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Saroglitazar: the World's First Drug for Treating Diabetic Dyslipidemia

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Abstract

Saroglitazar (Lipaglyn™) is the first indigenously developed new chemical entity by any Indian pharmaceutical company, ever. In February 2013, Drug Controller General of India has been approved Lipaglyn for treating diabetic dyslipidemia or hypertriglyceridemia in type 2 diabetes, not controlled by statins alone. The recommended dose of Lipaglyn is one tablet of 4 mg once a day. Saroglitazar is a dual (α/γ) peroxisome proliferator-activated receptors (PPAR) activator in the glitazar class, predominantly PPAR- α agonist with moderate PPAR- γ agonistic activity, thereby improving hyperglycemia and lipid abnormalities (i.e., reducing triglycerides and increasing high density lipoprotein cholesterol HDL-C) simultaneously. By conducting extensive phase I, II and III studies, pharmacokinetics, pharmacodynamics, tolerability, safety and efficacy of Saroglitazar were well studied by comparing with pioglitazone and placebo. Saroglitazar was found to be significantly decreased plasma triglycerides level and fasting plasma glucose level and also increased high density lipoprotein cholesterol level compared with placebo.

Diabetic dyslipidemia is a condition in which a person is diabetic and has elevated levels of the total cholesterol, low-density lipoprotein cholesterol (LDL-C) and the triglycerides and decrease in high-density lipoprotein cholesterol (HDL-C) concentration in the blood [1]. In 2013, 382 million people have diabetes worldwide, and it is projected to be 592 million by 2035 [2]. In any given country across the world, India has been known to have the largest number of diabetic people [3]. Estimates put forth by the WHO reveals that about 32 million people in India were presenting with diabetes in the year 2000, which has been projected to rise to 80 million by 2030 [4]. World over, it is estimated that 30% of all deaths occur due to cardiovascular diseases (CVD). In India, one out of every five persons is at serious risk of developing CVD. Research has shown that diabetes is one of the major risk factors for CVD. India has a Population of nearly 65 million diabetics and 77 million

pre-diabetics. 85 – 97 per cent of the diabetes patients suffer from dyslipidemia or lipid abnormalities [5]. Hence, addressing the problem of diabetes and dyslipidemia is crucial in tackling the health risk posed by CVD. The lipid changes associated with diabetes mellitus are attributed to increased free fatty acid flux secondary to insulin resistance (Figure 1). Optimal levels of LDL-C for adults with diabetes are <100 mg/dL, triglycerides are <150 mg/dL and HDL-C $\geq$ 40 mg/dL [6]. Although advances made in the prevention and management of cardiovascular disease, people with diabetes mellitus continue to have alarmingly high morbidity and mortality secondary to cardiovascular disease [7]. Epidemiologic studies make evident that diabetes mellitus is an independent risk factor for cardiovascular disease and that it amplifies the effects of other common risk factors, such as smoking, hypertension and hypercholesterolemia [8,9]. The Framingham Heart

Study found that both men and women with diabetes had an increased prevalence of hypertriglyceridemia and low HDL-C levels, but their total cholesterol and LDL-C levels did not differ from those in non-diabetic counterparts [10]. UK Prospective Diabetes Study gives similar results like total cholesterol levels of those with diabetes mellitus and control individuals did not differ, but women with diabetes had markedly higher LDL-C levels than non diabetic women. The plasma triglyceride levels of patients with diabetes were substantially increased, whereas HDL-C levels were markedly reduced in both men and women with diabetes compared with the non diabetics [11].

