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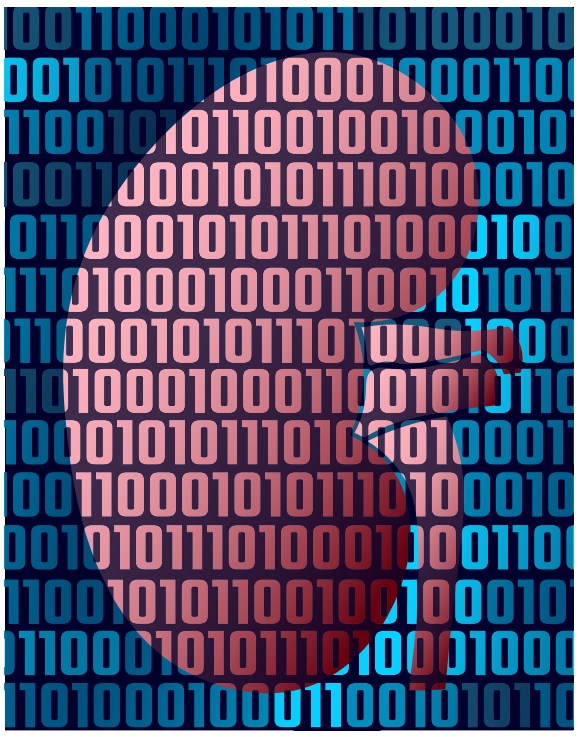
Machine Learning Technique Identifies and Classifies CKD Subtypes

By Eric Seaborg



Even among patients with similar levels of kidney function, an algorithm that considers a host of characteristics—including demographics, biomarkers from blood and urine, health status and behaviors, and medication use—can categorize patients into three clinically distinguishable clusters associated with distinct outcomes, such as chronic kidney disease (CKD) progression, cardiovascular disease, and death, according to a new study in *JASN*.

This style of "subtyping" of CKD using "multi-dimensional patient data holds the key to precision medicine," the authors write in "Subtyping CKD Patient by Consensus Clustering: The Chronic Renal Insufficiency Cohort (CRIC) Study." The approach could provide a better clinical picture of the course of a patient's kidney disease compared with simply considering traditional risk factors, the study authors state.

The 2012 KDIGO (Kidney Disease: Improving Global Outcomes) classification guidelines stage kidney disease using a patient's estimated glomerular filtration rate (eGFR) and urine albumin excretion relative to urine creatinine ratio (UACR), and this new subtyping technique provided additional useful information beyond these measures, the authors say, adding that staging CKD using eGFR and UACR "does not fully capture the underlying patient heterogeneity."

Toward personalized medicine

The study is a step toward more personalized, precision medicine, according to Sushrut S. Waikar, MD, MPH, one of the lead authors of the study and professor of medicine at Boston University School of Medicine and chief of nephrology at Boston Medical Center.

"The term chronic kidney disease doesn't refer to a single entity, but rather is an umbrella term that encompasses a large number of underlying disease pathologies," Waikar told *ASN Kidney News*. "Clinically we often don't make specific pathological diagnoses [of CKD], for example, with a kidney biopsy. As a result, we group together a potentially large number of diseases under an umbrella term like hypertensive kidney disease. But is hypertensive kidney disease a single disease or is it an umbrella term for 10 different diseases, each of which has a different etiology and potential treatments? And the same question can be asked for diabetic

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Overcoming Patient, Clinician Vaccine Hesitancy Key to COVID-19 Vaccination Effort

By Bridget M Kuehn

Only about one-third of the staff in the dialysis program at the University of Virginia Health system has been vaccinated against coronavirus infectious disease 2019 (COVID-19) so far, according to the program's administrator, Debbie Cote, BN, MSN. The main reason for the slow uptake is that many are concerned about the speed of the vaccines' development process and the lack of information about long-term side effects, Cote said in an interview with *Kidney News*.

"From my own staff, what I've heard is they would take the vaccine, but they don't want to be first," said Nancy Colobong Smith, MN, CNN, director of the American Nephrology Nurses Association (ANNA). Colobong Smith said her staff at the University of Washington Medical Center in Seattle are evenly divided among those who will take the vaccine, those who are unsure, and those who say they definitely will not take the vaccine.

Vaccine hesitancy among clinicians and patients is presenting a major challenge to the rollout of COVID-19 vaccines in the United States. A survey by the Kaiser Fam-

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ily Foundation (KFF) found that although 71% of Americans say they will definitely or probably get the vaccine, a substantial number remain skeptical (1). The largest group to report they would probably or definitely not get the vaccine were people who identified as Republicans (42%), according to the KFF survey. Additionally, 35% of individuals living in rural areas and 35% of Black adults also said they would probably or definitely not get the shot, as did 29% of healthcare workers.

"Many who are hesitant are in wait-and-see mode, and their concerns include worries about side effects and whether the vaccine can cause COVID-19, which may dissipate as people get more information and see the vaccine introduced successfully among people they know," Kaiser Family Foundation CEO Drew Altman wrote in a statement about the survey.

Trust gap

Kathleen Dooling, MD, MPH, co-lead for CDC's Advisory Committee on Immunization Practices COVID-19 Work Group, acknowledged that historical and ongoing mistreatment of Black people in US medical care has contributed to mistrust of the vaccine in this group. But she noted that vaccine manufacturers have worked to build trust in the vaccines by ensuring that some clinical trials were inclusive.

"There is a trust gap," she said. But she said she hopes to build trust and "make this vaccine something that everybody wants to get because it is safe and effective."

Dooling spoke during a recent ASN webinar (2) on "Safety and Efficacy of COVID-19 Vaccines in Dialysis."

Webinar participant Richard Knight, MBA, president of the American Association of Kidney Patients, emphasized the importance of patient education and healthcare provider credibility and trust in helping overcome vaccine hesitancy among patients who are Black or from other underrepresented groups that have been disproportionately affected by COVID-19.

"We need to come up with a message that will encourage people," Knight said. He noted the benefits of being vaccinated far outweigh the risks for dialysis patients despite some unanswered questions. He recommended being honest with patients about the unknowns and benefits. He also recommended that dialysis patients be vaccinated by their dialysis providers.

The trust gap extends to some health workers and other groups as well. Some staff have told Cote that they don't trust the vaccine because it was developed during a certain administration. Others have shared conspiracy theories about the vaccine.

"There's a lack of trust in the government," Cote said.

The KFF survey also found that vaccine-hesitant individuals were more likely "to harbor misconceptions about the pandemic and related health measures."

Beliefs about personal responsibility also factor in. A report from the KFF found that rural residents (3) were more likely to see getting vaccinated as a personal choice rather than a responsibility to help protect the community.

"Effective messages need to be delivered by trusted messengers and take into account these strongly held beliefs in order to have successful vaccine uptake in rural America," the report's authors wrote.

Clinician leadership key

Physicians and other clinicians have a key role to play in boosting patient acceptance of vaccines. The KFF survey found that 85% of patients trust their own physicians or healthcare providers to provide them reliable vaccine information, whereas about 70% trust federal authorities like the CDC. But hesitancy among some healthcare workers could undermine this.

"That's problematic in terms of how they may be advising the patients," Knight said. "[Patients] will miss out on something that can really have an impact, not just on their quality of life, but on their ability to continue living. It's very serious."

Overcoming hesitancy among healthcare workers is "a strong leadership challenge," Knight said. He emphasized the importance of educating staff about the vaccine and ensuring that clinicians talk with patients about the vaccine from the perspective of "what's in the best interest of the patient," regardless of the staff member's personal views.

Colobong Smith recommended that institutions be honest and transparent with

staff about what is known and not known about the vaccines so far and about the devastating effects COVID-19 has had on some patients and staff. She also recommended extra efforts to reach out to groups at elevated risk. She noted that her institutions have held virtual town halls, including some specifically for people of color, led by individuals from those groups, as well as holding some town halls in Spanish.

The Virginia Department of Health's Office of Health Equity recently featured National Institute of Allergy and Infectious Diseases Director Anthony Fauci, MD, as the keynote speaker about vaccine acceptance during a "Facts and Faith Fridays" webinar. The webinar targeted thought leaders in the faith community who are in a position to reach out to their communities to urge vaccine acceptance.

"All of that is helpful, as well as giving people easy access to quality evidence and sources," Colobong Smith said. She noted that ANNA (4), the American Nurses Association (5), and CDC (6) all have COVID-19 vaccine information.

The University of Virginia Health system sends daily COVID-19 updates, including information about hospital occupancy and staff vaccination numbers, Cote said. Additionally, leaders and other staff who have been vaccinated are encouraged to share their own experiences with the vaccine. Both Cote and Colobong Smith noted that most reactions to the vaccine are mild and brief.

"People are just trying to get the word out that it is safe and reassure people," Cote said.

For patients, dialysis patient advocate Elizabeth Fortune recommended using a shared decision-making process that engages physician, patient, and the rest of the care team. She noted that at her dialysis center, social workers routinely provide information, including pamphlets, about many topics. She also recommended sharing information from multiple sources.

"The social workers need to be involved because they do—at least in my clinic—more one-on-one education," she said.

Some patients may not need much convincing. Many patients who recognize they are at higher risk from COVID-19 are eager to be vaccinated, noted Cote.

"There sometimes is less apprehension in patients than there is in staff," she said.

However, many healthcare workers have also jumped at the chance to be vaccinated, and even some who were initially hesitant are changing their minds as growing numbers of people are vaccinated, said Colobong Smith. She has been helping to vaccinate healthcare workers in her system, and many are excited to share photos of their vaccinations on social media to help reassure friends and family who worry about their safety during the pandemic.

"It's about us as healthcare providers, as people, but also about our communities and the people that care about us and that we care about," she said. "It's all of that together." ■

References

1. Kaiser Family Foundation. KFF Launches New COVID-19 Vaccine Monitor to Track the Public's Confidence in the Vaccine and Experiences for the Duration of the Pandemic. December 15, 2020. https://www.kff.org/coronavirus-covid-19/press-release/kff-launches-new-covid-19-vaccine-monitor-to-track-the-publics-confidence-in-the-vaccine-and-experiences-for-the-duration-of-the-pandemic/
2. American Society of Nephrology. Safety and Efficacy of COVID-19 Vaccines in the Dialysis Population (webinar). January 7, 2021. https://goto.webcasts.com/viewer/event.jsp?ei=1416384&tp_key=2914871054
3. Kirzinger, A., et al. Vaccine Hesitancy in Rural America (Kaiser Family Foundation). January 7, 2021. https://www.kff.org/coronavirus-covid-19/poll-finding/vaccine-hesitancy-in-rural-america
4. American Nephrology Nurses Association. Coronavirus Disease (COVID-19): Information & Resources. January 14, 2021. https://www.annanurse.org/article/coronavirus
5. American Nurses Association. COVID-19 Vaccines. January 2021. https://www.nursingworld.org/practice-policy/work-environment/health-safety/disaster-preparedness/coronavirus/what-you-need-to-know/covid-19-vaccines/
6. Centers for Disease Control and Prevention. COVID-19 Vaccines. January 15, 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/index.html

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Shared Decision-Making for the Integrated Care of End-Stage Kidney Disease Patients

By Hajeong Lee

End-stage kidney disease (ESKD), which requires kidney replacement therapy (KRT) or comprehensive conservative management, burdens patients, their families and caregivers, and the healthcare system. The selection of the type of KRT for individual patients is therefore decided based on not only each patient's medical condition but also his or her family support, social and financial resources, and the healthcare resources he or she receives.

Most decisions regarding KRT have been based on physician- or healthcare system/stakeholder-centered determinations rather than "patient-centered" choices, and thus many patients with ESKD feel insufficiently involved in their treatment options. However, it is also important to improve a patient's sense of well-being by maintaining his or her daily life, both functionally and psychologically, which is not measured by any laboratory calculation.

Recently, the Kidney Disease: Improving Global Outcomes Controversies Conference recommended that patient-reported outcome measures (PROMs) should be implemented in clinical trials and registries of rare kidney diseases (1). The PROMs are tools that open a physician's ears to the patient and are good triggers to cultivate "shared decision-making." Shared decision-making implies that medical decisions are made collaboratively in accordance with the best available evidence provided by the clinician and the values and preferences of the patient. Furthermore, shared decision-making allows improved communication between physician and patient, enhancing the patient's compliance, motivating a patient's self-monitoring, and reducing emergency department utilization (2). However, remaining challenges should be overcome for PROMs to progress to shared decision-making and finally be incorporated into the healthcare system.

Barriers to the use of shared decision-making in caring for patients with ESKD are present at three levels.

1. From the clinician's view, barriers include limited time and resources, a lack of confidence in communication, and a lack of consensus on when and how to educate patients.
2. From the patient's view, barriers are a low level of health literacy, minimal awareness of kidney health, a low readiness to learn, different intellectual and socioeconomic levels, and complex co-morbidities.
3. From the healthcare system's view, there are problems to be solved, such as a limited budget for education or communication, a lack of standardized decision aids, and the absence of multidisciplinary team care with clear roles.

Fortunately, there has been a quality paradigm shift in the care of patients with kidney diseases to focus more on patient-reported outcomes, but all three levels of barriers should additively be conquered to accomplish true patient-centered care. The final goal for shared decision-making in caring for patients with ESKD is individualized care that allows patients to achieve the best outcomes from the viewpoint of patients themselves rather than the healthcare provider or system. As healthcare providers, let us make patient-centered care and shared decision-making priorities for nephrology in 2021. ■

Hajeong Lee, MD, PhD, is a professor in the Division of Nephrology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea.

References

1. Aymé S, et al. Common elements in rare kidney diseases: Conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2017; 92:796–808. doi: 10.1016/j.kint.2017.06.018
2. Elwyn G, et al. Shared decision making: A model for clinical practice. *J Gen Intern Med* 2012; 27:1361–1367. doi: 10.1007/s11606-012-2077-6

ERRATUM

The January 2021 article "Prioritizing COVID-19 Vaccination in Dialysis" lacked the following disclosures in its conflict of interest statement:

Daniel E. Weiner, MD, MS, FASN, received research funding paid to his institution from AstraZeneca for site-PI duties in the DAPA-CKD trial.

Jerry Yee, MD, FASN, reported consultancy agreements and honoraria with AstraZeneca.

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kidney disease. [This study is a step toward] trying to identify the heterogeneity underlying what we think are common forms of kidney disease."

Each patient is unique, says the other lead author, Zihe Zheng, MBBS, MHS, a doctoral candidate in the department of biostatistics at the University of Pennsylvania Perelman School of Medicine: "Patients are different, and people with similar kidney function are still different. This heterogeneity is something we really want to highlight [in this study]. Our main focus is to classify patients to find out how they are different from each other in the expectation that that will shine some light on the underlying pathophysiology."

72 baseline characteristics

The study used data from the CRIC project, an ongoing prospective cohort study of adults with CKD stage 2 to 4. Participants were recruited from 2003 through 2008 from clinical centers in seven U.S. cities. Since then, they have been followed through annual clinic visits during which investigators collect health information and urine and blood specimens for an extensive testing menu.

The researchers analyzed this database using a machine learning method called unsupervised consensus clustering. Consensus clustering refers to a process of using several algorithms to look for similarities that is "unsupervised" because researchers did not decide in advance how the groups should look. The algorithms looked at 72 baseline characteristics of the patients out of 822 variables measured in each patient at the CRIC study baseline. The 72 variables were selected based on a literature review for those most clinically relevant to CKD.

Three clusters

"The algorithm revealed three unique CKD subgroups that best represented patients' baseline characteristics," the authors write. Cluster 1 included patients with "relatively favorable levels" of bone and mineral, cardiac, and kidney function markers; diabetes; and obesity. The patients used fewer medications than members of the other clusters. Patients in cluster 2 had a higher prevalence of diabetes, had greater markers of obesity, and used more medications. Patients in cluster 3 had even higher levels of diabetes and obesity, and had the least favorable levels of bone and mineral, cardiac, inflammation, and kidney function markers.

The cluster membership was strongly associated with patients' future risks of kidney disease progression, cardiovascular events, and death, with risks escalating from cluster 1 through 3. "We showed a strong independent association between the cluster membership and future adverse events, after controlling for the known CKD risk factors, such as eGFR, UACR, blood pressure and diabetes status, etc., to be at the same level," the authors write. "The cluster membership provided a simple metric of summarizing the patient heterogeneity and comorbidity profiles encoded in the 72 baseline variables."

Consensus clustering has been used as a phenotyping tool in other heterogeneous conditions such as heart disease, type 2 diabetes, and several forms of cancer, and the authors write that "identification of clinical meaningful subgroups among CKD patients provides an important step toward patient classification and precision medicine in nephrology. Being able to characterize this heterogeneity early is an important step towards individualizing follow-up strategies for these patients."

