ASN American Society of Nephrology

KidneyNews

January 2023 | Vol. 15, Number 1

Nephrology Rapidly Transitioning to Race-Free Kidney Function Estimates Despite Hurdles

By Bridget M. Kuehn

Approximately 70% of laboratories using the Epic electronic health records system had implemented a recommendation to use race-free kidney function estimates as of late 2022, according to Paul Palevsky, MD, past president of the National Kidney Foundation (NKF) and professor at the University of Pittsburgh, PA.

The recommendation to use the race-free estimates was issued by the joint NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Diseases in September 2021.

"That is a remarkable uptake in a year," said Palevsky during a 2022 Kidney Week session titled "Implementing the Race-Free eGFR Equations in Clinical Practice: Where Are We Now?" He noted that two of the largest commercial laboratories, Labcorp and Quest Diagnostics, made the switch, as did the Veterans Affairs Health System.

The session highlighted rapid progress toward implementation of the NKF-ASN task force's recommendations despite ongoing challenges (1). Task force Co-Chairs Neil Powe, MD, MPH, and Cynthia Delgado, MD, both professors at the University of California, San Francisco, moderated the session. As part of its 2021 report, the task force recommended immediate implementation of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation refit without a race adjustment, greater use of cystatin C to measure glomerular filtration rates (GFRs), and more research on GFR and health disparities.

"The underlying reason for the task force recommendation was the recognition that the use of race in clinical algorithms is problematic and inappropriate—race is a social and not a biological construct," Palevsky explained. "When assessing race in clinical algorithms, we risk accepting health inequities as immutable facts rather than injustices driven by social factors."

Medication and transplant

The recommendations have immediate implications in nephrology for both medication dosing and transplant evaluations.

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Value-Based Payment Models Aim to Boost Patient-Centered Care

By Bridget M. Kuehn

It takes a multidisciplinary team, including a nurse coordinator, psychologist, and pharmacist, to successfully run the Kidney Care First (KCF) program at The University of Alabama at Birmingham (UAB). The program's lead nephrologist, Gaurav Jain, MD, a professor and associate division director of nephrology at UAB, described his experience during a Kidney Week 2022 session entitled, "Value-Based Payment Models Generating New Approaches to Kidney Disease Care." Jain and his colleagues chose to join the Centers for Medicare & Medicaid Services' (CMS') KCF value-based payment model (1) because they hoped it could decrease the cost of care and help boost patient transplant rates. Although assessing such outcomes will take more time, Jain said the program has already been rewarding and allowed him to access additional patient care resources. "It's a small program, but it gives me a lot of joy," he said. "It'll definitely make patients' lives better."

The KCF program and the Comprehensive Kidney Care Contracting (CKCC) options are part of the latest evolution of value-based payment models for kidney care, along with the mandatory ESRD Treatment Choices (ETC) model. CMS designed the programs to incentivize nephrology practices to improve care for patients with late-stage chronic kidney disease (CKD) or kidney failure, also known as end stage kidney disease (ESKD). Panelists

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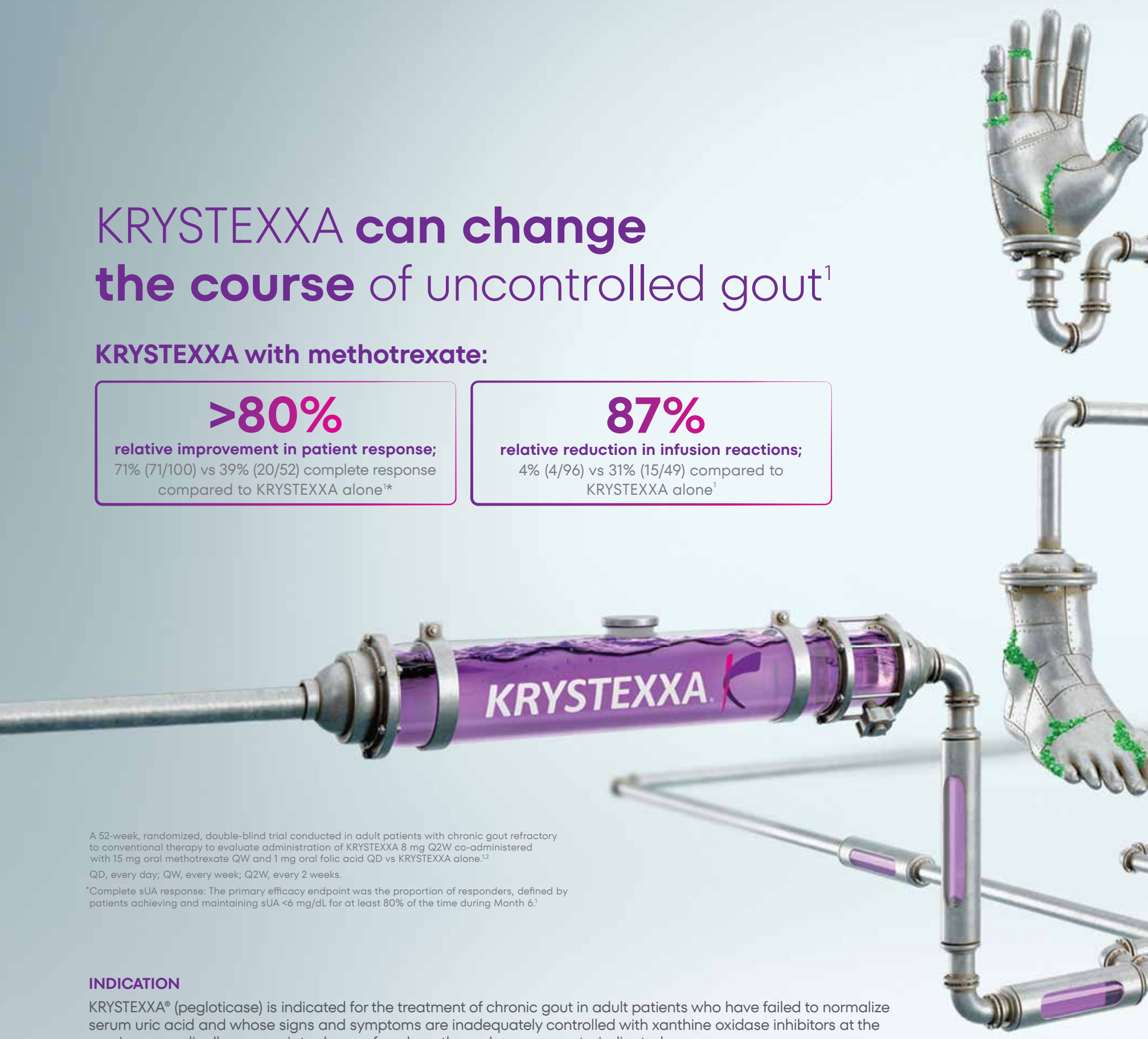
Inside

KRYSTEXXA **can change the course** of uncontrolled gout[1]



KRYSTEXXA with methotrexate:

>80%
relative improvement in patient response;
71% (71/100) vs 39% (20/52) complete response compared to KRYSTEXXA alone[1]*

87%
relative reduction in infusion reactions;
4% (4/96) vs 31% (15/49) compared to KRYSTEXXA alone[1]

A 52-week, randomized, double-blind trial conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg Q2W co-administered with 15 mg oral methotrexate QW and 1 mg oral folic acid QD vs KRYSTEXXA alone.[1,2]

QD, every day; QW, every week; Q2W, every 2 weeks.

*Complete sUA response: The primary efficacy endpoint was the proportion of responders, defined by patients achieving and maintaining sUA <6 mg/dL for at least 80% of the time during Month 6.[1]

INDICATION

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.

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

IMPORTANT SAFETY 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. Delayed hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Premedicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue 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 glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting KRYSTEXXA. Hemolysis and methemoglobinemia have been reported with KRYSTEXXA in patients with G6PD deficiency. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

CONTRAINDICATIONS:

- In patients with G6PD deficiency.
- In patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components.

Dissolve years of urate deposition[3]
ChangeTheCourse.com

WARNINGS AND PRECAUTIONS

Gout Flares: An increase in gout flares is frequently observed upon initiation of anti-hyperuricemic therapy, including KRYSTEXXA. 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 formally studied in patients with congestive heart failure, but some patients in the pre-marketing placebo-controlled clinical trials experienced exacerbation. Exercise caution in patients who have congestive heart failure and monitor patients closely following infusion.

ADVERSE REACTIONS

The most commonly reported adverse reactions (≥5%) are:

KRYSTEXXA co-administration with methotrexate trial:
KRYSTEXXA with methotrexate: gout flares, arthralgia, COVID-19, nausea, and fatigue; KRYSTEXXA alone: gout flares, arthralgia, COVID-19, nausea, fatigue, infusion reaction, pain in extremity, hypertension, and vomiting.

KRYSTEXXA pre-marketing placebo-controlled trials:
gout flares, infusion reactions, nausea, contusion or ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting.

Please see Brief Summary of Prescribing Information for KRYSTEXXA on following page.

References: 1. KRYSTEXXA (pegloticase) [prescribing information] Horizon. **2.** Botson J, et al. *J Clin Rheumatol*. 2022;28:e129-e134. **3.** Data on File. Horizon, March 2022.

HORIZON.

KRYSTEXXA®
pegloticase

KRYSTEXXA® (pegloticase) injection, for intravenous use

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

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

See full prescribing information for complete boxed warning.

- **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 hypersensitivity reactions have also been reported.**
- **KRYSTEXXA should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions.**
- **Pre-medicate with antihistamines and corticosteroids and closely monitor for anaphylaxis for an appropriate period of time after administration of KRYSTEXXA.**
- **Monitor serum uric acid levels prior to each infusion and discontinue 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. KRYSTEXXA is contraindicated in patients with G6PD deficiency.**

INDICATIONS AND USAGE

KRYSTEXXA® (pegloticase) is 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.

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

CONTRAINDICATIONS

KRYSTEXXA is contraindicated in:

- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency *[see Warnings and Precautions]*
- Patients with history of serious hypersensitivity reactions, including anaphylaxis, to KRYSTEXXA or any of its components

WARNINGS AND PRECAUTIONS

Anaphylaxis

In a 52-week controlled trial, which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of anaphylaxis. One patient randomized to the group treated with KRYSTEXXA co-administered with methotrexate (1%) experienced anaphylaxis during the first infusion and no patients experienced anaphylaxis in the group treated with KRYSTEXXA alone *[see Adverse Reactions]*.

During pre-marketing clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. 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, nausea or vomiting. 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 discontinue 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

In a 52-week, controlled trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone *[see Adverse Reactions]*, patients were pre-treated with standardized infusion reaction prophylaxis and were discontinued from treatment with KRYSTEXXA if serum uric acid levels increased to above 6 mg/dL at 2 consecutive visits after the initiation of KRYSTEXXA therapy to reduce the risk of infusion reactions. Infusion reactions were reported in 4% of patients in the KRYSTEXXA co-administered with methotrexate group compared to 31% of patients treated with KRYSTEXXA alone experienced infusion reactions *[see Adverse Reactions]*. In both treatment groups, the majority of infusion reactions occurred at the first or second KRYSTEXXA infusion and during the time of infusion. Manifestations of these infusion reactions were similar to that observed in the pre-marketing trials.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, KRYSTEXXA was not discontinued following 2 consecutive serum uric acid levels above 6 mg/dL. 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 discontinue 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

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, patients were administered gout flare prophylaxis similar to that in the pre-marketing, placebo-controlled trials. In this trial, the percentages of patients with any flare for the first 3 months were 66% and 69% for the group treated with KRYSTEXXA co-administered with methotrexate and the group treated with KRYSTEXXA alone, respectively. In the group treated with KRYSTEXXA co-administered with methotrexate, the percentages of patients with any flare for the subsequent 3 month increments of treatment were 27% during Month 6, 8% during Month 9 and 9% during Month 12. In the group treated with KRYSTEXXA alone, the percentages of patients with any flare were 14% during Month 6, 9% during Month 9 and 21% during Month 12.

During pre-marketing, 24-week controlled clinical trials with KRYSTEXXA alone, 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 *[see Dosage and Administration]*.

Congestive Heart Failure

KRYSTEXXA has not been formally studied in patients with congestive heart failure, but some patients in the pre-marketing, 24-week controlled clinical trials experienced exacerbation of congestive heart failure. 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 *[see Adverse Reactions]*.

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

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.

Co-administration with Methotrexate

A 52-week, randomized, double-blind trial was conducted in adult patients with chronic gout refractory to conventional therapy to evaluate administration of KRYSTEXXA 8 mg every 2 weeks co-administered with weekly administration of oral methotrexate 15 mg, compared to KRYSTEXXA alone. In this trial, patients who were able to tolerate two weeks on methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating KRYSTEXXA therapy. A total of 152 subjects were randomized, and of these, 145 subjects completed the 4-week methotrexate run-in period and received KRYSTEXXA (96 subjects received KRYSTEXXA co-administered with methotrexate and 49 received KRYSTEXXA plus placebo) during the treatment period. All patients received pre-treatment with an oral antihistamine, intravenous corticosteroid and acetaminophen. These patients were between the ages of 24 and 83 years (average 55 years); 135 patients were male and 17 and were female; 105 patients were White/Caucasian, 22 were Black/African American,

14 were Asian, 5 were Native Hawaiian/Other Pacific Islander and 5 identified as Other; 28 were Hispanic or Latino. Common co-morbid conditions among the enrolled patients included hypertension (63%), osteoarthritis (25%), hyperlipidemia (24%), gastroesophageal reflux disease (22%), obesity (20%), type 2 diabetes (18%) and depression (16%). Patients with an eGFR <40 mL/min/1.73 m² were excluded from this trial.

The most commonly reported adverse reaction during the methotrexate pre-treatment periods was gout flare. The most commonly reported adverse reactions that occurred in ≥ 5% in either treatment group during the KRYSTEXXA co-administered with methotrexate or KRYSTEXXA alone period are provided in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients in Either the KRYSTEXXA Co-administered with Methotrexate or KRYSTEXXA Alone Treatment Period

Adverse Reaction	KRYSTEXXA with Methotrexate (N=96) n (%)	KRYSTEXXA Alone (N=49) n (%)
Gout flare	64 (67%)	35 (71%)
Arthralgia	13 (14%)	5 (10%)
COVID-19	9 (9%)	3 (6%)
Nausea	5 (5%)	6 (12%)
Fatigue	5 (5%)	2 (4%)
Infusion reaction	4 (4%)[a]	15 (31%)
Pain in extremity	1 (1%)	3 (6%)
Hypertension	1 (1%)	3 (6%)
Vomiting	0	4 (8%)

[a] Included one case of anaphylaxis

KRYSTEXXA ALONE

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 24-week 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. These patients were between the ages of 23 and 89 years (average 55 years); 173 patients were male and 39 were female; and 143 patients were White/Caucasian, 27 were Black/African American, 24 were Hispanic/Latino and 18 were all other ethnicities. Common co-morbid conditions among the enrolled patients included hypertension (72%), dyslipidemia (49%), chronic kidney disease (28%), diabetes (24%), coronary artery disease (18%), arrhythmia (16%), and cardiac failure/left ventricular dysfunction (12%).

