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Research Article

Comparing the Efficacy and Tolerability of Oral Semaglutide and Weekly Injectable Dulaglutide: A Real-World Indian Experience

Binayak Sinha[1], Samit Ghosal[2*], Gangopadhyay KK[3], Debmalya Sanyal[4], Subir Ray[5], Anirban Mazumdar[4]

[1]Department of endocrinology, AMRI hospitals, Kolkata, India

[2]Department of internal medicine, Nightingale hospital, Kolkata, India

[3]Department of endocrinology, CK Birla Hospitals, Peerless Hospital, Kolkata, India

[4]Department of endocrinology, KPC medical college, Kolkata, India

[5]Department of endocrinology, Apollo hospitals, Kolkata, India

[*]**Corresponding author:** Samit Ghosal, Department of internal medicine, Kolkata- 700071, India

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Abstract

Background: Injectable dulaglutide (D) and oral semaglutide (S) are the two commonly used glucagon like peptide 1 receptor analogues (GLP1-RA), with minimal real-life comparative evidence in Type 2 Diabetes (T2D). Thus, a retrospective, multi-center, cohort study was conducted to compare them.

Materials and methods: A total of 243 patients with T2D from Kolkata, India, were started on D (n=89), S 3 mg (n=92), and S 7 mg (n=62). Anthropometric, clinical, and laboratory parameters were noted with doses of D (1.5 mg once a week), S 3 mg, and S 7 mg at baseline and at 3 months follow-up. ANOVA (2 group comparison) and Tukey's method (3 group comparison) was used for hypothesis testing of the mean difference (MD) using standard statistical software.

Results The baseline characteristics were matched except for duration of T2D. Individually S and D reduced weight, HBA1C, Systolic Blood Pressure (SBP), and alanine Aminotransferase (ALT) which was statistically significant. Comparing S 3 mg and 7 mg with D revealed a differential impact on weight with all other parameters being comparable. D 1.5 mg had greater weight loss compared to S 3 mg (-1.42, 95% CI -2.69 to -0.17), and a comparable outcome (0.85, 95% CI -0.44 to 2.15) with S 7 mg. In both groups the predominant adverse effect was gastrointestinal in nature.

Conclusion: Both D and S significantly improved anthropometric and metabolic parameters in this multi-centre cohort of T2D. D 1.5 mg was superior to S 3 mg in weight reduction, while other parameters were comparable.

Keywords: Dulaglutide; Semaglutide; Retrospective; Comparison

Introduction

Glucagon Like Peptide 1 Receptor Agonists (GLP-1RA) have revolutionized the management of type 2 diabetes (T2D). Apart from a significant impact on the metabolic parameters (glycemic control and weight reduction), GLP1-RA are capable of imparting organ-specific protection [1]. The LEADER trial, with liraglutide revealed a significant reduction in Major Adverse Cardiac Events (MACE) and Cardiovascular (CV) death [2]. Subsequent trials documented benefits in stroke (REWIND), Myocardial Infarction (HARMONY) and renal outcomes (FLOW trial) [3-5]. However, this data exists only with injectable GLP1-RAs.

Oral semaglutide, the first oral GLP1-RA, has been available in India since January 2022 [6]. In the absence of a dedicated cardiovascular or renal outcomes data, the positioning of oral semaglutide was aimed at achieving superior metabolic control compared to the prevalent standard of care. The randomized controlled PIONEER trials helped position oral semaglutide across the spectrum of diabetes management, from early diabetes (PIONEER 1) to T2D with mean duration of 15 years (PIONEER 8) [7,8]. In PIONEER 1 the mean glycosylated haemoglobin (HBA1C) reduction was 1.2% with 7 mg oral semaglutide and 1.4% with 14 mg oral semaglutide, and the mean reduction in weight was 1 kg with 7 mg oral semaglutide and 2.6 kg with 14 mg oral semaglutide. Oral semaglutide was superior to empagliflozin (PIONEER 2), sitagliptin (PIONEER 3), liraglutide (PIONEER 4), and dulaglutide, albeit at a dose of 0.75 mg, which is the starting dose of dulaglutide and not the maintenance dose (PIONEER 10) [9-12].

