Renal and Cardiovascular Benefits of Semaglutide in Type 2 Diabetes With CKD

The glucagon-like peptide-1 receptor ago
nist semaglutide improves renal outcomes and reduces cardiovascular mortality in pa

A Research Study to See How Semaglu
tide Works Compared to Placebo in People With Type 2 Diabetes and Chronic Kidney Disease (FLOW), an international, multi-
center trial, enrolled 3533 patients (mean age, 67 years) with type 2 diabetes and CKD. Eligible patients had an estimated glomerular filtration rate (eGFR) of 50 to 75 mL/min/1.73 m², with a urinary albumin to creatinine ratio of >300 and <5000.

Participants were randomly assigned to receive subcutaneous semaglutide (1.0 mg weekly) or placebo. Primary outcomes were major kidney disease events, a composite of kidney failure, 50% or greater reduction in eGFR, or death from renal or cardiovascular causes.

The trial was halted at a median follow-
up of 3.4 years based on the results of a prespecified interim analysis of efficacy. At that time, the primary outcome event rate was 5.8 per 100 patient-years with semaglutide versus 7.5 per 100 patient-years with placebo (hazard ratio [HR], 0.76). Similar patterns were shown for a composite of kidney-specific components of the primary outcome (HR, 0.79) and for death from cardiovascular causes (HR, 0.71).

Semaglutide also improved secondary outcomes, including a 1.16 mL/min/1.73 m² decrease in the mean annual eGFR slope. Major cardiovascular events (HR, 0.82) and all-cause mortality (HR, 0.80) also decreased. Numbers needed to treat were 45 to prevent one major cardiovascular event and 39 to prevent one death.

Patients in the semaglutide group had greater reductions in body weight (mean difference, 4.10 kg), glycated hemoglobin, and systolic blood pressure. Semaglutide was also associated with a lower rate of serious adverse events, mainly reflecting severe events related to infections or cardiovascular disorders.

Previous studies of glucagon-like peptide-1 receptor agonists in type 2 diabetes have not addressed clinically important kidney
disease. The FLOW trial “provides confidence that the use of semaglutide in patients with type 2 diabetes and chronic kidney disease will reduce the risk of kidney failure and slow the decline in the eGFR, as well as reduce the risk of cardiovascular events and death,” the researchers write. They discuss the mechanisms of semagl
tide’s kidney-protective effects, which are likely multifactorial [Petkovc V, et al.; FLOW Trial Committees and Investigators].


Findings

Among patients with lupus nephritis, exposure to the calcineurin inhibitor (CNI) tacrolimus is associated with greater long-term reduction in kidney function, reports a study in Nephrology Dialysis Transplantation.

The retrospective cohort study included 219 patients with lupus nephritis treated at the authors’ center between 2010 and 2022. Of these, 63 patients were exposed to tacrolimus, and 176 had never been treated with any CNI. Renal outcomes, diabetes status, cardiovascular events, and risk fac
tors were compared between groups at a median follow-up of 7.1 years.

The median follow-up was 89.6 months in the tacrolimus group and 88.9 months in those with no CNI exposure. The me
dian duration of tacrolimus exposure was 17.7 months. Disease flares were the most common indication for tacrolimus therapy, followed by pregnancy and side effects of previous immunosuppression.

Patients receiving tacrolimus had a greater decline in the estimated glomerular filtration rate (eGFR): median, ~6.8 mL/ min/1.73 m² compared with ~0.8 mL/ min/1.73 m² in the nonexposed group. The median annual eGFR slope was 1.1 for the tacrolimus group versus 0.1 mL/min/1.73 m² for the group without CNI. The rate of eGFR decline was related to the duration of tacrolimus treatment. Three patients in the tacrolimus group progressed to kidney fail
ture, all during active tacrolimus treatment.

After adjustment for potential con
founders, tacrolimus exposure was associ
ated with a -14.7 mL/min/1.73 m² decline in eGFR. On the sensitivity analysis, the tacrolimus-associated change in eGFR was greater in patients without a major disease flare: ~20.0 mL/min/1.73 m².

Tocrolimus Linked to Long-Term eGFR Decline in Lupus Nephritis

Tacrolimus is linked to long-term decline in eGFR in patients with lupus nephritis, according to a study published in the New England Journal of Medicine. The finding highlights the need for alternative treatments and emphasizes the importance of monitoring kidney function in patients receiving tacrolimus.

