LIRA 365 Plus-a real world experience of 19 months use of liraglutide in the obese Indian type 2 diabetic subjects

Abstract

Background: Data from Indian sub-continent regarding the safety and efficacy of long term usage (one year and beyond) of liraglutide is scanty. The present study endeavors to share some data from a real world scenario.

Aim: To evaluate the effect of liraglutide on body weight, blood pressure and glycemic control in obese Indian type 2 diabetic subjects.

Methodology: Single centered, retrospective, real world, observational study conducted on subjects taking liraglutide for a period of 19 months in the endocrine out-patient department.

Results: Data of 39 subjects were available for one year and beyond. Mean age was 47.89±11years. Mean duration of diabetes was 6.46±4.55years. Glycosylated hemoglobin (HbA1c) significantly decreased from 9.08±1.54% at baseline to 7.26±1.02% at end of therapy. Body weight significantly reduced from 88.27±10.68kg at baseline to 80.8±11.83kg at end of therapy and BMI significantly declined from 33.22±4.5 to 31±5.1 at end of therapy respectively. No major adverse effects were reported.

Conclusion: In our present study long term liraglutide therapy was associated with significant and sustained reduction in HbA1c and bodyweight. Liraglutide therapy, when tolerated for initial 3-6months, was associated with minimal gastrointestinal side effects and no gastrointestinal adverse event related drop-out. Liraglutide thus can be a natural choice of second line anti-diabetic agent in the subset of obese diabetic subjects.

Keywords: liraglutide, obesity, Indian, type 2 diabetes

Introduction

Metformin is the recommended first-line pharmacological therapy for type 2 diabetes mellitus (T2DM) both by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) The progressive nature of the disease often necessitates more intensive treatment regimens or combination therapy for subjects to achieve and/or maintain glycemic control. Despite the availability of several other anti-hyperglycemic agents (only 53% of subjects with T2DM achieve HbA1c <7.0%, which is the recommended glycemic target advocated by American Diabetes Association (ADA) and European Association for study of Diabetes (EASD).)

Achievement and/or maintenance of glycemic control are further complicated by widespread prevalence of obesity in majority T2DM. Although India is a developing country, the burden of obesity is not less than that in the Western world. The ICMR INDIAB-3 study extrapolated the data from three states and one union territory and projected the prevalence of generalized obesity, abdominal obesity and combined obesity in India to be 135million, 153million and 107million respectively and the country currently houses a diabetic population of nearly 70million people.

ThekgA1c paradox refers to the present scheme of intensive glycemic control aimed to prevent a micro and macro vascular complication which is contributing to the emerging unmet issue of weight gain. Hypoglycemia and weight gain are the collateral damage of tight A1c control and need to be critically evaluated. Weight gain happening during T2DM treatment can be clinically dangerous. Even mild to moderate overweight is believed to increase CVD risk & other complications. Weight management needs to be considered as key therapeutic goal. Keeping in mind the effect of weight reduction on various aspects of outcome in the diabetic patient, thekgA1C concept is coming into vogue which focuses on the benefits of weight reduction in the diabetic patient. Liraglutide is a known second line agent with benefits of weight loss along with HbA1c reduction. 5,7 HbA1c reduction and weight reduction data over 12weeks, 4 24weeks and 52weeks with liraglutide therapy is reported from among the Indian population, but long term data (beyond 52weeks) is not available. This retrospective single centre observational study aims to look at the effect of Liraglutide therapy with regards to safety, tolerability and weight loss among obese Indian T2DM. The present study is a real world scenario observational study with a mean follow-up period of 19months extending up to 40months. Obese T2DM subjects with a liraglutide usage of 12months and beyond were included in the present study.
Materials and methods

This is a single-centred, retrospective, real-world observational study conducted on subjects taking liraglutide for a period of 19 months in the Endocrine out-patient department (OPD) of KPC Medical College. KPC Medical College is a multispeciality hospital, situated in Eastern India with 650 bedded indoor facilities and a dedicated Endocrine Clinic. Database of subjects from the Endocrine OPD of the hospital was searched for subjects receiving liraglutide for at least 52 weeks and was taken up for subsequent analysis.

