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GLP-1 Receptor Agonist Use for Diabetes Mellitus is Associated With Reduced Psoriasis Disease Severity

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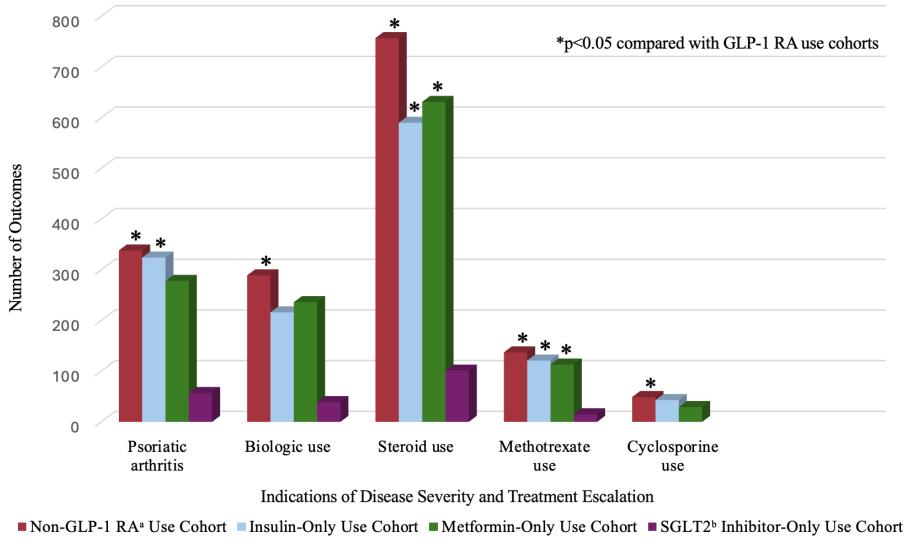
INTRODUCTION

Psoriasis is a chronic inflammatory skin disorder known to be linked to type 2 diabetes mellitus (T2DM), with 11.6% of psoriasis patients having comorbid T2DM.[1] Glucagon-like peptide-1 receptor agonists (GLP-1 RA) effectively treat T2DM, and recent studies demonstrate their potential role in modulating systemic inflammation for psoriasis treatment.[2] However, large-scale, real-world data comparing the effects of GLP-1 RAs with other antihyperglycemic medications on psoriasis disease severity and treatment escalation among patients with comorbid T2DM remains limited.

MATERIALS AND METHODS

Using the TriNetX Research Network, adults (≥18) with psoriasis and T2DM were identified using ICD-10-CM codes L40 and E11, respectively. A retrospective cohort analysis was initially conducted to ascertain whether any significant signal existed in psoriasis disease severity outcomes between patients treated with GLP-1 RAs and those treated with all non-GLP-1 RA antihyperglycemic therapies. This primary analysis was designed to reflect routine clinical practice, in which patients frequently receive multiple or sequential classes of diabetic medications. The composite 'all non-GLP-1 RA' group included insulin, metformin, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, sulfonylureas, meglitinides, thiazolidinediones, and alpha-glucosidase inhibitors. To further characterize and validate our findings from the primary analysis, additional subgroup comparisons were conducted across three distinct matched cohort analyses: (1) GLP-1 RAs versus insulin monotherapy, (2) GLP-1 RAs versus metformin monotherapy, and (3) GLP-1 RAs versus SGLT2 inhibitor monotherapy. For each experiment, individual 1:1 propensity score-matching was performed on age, sex, race, ethnicity, BMI, smoking, alcohol use, chronic kidney disease,

FIGURE 1. Comparative risk of psoriasis disease severity and treatment escalation among antihyperglycemic medications.



[a]GLP-1 RA: Glucagon-like peptide-1 receptor agonist
[b]SGLT2: Sodium-glucose cotransporter 2

TABLE 1.

Comparison of Psoriasis Disease Severity and Treatment Escalation Between Glucagon-Like Peptide-1 Receptor Agonists and Other Antihyperglycemic Medications

Outcome	Non-GLP-1 RA[a] / GLP-1 RA			Insulin Only / GLP-1 RA			Metformin Only / GLP-1 RA			SGLT2[b] Inhibitor Only / GLP-1 RA		
	Eligible Patients[c] (Outcomes)	RR[d] (95% CI)[e]	*P*-value	Eligible Patients (Outcomes)	RR (95% CI)	*P*-value	Eligible Patients (Outcomes)	RR (95% CI)	*P*-value	Eligible Patients (Outcomes)	RR (95% CI)	*P*-value
Psoriatic arthritis	2,911 (338) / 2,639 (259)	0.85 (0.73, 0.99)	0.031	2,772 (324) / 2,637 (259)	0.84 (0.72, 0.98)	0.027	2,899 (278) / 2,624 (259)	1.03 (0.88, 1.21)	0.72	703 (57) / 710 (61)	1.06 (0.75, 1.49)	0.74
Biologic use	3,137 (289) / 2,812 (211)	0.81 (0.69, 0.97)	0.018	3,137 (216) / 2,809 (211)	1.091 (0.91, 1.31)	0.35	3,063 (236) / 2,798 (211)	0.98 (0.82, 1.17)	0.82	793 (39) / 767 (45)	1.19 (0.79, 1.81)	0.41
Steroid use	1,182 (757) / 874 (383)	0.68 (0.63, 0.75)	<0.0001	1,032 (590) / 871 (382)	0.77 (0.70, 0.84)	<0.0001	1,167 (631) / 874 (383)	0.81 (0.74, 0.89)	<0.0001	264 (101) / 228 (91)	1.043 (0.84, 1.30)	0.71
Methotrexate use	3,226 (137) / 3,128 (73)	0.55 (0.42, 0.73)	<0.0001	3,213 (121) / 3,125 (73)	0.62 (0.47, 0.83)	0.001	3,174 (113) / 3,106 (72)	0.65 (0.49, 0.88)	0.0036	851 (15) / 836 (13)	0.88 (0.42, 1.84)	0.74
Cyclosporine use	3,428 (49) / 3,431 (30)	0.61 (0.38, 0.97)	0.031	3,431 (43) / 3,428 (30)	0.69 (0.44, 1.11)	0.13	3,424 (29) / 3,406 (29)	1.005 (0.60, 1.68)	0.98	≤10 / ≤10	N/A[f]	N/A

