ASN
Kidney News
January 2018 | Vol. 10, Number 1

Studies Find Persistent, Worsening Disparities in US Pre-ESRD Care

By Bridget M. Kuehn

Despite growing awareness of racial disparities in kidney care, 2 recent studies found that pre-dialysis or pre–end stage renal disease (ESRD) care for minorities hasn't improved and may actually be getting worse.

Data from the US Renal Data System (USRDS) show that over the last decade access to predialysis care for minorities actually worsened, according to Tanjala Purnell, PhD, MPH, an assistant professor of surgery in the division of transplantation at Johns Hopkins University School of Medicine. A second study found that fewer black patients are getting pre-ESRD care, and that black patients who do receive pre-ESRD care seem to benefit more than white patients. Both studies were presented at Kidney Week 2017.

"Clinicians need to be aware this is a problem we are still struggling to deal with," Purnell said.

Care by a nephrologist is recommended for patients in the later stages of chronic kidney disease, explained Purnell. Nephrology care improves access to transplant. It also ensures that patients start dialysis with fistula and has been linked with better quality of life and longer lifespans for patients receiving dialysis, she said.

Purnell and her colleagues analyzed data from the USRDS on 934,599 adults who initiated chronic dialysis between 2005 and 2015. They found that racial and ethnic disparities in pre-dialysis care actually worsened. Between 2005 and 2007, black patients were 14% less likely than whites to receive care by a nephrologist prior to starting dialysis, and Hispanic patients were 22% less likely than whites to receive such care. Between 2008 and 2010, blacks were 14% less likely to receive such care and Hispanics were 30% less likely. More recently, between 2010 and 2013 those figures declined further with black patients 19% and Hispanic patients 29% less likely to receive pre-dialysis care.

"We were disappointed and surprised," said Purnell. She and her colleagues have ruled out possible explanations like difference in access to primary care or insurance among subgroups of minority patients. Even older minority patients with Medicare are less likely to get the recommended pre-dialysis care. "It's across he board," she said. The one exception was young patients aged 18 to 24.

Purnell and her colleagues plan to meet with their nephrologist collaborators and to discuss the results with dialysis patients to try to understand what might be driving this trend and how to ensure more patients get pre-dialysis care.

"We want to bring patients to the table and find out what works and what doesn't," Purnell said.

Previous work by Purnell and her colleagues found that some patients, particularly those who are not having

Continued on page 3

Survival Rates Are Improving for US Patients with Kidney Failure

Individuals with end stage renal disease (ESRD) have a very high risk of premature death, but a new analysis indicates that their excess risk of all-cause mortality—over and above the risk in the general population—decreased significantly between 1995 and 2013 in the United States. The findings, which come from a study appearing in an upcoming issue of the *Clinical Journal of the American Society of Nephrology*, are encouraging and suggest that efforts to improve care for patients with kidney failure have resulted in improved survival.

Although registry data indicate that survival of patients with ESRD has improved in recent decades, general population survival has also benefited from public health efforts (such as smoking prevention) and medical advances (such as improved cardiovascular interventions).

To see if the longer life expectancy observed in ESRD registries simply reflects improved general population survival, a team led by Bethany Foster, MD, MSCE, of Montreal Children's Hospital and the Research Institute of the McGill University Health Centre, and Benjamin Laskin, MD, of The Children's Hospital of Philadelphia, applied time-dependent relative survival modeling to examine changes over time in the excess risk of death in persons with ESRD. Excess risk was defined as the mortal-

Continued on page 2

Inside

Survival Rates

Continued from page 1

ity risk in the ESRD population minus the expected risk in the age-, sex-, race-, and calendar-year matched general population.

In the analysis of information from the United States Renal Data System (USRDS) on almost 2 million children and adults diagnosed with ESRD from 1995 to 2013, the change over any 5-year interval in the excess risk of ESRD-related death varied by age, with decreases from 12% for ≥65 year olds to 27% for 0 to 14 year olds. Decreases in excess mortality over time were observed for all ages and both during treatment with dialysis and during time with a functioning kidney transplant, with the largest relative improvements observed for the youngest individuals with a functioning kidney transplant. Absolute decreases in excess ESRD-related mortality were greatest for the oldest patients.

"We showed that all age groups have had significant improvements in mortality risk over the past 22 years. Some of the improvements were due to improved access to kidney transplantation and to longer survival of kidney transplants, but there were also improvements that can only be attributed to improvements in the care provided to people treated with dialysis and to those with kidney transplants," said Foster. "This is important given the huge investment of resources in caring for these patients; we have shown that these investments have made a difference."

Foster noted that the investigators expected to find decreased mortality rates for all age groups except those in late adolescence and early young adulthood. "We expected this for several reasons. First, this age group often has difficulty adhering to the recommended treatments. Therefore, it was possible that they would not experience the same benefits from therapies as other age groups," she said. "Second, there may be a breakdown in the continuity of care when young people are transferred from a pediatric health care facility to an adult care facility that contribute to poorer outcomes. We discovered that young people in this age group had no improvements in mortality risk between 1995 and 2006 (unlike all other age groups), but started to have significant improvements after 2006. This may be because health care professionals became more sensitized to these problems in the early 2000s and have changed the way they care for these young people."

Although individuals with ESRD still have much higher risks of early death than people in the general population, it appears that the gap is gradually closing. "Things are getting better for all age groups. But one of the best ways to improve health in people with kidney failure is for them to get a kidney transplant, and the limited supply of suitable organs is still a major impediment to more progress in outcomes for people with kidney failure, Foster said. "Everyone needs to think about organ donation and sign their organ donor cards."

In an accompanying editorial, Kirsten Johansen, MD, of the University of California, San Francisco, noted that the study raises more questions than it answers, and it should provide a framework for future studies that are needed to examine which changes in practice patterns and clinical care may contribute to changes in mortality rates in patients with ESRD. "Analyses of differences in outcomes over time and across geographic regions are powerful tools we can apply to gain an understanding of the impact of changes or variations in practices on survival," she wrote. She also stressed the need to fully understand why the improvement occurred so that improvements can continue and future increases in mortality can be prevented. Newer data from 2013 to 2015 showed that the mortality rate among patients with ESRD stabilized or even increased, and the mortality rate in the United States as a whole has demonstrated a similar uptick.

According to the most recent data by the USRDS, adjusted mortality rates in 2015 for ESRD, dialysis, and transplant patients were 136, 166, and 29, per 1000 patient-years. Five-year survival rose from 36% in 2002 to 42% in 2010 among hemodialysis patients, from 42% to 52% among peritoneal dialysis patients, from 69% to 76% among deceased donor transplant patients, and from 77% to 88% among living donor transplant patients. Johansen noted that despite increases in life expectancy in recent years, patients with ESRD have lower 5-year survival rates than patients with cancer.

Study co-authors include Mark Mitsnefes, MD, Xun Zhang, PhD, and Mourad Dahhou, MSc.

The article, entitled "Changes in Excess Mortality from End-Stage Renal Disease in the United States from 1995-2013," and the editorial, entitled "Life Expectancy Gains for Patients with ESRD," are online at http://cjasn.asnjournals.org/.

Worsening Disparities

Continued from page 1

symptoms, may not want to see a specialist because they feel that would be accepting they will get worse.

"In the African American and Hispanic communities, we may need to educate patients about the benefit of seeing a specialist before they get sick," she said. Purnell suggested that more collaborative models of care where primary care physicians work more closely with nephrologists may also help.

A second study co-authored by Jennifer Bragg-Gresham, MS, PhD, an assistant research scientist at the Kidney Epidemiology and Cost Center at the University of Michigan, and her colleagues looked at USRDS data on 791,248 patients receiving dialysis who began treatment between 2006 and 2015. They found that 53.1% of black patients received pre-ESRD care compared with 60.1% of white patients. All patients receiving pre-ESRD care had a lower risk of death, but black patients appeared to benefit disproportionately, with a hazard ratio of death of 0.73 compared with 0.81 for white patients.

"The reason why pre-ESRD care is associated with superior survival among blacks is not clear," said Bragg-Gresham. "However, we speculate that either the health status of black patients reaching dialysis is better than their white counterparts or they are biologically more responsive to treatments given to them during their care."

She noted that previous studies have shown that black patients have better survival than white patients on dialysis, which may partly be explained by the fact that on average black patients start dialysis at a younger age, have fewer comorbid conditions, better nutritional status, and better laboratory measures than white patients. Bragg-Gresham and her colleagues plan to expand their analysis to look at whether disparities exist for other races and ethnicities.

Vanessa Grubbs, MD, associate professor at the University of San Francisco in the division of nephrology, said she is not surprised by the persistent disparities in kidney care. She said most efforts to reduce disparities have been very narrowly targeted and don't address larger societal issues like systemic racism.

"We tend to think everything that improves health happens in the hospital," she said. "We aren't looking at the larger things happening in this country."

Physicians often treat race as a biological construct rather than a social one, which may also contribute to disparities, she noted. For example, race-based adjustments to glomerular filtration rate, which are intended to account for higher than average muscle mass among African Americans, may delay referral to transplant for months or even years.

"That can definitely affect care," Grubbs said.

Physicians often cite distrust of health care among minorities as a reason for disparities in care, she said. But the number of minority physicians still lags, and many physicians don't address their patients' day-to-day experiences with racism or their family's history of dealing with institutional racism. Addressing those issues and reassuring patients that the care they are receiving is the same they would give a family member can help, she said.

"No one really speaks to the elephant in the room," Grubbs said. "It would be helpful if physicians just called it out."

"Racial and Ethnic Disparities in Access to Predialysis Nephrology Care in the US: Have We Made Any Progress over the Last Decade?" (Abstract SA-OR014)

"Pre-ESRD Nephrology Care Associated with Larger Survival Benefit for Black Compared to White Patients on Hemodialysis (HD)" (Abstract SA-OR037)

Perceived Discrimination and Social Disadvantage May Adversely Affect Kidney Health

By David White

Shedding further light on disparities in, and the impact of discrimination on, kidney disease rates and care was the focus of a Kidney Week 2017 session titled "Context Is King: Neighborhood and Social Networks as a Risk Factor for Chronic Disease."

Many studies about income and race disparities in the incidence of kidney diseases are well known, including higher incidence rates for lower income blacks and whites (1) and the heightened proportion of ESRD incidence across neighborhood poverty levels (2).

Deidra C. Crews, MD, ScM, FASN, outlined some of the more nuanced research on this subject in her presentation, "Disadvantage, Physiologic Stress, and Kidney Diseases in the United States," including work she and others conducted in the REGARDS study (REasons for Geographic And Racial Differences in Stroke study (3). In REGARDS, researchers examined the effect of the density of county-level poverty on ESRD risk, that is, whether or not poor counties being surrounded by other poor counties versus by more affluent counties affected ESRD risk. They found that greater density of county-level poverty was associated with greater individual risk of ESRD, but that household income was a stronger predictor of an individual's ESRD risk.

An often-cited finding that, overall, blacks survive dialysis at higher rates than whites led researchers to examine survival rates among younger (<50 years of age) blacks and whites of both higher and lower socioeconomic status (SES) (4). Over five years of follow-up, beginning after dialysis initiation, both the higher and lower SES young blacks fared worse than their white counterparts. In a study focused on earlier kidney disease, Crews and colleagues found higher rates of albuminuria in those with lower incomes (5). Although the association with income was noted for both white and black study participants, the association was strongest among blacks.