A total of 39 subjects were included in the analysis based on the inclusion criteria (adults T2DM between 18 to 75 years, eGFR > 30 and receiving liraglutide for more than 52 weeks). We have not analyzed any data of subjects who underwent hospitalization for acute illness during the entire observation period owing to the discontinuation of liraglutide therapy during the period of hospitalization.

Database search revealed, follow-up visit of the subjects were variable. Despite a written instruction to follow up every 1-3 months, subjects did not always comply. We have taken the nearest possible visit data for every 6 months, for a year and the last available data for those who continued liraglutide beyond a year for the analysis. Despite our best effort, irregularity in follow up, which is expected in real-world scenario, remained a great challenge in analyzing the data.

Liraglutide was used at a dose of 0.6, 1.2, or 1.8 mg/day depending on tolerability & affordability and all subjects received liraglutide in addition to existing anti-diabetic therapy (DPP4 inhibitor was discontinued in all once liraglutide was started). None of the subjects were on concomitant SGLT2 therapy. All subjects’ records with respect to HbA1c, fasting plasma glucose, and postprandial plasma glucose, blood pressure and body weight and adverse events and cause of stopping the therapy were collected. The data at baseline, at 6 month visit, at 12 month visit and at the point of stopping the therapy or the last data available for subjects who were still continuing on liraglutide were collected and evaluated.

Statistical methods

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

Normality of data was tested by simultaneous Anderson Darling test, Shapiro-Wilk test and graphically by QQ plot. Repeated measures ANOVA with post-hoc Bonferroni adjustment method has been used to find the significance of study parameters measured on three occasions between same/related groups of subjects. Mauchly’s test of sphericity was done to check the assumption of sphericity. Known as sphericity, the variances of the differences between all combinations of related groups must be equal. Unfortunately, repeated measures ANOVAs are particularly susceptible to violating the assumption of sphericity, which causes the test to become too liberal (i.e., leads to an increase in the Type I error rate; that is, the likelihood of detecting a statistically significant result when there isn’t one). If found to violate, it was subjected to Greenhouse-Geisser or Huynh-Feldt correction.

Statistical software

The Statistical software namely SAS Version 9.2 for Windows, Statistical Package for Social Sciences (SPSS) Version 21.0 for Windows were used for the analysis of the data and Microsoft word and Excel have been used to generate tables etc.

Result

A total of 39 subjects were included in the analysis based on the inclusion criteria. Database search revealed the results of 29 subjects at the 6th-month follow-up visit whereas the data for 10 subjects were missing. The 12th-month follow-up visit had data for 35 subjects and the data for 4 were missing. A total of 30 subjects had end of therapy data of 15 months and beyond (Table 1).

Table 1 Database search yield of included study subjects

| Study visits       | Number (% of subjects (data found from hospital records) | Number (% of subjects (data not found from hospital records) |
|--------------------|----------------------------------------------------------|-------------------------------------------------------------|
| Visit 1 (Baseline) | 39 (100%)                                                | 0 (0%)                                                      |
| Visit 2 (6 Months) | 29 (74.36%)                                              | 10 (25.64%)                                                 |
| Visit 3 (12 Months)| 35 (89.74%)                                              | 4 (10.26%)                                                  |
| Visit 4 (15 Months and beyond) | 30 (76.92%) | 9 (23.08%)                                                 |

All 39 subjects were started at a liraglutide dose of 0.6 mg/day and 3 subjects carried on with the same dose throughout the entire period of observation and three could reach a maximal dose of 1.8 mg/day, rest 33 were up titrated to a dose of 1.2 mg/day depending on their tolerability and affordability.

The subjects under study had a slight female preponderance (57.89% females versus 42.11% males), had an average age of 47.89±11 years with a 6.46±4.55 years of diabetes duration. The subjects under observation had a mean body weight of 88.27±10.68 kg, mean BMI of 33.22±4.51 kg/m², average fasting plasma glucose of 200.82±53.73 mg/dl and an average postprandial glucose of 261.08±75.84 mg/dl. The cohort of subjects in this study had a baseline HbA1c of 9.08±1.54% and had a mean follow up duration of 19.37±7.36 months (Table 2).

