Diabetes Ther (2021) 12:527–536
https://doi.org/10.1007/s13300-020-00984-x

ORIGINAL RESEARCH

Real-World Effectiveness Analysis of Switching From Liraglutide or Dulaglutide to Semaglutide in Patients With Type 2 Diabetes Mellitus: The Retrospective REALISE-DM Study

Akshay B. Jain · Steve Kanters · Reena Khurana · Jagoda Kissock · Naomi Severin · Sara G. Stafford

Received: November 13, 2020 / Accepted: December 11, 2020 / Published online: December 26, 2020

ABSTRACT

Introduction: Injectable semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that was previously shown to be superior to liraglutide and dulaglutide in head-to-head comparisons in GLP-1 RA-naïve individuals. It is hypothesized that semaglutide will cause further reductions in glycated hemoglobin A1c (HbA1c) and weight in type 2 diabetes mellitus (T2DM) patients previously treated with liraglutide or dulaglutide. The REALISE-DM study provides the first real-world evidence of the effectiveness and tolerability of semaglutide in patients switching from another GLP-1 RA.

Methods: This retrospective real-world effectiveness analysis included T2DM adults who were on a stable dose of liraglutide or dulaglutide prior to switching to semaglutide. The primary outcome was change in HbA1c. Secondary outcomes were the changes in weight and body mass index (BMI), the occurrence of gastrointestinal side effects (GSEs), and discontinuations. Linear mixed models were used to estimate changes in HbA1c, weight, and BMI, and logistic regression was employed to analyze GSEs and discontinuations.

Results: Six months after the 164 patients in this study had switched to semaglutide, their mean HbA1c had decreased by 0.65% (7.1 mmol/mol) (95% prediction interval [PI]: 0.48, 0.81% [5.2, 8.9 mmol/mol]) from a baseline of 7.9% (interquartile range [IQR]: 7.3, 8.8) (62.8 mmol/mol [IQR: 56.3, 72.7]), while their weight and BMI had reduced by 1.69 kg (95% PI: 1.01, 2.37) and 0.59 kg/m^2 (95% PI: 0.34, 0.84), respectively. Nineteen patients (11.6%) developed GSEs after switching.

Conclusions: This study supports switching T2DM patients on liraglutide or dulaglutide to injectable semaglutide to achieve further reductions in HbA1c and weight. Although a small number of GSEs occurred, semaglutide was well tolerated by the majority of the patients.

Keywords: Clinical physiology; Dulaglutide; GLP-1 RA; Liraglutide; Semaglutide; Type 2 diabetes mellitus

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-020-00984-x.

A. B. Jain (✉) · R. Khurana · J. Kissock · N. Severin · S. G. Stafford
Fraser River Endocrinology, Surrey, BC, Canada
e-mail: oxyjain@gmail.com

A. B. Jain · R. Khurana · N. Severin · S. G. Stafford
Department of Medicine, Division of Endocrinology at University of British Columbia, Vancouver, BC, Canada

S. Kanters
School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada

Key Summary Points

Why carry out this study?

Injectable semaglutide once weekly (OW) is a glucagon-like peptide-1 receptor agonist (GLP-1 RA) that was previously shown to be superior to liraglutide once daily (OD) and dulaglutide OW in head-to-head comparisons in GLP-1 RA-naïve individuals.

The REALISE-DM study provides real-world evidence of the effectiveness and tolerability of semaglutide OW in patients switching from another GLP-1 RA.

What was learned from the study?

Switching to semaglutide OW from liraglutide OD or dulaglutide OW is associated with further reductions in HbA1c, weight, and body mass index (BMI) in patients with T2DM.

Significant reductions in HbA1c, weight, and BMI postswitch support the use of semaglutide OW in patients previously treated with either liraglutide OD or dulaglutide OW.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13360382.

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) stimulate glucose-dependent insulin secretion, attenuate postprandial glucagon secretion, and slow gastric emptying, resulting in improved glycemic control and weight reduction in patients with type 2 diabetes mellitus (T2DM) [1].