Perceived discrimination based on race or gender

Another study by Crews and colleagues looked at perceived discrimination and longitudinal change in kidney function in urban adults. The study included 1620 participants with preserved baseline kidney function measured by estimated glomerular filtration rate (eGFR): 662 whites and 958 African Americans aged 30–64 years. Perceived racial and gender discrimination were self-reported, along with a general measure of experience of discrimination (6). Overall, high perceived gender discrimination was associated with lower baseline and follow-up eGFR. Among white women, a high experience of discrimination was associated with lower baseline eGFR, and among African American women, both perceived racial and gender discrimination were linked to lower follow-up eGFR.

Saban K et al. diagrammed the relation of cumulative life stressors to allostatic load—the cumulative impact of physiological wear and tear related to maladaptive stress patterns that predispose individuals to disease (7). Allostatic load is one example of how social disadvantage "gets under the skin," Crews said. She noted that social disadvantage is a strong risk factor for kidney diseases, and that even perceived discrimination is associated with kidney function decline among specific race/gender groups. Crews called for studies examining biological and behavioral mediators of social disadvantage and kidney outcomes, intervention studies targeting these mediators, and advocacy for policies supporting socially disadvantaged individuals' health.

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ASN Kidney News is published by the American Society of Nephrology
1510 H Street NW, Suite 800, Washington, DC 20005. Phone: 202-640-4660

www.asn-online.org

Postmaster: Please send address changes to *ASN Kidney News*, c/o Customer Service, American Society of Nephrology 1510 H Street NW, Suite 800, Washington, DC 20005.

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

ASN Kidney News (ISSN print 1943-8044 and online 1943-8052) is an official publication of the American Society of Nephrology, 1510 H Street NW #800, Washington DC 20005, and is published monthly 11 times a year except November. Periodicals postage paid at Washington, DC and at additional mailing offices. Subscription rates: $12 per year. To order, please email bhenkel@asn-online.org. Subscription prices subject to change. Annual ASN membership dues include $12 for *ASN Kidney News* subscription.

A Fresh Look for *Kidney News*

We are very proud to bring you *Kidney News*, issue after issue.

Kidney News strives to present you what is new and exciting in the world of kidney health and disease, and to support that information with reviews and opinions on how to usher that news into present day understanding and action.

As we approach a decade of serving our readership with the very best of kidney news, perspectives, and observations, we are making some changes. With this issue, we present a fresh new design for the magazine, including a more eye-catching cover and easier navigation. You will find that the paper itself still looks and feels familiar. However, we hope you will be struck by the improved features. The table of contents has been refreshed to make it easier to find the information you desire. And we wished this to become a more visual experience, so illustrations and supporting figures and tables will be more prominent and frequent. We hope the new colors and fresher formatting are appealing as well.

Kidney News remains committed to delivering the best, most expert, and accurate reporting of the news and events that shape the world of nephrology to keep you, our highly valued readers, informed, entertained, and involved. Please let us know how we may serve you better in this coming year.

—Richard Lafayette, MD, Editor-in-Chief, Kidney News

Exercise during Dialysis May Reduce Length of Hospital Stay

Exercise during dialysis reduces the length of stay for subsequent hospitalizations by three days, according to a recent study.

Patients on dialysis are often sedentary, which may contribute to poor outcomes. Yet efforts to engage patients in exercise outside of dialysis sessions have high drop-out rates, said Daniel March, PhD, a clinical trial facilitator at the University of Leicester in the United Kingdom. This has led to several small studies of whether engaging patients in exercise during dialysis would improve patient outcomes. So far, they have suggested that exercise is feasible and may improve patients' physical condition (Anding K, et al. *BMJ Open* 2015; 5:e008709 and de Lima MC, et al. *Ren Fail* 2013; 35:697–704.).

Although no large, long-term randomized, controlled trials have yet been published, two such trials of exercise during dialysis are currently underway in the United Kingdom. The PrEscription of Intra-Dialytic Exercise to Improve quAlity of Life in Patients with Chronic Kidney Disease (PEDAL) trial will enroll 380 hemodialysis patients and randomize them to either an 8-month program of cycling and muscle conditioning during dialysis or usual care. The CYCLE-HD trial will cluster randomize 130 hemodialysis patients to either three 30-minute sessions of cycling during dialysis a week or usual care (Graham-Brown MPM, et al. *BMC Nephrol* 2016; 17:69). The trial will examine the effects on cardiac structure and function.

March and his colleagues analyzed data on a subset of 35 patients (14 in the exercise group and 21 from the usual care group) from the CYCLE-HD trial. The rate of hospital admissions didn't change for the exercise group during the study, but the control group experienced a small drop in admissions. There was, however, a large difference in the length of stay between the groups. The length of stay dropped by 3 days or 73% among the exercise group and 11% among the control group. This advantage declined in the 6 months after the trial ended. The team presented their findings at Kidney Week 2017 ("A six month program of intradialytic exercise is effective in reducing length of hospital stay in hemodialysis patients," Poster 787).

March said it wasn't clear why there wasn't an effect of exercise on admissions. He noted it could be that the study didn't have an adequate number of patients to see a difference. But he suggested greater fitness among the exercise group may have explained their earlier discharge.

"We found that exercise during dialysis may reduce health care utilization, but we still need stronger evidence," he said. The group plans to continue collecting data from more trial participants. The trials themselves may also answer key questions about the effects on patient outcomes, cardiac health, quality of life, and physical function.

Kenneth Wilund, PhD, associate professor of kinesiology and community health at the University of Illinois at Urbana-Champaign, said the study provides an important "proof of concept" for the field, which has struggled to find ways to reimburse exercise specialists working with kidney disease patients.

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.

Distributed by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015
Revised: August 2017

ULR015 R6_Brf. L-TXF-0817-2

ASN President's Column

Mark D. Okusa, MD, FASN

The ASN communications team interviewed ASN President Mark D. Okusa, MD, FASN, about challenges and goals for nephrology in the near future.

WHAT ISSUES OR CHALLENGES DO YOU ANTICIPATE ASN AND THE DISCIPLINE OF NEPHROLOGY WILL NEED TO ADDRESS OVER THE COURSE OF THE NEXT YEAR?

The discipline of nephrology is at a crossroads. We face challenges that in some instances are common to other professional societies (e.g., health care delivery) and in other instances are unique to nephrology. ASN continues to staunchly advocate for the discipline of nephrology, establishing programs that undergird the future of nephrology.

First, our workforce or "pipeline" continues to remain a major concern. ASN has made major efforts toward improving the workforce, including sponsoring survey studies in collaboration with the George Washington University. Programs such as Kidney STARS and Kidney TREKS (and TREKS 2 in Chicago), to name a few, are ongoing efforts to continue to build the pipeline.

Nephrology as a profession has been affected by many factors including but not limited to the perception (rightly or wrongly) that nephrologists work harder and are paid less; care for sicker patients; and are challenged as a result of ceding to other disciplines nephrology procedures such as CRRT, kidney biopsies, and placement of dialysis catheters. The challenge facing many of us including ASN is how we define the practice of nephrology moving forward. What is the extent of nephrology practice? How do we assert the value of nephrology to health and science professionals, health care systems, and other stakeholders to ensure high-quality care for patients? Addressing these issues will be key to our future and to ensuring the health of our profession. I'm optimistic that through our collective efforts, both through programmatic and grassroots efforts at each institution and by every nephrologist, we will continue to maintain a vibrant subspecialty.

The 2017 Survey of Nephrology Fellows conducted by the George Washington University Health Workforce Institute and commissioned by ASN offered good news and perhaps a glimpse of the future. The survey report noted that in 2017 the job market improved for new nephrologists. So what do we need to do to accomplish the goal of reasserting the value of nephrology? We need to:

1. Define the scope of nephrology practice and articulate a vision for nephrology in the future.
2. Promote the development of a comprehensive kidney care model through collaboration with other societies and organizations.
3. Ensure exceptional kidney care through: i) educating trainees, ii) empowering patients in their care, and iii) implementing recommendations from the Nephrologists Transforming Dialysis Safety (NTDS) Project, a collaboration between ASN and the FDA, to reduce infections in dialysis patients.
4. Support the Kidney Health Initiative.
5. Advocate for NIH support for funding for kidney research at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of $150,000,000 annually for 10 years.
6. Champion the US Department of Health and Human Services' efforts to develop a Kidney Innovation Accelerator.

WHAT DO YOU FEEL CAN OR SHOULD BE DONE TO IMPROVE ASN'S MISSION AND GOALS?

Here is one example of how we are working to improve ASN's mission and goals. Over the past year ASN through implementation of the Strategic Plan has transitioned from advisory groups to ASN Communities. There are various communities including, to name a few, AKI, Basic Science, Patient Care Q & A, and Women's Health and Research. ASN members participate in discussion, networking, and collaborations on various topics. By reaching out to the entire membership of 17,000, ASN has the unique opportunity to learn from its members, which will allow ASN to better serve its membership, mission, and goals. We have already begun this process. Involvement by membership is robust, and the popularity of ASN Communities continues to grow. Thus with continued collaboration and networking facilitated by ASN Communities, the society overall will benefit.

> **"We are on the crest of a wave that will not only improve the lives of kidney patients but reinvigorate the field of nephrology."**

WHAT DO YOU HOPE TO ACCOMPLISH AS ASN PRESIDENT?

When I became Division Chief at the University of Virginia, my wife, Diane, gave me a large framed original photograph of a bridge that I placed on the wall of my office. This is a reminder of one of my lifelong career goals or strategies: it is important to build bridges for effective leadership and to accomplish one's goals. Over the past few years, ASN has begun to do just that. We have formed a number of strong collaborations with various international societies to initiate projects that will enhance the global health of kidney patients as well as enhance education and research. Over the next year I would like to continue to build bridges with these other societies within the US and globally. I would also like to ensure that we have a forum to listen to our patients and advocate on their behalf. This will necessitate strong support of ASN's advocacy efforts to apprise policymakers and administrators on Capitol Hill, at CMS, and at NIH regarding all aspects to improve outcomes and quality of life of patients with kidney diseases. Kidney diseases do not have borders, and collaboration and synergy will be key moving forward.

Disaster preparedness is another area in which I believe ASN can continue to lead. Recently the US has been besieged with a number of disasters, including those in Houston, Florida, and Puerto Rico. Numerous kidney patients were affected, and various organizations were challenged with providing dialysis and kidney care. ASN was instrumental in assisting with the coordination of care, organizing daily conference calls among key stakeholders and assisting the American Kidney Fund in raising financial support for those affected. As we have done in the past with disasters in Haiti and New Orleans, we will need to redouble our efforts in maintaining disaster preparedness in the event of future disasters.

WHAT ARE YOU MOST EXCITED ABOUT REGARDING ASN AND THE FUTURE OF NEPHROLOGY?

