OBSERVATIONS

Coadministration of Liraglutide With Tacrolimus in Kidney Transplant Recipients: A Case Series

Glucocorticoids commonly used in the posttransplant period have been demonstrated to reduce insulin sensitivity, impair α-cell function, and more recently, impair β-cell function and the incretin effect (1). Liraglutide is an incretin mimetic approved for the treatment of type 2 diabetes. One major concern about the use of liraglutide after transplantation is that it delays gastric emptying, which could potentially affect absorption of coadministered oral medications, such as tacrolimus, which has a narrow therapeutic index (2). This case series is the first to report on the safety of this drug combination in kidney transplant recipients (KTRs).

Nonpregnant, adult ($\geq$18 years of age), and clinically stable (estimated glomerular filtration rate [eGFR] $\geq$60 mL/min/1.73 m^2 and not experiencing allograft rejection or two serum creatinine values >30% of each other obtained at least 1 week apart within 4 weeks prior to enrollment) KTRs receiving unchanged tacrolimus doses for $\geq$4 weeks (goal trough concentration 5–15 ng/mL) were included. Patients with a history of preexisting diabetes or receiving antihyperglycemic agents or varying doses of glucocorticoids were excluded. The study was approved by the Henry Ford Hospital and the Wayne State University Institutional Review Boards. All participants provided written informed consent.

Measurements were performed before and after self-administration of a 21-day course of liraglutide (0.6 mg for 1 week, 1.2 mg during week 2, and 1.8 mg during week 3). Tacrolimus area under the curve (AUC)$_{0-12h}$ was measured with a previously validated multiple regression–derived limited sampling strategy (3). Fasting and postprandial (60 and 120 min after completion of a standardized test meal) blood glucose levels were measured. Body weight and safety and tolerability were captured. Descriptive statistics were performed.

Five patients had been exposed to concomitant liraglutide and tacrolimus therapy at our institution (age 55.4 ± 8.2 years, 3 male, 4 African American, BMI 30.1 ± 6.2 kg/m^2, eGFR 93.0 ± 21.3 mL/min/1.73 m^2). Two had prediabetes, and four were on chronic glucocorticoid therapy.

Primary and secondary outcomes assessed are included in Table 1. Compared with baseline, tacrolimus AUC$_{0-12h}$ appeared reduced after coadministration

Table 1—*Primary and secondary outcomes during coadministration of liraglutide with tacrolimus in KTRs*

	KTR 1	KTR 2	KTR 3	KTR 4	KTR 5‡
Primary outcomes					
Tacrolimus AUC					
Day 1 AUC$_{0-12\,h}$ (ng/mL)	157.1	146.2	149.4	128.2	115.4
Day 22 AUC$_{0-12\,h}$ (ng/mL)	123.3	126.5	101.0	107.1	N/A
Difference (ng/mL)	33.8	19.7	48.4	21.1	N/A
Tacrolimus blood concentrations (ng/mL)					
Day 1					
0 h	9.8	9.1	7.3	6.7	9.8
1 h	17.3	11.6	15.2	21.7	9.6
2 h	18.1	17.0	22.6	15.6	10.8
4 h	14.6	14.3	14.0	11.4	10.6
Day 22					
0 h	8.4	9.1	9.0	7.4	N/A
1 h	10.1	9.7	8.5	9.0	N/A
2 h	10.0	10.5	9.6	10.6	N/A
4 h	12.8	12.9	9.1	10.7	N/A
Secondary outcomes					
Blood glucose concentrations (mmol/L)					
Day 1					
Fasting	5.1	3.0	6.1	5.9	5.1
1 h postprandial	6.7	8.7	8.2	5.7	7.3
2 h postprandial	6.4	8.3	6.4	7.2	6.9
Day 22					
Fasting	5.0	5.3	6.1	4.9	N/A
1 h postprandial	6.7	5.6	6.3	5.1	N/A
2 h postprandial	6.3	6.5	5.7	5.7	N/A
Body weight (kg)					
Day 1	80.8	104.8	104.0	64.3	89.3
Day 22	78.6	103.3	100.1	63.5	N/A
Difference	2.2	1.5	3.9	0.8	N/A
Kidney function assessment					
Serum creatinine (μmol/L)					
Baseline	70.7	79.6	97.2	106.1	70.7
Day 14	79.6	61.9	97.2	97.2	88.4
Day 28	88.4	61.9	106.1	97.2	N/A
Difference*	17.7	−17.7	8.9	−8.9	N/A
eGFR (mL/min/1.73 m^2)					
Baseline	100	80	70	72	116
Day 14	86	106	69	84	93
Day 28	76	106	63	78	N/A
Difference†	24	−26	7	−6	N/A

‡One patient did not complete the 21-day course of liraglutide owing to a hospitalization on day 19 of therapy. After medical evaluation, it was determined that the admission was unrelated to liraglutide therapy. Since this patient did not complete liraglutide therapy, data from days 22 and 28 were excluded. However, the patient's tacrolimus trough level upon hospital admission on day 19 was 4.6 ng/mL and there were no adjustments made to the tacrolimus dose. Additionally, the patient remained euglycemic during hospitalization. *Difference in serum creatinine from baseline to day 28. †Difference in eGFR from baseline to day 28.

with liraglutide; however, trough concentrations were unaltered. Tacrolimus and maintenance corticosteroid doses remained unchanged, and there was no biopsy-proven evidence of acute rejection in any KTR. No patients experienced stage 1 acute kidney injury as defined by the Acute Kidney Injury Network criteria (≥ 26.5 μmol/L or ≥ 1.5- to 2.0-fold increase in serum creatinine from baseline). No differences were noted in fasting blood glucose (5.0 ± 1.2 vs. 5.3 ± 0.5 mmol/L). Liraglutide appeared to reduce blood glucose levels at 60 (7.3 ± 1.2 vs. 5.9 ± 0.5 mmol/L) and 120 min (7.1 ± 0.8 vs. 6.0 ± 0.4 mmol/L). Liraglutide administration was also associated with a reduction in body weight after 21 days of therapy (−2.1 ± 1.3 kg). No hypoglycemia or serious adverse events related to liraglutide therapy were reported. Nausea, reduced appetite, headache, injection site pain, and weakness were each reported by two KTRs. Indigestion was experienced by one KTR.

Evidence for the use of liraglutide in patients with chronic kidney disease is limited (4,5). These preliminary data suggest coadministration of liraglutide with tacrolimus does not clinically alter trough tacrolimus concentrations in stable KTRs with mild renal impairment. Clinical trials examining the efficacy and safety of liraglutide use in KTRs should be the focus of future research.

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