Liraglutide – Indian Experience

Majumder Anirban, Roy Chaudhri Soumyabrata, Sanyal Debmalya, Kingshuk Bhattacharjee1
Department of Endocrinology, KPC Medical College, Jadavpur, Kolkata, West Bengal, 1Department of Medical Sciences, JJT University, Rajasthan, India

Abstract

Liraglutide is an effective drug for the treatment of type 2 diabetes mellitus (T2DM). The aim of this review is to collate evidence on the real-world clinical effectiveness of liraglutide from the published Indian studies. A review of publications was conducted to identify observational studies that assessed the effectiveness of liraglutide among Indian T2DM. Total ten publications were retrieved and these observational studies are compared with the results of the liraglutide randomized controlled trial (RCT) program (Liraglutide Effect and Action in Diabetes [LEAD]). Liraglutide therapy demonstrated HbA1c reduction in the Indian population up to 2.26% and 2.54%, over 24 and 52 weeks, respectively. Among the LEAD trials, the HbA1c reduction at 24 weeks was maximum in LEAD-4 with 1.5% reduction at both doses used (1.2 and 1.8 mg) and up to 1.14% in LEAD-3 with a dose of 1.8 mg. The weight loss among Indian subjects was generally around 5 kg or more with maximum weight loss of 8.6 kg over 24 weeks. The maximal weight loss in LEAD studies was less than 3 kg with an exception of 3.24 kg in LEAD-6. In over 52 weeks of liraglutide therapy among Indian subjects, mean weight loss was 7.4 kg, which was 3.5 times more than that of LEAD program. Two Indian observational studies also demonstrated significant weight loss among nondiabetic obese subjects at a much lower than that of 3 mg anti-obesity dose. Gastrointestinal (GI) events are the commonly reported adverse events with Indian studies as well as LEAD program. Liraglutide therapy produces better glycaemic control and more weight loss among Indian T2DM subjects compared with RCTs conducted in western population with almost similar adverse consequences.

Keywords: Effectiveness, India, liraglutide, literature review, real-world, type 2 diabetes, weight

INTRODUCTION

Glucagon-like peptide-1 receptor agonists (GLP-1RA) are being recognized as an important therapeutic option in the management of type 2 diabetes mellitus (T2DM). Liraglutide is a unique GLP-1RA with 97% homology to endogenous human GLP-1 and a commonly prescribed anti-diabetic agent. In liraglutide, at the 34th position arginine has been replaced with lysine and a C-16 palmitic acid side chain has been attached to the lysine at the 26th position. The modifications in the structure lead to slow absorption from the subcutaneous tissue, resistance to degradation by endogenous dipeptidyl peptidase-4 (DPP4) enzyme and reversible albumin binding. This prolongs the half-life of liraglutide to 13 hours, enabling once daily administration.1,2

Liraglutide was first approved for treatment of T2DM as an adjunct to lifestyle therapy and in combination with oral anti-diabetic drugs (OADs) in Europe in 2009 and in the United States in 2010.3 It was approved for use in India in 2010. The approval of liraglutide was based on the outcomes from the Liraglutide Effect and Action in Diabetes (LEAD) phase 3 clinical trial program, which showed the anti-hyperglycemic efficacy of liraglutide in T2DM both as monotherapy and when combined with other glucose lowering anti-diabetic medications.4-9

Results from randomized controlled trials (RCTs) are obtained under supervised conditions and the clinical effects of the drugs may vary depending on a lot of practical factors. Although cost is a limiting factor for prolonged use of this drug in our country, there has been significant interest among Indian clinicians, as evidenced by recent publications. Ten observational studies have recently been published with liraglutide in a real-world setting (Jothydev et al., Kaur et al., Sanyal et al., Roy Chaudhri et al., Wagnoo et al., Verma et al., and Majumder et al.), from Liraglutide Effect and Action in Diabetes (LEAD) program. This review article is an attempt to collate evidence on the real-world clinical effectiveness of liraglutide from the published Indian studies.

Address for correspondence: Dr. Majumder Anirban, KPC Medical College, 1F, Raja Subodh Chandra Mullick Road, Jadavpur, Kolkata, West Bengal - 700 032, India. E-mail: dranirbanmazumdar@gmail.com

How to cite this article: Anirban M, Soumyabrata RC, Debmalya S, Bhattacharjee K. Liraglutide – Indian experience. Indian J Endocr Metab 2018;22:818-26.
various parts of India.\textsuperscript{[10-19]} We are presenting a review of the real-world experience with liraglutide in India.

