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Hybrid Telehealth Model Likely on the Horizon, Hurdles Remain

By Bridget M. Kuehn

When the pandemic hit more than 2 years ago, nephrologists and their patients had to pivot on a dime to adapt to telehealth technologies. Those technologies have proved popular with both nephrologists and patients. But now, clinicians face new challenges as they try to develop sustainable and equitable hybrid telehealth and in-person care models for the long term.

Provisions in the 2020 Coronavirus Aid, Relief, and Economic Security (CARES) Act enabled the Centers for Medicare & Medicaid Services to temporarily waive restrictions on where and how patients could receive telehealth (1). This policy change led to a rapid expansion of telehealth care. Before the changes, telehealth was allowed for patients on home therapies, such as home hemodialysis and peritoneal dialysis, through the Bipartisan Budget Act of 2018 (2). But there were restrictions on using telehealth for other kinds of kidney care. Medicare only covered telehealth visits in rural areas, and patients could not access telehealth visits from home. Audio visits were prohibited, and clinicians could only use Health Insurance Portability and Accountability Act-compliant video platforms. Clinicians were concerned the changes would expire with the end of the COVID-19 public health emergency. But in March 2022, Congress passed, and President Biden signed into law, a spending bill (3) that extended the provisions 5 months after the official end of the COVID-19 public health emergency.

"We commend the legislators for including critical telehealth extensions in this must-pass legislation, ensuring that patients do not fall off a 'telehealth cliff' immediately after the COVID-19 public health emergency ends," wrote Kyle Zebley, vice president of public policy at the American Telemedicine Association (ATA), in a statement (4). But the ATA and organizations representing physicians, such as the American Medical Association (5), want legislators to make the policies permanent this year.

Temporary reprieve

Nephrologist Susie Lew, MD, professor of medicine in the Division of Renal Diseases and Hypertension at George Washington University in Washington, DC, said the extension for at least 5 months is wise. She noted there are

Continued on page 7

Treating Mild Chronic Hypertension Improves Pregnancy Outcomes

By Timothy O'Brien

Chronic hypertension occurs in at least 2% of pregnancies in the United States and is associated with high rates of preeclampsia and other adverse pregnancy outcomes. There is ongoing debate over treatment strategies: Continuing antihypertensive therapy during pregnancy reduces the risk of severe hypertension but has not previously been shown to improve maternal, fetal, or neonatal outcomes.

Findings from a new trial reported in *The New England Journal of Medicine* suggest that pregnancy outcomes are improved by antihypertensive therapy for women with mild chronic hypertension, with a blood pressure target of less than 140/90 mm Hg.

The Chronic Hypertension and Pregnancy (CHAP) trial included 2402 pregnant women with mild chronic hypertension, defined as blood pressure of less than 140/90 mm Hg, enrolled from more than 70 US centers. The researchers found treatment for mild chronic hypertension was associated with a reduced risk of adverse pregnancy outcomes.

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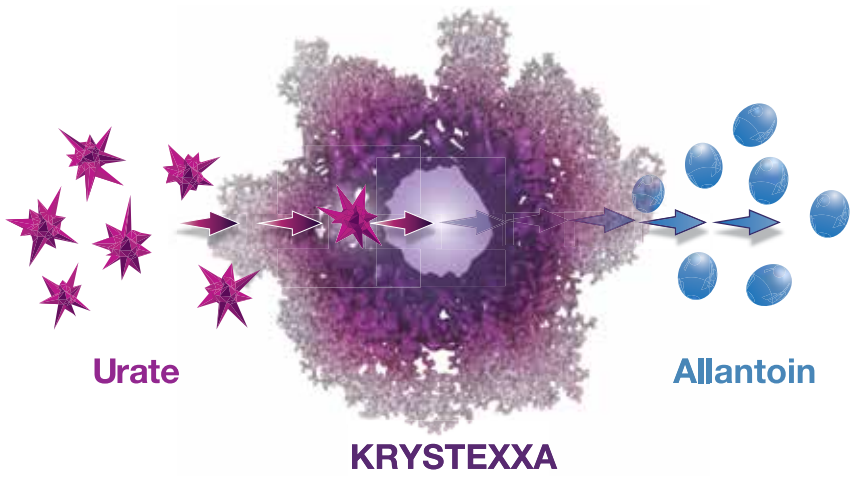
Inside

KRYSTEXXA (PEGLOTICASE) IS A RECOMBINANT INTO ALLANTOIN[1]



Artist's renditions.

RENAL EXCRETION OF ALLANTOIN IS UP TO 10 TIMES MORE EFFICIENT THAN EXCRETION OF URIC ACID[2]

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is indicated for the treatment of chronic gout in adult patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Important Limitations of Use: KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions. Patients should be premedicated with antihistamines and corticosteroids. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.

The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response.

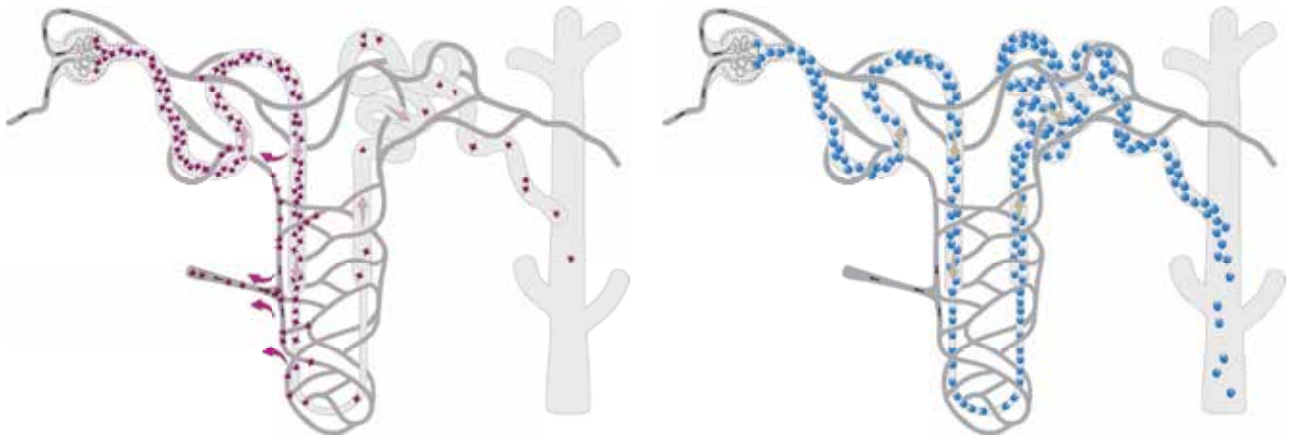
Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

In the event of anaphylaxis or infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** McDonagh EM, et al. *Pharmacogenet Genomics*. 2014;24:464-476. **3.** Terkeltaub R, et al. *Arthritis Res Ther*. 2006;8(suppl 1):S4.

HORIZON

URICASE ENZYME THAT CONVERTS URATE



Only 10% of uric acid filtered through the kidney is excreted[3]

vs

Nearly all of allantoin filtered through the kidney is excreted[2,3]

TO LEARN MORE, VISIT KRYSTEXXAHCP.COM

Inform patients of the symptoms and signs of anaphylaxis, and instruct them to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

Screen patients for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to these patients.

GOUT FLARES

An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including treatment with KRYSTEXXA. If a gout flare occurs during treatment, KRYSTEXXA need not be discontinued. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated.

CONGESTIVE HEART FAILURE

KRYSTEXXA has not been studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions in clinical trials with KRYSTEXXA are gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis and vomiting.

Please see Brief Summary of Prescribing Information, including Boxed Warning, for KRYSTEXXA on the following page.

KRYSTEXXA®
pegloticase

KRYSTEXXA® pegloticase

(pegloticase injection), for intravenous infusion

Brief Summary - Please see the KRYSTEXXA package insert for Full Prescribing Information.

WARNING: ANAPHYLAXIS and INFUSION REACTIONS; G6PD DEFICIENCY ASSOCIATED HEMOLYSIS and METHEMOGLOBINEMIA

- **Anaphylaxis and infusion reactions have been reported to occur during and after administration of KRYSTEXXA.**
- **Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Patients should be pre-medicated with antihistamines and corticosteroids.**
- **Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed.**
- **Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. Do not administer KRYSTEXXA to patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.

Gout refractory to conventional therapy occurs in patients who have failed to normalize serum uric acid and whose signs and symptoms are inadequately controlled with xanthine oxidase inhibitors at the maximum medically appropriate dose or for whom these drugs are contraindicated.

Important Limitations of Use:
KRYSTEXXA is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

WARNINGS AND PRECAUTIONS

Anaphylaxis

During pre-marketing clinical trials, anaphylaxis was reported with a frequency of 6.5% (8/123) of patients treated with KRYSTEXXA every 2 weeks and 4.8% (6/126) for the every 4-week dosing regimen. There were no cases of anaphylaxis in patients receiving placebo. Anaphylaxis generally occurred within 2 hours after treatment. Diagnostic criteria of anaphylaxis were skin or mucosal tissue involvement, and, either airway compromise, and/or reduced blood pressure with or without associated symptoms, and a temporal relationship to KRYSTEXXA or placebo injection with no other identifiable cause. Manifestations included wheezing, peri-oral or lingual edema, or hemodynamic instability, with or without rash or urticaria. Cases occurred in patients being pre-treated with one or more doses of an oral antihistamine, an intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of anaphylaxis and therefore the reported frequency may be an underestimate.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage anaphylaxis. Patients should be pre-treated with antihistamines and corticosteroids. Anaphylaxis may occur with any infusion, including a first infusion, and generally manifests within 2 hours of the infusion. However, delayed type hypersensitivity reactions have also been reported. Patients should be closely monitored for an appropriate period of time for anaphylaxis after administration of KRYSTEXXA. Patients should be informed of the symptoms and signs of anaphylaxis and instructed to seek immediate medical care should anaphylaxis occur after discharge from the healthcare setting.

The risk of anaphylaxis is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

Infusion Reactions

During pre-marketing controlled clinical trials, infusion reactions were reported in 26% of patients treated with KRYSTEXXA 8 mg every 2 weeks, and 41% of patients treated with KRYSTEXXA 8 mg every 4 weeks, compared to 5% of patients treated with placebo. These infusion reactions occurred in patients being pre-treated with an oral antihistamine, intravenous corticosteroid and/or acetaminophen. This pre-treatment may have blunted or obscured symptoms or signs of infusion reactions and therefore the reported frequency may be an underestimate.

Manifestations of these reactions included urticaria (frequency of 10.6%), dyspnea (frequency of 7.1%), chest discomfort (frequency of 9.5%), chest pain (frequency of 9.5%), erythema (frequency of 9.5%), and pruritus (frequency of 9.5%). These manifestations overlap with the symptoms of anaphylaxis, but in a given patient did not occur together to satisfy the clinical criteria for diagnosing anaphylaxis. Infusion reactions are thought to result from release of various mediators, such as cytokines. Infusion reactions occurred at any time during a course of treatment with approximately 3% occurring with the first infusion, and approximately 91% occurred during the time of infusion.

KRYSTEXXA should be administered in a healthcare setting by healthcare providers prepared to manage infusion reactions. Patients should be pre-treated with antihistamines and corticosteroids. KRYSTEXXA should be infused slowly over no less than 120 minutes. In the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate.

The risk of infusion reaction is higher in patients whose uric acid level increases to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed. Monitor serum uric acid levels prior to infusions and consider discontinuing treatment if levels increase to above 6 mg/dL. Because of the possibility that concomitant use of oral urate-lowering therapy and KRYSTEXXA may potentially blunt the rise of serum uric acid levels, it is recommended that before starting KRYSTEXXA patients discontinue oral urate-lowering medications and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

Life threatening hemolytic reactions and methemoglobinemia have been reported with KRYSTEXXA in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of the risk of hemolysis and methemoglobinemia, do not administer KRYSTEXXA to patients with G6PD deficiency [see Contraindications]. Screen patients at risk for G6PD deficiency prior to starting KRYSTEXXA. For example, patients of African, Mediterranean (including Southern European and Middle Eastern), and Southern Asian ancestry are at increased risk for G6PD deficiency.

Gout Flares

During the controlled treatment period with KRYSTEXXA or placebo, the frequencies of gout flares were high in all treatment groups, but more so with KRYSTEXXA treatment during the first 3 months of treatment, and decreased in the subsequent 3 months of treatment. The percentages of patients with any flare for the first 3 months were 74%, 81%, and 51%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. The percentages of patients with any flare for the subsequent 3 months were 41%, 57%, and 67%, for KRYSTEXXA 8 mg every 2 weeks, KRYSTEXXA 8 mg every 4 weeks, and placebo, respectively. Patients received gout flare prophylaxis with colchicine and/or nonsteroidal anti-inflammatory drugs (NSAIDs) starting at least one week before receiving KRYSTEXXA.

Gout flares may occur after initiation of KRYSTEXXA. An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, due to changing serum uric acid levels resulting in mobilization of urate from tissue deposits. Gout flare prophylaxis with a non-steroidal anti-inflammatory drug (NSAID) or colchicine is recommended starting at least 1 week before initiation of KRYSTEXXA therapy and lasting at least 6 months, unless medically contraindicated or not tolerated. KRYSTEXXA does not need to be discontinued because of a gout flare. The gout flare should be managed concurrently as appropriate for the individual patient.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the clinical trials experienced exacerbation. Two cases of congestive heart failure exacerbation occurred during the trials in patients receiving treatment with KRYSTEXXA 8 mg every 2 weeks. No cases were reported in placebo-treated patients. Four subjects had exacerbations of pre-existing congestive heart failure while receiving KRYSTEXXA 8 mg every 2 weeks during the open-label extension study. Exercise caution when using KRYSTEXXA in patients who have congestive heart failure and monitor patients closely following infusion.

Re-treatment with KRYSTEXXA

No controlled trial data are available on the safety and efficacy of re-treatment with KRYSTEXXA after stopping treatment for longer than 4 weeks. Due to the immunogenicity of KRYSTEXXA, patients receiving re-treatment may be at increased risk of anaphylaxis and infusion reactions. Therefore, patients receiving re-treatment after a drug-free interval should be monitored carefully.

ADVERSE REACTIONS

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

- Anaphylaxis [see Warnings and Precautions]
- Infusion Reactions [see Warnings and Precautions]
- G6PD Deficiency Associated Hemolysis and Methemoglobinemia [see Warnings and Precautions]
- Gout Flares [see Warnings and Precautions]
- Congestive Heart Failure [see Warnings and Precautions]

Clinical Trials Experience

The data described below reflect exposure to KRYSTEXXA in patients with chronic gout refractory to conventional therapy in two replicate randomized, placebo-controlled, double-blind 6-month clinical trials: 85 patients were treated with KRYSTEXXA 8 mg every 2 weeks; 84 patients were treated with KRYSTEXXA 8 mg every 4 weeks; and 43 patients were treated with placebo.

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug, and may not predict the rates observed in a broader patient population in clinical practice.

The most common adverse reactions that occurred in ≥5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction (Preferred Term)	KRYSTEXXA 8 mg every 2 weeks (N=85) N[a] (%)	Placebo (N=43) N (%)
Gout flare	65 (77%)	35 (81%)
Infusion reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion[b] or Ecchymosis[b]	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

[a] If the same subject in a given group had more than one occurrence in the same preferred term event category, the subject was counted only once.

[b] Most did not occur on the day of infusion and could be related to other factors (e.g., concomitant medications relevant to contusion or ecchymosis, insulin dependent diabetes mellitus).

Immunogenicity

Anti-pegloticase antibodies developed in 92% of patients treated with KRYSTEXXA every 2 weeks, and 28% for placebo. Anti-PEG antibodies were also detected in 42% of patients treated with KRYSTEXXA. High anti-pegloticase antibody titer was associated with a failure to maintain pegloticase-induced normalization of uric acid. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

There was a higher incidence of infusion reactions in patients with high anti-pegloticase antibody titer: 53% (16 of 30) in the KRYSTEXXA every 2 weeks group compared to 6% in patients who had undetectable or low antibody titers.

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity and assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the comparison of the incidence of antibodies to pegloticase with the incidence of antibodies to other products may be misleading.

Postmarketing Experience

General disorders and administration site conditions: asthenia, malaise, peripheral swelling have been identified during postapproval use of KRYSTEXXA. 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.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of KRYSTEXXA in pregnant women. Based on animal reproduction studies, no structural abnormalities were observed when pegloticase was administered by subcutaneous injection to pregnant rats and rabbits during the period of organogenesis at doses up to 50 and 75 times, respectively, the maximum recommended human dose (MRHD). Decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD, respectively.