"I think this is a step in the direction of using multi-dimensional data for risk prediction for chronic kidney disease," Waikar said. It remains to be seen whether mining the data in electronic medical records will be an approach that clinicians will be able to use to identify the prognosis and tailor the treatment for individual patients who share certain characteristics. "Can we identify the patients in clinical practice who would benefit from more intensive therapy and more intensive monitoring?" he asks.

As an example of the kinds of clues about treatment targets the information could provide, the study notes that inflammatory mechanisms are involved in the development and progression of CKD and its comorbidities such as cardiovascular disease. "The identified clusters may represent different states of inflammation which could, in part, explain the differences in risks of developing adverse clinical events," the authors write.

Girish N. Nadkarni, MD, MPH, assistant professor at Mount Sinai Health System in New York City, who was not involved in the study, said the study recognizes "that chronic kidney disease is quite a heterogeneous syndrome, and [the researchers] are trying to use data-driven techniques to tease out the heterogeneity. They are trying to show that this is not just one disease but a syndrome comprised of many different subtypes of different types of disease. There is great promise in this approach in order to discover unknown risk factors. This is the first step in a continuum of research trying to show that all chronic kidney diseases are not the same." ■

Slower CKD Progression with RASIs versus CCBs

Patients taking renin-angiotensin system inhibitors (RASIs) have slower progression of kidney disease than those taking calcium channel blockers (CCBs), according to a "real-world" study in the *American Journal of Kidney Diseases*.

With the use of 2007–2017 data from the Swedish Renal Registry, researchers identified two groups: 2458 new users of RASIs and 2345 patients starting treatment with CCBs. At a median follow-up of 4.1 years, rates of KRT initiation, death from any cause, and major adverse cardiovascular events (MACEs) were compared between the two treatment groups. Patients with stage 3 CKD taking the same medications were studied as positive controls.

"These findings suggest that RASi initiation might slow the progression of kidney disease compared with CCB in patients with advanced CKD, and offer similar cardiovascular protection," the investigators conclude [Fu EL, et al. Comparative effectiveness of renin-angiotensin system inhibitors and calcium channel blockers in individuals with advanced CKD: A nationwide observational cohort study. *Am J Kidney Dis*, published online ahead of print November 24, 2020. doi: 10.1053/j.ajkd.2020.10.006; https://www.ajkd.org/article/S0272-6386(20)31121-5/fulltext]. ■

COVID-19 Changed Kidney Care
Will Those Changes Stick?

By Nicole Fauteux

Throughout the COVID-19 pandemic, nephrologists have made adjustments to best care for patients. Now they are taking stock of how kidney care has changed and considering which of those changes might stick moving forward.

The challenges of delivering kidney care during the pandemic underscored the need for innovation. The experience of meeting those challenges also showed nephrologists that some improvements are well within reach and that emergency protocols adopted during the pandemic may become a new normal.

"I've stopped thinking that this is temporary," says Jeffrey Perl, MD, SM, FRCP, associate professor of medicine at the University of Toronto and staff nephrologist at St. Michael's Hospital Unity Health. Instead, he's asking, "What are we going to do to make healthcare safer for patients on renal replacement therapy no matter what comes at us?"

Perl would like to see what he calls the "COVID-19 mentality" stick around for the foreseeable future. First and foremost, that means a sustained focus on infection control—above and beyond what was previously standard in kidney care. He and his colleagues have applied for a grant to look at the impact the pandemic has had on dialysis-related infections. "Our hope is that infections are lower because of a heightened awareness around infection prevention among patients as well as providers."

What else has changed in kidney care?

- Dialysis centers instituted COVID-19 screening protocols, increased their capacity to treat infectious patients, and adopted telehealth to facilitate physician visits.
- Hospitals took steps to modify where and how they delivered dialysis, both to conserve supplies and to protect their patients and employees.
- Kidney transplantations came to a halt at many facilities, and hospitals with the capacity to receive patients developed new immunosuppression protocols that could influence future care.
- Home dialysis emerged as a model that is safer for patients and less vulnerable to disruption during times of pandemic.
- And healthcare providers of all stripes—and their patients—widely embraced the use of telehealth.

At the same time, providers encountered barriers to the widespread implementation of some of these practices, which may mean they are not sustainable over time. Nevertheless, American Society of Nephrology (ASN) members appear optimistic about what lies ahead. Here's what we learned from them about how recent changes to the status quo might inform future practice.

In-center dialysis

Brigitte Schiller, MD, FACP, FASN, chief medical officer at Satellite Healthcare based in San Jose, California, says in-center dialysis is normally a very predictable model of care, but with the arrival of COVID-19, she and her colleagues had to improvise. In a matter of days, they learned what they could about the novel coronavirus, set up a screening protocol, acquired additional personal protective equipment (PPE), enlisted nonclinical personnel to help in the clinics with screening and cleaning procedures, and adjusted workflows, introducing an extra shift at the end of the day to accommodate infected patients without exposing others. They also implemented telehealth options for physicians to continue to visit their patients at least once a month during dialysis in center or at home without worries about possible virus transmission.

In some urban areas, dialysis providers were able to dedicate entire centers to dialyzing people whose test results for COVID-19 were positive, but even that solution had its limitations. "Transportation companies weren't necessarily ready and equipped to transport infectious patients," Schiller says. "They didn't have masks for their own employees, and it was not clear how much they needed to deep-clean after each transfer, so we faced logistic obstacles in simply getting the patient to the treatment because of these additional risks."

Dialysis centers also found themselves navigating a changing regulatory environment. "The public health response varied from county to county," says Schiller, whose company operates in three states. "I can't imagine what the nationwide dialysis organizations had to go through with every state doing things differently. That causes a lot of additional logistical administrative work to implement something that required a really swift response."

Schiller would like to see coordination of policy and healthcare delivery increase before the next crisis occurs. "My real hope is that we learn to build a healthcare system that addresses the current fragmentation. We need solid, high-quality population health management, an underlying safety net, and agreement on how one approaches a threat. Then during a crisis, the incident command center needs to develop evidence-based and standardized policies and procedures, which providers can then execute in a locally adapted way."

Inpatient kidney care

The high incidence of acute kidney injury (AKI) among COVID-19 patients in intensive care units put enormous strain on hospital nephrology departments in New York City and other hotspots. The availability of hemodialysis machines and supplies was insufficient to meet the demand for kidney replacement therapy (RRT), relatively few clinicians on staff had experience with peritoneal dialysis, and skilled dialysis personnel were unable to work when they themselves became infected with SARS-CoV-2 (1).

"In St. Louis, we were fortunate," says Anitha Vijayan, MD, FASN, professor of medicine in the division of nephrology at Washington University School of Medicine. "Our case numbers were not as high as hard-hit areas. We were able to learn from reports out of Italy, New York, and elsewhere and take a strong approach to predicting dialysis requirements for inpatients with acute kidney injury."

Vijayan directs the Acute Dialysis Services at Barnes-Jewish Hospital, Missouri's largest hospital. As SARS-CoV-2 made its way inland from the coasts, Barnes-Jewish took many of the same steps used at other healthcare systems. The hospital suspended elective procedures and transitioned its intensive care units for COVID-19 care. In the nephrology unit, the hospital relied on its attending physicians so as not to expose trainees to the virus. The unit ordered and borrowed dialysis machines to prepare for a surge in AKI. Anesthesiologists and critical care physicians pitched in with hemodialysis catheter placement, and nurses were cross-trained to assist with dialysis care. The department instituted in-room dialysis rather than transporting infectious patients through the hospital and put them in rooms with video connections or glass doors to reduce the exposure of nurses monitoring their care.

BJC HealthCare, the hospital's parent organization, established a central command center, which could shift supplies in case of shortages. Vijayan, who served as the center's nephrology expert, worked with her colleagues to conserve essential dialysis fluids and supplies for continuous RRT for critically ill patients with AKI. They decreased the flow rate of continuous RRT and reduced the duration of intermittent hemodialysis treatment times, among other measures. Vijayan chairs the ASN COVID-19 Response Team In-Patient Kidney Care Subcommittee.

She attributes part of Barnes-Jewish's success in treating patients with COVID-19 to unprecedented collaboration within BJC and among all St. Louis healthcare organizations. "That sharing and coordination needs to remain in place," she says.

Transplantation

For kidney transplantation physicians, the experience of COVID-19 fell at two extremes. In coastal cities hard hit by COVID-19, these specialists found themselves sidelined as deceased- and living-donor transplantations were put on hold because of a lack of available hospital beds. The result was a boon for their counterparts at transplantation centers less affected by the pandemic.

"Contrary to what our expectations were, we started getting a lot of deceased-donor kidneys from centers that weren't doing transplants anymore," says Uday Nori, MD, FASN, transplantation nephrologist at The Ohio State University Wexner Medical Center. "We did more deceased-donor kidney transplants in 3 months than ever before. In 2019, we did 310 transplants, and [were] poised to surpass this number in 2020. This despite putting living-donor kidney transplantations on hold for more than 2 months."

While accommodating the increased volume of procedures, Nori and other transplantation physicians made adjustments to reduce their patients' risk of SARS-CoV-2 infection. They tailored their transplantation patients' immunosuppression regimens to give their bodies a fighting chance should they encounter the coronavirus (2).

"We stratified people as high and medium risk. We gave those at high risk of organ rejection the same induction treatment as before, involving antithymocyte globulin infusions. We gave the medium-risk patients a lower intensity of induction with basiliximab, a non–lymphocyte-depleting drug. There was a concern that this new approach would cause more rejections," Nori says, "but it turned out the patients did fine, and that's an important lesson. Maybe immunosuppression should be individualized rather than based on a one-size-fits-all protocol," he surmises, suggesting that stratification be used routinely to plan induction treatment in the future.

At the start of the pandemic, the transplantation center put a COVID-19 screening and testing plan in place for both kidney donors and recipients with the help of the National Kidney Registry. Scrupulous care was taken to isolate transplantation patients from staff treating patients with COVID-19 elsewhere at the medical center, and all post-transplantation patients were housed in a designated area. Follow-up care also had to change. Typically, transplant recipients return to clinical sites for wound care, stent and staple removal, and other consultations as many as nine times in 90 days after their procedures. The medical center limited the number of in-person encounters to a minimum and, like other providers, relied heavily on telehealth to monitor patients' recovery.

Screening, testing, isolation, and telehealth are all practices that have stood the test of time, in Nori's view. "These things are easy to do and don't require a lot of extra resources," he says. "They are common-sense practices to carry into the future."

Home dialysis

Might the COVID-19 pandemic be a catalyst for expanding the use of home dialysis? That question has been on the minds of many observers who would like to see this modality gain traction in the United States (3). Jeffrey Perl, who practices nephrology in Canada, where home dialysis is far more widely used, is a firm believer in its value. The pandemic provides another argument in favor of home therapies in his view, but, he adds, "There is much work to be done before COVID-19 alone can become a catalyst for change."

Perl says nephrologists are not sufficiently exposed to home dialysis during residency, and most feel uncomfortable managing it. Not every patient can self-dialyze at home without assistance. (That help is available in Europe and Canada, but assisted home dialysis is not typically covered in the United States.) And there simply are not enough nurses who can get folks started on dialysis at home.

Such home-training nurses need a full year of registered nursing under their belts plus at least 3 months of experience in the dialysis modality they will be teaching. This experience is especially difficult to obtain for peritoneal dialysis, according to Glenda Payne, MS, RN, CNN, cofounder and chief compliance officer at the National Dialysis Accreditation Commission and past president of the American Nephrology Nurses Association. "We have to grow that workforce," she says.

At the same time, she adds, a key opportunity for expanding home dialysis emerged when the US Centers for Medicare and Medicaid Services (CMS) clarified that dialysis centers may use the same machine for multiple patients. "This is a big deal. I think we will see nursing home programs bring in a small number of machines to treat a larger number of patients rather than transporting all their residents needing dialysis to a center," she predicts.

Telehealth

To support kidney care patients during the pandemic, providers have relied heavily on telehealth, and at least in the case of home dialysis, they've discovered that video visits have some unexpected advantages over in-person care. Perl recalls one case where "a glimpse into a patient's home during a virtual visit gave me insight into the challenges they faced dialyzing in their home environment." He was also able to meet patients' families and loop in other healthcare providers with greater ease. "We can now communicate with the patient as a unified health team," he says.

Perl would like the option of telehealth visits to continue for all nephrologists, but he has concerns about relying on telehealth in its current form. Many providers are scrolling through medical records and interacting with patients and others on a single screen; connectivity is poor in some patients' homes; others lack the technological know-how to reliably participate; and patients may be poorly prepared to make full use of virtual visits. Most importantly, Perl says, "For telemedicine to be successful, it requires a heightened level of self-management among patients. I worry about health literacy, and, in particular, socially isolated groups who may find telemedicine more of a challenge."

Payne also sees limits to the use of telehealth. "It would be very difficult for most patients beginning home dialysis to achieve competency through virtual training alone," she says. "There are a lot of technical, hands-on skills that you have to show and then watch the patient demonstrate."

Perl would like to see new tools developed and processes refined to make telehealth an effective delivery mechanism for all types of kidney care and all types of patients. "We have to step up our game and make sure that we come up with something that engages patients and is universally available," he says.

Preparing for whatever comes next

To be eligible for Medicare coverage, facilities must have an emergency preparedness plan, says Payne, but recent events have shown that many existing plans contained a major flaw. "They focused on things like hurricanes, tornadoes, earthquakes, flooding. It's become painfully clear that every emergency preparedness plan needs to focus on the risk of pandemic as well, particularly on having sufficient PPE."

Payne worked for the Center for Medicare & Medicaid Services (CMS) when Hurricane Katrina hit the Gulf Coast. She says the kidney community was viewed as a leader at the time because its members knew how to cooperate. They formed the Kidney Community Emergency Response (KCER) program to provide technical assistance during ensuing crises. Regular KCER and CMS calls during the pandemic have been "a life-saver" for the dialysis community, she says, as have calls and webinars organized by ASN.

The pandemic has also underscored the value of portable professional licensing. Payne would like more states to join the Enhanced Nurse Licensure Compact, which currently allows nurses in any of the 34 compact states to work where they are needed without obtaining additional licenses (4).

Research can also better prepare nephrologists for the resurgence of COVID-19 and other novel infectious diseases. According to Uday Nori, the Centers for Disease Control and Prevention and many other funding agencies are eager to underwrite projects so long as they relate to COVID-19 or SARS-CoV-2. He is cautious in evaluating the information that has flooded publications in recent months, but he believes that ongoing data collection will ultimately yield valuable knowledge. He is especially eager to see what emerges from an effort by Olivia Kates, MD, an infectious disease physician at the University of Washington in Seattle, who has established a registry to collect data on transplant recipients whose test results for COVID-19 were positive. "Hopefully that will be a goldmine that everybody can access and analyze to do their own research," Nori says.

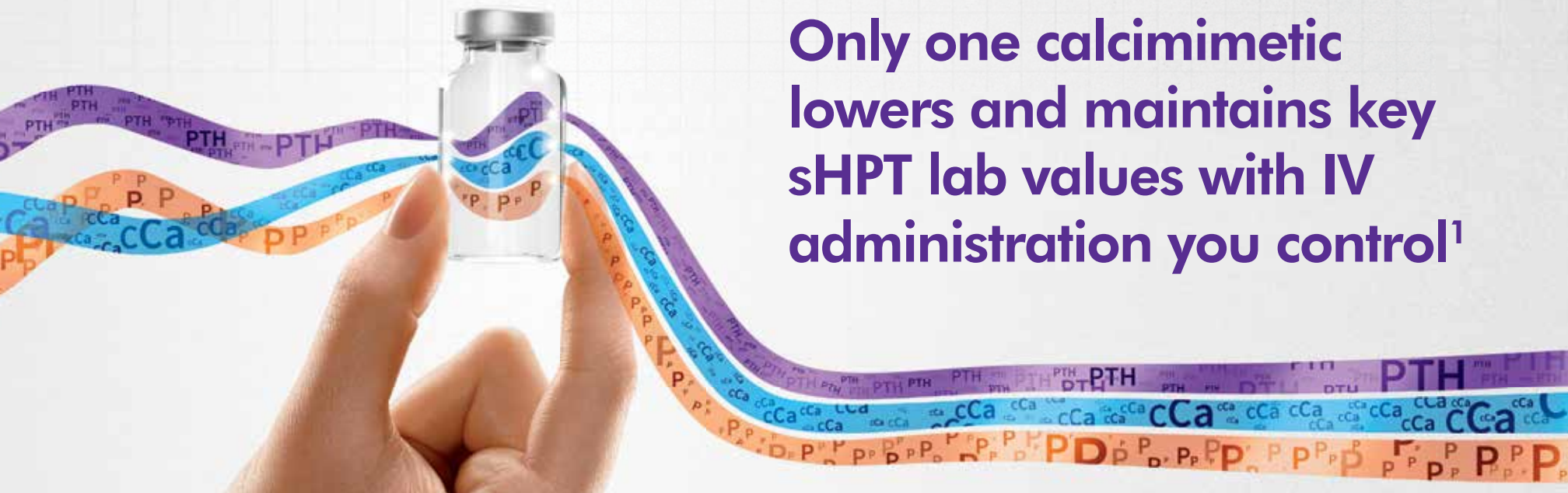
Perl anticipates that recent experience will encourage a more patient-centered approach to care. "COVID-19 has been a catalyst for us to reevaluate what really are the requirements for such frequent kidney care visits. What really are we trying to accomplish?" Perl asks, citing a recent study of 7454 patients receiving hemodialysis in Ontario. "Led by Alison Thomas, our group found more frequent blood work was not necessarily associated with better health outcomes (5). I would love to see more personalized care plans to consider different lengths of time between blood work, between clinic visits," he says. "We can potentially save money, reduce burden, improve patient-reported outcomes, and intensify our efforts on behalf of patients that need more care."