**Methods**

This literature review was conducted to collect evidence on the effectiveness and adverse effects of liraglutide, from the real-world studies in India. The PubMed database and Index Copernicus were searched. In the database search, no time limits were applied to ensure that no relevant publications were missed. Total ten publications were retrieved from the search evaluating the glycemic efficacy, weight loss, and adverse effect parameters in observational studies. Out of these, seven were on T2DM, two on obesity, and one evaluating the impact of starting very low dose on adverse parameters. The database search was executed on January 7, 2018. These seven observational studies on T2DM are compared with the results of the LEAD program.

**Characteristics of study design**

Indian observational studies with liraglutide had evaluated the efficacy (glycemic parameters and weight loss) and adverse consequences. Pertinent study design of these observations and LEAD program (a series of six-phase three RCTs) are presented in Tables 1 and 2.

**Patient baseline characteristics**

Number of subjects in all Indian observational studies with liraglutide was small compared with LEAD program, which comprised more than 4,000 patients. The mean age of patients with Indian T2DM on liraglutide was between 43.64 and 55.9 years at baseline. Three out of seven publications included more male than female subjects. The mean baseline HbA1c level before liraglutide treatment was between 7.78% and 9.08%. Mean baseline weight and mean baseline body mass index (BMI) were 85.71–98.9 kg/m\(^2\) and 33.22–36.2 kg/m\(^2\), respectively. Differences were observed in the baseline characteristics, especially regarding use of concomitant and previous anti-diabetic therapy and the information on the use of prior therapies varied between the studies. The baseline characteristics of patients of Indian studies and the LEAD program are presented in Tables 3 and 4.

**Clinical effectiveness**

The clinical effectiveness of anti-diabetic drugs on blood glucose control is measured by HbA1c, fasting plasma glucose (FPG), and post-prandial plasma glucose (PPG). The change in mean FPG, PPG, and HbA1c from baseline to end of study of both the Indian studies and LEAD program are shown in Tables 5 and 6.

**Change in body weight**

Reduction in body weight is associated with reduced risk of developing cardiovascular disease in obese patients with diabetes. Overall, liraglutide treatment both as monotherapy and in combination with oral therapy led to significant weight loss in patients with T2DM. Body weight reduction ranged from 1.18 to 8.65 kg in Indian subjects, whereas the LEAD program has reported a weight gain of 0.3 kg to a loss of 3.24 kg, as shown in Tables 7 and 8.

**Discussion**

The LEAD trial program consisted of a series of six phase-3 RCTs that was conducted at more than 600 sites, across 40 countries, comprising more than 4,000 patients, out of which around 2,700 patients received liraglutide therapy.\textsuperscript{[4-9]} All the LEAD trials were of 26 weeks duration with the sole exception of LEAD-3, which was a 52-week study.

Among the studies of liraglutide reported from India, three initial studies reported by Kesavadev \textit{et al.} (2012),\textsuperscript{[10]} Sanyal \textit{et al.} (2013),\textsuperscript{[18]} and Kesavadev \textit{et al.} (2014),\textsuperscript{[14]} were for a period of 24 weeks. However, as time progressed, it became relatively easier for the clinicians to gather data of subjects continuing liraglutide for a year and more. There were two publications from Kaur \textit{et al.} (2016)\textsuperscript{[12]} and Roy Chaudhuri \textit{et al.} (2016)\textsuperscript{[13]}

---

**Table 1: Study design of Indian studies and LEAD**

| Study design                        | Sample size | Study duration | Region            |
|-------------------------------------|-------------|----------------|-------------------|
| Kesavadev \textit{et al.} (2012)    | 14          | 24 weeks       | Trivandrum, Kerala|
| Sanyal \textit{et al.} (2013)       | 30          | 24 weeks       | Kolkata, West Bengal|
| Kesavadev \textit{et al.} (2014)    | 195         | 24 weeks       | Trivandrum, Kerala|
| Kaur \textit{et al.} (2014)         | 196         | 13 weeks       | Gurgaon, Haryana  |
| Kaur \textit{et al.} (2016)         | 96          | 52 weeks       | Gurgaon, Haryana  |
| Wagnoo \textit{et al.} (2016)       | 1,416       | 26 weeks       | 125 sites across India|
| Chaudhuri \textit{et al.} (2016)    | 39          | 82 weeks       | Kolkata, West Bengal|
| LEAD trials                         | 2,739       | (LEAD-1,2,4-6)-26 weeks | 600 sites across 40 countries |

