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Sex and Gender Differences Deserve More Study in Kidney Diseases

By Ruth Jessen Hickman

Before the National Institutes of Health (NIH) Revitalization Act, women were largely underrepresented in clinical trials, partly out of concerns for teratogenic effects. The act, passed in 1993, made it mandatory that clinical trials funded through NIH include data from women and minorities (1).

The percentage of women included in clinical trials has improved significantly since that time (2), although women are still underrepresented with respect to disease prevalence in some reports (3). However, data from men and women are often still aggregated together, and analyses based on sex are often not reported.

Clinical studies often lack sufficient statistical power to examine sex differences, said Christine Maric-Bilkan, PhD, a program director of the Division of Kidney, Urologic, and Hematologic Diseases in the NIH's National Institute of Diabetes and Digestive and Kidney Diseases. "There should be no barriers to reporting data by sex, and many journals are in fact insisting on papers including data by sex, so that should help," she said.

Females have also been underrepresented in the scientific research underlying these clinical trials. For example, most basic science studies are still performed on male kidneys, and much of what is known about basic physiology and pharmacokinetics is derived from studies performed in males (4). In 2015, the NIH released recommendations that sex be considered in the research design, analyses, and reporting of preclinical studies, although this was not mandated (5).

However, studies of sex differences are still scarce. "The vast majority of preclinical studies are being conducted in males, either in cells or animals," said Maric-Bilkan. "Unfortunately, this trend is not unique to any one research discipline or field, as a similar male bias has been reported across the board: neuroscience, immunology, cardiovascular, renal, etc."

Still, some fields have made more research progress in this area than others.

"If we compare ourselves to cancer or cardiology research, we in nephrology are a bit behind in terms of understanding how sex hormones and sex hormone receptors are playing a role in these diseases," said Eman Gohar, PhD, an instructor in the Division of Nephrology at the University of Alabama at Birmingham. One of her areas of expertise is sex differences in kidney diseases.

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Interim Report on Race and Kidney Function Addresses Process

By Eric Seaborg

The National Kidney Foundation-American Society of Nephrology (NKF-ASN) Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease released its highly anticipated interim report at the start of April. Published concurrently in *JASN* and the *American Journal of Kidney Diseases* (*AJKD*), the report lays out the process the task force is following.

It will take a couple more months to formulate the recommendations, according to a joint statement from the presidents of ASN and NKF, issued on March 9, 2021.

Although many stakeholders expressed hope for a recommended replacement for the use of a race factor in estimated glomerular filtration rate (eGFR) as soon as possible, the news that this report lacked recommendations was greeted mainly with an acknowledgment that the original timeline was overly ambitious for the complex undertaking. "Although I think I (and the medical community) all hoped for immediately actionable recommendations, it is understandable that this is a challenging task in the very short term,"

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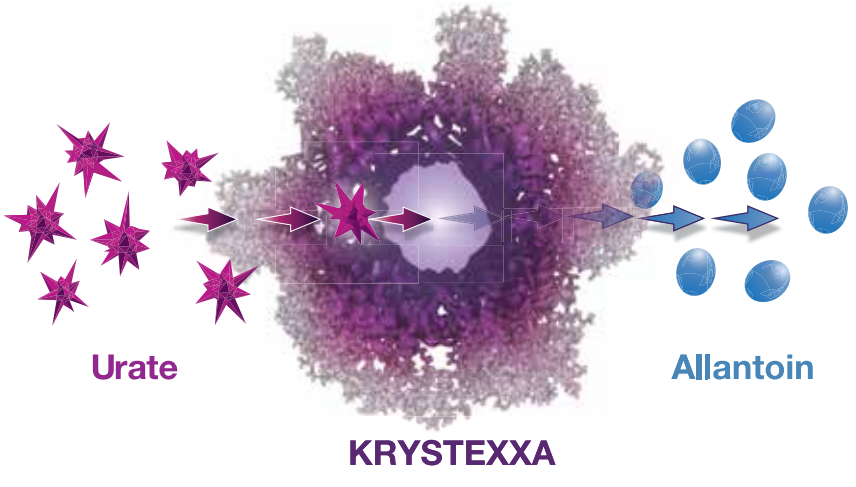
Inside

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



Artist's renditions.

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

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATIONS AND USAGE

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

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

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS AND INFUSION REACTIONS

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

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

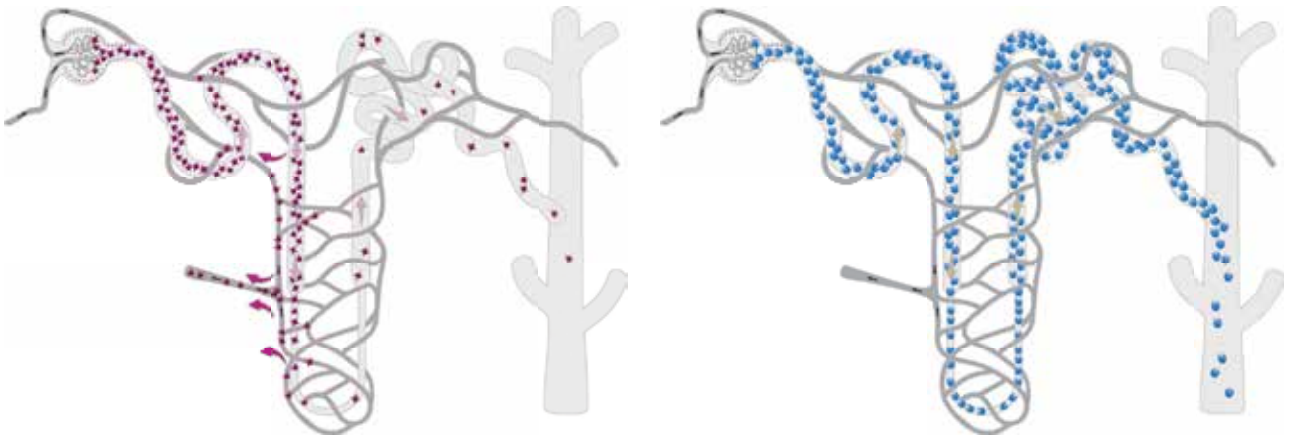
Concomitant use of KRYSTEXXA and oral urate-lowering agents may blunt the rise of sUA levels. Patients should discontinue oral urate-lowering agents and not institute therapy with oral urate-lowering agents while taking KRYSTEXXA.

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

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

HORIZON

URICASE ENZYME THAT CONVERTS URATE



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

VS

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

TO LEARN MORE, VISIT KRYSTEXXAHCP.COM

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

CONTRAINDICATIONS: G6PD DEFICIENCY ASSOCIATED HEMOLYSIS AND METHEMOGLOBINEMIA

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

GOUT FLARES

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

CONGESTIVE HEART FAILURE

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

ADVERSE REACTIONS

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

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

KRYSTEXXA® pegloticase

KRYSTEXXA®
pegloticase

(pegloticase injection), for intravenous infusion

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

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

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

INDICATIONS AND USAGE

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

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

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

CONTRAINDICATIONS

Glucose-6-phosphate dehydrogenase (G6PD) deficiency

WARNINGS AND PRECAUTIONS

Anaphylaxis

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

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

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

Infusion Reactions

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

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

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

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

G6PD Deficiency Associated Hemolysis and Methemoglobinemia

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

Gout Flares

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

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

Congestive Heart Failure

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

Re-treatment with KRYSTEXXA

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

Immunogenicity

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

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

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

Postmarketing Experience

General disorders and administration site conditions: asthenia, malaise, peripheral swelling have been identified during postapproval use of KRYSTEXXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

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

Renal Impairment

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

OVERDOSAGE

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

PATIENT COUNSELING INFORMATION

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

General Information

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

Anaphylaxis and Infusion Reactions

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

Glucose-6-phosphate dehydrogenase (G6PD) Deficiency

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

Gout Flares

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

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Interim Report on Race and Kidney Function

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said Elaine Ku, MD, director of the Nephrology Transition Clinic at the University of California, San Francisco (UCSF), who published a study earlier this year in *JASN* on modifying eGFR thresholds for transplant lists to lessen racial disparities.

The intense spotlight on racial inequities—in American society as a whole brought on by the Black Lives Matter movement and in healthcare highlighted by COVID-19—led ASN and NKF to form the task force in August 2020. Co-chaired by Cynthia Delgado, MD, and Neil R. Powe, MD, MPH, MBA, both at UCSF, the taskforce includes 14 members with broad expertise in healthcare disparities, epidemiology, health services research, genetic ancestry, clinical chemistry, patient safety and performance improvement, pharmacology, and social sciences, as well as two patients.

The task force members "collectively agreed on the confidentiality of deliberations (including refraining from social media commentary) to promote candid opinions and exchange of ideas," so it did not respond to requests for comment for this article.

The interim report lays out the history and rationale for the use of a race coefficient in eGFR, and the task force inventoried a wide range of potential approaches to eGFR in which race is considered and not considered, including those most widely used currently, those recently adopted at some institutions, and those that have been suggested and are under development. "The use of race to estimate GFR and possible replacements [has] shortcomings that the task force is currently examining," the report notes. "Nationwide, many institutions have made independent decisions to address race in estimation of GFR, but these approaches vary, and therefore, GFR estimates and subsequent care decisions are not standardized. Final recommendations will be made after the task force examines the strengths and weaknesses of existing and newer approaches to estimating GFR."

The importance of the work was underscored by the publication of an accompanying joint editorial by Josephine P. Briggs, MD, editor-in-chief of *JASN*, and Harold I. Feldman, MD, MSCE, editor-in-chief of *AJKD*. "The task force's interim report documents a process being undertaken with extraordinary care and thoroughness," they wrote. "As editors we recognize that journals have participated in the dissemination and perpetuation of science that casts race as a biologic construct. Much is being written about how race is a flawed concept, a societal construct that oversimplifies and at times distorts. The editorial teams of both *JASN* and A*JKD* are committed to re-examining our own roles and the language we use to talk about these problems."

All deliberate speed

There is an acknowledged race-against-time element because some institutions feel the pressure to change the equations they use—and some already have (see https://www.kidneynews.org/view/journals/kidney-news/12/10/11/article-p1_1.xml). In a press release announcing the task force interim report, ASN and NKF urged institutions "not to make any changes to how they estimate kidney function until the task force provides its recommendation for the best approach to replace the existing equations for estimating kidney function."

"I think there is definite concern that some institutions have already enacted changes that they feel are warranted, but it is unclear to me if these decisions were always supported by evidence-based data that outcomes would be improved through the changes that were implemented," UCSF's Ku said. "It is important that any systematic changes that are implemented are carefully considered and supported by evidence that they will achieve the intended goal of mitigating racial disparities in kidney disease outcomes."

"Due deliberation is needed, but preliminary recommendations to act on very soon would be great to avoid huge community variations in practice," said Richard Lafayette, MD, Professor of Nephrology at Stanford University Medical Center. "While it is reasonable for local communities to act quickly on behalf of their population, a deliberative, fully considered solution is a worthwhile goal."

The task force also notes the larger context that "assessing the inclusion of race in estimating GFR is part of a larger conversation in addressing racial disparities in kidney health."

"Beyond the inclusion of race in clinical algorithms like eGFR, ASN and NKF assert that racism manifests in many aspects of health care," ASN President Susan E. Quaggin, MD, FASN, said in a statement accompanying the release of the report. "Both organizations commit to providing resources and expertise to the essential job of dismantling systemic racism in kidney care, research, and education." ■

Clarification

The March *Kidney News* story, "Cold, Power, and Water Outages Temporarily Upend Dialysis Care in Texas," states, "Home dialysis patients could not dialyze without water and power, and home hemodialysis patients who can dialyze without water and power struggled to find ways to safely warm their dialysate fluid in freezing homes." For clarification, the statement should read: "Many home dialysis patients could not dialyze without power, and home dialysis patients who could dialyze without water and power struggled to find ways to safely warm their dialysate fluid in freezing homes. Deliveries of dialysate may also have been affected during the storm." ■

Sex and Gender

Continued from page 1

Researchers are increasingly realizing that sex and gender influence kidney function in both normal and pathophysiologic conditions. Noting that there is much to learn about the mechanisms underlying these differences, Maric-Bilkan stated: "There is increasing recognition that examining sex and gender differences in disease pathophysiology could lead to development of sex-specific therapeutic treatments."

Sex versus gender

To navigate this topic, it is important to clarify sex and gender. The US Institute of Medicine guidelines describe sex differences as biologic differences between men and women. These include differences due to sex hormones but also differences due to chromosomes and sex-specific gene expression. Gender refers to an individual's sense of themselves as a male or female in society (6). Although people often underscore the effects of sex hormones when discussing sex differences in this context, epidemiologic differences between the sexes in kidney disease incidence or progression might reflect a whole host of factors, including socially mediated ones.

But differences due to sex hormones, particularly estrogen, have been the focus of a great deal of the existing research. It is now well recognized that sex hormones have biologic effects extending beyond the reproductive system. Different receptor subtypes for estrogen and testosterone are widely found in many different parts of the body, including the kidney (4).

A large body of research implicates sex steroidal hormones as major contributors to normal and pathophysiologic sex differences in the kidney. The classic estrogen receptors, ERα and ERβ, act in the cell nucleus of kidney cells to stimulate gene expression. More recently, researchers have discovered a G-protein-linked estrogen receptor that can initiate more rapid signaling in kidney cells. Much remains to be learned about the exact location and intended function of these estrogen receptor subtypes in kidney cells, as well as for subtypes of androgen receptors (4).

Premenopausal women appear to be somewhat protected from kidney disease compared with age-matched men across multiple types of nephropathies. This relative protection seems to disappear during menopause. Women who undergo oophorectomy have a higher incidence of chronic kidney disease (CKD) as well, also suggesting a protective role for estrogens. Studies in animal models also strongly suggest that as a whole, estrogens, particularly estradiol, exert kidney-protective effects. In contrast, testosterone has been found to promote kidney disease progression in most animal models (4).

However, the picture is complex, especially when data from studies in humans are analyzed. The prevalence of CKD is higher in women than in men, but the prevalence of kidney failure is higher in men (4). Studies contrasting the rates of progression of CKD in men versus women have shown some conflicting results, although the authors of a 2019 systematic review posited that kidney disease progresses more quickly in men (7).

Why the discrepancies in prevalence?

The reasons for these discrepancies continue to be teased out, but multiple mediating factors have been proposed. The use of a single cutoff point of estimated glomerular filtration rate (GFR) to define CKD might lead to an overdiagnosis of CKD in women because it may not account for normal physiologic differences in rates (7). Differences due to sex hormones; sex chromosomes; renal hemodynamics size; and lifestyle factors such as smoking and healthcare use, including earlier initiation of dialysis in men compared with women, may also account for these discrepancies (8).

In some situations, social and cultural factors may mask underlying biologic and physiologic tendencies, making interpretation difficult. "We need to acknowledge differences in access to care, compliance with medications, speed of referral to dialysis, and discrepancies in kidney transplantation in men versus women," Gohar said.

Maric-Bilkan also underscored the need for more rigorous, well-designed observational studies that focus on defining sex differences in disease development and progression and that consider the sex-specific categorization of kidney disease severity. "These studies should address the role of sex-related biologic differences and differences in psychosocial, lifestyle, and other factors," she said. "They should take into account the menopausal status of the patients, hormone therapy use, and history of use of oral contraceptives, which may also affect kidney disease progression."

The pathways potentially mediating the nephroprotective effects of estrogen are still being elucidated.

Researchers know, for example, that sex hormones modulate endothelin, a potent vasoactive factor with disease implications for essential hypertension and kidney disease. Animal studies demonstrate important sex-related differences in endothelin receptor subtype expression, abundance, and function (9).

Immune signaling pathways have also been shown to be affected by sex and sex steroids, and these might also influence differences in kidney pathophysiology. Other potential avenues being explored include differential modulation of reactive oxygen species via redox signaling pathways (10). A research article published by Gohar and colleagues in the *Journal of the American Heart Association* demonstrates a novel function for the G-protein-coupled estrogen receptor in the kidney (10). Its activity was found to have a direct impact on sodium excretion, influencing blood pressure and kidney excretory function in female rats.

One challenge with working with estrogen as a potential therapy is its broad presence in multiple organ systems and resulting off-target effects. The potential risks/benefits of hormone replacement therapy in menopausal women were brought into question by the famous Women's Health Initiative outcomes, which unexpectedly raised concerns about the cardiovascular impact of such supplementation. Although later analyses have highlighted the importance of properly timing hormone replacement therapy and have raised questions about study design, many clinicians and patients still have concerns about its risks and benefits (11).

Treatments targeting specific subtypes of estrogen receptors may prove fruitful research avenues. For example, Gohar said, one could focus on the G-protein-coupled estrogen receptor that has been shown to elicit protective actions in the cardiovascular and renal systems in females, which might theoretically make them viable drug targets in postmenopausal women.

Much might be learned at the basic science level by studying models of kidney disease in which the female kidney is relatively protected, such as hypertension, acute kidney injury, and diabetic kidney disease. Uncovering the mechanisms that underlie this protection may ultimately contribute to the development of novel therapeutic choices in both women and men.

Gohar pointed out that women's kidneys are physiologically equipped to handle pregnancy, which poses huge challenges in fluid and electrolyte management. She suggested that improving our knowledge of female kidney physiology may ultimately lead to better understanding of preeclampsia and broader insights into pathologic changes in the kidney.

In addition to investigations into the contribution of sex hormones, research into other physiologic and social factors influencing epidemiology will be key. "Studies in other fields have brought to attention that X- or Y-linked genes, parental imprinting, or X mosaicism also contribute to sex differences," said Maric-Bilkan.

A thorough consideration of potential sex differences is also critical in initial study design. In an analysis of drugs withdrawn by the US Food and Drug Administration from 1997 to 2000, four out of 10 drugs had to be removed because of side effects in women (12). Women and men may experience different drug exposure resulting from differences in drug absorption, distribution, and metabolism as well as body weight. More research attention to these issues might allow for drug approvals in subsets of the population or might point the way toward adjustments of drug dosage in women that might lower toxicity.

Such study designs present research challenges, especially when women are stratified on the basis of premenopausal versus postmenopausal status. But such complexities at least need to be acknowledged and reported, Gohar said.

With the exception of treatments for diseases unique to each sex, very few diseases are currently treated differently in men versus women, Maric-Bilkan said. A better understanding of these issues would provide important data to help move toward more personalized medicine. Ideally, new therapeutic approaches to kidney disease could be tailored based on patients' gender and hormonal status.

"The more studies examining sex differences in renal function and pathophysiology, the more information we will have on what pathways may be targeted for drug development. Also, better understanding of disease pathophysiology could inform how existing therapies may be adapted and optimally used in both women and men," Maric-Bilkan said. ■

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The Nephropathologist Is Essential to Nephrology Fellowship Education

By Kammi J. Henriksen, MD

Nephrology and nephropathology have been intimately linked since the dawn of the kidney biopsy era in 1951 (1, 2). To develop an understanding of kidney physiology and kidney disease, the integration of structure and function is essential. Close clinicopathologic correlation is important to manage patients with kidney disease, from making the correct diagnosis to interpreting various prognostic features to developing treatment plans.

One of the core competencies established by the Accreditation Council for Graduate Medical Education (ACGME) is to demonstrate knowledge of nephropathology involving both native and transplant kidneys (3). Nephrology fellows must be able to incorporate the pathologic findings on light, immunofluorescence, and electron microscopy in order to arrive at a diagnosis. They must also become familiar with the various kidney disease-specific classification and reporting systems in order to understand prognostic and therapeutic implications. Throughout nephrology fellowship, access to nephropathology education and kidney biopsy material is vital.

Have we been successful at integrating nephropathology into nephrology training?

There are many ways in which nephropathology can be incorporated into nephrology fellowship training. Daily interactions, weekly/biweekly informal biopsy reviews (in person at the microscope or via videoconferencing), monthly biopsy conferences, and introductory nephropathology lectures are common. In addition, some centers have a dedicated pathology elective. Fellows may choose to attend regional or national kidney pathology conferences/workshops. Notably, there is a growing list of web-based learning opportunities (Table 1).

A survey of practicing nephrologists conducted in 2010 by Berns et al. (4) revealed that the majority (57%) felt competent and well trained in interpretation of kidney biopsy pathology, whereas ~40% reported some training but not enough to achieve competence, and <5% reported little or no training. More recently in 2017, a survey of nephrology fellowship program directors conducted by Mechery et al. (5) found that the majority of respondents (61%) were satisfied with nephropathology education for their fellows, whereas 36% were satisfied but thought there was room for improvement, and 3% were dissatisfied. Finally, a survey of nephrology fellows conducted by Rope et al. (6) in 2017 showed that a significant proportion of fellows (32%) would like to receive additional instruction in kidney pathology interpretation during fellowship.

What factors contribute to fellows developing competency in nephropathology?

Pathology education in nephrology fellowships varies across institutions and depends greatly on the presence of a nephropathologist on site, how involved the nephropathologist is, the frequency of nephropathology conferences, the volume of kidney biopsy material, and other factors. In the same survey by Mechery et al. (5), the vast majority of programs (82%) had a nephropathologist on site, and these program directors were more likely to be satisfied with their nephropathology education. Most program directors (72%) reported that their nephropathologists were "very involved" with teaching (versus 21% frequently involved, 2% infrequently involved, and 5% sometimes involved), and the very involved programs had a higher level of satisfaction. Not surprisingly, program directors at institutions with more kidney biopsies performed per year were also more likely to be satisfied with pathology education. When respondents were asked specifically about shortcomings, the most common answers were "not enough kidney biopsies performed," "lack of an in-house nephropathologist," and "lack of resources to schedule nephropathology conferences."

How can we improve pathology education for nephrology fellows?