During the pre-marketing placebo-controlled clinical trials, the most commonly reported adverse reactions that occurred in greater than or equal to 5% of patients treated with KRYSTEXXA 8 mg every 2 weeks are provided in Table 2.

Table 2. Adverse Reactions Occurring in 5% or More of Patients Treated with KRYSTEXXA Compared to Placebo

Adverse Reaction	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

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.

In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, approximately 26% of patients had pre-existing antibodies to pegloticase. Patients with an increase in titer from baseline or who were negative at baseline and developed an anti-pegloticase response at one or more post dose time points was 30% and 51%, for the KRYSTEXXA co-administered with methotrexate and KRYSTEXXA alone treatment groups, respectively. Patients with higher antibody titers were more likely to have faster clearance and lower efficacy.

During pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, 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.

Postmarketing Experience

The following adverse reactions 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.

General disorders and administration site conditions: asthenia, malaise, peripheral swelling

DRUG INTERACTIONS

Methotrexate

KRYSTEXXA 8 mg every 2 weeks has been studied in patients with chronic gout refractory to conventional therapy taking concomitant oral methotrexate 15 mg weekly. Co-administration of methotrexate with KRYSTEXXA may increase pegloticase concentration compared to KRYSTEXXA alone.

PEGylated products

Because anti-pegloticase antibodies appear to bind to the PEG portion of the drug, there may be potential for binding with other PEGylated products. The impact of anti-PEG antibodies on patients' responses to other PEG-containing therapeutics is unknown.

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 *[see Data]*.

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. In a 52-week, randomized, double-blind trial which evaluated KRYSTEXXA co-administered with methotrexate compared to KRYSTEXXA alone, 85% of patients had chronic kidney disease based on estimated glomerular filtration rate (eGFR) of ≥ 40 to < 90 mL/min/1.73 m² at baseline. In the pre-marketing 24-week controlled clinical trials with KRYSTEXXA alone, 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).

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, nausea or vomiting.
- 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 *[see Warnings and Precautions, Adverse Reactions]*
- 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 *[see Warnings and Precautions, Contraindications]*.

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 *[see Warnings and Precautions, Adverse Reactions]*. Advise patients that they should not stop KRYSTEXXA therapy if they have a flare.

Manufactured by:
Horizon Therapeutics Ireland DAC
Dublin, Ireland

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ASN American Society of Nephrology

KidneyNews

ASN Kidney News is published by the American Society of Nephrology
1401 H Street, NW, Suite 900, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1401 H Street, NW, Suite 900, Washington, DC 20005.

Publications mail agreement No. 40624074. Return undeliverable Canadian addresses to PO Box 503, RPO West Beaver Creek, Richmond Hill ON L4B 4R6

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1401 H Street, NW, Suite 900, Washington DC 20005, and is published monthly 11 times a year except November. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $20 for *ASN Kidney News* subscription.

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Nephrology Rapidly Transitioning

Continued from cover

Most drugs approved over the past 40 to 50 years have dosing recommendations based on creatinine clearance, explained Thomas Nolin, PharmD, PhD, associate dean for research and associate professor of pharmacy and therapeutics in the Department of Medicine at the University of Pittsburgh.

"What do we do with the hundreds of drugs we use every day that have drug-dosing recommendations based on creatinine clearance?" he asked. Nolin said he is working on an NKF Pharmacy Engagement Work Group with Wendy St. Peter, PharmD, professor with the College of Pharmacy at the University of Minnesota in Minneapolis, to find ways to improve the dosing information available for clinicians.

Guidance from the US Food & Drug Administration for drug manufacturers on drug pharmacokinetics in patients with kidney impairment in 2020 called for dosing information using contemporary estimated GFR (eGFR) calculators (2), which could have a major impact on dosing recommendations going forward, Nolin said. Already, some pharmaceutical companies have incorporated eGFR recommendations on dosing labels for newer drugs, including canagliflozin, he noted.

Eliminating race from kidney function estimates also has implications for kidney transplants, said John Friedewald, MD, professor of medicine and surgery in the Divisions of Nephrology and Hypertension and Organ Transplantation, respectively, at Northwestern University, Chicago, IL. He explained that race-based equations could overestimate kidney function for Black adults leading to delayed referral for transplant.

"Exposure to dialysis is our patient's greatest risk," Friedewald said. "Getting a transplant sooner is much better and increases longevity." Because of this, obtaining an accurate GFR is very important, he continued. He cited evidence that suggests the new recommendations would help reduce racial disparities in wait list time (3). "Timing is really important because you want to get patients [who] accumulated waiting time if they are preemptive (transplant candidates) so you can have time to find and evaluate appropriate living donors," he said.

Living donor evaluations also rely on an accurate GFR, Friedewald said. He noted that ideally, living donors have a GFR greater than 90 mL/minute body surface adjusted. However, transplant centers may consider people with GFRs between 60 and 90 mL/minute depending on several factors. They will also compare kidney function in the donor's kidneys and recommend leaving the donor with a better kidney. "GFR isn't the only thing that goes into evaluating a donor for approval," he said. "But GFR is one of the more important factors, and it is often a contraindication if someone does not have [an] adequate GFR. So, getting the right GFR is important."

Friedewald explained that a substantial number of potential donors could be misclassified based on eGFRs. One concern is that donors could be turned away during initial screening based on an inaccurate eGFR and never make it to the next step, he said. With the new equations, he noted, there may be more errors at the higher end of the GFR spectrum than at the lower end. Most transplant programs use a measured GFR to evaluate patients later in their candidacy. However, he expressed concern that inaccurate estimates during early screening could dissuade candidates from completing a donor evaluation.

"The answer here is to cast a wide net and not rely on an estimation equation alone to evaluate a living donor," he said. "For living-donor candidates, I stress [that] a measured GFR is preferred for accuracy and proper stratification."

Laboratory hurdles

The NKF's CKDintercept program (4) helped lay the ground for the rapid uptake of race-free kidney estimates, Palevsky said. Through the program, the NKF was already working with large commercial laboratories, pathology societies, and academic institutions to improve kidney disease diagnoses before the task force's recommendations. However, he noted that hurdles to implementing the cystatin C recommendations remain.

Palevsky explained that the number of laboratories able to run cystatin C tests remains low, at approximately 200 across the country. However, an analysis of data from Labcorp suggests that the number of cystatin C tests increased between 2012 and 2019 (5), but cystatin C tests are still orders of magnitude less common than creatinine tests, he noted. For example, in 2018, laboratories conducted approximately 110,000 cystatin C tests compared with about 39 million creatinine tests, he said. "We don't have clear-cut guidance on who should be tested with cystatin C," he said.

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend using cystatin C to confirm testing when creatinine-based estimates may be less reliable (6), and Palevsky cited a review of the evidence and circumstances where cystatin C may be appropriate (7). Some examples included patients whose eGFR is close to cutoff points or patients who are elderly, inactive, have cancer, are on a vegetarian diet, or are living with HIV or cirrhosis for whom creatinine-based tests may overestimate kidney function. He noted that creatinine might underestimate kidney function in other patients, such as bodybuilders.

Cystatin C cost barriers

There are also barriers to broader cystatin C implementation, including a much higher cost than for creatinine, Palevsky said. For example, he noted that a cystatin C test costs $18.52 compared with $5.12 for a creatinine test based on Medicare pricing.

Amy Karger, MD, PhD, a clinical pathologist and associate professor in the Department of Laboratory Medicine and Pathology at the University of Minnesota, noted that a lack of standardized reagents and methods had stymied wider use of cystatin C. However, she cited data from the College of American Pathologists (CAP) that show standardized assays increased between 2014 and 2019 (8). She recommended that nephrologists make sure their labs are using a standardized assay. "There are still some old, outdated platforms being used in clinical laboratories that don't use standard reagents," she said. "It's an important question to ask as a nephrologist if you are looking at bringing in that assay."

Traditionally, Karger noted, cystatin C was run primarily at reference labs or academic centers because it required specialized laboratory equipment. The 2019 CAP survey data show that only 7% of laboratories offered the test in-house, and 93% sent it to reference laboratories. More laboratory instrument manufacturers have made cystatin C tests available on equipment found in most clinical laboratories. However, it is still often considered a specialty test rather than a routine one because of low demand for the test, she explained. That may change as health systems push for greater access. She noted that the Veterans Affairs Health System started requiring at least one lab in each regional network to offer cystatin C testing by September 1, 2022.

Karger explained that low use of cystatin C tests in a health system could create financial disincentives for bringing the testing in-house. She said there are one-time and continuous costs for adding and maintaining a new assay. Spreading these costs over a few tests drives up individual test costs and can lead to wide variability in the costs of tests among health care systems implementing different test volumes. Palevsky noted that the price for a cystatin C test could be as high as $50 at some laboratories. As a result, many low-volume laboratories will opt to send out cystatin C tests, which creates additional barriers for clinicians trying to order creatinine and cystatin C concurrently, Karger added. "They are not going to get those results in the same time frame," she said.

Karger noted that working with manufacturers to make the tests more accessible and to lower reagent costs is a critical first step to overcoming these challenges. Greater use of the tests will help reduce the costs of reagents, she noted. She explained that updating clinical practice guidelines to include when it is appropriate to use cystatin C will help increase test volumes and justify reimbursement for the tests. "I encourage nephrologists to proactively engage their clinical laboratory directors about options for bringing testing in-house," Karger said. "If nephrology can lead efforts to support evidence-based utilization and increase test volumes, this can make in-house testing financially sustainable for clinical laboratories."

Palevsky agreed that nephrologists should be proactive about working with their colleagues in other specialties and laboratories regarding the use of the cystatin C test. He noted that the NKF published recommendations (9) to help laboratories implement race-free kidney function equations. However, he also cautioned that embracing the task force's advice is the first step in what must be a larger effort for the field of nephrology.

"While adopting race-free eGFR equations and increasing cystatin C use is important, these changes alone are inadequate for addressing the disparities in nephrology care," Palevsky concluded. "We need not lose sight of the bigger picture we need to achieve." ■

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Value-Based Payment Models

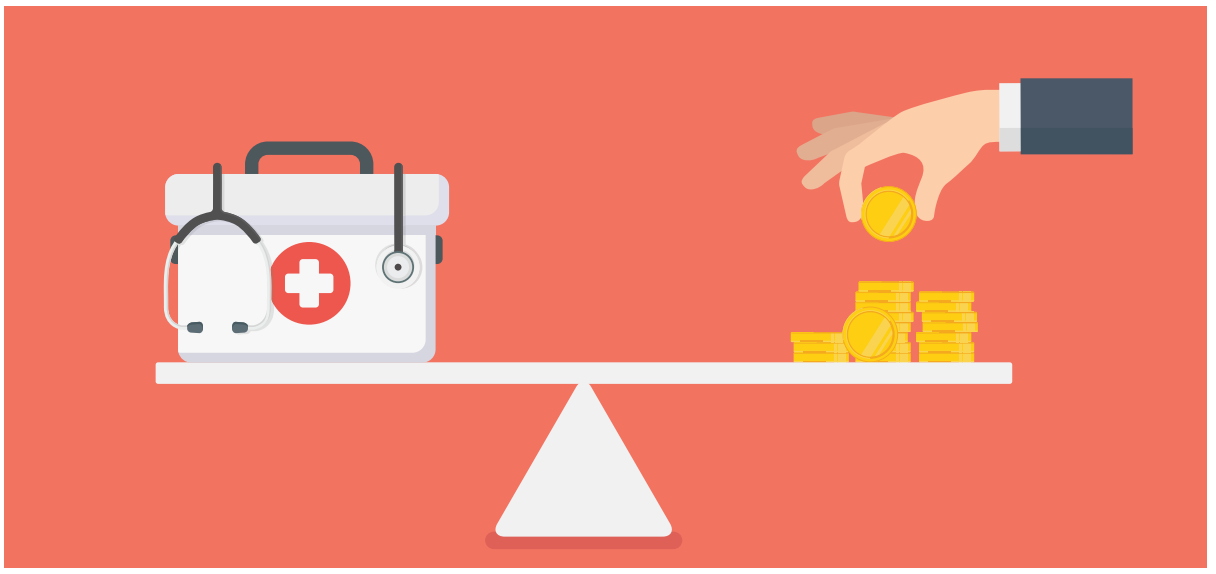
Continued from cover

at the Kidney Week session discussed what it is like to participate and how these new payment models have changed from earlier versions.

Misaligned incentives

Panelist Daniel Weiner, MD, MS, highlighted the evolution of value-based payment models in nephrology and the need to better align incentives with the program's goals. He noted that nephrology's "moonshot" came 50 years ago when in 1972 amendments to the Social Security Act extended Medicare coverage to patients with kidney failure (2). Weiner said that approximately 10,000 people at that time in the United States were receiving dialysis through a "hodgepodge" of programs funded by foundations or the Veterans Health Administration, but many patients did not have access to the treatments. "We got access for as many people—or almost as many people—in this country who needed a life-saving treatment," he said. But challenges and barriers to access remain, he noted.

One of those challenges has been the high cost of providing care for those with kidney failure. CMS pays approximately $50 billion yearly on the care of people with kidney failure or approximately 7% of Medicare's budget, comprised of $37 billion through traditional fee-for-service spending and $13 billion through Medicare Advantage in 2020. "Health care is the largest expenditure by the U.S. government, and dialysis is one of the largest line items in that expenditure," Weiner said. Of the $37 billion in fee-for-service spending on people with kidney failure in 2020, $12.6 billion was spent on outpatient dialysis.



CMS has created a series of value-based care initiatives to reduce costs while promoting the best possible care. The first was a "bundle" or pay-for-performance program mandated by the Medicare Improvements for Patients and Providers Act of 2008 for dialysis providers (3). Weiner noted, however, that CMS paid physicians under a separate monthly capitation program. "We actually get paid much better for caring for people who are receiving dialysis than we do for keeping somebody from needing dialysis," he said. "That's a misaligned incentive."

The Comprehensive End-Stage Renal Disease (ESRD) Care Model (4) created accountable care organizations for patients with kidney failure who shared the cost savings and losses with CMS based on quality measures. It incentivized the organizations to keep patients out of hospitals and as healthy as possible. Weiner noted that it included the use of patient navigators and patient advisory committees, but the program only included patients with kidney failure. There was a misaligned incentive because patients receiving a transplant—often among the healthiest patients at a dialysis organization—could hurt the organization's bottom line, he said.