LEAD: Liraglutide effect and action in diabetes; RCT: Randomized controlled trial
Glycemic control parameters: Plasma glucose and HbA1c

In the LEAD trials, when used as monotherapy, liraglutide showed significant improvements in the glycemic parameters compared with glimepiride and also when used in combination with one or two OADs. LEAD-1, LEAD-2, and LEAD-4 evaluated both doses of liraglutide (viz., 1.2 mg and 1.8 mg per day). LEAD-4 and LEAD-2 reported 1.5% and 1% reduction in HbA1c, respectively, which was similar at both the doses. A numerically improved HbA1c reduction of 1.13% with 1.8 mg dose versus a reduction of 1.08% with 1.2 mg dose was seen in LEAD-1. However, this marginal difference was not clinically significant and in real
Table 4: Patient demographics and baseline characteristics of LEAD studies individually (Adapted from Davies et al.)

| Study | Arm | Patients (n) | Age (years) | Gender (M/F), % | Weight (kg) | BMI (kg/m²) | Duration of diabetes (years) | HbA1c (%) | FPG (mg/dL) |
|-------|-----|--------------|-------------|-----------------|-------------|-------------|-----------------------------|-----------|-------------|
| LEAD-1 | Liraglutide: 1.2 mg | 228 | 57.7 (9.0) | 45/55 | 80.0 (17.1) | 29.8 (5.1) | 6.7 (4.0, 10.7) | 8.5 (1.1) | 176.4 |
|        | Liraglutide: 1.8 mg | 234 | 55.6 (10.0) | 53/47 | 83.0 (18.1) | 30.0 (5.1) | 6.5 (3.7, 10.5) | 8.5 (0.9) | 174.6 |
| LEAD-2 | Liraglutide: 1.2 mg | 241 | 57 (9) | 54/46 | 88.5 (19.1) | 31.1 (4.8) | 7 (5) | 8.3 (1.0) | 178.2 |
|        | Liraglutide: 1.8 mg | 242 | 57 (9) | 59/41 | 88.0 (16.3) | 30.9 (4.6) | 8 (5) | 8.4 (1.0) | 180.1 |
| LEAD-3 | Liraglutide: 1.2 mg | 251 | 53.7 (11.0) | 47/53 | 92.5 (19.2) | 33.2 (5.6) | 5.2 (5.5) | 8.3 (1.0) | 167.4 |
|        | Liraglutide: 1.8 mg | 247 | 52.0 (10.8) | 49/51 | 92.8 (20.7) | 32.8 (6.3) | 5.3 (5.1) | 8.3 (1.1) | 172.47 |
| LEAD-4 | Liraglutide: 1.2 mg | 178 | 55 (10) | 57/43 | 95.5 (18.5) | 33.2 (5.4) | 9 (6) | 8.5 (1.2) | 180.1 |
|        | Liraglutide: 1.8 mg | 178 | 55 (11) | 51/49 | 94.9 (19.2) | 33.5 (5.1) | 9 (6) | 8.6 (1.2) | 185.4 |
| LEAD-5 | Liraglutide: 1.8 mg | 232 | 57.6 (9.5) | 57/43 | 85.5 (19.4) | 30.4 (5.3) | 9.2 (5.8) | 8.3 (0.9) | 163.8 |
| LEAD-6 | Liraglutide: 1.8 mg | 233 | 56.3 (9.8) | 49/51 | 93.1 (20.1) | 32.9 (5.5) | 8.5 (6.2) | 8.2 (1.0) | 176.4 |

LEAD: Liraglutide effect and action in diabetes, BMI: Body mass index, FPG: Fasting plasma glucose