I am most excited about leading the society over the next year in innovation and discovery. Historically there has been very little advancement and innovation in the kidney space. There has been a lack of investment in research and development and there seems to be a lack of urgency. For example, there are no FDA-approved drugs for AKI, few drugs for treatment of CKD, and a lack of innovation in dialysis therapies. But new initiatives are changing the landscape of nephrology today! The Kidney Accelerator is a public-private partnership to incentivize the accelerated development and commercialization of technologies to reduce the number of patients with ESRD or to improve the quality of life of patients while on dialysis. ASN will participate in this multi-stakeholder effort to innovate in the kidney space. Next is the NIH/NIDDK Kidney Precision Medicine Project (KPMP). A critical barrier to advances in AKI/CKD therapies is the use of non-predictive animal models. The goal of KPMP is to obtain human kidney biopsies in order to define subgroup phenotypes, to identify critical pathways and targets for novel therapies, and ultimately to deliver individualized care for patients with kidney diseases. I am also excited about the Kidney Health Initiative, a partnership between the ASN and FDA to improve kidney health and safety, and the NTDS program, a project funded by the FDA to reduce infections in dialysis patients.

WHAT ELSE WOULD YOU LIKE TO SAY?

We are on the "crest of a wave" that will not only improve the lives of kidney patients but reinvigorate the field of nephrology. I would like to let our kidney patients know that we are here to serve you and improve your care and quality of life. As President of the ASN, I will commit my effort to ensuring that we achieve this aim.

Frequent Long Dialysis : Why Do Length and Frequency Help?

By Peter G. Kerr

Most dialysis in the developed world occurs as three sessions per week, typically about 4 hours per session. This provides us with fairly dismal outcomes—yes, we keep people alive for a period of time (hopefully for some, until they are transplanted)—but our outcomes are worse than breast cancer. It is not enough to claim that there have been improvements; we still have a long way to go. Most people working in nephrology accept that this is not something we should sit back and accept—we must strive for improved mortality for our patients. The question arises then: Is it our regimen of dialysis delivery that needs improvement? My tenet is yes, and that it needs to change.

Duration of dialysis

The first issue I would like to examine is time—the length of the dialysis session. There is strong observational data supporting the advantage of longer duration of dialysis sessions. The Dialysis Outcomes and Practice Patterns Study in particular draws on a large database representing (by means of random selection of units and patients) dialysis patients from 13 countries. These data demonstrate significantly improved mortality for relatively small changes in session length (compared with 4 hours per session; hazard ratios for death, 1.18 for 3.5 to 4 hours and 0.78 for 4.5 to 5 hours) (1). Similarly, the ANZDATA Registry in Australia showed major improvements in survival for 5 versus 4 hours per session. Unfortunately, the only randomized, controlled trial that examined this—the Hemodialysis Study, which strictly did not test the influence of time but rather, tested Kt/V, achieved the higher Kt/V predominantly by longer session length (mean 29 minutes difference)—did not show a benefit for the higher Kt/V. There are many reasons why this trial failed to show a benefit, many of which have been debated at length, but in terms of time, it may relate to the session length being under 4 hours, even in the high-dose group (2).

The next step up is prolonged dialysis sessions, such as are commonly practiced in nocturnal hemodialysis. Because of the length of session (typically 8 hours), this format is almost exclusively used in the home. Once again, trial evidence is lacking. Observational data from France, Canada, and Australia suggest that long-hours dialysis results in excellent outcomes, but undoubtedly, there is a selection bias, with home hemodialysis patients being younger, fitter, and more motivated than their peers in facilities. The only randomized, controlled trial to examine this was the nocturnal arm of the Frequent Hemodialysis Network (FHN) Trial, but this trial was significantly underpowered, used a composite end point of death and left ventricular hypertrophy (LVH), and is, therefore, difficult to interpret (3).

An important question to ask is why time helps. Several measurable values are improved with longer hours. These include better fluid management via slower ultrafiltration rates with better achievement of target weight, all while avoiding the use of antihypertensive agents. The achievement of target weight improves BP control and at least in some studies, improves LVH. Slower ultrafiltration rates are associated with better outcomes (4). In addition, although small molecule clearances may have little room for further improvement and at least in the Hemodialysis Study were not associated with improved outcomes, the clearance of larger molecules remains time dependent and is significantly improved by longer session length. This includes phosphate, which behaves like a larger molecule due to its hydration shell. Many patients using long-hours dialysis do not require phosphate binders, and some even require phosphate supplementation. As another marker middle molecule, β2-microglobulin clearance is also improved with longer hours and again, associates with better outcomes (2).

Increasing the frequency of dialysis

The other issue is frequency. There are two common approaches to increased frequency. The first is simply the avoidance of the long break. Several observational studies have pointed to the problems of the long break in traditional thrice weekly schedules. The main issue is the predominance of deaths clustered around the end of the long break (e.g., Monday morning in a Monday/Wednesday/Friday schedule), presumably related to volume and solute accumulation with more marked electrolyte abnormalities (5). Adopting a schedule of seven dialysis sessions in 2 weeks with no long break avoids this problem. This schedule is commonly adopted in Australian home hemodialysis, and it is associated with improved outcomes and avoids clustering of deaths on Monday morning. With maintenance of session length within these schedules, there is, of course, also an increase in overall hours by 17% per week.

The other approach is to dialyze five to six times per week with either maintained or even longer dialysis sessions (e.g., as seen in some nocturnal schedules) or "short daily" dialysis. The latter model was tested in the FHN Short Daily Trial and was associated with improved outcomes in the composite end point of that trial (6). In the FHN Trial, this model was conducted in facilities; however, this modality again lends itself to home hemodialysis, especially if simpler dialysis setups are used to diminish the burden of preparation for each dialysis session.

Why does frequency help? Fluid management is improved—the amounts of salt and water accumulated between dialysis sessions are low, and the rate of fluid removal is lower (unless adopting short daily schedules), allowing optimization of fluid status and BP control. Small molecule clearance is also improved (Figure 1), and if more hours per week are achieved, middle molecule clearance is improved.

Is there a downside? Time spent dialyzing is increased, and although nocturnal schedules avoid affecting lifestyle, it may make daytime schedules unpalatable. More frequent fistula needling may result in more access problems, such as was seen in the FHN Trial, but this was not seen in other reports of frequent dialysis. Costs may increase, although alternate-day schedules have only a small effect in this regard. Costs are offset by fewer hospital days.

As a final plea for frequent, long dialysis, let us remember that normal kidneys work 24 hours, 7 days a week, and that patients tend to do very well with a transplant—intuition would tell us that more dialysis is better. Although there may be some qualifications in that statement, I am convinced of a benefit for longer, more frequent dialysis. All of my dialysis patients commence on 5 hours per session three times per week, and all of my home dialysis patients use alternate-day scheduling, predominantly with 6 to 8 hours per (nocturnal) session. Increased hours and frequency are much easier in the home setting, and I am a strong advocate for this. ■

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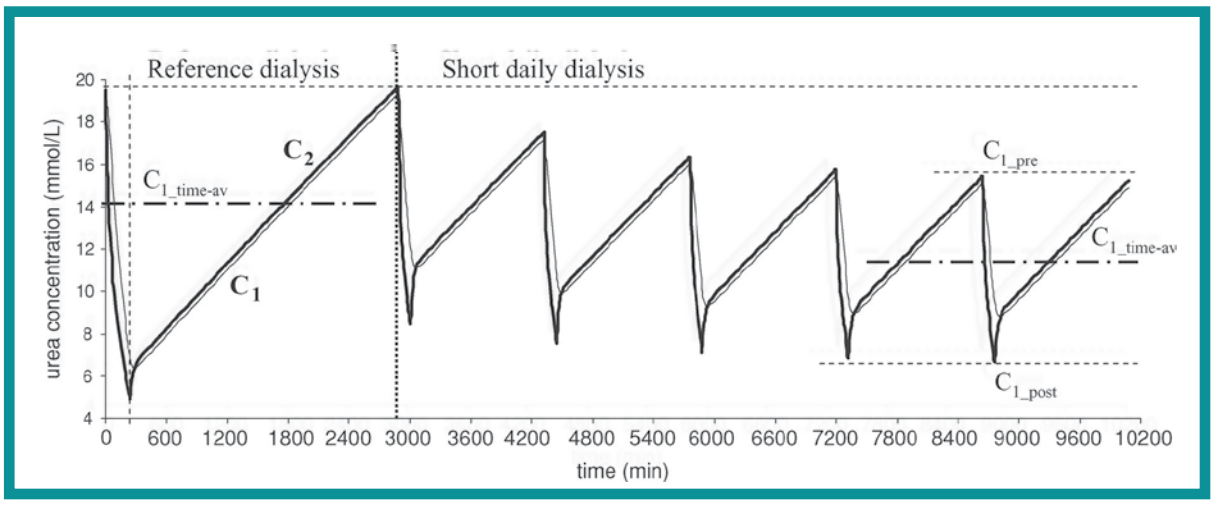
Figure 1. Intradialytic and interdialytic patient concentrations in the plasmatic (C1; bold line) and extraplasmatic (C2; thin line) compartments for a representative patient who was switched from reference dialysis (4 hours, three times per week) to six times per week 2-hour dialysis.



Reprinted with permission, Eloot S, et al. (7).

Barriers, Shortfalls, and Dangers of Frequent Hemodialysis

By Nalinee Saiprasertkit and Christopher T. Chan

Intensive home hemodialysis (IHHD) has become an apparent alternate treatment option for ESRD patients with several clinical benefits. Several studies have shown that, compared with in-center hemodialysis (HD), IHHD provided survival advantage, improvements in BP regulation, regression of left ventricular hypertrophy, restoration of left ventricular ejection fraction, normalization of phosphate control, better quality of life related to kidney disease, decreased recovery time from dialysis treatments, and improved pregnancy outcomes. Quality of sleep and sleep apnea have also been improved, especially in the case of nocturnal home HD (1, 2). Moreover, with more frequent therapies, it also eliminates the weekly 2-day gap between dialysis sessions over the weekends that can adversely affect patient outcomes (3).

In the latest US Renal Data System annual report, more than 80% of chronic patients with ESRD were treated with in-center HD in the majority of reporting countries (4–9). The highest rates of home HD were reported in New Zealand and Australia, with 18% and 9% of dialysis patients, respectively (4–9). Rates of 3% to 6% were seen in Canada, Denmark, Finland, the United Kingdom, Sweden, and The Netherlands (4–9). Despite its noteworthy benefits, the utilization rate of home HD has been low (4). In the latest US Renal Data System annual report, the overall use of home HD in the majority of reporting countries remains low. The highest rates of home HD were reported in New Zealand and Australia, with 18.3% and 9.4% of dialysis patients, respectively (5). Home HD was also used by 3.0% to 6.0 % of dialysis patients in Canada, Denmark, Finland, The Netherlands, Sweden, the United Kingdom, and Scotland. However, in all other countries, home HD either was not provided or was used by fewer than 3% of dialysis patients (5). There are several barriers to the implementation of home HD, including the lack of accessibility, physician experience, patient awareness, and caregiver burnout (1).

Barriers to home HD

Physician-related factors

Despite increasing evidence of benefits of home HD, physician interest in promoting home therapies remains an important challenge. In a recent survey of over 400 health care professionals from all over the world, 56% of respondents had no home HD patients in their units (8). The lack of adequately trained staff members and appropriate funding were identified as major barriers (8). Despite increasing evidence of benefits of home HD, it still remains an uncommon therapy, which is not an accessible option for patients in all countries. Physician interest in promoting home therapies is an important challenge. Nephrologists who lack experience with IHHD might have misconceptions concerning which patients are suitable for this therapy, resulting in IHHD not being offered as an option to the potential patients.

