Efficacy and tolerability of GLP-1 agonists in patients with type 2 diabetes mellitus: an Indian perspective

Mala Dharmalingam

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Abstract: Glucagon like peptide-1 (GLP-1) agonists have been able to address the unmet needs of type 2 diabetes patients across the world. Indian patients with type 2 diabetes have also been able to benefit from effects of GLP-1 analogues to a more or less similar extent compared with patients from other parts of the world. As there is no nationwide data on use of GLP-1 agonists in India, we used the clinical data from different studies and compared them with the global data on GLP-1 analogues. The review is limited to only two approved GLP-1 analogues in India: exenatide and liraglutide. The efficacy of GLP-1 analogues, in terms of glycated haemoglobin (HbA1c), fasting plasma glucose (FPG) and postprandial glucose (PPG), is found to be similar in Indian patients compared with the global data. The other beneficial effects such as weight loss, incidence of hypoglycaemia were found to be on similar lines in the Indian setting. In a single-centre study, liraglutide reduced the dose of antihypertensive medications due to its effect on blood pressure. The gastrointestinal adverse effects such as nausea and vomiting were major adverse events, but these were transient and varied from one particular agent to another. Liraglutide is found to be superior in terms of compliance compared with exenatide in the Indian setting. Overall, the GLP-1 analogues have presented a treatment option that gives patient a benefit of glycaemic control, weight loss and very low incidence of hypoglycaemia, but the cost of the therapy presents a major barrier.

Keywords: efficacy, GLP-1 agonists, India, tolerability

Introduction

Diabetes mellitus (DM) is a multifactorial, progressive disease predisposing the patients to an increased risk of developing various health complications. The most recent estimated figures released by the International Diabetes Federation (IDF) indicate that 8.3% of adults worldwide (382 million) have diabetes. The comparative prevalence figure for India is 9.09% (65 million). Baseline data of 20,554 Indian type 2 DM subjects, who participated in the observational Alcheive study, showed that prevalence of both macrovascular and microvascular complications was high due to poor glycaemic control (mean HbA1c = 9.2 ± 1.4) [Mohan *et al.* 2013].

The UKPDS (66,000 patient years of exposure [PYE] follow up) [Holman *et al.* 2008], DCCT (an average of 23.5 years of follow up) [Nathan *et al.*

2005] and STENO-2 (13.3 years follow up) [Gaede *et al.* 2008] studies present three important conclusions: intensive glycaemic therapy is associated with (i) significantly reduced risk of macrovascular and microvascular complications, (ii) sustained legacy effect of beneficial outcomes is observed despite the early loss of within trial differences in HbA1c levels between two treatment groups, (iii) reduction in the risk of any diabetes related end point. The relationship between incidence of complications and glycaemic control highlights the importance of adequate glycaemic control. However, glycaemic control continues to deteriorate over the course of type 2 diabetes [Cook *et al.* 2005]. This necessitates the use of various treatment options to achieve the recommended treatment goals of diabetes. The arsenal for the treatment of type 2 diabetes is growing and GLP-1 (glucagon-like peptide-1) analogues has added a new dimension to it.

Correspondence to:
Mala Dharmalingam MD, DM
M S Ramaiah Medical
College, Methikere,
Bangalore, 560001, India
endocrinology23@rediffmail.com

Glycaemic management in type 2 diabetes is becoming increasingly complex due to widening array of pharmacological agents. A joint committee was convened by the American Diabetic Association (ADA) and the European Association for Study of Diabetes (EASD) to examine the evidence and develop recommendations. The key message was to evaluate currently available therapies based on parameters such as efficacy, hypoglycaemia, weight, major side effects and cost [Inzucchi *et al.* 2012]. This can serve as a guide to clinicians and patients to develop a plan to meet the mutually set treatment goals.