We need to make a concerted effort to enhance nephropathology exposure during nephrology fellowship, especially considering that approximately one-third of fellows have reported a need for additional training in kidney biopsy interpretation (6). Fellowship programs should examine the frequency of their formal and informal nephropathology educational sessions and consider increasing them. The augmented use of teleconferencing may help improve the convenience and frequency of educational sessions. Fellows should be encouraged to pursue pathology electives/shadowing and to attend regional and national conferences/workshops with a nephropathology component. Finally, several high-quality web-based educational opportunities have become available (Table 1) due to the emergence of digital pathology and the social media revolution (7–9). These resources should be introduced at the beginning of nephrology fellowship and their use encouraged throughout, particularly at programs with limited resources for on-site nephropathology. ■

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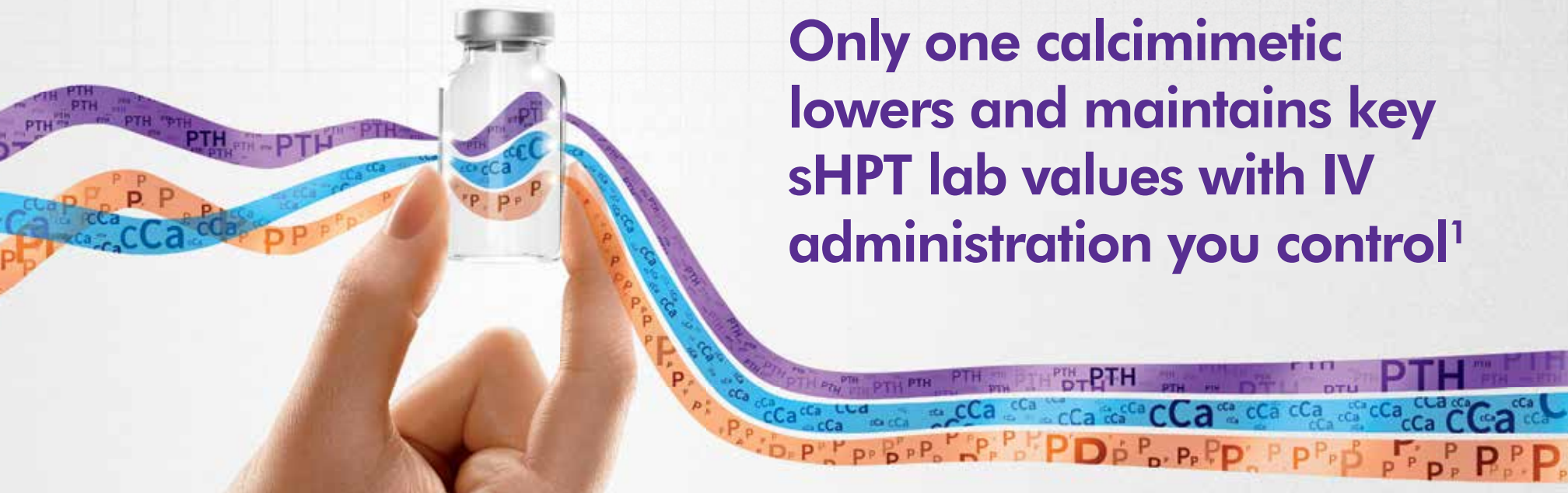
Table 1. Online nephropathology resources

GlomCon – Nephropathology Essentials	https://glomcon.org/glomerular-disease-study-trial-consortium/nephropathology-essentials-2018-2019/
Renal Fellow Network – Kidney Biopsy of the Month	https://www.renalfellow.org/category/kidney-biopsy-of-the-month/
AJKD – Atlas of Renal Pathology II	https://www.ajkd.org/content/atlasofrenalpathologyii
Renal Pathology Society – Webinar Series	https://renalpathsoc.org/Renal-Pathology-Society-Patient-Webinar-Series
Renal Pathology Society – Case of the Month (membership required for access)	https://renalpathsoc.org/
GlomCon Virtual Fellowship	https://edu.glomcon.org/fellowship
NephSIM Path 101	https://nephsim.com/pathology-approach/
Arkana Live Kidney Pathology Series (NephJC, NephSIM, KIDNEYcon)	https://www.arkanalabs.com/category/arkana-live/
Washington University in St. Louis Nephrology Web Series	https://www.youtube.com/channel/UC1mJLTtBsf6PT-buiv08vcOA



Only one calcimimetic lowers and maintains key sHPT lab values with IV administration you control[1]

Not an actual Parsabiv™ vial.
The displayed vial is for illustrative purposes only.

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

Indication

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

Limitations of Use:

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

Important Safety Information

Contraindication: Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred.

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

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

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

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

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

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

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

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

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

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium.

Reference: 1. Parsabiv™ (etelcalcetide) prescribing information, Amgen.

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

Visit **ParsabivHCP.com** for more information.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

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

Limitations of Use:

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

CONTRAINDICATIONS

Hypersensitivity

PARSABIV is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred with PARSABIV *[see Adverse Reactions (6.1) in PARSABIV full prescribing information]*.

WARNINGS AND PRECAUTIONS

Hypocalcemia

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

QT Interval Prolongation and Ventricular Arrhythmia

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

Seizures

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

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

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

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

Worsening Heart Failure

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

Upper Gastrointestinal Bleeding

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

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

Adynamic Bone

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

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

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

Description of Selected Adverse Reactions

Hypocalcemia

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

Hypophosphatemia

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

QTc Interval Prolongation Secondary to Hypocalcemia

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

Hypersensitivity

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

Immunogenicity

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

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

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

Lactation

Risk Summary

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

Data

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

Pediatric Use

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

Geriatric Use

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

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

OVERDOSAGE

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

AMGEN®

PARSABIV™ (etelcalcetide)

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

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

Detective Nephron

Detective Nephron, world-renowned for his expert analytic skills, trains budding physician-detectives, most recently L.O. Henle, in the diagnosis and treatment of kidney diseases. Mackenzie Ula Densa, a budding nephrologist, plans to present a new case to the master consultant.

Nephron (*gazing out the window*): 2021 has finally arrived. What do you have for us today, my dear apprentice?

Mac I have a 76-year-old woman with…

Nephron (*turning to face the door*): Who are you? Where is L.O. Henle?

L.O. Henle enters.

Henle Meet Dr. Mackenzie Ula Densa. She is our new budding nephrologist. We all call her Mac. I figure I can graduate myself to help you going forward.

Nephron You wish, Henle. And welcome, Mac.

Henle and Mac take a seat.

Nephron COVID-related thrombotic microangiopathy? COVID-related collapsing FSGS? What is it? Tell me! Tell me!

Mac Trust me; you are going to love this one!

Nephron Come on, spill the *beans*… no pun intended.

Mac Hmm…hold your horses. Didn't I mention hyperphosphatemia?

Nephron Stop! You are already sounding like Henle. I like you already. And phosphorus—what an amazing topic! Nephrologists love phosphorus cases (NOT).

Nephron What was her calcium and serum creatinine?

Henle (*laughing out loud*): Even better…she's on dialysis and has been on dialysis for years.

Nephron (*angry*): Oh, come on. End-stage renal disease—oops, my bad; kidney disease—patient with hyperphosphatemia. Let me guess: not taking her binders. What is the big deal here, Henle?

Mac (*surprised*): Shush. Let me tell you a bit more before you lose interest. She had chronic IgA nephropathy for years and then started dialysis 2 years ago and has been receiving long-term hemodialysis (HD) three times weekly through a tunneled central venous catheter. Her comorbid conditions include type 2 diabetes, hypertension, dyslipidemia, and hypothyroidism. Her medications include lisinopril, metoprolol, levothyroxine, pantoprazole, sertraline, clopidogrel, atorvastatin, allopurinol, and vitamins. She receives epoetin alfa, 6000 units, with each HD treatment but is currently not treated with vitamin D or etelcalcetide or cinacalcet.

Nephron (*bored, rolling his eyes*): And what is the phosphorus?

Mac Routine monthly laboratory test results showed that phosphate levels had been very well controlled, ranging between 3.5 and 5.5 mg/dL for the past few months. She is taking calcium acetate, 667 mg, two tablets three times daily; her parathyroid hormone values are in the low to normal range of 50 to 160 pg/mL since she started kidney replacement therapy. But the strange thing is that this month the patient had a serum phosphate level of 12.1 mg/dL.

Nephron Has she been getting adequate dialysis? What is her urea reduction ratio?

Mac Yes. It is >70%. The repeat value for phosphorous is 13.4 mg/dL.

Nephron Stop right there. Before we go any further, this is just diet related. Hyperphosphatemia in a dialysis patient is pretty simple. It's usually related to noncompliance with diet or binders. Ask her to stop drinking milk and eating beans! Come on, Henle, move on with it.

Mac (*wondering to herself about quick decision by Nephron*): For your information, her calcium level was 9.0 mg/dL: within the normal range. The patient's clinical status was unchanged at the time, and she insisted there had been no change in diet or medication adherence. She did admit to some unintentional weight loss recently.

Nephron Oh, no! Hmmm…acute kidney injury with hyperphosphatemia is exciting, a dialysis patient with hypercalcemia can be exciting, but hyperphosphatemia?

Mac The laboratory also confirms that the values are accurate.

Nephron (*jumping in*): Tell her to watch her diet more, and let's get a repeat value in 1 to 2 weeks.

Two weeks later

Henle Hmmm. The value is worse; now it is 18 mg/dL. The rest of her blood work shows no real changes.

Nephron (*shocked*): This is impressive! Let's break this down a bit further and deal with it as if she were not on dialysis. There are five ways to get high phosphorus levels in the laboratory results: acute phosphate load, acute extracellular shift of phosphate, acute kidney injury or chronic kidney disease, primary increase in tubular phosphate reabsorption, or spurious.

Mac Examples of marked tissue breakdown leading to acute phosphate overload can be tumor lysis syndrome, rhabdomyolysis, and, rarely, marked hemolysis or transfusion of stored blood.

Nephron Of course, and I assume all those test results were negative.

Mac Yes, creatinine kinase, lactate dehydrogenase, free light chains, haptoglobin, and uric acid were all in range and not suggestive of an acute process, as stated above.

Nephron Perfect! Sometimes dialysis patients are unable to recall all their medications. They have several other providers, and dialysis units don't always have the best medication reconciliation records. Hyperphosphatemia from exogenous sources is most commonly induced by the ingestion of large amounts of phosphate-containing laxatives and sometimes in some antiseizure medications as well.

Mac (*confused*): No, she is not taking any such medications. I specifically asked about Fleet's Phospho-Soda. I also don't think there is shifting going on, as is seen with lactate or ketoacidosis. No laboratory results suggestive of that, either.

Nephron Is there anything on her physical examination?

Henle Nothing specific except some trace edema bilaterally in the lower extremities. Her blood pressure was high, at 160/90 mm Hg.

Nephron Did you speak with the dialysis staff about any prescription changes of her dialysis?

Mac As mentioned earlier, she has been getting good dialysis with adequate clearance. I also spoke with her son, who lives with her, and she really has been very good with her diet.

Nephron (*puzzled*): Given that her kidney function is abnormal, I doubt this is a tubular phosphate absorption issue, which rules out hypoparathyroidism, fibroblast growth factor-23 overproduction, acromegaly due to insulin-like growth factor effects on phosphorus, or vitamin D overdose. These all seem unlikely!

Mac Yes, I agree. I didn't check a fibroblast growth factor-23 level, given that she is a dialysis patient, and it would be high anyway. Her 25-hydroxy vitamin D level is in the normal range, and her 1,25-vitamin D level is appropriately low.

Nephron Pseudo?! Hmm.… Spurious hyperphosphatemia due to interference with analytic methods may rarely occur in patients with hyperglobulinemia (immunoglobulin of any type in excess quantity), hyperlipidemia, hemolysis, and hyperbilirubinemia. You said there was no light chain concern and no signs of hemolysis. Is she jaundiced?

Henle and Nephron exit to visit the patient at the bedside. She is sitting comfortably with no acute discomfort. Her dialysis treatment has just completed. She does not appear pale or jaundiced. She has no edema. Her flowsheets report a fluid removal of 1.4 kg. She received epoetin alfa 6000 units today and alteplase 1 mg/mL after HD treatments to prevent clotting.

Nephron Henle, bedside rounds are the best. Brilliant!

Mac (*confused*): I don't understand. Did you just figure it out?

Nephron Fascinating information. Unexplained hyperphosphatemia in patients receiving dialysis is most often blamed on nonadherence to dietary restrictions or phosphate binders. In patients with a central catheter as HD access, the differential diagnosis of hyperphosphatemia must always include the use of tissue plasminogen activator (tPA), which may erroneously increase blood phosphate levels because of an improper blood-drawing technique. Why is she getting alteplase?

Mac and Henle are shocked.

Mac She has been getting tPA for the last month because of blood flow problems with the catheter. Alteplase and phosphorus?

Nephron (*jumping in*): Yes, in some cases we might erroneously observe increased blood phosphate levels because of an improper drawing technique. The label for the alteplase product administered does say it contains 1 g of phosphoric acid in a 100-mg vial, and it is used for pH adjustment.

A few days later

Mac (*surprised*): A peripheral blood draw for laboratory studies from the noncatheter site showed a phosphorus level of 4.0 mg/dL!

Nephron Fantastic. Spurious hyperphosphatemia it is. Tell the staff to be assured this is not real. However, they need to be retrained on the proper technique of drawing blood in a patient with a dialysis catheter. Simply drawing and discarding a volume of blood equal to the volume of the catheter lumen before drawing the blood sample will prevent contamination of the laboratory samples. Clearly, this concern arises with any catheter lock solution, not only alteplase. It is possible that a catheter tip clot may make contamination more likely because drawing blood through the catheter side holes will facilitate contamination with alteplase. Some suggest rinsing the catheter immediately after the 5- to 6-mL of blood has been discarded by attaching a 10-mL syringe and withdrawing and reinfusing 10 mL of blood before drawing laboratory samples to eliminate any possibility of contamination.

Mac Assumptions are bad in medicine. A systematic process is important for developing the differential diagnosis in every case, and sometimes visiting the bedside over and over again can lead to an accurate diagnosis.

Nephron Well done, both of you. Keep an open mind. Again, never assume. Make sure you have gone over all aspects of your differential diagnosis. We cannot assume patients are not eating the appropriate diet and not taking medications for their medical condition.

Henle and Mac (*with a wink*): We were not the one making assumptions this time.

Nephron (*laughing*): Don't even get me started on that one. Let's leave that for a discussion over my favorite New York-style coffee. ■

Detective Nephron was developed by Kenar D. Jhaveri, MD, professor of medicine at Donald and Barbara Zucker School of Medicine at Hofstra/Northwell. Thanks to Dr. Rimda Wanchoo, professor of medicine at Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, and Dr. Eugene Lin, editorial board member for ASN Kidney News *and assistant professor of Medicine and of Health Policy & Management at the University of Southern California, for their editorial assistance. Send correspondence regarding this section to kjhaveri@northwell.edu or kdj200@gmail.com.*

In adults who have T2D and diabetic nephropathy (ie, DKD) with albuminuria >300 mg/day,

INVOKANA® is the only SGLT2i indicated to slow the progression of **DKD**

and reduce the risk of hospitalization for heart failure[1-4]

INVOKANA® is the only T2D therapy approved by the FDA to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults who have T2D and diabetic nephropathy with albuminuria >300 mg/day[1]

In patients with DKD* and T2D

The landmark CREDENCE trial primary composite outcome[5]:

30% RRR

- **End-stage kidney disease†**
  (dialysis, transplant, or eGFR <15)
- **Doubling of serum creatinine**
- **Renal death‡**
- **CV death**

HR=0.70 (95% CI: 0.59, 0.82); *P*=0.00001

- **Reduced risk of hospitalization for heart failure[6§]**
  39% RRR‖ in hospitalization for heart failure
- **Proven safety profile in patients with an eGFR of 30 to <90[1,5]**
  Similar overall AEs with INVOKANA® vs placebo (35.1 vs 37.9 per 100 patient-years). Male GMI incidence was 0.84% vs 0.09% per 100 patient-years, respectively. DKA incidence was 0.22% vs 0.02% per 100 patient-years, respectively. No imbalance in fracture or amputation. Hypotension incidence was 2.8% vs 1.5%, respectively. Hypoglycemia incidence was 4.43 vs 4.89 per 100 patient-years, respectively.

‡There were not enough events to evaluate the risk of renal death (placebo, n=5; INVOKANA®, n=2). **INVOKANA® is not indicated to reduce the risk of renal death.**
§Prespecified secondary endpoint.

Learn more at INVOKANAhcp.com.

INDICATIONS

INVOKANA® (canagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD)
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day

Limitations of Use

INVOKANA® is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

INVOKANA® is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA® is likely to be ineffective in this setting based upon its mechanism of action.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA®, such as anaphylaxis or angioedema
- Patients on dialysis

WARNINGS AND PRECAUTIONS

- **Lower-Limb Amputation:** An increased risk of lower-limb amputations associated with INVOKANA® use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower-limb amputations was observed at both the 100-mg and 300-mg once-daily dosage regimens.

  Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA® in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA® in the two trials). Some patients had multiple amputations, some involving both lower limbs.

Please read additional Important Safety Information and Brief Summary of full Prescribing Information for INVOKANA® on the following pages.

Invokana® (canagliflozin) tablets

AE=adverse event; CREDENCE=Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DKA=diabetic ketoacidosis; DKD=diabetic kidney disease; GMI=genital mycotic infection; HR=hazard ratio; RRR=relative risk reduction; SGLT2i=sodium-glucose co-transporter 2 inhibitor; T2D=type 2 diabetes.
eGFR is measured in mL/min/1.73 m^2.
*With albuminuria >300 mg/day.
†End-stage kidney disease was defined as dialysis for ≥30 days, kidney transplantation, or an eGFR <15 mL/min/1.73 m^2 sustained for ≥30 days.
‖RRR was calculated using the following formula: 100 x (1–HR).

References: 1. INVOKANA® [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc. **2.** Jardiance® [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. **3.** Farxiga® [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP. **4.** Steglatro™ [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. **5.** Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380(24):2295-2306. Supplementary appendix available at: doi:10.1056/NEJMoa1811744. **6.** Mahaffey KW, Jardine MJ, Bompoint S, et al. Canagliflozin and cardiovascular and renal outcomes in type 2 diabetes mellitus and chronic kidney disease in primary and secondary cardiovascular prevention groups. *Circulation*. 2019;140(9):739-750.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

- **Lower-Limb Amputation: (cont'd)**
  Lower-limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

  Before initiating INVOKANA®, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores, or ulcers involving the lower limbs, and discontinue if these complications occur.
- **Volume Depletion:** INVOKANA® can cause intravascular volume contraction, which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine. There have been postmarketing reports of acute kidney injury which are likely related to volume depletion, some requiring hospitalizations and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INVOKANA® in patients with one or more of these characteristics, assess and correct volume status. Monitor for signs and symptoms of volume depletion after initiating therapy.
- **Ketoacidosis:** Ketoacidosis, a serious life-threatening condition requiring urgent hospitalization, has been identified in patients with type 1 and 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA®. Before initiating INVOKANA®, consider factors in patient history that may predispose to ketoacidosis. For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKANA® for at least 3 days prior to surgery. Monitor for ketoacidosis and temporarily discontinue in other clinical situations known to predispose to ketoacidosis. Ensure risk factors for ketoacidosis are resolved prior to restarting therapy. Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA® and seek medical attention immediately if signs and symptoms occur.
- **Urosepsis and Pyelonephritis:** Serious urinary tract infections, including urosepsis and pyelonephritis, requiring hospitalization have been reported in patients receiving SGLT2 inhibitors, including INVOKANA®. Treatment with SGLT2 inhibitors increases this risk. Evaluate for signs and symptoms and treat promptly.
- **Hypoglycemia With Concomitant Use With Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA® may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA®.
- **Necrotizing Fasciitis of the Perineum (Fournier's Gangrene):** Necrotizing fasciitis of the perineum, a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, has been identified in postmarketing surveillance in female and male patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA®. Serious outcomes have included hospitalization, multiple surgeries, and death. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA®.
- **Genital Mycotic Infections:** INVOKANA® increases risk of genital mycotic infections, especially in uncircumcised males or patients with prior infections. Monitor and treat appropriately.
- **Hypersensitivity Reactions:** Hypersensitivity reactions, including angioedema and anaphylaxis, were reported with INVOKANA®; these reactions generally occurred within hours to days after initiation. If reactions occur, discontinue INVOKANA®, treat, and monitor until signs and symptoms resolve.
- **Bone Fracture:** Increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA®. Prior to initiation, consider factors that contribute to fracture risk.

DRUG INTERACTIONS

- **UGT Enzyme Inducers:** Co-administration with rifampin lowered INVOKANA® exposure, which may reduce the efficacy of INVOKANA®. For patients with eGFR ≥60 mL/min/1.73 m^2, if an inducer of UGTs (eg, rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA® 200 mg and who require additional glycemic control.

  For patients with eGFR <60 mL/min/1.73 m^2, if an inducer of UGTs is co-administered with INVOKANA®, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA® 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control.
- **Digoxin:** There was an increase in the AUC and mean peak drug concentration of digoxin when co-administered with INVOKANA® 300 mg. Monitor appropriately.
- **Positive Urine Glucose Test:** Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.
- **Interference With 1,5-Anhydroglucitol (1,5-AG) Assay:** Monitoring glycemic control with 1,5-AG assay is not recommended in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** INVOKANA® is not recommended in pregnant women, especially during the second and third trimesters.
- **Lactation:** INVOKANA® is not recommended while breastfeeding.
- **Pediatric Use:** Safety and effectiveness in patients <18 years of age have not been established.
- **Geriatric Use:** Patients ≥65 years had a higher incidence of adverse reactions related to reduced intravascular volume, particularly with the 300-mg dose; more prominent increase in the incidence was seen in patients who were ≥75 years. Smaller reductions in HbA1c relative to placebo were seen in patients ≥65 years.
- **Renal Impairment:** The efficacy and safety of INVOKANA® for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to <50 mL/min/1.73 m^2). These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of the study. Patients with renal impairment using INVOKANA® for glycemic control may be more likely to experience hypotension and may be at a higher risk for acute kidney injury. INVOKANA® is contraindicated in patients with ESKD on dialysis.
- **Hepatic Impairment:** INVOKANA® has not been studied in patients with severe hepatic impairment and is not recommended in this population.

OVERDOSAGE

- In the event of an overdose, contact the Poison Control Center and employ the usual supportive measures.

ADVERSE REACTIONS

- The most common adverse reactions associated with INVOKANA® (5% or greater incidence) were female genital mycotic infections, urinary tract infections, and increased urination.

cp-68813v5

Please read Brief Summary of full Prescribing Information for INVOKANA® on the following pages.

Invokana®
(canagliflozin) tablets

Janssen Pharmaceuticals, Inc.

Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation.

 October 2020 cp-125458v3

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

INVOKANA®

(canagliflozin) tablets, for oral use

Brief Summary of Prescribing Information.

INDICATIONS AND USAGE

INVOKANA (canagliflozin) is indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
- to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD).
- to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria greater than 300 mg/day.

Limitations of Use

INVOKANA is not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients *[see Warnings and Precautions]*.

INVOKANA is not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA is likely to be ineffective in this setting based upon its mechanism of action.

CONTRAINDICATIONS

- Serious hypersensitivity reaction to INVOKANA, such as anaphylaxis or angioedema *[see Warnings and Precautions and Adverse Reactions]*.
- Patients on dialysis *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS

Lower Limb Amputation: An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. The risk of lower limb amputations was observed at both the 100 mg and 300 mg once daily dosage regimens. The amputation data for CANVAS and CANVAS-R are shown in Tables 3 and 4, respectively *[see Adverse Reactions]*.

Amputations of the toe and midfoot (99 out of 140 patients with amputations receiving INVOKANA in the two trials) were the most frequent; however, amputations involving the leg, below and above the knee, were also observed (41 out of 140 patients with amputations receiving INVOKANA in the two trials). Some patients had multiple amputations, some involving both lower limbs.

Lower limb infections, gangrene, and diabetic foot ulcers were the most common precipitating medical events leading to the need for an amputation. The risk of amputation was highest in patients with a baseline history of prior amputation, peripheral vascular disease, and neuropathy.

Before initiating INVOKANA, consider factors in the patient history that may predispose to the need for amputations, such as a history of prior amputation, peripheral vascular disease, neuropathy and diabetic foot ulcers. Counsel patients about the importance of routine preventative foot care. Monitor patients receiving INVOKANA for signs and symptoms of infection (including osteomyelitis), new pain or tenderness, sores or ulcers involving the lower limbs, and discontinue INVOKANA if these complications occur.

Volume Depletion: INVOKANA can cause intravascular volume contraction which may sometimes manifest as symptomatic hypotension or acute transient changes in creatinine *[see Adverse Reactions]*. There have been post-marketing reports of acute kidney injury which are likely related to volume depletion, some requiring hospitalizations and dialysis, in patients with type 2 diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA. Patients with impaired renal function (eGFR less than 60 mL/min/1.73 m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion or hypotension. Before initiating INVOKANA in patients with one or more of these characteristics, assess and correct volume status. Monitor for signs and symptoms of volume depletion after initiating therapy.

