New Dietary Approaches

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environment," Tyson said. They should also provide instructions on measuring serving sizes, cooking tips, and resources about new foods and address kidney-related diet concerns.

Nimrit Goraya, MD, a nephrologist at Baylor Scott & White Health in Temple, TX, also highlighted some barriers to healthy food access in racial and ethnic minority communities. Food insecurity, which has been linked (5) to a higher risk of CKD and progression to end-stage kidney disease, disproportionately (6) affects Black and Hispanic or Latinx households. The pandemic has increased food insecurity in the United States, particularly among these groups, she said.

Living in "food deserts" without easy access to supermarkets can also be a barrier to healthy eating. Goraya explained that individuals who live in areas with limited access to food resources may purchase energy-dense foods from gas stations or bodegas. This leads to individuals having a higher dietary acid load, which may contribute to higher acid excretion and CKD progression.

Making healthy foods easily available through vouchers or food banks can facilitate healthier eating, Goraya said. Family-based interventions that work to build trust in communities and engaging trusted community leaders can also help. For example, church-based programs have demonstrated success. Counseling on how to prepare healthy foods can also help, she said.

It is important to avoid stereotypes about what racial and ethnic minorities eat and to focus on individualized interventions. "Dietary patterns are diverse within cultures, and the breadth of that diversity should be recognized," Tyson said. Because of this, it is important to address a patient's individual needs and preferences, she said.

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High-Impact Trials Offer Potential Solutions to Clinical Conundrums

By Bridget M. Kuehn

A reduced dose of the inexpensive oral methylprednisolone reduced the risk of kidney failure by 41% over 4 years in patients with immunoglobulin A (IgA) nephropathy in the Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) study presented during Kidney Week 2021. The drug, however, was associated with an increased risk of severe infection, particularly in the first months of treatment. The TESTING trial results were among several results that promise to help solve "clinical conundrums" in the field of nephrology, presented during the High-Impact Clinical Trials session at Kidney Week 2021.

"These are exciting times in the field of nephrology," said Wendy St. Peter, PharmD, professor with the College of Pharmacy at the University of Minnesota in Minneapolis, who co-moderated the High-Impact Clinical Trials session at the meeting.

Steroid balancing act

IgA nephropathy is a common cause of kidney disease in younger adults and is a consequence of autoimmune attacks on the kidneys (1). Most studies' use of corticosteroids in these patients have not been adequately powered to assess kidney outcomes, said Vlado Perkovic, MBB, PhD, the TESTING trial's co-senior author and dean of medicine, University of New South Wales in Australia. To help fill this gap, the trial initially planned to randomize 503 patients with IgA to a full dose of methylprednisolone starting at 0.6–0.8 mg/kg/day to a maximum dose of 48 mg/day for 2 months, followed by gradual weaning from the drug over 4 to 7 months or placebo.

However, the identification (2) of an increased incidence of serious infections, including four that were fatal, in patients taking methylprednisolone led to the change in the trial protocol in which 241 patients were randomized to a reduced dose of methylprednisolone of 0.4 mg/kg/day to a maximum of 32 mg/day, followed by weaning. When the results from both steroid groups were analyzed after an average of 4 years of follow-up, there was a 47% reduction in a composite endpoint of 40% decline in estimated glomerular filtration rate (eGFR) or kidney failure compared with the placebo group and a 41% reduction in kidney failure, according to the data presented by Perkovic. A subgroup analysis of the lower dose group compared with placebo found a 73% reduction in the composite endpoint over an average of 2.5 years' follow-up. Perkovic noted that one patient in the lower dose group also died of a serious infection.

In the full dose group, for every 100 patients treated, methylprednisolone would precipitate about 12 fewer primary outcome kidney events but about 12 serious adverse events, Perkovic said. In the reduced dose group, for every 100 treated, there would be almost 17 fewer primary outcome kidney events with 2.4 serious events, he said. Perkovic said the results support existing guidelines that recommend nephrologists discuss the benefits and risks of corticosteroids with patients with IgA nephropathy who are at a high risk of kidney events.

"We provide additional data that will help inform those conversations by providing more precision about the risks and benefits of different approaches," Perkovic said. "[The results] suggest this should be offered to high-risk people."

The evidence shows that a lower dose of methylprednisolone is effective at reducing kidney-related events and resulted in fewer serious adverse events than higher doses, St. Peter said. "This is good news for patients with IgA nephropathy and their nephrologists who want them to get the benefits from an effective treatment but with less risk of a severe infection or other serious side effects that are common with higher steroid doses," she added.

New options for old challenges

Other high-impact studies presented during the session offered promising new options to solve longstanding challenges in nephrology, including a treatment for RNA inhibitor-reduced oxalate levels in patients with primary hyperoxaluria type 1 (PH1); a potential oral alternative to injectable therapies for anemia in patients with chronic kidney disease (CKD); and an inexpensive, older drug that may help control hypertension in patients with stage 4 CKD.