More recent policy developments, such as the 2019 Advancing American Kidney Health initiative (5), aim to reduce the number of U.S. individuals developing kidney failure by 25% by 2030, substantially increase the number receiving home dialysis by 2025, and double the number of kidneys available for transplant by 2030, Weiner noted. Newer, value-based care programs, such as the ETC model, have also added incentives to increase the number of patients on transplant lists and the number of patients on home dialysis, he said. But, he said, the pandemic and current staffing shortages make assessing their effects difficult. He worried that using transplant wait lists versus transplants might create misaligned incentives. "The key thing here is that it doesn't move upstream," he said.

He acknowledged that the fragmented nature of the U.S. health care system makes continuity of care for patients with chronic health conditions difficult. There are separate "silos" for care of kidney diseases, dialysis, and transplant care. Too often, patients in the early stages of kidney diseases go undetected because of a lack of screening for kidney diseases. "We're not screening adequately for albuminuria, and by the time people get to us, it is too late," he said. "We have to move much farther upstream."

Team-based care

The KCF model builds on the ETC model, according to CMS. To participate, Jain said a practice must have at least one nephrologist with approximately 200 patients with ESKD and at least 350 patients with stage 4 or 5 kidney disease. Smaller practices, he noted, can team up with other practice partners. He and his colleagues have teamed up with Banner Health in Phoenix, AZ, and the University of California, Los Angeles (UCLA).

The practices get an extra $35 monthly for each patient on home dialysis in addition to their monthly capitation payment, Jain said. They get a quarterly capitated payment for patients with advanced CKD equivalent to what they would get paid for patients on dialysis. The financial "backbone" of the program is a $15,000 bonus paid over 3 years for every patient who receives and maintains a transplant, Jain said. He said there is also a performance-based adjustment to the payments based on a predetermined set of quality metrics.

Session speaker Dylan Steer, MD, a nephrologist at the Balboa Nephrology Medical Group in La Jolla, CA, said the CKCC is an accountable care organization model that uses the same quality metrics as the KCF program. Participating organizations still get capitation payments but also share in Medicare cost savings or losses. The program has three shared savings options: graduated, 50%, or 100%. He noted that participation in the first cohort of CKCC has been high, with approximately 2400 aligned nephrologists and 200 transplant providers participating. Additionally, approximately 63,000 patients with kidney diseases and 54,000 patients with kidney failure receive care through one of the participating organizations. Patient activation is one of the key quality measures in both CKCC and KCF. Other quality measures include optimal kidney failure starts and depression remission, Steer said.

Patients must complete surveys assessing their activation every 6 months. The survey asks patients questions, such as whether they feel competent to carry out their medical treatments at home, if they are experiencing mental illness symptoms, or if they know what each medication does. It is often the first time that a patient has been asked these types of questions, Jain said, and it creates an opportunity to intervene. Steer said he was initially skeptical of the patient activation surveys but that the patient feedback has been very positive.

Steer and Jain emphasized the need for an upfront investment to succeed in either program. Jain's team includes a full-time registered nurse coordinator. There is also a nephropsychology clinic staffed one-half day each week by a psychologist who sees all of the program's patients. The psychologist helps talk with patients about the importance of sleep and medication compliance, helps patients with depression, or addresses the concerns of patients who are afraid to start dialysis. A pharmacist from Auburn University also works with patients 1 day each week, goes through patients' medications, and helps them troubleshoot. Jain also works with DaVita's CKD Insights program, which pulls all the CKD patient data into a platform that allows a patient navigator to identify patients who may be at risk for hospitalization or who need dialysis education or a dialysis access procedure. Jain said it is also essential to get help running the program's business and informatics side and to set aside enough time for the lead physician working in the program. "The nephrologists need to be at the center of the care," he said.

Jain emphasized the importance of choosing the right partners: "Find someone who is similar minded and similar sized and talk with [him or her] and assess [him or her]." He noted that he and his colleagues at Banner Health and UCLA have learned from each other.

Steer also emphasized the importance of picking the right partners, making sure participating nephrologists have dedicated time for the program, and working with the onsite team to troubleshoot as issues arise. He acknowledged that starting a value-based care program can be daunting but can also help to better align an institution's values with the care it provides. "You don't have to be perfect; just better," Steer concluded. ■

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Two More Studies Show Nova POC Creatinine/eGFR is As Accurate or More Accurate Than Laboratory Methods

Study One:

Accuracy Equal to Traceable Gold Standard Creatinine Method

Nova StatSensor capillary and venous whole blood POC specimens were directly compared to the same patient's venous samples measured by the laboratory gold standard ID-LCMS creatinine method. StatSensor POC concordance with ID-LCMS at a creatinine decision-making level of 1.2 mg/dL performed equally to the laboratory.

"Consequently, the sensitivity and specificity of the capillary blood testing post-calibration alignment was 100% and 98.3% respectively, indicating that the device is suitable to screen for CKD in POC settings and is a reliable method to assess a patient's renal status in the field."

Dubois JA et al. Creatinine standardization: a key consideration in evaluating whole blood creatinine monitoring systems for CKD screening. Analytical and Bioanalytical Chemistry (2022) 414:3279–3289.

Study Two:

Accuracy Better Than the Laboratory Jaffe Creatinine/eGFR Method

StatSensor Creatinine/eGFR showed better accuracy than the Jaffe creatinine/eGFR at identifying patients in the decision-making eGFR range of 60-89 when both methods were compared to the gold standard measured GFR.

"The performance of POC devices [StatSensor] to detect eGFR in the range 60–89 mL/min/1.73 m2 is of particular interest. With limited access to renal replacement therapy for severe kidney disease, it is advantageous to detect individuals with early disease who may benefit from renal protective measures. There was improved accuracy in this area compared to laboratory Jaffe measurements."

Currin S et al. Evaluating chronic kidney disease in rural South Africa: comparing estimated glomerular filtration rate using point-of-care creatinine to iohexol measured GFR. Clin Chem Med Lab 2021

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Malakoplakia in Kidney Transplant Recipients

By Kanza Haq

Malakoplakia is derived from Greek words, meaning "soft plaque." It is a rare, chronic, granulomatous disease that was first reported in 1902 by Leonor Michaelis and Carl Gutmann. Malakoplakia was initially thought to exclusively involve the urogenital tract, but it can affect any organ of the body and has been reported in the gastrointestinal tract, brain, bones, adrenal glands, lymph nodes, lungs, skin, and other organs (1). Most patients affected by malakoplakia have associated conditions characterized by some degree of immunosuppression, and it has been described in patients with solid organ transplant and kidney transplantation in particular. Other risk factors include recurrent urinary tract infections (UTIs), autoimmune diseases requiring steroid use, chronic systemic diseases, neoplasia, chemotherapy, alcohol abuse, and poorly controlled diabetes (2). Although it is more commonly seen in kidney transplant recipients, there are reported cases of malakoplakia in patients with liver, cardiac, and hematopoietic stem cell transplantation as well (3–5). Kidney transplant malakoplakia cannot only involve allograft parenchyma; it has also been reported in extra-renal sites (e.g., ureter, bladder, gastrointestinal tract, skin, submandibular gland, testicles, and prostate) (6–8).

Clinical features

Previous reports in kidney transplant recipients suggest a higher prevalence of malakoplakia in women and in patients with recurrent *Escherichia coli* UTI (8, 9). Following transplantation, the onset of malakoplakia has been reported within months and up to 1 decade or more later. Clinical presentation is very variable; it usually manifests as chronic dysfunction of the allograft, recurrent UTIs, or renal mass. *E. coli* is the predominant microorganism identified in most cases, although other organisms have been implicated, such as *Klebsiella*, *Proteus*, *Citrobacter*, *Corynebacterium*, and *Aerobacter* species (8–10).

Pathogenesis

The pathogenesis of malakoplakia is not well understood but thought to involve reduced levels of cyclic guanosine monophosphate (cGMP) in mononuclear cells, causing impaired lysosome function and intracellular lysis of phagocytosed bacteria (11). This leads to persistence of infection, and the granulomatous reaction generates the appearance of soft, yellowish nodules and plaques on gross examination. (Imaging and diagnostic features are elucidated in Table 1.)

Treatment/prognosis

Data about the therapeutic approaches to treat malakoplakia are limited, but the mainstay of treatment in transplant patients is reduction in immunosuppression and long-term antibiotics. Antibiotics having intracellular penetration are recommended, but ideal treatment duration still remains unclear. Treatment time of a few weeks to months has been described in previous reports with variable outcomes (8–10). The cholinergic agonist bethanechol has also been used with antibiotics to improve intracellular killing of the organisms by increasing cGMP levels. Some cases are refractory to antibiotic treatment and ultimately require surgical management. Prognosis of malakoplakia has improved over time, likely due to use of appropriate antibiotics and minimization of immunosuppressive regimens. The mortality rate has decreased, but non-recovery of renal function leading to graft failure is still seen (8–10). An important caveat is to consider graft rejection risk while reducing immunosuppression, especially in the early posttransplant period.

Conclusion

It is important to consider malakoplakia in the differential diagnosis for allograft dysfunction with a history of recurrent UTI or a mass in kidney transplant patients. Recognition and understanding of malakoplakia are important because it is a pathologic condition that has not been well studied and can contribute to loss of graft function and morbidity. More high-quality data are needed to elucidate treatment options for malakoplakia and to better understand long-term sequelae and its implications on prognosis. ■

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The author reports no conflicts of interest.

Figure 1. Hematoxylin and eosin (H&E) stain

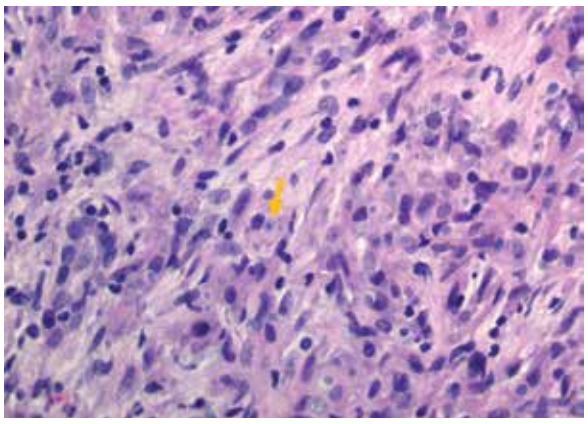
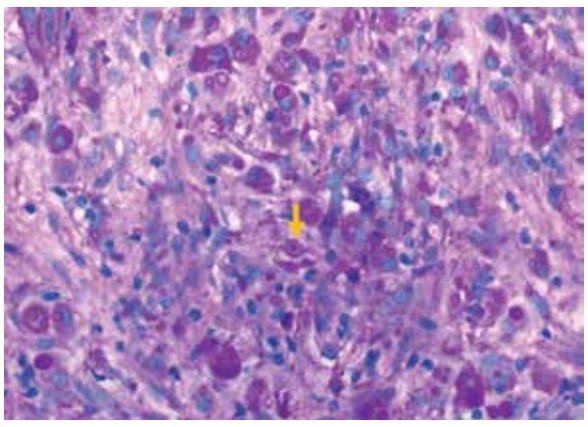


Figure 2. Periodic acid-Schiff (PAS) stain



Figures 1 and 2 illustrate high-power renal parenchyma showing histocytes with abundant PAS-positive, granular cytoplasm, and targetoid Michaelis-Gutmann bodies (arrows).

Table 1. Imaging and diagnostic features in malakoplakia

Imaging features	
Computed tomography	Ill-defined solid masses; solitary nodule mimicking neoplasms or post-transplant lymphoproliferative disorders; pseudo-tumoral lesions or diffuse infiltrative parenchymal involvement (10, 12–14)
Magnetic resonance imaging	Poorly defined low signal intensity nodules related to the presence of calcium and iron in the Michaelis-Gutmann bodies (15); findings in a previous report of increased uptake on a gallium scan and decreased uptake on dimercaptosuccinic acid (DMSA) in the involved area (16)
Diagnostic features	
Graft biopsy is required to establish the diagnosis and for timely treatment decisions. Pathognomonic biopsy findings are histocytes with granular cytoplasm (von Hansemann cells) and targetoid intra-cytoplasmic Periodic acid-Schiff (PAS)-positive inclusions, called Michaelis-Gutmann bodies (2) (Figures 1 and 2).	
Michaelis-Gutmann bodies are derived from remnants of partially phagocytosed bacteria with iron and calcium deposits. Identification sometimes may require special stains, such as the von Kossa stain for calcium and the Prussian blue stain for iron.	

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Painless Cannulation: Music to My Ears

By Ronak Patel and Yana Etkin

Cannulation during hemodialysis (HD) may not only be painful but is also associated with worse outcomes. Having a higher pain score during fistula cannulation is independently associated with missing HD sessions (1). It has been shown that missing just one session over a course of a few months is associated with a 68% higher rate of mortality (2). Moreover, untreated pain may increase the risk of developing needle phobia, tachycardia, and vasovagal syncope and contribute to future noncompliance. For all of these reasons, it is essential to consider managing pain with cannulation.

A number of strategies can help reduce pain associated with access cannulation, such as local anesthetic agents, topical heat, cryotherapy, and aromatherapy (3). Additionally, music interventions have been found to provide an effective complementary approach for the relief of acute, procedural, and cancer/chronic pain in the medical setting (4).

In a recent *CJASN* study, Inayama and colleagues (5) evaluated the role of music on decreasing pain during cannulation of HD access. The multicenter, single-blinded, crossover, randomized trial recruited 121 patients from five dialysis facilities in Japan who reported pain on cannulation. The treatment group listened to Mozart for 8 minutes before the cannulation procedure and underwent a cannulation while listening to music. To reduce the risk of bias, the authors set their control group as "white noise" rather than "no sound." Using a visual analog scale score, they found that cannulation pain can be reduced by 12% when patients listen to music. Although there was no significant difference in anxiety, vital signs, or stress markers, the ability to reduce pain with minimal cost was substantial.

There were important limitations to the study, such as gender and culture. Needle fear and needle phobia have been found to be more prevalent in women than in men (6), and yet, in this study, 71% of the participants were male. Although Mozart is appreciated by many people around the world, the music may not be familiar to some. We must consider how a patient's background may play a role in response to the type of music played. It is unclear if the therapeutic effect of Mozart's sonata is generalizable or is directly related to the "enjoyment" the person may experience listening to this particular music.

A study that examines combining various adjuncts listed above is lacking in the literature and would provide a better algorithm to reduce pain.

Overall, the outcomes of the study focused on patient satisfaction and could lead to improved, long-term use of access sites. Poor cannulation habits can lead to complications related to access. The 2019 Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines recommend rope ladder cannulation as the preferred cannulation technique for arteriovenous fistulas (7). However, patients who experience pain with cannulation may prefer the "area cannulation" technique in which the same site is repeatedly accessed, causing scarring, nerve damage, and then less pain in subsequent accesses. This technique leads to aneurysm formations, decreases the life span of the fistula, and should be avoided (7, 8). With pain reduction, the technique of area cannulation can finally be a thing of the past.