In India, the two most commonly used GLP1-RA are once weekly dulaglutide and oral semaglutide. Dulaglutide is prescribed usually at a dose of 1.5 mg weekly. The recommendation is to start oral semaglutide initially at a dose of 3 mg and up titrate to 7 mg, with the provision to escalate the dose further to 14 mg if glycemic and weight targets are not met with 7 mg. However, a small fraction of patients are uptitrated to 14 mg either due to the lack of requirement for additional metabolic benefits or gastrointestinal side effects. In the real-life IGNITE trial only 13.6% of T2D patients were uptitrated to the 14 mg dose [13]. In the present analysis only 6.64% of T2D patients were uptitrated to S 14 mg.

Hence, this real-life cohort study was conducted to compare the metabolic benefits of the commonly used preparations - once weekly injectable dulaglutide (1.5 mg) and oral semaglutide (3 mg and 7 mg).

Materials and Methods

Patient selection

Patients for this retrospective cohort study was selected from six tertiary care diabetes centres in the city of Kolkata, India. The pre-determined period selected for patient data collection was from 15th December 2022 to 15th March 2023. The decision was based on the launch date of oral semaglutide in India in January 2022, giving ample time to participating physicians to initiate and follow up patients for at least 3 months. In view of a pre-specified audit of all the five diabetes clinics' data indicating use of 3 mg and 7 mg of semaglutide and a rare up titration to 14 mg semaglutide, data related to the former along with 1.5 mg of once weekly dulaglutide was collected. An excel sheet was circulated online amongst the authors highlighting the demographic, clinical and laboratory parameters that would be captured for analysis. The inclusion criteria included T2D patients 18 years of age without any contraindication to incretin-based therapy. Patients with type 1 diabetes, pregnancy, lactating women, hepatic failure, eGFR <30 ml/min, heart failure), malignancies, and debilitating psychiatric or cognitive dysfunction were excluded from analysis. The demographic (patient identification number, age, gender, duration of diabetes), clinical (weight and laboratory parameters (HBA1C, Systolic Blood Pressure (SBP), Alanine Transaminase (ALT), Asparatate Transaminase (AST), creatinine, and low density lipoprotein cholesterol (LDL-C) were entered at baseline and at 3-months follow up. Since, the data was retrospective in nature missing data was anticipated and was entered in the excel sheet as NA. Having collected the patient consent form and ethical approval from the respective authorities, analysis of the data was initiated.

Statistical analysis

The baseline characteristics were expressed as frequency (percentage) in case of categorical variables and as mean ± Standard Deviation (SD) or median (interquartile range) in case of metric variables. P-value for interaction was used to assess whether the baseline characteristics were matched. Chi square test was employed for categorical variables and analysis of variance (ANOVA) in case of continuous variables using 0.5 as the significance level. Handling of missing data was based on exclusion of the concerned rows (in case of large number of variables missing) or data imputation (small number of missing variables). Prior to initiating analysis each variable was subjected to a screening for gross outliers by plotting boxplots with datapoints. Each variable column was re-structured after removing gross outliers (after accounting for the missing cells).

Statistical analysis was conducted using the R Statistical Software (v4.1.2; R Core Team 2021) and DATAtab Team (2023) statistical calculator.

While comparing oral semaglutide (3 mg & 7 mg) and dulaglutide (1.5 mg), the drug doses were considered as nominal or categorical variables. The comparative statistical analysis was conducted in a 2-phase manner:

1. The individual doses were assessed upon their effectiveness in reducing body weight, HBA1C, SBP, ALT, AST, creatinine, and LDL-C. In view of the independent variable being categorical and the dependent continuous, a one-way ANOVA with a significance level of 0.5 was used for analysis.

2. While comparing the 3 doses among themselves, Tukey's method with a family error rate (adjusted p-value) of 0.05 was used to assess difference between the groups. Tukey's method was chosen over ANOVA since the comparative groups had differing column lengths.

All statistical tests were 2-sided, with values considered significant if less than the pre-determined alpha of 0.05.

