%. Exploratory analyses suggested a one-half reduction in all-cause hospitalizations with intensive therapy.

There is continued debate over the optimal BP targets for patients with advanced CKD, who have often been excluded from treatment trials. This pilot study, suggests that an intensive SBP target is feasible for this group of patients, with no increase in adverse events.

The researchers point out challenges of their strategy, including the considerable investment of time and resources. The authors conclude, "Larger trials to determine optimal BP targets in advanced CKD and the risks and benefits associated with more intensive BP control are warranted" [Ku E, et al. Intensive home blood pressure lowering in patients with advanced CKD. *Am J Kidney Dis*, published online October 18, 2024. doi: 10.1053/j.ajkd.2024.08.010]. ■

Good Outcomes With Kidney Transplant From Donors Who Were HIV Positive

Kidneys from deceased donors who were HIV positive can be safely transplanted into recipients who are HIV positive, with outcomes similar to those of organs from donors who were HIV negative, concludes a study in *The New England Journal of Medicine*.

The observational noninferiority study included 408 kidney transplant candidates who were HIV positive at 26 US transplant centers. Among these patients, 198 received deceased-donor kidneys: 99 from donors who were HIV positive and 99 from donors who were HIV negative. Random allocation was not possible; patients received whichever organ was available first.

The two groups were compared on a primary composite safety outcome of death from any cause, graft loss, serious adverse events, HIV breakthrough infection, persistent failure of HIV treatment, or opportunistic infection. Efficacy outcomes of overall survival, survival without graft loss, organ rejection, infection, cancer, and HIV superinfection were assessed as well.

Primary outcome events occurred in 79 patients with donors who were HIV positive and in 77 patients with donors who were HIV negative. Adjusted relative risk was 1.00, demonstrating the noninferiority of kidney transplantation from donors who were HIV positive. Overall survival and survival free of graft loss were similar from 1 year through 3 years of follow-up. Serious adverse events, infections, surgical or vascular complications, and cancers were similar between groups.

Kidneys from donors who were HIV positive were associated with increased risk of HIV breakthrough infection: incidence rate ratio, 3.14. There was one possible case of HIV superinfection but no persistent failures of HIV treatment.

Since 2016, transplantation of kidneys from donors who were HIV positive to recipients who were HIV positive has been approved for research purposes under the US HIV Organ Policy Equity Act. Previous outcome studies have been small case series without a control group of recipients from donors who were non-HIV infected.

The new analysis supports the safety of transplantation of kidneys from deceased donors who were HIV positive, with outcomes similar to those of transplants from donors who were HIV negative. The increase in HIV breakthrough infections among recipients of HIV-positive organs may be attributed to nonadherence to antiretroviral therapy. The investigators conclude, "Taken together, these outcomes support the expansion of kidney transplantation involving donors and recipients with HIV from research to clinical care" [Durand CM, et al.; HOPE in Action Investigators. Safety of kidney transplantation from donors with HIV. *N Engl J Med* 2024; 391:1390–1401. doi: 10.1056/NEJMoa2403733]. ■

GLP-1RAs May Reduce Hyperkalemia in Type 2 Diabetes

In patients with type 2 diabetes, treatment with glucagon-like peptide-1 receptor agonists (GLP-1RAs) lowers the risk of hyperkalemia while reducing the need for discontinuation of renin-angiotensin system inhibitors (RASis) compared with treatment with dipeptidyl peptidase-4 inhibitors (DPP-4is), reports a study in *JAMA Internal Medicine*.

Using data from a population-based Swedish study, the researchers identified 33,280 adults with type 2 diabetes in the Stockholm region who initiated treatment with GLP-1RAs (13,633 patients) or with DPP-4is (19,647 patients) from 2008 through 2023. The mean age was 64 years, and 60% of patients were male. The median follow-up was 3.9 months.

Following a target trial emulation framework, the researchers compared rates of hyperkalemia and prolonged RASi use between the two treatments. Data analysis included an inverse probability of treatment weights to control for more than 70 potential confounders.

Rates of hyperkalemia were significantly lower for patients using GLP-1RAs compared with DPP-4is. Weighted hazard ratios (HRs) were 0.61 for any hyperkalemia (potassium >5.0 mEq/L) and 0.52 for moderate to severe hyperkalemia (potassium >5.5 mEq/L). At 12 months, absolute risk of hyperkalemia was 2.9% with GLP-1RAs versus 4.6% with DPP-4is.