Music during dialysis access cannulation provides no added risk to the patient or facility and is simple to implement in dialysis centers. The *CJASN* study (5) did highlight the use of music as an adjunct to reduce pain.

Outcomes of various pain management techniques during HD access cannulation were analyzed in a recent systematic review of 35 studies (3). Cryotherapy was found to be the best adjunctive technique to reduce cannulation pain. Authors concluded that other interventions, such as aromatherapy, thermotherapy, and transcutaneous electrical stimulation, need further testing in a larger population to ascertain the effectiveness of pain reduction. None of the studies included in the analysis combined alternative therapies together to achieve an augmented effect. There is a clear need for further studies to determine which combinations of adjuncts can provide the most pain relief for our patients. ■

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The authors report no conflicts of interest.

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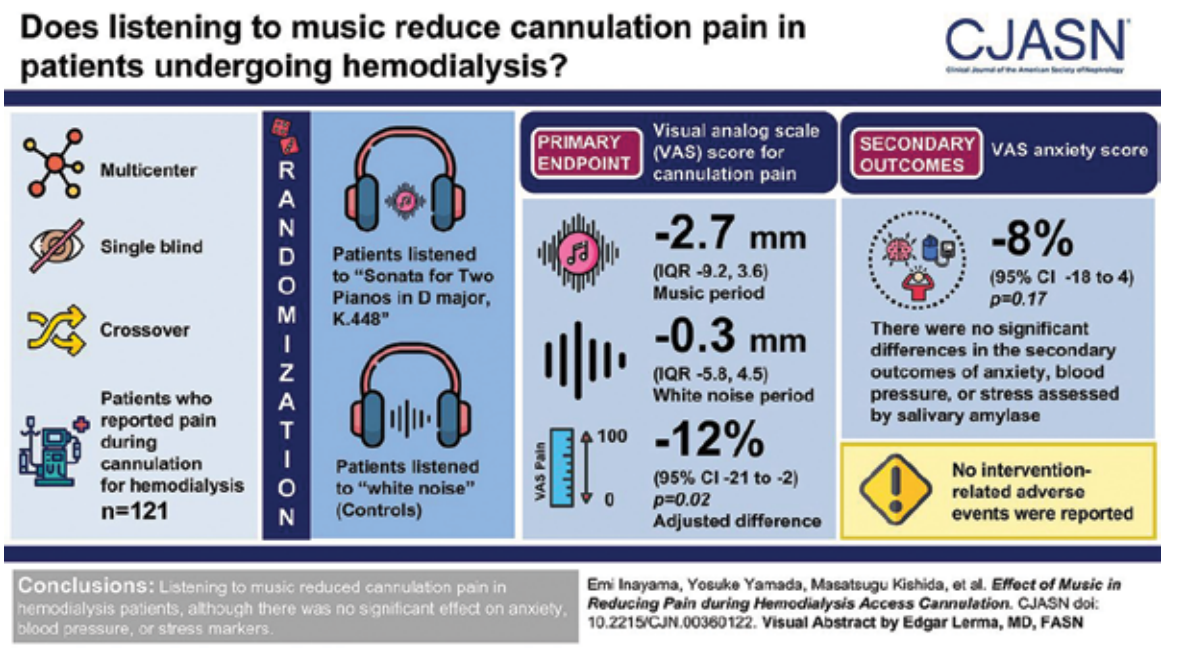

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Send your idea to the ASN *Kidney News* Fellows First column at kidneynews@asn-online.org

ASN President's Update

Priorities for 2023 Include: Transplantation, Nephrology Training, and Environmental Sustainability

By Michelle A. Josephson

Thank you to Anupam Agarwal and Susan Quaggin for their outstanding service to ASN. The entire kidney community owes them a debt of gratitude for their skilled and transformative leadership in 2020, 2021, and 2022. During their tenure, ASN accomplished an impressive number of meaningful achievements, some of which I have outlined in Table 1.

ASN was fortunate to have Anupam and Sue in charge during these challenging times. While bringing us through a pandemic, handling the tragic loss of our colleague and dear friend Barbara Murphy, and moving ASN forward, they served additional years and gave of themselves with grace, humility, and wisdom. The success of ASN Kidney Week 2022—our first in-person annual meeting since 2019—is a testament to how well they guided ASN while always keeping the needs of our patients and members as priorities. Anupam and Sue set a high bar, and they are hard acts to follow.

I recognize that you may not know me, so I thought it would be helpful to share a bit about myself. Starting at the beginning, I was born in Brooklyn (one of the five boroughs that form New York City) and mostly grew up there. My father was an allergist and immunologist who loved all aspects of his work in academic medicine: caring for his patients, conducting research, and teaching the next generation. His enthusiasm for the profession was so infectious that I became a physician, my younger brother is a hematologist-oncologist, and my younger sister is a physician's assistant who works with patients on peritoneal dialysis.

My father worked at the State University of New York Downstate Health Sciences University, where his friend and colleague, nephrologist Eli Friedman, worked as well. My mother, initially a nurse by training, became an epidemiologist, in large part inspired by working with Dr. Friedman on hepatitis B prevalence and transmission in dialysis patients (1). I started in the nephrology world working with Dr. Friedman on animal models he had developed to study diabetic nephropathy as well as participating in meetings to design a dialysis machine that could be carried around in a suitcase (2). During a summer spent at The Jackson Laboratory in Bar Harbor, ME, I was exposed to life as a bench science immunologist.

Perhaps it was these early experiences that helped me decide on a career in nephrology when, as a medicine resident, I was encouraged by Fredric Coe, Susan Fellner, Marshall Lindheimer, Mark Richter, and Gary Toback. During fellowship, I fell in love with transplant for the benefits it provided patients, the immunologic challenges, the medical complexities, and the multidisciplinary nature of the field. Transplant nephrology was not an area of focus for the University of Chicago (UC) nephrology faculty at the time, and patients were managed by the transplant surgeons. With that post-transplant care model, I saw the opportunity to make a difference in patient outcomes and address nonsurgical issues faced by our transplant recipients.

Although there were leading bench immunologists at UC, the challenge for me at the start of my career was a lack of clinical transplant nephrologists to create a program. This lack of on-site transplant nephrology propelled me to reach out to the relatively small group of transplant nephrologists nationwide at the time. They welcomed me into the transplant nephrology world, providing mentorship and opportunities as well as generously sharing their experience and expertise.

As a community, we should strive for a transplant system that maximizes patients' access to a kidney transplant.

At the end of fellowship, I readily accepted an opportunity to stay as the first official UC transplant nephrologist and founded the Clinical Transplant Nephrology Program. By accepting this position, my home became the city of Chicago, where I now live with my husband, Stephen Daiter, a photography dealer who runs a gallery and, when home from school, our daughter, Maya, as well as our dog, Ursa.

Over time, the one-person transplant nephrology program grew. I was able to recruit wonderful colleagues who have worked with me at different points, including James Chon, Amishi Desai, Pradeep Kadambi, Sambhavi Krishnamoorthy, Yousuf Kyeso, Basit Javaid, and Pratik Shah. I also started a transplant nephrology fellowship and have helped train more than 20 fellows (and counting!) who have contributed to several aspects of nephrology, making our field that much better. I could not be prouder of each of them.

On the national front, I worked closely with a number of groups besides ASN, including the American Board of Internal Medicine, American Society of Transplantation (AST), Kidney Disease: Improving Global Outcomes, National Kidney Foundation, and Women in Nephrology. After I had the honor of serving on the AST Board of Directors, ASN became my professional home, where I've worked closely with the dedicated members and staff on several initiatives and committees.

What is my focus for 2023? To start, I will continue to center any plans based on the four priorities outlined in the We're United 4 Kidney Health campaign (3). The campaign's four priorities provide direction while leaving room for all of us to find connection and meaning in our work, be it to intervene earlier to prevent, diagnose, coordinate care, and educate; transform transplant and increase access to donor kidneys; accelerate innovation and expand patient choice; or achieve equity and eliminate disparities. Progress in any of these domains is a win for our patients and for our specialty.

As a personal interest, as well as what would have been a focus of Barbara Murphy's tenure as ASN President in 2022, I enthusiastically embrace the opportunity to emphasize We're United 4 Kidney Health's second priority: transforming transplant. I see 2023 as a chance to build bridges between general nephrology and transplant nephrology. At times, our existing system does not serve patients as well as it could, making transplant more of a privilege than an equitably accessible treatment. As a community, we should strive for a transplant system that maximizes patients' access to a kidney transplant—no matter their means, their background, or where they live.

With bipartisan, bicameral interest in government to improve the transplant system, focusing on transplant is timely. Transplant is not a new emphasis for ASN, which has been helping to shape policy in this arena for years, including working closely with three consecutive presidential administrations. We are drafting several guiding principles that will underpin the transplant policy work for next year including: affirm that kidney transplant is the optimal therapy for kidney failure, articulate that the goal of the kidney transplant ecosystem should be to maximize access to a kidney transplant, and acknowledge that many simultaneous changes to the current approach to kidney transplant must occur urgently to achieve this goal.

With these principles forming the foundation, five objectives will guide everything we will do to transform transplant:

1. Expedite reforms necessary to maximize patient access to transplant.
2. Enable the use of more organs to allow more patients to receive a transplant.

3. Establish transparency to improve patient access to transplant and address barriers in the kidney transplant ecosystem.
4. Encourage investment in transplant-related research and innovation.
5. Embrace modern technology to increase every patient's access to transplant.

In addition to these principles and objectives, I am also passionate about finding ways to ensure we provide appropriate long-term care for transplant recipients. The COVID-19 pandemic exposed the many challenges faced by people who are immunosuppressed. Focusing on the health of transplant recipients will enhance their quality and length of life, reduce the need for new transplants, and increase the number of organs available for transplant (4).

During the next year, I will focus on advancing training, certification, and overall acknowledgment of transplant nephrology as an important part of medical care. This specific goal dovetails well with ongoing efforts to examine and reinvigorate nephrology training. In its final report, the ASN Task Force on the Future of Nephrology proposed three levels of training and competencies (5). The task force's 10 recommendations align with ASN's efforts to articulate the value of nephrology. Under Mark Rosenberg's leadership as the task force's chair, the final report is visionary, focusing on the "why" and the "what." Now is time for us to begin the "how." Implementation will be a multi-year process that starts today.

Another priority for 2023 is related to supporting several upcoming transitions. ASN's peer-reviewed journals (*JASN*, *CJASN*, and *Kidney360*) are migrating from an in-house operation to a commercial publisher (Wolters Kluwer), and this transition must go as smoothly as possible. By the end of this year, Josie Briggs and Rajnish Mehrotra, the editors-in-chief of *JASN* and *CJASN*, respectively, will complete their terms. For nearly a decade, Josie, Raj, and their editorial teams have expertly led the journals in publishing impactful scientific, clinical, and policy articles that shaped and reflected the high caliber of nephrology scholarship and discourse. Starting in 2024, with the guidance of the ASN leadership, the journal relationships will be restructured, with *JASN* serving as the "flagship journal" and its editor-in-chief working closely with the editors-in-chief of *CJASN* and *Kidney360* to produce the publications as a portfolio of journals.

On January 1, 2023, Uptal Patel succeeded Raymond Harris as chair of the Kidney Health Initiative (KHI) Board of Directors. A partnership between ASN and the US Food and Drug Administration (FDA), KHI includes more than 100 stakeholder members. Under Ray's deft leadership, KHI continued its momentum through the COVID-19 pandemic by increasing virtual connections with the member community. KHI has published 42 total manuscripts, including nine manuscripts in 2021 and six manuscripts in 2022. KHI's portfolio expanded across FDA centers by launching projects in xenotransplantation, initiating the first collaboration between KHI and FDA's Center for Biologics Evaluation and Research, and starting efforts to incorporate the input of care partners and people with kidney diseases through Patient Preferences, Patient-Reported Outcome Measures, and Human Centered Design tools.

ASN and the rest of the kidney community must concentrate on environmental sustainability at every level. This goal fits well with the recommendations of the ASN Task Force on the Future of Nephrology and provides an opportunity to work with other kidney organizations globally, particularly the European Renal Association (ERA) and the International Society of Nephrology (ISN). Last year, ASN issued a position statement on climate change (6) and published "Policy and Kidney Community Engagement to Advance toward Greener Kidney Care" (7). ASN, ERA, and ISN could partner to "support people with kidney diseases to survive climate change, diminish the contribution of kidney care to climate change, and advocate for public policy to address climate change as a contributor to kidney health" (6).

While I used this column to describe several of my priorities, they barely scratch the surface of what we must do together in 2023. Serving as ASN President is a once-in-a-lifetime opportunity, endeavor, and privilege. I look forward to working with you—the ASN membership, my fellow ASN Councilors (ASN Past President Sue Quaggin; President-Elect Deidra Crews; Secretary Prabir Roy-Chaudhury; Treasurer Keisha Gibson; and Councilors-at-Large: Jeffrey Berns, Linda Fried, Crystal Gadegbeku, and Patrick Nachman), and the ASN staff—to accomplish much this year. I wish you a happy, fulfilling, and successful 2023. Now let's get started! ■

Michelle A. Josephson, MD, FASN, is Professor of Medicine and Surgery, University of Chicago, IL, and is ASN President.

Table 1. Selected list of ASN's recent accomplishments

1. Initiated the Loan Mitigation Pilot Program for residents who match into nephrology fellowships.
2. Oversaw the We're United 4 Kidney Health campaign.
3. Produced high-quality Kidney Weeks regardless of format.
4. Revamped ASN's journal publishing enterprise.
5. Partnered with the National Kidney Foundation to remove race from the eGFR equation.
6. Launched several initiatives to ensure excellence in patient care (such as the Diabetic Kidney Disease Collaborative).
7. Completed myriad projects via the Kidney Health Initiative (KHI) and sponsored several KidneyX prizes.
8. Added a new grant to KidneyCure's portfolio (focused on diversity, equity, inclusion, and justice).
9. Partnered with Phairify to furnish members with comprehensive national, current, and nephrology-specific compensation, productivity, and practice information.
10. Advocated to the US federal government on many issues, including kidney transplant and screening for kidney diseases.

