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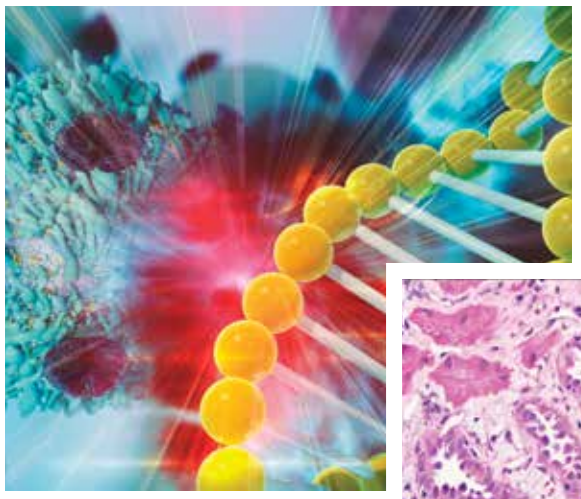
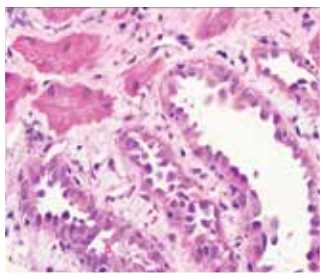
Immune Checkpoint Inhibitors for Cancer Treatment Have Renal Side Effects

By Eric Seaborg





Courtesy Ala Abudayyeh

Immunotherapy has successfully treated several recalcitrant forms of cancers and is on the cusp of revolutionizing treatment. But as with any new therapy, greater use is revealing side effects that must be managed, including dangers to the kidney.

Nephrologists need to be aware of these potential problems and the ways to counter them, according to Kenar D. Jhaveri, MD, professor of medicine in the division of kidney diseases and hypertension at Hofstra Northwell School of Medicine in Great Neck, N.Y. The most common of these problems are immune-mediated, including acute interstitial nephritis (AIN) and glomerular diseases, both of which can generally be countered with corticosteroids.

Immunotherapy is effective because it attacks cancer's secret weapon—its ability to hide from the immune system by keeping immune cells from recognizing cancer cells as invaders. The immune system is full of checks and balances to keep the body from attacking itself, and several years ago researchers discovered some of the "checkpoints" on T cells that act as brakes on their aggressiveness, including the proteins PD-1 (for programmed cell death 1), PD-L1, and CTLA-4 (for cytotoxic T-lymphocyte-associated protein 4). Many tumor cells express the ligands for these checkpoint receptors, and when triggered, the checkpoint proteins provide a brake or "off switch" that inhibits the T cell from attacking the tumor cell (Figure 1).

Researchers next developed drugs they dubbed immune checkpoint (ICP) inhibitors—monoclonal antibodies aimed at PD-1, PD-L1, and CTLA-4 that block them from binding to the tumor cells, thereby taking off the brake and allowing the T cell to recognize and attack tumor cells (Table 1).

"The U.S. Food and Drug Administration has approved ICP inhibitors for advanced or metastatic melanoma, non-small cell lung cancer, recurrent head and neck cancer, kidney cancer, urothelial cancer, and Hodgkin lymphoma," said Umut Selamet, MD, clinical instructor of nephrology and director of the onco-nephrology program at the University of California at Los Angeles. Selamet conducted most of her work on immune checkpoint inhibitors during her training at MD Anderson Cancer Center, with Ala Abudayyeh, MD, associate professor of nephrology at the University of Texas MD Anderson Cancer Center.

As one might expect, when more patients receive the drugs, their side effects come into better focus. And as these drugs take the brakes off the T cells, the cells may attack the patient's own tissues—and the kidneys are of particular concern.

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Proactive Nephrology Teams Leverage Electronic Tools to Prevent AKI

By Bridget M. Kuehn

By 6 a.m. each morning, an electronic dashboard displaying real-time information about the 8 to 10 patients at highest risk for acute kidney injury (AKI) is available for review by the nephrologists at Phoenix Children's Hospital.

"We have an entire day's work cut out for us and see who needs the attention," said Kanwel Kher, MD, chief of the division of nephrology at the hospital. "We have to evaluate them quickly, we can do that in about 10 to 15 minutes."

The nephrologists can access patients' complete charts through links in the dashboard, which is integrated with the hospital's electronic medical record system (EMR). Using a secure text message system, Kher and his colleagues can send their recommendations for reducing the patient's risk of AKI directly to the child's attending physician.

The effort is part of a growing movement in the field of nephrology to use electronic records, e-alerts, and other tools to more proactively prevent AKI and its progression in hospitalized patients. So far, the data on using e-alerts have been mixed. But some initiatives leveraging electronic

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Inside

Immune Checkpoint Inhibitors

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ICP inhibitors and transplant patients

Considering that immunosuppression is a key to transplant success, it is not surprising that ramping up the immune system with ICP inhibitors can cause problems for transplant patients. CTLA-4 inhibitors have been successfully used in kidney, liver, and heart transplant patients without rejection," according to a review that Jhaveri and colleagues published in the *Journal of Onco-Nephrology*.

"PD-1 inhibitors and the combination therapy of CTLA-4 and PD-1 inhibitors have been associated with cellular- and antibody-mediated rejection," Jhaveri said.

Jhaveri has also published a case of a kidney transplant patient who developed cancer, for which he was treated with a PD-1 inhibitor. The care team gave the patient a pre-emptive regimen of glucocorticoid and sirolimus, and he experienced no adverse immune response around the kidney transplant.

Table 1. FDA-approved ICP inhibitors

Anti-CTLA-4 drugs: Ipilimumab
Anti PD-1 drugs: Nivolumab, Pembrolizumab
Anti PD-L1 drugs: Atezolizumab, Durvalumab, Avelumab

Abbreviation: ICP = immune checkpoint

Immune-mediated effects

"The ICP-inhibitor–related problems are similar to those of other immune-mediated kidney conditions, as well as acute kidney reactions associated with antibiotics and proton pump inhibitors," Selamet said.

The main adverse effect associated with both the PD-1 inhibitors is AIN, and the main toxicities associated with the CTLA-4 inhibitor ipilimumab are AIN, glomerular diseases, and hyponatremia, according to Jhaveri. PD-1 inhibitors have been associated with acute graft loss in organ transplant patients, although solo use of CTLA-4 inhibitors has not.

The kidney injury develops more slowly for PD-1 inhibitors, at three to 10 months from the start of treatment, compared with CTLA-4 inhibitors, at two to three months.

The earliest and most obvious sign of a problem is a rise in serum creatinine, although "in urinalysis you may start to see some protein spilling, proteinuria, and sometimes hematuria and white blood cells in the urine," Selamet said. These signs should lead to the gold standard for diagnosis—a kidney biopsy.

Treatment for ICP-inhibitor–caused AIN and glomerular nephritis is similar to that of other immune-mediated AIN, consisting of a course of corticosteroids. "Some patients benefit from a short course of six weeks. Some patients need a full course of three months. And some are even extended to six months," Selamet said. She notes that the glomerular nephritis is generally harder to treat than AIN, and may require longer treatment, but that most cases lead to complete kidney recovery.

The rarer side effect of hyponatremia could be symptomatic of an endocrine problem. Hyponatremia can occur in cancer patients due to a syndrome of inappropriate antidiuretic hormone release, which may require intervention by an endocrinologist, Selamet said.

The first studies found the incidence of the side effects to be around 1 to 3%, but more recent studies suggest that it could be as high as 10 to 30%, Jhaveri said. It's hard to get a good handle on the rate of true injury, because some reports may rely on elevated lab tests without confirming the extent or source of the problem.

"A lot of times, the oncologists don't even call the nephrologists," Jhaveri said. "They see an increase in creatinine, and they just start treating with steroids, because they assume they know what it is. But it is not always the case. You can have other causes of kidney injury in a patient getting these drugs. Kidney biopsies are the definitive way to diagnose them."

Effects beyond the kidney

Kidney problems may be among the easier to spot because patients on immunotherapy receive regular lab workups that include renal tests. Cardiac problems are also common, and some of the most vulnerable other tissues are in the endocrine system, including the thyroid, pituitary, pancreas, and adrenal gland.

Patients have more generalized reactions as well. "We are seeing a number of nonspecific symptoms with these drugs, things like fatigue," said Howard Kaufman, MD, immediate past president of the Society for Immunotherapy of Cancer and a faculty member at Massachusetts General Hospital in Boston. "We can get isolated laboratory abnormalities, such as anemia. A lot of patients don't want to [report problems] because they don't want to go off the treatment. But if we can intervene when the side effects are minimal, the likelihood that they will stay on the treatment is higher, so I often have [to explain that to patients]. One thing I can say across the board with all of these side effects is the earlier they are identified and treated, the more rapidly they seem to come under control."

At the other extreme are patients who recognize they are having symptoms but don't realize they are side effects of their treatment or misunderstand their implications. "They go to the emergency room and say, 'I'm on chemotherapy.' The poor emergency room doctor may [be misled or may] not understand that immunotherapy is really different from chemotherapy," Kaufman said. Kaufman gives his patients cards explaining about their ICP inhibitor treatment, but not everyone carries them.

Trying to keep treatment going

Selamet said the treatment generally requires stopping the ICP inhibitors for both the glomerular nephritis and AIN: "The problem we have from the oncology side is that the drug is working against the tumor, so we don't want to stop it. But if it is causing side effects, then we do have to hold it. It is really important to recognize these side effects because if you catch them early and treat them, oftentimes you can restart the ICP inhibitors, and the patient will not get the same side effect again. But if they are incompletely treated or if the patient isn't diagnosed with the side effect until it is late, then it is much harder to keep them on ICP therapy. And at some point, the damage may not be reversible."

