ABSTRACT NUMBER: 2576

Glucagon-Like Peptide-1 Receptor Agonist Use and the Risk of Adverse Cardiac and Kidney Outcomes Among Patients with Systemic Lupus Erythematosus and Lupus Nephritis

April Jorge[1], Aakash Patel[1], Baijun Zhou[2], Yuqing Zhang[3] and Hyon K. Choi[4], [1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Massachusetts General Hospital, Boston, MA, [3]Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School; The Mongan Institute, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [4]Massachusetts General Hospital, Lexington, MA

Meeting: ACR Convergence 2024

Keywords: Cardiovascular, comparative effectiveness, Lupus nephritis, Renal, Systemic lupus erythematosus (SLE)

SESSION INFORMATION

Date: Monday, November 18, 2024

Session Type: Abstract Session

Title: Abstracts: SLE – Treatment II: Non-Cellular Lupus Therapeutics

Session Time: 1:00PM-2:30PM

Background/Purpose: Glucagon-like peptide-1 receptor agonists (GLP-1RA) are hypoglycemic agents with well-established cardioprotective properties and emerging data for kidney-protective benefits in patients with type 2 diabetes (T2D). We sought to determine whether GLP-1RA use will improve cardiovascular (CV) and kidney outcomes among patients with systemic lupus erythematosus (SLE) and lupus nephritis (LN).

Methods: We specified and emulated a pragmatic target trial to evaluate the impact of GLP-1RA vs. a comparator class of hypoglycemic agents, dipeptidyl peptidase 4 inhibitors (DPP4i), on CV and kidney outcomes among patients with SLE and T2D. We utilized a large, US multi-center electronic health record database, TriNetX, to identify patients with SLE (N= 96,511). We included all patients who met eligibility criteria of SLE, T2D, no prior end-stage kidney disease (ESKD), and no prior GLP-1RA or DPP4i use who initiated a GLP-1RA or DPP4i between 10/2006 and 8/2021. We used propensity score overlap weighting to emulate randomization between treatment groups. Covariates included demographics, LN, SLE severity index, medications for SLE and T2D, comorbidities, and healthcare utilization. CV outcomes included major adverse cardiovascular events, myocardial infarction, stroke, heart failure, and venous thrombosis (VTE). Kidney disease progression was defined as eGFR decline ≥ 30% or new-onset ESKD, and we assessed all-cause mortality. We also assessed the control outcome of genital infection, which was expected to be null. We used Cox regression to compare incidence rates for each outcome based on the weighted populations for a per-protocol analysis with censoring upon deviation from treatment strategy and a secondary intention-to-treat (ITT) analysis. We analyzed the subgroup with LN.

Results: There were 910 and 1004 initiators of GLP-1RA and DPP4i, respectively, with SLE and T2D; of

these, 267 and 324 patients had LN, respectively. Baseline covariates were balanced after propensity score overlap weighting **(Table 1)**. The mean age was 55 years, and 92% of patients were female; 48% were Non-Hispanic White, and 35% were Black. One-third had CKD ≥3. In the per-protocol analysis, the risks of MACE (HR 0.66 [95% CI 0.48-0.91]), VTE (HR 0.49 [0.24-0.97]), kidney disease progression (HR 0.77 [95% CI 0.60-0.98]), and all-cause death (HR 0.26 [95% CI 0.10-0.68]) were lower in the GLP-1RA users vs. DPP4i users **(Table 2)**. In the ITT analysis, the HRs were 0.80 (95% CI 0.62-1.03) for MACE, 0.79 (95% CI 0.65-0.96) for kidney disease progression, and 0.42 (95% CI 0.25-0.73) for all-cause death. Within the LN subgroup, GLP-1RA use was similarly associated with lower risks of MACE and kidney disease progression (**Table 3)**. There was no difference in the risk of the control outcome of genital infection (HR 1.02 [95% CI 0.69-1.50]).

Conclusion: In this study of patients with SLE and T2D, we found a lower risk of MACE, VTE, kidney disease progression, and all-cause mortality with use of GLP-1RA vs DPP4i. Our study is limited by a small sample size, and all SLE patients also had T2D as an indication for treatment. Overall, these findings support the potential benefits of GLP-1RA to reduce morbidity among patients with SLE and warrant further investigation.

