ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Dialysis in Disaster Zones

Back-to-Back Disasters Put Response Systems to the Test

By Bridget M. Kuehn

In the aftermath of Hurricane Irma, 130 dialysis patients from the island of St. Thomas found refuge in Puerto Rico. But Puerto Rico provided only a temporary respite on a multiple-stop journey for these patients. Soon, Hurricane Maria would bear down on the island leaving it, too, in ruins.

The plight of those 130 patients demonstrates the incredible challenges that faced dialysis providers, government agencies, and volunteer organizations responding to one of the worst hurricane seasons in memory. Hurricanes Harvey and Irma alone affected 50,000 dialysis patients at 750 dialysis facilities, according to Darlene Rodgers, CNN, RN, a nurse clinical consultant at ASN and Nephrologists Transforming Dialysis Safety who helped with the organizations' disaster response. An additional 6000 dialysis patients resided in Puerto Rico before Hurricane Maria hit.

Rodgers joined a panel of first responders at Kidney Week 2017 to share lessons learned from the 2017 hurricane season for nephrologists and dialysis providers. Among the key challenges they highlighted were the need for improved communications systems, coordinated disaster response among agencies and nonprofits, and solid disaster plans.

Island hopping

Dialysis patients evacuated from St. Thomas by Department of Health and Human Services staff and National Disaster Medical Assistance Teams from Colorado and Oregon faced repeated displacement.

In Puerto Rico, Jeffrey B. Kopp, MD, captain of the US Public Health Service's Kidney Disease Section, helped oversee their care. Initially, the patients were housed in hotels in Puerto Rico, along with 30 caregivers who were evacuated with them. However, many of the patients had serious comorbidities and mobility difficulties.

"It soon became apparent they were not thriving in the hotels," said Kopp. So, a special needs shelter was created at the convention center. The US Army helped set up mobile showers, and food service providers were contracted to provide meals. Patients

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Data Support Low-Protein Diet for Conservative Management of CKD

By Timothy O'Brien

Nutritional intervention strategies provide an alternative, conservative approach to management of chronic kidney disease (CKD)—allowing patients at least the possibility of delaying or avoiding dialysis, according to a comprehensive review published this month in *The New England Journal of Medicine*.

While questions remain, an analysis of the best available research evidence supports the concept of using a low-protein diet for conservative management of CKD—including a significantly lower risk of progression to end stage renal disease. "A low-protein diet appears to enhance the conservative management of non-dialysis dependent CKD and may be considered as a potential option for CKD patients who wish to avoid or defer dialysis initiation and to slow down the progression of CKD," said Kamyar Kalantar-Zadeh, MD, MPH, PhD, of the University of California Irvine.

Major new review of nutritional management in CKD

Of course, the notion of a low-protein, low-salt diet for patients with kidney disease is

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Disaster Zones

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were transported for dialysis at Fresenius and Atlantis facilities affiliated with their usual provider, Kopp said.

"They can quickly loop patients back into what they are used to," he said.

Volunteers including nurses, student nurses, and mental health professionals helped provide care for the patients at the shelter. The Federal Emergency Management Agency also hired emergency medical technicians to assist.

"Ideally, you vet [volunteers] very carefully," said Kopp. "My experience with Hurricane Katrina is that it is important to check their backgrounds."

Unfortunately, the providers and patients faced numerous challenges. It was a struggle to get patients' medications. Patients' prescriptions and medical histories had to be entered anew each time they were moved to a new facility with a new electronic medical system.

"Nothing in a disaster ever goes as planned," Kopp said. So he and his team just had to do what they could to make things work better each day.

"Then Maria appeared on the radar," Kopp said. A flight was quickly chartered to take the patients to Florida International University. "That turned out to be an excellent decision," he said.

It would not be the last stop for many patients. Some moved on to stay with family members throughout the US. Emory University in Atlanta now hosts 30 of the patients, said Janice Lea, MD, MSc, director of Emory Dialysis. Even when they arrived in Atlanta, providers had to relay their care information. Kopp said better systems are needed to ensure seamless transitions of patients' care information.

Through it all, Kopp said the patients were knowledgeable about their care and understanding about the austere conditions.

"These patients endured a tremendous amount of trauma," he said. "They showed a tremendous amount of tolerance and grace."

The eye of the storm

Those patients left behind in the Caribbean faced heart-breaking destruction and life-threatening disruptions in care.

British nephrologist James Tattersall, MBBS, MD, was selected by the International Society of Nephrology (ISN) Renal Disaster Relief Task Force to go to Tortola, one of the British Virgin Islands, in the aftermath of Irma and find out what was needed. On the wings of a small plane flown by a "daredevil" pilot Tattersall touched down on a runway newly cleared of planes and other debris. He was familiar with the island because his parents reside there.

On the ground, he found unfathomable devastation and trauma. A 56-ton catamaran had dropped on a building. Ninety percent of buildings were destroyed. The roofs of most houses had been torn off mid-storm, their contents strewn about the countryside, and their inhabitants left to weather the rest of the storm unprotected. Irma's wind top wind speeds of 185 miles per hour (mph) were simply too much for residences built to withstand 125 mph winds. Even hospitals, built to withstand 175 mph winds, faced devastation.

"By design, buildings would not survive that wind strength," he said.

The dialysis unit was flooded and windows were shattered in the hospital's intensive care unit. The electronic health records system was down. The island's only nephrologist was unable to return for 2 months. The UK military restored water, but power was unreliable and patients' dialysis sessions were frequently interrupted.

There were also no accommodations available for patients left homeless by the storm or those who had to ferry from nearby islands, he said. One patient began living in the hospital lobby. Clinically, Tattersall faced numerous challenges treating patients with life-threatening comorbidities and triaging patients who were unlikely to survive.

"I had difficult decisions to make," he said.

One of the biggest problems Tattersall faced was the complete lack of communications infrastructure left on the island. He relied on a GPS device to relay messages by text back to the UK and struggled to reliably connect with anyone on the island.

"Our communication is dependent on cell phones, but those are quite vulnerable," he said.

Coordination among the International Society of Nephrology, ASN, and Tattersall helped secure the first shipment of the medications needed for kidney patients on the island. Rodgers said ASN, ISN. and Tattersall held daily calls, and ASN tapped its members and US institutions for help. For example, the University of Miami helped acquire the medications and brought them to the airport. With the help of a pilot, Tattersall's brother then took the supplies to Tortola. Direct Relief, a US nonprofit, handled the next shipment of medications.

In the immediate aftermath of the storm, Tattersall met 2 patients with kidney transplants who couldn't get their immunosuppressant medications. Local police officers dug through the rubble of a pharmacy to find the medications, he said. The ASN team also helped connect prospective kidney transplant patients with their transplant centers in the US and UK, so these patients wouldn't miss out if a transplant became available.

Tattersall emphasized the importance of reliable methods of communication and "the need for focused aid informed by people in the disaster area."

Harvey headaches

In Houston, Hurricane Harvey dropped a record 51 inches of rain, leaving much of the city underwater. For dialysis providers in the area, like Stephen Fadem, MD, medical director of the Houston Kidney Center Integrated Service Network at DaVita, advance preparations paid off.

In the days prior to the storm, Fadem and his colleagues made disaster plans and started educating patients about how to protect themselves. For example, patients were instructed on what to eat, not to overhydrate, and to have a "go-bag" ready with medications and medical information in case they were displaced. Patients received an extra dialysis session prior to the storm.

His organization's main dialysis unit was on higher ground and equipped with a backup water system and generator. These features and having 10 staff members stay at a nearby hotel allowed the center to continue providing care for their patients and those who arrived from emergency shelters.

"Our dialysis unit waiting room looked like a bus station," he said. "I had never seen anything like this in a dialysis center."

Dialysis sessions were administered on a first-come, first-served basis and truncated to 2 hours to accommodate the increased demand. Ten staff members proved to be too few, and additional staff were brought in within a couple of days.

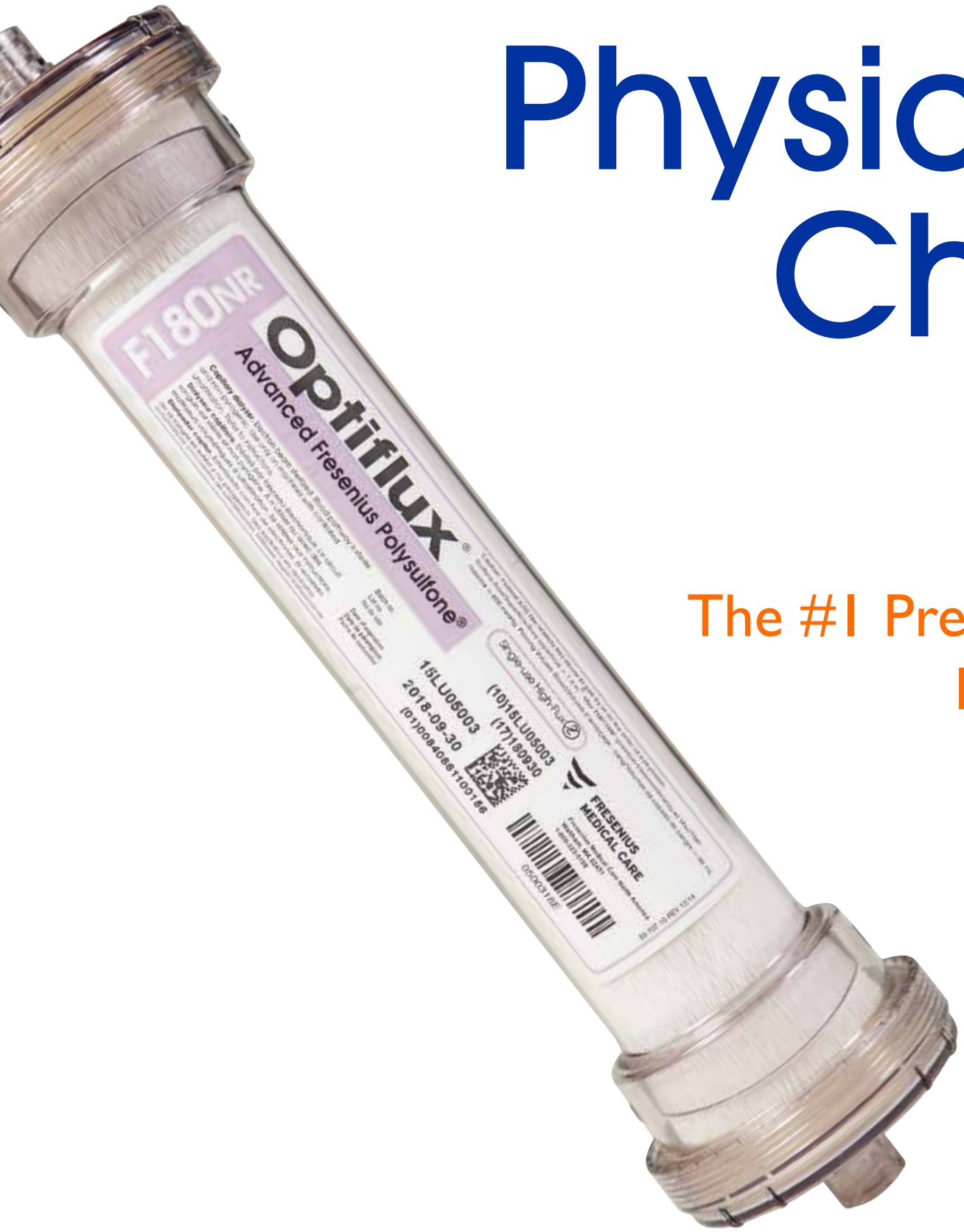
These efforts and "equal efforts" by other dialysis chains in Houston helped prevent a worse disaster, according to Fadem.

"We have a lot to learn," he said. "We did well, but [our disaster response] can be improved."

Advance preparations are critical, Fadem said. For example, his center was stocked with food, medications, and a gasoline truck. Staff and patients need curfew letters. Patients need a list of emergency numbers to call. For future disasters his team will work to have more multilingual patient education available, more staff nearby, and better patient records, including information about hepatitis B status.

"The most important take-home message is that this probably will happen again," Fadem said. "We need to take disaster management seriously and make it part of our daily routines."

The Physician's Choice



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Uloric
(febuxostat) 40 mg | 80 mg tablets

NOW WITH RECOMMENDED DOSING FOR GOUT PATIENTS WITH CKD STAGE 4[1]*

No dose adjustment is necessary in patients with mild to moderate renal impairment[1]
The dose of ULORIC is limited to 40 mg once daily in patients with severe renal impairment[1]

ULORIC IS NOT INDICATED TO TREAT CKD.[1]

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CKD=chronic kidney disease.

*Mild renal impairment (CKD stage 2) is defined as estimated glomerular filtration rate (eGFR) 60-89 mL/min/1.73 m^2; moderate renal impairment (CKD stage 3) is defined as eGFR 30-59 mL/min/1.73 m^2; severe renal impairment (CKD stage 4) is defined as eGFR 15-29 mL/min/1.73 m^2.[2]

INDICATION

ULORIC (febuxostat) is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout. ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

IMPORTANT SAFETY INFORMATION

- ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine.
- An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents, including ULORIC. If a gout flare occurs during treatment, ULORIC need not be discontinued. Prophylactic therapy (i.e., NSAIDs or colchicine) upon initiation of treatment may be beneficial for up to six months.
- Cardiovascular Events: In randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC [0.74 per 100 P-Y (95% CI 0.36-1.37)] than allopurinol [0.60 per 100 P-Y (95% CI 0.16-1.53)]. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.
- Hepatic Effects: Postmarketing reports of hepatic failure, sometimes fatal, have been received. Causality cannot be excluded. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted.

  Obtain liver tests before starting treatment with ULORIC. Use caution in patients with liver disease. If liver injury is detected, promptly interrupt ULORIC and assess patient for probable cause, then treat cause if possible, to resolution or stabilization. Do not restart treatment if liver injury is confirmed and no alternate etiology can be found.
- Serious Skin Reactions: Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported in patients taking ULORIC. Discontinue ULORIC if serious skin reactions are suspected.
- Adverse reactions occurring in at least 1% of ULORIC-treated patients, and at least 0.5% greater than placebo, are liver function abnormalities, nausea, arthralgia, and rash. Patients should be instructed to inform their healthcare professional if they develop a rash or have any side effect that bothers them or does not go away.