In Australia and New Zealand, where the prevalence of home HD is the highest, all nephrology trainees are required to have both peritoneal dialysis and home HD exposure (7). In contrast, a survey of recent nephrology trainees in the United States showed that only 15.8% of responders felt competent in the care of home HD patients (8). Furthermore, in a United States survey of practicing nephrologists, physicians who were practicing for less than 10 years were more likely to treat patients with home HD, perhaps as a result of more recent publications about the benefits of home HD (9). Adequate home HD exposure should thus be incorporated into all training programs. Indeed, if physicians are not adequately trained or exposed to home HD, they may not be able to effectively promote home therapies.

Patient-related factors

Patient-related factors are divided into two major categories: situational and psychological barriers (10). Situational barriers included inadequate housing or water or inadequate family support; these barriers are difficult or impossible to overcome, even if patients are motivated by the incentives of IHHD. In contrast, psychological barriers may include lack of confidence in their ability to conduct HD at home, fear of self-cannulation, fear of a catastrophic event, and quality of care at home; many studies have shown that these barriers could be settled with more thorough education and preparation as patients approach the need for dialysis (11–15). It is reasonable to assume that all patients are confronted to some degree with multiple concerns. These concerns are almost always surmountable with appropriate support (16).

Psychosocial barriers were also found to determine training and technique outcomes in IHHD. The burden of performing dialysis at home contributed to 16% of failures (17). This finding was also consistent with the finding of the Frequent Hemodialysis Network (FHN) Trial that the most common reason for dropping out was lack of partner/family support followed by patient-perceived burden of performing dialysis at home and inadequate dwelling (10, 18). It is tempting to hypothesize that development of targeted psychological support services could lower feelings of fear and burden and potentially facilitate the successful adoption of home HD.

Caregiver burden

The majority of home HD patients require the help of a family member, partner, or friend, referred to as the caregiver. Analyses of questionnaire data from the FHN Trial identified a high level of perceived caregiver burden as a concern among patients receiving IHHD; more than one half expressed worries about the burden of IHHD on their caregivers (19). This perceived high caregiver burden also significantly associated with low self-reported health-related quality of life scores and depression (19). The findings highlight the need to develop support networks for patients on IHHD that can readily aid the caregiver, reduce the levels of this perceived burden, and step in at times of potential crisis (20).

Risks of IHHD

Despite its important clinical advantages, IHHD also holds the same potential risks of other treatments, including increased vascular access-related events, high rate of buttonhole infection, and rapid decline of residual renal function (RRF).

Vascular access-related events

The increased rates of vascular access interventions and adverse events were shown in the FHN Trial. Patients receiving (in-center) short daily HD had a significantly shorter time to first vascular event (repair, loss, or access-related hospitalization) compared with those in the CHD group (hazard ratio [HR], 1.76; 95% confidence interval [95% CI], 1.11 to 2.79; p = 0.017). Most of these events were vascular access repairs or losses, and a higher risk was observed for patients dialyzing with an arteriovenous fistula (HR, 1.90; 95% CI, 1.11 to 3.25; p = 0.02) (21, 22). A similar trend was observed in the nocturnal cohort, although the time to first access-related event did not reach statistical significance (HR, 1.81; 95% CI, 0.94 to 3.48; p = 0.076) (18, 21). An association between dialysis frequency and vascular access-related events (infections and interventions) was also reported in an observational Australian study (23).

Buttonhole infection

Self-cannulation of arteriovenous access is a challenge for IHHD patients. Given the benefits of ease to delivery, decreased pain, and lower risk of hematoma, the buttonhole cannulation (BH) technique is widely used in IHHD. However, these benefits must be balanced against the increased risk of infection and septic complications. A randomized, controlled trial evaluating BH versus rope ladder cannulation in 140 patients on CHD found a higher rate of *Staphylococcus aureus* bacteremia and fistula abscesses requiring intravenous antibiotics in the group using the BH technique (p = 0.003) (24). An Australian cohort study in nocturnal HD patients also found that patients using the BH technique had an increased risk of septic dialysis-related events compared with those in the CHD group (incidence rate ratio, 3.0; 95% CI, 1.04 to 8.66; p = 0.04) (23). Furthermore, a systemic review in intensive HD also highlighted the infection risks of BH cannulation (25). Given the increased risk of infection, the patients should be informed and re-

Continued on page 10 >

Barriers, Shortfalls

Continued from page 9

ceive specialized training and frequent evaluations of their cannulation techniques. Strict adherence to aseptic technique in performing cannulations is essential. Moreover, each clinic should track and regularly review infection rates as part of quality indicators (26).

Rapid decline of RRF

It has been documented that preservation of RRF in dialysis patients improves quality of life as well as survival. A significant decline in RRF is appreciated during the first year of dialysis, especially in patients undergoing HD (27). The main contributor was dialysis hypotension, and the reduction in RRF might be even more pronounced among IHHD patients. In the FHN Trial, nocturnal HD seemed to promote a more rapid loss of RRF (18, 28). Nonetheless, the RRF in this study may have been underestimated because of differences in the timing of collections. It is unclear whether this effect would have been observed if RRF was measured by other means.

There are several potential barriers to the implementation of home HD, including among patients, physicians, and health care providers. Increased physician education along with appropriate workforce development and infrastructure might be the key to success in expansion of home HD programs. Properly identifying suitable patients for HD should equally be a priority for health care providers. In spite of multiple significant clinical benefits, IHHD also carries potential risks, such as other types of renal replacement therapy. Notwithstanding, these risks must be weighed against the potential advantages and should not be considered a limitation for considering IHHD in an appropriate candidate. Properly identifying suitable patients for HD should equally be a priority for health care providers.

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CRRT in the Surgical ICU – Duration and Mortality

For general surgery patients in the surgical ICU, the chances of survival to discharge decrease with each day of continuous renal replacement therapy (CRRT), according to a study in *JAMA Surgery*.

The retrospective study included 108 surgical ICU patients receiving CRRT at a tertiary care medical center from 2012 to 2016. The patients were 64 men and 44 women, mean age 62 years. Fifty-three patients were treated before or after general surgery; the remaining 55 were admitted before or for evaluation of liver transplantation. Survival to discharge after differing durations of CRRT was evaluated.

In the general surgery group, mean duration of CRRT was 3.2 days for patients who survived to discharge versus 7.2 days for those who died. Twelve general surgery patients required at least 7 days of CRRT; all of them died. Number of days of CRRT was the only factor independently associated with mortality: odds ratio 1.39 per day.

In the pretransplant group, mean duration of CRRT was 6.4 days for patients who survived or had a liver transplant compared to 8.0 days for those who died—a nonsignificant difference. Of 22 patients who required at least 7 days of CRRT, 13 died, for a mortality rate of 59.1%. In this group, the need for vasopressor therapy during CRRT was the only independent predictor of mortality: odds ratio 3.73.

The authors hypothesized that among patients admitted to a surgical service, there would be some duration of CRRT beyond which further treatment is futile. The new results suggest that, among general surgery patients admitted to a surgical ICU, the chances of survival decrease with each day of CRRT, and that continued treatment after 6 days may be futile.

In contrast, for patients with an identifiable, reversible indication such as liver failure before transplantation, duration of CRRT is not directly related to mortality. The study "supports the prolonged use of CRRT in patients who are admitted in anticipation of liver transplant," the researchers conclude [Tatum JM, et al. Analysis of survival after initiation of continuous renal replacement therapy in a surgical intensive care unit. *JAMA Surg* 2017; 152: 938–943].

No Benefit of ACE Inhibitors/Statins for Teens with Type 1 Diabetes

Treatment with angiotensin-converting enzyme (ACE) inhibitors, statins, or both does not affect albumin excretion in adolescents with type 1 diabetes, concludes a trial in *The New England Journal of Medicine*.

In a screening study of 4407 adolescents with type 1 diabetes, 1287 had increased albumin excretion, defined as the upper third of the albumin-to-creatinine ratio. Of these, 443 were randomly assigned to treatment with an ACE inhibitor, statin, or matching placebos in a 2-by-2 factorial design. The main outcome of interest was change in albumin excretion, assessed every 6 months over 2 to 4 years. Secondary outcomes included microalbuminuria, retinopathy, lipid levels, and other cardiovascular risk markers.

Change in albumin-to-creatinine ratio over time was unaffected by treatment with ACE inhibitor and/or statin. The incidence of microalbuminuria was lower with ACE inhibitor compared to placebo, but this difference was not considered significant. Statin treatment was associated with expected changes in lipid levels. However, there were no between-treatment differences in carotid intima-media thickness, other cardiovascular risk markers, glomerular filtration rate, or retinopathy progression. No serious unexpected adverse reactions occurred.

In adolescents with type 1 diabetes, puberty-associated increases in albumin excretion occur before the development of microalbuminuria and macroalbuminuria. This suggests that ACE inhibitors or statins might have beneficial effects for young diabetics with high albumin excretion.

However, the randomized, placebo-controlled trial shows no significant difference in albumin-to-creatinine ratio for young patients with type 1 diabetes taking ACE inhibitors or statins. Aside from statin-induced changes in lipid profiles, secondary outcomes are also similar between groups. The authors plan continued follow-up to assess any delayed "legacy effect" of early treatment [Marcovecchio ML, et al. ACE inhibitors and statins in adolescents with type 1 diabetes. *N Engl J Med* 2017; 377: 1733–1745].

Race Modifies HIV's Impact on Dialysis Survival

Even with modern antiretroviral therapy (ART), survival on dialysis is significantly lower for non-white patients with HIV infection, according to a study in *Kidney International*.

Using data from a nationwide dialysis provider, the researchers identified two groups of HIV-positive dialysis patients: 5348 patients who had HIV only and 1863 patients with HIV and hepatitis C virus (HCV) coinfection. In both groups, a large majority of patients were African American: 74.3% of the HIV-positive group and 81.6% of the HIV/HCV-positive group. Percentages of Caucasian patients were 13.2% and 9.0%, respectively.

A cohort of 410,545 HIV/HCV-negative patients were studied for comparison: 47.6% Caucasian and 29.0% African American. The effects of HIV- and HIV/HCV-positive status on mortality were assessed, along with the possible modifying effects of race.

In Caucasians, HIV status was not significantly related to mortality, but HIV/HCV infection was: hazard ratio (HR) 1.48. For non-Caucasians, both HIV- and HIV/HCV-positive status were associated with higher mortality: HR 1.44 and 1.77, respectively. The results were similar in secondary analyses using matched propensity scores.

The effects of HIV infection on dialysis outcomes are unclear, particularly in the era of widespread ART use. The new analysis suggests a "very concerning" reduction in survival associated with HIV-positive status in non-Caucasian patients: African American, Latino, Asian, and "other."

Across racial/ethnic group, dialysis survival is reduced for patients with HIV/HCV coinfection. The authors discuss the need for interventions targeting these vulnerable populations, possibly including early nephrology referral and therapy for HCV [Sawinski D, et al. Race but not hepatitis C co-infection affects survival of HIV+ individuals on dialysis in contemporary practice. *Kidney Int* 2017; http://dx.doi.org/10.1016/j.kint.2017.08.015].

The Changing Landscape of Nephrology: Will you Lead or Follow?

