ABSTRACT

Incidence of dyslipidemia among people suffering from diabetes is shooting up each year around the globe. A novel target to control this disorder has agonistic activity on peroxisome proliferator-activated receptors (PPAR-α and PPAR-γ) receptors simultaneously. While the α form has lipid lowering effects, γ leads to lowering in blood glucose. Saroglitazar (Lipaglyn), developed by Zydus Cadila, first new chemical entity (NCE) discovered and developed indigenously by an Indian Pharma Company, has agonistic activity on both PPAR-α and PPAR-γ receptors. Unlike other glitazars that were discontinued during their development, saroglitazar enjoys a high benefit-to-risk ratio. It is indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with Type 2 diabetes mellitus not controlled by conventional therapy. Dose recommended for Lipaglyn is 4mg once a day.

Key words: Saroglitazar, glitazar, diabetic dyslipidemia, PPAR-α & PPAR-γ agonist.

INTRODUCTION

Although there has been tremendous research in the areas dealing with prevention and management of cardiovascular diseases, yet people with diabetes mellitus still have critically high morbidity and mortality subsequent to cardiovascular diseases.[1] Almost 80% of diabetic population have associative dyslipidemia (low high density lipoprotein (HDL), increased triglycerides (TG), and postprandial lipemia) which necessitates a drug therapy for treatment. This pattern is mostly seen in diabetes mellitus type 2 (T2DM) and may be a treatable risk factor for consequent cardiovascular diseases.[2] Hypertriglyceridemia and reduced HDL commonly occur in poorly controlled diabetes mellitus type-1 and even ketoacidosis. [3] The leading cause of diabetic dyslipidemia is the increased free fatty-acid (FFA) release from insulin-resistant fat cells.[4-7] The inability of insulin to suppress FFA release leads to augmented hepatic very-low-density lipoprotein (VLDL) cholesterol production,[8] which parallels the extent of hepatic fat accumulation.[9] Activation of peroxisome proliferator-activated receptors (PPAR) - γ (predominantly expressed in adipose tissue) by thiazolidinediones (TZDs i.e. rosiglitazone and pioglitazone) may appear to lessen hepatic and skeletal insulin resistance through one or several mechanisms that control adipocyte signaling and metabolism.[10, 11-13]

The three PPAR receptors [PPAR-α, PPAR-β (or PPAR-δ, fatty acid activated receptor) and PPAR-γ] form a subfamily of nuclear receptors. These receptors function as lipid sensors and manage the regulation of expression of a large number of genes involved in metabolism. They form an obligate heterodimer with retinoid X receptor (RXR), which binds to peroxisome proliferator response elements (PPREs) located within the regulatory domains of target genes. Activation of the PPAR by its ligand results in recruitment of co-activators and loss of co-repressors that remodel the chromatin and activate transcription.[14]
PPAR-α is mainly expressed in liver and activation of the receptor results in increased hepatic lipid uptake and oxidation. Thus, the phenotype of the PPAR-α knock-out mouse in the fasted state is hypoglycemia, hypertriglyceridemia, hypoketonaemia and hepatic steatosis.[15]

So activators of PPAR-α are used to treat dyslipidaemia. They decrease plasma TG levels and increase HDL-C levels.[16] The latter effect is due to the increased hepatic production of major components of HDL-C, namely apolipoprotein (apo) A1 and AII.[17,18] PPAR-α also controls the genes involved in fatty acid oxidation (regulating plasma lipid levels) and hence maintains energy homeostasis[10, 19-21] (Table1). Various glitazars i.e. dual PPAR agonists with affinity towards both PPAR-α and PPAR-γ have been in clinical development[24] (Table 2).

Table 1: Principal location of PPAR subtypes and metabolic effects [22-23]

<table>
<thead>
<tr>
<th>Location</th>
<th>PPAR-α</th>
<th>PPAR-β</th>
<th>PPAR-γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actions in target tissues</td>
<td>↑ FA uptake</td>
<td>↑ FA uptake</td>
<td>↑ FA oxidation</td>
</tr>
<tr>
<td></td>
<td>↑ FA oxidation</td>
<td>↓ FA release</td>
<td>↑ Mitochondrial genesis</td>
</tr>
<tr>
<td></td>
<td>↑ Apo AI, Apo AII</td>
<td>↓ Pro-inflammatory cytokines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Insulin action</td>
<td>↑ Insulin resistance</td>
<td>↑ Body fat</td>
</tr>
<tr>
<td></td>
<td>▼ Circulating TG</td>
<td>▼ Body weight gain</td>
<td>▼ HDL-C</td>
</tr>
<tr>
<td></td>
<td>▼ HDL-C</td>
<td>▼ Atherosclerosis</td>
<td>▼ Liver fat</td>
</tr>
<tr>
<td></td>
<td>▼ Atherosclerosis</td>
<td>▼ Liver fat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▼ Body weight gain</td>
<td>▼ Insulin action</td>
<td></td>
</tr>
<tr>
<td></td>
<td>^ Vasoprotection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consequential effects