Ketoacidosis: Reports of ketoacidosis, a serious life-threatening condition requiring urgent hospitalization have been identified in clinical trials and postmarketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including INVOKANA. In placebo-controlled trials of patients with type 1 diabetes, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. The risk of ketoacidosis may be greater with higher doses. Fatal cases of ketoacidosis have been reported in patients taking INVOKANA. INVOKANA is not indicated for the treatment of patients with type 1 diabetes mellitus *[see Indications and Usage]*.

Patients treated with INVOKANA who present with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels, as ketoacidosis associated with INVOKANA may be present even if blood glucose levels are less than 250 mg/dL. If ketoacidosis is suspected, INVOKANA should be discontinued, patient should be evaluated, and prompt treatment should be instituted. Treatment of ketoacidosis may require insulin, fluid and carbohydrate replacement.

In many of the postmarketing reports, and particularly in patients with type 1 diabetes, the presence of ketoacidosis was not immediately recognized and institution of treatment was delayed because presenting blood glucose levels were below those typically expected for diabetic ketoacidosis (often less than 250 mg/dL). Signs and symptoms at presentation were consistent with dehydration and severe metabolic acidosis and included nausea, vomiting, abdominal pain, generalized malaise, and shortness of breath. In some but not all cases, factors predisposing to ketoacidosis such as insulin dose reduction, acute febrile illness, reduced caloric intake, surgery, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse were identified.

Before initiating INVOKANA, consider factors in the patient history that may predispose to ketoacidosis including pancreatic insulin deficiency from any cause, caloric restriction, and alcohol abuse.

For patients who undergo scheduled surgery, consider temporarily discontinuing INVOKANA for at least 3 days prior to surgery *[see Clinical Pharmacology (12.2, 12.3) in Full Prescribing Information]*.

Consider monitoring for ketoacidosis and temporarily discontinuing INVOKANA in other clinical situations known to predispose to ketoacidosis (e.g., prolonged fasting due to acute illness or post-surgery). Ensure risk factors for ketoacidosis are resolved prior to restarting INVOKANA.

Educate patients on the signs and symptoms of ketoacidosis and instruct patients to discontinue INVOKANA and seek medical attention immediately if signs and symptoms occur.

Urosepsis and Pyelonephritis: There have been postmarketing reports of serious urinary tract infections including urosepsis and pyelonephritis requiring hospitalization in patients receiving SGLT2 inhibitors, including INVOKANA. Treatment with SGLT2 inhibitors increases the risk for urinary tract infections. Evaluate patients for signs and symptoms of urinary tract infections and treat promptly, if indicated *[see Adverse Reactions]*.

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues: Insulin and insulin secretagogues are known to cause hypoglycemia. INVOKANA may increase the risk of hypoglycemia when combined with insulin or an insulin secretagogue *[see Adverse Reactions]*. Therefore, a lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with INVOKANA.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Reports of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious and life-threatening necrotizing infection requiring urgent surgical intervention, have been identified in postmarketing surveillance in patients with diabetes mellitus receiving SGLT2 inhibitors, including INVOKANA. Cases have been reported in both females and males. Serious outcomes have included hospitalization, multiple surgeries, and death.

Patients treated with INVOKANA presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed for necrotizing fasciitis. If suspected, start treatment immediately with broad-spectrum antibiotics and, if necessary, surgical debridement. Discontinue INVOKANA, closely monitor blood glucose levels, and provide appropriate alternative therapy for glycemic control.

Genital Mycotic Infections: INVOKANA increases the risk of genital mycotic infections. Patients with a history of genital mycotic infections and uncircumcised males were more likely to develop genital mycotic infections *[see Adverse Reactions]*. Monitor and treat appropriately.

Hypersensitivity Reactions: Hypersensitivity reactions, including angioedema and anaphylaxis, have been reported with INVOKANA. These reactions generally occurred within hours to days after initiating INVOKANA. If hypersensitivity reactions occur, discontinue use of INVOKANA; treat and monitor until signs and symptoms resolve *[see Contraindications and Adverse Reactions]*.

Bone Fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed in patients using INVOKANA in the CANVAS trial *[see Clinical Studies (14.2) in Full Prescribing Information]*. Consider factors that contribute to fracture risk prior to initiating INVOKANA *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Lower Limb Amputation *[see Warnings and Precautions]*
- Volume Depletion *[see Warnings and Precautions]*
- Ketoacidosis *[see Warnings and Precautions]*
- Urosepsis and Pyelonephritis *[see Warnings and Precautions]*
- Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues *[see Warnings and Precautions]*
- Necrotizing Fasciitis of the Perineum (Fournier's gangrene) *[see Warnings and Precautions]*
- Genital Mycotic Infections *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Warnings and Precautions]*
- Bone Fracture *[see Warnings and Precautions]*

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

Pool of Placebo-Controlled Trials for Glycemic Control: The data in Table 1 is derived from four 26-week placebo-controlled trials where INVOKANA was used as monotherapy in one trial and as add-on therapy in three trials. These data reflect exposure of 1,667 patients to INVOKANA and a mean duration of exposure to INVOKANA of 24 weeks. Patients received INVOKANA 100 mg (N=833), INVOKANA 300 mg (N=834) or placebo (N=646) once daily. The mean age of the population was 56 years and 2% were older than 75 years of age. Fifty percent (50%) of the population was male and 72% were Caucasian, 12% were Asian, and 5% were Black or African American. At baseline the population had diabetes for an average of 7.3 years, had a mean HbA_{1C} of 8.0% and 20% had established microvascular complications of diabetes. Baseline renal function was normal or mildly impaired (mean eGFR 88 mL/min/1.73 m^2).

Table 1 shows common adverse reactions associated with the use of INVOKANA. These adverse reactions were not present at baseline, occurred more commonly on INVOKANA than on placebo, and occurred in at least 2% of patients treated with either INVOKANA 100 mg or INVOKANA 300 mg.

Table 1: Adverse Reactions from Pool of Four 26–Week Placebo-Controlled Studies Reported in ≥ 2% of INVOKANA-Treated Patients*

Adverse Reaction	Placebo N=646	INVOKANA 100 mg N=833	INVOKANA 300 mg N=834
Urinary tract infections‡	3.8%	5.9%	4.4%
Increased urination§	0.7%	5.1%	4.6%
Thirst#	0.1%	2.8%	2.4%
Constipation	0.9%	1.8%	2.4%
Nausea	1.6%	2.1%	2.3%
	N=312	**N=425**	**N=430**
Female genital mycotic infections†	2.8%	10.6%	11.6%
Vulvovaginal pruritus	0.0%	1.6%	3.2%
	N=334	**N=408**	**N=404**
Male genital mycotic infections¶	0.7%	4.2%	3.8%

* The four placebo-controlled trials included one monotherapy trial and three add-on combination trials with metformin, metformin and sulfonylurea, or metformin and pioglitazone.

† Female genital mycotic infections include the following adverse reactions: Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Vulvovaginitis, Vaginal infection, Vulvitis, and Genital infection fungal.

‡ Urinary tract infections include the following adverse reactions: Urinary tract infection, Cystitis, Kidney infection, and Urosepsis.

§ Increased urination includes the following adverse reactions: Polyuria, Pollakiuria, Urine output increased, Micturition urgency, and Nocturia.

¶ Male genital mycotic infections include the following adverse reactions: Balanitis or Balanoposthitis, Balanitis candida, and Genital infection fungal.

Thirst includes the following adverse reactions: Thirst, Dry mouth, and Polydipsia.

Note: Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes.

Abdominal pain was also more commonly reported in patients taking INVOKANA 100 mg (1.8%), 300 mg (1.7%) than in patients taking placebo (0.8%).

Placebo-Controlled Trial in Diabetic Nephropathy: The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in CREDENCE, a study in patients with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day *[see Clinical Studies (14.3) in Full Prescribing Information]*. These data reflect exposure of 2,201 patients to INVOKANA and a mean duration of exposure to INVOKANA of 137 weeks.

- The rate of lower limb amputations associated with the use of INVOKANA 100 mg relative to placebo was 12.3 vs 11.2 events per 1000 patient-years, respectively, with 2.6 years mean duration of follow-up.
- Incidence rates of adjudicated events of diabetic ketoacidosis (DKA) were 0.21 (0.5%, 12/2,200) and 0.03 (0.1%, 2/2,197) per 100 patient-years of follow-up with INVOKANA 100 mg and placebo, respectively.
- The incidence of hypotension was 2.8% and 1.5% on INVOKANA 100 mg and placebo, respectively.

Pool of Placebo- and Active-Controlled Trials for Glycemic Control and Cardiovascular Outcomes: The occurrence of adverse reactions for INVOKANA was evaluated in patients participating in placebo- and active-controlled trials and in an integrated analysis of two cardiovascular trials, CANVAS and CANVAS-R.

The types and frequency of common adverse reactions observed in the pool of eight clinical trials (which reflect an exposure of 6,177 patients to INVOKANA) were consistent with those listed in Table 1.

Percentages were weighted by studies. Study weights were proportional to the harmonic mean of the three treatment sample sizes. In this pool, INVOKANA was also associated with the adverse reactions of fatigue (1.8%, 2.2%, and 2.0% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively) and loss of strength or energy (i.e., asthenia) (0.6%, 0.7%, and 1.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively).

In the pool of eight clinical trials, the incidence rate of pancreatitis (acute or chronic) was 0.1%, 0.2%, and 0.1% receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

In the pool of eight clinical trials, hypersensitivity-related adverse reactions (including erythema, rash, pruritus, urticaria, and angioedema) occurred in 3.0%, 3.8%, and 4.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Five patients experienced serious adverse reactions of hypersensitivity with INVOKANA, which included 4 patients with urticaria and 1 patient with a diffuse rash and urticaria occurring within hours of exposure to INVOKANA. Among these patients, 2 patients discontinued INVOKANA. One patient with urticaria had recurrence when INVOKANA was re-initiated.

Photosensitivity-related adverse reactions (including photosensitivity reaction, polymorphic light eruption, and sunburn) occurred in 0.1%, 0.2%, and 0.2% of patients receiving comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively.

Other adverse reactions occurring more frequently on INVOKANA than on comparator were:

Lower Limb Amputation: An increased risk of lower limb amputations associated with INVOKANA use versus placebo was observed in CANVAS (5.9 vs 2.8 events per 1000 patient-years) and CANVAS-R (7.5 vs 4.2 events per 1000 patient-years), two randomized, placebo-controlled trials evaluating patients with type 2 diabetes who had either established cardiovascular disease or were at risk for cardiovascular disease. Patients in CANVAS and CANVAS-R were followed for an average of 5.7 and 2.1 years, respectively *[see Clinical Studies (14.2) in Full Prescribing Information]*. The amputation data for CANVAS and CANVAS-R are shown in Tables 2 and 3, respectively.

Table 2: CANVAS Amputations

	Placebo N=1441	INVOKANA 100 mg N=1445	INVOKANA 300 mg N=1441	INVOKANA (Pooled) N=2886
Patients with an amputation, n (%)	22 (1.5)	50 (3.5)	45 (3.1)	95 (3.3)
Total amputations	33	83	79	162
Amputation incidence rate (per 1000 patient-years)	2.8	6.2	5.5	5.9
Hazard Ratio (95% CI)	--	2.24 (1.36, 3.69)	2.01 (1.20, 3.34)	2.12 (1.34, 3.38)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Table 3: CANVAS-R Amputations

	Placebo N=2903	INVOKANA 100 mg (with up-titration to 300 mg) N=2904
Patients with an amputation, n (%)	25 (0.9)	45 (1.5)
Total amputations	36	59
Amputation incidence rate (per 1000 patient-years)	4.2	7.5
Hazard Ratio (95% CI)	--	1.80 (1.10, 2.93)

Note: Incidence is based on the number of patients with at least one amputation, and not the total number of amputation events. A patient's follow-up is calculated from Day 1 to the first amputation event date. Some patients had more than one amputation.

Renal Cell Carcinoma: In the CANVAS trial (mean duration of follow-up of 5.7 years) *[see Clinical Studies (14.2) in Full Prescribing Information]*, the incidence of renal cell carcinoma was 0.15% (2/1331) and 0.29% (8/2716) for placebo and INVOKANA, respectively, excluding patients with less than 6 months of follow-up, less than 90 days of treatment, or a history of renal cell carcinoma. A causal relationship to INVOKANA could not be established due to the limited number of cases.

Volume Depletion-Related Adverse Reactions: INVOKANA results in an osmotic diuresis, which may lead to reductions in intravascular volume. In clinical trials for glycemic control, treatment with INVOKANA was associated with a dose-dependent increase in the incidence of volume depletion-related adverse reactions (e.g., hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration). An increased incidence was observed in patients on the 300 mg dose. The three factors associated with the largest increase in volume depletion-related adverse reactions in these trials were the use of loop diuretics, moderate renal impairment (eGFR 30 to less than 60 mL/min/1.73 m^2), and age 75 years and older (Table 4) *[see Use in Specific Populations]*.

Table 4: Proportion of Patients With at Least One Volume Depletion-Related Adverse Reaction (Pooled Results from 8 Clinical Trials for Glycemic Control)

Baseline Characteristic	Comparator Group* %	INVOKANA 100 mg %	INVOKANA 300 mg %
Overall population	1.5%	2.3%	3.4%
75 years of age and older†	2.6%	4.9%	8.7%
eGFR less than 60 mL/min/1.73 m^2†	2.5%	4.7%	8.1%
Use of loop diuretic†	4.7%	3.2%	8.8%

* Includes placebo and active-comparator groups

† Patients could have more than 1 of the listed risk factors

Falls: In a pool of nine clinical trials with mean duration of exposure to INVOKANA of 85 weeks, the proportion of patients who experienced falls was 1.3%, 1.5%, and 2.1% with comparator, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The higher risk of falls for patients treated with INVOKANA was observed within the first few weeks of treatment.

Genital Mycotic Infections: In the pool of four placebo-controlled clinical trials for glycemic control, female genital mycotic infections (e.g., vulvovaginal mycotic infection, vulvovaginal candidiasis, and vulvovaginitis) occurred in 2.8%, 10.6%, and 11.6% of females treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Patients with a history of genital mycotic infections were more likely to develop genital mycotic infections on INVOKANA. Female patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrence and require treatment with oral or topical antifungal agents and anti-microbial agents. In females, discontinuation due to genital mycotic infections occurred in 0% and 0.7% of patients treated with placebo and INVOKANA, respectively.

In the pool of four placebo-controlled clinical trials, male genital mycotic infections (e.g., candidal balanitis, balanoposthitis) occurred in 0.7%, 4.2%, and 3.8% of males treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Male genital mycotic infections occurred more commonly in uncircumcised males and in males with a prior history of balanitis or balanoposthitis. Male patients who developed genital mycotic infections on INVOKANA were more likely to experience recurrent infections (22% on INVOKANA versus none on placebo), and require treatment with oral or topical antifungal agents and anti-microbial agents than patients on comparators. In males, discontinuations due to genital mycotic infections occurred in 0% and 0.5% of patients treated with placebo and INVOKANA, respectively.

In the pooled analysis of 8 randomized trials evaluating glycemic control, phimosis was reported in 0.3% of uncircumcised male patients treated with INVOKANA and 0.2% required circumcision to treat the phimosis.

Hypoglycemia: In all glycemic control trials, hypoglycemia was defined as any event regardless of symptoms, where biochemical hypoglycemia was documented (any glucose value below or equal to 70 mg/dL). Severe hypoglycemia was defined as an event consistent with hypoglycemia where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained). In individual clinical trials of glycemic control *[see Clinical Studies (14.1) in Full Prescribing Information]*, episodes of hypoglycemia occurred at a higher rate when INVOKANA was co-administered with insulin or sulfonylureas (Table 5).

Table 5: Incidence of Hypoglycemia* in Randomized Clinical Studies of Glycemic Control

Monotherapy (26 weeks)	**Placebo (N=192)**	**INVOKANA 100 mg (N=195)**	**INVOKANA 300 mg (N=197)**
Overall [N (%)]	5 (2.6)	7 (3.6)	6 (3.0)
In Combination with Metformin (26 weeks)	**Placebo + Metformin (N=183)**	**INVOKANA 100 mg + Metformin (N=368)**	**INVOKANA 300 mg + Metformin (N=367)**
Overall [N (%)]	3 (1.6)	16 (4.3)	17 (4.6)
Severe [N (%)]†	0 (0)	1 (0.3)	1 (0.3)
In Combination with Metformin (52 weeks)	**Glimepiride + Metformin (N=482)**	**INVOKANA 100 mg + Metformin (N=483)**	**INVOKANA 300 mg + Metformin (N=485)**
Overall [N (%)]	165 (34.2)	27 (5.6)	24 (4.9)
Severe [N (%)]†	15 (3.1)	2 (0.4)	3 (0.6)
In Combination with Sulfonylurea (18 weeks)	**Placebo + Sulfonylurea (N=69)**	**INVOKANA 100 mg + Sulfonylurea (N=74)**	**INVOKANA 300 mg + Sulfonylurea (N=72)**
Overall [N (%)]	4 (5.8)	3 (4.1)	9 (12.5)
In Combination with Metformin + Sulfonylurea (26 weeks)	**Placebo + Metformin + Sulfonylurea (N=156)**	**INVOKANA 100 mg + Metformin + Sulfonylurea (N=157)**	**INVOKANA 300 mg + Metformin + Sulfonylurea (N=156)**
Overall [N (%)]	24 (15.4)	43 (27.4)	47 (30.1)
Severe [N (%)]†	1 (0.6)	1 (0.6)	0
In Combination with Metformin + Sulfonylurea (52 weeks)	**Sitagliptin + Metformin + Sulfonylurea (N=378)**		**INVOKANA 300 mg + Metformin + Sulfonylurea (N=377)**
Overall [N (%)]	154 (40.7)		163 (43.2)
Severe [N (%)]†	13 (3.4)		15 (4.0)
In Combination with Metformin + Pioglitazone (26 weeks)	**Placebo + Metformin + Pioglitazone (N=115)**	**INVOKANA 100 mg + Metformin + Pioglitazone (N=113)**	**INVOKANA 300 mg + Metformin + Pioglitazone (N=114)**
Overall [N (%)]	3 (2.6)	3 (2.7)	6 (5.3)
In Combination with Insulin (18 weeks)	**Placebo (N=565)**	**INVOKANA 100 mg (N=566)**	**INVOKANA 300 mg (N=587)**
Overall [N (%)]	208 (36.8)	279 (49.3)	285 (48.6)
Severe [N (%)]†	14 (2.5)	10 (1.8)	16 (2.7)

* Number of patients experiencing at least one event of hypoglycemia based on either biochemically documented episodes or severe hypoglycemic events in the intent-to-treat population

† Severe episodes of hypoglycemia were defined as those where the patient required the assistance of another person to recover, lost consciousness, or experienced a seizure (regardless of whether biochemical documentation of a low glucose value was obtained)

Bone Fracture: In the CANVAS trial *[see Clinical Studies (14.2) in Full Prescribing Information]*, the incidence rates of all adjudicated bone fracture were 1.09, 1.59, and 1.79 events per 100 patient-years of follow-up to placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. The fracture imbalance was observed within the first 26 weeks of therapy and remained through the end of the trial. Fractures were more likely to be low trauma (e.g., fall from no more than standing height), and affect the distal portion of upper and lower extremities.

Laboratory and Imaging Tests: *Increases in Serum Creatinine and Decreases in eGFR*: Initiation of INVOKANA causes an increase in serum creatinine and decrease in estimated GFR. In patients with moderate renal impairment, the increase in serum creatinine generally does not exceed 0.2 mg/dL, occurs within the first 6 weeks of starting therapy, and then stabilizes. Increases that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury *[see Clinical Pharmacology (12.1) in Full Prescribing Information]*. The acute effect on eGFR reverses after treatment discontinuation suggesting acute hemodynamic changes may play a role in the renal function changes observed with INVOKANA.

Increases in Serum Potassium: In a pooled population of patients (N=723) in glycemic control trials with moderate renal impairment (eGFR 45 to less than 60 mL/min/1.73 m^2), increases in serum potassium to greater than 5.4 mEq/L and 15% above baseline occurred in 5.3%, 5.0%, and 8.8% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively. Severe elevations (greater than or equal to 6.5 mEq/L) occurred in 0.4% of patients treated with placebo, no patients treated with INVOKANA 100 mg, and 1.3% of patients treated with INVOKANA 300 mg.

In these patients, increases in potassium were more commonly seen in those with elevated potassium at baseline. Among patients with moderate renal impairment, approximately 84% were taking medications that interfere with potassium excretion, such as potassium-sparing diuretics, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers *[see Use in Specific Populations]*.

In CREDENCE, no difference in serum potassium, no increase in adverse events of hyperkalemia, and no increase in absolute (> 6.5 mEq/L) or relative (> upper limit of normal and > 15% increase from baseline) increases in serum potassium were observed with INVOKANA 100 mg relative to placebo.

Increases in Low-Density Lipoprotein Cholesterol (LDL-C) and non-High-Density Lipoprotein Cholesterol (non-HDL-C): In the pool of four glycemic control placebo-controlled trials, dose-related increases in LDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in LDL-C relative to placebo were 4.4 mg/dL (4.5%) and 8.2 mg/dL (8.0%) with INVOKANA 100 mg and INVOKANA 300 mg, respectively. The mean baseline LDL-C levels were 104 to 110 mg/dL across treatment groups.

Dose-related increases in non-HDL-C with INVOKANA were observed. Mean changes (percent changes) from baseline in non-HDL-C relative to placebo were 2.1 mg/dL (1.5%) and 5.1 mg/dL (3.6%) with INVOKANA 100 mg and 300 mg, respectively. The mean baseline non-HDL-C levels were 140 to 147 mg/dL across treatment groups.

Increases in Hemoglobin: In the pool of four placebo-controlled trials of glycemic control, mean changes (percent changes) from baseline in hemoglobin were -0.18 g/dL (-1.1%) with placebo, 0.47 g/dL (3.5%) with INVOKANA 100 mg, and 0.51 g/dL (3.8%) with INVOKANA 300 mg. The mean baseline hemoglobin value was approximately 14.1 g/dL across treatment groups. At the end of treatment, 0.8%, 4.0%, and 2.7% of patients treated with placebo, INVOKANA 100 mg, and INVOKANA 300 mg, respectively, had hemoglobin above the upper limit of normal.

Decreases in Bone Mineral Density: Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry in a clinical trial of 714 older adults (mean age 64 years) *[see Clinical Studies (14.1) in Full Prescribing Information]*. At 2 years, patients randomized to INVOKANA 100 mg and INVOKANA 300 mg had placebo-corrected declines in BMD at the total hip of 0.9% and 1.2%, respectively, and at the lumbar spine of 0.3% and 0.7%, respectively. Additionally, placebo-adjusted BMD declines were 0.1% at the femoral neck for both INVOKANA doses and 0.4% at the distal forearm for patients randomized to INVOKANA 300 mg. The placebo-adjusted change at the distal forearm for patients randomized to INVOKANA 100 mg was 0%.