The first Indian publication by Jothydev et al. (2012) reported the most spectacular reduction of HbA1c up to 2.26% over 24 weeks. However, the numbers of subjects included were only 14 and the dose of liraglutide used was 1.8 mg/day, which was not always the dose majorly used in the Indian studies. In contrast, Sanyal et al. (2013) published the results of low-dose liraglutide (0.6 mg) over 24 weeks, demonstrating a much lesser drop of HbA1c (0.74%). However, the other two Indian data showed a robust reduction of HbA1c with Kaur et al. (2016) reporting a reduction of 1.4% and Roy Chaudhuri et al. (2016) reporting a reduction of 2.54% using varying doses of liraglutide between 0.6 mg and 1.8 mg per day. An overview of the changes in the mean HbA1c level achieved in 24 and 52 weeks by liraglutide treatment in Indian studies compared with the LEAD program is given in Figure 1 (Panel A).

With regard to the FPG reduction at 24 weeks, LEAD-4, which used rosiglitazone and metformin as concomitant medication, showed the most robust reduction of 39.6 mg/dL with 1.2 mg dose and 43.2 mg/dL with 1.8 mg dose. On the other hand, the Indian data showed a reduction of 38.5 mg/dL with low dose of liraglutide (0.6 mg) (Sanyal et al. 2013) and a more robust reduction of 48.5 mg/dL (Kesyadev et al. 2012) to 58.2 mg/dL (Kaur et al. 2016) with higher doses. At 1-year mark, LEAD-4 showed a reduction of FPG of 15.12 mg/dL and 25.56 mg/dL with 1.2 and 1.8 mg doses, respectively. However, the other two available Indian data of a duration of 52 weeks or more reported a robust reduction of 52.7 mg/dL (Kaur et al. 2016) and 59.65 mg/dL (Roy Chaudhuri et al., 2016). An overview of the changes in the mean FPG level achieved in 24 and 52 weeks by liraglutide treatment in Indian studies compared with the LEAD program is given in Figure 1 (Panel B).

PPG is important in the Indian subset as they have a predominantly carbohydrate-based diet. Indian observational data suggested a better reduction with liraglutide compared with the LEAD program. LEAD-5 produced the least reduction of 32.4 mg/dL at 24 weeks using a dose of 1.8 mg, while LEAD-6 achieved a maximum reduction of

life involves an extra financial burden which is a concern in poor-resource settings, especially in India, which is majorly an out-of-pocket market. In LEAD-3, over 52 weeks, 1.8 mg dose achieved a reduction of 1.14% in HbA1c versus 0.84% with 1.2 mg dose.
Anirban, et al.: Liraglutide – Indian Experience

Table 6: Change in glycemic parameters in LEAD trials individually

| Liraglutide dose | Baseline | At the end of study | Mean change | P       |
|----------------|----------|---------------------|-------------|---------|
|                | 1.2 mg   | 1.8 mg              | 1.2 mg      | 1.8 mg  | 1.2 mg | 1.8 mg |
| LEAD 1         |          |                     |             |         |
| HbA1c (%)      | 8.5      | 8.5                 | 7.42        | 7.37    | −1.08 | −1.13 |
| FPG (mg/dL)    | 176.4    | 174.6               | 146.14      | 145.98  | −28.26 | −28.62 |
| PPG (mg/dL)    | 232.2    | 232.2               | 187.20      | 183.60  | −45    | −48.6 |
| LEAD 2         |          |                     |             |         |
| HbA1c (%)      | 8.3      | 8.4                 | 7.3         | 7.4     | −1.00 | −1.00 |
| FPG (mg/dL)    | 178.2    | 181.8               | 149.40      | 151.20  | −28.80 | −30.60 |
| PPG (mg/dL)    | 214.2    | 219.6               | 172.80      | 172.80  | −41.40 | −46.80 |
| LEAD 3         |          |                     |             |         |
| HbA1c (%)      | 8.3      | 8.3                 | 7.46        | 7.16    | −0.84 | −1.14 |
| FPG (mg/dL)    | 167.4    | 171                 | 152.28      | 145.44  | −15.12 | −25.56 |
| PPG (mg/dL)    | 203.4    | 205.2               | 172.80      | 167.40  | −30.60 | −37.80 |
| LEAD 4         |          |                     |             |         |
| HbA1c (%)      | 8.5      | 8.6                 | 7.0         | 7.1     | −1.5  | −1.5  |
| FPG (mg/dL)    | 181.8    | 185.4               | 142.20      | 142.20  | −39.60 | −43.20 |
| PPG (mg/dL)    | 205.2    | 212.4               | 158.40      | 163.80  | −46.80 | −48.60 |
| Liraglutide dose | 1.8 mg   | 1.8 mg              | 1.8 mg      | 1.8 mg  | 1.8 mg | 1.8 mg |
| LEAD 5         |          |                     |             |         |
| HbA1c (%)      | 8.3      | 6.97                | −1.33       | <0.0001 |
| FPG (mg/dL)    | 163.8    | 135.9               | −27.9       | <0.0001 |
| PPG (mg/dL)    | 201.6    | 169.20              | −32.4       | NS      |
| LEAD 6         |          |                     |             |         |
| HbA1c (%)      | 8.2      | 7.08                | −1.12       | <0.0001 |
| FPG (mg/dL)    | 176.4    | 147.42              | −28.98      | <0.0001 |
| PPG (mg/dL)    | 171      | 100.80              | −70.2       | <0.0001 |