<table>
<thead>
<tr>
<th>Consequential effects</th>
<th>Location</th>
<th>PPAR-α</th>
<th>PPAR-β</th>
<th>PPAR-γ</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼ Circulating TG</td>
<td>Liver, endothelial cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑ HDL-C</td>
<td>Adipocytes, vascular cells</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>▼ Atherosclerosis</td>
<td>Skeletal muscle</td>
<td></td>
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<tr>
<td>↑ Liver fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▼ Insulin resistance</td>
<td></td>
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<tr>
<td>↑ Body weight gain</td>
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<tr>
<td>▼ Body fat</td>
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<tr>
<td>▼ Insulin action</td>
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<tr>
<td>^ Vasoprotection</td>
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</tbody>
</table>

Table 2: Dual PPAR-α/γ activators that have been in clinical development

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Company</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muraglitazar</td>
<td>Bristol-Myers Squibb</td>
<td>Approved then withdrawn from market in 2006 due to CV events (heart failure)</td>
</tr>
<tr>
<td></td>
<td>(United States of America)</td>
<td></td>
</tr>
<tr>
<td>Tesoglitazar</td>
<td>AstraZeneca (United Kingdom)</td>
<td>Discontinued following phase III trials due to elevated creatinine levels associate with decreased glomerular filtration</td>
</tr>
<tr>
<td>Ragaglitazar</td>
<td>Novo Nordisk (Denmark)</td>
<td>Discontinued 2002 due to bladder tumors in rodents</td>
</tr>
<tr>
<td></td>
<td>(outlicensed by Dr. Reddy’s)</td>
<td></td>
</tr>
<tr>
<td>Chiglitazar</td>
<td>Shenzhen Chipscreen, (China)</td>
<td>Development suspended in Phase II</td>
</tr>
<tr>
<td>Cevoglitazar</td>
<td>Novartis (Switzerland)</td>
<td>Discontinued in 2008 due to the lack of a sufficiently positive benefit/risk</td>
</tr>
<tr>
<td>Aleglitazar</td>
<td>Hoffman-La-Roche (Switzerland)</td>
<td>Halted at Phase III in 2013 due to GI bleeding, bone fractures, heart failure</td>
</tr>
<tr>
<td>TAK-559</td>
<td>Takeda (Japan)</td>
<td>Discontinued in 2005 in Phase III following abnormalities in liver enzymes</td>
</tr>
<tr>
<td>Naveglitazar</td>
<td>Eli Lilly (USA)</td>
<td>Discontinued in 2006 due to adverse preclinical findings in rodents</td>
</tr>
<tr>
<td>AVE-0847</td>
<td>Sanofi-Aventis (France)</td>
<td>Development terminated due to glitazar: reprioritization of product portfolio</td>
</tr>
<tr>
<td>Sipoglitazar</td>
<td>Takeda (Japan)</td>
<td>Discontinued in 2006 due to serious safety concerns</td>
</tr>
</tbody>
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Saroglitazar for diabetic dyslipidemia
For this review article, resources pertinent to the topic were searched in the months of September, October and November 2013 from online papers (pubmed, Science Direct) using the following key words - saroglitazar, glitazars, diabetic dyslipidemia, new antidiabetic drugs, novel antidiabetic drug targets. About 45 articles were retrieved (including abstracts) and 35 were used for preparation of the review which has been mentioned in the reference list. The articles were examined and the ones in which the information concerning the role of PPAR-α and PPAR-γ, chemistry, mechanism of action, pharmacokinetics, dosage, preclinical and clinical efficacy and safety studies for saroglitazar, were discussed in details were considered. All the data collected was then used to draft a comprehensive review article about this new drug saroglitazar, with an aim to cover all its important aspects.

**Basic Chemistry**

Saroglitazar, [(S)-a-ethoxy-4-{2-[2-methyl-5-(4-methylthio)phenyl]-1H-pyrrol-1-yl]-ethoxy}]-benzenepropanoic acid magnesium salt, (figure 1) is the first glitazar that has been given marketing authorization in India and is approved for the treatment of diabetic dyslipidemia. The empirical formula of saroglitazar is [CH$_{28}$NO$_4$S]$_2$ Mg and the molecular mass is 900 g/mole. It is an amorphous off-white powder.

