REVIEW ARTICLE

Will Oral Semaglutide be a Game-Changer in the Management of Type 2 Diabetes in Indian Context?

ARJUN BAIDYA*, SAURABH MISHRA†, ASHOK VENKATANARASU‡

*Associate Professor, Dept. of Endocrinology, NRS Medical College, Kolkata, West Bengal
†Consultant Physician and Diabetologist, Centre for Diabetes and Endocrine Diseases, Kanpur, Uttar Pradesh
‡Consultant Endocrinologist, Sanjeevani Thyroid Sugar and Hormones Clinic, Hyderabad, Telangana

ABSTRACT

The glucagon-like peptide-1 receptor agonists (GLP-1RAs) have important beneficial effects on glycemic control and body weight along with their pleiotropic effects on various systems of the body. However, until now these agents were administered via an injection posing a challenge to patient convenience. Oral semaglutide is a first in class oral GLP-1RA co-formulated with an absorption enhancer for the treatment of type 2 diabetes mellitus (T2DM). The clinical efficacy and safety of oral semaglutide has been extensively evaluated in the Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) program of clinical trials. This review shall elaborate on the unique diabetes situation in India and why the oral GLP-1RA (semaglutide) will be a game-changer in the Indian setting.

Keywords: Semaglutide, type 2 diabetes, GLP-1RAs, glucose-lowering drugs

Background

Type 2 diabetes mellitus (T2DM) accounts for almost 90% of all diabetes cases worldwide. The prevalence of diabetes around the world is likely to reach up to 592 million by the year 2035.[1] The genetic component among South Asians makes them up to four times more susceptible to T2DM compared to other ethnic groups.[2] The concept of an "Asian Indian Phenotype" was advanced by Mohan et al,[3] as the presence of insulin resistance along with abdominal obesity, higher C-reactive protein (CRP) and lower levels of adiponectin. Asian Indians have a lean-fat body composition with higher levels of central obesity (waist circumference, waist-to-hip ratio and visceral fat).

They also have more body fat for a given body mass index (BMI) compared to other ethnic groups.[4] Thus, the lean-fat Indian is at a larger risk of diabetes, which results from genetic predisposition along with other factors like lifestyle changes, rapid urbanization and changing dietary patterns.

The baseline data of Indian type 2 diabetic patients in an observational study showed high prevalence of micro- and macrovascular complications due to poor glycemic control (mean glycated hemoglobin [HbA1c] = 9.2 ± 1.4).[5] The relation between glycemic status and incidence of complications highlights the importance of optimum glycemic control in T2DM. The glycemic control, however, continues to deteriorate as the disease progresses.[6]

Obesity which is often described as 'Diabesity' in obese type 2 diabetics is a major risk factor leading to hypertension, hyperlipidemia, atherosclerotic cardiovascular disease (ASCVD), and its complications, and also to many types of cancers.[7] The prevalence of diabesity is reaching epidemic proportions around the globe with no clear guidelines for its optimum management.[8] In Indian adults aged 20 to 69 years, the prevalence of overweight will more than double while the prevalence of obesity will triple by 2040.[9]

Address for correspondence

Dr Arjun Baidya
Associate Professor
Dept. of Endocrinology, NRS Medical College, Kolkata, West Bengal
E-mail: arjun.baidya@gmail.com

The management of patients with T2DM has become individualized with different therapies available and owing to the presence of specific patient factors that influence the appropriate choice of medication. In 2018, the American Diabetes Association (ADA) presented a decision algorithm, which included the assessment of key patient characteristics including comorbidities like ASCVD, chronic kidney disease (CKD) or heart failure (HF). The presence of these comorbidities should allow preferential use of certain classes of glucose-lowering drugs as second-line therapy.[10]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an established class of glucose-lowering drugs that have a pleiotropic action on the pathophysiological defects of T2D – leading to effective glycemic control, loss of weight, minimal risk of hypoglycemia and a consistent safety profile.[11]GLP-1RAs have similar mechanisms of action but they vary in structure, pharmacokinetics and efficacy (their ability to reduce HbA1c, body weight and cardiorenal protection).[12,13]