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

References: 1. ULORIC (febuxostat) prescribing information. Takeda Pharmaceuticals. **2.** Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int Suppl*. 2013;3(1):1-150.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
ULORIC (febuxostat) tablet for oral use

INDICATIONS AND USAGE

ULORIC is a xanthine oxidase (XO) inhibitor indicated for the chronic management of hyperuricemia in patients with gout.

ULORIC is not recommended for the treatment of asymptomatic hyperuricemia.

CONTRAINDICATIONS

ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine *[see Drug Interactions]*.

WARNINGS AND PRECAUTIONS

Gout Flare

After initiation of ULORIC, an increase in gout flares is frequently observed. This increase is due to reduction in serum uric acid levels, resulting in mobilization of urate from tissue deposits.

In order to prevent gout flares when ULORIC is initiated, concurrent prophylactic treatment with an NSAID or colchicine is recommended.

Cardiovascular Events

In the randomized controlled studies, there was a higher rate of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) in patients treated with ULORIC (0.74 per 100 P-Y [95% Confidence Interval (CI) 0.36-1.37]) than allopurinol (0.60 per 100 P-Y [95% CI 0.16-1.53]) *[see Adverse Reactions]*. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of myocardial infarction (MI) and stroke.

Hepatic Effects

There have been postmarketing reports of fatal and non-fatal hepatic failure in patients taking ULORIC, although the reports contain insufficient information necessary to establish the probable cause. During randomized controlled studies, transaminase elevations greater than three times the upper limit of normal (ULN) were observed (AST: 2%, 2%, and ALT: 3%, 2% in ULORIC and allopurinol-treated patients, respectively). No dose-effect relationship for these transaminase elevations was noted.

Obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) as a baseline before initiating ULORIC.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (ALT greater than three times the upper limit of the reference range), ULORIC treatment should be interrupted and investigation done to establish the probable cause. ULORIC should not be restarted in these patients without another explanation for the liver test abnormalities.

Patients who have serum ALT greater than three times the reference range with serum total bilirubin greater than two times the reference range without alternative etiologies are at risk for severe drug-induced liver injury and should not be restarted on ULORIC. For patients with lesser elevations of serum ALT or bilirubin and with an alternate probable cause, treatment with ULORIC can be used with caution.

Serious Skin Reactions

Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN) have been reported in patients taking ULORIC. Discontinue ULORIC if serious skin reactions are suspected. Many of these patients had reported previous similar skin reactions to allopurinol. ULORIC should be used with caution in these patients.

ADVERSE REACTIONS

Clinical Trials Experience

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

A total of 2757 patients with hyperuricemia and gout were treated with ULORIC 40 mg or 80 mg daily in clinical studies. For ULORIC 40 mg, 559 patients were treated for ≥6 months. For ULORIC 80 mg, 1377 patients were treated for ≥6 months, 674 patients were treated for ≥1 year and 515 patients were treated for ≥2 years.

Most Common Adverse Reactions

In three randomized, controlled clinical studies (Studies 1, 2 and 3), which were six to 12 months in duration, the following adverse reactions were reported by the treating physician as related to study drug. Table 1 summarizes adverse reactions reported at a rate of at least 1% in ULORIC treatment groups and at least 0.5% greater than placebo.

Table 1: Adverse Reactions Occurring in ≥1% of Patients Treated with ULORIC and at Least 0.5% Greater than Seen in Patients Receiving Placebo in Controlled Studies

	Placebo	ULORIC		allopurinol*
Adverse Reactions	(N=134)	40 mg daily (N=757)	80 mg daily (N=1279)	(N=1277)
Liver Function Abnormalities	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

*Of the patients who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

The most common adverse reaction leading to discontinuation from therapy was liver function abnormalities in 1.8% of ULORIC 40 mg, 1.2% of ULORIC 80 mg, and in 0.9% of patients treated with allopurinol.

In addition to the adverse reactions presented in Table 1, dizziness was reported in more than 1% of patients treated with ULORIC although not at a rate more than 0.5% greater than placebo.

Less Common Adverse Reactions

In Phase 2 and 3 clinical studies the following adverse reactions occurred in less than 1% of patients and in more than one subject treated with doses ranging from 40 mg to 240 mg of ULORIC. This list also includes adverse reactions (less than 1% of patients) associated with organ systems from Warnings and Precautions.

Blood and Lymphatic System Disorders: anemia, idiopathic thrombocytopenic purpura, leukocytosis/leukopenia, neutropenia, pancytopenia, splenomegaly, thrombocytopenia.

Cardiac Disorders: angina pectoris, atrial fibrillation/flutter, cardiac murmur, ECG abnormal, palpitations, sinus bradycardia, tachycardia.

Ear and Labyrinth Disorders: deafness, tinnitus, vertigo.

Eye Disorders: vision blurred.

Gastrointestinal Disorders: abdominal distention, abdominal pain, constipation, dry mouth, dyspepsia, flatulence, frequent stools, gastritis, gastroesophageal reflux disease, gastrointestinal discomfort, gingival pain, haematemesis, hyperchlorhydria, hematochezia, mouth ulceration, pancreatitis, peptic ulcer, vomiting.

General Disorders and Administration Site Conditions: asthenia, chest pain/discomfort, edema, fatigue, feeling abnormal, gait disturbance, influenza-like symptoms, mass, pain, thirst.

Hepatobiliary Disorders: cholelithiasis/cholecystitis, hepatic steatosis, hepatitis, hepatomegaly.

Immune System Disorder: hypersensitivity.

Infections and Infestations: herpes zoster.

Procedural Complications: contusion.

Metabolism and Nutrition Disorders: anorexia, appetite decreased/increased, dehydration, diabetes mellitus, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypertriglyceridemia, hypokalemia, weight decreased/increased.

Musculoskeletal and Connective Tissue Disorders: arthritis, joint stiffness, joint swelling, muscle spasms/twitching/tightness/weakness, musculoskeletal pain/stiffness, myalgia.

Nervous System Disorders: altered taste, balance disorder, cerebrovascular accident, Guillain-Barré syndrome, headache, hemiparesis, hypoesthesia, hyposmia, lacunar infarction, lethargy, mental impairment, migraine, paresthesia, somnolence, transient ischemic attack, tremor.

Psychiatric Disorders: agitation, anxiety, depression, insomnia, irritability, libido decreased, nervousness, panic attack, personality change.

Renal and Urinary Disorders: hematuria, nephrolithiasis, pollakiuria, proteinuria, renal failure, renal insufficiency, urgency, incontinence.

Reproductive System and Breast Changes: breast pain, erectile dysfunction, gynecomastia.

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, cough, dyspnea, epistaxis, nasal dryness, paranasal sinus hypersecretion, pharyngeal edema, respiratory tract congestion, sneezing, throat irritation, upper respiratory tract infection.

Skin and Subcutaneous Tissue Disorders: alopecia, angio-edema, dermatitis, dermographism, ecchymosis, eczema, hair color changes, hair growth abnormal, hyperhidrosis, peeling skin, petechiae, photosensitivity, pruritus, purpura, skin discoloration/altered pigmentation, skin lesion, skin odor abnormal, urticaria.

Vascular Disorders: flushing, hot flush, hypertension, hypotension.

Laboratory Parameters: activated partial thromboplastin time prolonged, creatine increased, bicarbonate decreased, sodium increased, EEG abnormal, glucose increased, cholesterol increased, triglycerides increased, amylase increased, potassium increased, TSH increased, platelet count decreased, hematocrit decreased, hemoglobin decreased, MCV increased, RBC decreased, creatinine increased, blood urea increased, BUN/creatinine ratio increased, creatine phosphokinase (CPK) increased, alkaline phosphatase increased, LDH increased, PSA increased, urine output increased/decreased, lymphocyte count decreased, neutrophil count decreased, WBC increased/decreased, coagulation test abnormal, low density lipoprotein (LDL) increased, prothrombin time prolonged, urinary casts, urine positive for white blood cells and protein.

Cardiovascular Safety

Cardiovascular events and deaths were adjudicated to one of the pre-defined endpoints from the Anti-Platelet Trialists' Collaborations (APTC) (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) in the randomized controlled and long-term extension studies. In the Phase 3 randomized controlled studies, the incidences of adjudicated APTC events per 100 patient-years of exposure were: Placebo 0 (95% CI 0.00-6.16), ULORIC 40 mg 0 (95% CI 0.00-1.08), ULORIC 80 mg 1.09 (95% CI 0.44-2.24), and allopurinol 0.60 (95% CI 0.16-1.53).

In the long-term extension studies, the incidences of adjudicated APTC events were: ULORIC 80 mg 0.97 (95% CI 0.57-1.56), and allopurinol 0.58 (95% CI 0.02-3.24).

Overall, a higher rate of APTC events was observed in ULORIC than in patients treated with allopurinol. A causal relationship with ULORIC has not been established. Monitor for signs and symptoms of MI and stroke.

Postmarketing Experience

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

Blood and Lymphatic System Disorders: agranulocytosis, eosinophilia.

Hepatobiliary Disorders: hepatic failure (some fatal), jaundice, serious cases of abnormal liver function test results, liver disorder.

Immune System Disorders: anaphylaxis, anaphylactic reaction.

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis.

Psychiatric Disorders: psychotic behavior including aggressive thoughts.

Renal and Urinary Disorders: tubulointerstitial nephritis.

Skin and Subcutaneous Tissue Disorders: generalized rash, Stevens-Johnson Syndrome, hypersensitivity skin reactions, erythema multiforme, drug reaction with eosinophilia and systemic symptoms, toxic epidermal necrolysis.

DRUG INTERACTIONS

Xanthine Oxidase Substrate Drugs

ULORIC is an XO inhibitor. Based on a drug interaction study in healthy patients, febuxostat altered the metabolism of theophylline (a substrate of XO) in humans. Therefore, use with caution when coadministering ULORIC with theophylline.

Drug interaction studies of ULORIC with other drugs that are metabolized by XO (e.g., mercaptopurine and azathioprine) have not been conducted. Inhibition of XO by ULORIC may cause increased plasma concentrations of these drugs leading to toxicity. ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine *[see Contraindications]*.

Cytotoxic Chemotherapy Drugs

Drug interaction studies of ULORIC with cytotoxic chemotherapy have not been conducted. No data are available regarding the safety of ULORIC during cytotoxic chemotherapy.

In Vivo Drug Interaction Studies

Based on drug interaction studies in healthy patients, ULORIC does not have clinically significant interactions with colchicine, naproxen, indomethacin, hydrochlorothiazide, warfarin or desipramine. Therefore, ULORIC may be used concomitantly with these medications.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Limited available data with ULORIC use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. No adverse developmental effects were observed in embryo-fetal development studies with oral administration of febuxostat to pregnant rats and rabbits during organogenesis at doses that produced maternal exposures up to 40 and 51 times, respectively, the exposure at the maximum recommended human dose (MRHD). No adverse developmental effects were observed in a pre- and postnatal development study with administration of febuxostat to pregnant rats from organogenesis through lactation at an exposure approximately 11 times the MRHD *(see Data)*.

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 US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats dosed during the period of organogenesis from gestation Days 7 – 17, febuxostat was not teratogenic and did not affect fetal development or survival at exposures up to approximately 40 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day). In an embryo-fetal development study in pregnant rabbits dosed during the period of organogenesis from gestation Days 6 – 18, febuxostat was not teratogenic and did not affect fetal development at exposures up to approximately 51 times the MRHD (on an AUC basis at maternal oral doses up to 48 mg/kg/day).

In a pre- and postnatal development study in pregnant female rats dosed orally from gestation Day 7 through lactation Day 20, febuxostat had no effects on delivery or growth and development of offspring at a dose approximately 11 times the MRHD (on an AUC basis at a maternal oral dose of 12 mg/kg/day). However, increased neonatal mortality and a reduction in neonatal body weight gain were observed in the presence of maternal toxicity at a dose approximately 40 times the MRHD (on an AUC basis at a maternal oral dose of 48 mg/kg/day).

Febuxostat crossed the placental barrier following oral administration to pregnant rats and was detected in fetal tissues.

Lactation

Risk Summary

There are no data on the presence of febuxostat in human milk, the effects on the breastfed infant, or the effects on milk production. Febuxostat is present in rat milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ULORIC and any potential adverse effects on the breastfed child from ULORIC or from the underlying maternal condition.

Data

Animal Data

Orally administered febuxostat was detected in the milk of lactating rats at up to approximately 7 times the plasma concentration.

Pediatric Use

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

Geriatric Use

No dose adjustment is necessary in elderly patients. Of the total number of patients in clinical studies of ULORIC, 16% were 65 and over, while 4% were 75 and over. Comparing patients in different age groups, no clinically significant differences in safety or effectiveness were observed but greater sensitivity of some older individuals cannot be ruled out. The C_{max} and AUC_{24} of febuxostat following multiple oral doses of ULORIC in geriatric patients (≥65 years) were similar to those in younger patients (18 to 40 years).

Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (Cl_{cr} 30 to 89 mL/min). The recommended starting dose of ULORIC is 40 mg once daily. For patients who do not achieve a sUA less than 6 mg/dL after two weeks with 40 mg, ULORIC 80 mg is recommended. For patients with severe renal impairment (Cl_{cr} 15 to 29 mL/min), the dose of ULORIC is limited to 40 mg once daily.

Hepatic Impairment

No dose adjustment is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C); therefore, caution should be exercised in these patients.

Secondary Hyperuricemia

No studies have been conducted in patients with secondary hyperuricemia (including organ transplant recipients); ULORIC is not recommended for use in patients whom the rate of urate formation is greatly increased (e.g., malignant disease and its treatment, Lesch-Nyhan syndrome). The concentration of xanthine in urine could, in rare cases, rise sufficiently to allow deposition in the urinary tract.

OVERDOSAGE

ULORIC was studied in healthy patients in doses up to 300 mg daily for seven days without evidence of dose-limiting toxicities. No overdose of ULORIC was reported in clinical studies. Patients should be managed by symptomatic and supportive care should there be an overdose.

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Hypertension and CKD

High Nighttime Blood Pressure May Warn of Faster Kidney Disease Progression in Kids

Elevated nighttime blood pressure may be a warning sign that a child with kidney disease is at risk of faster progression, according to an abstract presented at Kidney Week.