The GLP-1 RA class of agents includes exendin-4-based molecules such as exenatide and lixisenatide, as well as human-analog molecules such as dulaglutide, liraglutide, and semaglutide. These agents have different molecular structures as well as inherent differences in their durations of action: exenatide is administered twice daily; liraglutide, lixisenatide, and oral semaglutide are administered once daily (OD); and dulaglutide, exenatide extended release, and injectable semaglutide are administered once weekly (OW) [2–7]. Cardiovascular risk reduction properties also vary between GLP-1 RA agents: exenatide and lixisenatide do not yield a significant reduction in major adverse cardiovascular events whereas dulaglutide, liraglutide, and semaglutide have shown cardiovascular benefit [8–12].

The American Diabetes Association/European Association for the Study of Diabetes consensus report recommends the use of GLP-1 RAs throughout the treatment pathway in patients with T2DM not controlled by metformin monotherapy as well as comprehensive lifestyle modifications, especially if there is concern about weight gain or hypoglycemia, or as an initial agent if metformin is contraindicated [13]. GLP-1 RAs are the only injectable antidiabetic agents besides insulin, and can be used in patients before or after insulin therapy.

Semaglutide is a GLP-1 RA indicated for the treatment of adults with insufficiently controlled T2DM as an adjunct to diet and exercise, and is administered as an OW subcutaneous injection, which was the only form of semaglutide available when the present study was conducted [14].

Head-to-head phase III trials have shown that subcutaneous semaglutide OW has greater potential to lower glycated hemoglobin A1c (HbA1c) levels than subcutaneous liraglutide OD or dulaglutide OW; however, semaglutide OW also leads to a higher incidence of gastrointestinal side effects (GSEs) in GLP-1 RA-naïve patients [15, 16]. While randomized trials are revered for their ability to optimize internal validity, they can be limited with respect to

external validity. Trials tend to be very selective of the subjects included, which may not reflect real-world settings [17].

Due to inherent differences between GLP-1 RA therapies, clinicians and patients may prefer to use one agent over another. In clinical practice, one may also consider switching to a different GLP-1 RA if the current agent is unable to achieve the expected glycemic control or weight loss, or if the patient is unable to tolerate a GLP-1 RA due to side effects. There are no studies to date that have investigated the effectiveness and safety of semaglutide OW in patients already receiving GLP-1 RA therapy. A previous model-based study predicted that switching to semaglutide OW from liraglutide, dulaglutide, or exenatide would result in further reductions in HbA1c and weight [14]. Previous randomized controlled trials have examined the effects of adding insulin to patients already on a GLP-1 RA regimen and whose T2DM was considered uncontrolled [18–20].

Here, we present results of the first study designed to investigate the effectiveness and tolerability of semaglutide OW in patients previously treated with liraglutide or dulaglutide in a real-world clinical setting. This study aimed to provide guidance to clinicians on the effectiveness and safety of switching to semaglutide OW in patients previously treated with liraglutide or dulaglutide, with a focus on trying to reduce GSEs and improve adherence.

METHODS

Study Design and Patients

This study was a retrospective chart review with longitudinal data carried out in a single Canadian endocrinology clinic with five endocrinologists on consecutive eligible patients. Patients who switched to semaglutide between March 2018 and June 2019 were included in the study; the follow-up period was from the date of the switch until March 2020. Nonpregnant adult patients with T2DM who had previously received a stable dose of liraglutide or dulaglutide for at least 3 months before switching to semaglutide OW at the discretion of their endocrinologist were eligible for inclusion. To eliminate the effect of insulin intensification on HbA1c reduction, cases with medical records indicating that insulin doses were increased at the time of switching to semaglutide OW or that bolus insulin was added in addition to existing basal insulin were excluded. Considerations for switching to semaglutide OW included, but were not limited to, a need to further reduce HbA1c (compared to the reduction achieved with dulaglutide and liraglutide), a desire for greater weight loss (compared to that achieved with dulaglutide and liraglutide), decreased frequency of administration (compared to liraglutide), cardiovascular protection (compared to dulaglutide, based on data available at the time the switch was conducted between March 2018 and June 2019), and the potential to reduce the doses of other concomitant diabetes medications, including insulin (compared to the doses of those medications when used with dulaglutide and liraglutide). HbA1c levels, weight, and body mass index (BMI) were recorded at baseline and subsequently at up to three regularly scheduled follow-up appointments. Weight was measured on a calibrated clinic scale at follow-up visits with patients wearing light indoor clothing and no footwear.

