Original Article

Once Weekly Dulaglutide Therapy in Type 2 Diabetic Subjects, Real-world Evidence from a Tertiary Care Diabetes Center in India

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Abstract

Aims: To evaluate the real-world efficacy, durability, and side-effect profile of once weekly GLP1RA: dulaglutide in Indian type 2 diabetes mellitus (T2DM) patients. **Materials and Methods:** A retrospective observational study. Data for efficacy (HbA1c and weight), adherence/discontinuation and patient reported side-effects, of 117 patients who were prescribed dulaglutide were analyzed. **Results:** Final analysis was done on complete data of 74 patients (6 months follow-up), this indicated that dulaglutide is effective (mean-reduction at 6 months of: HbA1c; 0.87% and weight; 3.8 kg). Subjects with a poorer glycemic control (greater HbA1c) or greater weight at initiation had a better fall in HbA1c and weight reduction at the end of the study. The most common side-effects were gastrointestinal (15% nausea and 6% loose motions). Also, 25% (n = 19) of our study subjects discontinued dulaglutide because of gastrointestinal side-effects. **Conclusion:** Our real-world experience is well aligned to systematic data of the randomized controlled trials (RCTs) regarding the efficacy of dulaglutide in the treatment of T2DM (our study vs. RCTs; HbA1c reduction: 0.87% vs. 0.78% to 1.64%, weight reduction: 3.8 vs. 0.3 to 3 kg). The most common side-effects and reason for discontinuation were gastrointestinal side-effects. Finally, by virtue of their observed benefit, we expect a superior cardiovascular risk-reduction with dulaglutide use in our population.

Keywords: Dulaglutide, real-world experience, type 2 diabetes mellitus

Introduction

The explosive increase in the prevalence of type 2 diabetes mellitus (T2DM) is projected to reach 1 in 3 adults by 2050, a substantial increase from 1 in 10 adults presently.[1] It is not just this expected increased prevalence of T2DM that is worrying but also the expected parallel increase of chronic complications, mainly cardiovascular disease (CVD) that presently will become a major public health concern, not just in India but also globally.[2]

The successful management of T2DM and CVD risk reduction is no more only a *glucocentric approach*, but present day practice entails assessing and addressing multiple risk factors including diet, physical activity, weight reduction, glycemic control, lipid/blood pressure management, etc. for an overall risk reduction to prevent chronic macro-vascular and micro-vascular complications.[3] Hence, it requires multiple, often complex risk reduction strategies that are patient centric and also require immense resources for optimal delivery. Recent advances in pharmacological research for T2DM therapy targeting the incretin axis (Glucagon like peptide-1 receptor agonist; GLP-1RA)[4] has definitely expanded the inventory of the health care provider managing T2DM, by not only providing a safe, effective, and sustained glycemic control and CVD risk reduction (weight loss and possible blood pressure reduction)[5-13] but also a likelihood of direct CVD reduction.[14,15] Further, another additional benefit of GLP-1RA from their glucose-dependent mechanism of action is lower risk of hypoglycemia as compared most other diabetes therapies.[4]

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Dulaglutide, a long acting GLP-1RA, has 90% structural homology to the endogenous human GLP-1 fragment 7–37. It is a once weekly subcutaneous injection, which got approval by the US Food and Drug Administration in September, 2014 for glycemic control in adults with T2DM.[16] The initial dose of dulaglutide is 0.75 mg, which can be later increased to a maximum of 1.5 mg, both the doses are available as a simple and convenient single dose disposable prefilled self-injector (0.75 mg/0.5 mL or 1.5 mg/0.5 mL). The primary mechanism for glycemic control with dulaglutide is a glucose dependent increment of insulin release from beta cells. This is further enhanced by improvements in other pathophysiological defects of T2DM including decreased glucagon secretion, slowing of gastric emptying, appetite suppression, and satiety enhancement (central and peripheral nervous system effects).[4] In addition, exciting preliminary data suggests that GLP-1 RA may reduce progressive beta cell failure by beta cell preservation. Finally, GLP-1RA's as a drug class in comparison to other anti-diabetic therapies may provide a pronounced benefit by virtue of their superior CVD risk reduction.[14,15] Importantly, results of the ongoing trial of once weekly dulaglutide (REWIND: Researching cardiovascular Events with a Weekly incretin in Diabetes) which in contrast to the other CV outcome trials of GLP1-RA's has recruited a large proportion of diabetics (69%) without established CVD and a mean HbA1c of 7.3% will provide valuable information regarding CV safety/benefits of dulaglutide use across a wide variety of diabetics that will be relevant to real-world clinical practice.[15]