Hypertension is a risk factor for kidney disease, and is linked to faster progression. Typically, physicians monitor blood pressure with readings during clinic visits. However, use of 24-hour ambulatory blood pressure monitoring is increasing, and emerging data suggest that high nighttime blood pressure may be a particularly important risk factor in kidney disease. For example, a recent study in adults with kidney disease suggested that elevated nighttime blood pressure may lead to worse organ damage (Wang C, et al. *PLoS One* 2015; 10:e0131546).

Now, Mónica Guzmán-Limón, MD, a nephrology and hypertension fellow at the McGovern Medical School at the University of Texas Health Science Center, and her colleagues show that nighttime hypertension is also an important risk factor for children with CKD. They analyzed results from 1195 24-hour blood pressure monitoring studies from 693 children ages 1 to 16 enrolled in the Chronic Kidney Disease in Children (CKiD) study. Children who had nocturnal only hypertension experienced faster kidney decline than children with normal blood pressure, and children who had elevated blood pressure both day and night had the fastest progression. For children with nonglomerular kidney disease, high nocturnal blood pressure was associated with worsening outcome with a Hazard Ratio (HR) of 1.80 compared to normotensive children (p=0.02), and those who had high blood pressure around the clock had a HR of 2.37 (p=0.001).

"Our study highlights the importance of normal nighttime blood pressure in children with chronic kidney disease," said Guzmán-Limón. "This study highlights the importance of ambulatory blood pressure monitoring to aid in the management of patients with chronic kidney disease."

The findings confirm the baseline data out of the CKiD study that nocturnal hypertension is more common than daytime hypertension, said Janis Dionne, MD, a clinical associate professor and pediatric nephrologist at the University of British Columbia, and show that having both high daytime and nighttime blood pressure is most strongly linked to the risk of progression.

"It reinforces that we need to use [24-hour ambulatory blood pressure monitoring] in pediatric hypertension and pediatric kidney disease," Dionne said. But she noted that payers poorly reimburse such monitoring, if it is reimbursed at all.

"Physicians need to advocate to get them done in their patients," she said.

Why nocturnal high blood pressure is associated with worse outcomes isn't yet clear. It might be a cause or marker of renal or systemic vascular changes, Dionne noted.

Guzmán-Limón suggested nighttime control of blood pressure may be an important means to delay kidney disease progression.

There is definitely room for improvement in hypertension treatment in this population, said Dionne, as many children with CKD and hypertension are not currently taking antihypertensive medication. But she noted that additional research is needed to determine if such treatment improves patient outcomes and, if so, what are the best treatment options.

"Nocturnal hypertension is common and is associated with CKD progression in chronic kidney disease" (Abstract 2756651)

Elevated Blood Pressure, Poorer Renal Function Seen in Teens Born Prematurely

By Bridget M. Kuehn

By adolescence, individuals who were born prematurely and low birth weight are already showing signs of kidney impairment, according to an abstract presented at Kidney Week.

Improved care in the neonatal intensive care unit has allowed many babies born prematurely to survive and thrive into adulthood. But some evidence has emerged that individuals who were born prematurely have an increased risk of developing chronic kidney disease later in life (Carmody JB and Charlton JR. *Pediatrics* 2013; 131:1168–1179).

"There is a growing recognition that individuals born preterm are vulnerable to renal disease," said Jennifer Charlton, MD, a pediatric nephrologist and associate professor at the University of Virginia Health System in Charlottesville.

It's not clear why, said abstract co-author Andrew South, MD, MS, assistant professor of pediatric nephrology at Wake Forest School of Medicine, but animal studies suggest that individuals born prematurely may not have a full complement of nephrons at birth.

"The nephrons, they do have to work harder and burn out sooner," he suggested. But it has been difficult to prove this hypothesis because it would be unethical to take kidney biopsies from healthy children.

So South and his colleagues have launched a study that will follow a cohort of adolescents (96 born prematurely and 43 born at term) to track kidney function over time non-invasively. In the abstract, they present results of measurements of blood pressure and kidney function at age 14. The results show that the former preemies have higher mean systolic ($p< 0.01$) and diastolic blood pressure ($p=0.03$) than the controls. They have significantly lower glomerular filtration rates (GFR) compared with the control group (β: -8.17 mL/min/1.73 m^2, 95% CI -15.93 to -0.4). The former preemies also had higher albumin.

The findings suggest that those born prematurely are already beginning to experience a decline in kidney function by early adolescence.

"It's an early indication those kidneys are working too hard," said South. He and his colleagues will continue to follow this cohort and assess their kidney function again at 19 and 24 years of age.

Adjusting for confounders reduced the differences between the two groups.

"It is wonderful that investigators are focusing research efforts on this understudied population," Charlton said. "Although their results were attenuated by adjustments for various confounders, their unadjusted results suggest higher blood pressure and lower renal function in the preterm group."

The results suggest that clinicians should carefully monitor kidney function in patients who were born prematurely, South said. By identifying kidney decline early, physicians may have an opportunity to prevent or delay progression.

"It suggests you could potentially intervene with drugs or other practices," he said.

Many questions remain to be answered such as when and how to follow these patients and educate their families, Charlton noted. Also, it is not clear whether acute kidney injury might contribute to the development of CKD in former preemies, whether these individuals have progressive disease, and what the long-term health consequences of mildly impaired GFR are.

"In my opinion, we are just beginning a fascinating journey to discover how renal health is affected by preterm birth," Charlton said.

"Renal Function and Blood Pressure in Adolescents Born Preterm and Very Low Birth Weight" (Poster 663)

Larger Blood Pressure Declines Linked with Kidney Harm in SPRINT Trial

By Bridget M. Kuehn

Greater reductions of mean arterial pressure were linked to reduced kidney function, according to an analysis of data from the SPRINT trial presented at Kidney Week.

The SPRINT trial demonstrated that tight blood pressure control—with a systolic target of less than 120 mm Hg—reduced the risk of death among non-diabetic patients at high risk of a cardiovascular event. But that tight control was associated with reduced kidney function.

To better understand the kidney-associated effects of tight blood pressure control, Rita Magriço, MD, of the Hospital Garcia de Orta in Portugal, and her colleagues took a second look at the SPRINT data. In their analysis, they grouped 1138 patients who received intensive blood pressure control based on whether their mean arterial pressure dropped by less than 20 mm Hg; between 20 and 39 mm Hg; or 40 or more mm Hg. They found that the roughly 10% of patients who achieved a 40 mm Hg or more drop in mean arterial pressure had a substantially elevated risk of chronic kidney disease (CKD) incidence compared with those whose pressure dropped between 20 and 39 mm Hg (HR 6.35 [95% CI, 2.82-14.29] vs. 2.14 [95% CI, 1.25-3.66]).

Based on their analysis, 43.5 patients would need to achieve a 20 mm Hg or less reduction for one to experience reduced death risk and one patient would experience CKD for every 65.4 treated. For those who reach a moderate target of a 20 to 39 mm Hg reduction, 41.7 would need to be treated and one would experience CKD for every 35.1 treated. By contrast, 95.2 patients would have to achieve a reduction of 40 mm Hg or more for one to benefit, while one patient would experience CKD for every 15.9 patients treated.

"The fact that in our analysis the benefit-risk relationship became less favorable with greater mean blood pressure reductions may be important for patients and physicians as they aim for the lowest cardiovascular risk with the lowest probability of side effects," Magriço said. "If this association is confirmed by prospective studies, future recommendations for hypertension treatment in this population should consider personalized targets rather than a fixed cutoff for every patient."

Lawrence Appel, MD, a professor at Johns Hopkins Bloomberg School of Public Health, cautioned that subgroup analyses of studies should be interpreted with caution as they are prone to false positives and false negatives.

"Be cautious, a subgroup analysis confined to small numbers of individuals can be misleading," he said.

He noted that a recent meta-analysis of 30 randomized clinical trials found a 14% reduction in all cause mortality among CKD patients who received tight blood pressure control (Malhotra R, et al. *JAMA Intern Med* 2017; 177:1498–1505).

Based on the results to date, he does not think physicians should avoid tight blood pressure control unless they have a compelling clinical reason. He said more study is needed on reaching a blood pressure target between 120 and 140 mm Hg for patients with diabetes.

In the meantime, he suggested that patients most likely to benefit from preventive interventions, like tight blood pressure control, are likely those in the earlier stages of disease.

"Most of the action in terms of prevention is in people with stage 3 kidney disease," Appel said. "That's where you have the greatest opportunity for prevention. In the more advanced stages, it is going to be hard."

"SPRINT Trial: Intensive Hypertension Treatment and Chronic Kidney Disease Incidence" (Abstract 2771812)

Diet and Kidney Diseases

Study Suggests Heart Benefits of Vegetarian Protein Sources

A plant-based protein appears to reduce heart damage in a mouse model of chronic kidney disease (CKD), according to a study presented at Kidney Week.

Cardiovascular disease is a common complication in patients with CKD. Ryohei Kaseda, MD, PhD, of the division of clinical nephrology and rheumatology at Niigata University School of Medical and Dental Sciences in Japan, and colleagues have previously shown that high-density lipoprotein (HDL) cholesterol may lose its beneficial effects in the setting of kidney dysfunction (Yamamoto S, et al. *J Am Coll Cardiol* 2012; 23:2372–2379). In their study, they looked at whether replacing animal protein with plant protein in the diet might restore the beneficial effects of HDL and reduce some of the cardiovascular harm associated with kidney disease.

"It has long been recognized that CVD and CKD are linked, so called cardio-renal association," he said. "Since there is evidence that plant-based diets are beneficial in CKD, we wished to assess if these nutritional interventions can benefit CKD-associated CVD."

Kaseda and his colleagues fed 10 12-week-old ApoE-deficient mice who had one kidney removed either a typical diet based on animal protein or a rice protein–based diet for 6 weeks. They found that the mice fed the rice protein–based diet had fewer atherosclerotic lesions compared with the animal protein diet (0.28 ± 0.06 vs. 0.67 ± 0.15 mm^2, p=0.038). HDL cholesterol from the mice on the plant-based diet also seemed to suppress inflammation in human endothelial cells in laboratory experiments.

Kaseda said the findings suggest nutritional interventions might help reduce cardiovascular complications in patients with CVD. But he noted that additional study is needed to characterize the differences in HDL composition and functionality on a plant protein vs. animal protein diet.

Connie Rhee, MD, MS, an assistant professor in the division of nephrology and hypertension at the University of California-Irvine who was not involved in the study, cautioned that more research on specific dietary interventions in pre-dialysis patients is needed. She said some studies have shown that low protein diets may be beneficial to patients with CKD, but studies on different sources of protein have had conflicting results (Ko GJ, et al. *Nutrients* 2017; 8:824).

"There is still not a lot known about the effect of the source or type of protein on the health and survival of CKD patients," Rhee said.

She and her colleagues recommend a low protein diet in pre-dialysis patients of 0.6 to 0.8 g/kg of body weight, of which at least 50% of that protein be of high biologic value like animal protein or dairy protein. By contrast, patients receiving dialysis are advised to eat a higher protein diet.

Some plant-based proteins like those from soybean and quinoa have high value protein, explained Rhee, but some plant-based proteins may not supply all the amino acids needed by the body. Patients who get insufficient levels of amino acids may experience protein energy wasting, which is an important predictor of death in patients with kidney disease, she said.

"There is a potential risk there could be loss of muscle mass," Rhee said. "They may not be getting essential amino acids to make protein in the body."

Rhee said she would like to see similar studies looking at varying proportions of plant vs. animal proteins that look at both cardiovascular and kidney outcomes. She also cautioned against clinical application of the findings until there is supporting evidence from human trials.

"We need rigorous prospective studies in humans before we pursue broad clinical applications," she said.

"Plant versus Animal Protein Improves Anti-Inflammatory Effects of HDL and Lessens CKD-Induced Atherosclerosis" (Poster TH-PO400)

Low-Protein Diet

Continued from page 1

by no means a new one. "However, reinvigoration of this idea is considered to have important clinical and public health implications because it may help with conservative and alternative management of CKD," Kalantar-Zadeh said. "If there is the opportunity to continue to manage CKD without dialysis therapy, if successful, then that will be the preferred option for many patients."

Along with Denis Fouque, MD, PhD, of Université Claude Bernard Lyon, France, Kalantar-Zadeh co-authored the review of current evidence on nutritional management of CKD, published in the November *NEJM*. In addition to other constituents, the review highlights new and emerging knowledge on the role of dietary protein in CKD progression.

As kidney disease progresses, protein-energy wasting is common, requiring dietary adjustments. The authors summarize animal studies suggesting that a low-protein diet has a "preglomerular effect"—enhancing the postglomerular effect of angiotensin-pathway modulators and thus lowering intraglomerular pressure. Experimental evidence also suggests that the protective effects of a low-protein diet interact synergistically with the direct effects of a low-sodium diet.

What does that mean for low-protein diets in humans? So far, the data have been inconsistent. Most controlled trials have supported the beneficial effects of restricted protein intake on CKD. However, the largest such trial, the Modification of Diet in Renal Disease (MDRD) study, concluded that a low-protein diet had only a minimal effect on progression of CKD, whereas Kalantar-Zadeh's review of secondary analyses suggests that the MDRD study was more effective than originally thought.

More recently, analysis of data from the Atherosclerosis Risk in Communities (ARIC) Study suggested that the source of protein matters. Risk of CKD was higher in individuals reporting a high intake of red and processed meats, but lower in those with a higher intake of nuts, legumes, and low-fat dairy products. "Altogether, the current evidence suggests that a low-protein diet mitigates proteinuria in both experimental models and human kidney disease," Kalantar-Zadeh and Fouque write.

That preliminary conclusion is supported by a meta-analysis of clinical trial data, published last month in the *Journal of Cachexia, Sarcopenia and Muscle*. The lead authors were Connie M. Rhee, MD, MSc, and Seyed-Foad Ahmad, MD, MPH, of the University of California Irvine. Csaba P. Kovesdy, MD, of the University of Tennessee, Memphis, is a coauthor of the new review, along with Kalantar-Zadeh, as the corresponding author.

In a systematic review, the authors identified 16 controlled trials of low-protein diet—with a protein intake of less than 0.8 g/kg/d—including comparison of clinical outcomes. To ensure meaningful sample size, the analysis was limited to randomized trials including at least 30 patients.