By Richard Lafayette, MD

It is said that the only constant in life is change. Throughout my career, health care policy changes have often been seen as harbingers of more difficult times for physicians in American medicine. Many of these changes, such as Medicare and Medicaid reform, the Health Maintenance Organization experience of the 1980s and 1990s, the consolidation of health insurance companies, and the enactment of the Affordable Care Act, had major impacts on the provision of health care. However, on balance, these changes have had positive effects, including allowing more patients access to see their physicians and to participate in preventive care programs, and for health care to start down the road of true reform. No doubt the changes required greater documentation, utilization of more restricted formularies, and ushered in the age of greater physician oversight, a pattern that continues today.

Presently, physicians in general and nephrologists in particular are under increasing pressure to conform their practice to administrative rules. Utilizing electronic medical records, constantly being subjected to measures of patient satisfaction, and most notably, entering an era where compensation is based on quality of care delivered rather than simple fee-for-service have greatly added to nephrologists' workload and anxiety.

The present day triple aim of providing patient-centered care that satisfies the patient, while delivering high-quality care and attending to cost-saving measures is highly desirable. However, how present day care delivery systems are to adapt to fulfill any or all of these aims effectively is yet to be determined. Without fail, the nephrologists with whom I meet speak of having to do more with less, and having to spend more time and energy to get anything accomplished. They are challenged with increased documentation rules, more barriers to providing patients with their medications, more metrics addressing their practice, and ever more limited resources to support their mission in terms of support staff in the practice and at dialysis units and, most notably, in trying to coordinate care with patients' insurance providers.

How do we, as nephrologists, ensure that our patients can continue to receive high quality care, that further increases in required reporting accomplish the goal of adding to and not detracting from patient care, and that we can find satisfaction in our chosen profession? Clearly, there are no simple answers. However, we must start by firmly advocating for our patients and our profession. Through the American Society of Nephrology and other professional organizations, there are opportunities to work as a community, together with our colleagues and our patients, and to try to have important conversations about the future. As providers of care, we are best suited to assess the present environment and see what works and what does not and cannot work in achieving not only the triple aim, but a quadruple aim that also accounts for physician satisfaction, so essential in assuring that devoted practitioners continue to provide care in the most productive, effective manner.

As the alphabet soup of EMRs, MACRA, ESCOs, and ACOs become more a fabric of our professional life dominating CKD, ESRD, AKI, RPGN, and our other more familiar acronyms, we must work together and be the leaders for designing and managing our practices (let alone research and teaching opportunities), utilizing all of our expertise and directly shaping the future.

We must get started. It will definitely be challenging, but there is much to be gained with activism and participation, or much to be lost if we fail to be involved. ■

Richard Lafayette, MD, is Editor-in-Chief of Kidney News.

Nephrology: We Define Our Future

By Amy Williams, MD

Over the past 10 years, much has changed in the specialty of nephrology and for nephrologists in all career tracks and professional settings. We have a deeper understanding of underlying mechanisms of disease and how to target therapy. Kidney Week 2017 was full of excitement and examples of discovery and translation to improve clinical care.

New care models have grown and matured, and there has been continued exploration of how to manage those with chronic kidney disease (CKD) and to identify those at risk for kidney disease earlier in their disease trajectory. Plus, there certainly is a market for our skills and knowledge with no shortage of individuals who need our expertise and care. To those thrilled with and fascinated by the complexity and power of the kidney, passionate about improving the outcomes of patients at risk for or with kidney disease—or dedicated to tapping into every resource to improve outcomes and decrease the burden of kidney disease through innovation—it is hard to understand why individuals don't choose nephrology as a career.

How then do we define our specialty's future? It can get a bit unnerving following the health care delivery and research funding conversations in Washington and watching the movement in the advanced CKD/dialysis industry. Yet we must participate and be active in the conversations, particularly around policy, for example, keeping an eye on any legislative proposals that could limit patient choice, make it more difficult for patients to access care, create silos of care, influence physicians' decision-making, and decrease patient-centered approaches to care, or overburden providers and patients with administrative tasks. Participating in the ASN Public Policy and Advocacy Community site is an easy way to gain understanding of new threats or of bills worth supporting, with a next step to raise the support of local legislators.

We must also find opportunities to elevate the importance of our contributions as nephrologists. As physicians, we have been trained to manage patients with complex chronic disease and have the most experience working in teams and in bundled and value-based payment models. As CMS and other insurers/payers build care bundles, and as alternative payment models become better defined, we can prove our value as partners by being involved early on in managing and educating about the risks of CKD and acute kidney injury (AKI) and subsequent disease progression, thereby improving outcomes—both medical and financial. Working across specialties and care sites to share knowledge and smooth transitions of care is a step we must take.

Through new collaborative partnerships, we can reach more patients and positively impact outcomes for the populations at risk for or with kidney disease. As always, self-reflection and occasional realignment are key to success. Our patients often have a disease trajectory that is not linear, but with many transitions (CKD–AKI–dialysis–transplant–dialysis, etc.). As we become more and more subspecialized, we must avoid creating silos within our specialty that decrease the overall advancement of care for patients throughout their lifetime.

Last, nephrology workforce concerns continue to loom, but most recent data point to possible stabilization or, thinking positively, maybe a sign that the worst is over. Reasons suggested for the decline in interest for nephrology are many: financial, how renal physiology is taught, lack of exposure to a breadth of renal diseases and patients, lack of enthusiastic mentors, and nephrologists' satisfaction in their careers. For each resident or learner the influencers may be different, but much of this we can change. We have an opportunity to take advantage of the uncertainty and chaos in health care delivery and funding for research and education by going to our strengths—the ability to manage the riskiest, most complex patients, lead effective teams, innovate and advance the science. Our specialty is essential in the new paradigms in medicine, population health, and health care delivery. It is our responsibility to make our contributions to medicine and the most vulnerable populations more visible.

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Could Deemed Status Become Reality for the Dialysis Industry?

Late 2017 found a push in the Senate to pass a companion bill to H.R. 3166, which would allow "deemed status" of ESRD facilities. Deemed status allows use of a survey by an accreditation agency to substitute for a survey by a state agency in outpatient dialysis facilities and could speed up the accreditation process.

The original law extending Medicare coverage to patients with ESRD prohibited the Centers for Medicare & Medicaid Services (CMS) from granting deemed status to accreditation agencies. If the Senate passes the companion bill and it is signed into law by the President, accreditation agencies will be able to apply for deemed status for surveys of outpatient dialysis facilities.

The dialysis industry has pushed for this change primarily to expedite initial surveys. Because CMS categorizes initial surveys as low priority ("Tier 3" for ESRD), there can be a long wait for an initial survey—as long as 28 months in some states. Because a new facility will not be reimbursed for the care they deliver to Medicare patients until the facility has successfully passed this survey, that wait can be very painful. If the bill becomes law, facilities will be able to pay accreditation organizations that achieve deemed status for ESRD to conduct their initial surveys, which should shorten the wait for Medicare certification and reimbursement.

When is Best to Initiate Dialysis in Critically Ill Patients with AKI?

By David White

One of the more challenging decisions in nephrology is if and when to initiate dialysis and the timing of that initiation for patients with acute kidney injury (AKI). Because the initiation of renal replacement therapy (RRT) is a crucial decision for patients with life-threatening changes in fluids, electrolytes, and acid–base balance, expect this to remain a topic of discussion and debate in 2018.

Ashita Tolwani, MD, MSc, laid out the advantages and drawbacks when considering early initiation of dialysis in patients with AKI in her talk "Timing of AKI Dialysis: Why the Answer Is Not That Simple" at Kidney Week 2017. Among the advantages of initiating RRT are improved fluid management, prevention of fluid overload, and unloading or resting stressed and damaged kidneys. Drawbacks include risk of hypotension, decreased renal recovery, and infections from catheters.

Tolwani noted the limitations of observational studies for RRT timing:

- Lack of uniform definition of "early" vs. "late."
- Better outcomes observed for the early group may be a result of a patient's good prognosis from the outset.
- Patients who received RRT too early might have recovered from AKI without its having ever become necessary.
- The studies do not account for the outcomes of patients who never received RRT.

A review of prospective controlled trials did not illuminate as clear a distinction as one might expect. Take for example two completed studies: "Artificial Kidney Initiation in Kidney Injury (AKIKI) Trial" [multicenter, France] (1) and "Early vs. Late Initiation of RRT in Critically Ill Patients with AKI (ELAIN) Trial" [single center, Germany] (2). Although the studies found different outcomes regarding the value of early vs. delayed initiation, they had significantly different base criteria. In AKIKI, which showed virtually no outcome differences between the early and delayed initiation, the following patient criteria were necessary:

- Adult, admission to an ICU + AKI compatible with acute tubular necrosis.
- Must be receiving invasive mechanical ventilation or catecholamine infusion.
- At least one of the following: serum creatinine >4.0 mg/dL or >3x baseline Cr, anuria for >12 h, oliguria (UO <0.3 mL/kg/h or <500 mL/day) for >24 h (KDIGO Stage 3).

In the ELAIN Trial, which demonstrated a significant difference in overall mortality probability, the criteria were significantly different:

- KDIGO stage 2 (serum creatinine 2x baseline Cr and/or urinary output <0.5 mL/kg/h ≥12 h) despite optimal resuscitation.
- Plasma NGAL >150 ng/mL.
- One of the following: a) severe sepsis; b) use of catecholamines; c) refractory fluid overload (worsening pulmonary edema, PaO_2/FiO_2 <300 mm Hg and/or fluid balance >10% of body weight); and d) development or progression of nonrenal organ dysfunction (SOFA [sequential organ failure assessment] score ≥2).
- Intention to provide full intensive care treatment for at least 3 days.

The trials also differed greatly in the patient cohorts studied. In AKIKI, 20% of participants were surgical patients, and in ELAIN, 93% of participants were surgical patients.

Looking for future guidance, Tolwani previewed the "Ongoing RRT Initiation RCT: STARRT-AKI (Canada) – Enrolling" which aims to enroll 2800 patients and "Ongoing RRT Initiation RCT: IDEAL-ICU study (France) – Initiated 2012" that has just completed.

With clinically based decisions of this nature involving so many factors, these studies are challenged to capture such important information as the inciting event that led to AKI, the degree of fluid overload, pre-existing comorbidities, and disease trajectory. Better trial design may inform better decision-making regarding the AKI-to-dialysis decision and the decision to terminate dialysis. Stay tuned as future trials unfold.

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Combining Genetics and Epigenetics Will Yield New Insights into Kidney Diseases

By Bridget M. Kuehn

Understanding DNA has helped science make major strides in understanding and treating disease. But "we [still] can't explain most of the variability leading to most human disease," said Andrew Feinberg, MD, MPH, director of the Center for Epigenetics at Johns Hopkins University in Baltimore. Changes in the genetic code explain only about 20% of disease risk, noted Feinberg, who presented a State-of-the-Art lecture at Kidney Week 2017.

Epigenetic studies may help unravel how the environment and gene–environment interactions contribute to that remaining disease risk. Already there is emerging evidence that epigenetic changes may contribute to kidney disease. Feinberg and others in the field are optimistic that further study of the role that these epigenetic changes play in the development of kidney disease and other ailments may lead to new treatments.

Epigenetic variability

Epigenetic variability is likely a major contributor to health and disease from the very earliest stages of development, Feinberg said.

The DNA found in the precursor cells of the heart and kidney is identical yet these two types of cells develop into vastly different organs. Their paths diverge because of epigenetic modifications, or chemical changes to the DNA that alter the expression of the genes.