What else can be done to better prepare for the next crisis? "The disproportionate impact of the pandemic on Black people raises the broader question of how we fix health disparities," Vijayan says. She would like to see healthcare systems, researchers, and physicians address the social determinants of health and inequities that currently exist in their communities. Schiller also stresses the need to tackle the fundamental issues that leave people vulnerable in times like the present. "The socioeconomic inequality in healthcare has been exposed painfully in this crisis," she says. "As a physician, this inequality is utterly unacceptable. Every life is precious." ■

Nicole Fauteux is the founder of Propensity LLC and a member of the Association of Health Care Journalists.

References

1. Goldfarb DS, et al. Impending shortages of kidney replacement therapy for COVID-19 patients. *Clin J Am Soc Nephrol* 2020; 15:880–882 doi: 10.2215/CJN.05180420
2. Transplant care transformed in the face of COVID-19. *Kidney News* 2020; 12:19.
3. Kidney Health Initiative. Accelerating technology development during a pandemic to bring more people with kidney failure home. May 8, 2020. https://khi.asn-online.org/uploads/AcceleratingHomeDialysisTechnology_KHIPositionPaper_May2020.pdf
4. National Council of State Boards of Nursing. List of NLC member states. https://www.ncsbn.org/nlc-memberstates.pdf
5. Thomas A, et al. The frequency of routine blood sampling and patient outcomes among maintenance hemodialysis recipients. *Am J Kidney Dis* 2020; 75:471–479. doi: 10.1053/j.ajkd.2019.08.016



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

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

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

Indication

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

Limitations of Use:

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

Important Safety Information

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

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

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

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

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

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

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

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

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

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

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

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

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

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

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE

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

Limitations of Use:

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

CONTRAINDICATIONS

Hypersensitivity

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

WARNINGS AND PRECAUTIONS

Hypocalcemia

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

QT Interval Prolongation and Ventricular Arrhythmia

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

Seizures

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

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

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

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

Worsening Heart Failure

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

Upper Gastrointestinal Bleeding

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

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

Adynamic Bone

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

ADVERSE REACTIONS

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

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

Clinical Trials Experience

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

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

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

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

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

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

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

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

[c] Paresthesia includes preferred terms of paresthesia and hypoesthesia

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

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

Description of Selected Adverse Reactions

Hypocalcemia

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

Hypophosphatemia

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

QTc Interval Prolongation Secondary to Hypocalcemia

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

Hypersensitivity

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

Immunogenicity

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

Data

Animal Data

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

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

Lactation

Risk Summary

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

Data

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

Pediatric Use

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

Geriatric Use

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

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

OVERDOSAGE

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

AMGEN®

PARSABIV™ (etelcalcetide)

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

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This Is the Way: Randomized Clinical Trial Shows ACEis and ARBs Can Safely Be Continued in Patients with COVID-19

By Swapnil Hiremath and Matthew A. Sparks

Severe acute respiratory coronavirus 2 (SARS-CoV-2) uses angiotensin-converting enzyme 2 (ACE2) to enter host cells. Early in the pandemic, several basic science studies were often cited and suggested that ACE inhibitors (ACEis) and angiotensin receptor blockers (ARBs) may have an effect to increase the abundance of ACE2 (1). Thus, logic would prevail that if anyone on ACEis or ARBs is at risk of infection, becomes infected, or develops coronavirus infectious disease 2019 (COVID-19), then these should be discontinued. However, the science of the renin angiotensin system (RAS) is far more intricate and interesting. The correct answer is that continuing ACEis or ARBs might indeed be harmful—or perhaps even beneficial. Thus, we and others (2) argued that empirical studies were needed to establish this rather than rely on biological plausibility and vacuous theorizing.

While much of the world was pontificating, some groups went on to design and conduct randomized clinical trials. REPLACE COVID is one such trial, recently published in *The Lancet Respiratory Medicine* (3). This trial began on March 31, 2020, within a few months of COVID-19 hitting North America and in the thick of the first wave. Over a period of 5 months, the required 152 patients were enrolled with global participation (20 hospitals representing 7 countries). Patients hospitalized with COVID-19, already on chronic ACEi or ARB, in whom equipoise was possible (e.g., excluding patients with hypo- or hypertension, hyperkalemia, severe acute kidney injury [AKI], or a compelling indication for ACEi/ARB), were randomized to either continue or stop their ACEi or ARB. Such an intervention is inherently open label, but the endpoints—primarily a global rank score, with secondary data on hospitalization, intensive care unit (ICU) length of stay, and mortality—were adjudicated by a blinded clinical panel.

In terms of the results, there was absolutely no difference in any of the outcomes, i.e., the primary global rank scores, nor all-cause death (10 in the continuation arm and 11 in the discontinuation arm), nor length of ICU or hospital stay. There was also no difference in the exploratory outcomes of ICU admission, ventilation, or hypotension requiring hemodynamics support. These results also question the oft-mentioned "sick day rules" for ACEis and ARBs, showing that patients hospitalized with a severe respiratory infection did not have an untoward effect. However, the debate on sick day rules is still ongoing (4). Thus, the REPLACE COVID trial does answer the question of whether ACEis or ARBs should be stopped in hospitalized patients with COVID-19 in the absence of classical clinical indications (e.g., hypotension). They should not be stopped!

These findings are also bolstered by the similar findings from the BRACE CORONA trial in a slightly less sick cohort of 659 patients. BRACE CORONA was conducted in Brazil and reported at the European Society of Cardiology but is not yet published (5). Some other questions in this area still remain: is infection with SARS-CoV-2 or the development of COVID-19 affected by being on ACEi or ARB, or can the addition of an ACEi or ARB to a RAS-naive patient be of benefit with COVID-19? The ongoing trials' list is available on the NephJC page (http://www.nephjc.com/news/covidace2) on the topic.

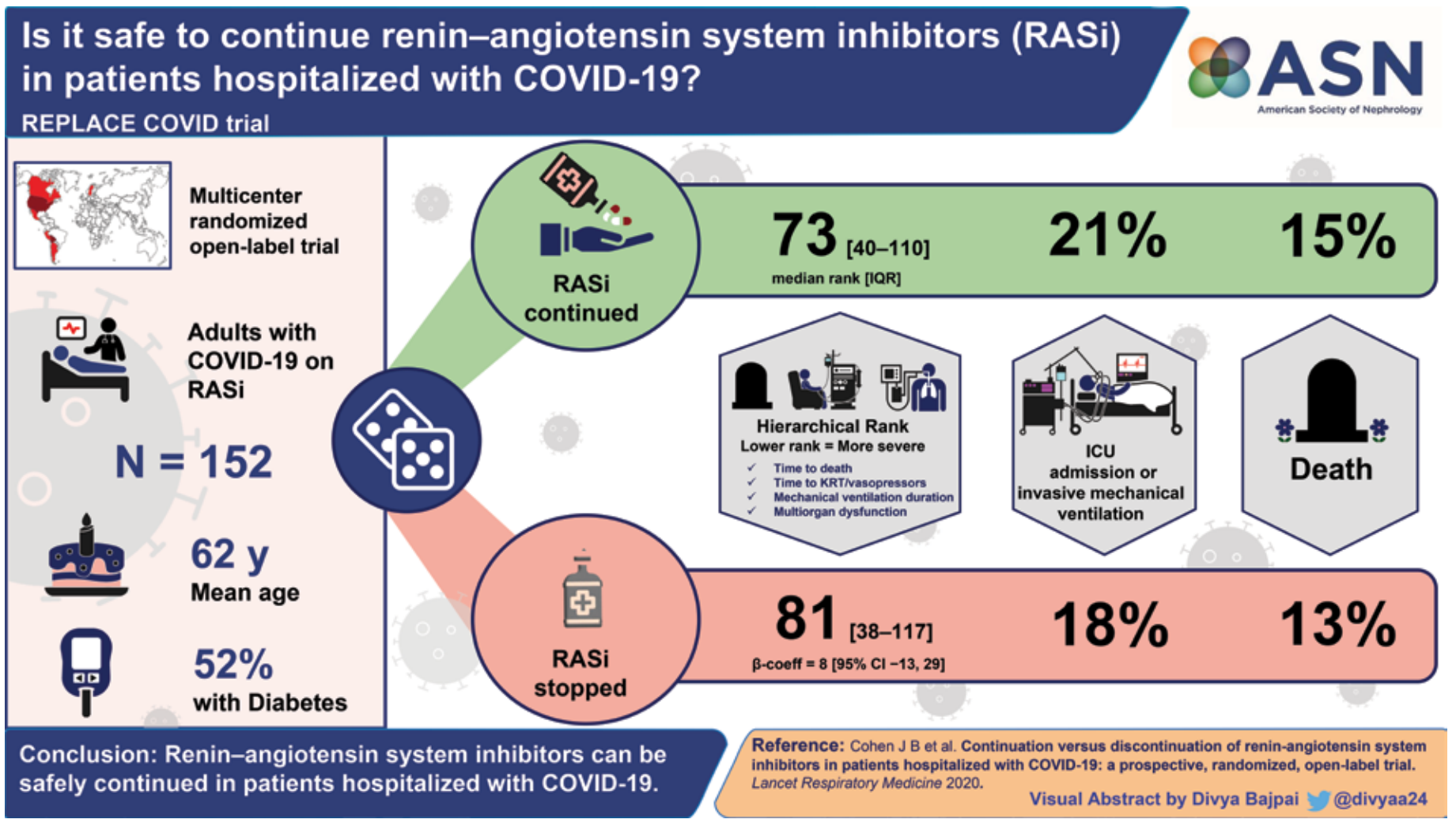
For now, let's celebrate the fact that nephrologists, cardiologists, infectious disease specialists, and other specialties came together and demonstrated that clinical trials are possible even at the height of a pandemic. This is the way!

Swapnil Hiremath, MD, MPH, is associate professor in the Division of Nephrology, Department of Medicine, University of Ottawa, Canada. Matthew A. Sparks, MD, FASN, is Assistant Professor of Medicine, Associate Program Director of Nephrology Fellowship, and Director of Medical Student Research in the Department of Medicine, Duke University, and staff physician for the Durham VA Health System, Durham, NC.

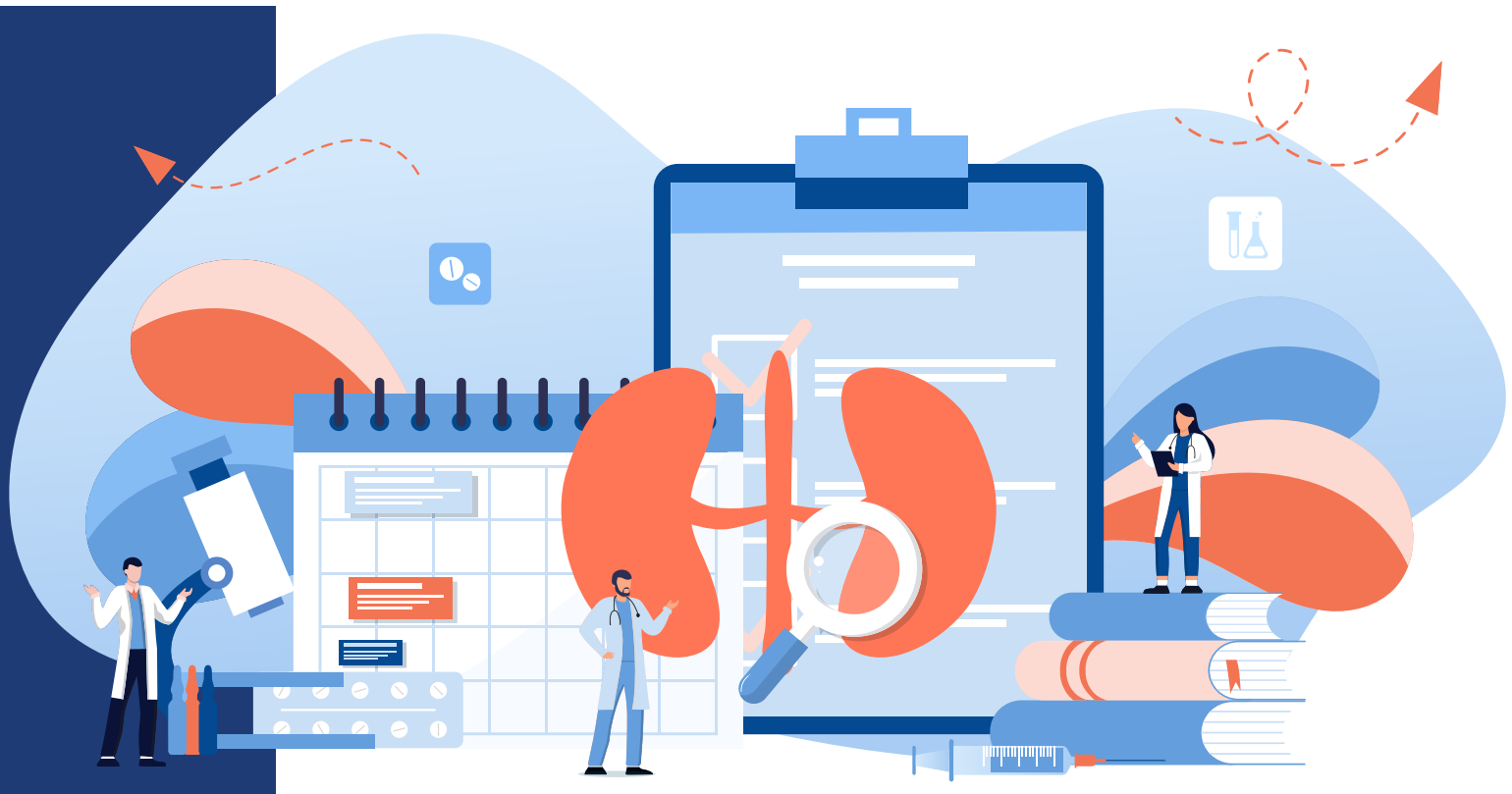
The authors report no conflict of interest.

References

1. Fang L, et al. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020; 8:e21. doi: 10.1016/S2213-2600(20)30116-8. Erratum in: *Lancet Respir Med* 2020; 88:e54. doi: 10.1016/S2213-2600(20)30235-6
2. Sparks MA, et al. Sound science before quick judgement regarding RAS blockade in COVID-19. *Clin J Am Soc Nephrol* 2020; 15:714–716. doi: 10.2215/CJN.03530320
3. Cohen JB, et al. Continuation versus discontinuation of renin–angiotensin system inhibitors in patients admitted to hospital with COVID-19: a prospective, randomised, open-label trial. *Lancet Respir Med* [published online ahead of print January 7, 2021]. doi: 10.1016/S2213-2600(20)30558-0; https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30558-0/fulltext#seccestitle160
4. Whiting P, et al. What are the risks and benefits of temporarily discontinuing medications to prevent acute kidney injury? A systematic review and meta-analysis. *BMJ Open* 2017; 7:e012674. doi: 10.1136/bmjopen-2016-012674
5. Lopes RD, et al. Effect of discontinuing vs continuing angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on days alive and out of the hospital in patients admitted with COVID-19: A randomized clinical trial. *JAMA* 2021; 325:254-264. doi:10.1001/jama.2020.25864



Visual Abstract by Divya Bajpai Dr. Divya Bajpai is associate professor, Department of Nephrology, Seth GSMC and KEM Hospital Mumbai



WARP SPEED
Nephrology Drug Development

By Kenar D. Jhaveri

Drug discovery and development is a lengthy and expensive process. Testing new agents in humans at an early stage can reduce the time and costs involved in identifying drugs that are likely to succeed in clinical studies. Implementation of a new drug in practice also requires the development of useful biomarkers of disease and of the drug's efficacy, as well as sensitive molecular imaging techniques.