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinical recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In 2 separate embryo-fetal developmental studies, pregnant rats and rabbits received pegloticase during the period of organogenesis at doses up to approximately 50 and 75 times the maximum recommended human dose (MRHD), respectively (on a mg/m2 basis at maternal doses up to 40 and 30 mg/kg twice weekly, in rats and rabbits, respectively). No evidence of structural abnormalities was observed in rats or rabbits. However, decreases in mean fetal and pup body weights were observed at approximately 50 and 75 times the MRHD in rats and rabbits, respectively (on a mg/m2 basis at maternal doses up to 40 and 30 mg/kg every other day, in rats and rabbits, respectively). No effects on mean fetal body weights were observed at approximately 10 and 25 times the MRHD in rats and rabbits, respectively (on a mg/m2 basis at maternal doses up to 10 mg/kg twice weekly in both species).

Lactation

Risk Summary

It is not known whether this drug is excreted in human milk. Therefore, KRYSTEXXA should not be used when breastfeeding unless the clear benefit to the mother can overcome the unknown risk to the newborn/infant.

Pediatric Use

The safety and effectiveness of KRYSTEXXA in pediatric patients less than 18 years of age have not been established.

Geriatric Use

Of the total number of patients treated with KRYSTEXXA 8 mg every 2 weeks in the controlled studies, 34% (29 of 85) were 65 years of age and older and 12% (10 of 85) were 75 years of age and older. No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients 65 years of age and older.

Renal Impairment

No dose adjustment is required for patients with renal impairment. A total of 32% (27 of 85) of patients treated with KRYSTEXXA 8 mg every 2 weeks had a creatinine clearance of ≤62.5 mL/min. No overall differences in efficacy were observed.

OVERDOSAGE

No reports of overdosage with KRYSTEXXA have been reported. The maximum dose that has been administered as a single intravenous dose is 12 mg as uricase protein. Patients suspected of receiving an overdose should be monitored, and general supportive measures should be initiated as no specific antidote has been identified.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

General Information

Provide and instruct patients to read the accompanying Medication Guide before starting treatment and before each subsequent treatment.

Anaphylaxis and Infusion Reactions

- Anaphylaxis and infusion reactions can occur at any infusion while on therapy. Counsel patients on the importance of adhering to any prescribed medications to help prevent or lessen the severity of these reactions.
- Educate patients on the signs and symptoms of anaphylaxis, including wheezing, peri-oral or lingual edema, hemodynamic instability, and rash or urticaria.
- Educate patients on the most common signs and symptoms of an infusion reaction, including urticaria (skin rash), erythema (redness of the skin), dyspnea (difficulty breathing), flushing, chest discomfort, chest pain, and rash.
- Advise patients to seek medical care immediately if they experience any symptoms of an allergic reaction during or at any time after the infusion of KRYSTEXXA.
- Advise patients to discontinue any oral urate-lowering agents before starting on KRYSTEXXA and not to take any oral urate-lowering agents while on KRYSTEXXA.

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

Inform patients not to take KRYSTEXXA if they have a condition known as G6PD deficiency. Explain to patients that G6PD deficiency is more frequently found in individuals of African, Mediterranean, or Southern Asian ancestry and that they may be tested to determine if they have G6PD deficiency, unless already known.

Gout Flares

Explain to patients that gout flares may initially increase when starting treatment with KRYSTEXXA, and that medications to help reduce flares may need to be taken regularly for the first few months after KRYSTEXXA is started. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

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Hybrid Telehealth Model Likely on the Horizon

Continued from cover

still pockets of SARS-CoV-2 transmission throughout the country. The move, she said, would help reduce transmission of the virus in health care settings. It also reduces the burden on practices that might have to suddenly convert patients with scheduled telehealth visits into in-person visits on short notice.

But nephrologist Eric Wallace, the medical director of telehealth and director at the Home Dialysis Academy at The University of Alabama at Birmingham (UAB), said he was disappointed that Congress chose a temporary, short-term extension of the COVID-19-era telehealth rules. Instead, he hoped that Congress would pass the Telehealth Extension and Evaluation Act (6), a bill that would have extended the rules for 2 years and put in place programs to evaluate what telehealth can do well and what it cannot. Wallace said he did not think 5 months would be enough time to gather the evidence necessary to make the best policy decisions. He explained that the short timeframe makes it harder for clinicians to plan and test telehealth programs. It may also deter health institutions from investing in telehealth. "Many people are not willing to make a giant investment without some sort of permanency," he said.

Wallace noted that clinicians and policymakers have already learned a lot about telehealth during the pandemic. For example, fears that it would lead to fraud and abuse or ramp up the cost of care have not materialized, he said. A recent review in the *Clinical Journal of the American Society of Nephrology* (7) about video-based telehealth care found that patients with kidney diseases were satisfied with telehealth care and felt it was comparable with in-person care. Both patients with chronic kidney disease and those undergoing dialysis said it improved their quality of life and reduced care costs. "There are things we know telehealth does very well," Wallace said.

Broadband and barriers

Studies have also identified the need to reduce disparities in telehealth care access. For example, a survey (8) of 298 patients with kidney diseases at the University of Pennsylvania found that more older patients had reduced access to video telemedicine. Patients who are non-White and older were also more likely to need help accessing the internet.

Another recent study in *JAMA Network Open* (9) found increased COVID-19 mortality in communities that lack broadband access. Although the study could not prove a causal relationship, it added evidence of the importance of universal broadband access as a social determinant of health. Wallace and Lew agreed. "Broadband is becoming a surrogate marker for socioeconomics," Wallace said, noting that broadband access is essential not just for accessing telehealth but also for education, commerce, and even purchasing medication. "It needs to be ubiquitous."

Last year, the Infrastructure Investment and Jobs Act (10) included $65 billion to expand broadband access in the United States. But Lew said it is unlikely that broadband access will reach all US residents because of geographic or financial barriers. She noted that many cities have extensive broadband networks, but not everyone can afford to subscribe or pay for a device to access it. Both Lew and Wallace suggested that efforts to make internet access more affordable may help. For example, Lew suggested making mobile phones available to those in need. The Federal Communications Commission currently offers eligible low-income households a $30 discount on broadband and a one-time $100 discount on a laptop, tablet, or desktop computer through the Affordable Connectivity Program. The program offers a $75 discount for those living on qualifying Tribal lands.

Telehealth hubs could also help, both Lew and Wallace recommended. "One way to solve that issue is instead of bringing broadband to a patient's home, bring it to a location that patients have access to," Lew said, for example, a business or other community gathering site. Wallace and his colleagues at UAB set up telehealth hubs at county health departments throughout the state.

Wallace also highlighted assisted telehealth during a presentation at Kidney Week 2021. Assisted telehealth sends a community health worker, equipped with satellite internet or another means of accessing the internet, to patients' homes to help them during telehealth visits. "We need a multipronged approach," he said.

Hybrid hope

Despite some of these challenges, both clinicians and patients are keen to continue with a hybrid in-person/telehealth model of kidney care. "A large majority of patients wish that telemedicine will continue in some form," Lew said, based on preliminary data of patients from a survey she conducted.

Continuing access to telehealth care is particularly important for patients with rare diseases, noted Wallace, who co-directs the Fabry Disease Clinic at UAB. He explained that many patients do not have easy access to rare disease specialists and that some of his patients drive 4–8 hours or even cross state lines to see him. Many states have enacted rules during the pandemic to allow patients to receive care from licensed physicians practicing in another state.

Wallace also emphasized the importance of giving patients a choice in how they access care. He recommended that rulemaking is needed to protect patient choice, create guardrails against potential abuse of telehealth visits, and ensure that patients still receive appropriate care, such as vitals monitoring. Wallace cautioned that if policymakers pass telehealth rules that make using it difficult for patients and physicians, they may not use it. He warned that it could reduce preventive care and drive up the numbers of patients needing dialysis at enormous costs to the US health care system.

"There is a return on investment of giving patients a choice," Wallace said. "Let's allow them to interact with the [health care] system how they want to but put some guardrails around it." ■

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Treating Mild Chronic Hypertension

Continued from cover

Women eligible for the trial had singleton fetuses at gestational age less than 23 weeks. In open-label fashion, they were randomly assigned to active treatment, consisting of antihypertensive medications recommended for use in pregnancy, or no treatment unless severe hypertension developed, which was defined as systolic blood pressure of 160 mm Hg or higher or diastolic blood pressure of 105 mm Hg or higher.

Pregnancy outcomes were compared between groups, including a composite primary outcome of preeclampsia with severe features, medically indicated preterm birth at less than 35 weeks' gestation, placental abruption, or fetal or neonatal death. Additionally, small-for-gestational-age birth weight under the 10th percentile for gestational age was evaluated as a safety outcome.

The primary outcome rate for those treated for mild chronic hypertension was 30.2% compared with 37.0% for the control group, with an adjusted risk ratio (RR) of 0.82. There was no significant difference in the rate of small-for-gestational age birth weight: 11.2% and 10.4%. Likewise, serious maternal complications were similar between the groups: 2.0% with treatment for mild chronic hypertension and 2.6% with the deferred strategy. The incidence of severe neonatal complications was 2.0% versus 2.6%.

The mild hypertension strategy was associated with a lower incidence of any preeclampsia: 24.4% versus 31.1%, RR 0.79. The study intervention was also associated with a lower incidence of preterm birth: 27.5% versus 31.4%, RR 0.87.

The CHAP results suggest that antihypertensive therapy for pregnant women with mild chronic hypertension, with a blood pressure target of less than 140/90 mm Hg, reduces the risk of adverse pregnancy outcomes including preeclampsia, without increasing the risk of small-for-gestational age birth weight. The researchers noted: "[W]e found that active treatment with antihypertensive drugs improved pregnancy outcomes without apparent harm" [Tita AT, et al. Treatment for mild chronic hypertension during pregnancy. *N Engl J Med*, published online ahead of print April 2, 2022; doi: 10.1056/NEJMoa2201295; https://www.nejm.org/doi/10.1056/NEJMoa2201295]. ■

Confronting Disinformation, Polarization, and Demagoguery

ASN Executive Vice President's Update

By Tod Ibrahim

Committed to creating a world without kidney diseases, the American Society of Nephrology (ASN)—together with other members of the kidney community—has produced incredible results in federal legislative and regulatory policy during the past decade, such as the landmark Executive Order on Advancing American Kidney Health. At a national level, patient advocates, health professionals, and policymakers are rallying around the four priorities of ASN's We're United 4 Kidney Health campaign: intervene earlier, transform transplant, accelerate innovation, and achieve equity.

Due to greater disinformation, polarization, and blowtorch politics, one in five people in the United States believes "The government, media, and financial worlds in the U.S. are controlled by a group of Satan-worshipping pedophiles who run a global child sex-trafficking operation" (1). It is not surprising, therefore, that ideologues in several states are damaging the relationship between patients and their caregivers. In the process, they are undermining public health, fueling racism, attacking people who are in the LGBTQ+ community, and assaulting access to reproductive health care. These threats compel ASN to consider leveraging its history of success in federal policy to create change at the state and local levels.

Public health

The federal government plays an essential role in health care policy, but public health is largely managed at the local and state levels. The COVID-19 pandemic highlights this dynamic. At the beginning of the pandemic, the federal government left each of the 50 US states to pursue individual policies, such as mandates to wear masks, socially distance, and close schools, as the Centers for Disease Control and Prevention is typically limited to providing advice (2).

This state-based approach resulted in politicizing the pandemic at local, state, and national levels, as well as diminishing trust in public health experts. Entering the 3rd year of the pandemic and nearing mid-term elections for every member of the House of Representatives, one-third of the Senate, and 36 governors, the politicization and skepticism are worsening. The Biden administration recently changed White House coronavirus response coordinators; Congress seems unwilling to continue federal funding for testing, treatment, and vaccines; and many states are declaring "mission accomplished" and prioritizing partisan political gain over citizens' health.

For example, the surgeon general of Florida has announced that "The Florida Department of Health is going to be the first state to officially recommend against the COVID-19 vaccines for healthy children" (3). The governor of Ohio is facing primary challengers who oppose his listening to health professionals while crafting the state's response to the pandemic (4). Either individually or through coalitions, such as the Council of Medical Specialty Societies, ASN has attempted to respond to as many of these threats as possible and provide updated information on its COVID-19 website (5).

According to the article, "Associations between governor political affiliation and COVID-19 cases, deaths, and testing in the United States," in the *American Journal of Preventive Medicine*, the political affiliation of a state's governor "may differentially impact COVID-19 incidence and death rates." The study adds, "Future state policy actions should be guided by public health considerations rather than political expedience and should be supported by a coordinated federal response" (6).

As health professionals and respected members of their communities, ASN members can provide guidance to local officials about the impact of policies on people with kidney diseases and promote kidney health. Polling consistently demonstrates that health professionals remain one of the most trusted occupations, and ASN members must make good on the public's trust by helping to guide policymakers (7).

Racism

A few months after insurrectionists attacked the US Capitol in January 2021 to overturn a fairly won presidential election, the governor of Georgia signed into law legislation that makes it much harder for the Peach State's citizens to vote. At the time the bill became law, 46 other states were considering similar legislation, empowered by a 2013 decision by the US Supreme Court (in Shelby County vs. Holder) that weakened a key provision of the Voting Rights Act of 1965 (8, 9).

ASN joined 16 other not-for-profit organizations representing more than 21.1 million patients and health professions in publishing an advertisement in *The Atlanta Journal-Constitution* highlighting the fact that Georgia's law would "disproportionately affect minority communities." Together, we urged "the people of Georgia and policymakers to consider the impact of this new law and find ways to create a more equitable, inclusive community that will attract visitors to help Atlanta and other cities in this state thrive" (10).

Besides making it harder for members of minority communities to vote, many states are also trying to prevent students from learning about racism in US history, especially how this past influences our present and future. At least 36 states have adopted or are considering legislation "to restrict education on racism, bias, the contributions of specific racial or ethnic groups to US history, or related topics" (11).

It is impossible for ASN to pursue health care justice and help address social determinants of health if US society refuses to acknowledge that the "racism embedded in laws, regulations, rules, and procedures" leads to "differential outcomes by race" (12). Data prove that kidney diseases are not experienced equally; across the United States, Black Americans are more likely to develop kidney diseases, more likely to progress to kidney failure, and less likely to receive optimal therapies, such as a kidney transplant, than are White Americans (13).

An analysis by the US Renal Data System demonstrates that Americans who live in areas with less access to resources were more likely to experience kidney failure than those with more access to resources, but racial and ethnic minorities were more likely to experience kidney failure in every area (14). If racial and ethnic differences in outcomes were prohibited from such studies, we would not understand such disparities.

ASN has opposed federal efforts to restrict education about racism in US history and its impact on health (15). However, local and state advocacy is needed to fully combat this assault. To achieve kidney health, patient advocates, health professionals, and policymakers must understand and address health disparities, which include dismantling systems that perpetuate discrimination.

LGBTQ+

At least nine states are poised to follow Florida's lead in enacting legislation "prohibiting classroom discussion about sexual orientation or gender identity in certain

Americans are affected by kidney diseases regardless of political affiliation, and it is critical that the kidney community—including ASN—takes the fight for kidney health to the local and state levels.

grade levels or in a specified manner" (16). Although the Florida legislation—formally titled "Parental Rights in Education" but better known as "Don't Say Gay"—defines "certain grade levels" as kindergarten through third grade, the wording of the legislation is vague enough to, in effect, eliminate any conversations about sexual orientation or gender identity at any grade in the Sunshine State's schools.

Additionally, the Florida law favors "the rights of parents" over the rights of students by requiring schools to notify parents each time students seek mental or physical health services for any reason. This part of the law will likely have a chilling effect on the willingness of students to discuss their sexual orientation or gender identity with school counselors (or seek important care), making schools an even more uncomfortable environment for people who identify as LGBTQ+.

The Florida law also deputizes private citizens to help with enforcement. If a school district fails to resolve a concern within the context of the law, anyone can "Bring an action against the school district to obtain a declaratory judgment that the school district procedure or practice violates this paragraph and seek injunctive relief." (Remember, one in five people in the United States believes "a group of Satan-worshipping pedophiles who run a global child sex-trafficking operation" [1] control the country.) The law permits courts to "award damages," "reasonable attorney fees," and "court costs to a parent who receives declaratory or injunctive relief."

A recent Alabama law criminalizes "gender-affirming healthcare for transgender youth, with a threat of 10 years in prison for medical providers" (17). This is the first law in the United States to make health care for transgender youth a felony, and health professionals will face prison if they provide "hormone treatment, puberty blockers[,] and gender reassignment surgery to minors."

In next month's issue of *ASN Kidney News*—and in celebration of Pride Month 2022—ASN President Susan E. Quaggin, MD, will focus on ASN's response to these attacks on the LGBTQ+ community.