"It's the grammar on top of the words of the DNA sequence," Feinberg said.

The addition of methyl groups to a stretch of DNA, for example, can act as a switch that turns on or off the expression of a gene or genes. These types of epigenetic changes underlie the characteristics that differentiate different organs as well as those that differentiate cancer cells from normal ones, he said.

There is variation in the methylation patterns among humans, just as there is variation in human genetics. Feinberg's work suggests that epigenetic variation is a driving force in evolution (Feinberg AP and Irizarry RA. *Proc Natl Acad Sci USA* 2010; 107 Suppl 1:1757–1764).

Having such variability may make it easier for organisms to adapt to changing environments.

"Different variants would be beneficial or harmful depending on the environment," he said.

These epigenetic variations may also contribute to disease risk. For example, Feinberg noted that a lot of cell death occurs during the early development of the kidneys. There may also be a good deal of variability in the process, he said. These differences could contribute to kidney resilience or vulnerability to kidney injury later in life.

"There is very good epidemiological data that epigenetics might play a role in kidney disease," said Katalin Susztak, MD, PhD, a professor of medicine and genetics at the University of Pennsylvania's Perelman School of Medicine.

Environmental exposures can alter a person's epigenetics and may explain these observational findings, Susztak said. For example, maternal over- or under-nutrition could cause epigenetic changes that make a child's kidneys more susceptible to kidney diseases or vulnerable to faster progression. In diabetic kidney disease, there is also evidence that a history of poor diabetes control may have lasting effects on outcomes even if an individual later achieves better control. These persistent effects might be explained by epigenetic changes.

"The epigenome is essentially the footprint of all the environmental changes that affect a human being from conception to death," she said.

Kidney clues

By tapping a large bank of kidney tissue samples, Susztak and her colleagues have identified epigenetic changes in patients with chronic kidney disease and diabetic kidney disease. She presented some preliminary findings from the studies at Kidney Week.

"The bigger question is, can we show a causal relationship between changes and disease development," she said.

To do that, she and her colleagues must next turn to cell and animal studies in which they will replicate these kidney disease–linked epigenetic changes and determine their physiological effects. Fortunately, new gene-editing technology called CRISPR CAS 9 technology can be used to make epigenetic changes as well as genetic ones.

So far, her work and that of others suggests that epigenetic changes play an important role in gene expression. Interestingly, genomewide association studies (GWAS) have suggested that genes linked to disease risk also play a role in regulating gene expression.

"There is a certain convergence between epigenome-wide association studies (EWAS) and GWAS changes," Susztak said.

This convergence has led Feinberg to propose that scientists combine EWAS and GWAS studies, along with environmental exposures that might cause epigenetic changes in order to better understand how these factors together may contribute to disease.

"We could save a fortune of National Institutes of Health money by combining these things," Feinberg said.

Both Susztak and Feinberg are optimistic that understanding how epigenetics contributes to disease may one day lead to new treatments that target disease-linked epigenetic changes.

"It would be very, very exciting if we could interfere with epigenetic changes and modify it and develop new therapies for kidney disease," Susztak said. ■

Asking the Right Question

By Pascale Lane

What in your field hasn't changed? What could be improved? What could be made less invasive? The impetus to improve on the way we currently do things will be a driving force in 2018.

This series of questions several years ago led to the Ellipsys® system for percutaneous placement of proximal radial arteriovenous fistulas for dialysis access. The system requires 2 mm arteries and veins. With the patient under sedation and local anesthesia, the device is placed through an antecubital venipuncture and threaded to the point where the vein lies adjacent to the proximal radial artery. The device is then activated, using nanotechnology to fuse the vessel wall tissues, creating an anastomosis. Day 1 bloodflow of 334 mL/minute was achieved. The entire procedure takes 23 minutes, and no adverse events were reported.

The primary endpoint was 2 needle hemodialysis within 100 days, and 86% met this goal. Patency at 12 months was 87%. These values are similar to those seen with surgical fistulae. About half of patients required an additional procedure to open up the vein or raise the vessel to facilitate access, particularly in heavier patients.

The device is currently available in Europe and under review by the FDA.

Imagine getting a fistula without an incision or a surgeon! Now, what other procedures and processes can we improve? ■

Pascale Lane, MD, FASN, is affiliated with the University of Oklahoma Health Sciences Center, and is a member of the KN *Editorial Advisory Board.*

Newer diabetic medications and the kidney

By Sonali Gupta and Joseph Mattana

The prevalence of diabetes is rapidly increasing and is projected to affect more than 400 million people by 2030 worldwide. Diabetic nephropathy remains the most serious microvascular complication and most frequent cause of end stage renal disease in the United States. There has been a pressing need for newer therapeutic agents to halt this expanding population and to limit the disease's associated morbidity, mortality, and expense. Newer antidiabetic medications acting via novel pathways are gaining increased acceptance in medical practice and their renal effects have been the subject of much recent study.

Although the sodium glucose cotransporter (SGLT) inhibitor called phlorizin, derived from the root bark of the apple tree, has been in use for over 150 years, it is only recently that its synthetic derivative, with a more specific and potent effect on the SGLT2 receptor in the kidney, has been approved by the FDA. Apart from its ability to cause glycosuria and better glycemic control, recent attention has been drawn to its cardio-renal profile including apparent renoprotective effects, along with optimization of body weight and blood pressure. In vitro and animal studies with empagliflozin have supported its counteracting action—by inhibiting glucose absorption in the proximal tubule—on glucose-induced inflammatory and profibrotic effects on renal tubules, thereby decreasing albuminuria, preventing hyperfiltration, and conferring renoprotective properties.

Results from EMPA-REG OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), CANTATA-SU (Canagliflozin Treatment and Trial Analysis verses Sulfonylureas), and dapagliflozin renal studies have been encouraging and support renoprotective effects (1–3). The subgroup analysis of CANVAS (Canagliflozin Cardiovascular Assessment Study) also demonstrated renal benefit of canagliflozin by targeting albuminuria, preventing deterioration in the estimated glomerular filtration rate, lowering renal replacement therapy requirement, and decreasing mortality from renal causes (4). However, questions have been raised regarding the potency of SGLT2 inhibitors in patients with established renal impairment. It is well known that renal autoregulation is impaired in diabetic kidneys and there are concerns for worsening renal function in the setting of volume depletion and the blood pressure–lowering properties of SGLT 2 inhibitors. A much awaited randomized, double blind, placebo controlled trial, the CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial is underway and includes patients with stage 2 or 3 chronic kidney disease and macroalbuminuria who are receiving standard of care including a maximum tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

Incretin-based therapies

Incretin-based therapies are another category of diabetic drugs that have received attention for their extra-pancreatic effects beyond controlling glucose. The two classes of drugs are: 1) agonists of glucagon-like peptide 1 receptor (GLP-1R) and 2) inhibitors of dipeptidyl peptidase 4 (DPP-4). The DPP-4 inhibitors mainly act by increasing the levels of the endogenous incretin hormone GLP-1, which has known anti-inflammatory properties. DPP-4 is highly expressed in human kidneys and levels are further upregulated in the setting of diabetes (5). Targeting DPP-4 inhibition has emerged as a potential therapeutic intervention to halt diabetic nephropathy early in its course. Preliminary data from preclinical and animal studies support a role for DPP-4 inhibitors in ameliorating early signs of renal injury, which appears to be mediated independent of its glucose-lowering effects, mainly through proteolytic, antifibrotic and anti-inflammatory actions (5).

Results from the SAVOR-TIMI 53 Trial (The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction) showed that treatment with saxagliptin reduced the urinary albumin-to-creatinine ratio, with a reduction in albuminuria in patients with moderate to severe renal impairment (6). However, the TECOS trial (Trial Evaluating Cardiovascular Outcomes with Sitagliptin) failed to show a clinically significant impact of sitagliptin on cardiovascular or renal outcomes, irrespective of the baseline glomerular filtration rate (7). Preliminary data support the stability of renal function with linagliptin and the lack of requirement for dose adjustment, even in severe renal insufficiency, although further research is needed to support these observations (8). CARMELINA (Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus) and MARLINA-T2D (Efficacy, Safety and Modification of Albuminuria in Type 2 Diabetes Subject With Renal Disease With Linagliptin) are two large trials that are underway and likely will provide answers to these questions.

In addition to experimental data for DPP-4 inhibitors, GLP1R agonists have also been shown to be renoprotective. Decreased albuminuria secondary to anti-inflammatory and anti-oxidative properties of GLP-1R agonists were shown in a rat model of diabetic nephropathy (9). Recently, the prespecified secondary renal outcomes in the LEADER trial, which had shown a reduction in cardiovascular events with liraglutide in patients with type 2 diabetes mellitus, were reported (10). In this study, the effect of liraglutide on the composite renal outcome of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end stage renal disease, or death due to renal disease was evaluated. Fewer patients on liraglutide experienced the renal outcome, mainly due to a reduction in the new onset of persistent macroalbuminuria, suggesting that liraglutide may have a favorable impact on the development and progression of diabetes-related renal disease (10).

With the excitement of having new agents to treat diabetes there are many questions to be answered, and further research is needed to evaluate their beneficial role in primary prevention of cardiovascular and renal events and to prevent renal disease onset and progression. Further clinical trials with predefined renal end points to assess the renoprotective effects of newer medications in these and other classes in patients with type 2 diabetes should provide many such answers over the coming years.

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Policy Update

CMS' Surprise: The Quality Payment Program in 2018

Keep an eye on the Quality Payment Program (QPP), created by the Medicare and Chip Access and Reauthorization Act of 2015 (MACRA), as the QPP enters its second performance year in 2018. The QPP is subdivided into two broad payment tracks: risk-bearing alternative payment models (APMs), such as downside risk Accountable Care Organizations (ACOs); and the Merit-Based Incentive Payment System, or MIPS, which aggregates scores across four domains to adjust payments based on performance. Between those two options is an important hybrid track for ACOs and participants in other alternative payment models that do not accept downside risk, called MIPS-APMs.

In its proposed rule of July 2017, CMS proposed several changes that meant MIPS would apply to fewer physicians, and would generally be less stringent. CMS also originally proposed completely removing the cost accountability domain from MIPS for 2018, despite the underlying statute requiring that cost account for 30% of the overall MIPS score by 2019. In addition, CMS proposed to reduce the quality measure "data completeness standards," effectively allowing clinicians to report quality scores based on a smaller subset of patients.

Under CMS' final rule, far fewer clinicians will now have to participate in MIPS. Under the new minimum threshold for MIPS' participation, clinicians must have $90,000 in annual Medicare billings and have 200 Medicare part B beneficiaries. CMS surprised many by reversing its proposed position regarding the cost domain and finalized a cost domain weight of 10% for the 2018 performance year, reducing the quality domain from 60% to 50%. CMS also declined to adopt the 90-day reporting period for quality. In 2018, the minimum score for avoiding negative penalties will rise to 15 from 3 in 2017.

These may seem like normal adjustments for phasing in a major new payment structure; however, health care analysts are trying to read the tea leaves in these steps. Why? The large increase in clinicians now exempt from MIPs requirements has many wondering if the new administration is softening the transition to a quality physician reimbursement system or possibly reconsidering the approach altogether. Also, the surprise move to finalize the cost domain at 10% overshadowed the accompanying announcement that the cost calculations in 2018 will not employ the new costs episodes that CMS has been developing for the QPP. Instead, CMS will use two measures from the previous Value Modifier—the Medicare Spending per Beneficiary measure, measuring the cost around a hospital episode, and the Medicare Per Capita Cost measure of total costs.

