# Late-breaking Trials Address Itch Relief in Dialysis, Cost-Saving Immunosuppression, and Disappointing Results for Supplements in Diabetes

## Itch Relief in Dialysis

Difelikefalin may offer dialysis patients some relief from the persistent itching associated with chronic dialysis, according to results from the KALM-1 trial presented during Kidney Week 2019.

The results were presented at the High Impact Clinical Trials session. Other trials presented during the session showed that azathioprine (AZA) may provide equivalent immunosuppression at a fraction of the price of mycophenolate mofetil (MMF), while vitamin D and omega-3 fatty acids failed to offer kidney protection for patients with diabetes.

Itching has proven to be a difficult-to-treat side effect of dialysis despite its substantial impact on patients' quality of life and mortality, said Steven Fishbane, MD, chief of nephrology at Northwell Health in Manhasset, New York. In fact, he noted he's seen negative trial result after negative trial result throughout his career. Currently, antihistamines are commonly used along with moisturizers or ultraviolet light therapy, Fishbane said. He said light therapy can work well but it adds to a patient's treatment burden.

"When you have [itching] chronically, it is a very tough sentence that affects quality of life," Fishbane said. "[It affects] sleep quality and is actually associated with infections, decreased erythropoietin response, and even mortality."

But Fishbane was buoyed by the promising results he presented from the KALM-1 trial. The phase 3 trial randomized 377 patients to receive intravenous difelikefalin or placebo after dialysis 3 times per week for 12 weeks. The trial met both its primary and secondary endpoints, with 51% of patients in the difelikefalin arm achieving a 3-point or greater reduction in itching intensity based on the Worst Itching Intensity Numerical Rating Scale (WI-NRSA) compared with 28% of the placebo group at 12 weeks, and 39% of the treatment group achieving a 4-point or greater reduction in WI-NRSA compared to 18% of the placebo group. He noted that patients were about 3 times more likely to experience a clinically meaningful reduction in itching in the difelikefalin group. Serious adverse events were similar between the 2 groups, but patients on difelikefalin were more likely to have diarrhea (9.5% vs. 3.7%), dizziness (6.9% vs. 1.1%), or vomiting (5.3% vs. 3.2%), but these symptoms resolved after a short time.

"We've got the first drug available to be able to treat uremic pruritis," Fishbane said. "The drug was effective. The drug was well tolerated in this really difficult population of patients with hemodialysis."

"This is a wonderful development," said Pascale Lane, MD, a pediatric nephrologist at the University of Oklahoma Medicine in Oklahoma City. She noted that in addition to demonstrating improved quality of life, the drug is convenient. "It can be given at the end of treatment when we've already got vascular access ready and it hangs around until they get dialyzed again," she said. ■

"Efficacy and Safety of Difelikefalin in Patients Undergoing Hemodialysis with Pruritus: Results from a Phase 3 Randomized, Controlled Study (KALM-1)" Oral Abstract 134

## Cost-Effective Immunosuppression

Azathioprine (AZA) could provide comparable protection against transplant rejection to mycophenolate mofetil (MMF) for kidney transplant patients taking a lower dose of a new more powerful formulation of cyclosporine while substantially reducing costs, according to another trial presented during the High Impact Clinical Trials session.

Paolo Cravedi, MD, PhD, assistant professor of nephrology at the Icahn School of Medicine at Mount Sinai Hospital in New York City, explained that in the mid-1990s two trials suggested that MMF provided a significant reduction in acute rejection compared to AZA when used with older formulations of cyclosporine. As a result, MMF, which costs 10 times more per dose, virtually replaced AZA.

"This choice had a major economic impact because switching patients from AZA to MMF over this time period cost over $1 billion," Cravedi said.

But results from the ATHENA randomized trial presented by Cravedi add to a growing body of evidence that suggests that AZA offers comparable rejection protection to MMF in kidney transplant recipients on low-dose, newer formulations of cyclosporine.

In the trial, 233 patients were randomized to receive MMF or AZA with a low-dose more stable microemulsion formulation of cyclosporin. At 3 years, 31.9% of the MMF patients had developed chronic allograft nephropathy vs. 32.4% of the AZA group and 18.5% vs. 21.1% had biopsy-proven acute cellular rejection. At 1-year posttransplant, 9.2% of the MMF group vs. 7% of the AZA group had subclinical acute cellular rejection and 5% vs. 6.1% had graft failure. The two groups had similar 3-year eGFR, and 16.1% of the MMF group vs. 18.4% of the AZA group successfully tapered their cyclosporine with only one episode of acute cellular rejection in each group.

"When we compared MMF versus AZA with the background of the new cyclosporine formulation, we couldn't find any benefit of MMF," Cravedi said. "They are virtually identical in terms of patient survival and graft survival." Cravedi said switching to AZA could save about $3500 per year per patient in costs.

Lane, who moderated a press briefing on the high impact trials, said the results of ATHENA were "very promising, especially from a cost saving perspective." However, she cautioned that most kidney transplant patients in the United States are not taking cyclosporine. Instead, tacrolimus is the calcineurin inhibitor of choice at most US transplant centers. Lane said these results would likely also hold true for patients taking tacrolimus, but it would be necessary to do a clinical trial to confirm this. As US policies aim to shift away from dialysis and to more kidney transplants, such potential savings may be even more important.

"Transplants are already more cost efficient [than dialysis]," Lane said. "Saving roughly 90% of the costs of one of the immunosuppressive agents could only make it even more cost-effective." ■

"Mycophenolate Mofetil vs. Azathioprine in Kidney Transplant Recipients on Steroid-Free, Low-Dose Cyclosporine Immunosuppression: The ATHENA Trial" Oral Abstract 135

## Vitamin D Disappoints in Diabetes

Results from a sub-analysis of the VITamin D and OmegA-3 TriaL (VITAL) did not find any benefit from either supplement in preventing or slowing kidney disease in patients with type 2 diabetes. Negative results from the primary analysis of the VITAL trial were published earlier this year showing no benefit of the supplements in cancer or cardiovascular diseases prevention.

The diabetic kidney disease portion of the trial randomized 1312 adults with type 2 diabetes to vitamin D or omega-3 supplementation or placebos and followed them for incidence or progression of kidney disease for 5 years. The purpose was to ask "whether we can use widely available and inexpensive and relatively safe supplements to prevent chronic kidney disease or progression early in the course of type 2 diabetes," said Ian DeBoer, MD, MS, professor in the Division of Nephrology and associate director of the Kidney Research Institute at the University of Washington in Seattle.

The trial did not find a significant difference in change in eGFR in either of the supplement groups, dashing hopes that such an inexpensive intervention might help prevent or stall kidney disease. The University of Oklahoma's Lane was not surprised by the findings. She noted that results from preclinical studies that had suggested potential benefits to such supplements have not been confirmed so far in clinical trials.

"We're beginning to see big scale trials of these [supplements] and almost all of them are coming up negative," she said. ■

"Effects of Vitamin D and Omega-3 Fatty Acid Supplementation on Kidney Function and Damage in Type 2 Diabetes" Oral Abstract 138

Other trials presented during the session included:

- The PARAGON-HF trial also showed that sacubitril/valsartan reduced the risk of renal events and slowed the progression of kidney disease in patients with heart failure and preserved ejection fraction. (Oral Abstract 132)
- Phase 2 results from the NOBILITY trial showed that obinutuzumab was superior to placebo at treating lupus nephritis. (Oral Abstract 136)
- The Preventing Early Renal Loss in Diabetes (PERL) Study did not find a significant benefit of allopurinol on patients with type 1 diabetes kidney outcomes. (Oral Abstract 137)