	Before Propensity Score Overlap Weighting			After Propensity Score Overlap Weighting		
	DPP4i	GLP-1RA	Std. Diff.	DPP4i	GLP-1RA	Std. Diff.
N	1004	910				
Age, mean (SD)	58.2 (12.0)	53.0 (11.3)	0.4454	55.0	55.0	<0.001
Female, n (%)	918 (91.4)	841 (92.4)	0.0361	92.3	92.3	<0.001
Race and Ethnicity, n (%)			0.1173			<0.001
Asian	19 (1.9)	6 (0.7)		0.9	0.9	
Hispanic	104 (10.4)	71 (7.8)		9.0	9.0	
Black	335 (33.4)	332 (36.5)		34.7	34.7	
Other	67 (6.7)	63 (6.9)		7.2	7.2	
White, Non-Hispanic	479 (47.7)	438 (48.1)		48.2	48.2	
Geographic Region, n (%)			0.0839			<0.001
East	200 (19.9)	202 (22.2)		20.7	20.7	
Midwest	159 (15.8)	168 (18.5)		17.0	17.0	
South	546 (54.4)	461 (50.7)		53.5	53.5	
West	99 (9.9)	79 (8.7)		8.9	8.9	
Lupus nephritis, n (%)	324 (32.3)	267 (29.3)	0.0635	29.3	29.3	<0.001
SLE Severity Index, n (%)			0.0264			<0.001
Mild	343 (34.2)	317 (34.8)		35.8	35.8	
Moderate	415 (41.3)	375 (41.2)		40.4	40.4	
Severe	246 (24.5)	218 (24.0)		23.9	23.9	
Charlson Comorbidity Index, mean (SD)	1.8 (1.8)	1.5 (1.4)	0.1781	1.6	1.6	<0.001
Comorbidities, n (%)						
CKD stage ≥3	366 (36.5)	293 (32.2)	0.0897	32.7	32.7	<0.001
Heart Failure	181 (18.0)	118 (13.0)	0.1402	14.9	14.9	<0.001
Cardiovascular disease	238 (23.7)	212 (23.3)	0.0096	23.1	23.1	<0.001
Obesity	275 (27.4)	416 (45.7)	0.3876	35.4	35.4	<0.001
Tobacco use, n (%)	246 (24.5)	246 (27.0)	0.0579	24.8	24.8	<0.001
SLE Medication use, n (%)						
Glucocorticoids	498 (49.6)	468 (51.4)	0.0365	49.4	49.4	<0.001
Hydroxychloroquine	351 (35.0)	366 (40.2)	0.1088	38.3	38.3	<0.001
Azathioprine	60 (6.0)	65 (7.1)	0.0471	6.1	6.1	<0.001
Methotrexate	80 (8.0)	85 (9.3)	0.0488	8.6	8.6	<0.001
Mycophenolate	112 (11.2)	93 (10.2)	0.0303	10.6	10.6	<0.001
Belimumab	14 (1.4)	32 (3.5)	0.1374	2.1	2.1	<0.001
Other Medications, n (%)						<0.001
ACEi or ARB	407 (40.5)	366 (40.2)	0.0065	38.4	38.4	<0.001
Insulin use	324 (32.3)	356 (39.1)	0.1433	32.9	32.9	<0.001
Metformin use	368 (36.7)	356 (39.1)	0.0509	35.2	35.2	<0.001
Sulfonylurea use	170 (16.9)	109 (12.0)	0.1412	13.0	13.0	<0.001

eGFR, mean (SD)	74.7 (28.6)	81.5 (27.0)	0.2416	79.0	79.0	<0.001
Healthcare Utilization						
Outpatient visits, median (IQR)	7 (1-17)	9 (2-17)	0.1010	7 (2-17)	7 (2-17)	<0.001
ER/Inpatient visits, n (%)	415 (41.3)	332 (36.5)	0.0996	37.8	37.8	<0.001
Hemoglobin A1c (%)	7.7 (3.0)	7.8 (2.5)	0.0310	7.6	7.6	<0.001

CKD, chronic kidney disease; CVD, cardiovascular disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; ER, emergency room

Table 1. Baseline Characteristics of GLP_1 Receptor Agonist and DPP4 Inhibitor Initiators with Systemic Lupus Erythematosus and Diabetes