Further confusing analysts, in October 2017, the Medicare Payment Advisory Commission called for the immediate repeal and replacement of MIPS. In an interview at that time, David Glass, principal policy analyst at MedPAC, said, "Time is of the essence to develop an alternative for MIPS." And in December, a report from the Health and Human Services Office of the Inspector General highlighted the challenges posed by ongoing physician confusion about the program.

Needless to say, the QPP, and its MIPS path to Medicare reimbursement, warrant careful watching.

KidneyX Accelerator Raises Hopes for Innovation in Kidney Space

Innovation in kidney care promises to be a significant theme in the kidney community in 2018, and it is hoped, well beyond. At ASN Kidney Week 2017, Department of Health and Human Services (HHS) Chief Technology Officer Bruce D. Greenstein announced HHS' commitment to launching a "KidneyX Innovation Accelerator" in 2018.

Although dialysis is a remarkable and life-saving technology, compared to other fields of medicine, nephrology has seen relatively few transformative new drugs or other therapeutics. Although kidney diseases are among the most complex, in part the relative dearth of innovation is due to perceptions of the market.

Angel investors, venture capitalists, and others are interested in making investments in the kidney field, Greenstein said, but have been hesitant to enter the space because the government has not demonstrated a path forward to do so. Given the outsize role the federal government plays in reimbursement for kidney care relative to other areas of medicine, potential investors are particularly sensitive to its signals in the field of nephrology. The announcement at Kidney Week in New Orleans heralded a new era, with all signals beginning to point toward demand for more innovation. As Greenstein told plenary attendees, the government's efforts in "making a very clear indication that this is a priority, and that we are moving forward to find a better way in the future, will begin to attract investors in this area."

In order to accomplish this goal, the Accelerator will provide three key ingredients. First, a public-private innovation fund will provide seed funding to promising opportunities for potential cures, therapies, and other products in order to accelerate breakthroughs in kidney care that may otherwise languish or never come to fruition. Second, bringing together in parallel NIH discovery efforts, FDA approval processes, and CMS payment indications will reduce the risk involved for companies and investors considering investing in the nephrology space, increasing the likelihood that new products will be commercialized and put in the hands of nephrologists and their patients. Third, and perhaps most important, the KidneyX Accelerator will create a sense of urgency to develop new kidney therapies—an urgency that patients and their families feel on a daily basis—across the disciplines of science, engineering, and finance.

Greenstein called upon the entire kidney community to get involved in the effort to foster innovation. "We admit readily that we do not have the answers for this. This Accelerator program should be seen as the beginning of a partnership with this community and others. We need everyone's help to go forward and make a difference."

Entitlement Reform and a Year of Austerity

Keep an eye out in 2018 for Congress and the Administration to once again target research and health funding for FY 2019 with deep cuts proposed at both the discretionary and mandatory level. A year ago, President Trump set the tone of federal budget negotiations for FY 2018 with the introduction of his "skinny budget." In a measure strongly condemned by then-ASN President Eleanor Lederer, MD, FASN, shortly after its introduction, the administration proposed deep cuts to funding for the National Institutes of Health, as well several other health programs.

In 2017, Congress listened to ASN's strong stance against the proposed cuts, providing for a $2 billion increase to the budget, and stopping a number of other harmful proposals from becoming law. However, the Republican tax reform package passed at the end of 2017 has been estimated by non-partisan sources to *increase* the federal deficit by as much as $1.5 trillion. This massive increase will likely be paid for by decreasing spending on mandatory funding programs, such as Medicare and welfare spending programs. Long a target of Speaker of the House Paul Ryan, these mandatory programs are already being eyed for a coordinated, systematic overhaul under reconciliation procedures—the same mechanism used to alter the Affordable Care Act and the tax code—by Congress and the White House, according to a recent *Politico* report.

Also, discretionary spending, a broad category of funding for agencies and programs ranging from the military to health research, will be targeted for cuts. In a July 7, 2017, memo to the heads of federal agencies, Office of Management and Budget Director Mick Mulvaney promised that the FY19 budget would "build on the ambitious plans laid out in the President's first budget" and instructed that FY19 budget requests only include proposals in line with the "President's commitment to reprioritize spending and redefine the proper role of the Federal Government." If the President's FY18 budget is an indication of the administration's spending priorities, health and research may bear the brunt of this reprioritization effort. Rumors on Capitol Hill corroborate this intelligence, with both Democrats and Republicans hinting that in FY19, programs and agencies will be lucky just to keep their funding steady.

Short-Acting Insulin Drug Approved to Treat Diabetes

In mid-December, the U.S. Food and Drug Administration announced it had approved Sanofi-Aventis US's (Bridgewater Township, NJ) Admelog (insulin lispro injection), a short-acting insulin indicated to improve control of blood glucose levels in adults and pediatric patients 3 years and older with type 1 diabetes and adults with type 2 diabetes. Admelog is the first short-acting insulin approved as a "follow-on" product [submitted through the agency's 505(b)(2) pathway, a shortened route based on comparative evidence with an approved drug].

"With [the] approval, we are providing an important short-acting insulin option for patients that meets our standards for safety and effectiveness," said Mary T. Thanh Hai, MD, deputy director of the Office of New Drug Evaluation II in the FDA's Center for Drug Evaluation and Research.

Patients taking the drug should be monitored more closely with regard to changes in insulin dosage, co-administration of other glucose-lowering medications, meal pattern, and physical activity, as well as in patients with renal impairment, hepatic impairment, or hypoglycemia unawareness, the FDA noted.

Sanofi-Aventis submitted a 505(b)(2) application that relied, in part, on the FDA's finding of safety and effectiveness for Eli Lilly's Humalog (insulin lispro injection) to support approval for Admelog. The application aimed to demonstrate scientific justification for reliance on the FDA's finding of safety and effectiveness for the reference product Humalog and provided Admelog-specific data from two Phase 3 trials.

"One of my key policy efforts is increasing competition in the market for prescription drugs and helping facilitate the entry of lower-cost alternatives," said FDA Commissioner Scott Gottlieb, MD. "In the coming months, we'll be taking additional policy steps to help to make sure patients continue to benefit from improved access to lower cost, safe and effective alternatives to brand name drugs approved through the agency's abbreviated pathways."

He noted that these efforts are "particularly important for drugs like insulin that are taken by millions of Americans every day for a lifetime to manage a chronic disease."

Therapy round-up

A recent, albeit early, study found that a combination of two Genentech drugs, Tecentriq (atezolizumab) and Avastin (bevacizumab), reduced the risk of disease worsening or death as an initial treatment in some individuals with advanced kidney cancer. Genentech is a division of Roche, and is headquartered in South San Francisco, CA.

Compared with Sutent (sunitinib; Pfizer, New York, NY), the combination treatment provided a statistically significant and clinically meaningful co-primary endpoint result in kidney cancer patients whose disease expressed the biomarker PD-L1 protein. The co-primary endpoint was investigator-assessed, progression-free survival for the first-line treatment of individuals with advanced or metastatic renal cell carcinoma.

Another study found that a group of diabetic patients with chronic kidney disease who received treatment for type 2 diabetes fared better with the drug metformin compared with sulfonylurea. The observational study used data from electronic pharmacy records of the US Veterans Health Administration.

Among 175,296 new users (veterans) of either a metformin or sulfonylurea monotherapy, 5121 deaths were observed (1).

Metformin monotherapy across all ranges of estimated glomerular filtration rate evaluated was associated with a lower mortality hazard ratio than sufonylurea monotherapy, the researchers found. An analysis of mortality risk differences also favored metformin. The largest absolute risk reduction was found in the group with moderately to severely reduced kidney function.

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UnitedHealth to Acquire DaVita Medical Group

In early December, UnitedHealth and Denver-based DaVita announced that UnitedHealth would spend $4.9 billion to acquire DaVita Medical Group, comprising a medical staff of about 2000 physicians in a group currently owned by one of the nation's largest dialysis companies. United Health Group's Optum segment has headquarters in Eden Prairie, MN, and has clinics or centers in more than 150 locations worldwide.

Under terms of the deal, Optum acquires from DaVita Medical Group physician groups in California, Colorado, Florida, Nevada, New Mexico, and Washington. The physician groups serve approximately 1.7 million patients per year in approximately 300 primary care centers, 35 urgent care centers, and six outpatient surgery centers. The acquisition will expand Optum's strategic care delivery portfolio, according to a joint statement from both companies.

According to UnitedHealth's third quarter 2017 highlights, all of Optum's segments showed double-digit percentage earnings growth. By the end of 2016, Optum had care management programs assisting people across the care continuum—physical and mental health, complex medical conditions, disease management and support, hospitalization, transplant, and post-acute care.

"Following this transaction, DaVita will continue to be a leader in population health management, with a focus on our US and international kidney care businesses," DaVita CEO Kent Thiry said. "We also expect to pursue other investments in health care services outside of kidney care."

Jeffrey Loo, an industry analyst with the investment research firm CFRA, noted that the acquisition "should mesh well with Optum's focus on primary care, urgent care, and outpatient care businesses."

According to MarketWatch.com, in dollar terms the acquisition is small potatoes compared with CVS's recent $69 billion acquisition of Aetna, a major health insurance company. UnitedHealth/Optum remains a step ahead of CVS, however, because it is now positioned to be a leading physician care platform for the transformed health care sector of the future, said Mizuho analyst Sheryl Skolnick.

Winning the ASN Policy Races for 2017

1

Secured GAO Report on Kidney Research

Highlighted that U.S. government invests <1% of Medicare kidney care costs in kidney research, bolstering case for more NIH funding

2

Championed NIH Kidney Research Funding

Championed NIH "Special Kidney Program" of dedicated $150 million per year for 10 years funding for kidney research

3

Advocated for Living Donor Protection Act

Collaborated with congressional champions and other stakeholders to advance bill to increase living donation

4

United Kidney Community on Capitol Hill

Brought together 22 patient and health professional organizations for 3rd Kidney Community Advocacy Day

5

Fought for Patient Access to Healthcare

Joined peer societies to fight to protect patients with pre-existing conditions and prevent cuts to Medicaid in repeal-replace debate

6

Influenced New Physician Payment System

Worked with Medicare to implement and shape improvements in the Quality Payment Program

7

Protected Equitable Grant Funding

Influenced revisal of the NIH Grant Support Index to support younger investigators

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Fellows Corner

Mentorship in the Modern Era

By Corey Cavanaugh

Corey Cavanaugh, DO

Many influences propelled me along the course that ultimately allowed me to train with some of the best minds in nephrology as an osteopathic medical graduate and current clinical nephrology fellow at Yale.

As many nephrologists will surely attest, it was the tutelage of talented mentors that led me to my career in nephrology. Surveys have explored the reasons behind why fellows are choosing *not* to pursue nephrology, and lack of mentorship is a particularly troubling reason. In one study, 33% of those polled attributed lack of quality teachers as the reason for choosing a non-nephrology specialty (1). As one of my favorite nephrologists and mentors once stated, with disappointment, "Sometimes there are simply not enough hours in the day to discuss a complex case with trainees." It seems that both trainees and nephrologists "get" that lack of quality mentorship is difficult for both parties to endure.