Majority of the cases of type 2 DM can be attributed to weight gain [IDF, 2013] and the patients often gain further weight, as the disease progresses. Weight gain can be a barrier for intensification [Davies, 2004] and can increase the cardiovascular risk [Bogers *et al.* 2007]. This can lead to loss of glycaemic control and increase the risk of complications to the patient. Before discussing the role of GLP-1-based therapies, it is important to summarize the unmet needs of the patient/clinicians. Progressive decline in beta-cell function, dysregulated release of glucagon by alpha-cells [Kahn *et al.* 2014], reduced incretin effect [Knop *et al.* 2007] and weight gain [Eckel *et al.* 2011]] are not adequately addressed by existing therapies. GLP-1 analogues have addressed these issues and have fulfilled the criteria to a certain extent of ideal antidiabetes treatment.

Physiological regulation of blood glucose is multifactorial and involves various systems. For example in addition to the insulin resistance and impaired beta-cell function, plasma glucagon concentrations are also inappropriately elevated [D'Alessio, 2011]. GLP-1 hormone causes glucose-dependent insulin release from beta cells, inhibition of glucagon release from alpha cells [Drucker, 2001], delay in gastric emptying, enhancement of satiety and reduction in energy intake [Gutzwiller *et al.* 1999] and improvement in insulin sensitivity [Zander *et al.* 2002]. This makes GLP-1 analogues an attractive treatment option, as the other therapies do not adequately address these issues.

Outcomes of the diabetes treatment are more important to clinicians and patients, as the glycaemic control should translate into benefits that outweigh risks associated with the treatment. Hence, the composite end point, defined in terms

of ADA goals, serves an effective barometer to compare the therapeutic options. A meta-analysis of seven clinical trials of GLP-1 analogue (liraglutide) revealed that proportion of patients achieving HbA1c <7.0% was significantly higher than comparator therapies. And 40% of patients treated with liraglutide achieved HbA1c <7.0% with no weight gain and no hypoglycaemia [Zinman *et al.* 2012]. This was the highest compared with the other therapies in the clinical trial. GLP-1 analogues offer patients an option of treatment that can provide glycaemic control with additional benefits of weight loss and no hypoglycaemia.

This review is limited to the efficacy and tolerability of the GLP-1 analogues in Indian clinical setting. As only two drugs in this class are approved in India, exenatide (twice a day) and liraglutide (once a day), the further discussion will be limited to these two drugs. Exenatide is an exendin-4 mimetic with 53% sequence identity to native GLP-1 molecule and because of its half-life of 2.4 hours, it is recommended twice a day [Amylin/Eli Lilly, 2009]. On the other hand, liraglutide is a GLP-1 analogue with 97% sequence identity to native GLP-1 and its half-life is approximately 13 hours [Novo Nordisk, 2009].

Efficacy

Currently there is a lack of nationwide data on the efficacy of GLP-1 analogues in the Indian setting. Hence, an attempt is made to compare the global efficacy data with that of published data on experience in Indian patients.

Glycaemic outcomes

HbA1c. An observational study on efficacy of exenatide twice daily was done by Bawa and colleagues for 1 year at a single centre in North India [Bawa *et al.* 2013]. The clinical use of exenatide was found to be associated with significant improvement in glycaemic control and major weight loss. The mean HbA1c at the end of 1 year was $7.2 \pm 0.8\%$ compared with the baseline mean: $8.8 \pm 1.3\%$ ($p < 0.05$). The ongoing therapies were continued except dipeptidyl peptidase 4 (DPP-IV) inhibitors or thiazolidinediones, which proved the beneficial effect of GLP-1 analogues as an add-on therapy. A meta-analysis of 21 randomized controlled trials reported that people with or without type 2 diabetes and a body mass index (BMI) $\geq 25\text{kg/m}^2$ receiving GLP-1RA therapy

(liraglutide OD, exenatide BID, or exenatide OW) at clinically relevant doses for at least 20 weeks achieved greater weight loss (weighted mean difference -2.9 kg, 95% confidence interval (CI) -3.6 to -2.2 kg) than people receiving 'control' treatments (placebo, oral antidiabetics or insulin) [Buse *et al.* 2011], and mean ($\pm$ SE) HbA1c fell by $0.73 \pm 0.03\%$ from mean (SD) $9.48(1.69)\%$ to $8.75(1.84)\%$ in 4551 patients participated in nationwide exenatide audit [Ryder *et al.* 2010].