An injectable RNA inhibitor called lumasiran reduced urinary oxalate levels by one-third in patients with PH1 who were not on dialysis and by 42% among those on dialysis, according to results from the Evaluate Lumasiran in Patients with Advanced Primary Hyperoxaluria Type 1 (ILLUMINATE-C) study presented at Kidney Week by its lead author Mini Michael, MD, MMed, associate professor at Baylor College of Medicine in Houston, TX. PH1 is a rare condition associated with oxalate overproduction, kidney disease, and multi-organ damage. The trial enrolled 21 patients and followed them for 6 months.

"[Oxalate] changes of this magnitude may change long-term patient outcomes," Michael said. She and her colleagues are continuing to follow patients to assess longer term outcomes.

"It is exciting to see a new therapy which has the potential to change the dynamic of a rare and serious disease [like PH1] that mainly affects the kidneys but can result in multi-organ damage," St. Peter said. She noted the condition often results in the need for dialysis, kidney transplant, or liver and kidney transplant. She said one remaining question is whether lumasiran will reduce kidney disease progression, the need for dialysis, or the need for kidney and liver transplantation.

Oral daprodustat may be an alternative to injectable erythropoiesis-stimulating agents (ESAs) for treating anemia in patients with CKD, according to a presentation by Ajay Singh, MBBS, MBA, a nephrologist at Brigham and Women's Hospital and Harvard University in Boston, MA. The results of the Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat (ASCEND) trials in patients on dialysis (3) and not on dialysis (4) were published in *The New England Journal of Medicine* simultaneously. The trials enrolled 6800 patients and showed that daprodustat was non-inferior to ESAs for treating anemia patients with CKD who were receiving dialysis and those who did not require dialysis. It was also non-inferior to ESAs when the researchers looked at major adverse cardiovascular adverse events.

In a press briefing about the results, Singh noted that many patients currently don't have access to ESA treatment. Additionally, patients may be more likely to comply with and tolerate an oral medication, he said.

"The nephrology community has been hoping that the new hypoxia-inducible factor prolyl hydroxylase inhibitor would represent a new era in the treatment of anemia in CKD, with better efficacy and/or safety than ESAs," St. Peter said. "It's a little disappointing that daprodustat was only shown to be non-inferior and not superior in efficacy or safety endpoints as ESAs. Regardless, it would be nice to have an oral option for anemia management, particularly in non-dialysis-dependent patients with CKD."

The Chlorthalidone in Chronic Kidney Disease (CLICK) study (5) randomized 160 patients with stage 4 CKD and hypertension to chlorthalidone or placebo and found the low-cost medication reduced systolic blood pressure by 11 mm Hg within 4 weeks, according to a presentation by Rajiv Agarwal, MD, of the Indiana University School of Medicine in Indianapolis. It also lowered albuminuria by one-half over 12 weeks.

"The results of the CLICK study dispelled the myth that thiazide diuretics are not effective for blood pressure man-

agement when eGFR is less than 30 mL/min/1.73 m^2," St. Peter said. "This study sets the stage for chlorthalidone to become a main component of blood pressure management in patients with stage 4 CKD."

St. Peter cautioned, however, that clinicians need to do more frequent monitoring in patients already receiving a loop diuretic because the combination increased the risk of hypokalemia and increased serum creatinine due to a combination diuretic effect.

Other studies presented during the High-Impact Clinical Trials session included the following:

- The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trial, presented by Faiez Zannad, showed that empagliflozin reduced cardiovascular death and heart failure hospitalization and slowed kidney decline in patients with heart failure with preserved ejection fraction with and without CKD (6).
  The ADVOCATE (A Phase 3 Clinical Trial of CCX168 [Avacopan] in Patients with ANCA [Anti-Neutrophil Cytoplasmic Autoantibody]-Associated Vasculitis) trial showed that patients with ANCA-associated vasculitis taking avacopan had better recovery of kidney function than patients taking prednisone, as explained by David Jayne (7). The US Food and Drug Administration approved use of avacopan for ANCA-associated vasculitis (8).
- Five-year follow-up results from the Ellipsys Vascular Access System pivotal trial of an ultrasound-guided, percutaneous outpatient technique for creating an arteriovenous fistula show that patients' use of the fistula remained above 90% at 5 years, and only one-half to one-quarter of patients needed a second procedure, said Jeffrey Hull, MD, director of the Richmond Vascular Center in Virginia, during a press briefing about the results.
- Another study presented by Aditi Sinha, MD, MBBS, PhD, professor of pediatrics at the All India Institute of Medical Sciences in New Delhi, showed no benefit to extending prednisone treatment for longer than 12 weeks for very young children with nephrotic syndrome. The open-label, multi-center study that randomized 172 children younger than 4 years with nephrotic syndrome to 12 or 24 weeks of prednisone found the proportions of patients who achieved sustained remission, relapse rates, or time-to-first relapse were not significantly different between the groups. Adverse effects were similar in the two groups, she said.