The Board of Record (Research Ethics Board [REB]# H18-03612) has reviewed and approved this study in accordance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2 2014). The Board of Record is the REB delegated by the participating REBs involved in a harmonized study to facilitate the ethics review and approval process. This study has been approved either by the Board of Record's full REB or by an authorized delegated reviewer. As this was a retrospective study where patient records were used, the Helsinki Declaration and consents to participate or for publication are not applicable here.

Study Outcomes

The primary outcome was the change in HbA1c over time after the initiation of semaglutide.

Secondary outcomes were changes in weight and BMI, the occurrence of GSEs based on patient reporting, and the number of patients who discontinued semaglutide to switch back to their previous therapy.

Statistical Analyses

To eliminate the impact of other glucose-lowering agents on the efficiency data, the statistical analyses only included the follow-up data when no additional new class of glucose-lowering agents or higher dose of insulin was needed. Given the repeated measures due to multiple visits from the same patients, methods were selected to account for the clustered nature of the evidence. Linear mixed models adjusting for differences in follow-up time (fixed effects) and repeated measures (random effects) were used to estimate changes in HbA1c, weight, and BMI over time. Using these models, changes in HbA1c (adjusted for baseline HbA1c levels [< 7% (53.0 mmol/mol), 7.0–8.4% (53.0–-68.3 mmol/mol), and ≥ 8.5% (69.4 mmol/mol)]), weight (adjusted for previous therapy [liraglutide or dulaglutide]), and BMI (adjusted for baseline BMI [< 35 or ≥ 35 kg/m^2]) were estimated at 3, 6, and 12 months. With respect to the inclusion of follow-up time in the model, the relationship between time on treatment and outcome was found to be nonlinear and monotonic. In all models, applying a log transformation made the relationship linear (i.e., changes were greater early on than later on) and so log(time) was included as a covariate in all models. Note that categorized covariates were used because relationships between baseline values and outcomes were found to be nonlinear. Model assumptions were verified graphically to ensure homoscedasticity, linearity, and a lack of high leverage points. One patient was removed from both the change in weight and BMI analyses for having an excessive decline. This outlier was removed due to its disproportionate influence on the model results.

Given that both GSE and discontinuation of semaglutide OW were one-time events, there was no need to adjust for repeated measures. As such, logistic regression was used to determine if differences in baseline characteristics (e.g., baseline BMI, baseline HbA1c, or previous therapy received) made these outcomes more likely.

The model with the lowest Akaike information criterion was considered the best-fitting model. All analyses were performed using R version 3.4.1 (http://www.r-project.org/), and the significance level p was ≤ 0.05 .

RESULTS

Patient Demographics

A total of 164 patients were analyzed in this study. Prior to switching to semaglutide OW, patients with T2DM had been treated with GLP-1 RA (liraglutide or dulaglutide) for a mean duration of 6.8 months. Ninety-six patients (58.5%) were male, and the median age at baseline was 58.0 years (interquartile range [IQR]: 51.0, 65.3) (Table 1). At baseline, the median HbA1c was 7.9% (IQR: 7.3, 8.8) (62.8 mmol/mol [IQR: 56.3, 72.7]). A total of 133 patients (81.1%) had HbA1c > 7.0% (53.0 mmol/mol), and 151 patients (92.1%) had HbA1c ≥ 6.5% (47.5 mmol/mol) (Table 1). The median baseline weight and BMI were 98.5 kg (IQR: 89.6, 113.0) and 33.1 kg/m^2 (IQR: 30.2, 37.8), respectively.

More patients (n [%]) switched to semaglutide OW from liraglutide than from dulaglutide (139 [84.8%] versus 25 [15.2%], respectively), and a total of 86 patients (52.4%) were on insulin therapy when they switched to semaglutide OW (Table 1).