In a clinical trial programme involving 4625 patients with type 2 diabetes, 65% of patients on liraglutide achieved HbA1c $<7\%$ (primary end-point) compared with comparator treatments (30–53%) [Zinman *et al.* 2012]. The trials included in the meta-analysis involved significant number of type 2 DM patients from India. The Association of British Clinical Diabetologists nationwide exenatide and liraglutide audits revealed the statistically superior HbA1c reduction in favour of liraglutide (-1.05%) compared with exenatide (-0.74%) ($p < 0.001$) [Ryder and Thong, 2011].

Fasting plasma glucose

GLP-1 analogues are associated with statistically significant greater reduction in fasting plasma glucose (FPG) of $7\text{--}74$ mg/dl, when administered as an add-on therapy [Cobble, 2012; Russell-Jones *et al.* 2009]. Bawa and colleagues observed reduction in FPG from 177.6 ± 38.5 (baseline) to 126.0 ± 25.0 (at the end of 1 year), after the treatment with exenatide twice daily, in Indian patients [Bawa *et al.* 2013]. Similar reductions were observed with liraglutide in a 24-week study by Kesavadev and colleagues [Kesavadev *et al.* 2011].

Postprandial glucose

GLP-1 analogues cause glucose-dependent insulin secretion from the beta cells and contribute to the improved postprandial glycaemic control. Clinical trials have shown consistent reduction in postprandial glucose (PPG) reduction ranging from 29 to 112 mg/dl [Russell-Jones *et al.* 2009; Marre *et al.* 2009; DeFronzo *et al.* 2005]. In a study done by Kaur and colleagues the reduction in PPG was observed to be in the range of $68.8\text{--}88.2$ mg/dl [Kaur *et al.* 2014]. This signifies the importance of GLP-1 analogues in controlling postprandial blood glucose as well.

Weight reduction. Systemic review was conducted by Vilsboll and colleagues to determine whether

GLP-1 receptor agonists result in weight loss in patients with BMI >25 with or without type 2 DM and they found that weight loss in the GLP-1R agonist groups for patients without diabetes (-3.2 kg, -4.3 to -2.1 ; three trials) as well as patients with diabetes (-2.8 kg, -3.4 to -2.3 ; 18 trials). This added benefit can provide clinicians a boon to treat patients, as weight gain increases the risk of cardiovascular adverse outcomes [Vilsboll *et al.* 2012].

Niswender and colleagues studied the relationship between weight change and related factors in subjects with type 2 diabetes included in seven phase III, randomized trials [Niswender *et al.* 2013]. The findings from the study are as follows.

1. A number of subjects experienced $>5\%$ weight loss during the trials (24.4% liraglutide 1.8 mg and 17.7% liraglutide 1.2 mg; 17.7% exenatide; 10.0% sitagliptin; 3.6–7.0% sulphonylurea; 2.6% thiazolidinedione; 2.6% glargine; and 9.9% placebo).
2. Across trials, higher initial BMI was associated with slightly greater weight loss with liraglutide.

These studies compared the effects of various anti-diabetic treatments on body weight and liraglutide caused weight reduction in a greater number of patients than that in any other group. Does weight reduction translate into beneficial outcomes for the patients? The LOOK AHEAD trial published interesting findings on the impact of weight loss on the risk factors. The magnitude of weight loss at 1 year was strongly ($p < 0.0001$) associated with improvements in glycaemia, blood pressure, triglycerides, and high-density lipoprotein (HDL) cholesterol but not with low-density lipoprotein (LDL) cholesterol ($p=0.79$) in patients with type 2 DM. Compared with weight-stable participants, those who lost 5–10% of their body weight had increased odds of achieving a 0.5% point reduction in HbA1c (odds ratio 3.52 [95% CI 2.81–4.40]), a 5 mmHg decrease in diastolic blood pressure (1.48 [1.20–1.82]), a 5 mmHg decrease in systolic blood pressure (1.56 [1.27–1.91]), a 5 mg/dl increase in HDL cholesterol (1.69 [1.37–2.07]), and a 40 mg/dl decrease in triglycerides (2.20 [1.71–2.83]) [Wing *et al.* 2011].