Reproductive health care

When Senate Bill 8 was signed into law last September, Texas outlawed abortion "after detection of an unborn child's heartbeat," essentially reducing the time for a legal abortion from 24 weeks to 6 weeks, likely reducing the number of abortions in Texas by 80%, and disproportionately making it harder for women who are of Black race, with lower economic status, or who live farther away from health facilities to access this medical procedure (18, 19).

The Texas Heartbeat Act, which also prohibits abortion after 6 weeks even in cases of rape or incest, is serving as a model for similar legislation in 13 other states. One of these states, Oklahoma, went a step further last month and made performing an abortion a felony punishable by a $100,000 fine and 10 years in prison. Four more states are considering bills to outlaw abortion after 15 weeks.

As with the Florida law concerning sexual orientation and gender identity, the Texas anti-abortion law deputizes the public to help with enforcement. Private citizens can earn $10,000 bounties "for successful lawsuits against anyone—from an Uber driver to a doctor—who 'aids or abets' a woman who gets an abortion once fetal cardiac activity can be detected" (20).

This vigilante justice is in addition to the fact that the law is "vaguely worded, leaves providers vulnerable to being sued[,] and puts patients at risk," according to the American College of Obstetricians and Gynecologists. As a result of the law, it has become harder for physicians "to treat medical crises," which is endangering patients, as they operate "in a climate of fear" (21).

Much has been written about how the COVID-19 pandemic served as an accelerant, quickening changes that were already underway in early 2020. For example, "telehealth use has increased 38X from the pre-COVID-19 baseline" (22). The pandemic has also accelerated radical individualism throughout the country. E pluribus unum—"Out of many, one" or if you prefer, "One out of many"—may no longer apply as a motto for the United States. The new motto is more akin to "Many out of one."

Hope

Several states have passed legislation to protect living organ donors, including states with liberal governments (such as California) and states with conservative governments (such as Texas) (23). Preceding federal protections for living donors, this legislation will likely trigger passage of federal legislation: Members of Congress continue to cite home-state versions as a motivation for supporting a parallel federal version, the Living Donor Protection Act of 2021 (HR 1255/S 377). Americans are affected by kidney diseases regardless of political affiliation, and it is critical that the kidney community—including ASN—takes the fight for kidney health to the local and state levels.

In its strategic plan, ASN seeks to achieve the goal of "Advocating for policies that empower patients and their care partners, the kidney care team and scientists, health systems, payers, and other stakeholders with a role in kidney health" (24). Through its members, ASN can accomplish this goal by helping confront disinformation, polarization, and demagoguery by focusing attention on the real challenges facing the more than 37 million people in the United States living with kidney diseases. ASN must leverage its track record at a federal level—which is based on a bipartisan, factual, and patient-centered approach—to engage in policy and advocacy at a state level to accomplish this goal. ■

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Glomerular Disease Corner

Recurrent Primary FSGS Posttransplant

By Sonia Rodriguez-Ramirez and Naoka Murakami

Visual Abstract by Paolo Nikolai So

Case description

A 23-year-old female with primary focal segmental glomerulosclerosis (FSGS), diagnosed at the age of 16, underwent a living-related kidney transplantation (KT). She was on hemodialysis for 2 years before transplant but still had residual urine output of 500 mL/day with a random urine protein-to-creatinine ratio (UPCR) of 1.5 g/gCr. On post-operative day 4, UPCR was noted as 14 g/gCr. A kidney allograft biopsy demonstrated diffuse effacement of podocyte foot processes with no evidence of acute rejection.

What are the risk factors and mechanisms of recurrent primary FSGS posttransplant? What treatment options (pre- and posttransplant) might benefit this patient?

Mechanisms of recurrent FSGS are not entirely understood.

Introduction

Primary FSGS is rare; however, it is the most common histopathologic pattern of glomerular injury in adult nephrotic syndrome. The Kidney Disease: Improving Global Outcomes (KDIGO) 2021 Clinical Practice Guideline for the Management of Glomerular Diseases proposed eliminating the term idiopathic from the FSGS lexicon and only using primary FSGS (1). Recurrent FSGS refers to the development of primary podocytopathy in KT recipients with a history of primary FSGS as the cause of end stage kidney disease. Recurrence may occur in more than 32% of cases (2) but is rare in patients with genetic FSGS (e.g., podocin mutations) and those without nephrotic syndrome at the initial presentation (3).

Risk factors

Several factors are associated with a higher risk of recurrence: younger age of disease onset, rapid progression of initial disease, living-related KT, history of recurrence in a previous kidney allograft, and native kidney nephrectomies (2).

A family history of FSGS, histologic subtype in the native kidney, and choice of transplantation immunosuppressive therapy have not been shown to alter the risk of recurrence.

Pathogenesis

Mechanisms of recurrent FSGS are not entirely understood. In addition to genetic and immunological modifiers, circulating factor(s) have been suggested, which may cause injury to the podocytes and/or glomerular capillary wall. Case reports demonstrated that re-transplantation of a kidney allograft removed from a KT recipient who developed biopsy-proven recurrent FSGS (4) resulted in complete resolution of proteinuria and reversal of histologic lesions, supporting the presence of circulating permeability factor(s) indirectly.

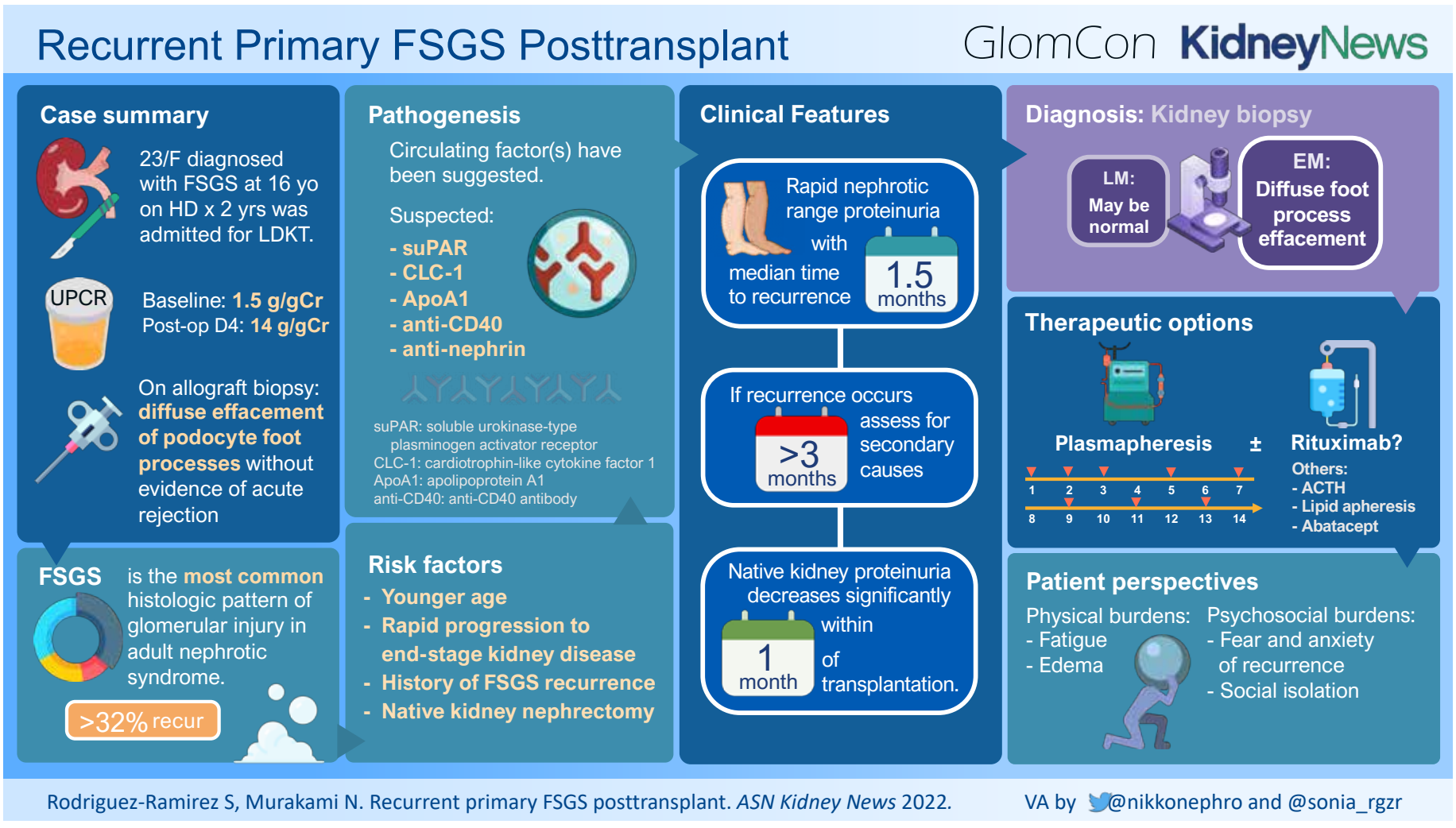
Several molecules (including soluble urokinase-type plasminogen activator receptor, cardiotrophin-like cytokine factor 1, apolipoprotein A1, anti-CD40 antibody, and anti-nephrin (5)) have been proposed as potential circulating factors. Nevertheless, none has been validated as a biomarker in clinical practice (6, 7).

Clinical manifestation and diagnosis

Patients with recurrent primary FSGS typically present with rapid nephrotic-range proteinuria with a median time to recurrence of 1.5 months (2). For the patients with nephrotic-range proteinuria after 3 months' posttransplantation, an evaluation for causes of secondary FSGS should also be performed (e.g., maladaptive response to hyperfiltration, viruses, drugs, and toxins).

Proteinuria from native kidneys decreases significantly within 1 month of transplantation; thus, proteinuria detected more than 1 month after KT is most likely derived from the allograft and should trigger further investigation (8).

A kidney allograft biopsy is critical to diagnose recurrent primary FSGS. As a spectrum of primary podocytopathy, early recurrence of primary FSGS may lack sclerotic lesions by light microscopy, and it may only involve diffuse podocyte foot process effacement by electron microscopy. Podocyte foot process effacement tends to be segmental in secondary forms (9).



HD, hemodialysis; LDKT, living donor kidney transplant; LM, light microscopy; EM electron microscopy; ACTH, adrenocorticotropic hormone.

Therapeutic options

For patients with recurrent primary FSGS, plasmapheresis is suggested to remove the hypothesized circulating permeability factor, with or without rituximab in combination (10). However, there is a lack of clear evidence of benefit with use of the rituximab in this setting (11).

Several additional treatment options for patients with recurrent FSGS who do not respond to initial therapy of plasmapheresis, with or without rituximab, have been explored, including adrenocorticotropic hormone (12), galactose (13), lipid apheresis (14), and abatacept (15). The clear benefit of these therapies should be tested in the future, and there are multiple ongoing clinical trials for primary FSGS, which may be effective for recurrent FSGS (16).

Consideration for re-transplantation

Patients who developed recurrent FSGS in the first KT are at very high risk (up to 75%) for recurrence in subsequent kidney allografts. Some clinicians have suggested that if a first graft is lost due to recurrent disease, then a second KT should be delayed for 1–2 years or avoided (17). This delay may result in the disappearance of the circulating factors responsible for the glomerular injury. However, the efficacy of this approach is not proven. A third KT in patients with two previous transplant losses due to recurrent FSGS should generally be avoided. Prophylactic plasmapheresis and rituximab do not appear to decrease the rate of recurrence after transplantation (18).

Perspectives from patients living with FSGS

Living with primary FSGS sets challenges for a patient's daily life. According to the patient forum organized by the National Kidney Foundation, the patients and their care partners shared that they experience not only physical symptom burden (e.g., fatigue and edema) but also psychosocial burden (e.g., fear and anxiety of FSGS recurrence after transplant). Participants reported that social isolation was frequently caused by the "invisible" nature of their disease, which made it difficult for others to understand possible complications in the lives of people with FSGS. This sometimes caused irreconcilable strains on friendships and workplace relationships. The lack of perceived importance of mental health relative to physical symptoms was pointed out (19).

Conclusions

Recurrence of primary FSGS after KT is immensely challenging. The understanding of pathogenesis, development of diagnostic biomarkers, and effective therapeutics are urgently needed. Future clinical trials that include a tight partnership with patients and their care partners are awaited. ■

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Indication

Parsabiv® (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

Parsabiv® has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information for Parsabiv®

Contraindication: Parsabiv® is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred.

Hypocalcemia: Parsabiv® lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv®. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv®.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv®. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv®.

Concurrent administration of Parsabiv® with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv® should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv®. Closely monitor corrected serum calcium in patients receiving Parsabiv® and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of Parsabiv®. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv®. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv®. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv® clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv® for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv® in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv®.

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv®. Monitor patients for worsening of common Parsabiv® GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv® therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv® to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

Please see Brief Summary of full Prescribing Information on adjacent page.

Visit **ParsabivHCP.com/efficacy** to see how Parsabiv® performed in clinical trials and real-world settings.

Parsabiv®
(etelcalcetide) Injection for intravenous use
2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Parsabiv®
(etelcalcetide) Injection for intravenous use

2.5mg/0.5mL | 5mg/1mL | 10mg/2mL

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

PARSABIV is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:

PARSABIV has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with chronic kidney disease who are not on hemodialysis and is not recommended for use in these populations.

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including face edema and anaphylactic reaction, have occurred with PARSABIV *[see Adverse Reactions (6) in PARSABIV full prescribing information]*.

WARNINGS AND PRECAUTIONS

Hypocalcemia

PARSABIV lowers serum calcium *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, seizures, QT interval prolongation, and ventricular arrhythmia.

QT Interval Prolongation and Ventricular Arrhythmia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). In these studies, the incidence of a maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*. Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to PARSABIV. Closely monitor corrected serum calcium and QT interval in patients at risk receiving PARSABIV.

Seizures

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to PARSABIV. Monitor corrected serum calcium in patients with seizure disorders receiving PARSABIV.

Risk of Hypocalcemia with Other Serum Calcium Lowering Products

Concurrent administration of PARSABIV with another oral calcium-sensing receptor agonist could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to PARSABIV should discontinue cinacalcet for at least 7 days prior to initiating PARSABIV *[see Dosage and Administration (2.4) in PARSABIV full prescribing information]*. Closely monitor corrected serum calcium in patients receiving PARSABIV and concomitant therapies known to lower serum calcium.

Monitoring Serum Calcium and Patient Education

Measure corrected serum calcium prior to initiation of PARSABIV. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with PARSABIV *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*. Educate patients on the symptoms of hypocalcemia and advise them to contact a healthcare provider if they occur.

Management of Hypocalcemia

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). PARSABIV dose reduction or discontinuation of PARSABIV may be necessary *[see Dosage and Administration (2.2) in PARSABIV full prescribing information]*.

Worsening Heart Failure

In clinical studies with PARSABIV, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. In clinical studies, heart failure requiring hospitalization occurred in 2% of PARSABIV-treated patients and 1% of placebo-treated patients. Reductions in corrected serum calcium may be associated with congestive heart failure, however, a causal relationship to PARSABIV could not be completely excluded. Closely monitor patients treated with PARSABIV for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]* and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterols and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range *[see Dosage and Administration (2.1) in PARSABIV full prescribing information]*.

ADVERSE REACTIONS

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

- Hypocalcemia *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*
- Worsening Heart Failure *[see Warnings and Precautions (5.2) in PARSABIV full prescribing information]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.3) in PARSABIV full prescribing information]*
- Adynamic Bone *[see Warnings and Precautions (5.4) in PARSABIV full prescribing information]*

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 with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other.

Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

Adverse Reaction*	Placebo (N = 513)	PARSABIV (N = 503)
Blood calcium decreased[a]	10%	64%
Muscle spasms	7%	12%
Diarrhea	9%	11%
Nausea	6%	11%
Vomiting	5%	9%
Headache	6%	8%
Hypocalcemia[b]	0.2%	7%
Paresthesia[c]	1%	6%

*Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

[a] Asymptomatic reductions in calcium below 7.5 mg/dL or clinically significant asymptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

[b] Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hyperkalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hospitalization for Heart Failure: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.6% PARSABIV, 3.1% placebo), below 7.5 mg/dL (27% PARSABIV, 5.5% placebo), and below 8.3 mg/dL (79% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus level below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.8%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (71 out of 995) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and post-natal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures 1.8 times the human exposure for the clinical dose of 15 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryo-fetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures 2.7 and 7 times exposures for the clinical dose, respectively.

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

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC. No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7- and 7-fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [^{14}C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [^{14}C]-etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [^{14}C]-etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

The safety and efficacy of PARSABIV have not been established in pediatric patients.