Table 7: Change in body weight in Indian studies

|                      | Baseline | At the end of study | Mean change | P       |
|----------------------|----------|---------------------|-------------|---------|
| Kesavadev et al. (2012)-24-week study | Body weight (kg) | 90.7±11.80 | 82.06±12.86 | −8.65 | <0.001 |
| Kesavadev et al. (2014)-24-week study | Body weight (kg) | 86.41±12.83 | 82.37±12.45 | −4.18 | <0.001 |
| Sanyal et al. (2013)-24-week study    | Body weight (kg) | 85.71±14.47 | 79.68        | −6.03 | <0.05  |
| Kaur et al. (2014)-13-week study      | Body weight (kg) | 100.1±17.5     | 96±16.5      | −4.1  | <0.001 |
| Kaur et al. (2016)-52-week study      | Body weight (kg) | 98.9±16.0      | 93.8±15.0    | −5.1  | <0.05  |
| Chaudhuri et al. (2016)-82-week study | Body weight (kg) | 88.27±10.68   | 80.8±11.83   | −7.25 | <0.0001 |
| Wagnoo et al. (2016)-26-week study    | Body weight (kg) | 92.5±14.6      | 84.8±12.9    | −8.1  | <0.0001 |

70.2 mg/dL with the same dose. Other LEAD trials showed a PPG reduction ranging from 41.4 mg/dL to 48.6 mg/dL. The Indian studies, on the other hand, showed a minimum reduction of 50.7 mg/dL (Sanyal et al. 2013)\[18\] at a low dose of 0.6 mg and a maximum reduction of 75.4 mg/dL at a dose of 1.2–1.8 mg (Kaur et al. 2016).\[12\] The 52-week studies also showed a similar trend whereby a reduction of 76.08 mg/dL and 47.3 mg/dL were reported by Roy Chaudhuri et al. (2016)\[15\] and Kaur et al. (2016),\[12\] respectively, whereas the two arms of LEAD-3 reported a PPG reduction of 30.6 mg/dL (with 1.2 mg dose) and 37.8 mg/dL (with 1.8 mg dose). An overview of the changes in the mean PPG level achieved in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD is given in Figure 1 (Panel C).

This accumulated Indian data now tend to suggest that liraglutide is effective in reducing all parameters of glycemic control over a period of 24 weeks and also in the long run, over a year or more, which is more than that of the LEAD program and at times with lower doses also.

Effect of liraglutide on weight and body mass index in diabetic patients

The vast majority of Indian subjects with T2DM are overweight or obese and the impact on weight should be considered while choosing the most appropriate glucose-lowering therapy for these subjects. In addition...
to providing significant glycemic control in LEAD studies, liraglutide reduced weight in most subjects. The maximal weight loss in the LEAD program was less than 3 kg, except in LEAD-6 which showed a weight loss of 3.24 kg over a 24-week period. In contrast, the 1.2 mg arm of LEAD-1 (used in addition to glimepiride 2–4 mg) showed a marginal (300 g) increase of weight over a period of 24 weeks. All Indian studies have reported a whopping weight loss in comparison to the LEAD program. The weight loss among Indian subjects (except for one study showing a weight loss of 1.1 kg over 24 weeks by Kesavadev et al., 2014) was generally around 5 kg or