Results

A total of 243 patient related data were taken up for analysis after having excluded 42 patients from the initial 285 patient recruited population in view of inadequate colection (n=12) and loss to follow up due to adverse effects (n=30). There were 92 patients on 3 mg oral semaglutide, 62 patients on 7 mg oral semaglutide, and 89 patients on 1.5 mg injectable once weekly dulaglutide. (Figure 1) In the overall cohort the mean age of patients was 52.58±10.57 years, duration of diabetes 7.35±8.05 years, with 54.48% being male. (Figure 2) The baseline characteristics of all the variables were matched between the three arms except for diabetes duration in view of a significantly higher number of missing data (n=90). (Table 1) There were no additions of any antihyperglycaemic agents in any of the groups as the follow up was after 3 months mirroring real world practice.

Figure 1: Patient selection process.

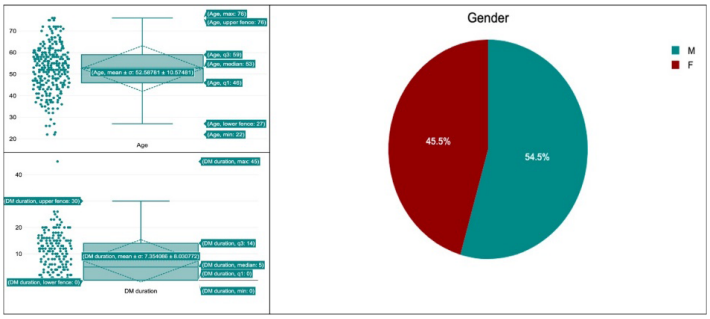

Figure 2: Baseline age, gender, and duration of diabetes in the entire cohort (M: male, F: female).

Characteristic	3 mg semaglutide	7 mg semaglutide	1.5 mg dulaglutide	p-value for interaction (ANOVA)
Age - years (Mean ±SD)	53.72 ±10.29	51.3±10.79	49.97±10.58	0.05
Male (%)	54.4	58.1	55.1	0.23 (chi square)
Female (%)	45.6	41.9	44.9	
DM duration in years (Mean ±SD)	12.2±6.69	7.61±6.15	11.71±7.95	0.02
Weight in kg (Mean ±SD)	82.69±14.38	86.98±15.05	85.31±13.19	0.25
Systolic blood pressure – mmHg (Mean ±SD)	131.99±14.36	131±16.74	131.02±14.39	0.92
Diastolic blood pressure – mmHg (Mean ±SD)	76±9.1	78.2±10.2	78.9±9.7	0.90
Glycated haemoglobin – %(Mean ±SD)	8.52±1.57	8.62±1.56	8.31±1.57	0.37
Alanine transaminase -IU/L (Mean ±SD)	46.9±27.93	50.2±30.47	42.21±19.12	0.16
Aspartate aminotransferase-IU/L (Mean ±SD)	35.23±13.62	40.33±15.95	37.66±20.8	0.12
Creatinine – mg/dL (Mean ±SD)	1.03±0.68	1.14±0.76	0.89±0.36	0.14
Low density lipoprotein cholesterol – mg/dL (Mean ±SD)	76.37±30.5	93.4±32.68	85.54±30.66	0.33
Background oral glucose lowering therapy (%)				
Metformin	96.5	92.8	89.5	0.93(chi square)
Sulfonylurea	78.2	65.5	57.8	0.58(chi square)
Sodium glucose transport protein-2 inhibitor	67.5	58.2	66.5	0.81(chi square)
Others (alpha glucosidase inhibitors, pioglitazone, glinides)	10.3	9.8	8.5	0.89(chi square)
Insulin	8.4	6.9	6.3	0.90(chi square)

Table 1: Baseline characteristics of the patients based on individual drug doses.