With regards to changes in the glycemic parameters, there was a significant reduction achieved for FPG, PPG and HbA1c measured on each of the three subsequent visits, p<0.0001 as determined by repeated measures ANOVA with both Greenhouse-Geisser correction and Huynh-Feldt correction, taking into account the violation of assumption of sphericity by Mauchly’s test of sphericity. Further post-hoc pair wise comparison test by Bonferroni adjustment method also revealed statistically significant reduction in FPG, PPG and HbA1c between each of the subsequent visits but not between 2nd and 3rd visit and 3rd and 4th visit respectively (Table 3). However, being a real-world data and of long follow-up, the anti-hyperglycemic therapies were modified in between to achieve the target HbA1c in majority of subject population. Hence, statistically significant reduction in FPG, PPG and HbA1c in our cohort is not the sole effect of liraglutide therapy.

Citation: Chaudhuri SR, Majumder A, Sanyal D, et al. LIRA 365 Plus: a real world experience of 19 months use of liraglutide in the obese Indian type 2 diabetic subjects. Adv Obes Weight Manag Control. 2016;5(4):277–282. DOI: 10.15406/aowmc.2016.05.00136

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Table 2 The baseline characteristic features

| Measure                                 | Baseline Mean±SD, n=38 | 2nd visit Mean±SD n=29 | 3rd visit Mean±SD n=35 | 4th visit Mean±SD n=26 | p (repeated measure ANOVA) Post-hoc test |
|-----------------------------------------|------------------------|------------------------|------------------------|------------------------|-----------------------------------------|
| FPG (mg/dl), Mean±SD                   | 200.82±53.73           | 147.66±29.77           | 141.17±50.91           | 135.27±49.8            | <0.0001                                 |
| PPG (mg/dl), Mean±SD                   | 261.08±75.84           | 196.52±37.48           | 185±53.74              | 177.67±63.66           | <0.0001                                 |
| HbA1c (%)                               | 9.08±1.54              | 7.78±0.75              | 7.41±0.99              | 7.26±1.02              | <0.0001                                 |

*p<0.05 considered as statistically significant, p computed by repeated measure ANOVA to find over-all significant difference between the three visits taking into account Mauchly’s test of sphericity followed by multiple comparison post-hoc test by Bonferroni method to find pairwise difference between two groups. a - probability of chance difference between baseline & 2nd visit, b- probability of chance difference between baseline & 3rd visit, c - probability of chance difference between baseline & 4th visit, d- probability of chance difference between 1st & 3rd visit, e- probability of chance difference between 2nd & 4th visit, f- probability of chance difference between 3rd & 4th visit.

Table 3 Changes in glycemic Parameters between 1st (baseline), 2nd (6months), 3rd visit (12months) and 4th visit (15months and beyond) respectively

| Parameter | Baseline n=38 | 2nd visit n=29 | 3rd visit n=35 | 4th visit n=26 | p (Repeated Measure ANOVA) Post-hoc Test |
|-----------|---------------|----------------|----------------|----------------|-----------------------------------------|
| FPG (mg/dl) | 200.82±53.73  | 147.66±29.77  | 141.17±50.91  | 135.27±49.8   | <0.0001                                  |
| PPG (mg/dl) | 261.08±75.84  | 196.52±37.48  | 185±53.74     | 177.67±63.66  | <0.0001                                  |
| HbA1c (%)   | 9.08±1.54     | 7.78±0.75     | 7.41±0.99     | 7.26±1.02     | <0.0001                                  |

*p<0.05 considered as statistically significant, p computed by repeated measure ANOVA to find over-all significant difference between the three visits taking into account Mauchly’s test of sphericity followed by multiple comparison post-hoc test by Bonferroni method to find pairwise difference between two groups. a - probability of chance difference between baseline & 2nd visit, b- probability of chance difference between baseline & 3rd visit, c - probability of chance difference between baseline & 4th visit, d- probability of chance difference between 1st & 3rd visit, e- probability of chance difference between 2nd & 4th visit, f- probability of chance difference between 3rd & 4th visit.