| Liraglutide dose | Baseline 1.2 mg | Baseline 1.8 mg | At the end of study 1.2 mg | At the end of study 1.8 mg | Mean change 1.2 mg | Mean change 1.8 mg | P |
|-----------------|----------------|----------------|---------------------------|---------------------------|-------------------|-------------------|---|
| LEAD 1          |                |                |                           |                           |                   |                   |   |
| Body weight (kg)| 80             | 83             | 80.3                      | 82.8                      | +0.3              | −0.2              | <0.0001 <0.0001 |
| LEAD 2          |                |                |                           |                           |                   |                   |   |
| Body weight (kg)| 88.5           | 88             | 85.9                      | 85.2                      | −2.6              | −2.8              | <0.0001 <0.0001 |
| LEAD 3          |                |                |                           |                           |                   |                   |   |
| Body weight (kg)| 92.5           | 92.8           | 90.4                      | 90.3                      | −2.1              | −2.5              | <0.0001 <0.0001 |
| LEAD 4          |                |                |                           |                           |                   |                   |   |
| Body weight (kg)| 95.5           | 94.9           | 94.5                      | 92.9                      | −1.0              | −2.0              | <0.0001 <0.0001 |
| Liraglutide dose|                | 1.8 mg         |                           |                           |                   |                   |   |
| LEAD 5          |                |                |                           |                           |                   |                   |   |
| Body weight (kg)| 85.5           | 83.7           | −1.8                      |                           |                   |                   | <0.0001 |
| LEAD 6          |                | 1.8 mg         |                           |                           |                   |                   |   |
| Body weight (kg)| 93.1           | 89.9           | −3.24                     |                           |                   |                   | NS |

LEAD: Liraglutide effect and action in diabetes

Figure 1 (Panel A): Changes in HbA1c in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD

Figure 1 (Panel B): Changes in FPG in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD
more with the maximum weight loss being reported of 8.6 kg over 24 weeks in a cohort of 14 overweight and obese T2DM subjects (Kesavadev et al. 2012). In the long run (over 52 weeks or more), a weight loss of 7.4 kg was about 3.5 times higher than the weight loss reported in LEAD-3 (−2.1 kg and −2.5 kg with 1.2 mg and 1.8 mg, respectively) (Roy Chaudhuri et al. 2016).

An overview of the changes in the mean weight achieved in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD is given in Figure 1 (Panel D).

**Effect of liraglutide on weight and body mass index in nondiabetic patients**

Liraglutide has been shown to be effective at inducing and sustaining weight loss among obese patients, and a 3-mg dose has been approved for chronic weight management in patients with obesity or who are overweight with a BMI ≥27 kg/m² and have a weight-related co-morbid condition.

Results from Indian observational studies also repeatedly demonstrated the ability of liraglutide to induce weight loss. A weight loss of 8 kg (±2.4 kg) from a baseline weight of 110 kg (±12.5 kg), and waist circumference reduction of 3.1 cm (±1.2 cm) from a baseline waist circumferences of 114 cm (±8.1 cm) was observed among 25 obese non-diabetic subjects after 12 weeks of liraglutide therapy, with a dose of 1.2 mg (Verma, 2012). Significant reduction of mean body weight (from 96.33 ± 14.45 at baseline to 90 ± 13.47 at 3 months and to 86.25 ± 13.19 at 9 months, \( P < 0.001 \)), BMI (from 34.99 ± 5.66 at baseline to 32.66 ± 5.17 at 3 months to 31.29 ± 4.97 at 9 months, \( P < 0.001 \)), and waist circumference (from 93.33 ± 5.43 at baseline to 90.33 ± 5.09 at 3 months to 88.5 ± 4.59 at 9 months, \( P < 0.001 \)) were reported after 3 and 9 months of liraglutide treatment, with a dose of 1.8 mg (Roy et al. 2016). Even a low dose (0.6 mg) of liraglutide showed a reduction of 6.03 kg over 24 weeks. Hence, in the scanty Indian data available, liraglutide at a dose much lower than that of 3 mg (as the approved anti-obesity dose) produced a substantial reduction in body weight of obese non-diabetic Indian subjects, which can make it a relatively less expensive anti-obesity agent in days to come.