Fig 1: Mechanism of dyslipidemia due to insulin

Saroglitazar

Saroglitazar (Lipaglyn™; Zydus Cadila, Ahmedabad, India) is a first-in class ‘glitazars’ discovered indigenously by an Indian Pharma Company ‘Zydus Research Centre’ and approved for launch in India by the Drug Controller General of India (DCGI) on 25th February, 2013 to be the world’s first drug targeted at healthcare need for treating diabetic dyslipidemia or hypertriglyceridemia in type 2 diabetes, not controlled by statins alone. The recommended dose of Lipaglyn is one tablet of 4 mg once a day [12]. The chemical name for saroglitazar is Benzenepropanoic acid, α -ethoxy-4-[2-[2-methyl-5-[4-(methylthio)phenyl]-1H-pyrrol-1-yl]ethoxy]-, magnesium salt (2:1), (α S). Structural formula of saroglitazar depicted in Figure 2.

Fig 2: Saroglitazar structural formula

Mechanism of Action

Glitazars are a new class of oral antidiabetic agents that activate nuclear receptors known as peroxisome proliferator-activated receptors (PPARs). Three PPAR subtypes have been characterized: PPAR- α , - γ , and - β/δ . Upon ligand binding, each receptor subtype mediates distinct physiological effects on glucose homeostasis and lipid metabolism (Figure 3). Activation of PPAR- γ reduces insulin resistance and improves glycemic control, whereas activation of PPAR- α reduces triglyceride levels and increases concentrations of HDL-C [13,14]. Saroglitazar is a dual (α/γ) PPAR activator in the glitazar class, predominantly PPAR- α agonist with moderate PPAR- γ agonistic activity, thereby improving hyperglycemia and lipid abnormalities (i.e., reducing triglycerides and increasing HDL-C) simultaneously. This drug targets the PPAR- α and - γ receptors, which are currently agonized separately in the thiazolidinediones for treatment of type 2 diabetes (pioglitazone and rosiglitazone), and the fibrates for treatment of dyslipidemia (fenofibrate and gemfibrozil) [15]. This approach of agonising both the sub types of a nuclear receptor PPAR was also anticipated to help reduce the pill burden and improve medication adherence in type 2 diabetic patients.

Pharmacokinetics

Saroglitazar was found to be safe and well tolerated in preclinical and clinical (Phase I/II) studies. In the single-dose pharmacokinetic study, saroglitazar was rapidly and well absorbed across all doses (0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64 and 128 mg), with a median time to the peak plasma concentration (t_{max}) of less than 1 hour (range 0.63–1 hour) under fasting conditions. The maximum plasma concentration ranged from 3.98 to 7,461 ng/mL across the dose range. The area under the plasma concentration–time curve increased in a dose-related manner. The average terminal half-life of saroglitazar was 5.6 hours. Saroglitazar was not eliminated via the renal route. Single oral doses of saroglitazar up to 128 mg were well tolerated [16].

Safety and Efficacy

A 24-week multicentric, randomized double blind study was conducted to evaluate safety and efficacy of saroglitazar 2 mg and 4 mg compared to pioglitazone 45 mg in diabetic dyslipidemia. The primary end point of the study was to assess the percent change in triglyceride levels after a 24 week treatment as compared to baseline. There was 45% decrease in serum triglycerides with saroglitazar 4 mg, which was statistically significant compared to baseline and also compared to pioglitazone 45 mg (15.5%). Saroglitazar reduced very LDL-C, LDL-C and total cholesterol significantly compared to pioglitazone and/or baseline. Apolipoprotein B, the marker of atherogenic dyslipidemia, was significantly reduced compared to baseline in the saroglitazar 4 mg arm, but not with pioglitazone 45 mg. The increase in HDL-C levels was observed in all treatment groups. Both

the glycemic parameters, fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c), were significantly reduced at week 24 as compared to baseline in the saroglitazar and pioglitazone arms. Saroglitazar 2 mg and 4 mg doses were well tolerated throughout the study. Less number of patients reported adverse events in the saroglitazar 2 mg and 4 mg arms as compared to the pioglitazone 45 mg arm. The most frequently reported adverse events were asthenia, gastritis, chest discomfort, peripheral edema, dizziness and tremors. Most of the adverse events were considered unrelated to treatment and were of mild intensity [15].