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdosage. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdosage. In the event of overdosage, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken *[see Warnings and Precautions (5.1) in PARSABIV full prescribing information]*.

AMGEN®

PARSABIV® (etelcalcetide)

Manufactured for:
KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

Patent: http://pat.amgen.com/Parsabiv/

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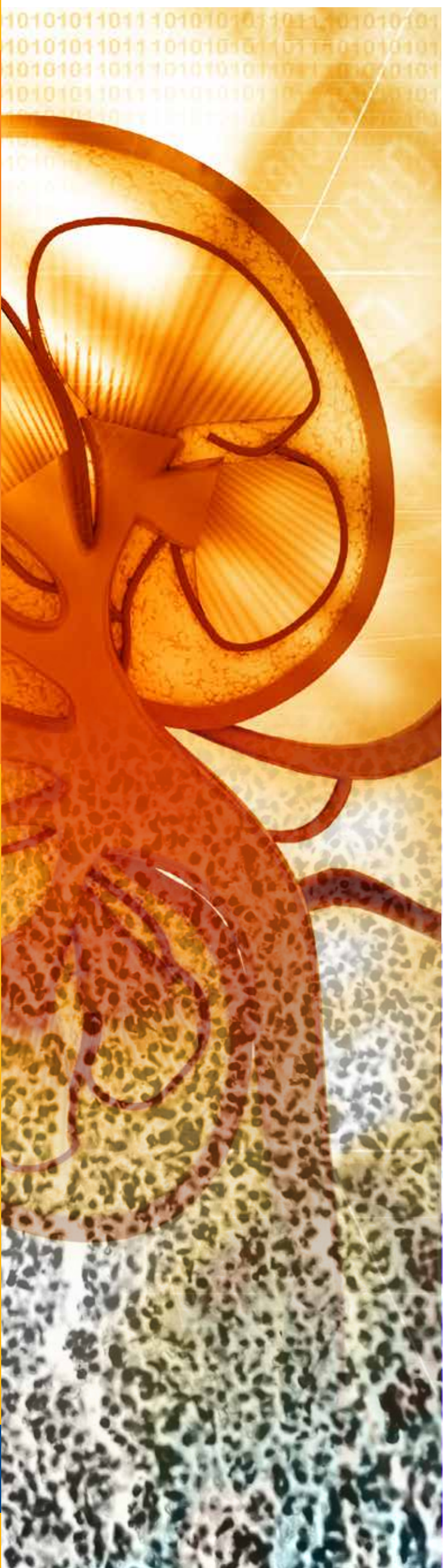


CANCER, CANCER THERAPY, AND THE KIDNEY 2022

By Kenar Jhaveri and Mayuri Trivedi

Traditionally, the field of hematology-oncology has elicited a feeling of despair and morbidity in many until a few years ago. However, with the growing advances in the field of oncology, there are a larger number of patients who are being diagnosed with cancers and an even larger number surviving cancer. With this change in the field of oncology, we—as nephrologists—encounter many patients who develop kidney diseases due to cancer or the therapy used for the treatment of cancer.

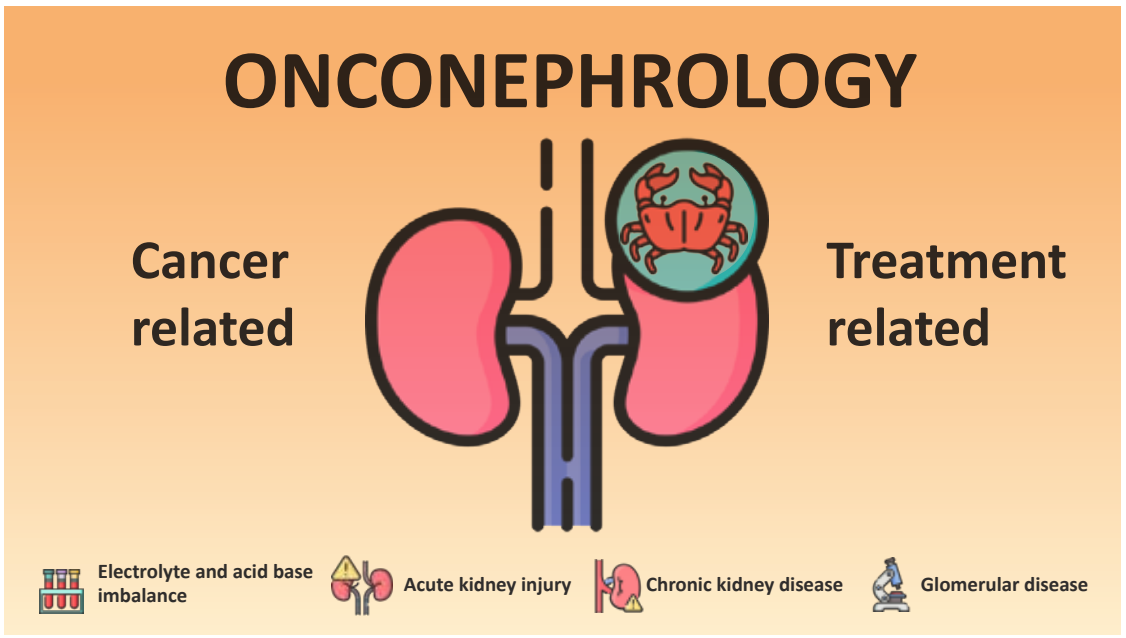
From electrolyte and acid-base imbalance to acute and chronic kidney disease, including glomerular diseases, nephrologists are seeing a growing number of patients in the inpatient and outpatient units who have had a tryst with some cancer. This is where the birth of onconephrology began. From being a highly specialized subspeciality to becoming the "need of the hour," this branch of nephrology is soon going to become a necessity.

In the next two issues of *Kidney News*, we will explore the various facets of onconephrology. We shall also feature editorials about recent original articles published in various journals that focus on onconephrology.

This year, several centers around the world are creating onconephrology services as well as clinics dedicated to the field. We hope that this will lead to better care for patients and new, original investigations.

As they say, necessity is truly the mother of invention. Thus is the beginning and an onward march of onconephrology!

Kenar D. Jhaveri, MD, is Editor-in-Chief of Kidney News. *Mayuri Trivedi, DM, is Assistant Professor with the Department of Nephrology, Lokmanya Tilak Municipal General Hospital, Mumbai, India.*



Malignancy-Related Membranous Nephropathy

By Prabhat Chauhan and Raja Ramachandran

The prevalence of malignancy in patients with membranous nephropathy (MN) ranges from 4% to 10% (1, 2). In adults, MN is the most common cause of nephrotic syndrome outside of diabetes and is well described but not well studied in patients with cancer.

In a recent article by Thet and colleagues (3) in *Translational Oncology*, the authors impart on an update on cancer risks in patients with a glomerular diseases. Thet et al. (3) used MN as a prototype to understand malignancy-related glomerular disease. Malignancy-related MN is a disease of the elderly, predominantly in the 7th decade (4). The diagnosis of cancer preceded the diagnosis of MN in one-fifth of the cases, and in 80%, neoplasm detection is within the first year of MN diagnosis (5). Patients with malignancy-related MN are older with a lower estimated glomerular filtration rate and serum albumin than those without neoplasms (6, 7).

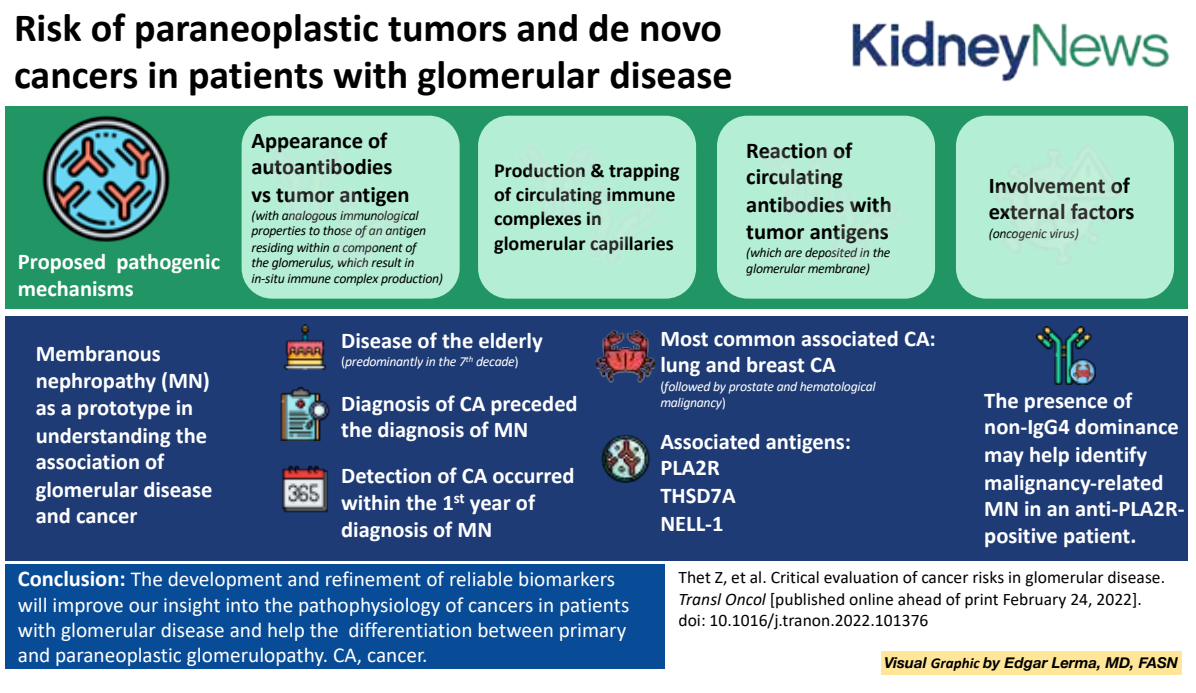
The most common malignancy-related MNs include lung and breast cancer, followed by prostate and hematological malignancy (4). In the article by Thet et al. (3), various strategies for screening cancers in patients with glomerular diseases are discussed. First, the authors highlight the lack of consensus among clinicians concerning cancer screening in glomerular diseases. Second, the practice ranges from a selective screening of older patients (8) with glomerular diseases to a risk-based, three-step approach (9), where the first two steps are limited to general screening, and the third step involves evaluating high-risk cases. Finally, after deliberating various strategies for screening cancers in patients with MN, the authors suggest adapting cancer-screening recommendations in the United States for solid organ cancers. Recently, 8F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) emerged helpful in detecting primary tumors in patients with cancer of an unknown primary site (10). However, before routinely adapting FDG-PET/CT to diagnose cancer in patients with MN, the tool will mandate cost-effectiveness and benefit-harm assessment.

Numerous reports describe anti-M-type phospholipase A2 receptor (PLA2R) and anti-thrombospondin type-I domain-containing 7A (THSD7A) in secondary MN, including malignancy-related MN (11). In addition, the recent discovery of neural epidermal growth factor-like 1 (NELL-1) as a culprit antigen in 33% of malignancy-related MN may dictate active surveillance for cancer (11).

The *Translational Oncology* (3) article also highlights the association of NELL-1-positive and seven septuple-negative status with malignancy-related MN. Importantly, the debate of malignancy causing secondary MN or a coincidental detection of MN (and anti-PLA2R anti-THSD7A antibodies) and cancer remains unresolved. The presence of non-immunoglobulin G4 (IgG4) dominance may help identify malignancy-related MN (7, 11). The other crucial aspect is deciding further therapy. A few reports suggest resolution of proteinuria with successful cancer treatment (12, 13), and hence, early detection and treatment of the cancer are paramount to treating MN per se.

To summarize, IgG subtyping and staining for NELL-1 and other antigens would identify the cohort of patients deserving extensive workup for malignancy. However, limited availability and lack of standardization (of the technique for antigen detection) remain a critical deterrent to differentiate primary and secondary MN successfully. Therefore, future research must develop and validate biomarkers to distinguish between primary and malignancy-related MN. ■

The most common malignancy-related [membranous nephropathies] include lung and breast cancer, followed by prostate and hematological malignancy.



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The authors report no conflicts of interest.

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Glomerular Diseases Associated with Stem Cell Transplant

By Ala Abudayyeh and Rimda Wanchoo

Allogeneic stem cell transplant (SCT) is used to cure several hematological disorders. The incidence of both acute kidney injury and chronic kidney disease (CKD) post-SCT remains high. A rare cause of CKD post-allogeneic SCT is development of glomerular disease, which by many is considered to be a manifestation of chronic graft-versus-host disease (GVHD) affecting the kidney (1). Based on mouse models, it has been proposed that GVHD could be a direct T cell-mediated injury or that the chronic systemic inflammatory state of GVHD leads to autoimmune induction and glomerulopathy (2). The incidence of nephrotic syndrome post-allogeneic SCT is reported to range from 0.4% to 6%, with a median onset after 100 days and up to 12 months post-allogeneic SCT (3). Based on case reports and retrospective studies, it has been reported that nephrotic syndrome appears shortly after cessation or tapering of immunosuppression, with or without chronic GVHD (1, 2).

The most common histological lesion seen is membranous nephropathy (MN), followed by minimal change disease. Other lesions that have been reported are focal segmental glomerulosclerosis, IgA nephropathy, and mesangial proliferative disease (1). In patients with proteinuria, it is recommended to assess for secondary causes, such as infections, drugs, and malignancy, and to do a kidney biopsy when safe (Figure 1).

In the last decade, we have started to recognize specific antibodies associated with primary MN, such as anti-M-type phospholipase A2 receptor (anti-PLA2R) in 70% of primary MN and anti-thrombospondin type-1 domain-containing 7A (anti-THSD7A) in 1%–5% of primary MN (4, 5). Other rare antigens have also been described in primary MN, such as neural tissue-encoding protein (NELL-1), semaphorin 3B (SEMA3B), protocadherin 7 (PCDH7), and serine protease HTRA1. Secondary MN has been associated with exostosin 1/exostosin 2 (EXT1/EXT2) and neural cell adhesion molecule (NCAM1) (6). For recognizing specific antigens associated with MN in SCT patients, both PLA2R- and NELL-1-associated MNs have been reported (7). In a recent study by Sethi et al. (6), protocadherin (FAT1) was identified as a unique antigen in MN associated with SCT, especially PLA2R-negative MN. All control cases, which included 15 time 0 kidney transplant biopsies, 73 other glomerulopathies, and 28 PLA2R-positive MN cases, were negative for FAT1 (6). In another case series by Nasr et al. (8), five patients with MN were noted to have extensive tubular basement membrane (TBM) deposits of IgG, C3, κ, and λ following allogeneic SCT. Only one patient had PLA2R, and the others were negative for PLA2R, THSD7A, EXT1/EXT2, NELL-1, PCDH7, and SEMA3B, which suggests that there are other unknown antibodies to the TBM leading to the injury as a form of renal GVHD (8).

Although podocyte diseases are rare, renal-limited thrombotic microangiopathy (TMA) post-SCT is not uncommon and remains a challenging topic from a mechanistic, diagnostic, and treatment aspect. However, there have been data indicating that the injury of renal vascular endothelium is analogous to renal GVHD, with C4d staining eluding to the presence of antibody and complement activation (9). Another finding connecting endothelial injury and TMA to GVHD includes elevated markers of endothelial injury, such as ST2 protein (receptor for interleukin-33), as well as angiopoietin 2, in patients with steroid refractory GVHD (10).

Treatment of glomerular diseases post-SCT has been guided by case reports and case series. Typically, treating with steroids initially and reinitiating immunosuppressive therapy, such as calcineurin inhibitors, mycophenolate mofetil, or cyclophosphamide, have been the standard of care. Rituximab has been used to treat SCT-associated MN and has proven to be effective (11). Treatment for renal TMA is challenging and often requires use of rituximab or anti-complement therapy. Data are sparse and mostly in the pediatric nephrology literature (12). ■

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The authors report no conflicts of interest.