Outcomes	Events, n		Follow-up Time, years		Incidence Rate (per 1000 person years)		Hazard Ratio (95% CI)
	DPP4i	GLP-1RA	DPP4i	GLP-1RA	DPP4i	GLP-1RA	
Per-Protocol							
Cardiovascular outcomes							
MACE	42	32	1.2	1.3	92.9	61.1	0.66 (0.48-0.91)
Myocardial infarction	6	3	1.3	1.4	12.8	5.6	0.43 (0.16-1.14)
Stroke	6	8	1.3	1.4	12.5	13.9	1.08 (0.51-2.31)
Heart Failure	26	23	1.2	1.4	55.7	44.1	0.78 (0.53-1.15)
VTE	13	7	1.2	1.4	26.5	12.6	0.49 (0.24-0.97)
Kidney outcome							
eGFR decline by ≥30% or new ESKD	68	58	1.1	1.3	158.1	117.5	0.77 (0.60-0.98)
All-cause death	11	3	1.3	1.4	21.6	5.6	0.26 (0.10-0.68)
Control outcome							
Genital Infection	24	27	1.2	1.3	52.4	52.2	1.02 (0.69-1.50)

MACE, major adverse cardiac events; VTE, venous thromboembolism; eGFR, estimated glomerular filtration rate; ESKD, end-stage disease. MACE includes myocardial infarction, ischemic stroke, or heart failure hospitalization.

Table 2. Cardiovascular and Kidney Outcomes Associated with GLP_1 Receptor Agonist versus DPP4 Inhibitor Use in Systemic Lupus Erythematosus

Outcomes	Events, n		Follow-up Time, years		Incidence Rate (per 1000 person years)		Hazard Ratio (95% CI)
	DPP4i	GLP-1RA	DPP4i	GLP-1RA	DPP4i	GLP-1RA	
Per-Protocol							
Cardiovascular outcomes							
MACE	23	18	1.0	1.2	193.0	122.2	0.64 (0.41-0.98)
Myocardial infarction	5	2	1.2	1.4	32.7	11.0	0.34 (0.10-1.09)
Stroke	4	2	1.2	1.4	25.3	14.7	0.58 (0.18-1.85)
Heart Failure	16	15	1.1	1.2	124.9	98.5	0.78 (0.48-1.28)
VTE	5	4	1.2	1.3	38.3	24.9	0.62 (0.25-1.56)
Kidney outcome							
eGFR decline by ≥30% or new ESKD	35	28	0.9	1.1	325.2	213.3	0.70 (0.49-1.00)
All-cause death	5	3	1.2	1.4	36.5	16.2	0.46 (0.16-1.37)
Control outcome							
Genital Infection	8	9	1.1	1.3	62.9	56.6	0.90 (0.48-1.68)

MACE, major adverse cardiac events; VTE, venous thromboembolism; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease. MACE outcome includes combined myocardial infarction, ischemic stroke, or heart failure hospitalization. Heart failure outcome includes heart failure hospitalization.

Table 3. Cardiovascular and Kidney Outcomes Associated with GLP_1 Receptor Agonists versus DPP4 Inhibitor Use in Lupus Nephritis

Disclosures: A. Jorge: Bristol-Myers Squibb(BMS), 12, Site investigator for a clinicl trial, Cabaletta Bio, 12, Site Sub-investigator for a clinical trial; **A. Patel**: None; **B. Zhou**: None; **Y. Zhang**: None; **H. Choi**: Ani, 1, Horizon, 1, 5, LG, 1, Protalix, 1, Shanton, 12, DSMB.

To cite this abstract in AMA style:

Jorge A, Patel A, Zhou B, Zhang Y, Choi H. Glucagon-Like Peptide-1 Receptor Agonist Use and the Risk of Adverse Cardiac and Kidney Outcomes Among Patients with Systemic Lupus Erythematosus and Lupus Nephritis [abstract]. *Arthritis Rheumatol.* 2024; 76 (suppl 9). https://acrabstracts.org/abstract/glucagon-like-peptide-1-receptor-agonist-use-and-the-risk-of-adverse-cardiac-and-kidney-outcomes-among-patients-with-systemic-lupus-erythematosus-and-lupus-nephritis/. Accessed November 18, 2024.