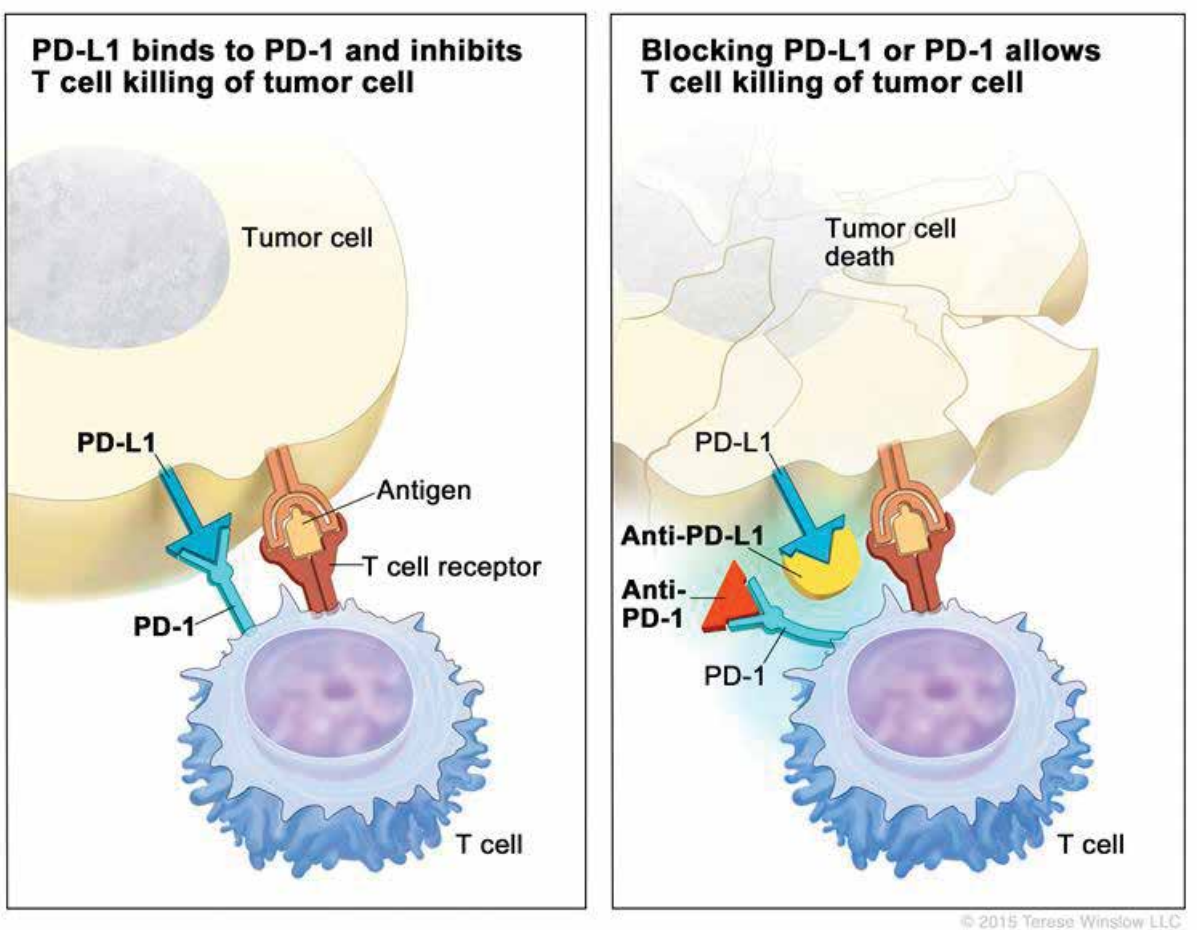
Often, when the side effects erupt, the immune system causes problems that go well beyond the kidney. There can be damage to the liver, lung, colon, or endocrine organs as well. "When it is more than one organ, you have more than one reason to stop the agent. Like other chemotherapy, when it becomes toxic, you try to change the cancer treatment," Selamet said.

In some cases, when patients are convinced the immunotherapy is needed to save their lives, they may decide that the side effects are worth the cost, and thus may progress to dialysis.

The need for clinicians to be familiar with immunotherapy agents and their side effects will only grow as more of them come on the market and the indications for their use expand. The currently approved agents are in a wide range of clinical trials and many others are in development. The first agents were approved in 2012, and their effectiveness has only increased researchers' enthusiasm about their potential.

"We think now that the immune system is really capable of mediating anti-tumor activity against almost any type of tumor," Kaufman said. "There are some types that have been holdouts that haven't responded and we are trying to understand why that is the case. We think eventually most cancers might be amenable to at least some form of immunotherapy."

Figure 1. Immune checkpoint inhibitors' mechanism of action



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Electronic Tools

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tools have shown promise at reducing AKI, and experts predict that they will increasingly become a routine part of practice as their use and the technology matures.

"Acute kidney injury is the most common complication of critical illnesses and has a dire impact on patients' outcomes," said Kianoush Keshani, MD, MS, a nephrology intensivist at the Mayo Clinic. "Anything that we can do to potentially avoid its development or progression to higher stages would potentially have an impact on mortality."

E-alerts

Electronic medical records contain important information that can be used to identify patients with AKI or those at risk. So, some hospitals have developed computer programs that can help alert physicians when a patient's creatinine levels have spiked or their urine production decreases, signaling kidney injury. Or they can warn physicians when a patient is receiving a medication or combination of medications that puts them at risk of such an injury.

"We want the electronic health record to assist clinicians to provide better care to patients," said Kashani.

Despite the promise of such electronic tools, the effects of these alerts on care processes or patient outcomes have been mixed. Technical, systems, and human level challenges have hampered their effectiveness. In some cases, alerts have come too late to be useful. In others, physicians haven't been able to easily access all the patient information they need to respond or the information didn't fit smoothly into their workflow. Many hospitals in the US still have very basic electronic health records and don't have the capacity to provide such alerts, Keshani said.

Physicians may also develop alert-fatigue when inundated with too many electronic warnings, he noted.

"If you go to the intensive care unit (ICU), there are so many alerts, so many alarms, that after a little while the providers get tired," he said. "They don't pay attention to any of those alerts and that has potential risk for the time that patients really need attention."

Some studies have shown that e-alerts can improve care processes and have identified what works and what doesn't. For example, Keshani noted physicians tend to ignore warnings not to use vancomycin, which can be nephrotoxic, but they are more receptive to prompts that suggest alternative antibiotics. The alerts also have been more successful in settings with high rates of AKI, such as the ICU, and when they are sent to higher-level physicians.

Next generation

To move beyond the limitations of e-alerts alone, many clinicians and centers have developed more sophisticated systems that leverage computers, pharmacists, and nephrologists' expertise.

Some hospitals have developed an electronic "sniffer" that ferrets out cases of AKI or those at risk, allowing nephrologists or others to continuously monitor patients. Keshani has one running on a laptop in his office that keeps track of all AKI cases in his center's ICUs.

"I know who, when, and what stage of acute kidney injury exists across all ICUs," he said.

At Cincinnati Children's Hospital Medical Center, the Nephrotoxic Injury Negated by Just-in-time Action (NINJA) project takes its sniffer to the next level. It collects data on every noncritically ill child who is exposed to 3 or more nephrotoxic medications or an intravenous aminoglycoside for 3 or more consecutive days. Each day at 11 a.m. hospital pharmacists and Stuart Goldstein, MD, director of the hospital's Center for Acute Care Nephrology, receive a secure e-mail detailing the findings. The findings and any relevant recommendations are then discussed with each child's clinician during rounds. The hospital also adopted a policy of testing creatinine levels daily to assess for acute kidney injury in each of these at-risk children. They've also created software that collects all the data, which is also reviewed by the quality improvement and research teams.

In its first 3 years, the program had become "part of the culture" at the hospital and has decreased the number of children exposed to 3 nephrotoxic medications by 38%, protecting 700 children from such exposures. It also reduced AKI rates by 68% averting almost 400 cases, Goldstein said.

"Our vision is that children should get nephrotoxic medications they need only for the time they need them," Goldstein said. NINJA allows the very precise and reliable collection of information on nephrotoxic drug exposure and disseminates it to health care teams "so they can make a decision near real time at the bedside," he said.

Twelve other pediatric hospitals have already implemented NINJA, with comparable results. By 2020, Goldstein expects 140 pediatric hospitals in the United States and Canada will be participating.

Preliminary data on the program at Phoenix Children's shows that there has been a 34% reduction in stage 1 AKI, a 56% reduction in stage 2 AKI, and a 61% reduction in stage 3 in the first 10 months of the program, according to Vinay Vaidya, MD, the hospital's Vice President and Chief Medical Information Officer and developer of the software for the dashboard. Next, they hope to add automated EMR alerts into the program.

"The alert can stop you just in time from adding that Toradol in a surgical patient who's already in stage one [AKI]," he said. But the dashboard allows more comprehensive views, so they "complement each other."

Physicians in other departments have also started leveraging the dashboard to look at their own patients or their departments. For example, a hematology oncologist is using it to reduce aminoglycoside-linked kidney damage and sends e-mails to his group about patients at risk.

"If you make it easy, generally most of the folks are eager to do the right thing," Vaidya said.

The next step for such automated monitoring programs is to use biomarkers like urinary neutrophil gelatinase-associated lipocalin (NGAL) to identify patients earlier through noninvasive urine tests, something both Goldstein and the Universtity of Alabama Children's team are working on. The Phoenix Children's team also has added NGAL to its dashboard. Goldstein is also working with multiple collaborators to find ways to use genetic data to personalize patients' AKI risk assessments.

All of these programs are part of a larger shift in the field of nephrology to become more proactive, said Keshani. He said this new model of nephrology care is more similar to the way infectious disease specialists practice by coming in each morning and reviewing all the antibiotics to ensure judicious use.

"This is the future that is coming into [nephrology] practice very, very quickly," Keshani said.

Longer Time on Dialysis Linked to Increased Transplant Failure

For non-preemptive living donor kidney transplant recipients, longer pretransplant dialysis exposure is associated with a higher risk of allograft failure, reports a study in the *American Journal of Kidney Diseases*.

The retrospective study included 77,607 adult, first-time, kidney-only living donor transplant recipients reported to the Scientific Registry of Transplant Recipients between 2000 and 2016. Of these, 51,390 underwent non-preemptive transplantation. Duration of pretransplant dialysis exposure was examined for association with kidney transplant failure from any cause including death. Median duration of dialysis exposure in the non-preemptive transplant group was 14 months.

Patients with longer pretransplant dialysis exposure were at higher risk of transplant failure. Compared to dialysis exposure of less than 3 months, hazard ratio for transplant failure from any cause increased from 1.16 for patients with 6 to 9 months of exposure to 1.60 for those with more than 60 months of exposure.

Time on dialysis varied considerably among transplant centers: median exposure was 11.0 months for centers in the 10th percentile versus 18.9 months for those in the 90th percentile. Pretransplant dialysis exposure was shorter at centers with higher proportions of living donor transplants.

Other factors associated with longer dialysis exposure were black race, low income, nonprivate insurance, less than high school education, and longer time not working for income. Even for patients with these characteristics, dialysis exposure varied between transplant centers.

The new results show that longer duration of dialysis before living donor kidney transplantation is associated with a higher risk of transplant failure from any cause. Duration of pretransplant dialysis exposure varies between centers and is associated with patient sociodemographic factors. "Strategies to increase the efficiency of living donor transplantation in non-preemptive recipients are warranted," the researchers conclude [Gill JS, et al. Variation in dialysis exposure prior to nonpreemptive living donor kidney transplantation in the United States and its association with allograft outcomes. *Am J Kidney Dis* 2017; DOI: https://doi.org/10.1053/j.ajkd.2017.11.012].

Higher BUN Linked to Higher Incidence of Diabetes

Elevated blood urea nitrogen (BUN) levels are associated with an increased risk of developing diabetes, according to a study in *Kidney International*.

The researchers analyzed a national cohort of more than 1.3 million US veterans enrolled in the VA Health Care System. All patients were initially free of diabetes. At the time of cohort entry, 8.77% of individuals had an elevated BUN level of greater than 25 mg/dL. Risk of incident diabetes associated with BUN was assessed over a median follow-up of nearly 5 years, including joint risk models of estimated glomerular filtration rate (eGFR) and BUN.