There is a potential solution to such a problem, albeit unconventional. As traditional classrooms become flipped and cadavers are traded out for ultrasound-based anatomy lessons, the mentor-mentee relationship must also be updated. Millennials spend significant portions of their lives on the web. From online dating to online universities, life is the web for some. The current cohort entering nephrology is more likely than ever to utilize the web for their medical education. The so-called FOAMed movement (Free Open Access Medical Education) is upon us. With the strong following of "Dr. Smith's ECG blog" among cardiologists, and EM-Crit.org for emergency medicine specialists and intensivists, the landscape of medical education is changing rapidly (2,3).

In nephrology, among the greatest sources of free information are the ASN discussion forums, in which award-winning educators actively respond to clinical queries from around the globe; even the most brilliant clinicians post case discussions when they're stumped. Trainees like me have the ability to pull back the curtain and analyze these discussions that would otherwise occur without any house staff involvement. Ideas are exchanged, studies are rediscovered, and guidelines are debated, all through the convenience of an email inbox.

NephJC is a Twitter-based online nephrology journal club that hosts bi-weekly chats and aims to stimulate powerful discussions among educators and trainees alike. Co-founded by Joel Topf, MD, and Swapnil Hiremath, MD, it consists of a team of nephrologists from five different countries who carefully choose contemporary nephrology articles for discussion.

As Topf et al. point out in their article *From Osler to Twitter*, over 2500 separate Twitter handles (profiles) have participated in the journal club over a two-year period (4). This takes a considerable amount of effort on the part of the organizers. Each article is chosen by a panel of 15 nephrologists, after which a summary of the chosen article is created. The article's authors are invited to join, and the online chat occurs on two separate evenings so as to accommodate European time zones (4). *One NephJC* chat covered a thought-provoking study by Titze and colleagues that suggested increased salt consumption decreases fluid intake. The article evaluated the sodium balance of cosmonauts in hermetically sealed rooms for months on end, simulating a trip to Mars. The discussion caused even the brightest minds in nephrology to grapple with the researchers' findings and struggle to reconcile the new data with our foundational understanding of salt and water homeostasis.

Twitter also offers open access to countless nephrologists around the world. On the @askrenal page, a nephrology-related query can be asked at any time of day. A tweet to @askrenal is usually met with a response in seconds. Other online resources such as the Renal Fellow Network blog allow trainees to create and publish their own searchable papers and introduce them to medical writing. Surprisingly, in a survey by Rope et al., as many as 34% of renal fellows used the Renal Fellow Network as an education tool (5, 6). Resources such as @AJKDonline, The Washington University Pathology Series, Arkana Pathology challenges, GlomCon, and others are all stimulating new educational tools that allow the exchange of ideas within the nephrology community and deliver information in a palatable manner to prospective trainees.

My hope is that these and other tools capture the hearts and minds of prospective trainees around the globe and expose them to the sheer excitement and curiosity of nephrologists—qualities that I admired the most in my mentors. However, these websites mean nothing without the discussion and interaction they hope to create. We need *you* in these discussions. So, create a Twitter handle and follow us. You may find yourself being a mentor to a learner like me. No, this isn't how your father envisioned we would be teaching and learning nephrology, but mentorship via social media could prove to be an exciting new frontier with a vast untapped potential with regard to revitalizing the future nephrology workforce.

Corey Cavanaugh, DO, is a clinical nephrology fellow at Yale University in New Haven, CT.

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Figure 1. A typical discussion on @askrenal among nephrologists

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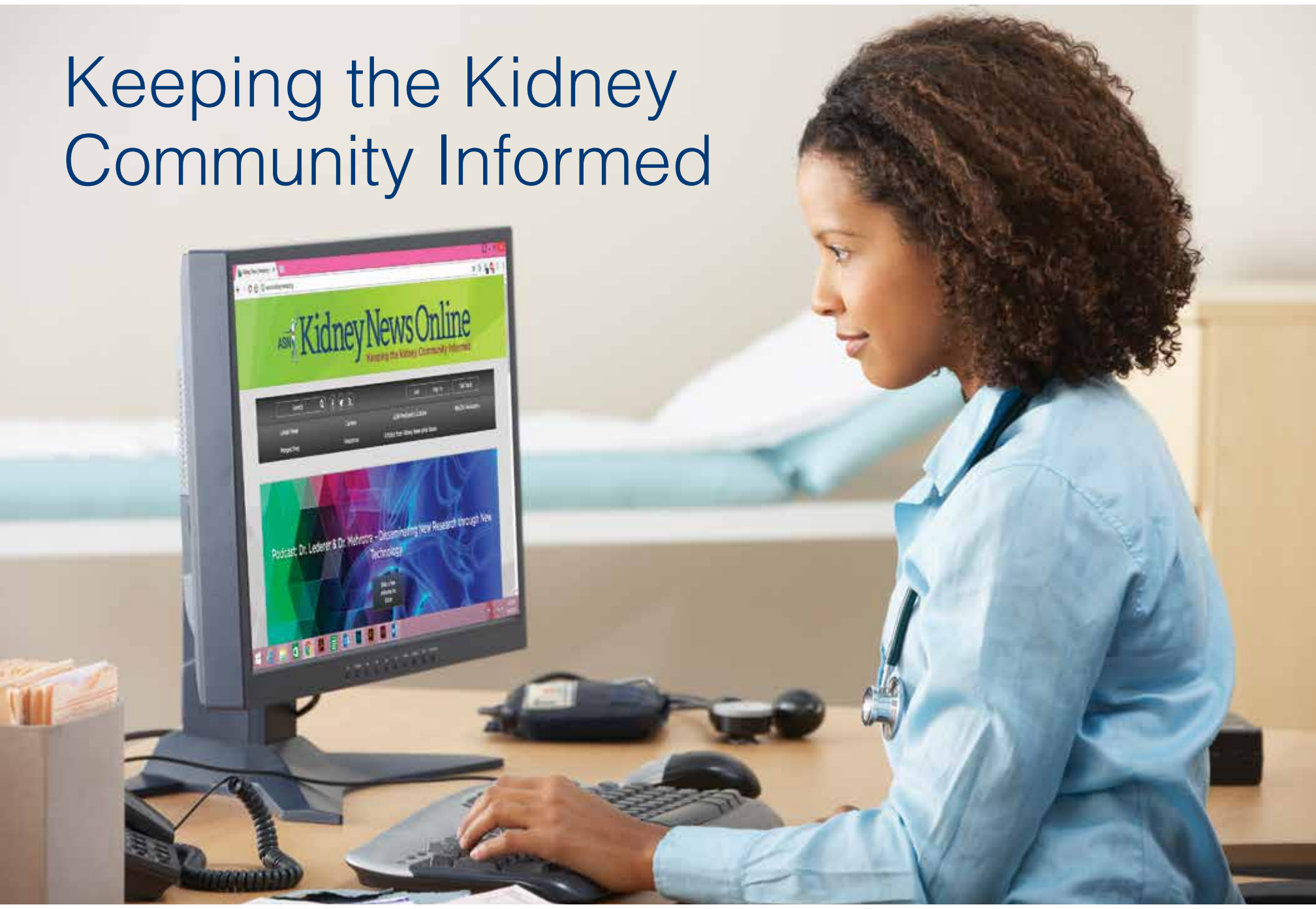

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INDICATIONS AND USAGE

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)

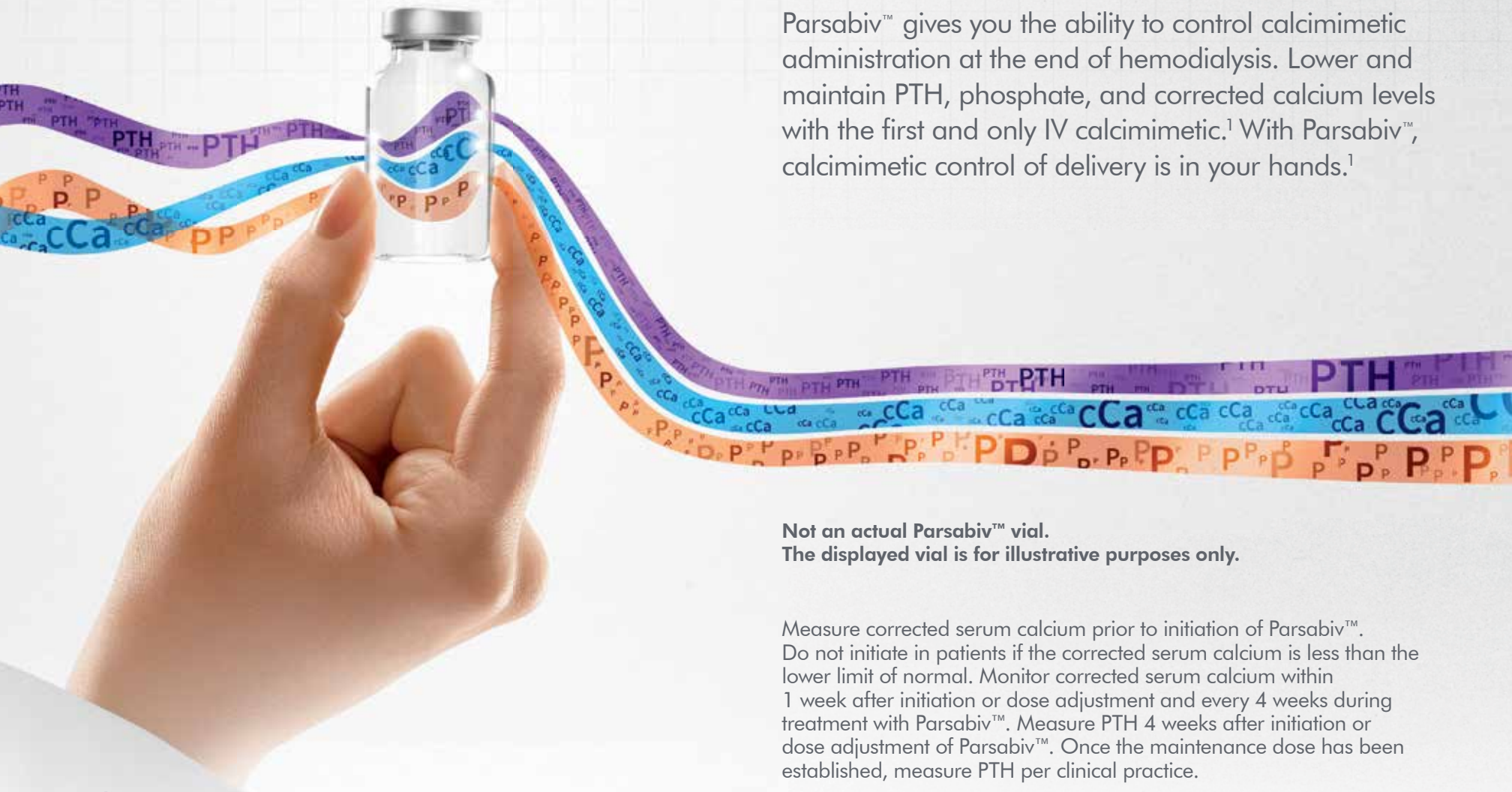
Manufactured for:
KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

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.