**Mechanism of action**

Saroglitazar aims at both PPAR-γ and PPAR-α receptors, whereas TZDs (used for treatment of type 2 diabetes) aims at PPAR-γ and the fibrates (used for treatment of dyslipidemia) aims at PPAR-α only. (Figure 2)

According to Zydus Cadila, saroglitazar has a predominant affinity for the PPAR-α isoform, and an intermediate affinity for PPAR-γ, and has exhibited advantageous effects on lipids and glycemic controls without any adverse effects. At a once daily dose of 4 mg, it brings down TG and LDL-C levels and raises HDL-C. It also shows a reduction in fasting plasma glucose and glycosylated hemoglobin.

**Preclinical Development**

The extensive preclinical studies of saroglitazar were conducted using various animal models for dyslipidemia & T2DM. These confirmed that saroglitazar has dual lipid lowering and anti-hyperglycemic effects. In hyperinsulinemic-euglycemic clamp study, saroglitazar showed significant improvement in glucose infusion rate indicating insulin sensitizing effect. Saroglitazar reduced TG levels by 90%, total serum cholesterol in cholesterol-fed rats by up to 77% and LDL-C by 67%. It also improved lipid clearance by up to 68%. In diabetic models, it reduced serum glucose by up to 65% and improved oral glucose tolerance by 59%. It also reduced fasting insulin and FFA levels in db/db mice and Zucker fa/fa rats.
Safety pharmacology studies indicated that saroglitazar does not affect central nervous system (CNS), cardiovascular system (CVS), respiratory system (RS) and gastrointestinal (GI) functions at several fold higher doses than therapeutic doses. Additionally, comparative mechanistic studies in rats and non-human primates employing molecular biomarkers demonstrated no carcinogenic risk to humans.

**Clinical Development** [36]

As a part of the 8 year long clinical development programme (Figure 3), extensive Phase-I, Phase-II and Phase-III clinical trials were carried out. Phase I was a prospective, randomized, double blind, placebo controlled, single-center study to evaluate the pharmacokinetics, safety and tolerability of saroglitazar in 136 healthy volunteers.

Phase II was a prospective, randomized efficacy and safety study of saroglitazar in 222 subjects, conducted during four phase II programs for proof of concept and dose finding. Saroglitazar doses studied were 0.5, 1, 2, and 4 mg once daily for 12 weeks.

Phase III study was conducted during two phase III programs. Results from the first Phase III programme with Pioglitazone as a comparator drug in diabetic patients showed that the 4 mg dose of saroglitazar led to a reduction in TG, LDL-C, fasting plasma glucose and glycosylated hemoglobin (HbA1c), and an increase in HDL-C thereby confirming its beneficial effects of both lipid and glycemic control in diabetic patients.

In the second Phase III study, saroglitazar was investigated in diabetic dyslipidemic patients inadequately controlled with conventional statins therapy. This study’s results confirmed that it had a pronounced beneficial effect on both the lipid and glycemic parameters in all subjects.

**Pharmacokinetic studies** [36]

**Absorption**

Saroglitazar is rapidly and well absorbed across all doses in the single-dose pharmacokinetic study, with a median time to the peak plasma concentration (tmax) of less than 1 h (range 0.63–1 h) under fasting conditions across the doses studied. The maximum plasma concentration (Cmax) extended from 3.98 to 7,461 ng/mL across the dose range (4 mg - 128 mg). The area under the plasma concentration-time curve (AUC) raised in a dose-dependent way. Multiple-dose studies in humans have demonstrated that saroglitazar does not undergo accumulation when administered once daily for 10 days.

**Distribution**

The average terminal half-life of saroglitazar is 5.6 h. The mean apparent oral volume of distribution (Vd/F) of saroglitazar following single-dose administration of 4 mg tablet is 20.14 ± 6.92 L. In vitro saroglitazar is 96% protein bound in human plasma. The mean plasma half-life (t1/2) of saroglitazar after single dose administration of 4 mg tablet is 2.9 ± 0.9 hours.

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**Figure 3: Saroglitazar’s clinical development timeline**

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</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Molecule Identified</td>
<td>IND Approved</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
<td>Phase III</td>
<td>NDA</td>
<td>Studies completed</td>
</tr>
</tbody>
</table>

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Metabolism

In healthy volunteers, saroglitazar 4 mg has an apparent oral clearance (CL/F), calculated to be 4.8 ± 0.93 L/hr. In vitro studies using pooled human liver microsomes showed that saroglitazar is metabolically stable. Saroglitazar (4mg) was found to be metabolized into three minor oxidative metabolites. The exposure of the most abundant oxidative metabolite was found to be less than 10% of the exposure of saroglitazar.