Efficacy of the individual drug doses

3mg oral semaglutide: There was significant reduction of weight (-1.17±2.96 kg, P=0.005, figure 3), HBA1C (-0.79±1.41%, P=0.000), SBP (-2.84±8.81mm of Hg, P=0.0001719), and ALT (-7.29±0.94IU/L, P=0.000) from baseline. The impact on AST, creatinine, and LDL-C were not significant from baseline. (Table 2)

7mg oral semaglutide: There was significant reduction of weight (-1.74±3.12kg, P=0.0005, figure 3), HBA1C (-0.84±1.06%, P=0.000), SBP (-4.5±9mm of Hg, P=0.00255), ALT (-7.31±0.6IU/L, P=0.000), AST (-7.67±5.51IU/L, P=0.038), and LDL-C (-16.6±14.66mg/dL, P=0.003) from baseline. There ws no significant change in serum creatinine levels from baseline. (Table 2)

1.5mg injectable dulaglutide: There was significant reduction of weight (-2.6±3.21kg, P=0.000, figure 3), HBA1C (-0.77±1.22%, P=0.000), SBP (-4.22±10.03mm of Hg, P=0.000), ALT (-6.83±2.04IU/L, P=0.000), AST (-6.26±15.29IU/L, P=0.005), and LDL-C (-10.46±18.39mg/dL, P=0.000) from baseline. The impact on creatinine was non-significant from baseline. (Table 2)

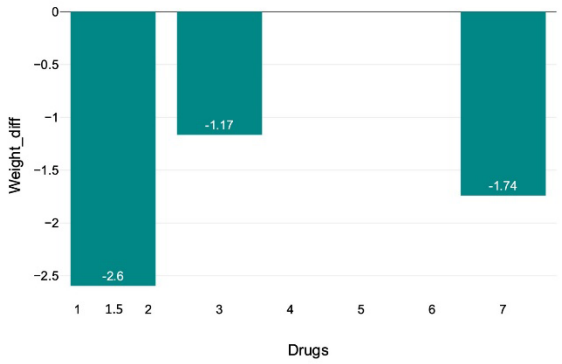

Figure 3: Effect of drugs (1.5 mg dulaglutide, 3 mg semaglutide and 7 mg semaglutide) on weight difference from baseline (weight_diff).

Characteristic	Weight loss (kg)	HBA1C reduction (%)	SBP reduction (mm of Hg)	ALT reduction (IU/L)	AST reduction (IU/L)	Creatinine reduction (mg/dL)	LDL-C reduction (mg/dL)
3 mg semaglutide							
Mean±SD	-1.17±2.96	-0.79±1.41	-2.84±8.81	-7.29±0.94	-7.4±19.61	0.03±0.23	-3.95±22.35
95%CI of the mean	-1.89 to -0.45	-1.09 to -0.49	-4.77 to -0.91	-7.6 to -6.99	-16.46 to 1.66	-0.04 to 0.09	-13.08 to 5.19
P-value	0.005	0.000 (1.291e-05)	0.0001719	0.000 (2.2e-16)	0.72	0.08	0.46
7 mg semaglutide							
Mean±SD	-1.74±3.12	-0.84±1.06	-4.5±9	-7.31±0.6	-7.67±5.51	0.13±0.59	-16.6±14.66
95%CI of the mean	-2.6 to -0.88	-1.1 to -0.57	-7 to -2.01	-7.47 to -7.15	-13.9 to -1.43	-0.14 to 0.39	-29.45 to -3.75
P-value	0.0005	0.000 (3.994e-10)	0.00255	0.000 (2.2e-16)	0.038	0.20	0.003
1.5 mg dulaglutide							
Mean±SD	-2.6±3.21	-0.77±1.22	-4.22±10.03	-6.83±2.04	-6.26±15.29	0.01±0.2	-10.46±18.39
95%CI of the mean	-3.28 to -1.91	-1.03 to -0.51	-6.41 to -2.04	-7.5 to -6.17	-10.1 to -2.42	-0.04 to 0.06	-14.93 to -5.99
P-value	0.000 (2.94e-09)	0.000 (2.876e-06)	0.000 (8.471e-05)	0.000 (2.2e-160	0.005	0.93	0.000 (7.272e-05)

Table 2: Analysis of individual drug doses on clinical and laboratory parameters.