Analysis of pooled data showed that the risk of progression to end stage renal disease was 4% lower for patients receiving a low-protein diet, compared to those receiving higher-protein diets (overall risk difference 0.04, 95% confidence interval 0.07 to 0.02). There was a trend toward a lower risk of death from any cause, although the difference was not significant.

Low-protein diets were also associated with a significant 1.46 mEq/L increase in serum bicarbonate

(95% confidence interval 1.04 to 1.87). There was no significant difference in serum phosphorus.

An additional meta-analysis compared outcomes for patients receiving very low-protein diets of less than 0.4 mg/kg/d with low-protein diets of 0.4 to 0.6 mg/kg/d. The results showed a significant 13% reduction in the risk of progression to ESRD with very low-protein diets. The estimated glomerular filtration rate was lower by 3.95 mL/min/1.73 m^2 in patients receiving very low-protein diets, along with a trend toward lower serum urea.

"An effective means to delay or defer dialysis therapy"

Thus the best available evidence points toward the possibility of dietary interventions for conservative management of CKD. For decades, dialysis has been considered a lifesaving treatment for patients with advanced kidney disease. Efforts to improve patient outcomes have generally focused on providing more dialysis and initiating dialysis earlier.

However, recent studies have questioned that assumption. "Discoveries in the past five or six years have encouraged us to rediscover conservative management as an option in addition to renal replacement therapy," Kalantar-Zadeh said. He points to a 2009 *NEJM* study showing a "substantial and sustained" decline in functional status after initiation of dialysis in nursing home residents with ESRD.

The focus on nutritional management is by no means intended to address resource constraints or challenges in access, nor to address the high costs of dialysis, according to Kalantar-Zadeh. "On the contrary, this is a decision for people who prefer an alternative to dialysis therapy," he said. "Nutritional therapy provides us with yet another option to help millions of CKD patients worldwide."

Just as nephrologists try to delay progression of CKD and ESRD with medications such as angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, "nutritional management gives us yet another angle for us to delay CKD progression, as well as to manage uremia," said Kalantar-Zadeh. "It allows us to be able to control symptoms and allow patients to add a few months to years if not longer without dialysis therapy—if that's their preferred choice. It's not necessarily 100% successful, but it may work in many patients, and should be tried."

Nutritional therapy may also play an important role in mitigating the increased risk of CKD and ESRD after nephrectomy—including living-donor and cancer nephrectomy. "A moderately low-protein diet—less than 1 g/kg/d—may help with the longevity of the solitary kidney," Kalantar-Zadeh said.

Further research is needed to provide a "more robust, evidence-based approach" to nutritional strategies for patients with kidney disease. Kalantar-Zadeh highlighted the importance of conducting studies under current clinical conditions—including the recent trend toward a diet higher in protein and lower in carbohydrates and fat. Such high-protein diets have become a popular weight-reduction strategy, but their effects on long-term kidney function remain unclear.

The *NEJM* review addresses many aspects of nutritional management for patients with CKD—not only protein but also sodium and fluids, potassium, phosphorus, calcium and vitamin D, and carbohydrates, fats, and dietary energy, and the microbiome, among other topics. It also includes tables and supplementary materials summarizing the low-protein diet and the evidence supporting its use in patients with CKD.

Kalantar-Zadeh acknowledged the significance of the publication of this major review of nutritional therapy for CKD, timed to correspond with Kidney Week—the largest and most important annual meeting of the world nephrology community. "For the ASN this is symbolically and strategically very important," he said.

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Diet and Kidney Diseases

High Dietary Phosphate Boosts Blood Pressure in Healthy People

High dietary phosphate levels are known to be harmful for patients with advanced kidney disease. Now an abstract presented at ASN Kidney Week 2017 suggests that high phosphate diets also may have detrimental effects on the cardiovascular health of healthy people.

In patients with advanced kidney disease there is evidence that a high-phosphate diet is associated with worse cardiovascular disease, said Kevin J. Martin, MD, a professor of internal medicine and director of the division of nephrology at St. Louis University, who was not involved in the study. In fact, patients are often urged to limit phosphorous in their diets, a tricky task given that food makers are not required to list this popular preservative on labeling, Martin explained. Phosphorous binding agents are also sometimes used, but he noted more evidence from clinical trials is needed to determine their effects (Cannata-Andía JB and Martin KJ. *Nephrol Dial Transplant* 2016; 31:541–7).

Epidemiological studies have also found higher dietary phosphate intake and blood phosphate concentration are linked to worse cardiovascular outcomes, noted one of the abstract's authors, Reto Krapf, MD, of the University of Basel in Switzerland. This is particularly concerning because phosphate levels appear to be increasing in Western diets.

To determine if increased dietary phosphate might have cardio-toxic effects, Krapf and his colleagues conducted a prospective study in which 20 healthy young people with normal kidney function were randomly assigned to a high- or low-phosphate diet for 11 weeks. At 6 weeks, both groups received a 600,000 U dose of vitamin D3.

Patients on the high-phosphate diet experienced increased systolic (plus 4.1) and diastolic blood pressure (plus 3.2) compared with baseline and with the low-phosphate group. The average heart rate in this group also increased by 4 beats per minute. Plasma renin/aldosterone concentrations and 24-hour urinary excretion rates of sodium, aldosterone, and free cortisol were comparable between the two groups. The vitamin D dose had no effect on blood pressure or pulse rate in the high-phosphate group, but it increased phosphate levels in the low-phosphate diet group.

At follow-up visits 2 months after the diet ended, the elevated blood pressures and pulse rate in the high-phosphate group returned to normal.

"By identifying the phenomenon of dietary phosphate–induced hypertension and acceleration of mean heart rate, we provide at least one important mechanism that explains the increased cardiovascular morbidity and mortality associated with increased phosphate intake," Krapf said. "Our study also identifies increased sympathetoadrenergic activity as the most likely cause of phosphate-induced hypertension."

Martin said the study was well done and extends the evidence regarding the vascular toxicity of high-phosphate diets into an otherwise healthy population.

"Just a high-phosphate diet is enough to raise blood pressure; that was kind of interesting," Martin said. He suggested it might help organizations like the National Kidney Foundation convince the US Food and Drug Administration to require phosphate labeling.

Krapf suggested that limiting phosphate in the diet might be a good step to protect kidney health.

"Hypertension is a very important cause of kidney disease and high phosphate intake or experimentally administered high phosphate loading has been shown to cause kidney disease and progressive renal failure," he said. "Thus, limiting phosphate intake in humans—both with normal and decreased renal function—may protect the kidneys both directly [by decreasing phosphate load] and indirectly [by decreasing blood pressure]."

"Effect of Dietary Phosphate Intake on Blood Pressure in Healthy Humans" (Abstract SA-OR027)

Lower Acid Diet May Boost Exercise Capacity, Especially in Elderly

By Bridget M. Kuehn

Eating a lower acid diet—typically lots of fruits and vegetables—may help boost exercise capacity, particularly for older patients, according to an abstract presented at Kidney Week.

Acid-producing diets, such as those rich in animal proteins, can exacerbate chronic kidney disease—so nephrologists often prescribe a low acid diet or bicarbonate supplements to balance a patient's acid load. High acid diets may also have ill effects on otherwise healthy individuals, particularly those who are experiencing age-related renal decline.

Now, Enni-Maria Hietavala, MS, a PhD student in the laboratory of Antti Mero at the University of Jyväskylä in Finland, shows that eating a low acid diet boosts exercise capacity. In the study, 88 healthy volunteers (22 adolescents, 33 young adults, and 33 elderly individuals) were assigned to eat a high acid or a low acid diet for 7 days and then switch to the other diet. At the end of each week, the participants were monitored as they performed a strenuous cycling test and provided blood samples.

The study found that base levels in the body declined for all participants during the high acid diet. Base levels were lower in both young and elderly women who performed suboptimally on the cycling test after eating the high acid diet. In young women, the maximum exercise workload was 19% shorter and the maximum cardiorespiratory capacity was lower after eating the high acid diet compared with the low acid diet.

Previously, Hietavala, MS, and her colleagues published a study showing that older people are more sensitive to the ill effects of a high acid diet on their exercise capacity (Hietavala Em, et al. *European Journal of Clinical Nutrition* 2015; 69:399–404).

"When you are young your kidneys work well and you have a large base buffer capacity," explained her coauthor Lynda Frassetto, MD, an emeritus professor of nephology at the University of California-San Francisco. But as people age they become less able to compensate. The current findings, if validated, suggest that eating a low acid diet should help individuals maintain muscle and bone mass via exercise, while promoting better kidney function, Frassetto said.

Bess Dawson Hughes, MD, a professor of medicine and director of the Bone Metabolism Laboratory at Tufts University in Boston, said the study will likely trigger additional research to find out if the benefits of a low acid diet on exercise capacity are sustained over time.

Alhough it is too soon to make clinical recommendations based on the results, they may have important implications for older adults.

"This diet modification is particularly important in elders whose exercise capacity is low," Dawson-Hughes explained. "It may enable people to have better functional capacity to live independently."

Bicarbonate supplements have been shown to help boost exercise capacity in elite athletes in some studies (Burke LM. *Nestle Nutr Inst Workshop* Ser 2013; 75:15–26), and Dawson-Hughes and her colleagues have also found improved muscle power in older women given bicarbonate supplements over 3 months (Dawson-Hughes B, et al. *Osteoporosis Int* 2010; 21:1171–1179). The low acid diet used by Hietavala was high in fruits and vegetables. This suggests that following current dietary recommendations for fruits and vegetables may be enough to help.

"If we were to do what is recommended by the dietary guidelines, we wouldn't have these [high] acid loads," Dawson-Hughes said. "It's another piece of evidence that we need those fruits and vegetables."

"Low Dietary Acid Intake May Help the Kidneys Improve Exercise Capacity" (Oral Abstract 068)

Have a tip or idea you'd like to share with your fellow peers and the broader kidney community?

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

Caffeine Consumption Linked to A Longer Life for CKD Patients

Consuming caffeine—the more the better—may help reduce the risk of early death among patients with chronic kidney disease, suggests a study presented at Kidney Week.

Drinking coffee has previously been shown to reduce the risk of an early death among the general population. Caffeine consumption has also been linked to better outcomes from some chronic diseases. For example, studies have shown that coffee and tea consumption help reduce the risk of death in patients with liver disease (Modi AA, et al. *Hepatology* 2010; 51:201–209), by exerting beneficial effects on the liver (Louise JM, et al. *J Hepatol* 2017; 67:339–348). Now, Miguel Bigotte Vieira, MD, of the Centro Hospitalar Lisboa Norte in Portugal, and his colleagues show that regular caffeine consumption may also yield life gains for CKD patients.

In their study, Bigotte Viera and colleagues looked at mortality rates in 2328 patients with CKD who participated in the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2010. The NHANES collects detailed health and nutritional data on a nationally representative sample of the US population.

Caffeine consumption was assessed based on reports of 24-hour consumption at the outset of the survey. The study grouped patients into 4 categories of caffeine consumption. The first consumed less than 29.5 mg/day of caffeine. That amount is less than the amount found in an iced tea, based on estimates from the Center for Science in the Public Interest. The second consumed between 30.5 to 101.0 mg/day—about the amount found in a soda or a cup of instant coffee. The third consumed between 101.5 and 206.0 mg/day—about the amount found in a cup or two of coffee. The fourth group consumed 206.5 to 1378.5 mg/day—the equivalent of multiple cups of coffee a day.

Compared with those in the lowest group of caffeine consumption those in the second group had a 12% reduction in the risk of dying (HR 0.88, 95% CI, 0.68–1.44). The benefits were even larger for the 3rd and 4th groups with a 22% (95% CI, 0.60–1.01) and 24% (95% CI, 0.59–0.97) lower risk of dying, respectively.

"Our study showed a dose-dependent protective effect of caffeine consumption on mortality among patients with CKD," said Bigotte Vieira. He noted the benefit persisted even when they adjusted for potential confounders like socioeconomic status, health factors, and other nutritional habits. He cautioned, however, that this observational study can't prove the survival benefit was caused by caffeine consumption.

"These results suggest that advising patients with CKD to drink more caffeine may reduce their mortality," he suggested. "This would represent a simple, clinically beneficial, and inexpensive option, though this benefit should ideally be confirmed in a randomized clinical trial."

"Caffeine consumption and mortality in chronic kidney disease" (Abstract 2784081)

Proton Pump Inhibitors Increase Risk of Developing CKD

Using proton pump inhibitors (PPIs) increases the risk of developing chronic kidney disease (CKD) or kidney failure by 33%, according to a meta analysis presented at Kidney Week.

PPIs are one of the most commonly prescribed medications worldwide. They are used to treat gastroesophageal reflux disease (GERD). But a growing number of studies have linked them to serious adverse effects including kidney disease, fractures, *Clostridium difficile* infections, and vitamin deficiencies (Wilhelm SM, et al. *Expert Rev Clin Pharmacol* 2013; 6:443–451).

To assess the potential kidney risks, Charat Thongprayoon, MD, of the Bassett Medical Center in Cooperstown, New York, and his colleagues analyzed data from studies that compared the risk of developing CKD or kidney failure among PPI users and non-users. They included 5 studies with 536,902 participants. The relative risk of kidney disease was one-third higher among PPI users (RR 1.33 95% CI, 1.18–1.51).

"This study demonstrates a significant association between the use of PPIs and increased risks of chronic kidney disease and kidney failure," said Thongprayoon.

He acknowledged that such observational data cannot prove that PPIs cause kidney injury, but he said the evidence is compelling enough to warrant more cautious use of these drugs.

"Although no causal relationship has been proven, providers should consider whether PPI therapy is indicated for patients," Thongprayoon said. "Chronic use of PPIs should be avoided if not really indicated."

Nephrologist Ziyad Al-Aly, MD, director of clinical epidemiology at VUS Department of Veterans Affairs St. Louis Health Care System, said the meta analysis helps synthesize the evidence to date linking PPIs with kidney disease. He noted there are a variety of potential mechanisms that might explain kidney-related adverse events in PPI users. The most plausible is that the drugs impair the ability of organelles called lysosomes, which act as the cell's "garbage incinerator," he explained.

"They impair the action of those organelles and they accelerate aging of the cells," he said.