On the basis of the substantially proven safety, efficacy, durability and pleiotropic (weight loss) outcomes data from a large number of globally representative T2DM subjects, enrolled in well designed and conducted randomized controlled trials (RCTs), we proposed to demonstrate similar benefits in a heterogeneous real-world T2DM patient population in India.

Materials and Methods

We intended to study the real-world safety, efficacy, and tolerability of dulaglutide in the outpatient setting at our center. Data were retrospectively evaluated for subjects who were prescribed protocol based weekly injections of dulaglutide during the period April 2016 to September 2016 at the Endocrinology and Diabetes clinic at Medanta, The Medicity Hospital in National Capital Region of India were captured.

Data used for the current investigation included laboratory [Glycosylated hemoglobin (HbA1c), fasting (FBG), and postprandial blood glucose levels (PPBG)] and anthropometric (weight and height) parameters at four serial timelines including baseline (initiation of treatment), and thereafter at 1, 3, and 6 months.

Ours was an observational study in design. We included a total of 117 T2DM subjects who were prescribed 0.75 mg dose of dulaglutide treatment for the first 2 weeks, and then increased to 1.5 mg, as a standard of care. We excluded subjects who were on pioglitazone currently, or immediately (3 months) prior to therapy, a drug which can contribute to weight gain, or its discontinuation may cause weight loss. We also obtained other relevant data on simultaneous use of sodium glucose transporter-2 inhibitor's (SGLT-2i), if they were prescribed during course of treatment for glycemic control. This allowed us sub-group analysis of subjects' naïve and exclusive to GLP-1 analogue therapy, and thus, observes primary outcomes more directly attributable to weekly dulaglutide use. The flow of study is as depicted in Figure 1.

Statistical analysis

Data were extracted from both manually entered and hospital information system prescriptions of our T2DM subjects. This was then entered into a pre-coded MS excel sheet. Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 21.0, IBM, USA. Descriptive statistics (mean, median, etc.) and non-parametric (Friedman and Wilcoxon Signed Rank) tests were applied for comparison of results at the four timelines. Pearson's correlation was done to observe correlations between baseline parameters and differences observed from end observation point. A P value of <0.05 was considered statistically significant for the interpretation of results.

Results

During the period from April 2016 to September 2016, a total of 117 T2DM subjects were initiated on weekly dulaglutide therapy as an add-on to their current therapeutic regimen for diabetes management. The follow-up period was up to 6 months after initiation (0.75 mg subcutaneously, weekly for first 2 weeks followed by 1.5 mg). All subjects were provided standard of care, including a diet and lifestyle counseling, injection technique explanation, and medication handout for observing, managing and reporting, if they experienced any

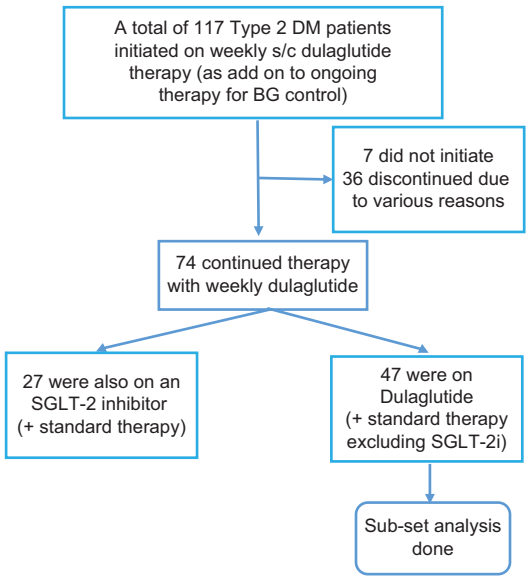

Figure 1: Flow of this study

of the already known side-effects of dulaglutide. They were counseled to follow-up at periodic intervals (4 weeks initially, then on completing 3 months and 6 months from initiation) as standard of care.