Based on the chart review, the recorded reasons for switching to semaglutide OW were: uncontrolled HbA1c (71 patients), to reduce the injection burden (49 patients), for further weight loss (42 patients), for cardiovascular protection (6 patients), and to reduce the amount of insulin or other medications used (25 patients). No reason was recorded for 8 patients. The total number of recorded reasons for switching medications was 201 (i.e., more than the total number of patients: 164), as some charts stated multiple reasons for the switch.

Table 1 Patient baseline characteristics

Number of patients	164
Age, years [IQR]	58.0 [51.0, 65.3]
Male	96 (58.5%)
Weight, kg [IQR]	98.5 [89.6, 113.0]
BMI, kg/m^2 [IQR]	33.1 [30.2, 37.8]
HbA1c, % (mmol/mol)	7.9 [7.3, 8.8] (62.8 [56.3, 72.7])
< 6.5% (47.5 mmol/mol)	13 (7.9%)
≥ 6.5% (47.5 mmol/mol)	151 (92.1%)
> 7.0% (53.0 mmol/mol)	133 (81.1%)
Patients receiving:	
Prior insulin	86 (52.4%)
Prior liraglutide	139 (84.8%)
Prior dulaglutide	25 (15.2%)

Data are median [IQR] or *n* (%)
BMI body mass index, *HbA1c* glycated hemoglobin A1c, *IQR* interquartile range

Dosing Information

Among the 139 patients on liraglutide OD at the time of the switch, 4 (2.8%), 29 (20.9%), and 106 (76.3%) were on doses of 0.6, 1.2, and 1.8 mg/day, respectively. Of the 25 patients on dulaglutide OW at the time of the switch, 2 (8%) and 23 (92%) patients were on doses of 0.75 and 1.5 mg/week, respectively. The median doses of liraglutide OD and dulaglutide OW prior to switching were 1.8 mg/day and 1.5 mg/week, respectively.

At the time of the switch, 48 (29.3%), 106 (64.6%), and 10 (6.1%) patients were started on 0.25, 0.5, and 1.0 mg/week of semaglutide OW, respectively. On study completion, the final recorded dose of semaglutide OW for the 147 patients who had continued on the medication was 0.25 mg/week for 1 patient (0.6%), 0.50 mg/week for 32 patients (21.8%), and 1.0 mg/week for 114 patients (77.6%). The median final dose of semaglutide OW was 1.0 mg/week.

Changes in HbA1c After Switching to Semaglutide OW

Following the switch to semaglutide OW, there was a 0.65% (95% prediction interval [PI]: 0.48, 0.81) (7.1 mmol/mol [95% PI: 5.2, 8.9]) reduction in HbA1c at 6 months.

Using linear mixed modeling, the change in HbA1c was estimated at 3, 6, and 12 months in patients with baseline HbA1c < 7% (53.0 mmol/mol), 7.0–8.4% (53.0–68.3 mmol/mol), and ≥ 8.5% (69.4 mmol/mol) (Table 2). The reduction in HbA1c was directly proportional to the baseline HbA1c level, with the greatest reduction seen in the ≥ 8.5% (69.4 mmol/mol) baseline HbA1c group (Fig. 1). At 12 months, there was a greater decrease in HbA1c in the ≥ 8.5% (69.4 mmol/mol) group than in the 7.0–8.4% (53.0–68.3 mmol/mol) group (− 1.49%; 95% confidence interval [CI] − 1.74, − 1.24 [− 16.3 mmol/mol; 95% CI − 19.0, − 13.6] versus − 0.58%; 95% CI − 0.79, − 0.38 [6.3 mmol/mol; 95% CI − 8.6, − 4.2]). Relative to the < 7% (53.0 mmol/mol) group, HbA1c was significantly reduced in both the 7.0–8.4% (53.0–68.3 mmol/mol) group (− 0.60%; 95 CI − 0.99, − 0.21 [− 6.6 mmol/mol; 95% CI − 10.8, − 2.3]; $p = 0.0031$) and the ≥ 8.5% (69.4 mmol/mol) group (–1.51%; 95% CI − 1.92, − 1.10 [− 16.5 mmol/mol; 95% CI − 21.0, − 12.0]; $p < 0.0001$).