Postmarketing Experience: Additional adverse reactions have been identified during post-approval use of INVOKANA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Ketoacidosis

Acute Kidney Injury

Anaphylaxis, Angioedema

Urosepsis and Pyelonephritis

Necrotizing Fasciitis of the Perineum (Fournier's gangrene)

DRUG INTERACTIONS

UGT Enzyme Inducers: Co-administration of canagliflozin with rifampin, a nonselective inducer of several UGT enzymes, including UGT1A9, UGT2B4, decreased canagliflozin area under the curve (AUC) by 51%. This decrease in exposure to canagliflozin may decrease efficacy.

For patients with eGFR 60 mL/min/1.73 m^2 or greater, if an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA 100 mg. The dose may be increased to 300 mg once daily in patients currently tolerating INVOKANA 200 mg and who require additional glycemic control.

For patients with eGFR less than 60 mL/min/1.73 m^2, if an inducer of UGTs (e.g., rifampin, phenytoin, phenobarbital, ritonavir) is co-administered with INVOKANA, increase the dose to 200 mg (taken as two 100 mg tablets) once daily in patients currently tolerating INVOKANA 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Digoxin: There was an increase in the AUC and mean peak drug concentration (C_{max}) of digoxin (20% and 36%, respectively) when co-administered with INVOKANA 300 mg *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Patients taking INVOKANA with concomitant digoxin should be monitored appropriately.

Positive Urine Glucose Test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary: Based on animal data showing adverse renal effects, INVOKANA is not recommended during the second and third trimesters of pregnancy.

Limited data with INVOKANA in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy *[see Clinical Considerations]*.

In animal studies, adverse renal pelvic and tubule dilatations that were not reversible were observed in rats when canagliflozin was administered during a period of renal development corresponding to the late second and third trimesters of human pregnancy, at an exposure 0.5-times the 300 mg clinical dose, based on AUC.

The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA_{1C} >7 and has been reported to be as high as 20-25% in women with a HbA_{1C} >10. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations*: Disease-associated maternal and/or embryo/fetal risk*: Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Animal Data: Canagliflozin dosed directly to juvenile rats from postnatal day (PND) 21 until PND 90 at doses of 4, 20, 65, or 100 mg/kg increased kidney weights and dose dependently increased the incidence and severity of renal pelvic and tubular dilatation at all doses tested. Exposure at the lowest dose was greater than or equal to 0.5-times the 300 mg clinical dose, based on AUC. These outcomes occurred with drug exposure during periods of renal development in rats that correspond to the late second and third trimester of human renal development. The renal pelvic dilatations observed in juvenile animals did not fully reverse within a 1-month recovery period.

In embryo-fetal development studies in rats and rabbits, canagliflozin was administered for intervals coinciding with the first trimester period of organogenesis in humans. No developmental toxicities independent of maternal toxicity were observed when canagliflozin was administered at doses up to 100 mg/kg in pregnant rats and 160 mg/kg in pregnant rabbits during embryonic organogenesis or during a study in which maternal rats were dosed from gestation day (GD) 6 through PND 21, yielding exposures up to approximately 19-times the 300 mg clinical dose, based on AUC.

Lactation: Risk Summary: There is no information regarding the presence of INVOKANA in human milk, the effects on the breastfed infant, or the effects on milk production. Canagliflozin is present in the milk of lactating rats *[see Data]*. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney.

Because of the potential for serious adverse reactions in a breastfed infant, advise women that use of INVOKANA is not recommended while breastfeeding.

Data: *Animal Data*: Radiolabeled canagliflozin administered to lactating rats on day 13 post-partum was present at a milk/plasma ratio of 1.40, indicating that canagliflozin and its metabolites are transferred into milk at a concentration comparable to that in plasma. Juvenile rats directly exposed to canagliflozin showed a risk to the developing kidney (renal pelvic and tubular dilatations) during maturation.

INVOKANA® (canagliflozin) tablets

Pediatric Use: Safety and effectiveness of INVOKANA in pediatric patients under 18 years of age have not been established.

Geriatric Use: In 13 clinical trials of INVOKANA, 2,294 patients 65 years and older, and 351 patients 75 years and older were exposed to INVOKANA *[see Clinical Studies (14.1) in Full Prescribing Information]*.

Patients 65 years and older had a higher incidence of adverse reactions related to reduced intravascular volume with INVOKANA (such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration), particularly with the 300 mg daily dose, compared to younger patients; a more prominent increase in the incidence was seen in patients who were 75 years and older *[see Dosage and Administration (2.1) in Full Prescribing Information and Adverse Reactions]*. Smaller reductions in HbA_{1C} with INVOKANA relative to placebo were seen in older (65 years and older; -0.61% with INVOKANA 100 mg and -0.74% with INVOKANA 300 mg relative to placebo) compared to younger patients (-0.72% with INVOKANA 100 mg and -0.87% with INVOKANA 300 mg relative to placebo).

Renal Impairment: The efficacy and safety of INVOKANA for glycemic control were evaluated in a trial that included patients with moderate renal impairment (eGFR 30 to less than 50 mL/min/1.73 m^2) *[see Clinical Studies (14.1) in Full Prescribing Information]*. These patients had less overall glycemic efficacy, and patients treated with 300 mg per day had increases in serum potassium, which were transient and similar by the end of study. Patients with renal impairment using INVOKANA for glycemic control may also be more likely to experience hypotension and may be at higher risk for acute kidney injury *[see Warnings and Precautions]*.

Efficacy and safety studies with INVOKANA did not enroll patients with ESKD on dialysis or patients with an eGFR less than 30 mL/min/1.73 m^2. INVOKANA is contraindicated in patients with ESKD on dialysis *[see Contraindications and Clinical Pharmacology (12.1) in Full Prescribing Information]*.

Hepatic Impairment: No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The use of INVOKANA has not been studied in patients with severe hepatic impairment and is therefore not recommended *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

OVERDOSAGE

In the event of an overdose, contact the Poison Control Center. It is also reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment as dictated by the patient's clinical status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. Canagliflozin is not expected to be dialyzable by peritoneal dialysis.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Lower Limb Amputation: Inform patients that INVOKANA is associated with an increased risk of amputations. Counsel patients about the importance of routine preventative foot care. Instruct patients to monitor for new pain or tenderness, sores or ulcers, or infections involving the leg or foot and to seek medical advice immediately if such signs or symptoms develop *[see Warnings and Precautions]*.

Volume Depletion: Inform patients that symptomatic hypotension may occur with INVOKANA and advise them to contact their doctor if they experience such symptoms *[see Warnings and Precautions]*. Inform patients that dehydration may increase the risk for hypotension, and to have adequate fluid intake.

Ketoacidosis: Inform patients that ketoacidosis is a serious life-threatening condition and that cases of ketoacidosis have been reported during use of INVOKANA, sometimes associated with illness or surgery among other risk factors. Instruct patients to check ketones (when possible) if symptoms consistent with ketoacidosis occur even if blood glucose is not elevated. If symptoms of ketoacidosis (including nausea, vomiting, abdominal pain, tiredness, and labored breathing) occur, instruct patients to discontinue INVOKANA and seek medical attention immediately *[see Warnings and Precautions]*.

Serious Urinary Tract Infections: Inform patients of the potential for urinary tract infections, which may be serious. Provide them with information on the symptoms of urinary tract infections. Advise them to seek medical advice if such symptoms occur *[see Warnings and Precautions]*.

Necrotizing Fasciitis of the Perineum (Fournier's Gangrene): Inform patients that necrotizing infections of the perineum (Fournier's gangrene) have occurred with INVOKANA. Counsel patients to promptly seek medical attention if they develop pain or tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, along with a fever above 100.4°F or malaise *[see Warnings and Precautions]*.

Genital Mycotic Infections in Females (e.g., Vulvovaginitis): Inform female patients that vaginal yeast infection may occur and provide them with information on the signs and symptoms of vaginal yeast infection. Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Genital Mycotic Infections in Males (e.g., Balanitis or Balanoposthitis): Inform male patients that yeast infection of penis (e.g., balanitis or balanoposthitis) may occur, especially in uncircumcised males and patients with prior history. Provide them with information on the signs and symptoms of balanitis and balanoposthitis (rash or redness of the glans or foreskin of the penis). Advise them of treatment options and when to seek medical advice *[see Warnings and Precautions]*.

Hypersensitivity Reactions: Inform patients that serious hypersensitivity reactions, such as urticaria, rash, anaphylaxis, and angioedema, have been reported with INVOKANA. Advise patients to report immediately any signs or symptoms suggesting allergic reaction, and to discontinue drug until they have consulted prescribing physicians *[see Warnings and Precautions]*.

Bone Fracture: Inform patients that bone fractures have been reported in patients taking INVOKANA. Provide them with information on factors that may contribute to fracture risk *[see Warnings and Precautions]*.

Pregnancy: Advise pregnant women, and females of reproductive potential of the potential risk to a fetus with treatment with INVOKANA *[see Use in Specific Populations]*. Instruct females of reproductive potential to report pregnancies to their physicians as soon as possible.

Lactation: Advise women that breastfeeding is not recommended during treatment with INVOKANA *[see Use in Specific Populations]*.

Laboratory Tests: Inform patients that due to its mechanism of action, patients taking INVOKANA will test positive for glucose in their urine *[see Drug Interactions]*.

Missed Dose: If a dose is missed, advise patients to take it as soon as it is remembered unless it is almost time for the next dose, in which case patients should skip the missed dose and take the medicine at the next regularly scheduled time. Advise patients not to take two doses of INVOKANA at the same time.

Active ingredient made in Belgium

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Licensed from Mitsubishi Tanabe Pharma Corporation

cp-22015v4

janssen

Immunotherapy and Novel Cancer Target Therapies in Kidney Transplant Recipients with Cancer

By Naoka Murakami and Ala Abudayyeh

Cancer is a major cause of death in patients with kidney transplants. The incidence of cancer after transplant is 3- to 100-fold higher than that in the general population, and cancer has been shown to be one of the most feared outcomes in patients with kidney transplants (1, 2). However, data on cancer screening and treatment efficacies of novel cancer therapies in patients with kidney transplants are lacking, as these patients have been typically excluded from clinical studies.

Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment and become standard therapy for many cancers. They work by enhancing the immune surveillance and cytotoxic killing of cancer cells. Notably, ICIs are double-edged swords: although they amplify immune response against cancer, they can also cause an immune-related adverse event (irAE), which manifests as acute allograft rejection in patients with kidney transplants.

The use of ICIs in patients with kidney transplants is challenging mainly for two reasons: the safety concern for high risk of rejection and the efficacy concern due to the use of maintenance immunosuppression. Initially, anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4; ipilimumab) was reported to be tolerated in transplant patients (3), but later, anti-programmed cell death protein 1 (anti-PD-1; e.g., nivolumab, pembrolizumab) has been shown to accelerate acute allograft rejection (4). A recent multicenter observational study examined the safety and efficacy of ICIs in 69 patients with kidney transplants from 23 institutions (5). The study showed that 42% of patients experienced acute allograft rejection with median onset of 24 days from ICI initiation to rejection. Once rejection occurred, 65% of patients experienced allograft failure and required dialysis. An increase of immunosuppression at the time of ICI initiation or use of mammalian target of rapamycin (mTOR) inhibitors was associated with lower risk of rejection (Figure 1). The efficacy of ICIs in advanced skin squamous cell carcinoma and melanoma, the two most common cancers in the cohort, was similar to that of non-transplant patients, supporting the data of the previous cohort study (6).

As the indication of ICIs expands and has become part of the first-line therapies for many cancers, it is estimated that approximately 40% of patients with cancer are eligible for ICIs in the United States (7). Additionally, novel therapies that may increase the acute rejection have been tested, such as chimeric antigen receptor T cell (CAR-T) therapy (8, 9) and personalized cancer vaccines. With knowledge of the risk of allograft rejection, our field should work hard to establish a better immunosuppression management strategy to mitigate acute rejection while achieving tumor response. Ongoing clinical trials to look at the choice of immunosuppressants (tacrolimus; NCT03816332) and mTOR inhibitors (NCT04339062) and further mechanistic analysis of the ICI-associated rejection are awaited. Throughout this difficult scenario of cancer treatment in patients with organ transplants, it is most important to assist patient-centered decision-making with multidisciplinary discussion involving patients, caregivers, oncologists, and transplant nephrologists. ■

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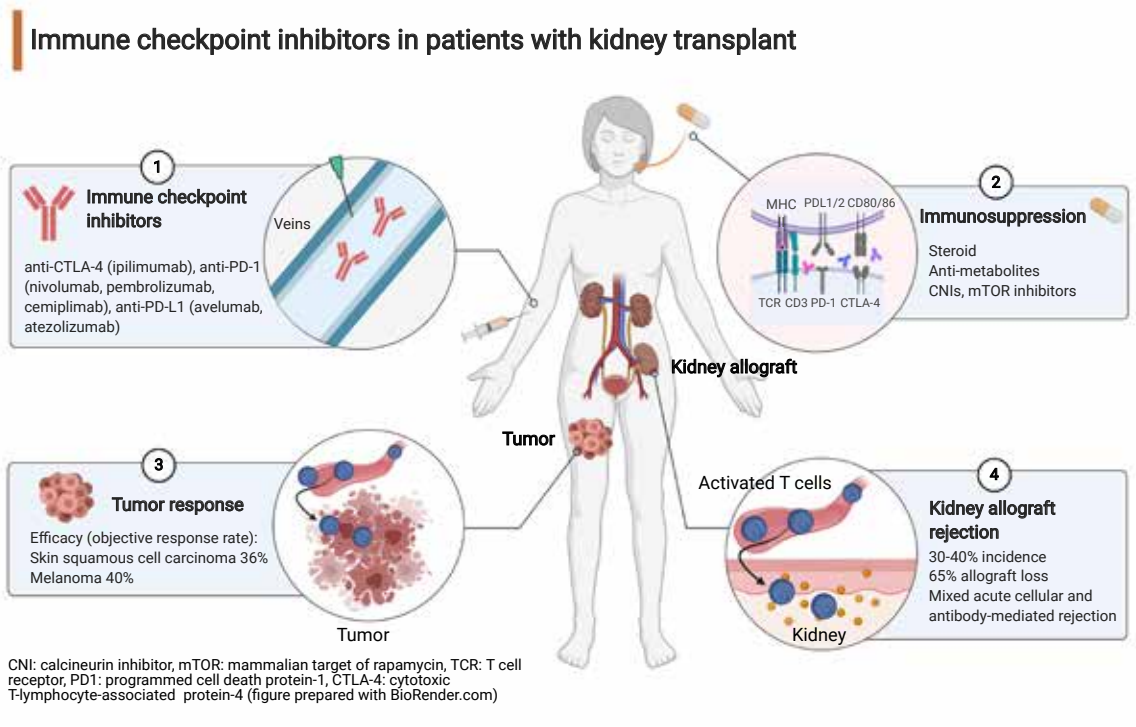
Our field should work hard to establish a better immunosuppression management strategy to mitigate acute rejection while achieving tumor response.

Figure 1.



CNI: calcineurin inhibitor, mTOR: mammalian target of rapamycin, TCR: T cell receptor, PD1: programmed cell death protein-1, CTLA-4: cytotoxic T-lymphocyte-associated protein-4 (figure prepared with BioRender.com)

There are several factors to consider when using immune checkpoint inhibitors (ICIs) in kidney transplant recipients. The choice of ICIs (factor 1) and immunosuppressants (factor 2) may affect the outcomes, such as tumor response (factor 3) and risk of acute allograft rejection (factor 4). PD-L1, programmed death ligand 1; MHC, major histocompatibility complex.

Tips and Tricks for the 2021 Nephrology Fellows—A Curated List of Fellow-Friendly Resources in the United States

By Pablo Garcia and Yuvaram Reddy

Dear Incoming Nephrology Fellows,

The transition from residency to fellowship is exciting and challenging. You have to adapt to your new role as a consultant, learn new clinical procedures, and be a role model for residents and medical students. As these skills grow during fellowship, you may find yourself wondering: What resources are out there? How do I find these resources? Which of these resources are right for me? We certainly felt that way during our fellowship. To help you navigate this transition, we compiled a list of free (or subsidized) training resources. We hope you find this useful.

This fellow-friendly resource guide focuses on the following areas: nephrology societies, annual general nephrology meetings, short courses and annual subspecialty nephrology meetings, and professional development opportunities (editorial internships, social media collaboratives, and other initiatives; see Figure 1 for a summary and timeline of key resources). Please note that while we attempted to be as inclusive as possible, it is possible that we may have unintentionally missed some resources. This guide is not meant to be exhaustive. For an updated guide with additional resources, please refer to the Renal Fellow Network (RFN). RFN has a curated list of conferences, internships, and opportunities for additional years of training. If you would like to add a resource to these guides, please contact the RFN editors. Your feedback can ensure that these guides are relevant for future nephrology fellows.

URLs:

Nephrology societies

1. **American Society of Nephrology:** https://asn-online.org/membership/join.aspx
2. **International Society of Nephrology:** https://www.theisn.org/join-the-isn/become-a-member/
3. **National Kidney Foundation:** https://kidney.org/professionals/physicians/fellows
4. **Renal Physicians Association:** https://www.renalmd.org/general/register_member_type.asp
5. **Women in Nephrology:** https://www.womeninnephrology.org/membership
6. **American Society of Diagnostic and Interventional Nephrology:** https://www.asdin.org/page/A4
7. **International Society for Peritoneal Dialysis:** https://ispd.org/join/
8. **American Society of Transplantation:** https://www.myast.org/

Short courses and nephrology subspecialty annual meetings

1. **Home Dialysis University:** https://ispd.org/
2. **Home Dialysis Academy of Excellence:** https://hdexcellence.org/
3. **KIDNEYcon:** http://kidneycon.org/
4. **Network of Minority Health Research Investigators Annual Workshop:** https://www.niddk.nih.gov/research-funding/research-programs/diversity-programs/network-minority-health-research-investigators-nmri
5. **Mount Desert Island Biological Laboratory Origins of Renal Physiology:** https://mdibl.org/course/origins-of-renal-physiology-fellows-2020/
6. **Nephrology Business Leadership University:** https://nbluniv.org/
7. **Annual Dialysis Conference:** https://annualdialysisconference.org/
8. **American Society of Diagnostic and Interventional Nephrology Annual Meeting**: https://www.asdin.org/
9. **American Transplant Congress:** https://atcmeeting.org/
10. **Renal Physicians Association Annual Meeting:** https://www.renalmd.org/page/calAnnualMeeting

Nephrology societies

Nephrology societies are a great way to feel connected with the kidney community. They help grow your network of peers, mentors, and (eventually) mentees.

Fortunately, most major societies provide free or subsidized registration for fellows (see Table 1). By joining these societies, you can access major nephrology journals (e.g., *JASN,* the *American Journal of Kidney Diseases*, and *Kidney International*), subsidized registration for national conferences (e.g., Kidney Week and the World Congress of Nephrology), networking opportunities, and training opportunities (such as travel grants, research grants, and educational grants). To benefit from free or subsidized rates, some societies require a letter from your fellowship program director.

Table 1 lists some general nephrology and subspecialty nephrology societies to consider joining when you start your nephrology fellowship.

Nephrology annual meetings

1. **ASN Kidney Week:** https://www.asn-online.org/education/kidney-week/
2. **ISN World Congress of Nephrology:** https://www.theisn.org/wcn/
3. **NKF Spring Clinical Meetings:** https://www.kidney.org/spring-clinical

Professional development opportunities

1. ***AJKD* editorial internship:** https://www.ajkd.org/content/edinternshipprogram
2. ***JASN* editorial fellowship:** https://jasn.asnjournals.org/content/editorial-fellowship-application-process
3. ***Kidney News*:** https://www.kidneynews.org/
4. **Renal Fellow Network editorial position:** https://www.renalfellow.org/2020/03/05/wanted-rfn-co-editor-asn-media-communications-committee-member/
5. **ASN Committees:** https://www.asn-online.org/about/committees/
6. **Nephrology Social Media Collective Internship:** https://www.nsmc.blog/
7. **GlomCon:** https://glomcon.org/
8. **Channel Your Enthusiasm: The Burton Rose Book Club:** http://www.rose-book.club/about
9. **Freely Filtered: A NephJC Podcast:** https://podcasts.apple.com/us/podcast/freely-filtered-a-nephjc-podcast/id1461664501
10. **Landmark Nephrology:** https://landmarknephrology.com/
11. **LIME:** https://www.cardionerds.com/letslime/
12. **NephJC:** http://nephjc.com/
13. **NephMadness:** https://ajkdblog.org/2021/03/01/welcome-to-nephmadness-2021/
14. **NephroWorldCup:** https://twitter.com/hashtag/NephroWorldCup
15. **NephSIM:** https://nephsim.com/
16. **Renal Fellow Network:** https://www.renalfellow.org/
17. **The Skeleton Key Group:** https://www.skeletonkey.group/

Renal Fellow Network curated lists

1. **Renal Fellow Network list of conferences:** https://www.renalfellow.org/conferences/
2. **Renal Fellow Network list of internships:** https://www.renalfellow.org/internships/
3. **Renal Fellow Network nephrology workforce article (Piecing Together the Adult Nephrology Workforce Puzzle):** https://www.renalfellow.org/the-nephrology-workforce/

Nephrology annual meetings

Annual meetings help the kidney community gather and discuss new developments in nephrology (e.g., the American Society of Nephrology's Kidney Week). For trainees, these meetings help hone your poster and oral-presentation skills, connect (or reconnect) you with peers and mentors who share your unique interests, and identify exciting career opportunities (academia, private practice, industry, government, or elsewhere). If you are attending these meetings for the first time, talk to your peers and mentors to plan ahead, and make the best use of your time during these meetings.

Table 2 lists some major nephrology annual meetings to consider attending during your fellowship.

Short courses and nephrology subspecialty annual meetings

Separate from general nephrology annual meetings, the kidney community also organizes several short courses and nephrology subspecialty annual meetings. These sessions cover niche topics for targeted audiences (think physician-scientists, business-oriented young leaders, trainees, home dialysis, or transplantation enthusiasts).

If you apply to attend these short courses and are selected to attend, most organizers pay for your travel and lodging. Since these courses last several days to 1 week and are usually in person, you should consider applying to these courses toward the end of your first year of fellowship so that you can attend these courses in your second year of fellowship.

Table 3 lists some short courses and nephrology subspecialty meetings to consider attending before you graduate from fellowship.

Professional development opportunities

Over the past decade, the kidney community has intentionally catalyzed the growth of unique professional development opportunities from editorial internships, positions on national committees, and social media collaboratives. These opportunities foster interest in nephrology and raise awareness about the breadth and depth of nephrology topics in an easy-to-understand, engaging manner. These collaboratives are often topical, timely, and highly engaging. We encourage you to consider participating during any phase of your fellowship.

Table 4 lists some professional development opportunities available for nephrology fellows (and virtually anyone interested in nephrology).