Out of 117 subjects initiated on weekly dulaglutide, 7 subjects did not start the therapy and 36 subjects discontinued because of specific reasons. The reasons for not starting, or discontinuation of dulaglutide are mentioned in Table 1.

Complete data for 74 subjects who were found to continue the therapy till the study end point period of 6 months were used for analysis. Of these, 47 (64%) were males and 27 (36%) females. The mean age of the subjects was 48.9 ± 9.1 years, mean HbA1c at baseline 8.99 ± 1.61%, and mean weight was 95.07 ± 15 kg. The baseline parameters of 74 subjects' naïve to dulaglutide and who completed 6 months follow-up are mentioned in Table 2a.

The mean HbA1c difference (reduction) observed at 6 months was 0.87% (range: −3.1 to +0.9%), and mean weight reduction was 3.8 kg (range: −25.4 to +3.9 kg).

Correlation between baseline HbA1c and HbA1c difference showed a Pearson's correlation coefficient of 0.600 ($P < 0.001$), indicating that reduction in HbA1c is linearly related and proportional to baseline HbA1c levels. Those subjects who had higher baseline HbA1c at initiation of therapy with dulaglutide showed a greater reduction in HbA1c levels with dulaglutide therapy. The linear relationship between baseline HbA1c and HbA1c difference is shown in Figure 2a.

Similarly, the weight difference observed at 6 months showed a statistically significant correlation with baseline weight of the subjects (Pearson's correlation coefficient: 0.320, *P* value: 0.005), indicating that subjects with greater weight at baseline are likely to observe more weight loss with this therapy. This linear relationship is shown in Figure 2b.

Non-parametric (Friedman) test was applied to repeated measurements at baseline and follow-up points. The results observed showed statistically significant differences observed for HbA1c, weight, FBG, and PPG (*P*-value < 0.001). The same are depicted in Table 3a.

Wilcoxon Signed Rank test to compare baseline and 6 month follow-up parameters showed results with statistically significant differences observed in reduction of all four parameters (HbA1c, weight, FBG, and PPG). (All *P* values <0.001) These are depicted in Table 4a.

Subset analysis

We did a subset analysis of the study subjects ($n = 74$), this included 47 subjects who were not on SGLT-2 inhibitors. In total, 26 (55.3%) were males and 21 (44.7%) were females. Mean glycosylated hemoglobin was 8.84% (range 6.5 to 11.5%) and mean weight was 93.45 kg (range 71 to 124 kg). Mean HbA1c difference (reduction from baseline and at 6 months of treatment) was 0.82% and mean weight difference (loss) was 3.55 kg. Baseline parameters of this subset are shown in Table 2b.

Table 1:Reasons cited for not starting or discontinuation of dulaglutide ($n=43$)

Reason	No. of patients (%)
GI side-effects: nausea, diarrhea, and stomach ache	19 (44.2)
Did not want to change current medication (did not start)	7 (16.2)
Fear of long-term side-effects	6 (14)
Cost of treatment	5 (11.6)
Lethargy	4 (9.4)
Poor response to treatment	1 (2.3)
Unable to use in travel	1 (2.3)

Table 2a: Patient's naïve to dulaglutide: Baseline parameters ($n=74$)

Parameter	Mean (Range)	SD
Height (cm)	165.52 (146-182)	8.7
HbA1c (%)	8.99 (6.1-14.4)	1.6
FBG (mg/dl)	164.74 (70-311)	46.2
PPBG (mg/dl)	237.3 (130-457)	65.1
Weight (kg)	95.07 (71-151.8)	14.9

Table 2b: Subset of patients on dulaglutide, not on any SGLT-2 inhibitor: Baseline parameters ($n=47$)

Parameter	Mean (Range)	SD
HbA1c (%)	8.84 (6.5-11.5)	1.3
FBG (mg/dl)	166.3 (109-289)	42.2
PPBG (mg/dl)	240.06 (130-457)	66.7
Weight (kg)	93.45 (71-124)	13.7

Table 3a: Comparison of repeated measures of parameters (Friedman Test): Dulaglutide group ($n=74$)

