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Short Communication

Saroglitazar: The revolution in India

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1. Introduction

Cardiovascular disease (CVD) is now one of the foremost causes of death and loss of disability-adjusted life years.[1] In the past few decades, age-adjusted cardiovascular death rates have declined in many developed countries, but the rates of CVD have increased in low- and middle-income countries.[2,3] The INTERHEART study has indicated that dyslipidemia and diabetes are amongst the stronger modifiable risk factors accounting for MI, in addition to other risk factors.[3] Dyslipidemia is a primary and major risk factor for coronary artery disease (CAD) and may even be a prerequisite for CAD, occurring before other major risk factors come into play. Increasing evidence also points to insulin resistance {which leads to an increase in levels of plasma triglycerides (TGs) and low-density lipoprotein cholesterol (LDL-C) and a decreased concentration of high-density lipoprotein cholesterol (HDL-C)} as an important risk factor for peripheral vascular disease, stroke, and CAD.[4,5] Asian Indians are known to be predisposed to a unique pattern of dyslipidemia with increased TG levels, lower HDL-C levels, and higher proportion of small-dense LDL cholesterol (sd LDL-C).[6] Dyslipidemia is highly prevalent in the population with type 2 diabetes mellitus (T2DM; insulin resistance).[7] Hypertriglyceridemia has been reported as an important risk factor for CVD.[8] Hypertriglyceridemia may be as prevalent as 50% in T2DM and is often unresponsive to statin treatment.[9,10] Epidemiological evidences suggested that plasma TG level is a strong predictor of CVD.[11,12] Current therapy for the management of hypertriglyceridemia is lifestyle therapy and pharmacotherapy with PPAR-α agonists (Fibrates), niacin, omega-3 fatty acids, or combination of these drugs with statins.[13]

Widely expressed in the liver, PPAR-α functions in the catabolism of fatty acids responsible for decreasing serum triglyceride levels and increasing HDL cholesterol levels in dyslipidemia. Therefore, PPAR α agonists have the potential to be used to ameliorate insulin resistance and hyperlipidemia.[14] But the efficacy of the current fibrates may be limited by an increased risk of myopathy, cholelithiasis, and venous thrombosis.[15] Fibrates also leads to a reversible increase in serum creatinine levels.[16] Moreover, PPAR-γ is highly expressed in adipocytes and is involved in adipocyte differentiation, lipid storage, glucose homeostasis, and adipocytokine regulation, which can improve insulin sensitivity and glucose tolerance.[17] The primary issue with the utility of classic full PPAR-γ agonists is that they exert a variety of side effects, chiefly weight gain due to edema and increased fat mass.[18] However, the side effects associated with PPAR activation may be circumvented through the combined activation of PPAR-α

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and -γ, which is known to result in a complementary and synergistic increase in lipid metabolism and insulin sensitivity.

2. Saroglitazar

Saroglitazar is the first glitazar class compound that has been approved as a therapeutic agent. Structurally, Saroglitazar is a non-TZD and nonfibrate molecule belonging to the aryl alkoxy propionic acid class. Saroglitazar was designed as a dual PPAR-α/γ agonist having strong PPAR-α effect with moderate PPAR-γ effect.

The journey of Saroglitazar from concept to market started in 2001, when the molecule was identified, followed by the preclinical safety and toxicity studies wherein Saroglitazar was found to be well tolerated in animal models, and found not to be genotoxic, hepatotoxic, myotoxic, nephrotoxic, cardiotoxic, or teratogenic at doses equivalent to or higher than efficacy doses. Saroglitazar further passed 2-year carcinogenicity studies in animal models (which was further confirmed by a mechanistic study using nonhuman primates employing molecular biomarkers).[19]

In 2005, pharmacokinetic properties of Saroglitazar were evaluated in Phase I, prospective, randomized, double-blind, placebo-controlled, single-center study. Saroglitazar was rapidly well absorbed across all doses in single-dose pharmacokinetic study. The AUC increased in a dose-related manner. The median time to reach maximum concentration for Saroglitazar 4 mg (Tmax) was found to be 0.71 ± 0.25 h under fasting conditions. The maximum plasma concentration (Cmax) was 337.07 ± 90.99 ng/ml for Saroglitazar 4 mg. The terminal half-life of Saroglitazar 4 mg was between 2.93 ± 0.87 h. Saroglitazar was not eliminated by the renal route. On the bases of various pharmacokinetic properties and plasma half-life, Saroglitazar did not show a potential for accumulation following once-daily repeat dosing in normal healthy subjects and was found to be safe and well tolerated up to 128 mg single dose in Phase I study conducted in healthy volunteers.[20]