In conclusion, there are an enormous number of resources available for nephrology fellows. We hope you leverage this guide to identify targeted resources that uniquely enhance your individual training and professional development. We hope that you use these free or subsidized resources and that you consider giving back to the future of the kidney community through your eventual mentorship, clinical service, teaching, and/or leadership. ■

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Table 1. Fellow-friendly nephrology societies

Society (Twitter handle)*	Benefits	Cost
American Society of Nephrology (@ASNKidney)	▪ Journal access: *JASN* and *CJASN* ▪ Discounted registration to Kidney Week ▪ Research and travel grants ▪ Case discussions on ASN Communities ▪ Nephrology board exam resources: free KSAP and NephSAP, discounted registration for BRCU ▪ Join national committees (policy and advocacy, quality, workforce and training, etc.) ▪ Subscription to *Kidney News* ▪ Subscription to *In the Loop* eNews briefing	Free
International Society of Nephrology (@ISNkidneycare)	▪ Journal access: *KI, KI Supplements,* and *KI Reports* ▪ Discounted registration to World Congress of Nephrology ▪ ISN grant opportunities ▪ ISN Academy (educational platform) ▪ ISN Emerging Leaders Program	Year 1: free; year 2: $25; years 3–5: $50
National Kidney Foundation (@nkf)	▪ Journal access: *AJKD* and *ACKD* ▪ Discounted registration to the NKF Spring Clinical Meetings ▪ Research and travel grants ▪ Access to KDOQI guidelines	Free
Renal Physicians Association (@RPANephrology)	▪ Discounted registration to RPA Annual meeting ▪ Join national committees (clinical practice, government affairs, health care payment, etc.) ▪ Billing and coding guide ▪ Public policy updates	Free
Women in Nephrology (@womeninnephro)	▪ Mentorship for junior nephrologists ▪ Lectures and opportunities focused on professional development and career advancement ▪ Open to all genders	Free
American Society of Diagnostic and Interventional Nephrology (@ASDINNews)	▪ Journal access: *Journal of Vascular Access* ▪ Annual scientific meeting ▪ Research grants ▪ Join ASDIN committees	$35
International Society for Peritoneal Dialysis (@ISPD1)	▪ Journal access: PDI ▪ Discounted registration to the Annual Dialysis Conference ▪ Research and travel grants	$60
American Society of Transplantation (@AST_Info)	▪ Discounted journal access: *AJT* and *CT* ▪ Join communities of practice ▪ Research and travel grants ▪ Journal clubs and webinars	$90

*Please see the online version of this article for links to join these societies.
Abbreviations: *JASN, Journal of the American Society of Nephrology*; *CJASN, Clinical Journal of the American Society of Nephrology*; ASN, American Society of Nephrology; KSAP, Kidney Self-Assessment Program; BRCU, Board Review Course and Update; NephSAP, Nephrology Self-Assessment Program; *AJKD, American Journal of Kidney Diseases*; *ACKD, Advances in Chronic Kidney Disease*; NKF, National Kidney Foundation; KDOQI, Kidney Disease Outcomes Quality Initiative; RPA, Renal Physicians Association; *KI, Kidney International*; ISN, International Society of Nephrology; ASDIN, American Society of Diagnostic and Interventional Nephrology; *PDI, Peritoneal Dialysis International*; *AJT, American Journal of Transplantation*; *CT, Clinical Transplantation*.

Continued on page 22 ›

Tips and Tricks

Continued from page 21

Table 2. Fellow-friendly general nephrology annual society meetings

Meeting*	Description	Cost#	Dates
ASN Kidney Week	Annual American Society of Nephrology meeting hosted in different cities	$250 (travel grants available)	October
ISN World Congress of Nephrology	Annual World Congress of Nephrology hosted in different countries around the world	$135	April
NKF Spring Clinical Meetings	Annual National Kidney Foundation meeting hosted in different cities	$175	April/May

*Please see the online version of this article for links to these meetings.
#These costs represent the 2019–2020 early-registration trainee rates. They are displayed to provide trainees with the last in-person registration costs listed before these meetings transitioned to a virtual (often cheaper) format due to the COVID-19 pandemic. These costs are subject to change.
Abbreviations: ASN, American Society of Nephrology; ISN, International Society of Nephrology; NKF, National Kidney Foundation.

Table 3. Fellow-friendly short courses and nephrology subspecialty annual meetings

Course (Twitter handle)*	Description	Cost	Application timeline#
Short courses			
Home Dialysis University	Two-day intensive event on home dialysis taught by international home dialysis leaders	Free travel and lodging ($100 registration fee)	3 times per year
Home Dialysis Academy of Excellence	Three-day event on home dialysis	Free travel and lodging (no registration fee)	September
KIDNEYcon (@KIDNEYcon)	Three- to 4-day event focused on education for trainees and networking	No registration fee (travel awards available)	April
Network of Minority Health Research Investigators Annual Workshop	NIDDK-sponsored meeting focused on research training and mentoring for young investigators	No registration fee (travel awards available)	April
Mount Desert Island Biological Laboratory Origins of Renal Physiology (@MDIBL)	One-week intensive course on renal physiology using basic science experiments	Free travel and lodging ($400 registration fee)	August
Nephrology Business Leadership University (@NBLUniv)	One-week course focused on the economics and business aspects of nephrology	Free travel and lodging (no registration fee)	August
Nephrology subspecialty annual meetings			
Annual Dialysis Conference (@AnnualDialysis)	Four-day multidisciplinary dialysis conference designed for health professionals involved in dialysis programs	$100 registration fee (Twenty fellows who submit interesting clinical cases receive a travel grant.)	March
American Society of Diagnostic and Interventional Nephrology Annual Meeting	Five-day conference focused on diagnostic and interventional radiology (e.g., role of diagnostic ultrasound for diagnostics, dialysis access for patients with kidney failure)	Free for fellows and physicians-in-training	February
American Transplant Congress	Five- to 6-day conference that brings together transplant physicians, scientists, nurses, organ procurement personnel, pharmacists, allied health professionals, and other transplant professionals. The educational offerings provide attendees the opportunity to learn cutting-edge advances in research and exchange of ideas and practice in the field of solid organ and tissue transplantation.	Free for trainee members	June
Renal Physicians Association Annual Meeting	Three- to four-day event focused on the regulatory, legislative, business, and clinical aspects of nephrology	$375 registration fee (free for fellows in 2021)	March

*Please see the online version of this article for links to these short courses and meetings.
#The timelines and registration fee for these events are subject to change.
Abbreviation: NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases.

Table 4. Fellow-friendly professional development opportunities

Professional development opportunities (Twitter handle)*	Description
Editorial training programs and committee internships	
***AJKD* editorial internship**	This year-long program provides editorial experience to nephrology fellows interested in research, education, teaching, or medical editing/writing. Interns have the opportunity to follow manuscripts from submission to publication, gaining experience in the peer-review process by using original submissions to develop skills in assessing manuscripts' novelty, validity, and clinical relevance.
ISN-*KI* editorial fellowship	This fellowship provides training opportunities for the review and critical evaluation of manuscripts and the management of editorial responsibilities within the context of a high-impact nephrology journal.
***JASN* editorial fellowship**	This year-long program provides fellows the opportunity to participate in all *JASN* editorial processes, including the editorial review of manuscripts, the development of editorial policy, and the identification of topics for invited manuscripts. Frequent "fellow-only" meetings with *JASN* senior leadership will be held to discuss specific topics in the editorial process.
Kidney News (@KidneyNews)	News magazine for ASN (and publisher of this article!), *Kidney News* enlists fellows for its Editorial Board.
Renal Fellow Network editorial position (@RenalFellowNtwk)	RFN is a highly trafficked blog. Fellows may serve as co-editor of RFN over a 2-year term. The co-editor will work with a larger team consisting of two faculty leads, the RFN co-editor, and a group of faculty advisors.
ASN Committees	ASN has several committees dedicated to overseeing various nephrology aspects such as education and training, policy and advocacy, and workforce and training. Trainees can apply to join select committees for a 1-year internship
Educational activities	
Nephrology Social Media Collective Internship (@NSMCInternship)	The Nephrology Social Media Collective Internship is a year-long, hands-on curriculum designed to cultivate leaders in medicine by instilling confidence, knowledge, competence, and professionalism in the use of social media. Each year, trainees (or attendings) can apply to join NSMC and partake in its year-long curriculum.
GlomCon (@GlomCon)	An online educational platform designed for clinicians and scientists to exchange ideas, participate in online conferences, and collaborate on basic science and clinical research projects related to glomerular disease
Social media collaboratives	
Channel Your Enthusiasm: The Burton Rose Book Club (@BookBurton)	A podcast that aims to be a light and joyful discussion among a group of nephrologists who go through the Burton Rose book, "The Clinical Physiology of Acid-Base and Electrolyte Disorders"
Freely Filtered: A NephJC Podcast (@NephJC_Podcast)	Freely Filtered is a twice-monthly podcast that discusses the most recent NephJC chat. It also discusses other big events in the world of nephrology.
Landmark Nephrology (@landmark_neph)	An online educational resource that highlights landmark clinical trials that have shaped the way we practice nephrology
LIME (@LetsLimeWith)	A webcast discussing Leadership & Innovation in Medicine & Education (LIME) run by @NephJC and @CardioNerds
NephJC (@NephJC)	A bi-weekly journal club that uses Twitter to discuss the research, guidelines, and editorials that drive nephrology. To learn how to join the NephJC discussions, read this tutorial (http://www.nephjc.com/how-to).
NephMadness (@NephMadness)	A free, online, annual, CME-granting, evidence-based, noncommercial learning initiative that leverages social media tools to teach the latest and greatest nephrology breakthroughs; sponsored by *AJKD* and the NKF
NephroWorldCup (@NephroWorldCup)	By combining the passions of football (soccer) and science, the Nephrology World Cup encourages individuals to learn from and about the diversity of scientific practice with their global colleagues and promote networking within the nephrology community.
NephSIM (@Neph_SIM)	A mobile-friendly teaching tool designed for anyone who wants to learn or teach nephrology
Renal Fellow Network (@RenalFellowNtwk)	The RFN was established on April 23, 2008, by the late Nathan Hellman. RFN was created to provide a forum to discuss interesting nephrology cases, scientific papers, and other topics germane to nephrologists, particularly fellows.
The Skeleton Key Group (@TheSkeletonKG)	An online platform designed by a multinational team of nephrology fellows who collaborate to present interesting and illustrative electrolyte cases

*Please see the online version of this article for links to these professional development opportunities.
Abbreviations: *AJKD*, American Journal of Kidney Diseases; ISN-KI, International Society of Nephrology and *Kidney International*; *JASN*, *Journal of the American Society of Nephrology*; ASN, American Society of Nephrology; NSMC, Nephrology Social Media Collaborative; GlomCon, Glomerular Disease Study & Trial Consortium; CME, continuing medical education; NKF, National Kidney Foundation; RFN, Renal Fellow Network.

Continued on page 24 >

Tips and Tricks

Continued from page 23

Figure 1. Summary and timeline of fellow-friendly resources

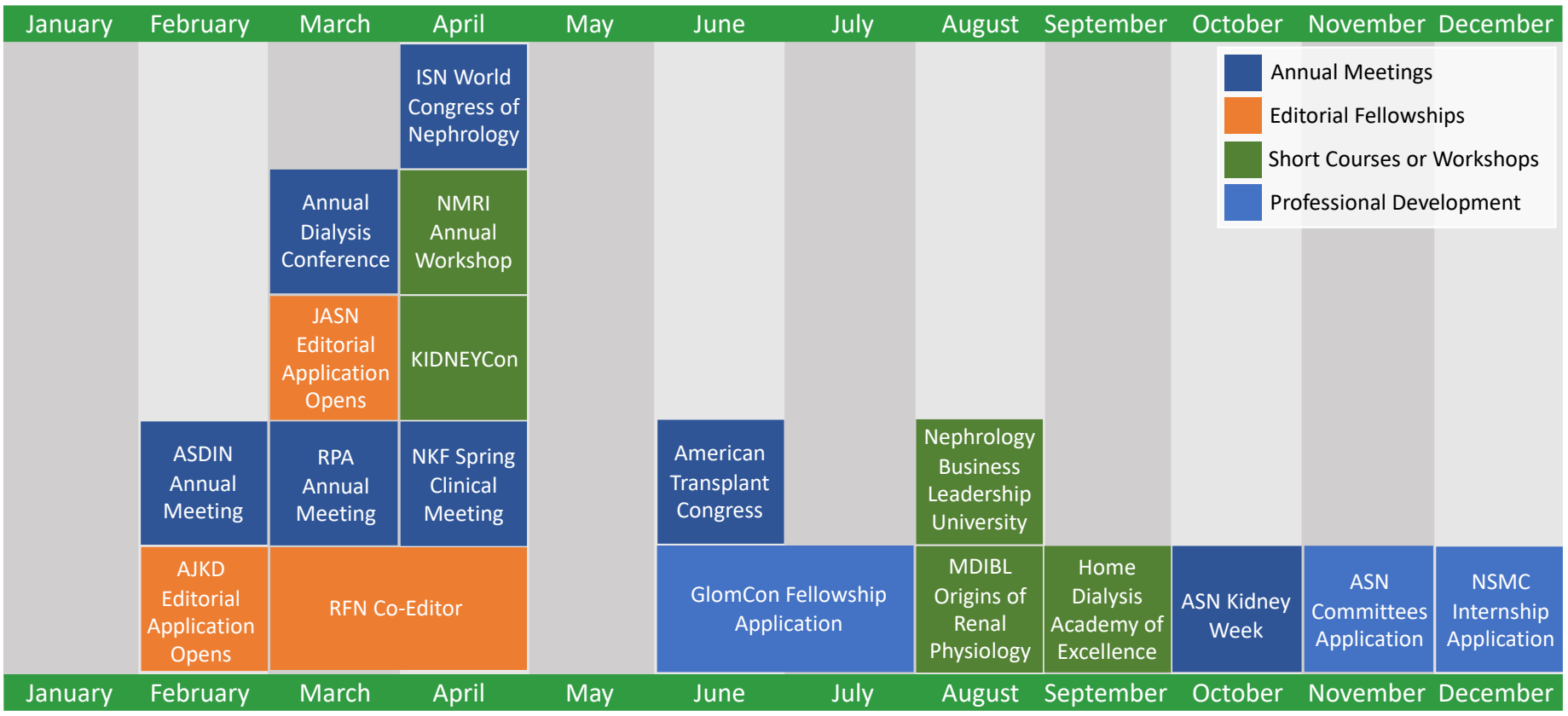


Figure created by: @PabloGarciaMD and @Yuv90

Abbreviations: ASDIN, American Society of Diagnostic and Interventional Nephrology; AJKD, American Journal of Kidney Disease; JASN, Journal of the American Society of Nephrology; RPA, Renal Physicians Association; RFN, Renal Fellow Network; ISN, International Society of Nephrology; NMRI, Network of Minority Health Research Investigators; NKF, National Kidney Foundation; GlomCon, Glomerular Disease Study & Trial Consortium; MDIBL, Mount Desert Island Biological Laboratory; ASN, American Society of Nephrology; NSMC, Nephrology Social Media Collective.

This figure presents a sample of key resources for nephrology fellows and anticipated application deadlines or annual meeting times. For a more thorough review of resources, refer to the main text and tables of this guide. The dark blue boxes represent anticipated meeting times for general nephrology society meetings. The orange boxes represent anticipated application times for editorial fellowships. The green boxes represent anticipated meeting times for short courses and workshops. The light blue boxes represent anticipated application times for professional development opportunities (positions on national committees, social medial collaboratives). These timelines are subject to change.

High Rate of AKI after Treatment for Infected Knee Replacements

Acute kidney injury (AKI) develops in nearly 1 out of 5 patients treated with antibiotic-loaded "spacers" for periprosthetic infection after total knee arthroplasty (TKA), reports a study in *The Journal of Bone and Joint Surgery*.

The retrospective study included 424 patients undergoing surgical treatment for periprosthetic infection after primary TKA at the Mayo Clinic from 2000 to 2017. Treatment included placement of high-dose antibiotic-loaded bone cement (ABLC) spacers in addition to systemic antibiotics. Mean age was 67 years; 15% of patients had pre-existing chronic kidney disease (CKD). AKI was defined as a creatinine increase or 1.5 times baseline or at least 0.3 mg/dL in any 48-hour period.

Nineteen percent of patients developed AKI while the ABLC spacers were in place. Risk of AKI was much higher among patients with pre-existing CKD: 45% versus 14%, odds ratio 5.0. None of the patients with AKI required acute dialysis.

AKI was more likely to occur when higher concentrations of vancomycin or aminoglycosides (over 3.6 g per batch of cement) were used in the ABLC spacers: odds ratio 1.9 and 1.8, respectively. Among patients without pre-existing CKD, independent risk factors for AKI included hypertension, perioperative hypovolemia, and atrial fibrillation. Diabetes trended toward significance.

Patients with AKI were not at an increased risk of a prolonged hospital stay or recurrent periprosthetic infection. At an average 6 years' follow-up, 8 patients had developed CKD, and 4 were receiving dialysis.

Two-stage exchange arthroplasty with ALBC spacer placement and intravenous or oral antibiotics is the most common treatment for periprosthetic infection after TKA. This contemporary cohort study suggests a high rate of AKI among patients undergoing this treatment, particularly those with pre-existing CKD.

Risk factors for AKI include indicators of reduced blood flow to the kidneys as well as high concentrations of vancomycin or aminoglycosides used in the spacers. The researchers add, "[W]hile higher antibiotic doses in ALBC spacers can lead to AKI, these doses are also a crucial factor for infection eradication" [Dagneaux L, et al. Acute kidney injury when treating infected total knee arthroplasties with antibiotic-loaded spacers: Incidence, risks, and outcomes. *J Bone Joint Surg Am*, published online ahead of print March 29, 2021. doi: 10.2106/JBJS.20.01825; https://journals.lww.com/jbjsjournal/Abstract/9900/Acute_Kidney_Injury_When_Treating_Periprosthetic.185.aspx].

How Long Do SARS-CoV-2 Antibodies Last in Dialysis Patients?

Nearly all dialysis patients infected with SARS-CoV-2 show sustained immune responses through 6 months' follow-up, according to a pre-proof paper in *Kidney International*.

The researchers screened for two types of SARS-CoV-2 antibodies in a cohort of 356 patients receiving hemodialysis at two UK dialysis centers. Specifically, samples were tested for antibodies to the nucleocapsid protein (anti-NP) and the receptor binding domain (anti-RBD) of the spike protein. Durability and functionality of immune responses to SARS-CoV-2 were assessed over time.

At initial screening, 38% of dialysis patients tested positive for one or both types of SARS-CoV-2 antibodies. Most patients (127 of 136) were positive for both anti-NP and anti-RBD. Two patients were positive for anti-NP but negative for anti-RBD, whereas 7 patients showed the opposite pattern.

At 6 months' follow-up in 301 patients, 64% were still positive for anti-NP and 85% for anti-RBD. Cellular immune responses were tested in 10 patients whose antibody responses had waned: 8 had detectable T cell responses.

Of the original 192 patients who were positive for anti-NP, 97% had persistent serologic or cellular immune responses at 6 months—even those with mild or asymptomatic SARS-CoV-2 infection. On assessment of clinical outcomes, patients who initially tested positive for SARS-CoV-2 antibodies were less likely to have polymerase chain reaction-positive infection, regardless of their 6-month antibody status.

Dialysis patients have high rates of SARS-CoV-2 infection with a high risk of poor outcomes. In this cohort study, close to 40% of in-center hemodialysis patients tested positive for SARS-CoV-2 antibodies.

Most patients remain antibody positive for 6 months, and nearly all have evidence of humoral or cellular immunity associated with reduced risk of subsequent SARS-CoV-2 infection. "Together, these data suggest that immune responses post-infection may be protective against reinfection," the investigators conclude [Clarke CL, et al. Longevity of SARS-CoV-2 immune responses in hemodialysis patients and protection against reinfection. *Kidney Int*, published online ahead of print March 24, 2021. doi: 10.1016/j.kint.2021.03.009; https://www.kidney-international.org/article/S0085-2538(21)00295-7/fulltext].

Acute Kidney Injury (AKI) Is Strongly Associated with COVID-19

AKI has been reported in up to 43% of hospitalized COVID-19 patients and is strongly associated with mortality[1]

Prime Plus Unique Kidney Injury Tests:

Urea, Creatinine, Ionized Magnesium, and Estimated plasma volume (fluid imbalance)

Other Prime Plus Tests:

Electrolyte disorders	Na, K, iCa, iMg, Cl, TCO_2
Metabolic acidosis	pH, PCO_2, HCO_3^-, Lactate
Acute respiratory distress	PCO_2, PO_2, SO_2%, Hb, Hct
Dysglycemia	Glucose

[1]Kellum JA et al. Targeting acute kidney injury in COVID-19. Nephrol Dial Transplant (2020) 35: 1652-1662.

STAT PROFILE Prime+®

Stat Profile Prime Plus® Blood Gas Critical Care Analyzer

nova® biomedical

novabiomedical.com

Preprints in Nephrology Research: PRO

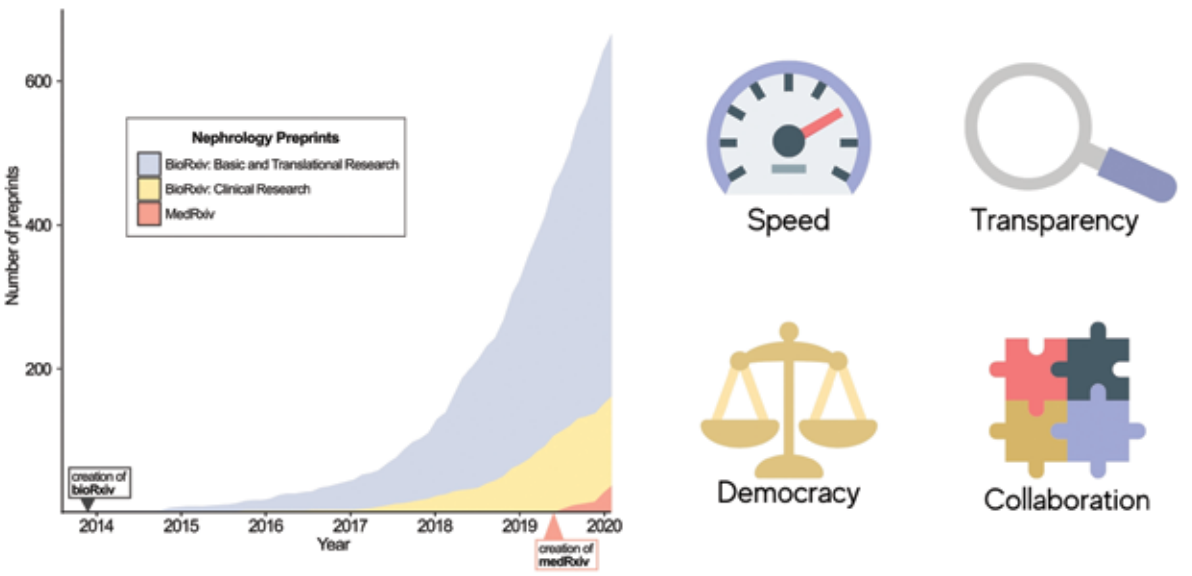
By Caitlyn Vlasschaert and Matthew B. Lanktree

Preprinting—the practice of posting full manuscripts in public forums ahead of formal peer review—has been around for decades (1, 2). In the 1950s, manuscripts were circulated within close networks of colleagues to discuss new ideas and supporting data before publication. The 21st century adaptation of this concept has taken the form of preprint servers such as bioRxiv.org and medRxiv.org. Preprints are steadily garnering acceptance in medicine, especially in the progressive field of nephrology. Nearly all general medicine and nephrology journals currently accept articles already shared as a preprint (3, 4). A National Library of Medicine (NLM) pilot will index preprints from National Institutes of Health (NIH)-funded research on eligible preprint servers in PubMed Central. What benefits can preprints bring to authors and the broader field of nephrology?