The therapy received by patients before switching to semaglutide OW (liraglutide or dulaglutide) did not have a significant impact on change in HbA1c (Table 2). The change in HbA1c differed between patients previously treated with dulaglutide and those previously treated with liraglutide by 0.08% (95% CI − 0.35, 0.51 [0.9 mmol/mol; 95% CI − 3.8, 5.6]; $p = 0.72$).

Table 2 Estimated change in HbA1c over time, stratified by baseline HbA1c levels and prior therapy

	Estimated change in HbA1c at 3 months, (95% CI)	Estimated change in HbA1c at 6 months, (95% CI)	Estimated change in HbA1c at 12 months, (95% CI)
Baseline HbA1c (%)			
< 7	0.33 (– 0.04, 0.70)	0.17 (– 0.17, 0.52)	0.02 (– 0.32, 0.36)
7.0–8.4	– 0.27 (– 0.50, – 0.05)	– 0.43 (– 0.63, – 0.24)	– 0.58 (– 0.79, – 0.38)
≥ 8.5	– 1.18 (– 1.44, – 0.92)	– 1.34 (– 1.57, – 1.1)	– 1.49 (– 1.74, – 1.24)
Prior therapy (%)			
Liraglutide	– 0.54 (– 0.76, – 0.32)	– 0.66 (– 0.84, – 0.48)	– 0.78 (– 0.97, – 0.59)
Dulaglutide	– 0.46 (– 0.87, – 0.05)	– 0.58 (– 0.98, – 0.18)	– 0.70 (– 1.11, – 0.29)
Baseline HbA1c (mmol/mol)			
< 53.0	3.6 (– 0.4, 7.6)	1.9 (– 1.9, 5.7)	0.2 (– 3.5, 3.9)
53.0–68.3	– 3.0 (– 5.5, – 0.5)	– 4.7 (6.9, – 2.6)	– 6.3 (– 8.6, – 4.2)
≥ 69.4	– 12.9 (– 15.7, – 10.1)	– 14.6 (– 17.2, – 12.0)	– 16.3 (19.0, – 13.6)
Prior therapy (mmol/mol)			
Liraglutide	– 5.9 (– 8.3, – 3.5)	– 7.2 (– 9.2, – 5.2)	– 8.5 (– 10.6, – 6.4)
Dulaglutide	– 5.0 (– 9.5, – 0.5)	– 6.3 (– 10.7, – 2.0)	– 7.7 (– 12.1, – 3.2)

Estimated values from a linear mixed model adjusting for differences in follow-up time (fixed effects) and repeated measures (random effects) using a logarithmic transformation of time
CI confidence interval, *HbA1c* glycated hemoglobin A1c

Changes in Weight After Switching to Semaglutide OW

The mean additional weight reduction was 1.69 kg (95% PI: 1.01, 2.37) 6 months after switching to semaglutide OW. Using linear mixed modeling, weight was estimated to have decreased over time from 3 to 6 and 12 months, with the greatest rate of additional weight loss occurring in the initial 3-month period post-switch (Fig. 2; Table 3).

The previous therapy received by patients before switching to semaglutide OW (liraglutide or dulaglutide) did not have a significant impact on the change in weight (Table 3). The change in weight over time differed between patients who were previously treated with dulaglutide and those who were previously treated with liraglutide by 0.97 kg (95% CI – 2.17, 4.11; $p = 0.55$).

In line with the changes in body weight, a reduction in mean BMI was also observed after patients switched to semaglutide OW (see the Supplementary Information).

Occurrence of GSEs After Switching to Semaglutide

Among the patients who had previously tolerated liraglutide or dulaglutide well, 19 (11.6%) developed GSEs after switching to semaglutide OW. A total of 17 (10.4%) patients discontinued semaglutide OW and switched back to their previous GLP-1 RA therapy. Eight patients discontinued because they could not tolerate the GSE, and the remaining nine patients discontinued because they felt that there were coverage issues, or that their home blood sugar readings were not controlled by semaglutide. Of the 17 patients who discontinued semaglutide OW, 1 patient discontinued at 0.25 mg/week, 7