Among patients with a BUN level of 25 mg/dL or less, there was no association between eGFR and incident diabetes. However, an elevated BUN of 25 mg/dL or higher was significantly associated with diabetes, even in those with eGFR of 60 mL/min/1.73 m^2: hazard ratio (HR) 1.27. For patients with elevated BUN and eGFR of less than 15 mL/min/1.73 m^2, the HR increased to 1.68.

Diabetes risk increased progressively with BUN level on spline analysis. In analyses considering eGFR as a continuous covariate, elevated BUN was associated with an increased risk of diabetes, HR 1.23; while eGFR was not related to incident diabetes. In two-stage residual inclusion analyses, each 10 mg/dL increase in BUN was associated with an increase in diabetes risk.

Previous reports have linked higher urea levels to increased insulin resistance and suppressed insulin secretion. The new study demonstrates a significant increase in diabetes incidence in veterans with elevated BUN levels, independent of eGFR. The results suggest a bidirectional relationship between diabetes and kidney disease: in addition to the known increase in kidney disease risk associated with diabetes, urea may be associated with increased diabetes risk [Xie Y, et al. Higher blood urea nitrogen is associated with increased risk of incident diabetes mellitus. *Kidney Int* 2017; DOI: 10.1016/j.kint.2017.08.033].

New Data on Long-Term Outcomes in Living Kidney Donors

At mid- to long-term follow-up, living kidney donors are at significantly increased risk of end stage renal disease (ESRD) and preeclampsia, concludes a meta-analysis in the *Annals of Internal Medicine*.

A systematic review identified 52 observational studies comparing a broad range of health outcomes in living kidney donors, with follow-up of 1 to 24 years. Meta-analysis included 118,426 living kidney donors and 117,656 controls.

The data showed no significant difference in all-cause mortality for living kidney donors compared to nondonors. Several other outcomes of concern were also similar between groups, including cardiovascular disease, hypertension, and type 2 diabetes. Health-related quality of life scores, including physical and mental health components, were comparable as well. Some evidence suggested a higher vitality score in donors versus controls.

Living kidney donation was associated with higher mean diastolic blood pressure and lower mean estimated glomerular filtration rate. Living donors were more likely to develop ESRD: incidence rate 0.5 versus 0.1 per 1000 person-years, relative risk (RR) 8.8. Female donors were at increased risk for preeclampsia: incidence rate 5.9 versus 3.1 per 100 pregnancies, RR 2.12.

Questions remain as to the long-term impact of living kidney donation on donor health and well-being. The new meta-analysis, including data on nearly 120,000 living kidney donors, finds increased relative risks of ESRD and preeclampsia, although the absolute risks are low.

Overall mortality, cardiovascular disease and type 2 diabetes risk, and psychosocial outcomes are similar to those of nondonors. The authors discuss the implications for informing prospective donors of the risks of living kidney donation [O'Keefe LM, et al. Mid- and long-term health risks in living kidney donors: a systematic review and meta-analysis. *Ann Intern Med* 2018; DOI: 10.7326/M17-1235].

Better Outcomes for ESRD Resulting from Granulomatosis with Polyangiitis

Since the 1990s, the risk of death has decreased for patients with end stage renal disease due to granulomatosis with polyangiitis (GPA-ESRD), reports a study in *Arthritis Care & Research*.

From the US Renal Data System, the researchers identified 5929 patients diagnosed with GPA-ESRD between 1995 and 2014, representing nearly all incident cases during that time. Trends in overall and cause-specific mortality were analyzed in subgroups of patients defined by year of ESRD onset: 1995–99, 2000–04, 2005–09, and 2010–14. The overall incidence of GPA-ESRD per million population increased from 0.81 in 1995–99 to 1.15 in 2005–09, stabilizing at 1.12 in 2010–14.

Mortality per 100 patient-years decreased throughout the period studied: from 19.0 in 1995–99, to 16.9 in 2000–04, to 16.2 in 2005–09, to 15.3 in 2010–14. The adjusted hazard ratio for death in the 2010–14 cohort was 0.77, compared to the 1995–99 cohort. The improvement in overall mortality was unaffected by further adjustment for body mass index, smoking, comorbid conditions, region, and initial ESRD therapy modality. On analysis accounting for competing risks, HRs were 0.61 for death from cardiovascular disease and 0.42 for death from infection.

Patients with GPA are at risk of kidney involvement leading to ESRD. The new study is the first to analyze US national trends in the incidence and mortality of GPA-ESRD.

The results show significant improvements in overall and cause-specific mortality from GPA-ESRD over the past two decades. While the specific factors responsible for gains cannot be identified, the findings "likely reflect improved management of both GPA and ESRD," the researchers write [Wallace ZS, et al. Improving mortality in end-stage renal disease due to granulomatosis with polyangiitis from 1995 to 2014. *Arthritis Care Res (Hoboken)* 2018; DOI: 10.1002/acr.23521].

High Rates of Overtreatment for Type 2 Diabetes in Older Adults

Overtreatment of type 2 diabetes is common and potentially harmful in older adults, according to a primary care study in *Diabetes, Obesity and Metabolism*.

The observational study included 1002 patients being treated for type 2 diabetes at five Dutch primary care centers, including 319 patients aged 70 years or older. These older patients were classified into subgroups according to Dutch guidelines, based on glycated hemoglobin targets: 7%, 7.5%, and 8%. Levels of personalized care for type 2 diabetes were assessed, focusing on overtreatment.

The analysis identified 165 patients aged 70 or older with an HbA1c target of greater than 7%. In this group, 54.0% of patients had microvascular complications, compared to 35.2% of those with lower HbA1c targets. Rates of macrovascular complications were 33.3% versus 17.7%, respectively. Patients with higher HbA1c targets were almost more likely to use five or more medications and more likely to be frail.

Of the 165 patients, 64 were overtreated: a rate of 38.8%, or 20% of all patients aged 70 years or older. Most overtreated patients were frail and used five or more medications. About 20% had episodes of hypoglycemia, while nearly 30% had accidents involving falls.

For patients with type 2 diabetes aged 70 or older, the risk of harm associated with HbA1c targets under the conventional 7% seem to outweigh the benefits. There are indications of overtreatment in this group of patients in the United States as well as Europe. In the Netherlands, more than 85% of patients with type 2 diabetes are managed in primary care.

The new study suggests that many older adults with type 2 diabetes are overtreated, with probable harmful consequences. "Personalized treatment in older people with type 2 diabetes is not common practice," the researchers write. They suggest that guidelines defining a lower HbA1c limit might be helpful to prevent overtreatment [Hart HE, et al. Overtreatment of older patients with type 2 diabetes mellitus in primary care. *Diabetes Obes Metab* 2017; DOI: 10.1111/dom.13174].

Kidney Disease in Childhood Increases Adult ESRD Risk

Any history of childhood kidney disease is associated with a substantially increased risk of end stage renal disease (ESRD) in adulthood, reports a study from Israel in *The New England Journal of Medicine*.

The historical cohort study included more than 1.5 million Israeli adolescents undergoing medical assessment before military conscription between 1967 and 1997. History of childhood kidney disease was assessed, including congenital anomalies of the kidney and urinary tract, pyelonephritis, and glomerular disease. When evaluated at a mean age of 17.7 years, all individuals had normal kidney function and blood pressure.

Risk of ESRD in adulthood was assessed by linkage to the national ESRD registry. During a mean follow-up of 30 years, 2490 individuals developed ESRD.

Any type of childhood kidney disease was associated with a fourfold increase in the risk of ESRD during adulthood: hazard ratio (HR) 4.19. Adjusted HRs were 5.19 for congenital anomalies, 4.03 for pyelonephritis, and 3.85 for glomerulonephritis.

Childhood kidney disease was also associated with younger age at ESRD onset, with an HR of 10.40 for risk of ESRD among adults younger than 40. The excess risk decreased with longer follow-up, but remained significant up to 40 years' follow-up.

Although most childhood kidney disease has a favorable prognosis, the impact on lifelong risk of chronic kidney disease has been unclear. This nationwide study shows an increased risk of ESRD among those with any history of childhood kidney disease, despite apparently normal kidney function in adolescence.

This risk may stem from hyperfiltration of remaining nephrons in patients with early kidney disease. The researchers conclude that their findings may imply "an even greater, albeit unmeasured, risk of the considerably more prevalent antecedent stages of chronic kidney disease" [Calderon-Margalit R, et al. History of childhood kidney disease and risk of adult end-stage renal disease. *N Engl J Med* 2018; 378:428–438].

Policy Update

Telehealth and Telemedicine Reimbursement Get Big Boost from Passage of Two-Year Budget Deal

By David White

Telehealth and telemedicine reimbursement received big boosts in the two-year budget deal signed into law by President Donald Trump on February 9, 2018, with one senator saying the law does more for Medicare coverage of telehealth than any past legislation.

The budget deal included parts of the Creating High-Quality Results and Outcomes Necessary to Improve Chronic (CHRONIC) Care Act advocated for by the American Society of Nephrology (ASN) and fellow members of the Telehealth/Remote Monitoring Coalition. Targeted at Medicare's telehealth and telemedicine reimbursement rules, the new law:

- adds the patient's home, without geographic restriction, to the list of originating sites for monthly telehealth assessments with a nephrologist, beginning in 2019, allowing for home dialysis monthly ESRD-related clinical assessments through telehealth in Medicare;
- eliminates geographic restrictions on telestroke consultation services, beginning in 2019;
- expands telehealth coverage under Medicare Advantage Plan B, beginning in 2020;
- gives Accountable Care Organizations more flexibility to use telehealth services; and
- extends for two years the Centers for Medicare & Medicaid Services' (CMS) Independence at Home demonstration, which establishes home-based primary care teams for Medicare beneficiaries with multiple chronic conditions and increases the cap on the total number of participating beneficiaries from 10,000 to 15,000.

Currently, Medicare pays only for certain telehealth services under Part B, normally in the form of face-to-face video conferencing. Under the new law, Medicare can pay for telehealth benefits, such as telemonitoring and medication therapy management, under private Medicare Advantage plans starting in 2020.

The next step is for Medicare to decide what services should be covered. *Bloomberg News* reported that CMS Administrator Seema Verma said during a February 6 conference that telehealth coverage provisions will be included in this year's Medicare payment rules, which are expected in the spring.

The three major rules that govern nephrologists' reimbursement and will need adjustments to implement the new law are the rules on the Quality Payment Program (QPP), End-Stage Renal Disease Prospective Payment System/Quality Incentive Program (ESRD PPS/QIP), and the Physician Fee Schedule. The ASN Quality Committee reviews these three rules annually and makes comments/recommendations for CMS to consider. The 2018 Physician Fee Schedule reflects CMS' intent to move further in this direction already. This year, it includes reimbursement for remote patient monitoring and CPT codes for telemedicine for the first time.

March Deadlines for Submission of 2017 Data for the Quality Payment Program

To potentially earn a positive payment adjustment under MIPS (Merit-based Incentive Payment System), send in data about the care you provided and how your practice used technology in 2017 to MIPS by the March 31, 2018, deadline. In order to earn the 5% incentive payment by significantly participating in an Advanced APM, just send quality data through your Advanced APM.