Preprinting increases the speed of research dissemination. The merits, and also challenges, of rapid dissemination have been tested during the COVID-19 pandemic (5). Scientists included rapidly shared data from preprints into meta-analyses to derive updated global prediction models that informed public health practices (6, 7). Concerns regarding poor quality preprints led to the implementation of additional safeguards on preprint servers (8). Overall, 31% of submissions to medRxiv were not posted, as they did not meet screening criteria (9). The COVID-19 pandemic has been a stress test exposing the weaknesses of preprinting, which ultimately is improving the process.

Preprinting has additional tangible benefits (Figure 1) (4). Similar to presenting data at late-breaking conference sessions, preprints generate interest and discussion, except the discussion is supported by greater detail and not just the headlines (9). Articles first shared as a preprint are read, shared, and cited more often than non-preprinted work (10, 11). The traditional peer-review process is limited to two to four solicited reviewers, whereas preprints are open access, allowing a wider network of peers to actively engage and provide feedback at the preprint stage. Preprints also provide a permanent public timestamp for novel ideas and findings, improving transparency. Overall, preprints promote rapid, collaborative, democratic, and transparent distribution of scientific results. ■

Figure 1. Rapid uptake and benefits of preprinting in nephrology



The left panel shows the number of kidney-related manuscripts uploaded to popular preprint servers since their inception (figure adapted from Vlasschaert et al. [4]). The right panel illustrates that the four main benefits of preprinting include faster speed of dissemination, improved transparency of the peer-review process, open and equitable access to research, and opportunity for collaboration on work in progress.

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Preprints in Nephrology: CON

By Jeffrey S. Berns

Publication of nephrology research in preprint servers, particularly medRxiv, which identifies itself as "the preprint server for health sciences," has rapidly expanded since the onset of the COVID-19 pandemic. Some of this material makes its way into peer-reviewed journals; much does not. Even well-known and respected authors are posting their research on such servers, likely, in part, due to the fact that most mainstream nephrology journals now accept submissions for peer review even if first posted on a preprint server. Having early access to important research, seemingly a primary goal of posting on a preprint server, can be valuable, as long as the material is accurate—and important. However, the peer-review process is imperfect—it slows access of information and does not always prevent flawed or erroneous material from publication (Table 1).

Keeping up to date and current with peer-reviewed medical and scientific literature is already an arduous task. Peer-review journals, including most that are open access, "narrow the funnel." Yet preprints turn the funnel upside down, making it virtually impossible to keep on top of all that is appearing in any given discipline.

Although some identify the ability to comment on and criticize a study posted on a preprint survey as a positive aspect, and it certainly can be, such comments and critiques are generally not monitored for accuracy or underlying conflicts of interest. As such, inappropriately positive or negative comments could influence interpretation and potentially even publication of preprints. It will be interesting to see studies of the impact—positive and negative, beneficial and harmful—of preprint material and clinical medicine. ■

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Dr. Berns is also a co-deputy editor of the *American Journal of Kidney Diseases* (*AJKD*). His comments reflect his personal view and opinions only, not those of *AJKD*.

Table 1. Concerns about preprint servers

Overwhelms ability to keep up with new information
Lack of traditional peer review and editorial oversight prior to posting/publication
Risk of widespread dissemination of false and/or harmful information by lay press
Not indexed for search via PubMed Central
NIH Preprint Pilot will allow indexing of NIH-funded COVID-19-related research from certain preprint servers
Requires separate searches of each preprint survey
Different search strategies
Disruption of current standards regarding publication primacy ("first to report")
Favors posting on preprint server over peer review
Early preprint posting of preliminary, incomplete results preempting peer-reviewed publication

There Is Another Way: Self-Publishing As a Form of Scientific Communication

By Tejas Desai

All of us have studied history, but rare is the person who lives through and shapes an instrumental period of humanity's record. We are that rare person. We live in a technological revolution where innovative ideas and disruptive forces, fueled by code, the microprocessor, and a self-awareness about our intrinsic capabilities, are changing nearly every aspect of our personal and professional lives (1). Those aspects that we suspect are prejudicial, exploitative, and/or simply inefficient are being reimagined into something closer to an ideal. Here, we shall focus on one such aspect that nearly all of us can agree is far from an ideal: scientific publishing.

It's time we tackle the manner in which we convey scientific information to each other. None of us were around when the conventions of scientific publishing were established, but all of us—producers (i.e., authors), judges (i.e., reviewers), and consumers (i.e., readers) of science—bear the burden of navigating through the publication process (2, 3). Currently, we have a system where scientific producers often pay to publish and forsake their rights to their product (i.e., paper), judges are expected to adjudicate science without remuneration, and consumers must purchase that product without the benefit of the first-sale doctrine (4). For decades we've convinced ourselves that we must use this route if science is to be shared (5). This may not be true anymore.

What if we could share science without these burdens? Can we innovate the manner in which we share scientific information? For that innovation to happen, first we would have to imagine a construct in which the producer of a scientific product makes available her/his work for free to anyone who wishes to read it. There would be no delay because the producer would decide when the science is ready to be shared. Then we would have to imagine the scientific consumer using that product and returning to the producer her/his assessment of it. Peer review(s) would be transformed into a non-anonymous, democratized effort in which the consumer would have first-pass scrutiny of the science. Finally, imagine the producer addressing the peer review(s) within the work itself so that the scientific product becomes a living document in which future consumers can read both the original version and the scientific discourse (i.e., the peer review and author response) that it generated. Transparent peer review could elucidate the science as much as or more than the original scientific product itself. Now you can stop imagining because such a construct already exists. It's called self-publishing (6, 7).

What I've asked you to imagine is a cursory description of self-publication. You would need to get into the details to understand the logistics of self-publishing and how it interfaces with other options, such as preprinting (Figure 1). Step back far enough, though, and you'll see that self-publishing is more than a disruptive publication method. Self-publication is a duty that the producer and consumer have to one another—a duty to release a good product in a timely manner to, and without payment from, the community. In return, the consumer must astutely judge the work and return a digitally signed assessment that is made transparent from which future consumers can learn. All of the responsibilities encompassed in this duty must be fulfilled in order to best serve scientific communication; so, it's not a surprise that self-publishing isn't for everyone (8, 9). For some though, the numerous avenues by which traditional publishers profit is the stimulus to enter the world of scientific self-publication (10, 11). For others, including myself, it is the lack of transparent and/or democratized peer review (12, 13). Whatever your reason(s), self-publishing offers you another choice to share your science.

Become an active member of the Technology Revolution (2015–?), and change the way science is shared! Choose to be a producer and/or consumer of self-published science and support this new construct of publishing (1). ■

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The views expressed here do not necessarily reflect Dr. Desai's views of the ASN or its affiliated publications or the official policy or position of any agency, organization, employer, or company.

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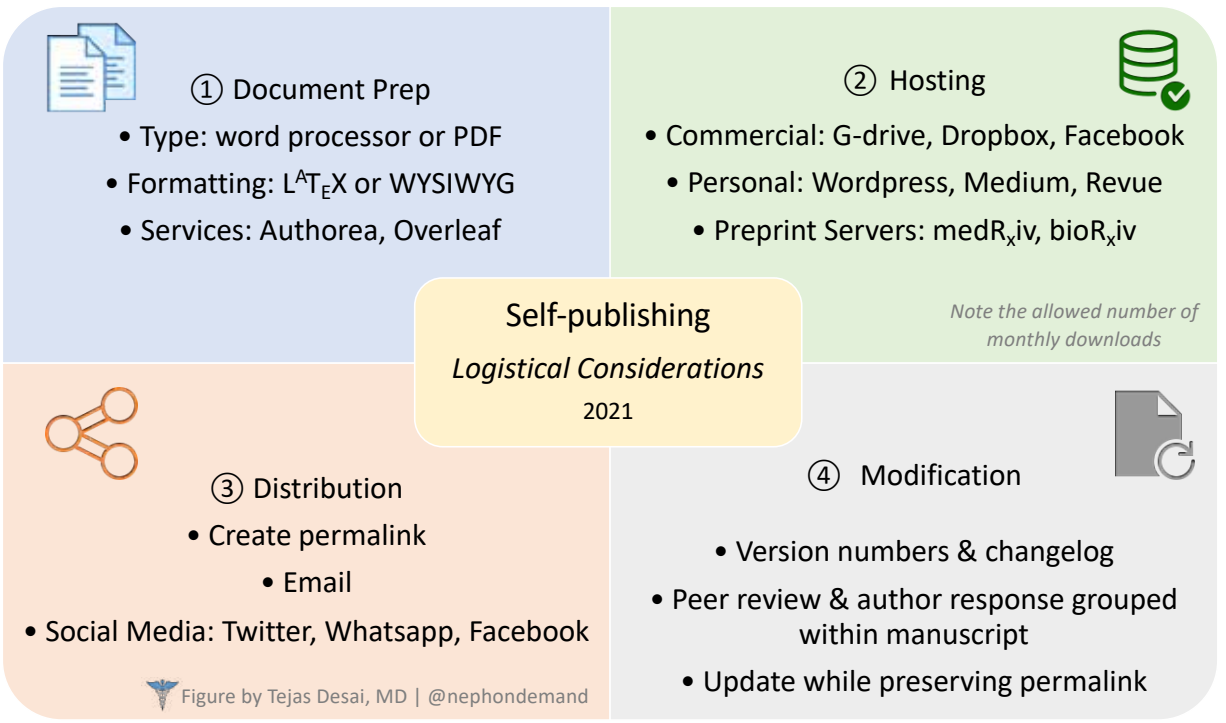
Figure 1. Logistical considerations for self-publishing



The Gut Microbiota and Metabolism of Immunosuppressive Medications

By John Lee

Studies have classically focused on how medications, such as antibiotics, affect the gut microbiota and how these microbiota changes lead to adverse outcomes. Indeed, the most common immunosuppressive medications, such as tacrolimus, have been reported to alter the gut microbiota in mouse models (1). Whether by immunosuppressive medications or by antibiotics, alterations in the gut microbiota in kidney transplant recipients have been associated with a variety of adverse outcomes, including urinary tract infections (2) and post-transplant diarrhea (3).

Recent data, however, suggest a role for the reverse: the gut microbiota's impact on the most commonly prescribed immunosuppressive medications: tacrolimus and mycophenolate mofetil. In a pilot study, researchers investigated whether the gut microbiota are related to the tacrolimus-dosing requirement and discovered that the gut abundance of a specific bacterium called *Faecalibacterium prausnitzii* early after transplantation was associated with higher tacrolimus dosage at 1 month after transplantation (4). *F. prausnitzii* is a common commensal gut bacterium that produces butyrate that is associated with anti-inflammatory properties and colonic health (5). A follow-up study found that *F. prausnitzii* and several other commensal bacterial taxa indeed directly metabolize tacrolimus into an immunosuppressive metabolite (M1) in vitro (6). Notably, M1 is a lesser effective immunosuppressant when compared to parent tacrolimus and is a novel metabolite unique to gut bacteria and not produced by the liver (6). A subsequent study then found that M1 can be detected in the blood of kidney transplant recipients after oral administration of tacrolimus, suggesting the presence of gut bacterial metabolism of tacrolimus in vivo (7). The extent to which gut bacteria metabolize tacrolimus and affect tacrolimus levels in kidney transplant recipients is not known, and so future studies are needed to understand how gut bacterial metabolism of tacrolimus impacts tacrolimus dosing and tacrolimus trough variability.

Although gut bacteria may metabolize tacrolimus to a lesser effective immunosuppressant, recent data suggest the reverse for mycophenolate mofetil. Enterohepatic recirculation of mycophenolic acid (MPA), the active form of mycophenolate mofetil, is a well-known phenomenon, and recent data highlight the role of the gut microbiota in reactivation of inactive MPA, specifically the role of bacterial beta-glucuronidase, which can convert glucuronidated MPA to active MPA (8). The investigators reported in mice that vancomycin administration eliminated bacterial beta-glucuronidase activity and prevented the mycophenolate mofetil-related side effects of weight loss (8). Finally, another study evaluated beta-glucuronidase activity in diarrheal fecal specimens in kidney transplant recipients and found that higher levels were associated with prolonged length of posttransplant diarrhea (9). How bacterial beta-glucuronidase activity influences MPA pharmacokinetics in kidney transplant recipients is unknown, and so future work is needed to understand how bacterial beta-glucuronidase activity may impact mycophenolate mofetil-related side effects and outcomes such as acute rejection.

Figure 1 shows a summary of the pathways for gut bacterial metabolism of tacrolimus and mycophenolate mofetil. Although some gut bacteria convert tacrolimus to a less-effective immunosuppressive medication, other bacteria convert inactivated MPA back to active MPA.

Future studies are needed to identify the specific bacteria and the extent to which they metabolize these medications. These studies will be particularly important, as these medications are utilized not only in kidney transplant recipients but also in other solid organ transplant recipients and in autoimmune diseases such as systemic lupus erythematosus. ■

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Dr. Lee has an investigator-initiated research grant from Biofire Diagnostics, LLC, and has a patent (US-2020-00487313-A1) on methods of detecting cell-free DNA in biological samples.

Alterations in the gut microbiota in kidney transplant recipients have been associated with a variety of adverse outcomes.

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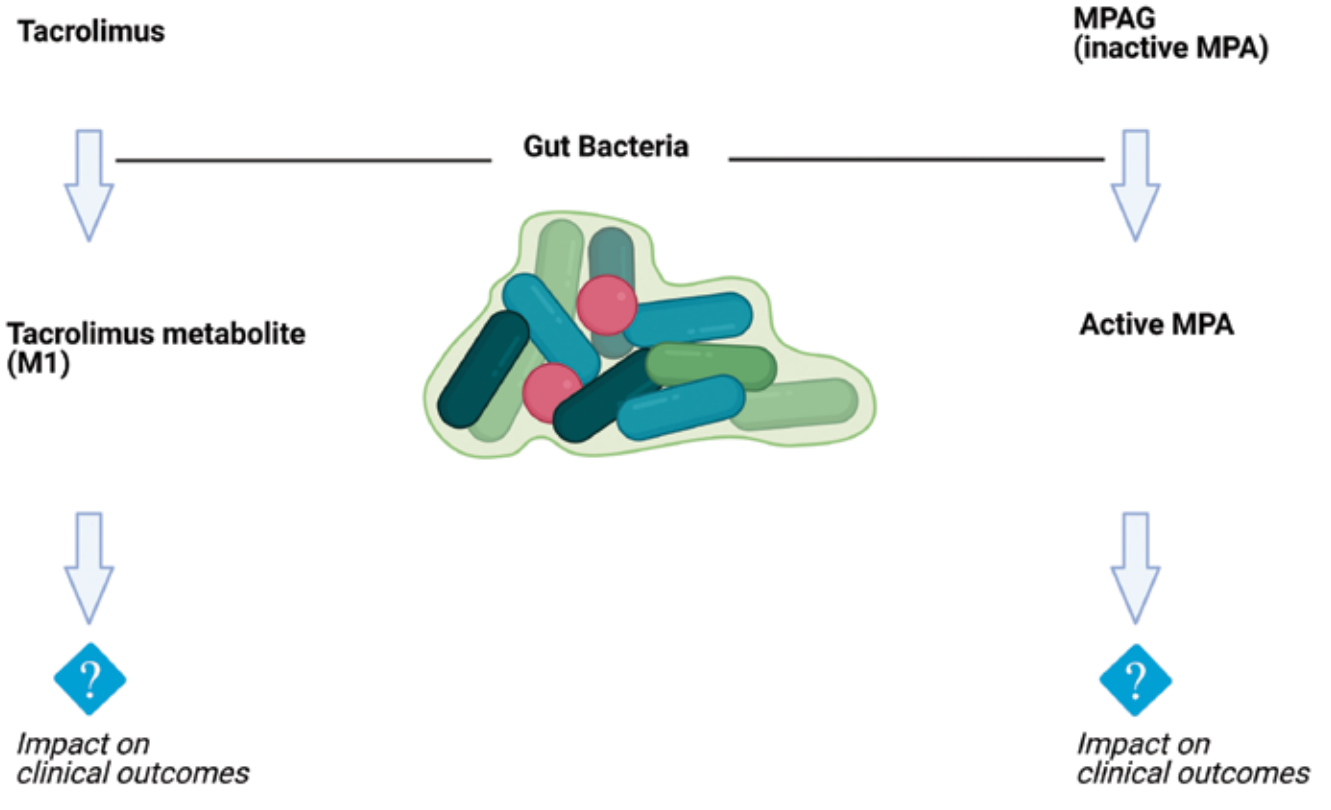
Figure 1. Different metabolism pathways of gut bacteria on tacrolimus and mycophenolate mofetil



On the left, parent tacrolimus is metabolized by gut bacteria into a tacrolimus metabolite, M1, that has lesser immunosuppressive effect than parent tacrolimus. On the right, inactivated MPA, glucuronidated MPA (MPAG), is metabolized by gut bacteria back into active MPA. MPA, mycophenolic acid.

Figure created by John Lee and Kenar Jhaveri using BioRender (biorender.com).

The VA MISSION Act of 2018—What This Means for Veterans Living with Kidney Diseases

By Susan T. Crowley

Fifty-one years ago, the fate of the daring US astronauts of the APOLLO 13 mission unfolded on national television. Launched to replicate the sensational success of NASA's lunar landing the previous year, the unlucky "13" spacecraft sustained damage to a critical environmental control module and had to not only abort the mission but creatively reengineer its way back to earth. What became known as NASA's "most successful failed mission" is a story of triumph, despite exceptional adversity, due to the courage, imagination, and determination of a network of people invested in a common goal—ensuring the well-being of its astronauts.

Fast forward half a century to the course of the Veterans Administration (VA), responsible for the care of 9 million US military veteran enrollees. Limited access to VA healthcare in some geographic regions of the United States had resulted in delays of care, which sparked a successive series of legislative actions to supplement veteran health services with non-VA care (Figure 1). The "Maintaining Internal Systems and Strengthening Integrated Outside Networks" (MISSION) Act (Public Law No. 115-182), signed into law in 2018, mandated the implementation of numerous initiatives targeting reforms in VA education, telehealth, opioid safety, caregiver support, health information exchange, and infrastructure investment. Most significantly, the MISSION Act required the establishment of an integrated network of community healthcare providers, informed by market assessments, supported by expanded VA payment authority for private-sector care, and managed under a consolidated payment system to supplement VA healthcare services where VA capacity limitations or geographic inaccessibility exist.

Although the impact of the MISSION Act on VA healthcare remains to be determined, the development of the VA Kidney Program, the office within VA Specialty Care Services, tasked with oversight of VA kidney health services, has over the past decade provided a lens to foresee the evolution of the rest of the nation's largest integrated healthcare system. Specifically, the VA's paradigm for the provision of outpatient dialysis services to veterans provides a proof of concept for the creation of durable public-private partnerships and for forecasting the need for augmented health information exchange, quality measurement, and cost controls to promote their sustainability.

Driven by high rates of diabetes and hypertension, kidney disease is common in the veteran population, accounting for 11% of the incident US end-stage kidney disease (ESKD) population (1). To meet the needs of a growing number of veterans with ESKD turning to the VA for care, in 2013, the VA developed a national bundled-rate contract and network of community providers for maintenance dialysis services. The resulting dramatic increase in annual expenditures for purchased dialysis care triggered several comparative analyses of VA and community care, which revealed significant health outcome differences for veterans, consistently favoring VA care (i.e., standardized mortality rate [SMR] is lower for veterans dialyzing in VA units as compared to veterans dialyzing in the community) (2–4).

Like dialysis services, kidney transplantation of veterans with ESKD also exemplifies the paradigm of VA/private-sector care. Although most veterans choose to undergo kidney transplant surgery in the community, a large fraction of these veterans choose the VA for some or all of their post-transplant care. Similar to the dialysis findings, greater degrees of veteran reliance on the VA for post-transplant care have been associated with significantly improved long-term patient survival (5).

Additional research is underway to determine the basis for the consistent observations of improved kidney health outcomes with VA care. Determining the proportionate contribution of VA collateral care, care coordination, and veteran preference for VA care, to the kidney health benefits of VA care, may not only inform how to bridge the divide, but may also suggest ways to mitigate health outcome disparities identified for other VA outsourced care.

In summary, VA kidney health services may be viewed as the vanguard of an evolving VA/private-sector paradigm to broaden access to essential health services as required by the MISSION Act. For veterans with kidney disease, dialysis and transplant services are nationally available either in the VA or via curated community partnerships. Additional cost controls and quality-of-care assessments are required to inform evidence-based decision-making related to outsourced kidney care and to build solutions to remedy unmet veteran healthcare needs. Like the APOLLO 13 mission was to NASA, the MISSION Act is the VA's challenge to swiftly and creatively reengineer itself. Through the development of novel purchasing mechanisms and trusted partnerships with community providers invested in veteran health, the VA is charting a new orbit to optimize veteran kidney health outcomes in the MISSION Act era.

Susan T. Crowley, MD, MBA, FASN, is the National Program Director for Kidney Disease & Dialysis, Veterans Health Administration, and Professor of Medicine, Department of Medicine, Section of Nephrology, Yale University School of Medicine, New Haven, CT.

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Figure 1. VA MISSION Act eligibility criteria for veteran care in the community

Access Standards	Primary Care, Mental Health, Non-institutional Extended care	Specialty Care
Drive Time	30 minutes	60 minutes
Wait Time	20 days	28 days

See Community Care: MISSION Act Update for more information: https://www.nachc.org/wp-content/uploads/2019/11/Office-of-Comm-Care-Iowa-FQHCs-110719.pdf.

Now approved for the treatment of adults with active lupus nephritis...

START WITH A STRONG FIRST LINE

Indications

LUPKYNIS is indicated in combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN). *Limitations of Use:* Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation.

Important Safety Information

BOXED WARNINGS: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing malignancies and serious infections with LUPKYNIS or other immunosuppressants that may lead to hospitalization or death.

CONTRAINDICATIONS: LUPKYNIS is contraindicated in patients taking strong CYP3A4 inhibitors because of the increased risk of acute and/or chronic nephrotoxicity, and in patients who have had a serious/severe hypersensitivity reaction to LUPKYNIS or its excipients.

WARNINGS AND PRECAUTIONS

Lymphoma and Other Malignancies: Immunosuppressants, including LUPKYNIS, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to increasing doses and duration of immunosuppression rather than to the use of any specific agent.

Serious Infections: Immunosuppressants, including LUPKYNIS, increase the risk of developing bacterial, viral, fungal, and protozoal infections (including opportunistic infections), which may lead to serious, including fatal, outcomes.

Nephrotoxicity: LUPKYNIS, like other calcineurin inhibitors (CNIs), may cause acute and/or chronic nephrotoxicity. The risk is increased when CNIs are concomitantly administered with drugs associated with nephrotoxicity.

Hypertension: Hypertension is a common adverse reaction of LUPKYNIS therapy and may require antihypertensive therapy.

Neurotoxicity: LUPKYNIS, like other CNIs, may cause a spectrum of neurotoxicities: severe include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremor, paresthesia, headache, and changes in mental status and/or motor and sensory functions.

Hyperkalemia: Hyperkalemia, which may be serious and require treatment, has been reported with CNIs, including LUPKYNIS. Concomitant use of agents associated with hyperkalemia may increase the risk for hyperkalemia.