Nephrology relied on only a handful of therapeutics during the 1970s to 2000s for managing anemia, bone-mineral disease, glomerular diseases, and transplantation-related events. In the past 2 decades, there has been a steady rise in novel therapeutics. The last 5 years saw a more rapid rise in the number of novel therapeutic targets and novel agents entering the kidney space (see Figure). The fields of oncology and cardiology have laid the path for us to follow. Targeted therapies and novel pathways along with out-of-the box thinking are required to move our field to the next level.

In this issue, along with the March 2021 issue, we take our readers to what the new therapeutics have to offer for our patients with kidney diseases. The time is now to speed up our process of offering novel agents to our patients and improve the care and outcomes of patients with kidney diseases.

Kenar D. Jhaveri, MD, is Editor-in-Chief of Kidney News.

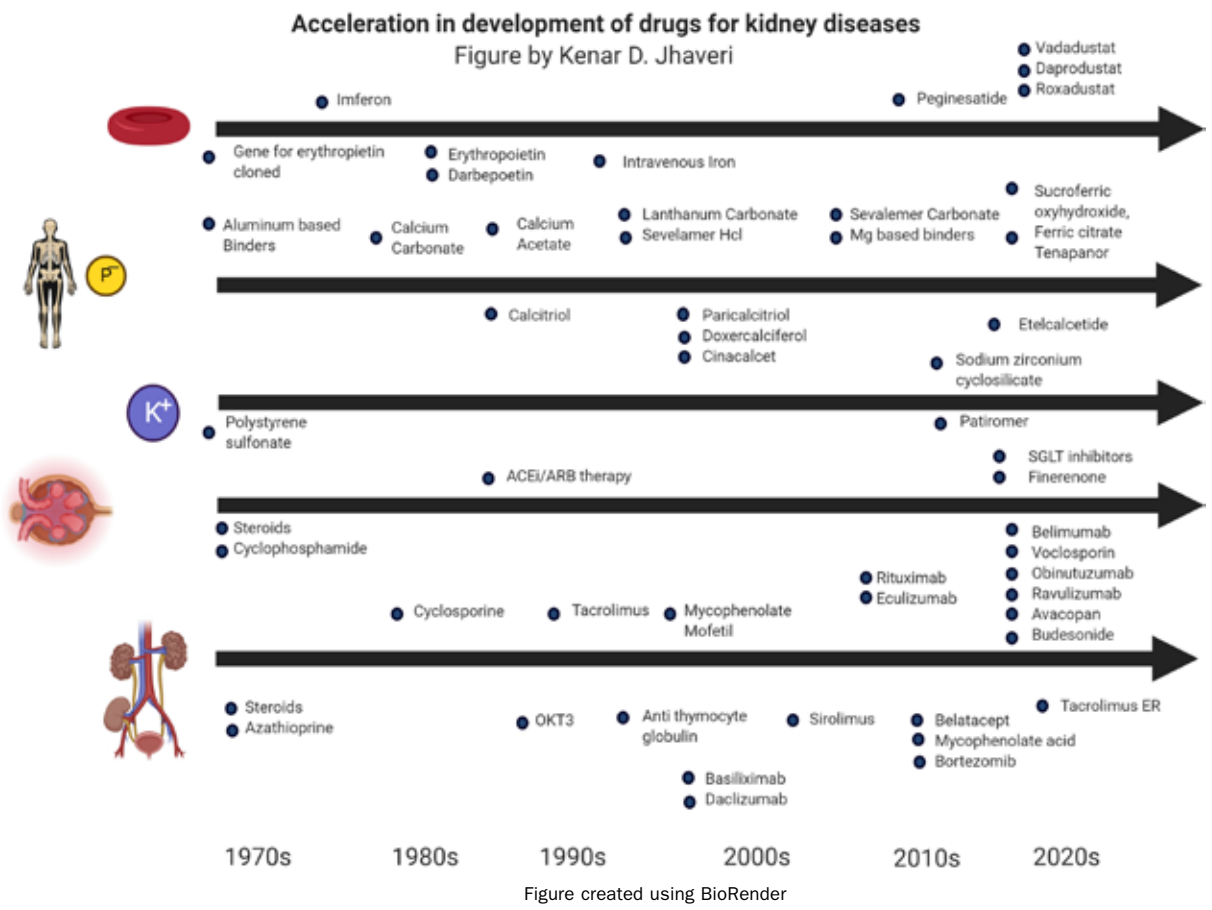


Figure created using BioRender

Novel Oral Potassium Binders

By Edgar V. Lerma

Appropriate and timely management of hyperkalemia is an important component of a nephrology practice. Hyperkalemia can result from increased K+ intake in the diet, impaired distribution between intracellular and extracellular spaces, and decreased kidney excretion. Risk factors associated with the development of hyperkalemia include older age, male sex, diabetes, underlying kidney disease, as well as intake of certain medications that affect the renin angiotensin aldosterone system (RAAS).

Prior to the advent of sodium zirconium cyclosilicate (SZC) and patiromer, only sodium polystyrene sulfonate (SPS) was available as a potassium exchange resin (1). Approved by the US Food and Drug Administration (FDA) in 1958, SPS has been mostly used in acute settings (Table 1). Although rare, the gastrointestinal (GI) toxicity of colonic necrosis was associated with high mortality if it happened.

Over the past several years, we have gained a much better understanding and newer tools with which to manage hyperkalemia, both in the acute and long-term scenarios. Although patiromer and SZC are advances, there are still limitations to consider.

The mechanism and onset of action make these agents quite useful in various clinical settings (2). Although SZC and patiromer have several advantages, including improved tolerability and an overall good safety profile, these agents can have a significant impact on financial costs with management of hyperkalemia.

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Novel Oral Potassium Binders

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In this pandemic era, the curtailment of patient exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by decreasing emergency room (ER) visits, reducing hospitalizations, and diminishing blood draws is a real benefit. Also, medical treatment of hyperkalemia and lessening of the burden on acute dialysis staff and available machines will help to prepare for any surge.

Financial data should be collected, and if the results are positive, actions should be taken to make these agents easily accessible, thereby potentially helping avoid ER visits, subsequent hospitalizations, and even the need for acute dialysis. Different practices should work on specific protocols to better manage hyperkalemia and include those protocols in quality improvement projects, i.e., regular assessment of the quality metrics, followed by appropriate action plans. This paradigm shift in the management of chronic hyperkalemia should open the doors for challenging endpoint studies in patients with kidney and cardiovascular diseases, where life-saving medications, such as RAAS inhibitors, mineralocorticoid receptor antagonists, and even beta-blockers, can be potentially titrated to the maximum dose. Another area of related interest may be how a more liberal diet affects the outcomes, nutritional status, and quality of life of patients (3). Many foods with health benefits (fruits and vegetables) also tend to be high in potassium.

There is a big push for home dialysis and urgent dialysis starts. A safe, effective, and well-tolerated potassium binder can make such a transition perhaps less challenging, particularly if hyperkalemia is one of the reasons driving the need for urgent-start kidney replacement therapy. This will give time for appropriate dialysis access placement, as well as evaluation and training, which will potentially translate into improved outcomes, including retention of patients on such dialytic modalities. The same applies to preemptive kidney transplantation, where a patient gets a transplant before going on dialysis. This is usually only possible if the patient has a potential living kidney donor, as the waiting time for a deceased kidney donation is quite protracted in most cases. However, at times, the living donor evaluation process may need to be delayed. A safe and effective K+ binder may help bridge the gap to a successful transplantation when the donor is ready.

In the future, cross-specialty training in hyperkalemia management is foreseeable. This should include trainees as well as clinical practitioners. Nephrology, cardiology, and diabetes specialists and primary care physicians should work collaboratively to optimize the medical management of patients, including keeping them on the medications and appropriately adjusted dosages as per kidney function.

The ultimate hope is that these novel oral K+ binders will help facilitate enhanced organ protection and at the same time, cause less hyperkalemia.

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Table 1. Agents approved for managing hyperkalemia

	Sodium polystyrene sulfonate (Kayexelate®) *15 g qD-QID (PO)* *30-50 g qD-BID (PR)*	Patiromer (Veltassa®) *8.4 g qD (PO), titrate up to 16.8 g or 25.2 g qD*	Sodium zirconium cyclosilicate (Lokelma®) *10 g TID (PO) for initial correction of K+ (for ≤ 48 h), then 5 g qOD or 15g qD for maintenance*
Year of Approval (US FDA)	1958	2015	2018
Mechanism of Action Selectivity for K^+ binding	Na^+ K^+ exchange resin Non-selective: also binds Ca^{2+} and Mg^{2+}	Ca^{2+} K^+ exchange polymer Non-selective: also binds Na^+ and Mg^{2+}	Crystalline compound traps K^+ in exchange for Na^+ and H^- Highly selective: also binds NH^{4+}
Components	Na^+ 1.5 g per 15 mg dose ± Sorbitol 20 g per 15 g dose	Ca^{2+} 1.6 g per 8.4 g dose Sorbitol 4 g per 8.4 g dose	Na^+ 400 mg per 5 g dose
Onset of Action	Variable	7 hours	1 hour
Site of Action	Colon	Distal colon predominantly	Entire GI tract
Separation required with other oral medications	3 hours before and 3 hours after	3 hours before and 3 hours after	2 hours before and 2 hours after
Adverse events	Nausea, vomiting, diarrhea, constipation, edema, GI bleeding, **bowel necrosis/ perforation** (SAE)	Nausea, diarrhea, constipation, hypomagnesemia	Nausea, diarrhea, constipation, peripheral edema

Dr. Lerma has received advisory board fees from AstraZeneca and research grants from ZS Pharma, Inc., which were involved with SZC studies.

References

1. Colbert GB, et al. Patiromer for the treatment of hyperkalemia. *Expert Rev Clin Pharmacol* 2020; 13:563–570. https://reference.medscape.com/medline/abstract/32511052
2. Palmer BF, et al. Clinical management of hyperkalemia [published online November 4, 2020]. *Mayo Clin Proc* doi: 10.1016/j.mayocp.2020.06.014
3. Palmer BF, Clegg DJ. Achieving the benefits of a high-potassium, paleolithic diet, without the toxicity. *Mayo Clin Proc* 2016; 91:496–508. doi: 10.1016/j.mayocp.2016.01.012

Does Veverimer Hold the Future for Metabolic Acidosis?

By Katherine Kwon

Veverimer is a novel agent for the treatment of metabolic acidosis in chronic kidney disease (CKD). It is a nonabsorbable polymer that selectively binds hydrochloric acid, leading to excretion of excess acid via the gastrointestinal tract. Veverimer completed a phase 3 clinical trial, demonstrating correction of serum bicarbonate when compared to placebo (1). However, in August 2020, the US Food and Drug Administration (FDA) declined to approve veverimer, requesting additional information on the likelihood of clinical benefit. This prompted manufacturer Tricida to create the VALOR-CKD trial. This ongoing trial will evaluate veverimer's efficacy against placebo on progression of kidney disease (2).

Metabolic acidosis in CKD is associated with a wide range of deleterious effects, including impaired muscle function, decreased bone density, and accelerated progression to end-stage kidney disease. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for management of CKD recommend treating metabolic acidosis with supplemental bicarbonate (3). However, bicarbonate and citrate (which metabolizes to bicarbonate) formulations include cations, such as sodium, potassium, or calcium, all of which can pose potential challenges in kidney patients who take them in large doses.

Veverimer allows for the correction of metabolic acidosis without the risks of the exogenous cations. It remains to be seen, however, if this correction leads to clinically meaningful outcomes for kidney patients. The VALOR-CKD trial seeks to answer this question but as a placebo-controlled trial, will not test efficacy against the current therapies in use. Existing therapies (sodium bicarbonate) are supported by several trials (albeit small) but do not have specific FDA approval for treating metabolic acidosis in CKD. Without a head-to-head trial, nephrologists and patients with kidney disease will need to decide if the anticipated extra cost of veverimer is worth it.

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The author reports no conflict of interest.

References

1. Wesson DE, et al. Veverimer versus placebo in patients with metabolic acidosis associated with chronic kidney disease: a multicentre, randomised, double-blind, controlled, phase 3 trial. *Lancet* 2019; 393:1417–1427. doi: 10.1016/S0140-6736(18)32562-5
2. Tricida, Inc. Evaluation of Effect of TRC101 on Progression of Chronic Kidney Disease in Subjects with Metabolic Acidosis (VALOR-CKD). ClinicalTrials.gov: NCT03710291. https://clinicaltrials.gov/ct2/show/NCT03710291
3. International Society of Nephrology. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3:1–150. https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

Fellows First

Voclosporin: Hope on the Horizon for Lupus Nephritis?

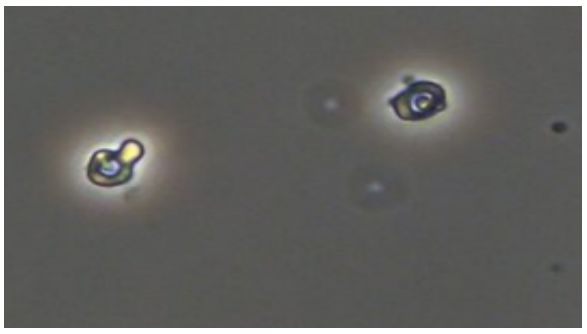
By Anna Gaddy

Ms. H is a 33-year-old Hispanic woman referred from a primary care clinic for proteinuria. Her only past medical history is hypertension on a single agent, amlodipine. She has had three children and had a tubal ligation for contraception. She reports that her pregnancies were uncomplicated with no history of preeclampsia or gestational diabetes. Her physical exam was unremarkable with blood pressure 130/70 mm Hg, and she has no edema.

Her laboratory data revealed a normal comprehensive metabolic panel with serum creatinine of 1.6 mg/dL and complete blood counts, although her serologies were noted for the following:

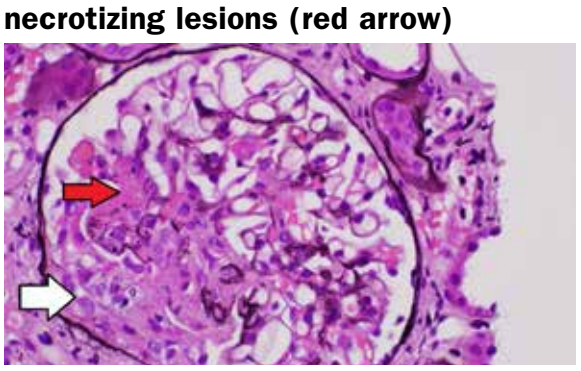
- double-stranded DNA titer 1:320 IU/mL
- C3 10 mg/dL (reference range 88–201 mg/dL), C4 5 mg/dL (reference range 15–45 mg/dL)
- spot urine protein/creatinine ratio of 4450 mg/g (reference range 0–200 mg/g)
- urinalysis was notable for 30 red blood cell/high-power field (RBC/hpf) (Figure 1)

Figure 1. Numerous dysmorphic RBCs were noted on the urine sediment



Courtesy Florian Buchkremer for Renal Fellow Network.

