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BRIEF REPORT

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Comparison of the glucagon-like-peptide-1 receptor agonists dulaglutide and liraglutide for the management of diabetes in solid organ transplant: A retrospective study

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are gaining popularity in the management of diabetes in solid organ transplant (SOT) recipients. There are no studies available comparing the two GLP-1RAs dulaglutide and liraglutide in SOT. We performed a retrospective chart review to assess the safety and effectiveness of these agents in adult SOT with diabetes at 6, 12 and 24 months. There were 63 and 25 recipients on dulaglutide and liraglutide, respectively. There was a sustained reduction in primary endpoints of weight, BMI and insulin requirement with dulaglutide when compared to liraglutide. Decrease in weight was 2%, 4% and 5.2% with dulaglutide and 0.09%, 0.87% and 0.89% with liraglutide at 6, 12 and 24 months respectively. BMI reduction followed the same trend in the two groups. The percentage reduction for insulin was 26% with dulaglutide and 3.6% with liraglutide. There was a 10% reduction in creatinine and a 15% increase in estimated glomerular filtration rate (eGFR) at the end of 24 months with dulaglutide. However, there was an increase in creatinine by 7% and an 8% decrease in eGFR at the end of 24 months with liraglutide.

KEYWORDS

dulaglutide, GLP-1 receptor agonist, post-transplant diabetes mellitus, solid organ transplantation

1 | INTRODUCTION

Poorly controlled diabetes mellitus in solid organ transplant (SOT) is often associated with a detrimental effect on long-term graft survival, increased cardiovascular morbidity, increased all-cause mortality, and substantial healthcare expenditure.[1,2] Human glucagon-like peptide-1 (GLP-1) is a member of the incretin family of glucoregulatory hormones that are rapidly secreted postprandially into the bloodstream from entero-endocrine L cells in the distal small intestine and the colon.[3,4] GLP-1 imparts its effect through glucose-dependent increased insulin secretion, decreased glucagon secretion (hepatic gluconeogenesis), delayed gastric emptying, increased satiety, and protection of β-cell mass.[3,4] The innate GLP-1 analogue has an extremely short half-life (1–2 min) that limits its therapeutic value.[3,4] Multiple GLP-1 analogues, formed by alteration of the molecular structure of the innate form of GLP-1, have been developed to recapitulate the physiological effects of GLP-1, but

with an extended duration of action.[3,4] Given their glucose-lowering ability, decreased risk of hypoglycemia and minimal drug interactions, they are widely used in the general population. A few retrospective studies, including one from our research group, have demonstrated the safety and effectiveness of GLP-1 analogues in SOT.[5] Some studies have compared the various GLP-1 analogues in a general population, but, to date, there have been no comparative studies in the SOT population.[6-14] In the present retrospective case series, we aimed to examine the efficacy and safety of the two widely used GLP-1 receptor agonists (GLP-1RAs) liraglutide and dulaglutide in SOT recipients. This study reports the first real-world experience of the two agents and will help inform clinicians' treatment decisions in the future.