Currently, many physicians who prescribe PPIs monitor their patients for signs of acute kidney injury, Al-Aly noted. However, a recent study by Al-Aly and his colleagues showed that even PPI-using patients without signs of acute kidney injury may be at risk of renal disease (Xie Y, et al. *Kidney Int* 2017; 91:1482–1494).

"It could be happening insidiously without that warning sign," he said.

He agreed that more caution should be used in prescribing these drugs. When they are indicated, such as when a patient has a bleeding ulcer, he said the lowest dose should be used for the shortest duration of time. He questioned why the drugs are being so widely prescribed and used, noting that data suggest 30–60% of PPI users may not need the drugs.

"When people who don't have a medical need to be on a PPI in the first place, all they are getting is the side effects," he said. "In that instance, the risks outweigh the benefits."

"Proton Pump Inhibitors and Risk of Chronic Kidney Diseases: A Meta-Analysis" (Abstract 2763180)

Excess Accumulation of Bone Drug in Rats With Compromised Kidneys

By Bridget M. Kuehn

A drug used to treat osteoporosis accumulates excessively in the bones of rats with chronic kidney disease, (CKD), according to a study presented at Kidney Week.

Bisphosphonates are currently not recommended in patients with CKD—despite the elevated risk of osteoporosis—because of potential safety concerns. The drug is cleared by the kidney, so in patients with impaired kidney function there is a concern about excess accumulation of the drug, said Mohammad Walid Aref, an MD/PhD candidate at the Indiana University-Purdue University-Indianapolis School of Medicine. But other experts point to the risk of more brittle bone rather than reduced excretion.

"The main concern about using these drugs is that they cause very low bone formation (adynamic bone), which could eventually result in more brittle bone," said bone disease specialist Susan Ott, MD, a professor of medicine at the University of Washington in Seattle.

Limited data are available on the use of this class of drugs in CKD because patients with the condition were excluded from clinical trials (Ott S. Intl Soc Nephrol 2012; 82:833–835). Some studies, however, have documented a risk of acute kidney injury in patients without kidney disease who are taking intravenous bisphosphonates. Others have suggested a potential benefit for patients with stage 3 disease, but no clear benefit has been shown for patients with later stages of disease (Ott SM. *Semin Dial* 2015; 28:363–369).

To better understand the dynamics of these drugs, Aref and his colleagues administered fluorescently labeled zolendronate to 25-week-old rats with CKD or without. Blood flow to the bones was measured using an injection of fluorescent microspheres. The rats were later euthanized, some 24 hours later, others 5 weeks out from the treatment. The animals' radius/ulna, distal femur, tibia, and 3rd lumbar vertebra were then examined using whole bone fluorescence imaging.

The animals with CKD had levels of blood urea nitrogen twice as high as the normal animals. The kidney-impaired animals also had higher levels of zolendronate in their bones at 24 hours and 5-weeks posttreatment. The authors also found nonsignificant differences in blood flow in the CKD animals compared with the normal controls. The results suggest that the accumulation of bisphosphonate may be caused by more blood flow and more bone surface, Aref said.

"It may be due to increased turnover and increased blood flow rather than a damaged kidney that can't filter them out," he noted.

The results add to the preclinical evidence on the dynamics of bisphosphonate in the setting of kidney disease, said Ott.

"This [finding] is consistent with the previous studies and has used a different technique which is interesting, and studied a different bisphosphonate that is known to have a stronger binding to the bone mineral," Ott wrote.

Ott noted that there are many more questions to be answered including how kidney disease affects skeletal uptake and whether worsening kidney disease impacts blood flow or whether the zolendronate itself may affect blood flow. She also questioned whether parathyroid hormone also may play a role since zolendronic acid would be expected to increase the hormone.

Aref and his colleagues are currently studying whether lower doses or different patterns of administering zolendronate change its accumulation in rats with CKD.

The study doesn't yet have implications for clinical care, Ott cautioned. "We still don't have any studies that show any benefit with these drugs in late stages of CKD on fractures," Ott said.

"Bisphosphonate Skeletal Accumulation is Increased in Early and Mid-Stage CKD" (Poster 0897)

Innovative Techniques, Trials, and Treatments Debut in Late-Breaking Trials

By Bridget M. Kuehn

Starting dialysis with a fistula has been shown to improve patient outcomes, but the challenge of getting a surgically created fistula in time to start dialysis is often hard to overcome. But trial results presented at Kidney Week suggest a minimally invasive technique for creating a fistula may one day allow interventional nephrologists to quickly and safely create fistulas.

The study was one of several late-breaking studies presented at the meeting that suggested innovative techniques, trial designs, and treatments might yield better results for patients with kidney disease and those at risk. Among them were a pragmatic trial examining the benefits of longer dialysis sessions in a real-world setting and studies aiming to reduce the kidney risks faced by patients undergoing cardiac procedures. Other trial results assessed the efficacy and safety of drugs tolvaptan, bardoxolone, and rituximab in select groups of patients with kidney disease.

Ultrasound guided access

The pivotal trial of an ultrasound-guided technique for creating an anastomosis between the proximal radial artery and perforating vein in an outpatient setting achieved its targets, according to Jeffrey Hull, MD, an interventional nephrologist at the Richmond Vascular Center and assistant clinical professor at Virginia Commonwealth University.

Instead of surgically creating such an access, in the trial the Ellipsys® Vascular Access System was used by interventional nephrologists to create fistulas for 107 patients at 5 outpatient vascular centers. The minimally invasive procedure takes on average 23 minutes, said Hull.

In the prospective trial, arteriovenous fistula with fused anastomoses were created for 95% (102) of the trial participants. The trial's goal of achieving primary flow and diameter endpoints for 49% of the patients was exceeded. In fact, 86% of the participants achieved brachial artery flow volume greater than or equal to 500 mL/min and a vein diameter of at least 4 mm.

"We created high-quality fistulas in the office setting," said Hull. "This was done by interventionists who had never done it before."

He said the company making the device hopes to achieve US Food and Drug Administration approval this year.

Kidney Week meeting attendee and *KN* Editor-in-Chief Richard Lafayette, MD, a nephrologist at the Stanford University Medical Center, called the study "a great advance toward moving the procedure into the hands of nephrologists."

Janice Lea, MD, MSc, professor of medicine and director of Emory Dialysis at Emory University in Atlanta, said she thought this study was the most "impactful" of the late-breaking trials.

"It could directly improve dialysis care by giving patients better vascular access without a lot of surgery," Lea said. She said she could definitely see it being very useful for patients who are new to dialysis, but she would like more data on whether it will benefit patients who've had multiple vascular access procedures, who have poor circulation, or other complicating factors.

"Real-world trial"

Longer dialysis sessions may lower the risk of early death among dialysis patients, suggest data from observational studies. To verify if this is true, Laura Dember, MD, of the University of Pennsylvania, and colleagues conducted a pragmatic trial comparing 4 hour and 15

minute dialysis with standard 4-hour sessions in 260 dialysis units operated by Fresenius and DaVita, the two largest dialysis providers in the United States.

"They are also called real-world trials because they are conducted under the circumstances the intervention will ultimately be applied rather than idealized experimental conditions," Dember said.

She explained that the interventions were carried out by the dialysis center staff and applied to 7035 incoming dialysis patients. The data used for the study analysis were all clinical data routinely collected during care. The trial was part of the National Institutes of Health Research Systems Collaborative that aims to advance the use of such pragmatic trials in the hopes of more efficiently producing results that will be generalizable in real-world clinical settings.

Unfortunately, the trial's independent data safety monitoring board decided to end the trial early because there wasn't a large enough difference in dialysis duration between the intervention and control group. She explained they were targeting a 30-minute difference in dialysis time between the 2 groups, but they only achieved a 10-minute difference.

"There was significant amount of resistance on the part of the patients [to longer dialysis duration]," explained Dember.

Despite not being able to answer whether longer dialysis improved outcomes, the trial did demonstrate that dialysis may be a promising setting for pragmatic clinical trials. The trial also offered valuable lessons that may aid future studies.

"We need to develop more effective approaches for engaging on the ground clinicians and patients if we are going to conduct large scale trials that are embedded in clinical care delivery," she said.

Protecting kidneys during heart care

Two other late-breaking studies demonstrated potential

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Innovative Techniques

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strategies to protect the kidneys from harm during heart procedures.

The contrast agents used to enhance imaging studies of individuals with suspected coronary artery disease may harm the kidneys, explained radiologist Marc Dewey, MD, of the Institute for Radiology at Charité Hospital in Berlin, Germany. Each year, 70 million such studies are conducted with intravenous contrast agents and 7 million are done with intracoronary agents in the United States and United Kingdom, he said. But there are limited data to guide clinicians to the least harmful choices.

So, he and his colleagues conducted a phase 3 trial comparing the kidney health effects of invasive coronary angiography (ICA) with intracoronary contrast agent with coronary computed tomography angiography (CTA) with intravenous contrast agent. The same contrast agent was used for both procedures. The study received no industry funding.

During the study, patients with suspect coronary disease were randomly assigned to undergo ICA (162) or CTA (165). The groups had comparable glomerular filtration rates prior to the procedures. After the procedures, 9 patients in the CTA group (6%, 95% CI 3-10%) and 21 patients in the ICA group (13%, 95% CI 8-19%) experienced a contrast-induced acute kidney injury.

"Coronary computed tomography angiography with IV contrast reduced acute kidney injury in patients with suspect coronary artery disease," he said. More trials are needed to confirm the results.

"It's encouraging that there are ways to potentially reduce the risk of kidney

injury [in heart patients]," said Lea.

A second phase 2 trial demonstrated a strategy for preventing acute kidney injury among cardiac patients. David Corteville, the medical director of Cardiac and Vascular Research Center of Northern Michigan, explained that 20% of patients undergoing cardiac surgery experience acute kidney injury.

The trial tested QPI, a small interfering RNA (siRNA) that reduces the expression of the p53 gene. The p53 gene promotes cell death, so according to the drug's manufacture Quark, the drug might prevent the death of normal kidney cells caused by acute kidney injury. The drug is also being studied to prevent ischemia-reperfusion injury in patients undergoing kidney transplant.

In the study, 341 patients undergoing nonemergency cardiac surgery at 41 sites were randomized to receive a single intravenous dose of QPI 4 hours after surgery or a placebo. Participants had at least one risk factor for acute kidney injury. Patients who received QPI had a 26% reduction in the relative risk of acute kidney injury compared with placebo (37% vs. 50%; p=0.02). The severity and duration of kidney injury was also reduced in the treated patients, Corteville said. Adverse events were comparable between the two groups. A phase 3 trial is planned to confirm the results.

In high risk patients with multiple risk factors for acute kidney injury the trial also showed a significant reduction (29%) in a composite endpoint of death, dialysis, or a 25% reduction in eGFR, said Shai Erlich, PhD, Chief Medical Officer of Quark Pharmaceuticals during a press briefing at Kidney Week.

Erlich explained that while the investigators hoped to see a trend in this direction, they did not expect that such a trend would be significant because the study wasn't designed to be large enough to detect such a difference.

"This exceeded our expectation that we would only see a trend," Erlich said.

A phase 3 trial is planned; if that trial is successful and the drug is approved for use in the US it is likely to be indicated only for those at high risk, Erlich said.

More research is needed to determine if the benefits outweigh the costs of the treatment, cautioned Lea. She noted that similar kidney injury–reducing drugs have proved not to be cost-effective. Additionally, she would like to see studies comparing QPI to conventional kidney sparing techniques, like administering IV fluids prior to surgery.

"I don't think it will be ready for primetime anytime soon," she said.

Other studies presented focused on the safety and efficacy of drug treatments:

- Results from the 23-center MENTOR trial showed that rituximab was noninferior to cyclosporine for treating patients with membranous nephropathy. At 6 and 12 months, the 2 drugs had comparable effects in achieving complete and partial remission. But at 24 months, rituximab appeared to reduce relapse and increase time to remission. Rituximab also had fewer adverse events than cyclosporine (13 vs 23).
- Data from the phase 3, multi-center REPRISE trial showed that tolvaptan slowed estimated glomular filtration rate decline in patients with autosomal dominant polycystic kidney disease by 35% over a year. However, elevated transaminase levels occurred more frequently in the tolvaptan-treated patients than in placebo-treated patients (5.6% vs 1.2%).
- The TSUBAKI trial tested whether bardoxolone could be safely used in patients with diabetic kidney disease at low risk of fluid overload. The drug had previously been shown to increase glomerular filtration rates in patients with diabetic kidney disease, but the Phase 3 BEACON trial was halted early because some patients experienced early fluid overload. The results of TSUBAKI suggested bardoxolone may provide a benefit for patients at low risk of fluid overload.

Policy Update

Medicare Intermediaries Target More Frequent Dialysis; ASN Responds

By David White

Multiple deadlines are available in December to voice your opinion with the Medicare Administrative Contractors (MACs) regarding their announced plans to limit reimbursement for dialysis that occurs more than three times per week exclusively to patients who meet specific acute condition requirements.

Seven MACs covering eight jurisdictions (WPS, Novitas Jurisdiction H, Novitas Jurisdiction J, NGS Jurisdiction K, NGS Jurisdiction 6, Noridian Jurisdiction E, Noridian Jurisdiction F, and First Coast, Palmetto, CGS), covering over half of the country, released nearly identical draft Local Coverage Decisions implementing restrictive guidance related to more frequent dialysis.

Deadlines for sending in comments regarding proposed dialysis coverage requirements

Noridian Jurisdiction E & F – December 15, 2017
CGS Administrators Jurisdiction 15 – December 24, 2017

Within a very narrow timeframe, the MACs separately announced almost identical plans to limit reimbursement for more frequent dialysis exclusively to patients who meet specific acute conditions outlined in a draft Local Coverage Determination (LCD). These draft LCDs propose that any claim linked to a Plan of Care (POC) that includes dialysis treatments occurring more than three times per week—for any chronic condition or acute condition not included on the list—will be denied.

The American Society of Nephrology (ASN) has been working with a wide range of kidney groups and coalitions, including the Renal Physicians Association, Kidney Care Partners, the Alliance for Home Dialysis, and others to advocate for rejection of the LCDs. ASN asks members to reach out to their respective MACs to voice their concerns.