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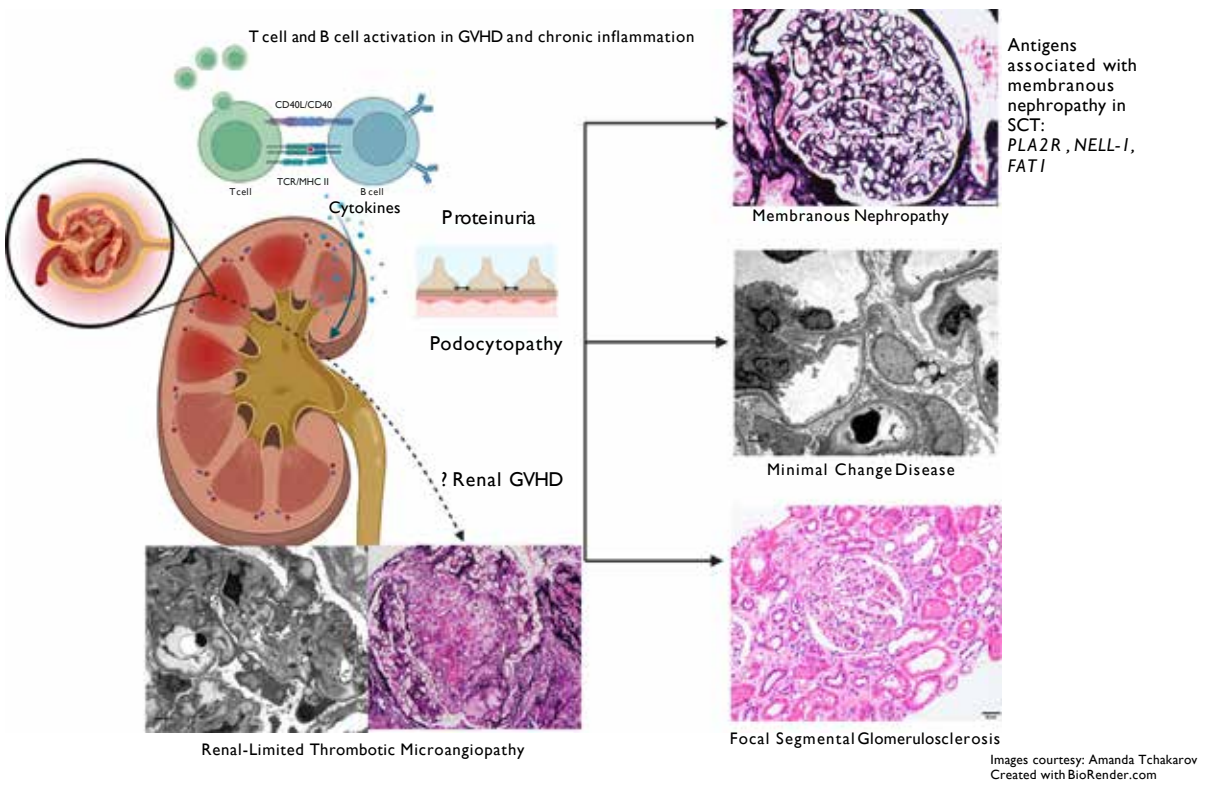
Figure 1. Glomerular diseases in stem cell transplant patients

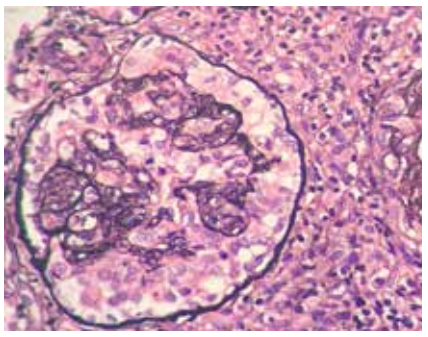


Spectrum of glomerular disease in stem cell transplant (SCT) patients. CD40L/CD40, cluster of differentiation 40 ligand/cluster of differentiation 40; TCR/MHC II, T cell receptor/major histocompatibility complex II.

Fellows First

Do You Know Your Drug Toxicities? Test Your Knowledge

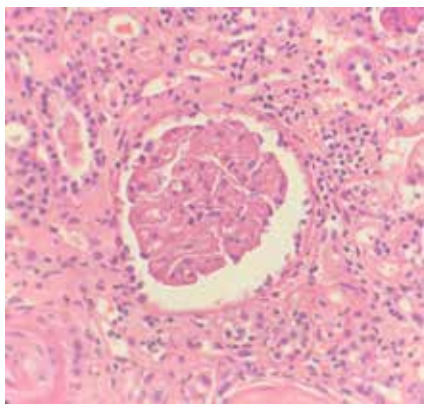
By Mythri Shankar

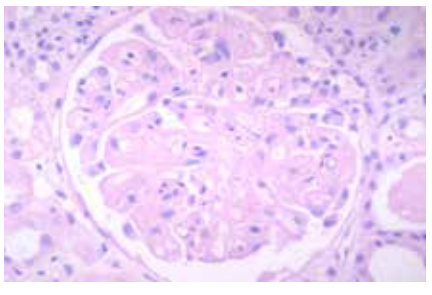


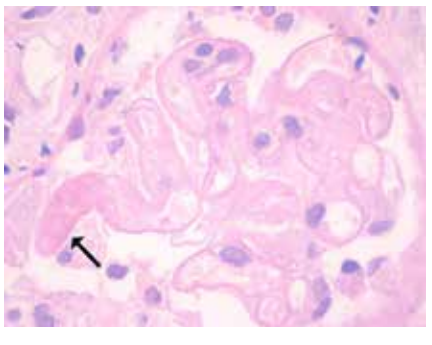
Light microscopy: Jones silver stain, proliferation of visceral epithelial cells and collapse of glomerulus known as collapsing focal segmental glomerulosclerosis (FSGS). Image credit: K.S. Vinay.

1. Collapsing glomerulopathy (CG)—high-dose pamidronate

Pamidronate has been found to be associated with CG in patients with multiple myeloma and breast cancer. In these patients, pamidronate is used in higher doses to prevent skeletal complications. It is hypothesized that pamidronate affects the glomerular epithelial cells (1).



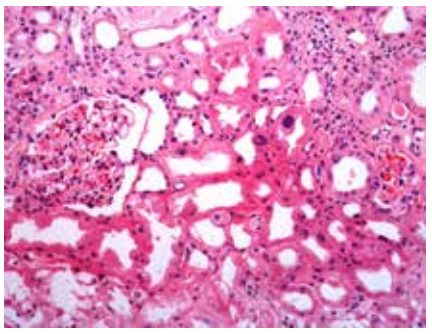




Light microscopy: Hematoxylin & eosin stain; mesangiolysis and glomerular capillary thrombosis suggestive of TMA. Arrow shows fibrin thrombi. Image credit: K.S. Vinay.

2. Thrombotic microangiopathy (TMA)—bevacizumab; anti-vascular endothelial growth factor (anti-VEGF) agent

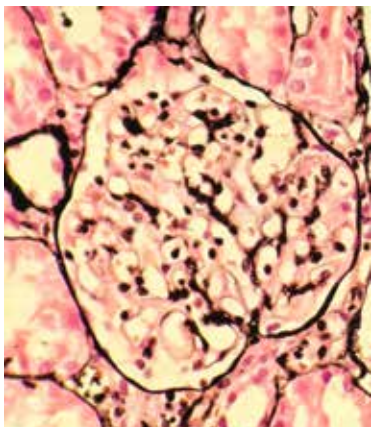
TMA can occur any time after the initiation of treatment with anti-VEGF agents. TMA is rarely systemic with positive hemolytic parameters. Usually, the presentation is kidney limited. Drug-induced TMA can be divided into immune-mediated (type 1) and non-immune-mediated (type 2) syndromes. Immune-mediated syndromes are idiosyncratic, dose independent, and antibody mediated. Non-immune-mediated syndromes usually occur when high doses of a drug are given for a long period of time or sometimes even with a single drug exposure. Anti-VEGF agents usually cause type 2 drug induced TMA. Some of the proposed mechanisms are direct endothelial injury, genetic predisposition, and increased platelet aggregation. The majority are reversible following discontinuation of the drug (2).



Light microscopy: Hematoxylin & eosin stain; acute tubular injury. Image credit: V. Mahesha.

3. Severe acute tubular necrosis (ATN)—ifosfamide

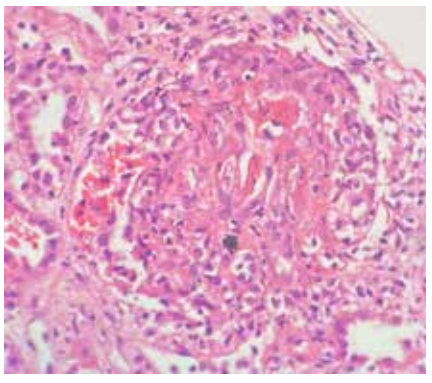
Ifosfamide is a chemotherapeutic agent usually used to treat metastatic germ cell testicular cancer and some types of pediatric sarcoma. Direct tubular injury is the most common complication of ifosfamide use. In vitro studies have shown that chloroacetaldehyde—a metabolite of ifosfamide—causes direct tubular injury. Also, another metabolite—acrolein—can lead to hemorrhagic cystitis (3).



Silver methenamine stain showing normal glomerulus. Image credit: K.S. Vinay.

4. Minimal change disease (MCD) and diffuse podocytopathy—doxorubicin

Doxorubicin (anthracycline antibiotic) is used in combination with other chemotherapeutic drugs to treat different types of cancers that affect the bladder, kidneys, breast, ovaries, and so on. It is also used to treat certain types of lymphomas and leukemias. Doxorubin causes severe ultra-structural changes to the podocytes in mice models as well as in humans, causing diffuse podocyte foot process effacement and MCD. Doxorubicin is one of the secondary causes of MCD. Treatment is withdrawal of the drug. Data are limited for the role of steroids in drug-induced MCD (4).



Light microscopy: Hematoxylin & eosin stain showing crescentic glomerulonephritis. Image credit: K.S. Vinay.

5. Lupus-like glomerulonephritis—ipilimumab

Ipilimumab is a completely humanized monoclonal antibody that targets cytotoxic T lymphocyte antigen 4. It is the first immune checkpoint inhibitor to be approved for the treatment of metastatic melanoma. Few cases of ipilimumab causing lupus-like nephritis are reported. An immune phenomenon has been postulated to cause this type of kidney injury. Early recognition and treatment with steroids pave the way to recovery (5). ■

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Pseudo-electrolyte Disorders in Patients with Cancer: When Seeing Is Not Believing

By Insara Jaffer Sathick and Aisha Shaikh

Pseudo-electrolyte disorders are laboratory artifacts, and failure to recognize this entity can lead to inadvertent treatment. The hallmark of pseudo-electrolyte disorders is that the patient does not exhibit classic signs or symptoms of the underlying electrolyte abnormality. This should prompt clinicians to rule out pseudo-electrolyte disorders before initiating therapy. Here, we highlight pseudo-electrolyte disorders seen in onconephrology practice.

Pseudo-hyponatremia

A *falsely low sodium level* is seen in conditions that reduce the water content of a given volume of plasma, such as 1) severe hyperproteinemia due to paraproteinemia, hypergammaglobulinemia, or intravenous immunoglobulin (IVIG) administration; 2) severe hyperlipidemia due to cholestasis/biliary obstruction; and 3) severe hypertriglyceridemia in the setting of cancer therapy, such as tamoxifen, capecitabine, fluorouracil, docetaxel, and paclitaxel (1–4). In pseudo-hyponatremia, serum osmolality is normal, and measurement of serum sodium by direct potentiometry will confirm the diagnosis.

Pseudo-hyperkalemia and pseudo-hypokalemia

A *falsely high potassium level* can be observed in severe thrombocytosis (>500,000/mm^3) caused by myeloproliferative disorders (5). In thrombocytosis, potassium is released from the platelets after the blood is collected due to in vitro clotting; hence, potassium is falsely elevated in the serum but not in plasma because the serum sample does not contain an anti-coagulant (heparin), whereas the plasma sample does, and the presence of the anticoagulant prevents platelet degranulation in the plasma sample (6). Conversely, reverse pseudo-hyperkalemia is observed in severe leukocytosis (>70,000/mm^3) caused by leukemia or lymphoma (7). This occurs due to fragility of the white blood cell membrane, making it prone to lysis by heparin or mechanical factors, such as centrifugation, pneumatic tube transport, or other mechanical factors. This form of pseudo-hyperkalemia is commonly observed in a plasma sample, hence, the term "reverse pseudo-hyperkalemia." Although this phenomenon can also occur in serum samples, it is less likely to occur in coagulated serum samples, likely because of fibrin clot formation stabilizing tumor cells during centrifugation. To circumvent pseudo-hyperkalemia, when suspected, a whole blood sample can be collected in a blood gas-analyzing vial with rapid transport to the laboratory for potassium measurement, which will help rule out true hyperkalemia. Interestingly, pseudo-hypokalemia, a falsely low potassium level, has also been observed in patients with leukemia and leukocytosis (>100,000/mm^3). This occurs if the blood sample is stored for a prolonged period at room temperature, resulting in increased Na-K-ATPase activity and movement of potassium into the leukocytes (8).

Pseudo-hypocalcemia

A *falsely low calcium level* has been described with the use of gadolinium. (Gadodiamide [Omniscan] and gadoversetamide [OptiMARK] specifically have been reported to cause this.) Gadolinium interferes with the colorimetric assay for calcium measurement, leading to pseudo-hypocalcemia (9). This is a transient phenomenon, as gadolinium is rapidly excreted by the kidneys.

Pseudo-hypercalcemia

A *falsely high calcium level* can occur in severe thrombocytosis and is due to in vitro secretion of calcium from activated platelets (10). Pseudo-hypercalcemia has been reported in patients with paraproteinemia due to binding of calcium to abnormal immunoglobulins. In these disorders, the total calcium is elevated, but ionized calcium is normal (11, 12).

Pseudo-hyperphosphatemia and pseudo-hypophosphatemia

These can also occur in the presence of paraproteins caused by plasma cell dyscrasias and lymphoplasmacytic disorders. They are due to assay interference by the paraproteins. Likewise, liposomal amphotericin B can cause pseudo-hyperphosphatemia and pseudo-hypophosphatemia (13). Pseudo-hyperphosphatemia can also occur if the blood sample is contaminated by heparin or t-PA or with the presence of hyperbilirubinemia and hyperlipidemia. Mannitol infusion can cause pseudo-hypophosphatemia by binding to molybdate, which is used in the colorimetric assay for phosphorus measurement (14).

It is critical to recognize these spurious electrolyte disorders to avoid unnecessary interventions that can potentially lead to harmful side effects. ■

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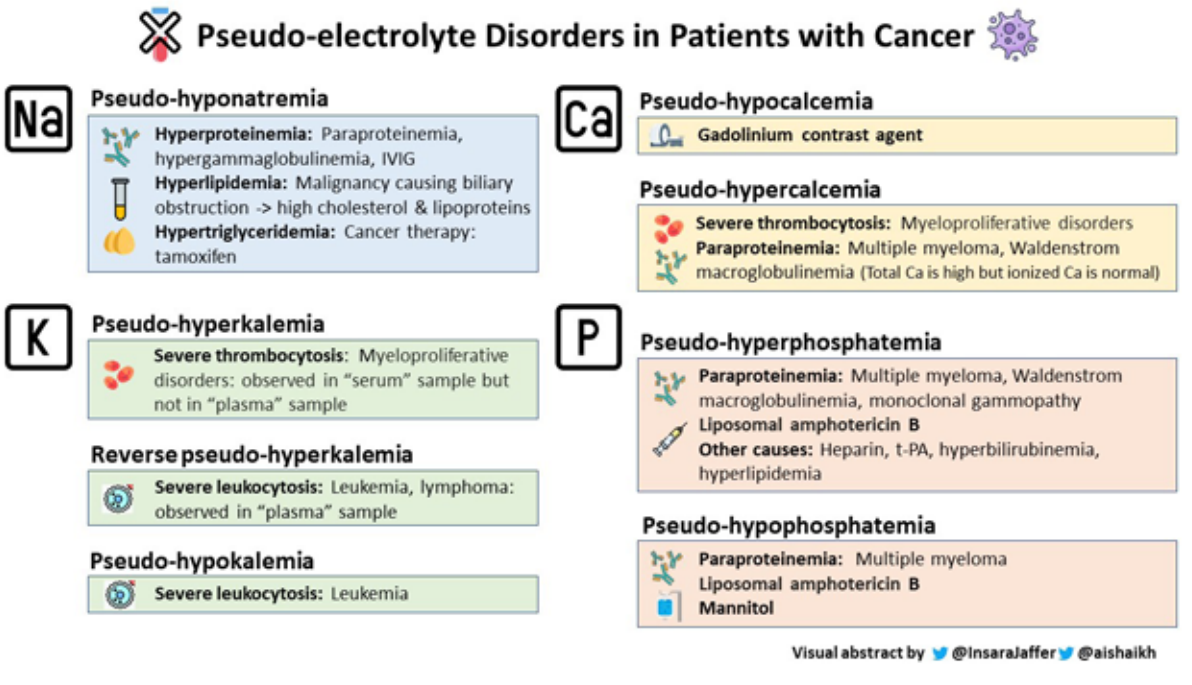


Immune Checkpoint Inhibitors and the Kidney: An Update

By Shruti Gupta and Paul E. Hanna

Immune checkpoint inhibitors (ICPis) have transformed the landscape of oncology, and they are now approved for the treatment of over one dozen different types of cancer. ICPis block immune checkpoints—the "brakes" of the immune system—and therefore activate cytotoxic T-cells to eliminate cancer cells. However, enhancement of T-cell activity also leads to autoimmune toxicities or immune-related adverse events (irAEs), which can affect multiple organ systems, including the kidneys. ICPi-associated acute kidney injury (ICPi-AKI) can have major repercussions, including discontinuation from therapy and prolonged courses of immunosuppression.