	Mean rank	*P*
HbA1c0	3.82	<0.001
HbA1c1	2.76	
HbA1c2	1.84	
HbA1c3	1.58	
Weight0	3.58	<0.001
Weight1	2.72	
Weight2	2.05	
Weight3	1.64	
FBG0	3.52	<0.001
FBG1	2.59	
FBG2	2.13	
FBG3	1.76	
PPBG0	3.80	<0.001
PPBG1	2.59	
PPBG2	1.89	
PPBG3	1.72	

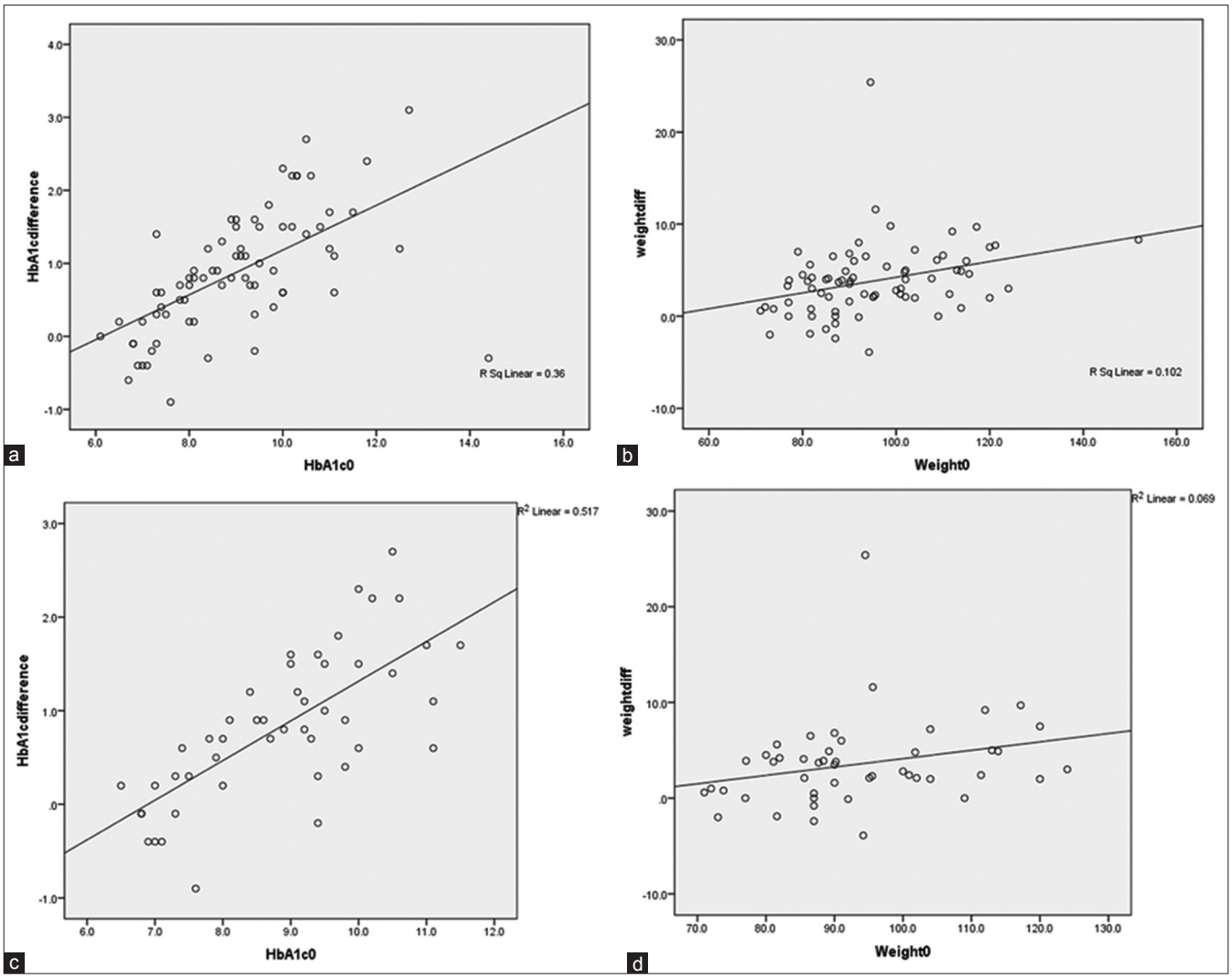

Figure 2: (a) Dulaglutide naïve group ($n = 74$), relationship between baseline HbA1c and HbA1c difference at 6 months (Pearson's correlation coefficient of 0.600 ($P < 0.001$). (b) Dulaglutide naïve group ($n = 74$), relationship between baseline weight and weight difference at 6 months (Pearson's correlation coefficient 0.320, P value = 0.005). (c) Patients on dulaglutide and not on any SGLT-2 inhibitor ($n = 47$), relationship between baseline HbA1c and HbA1c difference at 6 months (Pearson's correlation 0.719; P value <0.001). (d) Patients on dulaglutide and not on any SGLT-2 inhibitor ($n = 47$), relationship between baseline weight and weight difference at 6 months (Pearson's correlation 0.263; P value 0.074)

We did similar correlation between the baseline parameters and observed differences for HbA1c and weight, and the results showed Pearson's correlation between baseline HbA1c and HbA1c difference was 0.719 (P-value <0.001), and between weight and weight difference observed was 0.263 (P-value = 0.074; NS). Thus, a statistically significant difference was not observed for correlation between the weight and weight difference at 6 months, while the relationship was linear. The relationship is shown in Figures 2c and d.

Non parametric (Friedman) test applied to this subset, comparing repeated measurements showed statistically significant differences in the values of all four parameters compared (P value < 0.001) [Table 3b].