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Table 5 Changes in Body Weight and BMI from Visit 1 (Baseline) to subsequent follow-up visits (Visit 2, Visit 3 and Visit 4)

| Parameter     | Change from baseline to 2nd visit | Change from baseline to 3rd visit | Change from baseline to 4th visit |
|---------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Body weight (kg) | Mean±SD: -5.74±2.31               | Median (IQR): -5 (-3.5 to -7.0)  | Range: 0 to -9                    |
| BMI (kg/m²)    | Mean±SD: -2.13±0.94               | Median (IQR): -2 (-1.47 to -3)   | Range: 0 to -4                    |

Table 6 Percentage Change in Weight during the total follow-up period

| Overall Weight Loss during the total follow-up period | Number of subjects (%) |
|-------------------------------------------------------|-------------------------|
| 0 – 5 (%)                                             | 9 (23.07)               |
| 5.1 – 10 (%)                                          | 16 (41.02)              |
| >10 (%)                                               | 14 (35.9)               |

Table 7 Tolerability and reason for drop-outs in the study subjects

| Number of subjects (%)              |
|-------------------------------------|
| Total no of patient                 | 39 (100)                  |
| Nausea                              | 3 (7.69)                  |
| Nausea and Vomiting                 | 3 (7.69)                  |
| Nausea and Flatulence               | 1 (2.56)                  |
| Diarrhea                            | 1 (2.56)                  |
| Total Gastrointestinal (GI) Events  | 8 (20.51)                 |
| GI event related drop-outs          | 0                         |
| Documented hypoglycemia             | 0                         |
| Symptomatic hypoglycemia            | 2 (5.12)                  |
| Discontinued Liraglutide due to financial constraints | 7 (17.92) |
| Discontinued Liraglutide due to abnormal elevated amylase levels | 1 (2.56) |
| Discontinued Liraglutide due to weight gain | 1 (2.56) |
| Discontinued Liraglutide due to inadequate glycemic control | 3 (7.69) |
| Discontinued Liraglutide due to worsening renal function | 1 (2.56) |
| Discontinued Liraglutide for achieving target weight loss | 3 (7.69) |
| Switched to weekly GLP-1 analogue    | 1 (2.56)                  |

Discussion

Liraglutide is a novel, long-acting, injectable glucagon like peptide 1 receptor agonist which stimulates glucose dependent insulin secretion and suppresses glucagon secretion. The drug was approved for treatment of T2DM by the European Medicines Agency (July 3, 2009), and also by the US Food and Drug Administration (January 25, 2010). The LEAD (Liraglutide Effect and Action Diabetes) 3,4 program evaluated the safety and efficacy of liraglutide. Liraglutide, when used alone or in combination with other anti-diabetic medications, effectively controls hyperglycemia (HbA1c reductions up to 1.6%) and assists subjects in meeting established glycemic targets. In these LEAD series of trials, Liraglutide has also been associated with weight loss (1.8 to 3.4kg) and improved patient satisfaction and health-related quality of life, improved systolic blood pressure and beta-cell function. Liraglutide does not induce hypoglycemia and offers an alternative therapy to control blood glucose in subjects with T2DM. Beside the glucose lowering action, weight loss has been considered as an important additional benefit with liraglutide therapy.5,6
In another trial with Liraglutide 1.8mg and metformin run in for 12weeks and detemir add on in the randomized treatment group vis-à-vis placebo in the randomized control group, the control group showed weight loss of 1.02kg over and above the loss of 3.5kg in run-in period whereas the treatment group maintained the weight loss of the run in period.10 LEAD 3 was a 52week trial, and it showed a weight reduction of 2.1kg with a dose of 1.2mg and a reduction of 2.5kg with a dose of 1.8mg Liraglutide as monotherapy.11 These two are global data but in a controlled scenario of a clinical trial which does not always go parallel to the data generated from the real world experience.

As we browse through real world data generated from India, we come across Kesavadev et al.,12 who studied 1.8mg Liraglutide in 14 overweight and obese recently detected diabetics (Diabetes for <12weeks) for 24weeks.13 This study showed a huge weight loss of 8.65kg at 24weeks which was significantly greater than that seen in the LEAD Trials. In our previous observational study of 24weeks duration, low dose liraglutide13 (0.6mg) once a day demonstrated a statistically significant (p<0.05) mean weight reduction of 6.03kg and a decrease in BMI of 2.67kg/m2.14 The fasting and post prandial glucose reduced significantly (p<0.05) by 38.5mg/dl and 50.71mg/ dl respectively. There was no significant change in systolic blood pressure but diastolic blood pressure was significantly reduced by 7.2mm of Hg (p=0.004).13

