Use of GLP-1 Receptor Agonists and Risk of Acute Liver Injury: A Cohort Analysis in the OMOP CDM (GLP1-DILI)

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Background

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly prescribed to manage type 2 diabetes mellitus (T2DM) and, more recently, obesity. Although randomized controlled trials and post-marketing surveillance did not initially signal hepatotoxicity, several case reports have emerged suggesting an association between GLP-1 RAs and acute liver injury (ALI). For instance, liraglutide has been implicated in rare but serious liver-related adverse events, raising concerns among clinicians and regulators. With the usage of these agents growing rapidly due to new obesity indications, real-world assessment of their hepatic safety is urgently needed.

Methods

We conducted a new-user, active comparator cohort study using standardized OHDSI tools and definitions across multiple OMOP CDM-converted databases. Adult patients with T2DM and prior metformin exposure were included if they had no history of Type 1 diabetes, secondary diabetes, or acute liver injury in the 365 days prior to index exposure. The target cohort consisted of new users of GLP-1 RAs, while the comparator group comprised new users of DPP-4 inhibitors. Both cohorts required $\geqslant$365 days of observation prior to index and <30 days of prior insulin use.

The primary outcome (acute liver injury) was defined using diagnostic codes from the OHDSI Phenotype Library. Cohorts were propensity score matched 1:1 using large-scale covariates, and hazard ratios were estimated via Cox proportional hazards models. Study diagnostics included covariate balance (max absolute standardized mean difference < 0.1), empirical equipoise (preference score overlap > 0.25), and residual bias analysis using 130 negative control outcomes. Meta-analysis across databases was conducted using Bayesian methods.

The study utilized the OHDSI HADES suite (e.g., CohortMethod, Characterization, EvidenceSynthesis), and the full study package is openly available at: https://github.com/ohdsi-studies/Glp1Dili/. Preliminary results are accessible via the OHDSI Shiny dashboard.

We additionally plan to implement new secondary analyses assessing the risk of cholelithiasis, cholecystitis, chronic liver injury, and ALI defined by lab criteria (e.g., ALT $\geqslant$ 120 U/L + total bilirubin $\geqslant$ 2.0 mg/dL) prior to the OHDSI Symposium. These analyses are not yet completed but are currently in progress.

Results

From the US and Japan, over 4.4 million GLP-1 RA users and 1.89 million DPP-4 users were identified, with 1.46 million patients included after matching. Diagnostics were met across key databases, with balanced

covariates and sufficient preference score overlap. Negative control outcome calibration showed minimal residual bias (EASE < 0.25), with 88.3% of negative control HRs including the null.

Across qualified databases, the pooled hazard ratio for ALI did not indicate a significant difference between GLP-1 RAs and DPP-4 inhiitors. Kaplan-Meier plots and forest plots showed no elevated cumulative incidence of ALI in GLP-1 RA users. These findings offer real-world reassurance regarding hepatic safety, despite growing anecdotal concerns.

Although not included in the current results, we anticipate that secondary outcome analyses (e.g., cholelithiasis, chronic liver injury) will provide further insight into broader hepatic risks and will be shared with the OHDSI community as soon as available.

Conclusion

This multinational OHDSI network study found no significant increase in the risk of acute liver injury among new users of GLP-1 receptor agonists compared to DPP-4 inhibitors in T2DM patients. These findings offer important reassurance as GLP-1 RAs gain widespread adoption for diabetes and obesity management. Pending secondary analyses will extend these findings to other liver-related outcomes. The OHDSI community is encouraged to collaborate in extending this work across additional networks and comparators, such as SGLT2 inhibitors.

References

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