The previous success in clinical trials of exenatide and liraglutide renewed interest in the GLP-1 therapy area. The daily injection regime was inconvenient for some patients and hence, better patient convenience was needed for patient adherence and satisfaction.[14] The fear of injections and difficulty in administration along with the perception of injectable therapy was a major barrier to the use of GLP-1RA therapy.[11]

Semaglutide is a GLP-1RA with 94% structural homology to endogenous GLP-1, and it has three important structural differences that prolong its half-life but do not compromise receptor binding. The efficacy and safety of subcutaneous semaglutide is already demonstrated in numerous clinical studies. The efficacy of oral semaglutide was expected to correspond with subcutaneous semaglutide and was proved with the Peptide InnOvatioN for Early diabEtes tReatment (PIONEER) studies.[15] Oral semaglutide is co-formulated with SNAC {Sodium N-[8-(2-hydroxybenzoyl)amino] caprylate} which is an absorption enhancer and promotes semaglutide absorption across the gastric mucosa.

This review will specifically elaborate on why oral semaglutide will be ideal for Indian diabetic patients in the light of evidence from studies on oral and injectable semaglutide.

Diabetes and Prediabetes

The Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study was a national study designed to estimate the prevalence of diabetes and prediabetes in the Indian population. It was the largest ever study conducted to capture the diabetes scenario in India.

The evidence of prevalence were reported from 15 states, which represented 50.7% of the adult population of the country. The main factors identified to be driving the epidemic of diabetes in India were obesity, age and a family history of T2DM. Prediabetes prevalence in India was high and exceeded diabetes in many states implying a huge risk of progression to overt diabetes.[16] This finding is very important in the Indian context as it has been shown in several studies that Asian Indians progress faster through the prediabetes stage when compared with other ethnic groups.[17]

Beta-cell dysfunction was prominent even with mild dysglycemia in the Asian Indian population (impaired glucose tolerance [IGT] or impaired fasting glucose [IGF] or both). This finding is important as it highlights the need for primary prevention strategies focussing on preservation of beta-cell function and reduction in cell decline.[18]

Increase in beta-cell function and insulin biosynthesis was shown with semaglutide along with improved proinsulin to insulin ratios when compared with other antidiabetic agents including sulfonylureas, which increase insulin secretion with no effect on the biosynthesis of insulin. Also, reduction in insulin resistance was greater with semaglutide vs. placebo, sitagliptin or exenatide extended-release (ER).[19]

Glycemic efficacy of oral semaglutide

Oral semaglutide was effective in reducing HbA1c across the PIONEER trials. In the PIONEER 1 trial, oral semaglutide monotherapy significantly reduced baseline HbA1c compared with placebo after 26 weeks of treatment in patients with early T2DM.

In patients with established T2DM who were receiving background oral antidiabetic medications (PIONEER 2-4), 14 mg of oral semaglutide was more effective than empagliflozin 25 mg, sitagliptin 100 mg and similar to liraglutide 1.8 mg at week-26. Flexible dose adjustment of oral semaglutide was more effective than sitagliptin 100 mg for reducing HbA1c at 52 weeks in the PIONEER 7 trial.

In advanced T2DM patients receiving insulin, oral semaglutide significantly reduced HbA1c as compared to placebo at weeks-26 and week-52. In patients with moderate renal impairment (PIONEER 5), oral semaglutide 14 mg was significantly more effective

than placebo at reducing HbA1c at week-26. In high cardiovascular (CV) risk patients (PIONEER 6), oral semaglutide reduced HbA1c by a mean of −1.0% vs. −0.3% in the placebo group.