CMS Web Interface users (groups with 25 or more clinicians, including APM entities) have a shorter timeframe to submit quality data, as the submission window for this method closes March 16, 2018, at 8 p.m. Eastern Time. Go to qpp.cms.gov

WOMEN AND KIDNEY DISEASES

The risk of developing CKD is at least as high in women as in men, and possibly higher. Yet the number of women receiving dialysis is lower than the number of men, and women are more likely to donate kidneys but less likely to receive transplants.

The March 2018 World Kidney Day theme, "Kidneys & Women's Health: Include, Value, Empower," aims to shine a light on issues of equitable healthcare access for women with kidney diseases worldwide.

Here, we summarize recent reports providing insights into disparities in CKD care for women in the United States and around the world. We also review basic science findings regarding sex differences in animal models that could lay the groundwork for a variety of preclinical and clinical studies. Investigators are increasingly aware that results found in males do not always hold true in females, and that there are clear differences in the sexes that should be considered when preventing and treating health issues.

Sex, Gender, and CKD Care

Chronic kidney disease affects approximately 195,000 women worldwide and causes close to 600,000 deaths per year. A recent review in *Seminars in Nephrology* looks at patterns of care affecting the burden of CKD among women, noting important effects of sex, referring to biological differences; as well as gender, reflecting social differences.

Some biological differences between the sexes are well known but are typically not considered in CKD care. A prime example is anemia: although women typically have lower hemoglobin and hematocrit levels, current CKD guidelines do not include sex-specific targets for anemia. An issue of special importance is the possibility that women and men may have differing responses to erythropoiesis-stimulating agents.

There may also be important differences in calculation of dialysis dosage, with some studies suggesting overestimation of dialysis adequacy in women, as calculated by Kt/V. Other sex-related pathophysiologic differences warrant further study, including the higher rate of noncardiovascular deaths occurring among women, particularly at younger ages, according to study authors Juan-Jesus Carrero, MD, of Karolinska Institute and colleagues.

In an effort to provide a global perspective on CKD, gender, and access to care, the authors review gender-related differences in CKD and access to kidney care around the world, including differences by region in Africa and Asia and by country in Latin America. Women's access to care for CKD and end stage renal disease (ESRD) is affected by healthcare expenditures and gender social disparities.

But disparities in access to ESRD care are not limited to lower-income countries: women are consistently under-represented in hemodialysis clinics. These differences are not explained by a lower prevalence or incidence of CKD, nor by potential sex bias in estimated glomerular filtration rate.

Some evidence suggests that dialysis is initiated later in women, possibly reflecting lower awareness of kidney disease. Other studies have reported that kidney function declines more rapidly in women than men. However, an alternative explanation is that women have higher mortality on dialysis, or die before initiating dialysis. Thus even in the United States and other high-income countries, the lower rate of dialysis among women may result from "psycho-socioeconomic" rather than biological factors.

Studies consistently find that women tend to donate kidneys more often but are less likely to receive kidney transplants. Again, this finding is present in high-income as well as lower-income countries. In the Dialysis Outcomes and Practice Patterns study, 5.6% of US women on dialysis received kidney transplants compared to 7.0% of men. Similar gender disparities may prevail among children with kidney disease.

The assembled evidence highlights suboptimal understanding of biological differences in kidney disease between men and women, while also raising questions about gender-related differences in treatment for CKD and ESRD—including access to dialysis and transplantation—in women and girls.

"Research is needed urgently to elucidate the reasons behind these disparities, as well as to develop CKD treatment strategies tailored to women's unique healthcare needs," Carrero and colleagues conclude. ■

Carrero J-J, et al. Chronic kidney disease, gender, and access to care: a global perspective. Semin Nephrol *2017; 37:296–308.*

Women Less Likely to Have AVFs at Dialysis Initiation

Studies have shown gender disparities in care for many chronic diseases, and ESRD is no exception.

Studies from the early 2000s suggested that women had lower rates of hemodialysis initiation using an arteriovenous fistula (AVF), the preferred hemodialysis vascular access. A recent study in *Hemodialysis International* analyzed gender-related differences in AVF use at dialysis initiation, including variations between ESRD regional networks.

Mariana Markell, MD, and colleagues of SUNY Downstate School of Medicine, Brooklyn, analyzed US Renal Data System data on 202,999 patients initiating hemodialysis between 2006 and 2009. The analysis was limited to 187,577 patients who received predialysis nephrology care. The study examined gender disparities in AVF use at hemodialysis initiation, with adjustment for a wide range of potential confounders.

The results showed a persistent gender gap during the study period: 18.2% of women had an AVF at dialysis initiation, compared to 25.8% of men. On adjusted analysis, the rate of AVF use at dialysis initiation was 30% lower in women compared to men: odds ratio (OR) 0.69.

A wide range of other factors were also associated with a lower likelihood of AVF at initiation. These included lower body mass index; presence of diabetes, peripheral arterial disease, congestive heart failure, or chronic obstructive pulmonary disease; history of alcohol abuse; inability to ambulate; and being uninsured. The strongest factor was inability to ambulate: odds ratio 0.49. An AVF was more likely to be present in patients who had more than 12 months of predialysis nephrology care: OR 1.89, compared to those with less than 6 months of nephrology care.

The data also showed significant variations in AVF gender disparity between ESRD regions. Region 2 (New York) and region 12 (Midwest) had the largest disparities: OR 0.58 and 0.54, respectively. The disparity was smallest in region 16 (Alaska and Pacific Northwest) and region 18 (California): OR 0.80 and 0.79, respectively. Only region 16 had no statistically significant difference by gender.

The gender disparity was larger for black women compared to non-black women: OR 0.66 versus 0.70. Differences in gender disparity in AVF use were more pronounced in the youngest (19 to 45) and oldest (76 and older) age groups.

The findings add to previous reports of gender disparities in AVF use at dialysis initiation. These differences are present in all age groups and across races, and after controlling for other important patient and clinical characteristics.

The study also shows variations in AVF gender disparities across ESRD networks. Absolute rates of AVF use at dialysis initiation range as low as 15%—far below the 50% rate targeted by the "Fistula First" initiative.

While many factors could contribute to these differences, the findings suggest that practice-based factors may play an important role, Markell said.

"Further studies investigating physician or patient bias, geographic referral patterns, maturation failure and other reasons for access choice should be performed with gender as a focus, in order that all patients may have appropriate access to 'Fistula First,' regardless of gender or geographic location," he said. ■

Markell M, et al. Gender disparity in fistula use at initiation of hemodialysis varies markedly across ESRD networks—Analysis of USRDS data. Hemodial Int *2017 Jun 29. doi: 10.1111/hdi.12579.*

Research Reveals Important Differences between Male and Female Kidneys

By Tracy Hampton

Investigators who are designing clinical trials and preclinical studies have realized that results found in males do not always hold true in females, and that there are clear differences in the sexes that should be considered when preventing and treating a wide variety of health issues. Kidney researchers also note that because female physiology is optimized for successful reproduction—which entails large fluctuations in vascular, hemodynamic, and renal function—it's likely that female kidneys have important differences from those of males.

With this in mind, a team led by scientists at the Keck School of Medicine of the University of Southern California, Los Angeles, recently conducted a study to compare female and male nephron organization and physiologic function.

In their study, which was conducted in rodents and was published in the *Journal of the American Society of Nephrology (JASN)*, the investigators applied quantitative immunoblotting to generate profiles of transporters, channels, claudins, and selected regulators in both sexes.

"The study revealed significant differences: the female rat nephron excreted a saline volume challenge more rapidly than males, which was attributed to less sodium reabsorption by transporters in the early part of the kidney nephrons," said lead author and graduate student Luciana Veiras. "This increased volume flow to the later part of the nephrons where sodium transporters were more abundant and activated, a pattern that facilitates renal potassium elimination as well."

The researchers noted that this pattern could allow for fluid retention adaptations required of pregnancy and lactation.

"We know that pronounced fluid retention is required in pregnancy and lactation. We propose that the baseline transporter profile is positioned for upregulation of fluid reabsorption without accompanying hypertension: raising reabsorption in the early nephron—where it is lower than in males—would increase the salt, water, and potassium reabsorption needed to support the development of the offspring," said senior author Alicia McDonough, PhD. These are important areas for future consideration as they could impact the treatment of electrolyte disturbances during pregnancy, such as preeclampsia.

The findings relate to previous observations that female rodents are resistant to hypertension in response to hypertensive stimuli or genetic hypertension, and that female humans have lower rats of hypertension than males before menopause. The latest results suggested that female rats could maintain salt balance at lower blood pressures when faced with stimuli or injuries that decrease sodium excretion. "In fact, the female pattern of salt transport and transporters resembles what is seen in a male exposed to hypertensive stimuli. Said another way, the females are optimized for excreting salt, which explains why a rise in blood pressure is not necessary in order to maintain salt and water balance in response to hypertension stimuli," said Veiras. Interestingly, after menopause, female humans lose this "advantage," she said.

The *JASN* study also noted that the mouse female nephron has a similar transporter profile (lower in early nephron, higher in later nephron vs. males), but did not exhibit such pronounced differences in responses to saline and potassium challenges.

"This study demonstrates there are, indeed, sexual dimorphic characteristics of renal transporters as well as consequential physiologic differences at baseline," said Veiras. "While some sex-specific transporter differences had been reported previously in the literature, this study provides a comprehensive map of transporter abundance, activation, and the physiological impact important to understand sexual dimorphisms in function and pathophysiology. These baseline findings will be useful to investigators probing effects of gene manipulations, pathologic stimuli, or disease progression in the two sexes."

The findings lay the groundwork for a variety of preclinical and clinical studies that should be pursued. "Whether the differences determined for rats and mice pertain to humans is the most important question and warrants careful investigation, perhaps by combining non-invasive physiologic assays and urinary biomarkers," said McDonough.

Importantly, the findings reveal that sexual differences should be considered for the treatment of common kidney-related disorders including hypertension, diabetes, and kidney stones, which all involve renal transporters. ■

Luciana C. Veiras, et al. Sexual dimorphic pattern of renal transporters and electrolyte homeostasis. J Am Soc Nephrol *28; 12:3504-3517.*

Sex and Acute Kidney Injury

By Lisa M. Curtis

Enigmas abound in the clinical care and research related to acute kidney injury (AKI). Unfortunately, little conversion of research findings to changes in patient care has occurred.

The complexities associated with staging clinical AKI and identifying the timing of the insult, as well as the inability to identify characteristics that clearly define why and how certain patients recover while others progressively decline in renal function—some leading to chronic kidney disease (CKD)—all lead to an unsatisfying status of care for patients. Likewise, discordant findings in preclinical models of AKI have led to more questions than answers.

Sex remains a variable that has not often been examined specifically. Older studies, in both clinical and basic science investigations, have focused on male-only populations, owing to the lower incidence of AKI in females, or have been of mixed sex. Insufficient power in these latter studies to examine sex as a variable has resulted in an assumption of understanding without proper consideration that females may in fact exhibit different biology. With the advent of a focus on inclusion of women and females in research studies advocated by the National Institutes of Health NIH (1), a new awareness of the distinctions between women and men, and female and male subjects, is evolving.