Real-life data reflected similar findings: mean weight loss of 3.1 kg over 3 months and 3.7 kg over 6 months [Ryder and Thong, 2011].

Hypoglycaemia. Hypoglycaemia is a major barrier to the aggressive treatment of hyperglycaemia in DM and physicians find it difficult to manage simultaneously both efficacy (hyperglycaemia) and safety (hypoglycaemia) [Peyrot *et al.* 2012]. In a clinical trial comparing exenatide once weekly *versus* exenatide twice daily, no episode of major hypoglycaemia were found in either regimen group and the incidence of minor hypoglycaemia was very low [Drucker *et al.* 2008]. Nauck and colleagues found that the incidence of hypoglycaemia in the liraglutide arm (0.03–0.14 events/year) was comparable with the placebo and that of major hypoglycaemia was zero [Nauck *et al.* 2009]. The lower incidence of overall hypoglycaemia can be attributed to glucose-dependent insulinotropic action. GLP-1 analogues have become the therapy of choice in patients who require a minimal risk of hypoglycaemia due to work constraints, such as drivers.

B-cell function. Deterioration of B-cell function is directly proportional to the duration of diabetes. In the UKPDS study, B-cell function, in the 56% of subjects who remained on their allocated metformin therapy, decreased to 38% at 6 years ($p < 0.0001$) similar to that in the 36% of subjects treated by diet [UKPDS Study Group, 1995]. Hence, the therapies used in the treatment of DM should be weighed on the basis of their effect on B-cell function. Even though the direct effects of liraglutide and exenatide on beta cell mass have not been demonstrated directly due to unavailability of suitable noninvasive technology, beneficial effects on islet cell function have been consistently reported [Garber, 2011]. Indirect markers of B-cell function such as the proinsulin/insulin ratio, the disposition index, the first phase insulin response and insulin response to arginine stimulation test showed positive response after 1 week of once-daily liraglutide treatment, thus pointing towards a beneficial effect of liraglutide towards beta-cell preservation [Degen *et al.* 2004]. This mounting evidence highlights another beneficial effect of the GLP-1 analogues for the patients with diabetes.

Cardiovascular effects. Type 2 diabetes increases the risk of cardiovascular mortality by 4.9 times compared with those with no diabetes [Juutilainen *et al.* 2008]. These findings were noted in an 18-year follow-up study. Hence, most of the guidelines recommend assessing the cardiovascular risk reduction of the therapies before deciding to start them. GLP-1 analogue's action on

pancreatic islet cells, causing increase in insulin secretion and concomitant decrease in glucagon secretion, enhances glucose utilization and decreases dependency of cardiomyocytes on free fatty acids. This increases short-term and long-term cardiac function [Hermansen *et al.* 2012]. GLP-1 may also have beneficial effects on postprandial lipid profile, which can offer cardiovascular protection. Varanasi and colleagues observed statistically significant reduction in C-reactive protein and triglycerides in addition to glycaemic control [Varanasi *et al.* 2012]. These class effects were present to a more or less to similar extent in most of the GLP-1 analogues. However, treatment with liraglutide (a GLP-1 RA for 3 weeks) significantly reduced systolic blood pressure compared with that with placebo and the effect was sustained over a 26-week period. The same trend for liraglutide was further confirmed against all of the regimens investigated in LEAD 1–6 trials [Baggio and Drucker, 2007]. In a case series presented at ADA, liraglutide has been observed to reduce both systolic and diastolic blood pressures in Indian patients, requiring reduction in doses of antihypertensive medications [Kesavadev *et al.* 2011]. The data on impact of these cardiovascular effects on outcome in terms of cardiovascular risk reduction is currently not available.