**Side effect profile**

The LEAD program has demonstrated that liraglutide therapy is generally well tolerated, and the most commonly reported adverse event was nausea (7-40%) which was transient and subsided as the treatment progressed. Nausea was also a common adverse event in the Indian studies and reported incidences varies from 0.7% to 42.58%.

---

Figure 1 (Panel C): Changes in PPPG in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD

Figure 1 (Panel D): Changes in body weight in 24 and 52 weeks by liraglutide treatment in Indian studies compared with LEAD
Vomiting, diarrhea, dyspepsia, and constipation are the other adverse events reported in the LEAD program and the cumulative gastrointestinal (GI) adverse events ranged up to 54% in these trials. The GI events were often dose dependent and mild in nature and diminished gradually on continuation of therapy over 4–6 weeks or more. A majority of the adverse events of liraglutide therapy among Indian studies are also GI related. The cumulative GI adverse events in Indian studies varies from 11.28% (Kesavadev et al., 2015) to 63% (Kesavadev et al., 2012). In the long-term study by Chaudhuri et al. (2016), 8 out of 39 subjects (20.51%) complained of GI events. Majumder et al. (2017) highlighted the benefit of starting with a very low dose (0.2 mg). Though statistically not superior, starting with 0.2 mg liraglutide and weekly up-titration appeared to be better tolerated, with lower dropout rates, owing to lesser GI intolerance.

The risk of hypoglycemia as reported in the LEAD program was low across all the treatment arms and especially increased in combination with sulphonylureas (0.47–1.93 events per patient per year in LEAD-1, LEAD-5, and LEAD-6). Interestingly, the rate of minor hypoglycemia was significantly less with liraglutide plus OADs compared with exenatide plus OADs in LEAD-6. No major hypoglycemic episodes were reported in LEAD-4, the 26-week LEAD-2 main study phase and the 52-week LEAD-3 main study phase. Similarly, no hypoglycemic episodes were reported from short-term Indian studies except 3% mild hypoglycemia events reported from Kaur et al. (2016).

In the long-term study by Chaudhuri et al. (2016), no documented hypoglycemia for any of the subjects was observed; however, two subjects reported subjective hypoglycemia-like symptoms which was not confirmed by a glucometer reading. It will be worthwhile to note that a vast majority of the patients in this study were initiated with a strategy of gradual up-titration from a very low-dose (0.2 mg) liraglutide as followed in Majumder et al. and thus has also showed much lesser GI adverse events than in other published Indian studies.

As seen in the LEAD program, the Indian studies also reported similar GI adverse events and low risk for both major and minor hypoglycemics. The GI side effects was maximum in the initial 3 months leading to GI-related dropouts but were insignificant after 6 months of therapy.