The study analyzed data from 219 patients with lupus nephritis treated at a single center between 2010 and 2022. Patients were divided into two groups: those who received tacrolimus (n = 63) and those who did not (n = 176). The median duration of tacrolimus exposure was 17.7 months, and the median follow-up was 89.6 months for the tacrolimus group and 88.9 months for the control group.

The results showed a significant difference in the rate of eGFR decline between the two groups. The median annual eGFR slope was 1.1 mL/min/1.73 m² for the tacrolimus group and 0.1 mL/min/1.73 m² for the control group. This difference was statistically significant (P < 0.0001).

The study also found that the rate of eGFR decline was faster in patients who received tacrolimus, with a mean decrease of 6.8 mL/min/1.73 m² per year compared to 0.8 mL/min/1.73 m² in the control group. The median follow-up was 7.1 years.

The authors suggest that these findings highlight the need for alternative treatments for lupus nephritis and emphasize the importance of monitoring kidney function in patients receiving tacrolimus. Further studies are needed to explore the mechanisms behind the observed eGFR decline and to identify strategies to minimize its impact.

The New England Journal of Medicine

References:

1. Torres VE, Devuyst O, Chapman AB, et al; for the TEMPO 3:4
   Trial — A 36-month trial in patients with CKD Stages 1, 2, and 3
   2,4

2. The TEMPO 3:4 Trial was halted at a median follow-
   up of 3.4 years based on the results of a prespecified interim analysis of eff
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confidence that the use of semaglutide in patients with type 2 diabetes and chronic
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as well as reduce the risk of cardiovascular events and death,” the researchers write.

6. They discuss the mechanisms of semaglutide’s kidney-protective effects, which
are likely multifactorial [Petkovc V, et al.; FLOW Trial Committees and Investigators].


Findings


For your patients at risk for rapidly progressing ADPKD

JYNARQUE® (tolvaptan) could change the course of their disease

JYNARQUE is the first and only FDA-approved treatment indicated to slow kidney function decline in adults at risk of rapidly progress

ing ADPKD.

IMPORTANT SAFETY INFORMATION:

WARNING: RISK OF SERIOUS LIVER INJURY

• JYNARQUE® (tolvaptan) can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported.

• Measure transaminases (ALT, AST) and bilirubin before initiation, then monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity.

• Because of the risks of serious liver injury, JYNARQUE is available only through a Risk Evaluation and Mitigation Strategy Program called the JYNARQUE REMS Program.

CONTRAINDICATIONS:

• History, signs or symptoms of significant liver impairment or injury. This contraindication does not apply to uncomplicated polycystic liver disease.

• Taking strong CYP3A inhibitors

• With incorrect reconstitution and sodium concentrations

• Unable to sense or respond to thirst

• Hypovolemia

• Hypersensitivity (e.g., anaphylaxis, rash) to JYNARQUE or any component of the product

• Uncorrected urinary outflow obstruction

• Anuria

Serious Liver Injury: JYNARQUE can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported in the post-marketing JYNARQUE experience. Discontinuation in response to laboratory abnormalities, signs, or symptoms of liver injury (such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine or jaundice) can reduce the risk of severe hepatotoxicity. To reduce the risk of significant or irreversible liver injury, assess ALT, AST and bilirubin prior to initiating JYNARQUE, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter.

Hypertension: Dehydration and Hypovolemia: JYNARQUE therapy increases free water clearance which can lead to dehydration, hypovolemia and hypotension. Instruct patients to drink water when thirsty, and throughout the day and night if awake. Monitor for weight loss, tachycardia and hypotension because they may signal dehydration. Ensure abnormalities in sodium concentrations are corrected before initiating therapy. If serum sodium increases above normal or the patient becomes hypovolemic or dehydrated, fluid intake cannot be increased, suspend JYNARQUE until serum sodium, hydration status and volume status parameters are within the normal range.

Inhibitors of CYP3A: Concomitant use of JYNARQUE with drugs that are moderate or strong CYP3A inhibitors

ADPKD=autosomal dominant polycystic kidney disease.
Tacrolimus exposure was also associated with higher hemoglobin A1c: 37.4 mmol/mol versus 35.6 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.


**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

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