Lupkynis™ (voclosporin) capsules 7.9 mg

Using LUPKYNIS™ (voclosporin) in combination with MMF and steroids can transform your first-line regimen[1,a,b]

- ✓ Significantly greater complete renal response rates with LUPKYNIS vs standard of care alone
- ✓ Faster proteinuria reductions than standard of care alone
- ✓ Outcomes achieved with a low-dose steroid regimen
- ✓ Novel CNI with no drug level monitoring required[1,2]

[a]Complete renal response was achieved in 40.8% of patients with LUPKYNIS and 22.5% with control. Proteinuria reductions (UPCR ≤0.5 mg/mg) were achieved at a median time of 169 days with LUPKYNIS vs 372 days with control.[1]

[b]Complete renal response was defined as a confirmed UPCR of ≤0.5 mg/mg; eGFR ≥60 mL/min/1.73 m^2 or no confirmed decrease from baseline in eGFR of >20% or no treatment- or disease-related eGFR-associated event at time of assessment; presence of sustained, low-dose steroids (≤10 mg prednisone from Weeks 44-52); and no administration of rescue medications. Proteinuria reduction was based on time to UPCR of ≤0.5 mg/mg.[1]

CNI=calcineurin inhibitor; eGFR=estimated glomerular filtration rate; MMF=mycophenolate mofetil; standard of care=MMF + steroids; UPCR=urine protein/creatinine ratio.

See how LUPKYNIS can impact your appropriate patients with lupus nephritis at LUPKYNISpro.com

QTc Prolongation: LUPKYNIS prolongs the QTc interval in a dose-dependent manner when dosed higher than the recommended lupus nephritis therapeutic dose. The use of LUPKYNIS in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.

Immunizations: Avoid the use of live attenuated vaccines during treatment with LUPKYNIS. Inactivated vaccines noted to be safe for administration may not be sufficiently immunogenic during treatment with LUPKYNIS.

Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another CNI immunosuppressant. If PRCA is diagnosed, consider discontinuation of LUPKYNIS.

Drug-Drug Interactions: Avoid co-administration of LUPKYNIS and strong CYP3A4 inhibitors or with strong or moderate CYP3A4 inducers. Reduce LUPKYNIS dosage when co-administered with moderate CYP3A4 inhibitors. Reduce dosage of certain P-gp substrates with narrow therapeutic windows when co-administered.

ADVERSE REACTIONS

The most common adverse reactions (≥3%) were glomerular filtration rate decreased, hypertension, diarrhea, headache, anemia, cough, urinary tract infection, abdominal pain upper, dyspepsia, alopecia, renal impairment, abdominal pain, mouth ulceration, fatigue, tremor, acute kidney injury, and decreased appetite.

SPECIFIC POPULATIONS

Pregnancy/Lactation: May cause fetal harm. Advise not to breastfeed.

Renal Impairment: Not recommended in patients with baseline eGFR ≤45 mL/min/1.73 m^2 unless benefit exceeds risk. If used in this population, reduce LUPKYNIS dose.

Hepatic Impairment: For mild or moderate hepatic impairment, reduce LUPKYNIS dose. Avoid use with severe hepatic impairment.

Please see Brief Summary of Prescribing Information including Boxed Warning on adjacent pages.

References: 1. LUPKYNIS [package insert]. Rockville, MD: Aurinia Pharma U.S., Inc., 2021. **2.** Kuglstatter A, Mueller F, Kusznir E, et al. Structural basis for the cyclophilin A binding affinity and immunosuppressive potency of E-ISA247 (voclosporin). *Acta Crystallogr D Biol Crystallogr.* 2011;67(pt 2):119-123.

Aurinia™

Lupkynis™ (voclosporin) capsules 7.9 mg

LUPKYNIS™ (voclosporin) capsules, BRIEF SUMMARY
SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

BOXED WARNINGS: MALIGNANCIES AND SERIOUS INFECTIONS

Increased risk for developing malignancies and serious infections with LUPKYNIS or other immunosuppressants that may lead to hospitalization or death.

INDICATIONS AND USAGE

LUPKYNIS is indicated with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis (LN). Limitations of Use: Safety and efficacy of LUPKYNIS have not been established in combination with cyclophosphamide. Use of LUPKYNIS is not recommended in this situation.

CONTRAINDICATIONS

LUPKYNIS is contraindicated in patients taking strong CYP3A4 inhibitors because these medications can significantly increase exposure to LUPKYNIS, which may increase the risk of acute and/or chronic nephrotoxicity, and in patients who have had a serious/severe hypersensitivity reaction to LUPKYNIS or its excipients.

WARNINGS AND PRECAUTIONS

Lymphoma and Other Malignancies: Immunosuppressants, including LUPKYNIS, increase the risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

Serious Infections: Immunosuppressants, including LUPKYNIS, increase the risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Viral infections reported include cytomegalovirus and herpes zoster infections.

Nephrotoxicity: LUPKYNIS, like other calcineurin inhibitors (CNIs), can cause acute and/or chronic nephrotoxicity. The risk is increased when CNIs are concomitantly administered with drugs associated with nephrotoxicity. Consider the risks and benefits of LUPKYNIS treatment in light of the patient's treatment response and risk of worsening nephrotoxicity, including in the following situations:
1) Longer treatment duration beyond one year. Safety and efficacy of LUPKYNIS have not been established beyond one year.
2) Co-administration with drugs associated with nephrotoxicity. The risk for acute and/or chronic nephrotoxicity is increased when LUPKYNIS is concomitantly administered with drugs associated with nephrotoxicity.

Hypertension: Hypertension is a common adverse reaction of LUPKYNIS therapy and may require antihypertensive therapy.

Neurotoxicity: Like other CNIs, LUPKYNIS can cause neurotoxicities. The most severe ones include posterior reversible encephalopathy syndrome (PRES), delirium, seizure, and coma; others include tremor, paresthesia, headache, mental status changes, and changes in motor and sensory functions.

Hyperkalemia: Hyperkalemia, which may be serious and require treatment, has been reported with CNIs including LUPKYNIS. Concomitant use of agents associated with hyperkalemia may increase the risk for hyperkalemia.

QTc Prolongation: LUPKYNIS prolongs the QTc interval in a dose-dependent manner after single dose administration at a dose higher than the recommended lupus nephritis therapeutic dose. The use of LUPKYNIS in combination with other drugs that are known to prolong QTc may result in clinically significant QT prolongation.

Immunizations: Avoid the use of live attenuated vaccines during treatment with LUPKYNIS. Inactivated vaccines noted to be safe for administration may not be sufficiently immunogenic during treatment with LUPKYNIS.

Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with another CNI immunosuppressant. If PRCA is diagnosed, consider discontinuation of LUPKYNIS.

ADVERSE REACTIONS

Clinical Trials Experience

A total of 355 patients with LN were treated with voclosporin in the Phase 2 and 3 clinical studies of whom 224 were exposed for at least 48 weeks. A total of 267 patients received at least 1 dose of LUPKYNIS 23.7 mg twice a day with 184 exposed for at least 48 weeks. A total of 88 patients received at least 1 dose of voclosporin 39.5 mg twice a day with 40 exposed for 48 weeks. Patients received background treatment with MMF 2 g daily and an IV bolus of corticosteroids followed by a pre-specified oral corticosteroid taper dosing schedule.

Adverse Reactions in ≥3% of Patients Treated with LUPKYNIS 23.7 mg BID and ≥2% Higher than Placebo in Studies 1 and 2

Adverse Reaction	LUPKYNIS 23.7 mg twice a day (n=267)	Placebo (n=266)
Glomerular filtration rate (GFR) decreased*	26%	9%
Hypertension	19%	9%
Diarrhea	19%	13%
Headache	15%	8%
Anemia	12%	6%
Cough	11%	2%
Urinary tract infection	10%	6%
Abdominal pain upper	7%	2%
Dyspepsia	6%	3%
Alopecia	6%	3%
Renal Impairment*	6%	3%
Abdominal Pain	5%	2%
Mouth ulceration	4%	1%
Fatigue	4%	1%
Tremor	3%	1%
Acute kidney injury*	3%	1%
Decreased appetite	3%	1%

**GFR decreased was the most frequently reported renal adverse reaction. Other renal adverse reactions were renal impairment, acute kidney injury, blood creatinine increased, azotemia, renal failure, oliguria, and proteinuria.*

Other adverse reactions reported in less than 3% of patients in the LUPKYNIS 23.7 mg group and at a 2% higher rate than in the placebo group through Week 48/52 included gingivitis and hypertrichosis. Studies 1 and 2 were integrated to represent safety through 48/52 weeks for placebo (n=266), LUPKYNIS 23.7 mg twice a day (n=267), and voclosporin 39.5 mg twice a day (n=88). Exposure adjusted incidence rates were adjusted by study for all the adverse events reported in this section.

DRUG INTERACTIONS

Effect of Other Drugs on LUPKYNIS

Strong and Moderate CYP3A4 Inhibitors: Voclosporin is a sensitive CYP3A4 substrate. Co-administration with strong or moderate CYP3A4 inhibitors increases voclosporin exposure, which may increase the risk of LUPKYNIS adverse reactions. Co-administration of LUPKYNIS with strong CYP3A4 inhibitors (e.g., ketoconazole,

itraconazole, clarithromycin) is contraindicated. Reduce LUPKYNIS dosage when co-administered with moderate CYP3A4 inhibitors (e.g., verapamil, fluconazole, diltiazem). Avoid food or drink containing grapefruit when taking LUPKYNIS.

Strong and Moderate CYP3A4 Inducers: Voclosporin is a sensitive CYP3A4 substrate. Co-administration with strong or moderate CYP3A4 inducers decreases voclosporin exposure, which may decrease the efficacy of LUPKYNIS. Avoid co-administration of LUPKYNIS with strong or moderate CYP3A4 inducers.

Effect of LUPKYNIS on Other Drugs

Certain P-gp Substrates

Voclosporin is a P-gp inhibitor. Co-administration of voclosporin increases exposure of P-gp substrates, which may increase the risk of adverse reactions of these substrates. For certain P-gp substrates with a narrow therapeutic window, reduce the dosage of the substrate as recommended in its prescribing information, if needed.

OATP1B1 Substrates

The effect of LUPKYNIS on OATP1B1 substrates (e.g., statins) has not been studied clinically. However, voclosporin is an OATP1B1 inhibitor in vitro, and information suggests an increase in the concentration of these substrates is possible. Monitor for adverse reactions of OATP1B1 substrates when used concomitantly with LUPKYNIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Avoid use of LUPKYNIS in pregnant women. The available data on the use of LUPKYNIS in pregnant patients are insufficient to determine whether there is a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with systemic lupus erythematosus (SLE). LUPKYNIS may be used in combination with a background immunosuppressive therapy regimen that includes mycophenolate mofetil (MMF). MMF used in pregnant women and men whose female partners are pregnant can cause fetal harm (major birth defects and miscarriage). Refer to the MMF prescribing information for more information on its use during pregnancy. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

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

Lactation

There are no available data on the presence of voclosporin in human milk, the effects on the breastfed infant, or the effects on milk production. Voclosporin is present in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adult patients treated with LUPKYNIS such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 7 days after the last dose of LUPKYNIS (approximately 6 elimination half-lives).

Females and Males of Reproductive Potential

LUPKYNIS may be used in combination with a background immunosuppressive therapy regimen that includes MMF. If LUPKYNIS is administered with MMF, the information for MMF regarding pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to MMF prescribing information for additional information.

Pediatric Use: The safety and efficacy of LUPKYNIS in pediatric patients has not been established.

Geriatric Use: Clinical studies of LUPKYNIS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. 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.

Renal Impairment

Use of LUPKYNIS is not recommended in patients with a baseline eGFR ≤45 mL/min/1.73 m^2 unless the benefit exceeds the risk. If used in patients with severe renal impairment at baseline, LUPKYNIS should be used at a reduced dose. No dosage adjustment is recommended in patients with mild or moderate renal impairment at baseline. Monitor eGFR closely. After initiating therapy, dosing adjustments should be made based on eGFR.

Hepatic Impairment

Reduce LUPKYNIS dosage in patients with mild/moderate hepatic impairment. Avoid LUPKYNIS in patients with severe hepatic impairment.

OVERDOSAGE

Symptoms of accidental overdose may include tremor, headache, nausea and vomiting, infections, tachycardia, urticaria, lethargy, and increases in blood urea nitrogen, serum creatinine, and alanine aminotransferase levels. General supportive measures and symptomatic treatment are recommended in cases of overdose.

To report SUSPECTED ADVERSE REACTIONS, contact Aurinia Pharma U.S., Inc. at 1-833-672-0028 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This brief summary is based on LUPKYNIS Prescribing Information (FPI-0009) issued January 2021.

Additional information can be found at LUPKYNISpro.com.

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Metabolomics Approaches Confer a Deeper Biologic Understanding of Kidney-Related Diseases

By Alexander M. Buko

A Q&A

Human Metabolome Technologies (HMT) Vice President Alex Buko, PhD, addresses the use of metabolomics to further understanding of kidney diseases. At HMT, Dr. Buko provides scientific and statistical support for preclinical and clinical studies in metabolomics.

1 Metabolomics is fast becoming a significant technology applied to kidney disease research. What is metabolomics?

Metabolomics is the measurement and analysis of small organic molecules in biologic samples: cells, tissues, organs, and biofluids. It provides a snapshot of the biologic system as a whole, taking into account internal and external factors such as genetics, microbiome, lifestyle, and disease. The organic compounds analyzed cover a wide range of chemical species including sugars, amino acids, organic acids, nucleic acids, acylcarnitines, small- to very long-chain fatty acids, bile acids, and a whole cast of steroids and lipids. Owing to the wide range of chemical species, different analytic methods need to be used to capture the kidney, urine, or plasma metabolome. Concerning kidney function, metabolites of research interest include creatinine, urea, uric acid, glucose, triglycerides, kynurenines, amino acids, and bile acids. Current clinical approaches in nephrology include measuring metabolites like urea, creatinine, and uric acid, which complement other tests, such as cystatin C, parathyroid hormone, and albumin.

The number of endogenous metabolites present in the human body, according to the Human Metabolome Database (HMDB) (1), is >90,000. Altogether, metabolites in the HMDB are linked to >660 diseases. Small molecule metabolites are linked to >27,000 single nucleotide polymorphisms, 2000 enzymes, and hundreds of pathways. They build a network of signaling and information flow representing the biochemical profile of an individual. In patients with chronic kidney disease (CKD), many metabolomics studies have revealed associations among blood metabolites, estimated glomerular filtration rate (eGFR), and clinical phenotypes representing disease status and progression.

The central dogma of molecular biology states that DNA makes RNA, and RNA makes proteins. These proteins turn over metabolites, with metabolites representing an endpoint of protein expression. Whereas an individual's DNA is static, the metabolome is dynamic and a functional system of cellular programming. In addition, the metabolome differs throughout the body, so the analysis of organs such as the kidneys will be different from that of other organs or biofluids such as blood and urine. Even within tissues, there can be heterogeneity across an organ's cross-section. Hence, metabolic profiles of patients with kidney diseases can represent their clinical status at the molecular level.

2 Many metabolites can then be measured. Why would kidney disease be an emerging area for applying metabolomics?

Changes in circulating metabolites may be of interest for different reasons, based on the specific cohort or clinical study in a host of different diseases. To this point, kidney disease is not unique; however, there are some special reasons that may enable metabolomics to be particularly adaptive and successful in this area. The kidney has a broad and complicated impact on circulating metabolites because of its unique biologic function to filter blood and remove circulating toxins. Hence, an enhanced level of a metabolite may be reflective of kidney failure and could provide early detection of chronic disease, measure disease prognosis, be a marker for therapeutic efficacy, shadow organ health, or provide researchers with a better understanding of the complex kidney biochemistry. Some of these metabolites may in fact act as ligands for specific receptors elsewhere in the body and can facilitate interaction with other organs such as the liver and brain.

Part of the problem in understanding the complex biochemistry of kidney function is how to aptly measure the large metabolic space covered by polar and nonpolar metabolites.

3 Where can metabolomics enable CKD research?

One of the most common measurements for kidney disease is the GFR. However, because human biology is so complex, GFR does not fully reflect individual kidney functions or discriminate between disease cause and progression. The effects of diet, lifestyle, microbiome, medication, and comorbidities require a finer understanding of the disease phenotype than the general measurements of cholesterol, uric acid, glucose, creatinine, and eGFR typically provide to the clinician. Many metabolites have been observed to change in blood with kidney dysfunction (2–4), among them the amino acids citrulline, glutamine, and several others. The impact of kidney function on peripheral metabolites in plasma and serum and on urine metabolism is complex, with both direct and indirect effects. Intra-organ communication and feedback add further complexity, which is not completely understood. Despite the diversity among patients, metabolomics is offering new insights and new directions to understanding CKD and drug development (5–7).

At HMT, we have a lot of experience with the metabolome of the gut microbiome and its interactions with other organs and the brain. Whereas many metabolomics studies continue to identify the best mix of biomarkers for CKD diagnosis, an emerging subject is the effect of the microbiome on CKD development (8). Indoxyl sulfate and p-cresyl sulfate, which are colon-derived metabolites of bacterial origin, are found at higher levels in end-stage kidney disease (ESKD) than in healthy individuals and are not removed by dialysis. Phenyl sulfate, another gut metabolite, has also been observed in diabetic kidney disease. Phenyl sulfate was observed to correlate with albuminuria. In addition, another gut metabolite, trimethylamine-N-oxide (TMAO), has been associated with cardiovascular disease (CVD) and cholesterol transport (9). TMAO is primarily excreted by the kidney and is associated with ESKD (10). These biomarkers and others are under investigation for larger validation studies and other related diseases (11).

4 You mentioned many different types of metabolites, from TMAO to lipids. How can we decide which technology would best be used to discover biomarkers for disease progression or patient stratification?

Part of the problem understanding the complex biochemistry of kidney function is how to aptly measure the large metabolic space covered by polar and nonpolar metabolites. The presence of polar metabolites, such as asymmetric dimethylarginine (ADMA), TMAO, and phosphate sugars, and nonpolar long-chain fatty acids, bile acids, steroids, and lipid complexes presents an analytic challenge. Many different technologies are successfully used to measure different segments of this metabolic space, including nuclear magnetic resonance (NMR), gas chromatography-mass spectrometry (GC-MS), various forms of liquid chromatography (LC)-MS, imaging MS, and capillary electrophoresis (CE)-MS. Each method has its advantages and limitations. The differences among these technologies include unique coverage of metabolic space, sensitivity for certain classes of metabolites, ability to identify novel metabolites, sample throughput, and instrument dynamic range. NMR has the advantage of being nondestructive, and samples do not need preparation or extraction and can be reused. However, NMR lacks the sensitivity, resolution, and specificity of the MS-based techniques.

Many successful NMR applications have been published in kidney disease studies. MS-based techniques, however, are the most widespread. Owing to the large variations and complexities of the metabolome, no single MS-based technique is capable of systematic broad detection and measurements. Various reverse-phase LC methods coupled with high-performance MS are mainstream methods to sample a broad range of polar to nonpolar spaces. Very polar metabolites require a different approach with hydrophilic interaction LC (HILIC) CE methods. The complexity and number of isobaric metabolites in the lipid space place an even higher burden on specialized chromatography and MS. In the search for the right method to use in a study, prior knowledge of a metabolite of interest, focused metabolic pathway, or specific chemical class allows for more unique solutions. Unbiased methods—called untargeted metabolomics—generally provide nonquantitative metabolite data but cover a large range of metabolic space. If a particular metabolite or family is known to be of interest, a targeted approach providing quantitative data might be the method of choice. It may be advisable to consider several different methods before choosing one or more methods for metabolomic studies.

Most laboratories today use extensive metabolite libraries for the annotation of known and validated metabolite identification and high-resolution mass spectrometers that can provide elemental formulas for the identification of novel or unknown metabolites. As the size of the metabolome continues to grow, metabolite libraries continue to expand.

5 What biomarkers are currently useful for preclinical or clinical studies for research in drug development, and what limits the commercial development of research-grade biomarkers?

The issues today, concerning not only biomarkers but also omics discovery in general, are found in the translation from discovery and preclinical to clinical use. In detail, these issues include acceptance of common practices, variations in size and composition of study groups, reliance on the discovery of single analytes, the lack of appropriate validation studies, and the challenges of combining different datasets from orthogonal methods (combining RNA with proteomics with metabolomics, for example (7). Hence, aside from the accepted clinical measurements, there is a growing literature of promising new metabolites and panels that can be used for research. However, owing to different methodologies, pathologic conditions, and cohort selections, investigators today must conduct their own targeted or untargeted research to feel confident about any metabolite panel chosen for disease progression or clinical study. The good news is that organizations such as ASN are bringing together data and studies, facilitating data sharing, and providing the driver to move these discoveries to a common consensus that pushes commercialization of critical biomarkers and also focuses on the needed biochemistry to enable drug discovery.

6 What can we expect in the future?

Metabolomics is a growing, powerful, and enabling tool for CKD research. Coupled with a strategic cohort study design and size, metabolomics is capable of providing needed data for a deeper understanding of kidney function and dysfunction. We at HMT view metabolites as an important starting point for biomarker discovery and hypothesis generation. Metabolomics has the capability to measure polar and lipid metabolites in kidney tissue, circulating plasma, and urine, linking disease status to molecular processes. The technologies to measure metabolites in patient samples already exist, so the technology and assay development from research to validation to commercialization are already in place. In the future, we expect to see metabolomics playing a leading role in CKD study, diagnosis, and drug development. ■

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Cultivating Interest in Nephrology by Engaging in Opportunities and Seeking out Mentors

By Tanima Arora

As a starry-eyed international medical student looking for opportunities to gain clinical experience in the United States, I was beyond thrilled to receive an offer from Yale School of Medicine to complete a month-long clerkship in pediatric nephrology. Did I want to pursue a career in nephrology back then as a final-year medical student? Honestly, I wasn't sure. Kidney physiology, as fascinating as it is, was also extremely daunting to me. As a medical student, I would have a subclinical panic attack anytime I was asked to, for instance, "calculate eGFR in CKD" or explain "renal tubular acidosis" in detail. I was nervous, to say the least, but did I decide to keep an open mind and take this remarkable opportunity to learn? Absolutely, yes!

And so my journey in the world of nephrology began, surrounded by exceptional mentors, interesting patients, fascinating research, and most important, a sense of belonging. In addition to the complexity of kidney pathophysiology and satisfaction of caring for and improving the quality of life of critically ill patients, what struck me the most was the passion and commitment of the workforce toward creating an innovative and fun learning environment for students. Thus, invigorated and inspired by this intensive, albeit short, exposure to nephrology, I decided to dedicate myself toward kidney research and gain more experience in this wonderful field.

My postdoctoral training (a full-time research trainee position) at Yale allowed my academic and professional growth to flourish, as I gained independence in conducting and managing research projects, presenting posters, publishing papers, contributing at conferences, and building connections, both in person and via social media. My budding interest in nephrology was recognized by numerous members of the kidney world, and I was lucky enough to partake in wonderful opportunities to participate in unique educational activities such as ASN Kidney STARS, ASN Kidney TREKS, and NephSIM Nephrons.

The crux of my interest and passion for nephrology is the incredible mentorship I have received over the years. Not only was I blessed with extraordinary mentors at Yale, but through participating in various educational activities, I also connected with some of the brightest minds in nephrology and gained more mentors. Each provided support, motivation, and guidance and created a nurturing, stimulating environment for me to consistently face challenges, grasp new opportunities, and grow, both professionally and personally.

The crux of my interest and passion for nephrology is the incredible mentorship I have received over the years.