Recent clinical studies are targeting female sex as a variable. At times, however, these studies are complicated by the inclusion of women across an age spectrum that includes the menopausal shift. In addition, the reality of comorbidities in patients has made deciphering a sex-specific effect challenging. Studies in which the initiation of the insult can be identified in advance (e.g., cardiac procedures, renal transplantation) are few and have had conflicting outcomes, perhaps owing to the presence of preexisting kidney or vascular disease, which may mask a female sex–defined protection.

The key is to remain persistent in our curiosity and perseverance to uncover the amazing physiology and pathophysiology of kidneys, male and female, so that robust changes can come to the care of patients with AKI.

Basic science studies into the injury and reparative mechanisms in AKI allow for better precision in defining the insult and also allow for the absence of other comorbidities. A caveat to such studies of AKI is the lack of complete concordance between rodent models of AKI and the multiple manifestations of human AKI. As noted by ASN Past President Bruce Molitoris, MD, FASN, and colleagues a number of years ago, AKI models are "imperfect, but indispensable" (2).

Two primary rodent models of AKI are renal ischemia-reperfusion injury (IRI), which is induced by clamping the renal pedicle, or systemic administration of a toxin, principally cisplatin, heavy metals, or other nephrotoxins. IRI is further complicated by variations in clamping of one kidney only, with or without contralateral nephrectomy, or bilateral pedicle clamping, often with varying durations of ischemia. Dosing schemes for administering a nephrotoxin may also vary, both in absolute amount as well as temporal administration differences, and a variety of agents may be used.

Notably, these studies rely on our basic understanding of renal physiology, much of which has been done in male rodents. Mechanistic studies of sex-specific differences in AKI are only beginning to be done, and clearly more research is needed. One overriding question worthy of investigation is deciphering why females, both humans and rodents in our models, exhibit a decreased susceptibility to AKI. In that distinction may lie novel and innovative treatments that can be applied to men and women, as well as new biomarkers to help stage and effectively treat preemptively in the course of injury.

As Albert Einstein said, "If we knew what it was we were doing, it would not be called research, would it?" The key is to remain persistent in our curiosity and perseverance to uncover the amazing physiology and pathophysiology of kidneys, male and female, so that robust changes can come to the care of patients with AKI. ■

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Exposure to women's health issues in training, practice is topic of new survey

By Monica Reynolds, Keisha Gibson, Laura H. Mariani, and Michelle A. Hladunewich

This year's World Kidney Day falls on International Women's Day, offering the nephrology community an excellent time to reflect on the theme, "Kidneys & Women's Health: Include, Value, Empower."

What progress have we made in addressing women's kidney health? Why do so many unanswered questions remain? Most important, how do we as nephrologists currently care for women with chronic kidney disease (CKD)? How do we empower them?

For many of us, topics in women's health are fraught with anxiety owing to a poor knowledge base, uncertainties in the literature, or a lack of clinical experience. Yet our patients rely on us to provide the most up-to-date knowledge on these topics in order to help them make informed decisions about the life-altering events associated with kidney diseases.

Although many nephrologists have a general sense of the risks and disparities that affect women with CKD, this information is not often at the forefront of the clinical visit because women of childbearing age still represent a minority of patients seen from day to day.

Preconception counseling takes dedicated time and can elicit a variety of emotions from both the patient and provider. Reviewing a detailed obstetrical history provides insight into a woman's risk for future proteinuria, hypertension, end stage renal disease (ESRD), and cardiovascular disease, but it is unclear if this is standard practice among nephrologists. Clinical training in women's health is also vague and likely largely dependent on a preceptor's personal experience. Without adequate exposure and structured didactics, discussions of safe contraception methods, fertility preservation options, optimal pregnancy timing, or appropriate anti-hypertensive and immunosuppressive agents for use while pregnant or breastfeeding may simply fall short.

CureGN is an observational prospective cohort study of biopsy-proven primary membranous nephropathy, focal segmental glomerulosclerosis, minimal change disease, and IgA nephropathy. With current enrollment including over 475 women aged 13 to 55, the study seeks to answer disease-specific questions about both pregnancy and women's health.

The women's health working group of CureGN is interested in your experience caring for women with CKD, and is conducting an international survey to better understand what limits your ability to provide reproductive counseling to women with CKD/ESRD, and what resources would be helpful to better serve this population.

We hope to improve the current state of clinical care for this growing population and help shape the future teaching of these clinically relevant and essential topics.

If you are an adult nephrologist, please visit https://www.surveymonkey.com/r/womens-health-nephrology to complete the survey, which is anonymous and should take less than 10 minutes to complete.

Results of the survey will allow us to compare adult nephrologists' exposure to women's health issues in training and current practice, their confidence in counseling and managing these issues, and ways to improve care in the future. We greatly appreciate your participation in this vital research. ■

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Calcimimetics in End Stage Renal Disease

By Susan Ziolkowski and Graham Abra

Chronic kidney disease–mineral bone disorder (CKD-MBD) is a universal complication of advanced chronic kidney disease, and is characterized by bone disease, calcification of extraskeletal tissue, and multiple biochemical abnormalities.

Specific CKD-MBD laboratory abnormalities, such as hyperphosphatemia, hyperparathyroidism, hypocalcemia, and elevated fibroblast growth factor 23 levels, are each independently associated with mortality in dialysis patients (1, 2).

Management of CKD-MBD

Treatment for CKD-MBD generally starts with counseling about a low-phosphorus diet and phosphate binders to limit gastrointestinal phosphorus absorption (3–5). Clinically meaningful reductions in serum phosphorus levels can also be achieved by increasing weekly dialysis time. Next, calcitriol or another active vitamin D agent is typically started to reduce parathyroid hormone (PTH) levels to goal. Neither the Kidney Disease Outcomes Quality Initiative nor the Kidney Disease Improving Global Outcomes (KDIGO) guidelines give preference to any specific active vitamin D agent.

Cinacalcet is often started when adequate PTH control is not achieved with the above measures or if worsening hyperphosphatemia or hypercalcemia complicates therapy. Cinacalcet, the first calcimimetic medication approved by the Food and Drug Administration (FDA) as a treatment for secondary hyperparathyroidism, is effective in decreasing PTH, calcium, and phosphorus levels, and it has reduced the need for parathyroidectomy (6, 7). Cinacalcet acts by binding to the calcium-sensing receptor of the parathyroid gland, "mimicking" the effect of calcium and decreasing PTH levels.

A new intravenous calcimimetic, etelcalcetide, has recently been approved by the FDA. In the phase 3 trial, the primary efficacy end point (achieving more than a 30% reduction from baseline in mean predialysis PTH levels during weeks 20 to 27) was achieved, proving noninferiority of etelcalcetide to cinacalcet (Table 1). In addition, the secondary end point, a more than 50% reduction of PTH levels, was achieved more frequently in the etelcalcetide group (8).

Notably, nausea and vomiting occurred at similar rates between etelcalcetide and cinacalcet, indicating a possible centrally mediated mechanism. Etelcalcetide is associated with a higher incidence of hypocalcemia; however, few patients developed related symptoms, including muscle cramping and parasthesias (8).

Etelcalcetide is a dialyzable peptide that must be given posthemodialysis to avoid drug removal. It has not been tested in patients on peritoneal dialysis or home hemodialysis.

New KDIGO guidelines, released in July 2017, do not change the target PTH level, which remains within two to nine times the upper limit of normal for the assay (9). The work group did not prioritize any PTH-lowering treatment (calcimimetics, calcitriol, or other active vitamin D agents), suggesting that all were suitable as first-line drugs.

Cinacalcet, cardiovascular disease, and mortality

Early randomized, placebo-controlled trials showed a reduction in the risk of cardiovascular hospitalization with cinacalcet use (10). The Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) Trial randomized 3883 hemodialysis patients with moderate to severe secondary hyperparathyroidism to cinacalcet or placebo (11). Participants were followed for up to 64 months, with a primary composite end point of time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event.

The unadjusted intention to treat analysis of the primary composite end point was not significantly different between the two groups (relative hazard, 0.93; 95% confidence interval, 0.85 to 1.02; p = 0.11). Differences in baseline characteristics, including older age in the cinacalcet arm and initiation of commercially available cinacalcet or parathyroidectomy in the placebo arm, may have attenuated the differences between the two groups.

A secondary analysis comparing older versus younger EVOLVE Trial participants revealed a significant reduction in the primary composite outcome in participants ≥65 years old, although an observational study showed conflicting results (12, 13).

Cinacalcet, fractures, and parathyroidectomy

Dialysis patients have a higher incidence of fractures, with increased morbidity and mortality compared with the general population (14). Secondary hyperparathyroidism is a major contributor to bone disease in ESRD, and treatment with cinacalcet improves histopathologic changes seen on bone biopsy (15). In the EVOLVE Trial, the effect of cinacalcet on clinical fracture was not statistically significant (relative hazard, 0.89; 95% confidence interval, 0.75 to 1.07) (11). However, when accounting for differences in baseline characteristics, multiple fractures, and/or events prompting discontinuation of study drug, cinacalcet reduced the rate of clinical fracture by 16% to 29% (16). Furthermore, parathyroidectomy occurred in 7% of cinacalcet-treated patients and 14% of placebo-treated patients (relative hazard, 0.44; 95% confidence interval, 0.36 to 0.54). Independent predictors of parathyroidectomy included younger age, female gender, geographic region, and absence of history of peripheral vascular disease (11).

Challenges and new developments

There are multiple practical challenges to current successful calcimimetic prescribing. Prescribers often encounter barriers owing to insurance prior authorization policies. Cinacalcet often comes at significant patient cost under Medicare Part D, and some patients are unable to afford copays. The wholesale annual cost of cinacalcet dosed at 30 to 60 mg per day ranges from $10,000 to $19,400, respectively. Gastrointestinal side effects of cinacalcet also limit patient adherence.

Dialysis facilities already provide dietary phosphorus restriction counseling and active vitamin D agents.

In January 2018, dialysis providers became responsible for providing both cinacalcet and etelcalcetide for Medicare patients and likely, many private insurers as well. This represents an opportunity to address many of the practical prescribing issues noted here.

In conclusion:

- Management of CKD-MBD in ESRD includes dietary phosphorus restriction, phosphate binders, active vitamin D agents, and calcimimetics.
- Cinacalcet use is associated with lower rates of parathyroidectomy and possibly, fewer bone fractures.
- Data on the effect of cinacalcet on cardiovascular disease and mortality remain uncertain.
- Compared with cinacalcet, etelcalcetide more effectively lowers PTH, with a similar incidence of nausea and vomiting but higher rates of hypocalcemia.
- Physicians will need to individualize CKD-MBD care by carefully evaluating the value and benefit against the risks and costs of different approaches as dialysis facilities began taking on the provision of calcimimetics in January 2018.

Susan Ziolkowski, MD, is Ruth L. Kirschstein National Research Service Award (NRSA) Individual Postdoctoral Fellow, and Graham Abra, MD, is a clinical assistant professor at Stanford University. Abra is also director, Medical Clinical Affairs, at Satellite Healthcare.