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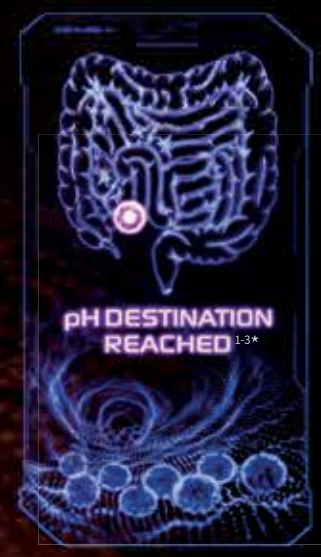
For adults at risk of rapid disease progression,

TARPEYO: First and only treatment FDA approved to reduce proteinuria in IgA Nephropathy[1]



TARPEYO® (budesonide) delayed release capsules is designed to deliver treatment to an area of the ileum to target mucosal B cells, which are responsible for the production of galactose-deficient IgA1 antibodies, causing immunoglobulin A Nephropathy (IgAN).[1,2,4]

*Drug release is initiated in the ileum by the pH-dependent disintegration of the enteric coat.[1,3]

Indication

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

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

Important Safety Information

Contraindications: TARPEYO is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of TARPEYO. Serious hypersensitivity reactions, including anaphylaxis, have occurred with other budesonide formulations.

Warnings and Precautions

Hypercorticism and adrenal axis suppression: When corticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Corticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic corticosteroid is recommended. When discontinuing therapy *[see Dosing and Administration]* or switching between corticosteroids, monitor for signs of adrenal axis suppression.

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C, respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure to oral budesonide. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B).

Risks of immunosuppression: Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressive doses of corticosteroids. Avoid corticosteroid therapy in patients with active or quiescent tuberculosis infection; untreated fungal, bacterial, systemic viral, or parasitic infections; or ocular herpes simplex. Avoid exposure to active, easily transmitted infections (eg, chicken pox, measles). Corticosteroid therapy may decrease the immune response to some vaccines.

TARPEYO®
(budesonide) delayed release capsules • 4 mg
DIRECT BY DESIGN

Designed to deploy in the ileum[1,2,4†]

- Designed to deliver treatment to the area of the ileum, including the Peyer's patches, where mucosal B cells are located
- Mucosal B cells express glucocorticoid receptors and produce galactose-deficient IgA1 antibodies, causing IgAN
- Through anti-inflammatory and immunosuppressive effects at the glucocorticoid receptor, TARPEYO can modulate B cell numbers and activity

Statistically significant reduction in UPCR with TARPEYO plus RASi vs RASi alone at 9 months[1‡§]

- **Primary endpoint:** Significant reduction (34%) in UPCR from baseline was achieved in the TARPEYO plus renin-angiotensin system inhibitor (RASi)-treated group (n=97) vs 5% with RASi alone (n=102) at 9 months[1‡§‖]
  - At the 12-month observational follow-up, a 53% reduction in UPCR from baseline was reported with TARPEYO plus RASi vs 9% with RASi alone[3§¶#]

Additional data presented beyond the primary endpoint of 9 months should be interpreted cautiously.

eGFR data with TARPEYO plus RASi vs RASi alone at 9 months

- **Secondary endpoint:** At 9 months, absolute change in eGFR was -0.6 mL/min/1.73 m^2 with TARPEYO plus RASi (n=97) vs -4.0 mL/min/1.73 m^2 with RASi alone (n=102)[3§**]

These interim secondary endpoint data were not prospectively controlled for multiplicity and need cautious interpretation. The clinical significance of these results is unknown. Confirmatory clinical trial results are required to draw any conclusions. It has not been established whether TARPEYO has demonstrated a benefit in slowing kidney function decline in patients with IgAN.[3]

Demonstrated safety profile

- 87% of patients in the TARPEYO plus RASi-treated group reported adverse reactions vs 73% of patients on RASi alone[1,3]
- In clinical studies, the most common adverse reactions of TARPEYO plus RASi (occurring in ≥10% of patients treated with TARPEYO plus RASi and at a higher incidence than RASi alone) were: hypertension, peripheral edema, muscle spasms, and acne[1,3]
- The safety profile is generally consistent with the well-established safety profile of the active ingredient, budesonide[3]

Study Design: NefIgArd is an ongoing, phase 3, randomized, double-blind, multicenter study to evaluate the efficacy and safety of TARPEYO 16 mg/day vs placebo in patients with primary IgAN as an addition to optimized RAS blockade therapy. Part A of the study (n=199) included a 9-month blinded treatment period and a 3-month follow-up period. The primary endpoint was UPCR at 9 months; eGFR was a secondary endpoint. Part B, a confirmatory validation study in which no treatment will be administered, will assess eGFR over 2 years.[1,3]

†It has not been established to what extent the efficacy of TARPEYO is mediated via local effects in the ileum vs systemic effects.[1]
‡31% reduction (95% CI, 16-42) in UPCR with TARPEYO plus RASi vs RASi alone (*P*=0.0001).[1††]
§All patients with a UPCR/eGFR reading regardless of use of prohibited medication at 9 months and 12 months.[1,3]
‖Adjusted geometric least squares mean ratio of UPCR relative to baseline were based on a longitudinal repeated measures model.[1]
¶49% reduction (95% CI, 37-58) in UPCR with TARPEYO plus RASi vs RASi alone.[3]
#Full analysis set (TARPEYO=97, placebo=102). Not all patients in the full analysis set contributed data at each postbaseline time point, including at 12 months.[3]
**Absolute changes derived from geometric least square mean ratios using the pooled baseline geometric mean.[3]
††The estimate of the ratio of geometric mean ratio of UPCR relative to baseline comparing TARPEYO 16 mg plus RASi with RASi alone was reported as percentage reduction along with the respective 95% confidence interval from the longitudinal repeated measures model and *P* values.[1]

Learn more about how TARPEYO works at TARPEYOhcp.com

Warnings and Precautions (cont'd)

Other corticosteroid effects: TARPEYO is a systemically available corticosteroid and is expected to cause related adverse reactions. Monitor patients with hypertension, prediabetes, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma, cataracts, a family history of diabetes or glaucoma, or with any other condition in which corticosteroids may have unwanted effects.

Adverse reactions: In clinical studies, the most common adverse reactions with TARPEYO (occurring in ≥5% of TARPEYO patients and ≥2% higher than placebo) were hypertension (16%), peripheral edema (14%), muscle spasms (13%), acne (11%), dermatitis (7%), weight increase (7%), dyspnea (6%), face edema (6%), dyspepsia (5%), fatigue (5%), and hirsutism (5%).

Drug interactions: Budesonide is a substrate for CYP3A4. Avoid use with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and cyclosporine. Avoid ingestion of grapefruit juice with TARPEYO. Intake of grapefruit juice, which inhibits CYP3A4 activity, can increase the systemic exposure to budesonide.

Use in specific populations

Pregnancy: The available data from published case series, epidemiological studies, and reviews with oral budesonide use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with IgAN. Infants exposed to in utero corticosteroids, including budesonide, are at risk for hypoadrenalism.

Please see brief summary of Full Prescribing Information on the adjacent pages.

References: 1. TARPEYO. Prescribing Information. Calliditas Therapeutics AB; 2021. **2.** Barratt J, Rovin BH, Cattran D, et al. Why target the gut to treat IgA nephropathy? *Kidney Int Rep.* 2020;5(10):1620-1624. doi:10.1016/j.ekir.2020.08.009 **3.** Data on file. Calliditas Therapeutics AB. **4.** Fellström BC, Barratt J, Cook H, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet*. 2017;389(10084):2117-2127. doi:10.1016/S0140-6736(17)30550-0

calliditas THERAPEUTICS

TARPEYO® (budesonide) delayed release capsules Brief Summary of Prescribing Information

4 CONTRAINDICATIONS

TARPEYO is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of TARPEYO. Serious hypersensitivity reactions, including anaphylaxis have occurred with other budesonide formulations.

5 WARNINGS AND PRECAUTIONS

5.1 Hypercorticism and Adrenal Axis Suppression

When corticosteroids are used chronically, systemic effects such as hypercorticism and adrenal suppression may occur. Corticosteroids can reduce the response of the hypothalamus-pituitary-adrenal (HPA) axis to stress. In situations where patients are subject to surgery or other stress situations, supplementation with a systemic corticosteroid is recommended. When discontinuing therapy *[see Dosing and Administration (2)]* or switching between corticosteroids, monitor for signs of adrenal axis suppression.
Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure of oral budesonide. Avoid use in patients with severe hepatic impairment (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B) *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

5.2 Risks of Immunosuppression

Patients who are on drugs that suppress the immune system are more susceptible to infection than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible patients or patients on immunosuppressant doses of corticosteroids. Avoid corticosteroid therapy in patients with active or quiescent tuberculosis infection, untreated fungal, bacterial, systemic viral or parasitic infections, or ocular herpes simplex. Avoid exposure to active, easily-transmitted infections (e.g., chicken pox, measles). Corticosteroid therapy may decrease the immune response to some vaccines.
How the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, consider therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG). If exposed to measles, consider prophylaxis with pooled intramuscular immunoglobulin (IG). If chickenpox develops, consider treatment with antiviral agents.

5.3 Other Corticosteroid Effects

TARPEYO is a systemically available corticosteroid and is expected to cause related adverse reactions. Monitor patients with hypertension, prediabetes, diabetes mellitus, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where corticosteroids may have unwanted effects.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypercorticism and adrenal suppression *[see Warnings and Precautions (5.1)]*
- Risks of immunosuppression *[see Warnings and Precautions (5.2)]*
- Other corticosteroid effects *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of TARPEYO has been evaluated in a randomized controlled study in 197 patients.
The most common adverse reactions reported in greater than or equal to 5% of TARPEYO-treated patients are listed in Table 1. The majority of adverse reactions were mild or moderate in severity.

Table 1: Reported adverse reactions occurring in greater than or equal to 5% of TARPEYO treated patients, and greater than or equal to 2% higher than Placebo

Adverse Reaction	TARPEYO 16 mg (N=97)	Placebo (N=100)
	n (%)	n (%)
Patients with any Adverse Reaction	84 (87)	73 (73)
Hypertension	15 (16)	2 (2)
Peripheral edema	14 (14)	4 (4)
Muscle spasms	13 (13)	4 (4)
Acne	11 (11)	2 (2)
Dermatitis	7 (7)	1 (1)
Weight increased	7 (7)	3 (3)
Dyspnea	6 (6)	0 (0)
Face edema	6 (6)	1 (1)
Dyspepsia	5 (5)	2 (2)
Fatigue	5 (5)	2 (2)
Hirsutism	5 (5)	0 (0)

Most adverse reactions that occurred at a greater incidence for TARPEYO compared to placebo were consistent with hypercortisolism.

7 DRUG INTERACTIONS

7.1 Interaction with CYP3A4 Inhibitors

Budesonide is a substrate for CYP3A4. Avoid use with potent CYP3A4 inhibitors; e.g. ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, and cyclosporine.
Avoid ingestion of grapefruit juice with TARPEYO. Intake of grapefruit juice, which inhibits CYP3A4 activity, can increase the systemic exposure to budesonide.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary The available data from published case series, epidemiological studies and reviews with oral budesonide use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with IgA Nephropathy. Infants exposed to in-utero corticosteroids, including budesonide, are at risk for hypoadrenalism *(see Clinical Considerations)*.
In animal reproduction studies with pregnant rats and rabbits, administration of subcutaneous budesonide during organogenesis at doses approximately 0.3 times or 0.03 times, respectively, the maximum recommended human dose (MRHD), resulted in increased fetal loss, decreased pup weights, and skeletal abnormalities. Maternal toxicity was observed in both rats and rabbits at these dose levels *(see Data)*.
The estimated background risk of major birth defects and miscarriage of the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations *Disease-Associated Maternal and/or Embryo/Fetal Risk* IgA nephropathy in pregnancy is associated with adverse maternal outcomes, including increased rates of cesarean section, pregnancy-induced hypertension, pre-eclampsia and preterm delivery, and adverse fetal/neonatal outcomes, including stillbirth and low birth weight.
Fetal/Neonatal Adverse Reactions Hypoadrenalism may occur in infants born to mothers receiving corticosteroids during pregnancy. Infants should be carefully observed for signs of hypoadrenalism, such as poor feeding, irritability, weakness, and vomiting, and managed accordingly *[see Warnings and Precautions (5.1)]*.
Data *Animal Data* Budesonide was teratogenic and embryo-lethal in rabbits and rats.
In an embryo-fetal development study in pregnant rats dosed subcutaneously with budesonide during the period of organogenesis on gestation days 6 to 15 there were effects on fetal development and survival at subcutaneous doses up to approximately 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose (MRHD) on a body surface area basis).
In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis on gestation days 6 to 18, there was an increase in maternal abortion, and effects on fetal development and reduction in litter weights at subcutaneous doses from approximately 25 mcg/kg (approximately 0.03 times the MRHD on a body surface area basis).
Maternal toxicity, including reduction in body weight gain, was observed at subcutaneous doses of 5 mcg/kg in rabbits (approximately 0.006 times the maximum recommended human dose on a body surface area basis) and 500 mcg/kg in rats (approximately 0.3 times the maximum recommended human dose on a body surface area basis).
In a peri- and post-natal development study, subcutaneous treatment of pregnant rats with budesonide during the period from Day 15 post coitum to Day 21 post partum, budesonide had no effects on delivery, but did have an effect on growth and development of offspring. In addition, offspring survival was reduced and surviving offspring had decreased mean body weights at birth and during lactation at exposures ≥ 0.012 times the MRHD (on a mg/m^2 basis at maternal subcutaneous doses of 20 mcg/kg/day and higher). These findings occurred in the presence of maternal toxicity.

8.2 Lactation

Risk Summary Breastfeeding is not expected to result in significant exposure of the infant to TARPEYO. Lactation studies have not been conducted with oral budesonide, including TARPEYO, and no information is available on the effects of the drug on the breastfed infant or the effects on the drug on milk production. One published study reports that budesonide is present in human milk following maternal inhalation of budesonide *(see Data)*. Routine monitoring of linear growth in infants is recommended with chronic use of budesonide in the nursing mother. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TARPEYO and any potential adverse effects on the breastfed infant from TARPEYO, or from the underlying maternal condition.
Data One published study reports that budesonide is present in human milk following maternal inhalation of budesonide, which resulted in infant doses approximately 0.3% to 1% of the maternal weight-adjusted dosage and a milk to plasma ratio was approximately 0.5. Budesonide was not detected in plasma, and no adverse events were noted in the breastfed infants following maternal use of inhaled budesonide.
Assuming a daily average milk intake of about 150 mL/kg/day and a milk to plasma ratio of 0.5, the estimated oral dose of budesonide for a 5-kg infant is expected to be less than 2 mcg/day for a maternal dose of 16 mg TARPEYO. Assuming 100% bio-availability in the infant this is about 0.1% of the maternal dose and about 3% of the highest inhaled dose used clinically for asthma in infants.

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of TARPEYO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic Impairment

Patients with moderate to severe hepatic impairment (Child-Pugh Class B and C, respectively) could be at an increased risk of hypercorticism and adrenal axis suppression due to an increased systemic exposure to budesonide *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*. Avoid use in patients with severe hepatic impairments (Child-Pugh Class C). Monitor for increased signs and/or symptoms of hypercorticism in patients with moderate hepatic impairment (Child-Pugh Class B).