In comment letters to the MACs, ASN objects to the proposed policy change on the grounds that the change:

Violates the physician-patient relationship

ASN maintains that, as currently written, the draft LCD interferes with the patient-physician relationship in several ways. By proposing to establish a blanket denial policy for any claim linked to a POC that includes a dose of dialysis of more than three treatments per week, and by limiting the conditions that qualify as "medical justification" for more than three treatments per week to only a few acute conditions while excluding chronic conditions, the MACs inappropriately infringe upon the physician-patient relationship and establish substantial barriers to prescribing optimal treatments for individual patients.

Discourages medically justified individualized care

Clinical literature, as well as best practices and international guidelines, recognize that some patients with kidney failure may require more than three treatments per week on an ongoing basis in order to achieve and maintain optimal health, ASN said in comment letters. A peer-reviewed *American Journal of Kidney Diseases* Supplement on *Intensive Hemodialysis* published in November 2016 catalogs the literature supporting the prescription of additional hemodialysis sessions for the treatment of a number of different chronic conditions (1). Studies report that patients prescribed more than three treatments per week have been able to achieve improvements in, among other things, left ventricular hypertrophy, hypertension (using fewer medications), hyperphosphatemia, depression, posttreatment recovery time, sleep disturbances, and restless legs syndrome.

Does not recognize both acute and chronic conditions and care needs

ASN is concerned that if the LCD limits the conditions for more than three dialysis treatments per week to "acute" clinical conditions, this limitation would not be consistent with the clinical literature. As reflected in the names of conditions such as "chronic systolic [or diastolic] (congestive) heart failure," as well as others without the modifier "chronic," many conditions where more frequent hemodialysis is beneficial are chronic rather than acute in nature. Moreover, ASN asserts that it is contrary to best practices to treat patients when they have an acute episode, then stop the treatment approach that addressed the issue. Such a shortsighted strategy will, predictably, lead to another acute episode for many patients and risk re-hospitalization and resource use requirements that far exceed those of an additional weekly dialysis session.

Violates current CMS policy

ASN maintains that the proposed LCDs exceed the bounds of the MACs' authority in trying to restrict what conditions can be covered for more than thrice-weekly dialysis with medical justification. As CMS rules and guidance have made clear, the decision regarding medical justification must be made on an individual patient basis, making the proposed LCDs contrary to current CMS policy. CMS would have to rely upon notice-and-comment rulemaking, which is beyond the scope of the LCD authority.

- ***Case Study # 1***

Patient: A 30-year-old man with primary hyperoxaluria complicated by kidney failure.

Prescribed Treatment: To control his hyperoxalosis and prevent other end-organ damage, he required hemodialysis six times per week; he elected to perform this in-center.

Results: The patient was otherwise well, and he worked part-time as allowed by his dialysis schedule. He had no hospitalizations while receiving dialysis and ultimately received a successful liver-kidney transplant.

This is a good example of a patient with a chronic condition (hyperoxaluria) that is controlled by more frequent dialysis, with the POC calling for frequent dialysis. He was stable, and, therefore, more frequent care-planning would not have had value justifying its resource cost. He was seen most weeks by his physician, but not every week—and this was appropriate for his clinical state.

- ***Case Study #2***

Patient: An 80-year-old man treated with hemodialysis for more than 10 years with three hospitalizations in a six-week period due to fluid overload in the setting of heart failure with preserved ejection fraction. Despite aggressive education, he continued to gain substantial weight between sessions; this weight gain was in part due to chronic odynophagia, making fluids easier for him to swallow than solids. Each hospitalization came toward the end of the long interdialytic interval (Mondays, given that he was typically treated on a Tuesday/Thursday/Saturday schedule). His spKt/V at dialysis was ~1.8, consistent with adequate dialysis. He does not tolerate more than 2.5 to 3 kg of ultrafiltration per session, developing hypotension.

Prescribed Treatment: To control volume overload, he agreed to a fourth weekly dialysis treatment on Mondays.

Results: The fourth regularly scheduled session was documented in his POC. Following this prescription change, he had no further emergency department visits or hospitalizations for fluid overload. Given prior trends, if more than thrice-weekly dialysis was not provided routinely, he would be virtually certain to experience re-hospitalization; accordingly, integrating this into his POC (as opposed to writing weekly revisions to his dialysis prescription) was the most prudent course of action.

- ***Case Study Discussion***

ASN asserts that in these case studies, the provision of more than thrice-weekly dialysis was critical to the patient's health in the long-term (chronic need), not just in the short-term (acute need). Also, in both cases, the proposed new requirement that the patient's nephrologist file an acute order with medical justification for the additional dialysis session every week—as would be necessary under the proposed LCD—would make provision of optimal care more challenging for nephrologists, creating an administrative burden with no clinical utility. It would also create uncertainty and increased risks for the patient, and may increase tensions among physicians, patients, and dialysis facilities, with facilities objecting to medically indicated and prescribed additional treatments due to inappropriately strict criteria and resulting uncertainty of payment as delineated in the proposed LCD.

The ABCs of MACs

A. Medicare divides the country into 12 geographical jurisdictions.

B. It contracts with private companies to serve as MACs to process Medicare Part A and Part B medical claims.

C. MACs make Local Coverage Determinations (LCDs), but only Medicare can make national policy through the rulemaking process governed by the Administrative Procedures Act (2).

D. MACs pay $386 billion in Medicare benefits annually.

E. MACs process more than 1.2 billion Medicare FFS claims annually, 218 million Part A claims and more than 1 billion Part B claims (3).

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1. http://www.ajkd.org/issue/S0272-6386(16)X0004-2
2. 5 U.S.C. & 500 et seq.
3. https://www.cms.gov/Medicare/Medicare-Contracting/Medicare-Administrative-Contractors/What-is-a-MAC.html

Practice Pointers

Lupus Nephritis in 2017: An Update

By Wai Lang Lau, MD, and Gerald B. Appel, MD, FASN

In light of recent progress in the genomics of complex traits, where do we stand with glomerular disease?

Renal involvement is clinically apparent in approximately 50% of systemic lupus erythematosis (SLE) patients and a frequent cause of significant morbidity and mortality (1). On renal biopsy, virtually all lupus patients have some findings indicative of kidney pathology. The clinical presentation of lupus nephritis is highly varied, ranging from asymptomatic hematuria and/or proteinuria to the full nephrotic syndrome or even rapidly progressive glomerulonephritis. In the kidney, the cornerstone mechanism of damage is the formation and deposition of immune complexes (including DNA nucleosome complexes and anti-DNA antibodies), which may occur by nonspecific trapping of circulating immune complexes, in situ formation, or interaction with negatively charged components of the glomerular capillary wall. In general, immune deposits in the mesangium and subendothelial location incite an active inflammatory response, whereas those in a subepithelial location do not as they are separated from the circulation by the glomerular basement membrane. Immune complex formation is followed by the binding and activation of complement and ensuing inflammatory cascades. However, a variety of other mechanisms may be at play, including activation of the coagulation system causing a thrombotic microangiopathy, podocytopathies associated with heavy proteinuria but no active inflammatory lesions, and interstitial or vascular renal disease.

The role of renal biopsy and clinical pathologic correlations

In lupus nephritis, the kidney biopsy provides diagnostic and prognostic information and can serve as a guide to therapy. Current classification describes six classes of pathology (Table 1).

Multiple studies have shown the prognostic value of this classification. In general, classes I and II have a mild presentation and benign clinical course. Treatment is targeted at blood control with antiproteinuric agents and angiotensin-converting enzyme-I (ACE-I) or angiotensin receptor blockers (ARBs). Classes III and IV are associated with active urinary sediment, substantial proteinuria, and progressive renal damage and thus, deserve vigorous therapy. Class V, membranous lupus nephropathy, is associated with heavy proteinuria (often the nephrotic syndrome) and requires special therapeutic considerations. Patients with class VI, sclerosing lesions, do not respond to immunosuppressive therapy and should be prepared for dialysis and/or transplantation.

Treatment of classes III and IV is divided into two phases: induction and maintenance

Early National Institutes of Health (NIH)-sponsored trials showed that intravenous steroids and six monthly intravenous high doses of cyclophosphamide (0.5 to 1.0 g/m^2) followed by quarterly maintenance doses resulted in more clinical remissions than treatment with either steroid or cyclophosphamide alone (2). With concerns about cyclophosphamide toxicity, including infection, infertility, and malignancy development, the Eurolupus Group studied 90 proliferative lupus nephritis patients randomized to receive either a low-dose cyclophosphamide regimen (six pulses of 500-mg doses every 2 weeks) or a high-dose regimen (six monthly pulses) similar to the NIH regimen. Both groups were then maintained on azathioprine, 2 mg/kg per day. At short- and long-term follow-up, there was no significant difference in efficacy or adverse effects. However, the number of patients with severe infection was twice as high in the high-dose cyclophosphamide group, providing support for the low-dose treatment course (3). This new regimen has been validated in other populations, including African Americans, and is now considered one of two standard induction therapies for lupus nephritis.

The alternative standard induction regimen uses mycophenolate mofetil. The Aspreva Lupus Management Study (ALMS) (4), a multicenter, multicultural trial of 370 patients with class III, IV, or V lupus nephritis, randomized induction to either mycophenolate mofetil or six monthly intravenous cyclophosphamide pulses. Both arms initially received high-dose corticosteroids, which were tapered. The trial showed similar efficacy and toxicity with both regimens in a broad range of racial and geographic groups.

Thus, the recommendations by most nephrology and rheumatology organizations are to use either cyclophosphamide or mycophenolate combined with corticosteroids as induction treatment for severe active lupus nephritis. Individual preference, compliance, tolerability, and specific clinical scenarios all influence selection. However, if patients fail therapy with one agent, they are most often switched to rescue with the second therapeutic regimen.

Maintenance therapy of proliferative lupus nephritis

After remission through induction has been achieved, a number of studies have defined optimal maintenance treatment. An early trial randomized 59 patients with class III or IV lupus nephritis postinduction with 6 months of monthly pulse cyclophosphamide to receive either quarterly intravenous cyclophosphamide pulses (0.5 to 1.0 g/m^2) or daily oral azathioprine or mycophenolate (5). At follow-up, the study showed that maintenance with either mycophenolate or azathioprine was more efficacious and significantly safer than continuing long-term therapy with intravenous cyclophosphamide. A study by the Euro Lupus group that randomized patients to azathioprine or mycophenolate after induction showed no significant difference in the very good outcome seen in the largely Caucasian European population studied (6). More recently, 227 patients from the ALMS who had a good clinical response to either cyclophosphamide or mycophenolate induction were rerandomized to receive either mycophenolate (1 g twice a day) or azathioprine (2 mg/kg per day) double blind for another 3 years. At follow-up, mycophenolate was superior to azathioprine in maintaining renal response and preventing relapse (7). This was true in different geographic areas, among different racial groups, and regardless of which induction regimen was used.

At present, both mycophenolate and azathioprine seem effective agents for maintenance therapy. Mycophenolate may have advantages in non-Caucasian populations. Azathioprine should be used in women contemplating pregnancy. Cost may be a factor for some patients, and mycophenolate is generally more expensive. Mycophenolate can be used with allopurinol or febuxostat for patients with gout, whereas azathioprine should not be used with xanthine oxidase inhibitors.

Rituximab is a chimeric mAb directed against CD20, an antigen expressed on the surfaces of mature

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Table 1

1. **Class I (minimal mesangial lupus nephritis):** normal light microscopy with mesangial immune deposition on IF and/or EM.
2. **Class II (mesangial proliferative lupus nephritis):** mesangial hypercellularity on light microscopy with mesangial immune deposition.
3. **Class III (focal lupus nephritis):** inflammatory injury affecting less than 50% of the glomeruli by light microscopy with crescents, fibrinoid necrosis, and/or subendothelial immune deposition. Both classes III and IV are classified as A with active lesions of proliferation and necrosis, C with chronic lesions of sclerosis and fibrosis, or A/C with a combination of these lesions.
4. **Class IV (diffuse lupus nephritis):** inflammatory injury as in class III affecting greater than 50% of the glomeruli, again classified as A, C, or A/C. This class is further divided into segmental or global depending on the extent of injury to the individual glomerular tuft, greater than 50% in the latter category.
5. **Class V (lupus membranous nephritis):** glomerular capillary thickening on light microscopy with subepithelial immune deposition on EM/IF.
6. **Class VI (advanced sclerosing lupus nephritis):** over 90% glomerulosclerosis.

IF = immunofluorescence; EM = electron microscopy.

Practice Pointers

Lupus Nephritis

Continued from page 17

and immature B cells. The Lupus Nephritis Assessment with Rituximab Study investigated the addition of rituximab (1000 mg on days 1, 15, 168, and 182) versus placebo in 144 patients with class III/IV disease on full induction with steroids and mycophenolate. At 52 weeks, the rituximab arm did not result in a statistically significant clinical improvement in complete/partial renal response (8). Thus, at this time, rituximab is not considered a first-line induction agent for lupus nephritis. However, some observational studies suggest efficacy in patients who have failed induction therapy with other agents. A systematic analysis of 26 reports encompassing about 300 lupus nephritis patients refractory to standard therapy treated with rituximab showed the achievement of complete or partial response in greater than 50% (9). Moreover, the ongoing Rituximab and Mycophenolate without Oral Steroids in Lupus Nephritis (RITUXILUP) Trial is a phase 3 randomized multicenter United Kingdom study that tests rituximab as a potential steroid-sparing drug in treating proliferative disease (NCT 01773616).

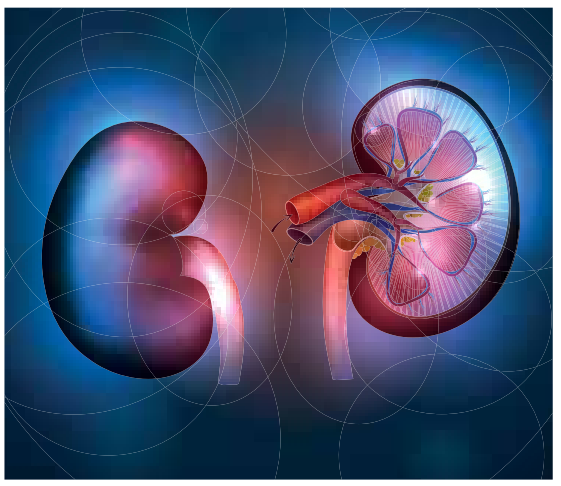
Treatment of class V—membranous lupus nephropathy

For class V lupus, membranous nephritis, use of immunosuppressant agents is controversial. However, most nephrologists would treat when the proteinuria exceeds 3 g/d, despite the use of ACE-I/ARB agents. In the ALMS, 60 of 370 patients had class V lupus nephritis. At 24 weeks, there was no difference in study end points between treatment with mycophenolate and monthly intravenous cyclophosphamide. Thus, mycophenolate and prednisone seem to be a good first-line agent for treatment. Other choices include cyclophosphamide (intravenous/PO) or a calcineurin inhibitor along with corticosteroids.