**CONCLUSION**

Liraglutide therapy improved glycaemic control with low risk of hypoglycemia and facilitated clinically relevant weight loss in both short- and long-term real-world studies among Indian subjects with T2DM. The glycemic efficacy and weight loss seen in Indian studies are far more impressive than seen in the LEAD program. Liraglutide therapy, at a much lower dose than 3 mg daily, also significantly improved weight loss in obese non-diabetic Indian subjects. The frequency of GI adverse effects in the Indian real-world studies was nearly in accordance with the results seen in the LEAD trials. Most of GI side effects and GI adverse event related drop outs were observed in the initial 3–6 months starting of therapy. When tolerated for initial three-six months, liraglutide therapy was associated with minimal GI side effects and no GI adverse event related dropout in the Indian real world studies. Moreover, starting with a very low-dose (0.2 mg) liraglutide and weekly up-titration appears to be better tolerated and further reduces the GI adverse event related dropouts.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Malm-Erjefält M, Björnsdottir I, Vanggaard J, Helleberg H, Larsen U, Oosterhuis B et al. Metabolism and excretion of the once-daily human GLP-1 analogue liraglutide in healthy subjects and it’s in vitro degradation by dipeptidyl peptidase 4 and neutral endopeptidase (Abstract 891). Diabetologia 2008;51(Suppl. 1):S356.
2. Agero H, Jensen LB, Elbrønd B, Rolan P, Zdravkovic M. The pharmacoekinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. Diabetologia 2002;45:195-202.
3. Bode B. Liraglutide: A Review of the First Once-Daily GLP-1 Receptor Agonist. Am J Manag Care 2011;17:S59-S70.
4. Buse JB, Rosenstock J, Sesti G, Schmidt WE, Montanya E, Brett JH, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: A 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374:39-47.
5. Garber A, Henry R, Ratnur R, Garcia-Hernandez PA, Rodriguez-Pattz R, Olvera-Alvarez I, et al. Liraglutide versus gliclizide monotherapy for type 2 diabetes (LEAD-3 Mono): A randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009;373:473-81.
6. Marre M, Shaw J, Brandle M, Bebakar WM, Kamaruddin NA, Strand I, et al. Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). Diabet Med 2009;26:268-78.
7. Nauck M, Frid A, Hermansen K, Shah NS, Tankova T, Mitha IH, et al. Efficacy and safety comparison of liraglutide, gliclizide, and placebo, all in combination with metformin, in type 2 diabetes: The LEAD (liraglutide effect and action in diabetes)-2 study. Diabetes Care 2009;32:84-90.
8. Russell-Jones D, Vaag A, Schmitz O, Sethi BK, Lalic N, Antic S, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): A randomised controlled trial. Diabetologia 2009;52:2046-55.
9. Zinman B, Gerich J, Buse JB, Lewin A, Schwartz S, Raskin P, et al. Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with type 2 diabetes (LEAD-4 Met+TZD). Diabetes Care 2009;32:1224-30.
10. Kesavadev J, Shankar A, Krishnan G, Jothidev S. Liraglutide therapy beyond glycemic control: An observational study in Indian patients with type 2 diabetes in real world setting. Int J Gen Med 2012;5:317-22.
11. Wangnoo SK, Kumar S, Bhattacharyya A, Tripathi S, Akhtar S, Shetty R, et al. Liraglutide effect and action in diabetes-In (LEAD-In): A prospective observational study assessing safety and effectiveness of liraglutide in patients with type 2 diabetes mellitus treated under routine clinical practice conditions in India. Indian J Endocr Metab 2016;20:838-45.
12. Kaur P, Mahendra S, Mithal A. Long-term efficacy of liraglutide in Indian patients with Type 2 diabetes in a real-world setting. Indian J
13. Kaur P, Mishra SK, Mittal A, Saxena M, Makkar A, Sharma P. Clinical experience with Liraglutide in 196 patients with type 2 diabetes from a tertiary care center in India. Indian J Endocrinol Metab 2014;18:77-82.
14. Kesavadev J, Shankar A, Gopalakrishnan G, Jothydev S. Efficacy and safety of liraglutide therapy in 195 Indian patients with type 2 diabetes in real world setting. Diabetes Metab Syndr 2015;9:30-3.
15. Roy Chaudhuri S, Sanyal D, Majumder A, Bhattacharjee K. LIRA 365 Plus-A Real World Experience of 82 week Use of Liraglutide in the Obese Indian Type 2 Diabetic Subjects. Adv Obes Weight Manag Control 2016;5:00136.
16. Roy Chaudhuri S, Sanyal D, Majumder A, Bhattacharjee K. Short Term Outcomes of Low Dose Liraglutide in Obese Non Diabetic Indian Subjects-A Real World Experience. Diabetes Obes Int J 2016;1:000140.
17. Verma A. Non-diabetic use of liraglutide. Indian J Endocrinol Metab 2012;16:864-5.
18. Sanyal D, Majumdar A. Low dose liraglutide in Indian patients with type 2 diabetes in the real world setting. Indian J Endocrinol Metab 2013;17(Suppl 1):S301-3.
19. Anirban M, Bhattacharjee K. Beginning With Very Low Dose (0.2mg) Liraglutide in Indian Type 2 Diabetic Patients Appears Better Tolerated: Experience from Real Life Practice. J Diabetes Metab Disord Control 2017;4:00127.
20. Davies MJ, Kela R, Khunti K. Liraglutide – Overview of the preclinical and clinical data and its role in the treatment of type 2 diabetes. Diabetes Obes Metab 2011;13:207-20.
21. Saxenda [package insert]. Novo Nordisk: Plainsboro, NJ, 2015. Available from: https://www.accessdata.fda.gov/drugsatfda.../206321. [Last accessed on 2018 May 13].