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First Fabulous Fifty – An Initial Experience of Dulaglutide from a Tertiary Care Centre in Eastern India

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Abstract

Objective: This retrospective single centred real world observational study was undertaken with the aim to introspect the glycaemic control, weight loss, changes in lipid parameters, adverse events and treatment adherence with Dulaglutide therapy.

Methodology: Single centered, retrospective, real world, observational study conducted on subjects taking liraglutide for a mean duration of 41 weeks in the endocrine out-patient department.

Results: Data of 45 subjects were available. Mean age was 46.67 ± 5.53years. Glycosylated haemoglobin (HbA1c) significantly decreased from 8.68 ± 0.43% at baseline to 7.58 ± 0.19% at end of therapy. Body weight significantly reduced from 74.2 ± 8.07 kg at baseline to 69.27 ± 4.74kg at end of therapy and BMI significantly declined from 33.06 ± 4.5 to 30.09 ± 0.93 at end of therapy respectively. Nausea, vomiting and diarrhoea (15.55%) were the major adverse events noted in the study. Only one patient developed acute pancreatitis (2.22%).

Conclusion: Treatment with Dulaglutide resulted in clinically meaningful HbA1c, FPG and weight reductions. The overall safety profile is consistent with the GLP-1 receptor agonist class. However, Dulaglutide did not show statistically greater reduction of glycaemic parameters in the subset of Indian patients compared to RCT data of Western population.

Keywords: *Dulaglutide, obesity, Indian, type 2 diabetes*

Introduction

Glucagon-like peptide-1 (GLP-1) agonists act at GLP-1 receptors in pancreatic beta cells to increase glucose-dependent insulin secretion, in pancreatic alpha cells to decrease glucagon release and slow gastric emptying. Over the years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become integral in diabetes management as demonstrated by various publications from India [1–7]. Short-acting GLP-1 RAs requires either a once-daily (e.g. liraglutide) or twice-daily dosing (e.g., exenatide and lixisenatide). Studies published as back as 2005 from India by Vijan et. Al [8]. Showed that the injection burden was definitely an issue to be considered. When adherence to injectable treatment was looked into, the increased number of injection burden was found to be responsible for missed doses and non-adherence to treatment (GAAP study) [9]. Dulaglutide is longer acting GLP-1RA for the treatment of type 2 diabetes mellitus (T2D) and requires once-weekly dosing [10]. Hence the launch of Dulaglutide since march 2016 in India, the novel once weekly GLP1 RA was an welcome step and expected to increase the adherence to GLP1 RA treatment. However, adverse effects if any with one shot of the weekly once Dulaglutide would carry on for the entire week relentlessly. This retrospective single centred real world observational study was undertaken with the aim to introspect the glycaemic control, weight loss, changes in lipid parameters, adverse events and treatment adherence with Dulaglutide therapy.

Materials and Methods

This retrospective real world observational study was conducted in the Endocrinology Department of KPC Medical College and Hospital. It is a 700 bedded tertiary care hospital, situated in the southern fringes of the city of Kolkata, in the eastern part of India. The Endocrine out-patient database was frisked to tease out the initial 50 patients who were prescribed Dulaglutide over and above standard of care (with the exception that DPP 4 inhibitors if any on board) and weren't lost to follow-up thereafter irrespective of the fact whether they were able to initiate or carry on Dulaglutide therapy continuously or not. No patients with e GFR <30, family history of medullary carcinoma of the thyroid and history of pancreatitis were offered the Dulaglutide as a standard of care of the Department.

The inclusion and exclusion criteria used while selecting the cohort of patients were as follows:

Inclusion Criteria:

1. Adult type 2 diabetes between 18–75 year age
2. HbA1C >= 7% and < 11% on a combination of OAD ± insulin

3. First 50 patients to be prescribed Dulaglutide therapy and who came for a second follow up irrespective of whether he/she had started Dulaglutide.

Exclusion Criteria:

1. Patients who were initially prescribed Dulaglutide but were lost to follow up after 1st visit
2. Pregnancy
3. Hospitalisation during follow-up

Statistical Analysis

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SEM and results on categorical measurements are presented in Number (%). Significance is assessed at a level of 5 %.

The following assumptions on data are made.

Assumptions:

1. Cases of the samples should be independent.
2. The populations from which the samples are drawn have the same variance (or standard deviation).
3. The samples drawn from different populations are random.

Normality of data tested by Anderson Darling test, Shapiro-Wilk, Kolmogorov-Smirnoff test and visually by QQ plot. Paired t-test has been used to find the significance of study parameters within groups of patients measured on two occasions.

