Original Article

Efficacy and Safety of Dulaglutide in Type 2 Diabetes Patients in Endocrinology Clinics of Islamabad, Pakistan

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Abstract

Objective: Our objective was to ascertain the efficacy and safety of once weekly Dulaglutide among patients with Type 2 diabetes of Pakistani origin. **Methods:** This prospective cohort study was conducted at the Endocrinology Clinics of Shifa International Hospital, Islamabad and Umar Diabetes and Foot Care Centre, Islamabad, Pakistan during the period from July 2020 to December 2020. Dulaglutide at the dose of 1.5 mg once weekly was initiated in patients with BMI >28 and suboptimal glucose control in the background of Type 2 Diabetes who were also taking one or more of oral anti-diabetic and/or insulin therapy. **Results:** Mean age of patient cohort (n = 148) was 49.51 years (SD +/- 12.15) with 53.5% (n = 85) having type 2 diabetes for a duration of over 10 years. Mean weight was 93.2 kg at baseline with end of study mean weight being 90.7 kg. Mean HbA1c at baseline was 9.2%, which improved to 8.05% at the end of study. The main side-effects were nausea in 32%, vomiting in 8%, and diarrhea in 7% with 19% discontinuation rate due to cost and side-effects. **Conclusion:** Dulaglutide as a therapy demonstrated favorable HbA1c and weight reduction in obese type 2 diabetes patients of Pakistani origin.

Keywords: Dulaglutide, real world evidence, type 2 diabetes

Introduction

Type 2 diabetes mellitus is a complex metabolic condition defined by deranged glucose regulation. The incidence is rising exponentially with numbers tripled within the last two decades from under 19 up to over 45 million, and this is expected to double by 2045.[1] This rapid increase is primarily due to increasing prevalence of obesity and overweight and reduced physical activity.[2] Even more concerning is the skewed distribution and it is estimated that 80% of world's population with diabetes will be living in countries with low socioeconomic status by 2045.[3]

Cardiovascular diseases are the leading cause of death globally and diabetes is an independent risk factor with the risk of cardiovascular diseases over two fold, despite addressing other cardiac risk factors.[4] It is therefore strongly desired to have access to pharmacotherapies that manage glycemic control in addition to providing cardiovascular benefit and reduce all-cause mortality.[5] Fortunately, two emerging classes of anti-diabetic therapies have shown a ray of hope to meet this cardiometabolic goal.[6] Among them, glucagon like peptide (GLP-1) agonists are now established class of therapies that are designed to exploit gut incretin phenomenon thereby enhancing insulin secretion in response to oral glucose load in the form of meal. The CVOT trials demonstrated additional advantages in terms of cardiovascular, weight, and multiple pleiotropic benefits thus securing them an established place as second line therapies in diabetes management, in particular, in the presence of established cardiovascular disease or risk factors.[7]

Pakistan, a South Asian country, currently ranks fourth in terms of diabetes prevalence and this number is expected

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to rise placing third in the next 15 years.[8] This necessitates urgent measures to develop comprehensive strategies both in primary prevention by addressing risk factors of diabetes as well as to afford cost-effective evidence-based anti-diabetic therapies to Pakistani population in pace with global practice.[9] Unfortunately, despite high prevalence of diabetes and impaired glucose tolerance in south Asian countries, population from this part of the world is underrepresented in major international trials. This leads to an uncertainty for a physician practicing in these countries to offer therapies with cardiovascular benefits in the absence of data pertaining to desired benefits seen in other ethnicities enrolled in trials.

GLP-1 agonist, specifically once weekly dulaglutide, has proven to be an effective therapy both in optimizing glycemic control and in reducing cardiovascular risk.[10] Additionally, it is distinguished from other GLP-1 agonists currently available with evidence to demonstrate its role in primary prevention. Despite these advantages, these drugs are expensive and require careful patient selection that is deemed to derive most benefits. Due to lack of reliable evidence base confirming benefits of dulaglutide in Pakistan population, we sought to assess its efficacy and safety in Pakistani cohort, and to ascertain if metabolic benefits in terms of improved glycemic control and weight as observed in international trials are replicated in our cohort.

Methods

This was an observational, non-randomized, prospective follow-up real world study conducted in the endocrinology clinics of Shifa International Hospital, Islamabad and Umar Diabetes and Foot care Centre, Islamabad. As a real world study, physicians prescribed dulaglutide in eligible candidates in addition to other therapies upon their discretion to optimize glycemic control. Data collection form was designed to collect patient demographic characteristics (age, gender, education, and occupation), weight, HbA1c, serum creatinine level and adverse events throughout the study period.