A 16-week prospective, multicenter, randomized, double-blind, placebo controlled, three-arm Phase III study was conducted to evaluate the safety and efficacy of saroglitazar compared with placebo in patients with type 2 diabetes having hypertriglyceridemia (>200 and <500 mg/dL) not controlled with atorvastatin 10 mg therapy. A total of 302 subjects were randomized to receive 12 week treatment with saroglitazar 2 mg ($n = 101$) or saroglitazar 4 mg ($n = 99$), or matching placebo ($n = 102$), after 4-week run-in period. At week 12, saroglitazar 2 mg and 4 mg was found to be significantly reduced mean plasma triglyceride levels by $-45.5 \pm 3.03\%$ and $-46.7 \pm 3.02\%$, respectively, compared with placebo ($P < 0.001$). Saroglitazar 2 mg also caused a significant decrease in non-HDL-C, very LDL-C, total cholesterol; saroglitazar 4 mg also significantly reduced LDL-C and apolipoprotein B levels, compared with placebo. After the 12-week treatment, saroglitazar (2 and 4 mg) caused a significant increase in HDL-C level compared with

placebo. There was also a statistically significant decrease in FPG level after 12-weeks of treatment with saroglitazar 2mg (-23.6 ± 7.92 mg/dL) and 4 mg (-25.4 ± 7.92 mg/dL) compared with placebo. Both doses of saroglitazar were well tolerated. There were similar numbers of adverse events in the saroglitazar and placebo arms. Following are the frequently reported adverse events: dyspepsia, gastritis, chest pain, pain and pyrexia. Most of the adverse events were not related to treatment and were mild to moderate in intensity [17].

Other Glitazars

The first PPAR- α/γ dual agonist to be reported was KRP-297 (MK-0767) shown effectiveness in diabetic dyslipidemia in animal models [18]. However, further development was discontinued due to toxicity. Muraglitazar (BMS-298585) was the first PPAR- α/γ dual agonist reviewed by the US FDA advisory committee. This was reported to exhibit potent in vitro activities against both PPAR- α and PPAR- γ subtypes and exerts excellent glucose and lipid-lowering effects in rodent models but its development was discontinued due to increased CV risk [19]. Other than these two, researchers also discovered farglitazar (MK-0676), tesaglitazar (AZ-242), ragaglitazar (DRF-2725) and imiglitazar (TAK-559) as PPAR- α/γ dual agonists. They were effective in animal models; however, further development was discontinued due to various toxicological reasons or a risk benefit assessment. An important observation is that most of these failed compounds had higher selectivity towards PPAR- γ receptor [20].

Fig 3: Physiological effects of peroxisome proliferator-activated receptors α and γ