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Table 1. Cinacalcet vs. etelcalcetide in CKD-MBD

	SENSIPAR (cinacalcet)	**PARSABIV** (etelcalcetide)
Mechanism of Action	A small module compound that binds to the transmembrane domain of the CaSR	A synthetic peptide binding directly to the extracellular domain of CaSR
Route	Oral	Intravenous
Efficacy: % of patients with >30% iPTH reduction	63.9%	77.9%
Safety: % patients with Adverse Reactions		
• cCa decrease	68.9%	59.8%
• Nausea	18.3%	22.6%
• Vomiting	13.3%	13.8%

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

Creating a Stronger Nephrology Community
Two years of ASN Communities

By Richard Glassock, MD, and Roger Rodby, MD, with Zach Cahill, Senior ASN Communities Associate

Increasingly in the 21st century, nephrologists and other physicians are turning to social media (SoMe) and internet-based forums to teach the next generation, treat their patients better, and bolster their knowledge. From blogs to Twitter, there are an overwhelming number of non-traditional learning and teaching resources available to nephrologists (1–3).

For the past two years, ASN Communities has been a vital addition to this space by providing an online venue for nephrologists around the world to have detailed discussions about complex questions, share their knowledge with peers, and create the peer-to-peer relationships that many only find in academia. ASN Communities combines the best of other SoMe platforms into a professional, iterative, educational experience for both the mundane and the most complex questions of physicians around the world.

ASN leverages new paradigms for medical education

Over the past few years, ASN has grown to recognize and take advantage of the new paradigms and evolutions of medical education. ASN Communities is one result of this recognition. While participation is limited to ASN members, 61% of the membership have visited the site at least once. ASN Communities benefits from not being a US-dominated platform, with 30% of logins and 26% of posts originating from outside North America. To date there have been 15,731 posts by 1600 different contributors.

We have learned a lot from the "real world" experiences that dominate the discussions on Communities. Of course, the format encourages posting of the exotic, the unusual, the difficult, and the frustrating cases. But in many instances great pearls of wisdom are uncovered and shared. It is humbling to realize how deficient the evidence base really is concerning resolution of complex problems in nephrology. We have also learned more about the difficulties in applying clinical judgment when data points are missing. Questions are frequently posted about cases that, while we may have an answer or opinion, we realize opinion alone is hardly enough for a forum as important as this. We try very carefully not to be anecdotal, but to supply the proper data to back up any opinions or advice.

The electronic nature of the exchanges carried out on Communities can never exactly duplicate an actual consultation, but the opportunity to receive timely opinions from a diverse array of experienced clinicians is priceless.

Nothing gives us greater professional joy than to learn and teach. The Communities audience is by definition receptive, appreciative, and smart. The questions asked are often complex, and answering them in a manner that is both informative and understandable is a challenge. We may think we know an answer, but backing it up with evidence-based data, and putting it into a cogent form can be daunting. In the end, through this process we always learn something.

We would be remiss to not mention the relationships created through this process. We met so many people at last year's Kidney Week who randomly came up and thanked us for our contributions to Communities. Many of these individuals are international nephrologists we would never have met otherwise. Posting takes time, but those comments make it all worthwhile.

Involvement in Communities provides an unrivaled opportunity to work with the best in the field. We have greatly benefited from working closely with each other in a rewarding academic endeavor with colleagues whose skills we greatly admire.

Medicine can often be a lonely, unforgiving, and sometimes frightening profession. ASN Communities provides solace to these emotions, an outlet to use the cognitive skills that attracted us to nephrology, and an opportunity to knit the global nephrology community closer together. Congratulations to ASN for conceiving this novel communication approach, and to the staff that make it function so smoothly.

"My first post in Communities was on January 19, 2016, on a thread about the use of sodium bicarbonate. Since then I have contributed >1250 discussion posts, averaging out to about three a day! No wonder people ask me how I ever find the time to do this. My answer is always twofold: My kids are in college now (time) and I make the time because I truly enjoy it (interest).

As I have gotten older, I appreciate the role that experience plays in the practice of nephrology. I've hardly seen it all, but I've seen a lot. Take that and my penchant for medical education, 30+ years as an Attending in an academic center, 17 years as Fellowship Program Director and my essentially boundless access to medical information through the internet, and I feel ASN Communities was created for me. I am learning and teaching. What more could I ask for? This really is a great use of my time."

–Roger Rodby, MD

"Time flies quickly when you are having fun. Participation in the Patient Care and Open Forum parts of the ASN Communities over the past 24 months has been interesting, challenging, gratifying and educational. For me it has been a privilege to be a moderator and it has given new meaning to the joy of being a nephrologist in the global sense."

–Richard Glassock, MD

Richard Glassock, MD, is Emeritus Professor at the David Geffen School of Medicine at UCLA, and Roger Rodby, MD, FASN, is Professor of Medicine at Rush University Medical Center. Both are Community Leaders for the Patient Care Q&A Community.

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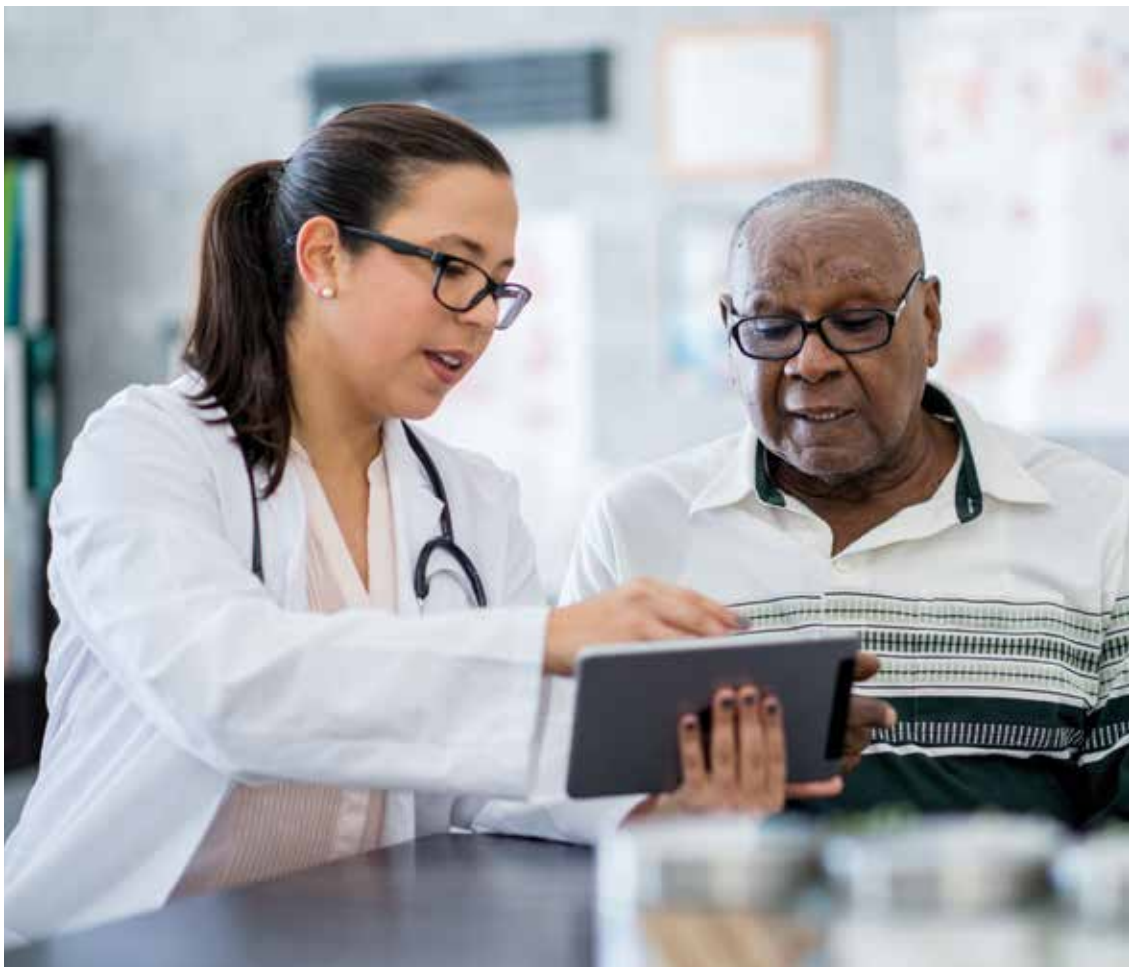

Chronic Kidney Disease: Achieving Better Outcomes

By Derek L. Forfang

I was recently honored to be one of the patients at a roundtable discussion on care models for early detection and better management of chronic kidney disease (CKD). The Rogosin Institute sponsored this roundtable to bring together key stakeholders from the kidney community and the leaders of the local community in Brooklyn, New York. The discussion centered on how to achieve better outcomes for patients at earlier stages of CKD.

My kidneys failed 20 years ago when I was 32 years old. I was told in my mid-20s that I was spilling protein into my urine but did not understand what that meant. I was never told about CKD or the stages of CKD. As a matter of fact, I did not hear those terms until I started advocating about kidney disease 5 years after my kidneys failed. Although I am a type 1 diabetic, I had never been told about my risks of kidney failure, and no one ever discussed steps that might slow its progression or diet precautions after I was diagnosed.

Like many of us with kidney disease, I "crashed" into the emergency department.

I had 42 pounds of fluid on. I went into the hospital weighing 215 lbs. and left 4 days later weighing 173 lbs. I was able to breathe and move my legs again, and there was a catheter in my neck. I remember my son saying, "There you are, I knew you were in there."

This scenario happens much too frequently: 52% of renal patients crash into dialysis or start dialysis in an inpatient setting (1), and 24% of patients crash without ever being diagnosed with CKD (2). Crashes increase costs per patient by approximately $53,000 during the first year on dialysis (3), and 74% of patients start dialysis without the preferred vascular access in place (4).

Although I was seeing physicians for my kidney disease, there was little to no coordination of my care with specialists. I was one of the 25% of new ESRD patients who had not seen a nephrologist (5). It is strange as a patient advocate that I see a lot of statistics and sometimes forget that I am part of them, but I remember the start of treatment for my kidney failure clearly: it was a horrible experience for both me and my family.

Therefore, I am very passionate that others with CKD do not share my experiences. The first year or so on dialysis, I just struggled to survive; I felt like my body was falling apart. I see how smoother starts on renal replacement therapies (RRTs) can improve patient outcomes.

Here is a list of issues that I feel need to be included in a CKD care model:

- Patient activation to assist each patient in being active in his or her own care;
- Patient-centered care planning, focusing on that patient's life goals, values, and culture;
- Education on diet, disease, medications, RRT options (including preemptive transplantation), and palliative care if appropriate;
- Preserving residual kidney function: we like to pee!
- Mental health care;
- Coordination of care;
- Hope.

I watched my grandfather and mother struggle with kidney disease. They had bouts of depression, and I could see in their eyes when they had just lost hope. My mother only lived about a year after starting dialysis, passing at 60 years old. My grandfather lasted about 4 years after his diagnosis. I often think of them both, especially knowing what could have been done better in their care. I have also seen that, when other patients lose hope, their outcomes are never good.