Groupwise comparison

3mg oral semaglutide compared to 7 mg oral semaglutide: The two doses were comparable across all the variables. Although there was greater mean reduction in weight (-0.57, 95% CI -1.95 to 0.79), SBP (-1.66, 95% CI -5.63 to 2.31), ALT (-2.20, 95% CI -11.22 to 6.80), and LDL-C (-12.65, 95% CI-35.33 to 10.03), the difference was not significant. (Table 3)

3mg oral semaglutide compared to 1.5 mg injectable dulaglutide: Oral semaglutide (3 mg) and 1.5 mg injectable dulaglutide were comparable across all the parameters except for weight (-1.42, 95% CI -2.69 to -0.17), in favor of the latter. (Table 3)

7mg oral semaglutide compared to 1.5 mg injectable dulaglutide: The two doses were comparable across all the variables. (Table 3)

Characteristics	Weight loss (kg)	HBA1C reduction (%)	SBP reduction (mm of Hg)	ALT reduction (IU/L)	AST reduction (IU/L)	Creatinine reduction (mg/dL)	LDL-C reduction (mg/dL)
1.5 mg Vs 3 mg							
Mean difference	-1.42	-0.02	1.38	-2.65	-1.13	0.01	6.51
95% CI of the mean	-2.69 to -0.17	-0.48 to 0.43	-2.09 to 4.86	-10.85 to 5.53	-11.48 to 9.22	-0.11 to 0.15	-4.64 to 17.66
P-value (adjusted)	0.01	0.99	0.61	0.72	0.96	0.95	0.34
7 mg Vs 1.5 mg							
Mean difference	0.85	-0.06	-0.27	-4.86	-1.4	0.11	-6.14
95% CI of the mean	-0.44 to 2.15	-0.56 to 0.43	-4.24 to 3.68	-13.94 to 4.20	-24.23 to 21.42	-0.06 to 0.29	-27.47 to 15.19
P-value (adjusted)	0.27	0.94	0.98	0.41	0.98	0.28	0.77
7 mg Vs 3 mg							
Mean difference	-0.57	-0.04	-1.66	-2.2	-0.27	0.09	-12.65
95% CI of the mean	-1.95 to 0.79	-0.53 to 0.45	-5.63 to 2.31	-11.22 to 6.80	-24.34 to 23.80	-0.09 to 0.29	-35.33 to 10.03
P-value (adjusted)	0.58	0.97	0.58	0.83	0.99	0.44	0.38

Table 3: Comparison of the 3 drug doses (3 mg oral semaglutide, 7 mg semaglutide, and 1.5 mg injectable dulaglutide).

Adverse effects

Gastrointestinal (GI) adverse effects were the most common adverse event in all the three groups accounting for 37.93% of the overall adverse events. The GI adverse events were comparable between three groups. (Table 4) The dropout rate from this cohort due to GI side effects was 10.48% (15 inD 1.5 mg group, 5 in S 3mg group, and 10 in S 7 mg group).

Adverse effects	Drugs							
	1.5 mg Dulaglutide		3mg Semaglutide		7 mg Semaglutide		Total	
	n	%	n	%	n	%	n	%
No adverse effects	50	34.48%	13	8.97%	19	13.1%	82	56.55%
GI S/E	23	15.86%	18	12.41%	14	9.66%	55	37.93%
Heaviness in head	0	0%	2	1.38%	0	0%	2	1.38%
Herpes	0	0%	1	0.69%	0	0%	1	0.69%
Disturbed sleep	1	0.69%	1	0.69%	1	0.69%	3	2.07%

Increase urinary frequency	1	0.69%	0	0%	1	0.69%	2	1.38%
Total	75	51.72%	35	24.14%	35	24.14%	145	100%

Table 4: Adverse events related to the interventions.