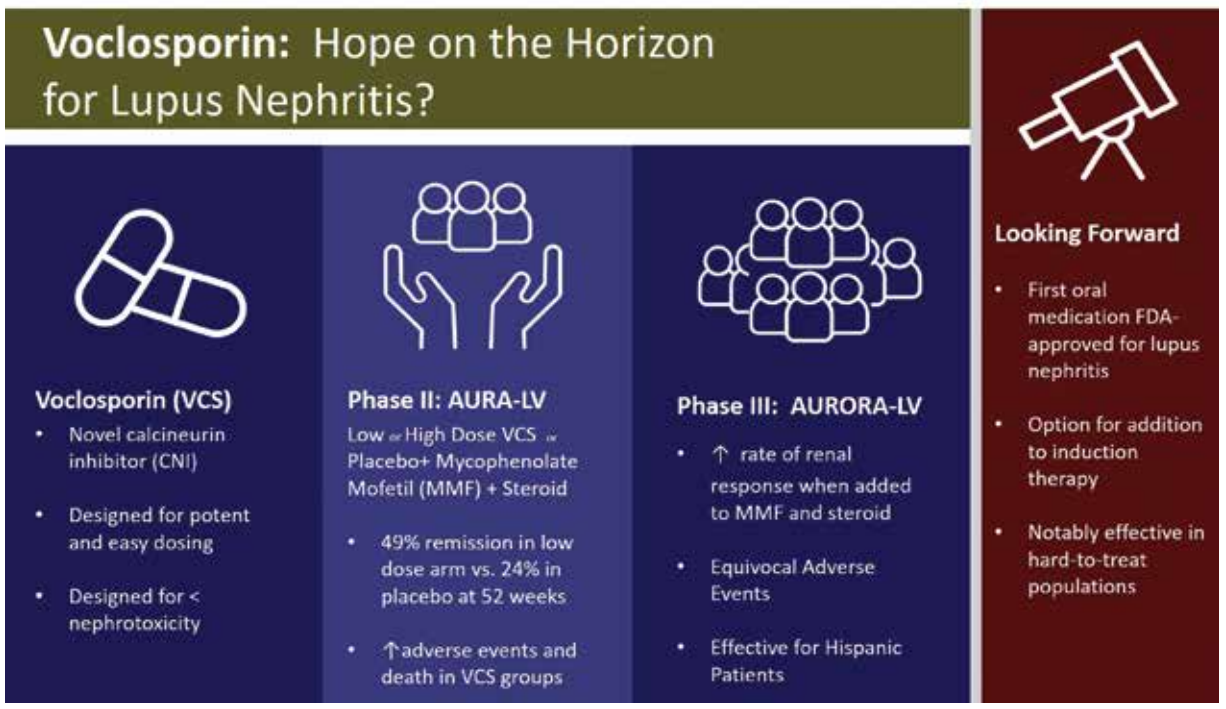
Figure 2. Lupus nephritis class III with focal crescentic (white arrow) and necrotizing lesions (red arrow)



A background of mild segmental mesangial hypercellularity is noted (silver stain, ×400). Courtesy Sam Albadri for Renal Fellow Network.

A kidney biopsy shows class III lupus nephritis (LN) with occasional crescents (<50%) (Figure 2). Ms. H asks you about treatment options. Her sister had LN, and cyclosporine caused gastrointestinal discomfort, hirsutism, and required multiple lab draws (for monitoring of levels), so she wants to avoid this regimen if possible. One year ago, your choice would have been mycophenolate mofetil (MMF) with a steroid taper for induction or perhaps rituximab or even a cyclophosphamide-based regimen. However, in 2021, treatment options for LN are quickly evolving. Kidney Week 2020 was rife with new developments in glomerular disease, including a session on the phase 3 clinical trial of voclosporin (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events [AURORA]) for induction of remission in patients with LN).

Figure 3. Voclosporin characteristics and clinical trial progress



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Voclosporin is a semi-synthetic analogue of cyclosporin A with enhanced potency and more predictable metabolism. This is because voclosporin is metabolized into smaller metabolites that do not competitively antagonize the parent compound like cyclosporine does. Thus, voclosporin does not require monitoring of levels. Like tacrolimus and cyclosporine, voclosporin inhibits calcineurin and prevents interleukin-2 (IL-2)-mediated T-cell activation. There are also data that calcineurin inhibitors (CNIs) can potentially directly stabilize podocyte foot processes and protect against injury (1, 2). Voclosporin achieves its immunomodulatory effect at lower doses than cyclosporine (3). Therefore, the hope is that heart- and kidney-associated toxicity seen with traditional CNIs will be lower (4). Because of this, voclosporin has the potential to improve remission rates and long-term outcomes (Figure 3).

In 2018, the phase 2 Aurinia Urinary Protein Reduction Active-Lupus with Voclosporin (AURA-LV) trial (5) demonstrated that voclosporin was efficacious when combined with MMF and a rapid steroid taper to induce remission in LN. The AURA-LV trial was composed of 265 patients with a kidney biopsy showing active class III, IV, or V LN within 6 months of screening. All patients received daily MMF and oral corticosteroids. The three comparison groups were 88 patients who received placebo, 89 patients receiving low-dose voclosporin (23.7 mg twice daily), and 88 patients receiving high-dose voclosporin (39.5 mg twice daily). In this study, significantly more individuals achieved complete remission with either low- or high-dose voclosporin than with placebo, and this effect persisted at 48 weeks in the low-dose group. Overall, with the addition of low-dose voclosporin, complete kidney remission was achieved by just under 30% of participants compared to only 20% of participants in the placebo group.

Not all of the AURA-LV results were encouraging, as both high-dose voclosporin and low-dose groups experienced significantly more serious adverse events (25.0% in low dose and 28.1% in high dose) compared to the placebo group (15.9%). Particularly concerning was that 10 deaths (11.2%) occurred in the low-dose voclosporin arm, compared to two in the high-dose arm and one in the placebo arm. However, only 3 of the 12 deaths in patients receiving voclosporin were related to infections. The most common serious adverse events in the AURA-LV trial were infection and gastrointestinal side effects.

The wait for phase 3 data came to an end as the AURORA trial data were presented at the Annual European Congress of Rheumatology (EULAR); then, at ASN Kidney Week 2020 Reimagined, the pooled results from phases 2 and 3 were presented (5). This pooled analysis combined data from the low-dose arm of the AURA-LV trial with data from the AURORA trial, as all study patients in the latter trial received 23.7 mg daily, randomized with placebo on a background of steroids and MMF—a total of 534 patients. The efficacy seen in AURORA was re-demonstrated, as voclosporin significantly improved the kidney response by 18% at one year (40.8% versus 22.5% in placebo). Subgroup analysis of the AURORA trial showed that 38.6% of Hispanic/Latinx participants receiving voclosporin achieved kidney remission (6, 7) compared to only 18.6% of those in the control arm. This is an exciting finding given the historically poor outcomes in this patient population.

Importantly, the increase in adverse events and death seen in the phase 2 AURA-LV trial was not appreciated in the phase 3 trials, with only 20.8% of participants taking voclosporin experiencing serious adverse events compared to 21.3% in the control group. It is worth noting that the definition of complete kidney remission of LN is defined as a urine protein-to-creatinine ratio of equal to or less than 0.5 mg/g, an estimated glomerular filtration rate (eGFR) of greater than or equal to 60 mL/min/1.73 m^2, or no loss of eGFR more than 20% of baseline and importantly, no rescue medications. Since CNIs are known to decrease proteinuria by nonimmunologic mechanisms (8), the endpoint of proteinuria may not tell a complete story, as immune damage may still be occurring even with diminished proteinuria. We await the final peer-reviewed publication of this trial before we can make any major conclusions.

Overall, the unpublished data of voclosporin appear to show improved remission rates and facilitate the early taper of corticosteroids, with no apparent increase in adverse

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Voclosporin

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events in phase 3 clinical trials. Important questions still remain about the long-term effects of voclosporin on cardiovascular and kidney function. However, the potential to give a medication without the need for monitoring has made voclosporin the first FDA-approved CNI for the treatment of LN. The encouraging results demonstrated in AURORA, along with data on the novel monoclonal antibody belimumab as an add-on therapy in the Efficacy and Safety of Belimumab in Patients with Active LN (BLISS-LN) trial (9), made 2020 an exciting year for the advancement of management of LN. ■

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The author reports no conflict of interest.

References

1. Wang L, et al. Calcineurin (CN) activation promotes apoptosis of glomerular podocytes both in vitro and in vivo. *Mol Endocrinol* 2011; 25:1376–1386. doi: 10.1210/me.2011-0029
2. Shen X, et al. Calcineurin inhibitors cyclosporin A and tacrolimus protect against podocyte injury induced by puromycin aminonucleoside in rodent models. *Sci Rep* 2016; 6:32087. doi: 10.1038/srep32087
3. Li Y, et al. Pharmacokinetic disposition difference between cyclosporine and voclosporin drives their distinct efficacy and safety profiles in clinical studies. *Clin Pharmacol* 2020; 12:83–96. doi: 10.2147/CPAA.S255789
4. Sanders ML, Langone AJ. Drugs in development for prophylaxis of rejection in kidney-transplant recipients. *Transpl Res Risk Manag* 2015; 7:59–69. doi: 10.2147/TRRM.S61446; https://www.dovepress.com/drugs-in-development-for-prophylaxis-of-rejection-in-kidney-transplant-peer-reviewed-fulltext-article-TRRM
5. Rovin BH, et al. A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis. *Kidney Int* 2019; 95:219–231. doi: 10.1016/j.kint.2018.08.025
6. Rovin BH, et al. Management of lupus nephritis (LN) with voclosporin: An update from a pooled analysis of 534 patients. American Society of Nephrology Kidney Week 2020. October 22, 2020. Abstract PO1917. https://www.asn-online.org/education/kidneyweek/2020/program-abstract.aspx?controlId=3446491
7. Arriens C, et al. Scientific Abstracts, Oral Presentations: Other orphan diseases. OP0277: AURORA phase 3 study demonstrates voclosporin statistical superiority over standard of care in lupus nephritis (LN). *Ann Rheum Dis* 2020; 79:172–173. https://ard.bmj.com/content/79/Suppl_1/172.2
8. Bensman A, Niaudet P. Non-immunologic mechanisms of calcineurin inhibitors explain its antiproteinuric effects in genetic glomerulopathies. *Pediatr Nephrol* 2010; 25:1197–1199. doi: 10.1007/s00467-010-1469-2
9. Furie R, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. *N Engl J Med* 2020; 383:1117–1128. doi: 10.1056/NEJMoa2001180

Novel Therapeutics in Kidney Transplantation

Belatacept, Bortezomib, Battlestar Galactica

By Samira S. Farouk

"Continue FK, MMF, pred."

Most nephrologists learn early in their training that the most common immunosuppressant regimen for patients with a kidney transplant consists of a calcineurin inhibitor (CNI), mycophenolic acid (usually mycophenolate mofetil [MMF]), with or without some corticosteroid. Let's take a quick look at two emerging outside-the-box immunosuppression tools.

The new kid on the block

CNIs have long been a thorn in kidney transplantation's side—with a laundry list of adverse effects ranging from tremors to electrolyte disturbances to paradoxical nephrotoxicity (1). One newer drug that has provided a CNI-free option in some patients is belatacept (approved by the US Food and Drug Administration [FDA] in 2011 for use in kidney transplantation), a fusion protein of the Fc fragment of human immunoglobulin G1 (IgG1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that interrupts the co-stimulatory step or "signal 2" of T cell activation. An analysis of efficacy and safety outcomes of the open-label Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT) study at 7 years (2), although not perfect, found higher patient and graft survival and mean estimated glomerular filtration rate (eGFR) in the belatacept group when compared to cyclosporine (despite higher rates of acute rejection in the belatacept groups). Belatacept is given as monthly infusions and provides a potential CNI alternative in patients with evidence of CNI toxicity or who experience challenges with adherence. Belatacept has been used for both induction and maintenance immunosuppression in kidney transplantation, with practices varying by transplant center (3–6).

Pesky plasma cells

Long-lived plasma cells (LLPCs) are terminally differentiated B cells arising from germinal centers that produce antibodies. LLPCs play a key role in antibody-mediated rejection (AMR) of the kidney transplant. Unfortunately, mainstays of AMR treatment, including intravenous Ig, plasmapheresis, and rituximab, are unable to target the majority of mature plasma cells (PCs) that do not express CD20 (8). Bortezomib, a first-generation proteasome inhibitor with a long track record in myeloma therapy, has been shown to reduce antibody levels before or after transplantation by inducing PC apoptosis (9). Carfilzomib, a second-generation proteasome inhibitor with minimal neurotoxicity (as opposed to bortezomib), has demonstrated efficacy in LLPC elimination and reduced antibody levels, although antibody rebound was also observed (10). The use of proteasome inhibitors to target LLPCs represents a needed advance in the treatment of AMR, as the persistence of LLPCs presents an ongoing challenge in improving long-term allograft survival. An improved understanding of PC biology, including its generation and survival, has allowed for development of and trials of newer therapies, including chemokine and cytokine antagonism (10).

Advances in immunosuppression that result from our better understanding of immune biology have the potential to improve allograft outcomes by either providing less toxic immunosuppressant options or allowing options to treat rejection more effectively. ■

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The authors report no conflict of interest.

References

1. Farouk SS, Rein JL. The many faces of calcineurin inhibitor toxicity—What the FK? *Adv Chronic Kidney Dis* 2020; 27:56–66. doi: 10.1053/j.ackd.2019.08.006
2. Vincenti F, et al. Belatacept and long-term outcomes in kidney transplantation. *N Engl J Med* 2016; 374:333–343. doi: 10.1056/NEJMoa1506027. Erratum in: *N Engl J Med* 2016; 374:698. doi: 10.1056/NEJMx160003
3. Adams AB, et al. Belatacept combined with transient calcineurin inhibitor therapy prevents rejection and promotes improved long-term renal allograft function. *Am J Transplant* 2017; 17:2922–2936. doi: 10.1111/ajt.14353
4. Cicora F, et al. Belatacept-based, ATG-Fresenius-induction regimen for kidney transplant recipients: A proof-of-concept study. *Transpl Immunol* 2015; 32:35–39. doi: 10.1016/j.trim.2014.10.002
5. Kumar D, et al. Belatacept as an alternative to calcineurin inhibitors in patients with solid organ transplants. *Front Med (Lausanne)* 2017; 4:60. doi: 10.3389/fmed.2017.00060
6. Ferguson R, et al. Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. *Am J Transplant* 2011; 11:66–76. doi: 10.1111/j.1600-6143.2010.03338.x
7. Radbruch A, et al. Competence and competition: The challenge of becoming a long-lived plasma cell. *Nat Rev Immunol* 2006; 6:741–750. doi: 10.1038/nri1886
8. Ajaz B, et al. Plasma cell CD20 expression: Primary aberrant expression or receptor up-regulation. *Leuk Lymphoma* 2014; 55:444–446. doi: 10.3109/10428194.2013.802782
9. Lee J, et al. The effect of bortezomib on antibody-mediated rejection after kidney transplantation. *Yonsei Med J* 2015; 56:1638–1642. doi: 10.3349/ymj.2015.56.6.1638
10. Woodle ES, et al. Plasma cell targeting to prevent antibody-mediated rejection. *Am J Transplant* 2020; 20:33–41. doi: 10.1111/ajt.15889

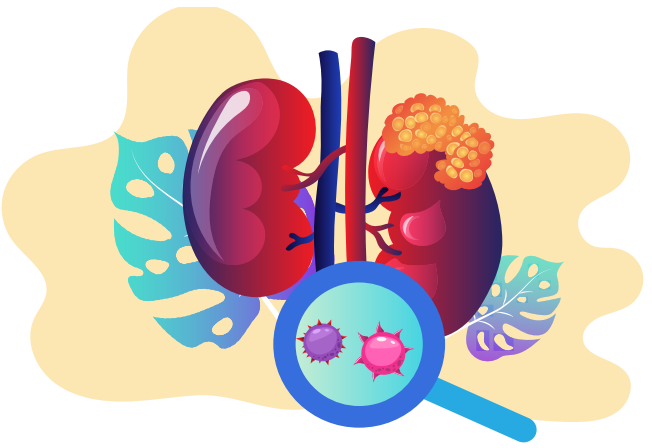
Diabetic (and Non-Diabetic) Kidney Disease Enters a New Era

By Susan Murray and Matthew A. Sparks

The year 2019 proved an incredibly important year for the treatment of patients with diabetic kidney disease (DKD). The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was a game changer; it demonstrated impressive cardiovascular- and kidney-protective effects of the sodium glucose co-transporter-2 (SGLT2) inhibitor canagliflozin in patients with DKD (1). CREDENCE was important because it was the first trial of SGLT2 inhibitors to include kidney endpoints as primary targets of the trial and led to the US Food and Drug Administration (FDA) extending the indication for canagliflozin specifically for reducing the risk of end-stage kidney disease (ESKD) in patients with type 2 diabetes. SGLT2 inhibitors quickly became a cornerstone of the treatment of diabetic nephropathy. Reflecting this, SGLT2 inhibitors were enshrined in the 2020 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. It recommended that patients with type 2 diabetes, chronic kidney disease (CKD), and an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2 should be treated with metformin and an SGLT2 inhibitor (2).

The year 2020 continued to raise the bar for therapeutics in kidney disease and extended the use of SGLT2 inhibitors to patients without diabetes. The Dapagliflozin and Prevention of Adverse Outcomes in CKD (DAPA-CKD) trial showed that the heart- and kidney-protective effects of dapagliflozin occurred in those with, and importantly without, diabetes mellitus (3). Dapagliflozin resulted in a 5% absolute risk reduction of ESKD, death from cardiovascular or kidney causes, or a sustained 50% fall in eGFR compared to placebo.