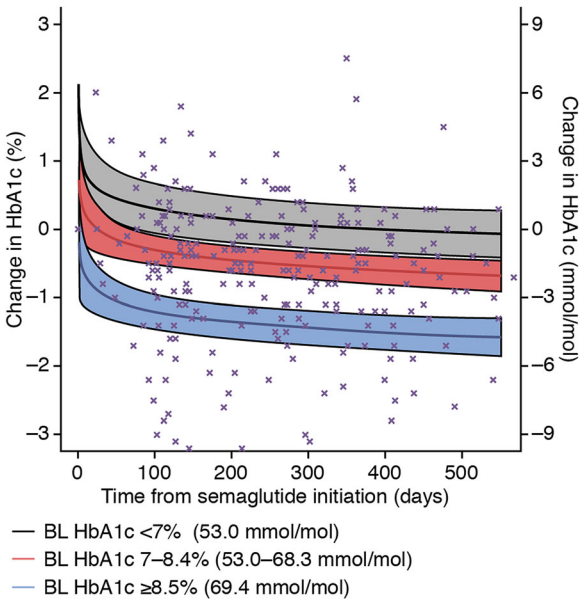

Fig. 1 Change in HbA1c over time after semaglutide OW initiation, stratified by baseline HbA1c level. *BL* baseline, *HbA1c* glycated hemoglobin A1c, *OW* once weekly

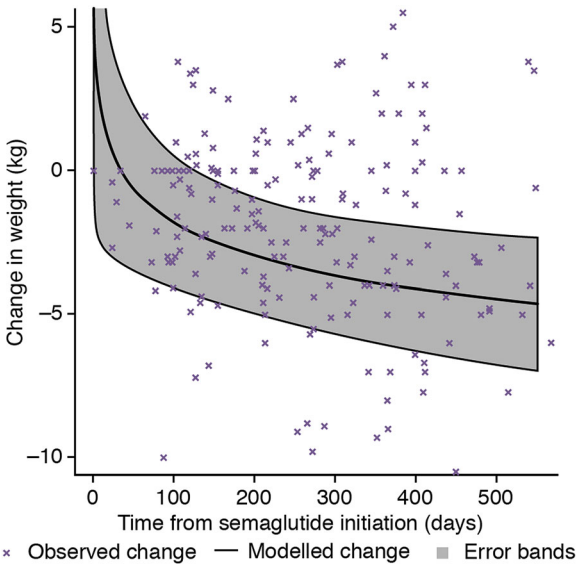

Fig. 2 Change in weight over time after semaglutide OW initiation. *OW* once weekly

patients at 0.5 mg/week, and 9 patients at the 1.0 mg/week dose.

The number of patients with GSEs was small, and there was no significant contribution from the GSEs to the reductions in HbA1c and body weight. Furthermore, logistic regression modeling of discontinuation did not support an association between any of the baseline characteristics (previous treatment, HbA1c, weight, etc.) or starting dose of semaglutide OW and risk of discontinuation.

DISCUSSION

This is the first real-world study ($n = 164$) to demonstrate that switching to semaglutide OW from liraglutide OD or dulaglutide OW is associated with further reductions in HbA1c, weight, and BMI in patients with T2DM, most of whom were considered uncontrolled on their previous therapy. The reasons for switching to semaglutide OW included a need to reduce HbA1c or weight further (as compared with the reductions achieved with dulaglutide and liraglutide), decreased frequency of administration (compared to liraglutide), and cardiovascular protection (compared to dulaglutide). The degree of reduction in HbA1c was found to be directly proportional to the baseline HbA1c at the time of the switch, with significant changes seen in patients with prior uncontrolled HbA1c. In patients who were already at their target HbA1c < 7.0% (53.0 mmol/mol), switching to semaglutide OW from liraglutide OD or dulaglutide OW did not lead to significant changes in their HbA1c levels. Neither the change in HbA1c nor the change in weight were found to be influenced by previous therapy. The reduction in BMI was greatest in patents who had a higher baseline BMI.