The physician designated an initial visit as baseline data collection time point with initiation of dulaglutide and end point was the follow-up visit after 6 months. Study population were the diabetic patients visiting the Outpatient clinic of Department of endocrinology, Shifa International Hospital, Islamabad and Umar Diabetes and Foot Care center, Islamabad, from July 2020 to December 2020, and meeting predefined inclusion criteria including patients older than 18 years and of either gender and having type 2 diabetes for at least 6 months before enrollment to study. At least one prescription of dulaglutide was required to include participants in final analysis.

Statistical analysis was performed by SPSS version 21 (IBM, Armonk, NY, USA). Ethical approval was obtained from IRB Shifa International Hospital and date of approval was 17th August 2020.

Results

Data was analyzed for 148 participants, 57.40% (n = 85) being male and 42.60% (n = 63) being female, having a mean age of 49.51 (SD ± 12.15) years. A large proportion of the participants was employed in private sector (44.6%, n = 66), whereas 36.5% (n = 54) were unemployed. Majority had attained minimum expected education at primary school level, with 47.3% (n = 70) having completed secondary school, and 38.5% (n = 57) having completed college education.

The mean duration between participants' diagnosis and initiation of therapy for Type 2 DM for enrollment in this study was 11.63 years (SD ± 7.49). Mean weight was 93.70 kg (SD ± 17.85 kg) at baseline with a mean BMI of 33.64 (SD ± 6.82). Mean resting heart rate (RHR) was 77.45 (SD ± 6.46), whereas mean HbA1c was 9.34 (SD ± 1.92) and mean serum creatinine level was 0.85 (SD ± 0.401) [Table 1].

About 63.7% (n = 93) participants suffered from dyslipidemia, 16.9% (n = 25) suffered from hypertension, 16.9% (n = 25) had coronary artery disease, 11.6% (n = 17) had retinopathy, 26.4% (n = 39) had neuropathy, and 20.9% (n = 31) had nephropathy [Table 1].

Prior to starting Dulaglutide, study participants were being treated with maximum doses of sulfonylureas in 45.2% (n = 66), metformin in 98% (n = 145), DPP-4 inhibitors in 67.3%, basal insulin in 38.1%, (n = 56), pre-mixed insulin in 39.9% (n = 59), and basal insulin bolus regimen in 19.6% (n = 29) either alone or in combination before addition