2 | METHODS

We performed a retrospective chart review of SOT recipients with type 2 diabetes (diagnosed pre- or post-transplant) treated with dulaglutide or liraglutide between October 30, 2014 and January 1, 2018. The aim of the study was to analyse the efficacy and safety of dulaglutide versus liraglutide in the management of type 2 diabetes in SOT recipients. Inclusion criteria were age >18 years, history of SOT, and follow-up of >6 months for either treatment. Exclusion criteria were a history (personal or family) of medullary or thyroid C-cell carcinoma, pancreatitis, multiple endocrine neoplasia syndrome type 2, and severe gastrointestinal (GI) disease. We identified a total of 108 patients, of whom 88 fulfilled the inclusion criteria and comprised the final study group: 63 patients treated with dulaglutide and 25 treated with liraglutide. We collected data at baseline, 6, 12 and 24 months. In the dulaglutide group, patients were initially started on a dose of 0.75 mg once weekly, which was increased as clinically indicated to a maximum of 1.5 mg once weekly. Liraglutide was initiated at 0.6 mg once daily subcutaneously; based on the response, the dose was then increased to 1.2 mg once daily. If the optimal glycemic response was not achieved after an additional week of treatment, the dose was further increased to 1.8 mg once daily. The lower initial dose (0.6 mg daily) was intended to reduce GI symptoms. The primary endpoints were change in weight (kg), body mass index (BMI [kg/m^2]), insulin requirements (units), cardiovascular morbidity, graft survival, and all-cause mortality. Safety endpoints included: severe and non-severe hypoglycaemia, data on which were extracted from the chart review; GI side effects (self-reported nausea, vomiting, diarrhoea, abdominal pain, decreased appetite); pancreatitis; gallstones; and new diagnosis of malignancy. Secondary endpoints were: glycated haemoglobin (HbA1c [mmol/mol]); renal function (creatinine [mg/dL], and estimated glomerular filtration rate [eGFR], calculated according to the *Chronic Kidney Disease* [CKD] Epidemiology Collaboration formula [mL/min/1.73 m^2]); and liver function (units/L). We calculated the mean, median and percentage values for the available data and performed statistical analyses with a two-tailed paired *t*-test using GraphPad InStat 3 software.

All data were collected according to our institutional review board-approved protocol (#2018H0153). As our study was a retrospective chart review, involving the use of existing data and no or minimal risk to participants, it had an institutional review board and patient consent "exempt" status under human subject regulations.

3 | RESULTS

Baseline characteristics and primary/secondary endpoints are shown in Tables 1 and 2, respectively. Baseline characteristics were comparable in terms of age, gender, race, family history, CKD stage, and baseline cardiovascular characteristics. Percentage decreases in weight were 2%, 4% and 5.2% with dulaglutide, and 0.09%, 0.87% and 0.89% with liraglutide, at 6, 12 and 24 months, respectively. *P* values indicated statistical significance throughout the follow-up period of 24 months. BMI followed a similar trend, with percentage reductions of 2.4%, 6% and 8% with dulaglutide, and minimal decreases of 0.24%, 1.4% and 0.54% with liraglutide, at 6, 12 and 24 months, respectively (*P* values <0.05 throughout the study period). We converted all the insulin forms to equivalent doses of insulin glargine for statistical analysis. The percentage reduction in insulin requirement was 26% with dulaglutide versus 3.6% with liraglutide at the end of follow-up (*P* = 0.01). The baseline insulin requirement in the dulaglutide group was 23 units, compared with 50 units in the liraglutide group. Renal and hepatic function were closely monitored. Both eGFR and creatinine level improved over the 24-month follow-up period in patients in the dulaglutide group. There was a 10% reduction in creatinine level and a 15% increase in eGFR at the end of follow-up with dulaglutide (baseline creatinine level 1.73 mg/dL and eGFR 47 mL/min/1.73 m^2), whereas in the liraglutide group there was an increase in creatinine level of 7% at the end of 24 months. This trend was reflected in a decrease in eGFR of 8% with liraglutide at the end of the study period (baseline creatinine and eGFR 1.85 mg/dL and 42.48 mL/min/1.73 m^2, respectively). There was no increased incidence of transaminitis. The immunosuppressive regimen remained stable in patients, with no increased doses for patients on either of the GLP-1RAs. There was one graft failure, one angina episode, and two deaths in each of the dulaglutide and liraglutide groups throughout the follow-up.