Central nervous system effects. The presence of GLP-1 receptors in the area postrema and nucleus of the solitary tract has led to the various studies in the role of GLP-1 in potential therapeutic areas such as Alzheimers and Parkinson's disease. However, these studies are still in the experimental stage. Weight reduction associated with GLP-1 analogue therapy is the result of combined central and peripheral actions: collectively promoting satiety, decreasing hunger sensation and ultimately leading to reductions in food intake [van Bloemendaal *et al.* 2014]. There is no clinical data available on the impact of GLP-1 analogues on central nervous system in Indian setting.

In a nutshell, beneficial effects of GLP-1 analogues such as glycaemic control, weight reduction, reduction in systolic blood pressure have been observed in Indian patients, despite having relatively lower BMI compared with the rest of the world.

Tolerability

The following part of the discussion will focus on tolerability aspects of GLP-1 analogues.

Gastrointestinal adverse events

Nausea and diarrhoea were very common, whereas vomiting, constipation, abdominal pain and dyspepsia were most frequently reported adverse reactions during clinical trials with GLP-1 RAs [Garber *et al.* 2011; Zinman, 2009; Russell-Jones, 2009; Russell-Jones *et al.* 2009; Buse, 2010; Pratley, 2011]. These gastrointestinal adverse reactions are transient and usually diminish within a few days or weeks on continued treatment. These events vary in severity depending on the choice of drug. For example, a smaller proportion of patients reported nausea or vomiting after liraglutide treatment compared with patients treated with exenatide (25.5% of the study population *versus* 28% with twice-daily exenatide; vomiting, 6.0% of the study population *versus* 9.9% with twice-daily exenatide) [Buse *et al.* 2010]. Similarly, nausea and vomiting due to taspoglutide treatment were usually resolved within 1 day, and subsequent taspoglutide administrations were less likely to induce nausea [Nauck *et al.* 2009].

Kesavadev *et al.* [2011] studied efficacy and safety of liraglutide (GLP-1 analogue) in overweight and obese DM patients in India. Efficacy and tolerability of liraglutide was noted in the study. Nine patients reported adverse events (AEs). Nausea was the most common AE ($n=6$) followed by feeling of satiety ($n=3$), and vomiting ($n=1$). Nausea persisted for 1–2 weeks in five of six patients, while in one patient it subsided after 5 days of therapy. Vomiting was seen in one subject for the first 3 days, while feeling of satiety was noticed for 1 month in three patients. All AEs were self-limiting and of minimal clinical significance. None of the patients reported any serious AE [Kesavadev *et al.* 2012].

An observational study in 196 patients reported glycaemic control with low risk of hypoglycaemia with significant weight loss and low incidence of minor hypoglycaemia in obese Indian patients with type 2 DM [Kaur *et al.* 2014]. In the same study out of 175 patients, 44 (25%) experienced adverse drug reactions (ADR). Most common AEs were nausea, burping and eructation (10%) and diarrhoea (4.7%). Nausea associated with liraglutide was transient, decreasing after 4 weeks of therapy. However, liraglutide had to be discontinued in seven patients due to ADRs not responding to symptomatic treatment (one had intractable nausea and vomiting, four had severe diarrhoea) [Kaur *et al.* 2014].

Conclusion

GLP-1 analogues improved overall glycaemic control, and are well tolerated. The maximum benefits are seen if initiated early in the course of the disease. Clinically significant reduction in body weight, systolic blood pressure and improvement in lipid profile are seen with GLP-1 analogue therapy in addition to glycaemic control. The gastrointestinal AEs were observed in Indian patients and were well tolerated in maximum number of patients. These AEs are class specific, but vary in intensity depending on the agent used. In a nutshell, GLP-1 analogues present a new way of tackling diabetes, but cost is a major concern in India, as the cost of the drug is paid as an out of pocket expense.

Conflict of interest statement

The author declares that there is no conflict of interest.

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