Proportion of patients who achieved ADA recommended target of HbA1c <7.0% was persistently greater with 7 and 14 mg of oral semaglutide as compared with placebo and active comparators. Fasting plasma glucose was also generally reduced in patients on oral semaglutide, compared to the placebo and active comparator groups.[20]

Obesity

Obesity in India has been rampantly increasing in prevalence and the recent trends indicate a rate any where between 13% to 50% among the urban population and 8% to 38.2% in rural population of obesity. Obesity among Asian Indians has distinctive features like greater truncal, intra-abdominal, subcutaneous and total adipose tissue when compared with Caucasians.[21] Several comorbid conditions are associated with obesity like hypertension, hyperglycemia, dyslipidemia, nonalcoholic fatty liver disease (NAFLD), etc. This constellation of conditions is broadly defined as metabolic syndrome.[22]

NAFLD is an important component of metabolic syndrome which can progress to fibrosis and even cirrhosis in the presence of portal inflammation (nonalcoholic steatohepatitis [NASH]).[23] Approximately one-fourth of the urban Indian population has NAFLD and according to a case-control study, Asian Indians in North India with NAFLD have increased adipose tissue, fasting hyperinsulinemia, IGT and metabolic syndrome.[24] The improvement in NAFLD/NASH with GLP-1RAs is thought to be through an indirect mechanism – through which these drugs aid in reducing inflammation.[25]

Dyslipidemia is described as an increased level of total and low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol and hypertriglyceridemia (present alone or in concurrence).[26] In Asian Indians with insulin resistance, the plasma adipose tissue metabolites, fatty acids and leptin are higher along with lower adiponectin levels.[27] In a study conducted with oral semaglutide to assess its effects on postprandial glucose and lipid metabolism, it was found that fasting LDL and total cholesterol concentrations were lower with oral semaglutide compared with placebo.

Treatment with oral semaglutide also resulted in lower fasting and postprandial triglycerides than with placebo. In the PIONEER 6 trial, improvements in elevated total cholesterol, LDL and triglycerides, reduced HDL were seen with oral semaglutide. The trial met its primary objective of proving CV safety of oral semaglutide.[28]

Body weight reduction with oral semaglutide

In the PIONEER clinical trial program, greater number of patients achieved a weight loss of ≥5% across clinical trials with oral semaglutide 7 and 14 mg (13-44%) versus placebo (3-15%) and active comparators (10-36%) at week-26, which was sustained at the end of the trial. Other body size measures like BMI and waist circumference were also reduced with oral semaglutide compared with placebo and active comparators.[20]

Atherosclerotic Cardiovascular Disease

According to the Global Burden of Disease study, 24.8% of all deaths in India are associated with cardiovascular disease (CVD). Ischemic heart disease and stroke are responsible for 21.1% of all deaths in India.[29] T2DM and the associated microvascular (retinopathy, neuropathy and nephropathy) and macrovascular (coronary artery disease, peripheral arterial disease and stroke) complications contribute substantially to the morbidity and mortality of the disease. The core pathophysiological mechanism leading to arterial lumen narrowing is atherosclerosis. Recent studies have indicated the central role played by endothelium and inflammation in atherosclerosis.[30]

In animal studies, semaglutide reduced the size of the aortic atherosclerotic plaque lesion independent of its effect on diabetes, body weight, and lipids.[25] It is important to note that the findings from the cardiovascular outcomes trial (CVOT) with semaglutide showing effects – consistent with reduction in atherosclerotic burden, suggest that the findings seen in animal studies may translate to humans.[14]

The largest cause of diabetes associated morbidity and mortality is CVD. The international diabetology and cardiology guidelines have been updated to put forth a combined approach for the management of T2DM and CVD. The GLP-1RAs or sodium-glucose co-transporter 2 inhibitors (SGLT2i), which have a demonstrated CV benefit are recommended as first- or second-line agents in this regard.