We used HbA1c as a secondary rather than a primary endpoint as HbA1c is thought to be an unreliable measure of glucose control immediately post-transplant, due to anaemia and fluctuating renal function. The mean baseline HbA1c was 7.5% in both treatment groups. There was a trend towards a persistent decrease in HbA1c throughout the follow-up for dulaglutide (decreases in HbA1c of 10%, 5.3% and 8.4% at 6, 12 and 24 months, respectively), whereas in the liraglutide group, there was an initial decrease followed by an increase in HbA1c (percentage decreases of 5.3% and 3% at 6 and 12 months, followed by an increase of 2% in HbA1c at 24 months). For this reason, ~14% of patients in the dulaglutide and 8% in the liraglutide group were able to completely discontinue all antidiabetic medications and were maintained only on the GLP-1RA. Approximately 42%, 52% and 16% of patients in the dulaglutide and liraglutide groups required dose adjustments to 1.5 mg dulaglutide, 1.2 mg liraglutide and 1.8 mg liraglutide. Although the rate of cardiovascular morbidity was higher

TABLE 1 Baseline characteristics of the patients in the dulaglutide and liraglutide study groups

Characteristic	Dulaglutide (n = 63)	Liraglutide (n = 25)	*P*
Median (range) age, years	58 (30, 74)	57 (35, 76)	0.42
Men, %	68	72	0.73
Race/ethnicity, %			0.92
White	71	68	
Black	23	28	
Hispanic	5	4	
Other	1		
Type of organ transplant, %			0.95
Kidney	81	84	
Liver	16	4	
Liver-kidney	1.5	8	
Heart	1.5	4	
Immunosuppression based on drug class, %			0.9
CNI	81	64	
CCI	57	60	
mTOR inhibitors	54	64	
Maintenance steroid	21	8	
Belatacept	3	8	
Steroid used for rejection	22	4	
Patients with PTDM onset, %			0.9
<1 month after transplant	86	68	
>1 month after transplant	14	32	
CKD stage, %			0.9
1	1.5	0	
2	25.6	24	
3a	22.2	16	
3b	30.15	44	
4	20.6	16	
5 and ESRD	0	0	
History of cardiovascular disease[a] before GLP-1RA treatment, %	33	40	0.47
Baseline HbA1c, %	7.5	7.5	0.99
Baseline insulin, units	23	50	0.01
Baseline creatinine, mg/dL	1.6	1.8	0.69
Baseline eGFR, mL/min/1.73m^2	48	42.48	0.08
Baseline weight, kg	98.9	112.6	0.04
Baseline BMI, kg/m^2	32.8	36.8	0.04
Time since transplant, days	2140	2933	0.09
Antidiabetic therapy pre-GLP-1RA treatment			0.8
1 OAD	4	8	
2 OAD	16	9	
3 OADs	0	7	

(Continues)

in the liraglutide group than in the dulaglutide group, given the small sample sizes, firm conclusions about this cannot be drawn (rates of coronary artery disease, stroke, congestive heart failure and all-cause mortality were 1.5%, 0%, 0% and 3%, respectively, in the dulaglutide group, and 8%, 4%, 8% and 4%, respectively, in the liraglutide group). The beneficial effects of dulaglutide compared to liraglutide on

TABLE 1 (Continued)

Characteristic	Dulaglutide (n = 63)	Liraglutide (n = 25)	*P*
Insulin only	44	46	
Insulin + OAD	36	30	
No OAD	0	0	

BMI, body mass index; CCI, cell cycle inhibitors; CKD, chronic kidney disease; CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; mTOR, mammalian target of rapamycin; OAD, oral antidiabetic agent; PTDM, post-transplant diabetes mellitus.
[a]Angina, non-fatal myocardial infarction, stroke, congestive heart failure.

TABLE 2 Primary and secondary outcomes in the dulaglutide and liraglutide groups at the end of the follow-up period