[a]GLP-1 RA: Glucagon-like peptide-1 receptor agonist
[b]SGLT2: Sodium-glucose cotransporter 2
[c]The counts in the number of "eligible patients" for each outcome differ slightly because each analysis was conducted independently. For each specific outcome (eg, psoriatic arthritis, biologic use, steroid use, methotrexate use, and cyclosporine use), only patients with that outcome documented prior to the study period were excluded. As a result, the denominators vary slightly across outcomes.
[d]RR: Risk ratio
[e]CI: Confidence interval
[f]N/A: Not applicable

atherosclerotic cardiovascular disease, and heart failure. Patients with type 1 diabetes mellitus, gestational diabetes, other autoimmune conditions, transplant history, malignancy, concurrent use of multiple antihyperglycemic medication classes in the monotherapy experiments (subgroup analyses 1 through 3), or documentation of the target outcome prior to the study period were excluded. Indications of disease severity and treatment escalation, including recorded diagnoses of psoriatic arthritis and patterns of psoriasis medication utilization, following GLP-1 RA initiation were evaluated using risk ratios (RR). Statistical significance was defined as $P<0.05$.

RESULTS

Compared with composite 'all non-GLP-1 RA' use, GLP-1 RA use was associated with significantly decreased risks of psoriatic arthritis (RR 0.85, $P=0.031$), biologic use (RR 0.81, $P=0.018$), steroid use (RR 0.68, $P<0.0001$), methotrexate use (RR 0.55, $P<0.0001$), and cyclosporine use (RR 0.61, $P=0.031$; Figure 1). Compared with insulin-only use, GLP-1 RA use was associated with significantly decreased risks of psoriatic arthritis (RR 0.84, $P=0.027$), steroid use (RR 0.77, $P<0.0001$), and methotrexate use (RR 0.62, $P=0.001$). Compared with metformin-only use, GLP-1 RA use was associated with significantly decreased risks of steroid use (RR 0.81, $P<0.0001$) and methotrexate use (RR 0.65, $P=0.0036$). Compared with SGLT2 inhibitor-only use, GLP-1 RA use was not associated with a significant difference in psoriasis treatment escalation ($P>0.05$; Table 1); however, within this comparison, reported outcomes for cyclosporine use were ≤10, and therefore suppressed by TriNetX's patient privacy policy, precluding risk quantification.

DISCUSSION

In our study, GLP-1 RA use was associated with a reduced risk of psoriasis treatment escalation compared with common antihyperglycemic medications. This association is biologically plausible, as GLP-1 RAs decrease IL-17, IL-23, and TNF-α in psoriatic skin, while increased GLP-1 receptors on immune cells are found within psoriasis plaques.[2,3] Prior studies also show that clinical improvements in psoriasis with GLP-1 RAs occur independently of metabolic change, further suggesting a direct immune-cutaneous effect that may be distinct from other insulin-targeting therapies.[3,4] Additionally, SGLT2 inhibitors have been associated with reduced cutaneous inflammation and attenuated psoriasis severity in experimental models.[5] Consistent with these shared anti-inflammatory effects, no significant difference was observed between GLP-1 RAs and SGLT2 inhibitors in our study, suggesting that the reduction in cutaneous inflammation associated with SGLT2 inhibitors may confer comparable effects on psoriasis. Overall, our study found that GLP-1 RA use was associated with a reduced risk of psoriasis treatment escalation when compared with other common antihyperglycemic medications.

Our study's limitations include its retrospective design, reliance on ICD-10-CM coding, and potential for residual confounding, with unmeasured factors including disease severity, medication adherence, and lifestyle variables that could not be accounted for. Prospective studies should compare the effectiveness of GLP-1 RAs with other antihyperglycemic medications to further inform integrated therapeutic approaches for patients with psoriasis and T2DM.

DISCLOSURES

SNT is an investigator/speaker for Bioventus, Kerecis, Boehringer Ingelheim, Regeneron, and Castle Biosciences. The other authors have no relevant conflict of interest to declare.

Ethics Approval/Statement:
Data accessible via TriNetX is presented in aggregate form and only contains anonymized data as per the deidentification

standard defined by the US Health Insurance Portability and Accountability Act (HIPAA) in section 164.514(a). Given that this study used only deidentified data and did not involve individually identifiable patient data, this study was exempt from Institutional Review Board Approval.

Data Sharing Statement:

The data that support the findings of this study were obtained from the TriNetX Research Network and are available to other researchers upon request and with appropriate access permissions. Deidentified aggregate-level data, a data dictionary describing the variables used, and the statistical code used for cohort creation and outcome assessment can be shared upon reasonable request to the corresponding author. Data access requires institutional credentials or collaboration with an institution that maintains a TriNetX license. Analyses may be replicated or extended within the TriNetX platform. There are no additional restrictions on the use of the shared materials beyond those imposed by the TriNetX user agreement.

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