Wilcoxon Signed Rank test was applied comparing the baseline and 6 month time point parameters showed statistically significant results for all parameters compared, even in the subset treatment group (P-value < 0.001) [Table 4b].

There were no statistical differences observed in between the two groups (dulaglutide only: $n = 47$; dulaglutide and SGLT2i: $n = 27$) at baseline and at 6 months with respect to weight or HbA1c reduction.

Discussion

Our study assessed real-world safety, efficacy (glycemic and weight benefits), and tolerability of dulaglutide a once weekly dosed GLP-1RA in patients with T2DM. For ease of understanding, we have divided this section into two major parts:

- Comparison (Efficacy: glycemic control and weight loss; Safety: side-effects; Adherence/discontinuation) with published RCT's (AWARD trials)[5-13,17]

Table 3b: Comparison of repeated measures of parameters (Friedman Test): Dulaglutide patients not on any SGLT2 inhibitor (*n*=47)

	Mean rank	*P*
HbA1c0	3.90	<0.001
HbA1c1	2.76	
HbA1c2	1.70	
HbA1c3	1.64	
Weight0	3.48	<0.001
Weight1	2.67	
Weight2	2.09	
Weight3	1.77	
FBG0	3.68	<0.001
FBG1	2.51	
FBG2	2.13	
FBG3	1.68	
PPBG0	3.80	<0.001
PPBG1	2.65	
PPBG2	1.80	
PPBG3	1.76	

Table 4a: Wilcoxon Signed Rank test to compare baseline and 6 month follow-up: Dulaglutide naïve patients (*n*=74)

	Z score	*P*
HbA1c 6 months vs. baseline	−7.274	<0.001
Weight 6 months vs. baseline	−6.690	<0.001
FBG 6 months vs. baseline	−6.839	<0.001
PPBG 6 months vs. baseline	−7.211	<0.001

Table 4b: Wilcoxon Signed Rank test to compare baseline and 6 month follow-up: Dulaglutide naïve patients not on any SGLT2 inhibitor (*n*=47)

	Z score	*P*
HbA1c 6 months vs. baseline	−5.927	<0.001
Weight 6 months vs. baseline	−5.001	<0.001
FBG 6 months vs. baseline	−5.676	<0.001
PPBG 6 months vs. baseline	−5.836	<0.001

- Comparison with other select real-world published data (Efficacy: glycemic control and weight loss; discontinuation rates).[18,19]