Recently, Gupta et al. (1) conducted a multicenter study of 429 cases of clinically adjudicated and/or biopsy-proven ICPi-AKI from 30 sites across 10 countries, highlighting key risk factors, clinical features, and outcomes of ICPi-AKI. Compared with contemporaneous controls who received ICPis but did not develop ICPi-AKI, patients with ICPi-AKI were more likely to have lower baseline kidney function, receive proton pump inhibitors, and have a history of extrarenal irAEs (e.g., rash or hepatitis). ICPi-AKI occurred at a median of 16 weeks (interquartile range [IQR] 8–32) after ICPi initiation. Urinalysis findings were neither sensitive nor specific for ICPi-AKI. The most common lesion on biopsy was acute tubulointerstitial nephritis (ATIN); however, other lesions were present in up to 20% of patients. The majority of patients (82%) were treated with corticosteroids, and early initiation of corticosteroids (e.g., within 3 days of ICPi-AKI) was associated with a higher odds of kidney recovery (Figure 1).

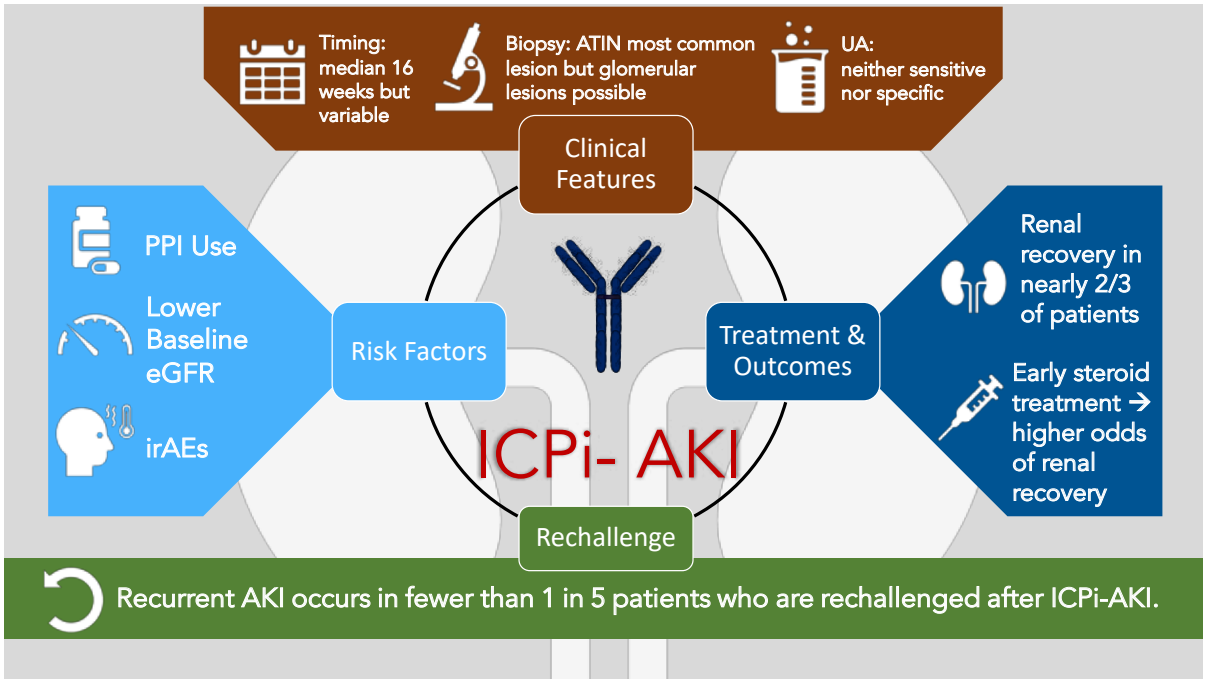
Some of the most compelling findings were outcomes after rechallenge. A total of 121 of the 429 patients (28.2%) were rechallenged with an ICPi after ICPi-AKI. Of these, only 20 (16.5%) developed recurrent ICPi-AKI, of whom 60% had kidney recovery at a median of 34 days (IQR 27–38) following recurrent ICPi-AKI. These findings collectively show that rechallenge should be strongly considered after ICPi-AKI.

There is considerable debate about the utility of a kidney biopsy in patients with ICPi-AKI. Biopsy may be relatively contraindicated in patients with a history of nephrectomy or in those for whom anticoagulation cannot be safely discontinued (2). However, biopsy should be strongly considered in patients with a plausible alternative etiology for AKI and/or atypical features (e.g., hematuria or heavy proteinuria) (2, 3). ATIN is the most common lesion on kidney biopsy, although other lesions have been reported. One meta-analysis found that pauci-immune glomerulonephritis (GN), podocytopathies, and C3 GN are the most frequently observed lesions, although immunoglobulin A nephropathy and amyloidosis have also been reported (4). The pathophysiology behind these lesions is not well understood but may be related to both T-cell hyperactivity and B-cell-driven, autoantibody-mediated disease.

In addition to AKI, ICPis are also associated with a number of electrolyte disturbances, most commonly, hyponatremia, hypokalemia, and hypercalcemia (5–7). The incidence of hyponatremia varies from 1.2% in clinical trials to 62% in real-world studies (7, 8). Risk factors for hyponatremia include use of ipilimumab, diuretics, and non-White race (7). Hyponatremia may occur in the setting of endocrinopathies, such as hypophysitis, adrenalitis, and thyroid dysfunction; however, volume shifts and the syndrome of inappropriate diuretic hormone secretion are likely more common causes. Hypokalemia may occur from gastrointestinal losses in the setting of ICPi-mediated colitis or renal losses in patients with renal tubular acidosis. Hypercalcemia has been observed in patients with elevated parathyroid hormone-related peptide, sarcoid-like granulomas, and hyperprogression of disease (9–12) (Figure 2).

Given the rapid and dramatic growth in ICPi therapy, there is considerable interest in understanding mechanisms behind ICPi-AKI and electrolyte abnormalities, as well as addressing challenges related to diagnosis and management of ICPi-AKI. Biomarkers with anatomic specificity are needed to distinguish ICPi-AKI from other causes and to identify potential therapeutic targets. Additionally, prospective studies measuring hormone levels and fractional excretion of electrolytes may help shed further light on the mechanisms behind electrolyte abnormalities. ■

Figure 1. Immune checkpoint inhibitor-associated acute kidney injury



AKI, acute kidney injury; ATIN, acute tubulointerstitial nephritis, eGFR, estimated glomerular filtration rate; ICPi-AKI, immune checkpoint inhibitor-associated AKI; irAEs, immune-related adverse events; PPI, proton pump inhibitor; UA, urinalysis.

Figure 2. Common electrolyte disorders associated with immune checkpoint inhibitors

GI, gastrointestinal; HyperCa+, hypercalcemia; HypoCa+, hypocalcemia; HypoK+, hypokalemia; HypoNa+, hyponatremia; HypoPhos−, hypophosphatemia; PTHrP, parathyroid hormone-related peptide; RTA, renal tubular acidosis; SIADH, syndrome of inappropriate anti-diuretic hormone release.

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Dr. Gupta is the president and co-founder of the American Society of Onconephrology and receives research funding from the National Institutes of Health, BTG International, and GE Healthcare. Dr. Hanna reports no conflicts of interest.

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Sickle Cell Disease and the Kidney

By Pooja Amarapurkar, Pooja Kalantri, Levard Roberts, and Jose Navarrete

Sickle cell disease and sickle cell trait are associated with several kidney abnormalities. The inner medullary environment of the kidney with low oxygen tension, hyperosmolarity, and acidemia is an ideal setup for hemoglobin polymerization and sickling. Repeated hemolysis, vaso-occlusive episodes, subsequent reperfusion injury, oxidative stress, and inflammation lead to acute and chronic kidney disease (CKD) (1, 2). The various kidney manifestations of sickle cell disease are summarized in Table 1.

Glomerular hyperfiltration and lower mean arterial pressure occur in early years of life. With advancing age, a decline in glomerular filtration rate (GFR) is noted (1–3). Approximately 60% of all patients with sickle cell disease over the age of 45 have some amount of albuminuria. There is a steeper decline in kidney function among adults with albuminuria compared with those without (4).

CKD in sickle cell disease is highly influenced by genetic factors. Coinheritance of alpha-thalassemia is associated with a reduced risk of hemolysis and protection from albuminuria (5). The presence of haplotypes of the APOL1 gene, MYH9 gene, and polymorphism in the bone morphogenic protein receptor 1B promotes albuminuria and CKD in patients with sickle cell disease (6).

The occurrence of nephrotic syndrome due to sickle cell disease is uncommon and is associated with a poor kidney outcome. Human parvovirus B19 infection is an important cause of nephrotic syndrome in this population (7). Sickle cell disease-related end stage kidney disease accounts for 0.1% of the dialysis population in the United States (8). These patients are younger and have high mortality (9). Acute kidney injury (AKI) may occur in approximately 2.3%–13.6% of patients with sickle cell disease who are admitted for vaso-occlusive episodes or acute chest syndrome. Figure 1 describes the pathophysiology of AKI in sickle cell disease (10).

Patients with sickle cell disease should be screened for proteinuria annually starting at age 10. A combination of cystatin C-creatinine-based GFR, a trend rather than an absolute value of creatinine and trend in albuminuria, is preferred to diagnose and follow kidney disease in sickle cell disease. Albuminuria >300 mg/g, decline in kidney function, nephrotic syndrome, persistent hematuria, and hypertension must prompt referral to nephrology (11, 12). Hemodialysis and peritoneal dialysis are well tolerated (13).

Increased incidence of APOL1 risk alleles, higher infection risk, blood group incompatibility, pulmonary hypertension, and inability to tolerate side effects of immunosuppressive drugs are some reasons for lower rates of transplantation in sickle cell disease. Even with these limitations, patients have significantly better outcomes after kidney transplant compared with dialysis (14).

There is no specific treatment for sickle cell disease-related kidney disease. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers remain the mainstay therapy. With patients living longer, the burden of CKD is increasing in this population. Thus, a multidisciplinary approach with hematologists and nephrologists is needed to manage these patients. At our institution, Emory University School of Medicine, we have successfully implemented a CKD clinic for sickle cell disease patients. This clinic has improved access and timeliness to nephrology care. It serves as a great platform for epidemiological, clinical, and basic science research and helps deliver comprehensive care to patients with sickle cell disease. We hope to collaborate with other centers to improve care for this vulnerable population. ■

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The authors report no conflicts of interest.

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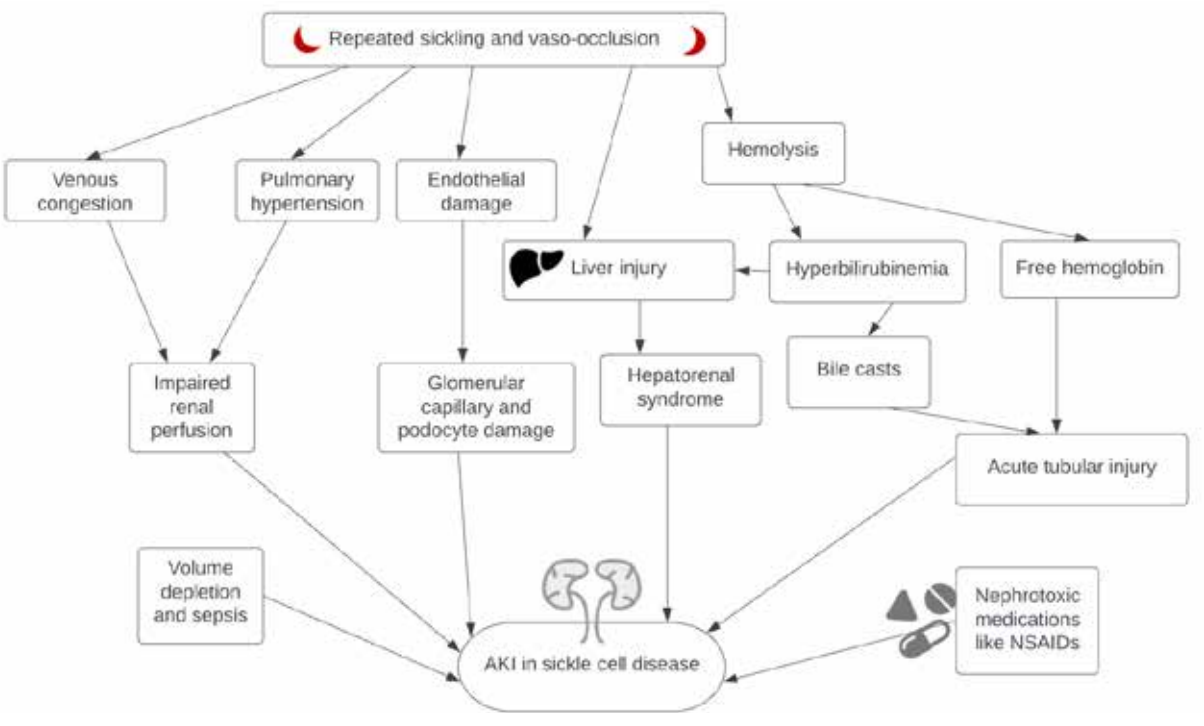
Table 1. Kidney manifestations of sickle cell disease

Glomerular hyperfiltration: Early childhood and young adults
Albuminuria
Glomerular pathology: • Focal segmental glomerulonephritis • Membranoproliferative glomerulonephritis • Thrombotic microangiopathy
Proximal tubular hyperfunction: • Increased phosphate secretion • Increased creatinine secretion
Tubular iron deposits
Hyposthenuria (decreased urinary concentration ability)
Impaired distal tubular hydrogen ion and potassium handling (hyperkalemia and metabolic acidosis)
Hematuria
Renal papillary necrosis
Renal medullary carcinoma

Figure 1. Pathophysiology of acute kidney injury in sickle cell disease



Sickle Cell Disease and the Kidney

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Overview of Onconephrology in Europe: An Essential Subspecialty with Increasing Importance

By Sheila Bermejo

Cancer is a worldwide epidemic that has increased its prevalence exponentially over the last decades. In 2020, 19.3 million new cases of cancer were diagnosed, and there were 10 million deaths from cancer worldwide (1). Cancer patients are susceptible to chemotherapy and immunotherapy treatments that can cause renal complications, such as acute kidney injury (secondary to glomerular disease, acute interstitial nephritis, or acute tubular necrosis), electrolyte disorder, proteinuria, and others (2). Additionally, a higher prevalence of cancer has been demonstrated in patients with chronic kidney disease from various types, those with a kidney transplant, and patients on kidney replacement therapy (Figure 1). Because of a lack of randomized clinical trials that test oncologic treatments in the population with renal diseases, patients with a lower glomerular filtration rate have less opportunity to receive some oncologic treatments. Thus, it is important to optimize their renal function with nephrologist intervention.

For these reasons, multidisciplinary care is important for cancer patients with diminished kidney function. Based on this idea, onconephrology was born. Onconephrology was originally considered a subspecialty that has increased in importance over the last decade, with the purpose to address accurate care of cancer patients and to diagnose and prevent complications. This increase in interest and importance of onconephrology has been evident in multiple ways (3). For example, the number of oral presentations dedicated to onconephrology topics at ASN Kidney Week has increased in the last several years. Likewise, this is also seen in Europe. During the last two European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) congresses (2020 and 2021), there has been an increase in onconephrology topics. In 2020, ERA-EDTA offered a symposium, "New immune therapies and onconephrology." In addition, a pre-congress course was dedicated to onconephrology (4). During the most recent congress in 2021 (58th ERA-EDTA Congress), there was a symposium dedicated to onconephrology with three lectures and a second symposium, entitled "AKI in special situations," in which one of the lectures was "AKI in oncology patients" (5).