A small NIH trial randomized 42 patients with class V lupus nephritis to receive alternate-day prednisone, prednisone plus intravenous cyclophosphamide every other month, or prednisone and daily cyclosporin for a 1-year period. The study concluded that the cyclophosphamide and cyclosporin arms were more than twice as likely to experience a remission of proteinuria than the prednisone arm. Relapses occurred significantly more often after cyclosporin than after cyclophosphamide (10). However, because most cyclosporin patients later respond to cyclophophosphamide, many feel that calcineurin inhibitors are reasonable treatment agents for class V patients. A combined study of patients from two randomized, controlled trials of almost 500 patients included 84 with class V lupus nephritis treated with cyclophosphamide or mycophenolate. Both groups had equal efficacy and side effect profiles (11). Thus, for class V patients with heavy proteinuria, calcineurin inhibitors, cyclophosphamide, and mycophenolate are all reasonable therapies. Indeed, there is uncontrolled evidence that rituximab also is effective in this population. A prospective observational study of 50 patients (44% of whom had pure class V lupus nephritis) (12) using the RITUXILUP Trial regimen (intravenous rituximab, intravenous methylprednisolone, and mycophenolate) attained complete and partial remissions in 52% and 34% of patients, respectively, after 1 year.

Future Therapies

Future treatments of lupus nephritis rest on a better understanding of the immune pathogenesis of the disease. Key players include T and B cells, plasma cells, the costimulatory factors that nurture these cells, and the cytokines that upregulate the inflammatory cascade. Trials of some available agents are ongoing. Rituximab with mycophenolate is being studied as a steroid-sparing regimen in the RITUXILUP Trial as mentioned above. There is interest in multitargeted therapy for severe lupus nephritis, because a positive randomized multicenter Chinese study looked at induction therapy with monthly intravenous cyclophosphamide versus treatment with mycophenolate and tacrolimus, with both groups receiving corticosteroids. Results revealed significantly more complete and partial remission in the mycophenolate/tacrolimus arm (13).



Anifrolumab, a mAb against the IFN-α receptor I, blocks the effects of IFN-α, a major regulatory cytokine in approximately 50% of SLE patients (14, 15). In a randomized, controlled study of over 300 patients, anifrolumab provided added efficacy in induction when added to mycophenolate and corticosteroids (16). Belimumab, a humanized anti-BLyS mAb, is being evaluated for active lupus nephritis as an add-on drug (versus placebo) to standard of care induction therapy (NCT 01639339). Another trial, the CALIBRATE Study, will test cyclophosphamide, rituximab, and oral prednisone followed by belimumab (NCT 02260934). Obinutuzumab, a humanized anti-CD20 mAb, causes more complete peripheral and lymphoid tissue B cell depletion than rituximab (17). A phase 2 study is currently underway for patients with active lupus nephritis (NCT 02550652). Voclosporin, a novel calcineurin inhibitor with enhanced stability and activity relative to cyclosporin, is currently being studied as add-on therapy as well (NCT02141672). Finally, ACTHAR gel is being studied in both proliferative and membranous lupus.

This is an exciting time for those treating patients with lupus nephritis. We already have good therapies for induction and maintenance that have been studied in large controlled, randomized trials. It is clear that treatments will evolve further as we learn more about the complex immunologic pathways involved in the disease. The quest for more effective and safer therapeutic options for lupus nephritis is paramount.

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Findings

Gestational Diabetes Linked to Higher CKD Risk in Black Women

Very long-term follow-up suggests a twofold increase in chronic kidney disease (CKD) risk among black women with pregnancies affected by gestational diabetes mellitus, reports a study in *American Journal of Kidney Diseases*.

The researchers analyzed data on 2747 women, aged 18 to 30, from the community-based "Coronary Artery Risk Development in Young Adults" (CARDIA) study. Of these, 820 women were nulliparous at baseline, had one or more pregnancies lasting 20 weeks or longer, and had available data on kidney function at up to 25 years of follow-up. Associations between gestational diabetes and CKD were assessed, with adjustment for a wide range of other factors.

Overall, 12.3% of women reported a pregnancy affected by gestational diabetes. At a mean follow-up of 20.8 years, 12.8% of women had developed CKD. Of 105 cases of CKD, 98 were defined by albuminuria only (urine albumin-creatinine ratio of 25 mg/g or higher).

Gestational diabetes was associated with an increased risk of CKD only among black women: adjusted hazard ratio (HR) 1.96 (95% confidence interval 1.04 to 3.67). For white women, the association was nonsignificant, with an HR of 0.65 (95% confidence interval 0.23 to 1.83). Among black women, CKD developed in 31.0% of those with gestational diabetes versus 15.6% of those without gestational diabetes. Among white women, the figures were 6.8% versus 10.0%, respectively.

The study was designed to determine whether gestational diabetes is associated with incident CKD, after controlling for prepregnancy factors associated with both conditions. The results show a significant long-term increase in CKD, defined by albuminuria, among black but not white women with a history of gestational diabetes. "Pregnancy may present a window of opportunity to identify women at risk for CKD and implement prevention strategies," the researchers write [Dehmer EW, et al. Association between gestational diabetes and incident maternal CKD: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Kidney Dis* 2017; DOI: http://dx.doi.org/10.1053/j.ajkd.2017.08.015].

Early Conversion to Belatacept: A Case-Control Study

In kidney transplant recipients with low kidney function, early conversion from tacrolimus- to belatacept-based immunosuppression leads to a small but significant increase in estimated glomerular filtration rate (GFR), reports a study in *Transplantation*.

The retrospective study included two groups of 30 matched transplant recipients with low but stable eGFR: typically less than less than 40 mL/min/m^2 (median 23 mL/min/m^2. From 2012 to 2016, the study center had a protocol to convert patients with low kidney function at least 1 month posttransplant from tacrolimus to belatacept. Cases were matched on a wide range of variables to controls maintained on calcineurin inhibitors (CNIs).

Mean change in GFR during the first 4 months after conversion was 11 mL/min/m^2 in patients converted to belatacept versus 4.8 mL/min/m^2 in the control cohort. This was despite a 16.7% rate of acute rejection in the conversion group, compared to zero in the control group. The improvement in kidney function was still present after 1 year. The two groups had similar allograft and patient survival at 2 years.

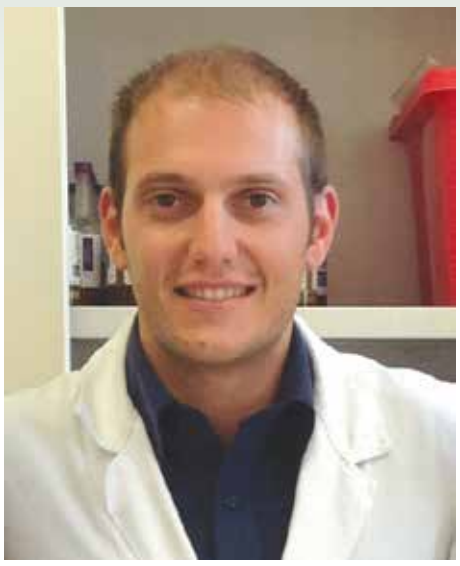
Previous reports from the BENEFIT trial showed better kidney function in patients started on belatacept-based immunosuppression after kidney transplantation, compared to CNIs. Less is known about the effects of converting from CNI- to belatacept-based therapy.

This retrospective study reports a "modest increase" in kidney function with early conversion from tacrolimus to belatacept in kidney recipients with low but stable eGFR [Elhamahmi DA, et al. Early conversion to belatacept in kidney transplant recipient with low glomerular filtration rate [*Transplantation* 2017; DOI: 10.1097/TP.0000000000001985].

Fellows Corner

Critical Care Nephrology: an Appealing Subspecialty for Young Nephrologists

By Marco Florentino



Marco Fiorentino

Many exciting opportunities and subspecialties have emerged within the field of nephrology. Among these, critical care nephrology has become an important specialty in both clinical and research settings. Acute kidney injury (AKI) is an increasingly recognized adverse outcome among critically ill patients, and its impact is both devastating and often underestimated (1).

Several critical care nephrology programs have been created in recent years to provide clinical care, research, and educational programs to interested trainees. The Center for Critical Care Nephrology in Pittsburgh is an example of the growing interest in promoting a multidisciplinary model of basic, translational, and clinical research to prevent and cure AKI in critically ill patients. However, the role of the nephrologist in the intensive care unit (ICU) is still an area of debate, as opinions regarding whether a nephrologist should be consulted vary widely across different institutions (2).

Both the prompt identification of high-risk patients as well as the correct management of AKI require a strong collaboration between critical care physicians and nephrologists. AKI is a multifactorial syndrome with a wide range of prevalence, pathophysiology, and different therapeutic approaches in the ICU, and nephrologists must have adequate intensive care training to ensure high-quality and efficient care of these patients. Complicated electrolyte and acid-base disorders are common in the ICU and require a robust knowledge of renal physiology. As such, the nephrologist needs to be an early and active participant in guiding and assisting critical care teams in the interpretation of data.

Furthermore, the nephrologist must play an active role in implementing strategies to minimize the risk of severe complications. He or she may assist with avoiding potentially harmful interventions such as the use of nephrotoxic medications, contrast exposure, and with over- or underdiuresis. In addition, the nephrologist can ensure early and appropriate implementation of certain treatment strategies. Early nephrology engagement is crucial when renal replacement therapy (RRT) is required, not only with regard to appropriate timing, but also in relation to choosing the optimal modality, etc. Other therapeutic options such as plasmapheresis and hemadsorption may be appropriate and are also often under the control of nephrologists. A multidisciplinary team consisting of the nephrologist, critical care physician, nurse, and pharmacist is often suggested in the ICU to deliver the right prescription in order to personalize the treatment and maximize its efficacy.

Recently, Ronco and colleagues provided a practical algorithm to better identify patients at high risk for AKI. They proposed that a Nephrology Rapid Response Team (NRRT) manage these high-risk patients, defining AKI causes and stages and aiming to avoid renal and non-renal long-term consequences (3). Moreover, drugs and iatrogenic interventions may often overlap with other AKI exposures and contribute to AKI. The nephrologist may be invaluable in assisting in drug prescription and dosing in ICU patients: potential nephrotoxic drugs may be substituted with less or non-nephrotoxic ones or they may be dosed according to patients' renal function. This is a big issue in ICU patients, since all formulas that estimate renal function assume a stable serum creatinine. Thus, a strong collaboration between nephrologists and pharmacists is crucial to find the right balance between risks and benefits of medications.

Last, adequate follow-up of AKI patients after ICU and hospital discharge is required because evidence has shown that even partial recovery from AKI episodes increases the risk of progression to chronic kidney disease and premature mortality (4, 5).

Value of collaboration between young nephrologists and intensivists

Beyond the advantages of collaboration between intensivists and nephrologists at the bedside, young nephrologists should partner with intensivists and other specialists in research programs. Many aspects of AKI are still unknown. There is a general consensus about the weakness of the standard criteria for AKI, and the search for the "kidney troponin" is ongoing. Several AKI biomarkers have been evaluated in past years and, more recently, cell-cycle arrest biomarkers have been validated as an early alarm. However, many questions remain about which populations would benefit from such testing, as well as the methods for using these biomarkers in clinical practice. Accurate clinical trials of the biomarkers are not possible until these questions are answered.

There is also discordance about whether or not early initiation of RRT in critically ill patients results in better outcomes (6, 7). In addition, much is still unknown about the pathogenesis of AKI (e.g., septic-AKI vs. non-septic AKI) and the non-pharmacological management of AKI (e.g., preferred type and amount of fluid for resuscitation). Research collaboration between intensivists and nephrologists will be critical in improving outcomes in AKI patients.

Many exciting educational opportunities for fellows and young nephrologists are available in critical care nephrology (Table 1). Several multidisciplinary training programs and courses on topics such as AKI and continuous RRT are available around the world. Attending these courses could not only improve AKI knowledge and increase awareness of critical care nephrology, but it could also help foster interest in the field for future nephrology trainees.

Critical care nephrology is an emerging and challenging area in our field that deserves our continued attention. The new generation of nephrologists must be ready to collaborate with intensivists to improve the care of ICU patients, educate multidisciplinary teams, develop procedures and protocols, and perform basic and clinical research to better understand AKI pathophysiology.