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Nephrology Teams Can Help Address Patients' Psychosocial Needs

By Karen Blum

Patients with chronic kidney disease have a high symptom burden that can impact their outlook on life and self-confidence to manage disease. With the recognition of these features, nephrology teams can offer targeted solutions to help patients improve their quality of life, according to a presentation at Kidney Week 2021.

More than 60% of patients receiving dialysis reported feeling depressed, worried, or frustrated in a recent survey (1), said Daniel Cukor, PhD, director of behavioral health at the Rogosin Institute in New York. "There's a really high emotional toll being a patient with end stage renal disease [ESRD]," he said.

About 6% of patients in the general population experience depression, according to another study looking at the prevalence of depression in patients with different medical conditions (2). However, depression among people with ESRD is estimated to range from 22% to 37%, akin to prevalence in patients with ovarian or brain cancers or those who experienced heart attack, hypertension, or type 2 diabetes.

There are four models of thinking that explain why the emotional toll is so high for patients with kidney disease, Cukor said.

1) Coping model. This involves a patient's interpretation of whether he or she has the power, ability, or resources to respond to, adjust to, or fight a particular event or challenge. This evaluation determines a person's ability to cope. The greater the threat or challenges, the larger the coping response an individual must mount in response.

The demands for ESRD are multifaceted. Kidney failure taxes the body and spirit. Treatments, although life saving, also pose a high burden on patients. Additionally, some patients may have lifestyle changes imposed on them, such as needing to stop work or travel. This may impact future plans, such as how they were going to spend their retirement years.

To help, Cukor said, clinical teams can provide support to decrease the amount of demand on patients while increasing the available psychological resources. They can conduct patient-centered team meetings to really hear about what's bothering patients and their families; connect them to any needed resources and to patient ambassador programs; and offer support groups or family counseling sessions.

2) Cognitive behavioral model. In this model, patients believe that bad things, such as needing dialysis, are internal (meaning because of them), widespread, and unlikely to change in the future. These are hallmarks of depressive thinking.

If patients think managing their condition is too hard, it can launch a negative, vicious cycle where they begin to isolate from friends and family, to skip clinical visits, or to not maintain open communication with the care team. Turning that around to a more positive outlook, patients will engage more and feel more mastery over their condition.

Clinical teams can support patients here by offering cognitive behavioral therapy, which includes a process called cognitive restructuring—a careful evaluation of people's thoughts and whether they contribute to a positive or negative cycle and helping people reframe and think more positively about their situation. Psychologists or counselors with the program also could help people accept that their life may be different now and offer existential coaching, helping patients work to derive meaning and enjoyment from activities they still are able to do.

3) Learned helplessness. If a patient's life revolves around dialysis—waking up in the morning and prepping for treatment, going to dialysis, and then recovering from treatment multiple times a week—it can be very challenging and demanding. As a result, other rewarding life activities, including socializing, tend to fade out because all of the person's energy is consumed by the dialysis cycle and thinking it's never going to get better. Patients tend to give up on everything else and have a negative outlook.

In this case, clinical teams can offer better patient engagement, finding strategies to partner with patients to keep their motivation high and keep them active in care. Motivational interviewing can help people understand for themselves what their drivers are. They also could consider pharmacological or non-pharmacological treatments for depression. Teams can help patients start rescheduling some of the activities they've given up that they enjoyed, such as calling or visiting a friend or going out to dinner. "If [people] look at [their] week, and it's not only medical related, [they] tend to feel a lot better and a lot more engaged in their care," Cukor said.

4) Symptom burden. A high symptom burden has been reported in patients from a 2005 survey of 162 dialysis patients from three centers (3). In that study, over 50% of patients reported mood or sexual issues, sleep difficulties, pain, and skin and gastrointestinal issues.

Poor sleep, in particular, can lead to a cycle of fatigue, napping, decreased satisfaction with sleep, and anticipatory anxiety related to sleep, Cukor said. Symptom burden also can lead to a cycle of depression where patients aren't sleeping well, aren't active, feel tired, and don't have energy for preferred activities. Pain, too, can start a cycle of not sleeping well or feeling anxious or depressed.

Symptoms should be thought of as interconnected gears, with one factor having the power to impact others. Clinical teams should focus on the interference caused by symptoms, to help patients return to more positive health cycles. Helping someone with pain, for example, may allow that person to get better sleep, which can in turn lead to improved mood.

"Targeting symptoms as clinical entities that are worth treating is really important," Cukor said. "They're not just merely comorbidities but are real difficulties that people are going through. Even if you can't solve all of them, if you can alleviate some of them, that would be quite a significant contribution to the patient's quality of life."

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