The bigger news from DAPA-CKD was that the benefit of SGLT2 inhibitors extended to those even without diabetes. Of the 4304 randomized participants, 33% did not have diabetes. Importantly, the safety profile of dapagliflozin in patients without diabetes was impressive. The recent Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection



Fraction (EMPEROR-Reduced) showed that in a study of 3730 patients with heart failure and an ejection fraction of <30%, cardiovascular death and admissions with heart failure were lower in those taking empagliflozin compared to placebo. A decline in eGFR was a secondary outcome of the study, and those on empagliflozin showed a slower rate of decline in eGFR over a median of 16 months of the study. Only 50% of enrolled pa-

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Diabetic (and Non-Diabetic) Kidney Disease

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tients in EMPEROR-Reduced had diabetes mellitus (4). We await the results of The Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY), which aims to assess the effect of empagliflozin on kidney disease progression or cardiovascular death. EMPA-KIDNEY is also enrolling patients without diabetes and pushing the eGFR inclusion criteria to 20 mL/min/1.73 m^2 without the need for albuminuria if eGFR is between 20 and 45 mL/min/1.73 m^2. These trials are paving the road for use of SGLT2 inhibitors in DKD and non-diabetic proteinuric CKD and in patients with congestive heart failure and kidney disease.

This year also saw the introduction of another new agent for use in patients with DKD. Finerenone is a non-steroidal mineralocorticoid receptor antagonist. It functions similarly to other mineralocorticoid receptor antagonists, such as spironolactone or eplerenone, but without appreciable effects on the glucocorticoid, androgen, and progesterone receptors (5). In November 2020, the results from the Efficacy and Safety of Finerenone in Subjects with Type 2 Diabetes Mellitus and DKD (FIDELIO-DKD) trial were published. The study showed that compared to placebo, finerenone led to a 3% absolute risk reduction in a composite endpoint, consisting of death from kidney causes or kidney failure or a decrease of eGFR by 40% from baseline (6). The majority of this outcome was driven by patients who experienced a sustained decrease in eGFR. As with other mineralocorticoid receptors, hyperkalemia is a concern with finerenone. In FIDELIO-DKD, hyperkalemia-related events were seen in twice as many people in the finerenone group as in the placebo group (18% vs. 9%), and 2.3% of the finerenone group discontinued treatment due to hyperkalemia, compared to 0.9% of the placebo group.

It is truly a remarkable time for the treatment of individuals with DKD, and with more major trials expected in the coming years, we are hopeful that these therapies will be widely used to diminish the need for kidney replacement therapy. ■

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The authors report no conflict of interest.

References

1. Perkovic V, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380:2295–2306. doi: 10.1056/NEJMoa1811744
2. de Boer IA, et al. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int* 2020; 98:S1–S115. doi: 10.1016/j.kint.2020.06.019
3. Heerspink HJL, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; 383:1436–1446. doi: 10.1056/NEJMoa2024816
4. Packer M, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; 383:1413–1424. doi: 10.1056/NEJMoa2022190
5. Haller H, et al. Finerenone: A new mineralocorticoid-receptor antagonist without hyperkalemia: An opportunity in patients with CKD? *Curr Hypertens Rep* 2016; 18:41. doi: 10.1007/s11906-016-0649-2
6. Bakris GL, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med* 2020; 383:2219–2229. doi: 10.1056/NEJMoa2025845

Rituximab and Obinutuzumab for Membranous Nephropathy

By Sahar Semnani and Eugene Lin

The last two years have brought several promising trials with novel therapies for the treatment of membranous nephropathy, the most common etiology of nephrotic syndrome in adults (1, 2).

Currently, the mainstay of treatment is steroids in combination with alkylating agents (modified Ponticelli regimen) or calcineurin inhibitors (3). With the identification of auto-antibodies against the phospholipase-2 receptor (PLA2R) comes the potential for new therapies (4, 5), including monoclonal antibodies against CD20 on B-lymphocytes: rituximab and obinutuzumab (4).

In 2019, the MENTOR randomized controlled trial showed that rituximab was non-inferior to cyclosporine in inducing complete or partial remission of proteinuria and was superior in maintaining remission after 24 months (6). The RI-CYCLO trial, a smaller pilot study (unpublished) that was presented as an abstract at Kidney Week 2020 Reimagined, suggested similar efficacy between rituximab and cyclophosphamide in complete or partial remission of proteinuria (7). The STARMEN trial, on the other hand, was less favorable for the combination of rituximab and tacrolimus when randomized against the modified Ponticelli regimen (8). The ongoing clinical trial NCT00977977 will shed light on the safety and efficacy of combining rituximab with cyclosporine in patients with membranous nephropathy (9).

Because up to 40% of patients do not respond to rituximab (6), obinutuzumab has garnered interest as an alternative therapy for refractory membranous nephropathy and has demonstrated promise in small studies (10, 11). Although larger trials have not been conducted, obinutuzumab has shown excellent B-cell cytotoxic profiles in treating B-cell malignancies (12). An upcoming trial comparing obinutuzumab to tacrolimus will begin recruiting early this year (11, 13).

These ongoing investigations and trials should generate optimism so that we may soon have alternatives to the Ponticelli regimen for membranous nephropathy, which has been the mainstay of first-line therapy for over 30 years (4). Given the toxicity of alkylating agents and difficulty of administration in many, such a development would be very welcome. ■

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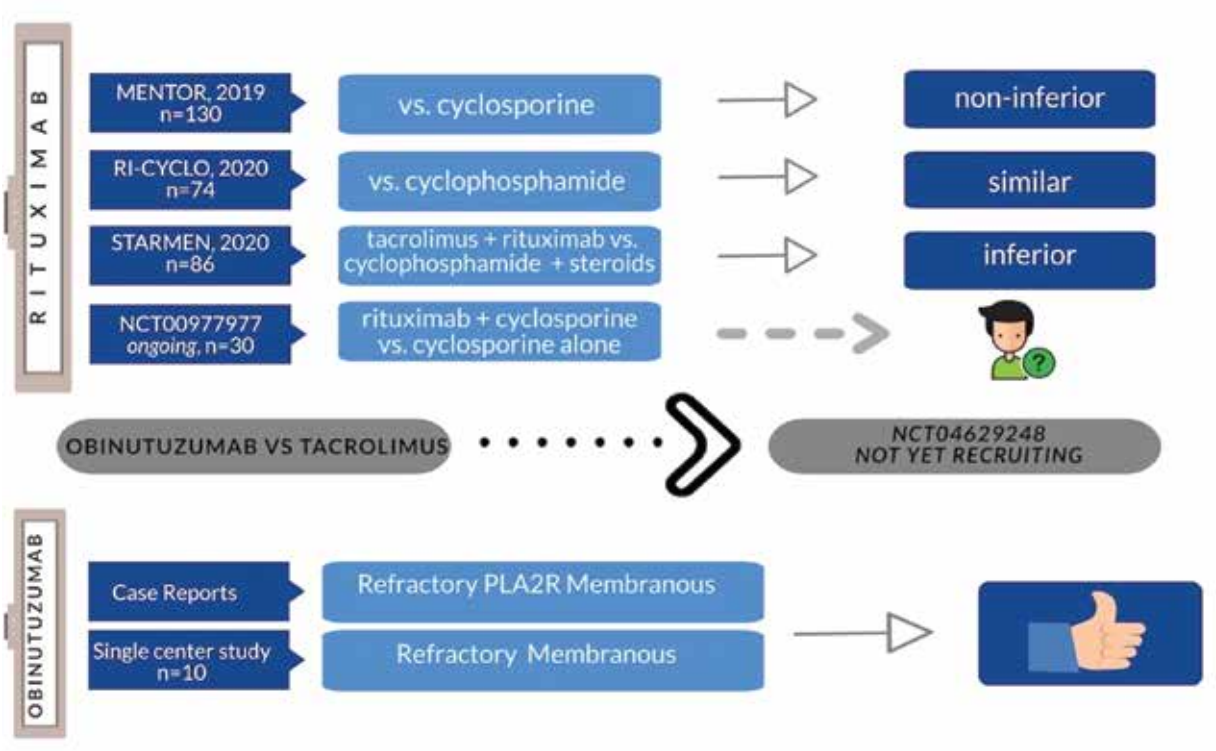
The authors report no conflict of interest.

References

1. Rojas-Rivera JE, et al. Treatment of idiopathic membranous nephropathy in adults: KDIGO 2012, cyclophosphamide and cyclosporine A are out, rituximab is the new normal. *Clin Kidney J* 2019; 12:629–638. doi: 10.1093/ckj/sfz127
2. Singh L, et al. Understanding podocytopathy and its relevance to clinical nephrology. *Indian J Nephrol* 2015; 25:1–7. doi: 10.4103/0971-4065.134531
3. Ferreira F, Nunes AT. New treatments in membranous glomerulopathy—from the pitfalls of rituximab to a new era of biological treatments. *Port J Nephrol Amp Hypertens* 2020; 34:160–164. http://doi.org/10.32932/pjnh.2020.10.087
4. Waldman M, Austin HA 3rd. Treatment of idiopathic membranous nephropathy. *J Am Soc Nephrol* 2012; 23:1617–1630. doi: 10.1681/ASN.2012010058

Recent clinical trials investigating antibodies against CD20 for the treatment of primary membranous nephropathy



5. Salvadori M, Tsalouchos A. Editor's pick: New aspects of pathogenesis and treatment of membranous glomerulopathy after the MENTOR study. *EMJ Nephrol* 2020; 8:46–53. https://www.emjreviews.com/nephrology/article/editors-pick-new-aspects-of-pathogenesis-and-treatment-of-membranous-glomerulopathy-after-the-mentor-study/
6. Fervenza FC, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med* 2019; 381:36–46. doi: 10.1056/NEJMoa1814427
7. Delbarba E, et al. Rituximab vs. cyclophosphamide in the treatment of membranous nephropathy: The RI-CYCLO trial. American Society of Nephrology, Kidney Week. October 22, 2020; PO2638. Accessed December 21, 2020. https://www.asn-online.org/education/kidneyweek/2020/program-abstract.aspx?controlId=3470922
8. Fernández-Juárez G, et al. The STARMEN trial indicates that alternating treatment with corticosteroids and cyclophosphamide is superior to sequential treatment with tacrolimus and rituximab in primary membranous nephropathy. *Kidney Int* [Published online ahead of print November 7, 2020]. doi: 10.1016/j.kint.2020.10.014; https://www.kidney-international.org/article/S0085-2538(20)31251-5/fulltext
9. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Rituximab plus cyclosporine in idiopathic membranous nephropathy. ClinicalTrials.gov: NCT00977977. Accessed December 20, 2020. https://clinicaltrials.gov/ct2/show/NCT00977977
10. Klomjit N, et al. Successful treatment of patients with refractory PLA2R-associated membranous nephropathy with obinutuzumab: A report of 3 cases. *Am J Kidney Dis* 2020; 76:883–888. doi: 10.1053/j.ajkd.2020.02.444
11. Sethi S, et al. Obinutuzumab is effective for the treatment of refractory membranous nephropathy. *Kidney Int Rep* 2020; 5:1515–1518. doi: 10.1016/j.ekir.2020.06.030
12. Marcus R, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med* 2017; 377:1331–1344. doi: 10.1056/NEJMoa1614598
13. Hoffmann-La Roche. A phase III randomized, open-label active comparator-controlled multicenter study to evaluate efficacy and safety of obinutuzumab in patients with primary membranous nephropathy. ClinicalTrials.gov: NCT04629248. Accessed December 29, 2020. https://clinicaltrials.gov/ct2/show/NCT04629248

Novel Agents in CKD-MBD

A Second Lease on Life or Flogging a Dead Horse?

By Mayuri Trivedi and Sanjeev Nair

Mineral bone disease (MBD) has proven to be a Pandora's box for most clinicians treating chronic kidney disease (CKD), including end-stage kidney disease (ESKD). Although the body of literature highlighting the various bone metabolic abnormalities associated with ESKD as definite risk factors for mortality, cardiovascular disease, increased risk of fractures, and other musculoskeletal complications grows stronger, the therapeutic agents to deal with these abnormalities continue to keep us on edge (Table 1).

In recent years, a few novel agents have been promoted as game changers in the management of this important complication of ESKD. Time will tell whether they will be successful in matching the hype and actually improving patient outcomes.

Currently approved treatments for the mineral bone abnormalities in ESKD include phosphate binders to treat the hyperphosphatemia and calcimimetic drugs and active vitamin D analogs to treat the associated secondary hyperparathyroidism. In 2012, a randomized, placebo-controlled trial, EVOLVE, with cinacalcet, a first-generation calcimimetic agent, did not significantly reduce the risk of death or non-fatal cardiovascular events in ESKD patients with secondary hyperparathyroidism (1). Recently, a second-generation intravenous calcimimetic agent, etelcalcetide, was approved to be used thrice per week post-regular hemodialysis (2). It reportedly reduces the parathyroid hormone (PTH) levels by at least 30% from baseline by 20–27 weeks of use, along with lowering serum phosphate and fibroblast growth factor (FGF)-23 levels. This was achieved without loading the patient with calcium, thus minimizing the risk of soft tissue and arterial calcification similar to cinacalcet albeit with lesser gastrointestinal side effects and a convenient thrice-weekly post-dialysis dosing. However, despite this proposed benefit, the drug does seem to share the hypocalcemia potential of the calcimimetic drug class with an increased incidence of hypocalcemia-related life-threatening complications compared to placebo.

Phosphate binders are commonly used drugs in kidney disease. A new kid on the block, tenapanor, is a minimally absorbed novel drug that inhibits the gastrointestinal sodium/hydrogen exchanger 3 (NHE3) and is used as an anti-constipation agent in irritable bowel syndrome. It acts by reducing paracellular phosphate transport in the intestine and thus acts via a non-phosphorus binding mechanism to reduce serum phosphate levels by as much as 1–1.2 g/dL over an 8-week period of use. Apart from soft stools and increased bowel movements, this drug did not differ significantly from placebo and shows some potential in improving the management of MBD (3). In the absence of good quality data, however, we will have to wait to see whether tenapanor will prove beneficial in the treatment of MBD. We are awaiting publication of the phase 3 clinical trial, called the PHREEDOM study, looking at tenapanor versus placebo in patients with ESKD on dialysis (4).

Ferric citrate is a relatively more researched novel agent, which is an oral, calcium-free, iron-based phosphate binder that not only helps in reducing serum phosphate levels but also helps in treatment of another common complication of CKD, i.e., anemia. So apart from phosphate reduction, the added improvement of iron parameters can potentially cut costs and reduce the pill burden for these patients. Block et al. (5), in their recent study, showed a beneficial effect on the biochemical parameters with an excellent safety profile.

The advent of newer agents for the treatment of MBD in CKD may help in improving the cardiovascular outcomes. However, robust data with randomized controlled trials that measure patient-centric outcomes as well as hard outcomes like mortality benefit are needed to back the claims that inspire the hope of improved outcomes. The results of the recently announced HiLo trial will be important to watch. HiLo is a multi-center, pragmatic, randomized controlled trial that aims to study all-cause mortality and all-cause hospitalizations in ESKD patients with high-phosphate (≥6.5 mg/dL) or low-phosphate (≤5.5 mg/dL) levels (6). Another similar trial, the results of which may have an impact on our approach to MBD management, is the PHOSPHATE trial (7).

Regardless of the final status of these drugs, the management of MBD must move beyond surrogate outcomes like biochemical improvements and be measured by its impact on patient-centric outcomes, as well as hard outcomes, including improved cardiovascular and mortality outcomes in the long run. ■

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The authors report no conflict of interest.

References

1. Chertow GM, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med* 2012; 367:2482–2494. doi: 10.1056/NEJMoa1205624
2. Block GA, et al. Effect of etelcalcetide vs placebo on serum parathyroid hormone in patients receiving hemodialysis with secondary hyperparathyroidism: Two randomized clinical trials. *JAMA* 2017; 317:146–155. doi: 10.1001/jama.2016.19456
3. Block GA, et al. Efficacy and safety of tenapanor in patients with hyperphosphatemia receiving maintenance hemodialysis: A randomized phase 3 trial. *J Am Soc Nephrol* 2019; 30:641–652. doi: 10.1681/ASN.2018080832
4. Ardelyx. Ardelyx Announces Positive Topline Results from Pivotal Phase 3 PHREEDOM Study Evaluating Tenapanor in CKD Patients on Dialysis. Published December 3, 2019. Accessed December 25, 2020. https://ir.ardelyx.com/news-releases/news-release-details/ardelyx-announces-positive-topline-results-pivotal-phase-3
5. Block GA, et al. A pilot randomized trial of ferric citrate coordination complex for the treatment of advanced CKD. *J Am Soc Nephrol* 2019; 30:1495–1504. doi: 10.1681/ASN.2018101016
6. Edmonston DL, et al. Design and rationale of HiLo: A pragmatic, randomized trial of phosphate management for patients on maintenance hemodialysis. *Am J Kidney Dis* [published online ahead of print December 3, 2020]. doi: 10.1053/j.ajkd.2020.10.008; https://www.ajkd.org/article/S0272-6386(20)31131-8/fulltext
7. Pragmatic Randomised Trial of High Or Standard PHosphAte Targets in End-stage Kidney Disease (PHOSPHATE). ClinicalTrials.gov: NCT03573089. https://clinicaltrials.gov/ct2/show/NCT03573089

Table 1. Reasons for skepticism among nephrologists regarding novel drugs for MBD

■ There is a lack of randomized controlled trial data with hard outcomes (mortality/cardiovascular endpoints).
■ Existing trials are placebo controlled with surrogate outcomes or observational studies.
■ Introduction of novel agents into the market only requires demonstration of phosphorus lowering with a favorable safety profile.