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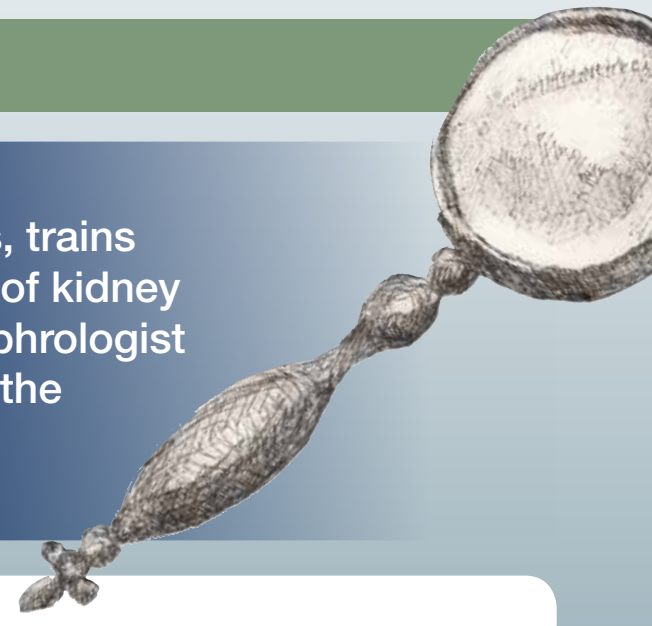
Table 1. Conference and training opportunities focusing on AKI and critical care nephrology

Conferences
AKI & CRRT, Annual International Conference in Advances in Critical Care Nephrology; University of California, San Diego, CA
Annual Vicenza Course on AKI & CRRT, IRRIV International Renal Research Institute; Vicenza, Italy
Critical Care Nephrology: Update; Early Program of American Society of Nephrology (ASN) meeting
Annual AKI Symposium, The Center for Critical Care Nephrology, University of Pittsburgh, PA
International Symposium on AKI in Children; Center for Acute Care Nephrology, Cincinnati, OH
International Conference on Pediatric Continuous Renal Replacement Therapy (PCRRT)
Annual UAB CRRT Academy Symposium, University of Alabama at Birmingham
Fellowships and Training Programs
Nephrology/Critical Care Track, UT Southwestern Medical Center, Dallas, TX
Critical Care Nephrology Fellowship, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA
Pediatric Critical Care Nephrology Fellowship, Baylor College of Medicine, Houston, TX
Combined Nephrology – Critical Care Medicine Track, Allegheny General Hospital, Pittsburgh, PA
Critical Care Nephrology and Acute Renal Failure, Mayo Clinic, Division of Nephrology and Hypertension, Rochester, MN
Critical Care Nephrology Curriculum, Division of Nephrology, University of Maryland School of Medicine, Baltimore, MD
Nephrology/Critical Care Track, Henry Ford Health System, Detroit, MI

Detective Nephron

Detective Nephron, world-renowned for expert analytical skills, trains budding physician-detectives on the diagnosis and treatment of kidney diseases. Wildly waving a stack of paper records, budding nephrologist L.O. Henle and medical student Ms. Curious Tubule run down the hall toward Detective Nephron's office.



Henle (*with a smile*): A case for you sir!

The detective sits facing the window. He has been experiencing some gastric reflux lately and has given up coffee. He is disgruntled as he misses it.

Nephron (*curious*): Finally, something that might put an end to this utter boredom.

Henle It's a case of acute kidney injury (AKI).

Nephron (*smiling*): Ah yes. That's what they call it these days. Gone are the days of renal failure and kidney failure. God forbid that we use big words like "failure" these days. "Injury"… oh well.

Tubule So this is a 70-year-old male with really no past medical history and now noted to have some elevation in serum creatinine for the past 3 months or so. It's 2.3 mg/dL. It was apparently normal 5 months ago with a level of 0.8 mg/dL per records.

Nephron (*interrupting*): I don't need any of that information. Do you have a urinalysis?

Tubule He was found to have a serum bicarbonate of 8 mmol/L. His sodium was 140 mmol/L, chloride was 103 mmol/L. That gives him a serum anion gap of….

Nephron (*surprised look*) …

Tubule . . . Yes, it's bland, no red cells, no white cells, no casts, nothing at all.

Henle Also, we even went ahead and did a spot urinary protein/creatinine ratio and it was 0.2. Fractional excretion of sodium (FeNa) was >1%.

Nephron Interesting. So let's start from the basics!

Tubule Usually, AKI can be looked at from three angles—pre-renal, intra-renal and post-renal.

Nephron Remember there are only two body systems in my nephrocentric mind … renal and extra-renal. So is the problem in the kidney or out of the kidney?

Tubule Well, FeNa points toward an intrinsic pathology.

Henle (*stepping in*): Precisely.

Nephron Is the patient an oliguric Caucasian man?

Tubule (*not chuckling*): Huh?

Nephron (*laughing loudly*): The original studies in which a condition was called "pre-renal" based on FeNa were done by Schrier et al. They were in oliguric Caucasian men. So if a case involves chronic kidney disease, women, or non-oliguric AKI, the value of FeNa is not known. But we still use it in practice… as long as you know its limitations.

Pause.

Nephron Volume exam?

Tubule (*happy*): Euvolemic.

Nephron Trial of fluids?

Tubule Yes, of course. It would be too easy for you otherwise! And no improvement with volume repletion.

Nephron So in a patient who is not fluid overloaded, a fluid challenge and no improvement in kidney function rules out pre-renal. This is even better than the FeNa!

Henle He also has no post-renal issues because he has no post-void residual and no hydronephrosis on my bedside point-of-care ultrasound exam.

Nephron (*jumping in*): Good work on the point-of-care ultrasound exam, Henle. It's about time nephrologists do their own imaging. How small or big are his kidneys?

Tubule 13 cm on the right and 12.5 cm on the left.

Henle (*confident*): Well, given he is 5 feet 6 inches tall, those kidneys sound a bit too big to me. He is not a diabetic and he has no known HIV disease to my knowledge. To me that size is concerning!

Nephron So what is your differential for large kidneys?

Henle As I mentioned, diabetic nephropathy, HIV-related disease, acute interstitial nephritis (AIN), and/or infiltrative diseases of some kind such as leukemias or amyloidosis.

Tubule He is not on any medications except a multivitamin. He denies taking any nonsteroidal pain medications (NSAIDS). His last HbA1c was 5.4. He has a normal white count, normal hemoglobin, and does not endorse bone pain.

Nephron So let's end this confusion once and for all. He is not a diabetic, nor does he have any signs of a malignancy. He is not on any obvious medications causing AIN, nor does he have any chronic viral diseases such as HIV.

Henle Hmmm. Could he have amyloidosis? But he has no signs of nephrotic syndrome? He has no edema on exam, and he has normal albumin, normal cholesterol, and no signs of proteinuria.

Nephron (*with a smirk*): Could he have vascular amyloidosis?

Tubule (*relieved*): Well, he could but his free light chain ratio and serum immunofixation are in range for his kidney dysfunction.

Nephron What is his urine glucose?

Henle (*jumping in*): Not elevated and his electrolytes don't suggest any signs of Fanconi syndrome either.

Nephron What do we think?

Tubule With all of the above workup negative, I feel lost and confused. Perhaps we have to move to a kidney biopsy?

Nephron Let's go back to an older technique we call "history taking." I think that he is not telling us everything … or "we" are not asking the right questions. Take a more detailed history on any new medications, herbals, over the counter medications, and so forth.

Tubule and Henle leave the room.

Tubule (*returning*): Nothing. The only symptom he had a few months ago was some gastric reflux, for which he took some over the counter omeprazole and calcium carbonate with some relief. He takes them occasionally and in some cases daily. But no real nephrotoxic medications.

Henle (*jumping in*): Really? He is taking a proton pump inhibitor (PPI)?

Tubule So?

Nephron (*excitement in his eyes*): PPIs are increasingly being associated with AKI from AIN and eventually CKD as well.

The detective's eyes brighten as he suddenly looks up at Ms. Tubule for a split second, then backs down again.

Nephron Fascinating.

Henle and Ms. Tubule appear puzzled.

Nephron Please get a kidney biopsy!

Tubule and Henle return a day later.

Tubule It is AIN!

Henle We told him to stop the omeprazole.

Nephron So you are sure it is the PPI causing his AKI or CKD?

Tubule I think so!

Nephron (*continues on*): While PPIs have an excellent overall safety profile, concerns have been raised about recent adverse renal events, specifically their association with AIN and hypomagnesemia. While only a small proportion of patients develop AIN from PPIs, these drugs are now a common cause of drug-induced AIN in the developed world due to their widespread and prolonged use. PPI-induced AIN is often subtle and without systemic allergic manifestations; subclinical, leading to gradually progressive kidney failure; delayed, median time from drug initiation to AIN diagnosis often exceeds 6 months; and often unsuspected prior to a biopsy.

Henle (*showing off from a review article he just read*): It is not until recently that new studies performed by many around the world have demonstrated this association. First, two population-based studies described a higher risk of AIN and AKI in patients prescribed PPIs as opposed to H2 blockers such as ranitidine. Second, evidence suggests that on intermediate to longer term follow-up, patients have a lower estimated glomerular filtration rate (eGFR) after an episode of PPI-induced AIN and patients prescribed PPIs have higher CKD risk.

Tubule *(curious)*: Is it a class effect?

Nephron Yes. Possibly.

Nephron Yes, I think it is a class effect. Moreover, new users of PPIs in comparison to H2 blocker users had a higher risk of eGFR less than 60 mL/min/1.73 m^2, had a greater than 30% decrease in eGFR, and end stage kidney disease (ESKD) with greater than 50% decrease in eGFR after adjusting numerous factors and co-morbidities of participants.

Henle Why does this happen? Is it just allergic?

Nephron The purported mechanism of PPI-induced nephrotoxicity is either from impaired lysosomal acidification and proteostasis or due to hypomagnesemia, both of them causing increased oxidative stress, dysfunction, and accelerated wear and tear damage in human renal endothelial cells.

Tubule So if I had to summarize, PPIs can cause AIN, CKD, and if continued and not interrupted, can lead to ESKD as well. In addition, we know the electrolyte disorder of hypomagnesemia is linked with it as well.

Nephron Precisely!

Henle In causing AIN, how do PPIs compare to antibiotics and NSAIDS?

Nephron Excellent question! Let me take you on a historical adventure. If the year was 1965, probably the only known AIN-causing medication class was antibiotics. If the year was 1978 or 1981, NSAIDS started to trickle in. In the late 1980s to early 2000s, NSAIDS overtook antibiotics as the number 1 cause of drug-induced AIN. And if you take the years from the mid-2000s until now, PPIs and antibiotics lead the way in the number of drug-induced AIN cases followed by NSAIDS. Keep in mind that "evidence based" or "not evidence based," many patients are placed on PPIs from hospital discharges, as it is part of some form of "prophylaxis." Unfortunately, perhaps some never discontinue their use. Be vigilant my detectives! When needed, these agents are a great treatment for ulcers, *H. pylori*, and gastric reflux, but so are NSAIDS for severe pain. Like everything, we have to watch for any known effects on the kidney in our nephrocentric minds!

Tubule Fascinating.

Nephron Very well then. And so, yet again, the kidney is a bystander here and commonly used drugs can be a missed cause of CKD and ESKD. Good work my pupils. Let's go before this drug causes a stress ulcer in all nephrologists out there.

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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)

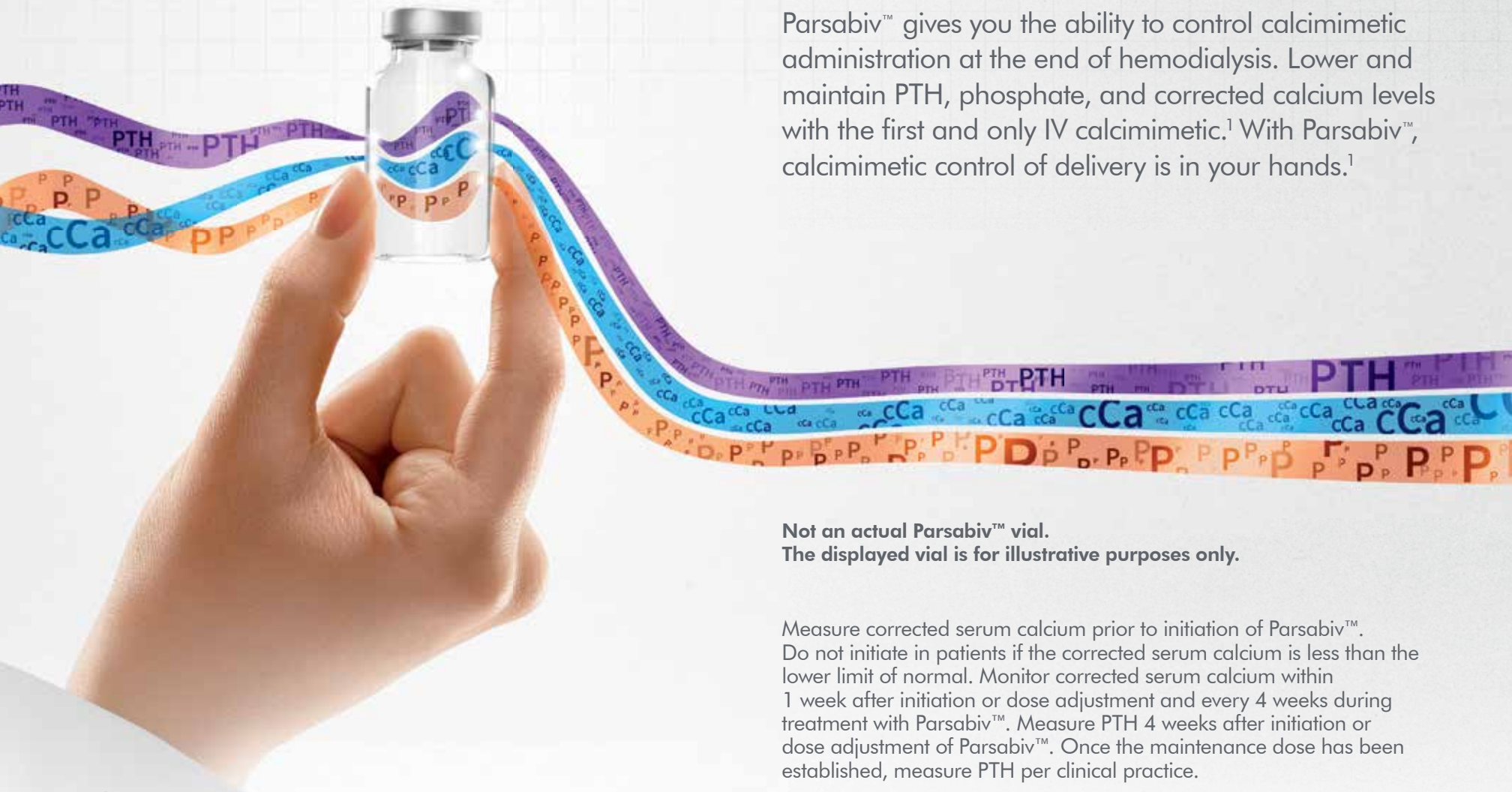
Manufactured for:
KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

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

02-17

Parsabiv™—

the control of calcimimetic delivery you've always wanted, the sustained lowering of sHPT lab values your patients deserve[1]



Parsabiv™ gives you the ability to control calcimimetic administration at the end of hemodialysis. Lower and maintain PTH, phosphate, and corrected calcium levels with the first and only IV calcimimetic.[1] With Parsabiv™, calcimimetic control of delivery is in your hands.[1]

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

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.

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

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

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

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

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

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

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

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone.

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.