Statistical software: The Statistical software namely SAS (Statistical Analysis System) version 9.2 for windows, SAS Institute Inc. Cary, NC, USA and Statistical Package for Social Sciences (SPSS Complex Samples) Version 21.0 for windows, SPSS, Inc., Chicago, IL, USA were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs and tables.

Results and Analysis

In the present analyses, a total of 50 patients with T2D were included out of which 45 did actually initiate the drug as was revealed in the first follow-up visit. Patient numbers for gender, age, height, BMI, duration of diabetes, baseline blood pressure, FPG, PPPG, HbA1c, Cholesterol, HDL, LDL, TG and duration of follow up are listed in Table 1. Out of 45, 24 were female and 21 were male having a mean age of 46.67 ± 5.53 years .The patients had a mean height, mean body weight of 74.2 ± 8.07 kg and mean BMI of 33.06 ± 1.47 kg /m^2. The mean FPG was 169.18 ± 11.38 mg/dl, PPPG was 222.46 ± 23.77 mg/dl and mean Hba1c was 8.68+- 0.43% before the initiation of Dulaglutide. The baseline demographic and clinical characteristics of the study subjects are enumerated in (Table 1). Post analysis it was revealed that the mean follow up period for the 45 patients who ultimately initiated dulaglutide therapy was 41.2 ± 11.71 weeks.

HbA1c, FBG reductions and weight changes

All the glycaemic parameters viz. FPG, PPPG and HbA1C had statistically significant reductions, with the respective p values achieved being 0.044, 0.018 and 0.032 during the study period. FPG was reduced by 31.14 ± 0.17 mg/dl, PPPG was reduced by 53.02 ± 10.52 mg/dl and HBA1C was also reduced by 1.10 ± 0.24%. (Table 2) In this small subgroup of patients 22.2% achieved a target HBA1C of less than 7% and 55.56% achieved a target of less than 7.5%, which is a significant proportion considering the fact that the average HBA1C of Indian Diabetic patients undergoing treatment is far higher than this (18). 26.67% of patients were able to achieve a reduction of greater than 1% HBA1C , 17.78% achieved a reduction between 0.5%-1.0%, however interesting is the fact that 37.78 % showed no change in HBA1C and 13.33 % were showing an increased HBA1C than that at baseline (Table 3, 4).

Table 1. Baseline Characteristics of the Patients (N = 45)

Demographic & Clinical Profile	Values
Male, n (%)	21 (46.67)
Female, n (%)	24 (53.33)
Age(years), Mean ± SEM	46.67 ± 5.53
Height (centimeters), Mean ± SEM	161.63 ± 11.42
Body weight (Kg), Mean ± SEM	74.2 ± 8.07
SBP (mmHg), Mean ± SEM	133.68 ± 12.11
DBP (mmHg), Mean ± SEM	84.03 ± 10.51
BMI (kg/m^2), Mean ± SEM	33.06 ± 1.47
BMI – 23 -29.9	22 (48.89%)
BMI - 30–34.9	11 (24.44%)
BMI - 35–39.9	11 (24.44%)
BMI - ≥ 40	1 (2.22%)
FPG (mg/dL), Mean ± SEM	169.18 ± 11.38
PPPG (mg/dL), Mean ± SEM	222.46 ± 23.77
HbA1c(%), Mean ± SEM	8.68 ± 0.43
Total Cholesterol (mg/dL), Mean ± SEM	165.68 ± 6.23
LDL- Cholesterol (mg/dL), Mean ± SEM	115.06 ± 27.2
HDL- Cholesterol (mg/dL), Mean ± SEM	42.35 ± 1.70
Triglycerides (mg/dL), Mean ± SEM	189.87 ± 12.35
Duration of follow-up (weeks), Mean ± SEM	41.2 ± 11.71

Table 2. Change in study parameters during the follow-up period, (N = 45)**

Parameter	Baseline Mean ± SEM	Follow-up** Mean ± SEM	P value
Body weight (kg)	74.2 ± 8.07	69.27 ± 4.74	<0.001
BMI (kg/m^2)	33.06 ± 1.47	30.09 ± 0.93	0.041
SBP (mmHg)	133.68 ± 12.11	130.92 ± 3.63	0.731
DBP (mmHg	84.03 ± 10.51	81.65 ± 8.03	0.930
FPG(mg/dl)	169.18 ± 11.38	138.04 ± 11.21	0.044
PPPG(mg/dl)	222.46 ± 23.77	169.44 ± 13.25	0.018