Elimination

Saroglitazar was not eliminated via the renal route. Preclinical studies have shown that saroglitazar is mainly eliminated by the hepatobiliary route. There was no effect of gender on the pharmacokinetics of saroglitazar, except for the terminal half-life, which was significantly shorter in females than in males. Food had a small effect on the pharmacokinetics; however, it was not consistent in males and females. Single oral doses of saroglitazar up to 128 mg were well tolerated. The pharmacokinetics of saroglitazar supports a once daily dosage schedule. These data are consistent with high transepithelial permeability of saroglitazar (162 nm/s) as seen in the well-established human Caco-2 cell model for intestinal absorption.

Indications and Usage

Saroglitazar is indicated for the treatment of diabetic dyslipidemia and hypertriglyceridemia with diabetes mellitus type-2 not controlled by statins therapy. Clinical studies have demonstrated reduction in TG, LDL-C, VLDL-C, non-HDL cholesterol and an increase in HDL-C. It has also shown favorable glycemic indices by reducing the fasting plasma glucose and glycosylated hemoglobin in diabetic patients. It is best taken before the first meal of the day. Recommended oral dose is 4mg once daily.

Safety & Tolerability

No serious adverse events were reported. Saroglitazar did not show any clinically relevant findings in clinical laboratory investigations, physical examinations, vital signs and electrocardiograms. A total of 22 adverse effects (AE) in 11 subjects were reported during the study, included rash/itching, abdominal pain, nausea, cough, cold, headache, backache, body pain, calf pain, fever, malaise, giddiness, dyspepsia and diarrhea; however, they were mild to moderate in intensity.

None of the AEs required any treatment for resolution. No potential carcinogenic concern for humans was identified, which was confirmed by a mechanistic study in non-human primates employing molecular biomarkers. Saroglitazar was found to be non-mutagenic and non-genotoxic in a battery of genetic toxicology studies, including the Ames mutagenicity test, chromosomal aberration assay using the peripheral human blood lymphocytes and the mouse micronucleus assay.

Interactions

Saroglitazar does not significantly inhibit CYP1A2, 2C9, 2C19, 2D6 and 3A4 at concentration of 10 μM. Similarly, saroglitazar did not show any potential for CYP3A4 enzyme induction when tested up to 100 μM concentration in luciferase based reporter assay in transiently transfected HepG2 cells.

Saroglitazar vs. current therapies

Statins are considered a first-line treatment for lowering LDL-C in patients with Atherogenic Diabetic Dyslipidemia (ADD). These drugs decrease the LDL-C levels by as much as 50% with additional benefit on HDL-C and TG levels. But the most common problem with statins use is their effect on muscle function. Muscle symptoms range from myalgia to myositis. Hepatic function is also known to be affected by statins use. Recent studies also shows that statins therapy for long term, especially in high dose can worsen the glycemic control and can lead to new onset of T2DM.
Fibrates i.e. PPAR-α agonists are beneficial in the treatment of ADD. They lower TG, and raise HDL-C levels with minimal impact on LDL-C. But, common adverse effects include gastrointestinal complaints (nausea, abdominal pain) affecting approximately 5% patients. Fibrates can also cause myopathy. The risk for myopathy appears to be elevated in patients with renal dysfunction, and fibrates generally should be avoided in such population. Fenofibrate increase serum creatinine concentrations to a greater extent than does gemfibrozil.

Interventions to improve glycemia usually lower triglyceride levels. In general, glucose-lowering agents do not change or have only a modest effect on raising HDL levels. However, the HDL composition may change in a direction thought to be antiatherogenic. TZDs may increase HDL and LDL levels, but the long-term effect of such changes is unknown. Rising HDL cholesterol levels in diabetic patients is very difficult since the most effective agent raising HDL cholesterol levels is niacin, which is relatively contraindicated in diabetic patients.

Saroglitazar has shown to optimize glycemic control and lipid parameters, and minimize PPAR-related adverse effects in the treatment of patients with T2DM. Preclinical and clinical studies have shown favorable effects of saroglitazar on insulin sensitivity and dyslipidemia. The overall toxicity profile from clinical and non-clinical safety studies with saroglitazar was very much acceptable.

Saroglitazar treatment produced significant dose-dependent improvements in HbA1c, Fasting Plasma Glucose concentration and significant improvements in all lipid parameters, including LDL-C. Essentially, saroglitazar appears to be safe and well tolerated over the course of the study duration.

**CONCLUSION**

Saroglitazar has been approved by Drug Controller General of India (DCGI) for launch in India in June 2013. With increasing cases of lifestyle disorders along with diabetic dyslipidemia, saroglitazar is bound to help several patients suffering from it, also providing a big market opportunity for the pharmaceutical companies. Simultaneous agonistic activity on PPAR-α & PPAR-γ is a novel treatment option for diabetic dyslipidemia & other such discoveries in this area shall benefit many.

**ACKNOWLEDGEMENT**

Not reported.

**REFERENCES**