References

- Taskinen MR. Diabetic dyslipidemia. *Atheroscler Suppl* 2002;**3**(1):47-51
- International Diabetes Federation. Diabetes Atlas [Online]. 2014 [cited 2014 Jan 20]. Available from: <http://www.idf.org/diabetesatlas>
- United Nations. World Urbanization Prospects: 1999 Revision [Online]. 1999 [cited 2014 Jan 20]. Available from: <http://www.un.org/esa/population/pubsarchive/urbanization/urbanization.pdf>
- International Diabetes Federation. Diabetes Atlas 2003 [Online]. 2003 [cited 2014 Jan 20]. Available from: http://www.idf.org/sites/default/files/IDF_Diabetes_Atlas_2ndEd.pdf
- Pharmabiz.com. Zydus pioneers breakthrough with Lipaglyn to treat diabetic dyslipidemia [Online]. 2013 [cited 2014 Jan 20]. Available from: <http://pharmabiz.com/PrintArticle.aspx?aid=75719&sid=2>
- American Diabetes Association. Management of dyslipidemia in adults with diabetes. *Diabetes Care* 1998;**21**(1):179-182
- Mooradian AD. Cardiovascular disease in type 2 diabetes mellitus: current management guidelines. *Arch Intern Med* 2003;**163**(1):33-40
- Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;**16**(2):434-444
- Almdal T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Arch Intern Med* 2004;**164**(13):1422-1426
- Kannel WB. Lipids, diabetes, and coronary heart disease: insights from the Framingham Study. *Am Heart J* 1985;**110**(5):1100-1107
- [No authors listed]. U.K. Prospective Diabetes Study 27. Plasma lipids and lipoproteins at diagnosis of NIDDM by age and sex. *Diabetes Care* 1997;**20**(11):1683-1687
- Central Drugs Standard Control Organization. List of approved drugs from 01-01-2013 to 31-12-2013 [Online]. 2013 [cited 2014 Jan 20]. Available from: [https://www.google.co.in/url?sa=t&rct=j&q=&esrc=s&source=web&cd=4&cad=rja&uact=8&ved=0CDsQFjAD&url=http%3A%2F%2Fwww.cdsc.nic.in%2Fwritereaddata%2FNew%2520Drugs%2520approved%2520updated%25202013%2520\(4\).doc&ei=b-1AU5PPE8iMrQf2YGQBA&usg=AFQjCNGH6H1jF9vK_3kDngkIqCCrWFjtUw&bvm=bv.64367178,d.bmk](https://www.google.co.in/url?sa=t&rct=j&q=&esrc=s&source=web&cd=4&cad=rja&uact=8&ved=0CDsQFjAD&url=http%3A%2F%2Fwww.cdsc.nic.in%2Fwritereaddata%2FNew%2520Drugs%2520approved%2520updated%25202013%2520(4).doc&ei=b-1AU5PPE8iMrQf2YGQBA&usg=AFQjCNGH6H1jF9vK_3kDngkIqCCrWFjtUw&bvm=bv.64367178,d.bmk)
- Lee CH, Olson P, Evans RM. Minireview: lipid metabolism, metabolic diseases, and peroxisome proliferator-activated receptors. *Endocrinology* 2003;**144**(6):2201-2207
- Kota BP, Huang TH-W, Roufogalis BD. An overview on biological mechanisms of PPARs. *Pharmacol Res* 2005;**51**(2):85-94
- Zydus Discovery. Product Monograph: Lipaglyn [Online]. 2013 [cited 2014 Jan 20]. Available from: lipaglyn.com/downloads/Lipaglyn_Product_Monograph.pdf
- Jani RH, Kansagra K, Jain MR, Patel H. Pharmacokinetics, safety, and tolerability of Saroglitazar (ZYH1), a predominantly PPAR α agonist with moderate PPAR γ agonist activity in healthy human subjects. *Clin Drug Investig* 2013;**33**(11):809-816
- Jani RH, Pai V, Jha P, Jariwala G, Mukhopadhyay S, Bhansali A et al. A multicenter, prospective, randomized, double-blind study to evaluate the safety and efficacy of Saroglitazar 2 and 4 mg compared with placebo in type 2 diabetes mellitus patients having hypertriglyceridemia not controlled with atorvastatin therapy (PRESS VI). *Diabetes Technol Ther* 2014;**16**(2):63-71
- Murakami K, Tobe K, Ide T, Mochizuki T, Ohashi M, Akanuma Y et al. A novel insulin sensitizer acts as a coligand for peroxisome proliferator-activated receptor- α (PPAR- α) and PPAR- γ : effect of PPAR- α activation on abnormal lipid metabolism in liver of Zucker fatty rats. *Diabetes* 1998;**47**(12):1841-1847
- Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005;**294**(20):2581-2586
- Rubenstrunk A, Hanf R, Hum DW, Fruchart JC, Staels B. Safety issues and prospects for future generations of PPAR modulators. *Biochim Biophys Acta* 2007;**1771**(8):1065-1081

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