	Dulaglutide	Liraglutide	*P*[a]
Decrease in weight at 6 months, %	2 (baseline median weight 98.7 kg)	0.09 (baseline median weight 98.3 kg)	0.003
Decrease in weight at 12 months, %	4	0.87	0.005
Decrease in weight at 24 months, %	5.2	0.89	0.05
Decrease in BMI at 6 months, %	2.4 (baseline median BMI 32.8 kg/m^2)	0.24 (baseline median BMI 32.3 kg/m^2)	0.01
Decrease in BMI at 12 months, %	6	1.4	0.009
Decrease in BMI at 24 months, %	8	0.54	0.04
Change in creatinine level at 24 months, %	−10 (baseline median creatinine 1.73)	+7 (baseline median creatinine 1.85)	0.02
Change in eGFR at 24 months, %	+15 (baseline median eGFR 47 mL/min/1.73 m^2)	−8 (baseline median eGFR 42.48 mL/min/1.73 m^2)	0.03
Graft survival, %			
6 months	100	100	
12 months	98.2	100	
24 months	98.2	96	
Decrease in insulin units pre- and post-treatment, %	26	3.6	0.01
Change in HbA1c at 6 months, %	−10 (median baseline HbA1c 7.5%)	−5.3 (median baseline HbA1c 7.5%)	0.81
Change in HbA1c at 12 months, %	−5.3	−3	0.97
Change in HbA1c at 24 months, %	−8.4	+2	0.49
OHA treatment before and after GLP-1RA treatment	Remained same (3 OHAs pre- and post-dulaglutide	Increased from 3 OHAs to 4 OHAs pre- and post-liraglutide	

BMI, body mass index; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; OHA, oral anti-hyperglycaemic agent.
[a]Mann–Whitney test.

weight, BMI, renal function, insulin use, HbA1c and graft survival were maintained in the subgroup analysis involving renal transplant recipients only (Supporting Information, Table S1).

3.1 | Safety and adverse events

The incidence of non-severe hypoglycaemia was higher in the liraglutide group compared to the dulaglutide group (24% vs. 6.3% Supporting Information, Table S2). There was no episode of severe hypoglycaemia requiring hospitalization in either group. Rates of GI side effects of nausea, vomiting, diarrhoea, abdominal pain and decreased appetite were higher in the liraglutide group (8%, 4%, 12%, 4% and 4%) than in the dulaglutide group (3%, 1.5%, 3%, 0% and 0%). For reasons that are not clear, 4% of patients in the liraglutide group had cholelithiasis compared to 0% in the dulaglutide group. There were no adverse events of pancreatitis, pancreatic cancers, thyroid cancers or injection site infection in either group (Supporting Information, Table S2). One patient developed post-transplant lymphoproliferative disorder in the dulaglutide group. This disorder is not uncommon in SOT recipients, and the incidence was thought to be unrelated to the study drug.

4 | DISCUSSION

The GLP-1RAs dulaglutide and liraglutide improve glycaemic control and reduce weight in people with type 2 diabetes.[13] To date, only

one phase III clinical trial (AWARD 6) has directly compared dulaglutide with liraglutide treatment in the general population.[13] Both these agents are used in SOT recipients, based on the extrapolation of data from the general population. The AWARD 6 trial was a head-to-head trial comparing the safety and efficacy of once-weekly dulaglutide with that of once-daily liraglutide in metformin-treated patients with uncontrolled type 2 diabetes.[13] The study found that once-weekly dulaglutide was non-inferior to once-daily liraglutide with regard to least-squares mean reduction in HbA1c, with similar safety and tolerability profiles over a follow-up of 26 weeks.[13] By contrast, the present study showed favourable efficacy and safety profiles for dulaglutide when compared to liraglutide. These results could be secondary to the structural differences between these two GLP-1RAs, resulting in unique clinical profiles, glycaemic control, effects on weight/BMI, and safety and tolerability. Dulaglutide and liraglutide are classified as long-acting GLP-1 analogues with 97% and 90% identity, respectively, to native GLP-1. Although both these agents are long-acting, dulaglutide has a longer duration of action and requires weekly dosing compared to daily dosing with liraglutide. This long duration of action of dulaglutide is attributable to the GLP-1 portion of the molecule being fused to an IgG4 molecule, limiting renal clearance and prolonging activity.[4] Dulaglutide also results in less formation of anti-drug antibodies compared to liraglutide.[4] Meanwhile, the greater half-life of the relatively long-acting dulaglutide allows enhanced effects on weight, BMI, HbA1c and insulin requirement compared with liraglutide, with these structural and functional differences leading to different durations of action and bioavailability. The differing GI tolerability profiles could be secondary to the differences between these two agents in: delayed gastric emptying time; effect on the pancreas; increase of insulin secretion; glucagon secretion inhibition via the paracrine release of somatostatin effect; and effect on satiety. It is known that shorter-acting GLP-1RAs exert their effect mainly via increased GI emptying time, whereas the longer-acting agents work more on the pancreas and the CNS satiety centres.[4] It is important to understand these specific characteristics so that the choice of GLP-1RA can be tailored to the individual patient appropriately. Head-to-head clinical trials are the best way to elucidate variations in efficacy and tolerability, and are warranted in SOT populations.