Of 21,751 patients using RASis at the time that they started treatment of study drugs, 2351 stopped RASi therapy during follow-up. The incidence of RASi discontinuation was significantly lower with GLP-1RAs: weighted HR, 0.89. Subgroup and sensitivity analyses showed similar associations for groups defined by age; sex; kidney function; atherosclerotic cardiovascular disease; and adherence to sodium-glucose cotransporter-2 inhibitors, insulin, or RASis.

Hyperkalemia is a common symptom in patients with type 2 diabetes that may limit the use of guideline-recommended RASi therapy. Recent reports suggest that GLP-1RAs may increase potassium excretion and thus reduce the risk of hyperkalemia.

This population-based cohort study adds further evidence that GLP-1RA use reduces hyperkalemia while promoting sustained RASi use in type 2 diabetes compared with DPP-4is. While acknowledging the limitations of their study, the investigators conclude, "Treatment with GLP-1RAs may enable wider use of the guideline-recommended cardioprotective and renoprotective medications and contribute to improving clinical outcomes in this population" [Huang T, et al. GLP-1RA vs DPP-4i use and rates of hyperkalemia and RAS blockade discontinuation in type 2 diabetes. *JAMA Intern Med* 2024; 184:1195–1203. doi: 10.1001/jamainternmed.2024.3806]. ■

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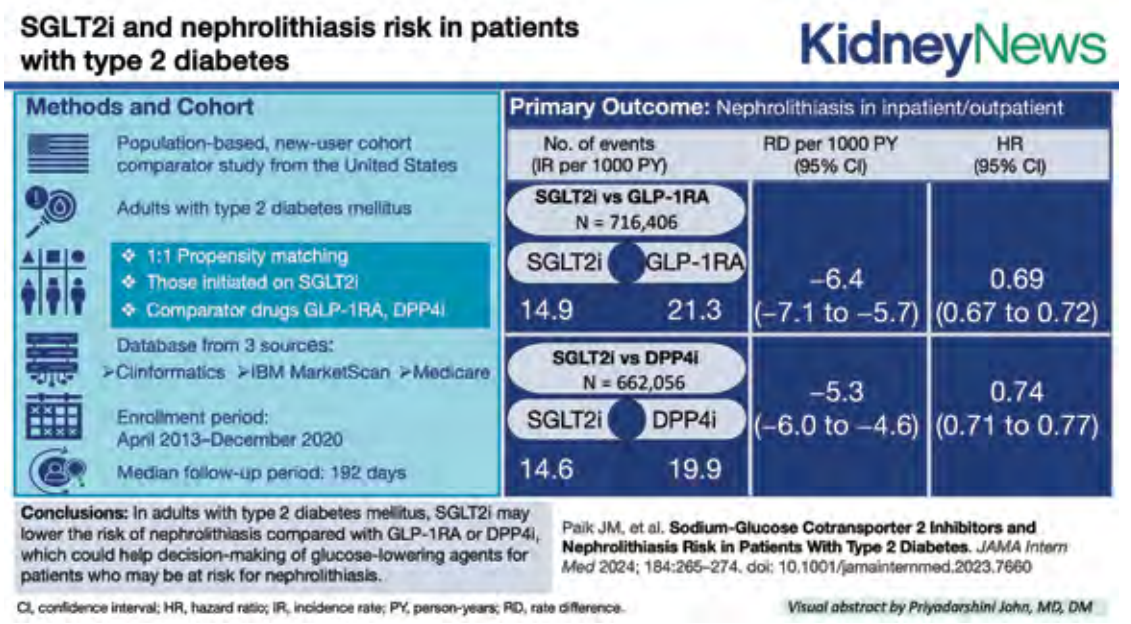
Correction

The visual abstract from the article "SGLT2i: The New Wonder Drugs for Kidney Stone Prevention?" by Amy A. Yau and David S. Goldfarb in the June 2024 issue of *Kidney News* contained an error.

The 95% confidence interval calculations of rate difference comparing sodium-glucose cotransporter-2 inhibitors (SGLT2is) with glucagon-like peptide-1 receptor agonists (GLP-1RAs) and with dipeptidyl peptidase 4 inhibitors (DPP4is) were incorrectly labeled as "–7.1 to 5.7" and "–6.0 to 4.6," respectively. These should have been labeled as "–7.1 to –5.7" and "–6.0 to –4.6." The corrected visual abstract is shown below. ■



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