Discussion

To our knowledge this is the first study comparing the relative pros and cons of treatment with oral semaglutide and dulaglutide, in India. Analysis of this real-world retrospective cohort study with 243 patients from six tertiary care diabetes centres illustrates an impressive effect of oral semaglutide (3mg and 7 mg) as well as 1.5 mg once weekly injectable dulaglutide on HBA1C and weight reduction. In addition oral semaglutide 3 mg provided a significant reduction in mean SBP and ALT while with 7 mg oral semaglutide there was a significant mean reduction in SBP, LDL-C, ALT and AST. Once weekly 1.5 mg dulaglutide resulted in significant reduction of SBP, ALT, AST and LDL-C. Once weekly 1.5 mg injectable dulaglutide was superior to 3 mg oral semaglutide in reduction of body weight, while the 7 mg dose was comparable to 1.5 mg once weekly injectable dulaglutide in reduction of body weight, HBA1C, SBP, ALT, AST, and LDL-C. Thus 1.5 mg injectable dulaglutide and 7 mg oral semaglutide are comparable in improving body weight, glycaemia, lipid lowering and improvement of liver function. The 3 mg dose of oral semaglutide, though useful in metabolic control, should therefore be used only as a starting dose as recommended. Gastrointestinal adverse events were the predominant side effect with 15.86% attributed to 1.5 mg once weekly injectable dulaglutide, 12.41% to 3 mg oral semaglutide, and 9.66% to 7 mg oral semaglutide.

GLP1-RA along with sodium glucose co-transporter 2 inhibitors have become the backbone of modern day T2D management strategy. This promotion in the treatment hierarchy was from the dual perspective of achieving metabolic control as well as providing organ protection [14]. SGLT-2is have been preferred to injectable GLP1-RA as GLP1RA are expensive and injectable. The introduction of semaglutide in oral form, is thus a major scientific breakthrough [15], making GLP1-RA more acceptable to the patients as well the physician. From a metabolic perspective, oral semaglutide is superior to SGLT-is, DPP-4 inhibitors, as well as injectable GLP1-RAs [16]. In the PIONEER 10 study, both 7 mg and 14 mg semaglutide was shown to be superior to once weekly dulaglutide in improving HBA1c and body weight [12]. However, the dose of dulaglutide used was 0.75 mg, which is half the usually prescribed dose. This may have skewed the data in favor of oral semaglutide. In the absence of a randomized controlled trial or RWE comparing oral semaglutide with 1.5 mg of once weekly injectable dulaglutide, this retrospective cohort study provides a novel insight into their comparable properties.

The main limitation of the study was its retrospective design. This could have resulted in selection bias. In addition this study is of short duration with a relatively restricted sample size. Though, the data was collected from a single city in eastern India, Kolkata's population is diverse and includes representation from all parts of India. Some of the variables had a very large number of missing content resulting in a wide confidence interval of the mean (lesser precision of estimation). This was typically encountered with diabetes duration, ALT, and AST.

The main strength of the study was its multi-centric nature, involving six prominent diabetes clinics with computerized electronic medical record keeping facilities. The dropout due to missing data as well due to GI side effects were negligible, making this analysis the first and the biggest database analysis from India. In addition, the analysis of the metric variables was carried out after omitting gross outliers, thereby improving the precision of the final estimates.

Oral semaglutide (3 mg and 7 mg) as well as 1.5 mg once weekly injectable dulaglutide have impressive metabolic effects in T2D patients being treated with lifestyle modification and standard-of-care oral antihyperglycemic agents. Although, 1.5 mg once weekly dulaglutide appears to be marginally superior to oral semaglutide in reducing body weight, all the 3 preparations of dulaglutide and semaglutide collectively are comparable on all other end points.

Conclusion

Dulaglutide and both the doses of semaglutide had significant impact on reduction of weight, HBA1C, SBP, ALT, AST (D and 7 mg S), and LDL-C (D and 7 mg S). Dulaglutide 1.5 mg weekly and 3 mg and 7 mg semaglutide are comparable in all aspects of efficacy and tolerability, except reduction in body weight was superior with dulaglutide when compared with 3 mg of semaglutide. A larger prospective study is required to confirm these findings.

External grant/support: None

Conflict of interest: None

Authors' contribution: All the authors participated proactively in the project. There was nearly equal contribution in providing patient details from all the 6 centers. The project was conceptualized by Dr. Binayak Sinha and the statistical analysis conducted

by Dr. Samit Ghosal. All the authors took turn in preparing the manuscript and editing it repeatedly until the final format was accepted universally by all.

Authors' approval: All the authors approve submission of the current manuscript for submission.

Ethics and patient approval: The project was passed by the respective institutional ethical committee and signed patient consent form were procured prior to conducting the analysis.

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