Many questions and topics were discussed at the roundtable and will be shared in upcoming issues of *Kidney News*. From my point of view, we have many things to do, and we need to think big.

Perhaps we should focus on the stages of CKD individually, looking at a model for early detection and slowing progression or halting CKD. Or maybe we focus on a separate model that improves transition to ESRD and a smooth start to RRT. Or we focus on one model that encompasses it all. We cannot leave out people with any stage of CKD.

I feel such a sense of urgency to address CKD and the vulnerable people who have it and do not even know they have it. CKD affects more than 30 million people in the United States, and astonishingly, 96% of those with early kidney disease do not know they have it. People at the highest risk include those with diabetes and hypertension. Minority populations are also disproportionately affected by CKD: Compared with Caucasians, four times as many African Americans and twice as many Hispanics develop CKD.

One thing we can all do immediately is engage patients in their own care. A provider recently said to me, "I keep telling my patients exactly what they need to do to improve their care, but they don't listen to me. How can I get my patients engaged?"

My answer is, stop talking and listen. Put down the laboratory values and start the conversation with "How have you been doing; are you able to do the things you like or need to do?" If we as patients understand the steps we need to take to keep working, camping, doing a hobby that we enjoy, traveling, etc., then you have a better chance to get us engaged. We are all individuals, and having a care plan that is developed with our interests in mind is key. This also applies to a more palliative approach. Some patients (e.g., the elderly or those with a short life expectancy) may not want to transition to RRT at all. The plan should start with us (the patients) and our families. Be sure that we have the information needed to make shared decisions and set goals.

Derek L. Forfang is a member of the National Kidney Foundation's Public Policy Committee as well as its Kidney Advocacy Committee. He also serves as Chair of the National Forum of ESRD Networks' Kidney Patient Advisory Council and Chair of the ESRD Network 17 Patient Advisory Committee. He is a member of the Kidney Health Initiative Patient Advisory Committee.

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Distracted by Dialysis: Effects on Nephrology Fellowship and Careers

By Mary Mallappallil

At the 2017 American Society of Nephrology (ASN) Training Program Directors (TPD) meeting in New Orleans, preliminary information about the nephrology fellowship match predicted that the recent trend of unfilled positions would continue for the present. Despite that information, there was an unambiguous optimism owing to the improvement in job opportunities for new graduates over the past year.

The most recent ASN annual exit survey of nephrology fellows reported that "perceptions of local nephrology job opportunities were much improved compared to earlier years for both US medical graduates and international medical graduates." Furthermore, new "fellows' anticipated salaries in 2017 were higher than in previous years."

The other important information from the survey included concerns that persist, mostly related to lifestyle issues. Weekend duties, overnight calls, location, salary, practice setting, and length of each workday were very important in work selection. Overall, it seemed that 2014 and 2015 were the worst years for nephrology fellowship, with the lowest number of jobs for new graduates. Not surprisingly, during these years, existing nephrology trainees were least likely to advise medical students to enter nephrology as a career. Overall, it seems to be the start of the end of a bleak period for those involved with nephrology fellowship.

How did we get here?

It seems intuitive that fellowship trends would follow the patterns in the specialty with a lag time. To look into the future, a look backward into the past would help explain the trajectory of our cherished field for some actionable insight to sustain nephrology training and careers. Keeping in mind that no authentic progress follows a straight and easy path, this journey too has been in jumps and starts—and at times, even in the wrong direction.

In the early years, nephrology was centered on physiology, the mysteries of fluid, acid-base, and electrolyte metabolism, while delving into the secrets of the kidney. Dialysis therapy was rare and was used for viable patients with acute kidney injury. It was an innovation from World War II, a procedure performed by excited renal fellows who prepared the dialyzer, dialysate, and related equipment and supplies after having dealt with the challenge of temporary vascular access.

Chronic hemodialysis was the culmination of many endeavors, including lasting vascular access, successful anticoagulation, safe and repeated administration of ambulatory hemodialysis, and federal government funding via the 1972 Social Security amendment allowing for the Medicare kidney disease entitlement provision. Sustainable organ replacement! The increasing cost of caring for renal patients was noted as early as 1973 when a New York newspaper published an editorial about dialysis and named it "Medicarelessness."The message was: While providing life-sustaining therapy ahead of all other specialties on the one hand, the rest of nephrology needs to be taken with a pinch of salt.

Fascination with dialysis, secure payments fostered growth

With renal replacement therapy in place, what did we do with it?

The fascination of dialysis was explored in detail, including who, when, and how people should get it, and how much they should get. Secure payments ensured that no one who needed dialysis in the United States would be denied on the basis of cost. The next few decades saw the trainee metamorphose from a physician-scientist to a physician-businessman/businesswoman. The initial trainees became owners of private dialysis units, essentially small business owners. The new treatment was provided on a trial and error basis, with best practices becoming clear only over time.

The subsequent decade brought about innovative anemia therapy and exploding cost, still paid for by the federal government but with growing concerns regarding the cost. Big business had already turned their attention to the dialysis boom. However, the gradual increase in work with fixed payments for dialysis made it progressively less desirable to American medical students, and a large number of foreign medical graduates entered the field.

The way to make a profit was to increase the number of patients on dialysis. With business models describing the number of dialysis patients needed to cover cost, there was a rush to save all patients with kidney failure, which would, in return, sustain the dialysis unit. The available funds attracted industry, including chain dialysis centers, and led to the churning out of algorithm-based therapies, use of physician extenders, and growing logistics and regulations.

In the midst of all this, both science and scientist suffered.

The success of having organ replacement and delving into delivery, payment, and outcome logistics came at the opportunity cost of discovering prevention and cures for kidney failure.

We are actually working backward in nephrology. Most specialties have fractured therapies, and none have so successfully combated organ failure on a commercial level. Yet this preliminary success seems to have become a crutch. If, for example, the heart could be commercially replaced by visiting an outpatient facility, can we be certain that medications, interventional therapies, pacemaker and defibrillator device therapies, trans-catheter aortic valve replacement, or any of the other diagnostics or therapeutics that we have today would exist?

"In the midst of [algorithm-based therapies, use of physician extenders, and growing logistics and regulations] both science and scientist suffered."

Cost concerns

The huge growth curve in expenditures for dialysis patients was not lost on the federal government. In the presence of other insurance, Medicare would only cover dialysis after the first 2.5 years, a noteworthy time point given that the initial dialysis mortality was 50% at 2 years. In 2011, Medicare started to trim costs further, starting by bundling payments, and the nephrology community accepted the payment of $240 per dialysis treatment. The next instrument to cut costs came in the form of quality improvement. Medicare placed 2% of payments on hold to be paid out only if quality indicators were met.

The unforeseen complication of this cost cutting is the response from potential trainees. Two years after the cuts, there was a drop in nephrology job opportunities, and not

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Distracted by Dialysis

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surprisingly, we saw the highest number of unfilled nephrology fellowship spots. In a field with poor job prospects, only the very dedicated will enter fellowship given the price of uncertainty in future employment.

Practice patterns

In addition to lower reimbursements, practice patterns also have resulted in fewer jobs.

With trainees focused on dialysis and dialysis delivery, "expectation transfer," the use of technology in a new way, occurred, with procedures in the realm of nephrology being exported to become integral parts of other fields. The list of procedures that have been lost to other fields is long and growing. Arteriovenous fistulas and grafts, initially placed by nephrologists, were handed off early to vascular surgeons. Hemodialysis catheter placement and kidney biopsies are now frequently performed by interventional radiologists. Peritoneal dialysis catheters are placed by general surgeons. Renal ultrasounds are done by radiologists. Continuous renal replacement therapies have now entered the realm of critical care intensivists, and urinalysis is done in the pathology laboratory.

What is left but dialysis for the nephrologist?

It seems that we have completely abandoned our scrubs for suits! The only procedure that we have left seems to be using electronic medical records to put in an order for a 2K dialysate.

This state of affairs has all happened as the nephrology community has been distracted by dialysis. At the 2017 ASN TPD meeting, program directors discussed renal fellows not doing and not needing to do kidney biopsies owing to "logistics." There was a question about the number of procedures needed to claim that a fellow was board eligible with regard to kidney biopsies. The TPDs split about 50:50 concerning the need for procedural comfort with kidney biopsies. Half of the TPDs at the meeting discussed that, because the procedure was done by radiology in the real world and is now a required procedure for interventional radiology training, it was unrealistic and unfair to have trainees do kidney biopsies in order to be deemed board eligible.

How has all of this change affected trainees? It is not surprising that nephrology is one of the lowest paid specialties, and although nephrology jobs have been lost, ironically, we have created jobs for interventional radiologists, vascular surgeons, hospitalists, and critical care intensivists. In some hospitals, hospitalists do more procedures that nephrologists and are expected to put central lines in, tap joints, do lumbar punctures, and read basic radiographic studies among other tests. Becoming a hospitalist straight out of residency often results in a higher salary compared with that of a new nephrology graduate, despite nephrology graduates having completed 2 additional years of fellowship training.

At the 2017 ASN Kidney Week opening plenary, then-President Eleanor Lederer, MD, FASN, addressed the community with a key message: Disengage from being solely identified as dialysis doctors and instead, reclaim the title of nephrologists. This is a laudable goal, but we need to be mindful of the many challenges we face in this pursuit.

Growing our field and making it more attractive to students and residents requires research and new therapies. Yet those in fellowship may not be able to apply for NIH funding owing to work visas. And fueled by the embers of unsustainable cost, the US Government Accountability Office report noted that National Institutes of Health (NIH) kidney disease research funding is inadequate. To put this in perspective, total NIH funding is less than government expenditures on kidney disease care alone.

"The lack of stringent research requirements along with time-consuming education about the dialysis business can keep many trainees, who are usually the engine of innovation, disconnected from efforts to move the field of nephrology forward."

The lack of stringent research requirements along with time-consuming education about the dialysis business can keep many trainees, who are usually the engine of innovation, disconnected from efforts to move the field of nephrology forward. We continue to use classification systems for acute and chronic kidney disease that are focused on the suspected timeline of kidney damage. Podocytopathies have been defined in the past decade as the basis of glomerular diseases after a half-century of syndromes on the basis of microscopic pathology. Renal cyst enlargement with imaging is still being used to determine progression of autosomal dominant polycystic kidney disease, because it is found to precede the rise in serum creatinine. A frustration voiced by trainees is that, despite the plethora of scientific investigations and extraordinary new mechanistic insights into renal disease, there has been little in the way of new and innovative therapies in nephrology in recent years.

Although innovation may seem to be a herculean task, it has happened in other specialties. Rheumatology had a very limited therapeutic armamentarium in the 1980s, with gold as a major therapy, until biological therapeutic agents appeared on the scene. It started with the TNF inhibitors, and from then on, there seemed to be no turning back. Now, fellowships like hematology-oncology and rheumatology are competitive fields attracting the best among both American and international medical graduates. Physicians like the novelty of new therapeutics and the empowerment of helping others in addition to a good lifestyle.