The recent formation of the American Society of Onconephrology (ASON) in the United States demonstrates the advances of this subspecialty, but this type

Figure 1. The spectrum of renal diseases in cancer patients

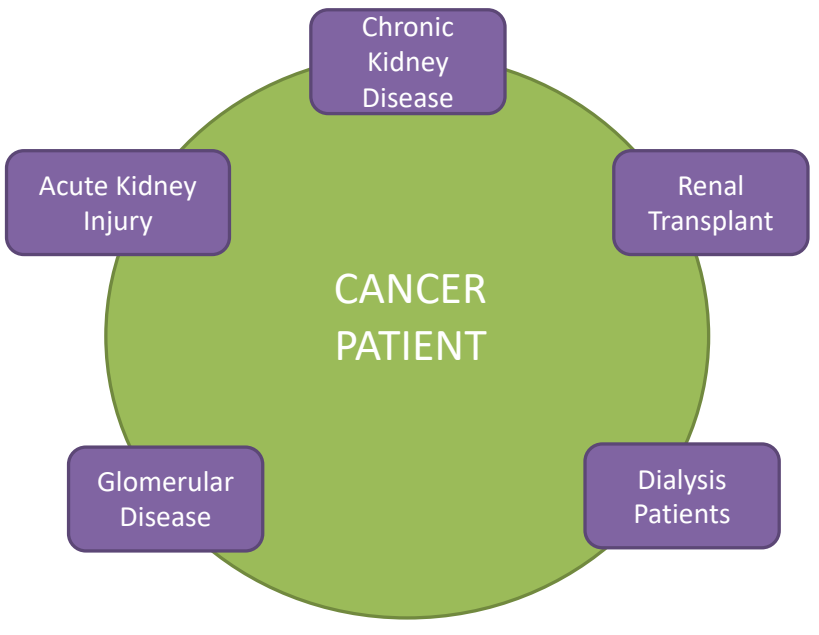
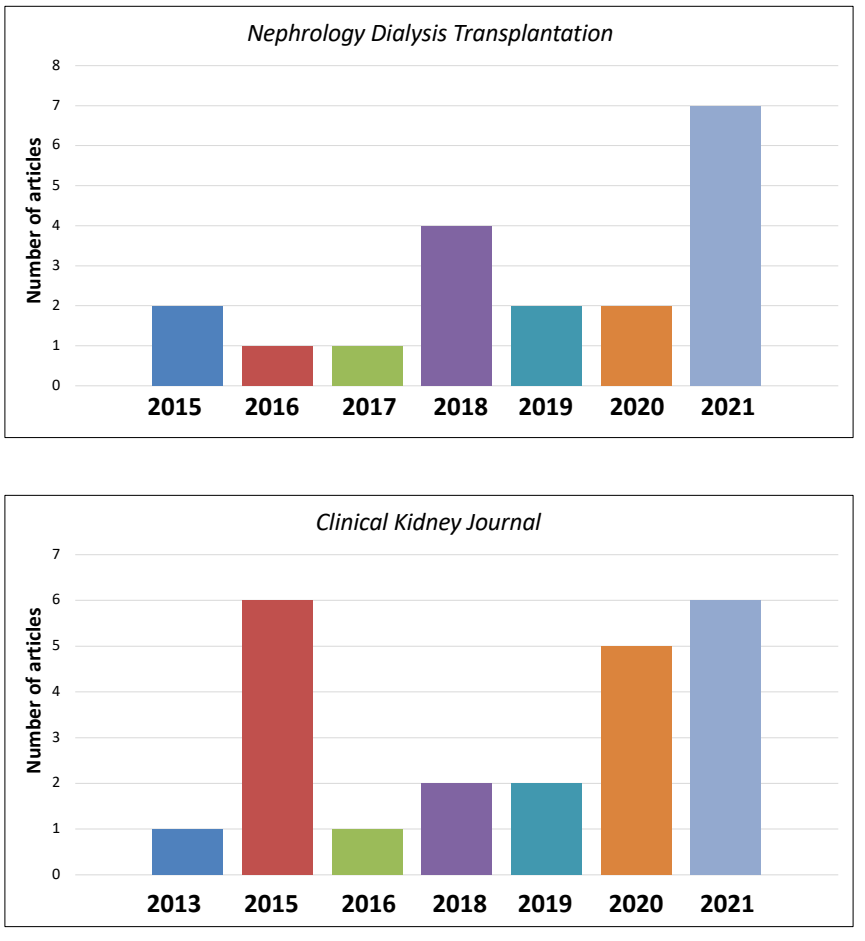


Figure 2. Distribution of onconephrology articles published in recent years in two European journals



of international society is lacking in Europe. However, this important increase in the prevalence of onconephrology is observed in the European congress and also reflected in European journals. Two major European journals, *Nephrology Dialysis Transplantation* (*NDT*) and *Clinical Kidney Journal* (*CKJ*), have published many onconephrology articles (Figure 2). In both onconephrology publications, 15 (37.5%) are reviews, 11 (27.5%) abstracts, 11 (27.5%) original articles, 5 (12.5%) editorials, 1 (2.5%) a letter, and 1 (2.5%) a meeting report.

In Spain, a working group called "Onconephrology" has been created by the Spanish Society of Nephrology. The working group holds regular meetings and multicenter collaborative projects are proposed in different hospitals with onconephrology units, as well as training courses for nephrologists in this subspecialty (6).

Recognition of the importance of onconephrology has increased recently because of the increase in the number of cancer patients with kidney impairment and the need for a multidisciplinary approach in caring for these patients. This need is reflected in the increase of onconephrology in both research and education in Europe, with an aim to optimize the care of cancer patients with kidney impairment and to improve their survival and quality of life. ■

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Performance of GFR Estimating Equations in Patients with Solid Tumors

By Paul E. Hanna and Meghan E. Sise

Important decisions about diagnosing kidney disease, managing drug dosing, and considering kidney replacement therapy rely on an accurate estimation of the glomerular filtration rate (GFR), especially in patients with cancer (1, 2). Despite its continued use, the Cockcroft-Gault equation (3), originally created to assess kidney function based on serum creatinine in 1976, has significant limitations that may be even greater in patients with cancer who have sarcopenia. To address this, Costa E Silva and colleagues (4) compared the measured GFR using chromium-51-labeled ethylenediamine tetraacetic acid (^{51}Cr-EDTA) clearance in 1200 patients with solid tumors to test six GFR estimating equations. They reported both the bias (median of the differences between measured GFR and estimated GFR) and accuracy (1 minus the percentage of GFR estimates within 30% of measured GFR in mL/min/1.73 m^2 [1–P30]) of each equation (Table 1). The 2012 Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation, using both serum creatinine and cystatin C, performed the best among all equations. Among the GFR estimating equations that used serum creatinine alone, Cockcroft-Gault and 2009 CKD-EPI had the greatest bias, and Cockcroft-Gault had the least accuracy (Table 1).

Creatinine is a byproduct of muscle breakdown that lacks both sensitivity and specificity for measuring acute kidney injury (AKI) and CKD. Because creatinine is a muscle-derived biomarker, patients with advanced malignancies, who commonly exhibit muscle wasting, have 1) overestimation of their baseline estimated GFR when relying on creatinine-based equations and 2) underestimation of severity of AKI events when relying on accumulation of creatinine (9). Attempts to overcome these limitations in patients with cancer led to the development of population-specific GFR estimating equations, such as the Martin formula (10), the Wright formula (11), and the Calvert dose-determining formula (12); yet, even these did not generalize well and are not widely used (13, 14). Cystatin C is a low molecular weight protein that is released by all nucleated cells and freely filtered by the glomerulus and is used to estimate GFR. A major limitation of cystatin C is that it can be influenced by concurrent inflammation, history of smoking, obesity independent of the GFR (15), and corticosteroid therapy (16).

In subgroup analyses, the authors showed that several patient-specific factors strongly influenced the accuracy of GFR estimation. Creatinine-based equations were much more likely to overestimate GFR in women and in those with low body mass index (BMI [<25 kg/m^2]). In these populations, the CKD-EPI 2012 equation that uses cystatin C alone was most accurate. This suggests that GFR estimation could be personalized based on patient-specific factors such as BMI and sex. The authors also demonstrate that in patients with measured GFR <60 mL/min/1.73 m^2, all equa-

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Table 1. Bias and accuracy of different GFR estimating equations

Marker, equation	Bias (mGFR – eGFR) mL/min/1.73 m^2	Accuracy (1–P30)
Cr, CG (3)	–8.1 (–9.4 to –6.7)	24.9 (22.4 to 27.3)
Cr, MDRD (5)	–4.8 (–6.0 to –3.6)	18.2 (16.0 to 20.3)
Cr, CKD-EPI (6)	–8.1 (–8.9 to –7.1)	19.1 (16.8 to 21.2)
Cr, CamGFRv2 (7)	6.1 (5.3 to 6.9)	7.2 (5.7 to 8.7)
Cys, CKD-EPI (8)	4.6 (3.7 to 5.5)	12.3 (10.3 to 14.3)
Cr-Cys, CKD-EPI (8)	–2.0 (–2.6 to –1.1)	7.8 (6.3 to 9.4)

Bias and accuracy of different GFR estimating equations (eGFR) when compared with measured GFR (mGFR); data and 95% confidence intervals are presented. Cr, creatinine; Cys, cystatin C; CG, Cockcroft-Gault; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; CamGFRv2, Cambridge University Hospitals National Health Service (NHS) Foundation Trust; P30, proportion of estimates within 30% of mGFR. Adapted from Costa E Silva et al. (4).

Performance of 2012 CKD-EPI equation vs. Cockcroft-Gault equation in adults with solid tumors

KidneyNews

PROSPECTIVE

April 2015 to September 2017

58.8 years mean age

78.4 mL/min/1.73 m^2 measured GFR

n = 1200

Equation (filtration marker)	Bias (median), mL/min/1.73 m^2	Accuracy (1–P30), %
Cockcroft-Gault (CG) ($eGFR_{Cr}$)	–8.1 (–9.4 to –6.7)	24.9 (22.4 to 27.3)
CKD-EPI ($eGFR_{Cr}$)	–8.1 (–8.9 to –7.1)	19.1 (16.8 to 21.2)
CKD-EPI ($eGFR_{Cr\text{-}Cys}$)	–2.0 (–2.6 to –1.1)	7.8 (6.3 to 9.4)

Bias was defined as the median of the differences between mGFR and eGFR, whereas accuracy was defined as the percentage of estimates that differed by more than 30% from the measured GFR (1–P30).

Conclusions: The CG equation should not be preferred over the CKD-EPI equation, and $eGFR_{Cr\text{-}Cys}$ can be used as a confirmatory test in adults with solid tumors. Hence, a major policy implication would be to adopt general practice guideline-recommended methods for GFR evaluation in oncology practice and clinical trials.

Costa E Silva VT, et al. A prospective cross-sectional study estimated glomerular filtration rate from creatinine and cystatin C in adults with solid tumors. *Kidney Int* 2022; 101:607–614. doi: 10.1016/j.kint.2021.12.010

Visual Graphic by Edgar Lerma, MD, FASN

Performance of GFR Estimating Equations in Patients with Solid Tumors

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tions overestimated GFR. Although the new 2021 CKD-EPI race-free equation that uses both creatinine and cystatin C (17) was not used in this study, it would be reasonable to use as a new standard of care.

This serves as a call to action to change practice and personalize our approach to estimating GFR, especially in this vulnerable population of patients with cancer where treatment decisions hinge on accurate assessment of kidney function and in whom the rate of AKI is so high (18). Inaccurate assessments of kidney function could potentially preclude patients from lifesaving treatments, expose them to toxic drug levels, and delay diagnosis and treatment of AKI. Future studies are needed to determine the performance of the 2021 equations and determine the best and most cost-effective strategies for implementation of these important findings into routine cancer care. ■

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The authors report no conflicts of interest.

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Acute Kidney Injury and Risk of Nephropathy in Children with Diabetes

By Leena Mamilly and Mahmoud Kallash

Diabetic nephropathy is the leading cause of chronic kidney disease (CKD) in the United States and one of the most common complications of diabetes mellitus, increasing the risk of cardiovascular disease in individuals with diabetes. Risk factors for developing diabetes-related kidney disease include poor glycemic control, hypertension, older age, dyslipidemia, and genetic factors, among others (1). Jia Xin Huang, MD, et al. (2) recently published an article about the role of acute kidney injury (AKI) and diabetic ketoacidosis (DKA) in the development of proteinuria in children with diabetes.

The study is a well-designed retrospective chart review of 2345 children with type 1 diabetes mellitus (T1DM), cared for in two academic tertiary care children's hospitals in the United States. Children were included if they were diagnosed with T1DM for at least 1 year and had at least one urine microalbumin measurement. The study reports DKA episodes in 41% of the cohort with 560 unique episodes of AKI. A total of 183 children (7.8%) developed microalbuminuria. Similar to previous studies (3), older age at the time of diagnosis of T1DM and higher mean hemoglobin A1c were associated with a higher hazard rate for development of microalbuminuria. Uniquely, the study found that each AKI induced by DKA increased the hazard rate of developing microalbuminuria by a ratio of 1.56 (95% confidence interval, 1.3–1.87). Furthermore, the hazard rate of microalbuminuria increased with the number of AKI-associated DKA episodes, increasing by >3-fold for patients with two AKI episodes and >5-fold for those with four or more AKI episodes. Although the hazard rate increased for moderate or severe DKA episodes, as well as more severe AKI, DKA episodes without AKI were not associated with an increased hazard rate of microalbuminuria.

Despite what is known about AKI episodes increasing the risk of kidney function decline in children with CKD (4, 5), there have been no studies that addressed this matter in children with T1DM. Other strong points about this study are that it included a relatively large number of children with T1DM and a long duration of follow-up (mean of 6.5 ± 3 years), which allow for detection of early microalbuminuria. In the statistical analysis, the authors distinguished between possible and confirmed microalbuminuria, with the latter being based on two abnormal morning urine samples or abnormal 24-hour urine albumin. Such distinction is essential in distinguishing abnormal random urine albumin levels that later normalize on further testing and do not represent true positive screens.

The study had some limitations, primarily related to the retrospective study design. Classification of AKI severity assumed a normal baseline kidney function in all children before the AKI episode. Height measurements used in the Schwartz formula were also estimated in some of the calculations. Furthermore, some DKA episodes might have been missed due to their occurrence in institutions outside of the centers where the study was held. Another limitation to the study was the lack of differentiation between prerenal etiology (as often seen in DKA-induced AKI) and intrinsic AKI. In such cases, checking specific urinary biomarkers (such as neutrophil gelatinase-associated lipocalin) may help differentiate between the causes.

In current clinical practice, urine albumin excretion is used as the primary screening method to detect the onset of diabetic nephropathy. However, several other biochemical markers have been identified that represent different mechanistic factors in diabetes-related kidney disease. Some such markers have been shown to appear much earlier than microalbuminuria (6, 7). With this consideration in mind and combined with the fact that DKA episodes without AKI were not associated with higher risk for microalbuminuria, it should be studied further whether it is the background of diabetes-related kidney disease that increases the risk of AKI in some children in the context of DKA.

AKI has been recognized as a predictor of CKD in both adults and children (8). Although the pathophysiology of this progression remains unclear, it is suspected that AKI in the context of DKA can have the same consequence in individuals with diabetes. Knowing that kidney damage in diabetes is a process that may start as early as the first few years after diagnosis (9), the inflammation, oxidative stress, hypoperfusion, and endothelial dysfunction associated with DKA and/or AKI episodes might accelerate the progression of diabetes-related kidney damage. The study discussed highlights and confirms this association between AKI and microalbuminuria as a sign of diabetic nephropathy. Findings from this study are of substantial importance and are expected to lead to further research exploring the progression of diabetes-related kidney disease and its relation to acute diabetes complications. ■

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The authors report no conflicts of interest.

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Findings

In Women with ADPKD, Aneurysm Risk Increases after Age 50

An analysis of a large cohort of patients with autosomal-dominant polycystic kidney disease (ADPKD) adds new knowledge about risk factors for intracranial aneurysm (IA), including an increase in IA risk for women after menopause, according to a pre-proof paper in *Nephrology Dialysis Transplantation*.

The cross-sectional, population-based study included 2449 patients with ADPKD (median age, 55 years) from 26 nephrology centers in western France. On genetic analysis in 2386 patients, 67.6% had *PKD1* pathogenic variants, and 19.0% had *PKD2* pathogenic variants. The researchers analyzed the frequency of diagnosis of ruptured and unruptured IA, along with risk factors for this vascular complication.

At the time of enrollment, 4.65% of patients had previously been diagnosed with IA, ruptured or unruptured. Nearly one-half of patients had a positive family history of IAs. Aneurysms occurred at all stages of chronic kidney disease; most were small, saccular, and located in the anterior circulation. More than one-fourth of patients (26.3%) had multiple IAs.

Cumulative probability of IA diagnosis increased from 1.3% at age 40 to 3.9% at age 50, to 6.2% at age 60, and to 8.1% at age 70. Probabilities of ruptured aneurysm were 0.9%, 1.8%, 2.6%, and 3.2%, respectively.

