Original Article

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Insulin Resistance in T2DM – Focus on Lobeglitazone

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Abstract

Insulin resistance (IR) is a key underlying pathophysiology in type 2 diabetes mellitus (T2DM). Thiazolidinediones (TZDs) are oral antidiabetic drugs (OADs) that can address IR. However, their use has been limited due to the associated adverse effects. A novel TZD – Lobeglitazone – has been introduced, which is a dual agonist of peroxisome proliferator-activated receptor (PPAR) and has been reported to have a favorable safety and efficacy profile. This paper summarizes some key characteristics of this agent and the findings from two recent studies conducted in Korea and India.

Keywords: *Type 2 diabetes mellitus, Lobeglitazone, insulin resistance*

Introduction

Diabetes, a progressive disease, is one among the most rapidly escalating health crises globally of the current century. By 2045, 124.9 million people aged 20 to 79 years are estimated to be affected by diabetes in India.[1]An evaluation of the prevalence of diabetes among adults in our country, from the National Non-communicable Disease Monitoring Survey, noted the prevalence of diabetes to be 9.3% and that of impaired fasting glucose to be 24.5%.[2]It is known that diabetes is associated with a range of complications, both macrovascular and microvascular. A recent systematic review of the prevalence of diabetes and associated complications noted that the prevalence of diabetes varied between 2.02% and 40.3%. Additionally, prediabetes prevalence varied between 2.4% and 47.6%. The prevalence of chronic complications was noted as follows: nephropathy – between 0.9% and 62.3%, retinopathy - 4.8% to 21.7%, neuropathy - between 10.5% and 44.9%.[3]

There are various classes of medications available for decreasing glucose levels, including metformin, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, dipeptidyl peptidase-4inhibitors, thiazolidinediones (TZDs), sulfonylureas, and insulin.[4] Yet, despite the availability of so many drugs, the levels of diabetes control are still low across the country.[2]

A dysfunction of pancreatic β-cells and insulin resistance (IR) are major players in type 2 diabetes mellitus (T2DM) and TZDs are known to address IR.[5] TZDs are a class of oral antidiabetic drugs (OADs) that have high efficacy and no associated hypoglycemia.[4]These agents have effects on the adipose tissue.[6] They activate peroxisome proliferator-activated receptor γ (PPAR-γ),[5,6] and work by a reduction in visceral fat mass and activity, an increase in subcutaneous fat mass, and a reduction in hepatic triglycerides.[6] This leads to an improvement in insulin sensitivity.[5]However, there may be some unwanted effects with the use of these agents, like weight gain and risk of heart failure.[4]It is known that the use of pioglitazone and rosiglitazone has plummeted owing to cardiac and bladder cancer issues.[5]Thus, there is a need for an effective and safer agent to tackle IR in T2DM.

Lobeglitazone has been introduced as a novel TZD that has shown favorable outcomes in T2DM.[6]The drug received approval for type 2 diabetes management in Korea in 2013.[5] It has been authorized in India as well.[6] Several studies have assessed the efficacy and safety of lobeglitazone in T2DM. Lobeglitazone appears to have a favorable safety profile. The occurrence of peripheral edema, a common adverse effect of TZDs, has been reported to range between 3.6% and 28.9% with pioglitazone across studies.[5]On the contrary, a recent real-world study noted edema in 1.97% patients with lobeglitazone.[7]Additionally, as an additional therapy to metformin, no significant difference has been reported in mean weight gain between lobeglitazone and pioglitazone.[5]The use of TZDs over the long term has also been reported to adversely affect bone mineral density (BMD), as observed with rosiglitazone.[5] However, lobeglitazone has been found not to cause significant changes in total hip and femur neck BMD in comparison with placebo.[7]

Two studies have been published in recent years that substantiate the favorable effects of lobeglitazone in patients with T2DM. This paper discusses some characteristics of this novel TZD and the evidence from these two studies.

Discussion

Structure and pharmacokinetics of lobeglitazone

The structure of rosiglitazone was changed to incorporate a p-methoxyphenoxy group at the pyrimidine component's position-4 to develop lobeglitazone. Therefore, its binding affinity to PPAR-γ is augmented, as much as 12-fold greater compared to the other two TZDs – rosiglitazone and pioglitazone. There is a 2,4-thiazolidinedione group connected to an ethoxy-benzyl N-methylamino group.[5,8] In addition to PPAR-γ, lobeglitazone can also bind to PPAR-α.[8]So, it is a dual agonist of PPAR-α and γ, which sets it apart from rosiglitazone and pioglitazone.[6]

Among healthy individuals (males), peak plasma levels have been reported at 1 to 3 hours following a single oral dose. It has a half-life of 7.8-9.8 hours. Further, in healthy male individuals, following repeated dosing as a once-daily regimen, steady-state concentrations were attained by the fifth day, with no notable drug accumulation. The clearance of lobeglitazone has been reported to occur primarily through hepatic metabolism, with renal excretion projected to be less than 1%.[5]