Parameter	Baseline Mean ± SEM	Follow-up** Mean ± SEM	P value
HbA1c (%)	8.68 ± 0.43	7.58 ± 0.19	0.032
Total Cholesterol (mg/dL)	165.68 ± 6.23	142.11 ± 6.17	0.020
LDL- Cholesterol (mg/dL)	115.06 ± 27.2	71.95 ± 5.57	0.43
HDL- Cholesterol (mg/dL)	42.35 ± 1.70	42.26 ± 3.15	0.178
Triglycerides (mg/dL)	189.87 ± 12.35	137.21 ± 10.05	0.068
p < 0.05 considered as statistically significant, p computed by paired-t-test, ** Calculated as per the data available at last follow-up visit			

Table 3. Proportion of patients achieving HbA1c less than 7%, 7%-7.5%, 7.5%-8.5% and beyond, (N = 45)

Follow-up HbA1c (in %)	Number of subjects	% of subjects
<7%	8	17.78
7%-7.5%	10	22.22
7.5–8.5%	8	17.78
>8.5%	2	4.44
Drop-out	17	37.78

Table 4. Change in HbA1c from baseline to follow-up, (N = 45)

Change in HbA1c (in %)	Number of subjects	% of subjects
Drop of 1% and more	12	26.67
Drop of 0.5% to 1%	8	17.78
Drop of less than 0.5%	2	4.44
Increase from baseline	6	13.33
Drop out at 3 months	17	37.78

The statistical analysis of the cohort of 45 patients revealed a weight loss of 4.93 ± 3.33 kg which had a p value of <0.001 and thereby also achieved a statistically significant reduction in BMI from an initial value of 33.06 ± 1.47 kg/m^2 to 30.09 ± 0.93 kg/m^2 (p value 0.041). (Table 2) Weight benefits were more robust with 40% showing a weight loss of 5% or less from the baseline and another 20%showing a weight loss between 5.1–10 % from the baseline. 3 patients who had Insulin and Pioglitazone on board showed an increase in weight from the baseline and as many as 28.87% of patient showed no appreciable change in bodyweight despite addition of Dulaglutide reiterating the presence of non-responders to GLP 1 RA therapy with respect to reduction of weight (Table 5).

Table 5. Percentage Change in Weight during the 3 months follow-up period, (N = 45)

	Number of subjects	% of subjects
Weight gain	3	6.67
Weight loss (Less than 5%)	14	31.11
Weight loss (5.1% to 10%)	9	20
Weight loss (Greater than 10%)	2	4.44
Drop out	17	28.89

Blood pressure and lipid changes

When the blood pressure and lipid data of the 45 patients were analysed, systolic and diastolic pressure did not show any statistically significant reduction and amidst the lipid parameters only the total cholesterol values showed a significant reduction with a p value of 0.20 (Table 2).

Hypoglycaemia Gastrointestinal adverse events

Nausea, vomiting and diarrhoea (15.55%) were the major adverse events noted in the study. Only one patient developed acute pancreatitis (2.22%). Ten patients (22.22%) had to discontinue Dulaglutide due to financial constraints. (Table 6, 7)

Table 6. Reason for Drop-out

Reason for Drop-out	Number of subjects	% of subjects
Financial constraint	10	22.22
Nausea/Vomiting	6	13.33
Acute Pancreatitis	1	2.22
Diarrhea	1	2.22

Table 7. Adverse Effect Profile

Reason for Drop-out	Number of subjects	% of subjects
Nausea/Vomiting	6	13.33
Acute Pancreatitis	1	2.22
Diarrhea	1	2.22

Discussion

In this analysis of the 45 patients who (out of the 50 patients prescribed) we observed significant reduction of HbA1c with the initiation of Dulaglutide which was similar in either sex and as expected with all anti diabetic agents the fall was greater in the group with a higher baseline HbA1c (8.5% and above) and the drop of HbA1c achieved was 1.1 ± 0.24%. Fasting plasma glucose was reduced by 31.14 ± 0.14 mg/dl and the post prandial values dropped by 53.02 ± 10.52 mg/dl at the end of the analysis period. The change in the glycaemic indices namely HbA1c, FPG and PPPG all achieved statistical significance with p values of 0.032, 0.044 and 0.018 respectively.