MBD = mineral bone disease

Update on SARS-CoV-2 Vaccination for Kidney Transplant Recipients

By Victoria Hall and Deepali Kumar

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has had a significant impact on transplantation, with mortality rates in transplant recipients ranging from 10% to 20% (1). Although some antiviral and anti-inflammatory therapies for COVID-19 have become available, they need to be given within a short time window during the course of illness to be effective (2, 3). Thus, the recent US Food and Drug Administration (FDA) Emergency Use Authorization of highly efficacious mRNA-based SARS-CoV-2 vaccines by Pfizer/BioNTech and Moderna provides hope for reducing infection rates (4).

Both the Pfizer/BioNTech and Moderna vaccines were rigorously evaluated in >70,000 individuals and found to have an efficacy of 94.1%–95% in phase 3 placebo-controlled trials (5, 6). Local and systemic adverse events, such as fever, chills, and headache, occurred and were more common after the second dose (5, 6). Immunocompromised patients, including kidney or kidney-pancreas transplant recipients, were not included in the two large trials, and therefore, safety and efficacy data are lacking. Nevertheless, despite the lack of vaccine data, the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) stated that immunocompromised patients can receive the vaccine after being counseled regarding risks and benefits, lack of data, and the potential for lower efficacy (7).

Experts with the American Society of Transplantation (AST) have reviewed the available information for the safety and efficacy of mRNA vaccination and recommended that transplant candidates, recipients, and their household contacts receive the vaccine when it is available to them (8). This is consistent with recommendations from other transplant societies, such as the Canadian Society of Transplantation (CST) and The Transplantation Society (TTS) (9). Although mRNA vaccines have not specifically been tested in kidney or kidney-pancreas transplant recipients, mRNA technology has been used in investigational vaccines for cancer and other infectious diseases. Given the relatively high mortality from COVID-19 in transplant patients, it is clear that the benefits of vaccination outweigh any theoretical risks of systemic or off-target effects, such as graft dysfunction. The efficacy of the vaccine is likely to be lower in transplant recipients than outlined in the trials; however, it is also likely that patients with a functioning transplant will derive at least partial benefit.

The AST guidance also outlines issues regarding timing of vaccination in relation to transplant immunosuppression in order to maximize immune responses (8). Vaccines should be given prior to transplant when possible. In the post-transplant setting, the SARS-CoV-2 vaccine can be given starting 1 month after transplant, although a longer time period is suggested if T or B cell ablation is given. It is also suggested to wait to start the vaccination series 90 days after developing COVID-19 or receipt of convalescent plasma or monoclonal antibody. Since no vaccine co-administration studies are available, it is reasonable to avoid giving other vaccines within 14 days of a SARS-CoV-2 vaccine. Importantly, since vaccination is a 2-dose series, deferring transplant to complete vaccination doses is not suggested as a routine (Table 1).

The prioritization of kidney or kidney-pancreas transplant recipients is likely to occur in phase 1c, as defined by the CDC (7), in which several groups of high-risk individuals are noted. Some transplant

recipients who are healthcare workers or other essential workers or reside in long-term care facilities may receive the vaccine sooner. A state-defined prioritization and distribution scheme, as well as vaccine availability, will likely define when transplant recipients are vaccinated. In addition, several other types of SARS-CoV-2 vaccines are under review or being developed and may become available in the future. The AST guidelines are updated as new information becomes available and provide an excellent "go-to" resource for transplant professionals on SARS-CoV-2 vaccination.

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References

1. Kates OS, et al. COVID-19 in solid organ transplant: A multi-center cohort study. *Clin Infect Dis* [published online ahead of print August 7, 2020]. doi: 10.1093/cid/ciaa1097; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7454362/
2. Horby P, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med* [published online ahead of print July 17, 2020]. doi: 10.1056/NEJMoa2021436; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7383595/
3. Beigel JH, et al. Remdesivir for the treatment of Covid-19—final report. *N Engl J Med* 2020; 383:1813–1826. doi: 10.1056/NEJMoa2007764
4. U.S. Food and Drug Administration. COVID-19 Vaccines. January 2021. https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines
5. Polack FP, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; 383:2603–2615. doi: 10.1056/NEJMoa2034577
6. Baden LR, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* [published online ahead of print December 30, 2020]. doi: 10.1056/NEJMoa2035389; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7787219/
7. Dooling K, et al. The Advisory Committee on Immunization Practices' Interim Recommendation for Allocating Initial Supplies of COVID-19 Vaccine—United States, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69:1857–1859. doi: 10.15585/mmwr.mm6949e1
8. American Society of Transplantation. COVID-19: Vaccine FAQ Sheet. January 25, 2021. https://www.myast.org/sites/default/files/2021%2001%2025%20COVID19%20VACCINE%20FAQS_update%20v%203.pdf
9. Canadian Society of Transplantation. National Transplant Consensus Guidance on COVID-19 Vaccine. January 23, 2021. https://www.cst-transplant.ca/_Library/Coronavirus/National_Transplant_Consensus_Guidance_on_COVID_vaccine-20210123_FINAL.pdf

Table 1. Recommendations for giving the SARS-CoV-2 vaccine in patients with kidney and kidney-pancreas transplants

- Patients should be counseled regarding risks and benefits, lack of data, and the potential for lower efficacy while on immunosuppressive medications.
- Give prior to transplant when possible.
- Give 1 month post-transplant and longer if T- or B cell ablation given.
- Wait 90 days after developing COVID-19 or receipt of convalescent plasma or monoclonal antibody.
- Avoid giving other vaccines within 14 days of a SARS-CoV-2 vaccine.
- Deferring transplant to complete vaccination doses is not suggested.

NEWS FLASH

SGLT2 Inhibitors as Protective for Acute Kidney Injury

Highlight of a recent study in *CJASN*, "Network Meta-Analysis of Novel Glucose-Lowering Drugs on Risk of Acute Kidney Injury"

By Huilin Tang

Acute kidney injury (AKI) can be a complication seen in patients with type 2 diabetes mellitus (T2DM) who are on glucose-lowering agents. Diabetic kidney disease is a major cause of chronic kidney disease, and the presence of diabetes is an independent risk factor for both AKI and poor clinical outcomes.

Sodium glucose co-transporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP-1RAs) are new classes of glucose-lowering agents for treating T2DM. However, little is known about the comparative effects of these three glucose-lowering agents on AKI.

Network meta-analysis is a method that enables comparison of these three glucose-lowering agents in the same analysis. Thus, we applied a network meta-analysis to analyze data from 20 event-driven cardiovascular or kidney outcome randomized clinical trials. Of the 20 trials analyzed, 18 included patients with T2DM only, and two trials included patients with or without T2DM. Of the 18 trials, which included a total of 156,690 patients with T2DM receiving these glucose-lowering agents, 2051 AKI events occurred. Interestingly, patients taking SGLT2 inhibitors had a lower risk of AKI than those taking placebo by 24%, whereas both DPP-4 inhibitors and GLP-1RAs had no effect on risk of AKI.

Moreover, SGLT2 inhibitors were significantly associated with a lower risk of AKI than DPP-4 inhibitors (odds ratio [OR] = 0.68) and GLP-1RAs (OR = 0.79). Among the three glucose-lowering agents, SGLT2 inhibitors were the lowest risk for AKI. When we analyzed 20 trials involving patients with or without T2DM, the results remained similar. Therefore, these data suggest that SGLT2 inhibitors may protect against AKI. However, several limitations should be considered, including the various definitions of AKI used in the different trials and AKI not being reported as the primary outcome in the included trials.

As SGLT2 inhibitors cause an acute drop in glomerular filtration rate, our finding of a protective effect for these agents is perhaps surprising and raises questions about the mechanism of AKI. The multifactorial nature of AKI means there are likely multiple mechanisms that lead to the protection against AKI seen with SGLT2 inhibitors. It is possible that the acute reduction in glomerular filtration rate seen with SGLT2 inhibitors appears to confer protection against AKI, potentially through reducing kidney oxygen demands further.

The results of this study suggest that SGLT2 inhibitors not only clearly prevent progressive loss of kidney function and kidney failure but also specifically reduce the risk of AKI.

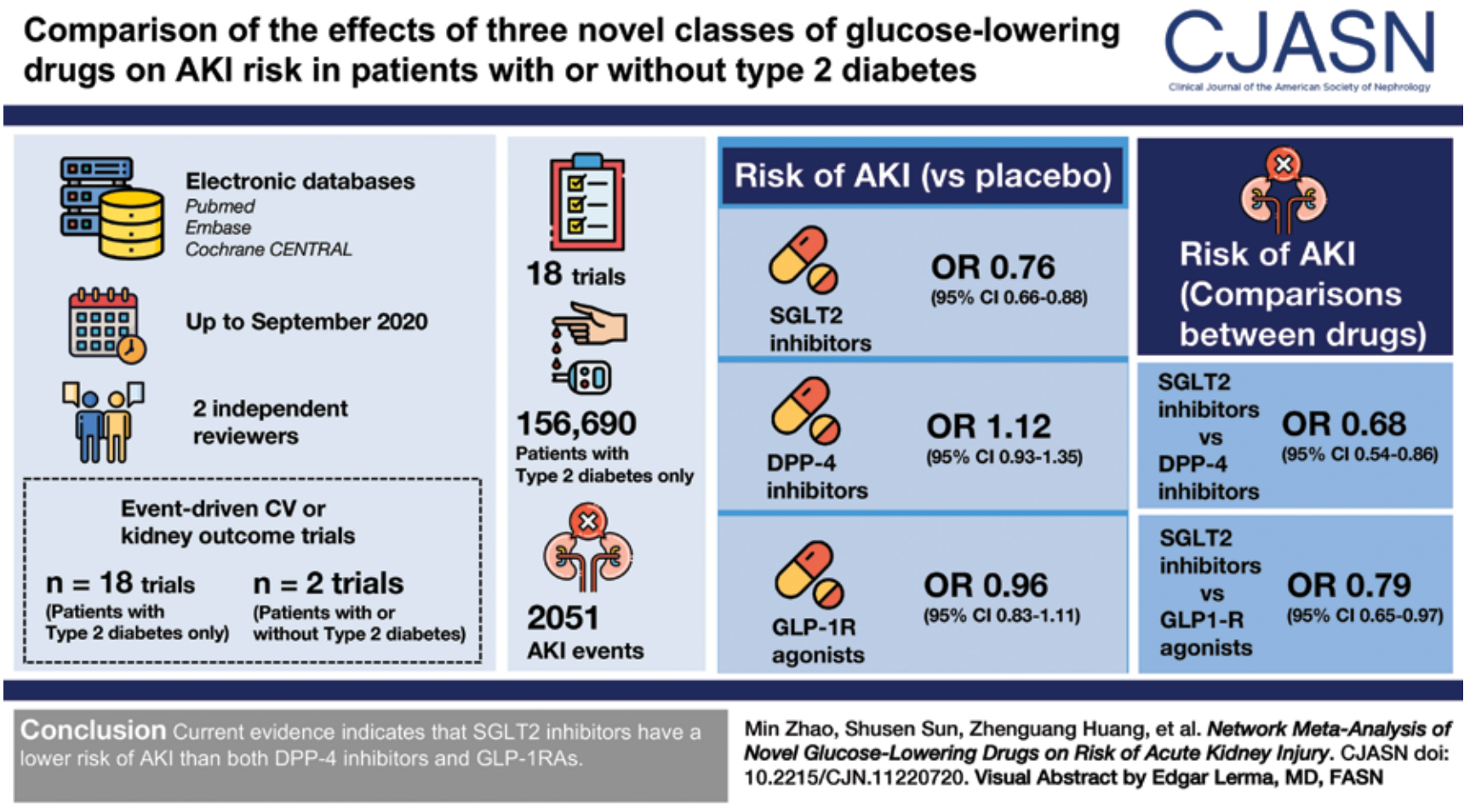
For details on the study, check out our findings in the January 2021 issue of *CJASN* (1). ■

Huilin Tang, MS, is affiliated with the Institute for Drug Evaluation, Peking University Health Science Center. Study co-authors Min Zhao, MS, and Zhenguang Huang, MS, are affiliated with the Department of Pharmacy, The First Affiliated Hospital of Guangxi Medical University; Shusen Sun, PharmD, with the College of Pharmacy and Health Sciences, Western New England University; and Tiansheng Wang, PharmD, with the Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill.

The author reports no conflict of interest.

Reference

1. Zhao M, et al. Network meta-analysis of novel glucose-lowering drugs on risk of acute kidney injury. *Clin J Am Soc Nephrol* 2021; 16:70–78. doi: https://doi.org/10.2215/CJN.11220720



Source: Zhao M, et al. Network meta-analysis of novel glucose-lowering drugs on risk of acute kidney injury. *Clin J Am Soc Nephrol* 2021; 16:70–78. 10.2215/CJN.11220720

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Controversy in Nephrology: Has Continuous Kidney Replacement Failed Its Promise?

By Richard A. Lafayette

More than 35 years ago, continuous arteriovenous hemofiltration (CAVH) was introduced by Kramer and colleagues (1) in order to optimize volume in hemodynamically compromised individuals with insufficient urine output. The successful treatment of congestive heart failure, despite cardiogenic shock, was heralded as a major advance, but soon limitations in solute clearance and complications of critical limb ischemia had clinicians looking for better solutions. This ushered in an era of multiple continuous dialytic techniques, including slow continuous ultrafiltration (SCUF), continuous venovenous hemofiltration (CVVH), continuous venovenous hemodiafiltration (CVVHDF), and sustained low-efficiency dialysis (SLED), which have become commonplace in intensive care units (ICUs). Benefits of these continuous renal replacement therapies (CRRTs) were quickly acknowledged. Clinicians could achieve excellent solute control throughout the day and remove substantial amounts of volume to keep up with or exceed input, and hemodynamic consequences appeared minimal. In fact, the blood pressure frequently stabilized.

Shortly thereafter, intensivists were galvanized by studies suggesting that critically ill patients could benefit from numerous "goal-directed" therapies targeting optimal organ perfusion by careful adjustment of numerous parameters, including mean arterial pressure, central venous pressure, mixed venous O_2 saturation, and serum lactate levels (2). Thus, the combination of rigorous control of volume and solutes in patients with acute kidney injury (AKI) or fluid overload was immediately appealing, and CRRTs seemed a perfect fit to the goal-directed approach. However, subsequent studies have demonstrated limited efficacy in aggressively pursuing targets, as compared to more general efforts assuring adequate volume support and early use of antibiotics (3). Still, the notion of early and aggressive replacement of kidney function in a highly efficient manner, one that takes advantage of the full day while limiting hemodynamic consequences, is quite attractive.

Nonetheless, several research findings from randomized controlled trials (RCTs) now seem generalizable to most patients in the ICU. First, "early" initiation of kidney replacement therapy does not improve care or outcomes in the ICU and may subject many patients, who will never require it, to dialysis. "Early" is before there are absolute indications (uremia or unmanageable hyperkalemia or fluid overload) or relentless advanced azotemia. This finding, on the basis of multiple RCTs (4, 5), likely sheds light on the fact that despite improved volume and solute control afforded by kidney replacement therapy, these potential gains are offset by potential risks of kidney replacement therapy. Secondly, for a "typical" hemodynamically compromised patient in the ICU, continuous therapies do not result in better outcomes of interest than does intermittent hemodialysis. That is to say that despite evidence for greater hemodynamic stability and greater ability to control volume status, key outcomes, such as mortality, ventilator days, ICU length of stay, and even kidney recovery rates, in no way are improved (6–9). This is regardless of using a hemofiltration or hemodialysis approach or higher or lower doses of kidney replacement therapy. Thus, it has been stated that for typical ICU patients with hemodynamic instability and pressor requirements, the most reasonable approach is to manage them with intermittent hemodialysis. The advantages are that the patients can be more flexible for other procedures and be off the dialysis machine for parts of the day. Additionally, the associated costs tend to be more acceptable for intermittent dialysis as compared to continuous kidney replacement.