10 OVERDOSAGE

Reports of acute toxicity and/or death following overdosage of corticoids are rare.
In the event of acute overdosage, no specific antidote is available. Treatment consists of supportive and symptomatic therapy.

Please see Full Prescribing Information for TARPEYO at TARPEYOhcp.com

US-NEF-2100056-B v 2.0

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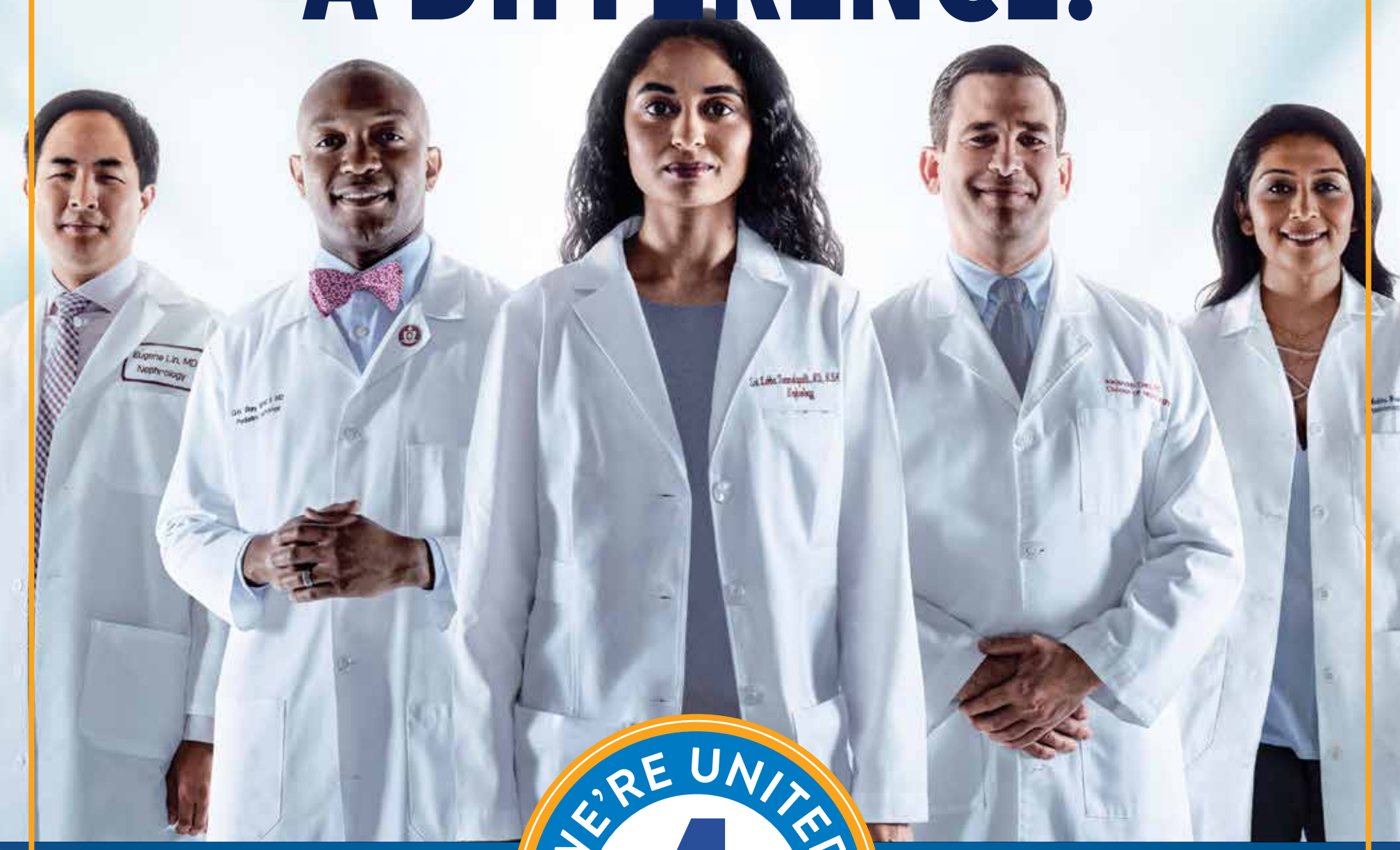

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Can Medicare's End-Stage Renal Disease Treatment Choices Model Meaningfully Increase Home Dialysis Use and Transplantation?

By Christina Chang and Eugene Lin

The nephrology community is in the middle of a randomized trial, aimed at increasing home dialysis use and kidney transplants (1). Experts broadly agree that both modalities are under-used in the United States. The policy experiment—known as the End-Stage Renal Disease Treatment Choices (ETC) model—is being implemented by the Center for Medicare & Medicaid Innovation. ETC randomized 30% of the country to mandatory participation and holds participating providers financially accountable for home dialysis and transplant waitlisting rates.

A recent study in *JAMA Health Forum* (2), however, questions the model's efficacy. Using data from all eligible dialysis facilities and managing clinicians under the ETC model, the authors analyzed 18,621 patients initiating dialysis during the first 8 months of the policy. The study found that participating regions (i.e., those subject to ETC's payment adjustments) did not have statistically different home dialysis rates compared with control regions (only 0.1 percentage points over a base of 20.6%). The study raises a provocative question: Will ETC's large financial incentives succeed in boosting home dialysis and transplantation rates?

Still, it is probably too soon to dub ETC a policy failure. Given that the financial incentives of the model increase over time and that scaling home dialysis programs can be difficult, future analyses may demonstrate a positive effect on increasing home dialysis use and kidney transplants. However, if ETC is unable to achieve its aims, policymakers must ask, "Why? Were the financial incentives large enough to effect change? Is home dialysis uptake inelastic to incentives because other constraints (e.g., disruptions to the supply chain and patient reticence to home therapies) predominate?

This year, look for studies examining why home dialysis uptake remains sluggish. Moreover, as additional data on ETC are released, look for whether the policy adequately addresses inequities in home dialysis use and transplantation (3). Irrespective of what investigators find, ETC provides a unique opportunity to test whether financial incentives can effectively promote these underutilized modalities. ■

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Disclosures: Ms. Chang reports no conflicts of interest. Dr. Lin receives salary support from the National Institute of Diabetes and Digestive and Kidney Diseases (grants K08 DK118213 and R03 DK131239) and ASN's KidneyCure and receives consulting income from Acumen, LLC, a federal contractor. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Results from the first year of a nationwide randomized clinical trial that provides financial incentives to ESKD facilities and managing clinicians to increase home dialysis rates

KidneyNews

US Center for Medicare & Medicaid Innovation

End-Stage Renal Disease Treatment Choice (ETC) model

Medicare patients with ESKD
≥66 years
(initiated dialysis in 2021)

302
Hospital Referral Regions (HRRs)
Data collection thru 12/31/2021

18,621
Eligible patients

74.8 [1.05]
Mean [SD] Age

57.9% Men
42.1% Women

5.2% Asian
17% Black
4.3% Hispanic

Any home modality in 1st 90 days, %

20.60 [7.77]
Value in control HRRs, Mean [SD]

0.12 [-1.42 to 1.65]
Between treatment and control HRRs, Mean difference [95% CI]
p=0.89

None of the secondary outcomes differed significantly between groups

Conclusion The trial results found that in the first year of the US Center for Medicare & Medicaid Innovation–designed ETC model, HRRs assigned to the model did not have statistically significantly different rates in home dialysis compared with control HRRs. This raises questions about the efficacy of the financial incentives provided, although further evaluation is needed, as the size of these incentives will increase in subsequent years.

Yunan Ji, Liran Einav, Neale Mahoney, Amy Finkelstein. ***Financial Incentives to Facilities and Clinicians Treating Patients With End-stage Kidney Disease and Use of Home Dialysis A Randomized Clinical Trial.*** JAMA Health Forum. 2022;3(10):e223503. doi:10.1001/jamahealthforum.2022.3503

Visual Graphic by Edgar Lerma, MD, FASN

2023: Year of Flozination and Hypertension

By Kenar D. Jhaveri and Swapnil Hiremath

As November 2022 rolled in, and ASN Kidney Week and the American Heart Association were in session, several major publications appeared in high-impact medical journals that will change practice in 2023 and beyond.

In our opinion, the 10 published studies discussed below highlight the end of 2022.

10 Anticoagulation in patients with chronic kidney disease (CKD) and kidney failure is challenging. Although no one likes warfarin, and the direct oral anticoagulants are easier to use, there are no trials in this space for patients with kidney failure on dialysis. The RENAL-AF (1) trial was published at the end of 2022 to help answer this question. This was a prospective, randomized, open-label, blinded-outcome evaluation of apixaban vs. warfarin in patients receiving hemodialysis with atrial fibrillation and a CHA_2DS_2-VASc score ≥2. Patients were randomized 1:1 to apixaban (5 mg twice daily; 2.5 mg twice daily with age ≥80 years and/or weight ≤60 kg) or dose-adjusted warfarin. The 1-year rates for major or clinically relevant, non-major bleeding were 32% and 26% in apixaban and warfarin groups, respectively, whereas 1-year rates for stroke or systemic embolism were 3.0% and 3.3% in apixaban and warfarin groups, respectively. Death was the most common major event in the apixaban (21 patients [26%]) and warfarin (13 patients [18%]) arms. Unfortunately, enrollment was very slow, and there was inadequate power to draw any firm efficacy conclusions. As a result, the study was terminated early. But it was very clear that clinically relevant bleeding events were approximately 10-fold more likely than stroke or systemic embolism among this population on anticoagulation. Whether we even need to give anticoagulation in patients with kidney failure on dialysis for atrial fibrillation is the bigger question for the next trial.

Anticoagulation in patients with chronic kidney disease and kidney failure is challenging.

9 Dialysis-related studies are important for our community. An interesting study published in 2022 assessed the association between nephrologist ownership of freestanding dialysis facilities and certain clinical outcomes (2). Reassuringly, patient treatment by nephrologist owners at their owned facilities was associated with a 2.4% higher probability of home dialysis, a 2.2% lower probability of receiving an erythropoiesis-stimulating agent, and no significant difference in anemia or blood transfusions. Patient treatment by nephrologist owners at their owned facilities was not associated with differences in missed treatments, transplant waitlisting, mortality, hospitalizations, 30-day readmissions, hemodialysis adequacy, or fistula or long-term dialysis catheter use. This was a fascinating study showcasing how profit motives did not compromise patient-centered nephrologists' care within the constraints of this cross-sectional examination.

8 Hypertension (HTN) management is an important problem in general medicine, cardiology, and nephrology. Having more agents using novel pathways will add to the armamentarium for the battle against HTN. The next two trials published in November 2022 highlighted two novel agents for HTN management. PRECISION, a multicenter, blinded, randomized, parallel-group, phase 3 study, supports the role of endothelin (ET) receptor antagonists (ERAs) in the treatment of resistant HTN (3). Although the ET pathway has been implicated in the pathogenesis of HTN, it is currently not targeted therapeutically, and this could contribute to the failure to control HTN with currently available drugs. ET-1 is a vasoconstrictive peptide that causes neurohormonal and sympathetic activation, increased aldosterone synthesis and secretion, endothelial dysfunction, vascular hypertrophy and remodeling, and fibrosis. ET-1 acts through two receptors: ETA and ETB. Activation of ETA receptors in vascular smooth muscle cells results in vasoconstriction, whereas ETB receptor activation results in vasoconstriction in the vascular smooth muscle cells and vasodilation through nitric oxide release in endothelial cells. Aprocitentan is a novel, oral, dual ETA/ETB antagonist that has demonstrated a more favorable tolerability (less edema from unopposed ETB stimulation in single ETA inhibitors such as atrasentan) and improved safety profile in early clinical trials compared with other ERAs studied (4). Importantly, aprocitentan has a longer half-life and less liver toxicity than the dual ETA/ETB inhibitor bosentan used in pulmonary HTN. The unique design of the study, including a 4-week, double-blind, placebo-controlled treatment phase; a 32-week single-blind, active-treatment phase; and a 12-week, double-blind, placebo-controlled withdrawal phase provides robust data on short-term and, importantly, long-term safety and efficacy of aprocitentan with both office and ambulatory blood measurement. The safety profile, long half-life (44 h), and low potential for drug–drug interactions are conducive for a chronic treatment to be used for patients who often have several comorbidities and are treated with multiple agents. The effect shown in this study was consistent across multiple key subpopulations. Importantly, these results open the possibility of aprocitentan being used in other kidney diseases.

7 Aldosterone synthase inhibitors target a likely cause of treatment resistance by suppressing hormone synthesis rather than by blocking the downstream mineralocorticoid receptor. The first aldosterone synthase inhibitor to enter clinical development (osilodrostat) was associated with off-target inhibition of cortisol synthesis and was ultimately repurposed to treat excess cortisol states rather than HTN (5). Preclinical and phase 1 studies have shown that baxdrostat has high selectivity (selectivity ratio, 100:1) for aldosterone synthase compared with the enzyme required for cortisol synthesis (11β-hydroxylase), which shares 93% sequence similarity with aldosterone synthase. In a recent phase 2 trial of 248 patients published in 2022 (6), the investigators examined the efficacy and safety of baxdrostat in patients with treatment-resistant HTN. The difference in the change in systolic blood pressure between the 2-mg group and the placebo group was –11.0 mm Hg, and the difference in this change between the 1-mg group and the placebo group was –8.1 mm Hg. No deaths occurred during the trial, no serious adverse events were attributed by the investigators to baxdrostat, and there were no instances of adrenocortical insufficiency. Baxdrostat-related increases in the potassium level of 6.0 mmol/L or greater occurred in two patients, but these increases did not recur after withdrawal and reinitiation of the drug. This class would potentially serve to be more effective at removing circulating aldosterone (and consequent target organ damage), as well as for those who are intolerant of existing mineralocorticoid antagonists, especially the high doses often required in primary aldosteronism.