That sense of belonging that I first felt during my nephrology clerkship has only grown stronger, and I feel confident that as I embark on this next phase of my career, the kidney world will take care of me and continue to cultivate my passion for nephrology. ■

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TRICIDA

This article is part of a series about peritoneal dialysis. Additional articles will appear in upcoming issues.

A Practical Patient-Centric Approach to the Peritoneal Dialysis Prescription

By Sehrish Ali, Natasha Dave, and Ankur Shah

Once the decision to pursue peritoneal dialysis (PD) is made, two primary modalities are available from which patients can choose: continuous ambulatory PD (CAPD) and ambulatory PD (APD). CAPD involves manually performed exchanges using gravity to fill and drain the peritoneal cavity, and APD involves exchanges that are performed using a cycler over several hours, typically during the night. The selection of a PD modality is dependent on an individual's lifestyle because there is no difference in patient and technique survival (1).

Subtypes of APD include continuous cycling PD (CCPD), nightly intermittent PD (NIPD), and tidal PD (TPD) (2). CCPD consists of overnight exchanges with a day dwell, and NIPD encompasses only overnight exchanges without a day dwell. TPD is an alternative form of APD in which the peritoneum is not completely drained between exchanges (Figure 1).

We use the following approach to determine modality and initial prescription. We begin with an assessment of the patient's lifestyle. Given that CCPD is a predominantly nocturnal therapy, a detailed sleep history is critical. This should include the average times when the patient goes to bed, falls asleep, and wakes up. This history can help determine the total amount of time available for cycler-assisted dialysis. In patients who report shorter sleep periods, the history is expanded to include activities immediately before and after bedtime, because some may be amenable to being performed during cycler-assisted dialysis. After understanding the patient's sleep schedule, the nephrologist and patient can work together to determine whether it would be feasible to perform exchanges during the day. This typically depends on the employment status, field, and lifestyle of the patient. The adept nephrologist will develop a prescription that works around the patient's lifestyle, allowing the patient to maintain a maximal quality of life. For example, a patient may report sleeping only 6.5 hours per night, but further history taking reveals that the patient reads for 1 hour before falling asleep and has a sleep latency of 30 minutes. This patient could reasonably receive 8 hours of cycler-assisted dialysis overnight. Volumes are titrated to tolerance, and dwell time typically targets 2 hours per exchange, which can be adjusted when transport status is determined by peritoneal equilibrium testing. Patients who are rapid transporters will benefit from shortened exchanges and slow transporters from longer exchanges (Figure 2).

Example prescriptions

- 32-year-old, 104-kg man, rapid transporter, works 9 to 5, sleeps 10 to 7; CCPD with four cycles over 9 hours of 3 L with a 2-L last fill
- 58-year-old, 78-kg woman, slow transporter, works from home, sleeps 9 to 7; CAPD with four manual exchanges of 2 L daily, scheduled at 8 am, noon, 4 pm, and 8 pm
- 36-year-old, 74-kg woman, slow transporter, works an office job, sleeps 10 to 6; CCPD with two exchanges over 8 hours of 2 L, last fill of 2 L, and midday exchange when home from work
- 46-year-old, 66-kg man, rapid transporter, works service job with variable hours, sleeps 11 to 6; CCPD with four cycles over 7 hours of 2 L with a 1.5-L icodextrin last fill.

We determine dialysis adequacy by using a holistic approach, including assessment of volume status, nutrition, electrolyte derangements, uremic symptoms, burden of therapy, and small solute clearance, as recommended by the 2020 International Society for Peritoneal Dialysis guideline. The evidence supporting this recommendation was reviewed in a prior *Kidney News* article (3). However, the Centers for Medicare & Medicaid Services quality metrics in the United States require that combined peritoneal and residual kidney Kt/V urea (whereby K is the clearance, t is time on dialysis, and V is the volume of distribution of urea) in PD patients be >1.7. If the prescription is deemed inadequate, then the prescription is adjusted to increase clearance, either by increasing dialysate fluid quantity or time or by adding an exchange (4).

Regardless of modality, dialysate composition in the United States is dextrose based and typically includes a sodium concentration of 132 mM, potassium 0 mEq/L, calcium 2.5 to 3.5 mEq/L, magnesium 0.25 to 0.75 mM, and lactate 35 to 40 mM. The dextrose concentrations available include 1.5, 2.5, and 4.25 g/dL (5). The tonicity of the dialysate may be increased to improve ultrafiltration and clearance. Attention should be given to uncontrolled hyperglycemia and hyperlipidemia and changes in peritoneal membrane function. Icodextrin, a branched glucose polymer derived from maltodextrin with minimal absorption that functions through colloid osmosis rather than crystalloid osmosis, may be used for the day dwell to improve ultrafiltration without worsening the hyperglycemia and limiting peritoneal absorption.

Writing a prescription requires a good foundation of knowledge of PD modalities and comprehension of your patient's daily life and transporter status. Understanding the patient's sleep patterns, lifestyle, occupation, and preferences for PD modality type will help in writing the appropriate prescription (6). Thankfully, prescriptions can be adjusted, and modalities can be switched if necessary. It is important to approach PD in a holistic fashion to ensure that dialysis is adequate and quality of life is upheld. ■

Figure 1. Overview of PD modality types

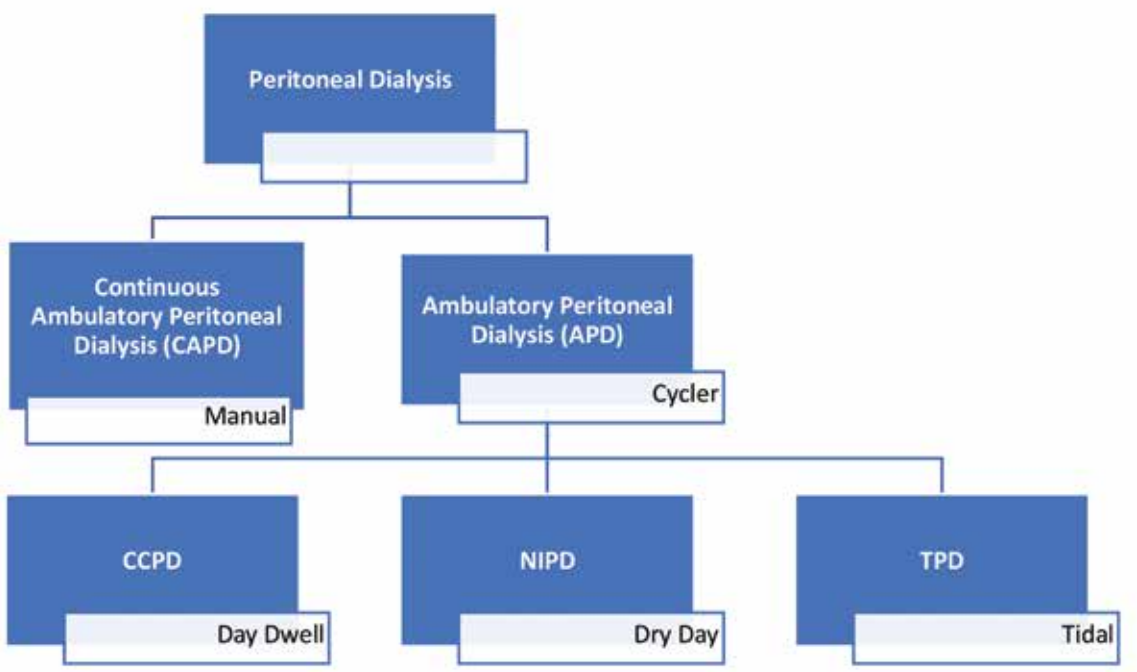
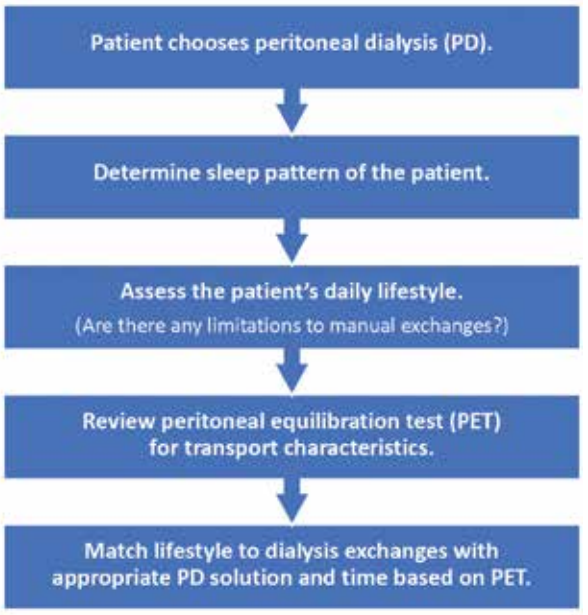


Figure 2. Chronology for determining the peritoneal dialysis prescription



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Drs. Ali and Shah report no conflicts of interest. Dr. Dave is a nephrologist and medical director for Strive Health and reports serving on a medical advisory board for Tricida Pharmaceuticals.

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Findings

Terlipressin Increases "Verified Reversal" of Hepatorenal Syndrome

The synthetic vasopressin analog terlipressin improves kidney function in patients with type 1 hepatorenal syndrome (HRS-1)—but with a high rate of serious adverse events, reports a clinical trial in *The New England Journal of Medicine*.

The CONFIRM Study (A Multi-Center, Randomized, Placebo Controlled, Double-Blind Study to Confirm Efficacy and Safety of Terlipressin in Subjects with Hepatorenal Syndrome Type 1), a randomized, phase 3 trial, included 300 adults with cirrhosis and HRS-1 treated at 60 North American centers. In a 2:1 ratio, patients were assigned to 30 days of treatment with terlipressin or placebo; concomitant albumin therapy was "strongly recommended" for both groups.

The main efficacy outcome was reversal of HRS, verified by two consecutive serum creatinine levels of 1.5 mg/dL or less (at least 2 hours apart) and survival free of kidney replacement therapy for at least 10 days after the end of treatment.

Terlipressin was associated with a higher rate of verified reversal of HRS: 32% compared to 17% in the placebo group. Secondary outcome analysis also favored terlipressin, including any serum creatinine level of 1.5 mg/dL or less within 14 days, 39% versus 18%; HRS reversal without kidney replacement therapy within 30 days, 34% versus 17%; HRS reversal among patients with systemic inflammatory response syndrome, 37% versus 6%; and verified reversal of HRS without recurrence by 30 days, 26% versus 17%.

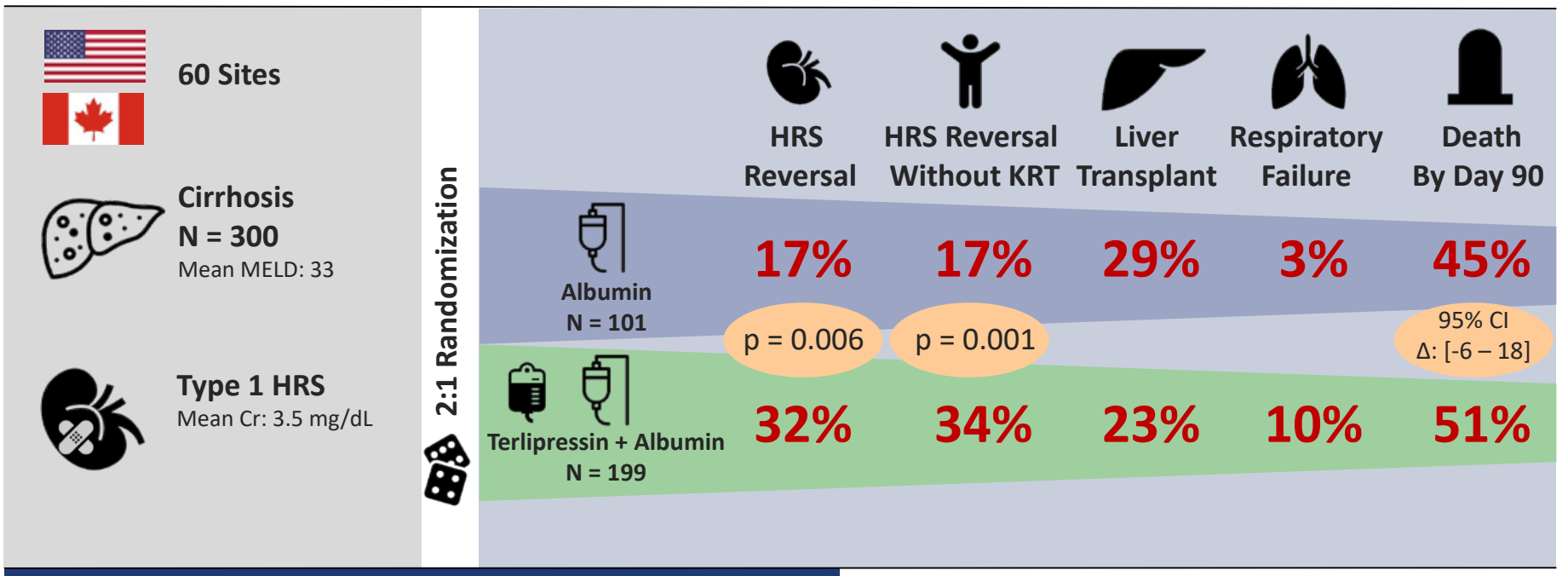
By 90 days, 23% of patients in the terlipressin group and 29% in the placebo group had undergone liver transplantation. Ninety-day mortality rates were 51% and 45%, respectively. Terlipressin was associated with higher rates of adverse events, including abdominal pain, nausea, diarrhea, and respiratory failure. Adverse outcomes included an 11% rate of death due to respiratory disorders in the terlipressin group compared to 2% in the placebo group.

With its vasoconstrictor activity, terlipressin is used as a treatment for HRS-1 in some parts of the world and is included in European clinical practice guidelines. The CONFIRM trial was designed to confirm the efficacy of terlipressin plus albumin for adults with cirrhosis and HRS-1.

The results show significant improvements in verified reversal of HRS-1 and initial survival in patients treated with terlipressin compared to placebo. However, terlipressin is associated with substantial rates of serious adverse events, including respiratory failure. The researchers write, "Terlipressin should be used with caution in patients who have the most advanced liver disease" [Wong F, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. *N Engl J Med* 2021; 384:818–828. doi: 10.1056/NEJMoa2008290]. ■

Does terlipressin reverse type 1 hepatorenal syndrome (HRS-1) in patients with cirrhosis?

ASN KidneyNews



CONCLUSION: In this trial involving adults with cirrhosis and HRS-1, terlipressin was more effective than placebo in improving kidney function but was associated with serious adverse events, including respiratory failure.

Wong F, Pappas SC, Curry MP, et al. **Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome.** *N Engl J Med*. 2021 DOI: 10.1056/NEJMoa2008290

@ssfarouk @Nephro_Sparks

Laxative Use Increases with Progression to ESRD

For patients with advanced chronic kidney disease (CKD), the transition to dialysis and end-stage kidney disease (ESKD) is associated with substantially increased use of laxatives, reports a study in *Nephrology Dialysis Transplantation*.

With the use of data from the US Renal Data System Transition of Care in CKD Study, the researchers analyzed patterns of laxative use among 102,477 military veterans who transitioned to ESKD between 2007 and 2015. The analysis focused on the proportion of patients who filled a prescription for any type of laxative during 6-month periods before and after the transition to ESKD. Factors associated with pre-ESKD laxative use were analyzed as well.

Patients used more laxatives as they approached ESKD. The proportion of laxative use peaked at 37.1% in the first 6 months after dialysis transition, remaining stable thereafter. Stool softeners were the most commonly used product (about 30% of users), followed by hyperosmotic agents (about 20%), and stimulants (about 10%).

Pre-ESKD laxative use was independently associated with use of medications, including the following: anticoagulants, odds ratio (OR) 4.24; iron supplements, OR 3.42; non-opioid analgesics, OR 2.51; antihistamines, OR 2.47; and opioid analgesics, OR 2.11. Positive associations were also noted for people who are Black and those with anemia, depression, and liver disease.

Constipation is common in patients with advanced CKD, especially after progression to ESKD and dialysis. The new findings document the high prevalence of laxative use during this transition period—a pattern that may reflect the increased use of medications can induce constipation. "[P]otential changes in practice habits to avoid unnecessary laxative use could contribute to a lower overall pill and economic burden in this relevant population," the researchers write [Sumida K, et al. Laxative use in patients with advanced chronic kidney disease transitioning to dialysis. *Nephrol Dial Transpl*, published online ahead of print October 10, 2020. doi: 10.1093/ndt/gfaa205; https://academic.oup.com/ndt/advance-article-abstract/doi/10.1093/ndt/gfaa205/5920411?redirectedFrom=fulltext]. ■

COVID-19-Associated AKI Linked to Sharper Declines in eGFR

For patients with COVID-19-associated acute kidney injury (AKI), the postdischarge rate of decrease in kidney function is greater than in AKI patients without COVID-19, reports a paper in *JAMA Network Open*.

The retrospective study included two groups of patients with AKI treated at five hospitals in a New England health system from March through August 2020. One hundred eighty-two patients had COVID-19-associated AKI, with positive results on a SARS-CoV-2 reverse transcription-polymerase chain reaction test at a study hospital. Another 1430 patients had AKI not associated with COVID-19. In both groups, all patients survived past discharge, did not require dialysis within 3 days after discharge, and had at least one subsequent outpatient creatinine level measurement.

Mixed-effects models were used to compare the postdischarge slope in estimated glomerular filtration rate (eGFR) for AKI patients with and without COVID-19. In a subgroup of 319 patients who did not have AKI recovery by discharge, time to recovery was compared between groups.

The sample included roughly equal numbers of men and women; median age was 69.7 years. Patients with COVID-19-associated AKI were more likely to be Black (40.1% versus 15.7%) or Hispanic (22% versus 8.8%). Overall comorbidity was lower in the COVID-19 group, but rates of pre-existing chronic kidney disease and hypertension were similar. Patients with COVID-19-associated AKI were more likely to be excluded due to in-hospital death. Median follow-up was longer in the COVID-19 group: about 90 versus 60 days.

The AKI patients with COVID-19 had a greater postdischarge decrease in eGFR: –11.3 mL/min/1.73 m^2/y before and –12.4 mL/min/1.73 m^2/y after adjustment for comorbidity. The difference remained significant in a fully adjusted model: –14.0 mL/min/1.73 m^2/y. In the subgroup analysis of patients whose eGFR did not return to normal by discharge, those in the COVID-19 group were less likely to have AKI recovery during follow-up: adjusted hazard ratio 0.57.

AKI has been reported to occur in more than one-half of patients hospitalized with COVID-19 and more than three-fourths of those admitted to the Intensive Care Unit (ICU). There are few data on the intermediate- and long-term outcomes of COVID-19-associated AKI.

The new study suggests that among hospitalized patients with AKI, cases associated with COVID-19 have a greater rate of decrease in eGFR after discharge. The difference in outcomes is unrelated to differences in comorbidity or AKI severity. "Identifying predictors of longitudinal eGFR decrease in patients with COVID-19-associated AKI may help prioritize which patients need close outpatient follow-up during the pandemic," the researchers write [Nugent J, et al. Assessment of acute kidney injury and longitudinal kidney function after hospital discharge among patients with and without COVID-19. *JAMA Netw Open* 2021; 4:e211095. doi: 10.1001/jamanetworkopen.2021.1095].

Policy Update

Improving Kidney Payment Model, Increasing Transparency in Transplant Waitlisting, and Creating Medicare Coverage on Innovative Devices

The American Society of Nephrology (ASN) is actively engaging with the federal government on multiple fronts on a host of issues, from COVID-19 to addressing equity in kidney healthcare. Three current fronts of activity focus on the kidney care payment models, transplant access, and support for payment pathways for innovative devices.

Payment models

Even before the recent delay in the voluntary Kidney Care Choices (KCC) Model, ASN had engaged the Center for Medicare and Medicaid Innovation (CMMI) to advocate for changes in the model based on ASN members' concerns. With ASN's request for CMMI to use the delay until January 1, 2021, to address multiple issues to improve the model, the first item raised was getting Medicare to address the issue of those nephrologists and practices that were planning to participate in KCC and would have been in an Alternative Payment Model (APM) in 2021 and not reporting in the Merit-based Incentive Payment System (MIPS). Medicare has indicated that nephrologists affected in this way will be allowed to file "hardship exemptions" due to COVID-19 and will be excused from reporting in MIPS if they wish—meaning they will receive no adjustment up or down for 2021.

Second, ASN asked CMMI to address modifications to the following areas of concern:

1. Withholding 30% of payments to avoid clawbacks from participants whose payment exceeded their performance will severely affect cash flow for all practices, particularly small ones, and in many cases preclude participation.
2. Removing the facility fee will negatively impact the ability of some groups to participate in the model, thereby limiting the scope of kidney patient participation, which is key to the model's success.
3. Compensating with a transplant bonus may help make up for these two cash flow issues in the longer term. However, because it is paid over 3 years, it cannot overcome the immediate cash flow challenges these two issues create in the short term as well as the challenges of payment of the bonus in the last 2 years of the model.
4. Overcoming challenges of administering the patient activation measure (PAM) and providing a sufficient opportunity to improve PAM scores. Administering the PAM will be challenging for nephrologists with patients in multiple facilities.
5. Increasing the payment levels of the chronic kidney disease (CKD) Quarterly Capitated Payment (QCP).

ASN believes the payment pathways of the KCC Model are vitally important steps to improving kidney care, but that the above issues must be addressed for the program to have a chance at success. ASN will update readers as the year progresses.

Transplant access

Transplant issues for 2021 are shaping up as challenging, as always, but also are providing opportunities for change. On March 30, the Biden administration allowed the long-awaited Organ Procurement Organization (OPO) Metric final rule to take effect. ASN supported this step to provide more transparency and objectivity in the OPO performance-rating system with real consequences for underperforming OPOs. ASN also supports more transparency in the area of transplant centers. First, however, it is engaging the Health Resources and Services Administration (HRSA) to address transplant waitlist challenges and the need for increased access to waitlist data for nephrologists and healthcare professionals. These advocacy efforts are designed to both increase access to transplantation and provide the transparency needed to address inequities in the transplant process.

Recently published research in *JASN* demonstrated that waitlist practices have not improved waitlist times over the last two decades (1). "Our study highlights the failure to improve waitlisting for ESRD [end-stage renal disease] patients that greatly impacts our most vulnerable patients over the past two decades," said Sumit Mohan, MD, MPH, FASN, one of the study's authors.

Payment pathways for innovative devices

The lack of innovation in kidney care remains an important issue. By addressing the payment for innovation in all of healthcare, ASN is urging the Centers for Medicare & Medicaid Services (CMS) to implement the Interim Final Rule (IFR) "Medicare Program: Medicare Coverage of Innovative Technology (MCIT) and Definition of 'Reasonable and Necessary.'" MCIT will provide a Medicare coverage pathway for US Food and Drug Administration (FDA)-designated breakthrough medical devices. The MCIT program will provide national Medicare coverage as early as the same day as FDA market authorization for breakthrough devices, and coverage would last for 4 years. The goal is that this new coverage pathway will offer beneficiaries nationwide predictable access to new, breakthrough devices to help improve their health outcomes.

ASN has long advocated for streamlined approaches to Medicare coverage of innovative medical devices and diagnostics that improve health outcomes for beneficiaries who suffer from kidney diseases—especially kidney failure. Although ASN's comments have most recently dealt with the Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies (TPNIES) in the ESRD bundle, ASN urged CMS to implement the MCIT program on May 15, 2021, as scheduled.

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