The wages of distraction: lack of focus on the "why"

The emergence of new biomarkers begs to reclassify acute kidney injury, chronic kidney disease, and GN not just temporally but on the basis of why—which is the most important question in science. Work on the "why" is slow to elicit an answer, especially if a distracted community is focused elsewhere.

Greater emphasis on pathophysiology would likely lead to vistas of therapy. Biomarkers could tease out nuances of unclear pathophysiology—for example, at what points do dehydration, Meso-American nephropathy, and acute tubular necrosis occur in the setting of volume depletion? Some may argue that this may come at an opportunity cost of both time and expense, which could be well invested in therapeutics, but investment in both our understanding of disease mechanism and therapy is needed. With the data that more healthcare dollars are spent on kidney patients than the entire NIH budget (a wallet-opening fact), the Health and Human Services Chief Technology Officer announced the Health and Human Services' intent to launch a Kidney Innovation Accelerator, which would establish a public-private innovation fund for real breakthroughs.

With all of these changes, will we survive as a specialty? Will nephrology fellowship continue to exist?

In the process of being torn apart, we often discover that it is just a part of reinventing ourselves. Yet we must be careful to avoid other unintended consequences. With the new seamless care delivery systems, it seems that the nephrologist will also become the primary care doctor for those with chronic kidney disease. There would be an increase in the number of patients and jobs with a change in the role of the nephrologist. Will the former nephrologist, who evolved into a perceived role as a dialysis doctor, now become a new version of a primary care provider? Will the heroic innovations of renal replacement therapy be replaced by mundane medical work?

With the growth and attention to dialysis, the leaders in our field changed from the likes of Kolff, Schreiner, Merrill, and Scribner to multinational chain dialysis companies along with regulatory and payment agencies—and with this came a shift toward mundane medical work. Commercialization, other than the obvious economic implications, has also meant a change in our champions.

We have been distracted by dialysis long enough. We need to get our focus back. Let us do more of our own procedures, not fewer procedures. Let us be more and not less. Let us be ambitious, and less easily satisfied. Let us focus on prevention and better treatment of earlier stages of CKD, with new therapies as a key to sustaining our field and its training programs.

This year's Match is predicted to be no different with regard to the number of candidates entering nephrology. However, with the decreased supply, the nephrologist's market seems to be getting better, with more job opportunities for graduating fellows.

The urgency to develop the field is seen from both those entering nephrology and those not entering it. Breakthroughs in physiology over the past decade seem to be reaching the threshold for application in both diagnostics and therapeutics. On the verge of breakthroughs in nephrology, the pendulum seems to have started to swing in the right direction.

Mary Mallappallil, MD, is the training program director for nephrology fellowship at the State University of New York at Downstate.

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Fellows Corner

Tales from the Subcontinent: Trials, Triumphs, and Lessons in Tenacity from My Time Conducting Research in India

By Christi Bradshaw

Christi Bradshaw

"Why India?"

Along with sunscreen and mosquito repellent, this query was my steadfast travel companion throughout my time on the subcontinent. The only thing more ubiquitous were the auto rickshaws that careened haphazardly through the streets (effectively hailing them eventually became one of my triumphs). Conducting research in any setting has its unique set of challenges, and adding cultural uncertainty to the mix is perhaps a thing some people would prefer to avoid. I decidedly fall outside that group.

My decision to travel to India to conduct nephrology research was influenced by many factors. I am fortunate to have had the opportunity to travel extensively in my 30-something years on earth, with a few excursions centering on medical work or volunteering in South India. My savoring of cultural unfamiliarity has not only helped fuel an insatiable curiosity, but has also rewarded me with an enhanced sense of community and an elevated respect for other perspectives. Because of my familial connection (my in-laws are from the subcontinent) and my desire to understand the plight of persons on dialysis in a country where out-of-pocket health care costs are irregularly subsidized, choosing India as the site of my research held an undeniable appeal.

The premise of my research project was built on the idea that many persons with end stage renal disease (ESRD) in India often experience an extraordinary financial burden, to the point where selling possessions and property and borrowing extensively are the only ways to fund their care. Data collected by government-sponsored surveys has revealed that approximately 70–80% of the population has no health insurance (1). This figure is in contrast to the 9% of persons in the United States without health care coverage as of 2016 (2).

Although there are government schemes in place that subsidize health expenses for persons below the poverty line (3, 4), this financial aid typically only applies to inpatient costs and does not mitigate the indirect monetary losses associated with transport to and from medical facilities and disruption in employment. Moreover, India's healthcare expenditure as a percent of its gross domestic product (GDP) is below the global average (4.7% versus 9.9% [5]). Therefore, not only is comprehensive health coverage hard to come by, but the government seems to be lagging behind in its investment in health care as well.

How do these circumstances affect our kidney patients? To date, information on the economic plight of persons on chronic dialysis in India is scarce. Public hospital facilities provide dialysis (often twice weekly) at a discounted cost. Even then, the cost of dialysis sessions alone can reach 6000 rupees (6) ($94) per month. When compared to an average monthly wage of 7500 rupees (7) ($118), it is not difficult to appreciate the financial strain that dialysis places on a household, especially when indirect costs are considered. Furthermore, over 90% of nephrologists and dialysis facilities are in the private sector (8), where out-of-pocket costs can skyrocket.

With this state of affairs serving as a background, I leapt into the murky waters otherwise known as the Indian research apparatus. If I thought renal physiology could be inscrutable at times, it paled in comparison to the bureaucratic gymnastics I had to perform to get my study off the ground. In addition, the clinical obligations that accompany being a physician in the second most populous country in the world can understandably leave little room for anything else, research included. I found it difficult to effectively convince local nephrologists of the value of my study, especially when the onus of submitting study documents to their respective hospital institutional review boards fell squarely on their already heavy-laden shoulders. At times, physician reticence was also accompanied by skepticism regarding my motives ("Why India?!"). It was primarily due to the unceasing advocacy of a few talented and committed souls that I was able to eventually clear these hurdles.

My commitment (and ability to withstand regular 100+°F temperatures) having been tested, I am thrilled to say that my research is slowly but steadily progressing. Data collection has been completed at three sites and we are starting enrollment at two more.

I have met spectacular people along the way, all of whom have been willing to overlook the peculiarity of my non-native quest to help persons with ESRD in a country that is not my own. In addition to my research and nephrology colleagues, credit and gratitude is also due to the dialysis patients themselves. I was met with a receptiveness and warmth that is a testimony to the underlying sense of common humanity we all share—something that seems increasingly marginalized these days. I hope that by arming the nephrology community in India with concrete data on the financial hardships experienced by persons with ESRD, this research can provide an impetus for health policy change in the future.

Yes, there were challenges. Yes, there was weariness. However, there was also fun and a sense of accomplishment. Despite the exotic packaging, the ups and downs were not so different from those that accompany the research process in any setting. Stepping outside one's comfort zone can take many forms, but the personal growth and potential to effect positive change that can arise from that effort often outweigh the discomfort. As for the discomfort of dodging those careening rickshaws, I recommend calling their bluff; the drivers are more disciplined than they look. ■

Christi Bradshaw is a third year nephrology research fellow at Stanford.

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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)

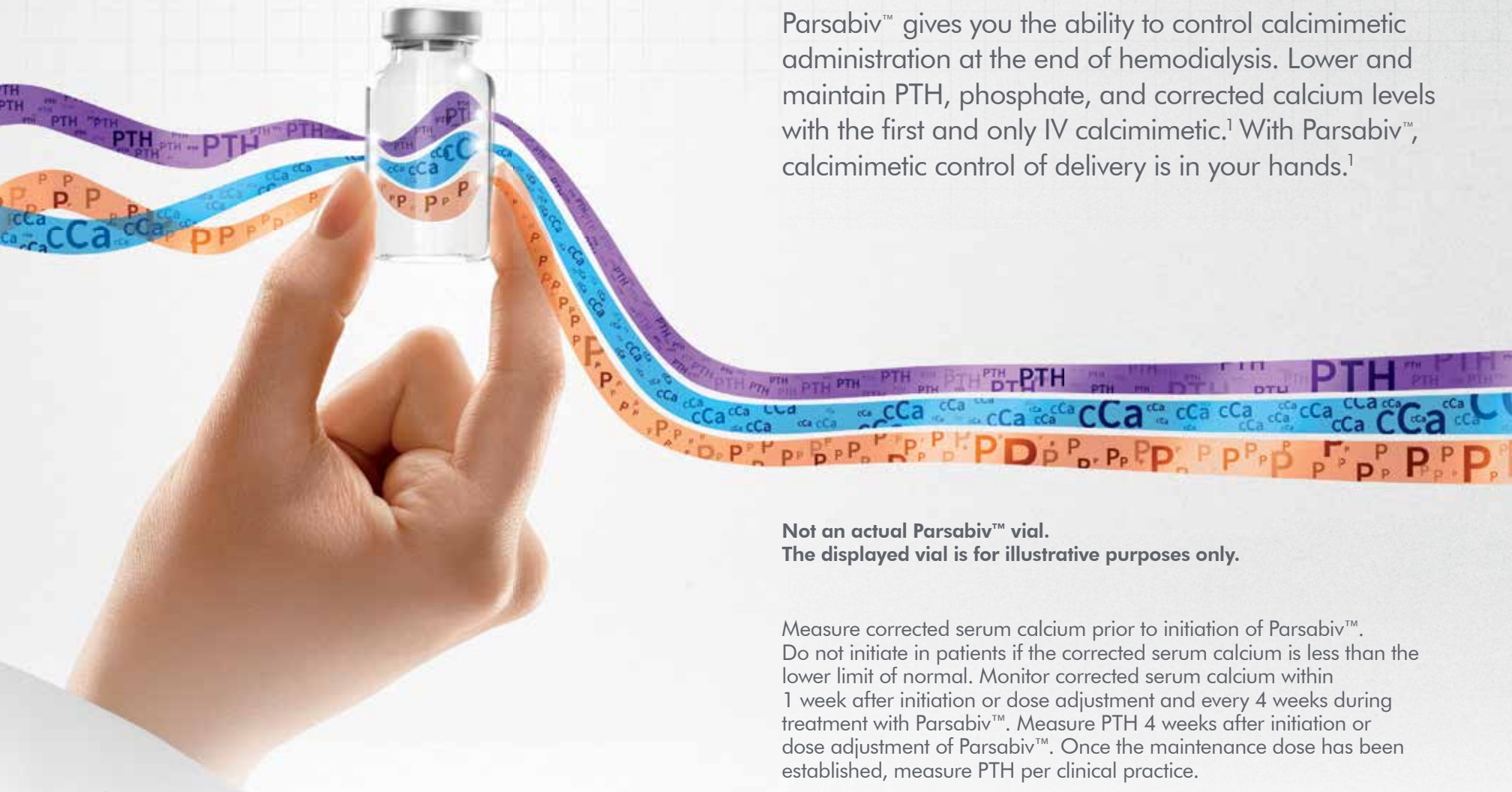
Manufactured for:
KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

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.