In patients younger than 50 years old, IA risk was similar for men and women. After 50, however, IA risk was substantially higher in women: up to 10.8% compared with 5.4% in men. The frequency of IA diagnosis was more than twice as high in patients with *PKD2* pathogenic variants compared with *PKD1* variants. In addition to female sex and *PKD1* genotype, hypertension before age 35 and smoking were independent risk factors for diagnosed IA.

Patients with ADPKD are at high risk of IA. Risk factors for IA have important implications for screening using magnetic resonance imaging. In previous reports, a personal or family history has been the main risk factor for IA.

The new finding demonstrates the "complex and multifactorial" determinants of IAs in a large population of patients with ADPKD receiving real-life clinical care. Women appear more likely to be diagnosed with ruptured or unruptured IAs, particularly after age 50. The investigators note, "This parallels observations made in the non-ADPKD population and suggests a possible protective role of estrogens" [Lefèvre S, et al. Diagnosis and risk factors for intracranial aneurysms in autosomal polycystic kidney disease: A cross-sectional study from the Genkyst cohort. *Nephrol Dial Transpl*, published online ahead of print February 2, 2022. doi: 10.1093/ndt/gfac027; https://academic.oup.com/ndt/advance-article/doi/10.1093/ndt/gfac027/6520449?login=false]. ■

The Missing Link between Chronic Kidney Disease and Peripheral Arterial Disease

By Chelsea C. Estrada and Sandeep K. Mallipattu

Peripheral arterial disease (PAD) is three times as prevalent in patients with chronic kidney disease (CKD) compared with their non-CKD counterparts (1). This increased susceptibility has been attributed to the uremic milieu; however, specific mechanisms remain unknown. Recently, in the *Journal of Clinical Investigation*, Arinze and colleagues (2) shed new light on the detrimental impact of dietary and gut-converted, tryptophan-based uremic toxins (indoxyl sulfate and its metabolites) on neovascularization in PAD.

In a series of elegant studies, the investigators demonstrated that serum from patients with uremia, as well as indoxyl sulfate alone, induced a dose-dependent reduction in Wnt-β-catenin signaling in endothelial cells, which was exacerbated under hypoxic conditions. Interestingly, this effect was observed at levels of indoxyl sulfate consistent with that in patients with early-stage CKD. With the use of zebrafish and mouse models, the researchers demonstrated that this loss in Wnt-β-catenin signaling translated to decreased angiogenesis, capillary density, and vascular perfusion. The authors also identified that the reduction in active β-catenin was dependent on aryl hydrocarbon receptor activation. Importantly, in a mouse model of CKD and PAD, aryl hydrocarbon receptor inhibition restored Wnt-β-catenin signaling to that of non-uremic levels and restored neovascularization. The authors corroborated these findings in plasma from patients with CKD and PAD, where levels of indoxyl sulfate and its metabolites were predictive of subsequent adverse limb events in patients followed for up to 2 years.

Significant questions raised by these studies include the possibility of inhibiting aryl hydrocarbon receptor signaling as a therapeutic target in PAD, with or without CKD. Many of the same authors also previously demonstrated that aryl hydrocarbon receptor inhibition decreased the time to occlusion in a pro-thrombotic CKD murine model (3). Aryl hydrocarbon receptor inhibitors are currently in clinical trials for solid tumors and have been shown to reduce tumor growth when used in combination with immune checkpoint inhibition (4).

With the exceedingly high incidence of cardiovascular mortality in patients with CKD and kidney failure on dialysis, the role of aryl hydrocarbon receptor pathway antagonism in coronary circulation ischemia might also serve as another important avenue for future investigation. This study also resurfaces important questions that have been raised by nephrologists for decades: How can we optimize the dialysis prescription to enhance removal of these protein-bound tryptophan derivatives? Does modulating the dietary regimen to reduce the accumulation of indoxyl sulfate levels improve clinical outcomes? Taken together, Arinze et al. (2) highlight the critical need for randomized clinical trials to assess the therapeutic impact of targeting this pathway in patients with CKD and kidney failure on dialysis. ■

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President's Budget: Status Quo for Kidney Health

In April 2022, the Office of Management and Budget released the annual President's Budget for fiscal year (FY) 2023. The President's Budget is a non-binding request to Congress that describes the priorities of the current administration. In the words of President Biden, "Don't tell me what you value. Show me your budget, and I will tell you what you value."

The priorities of the current administration are clear. For the Department of Health and Human Services, the budget prioritizes "tackling the COVID-19 pandemic, expanding access to care, addressing health disparities, strengthening behavioral health, and promoting the well-being of children, families, and seniors." The focus on these priorities can be seen throughout the budget, at times even at the expense of existing programs. Below are several line items and issues that affect kidney health professionals.

COVID-19

The FY 2023 budget includes an effort totaling $81.7 billion in mandatory funding to fight COVID-19 and to respond to future pandemics. Available over 5 years, this funding is budgeted across the Office of the Assistant Secretary for Preparedness and Response, Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and Food and Drug Administration. This funding is in addition to a now-stalled $10 billion in COVID-19 funding currently under consideration by Congress that would be used to purchase and develop COVID-19 tests, vaccines, and therapeutics.

Kidney Innovation Accelerator (KidneyX)

KidneyX is slated to receive $5 million in FY 2023, the same total that it received in FY 2022 congressional appropriations. ASN and congressional allies are calling on the Biden administration to support a full $25 million for KidneyX. This funding is essential to continue accelerating innovation in kidney health by supporting additional innovators through the Artificial Kidney Prize, which seeks to promote the integration and advancement of prototype artificial kidneys, and provide prizes in other essential areas, such as the diagnosis and prevention of kidney diseases. Recent advancements in regenerative medicine and xenotransplantation demonstrate the promise and importance of fostering responsible innovation in kidney health.

NIH

The FY 2023 budget includes $63 billion for the NIH, a $16 billion (34%) increase in new and mandatory funding over FY 2022 funding levels. This budget includes more than $12 billion of new COVID-19 funding (referenced above) that would support NIH research and development of vaccines, diagnostics, and therapeutics against high-priority viral families; support biosafety and biosecurity; and expand laboratory capacity and clinical trial infrastructure.

The budget also calls for the proposed Advanced Research Projects Agency for Health (ARPA-H). Modeled after the groundbreaking Defense Advanced Research Projects Agency, which supported the development of products ranging from the internet to mRNA vaccines, ARPA-H holds promise to revolutionize health care research and development and may serve as a viable new vehicle to advance the state of kidney care.

The FY 2023 budget calls for ARPA-H to be housed within the NIH to promote medical and scientific innovation. Many policymakers and stakeholders in the scientific community have raised concerns of housing ARPA-H within the NIH, claiming that its location will limit the new program's independence and ability to take calculated risks that push the envelope and help fund generational advances versus the incremental, basic science approach that has been perfected by the NIH.

In addition, the $5 billion in funding proposed for ARPA-H would—combined with the new COVID-19 funding—total $2 billion more than the total increase proposed for the NIH, meaning funding for the project would need to come out of the budgets of the 17 investigative centers at the NIH. This proposal has deeply worried advocates for medical research, and ASN has joined the call for ARPA-H to be supported by funding in addition to the regular increases for the NIH.

This ARPA-H budget adjustment will be felt by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). NIDDK is budgeted to receive a total of only $2.34 billion, a $2 million or .09% increase over FY 2022 funding levels. ASN and the entire kidney community remain united in advocating that the final appropriations for NIDDK are higher than what the FY 2023 budget presents. During Kidney Health Advocacy Day, ASN members advocated for a $632 million increase for NIDDK to keep pace with medical inflation and provide dedicated COVID-19 funding. To date, NIDDK has not received any dedicated funding to study COVID-19; thus, this research may come at the expense of other critical kidney health research projects.

Finally, the FY 2023 budget also provides an increase of $350 million to enhance health disparities and inequities research, including a $210 million increase for the National Institute on Minority Health and Health Disparities.

Agency for Healthcare Research and Quality (AHRQ)

The FY 2023 budget outlines $376 million for the AHRQ, with $34 million specifically for research on health costs, quality, and outcomes. This is a $38 million increase over FY 2022 funding levels.

AHRQ provides scientific and administrative support for the U.S. Preventive Services Task Force (USPSTF), which is budgeted for $12 million in FY 2023. This is the same total that USPSTF received in FY 2022 congressional appropriations, and the budget commits that the funding will be used to conduct evidence reviews and develop approximately 8–12 screening recommendations in FY 2023. At the urging of ASN and other organizations within the kidney community, USPSTF has added Screening for Chronic Kidney Disease to the list of preventive services topics under active consideration for one of the 8–12 recommendations made in 2023.

Centers for Medicare & Medicaid Services (CMS)

The FY 2023 budget estimates $1.4 trillion in mandatory and discretionary spending for the CMS. This is a $53 billion increase over FY 2022 funding levels. Specifically, the FY 2023 budget invests $35 million in a new initiative to systematically identify and resolve barriers to equity in each CMS program through research, data collection and analysis, stakeholder engagement, building upon rural health-equity efforts, and technical assistance.

The FY 2023 budget also outlines several legislative proposals for consideration by Congress, including:

- beginning Physician Fee Schedule Conversion Factor updates in calendar year 2025 instead of 2026 as planned,
- providing Medicare coverage and reimbursement to community health workers acting under Medicare's Physician Fee Schedule for select care management services, effective in calendar year 2024, and
- allowing CMS to certify new entities as Organ Procurement Organizations (OPOs) while weakening oversight of OPOs by allowing CMS to recertify certain OPOs that do not meet the criteria—recently put in place at the urging of ASN and other stakeholders—for recertification based on outcome measure performance.

Congress has been increasing oversight of OPOs, including establishing objective and verifiable methods to measure their performance. Concerns still remain about how OPOs serve their communities, especially Americans of Black race, and it is essential that Congress and the administration have the tools to continue to ensure accountability in this important part of the transplant system and not weaken oversight by allowing failing OPOs to be recertified.

The FY 2023 budget reiterates the administration's support for the End-Stage Renal Disease Treatment Choices (ETC) model, which runs from January 2021 to June 2027. The budget highlights the October 2021 changes to the ETC model that aim to encourage dialysis facilities and health care providers to decrease disparities in the rates of home dialysis and kidney transplantation among patients with lower socioeconomic status. Fittingly, the budget notes that the ETC model was the first payment model to address health equity.

CDC

The CDC's Chronic Disease Prevention and Health Promotion program is budgeted for $1.6 billion in FY 2023. This is a $274 million increase over FY 2022-enacted levels. This program helps people and communities prevent chronic diseases, including kidney diseases, and promotes health and wellness for all. ASN will continue to advocate with kidney stakeholder organizations that no less than $15 million of this line item is used to promote kidney disease awareness, surveillance, and disease prevention.

Health Resources and Services Administration (HRSA)

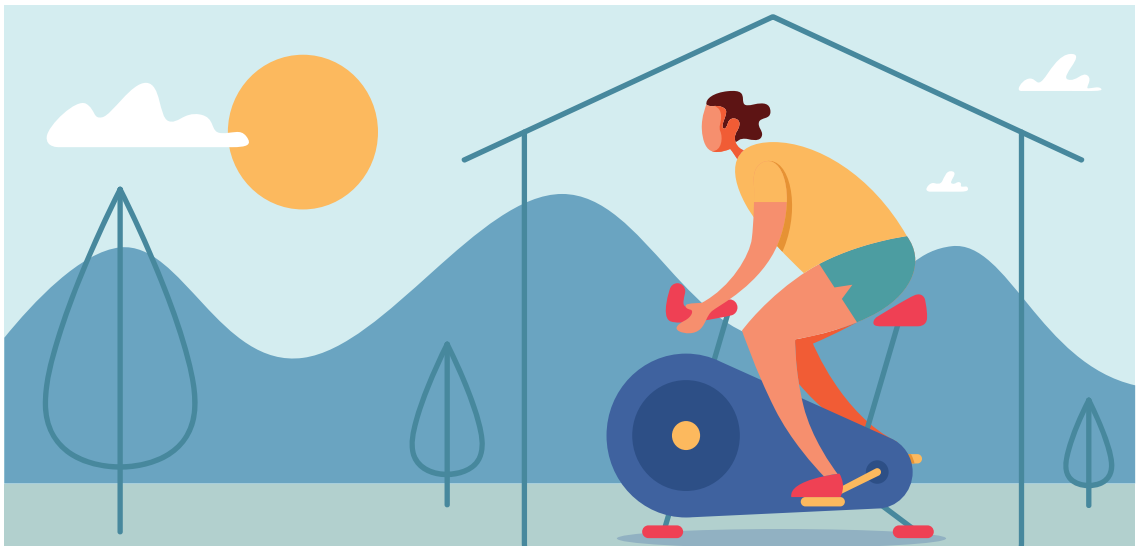
The HRSA includes several programs that support kidney health, including programs to support the health workforce, telehealth, and transplantation. Funding for these programs is mixed in the FY 2023 budget. All HRSA workforce programs are slated to receive $2.1 billion, an increase of $324 million, and the budget provides $133 million, an increase of $15 million, to expand the diversity of the health professions workforce, although the specific allocation that may be used to support kidney health professionals is unstated. In addition, the budget includes $44 million for a new Office for the Advancement of Telehealth, an essential program, as Congress determines which expanded telehealth flexibilities, as part of the COVID-19 Public Health Emergency, to retain.

However, the budget also proposes decreasing the funding for organ transplantation efforts, proposing a $1 million decrease for a total of $29 million. Facing a nearly 100,000-person waitlist for a transplant, people with kidney failure must have increased access to transplantation. Unified federal oversight of the transplant system, as proposed by many stakeholders in the kidney health community, would help ensure this important therapy is prioritized across the federal government, including in future budgets.

Although the Biden administration's attention to health equity and COVID-19 throughout the FY 2023 budget is commendable, the budget maintains the status quo of kidney health programs and does not substantially propose increasing investment on behalf of this critical population. Ultimately, Congress, with input from advocacy organizations such as ASN, will decide how closely to follow this budget. ASN will continue to fight for increased investment in the health of the 37 million Americans living with kidney diseases and to create a world without kidney diseases. ■

Exercise Therapy Enhances Exercise Capacity and Cardiorespiratory Fitness in Patients with CKD

By Patrick C. Ahearn and Xingxing S. Cheng



Chronic kidney disease (CKD) is associated with physical function decline and worsening comorbidity burden. A recent study published in the *Journal of the American Society of Nephrology* (1) reports findings from the LANDMARK III study, a years-long, longitudinal randomized study of a multi-disciplinary, clinic-based and lifestyle intervention for Australian patients with CKD stages 3a–4. The intensive intervention required a treatment team of nurse practitioners, exercise physiologists, dieticians, diabetes educators, psychologists, and nephrologists. Risk factors addressed included blood pressure, weight, and cardiorespiratory fitness. The 81 intervention-group patients attended 4 weeks of behavior and lifestyle intervention and 8 weeks of center-based supervised exercise, followed by interval review for ongoing adherence (scheduled telephone calls at least once a month with gym-refresher sessions as needed). Over the 3-year follow-up, 16% of patients dropped out each year due to death, dialysis initiation, patient choice, or funding cessation.

This publication focuses on the trial's secondary outcomes, including physical activity levels, cardiorespiratory fitness (peak oxygen consumption [VO_2]), exercise capacity (peak metabolic equivalent and 6-minute walk distance), and neuromuscular fitness. Physical activity level improved markedly in the intervention arm: 63% met recommended guidelines for physical activity compared with 29% at baseline; in contrast, those in the usual care group who met the target decreased by 8%. Cardiorespiratory fitness and exercise capacity improved in the intervention group compared with the control group at 1 year, and the difference persisted in years 2 and 3. Similar effects, albeit less marked, were on neuromuscular strength. Measures of body composition (body mass index and waist circumference) improved in the intervention arm, but neither blood pressure nor biochemical markers (creatinine, glucose, or lipid) differed between the groups.

Compared with other studies on exercise interventions in patients with CKD (2–4), this study is notable for the intensity of its intervention, long follow-up, and comprehensiveness of its outcomes. The resulting improvements are impressive, may potentially improve hard outcomes such as hospitalization and mortality, and serve as a proof-of-concept for the efficacy of exercise interventions. However, many medical homes that care for CKD patients will likely face steep barriers to implementation of such broad and intensive intervention. Interdisciplinary relationships are often disincentivized under current reimbursement structures. Furthermore, practices serving underserved communities may have difficulty recruiting qualified practitioners regardless of incentives. Patients may also lack the resources to attend such intensive programs, with low uptake and high drop-out even if the programs were in place. CKD providers should take heart that progress against physical decline is possible, while planning for the challenging path toward widespread practice change. ■

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The authors report no conflicts of interest.

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