By 2008, the pivotal Phase III studies (PRESS V and VI) were initiated. PRESS V study was a multicenter, prospective, randomized, double-blind, active control, interventional, Phase III study conducted in India. The objective of this study was to evaluate the safety, tolerability, and efficacy of Saroglitazar 2 and 4 mg as compared to high-dose pioglitazone (45 mg) in patients with diabetic dyslipidemia. A total of 122 patients with hypertriglyceridemia with T2DM (body mass index >23 kg/m^2; hypertriglyceridemia: TG > 200–400 mg/dL; glycated hemoglobin [HbA1c] > 7–9%) were randomly assigned to either Saroglitazar (2 or 4 mg once a day) or pioglitazone 45 mg once a day. The primary endpoint was change in plasma TG level at 24 weeks, while, the secondary endpoints were change in lipid profile and fasting plasma glucose at week 24. For safety evaluation, all randomized patients who received at least a single dose were included. Saroglitazar 4 mg was found to significantly reduce ($p < 0.001$) plasma TG from baseline by 45% (absolute change ± standard deviation [SD]: −115.4 ± 68.11 mg/dL), as compared to pioglitazone −15.5% (absolute change ± SD: −33.3 ± 162.41 mg/dL) at week 24. Saroglitazar 4 mg treatment also demonstrated a marked reduction in LDL-C (5%), very LDL (VLDL-C) (45.5%), total cholesterol (7.7%), and apolipoprotein-B (10.9%). Saroglitazar treatment was found to be safe and well tolerated. No serious adverse events were reported in Saroglitazar treatment arm and no persistent change in laboratory parameters.[21]

PRESS VI study was a multicenter, prospective, randomized, double-blind, placebo control, interventional, Phase III study conducted in India. The objective of this study was to evaluate the safety, tolerability, and efficacy of Saroglitazar 2 and 4 mg as compared to placebo in patients with hypertriglyceridemia (>200 and <500 mg/dL) in T2DM not controlled with atorvastatin 10 mg once a day therapy. A total of 302 subjects were randomized to receive one of the treatments, Saroglitazar 2 mg ($n = 101$) or Saroglitazar 4 mg ($n = 99$) or a matching placebo ($n = 102$) for a period of 12 weeks. The primary endpoint was the change in plasma TG level compared with baseline and the placebo arm at the end of week 12. The secondary exploratory endpoints were change in lipid profile and fasting plasma glucose at week 12. At week 12, Saroglitazar 4 mg was found to significantly reduce mean plasma TG levels by 46.7 ± 3.02% (mean ± SE), and the difference was statistically significant ($p < 0.001$) compared with placebo. Saroglitazar also demonstrated a significant decrease in levels of non-HDL-C, VLDL-C, total cholesterol, and fasting plasma glucose. Additionally, Saroglitazar 4 mg also significantly reduced LDL-C and apolipoprotein B levels. Saroglitazar was found to be safe and well tolerated by patients.[22]

Gastritis, asthenia, and pyrexia were the most commonly reported adverse effects in the clinical trials. Most of the adverse events reported were mild to moderate in intensity and were not related to treatment. In vitro studies done by using human cytochrome P-450 isozymes did not reveal any potential for clinically significant drug interactions with other drugs. The PRESS V study found no clinically significant changes in electrocardiography (ECG), two-dimensional echocardiography (2D ECHO), or ultrasonography findings in any of the treatment groups. In the PRESS VI study, after 12 weeks of treatment, there were no significant changes in hemoglobin, liver enzymes (ALP, ALT, AST, and g-glutamyl transferase), renal function (creatinine, enhanced glomerular filtration rate, and blood urea nitrogen), creatine phosphokinase, and high-sensitivity C-reactive protein in the Saroglitazar and placebo arms. There was no edema or weight gain reported in any of the study arms. During PRESS VI study, subjects were monitored for cardiac events, ECG abnormalities, and cardiac function by 2D ECHO at the start of the study, at the end of 12 weeks, and at 24 weeks after the last dose of the study drug. There were no adverse events reported as far as cardiac safety is concerned. Though considered safe, Saroglitazar should be given with caution in patients with hepatic or renal impairment.[19–22]

The two Phase III, prospective, randomized, controlled, multicenter clinical trials (prospective, randomized efficacy and safety of Saroglitazar (PRESS V and PRESS VI))[21,22] led to an approval of Saroglitazar by Drug Controller General of India (DCGI). And following approval, Saroglitazar was launched in the Indian markets in 2013 and is now an option for the treatment of hypertriglyceridemia and dyslipidemia associated with diabetes in India.