Whereas these two trials were lean in terms of numbers, later two studies by Kesavadev et al.,13 and Kaur et al.,14 had more robust numbers of 195 subjects and 196 subjects respectively and 24weeks and 12weeks in duration respectively. Kesavadev et al.,13 reported statistical significant reduction in fasting plasma glucose (p<0.001), HbA1c (p=0.006), weight (p<0.001) and diastolic blood pressure (p<0.001) over 24weeks follow up. In the same line, Kaur et al reported a significant (p=0.007) HbA1c drop of 9.2±1.9% at baseline to 7.6±0.9% at week 12 and body weight also dropped to a significant (p<0.001) 96.0±16.5kg from the initial figure of 100.1±17.5kg.

The recently published paper by Kaur et al.15 shared 52weeks experience with Liraglutide which is the maximum duration of observation available from Indian subcontinent. Data of 74 obese subjects were available whose mean duration of diabetes was 11.6±6.3years. The drop in HBA1c was 8.9±1.3% at baseline to 7.4±1.2% at 52weeks and the drop in body weight was from 98.9±16.0kg at baseline to 93.8±15.0kg at the end of 52weeks. Although Kaur et al did change the dose of liraglutide and other anti-diabetic medications as per clinical judgment, they have attributed the sustained HbA1c lowering to Liraglutide therapy, which probably is not backed by evidence due to change of dosage of other anti-diabetic drugs as well as that of liraglutide.

We had an average follow up duration of 19.37±7.36months and the longest follow up data from India as of now. The baseline HbA1c in our subjects was 9.8±1.54% and it dropped to 7.78±0.75% at 6month, then to 7.41±0.99% at 52weeks and to 7.26±1.02 % at the end of 12month of the study. Due to the time span required to observe the benefits, it is postulated that the CV benefits of liraglutide are possibly mediated by changes in the atherosclerotic process and hence long term usage of Liraglutide may be associated with CV outcome benefits in addition to the benefits of A1C reduction and weight reduction. Dose-dependent nausea, vomiting, and diarrhea are the most commonly reported adverse events with Liraglutide therapy and an important cause of drop out, However those who tolerated the drug in first few months, (as evidenced in our study cohort that included the subjects continuing Liraglutide for 52weeks or longer), is expected to continue the drug for long time. In this group of subjects, where no gastrointestinal adverse event related drop out was noted, it is likely that they will benefit in cardiovascular front. Supplemented with robust enhancement of beta cell function and improved A1C control, long term use of Liraglutide is warranted for CV benefit in majority of T2DM who can afford, because in long term use, gastrointestinal side effects, which is the principal cause of discontinuation during the first few months of therapy, does not seem to bother much.
Limitations of the study

The study has few limitations:

a. Firstly, it is a retrospective design observational study; hence it is not a gold standard study design to establish the cause and effect direction. Further, adequately powered properly designed randomized studies are warranted to establish the antecedent outcome relationship in a biologically plausible background.

b. Secondly, the subjects were on concomitant medications like anti-hypertensive and anti-diabetic medications, hence the changes in the outcome parameters cannot be solely attributed to the liraglutide therapy.

c. Third, the sample size is small. Although the sample size of this real world observational study is meager, it adds to the present body of medical literature on the usage of liraglutide therapy in underdeveloped and developing countries where the long term data of this medication usage is primarily restricted due to affordability in long run. In our previous published study, 23.33% discontinued liraglutide due to financial constraint. The penetration of health insurance in India is low by international standards. According to a few nationwide studies in 2014, only 17%-25% of India’s population was insured. Also, private health insurance schemes, which constitute the bulk of insurance schemes, availed by the Indian population, do not cover costs of outpatient consultation or outpatient medication. Only hospitalisation and associated expenses are covered.

Conclusion

Long term liraglutide therapy in high risk T2DM subjects has shown to improve cerebrovascular and cardiovascular outcomes as per LEADER trial. In our present study long term liraglutide therapy was associated with significant and sustained reduction in HbA1c and bodyweight. Liraglutide therapy, when tolerated for initial 3-6 months, was associated with minimal gastrointestinal side effects and no gastrointestinal adverse event related drop-out. Liraglutide thus can be a natural choice of second line anti-diabetic agent in the subset of obese diabetic subjects.

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None.

Conflict of interest

The author declares no conflict of interest.

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