The CAPTURE study found that almost one out of three adults with T2DM had established CVD. Most of the burden was contributed by ASCVD with coronary artery disease, carotid artery disease and stroke with

maximum contribution. The management of most participants was not according to recent guidelines on diabetes and cardiac disease. There was an unmet need of reducing risk through interventions based on current evidence.[31]

Cardiovascular safety of oral semaglutide

The PIONEER 6 trial was a CVOT designed to establish the CV safety of oral semaglutide; it was not powered for proof of superiority and CV benefit. The investigators concluded the noninferiority of oral semaglutide safety profile to placebo, on a background of standard care. The CVOT of oral semaglutide to prove superiority in major adverse CV event (MACE) reduction is ongoing as A Heart Disease Study of Semaglutide in Patients with Type 2 Diabetes (SOUL). Pooled analysis, which combined data from CVOTs of oral and injectable semaglutide showed that the once-daily oral and once-weekly injectable showed very similar effects on glycemic and body weight control. Post-hoc analyses suggest a potential for improved CV outcomes with semaglutide irrespective of the route of administration.[32]

Hypoglycemia

There is a huge corpus of evidence available suggesting that intensive glycemic control with a goal of euglycemia should be instituted as early as possible in diabetic patients. The Diabetes Control and Complications Trial (DCCT) and Stockholm Diabetes Intervention Study (SDIS) showed reduction in the incidence of microvascular complications with intensive glycemic control in type 1 diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) and Kumamoto study found that tighter glycemic control can delay the onset and progression of micro- and macrovascular complications in T2DM patients.[33-37]

However, due to the risk of hypoglycemia, strict glycemic control is not achieved in majority of patients in real life clinical settings, and this was also a major finding in the above studies. In the DCCT, there was a threefold increase in severe hypoglycemia with intensive therapy as compared with conventional therapy–during the study. In the UKPDS, major hypoglycemic episode in a year was significantly higher in the intensive treatment group.[33,35]

The risk of hypoglycemia is increased with insulin excess (exogenous insulin or agents causing release of insulin), and faulty glucose regulation. Progressive beta-cell failure in T2DM increase the characteristics and severity of hypoglycemic episodes.[37]

Hypoglycemia is a significant barrier to patient adherence to medications leading to suboptimal glycemic control along with the risk of development of complications. Recurrent hypoglycemia worsens the quality of life and can also prove fatal.[38]

In a cross-sectional study conducted in an Indian hospital, to find out proportion of T2DM patients reporting at least one or other symptom of hypoglycemia, almost 96% of subjects reported one or the other symptoms of hypoglycemia. Severe hypoglycemia episodes were reported by 19% patients and 8% patients required admission due to hypoglycemia. This study showed the reported prevalence of hypoglycemia among T2DM patients and the urgent need for intervention.[39]

GLP-1RAs have an inherently low propensity to cause hypoglycemia, which was also consistent with oral semaglutide. The PIONEER 4 study was associated with very low proportions of patients experiencing severe or blood-glucose confirmed hypoglycemia (1% and 2% patients, compared with 2% in placebo group). In the PIONEER 8 study, the number of such events was higher in patients having a background of insulin therapy, but the addition of oral semaglutide to insulin did not increase the proportion of patients with hypoglycemia compared to placebo. Most events occurred in patients receiving basal-bolus background therapy with insulin.[40]

Conclusion

Oral semaglutide is a revolutionary new drug in the management of T2DM which overcomes the injectable barrier associated with GLP-1RA therapy. It is administered as a co-formulation with an absorption enhancer called SNAC. Oral semaglutide has glycemic control and weight reduction benefits–consistent with the GLP-1RA class. India is fast becoming the type 2 diabetes capital of the world with associated conditions like obesity and ASCVD complicating the picture. The pleiotropic benefits of GLP-1RAs are well known and are consistent with oral semaglutide. All guidelines relating diabetes and cardiology have evolved and now recommend a cardiovasculocentric approach to T2DM as opposed to earlier more glucocentric approach.

With oral semaglutide, we have robust data on the clinical efficacy and safety of oral semaglutide, as well as the added advantage of once-daily oral administration, improving patient convenience. The beneficial effects with oral semaglutide like superior

glycemic control, weight loss, CV safety and minimal risk of hypoglycemia make it a game-changer for T2DM management in India.

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