Perhaps these findings should not be so surprising. One of the major findings regarding kidney replacement therapy over the past decade has been that dose and frequency, beyond a certain minimum, do not improve outcomes. That is to say that once those solutes are under control and not causing immediate harm, further therapy does not appear to be useful. Thus, the evaluation of the improved stability of 6 times per week dialysis versus 3 sessions, the improved time, and the improved volume control did not equate to improved survival or improved rates of kidney recovery. Similarly, for continuous therapies, increasing the clearance rates did not result in improved survival (10).

One of the major findings regarding kidney replacement therapy over the past decade has been that dose and frequency, beyond a certain minimum, do not improve outcomes.

Understanding exactly why this occurs is difficult, as trials have not been able to incorporate tests for associated components of the dialytic technique. Is it possible that rigorous control of blood pressure in the ICU is not meaningful and that patients with frequent exacerbations of hypotension may do as well as those with well-controlled stable blood pressure? Can it be that volume control that is episodic in nature and ultimately less efficient in getting to goal is none the worse for severely ill ICU patients? Perhaps these are true. However, it seems more likely that there is a tradeoff. That is to say that exposure to dialysis, whether intermittent or continuous is, by its very nature, hazardous. There are changes in many electrolytes and solutes and in volume status that may not be as controlled as we would hope. There is the extracorporeal circuit with risks for contamination, infection, and direct allergic and immunologic reactions to the artificial membranes. There are the hazards of being stuck on and requiring various forms of anticoagulation. Additionally, there could be harm from aggressive therapy that does not allow recognition of the earliest stages of kidney recovery, wherein dialysis could be discontinued and its potential for further harm averted.

Further research into dialytic techniques may revolutionize the practice of intensive care nephrology. However, for now, it would appear that optimal communication is necessary among all of those who take care of critically ill patients at risk for, or suffering from, AKI. The large number of completed trials together suggests that kidney replacement therapy should be utilized only when it is absolutely needed and no earlier and should be used as sparingly as tolerated to achieve manageable volume, solute, and electrolyte control. Early kidney replacement, continuous therapy, and ever-increasing desires to normalize every laboratory and physiological measure have not lived up to their promise to improve patient outcomes. More understanding is certainly needed and essential. ■

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1. Kramer P, et al. Intensive care potential of continuous arteriovenous hemofiltration. *Trans Am Soc Artif Intern Organs* 1982; 28:28–32. PMID: 7164248
2. Rivers E, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345:1368–1377. doi: 10.1056/NEJMoa010307
3. Rowan KM, et al. Early, goal-directed therapy for septic shock—a patient-level meta-analysis. *N Engl J Med* 2017; 376:2223–2234. doi: 10.1056/NEJMoa1701380
4. Gaudry S, et al. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: A systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet* 2020; 95:1506–1515. doi: 0.1016/S0140-6736(20)30531-6
5. Bagshaw SM, et al. Timing of initiation of renal-replacement therapy in acute kidney injury. *N Engl J Med* 2020; 383:240–251. doi: 10.1056/NEJMoa2000741
6. Lins RL, et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: Results of a randomized clinical trial. *Nephrol Dial Transplant* 2009; 24:512–518. doi: 10.1093/ndt/gfn560
7. Vinsonneau C, et al. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: A multicentre randomised trial. *Lancet* 2006; 368:379–385. doi: 10.1016/S0140-6736(06)69111-3
8. Mehta RL, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 2001; 60:1154–1163. doi: 10.1046/j.1523-1755.2001.0600031154.x
9. Schefold JC, et al. The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): A prospective randomized controlled trial. *Crit Care* 2014; 18:R11. doi: 10.1186/cc13188
10. Palevsky PM, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; 359:7–20. doi: 10.1056/NEJMoa0802639
11. McIntyre CW, Rosansky SJ. Starting dialysis is dangerous: How do we balance the risk? *Kidney Int* 2012; 82:382–387. doi: 10.1038/ki.2012.133

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

Peritoneal Dialysis Myth Busters

By Ankur Shah and Natasha Dave

Peritoneal dialysis (PD) is associated with improved quality of life, is cost effective, and has outcomes comparable with those of hemodialysis (HD). Despite this, there is a big discrepancy in the percentage of US patients using PD: 10.1% versus HD at 89.9% (1). One reason for this difference is likely the number of myths surrounding appropriate PD candidates. These myths are often based on tradition or authority as opposed to evidence. Ready acceptance of such beliefs without re-examining them can lead to improper care. A myth we noted in a previous article in this series is the negligible mortality difference between HD and PD. This month, our post will focus on candidacy for PD and the circumstances in which it is believed to be inferior or inadvisable (2).

Myth 1: PD is not a good option for patients with diabetes

Concerns over hyperglycemia and peritoneal dextrose absorption are not unfounded; however, studies comparing the outcomes in diabetic patients using both dialysis modalities have not consistently shown a superior modality. In 2015, the European Renal Best Practice Diabetes Guideline Development Group published a systematic review of 25 observational studies of patient survival by modality. The authors found that patient outcomes were inconsistent; no mortality differences were detected in an intention-to-treat analysis across subpopulations and follow-up periods. There was a significant heterogeneity in study design and in outcomes among studies, leaving the authors to find that no conclusion could be made regarding mortality (3). In the absence of a clear superior dialysis type, modality selection should be based on patient preference. Care should be taken to avoid hypertonic dextrose solutions, given their higher glucose content; however, this is not a contraindication to the modality. A multidisciplinary approach to the management of diabetes and hyperglycemia is recommended.

Myth 2: PD is not a good option in obese patients

A second misconception is that body habitus may preclude the use of traditional exit sites. Presternal exit sites are good options for obese patients who are motivated to use PD. Although the implantation technique is more difficult, the disadvantages in comparison with a traditional catheter are minimal (4).

Another common misconception is that adequate dialysis is difficult to achieve in obese patients. First and foremost, it should be noted that the conventional methods of evaluating adequacy are not reliable in obese patients. Adequacy, or Kt/V (whereby K is the clearance of urea, t is time with dialysis, and V is volume of distribution of urea), is unlikely to be accurate in obese patients because the V calculation does not account for the lack of significant urea content of fat, owing to the low water content. Inasmuch as the volume of distribution of urea is total body water, and the Watson equation estimates total body water from height, weight, sex, and age, miscalculations of total body water based on assumptions about body habitus from total body weight can cause miscalculations of Kt/V. Despite that, in cases where Kt/V is used to calculate adequacy in obese patients, clearance can be obtained (2). Furthermore, a retrospective cohort study found that overweight and obese patients using PD survived longer than did those with lower body mass index, even after adjustment for transplantation and modality failure (5). Regardless, dialysis should be individually based; it should be provided for symptomatic relief and should not be based on arbitrary numbers. This sentiment is also shared by the latest recommendations from the International Society for Peritoneal Dialysis, in which its guideline released in February 2020 endorses a more personalized approach to PD patients as opposed to a one-size-fits-all approach.

Myth 3: PD is not a good option for patients with autosomal-dominant polycystic kidney disease (ADPKD)

Many practitioners avoid PD in patients with ADPKD over a concern about increased intra-abdominal pressure. A systematic review and meta-analysis of 12 studies in 17,040 patients found no significant differences in adequacy, technique failure, or PD-related complications between those with ADPKD and those without (6). Although the risk of hernia or leak is higher in patients with ADPKD, studies have not shown a resulting increased risk of transfer to HD (7, 8). Notably, in patients undergoing hernia repair, PD does not need to be withheld; low-volume supine dialysis can be performed as the wound heals.

Myth 4: PD is not a good option for elderly patients

Elderly patients have several perceived barriers that preclude PD as a viable dialysis option. Some of them include visual impairment, restricted dexterity, and mild cognitive impairment. However, if PD is the patient's modality of choice, it is important to recognize that these issues can be overcome with extended training or assisted PD (9). Currently, there is no general recommendation about an ideal dialysis modality for this population. Observational trials have produced mixed outcomes, and randomized controlled trials are not feasible (9). With unclear evidence, patients should be counseled about the full spectrum of dialysis modalities, and shared decision-making should guide the choice. In two closely matched cohorts of PD and HD patients over the age of 65, quality of life was similar if not better in those using PD, suggesting its suitability for this population (10).

Myth 5: PD is not a good option for patients who have experienced kidney graft failure

Individuals requiring dialysis after graft loss are believed by some to be poor candidates for PD. This outlook may be due to prior surgery, immunosuppression, and less predictable residual kidney function. Four analyses of this population have been made, and all have shown no difference in mortality between HD and PD (11–13). More contemporary cohorts have shown better survival than earlier cohorts regardless of modality. Despite these findings, PD was initiated in only 18% of patients with allograft loss in the largest cohort, suggesting significant potential improvement.

Myth 6: PD is not a good option because infections (peritonitis) are more likely to develop

Frequently, concerns over peritonitis lead to avoidance of PD. Interestingly, patients receiving HD are at an increased risk for bloodstream infection. Furthermore, the mortality of bacteremia and sepsis in the end stage kidney disease (ESKD) population far outweighs that in patients with peritonitis (14, 15).

Myth 7: Certain patients and comorbid conditions are associated with PD failure and discontinuation

Switching from PD to HD can be disruptive and is associated with a decreased quality of life and higher cost. However, the avoidance of PD because of concerns about failure or discontinuation, based on a particular demographic or comorbid condition, is unfounded. Shen et al. (16) evaluated the factors leading to technique failure and modality discontinuation in 1587 patients from 1996 to 1997 using the United States Renal Data System database. In their study, technique failure was defined as switching from PD to HD for ≥30 days. That study found no association of diabetes, obesity, or education level with technique failure. Furthermore, the following risk factors were identified: male gender, Black race, systolic blood pressure of 140 to 160 mm Hg, retirement, or disablement. The authors concluded that sociodemographic factors outweighed clinical factors, noting that increased social and financial support would help avoid technique failure. Paradoxically, a more recent review found that time to technique failure showed no differences related to gender, race, or body mass index. From 2009 to 2014, Workeneh et al. (17) followed up 128 incident PD patients and found that the principal reasons for PD withdrawal included peritonitis (30%); catheter dysfunction (18%); ultrafiltration failure (16%); patient choice or lack of support (16%); and hernia, leak, or other surgical complications (6%).

In conclusion, there are many myths concerning candidacy for PD. As nephrologists, we must be comprehensive and impartial when discussing dialysis modalities. Furthermore, in the absence of contraindications, we must focus on inclusivity and work to better accommodate our patients who choose PD as their preferred modality. ■

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References

1. Saran R, et al. US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* 2020; 75 (1 Suppl 1):A6–A7. doi: 10.1053/j.ajkd.2019.09.003
2. Lee MB, Bargman JM. Myths in peritoneal dialysis. *Curr Opin Nephrol Hypertens* 2016; 25:602–608. doi: 10.1097/MNH.0000000000000274
3. Couchoud C, et al. Dialysis modality choice in diabetic patients with end-stage kidney disease: A systematic review of the available evidence. *Nephrol Dial Transplant* 2015; 30:310–320. doi: 10.1093/ndt/gfu293
4. Twardowski ZJ, et al. Four-year experience with swan neck presternal peritoneal dialysis catheter. *Am J Kidney Dis* 1996; 27:99–105. doi: 10.1016/s0272-6386(96)90036-0
5. Snyder JJ, et al. Body size and outcomes on peritoneal dialysis in the United States. *Kidney Int* 2003; 64:1838–1844. doi: 10.1046/j.1523-1755.2003.00287.x
6. Zhang T, et al. Is peritoneal dialysis a suitable renal replacement therapy option for polycystic kidney disease patients? *Kidney Blood Press Res* 2018; 43:1539–1553. doi: 10.1159/000494020
7. Dupont V, et al. Outcome of polycystic kidney disease patients on peritoneal dialysis: Systematic review of literature and meta-analysis. *PLoS One* 2018; 13:e0196769. doi: 10.1371/journal.pone.0196769
8. Jankowska M, et al. Peritoneal dialysis as a treatment option in autosomal dominant polycystic kidney disease. *Int Urol Nephrol* 2015; 47:1739–1744. doi: 10.1007/s11255-015-1087-9
9. Segall L, et al. Dialysis modality choice in elderly pa-

tients with end-stage renal disease: A narrative review of the available evidence. *Nephrol Dial Transplant* 2017; 32:41–49. doi: 10.1093/ndt/gfv411
10. Brown EA, et al. Broadening options for long-term dialysis in the elderly (BOLDE): Differences in quality of life on peritoneal dialysis compared to haemodialysis for older patients. *Nephrol Dial Transplant* 2010; 25:3755–3763. doi: 10.1093/ndt/gfq212
11. Perl J, et al. Impact of dialysis modality on survival after kidney transplant failure. *Clin J Am Soc Nephrol* 2011; 6:582–590. doi: 10.2215/CJN.06640810
12. Davies SJ. Peritoneal dialysis in the patient with a failing renal allograft. *Perit Dial Int* 2001; 21 (Suppl 3):S280–S284. PMID: 11887836
13. de Jonge H, et al. Comparison of peritoneal dialysis and haemodialysis after renal transplant failure. *Nephrol Dial Transplant* 2006; 21:1669–1674. doi: 10.1093/ndt/gfl010
14. Pérez Fontan M, et al. Peritonitis-related mortality in patients undergoing chronic peritoneal dialysis. *Perit Dial Int* 2005; 25:274–284. PMID: 15981776
15. Abou Dagher G, et al. Sepsis in hemodialysis patients. *BMC Emerg Med* 2015; 15:30. doi: 10.1186/s12873-015-0057-y
16. Shen JI, et al. Determinants of peritoneal dialysis technique failure in incident US patients. *Perit Dial Int* 2013; 33:155–166. doi: 10.3747/pdi.2011.00233
17. Workeneh B, et al. Causes for withdrawal in an urban peritoneal dialysis program. *Int J Nephrol* 2015; 2015:652953. doi: 10.1155/2015/652953

Policy Update

2020's Kidney Policy Advances Create Momentum for More

The year 2020 was an incredibly difficult one for the world, the nation, and the kidney community. In facing significant and new challenges, the American Society of Nephrology (ASN) shifted policy priorities to reflect the changing environment while still advocating for kidney patients and the kidney care professionals treating them and conducting research on their behalf. Pivoting traditional in-person congressional office visits with the ASN Policy and Advocacy Committee and the ASN Quality Committee to virtual ones, ASN delivered key policy messages to influence both coronavirus infectious disease 2019 (COVID-19) stimulus packages and the annual appropriations process.

After months of negotiations among the House, Senate, and administration leadership, the fiscal year 2021 (FY21) appropriations bill and COVID-19 relief legislation were signed into law on December 27, 2020, avoiding a government shutdown.

The package included a number of ASN policy priorities, including the following:

- Lifetime immunosuppressive drug coverage: the entire immuno bill is estimated to save $400 million over 10 years. This is a long overdue and hard-won victory for the entire community on behalf of kidney patients.
- The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) received an increase of $37 million for FY21, a 1.7% increase that came as part of a total $1.25 billion increase for the National Institutes of Health (NIH) overall for FY21.
- KidneyX received $5 million for FY21, similar to the amount received in FY20, and funding to help launch additional prize competitions to catalyze innovation in kidney care, including the Artificial Kidney Prize.
- NIH also received an additional $1.25 billion for COVID-related funds to support "research and clinical trials related to long-term COVID-19" in addition to the funds for FY21.
- The National Institute on Minority Health and Health Disparities (NIMHD) received direction in report language from Congress in the bill that it has provided "sufficient funding for NIMHD to establish a comprehensive center initiative aimed at a wide variety of chronic diseases," specifically naming kidney diseases as a priority area and instructing NIMHD to work with NIDDK, among other NIH institutes and centers.
- The Centers for Disease Control and Prevention received $2.5 million for kidney disease in the Chronic Disease Prevention and Health Promotion program.
- The Federal Communications Commission (FCC) received an additional $250 million for COVID-related telehealth, along with an additional $7 billion for the FCC for broadband infrastructure.

ASN is appreciative of all the member volunteers and partner patient and health professional organizations that helped these policy successes come to fruition. ASN is now prepared to build off of the momentum closing out 2020 and continue to secure additional policy victories this year. The March 2021 issue of *ASN Kidney News* will include a detailed overview of ASN's priorities for the new administration and new Congress.

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