Amidst the other parameters measured and the lipid parameters did not achieve statistical significance - except for the total cholesterol value which showed a drop of 23.57 ± 0.06 mg/dl and had a p value of 0.020 which was statistically significant. Weight however showed an overwhelming drop of 4.93 ± 3.33 kg and BMI also showed a drop of 2.97 ± 0.54 kg/m^2 -both thus achieving statistical significance with p values of < 0.001 and 0.041. When we compare this data with the data of the various AWARD trials some stark differences do stand out all of which can perhaps be explained and some of which can be expected as a part of standard differences which occur in between RCTs and RWE (real world evidence) generated data. Dulaglutide being an once weekly GLP-1RAs is structurally a large molecule and is expected to have a more profound action over fasting plasma glucose

rather than on the post prandial plasma glucose levels [11], however in this real world generated data the same was not reflected due to the heterogeneity of concomitant anti diabetic medication which perhaps played a differential role in the control of fasting and post prandial blood glucose levels. AWARD 3 assessed dulaglutide monotherapy at 1.5 gm dose over a 52 week period and achieved an HbA1C reduction of 0.78 ± 0.06 % and this data from the series of AWARD studies was less than the HbA1c reduction achieved in the subset of patients which we included in our study cohort [12]. AWARD 2 studied the effect of Dulaglutide on top of existing glimepiride and metformin therapy and over a period of 72 weeks and the HbA1c reduction of 1.08 ± 0.06 achieved, was a wee bit less than that achieved in our subjects; who, however had a mean duration of follow up of just over 41 weeks [13]. AWARD 1 studied Dulaglutide 1.5 mg in addition to Pioglitazone (30- 45 mg) and Metformin (2000- 3000mg) over a period of 24 weeks and showed a robust reduction of HbA1c of -1.51 ± 0.06 which was substantially greater than that achieved in our real world study of just over 41 weeks [14]. This discrepancy between the two reductions achieved may be attributed to the fact that both Pioglitazone and Metformin were used in lower doses of 7.5–15 mg and 1500–2000 mg respectively. AWARD-4 [15] studied prandial doses of insulin Lispro in addition to Dulaglutide over a period of 26 weeks and the combination achieved the highest HbA1c reduction of -1.64%(95% CI -1.50 to - 1.78) and AWARD-10 studied effect of Dulaglutide 1.5 mg and SGLT2 inhibitor combination over a similar time period and achieved a HbA1c reduction of 1.34% [16]. The HbA1c reductions in these two RCTs were however significantly more than that achieved in our real world data of just over 41 weeks of Dulaglutide therapy.

In general, Incretin based therapies are more efficacious in the south-east Asian population suffering from Type 2 Diabetes than in their counterparts coming from the Western world [17]. With the previously available once daily GLP1RA – Liraglutide; the Indian experience (1–7) when taken together also showed superior glycaemic control and weight reduction than all the LEAD trials [18] which were RCTs performed with the same drug in Western population used at a dose of 1.8 mg /day – a dose which was not always used in the Indian real world studies. Doses as low as 0.6 mg/day were used and 1.2 mg/day rather than 1.8mg/day was the most frequently used dosage) [19].

The weight loss achieved by the subjects in this real world study is quite robust – a loss of 4.93 ± 3.33 kg. Considering the impact of weight loss on remission of diabetes as shown in the DIRECT trial [20] published in The Lancet, this weight loss, if it can be sustained over longer periods may have substantial role to play in redirecting the future management of diabetes in these subjects. If we closely assess the data 15 out of 50 subjects were not able to carry on Dulaglutide and dropped out on economic grounds. Of these, five patients came back to state that although prescribed reconsidering their finances they were unable to start the drug. Of the rest, ten more patients dropped out within the observation period, cumulating to a drop-out rate of 30% within the first year. GLP-1 RAs usually are thought to exert their cardiovascular benefit via modification of the atherosclerotic pathway [21] due to the delayed bifurcation of the outcomes graph in contrast to that of SGLT2 inhibitors [22]. Thus choosing the right patient who can carry on the GLP-1 therapy for longer periods to harness the CV outcome benefits also should be a clinical consideration before initiating the therapy.

GI Side effect and Drop-out

The incidence of gastrointestinal adverse events on dulaglutide treatment was observed in 41.47 % of patient's. Out of 45 subjects, 18 had stopped treatment. Limitations in these analyses restrict the application of these data to the larger population of patients with T2D. No placebo or active comparator data were included in the analyses. The number of patients was small and may not necessarily be representative of the entire T2D patient population in clinical practice. The mean duration of diabetes of years and the mean age of 46 years were typical for the real world study, but may differ from the wider T2D population. Moreover, the durations of the study in the present analysis were limited to 32.2 weeks, which may not reflect the effect of longer-term use of dulaglutide.

Conclusion

Treatment with dulaglutide resulted in clinically meaningful HbA1c, FBG and weight reductions. The overall safety profile is consistent with the GLP-1 receptor agonist class. However, Dulaglutide did not show statistically greater reduction of glycaemic parameters in the subset of Indian patients compared to RCT data of Western population.

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