Although this study was designed retrospectively, the outcomes reported here reflect a model-based approach described by Overgaard et al. [14], who suggested that switching from liraglutide, dulaglutide, or exenatide to semaglutide OW results in reduced HbA1c levels and weight. Treatment adherence can undoubtedly be enhanced by switching from OD to OW GLP-1 RA injections, leading to further reductions in HbA1c and weight. Semaglutide therefore provides a further treatment option for patients for whom metformin and lifestyle changes have failed and who are

Table 3 Estimated change in weight over time in patients overall and patients stratified by prior therapy

	Estimated change in weight at 3 months, (95% CI)	Estimated change in weight at 6 months, (95% CI)	Estimated change in weight at 12 months, (95% CI)
Overall (kg)	– 0.96 (– 1.84, – 0.08)	– 1.69 (– 2.37, – 1.01)	– 2.41 (– 3.14, – 1.68)
Prior therapy:			
Liraglutide (kg)	– 1.04 (– 2.02, – 0.06)	– 1.85 (– 2.59, – 1.11)	– 2.66 (– 3.44, – 1.88)
Dulaglutide (kg)	– 0.25 (– 0.47, – 0.04)	– 0.49 (– 0.67, – 0.31)	– 0.72 (– 0.91, – 0.54)

Estimated values from a linear mixed model that adjusted for differences in follow-up time (fixed effects) and repeated measures (random effects) using a logarithmic transformation of time
CI confidence interval

still considered uncontrolled on liraglutide or dulaglutide. Semaglutide has the added benefit of being administered OW (compared with OD liraglutide), which could improve adherence and quality of life.

The majority of patients tolerated switching from GLP-1 RA therapy to semaglutide, but GSEs occurred in a small number of patients. This finding is in line with previous head-to-head randomized controlled trials comparing semaglutide with liraglutide or dulaglutide in GLP-1 RA-naïve patients, which indicated that semaglutide induces higher rates of nausea [15, 16]. We are not aware of any data on the incidence of GSEs in patients receiving semaglutide who had previously tolerated other GLP-1 RAs. Semaglutide is thought to be a more potent therapy than liraglutide or dulaglutide [21], so semaglutide therapy may increase the intensity of delayed gastric emptying and the incidence of GSEs.

The limitations of this study include its single-center retrospective design and the low number of patients who switched from dulaglutide versus those who switched from liraglutide, meaning that comparisons stratified by previous therapy may not have attained sufficient statistical power. This imbalance was expected, as liraglutide was approved before dulaglutide in Canada. Postswitch differences in weight reduction between previous liraglutide patients and previous dulaglutide patients did not reach significance; a greater sample size of dulaglutide patients could help to elucidate this difference in weight reduction. The small size of the study implies a possible association between switching from liraglutide OD or dulaglutide OW to semaglutide OW and further reductions in HbA1c, weight, and BMI in patients with T2DM. Previous clinical studies have, however, demonstrated efficacy and safety outcomes of liraglutide and dulaglutide: AWARD 6, a head-to-head phase III clinical trial comparing liraglutide OD with dulaglutide OW in GLP-1 RA-naïve patients, demonstrated comparable reductions in HbA1c, GSE incidence, and tolerability but greater weight loss with liraglutide [22]. The real-world setting of this study is a strength, and our results corroborate the findings of previous clinical trials [15, 16].

CONCLUSIONS

The real-world evidence presented in this study indicates that switching to semaglutide OW from liraglutide OD or dulaglutide OD is associated with further reductions in HbA1c, weight, and BMI in patients with T2DM. In patients with HbA1c < 7.0% (53.0 mmol/mol), switching to semaglutide OW from liraglutide OD or dulaglutide OW did not cause any significant change in HbA1c levels, although this switch may help to improve patient adherence if the switch is from OD GLP-1 RA injections. Results are congruous with previous clinical

trials [15, 16]. Significant reductions in HbA1c, weight, and BMI postswitch support the use of semaglutide OW in patients previously treated with either liraglutide or dulaglutide. Future prospective randomized clinical trials with larger sample sizes are needed to help corroborate the findings noted in our study.

ACKNOWLEDGEMENTS

The authors thank all those involved in the conduct of the trial and the participants of the study.

Funding. The medical writing, editorial support of this study, and the journal's rapid service fee were supported by Novo Nordisk Canada.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Medical Writing and/or Editorial Assistance. The authors thank Jin Heppell and Helen Marshall of Watermeadow Medical, an Ashfield Company, part of UDG Healthcare plc, for medical writing and editorial support (funded by Novo Nordisk Canada).