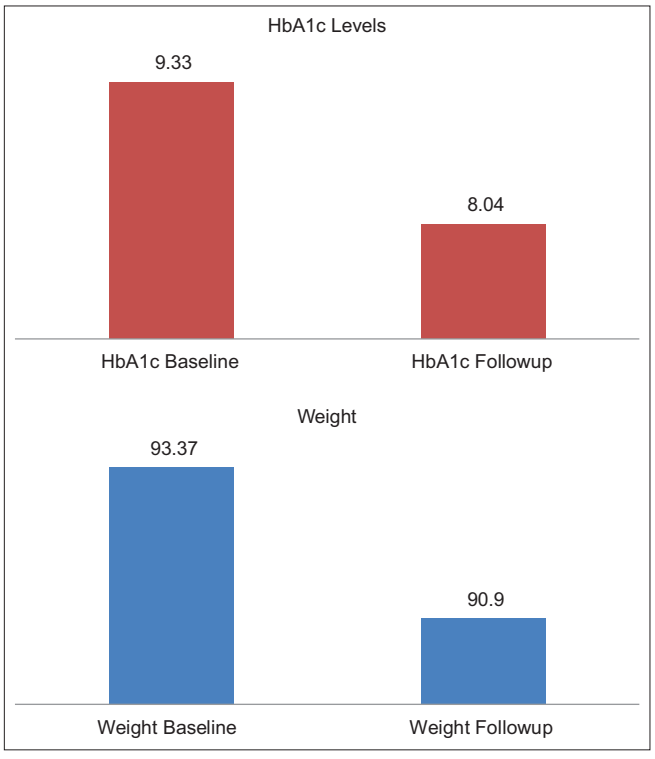

Figure 1: Change in HbA1c and Weight at baseline and at 6 months

Table 1: Participant characteristics and outcomes, *n*=148

Dulaglutide Study Table - 1		
Age	49.5±12.2	
Gender		
Male	85 (57.4%)	
Female	63 (42.6%)	
Duration of Diabetes (Years)	11.6±7.5	
Participants on Sulfonylurea	66 (45.2%)	
Participants on Metformin	145 (98.0%)	
Participants on Thiazolidinedione	3 (2.0%)	
Participants on DDP4 Inhibitors	103 (69.6%)	
Participants on OtherGLP1RA	7 (5.0%)	
Participants on BasalInsulin	56 (38.1%)	
Participants on PreMixedInsulin	59 (39.9%)	
Participants on BasalBolusRegimen	29 (19.6%)	
Participants on Dulaglutide		
0.75 mg once weekly	1	
1.50 mg once weekly	147	
	Before Dulaglutide (Baseline)	**After Dulaglutide (Follow-up)**
Creatinine level	0.85±040	1.6±8.7
HbA1c level	9.34±1.92	8.0 1.4
Pulse (beats/min)	77.4±6.5	78.3 10.0
Weight (kg)	93.4±17.9	90.9±16.7
BMI	33.64±6.83	33.18±8.12
Diastolic Blood Pressure (mmHg)	82.17±8.77	79.24±7.70
Systolic Blood Pressure (mmHg)	128.92±15.55	122.26±12.59
Presence of Dyslipidemia	93 (63.7%)	84 (57.1%)
Presence of Hypertension	75 (50.7%)	69 (46.6%)
Presence of Coronary Artery Disease	25 (16.9%)	23 (15.6%)
Presence of Retinopathy	17 (11.6%)	20 (13.7%)
Presence of Neuropathy	39 (26.4%)	29 (19.7%)
Presence of Nephropathy	31 (20.9%)	28 (19.0%)

Table 2: Results of paired samples *t*-test

Paired Samples Test								
	Paired Differences					*t*	df	Sig. (2-tailed)
	Mean	Std. deviation	Std. error mean	95% confidence interval of the difference				
				Lower	Upper			
HbA1c at Baseline	1.29358	1.47033	0.12086	1.05473	1.53243	10.703	147	0.000
HbA1c at Follow-up								
Pulse at Baseline	-0.9116	10.5083	0.8667	-2.6245	0.8013	-1.052	146	0.295
Pulse at Follow-up								
BMI at Baseline	0.52537	8.22030	0.68983	-0.83838	1.88912	0.762	141	0.448
BMI at Follow-up								
Creatinine at Baseline	-0.75712	8.71259	0.75833	-2.25729	0.74304	-0.998	131	0.320
Creatinine at Follow-up								
Systolic BP at Baseline	6.65541	12.04284	0.98992	4.69910	8.61171	6.723	147	0.000
Systolic BP at Follow-up								
Diastolic BP at Baseline	2.92568	7.12292	0.58550	1.76859	4.08276	4.997	147	0.000
Diastolic BP at Follow-up								

of Dulaglutide to the treatment regimen [Table 1]. DPP-4 inhibitors were discontinued once dulaglutide was introduced and dosage of other medications was adjusted.

After intervention was initiated, mean HbA1c reduced to 8.04% at follow-up, which was statistically significant (p value <0.05) in our study. Mean reduction in weight

between baseline and follow-up assessment was 2.46 kg, although this was not statistically significant [Figure 1]. There was no significant difference noted between baseline and follow-up groups in terms of blood pressures, pulse rates, serum creatinine, or BMI [Appendix 1 and Table 2].

The main side-effects reported in our study group after start of Dulaglutide was of gastrointestinal nature with nausea reported in 32%, vomiting in 8%, and diarrhea in 7% of study participants. Around 2% of participants reported other side-effects including headaches and dizziness. In addition, Dulaglutide was discontinued in 19% of our study population mainly due to cost and side-effects.

Discussion

Dulaglutide is the first weekly GLP-1 agonist approved to be used in clinical practice in Pakistan. Although, established as a safe and effective therapy in the management of type 2 diabetes, there is insufficient study data pertaining to safety and efficacy of dulaglutide in diabetes population of Pakistani origin. Major international trials have shown Dulaglutide to be an effective treatment for type 2 diabetes with an acceptable tolerance and safety profile.[5-7] The Award 1-5 programme comprising phase 3 trial studies for dulaglutide, demonstrated mean HbA1c reduction between 0.7 and 1.48% and weight loss ranging between 0.4 and 2.9 kg when drug is administered at 1.5 mg weekly dosage for 26–52 weeks, either as monotherapy or in comparison with Sitagliptin, Exenatide or insulin Glargine.[11,12] Our study has demonstrated and confirmed similar findings with mean reduction of HbA1c by 1.2% and body weight of 2.46 kg following 6 months' use in local Pakistani population.

