Tacrolimus exposure was also associated with higher hemoglobin A_{1c}: 37.4 mmol/mol versus 33.6 mmol/mol. Cardiovascular events and cardiovascular risk factors were not significantly different between groups.

Tacrolimus, in combination with mycophenolate and corticosteroids, is an effective treatment option for patients with active lupus nephritis. CNIs have known renal and cardiovascular adverse effects in kidney transplant recipients. However, in the absence of long-term follow-up data, there are persistent concerns about the safety of tacrolimus in lupus nephritis.

The new study shows "clinically meaningful" long-term declines in kidney function associated with tacrolimus treatment in patients with lupus nephritis. The effect on an eGFR decline is greater with longer duration of treatment but appears independent of indications of tacrolimus therapy. The researchers conclude: "[O]ur study supports the need for increased vigilance [toward] tacrolimus treatment, especially in [patients with lupus nephritis] with an increased risk of developing ESKD [end stage kidney disease]" [van Schaik M, et al. Long-term renal and cardiovascular risks of tacrolimus in patients with lupus nephritis. *Nephrol Dial Transpl*, published online May 20, 2024. doi: 10.1093/ndt/gfae113].

Anti-CD38 Shows Safety in Antibody-Mediated Rejection

The investigational CD38 monoclonal antibody felzartamab has a low rate of serious adverse events in the treatment of antibody-mediated kidney transplant rejection, according to a clinical trial report in *The New England Journal of Medicine*.

The phase 2 randomized, double-blind trial included 22 kidney transplant recipients with antibody-mediated rejection occurring after at least 180 days. Median time from transplant to study enrollment was 9 years. In equal numbers, patients were assigned to felzartamab (nine infusions at a dose of 16 mg/kg of body weight) or to placebo. Treatment continued for 6 months, followed by a 6-month observation period.

Safety and side-effect profiles were evaluated as the primary outcome. A range of secondary efficacy outcomes were evaluated as well, including resolution of antibody-mediated rejection.

Eight patients in the felzartamab group

Continued on page 26 >

Anti-CD38 Shows Safety in Antibody-Mediated Rejection

Continued from page 25

experienced mild to moderate infusion reactions. Serious adverse events, primarily infection-related, occurred in one patient with felzartamab versus four patients with placebo. Graft loss occurred in one patient in the placebo group; there were no deaths in either group.

Renal biopsy performed at 24 weeks showed resolution of morphologic antibody-mediated rejection in 82% of patients (9 of 11) assigned to felzartamab versus 20% (2 of 10) in the placebo group. Other efficacy outcomes also favored felzartamab: microvascular inflammation, median score of 0 versus 25; a molecular score indicating probability of antibody-mediated rejection, 0.17 versus 0.77; and donor-derived cell-free DNA level, 0.31% versus 0.82%.

At 52 weeks, antibody-mediated rejection occurred in three of the nine patients who responded to felzartamab. Recurrence was associated with rising rejection-related molecular scores and natural killer cell burden.

CD38 is a promising target for depletion of plasma cells producing donor-specific antibodies and natural killer cells, which are believed to contribute to microvascular inflammation. A different anti-CD38 therapy has been approved for depletion of malignant plasma cells in multiple myeloma.

The new phase 2 trial shows "an acceptable safety profile" and "potential therapeutic benefit" of felzartamab for late active or chronic active antibody-mediated rejection after kidney transplantation. "[F]elzartamab may have the potential to effectively and safely reverse ongoing antibody-mediated rejection," the investigators conclude. The study "underscores the potential of felzartamab as a therapeutic option warranting further investigation in the context of late or even early rejection after organ transplantation" [Mayer KA, et al. A randomized phase 2 trial of felzartamab in antibody-mediated rejection. *N Engl J Med,* published online May 25, 2024. doi: 10.1056/NEJMoa2400763].

No Decrease in CKD Admissions With "ICD-Pieces"

A primary care intervention to promote guideline-based care for patients with the "kidney dysfunction triad" does not lead to reduced rates of hospitalization due to chronic kidney disease (CKD), reports a pragmatic trial in *The New England Journal of Medicine*.

The cluster-randomized Improving Chronic Disease Management with Pieces (ICD-Pieces) trial evaluated a multidisciplinary intervention to promote guideline-directed therapy for patients with CKD. The intervention included a personalized algorithm, based on electronic health record data, to identify patients with the triad of CKD, type 2 diabetes, and hypertension, as well as practice facilitators who assisted primary care practitioners in implementing evidence-based interventions.

A total of 11,182 patients at 141 clinics in four large health systems were assigned to intervention or usual-care groups. All-cause hospitalization at 1 year was compared between groups, along with secondary outcomes. Patient characteristics were similar between intervention and usual-care groups.

Rates of hospitalization for any cause were not significantly different between groups: 20.7% for patients assigned to the ICD-Pieces intervention and 21.1% in the usual-care group. Secondary outcomes were similar as well, including emergency department visits, hospital readmissions, cardiovascular events, dialysis, and death from any cause.

The ICD-Pieces intervention was associated with a higher rate of acute kidney injury: 12.7% versus 11.3%. Other adverse events were comparable between groups.

Patients with the kidney dysfunction triad are at high risk for cardiovascular events and kidney failure. Although several guideline-directed therapies targeting these patients have been developed, few studies have evaluated the effects on morbidity and mortality.

The new pragmatic trial shows no significant effect of ICD-Pieces implementation on CKD hospitalization rates. "[T]he use of an EHR [electronic health record]-based algorithm and practice facilitators embedded in primary care clinics did not translate into reduced hospitalization at 1 year," the researchers write. They discuss implications for future clinical trials of multicomponent interventions for patients with multiple chronic diseases [Vazquez MA, et al.; ICD-Pieces Study Group. Pragmatic trial of hospitalization rate in chronic kidney disease. *N Engl J Med* 2024; 390:1196–1206. doi: 10.1056/NEJMoa2311708].