Comparison with published RCT's

The Assessment of Weekly AdministRation of LY2189265 (dulaglutide) in Diabetes (AWARD) clinical trial program consists of nine completed RCT's (AWARD-1 to AWARD-6 and AWARD-8 to AWARD-10)[5-13] comparing dulaglutide 1.5 mg and/or dulaglutide 0.75 mg to a variety of commonly approved T2DM medications. Of the various parameters studied, the important ones relevant to our study (safety, efficacy, and tolerability) will be discussed. The AWARD trials included comparisons across the various stages of the T2DM treatment continuum: monotherapy[7] (AWARD-3), concomitant sulfonylurea (SU) (AWARD-8),[11] metformin (AWARD-5 and AWARD-6),[9,10] metformin and thiazolidinedione (TZD) (AWARD-1),[5] metformin, and SU (AWARD-2),[6] in combination with prandial insulin with or without metformin (AWARD-4),[8] titrated doses of Glargine (AWARD-9)[12], and SGLT2i (AWARD-10)[13] with a study duration ranging from 24 to104 weeks. The age mean of subjects in these trials[16] was 54.1 to 59.4 years (Our study: mean age of the subjects was 48.9 ± 9.1 years), mean HbA1c of 7.6 to 8.5%[16] (Our study: HbA1c at baseline 8.9 ± 1.6%), mean weight of 85.5 to 96.0 kg[16] (Our study: mean weight was 95.1 ± 15 kg), and pre-trial drug treatment for diabetes ranging from anti-hyperglycemic medication naive to third-line therapy. As we can see above in comparison to the RCT study population which is more homogeneous, real-world patient population includes a far more heterogeneous patient population. Hence, the data obtained from real-world studies further enhances the usability of dulaglutide across a far greater spectrum of patients who can, hence, be provided all the possible benefits of dulaglutide.

Efficacy (Glycemic control)

Consistently, dulaglutide has demonstrated early reduction in FBG and PPG, and it even reduces HbA1c in patients with T2DM as early as 4 weeks after the start of treatment.[7-9] The range of HbA1c reduction from baseline to the primary end point with dulaglutide (1.5 mg) in the AWARD trial was − 0.78% to − 1.64%.[16] In our real-world study population, we have demonstrated a statistically significant HbA1c reduction at 6 months of 0.87%, (Range:−3.1 to + 0.9%). Our study analysis indicates that patients with a greater HbA1c at baseline show a far superior HbA1c reduction that persists at the end of 6 months. This strengthens the fact that dulaglutide provides a durable (our data: 6 months) and efficacious glycemic control across a wide variety of patient populations with T2DM. Our study subset which included patients prescribed dulaglutide but not SGLT2i (*n* = 47), the mean HbA1c difference (reduction at 6 months) was 0.82%. Like in the total study population the subgroup analysis indicated significantly better glycemic control at 6 months of completed treatment. A statistically similar linear relation of baseline HbA1c to HbA1c change was seen in the subgroup [Figure 2c].

Efficacy (Weight reduction)

Excess weight or obesity is contributory not only to the development of T2DM but is definitely and independently linked to poor cardiovascular outcomes and other T2DM related comorbidities.[20] Another therapy related concern in patients on diabetes treatment is that some drugs, including insulin, SUs, glinides, and TZDs, are associated with weight gain.[21] This treatment related weight gain may not only offset the clinical benefits provided by superior glycemic control by increasing the cardiovascular disease risk but also may also discourage patients from initiating/enhancement of therapy for better glycemic control. In the AWARD clinical trials, patients experienced a weight change of −0.9 to −3.0 kg with dulaglutide 1.5 mg.[16] Comparatively, greater weight change

was seen in our study subjects (mean weight reduction was 3.8 kg at 6 months). The range (−25.4 to +3.9 kg) of weight change was very variable, which may possibly be explained by varied degree of compliance with life style changes or use of concomitant drugs (diabetes related and/or non-related) effecting weight. Although ideal, it was out of the scope of the present investigation to capture all these very relevant data. Weight changes in the study subset (not on SGLT2i) was −3.6 kg which was statistically significant at the end of 6 months of continuous dulaglutide treatment along with the standard of care therapy. Although a linear correlation was observed between the baseline weight and the mean weight change, it failed to reach statistical significance in the subgroup. This may be because of the less number of patients in the subgroup.