6 Anticoagulation in patients with kidney failure on dialysis is important, as we discussed earlier. Yet another study—the AXADIA trial—was a prospective, randomized, open, blinded outcome assessment of apixaban vs. vitamin K antagonists (VKAs) for atrial fibrillation in patients on hemodialysis (7). The two arms were either apixaban (2.5 mg twice per day) or the VKA phenprocoumon (international normalized ratio [INR], 2.0–3.0). The composite primary safety outcome was defined by a first event of major bleeding; clinically relevant, non-major bleeding; or all-cause death. The primary efficacy outcome was a composite of ischemic stroke, all-cause death, myocardial infarction, and deep vein thrombosis and/or pulmonary embolism. Composite primary safety outcome events occurred in 22 patients (45.8%) on apixaban and in 25 patients (51.0%) on VKA (hazard ratio [HR], 0.93; 95% confidence interval [CI], 0.53–1.65; p (noninferiority) = 0.157). Composite primary efficacy outcome events occurred in 10 patients (20.8%) on apixaban and in 15 patients (30.6%) on VKA. There were no significant differences regarding individual outcomes (all-cause mortality, 18.8% vs. 24.5%; major bleedings, 10.4% vs. 12.2%; myocardial infarctions, 4.2% vs. 6.1%, respectively). In summary, comparing apixaban with VKA in patients with atrial fibrillation on hemodialysis with long follow-up, no differences were observed in safety or efficacy outcomes. Interestingly, even on oral anticoagulation, patients with kidney failure on hemodialysis with atrial fibrillation remain at high risk of cardiovascular events. Should we move to using an agent that does not require monitoring of INR?

5 We often get asked by our surgical and anesthesia colleagues to perform dialysis on the day before or the day of surgery in patients with kidney failure on hemodialysis. There really were not much data for that statement until a recent study, again in 2022, that may change the way we should practice perioperative hemodialysis. A retrospective cohort study of over 1 million procedures among more than 340,000 patients with kidney failure on hemodialysis looked at 1-, 2-, or 3-day intervals between the most recent hemodialysis treatment and the surgical procedure (8). The authors found that the longer intervals between the last hemodialysis session and surgery were significantly associated with higher risk of 90-day mortality in a dose-dependent manner regardless of the number of days they compared. In addition, undergoing hemodialysis on the same day as surgery was associated with a significantly lower hazard of mortality vs. without same-day hemodialysis. In the analyses that evaluated the interaction between the hemodialysis-to-procedure interval and same-day hemodialysis, undergoing hemodialysis on the day of the procedure significantly attenuated the risk associated with a longer hemodialysis-to-procedure interval. Yes, the study design is retrospective, the magnitude of the absolute risk differences is small, and the findings are susceptible to residual confounding, but we may have to face the possibly that our surgical and anesthesia colleagues do have a point.

4 Next is the MyTEMP study (9) that focused on temperature used in maintenance hemodialysis and use of cooled dialysate or not. MyTEMP was a pragmatic, two-arm, parallel-group, registry-based, open-label, cluster-randomized superiority trial done at 97 hemodialysis

centers with 15,413 patients undergoing approximately 4.3 million treatments in Ontario, Canada. Interestingly, rather than patients, centers were randomized in this cluster-randomization design. The intervention was personalized cooler dialysate (temperature, 0.5°C–0.9°C below each patient's pre-dialysis body temperature with a lowest recommended dialysate temperature of 35.5°C or a standard temperature dialysate of 36.5°C for all patients and treatments). The study showed that the mean dialysate temperature was 35.8°C in the cooler dialysate group and 36.4°C in the standard temperature group. The primary outcome of major adverse cardiovascular outcomes occurred in 1711 of 8000 patients (21.4%) in the cooler dialysate group vs. 1658 of 7413 patients (22.4%) in the standard temperature group. The blood pressure had no major difference. The popularity of cooler dialysate as a blanket option for the whole dialysis unit is called into question by this study, although the risks and benefits of cooler dialysate in some patients on hemodialysis who are susceptible or high risk may need further study.

3 We often wonder, as renin-angiotensin system (RAS) inhibitors are kidney protective, does stopping them at stage 4–5 CKD increase the glomerular filtration rate (GFR) and provide some breathing space in the relentless path to dialysis? To this end, the STOP ACEi (angiotensin-converting enzyme inhibitor) investigators (10) sought to assess whether discontinuing RAS inhibitors in patients with progressive stage 4–5 CKD would slow the GFR decline. Just over 400 participants were randomized in a 1:1 fashion to continue RAS inhibitors or to discontinue them. The STOP ACEi trial did not find any benefit by stopping ACEi (or angiotensin receptor blockers) in advanced CKD for the primary outcome of GFR decline. Indeed, the discontinuation arm had a 6% numerically higher risk of needing dialysis and a numerically higher risk of cardiovascular events as well. Strengths are obvious in the numbers and large randomized clinical trial study. The study cohort included primarily participants who were White, limiting the generalizability of these findings to other ethnicities. The open-label nature of this study may have contributed to bias, particularly with respect to subjective end points (e.g., quality of life), and the indication for starting dialysis. Nevertheless, perhaps in the era of good anti-hyperkalemia agents, stopping RAS inhibitors is probably not needed unless they are hypotensive.

2 The final top 2 studies published in November 2022 really are a win for nephrology and the cardiovascular community. The sodium glucose cotransporter 2 (SGLT2) inhibitors, or flozins, have truly arrived. A meta-analysis published in *Lancet* (11) really highlights the importance of this. Thirteen trials involving 90,413 participants were included. In total, 82% were patients with type 2 diabetes, and the remainder did not have diabetes. Compared with placebo, adding an SGLT2 inhibitor reduced the risk of kidney disease progression by 37% (relative risk, 0.63; 95% CI, 0.58–0.69) with similar relative risks in patients with and without diabetes. In the four CKD trials, relative risks were similar irrespective of the primary kidney diagnosis. SGLT2 inhibitors reduced the risk of acute kidney injury and cardiovascular death and hospitalization for congestive heart failure each by 23% regardless of whether participants had diabetes. SGLT2 inhibitors also reduced the risk of cardiovascular death but did not significantly reduce the risk of non-cardiovascular death. For all outcomes, results were broadly similar irrespective of trial mean baseline estimated GFR. Per authors, based on estimates of absolute effects, the absolute benefits of SGLT2 inhibition outweighed any hazards of ketoacidosis or amputation.

1 The EMPA-KIDNEY trial tops the list. EMPA-KIDNEY (12) is a multinational, randomized, parallel-group, double-blind, placebo-controlled trial of the SGLT2 inhibitor empagliflozin. The primary outcome of kidney disease progression or cardiovascular death occurred in 432 of 3304 patients (13.1%) in the empagliflozin group vs. 558 of 3305 patients (16.9%) in the placebo group—a 28% risk reduction with empagliflozin. This was greater than the 18% that had been required for the power calculations. Hospitalization due to any cause was significantly lower in the empagliflozin group, occurring at a rate of 24.8/100 patient-years vs. 29.2 hospitalizations/100 patient-years in the placebo arm, indicating a 14% relative risk reduction. This is one of the largest flozin studies to date for patients with kidney diseases with and without diabetes. There were more than 800 patients with immunoglobulin A nephropathy in this study as well (13). This looks like yet another win for flozinate. There was significant benefit in terms of the primary outcome with empagliflozin, with good safety and tolerability. The benefits extend into populations without diabetes (confirming DAPA-CKD [14]) and down to a GFR of 20 mL/min/1.73 m^2.

The end of 2021 saw more glomerular disease trials; the end of 2022 heading into 2023 showcased more magic of flozination and highlighted novel, anti-HTN medication pathways. ■

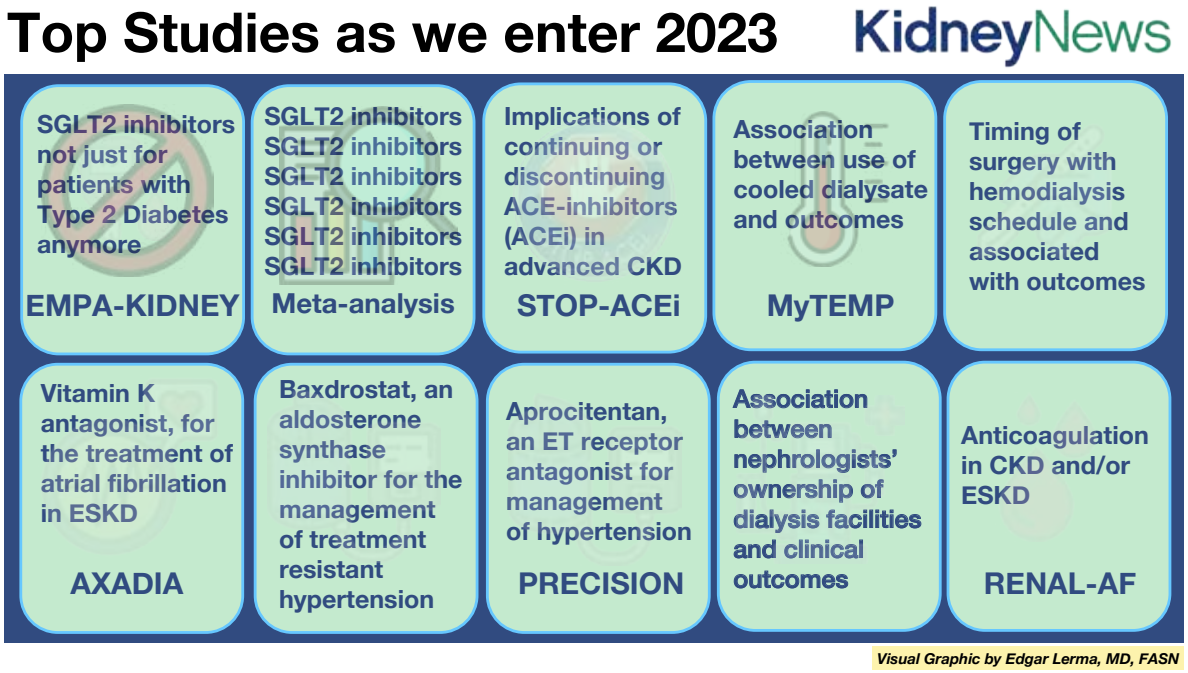

Figure created by Dr. Edgar Lerma to summarize the top 10 top studies.

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The authors report no conflicts of interest.

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Post-AKI Care Is a Research Priority

By Jia H. Ng

Acute kidney injury (AKI) occurs in 16%–25% of patients who are hospitalized and is linked to death and higher risk of chronic kidney disease and permanent kidney failure (1–4). As recovery from moderate to severe AKI may take several months, patients are discharged to recover through self-management and outpatient care. Yet, studies investigating AKI intervention outside of the hospital setting are limited.

Research studies on pharmacotherapy to treat AKI have shown disappointing results, leading to increased interest in improving processes of care for AKI. This is because the health care needs of patients with AKI are variable and dynamic. Depending on the type of AKI, severity of AKI, kidney recovery, and comorbidities, each patient will need a different care plan. Some patients will need full nephrology care at the dialysis unit, whereas some patients will need intermittent monitoring of kidney function, medication dosing adjustment, and resumption of nephroprotective medication. However, there is no clear evidence for how to care for patients who survive an episode of AKI after hospitalization. Barriers to developing interventions for post-AKI care are numerous and include: 1) a lack of understanding about the different phenotypes of AKI and their recovery period; 2) heterogeneity in the definition of kidney recovery; 3) suboptimal transition of care plans due to poor communication channels; and 4) high variability in care delivered after hospital discharge in terms of specialties (nephrology vs primary care), modalities (in-person vs televisits), and frequency of follow-up (5, 6).

Interventions to improve post-AKI care

Research communities and professional AKI workgroups recognize the need to improve post-AKI care. The Acute Disease Quality Initiative and the AKINow: Recovery/Post-AKI Workgroup have included post-AKI care as part of their research priorities (5, 6). Additionally, the National Institute of Diabetes and Digestive and Kidney Diseases recently awarded grant funding to the University of Pittsburgh, Cleveland Clinic, and Vanderbilt University Medical Center for the Caring for Outpatients after AKI study. The goal of the 5-year project is to assess interventions to improve clinical and patient-centered outcomes after a patient has developed an AKI.

Thus, for 2023, we anticipate more publications related to the following:

1. Identification of best practices and interventions to improve clinical and patient-centered outcomes
2. More effort into understanding and improving processes for post-AKI care
3. Review standardized definition of AKI recovery and outcome measures
4. The use of digital technology to improve post-AKI care (e.g., telemedicine, digital mobile platforms, and better health information technology interoperability)
5. Effective education for health providers, patients, and care partners. ■

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The author reports no conflicts of interest.

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Dialysis Companies Continue to Face Economic Challenges

By Katherine Kwon

Dialysis companies will continue to face a challenging economic environment in 2023. That is the conclusion the market has drawn, based on the trend in stock prices for the publicly traded large dialysis organizations, DaVita and Fresenius Medical Care (FMC). Fewer patients needing dialysis, higher labor costs, and anemic reimbursement updates are all dragging down the bottom line.

The COVID-19 pandemic, entering its fourth year, has precipitated multiple adverse impacts on the business of providing dialysis to patients with end stage kidney disease (ESKD). Analysis of the U.S. Renal Data System population data suggested that the population of patients with ESKD had an absolute decrease of 0.6% in the first year after the pandemic started and a decrease of 3.5% from the expected population, based on the pre-pandemic established rate of growth (1). Higher mortality from COVID-19 in patients with ESKD, as well as in patients with advanced chronic kidney disease (CKD), has led to fewer patients needing dialysis treatments.

Labor costs have increased significantly across all segments of the health care market, and dialysis staff are no exception. In a second-quarter earnings call last year, FMC described higher staff turnover rates and reported paying significant wage premiums to temporary staffing agencies, while it struggled with a shortage of permanent dialysis nurses (2). DaVita blamed rising labor costs in its third-quarter earnings call in which the company reported it had fallen far short of earnings' expectations (3). Despite rapidly rising labor costs, the Centers for Medicare & Medicaid Services has adopted only a 3.1% increase in the bundled payment rate for dialysis in 2024 (4). This will not be expected to cover the total increase in labor costs. There have already been reports of units closing due to staffing shortages (5, 6).

The medium-term outlook does not suggest that these conditions will improve any time soon. The viral forecast is for continued waves of illness, with influenza and other respiratory viruses adding to the toll on top of new COVID-19 variants. These will continue to lead to excess mortality in patients with ESKD. Although robust vaccination uptake can reduce mortality losses, the illness will still contribute to missed treatments and higher hospitalization rates, which also adversely impact dialysis units' financial performance.

Continued pressures could trigger larger-scale changes at both companies. In October 2022, an investment firm with a history of initiating corporate restructuring acquired a significant stake in the parent company of FMC, Fresenius SE & Co. (7). This led to speculation that the dialysis division may be placed up for sale. Given the approximate 40% share of the dialysis market held by FMC, an ownership change would be a major shakeup. DaVita is less vertically integrated than FMC and may push further into value-based CKD care to make up lost revenue from dialysis.

What does all this mean to nephrologists? Unit closures will probably continue. This can force patients to travel farther for life-saving care and depending on the market, may force them to change nephrologists. Losing patients with ESKD is a significant financial hit under both fee-for-service and value-based care payment models. Joint-venture opportunities, which allow nephrologists to own a fraction of a dialysis unit, are financially more risky in such an adverse environment. Medical directorships, which are paid by the dialysis company to the physician, may also be aggressively renegotiated.