Similar to other GLP-1 agonists, the most common, albeit transient in majority, side-effects observed with Dulaglutide are gastrointestinal in origin (nausea, vomiting, and diarrhea). AWARD trials reported nausea and vomiting as side-effects in 15– 29% and 6–17% of the study cohort on dulaglutide 1.5 mg weekly, respectively.[12] This was broadly similar to our study, which showed nausea in around 32% of patients and vomiting in 8% of patients taking dulaglutide 1.5 mg weekly.

Since 2016, the only other approved GLP-1 agonist in Pakistan is once daily liraglutide.[13] Real-world data derived from retrospective observational study from Pakistan has shown mean HbA1c reduction between 0.94 and 1.76% at 3–6 months with liraglutide and the mean weight loss of 1.38–5.43 kg.[13,14] While the maximum licensed dose of liraglutide is 1.8 mg once daily, average administered dose in Pakistan remains 1.2 mg daily primarily due to cost issues.[14] In comparison, our present study has shown that fixed dose once weekly dulaglutide has comparable efficacy to liraglutide in terms of glycemic control and weight loss with no significant cost difference. This is in addition to significant reduction in the number of injections with 52 injections yearly with dulaglutide compared with 365 injections with liraglutide, thus leading to better patient satisfaction and adherence.

Strengths and limitations

The strength of the study derives from the fact that this is the first study aimed at ascertaining feasibility, efficacy, and safety of once weekly GLP-1 agonist in Pakistani population. As an observational, real world study, the participants in this study represent people with type 2 DM routinely seen in secondary and tertiary care centers with poorly controlled type 2 DM (mean baseline HbA1c 9.34%) and a host of associated co-morbidities. This, therefore, provides evidence in the use and benefit of dulaglutide in routine practice at discretion and judgment of the prescribing physician. This is particularly beneficial when considering a relatively expensive drug such as dulaglutide to be prescribed in specific cohort of population who are otherwise underrepresented in controlled trials.

In accordance with the nature and characteristics of real world studies, there are inherent limitations in our study, the primary being lack of structured randomization and controlled settings that reduces the validity and significance of study outcome. The study duration is relatively short, which further limits the strength of data when considering long-term safety and efficacy. Furthermore, a prospective design is associated with bias and confounding factors, which must be taken into account when interpreting findings. Indeed, we were unable to assess the effect of dulaglutide on lowering systolic blood pressure and lipids level owing to incomplete data.

Nevertheless, our study, despite limitations in its scope and duration, achieved its primary purpose, which was to assess the efficacy of once weekly dulaglutide in improving glycemic control and its weight loss effect in Pakistani cohort. It provides useful and clinically meaningful information to healthcare professionals practicing in Pakistan and the data derived from this study will add to the confidence and serve its informative purpose when making prescribing decisions for dulaglutide in Pakistani population.

Further large scale studies incorporating multiple centers with larger study cohort and duration as well as assessing cardiovascular and cost benefits are warranted to further strengthen the utility of dulaglutide in Pakistani population.

Conclusion

Our study has demonstrated that Dulaglutide is a safe and effective treatment in improving glycemic control and weight loss in people with type 2 diabetes of Pakistani origin.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Appendix 1: Paired samples test

	Paired Differences					*t*	df	Sig. (2-tailed)
	Mean	Std. deviation	Std. error mean	95% Confidence Interval of the Difference				
				Lower	Upper			
Weight at Baseline Weight at Follow-up	2.4627	11.6758	0.9798	0.5256	4.3997	2.513	141	0.013
Serum Cr at Baseline Serum Cr at Follow-up	-0.75712	8.71259	0.75833	-2.25729	0.74304	-0.998	131	0.320
Serum HbA1c at Baseline Serum HbA1c at Follow-up	1.29358	1.47033	0.12086	1.05473	1.53243	10.703	147	0.000
Pulse at Baseline	-0.9116	10.5083	0.8667	-2.6245	0.8013	-1.052	146	0.295
Pulse at Follow-up								
BMI at Baseline	0.52537	8.22030	0.68983	-0.83838	1.88912	0.762	141	0.448
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