Safety (adverse side-effects)

The most frequent adverse side-effects (ASEs) associated with dulaglutide treatment are gastrointestinal including nausea, vomiting, and diarrhea. Across the AWARD study patients on dulaglutide: 8–29% of patients had nausea, 4–17% had vomiting, and 8–17% diarrhea.[16] Comparatively, in our study, we reported nausea in 15% and diarrhea in 6% of the T2DM subjects on dulaglutide. As per the RCT data, the ASEs are mild to moderate in severity, peak at 2 weeks, and rapidly decline over the next 4 weeks.[22] The majority of gastrointestinal side-effects are reported during the first 2–3 days after the initial dose and decline with subsequent doses.[22]

Discontinuation

In the AWARD studies, discontinuation of dulaglutide treatment in the study subjects because of ASEs (all included) was generally low with 1–11%.[5-13] Interestingly, in the AWARD-5 after 104 weeks of treatment, 21% of patients discontinued treatment.[9] Like the AWARD-5 study result, 25% ($n = 19$) of our real-world study subject also discontinued dulaglutide because of ASEs (gastrointestinal only).

Comparison with RCT on combination therapy of SGLT2i and long-acting GLP-RA

The DURATION-8 trial investigated the efficacy and safety of combination therapy including both SGLT-2i (Dapagliflozin) and a long-acting GLP1-RA (Exenatide QW) versus the two drugs given separately over a period of 52 weeks.[23] The study results indicated that a combination of SGLT2i and long-acting GLP1-RA were associated with greater HbA1c, weight, and BP reductions that either of the drugs given alone.[23] In contrast, our study did not show any statistical difference in either HbA1c or weight reduction at 24 weeks with the combination of SGLT-2i and dulaglutide when compared to dulaglutide alone. The possible reasons may be the limited number of patients, shorter duration of study, or a greater heterogeneity of our study population.

Comparison with other select real-world data

Two real-world studies have been used for comparison in this section.[17,18] Study 1 (S1) includes retrospective data from a cohort (38 million patients from 49 US states) obtained from the Quintiles Electronic Medical Record database (Q-EMR).[17] This real-world study describes the efficacy (glycemic control and weight changes) of once a week GLP-1RA's including dulaglutide ($n = 201$). The mean HbA1c reduction in S1 was −0.6% (SD: 1.5) for dulaglutide. At the end of the same time interval of 6 months as in our study, we observed an HbA1c reduction of 0.87% (total study group) and 0.82% (subgroup of subjects not on SGLT2i). At 6 months in S1 T2DM patients on dulaglutide lost −2.7 (SD: 5.7) kg.[17] Comparatively, our patients with T2DM in whom dulaglutide was introduced as an add-on treatment, lost greater weight [3.8 kg (total) and 3.6 kg (subgroup)] at the study end. Study 2 (S2) like S1 was a retrospective study with the data obtained from health insurance database of HealthCore Integrated Research Database.[18] The patients in S2 were distributed over the 50 US states and included 308 patients (on dulaglutide in combination with other standard of care treatment for T2DM).[18] The follow-up period was 6 months (similar to our study and S1). The HbA1c reduction in S2 was 0.9%.[18] This glycemic benefit is similar to what we have demonstrated − 0.87% (total study group) and −0.82% (subgroup of subjects not on SGLT2i). In S2 discontinuation, rates over 6 months in patients prescribed dulaglutide was 37% (>45 days between prescription fills).[18] An exact percentage (compared to S2) of our patients (43 out of 117 patients: 36.7%) of our study subjects discontinued dulaglutide because of various reasons [Table 1].

Conclusion

In conclusion, the once weekly GLP1RA dulaglutide, with its multiple clinical benefits, including effective and durable glycemic control, a sustained weight reduction, likely (minimal) blood pressure reduction and possible cardiovascular disease reduction, is a promising choice for optimal management of T2DM. It is majorly because of the above reason, that despite being injectable, GLP1RAs have been promoted in the hierarchy of treatment in the recently updated guidelines for the standards of care for optimal treatment of T2DM.[24]

A weekly injectable option of GLP1RA definitely adds to the convenience for the patient and, our real-world study has reinforced the clear benefits, validating further the evidence of its efficacy for the clinical parameters studied.

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Conflicts of interest

There are no conflicts of interest.

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