Recent clinical evidence on the role of lobeglitazone in T2DM

One of the recently published studies on the efficacy of lobeglitazone presents a real-world assessment of the agent in T2DM patients in Korea.[7] The second study is an Indian randomized, double-blind study that compared the efficacy of this agent with pioglitazone as an add-on to metformin therapy.[6]

Kim and colleagues conducted a multicenter, observational study to determine the safety and efficacy of lobeglitazone in real-world settings.[7] The study included 2228 patients with T2DM who had been given 0.5 mglobeglitazone for over 1 year. The investigators obtained data on the patients from medical records. The parameters evaluated included glucose level, glycosylated hemoglobin (HbA1c), and lipid levels at 3, 6, 12, 18, 24, 36, 42, and 48 months following treatment administration. Safety was assessed based on major adverse events, including weight gain, edema, hypoglycemia, fractures, bladder cancer, congestive heart failure, among others, and any adverse events observed over the treatment period. The efficacy analysis set of the study

included 1651 patients. There was an improvement in glucose levels from 174.71±58.13 at baseline to 139.10±44.88 at follow-up with lobeglitazone treatment. Additionally, a significant reduction in HbA1c was noted from 8.17±1.36% 7.12±1.13%. Furthermore, irrespective of statin administration, lobeglitazone therapy was associated with a significant reduction in total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides, and an increase in high-density lipoprotein cholesterol (HDL-C). Patients given lobeglitazone exhibited a decrease in HbA1c over the initial 6 months of treatment. Subsequently, the levels exhibited consistency from 6 to 42 months. The mean treatment difference in HbA1c and glucose level is shown in Table1.

Table 1. Mean treatment difference in HbA1c and glucose

Parameter	Treatment difference (Mean ±Standard deviation)
HbA1c (%)	-1.05±1.35
Glucose (mg/dL)	-34.05±62.00

The second study of interest is the one conducted by Joshi *et al* in India.[6] According to the authors, there had been no prior study on this agent conducted in the country before the start of this one. Therefore, this study holds relevance in the Indian scenario. A multicenter, randomized, double-blind study was conducted over a period of 16 weeks that randomly allocated patients with HbA1c 7.5% or higher and up to 10.5% into two equal groups. The study compared the efficacy of once-daily lobeglitazone 0.5 mg and once-daily pioglitazone 15 mg in patients having insufficient glycemic control on metformin. In the lobeglitazone arm, a statistically significant decrease was noted in HbA1c at 16 weeks (Table 2). Additionally, there was a statistically significant decrease in fasting glucose and postprandial glucose in the lobeglitazone arm (Table 2). A statistically significant reduction in IR was noted in the lobeglitazone arm. With regard to change in fasting insulin, homeostasis model assessment (HOMA)-β, and HOMA-IR, lobeglitazone was not inferior to pioglitazone. Furthermore, 11.7% of the patients in the lobeglitazone group and 12.2% in the pioglitazone group developed treatment-emergent adverse events (similar).

Table 2. Changes in HbA1c, fasting glucose, and postprandial glucose at 16 weeks

Variable	LS mean (SE) change		LS mean difference
	Lobeglitazone	Pioglitazone	
HbA1c (%)	-1.01 (0.09)	-1.06 (0.08)	0.05 (0.12)
FPG (mg/dL)	-41.31 (3.25)	-35.54 (3.09)	-5.76 (4.32)
PPG (mg/dL)	-41.24 (5.81)	-32.87 (5.57)	-8.37 (7.72)

LS: Least squares; SE: Standard error; FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose

Kim and colleagues put forward data on the durability of the effects of lobeglitazone in T2DM in real-world scenarios and validated its safety over the long run while Joshi and colleagues noted that the drug was safe and effective in Indian T2DM patients while being non-inferior to pioglitazone.

Conclusion

TZDs are a class of agents that target IR, which is a major underlying pathology in T2DM. The concerns of heart failure and bladder cancer, among some other adverse effects, have limited the use of these agents in the management of type 2 diabetes. However, a novel TZD, lobeglitazone, with its dual PPAR agonist activity, seems to hold

promise as a potential agent in the management of T2DM patients. Several studies over the years, involving a large number of patients (with over 2000 patients in the study by Kim and colleagues alone), have put forward data on its efficacy and safety in T2DM management. Two recent studies from Korea and India, discussed in detail in this paper, also affirm the effects of this agent in addressing IR and improving glycemic variables in T2DM patients, while having a favorable safety profile. The agent has also been shown to have favorable effects on lipid levels. On account of its insulin sensitizing effect, lobeglitazone could be a valuable addition to the diabetes therapeutic armamentarium.

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