Disclosures. Akshay B. Jain: CME honoraria and advisory boards for Novo Nordisk, Eli Lilly, and AstraZeneca; research funding for Novo Nordisk. Steve Kanters: no disclosures. Naomi Severin: advisory boards for Novo Nordisk and AstraZeneca. Reena Khurana: advisory boards for Novo Nordisk and Eli Lilly. Jagoda Kissock: advisory boards for Novo Nordisk. Sara G. Stafford: CME honoraria and advisory boards for Novo Nordisk, Eli Lilly, and AstraZeneca; research funding for Novo Nordisk and AstraZeneca.

Compliance with Ethics Guidelines. The Board of Record (Research Ethics Board [REB]# H18-03,612) has reviewed and approved this study in accordance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS2, 2014). The Board of Record is the REB delegated by the participating REBs involved in a harmonized study to facilitate the ethics review and approval process. This study has been approved either by the Board of Record's full REB or by an authorized delegated reviewer. As this is a retrospective study where patient records were used, the Helsinki Declaration and consents to participate or for publication are not applicable here.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet. 2006;368:1696–705.

2. US FDA. Prescribing Information: Byetta® (exenatide) injection. Silver Spring: US Food and Drug Administration; 2009.

3. US FDA. Prescribing Information: Adlyxin (lixisenatide) injection, for subcutaneous use. Silver Spring: US Food and Drug Administration; 2016.

4. US FDA. Prescribing Information: Bydureon® (exenatide extended-release) for injectable suspension, for subcutaneous use. Silver Spring: US Food and Drug Administration; 2018.

5. US FDA. Prescribing Information: Ozempic (semaglutide) injection, for subcutaneous use. Silver Spring: US Food and Drug Administration; 2019.

6. US FDA. Trulicity (dulaglutide) injection, for subcutaneous use. Silver Spring: US Food and Drug Administration; 2017.

7. US FDA. Victoza® (liraglutide) injection, for subcutaneous use. Silver Spring: US Food and Drug Administration; 2017.

8. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–44.

9. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–22.

10. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394:121–30.

11. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373:2247–57.

12. Holman RR, Bethel MA, Mentz RJ, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377:1228–39.

13. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes 2020. Diabetes Care. 2020;43(Suppl. 1):S98-110.

14. Overgaard RV, Lindberg SO, Thielke D. Impact on HbA1c and body weight of switching from other GLP-1 receptor agonists to semaglutide: a model-based approach. Diabetes Obes Metab. 2019;21:43–51.

15. Capehorn MS, Catarig AM, Furberg JK, et al. Efficacy and safety of once-weekly semaglutide 1.0mg vs once-daily liraglutide 1.2mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10). Diabetes Metab. 2020;46:100–9.

16. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinol. 2018;6:275–86.

17. Heneghan C, Goldacre B, Mahtani KR. Why clinical trial outcomes fail to translate into benefits for patients. Trials. 2017;18:122.

18. Aroda VR, Bailey TS, Cariou B, et al. Effect of adding insulin degludec to treatment in patients with type 2 diabetes inadequately controlled with metformin and liraglutide: a double-blind randomized controlled trial (BEGIN: ADD TO GLP-1 Study). Diabetes Obes Metab. 2016;18:663–70.

19. Blonde L, Rosenstock J, Del Prato S, et al. Switching to iGlarLixi versus continuing daily or weekly GLP-1 RA in type 2 diabetes inadequately controlled by GLP-1 RA and oral antihyperglycemic therapy: the LixiLan-G randomized clinical trial. Diabetes Care. 2019;42:2108–16.

20. Linjawi S, Bode BW, Chaykin LB, et al. The efficacy of IDegLira (insulin degludec/liraglutide combination) in adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist and oral therapy: DUAL III randomized clinical trial. Diabetes Ther. 2017;8:101–14.

21. Holst JJ, Madsbad S. Semaglutide seems to be more effective the other GLP-1Ras. Ann Transl Med. 2017;5:505.

22. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet. 2014;384:1349–57.