Nephrology has suffered for decades from being too dependent on dialysis as the major source of revenue. The advent of nephrology-specific, value-based care payment models under the 2019 Advancing American Kidney Health executive order had already started revaluing care of patients with earlier stages of CKD. This movement has been enhanced by the advent of new treatment options that are more effective at preserving kidney function and preventing kidney failure. Nephrology practices should continue to search for ways to diversify their income streams, including value-based care arrangements, ancillary services, and research. This will offer some protection from the anticipated continuing pressures in dialysis care. ■

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The author reports no conflicts of interest.

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The 2022 Nephrology Match: More Filled Programs, More Filled Positions…and More Offered Positions

By Samira S. Farouk

It's that time of year again—results of the 2022 National Resident Matching Program (NRMP) Medicine and Pediatric Specialties Match are out. Among 39 specialties (including adult, pediatric, addiction, and multidisciplinary specialties), a total of 3361 programs offered 8724 positions. Of all positions, 88% were filled, with cardiovascular disease, interventional pulmonology, and oncology filling all offered positions (1).

In 2009, nephrology's "heyday," 95% of 367 offered positions filled—with 89% of adult nephrology programs filling (2). These numbers reached a decade-nadir in 2016 with 59% of 466 offered positions filled and only 41% of programs filling. For the 2023 academic year (AY), 178 adult nephrology programs offered 493 positions (an increase of 9 from AY 2022), with 58% (a 7% increase from AY 2022) and 73% (a 5% increase from AY 2022) of programs and offered positions filling, respectively (1, 2). Out of 42 pediatric nephrology programs and 67 offered positions for this year's match, 17 of 42 (40%) and 36 of 67 (54%) programs and offered positions were filled, respectively (1).

Among adult specialties, nephrology ranked 5th in offered positions, 6th in filled positions, 11th in percentage of programs filled, and 12th in percentage of positions filled in the 2022 Match (Figures 1 and 2). Since 2009, the number of nephrology offered positions has increased by over 30%, with the number of filled positions increasing by only 3% (2). The number of new spots included in the few years after the 2009 Match was likely a result of the "all in" match policy (3) and the inclusion of existing positions, which were not listed previously. Although the number of filled positions has modestly increased over the last few years, we have a clear supply-greater-than-demand mismatch. One potential solution, although with its own challenges, was outlined in a 2017 editorial: "We believe that these trends and hiring practices are not good for nephrology and that radical solutions are needed to reverse the ongoing disinterest in our field. We believe that the best way to save nephrology is to reduce the number of training program slots to <300" (4).

A 2020 focus group study of 25 internal medicine residents (5) cited several well-known factors associated with lack of interest in nephrology as a subspecialty: high complexity; low compensation and prestige; and lack of exposure, advances, and mentors. Although the nephrology community's efforts to address some of these challenges may be contributing to slowly recovering Match statistics, the supply of offered positions continues to increase. Let's keep calm, keep recruiting, and think about innovative approaches to tackle the supply-demand inequality.

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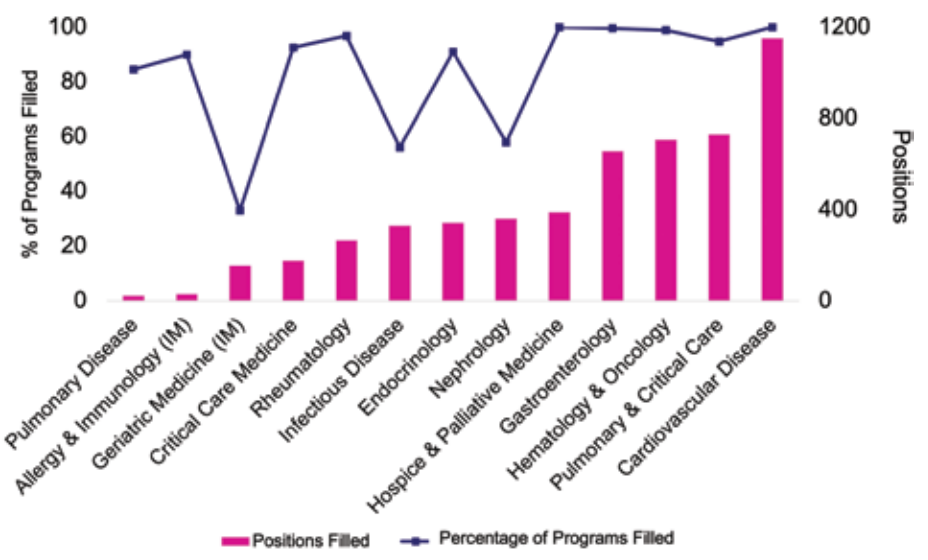
Figure 1. Adult specialty spots offered, filled, and percentage filled

Data based on 2022 NRMP statistics.

Figure 2. Adult specialty spots filled and percentage of programs filled



Data based on 2022 NRMP statistics.

What Is New in the Glomerular Diseases' Armamentarium?

By Mayuri Trivedi

Glomerular diseases are probably one of the most satisfying subspecialities of nephrology.

As we step into the new year of 2023, we eagerly look forward to all that can help us fight glomerular diseases better and faster and with maximum efficiency. We review some of the late-breaking trials from Kidney Week 2022, which will help us keep our eyes open for the real action in the world of glomerulonephritis.

Roccatello et al. (1) have aimed to study the safety and efficacy of an intensified B-cell depletion induction therapy (IBCDT) in lupus nephritis (LN). The proposed regimen was comprised of weekly rituximab (375 mg/m^2) and two more doses after 1 and 2 months. It also included two infusions of 10 mg/kg cyclophosphamide (three methylprednisolone pulses), followed by oral prednisone (tapered to 5 mg/day by the third month) without an immunosuppressive maintenance regimen, compared with standard of care in biopsy-proven LN. At the end of 1 year, they found that the IBCDT was as efficacious as the conventional therapy of LN (with the advantage of not requiring any further maintenance therapy and much lower doses of steroids compared with conventional therapy). Now, that seems to be a promising, new regimen given the fact that patients with lupus have a very long and intense amount of immunosuppression.

The Safety and Efficacy Study of VIS649 for IgA [immunoglobulin A] Nephropathy (NCT04287985) is a global, multicentric, randomized controlled trial that has evaluated monthly intravenous sibeprenlimab (a humanized IgG2 monoclonal antibody that prevents the A proliferation-inducing ligand) in IgA nephropathy vs. placebo. In this interim analysis of a phase 2 study, Kooienga et al. (2) have demonstrated an acceptable tolerability and safety profile with a significant reduction in the urinary protein excretion and stabilization of the estimated glomerular filtration rate when compared with the placebo at 9 months of study. Depending on the final results, this study marks an intense attack on the pathobiology of IgA nephropathy treatment.

Barratt et al. (3) explored the use of cemdisiran, a subcutaneously administered, investigational RNA interference therapeutic that completely inhibits the hepatic production of C5 of the complement cascade for the therapy of patients with IgA nephropathy with proteinuria greater than 1 g/day. This phase 2, randomized, double-blinded, placebo-controlled trial (A Study of Cemdisiran in Adults with Immunoglobulin A Nephropathy [IgAN]; NCT03841448) in adults has shown a promising result in reduction of proteinuria at week 32 of the study with an acceptable safety profile, including lack of infections with encapsulated organisms.

As we await the opening of the Pandora's box of glomerular diseases therapy, we hope that we improve our knowledge and are able to offer more precise and less toxic therapy to our patients. Keep a look out please!

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The author reports no conflicts of interest.

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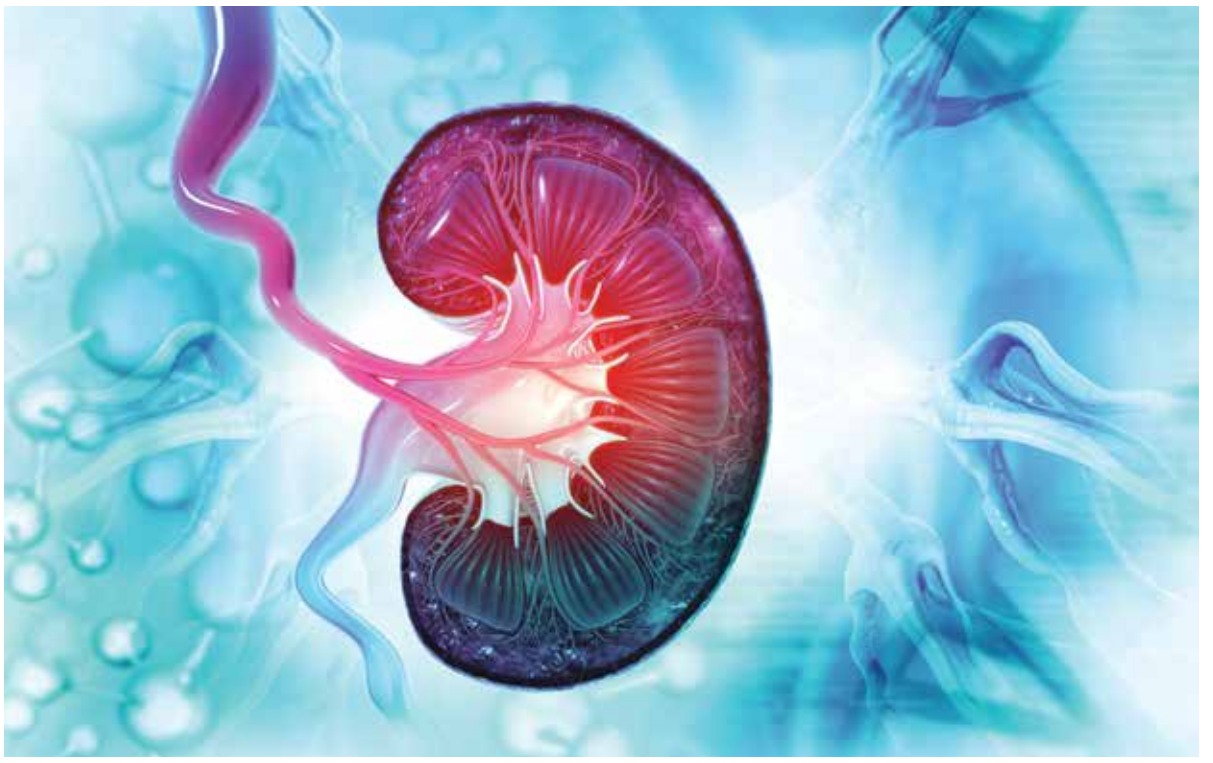
New Era in Treatment of Anemia in Chronic Kidney Disease?

By Arash Rashidi



Treatment of anemia in patients with chronic kidney disease (CKD) has been a matter of debate over the past 20–30 years. Earlier landmark trials, such as CHOIR (1), CREATE (2), and TREAT (3), tried to address appropriate hemoglobin levels in patients and whether treatment with erythropoiesis-stimulating agents (ESAs) had any short- or long-term complications.

The discovery of the hypoxia-inducible factor (HIF), one of the key regulators that controls how cells respond to hypoxic conditions, has diverted recent trials in this direction. HIF enhances kidney and hepatic erythropoietin synthesis and iron uptake by the intestine and opposes the deleterious effects of hepcidin. This discovery led to the creation of HIF prolyl hydroxylase inhibitors (HIF-PHIs), which are newer medications being developed to treat anemia in patients with CKD. These drugs offer the advantage of being dosed orally as opposed to existing ESAs, which are administered either intravenously or subcutaneously. This process triggers multiple phenomena, including an increase in erythropoietin and transferrin production and in iron bioavailability and a decrease in hepcidin levels, which all aid in treating anemia in patients with CKD.

In the PRO2TECT study (4), patients with CKD who were not on dialysis were randomized to receive either vadadustat, an HIF-PHI, or darbepoetin. The study included two, phase 3, randomized, open-label, active-controlled, noninferiority trials to compare vadadustat with darbepoetin alfa. The study showed that vadadustat was noninferior to darbepoetin alfa with regard to hematologic efficacy, but vadadustat was inferior to darbepoetin alfa in the time to the first occurrence of major adverse cardiovascular events, which were defined as the composite of all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke.

The ANDES trial (5) was a randomized clinical trial in 916 patients with CKD with anemia who were not on dialysis. The study found that oral roxadustat was superior to placebo in hemoglobin correction and maintenance with the same overall tolerability. In the OLYMPUS trial (6), nondialysis patients with CKD with anemia received roxadustat versus placebo. The study showed a significant increase in the hemoglobin level and a decreased need for blood transfusions in the roxadustat group with a side effect profile similar to that of placebo. The ALPS study had similar findings (7). In the HIMALAYAS study (8), 1043 patients with anemia, who were new to dialysis and had never received an ESA, received either roxadustat or epoetin alfa. The study showed that roxadustat was noninferior to epoetin alfa in correcting and maintaining hemoglobin levels, with comparable adverse-event rates with either treatment. Vadadustat demonstrated comparable efficacy (maintenance of target hemoglobin level) and safety noninferiority to ESAs in its phase 3 INNO2VATE global clinical trial involving 3950 patients on dialysis (9) (Table 1).

Five HIF-PHIs (including roxadustat and vadadustat) have been approved in Japan; roxadustat has also been approved in China, South Korea, Chile, and the European Union, but recently, the US Food and Drug Administration (FDA) voted against roxadustat and vadadustat. FDA's Cardiovascular and Renal Drugs Advisory Committee indicated that roxadustat's benefit-risk profile does not support approval for anemia of CKD in adults. The FDA questioned signals of increased all-cause death, major adverse coronary events, thrombotic events, thrombosis in vascular access sites among patients receiving dialysis, infections, and seizures in patients who received roxadustat compared with control patients. Similar concerns were raised about vadadustat. Now, we should wait and see if the FDA will approve daprodustat to treat anemia in patients with CKD who are and are not on dialysis in February 2023. ■

Table 1. Summary of major trials on HIF-PHI agents in patients with CKD on dialysis and not on dialysis

Study (reference)	Population	HIF-PHI	Outcome
PRO2TECT (4)	CKD-nondialysis	Vadadustat vs. darbepoetin	Vadadustat was not inferior to darbepoetin regarding hemoglobin correction.
ANDES (5)	CKD-nondialysis	Roxadustat vs. placebo	Roxadustat was superior to placebo.
OLYMPUS (6)	CKD-nondialysis	Roxadustat vs. placebo	Roxadustat was superior to placebo.
ALPS (7)	CKD-nondialysis	Roxadustat vs. placebo	Roxadustat was superior to placebo.
HIMALAYAS (8)	CKD-on dialysis	Roxadustat vs. epoetin alfa	Roxadustat was noninferior to epoetin alfa.
INNO2VATE (9)	CKD-on dialysis	Vadadustat vs. darbepoetin	Vadadustat was not inferior to darbepoetin.

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The author reports no conflicts of interest.

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