AWARD 6 had a shorter duration (26 weeks) than the present study and thus might not be able to capture the differences that we observed.[13] The present study also showed an initial decrease in HbA1c at 6 and 12 months but an increase in HbA1c in the long run (24 months). AWARD 6 did not monitor the changes in renal function.[13] Renal dysfunction is one of the frequent complications in SOT, probably resulting from haemodynamic fluctuations and use of chronic immunosuppressive agents. In the present cohort, 72% and 76% of patients had advanced CKD (stages 3 and 4) in the dulaglutide and liraglutide groups, respectively. In the dulaglutide group, renal function not only remained stable but also showed a trend towards improvement despite the advanced CKD; however, in the liraglutide group, there was a trend towards worsening renal function. The renal injury observed in the liraglutide group could be attributed to increased glucose drag and glomerular hyperfiltration in the setting of obesity with liraglutide treatment. Dulaglutide could therefore be a valuable asset in the management of type 2 diabetes in SOT patients with renal dysfunction and metabolic syndrome. One of the biggest reasons for high non-adherence to treatment in people with type 2 diabetes is the high pill burden and multiple daily injections of insulin.[2] In the present study, more patients were able to reduce their medication burden in the dulaglutide group compared to the liraglutide group. Dulaglutide has the advantage of convenient once-weekly dosing due to the long half-life of 5 days for both doses (0.75 mg and 1.5 mg), which patients favour and which may improve their adherence to treatment. The long-acting GLP-1RA doesn't impair the counterregulatory response of glucagon to hypoglycemia. This is the likely reason for no episodes of severe hypoglycaemia in either group.[2,4] However, with dulaglutide, there was a lesser incidence of non-severe hypoglycaemia, which could be secondary to its longer bioavailability. There were no increased incidences of serious events, including pancreatitis, transaminitis or malignancy, in our study. This could be secondary to the careful exclusion of patients with personal or family history before the initiation of the drug. The overall graft survival and all causes mortality were similar in both the groups and were thought to be unrelated to the GLP-1RA use. The cardiovascular morbidity was comparable in the two groups. Similar to previous studies, no significant interactions and dose adjustments were required in immunosuppressive agents with either of the agents.

Limitations of the present study include the small number of patients, and the retrospective, observational design. In addition, the cohort comprised mainly white men and renal transplant recipients, which may affect the generalizability of the findings.

In conclusion, there was a sustained reduction in weight, BMI, insulin requirement and HbA1c with dulaglutide when compared to liraglutide. Both agents had a favourable side effect profile, with no interference with immunosuppressants. The beneficial effect persisted for 2 years of follow-up, suggesting it is valuable as a long-term treatment option. Despite having a retrospective design, the present study is the first, extensive, real-world study on the efficacy, safety and patient tolerability of dulaglutide versus liraglutide in SOT recipients and is therefore noteworthy. Further large-scale, prospective trials are warranted to analyse the effect of these agents on microvascular and macrovascular complications in SOT recipients.

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CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and conduct of the study. P.S., S.M. and D.W. contributed to the acquisition, analysis and interpretation of data. P.S. and S.M. wrote the first draft of the manuscript. T.P.,

K.W., P.S., S.M. and D.W. reviewed, edited and approved the manuscript.

DATA AVAILABILITY

The datasets generated during and/or analysed during this study are not publicly available because of institutional review board restrictions, but are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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