REG.NO:D7635654-AFINJ JOHP-ISSN: 2348-7704

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JOHP

Journal of Hospital Pharmacy
An Official Publication of Bureau for Health & Education Status Upliftment
(Constitutionally Entitled as Health-Education, Bureau)

Exploring the Safety and Effectiveness of Saroglitazar Superior to Other Drugs in the Management of Diabetic Dyslipidemia

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***Abstract*:**

The study is aimed to explore the safety and effectiveness of saroglitazar superior to other drugs in the management of diabetic dyslipidemia. The drug that is first approved forthe treatment of diabetic dyslipidemia by FDA. Using search terms: Saroglitazar, Glitazars, Diabetic dyslipidemia, new anti-dyslipidemic drugs, novel antidiabetic drug targets, PPAR- α, PPAR-γ. A total of approximately 38 articles were collected and selected 36 articles basedon the relevance of the topic from 2002-2024.The publications were reviewed. Subsequently,all gathered data were utilized and concluded that Saroglitazar is safe and effective for the treatment of diabetic dyslipidemia. It is superior in action as well as safer when compared toother drugs for treatment of diabetic dyslipidemia. It caused mild ADRs that does not requiremedical intervention. Saroglitazar is safe and effective for the treatment of diabetic dyslipidemia and do not cause any serious ADRs

IndexTerms - Diabetic Dyslipidemia, Saroglitazar, glitazars, new antidyslipidemic drugs,Novel antidiabetic drug targets.

Access this Article Online	Quick Response Code:
Website: http://www.journalofhospitalpharmacy.in	
Received on 18/08/2024	
Accepted on 10/09/2024 © HEB All rights reserved	

INTRODUCTION

The trio of high triglycerides (TG), elevated small dense low density lipoprotein cholesterol (sd-LDL-C), and low high density lipoprotein cholesterol (HDL-C) is known as dyslipidemia (DD), also referred to as atherogenic dyslipidemia [1]. Dyslipidemia is believedto affect 30–60% of T2DM patients[2].More than 90% of India's 74 million adult patients withdiabetes (1 in 12) are expected to have atherogenic dyslipidemia, and an additional 70 million people with prediabetes may also have dyslipidemia[3].According to an Indian study, the baseline prevalence of dyslipidemia in individuals with diabetes was 97.8% in females and 85.5% in males[4].Insulin resistance is the major cause for the diabetic dyslipidemia, which result in the increased accumulation of FFAs, TG, LDL, VLDL and free glucose level[6].

3-step approach for treatment for diabetic dyslipidemia are: First, changes to healthy diet and life style, which include reduced intake of cholesterol, cholesterol- raising fat and total energy. Second, maintain a proper glycemic control, with low glucose diet and hypoglycaemic drugs. Third, Antihyperlipidemic drugs are used.

Saroglitazar the dual PPAR agonist that is approved by India for the treatment of diabetic dylipidemia which is not controlled by statins [5].A possible treatment for diabetic dyslipidemia is saroglitazar, a dual PPAR-α/γ agonist. Both glycemic indices (fasting blood glucose and glycated hemoglobin) and dyslipidemia (TGs, apolipoprotein B, non-HDL-C) significantly improve as a result of it. Phase III clinical study findings show that saroglitazardoes not have the typical adverse effects associated with pioglitazone and fibrates. More saroglitazar clinical trials will confirm the drug's role in treating diabetes, dyslipidemia, and related cardiovascular risks [6]. Thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, may appear to reduce skeletal and hepatic insulin resistance by activating peroxisome proliferator-activated receptor (PPAR)-γ, which is primarily expressed in adiposetissue via one or more mechanisms that regulate adipocyte signaling and metabolism[6]. PPAR-α activators have been used to treat dyslipidemia. They increase HDL-C levels and lower plasma TG levels [7]. Fever, malaise, giddiness, dyspepsia, diarrhea, rash/itching, stomach pain, nausea, cough, cold, headache, backache, body pain, and calf pain are some ofthe side effects showed by saroglitazar, which are mild and no need of medical assistance [28].

METHODOLOGY

The article assessment was done to ensure the safety and efficacy of Saroglitazar andto ensure their superiority over other drugs for the treatment of diabetic dyslipidemia. By using the following search terms: Saroglitazar, Glitazars, Diabetic dyslipidemia, Dyslipidemia, Diabetes, new anti-dyslipidemic drugs, novel antidiabetic drug targets, PPAR-α, PPAR-γ. Appraised various online papers from various journals like PubMed, Science Direct, NCBI, Journal of Clinical Lipidology, World Journal of Diabetes, Journal for hepatology, Journal for biological chemistry, International journal for molecular science, European journal of pharmacology, Journal of international association of the study of the liver, Journal of young pharmacist, Journal of diabetes science and technology additional services and information from year 2002-2024. A total of approximately 38 article were collected and selected 36 articles based on the relevance of the topic. The publications were reviewed, and those that included detailed discussions of preclinical and clinical effectiveness,dose, pharmacokinetics, mechanism of action, chemistry, safety investigations, and the rolesof PPAR-α and PPAR-γ were given special consideration. Subsequently, all gathered data were utilized.

INSULIN RESISTANCE A MAJOR CAUSE OF DIABETICDYSLIPIDEMIA

Insulin resistance is having a major role in development of Diabetic dyslipidemia. Insulin resistance result in increase in the FFAs by decreasing apoB degradation, it also stimulates MTP activity which result in the production of VLDL [6].VLDL are 2 types: VLDL1 and VLDL2.VLDL result in the increased sdLDL and decreased HDL-C. Suppression of LPL alsoresults in increased chylomicrons [6]. Insulin resistance can result in the decreased expression of ABCG5/G8 result in decreased cholesterol secretion from intestine [6]. These all collectivelyresult in Diabetic dyslipidemia [6]. The 3 major sites of insulin resistance are,

PPAR-α AND LIPID METABOLISM

A nutritional sensor called PPARα enables the modification of the rates of lipogenesis,ketone body production, and fatty acid (FA) catabolism in response to famine and feeding [9].PPARα is a transcriptional regulator of genes involved in FA transport, hepatic glucose synthesis (unique to rodents), peroxisomal and mitochondrial β-oxidation [10]. In rat models of systemic inflammation, atherosclerosis, and non-alcoholic steatohepatitis (NASH), PPARαadversely controls pro-inflammatory and acute phase response (APR) signaling pathways [11],[12].

PPAR-γ AND GLUCOSE HOMEOSTASIS

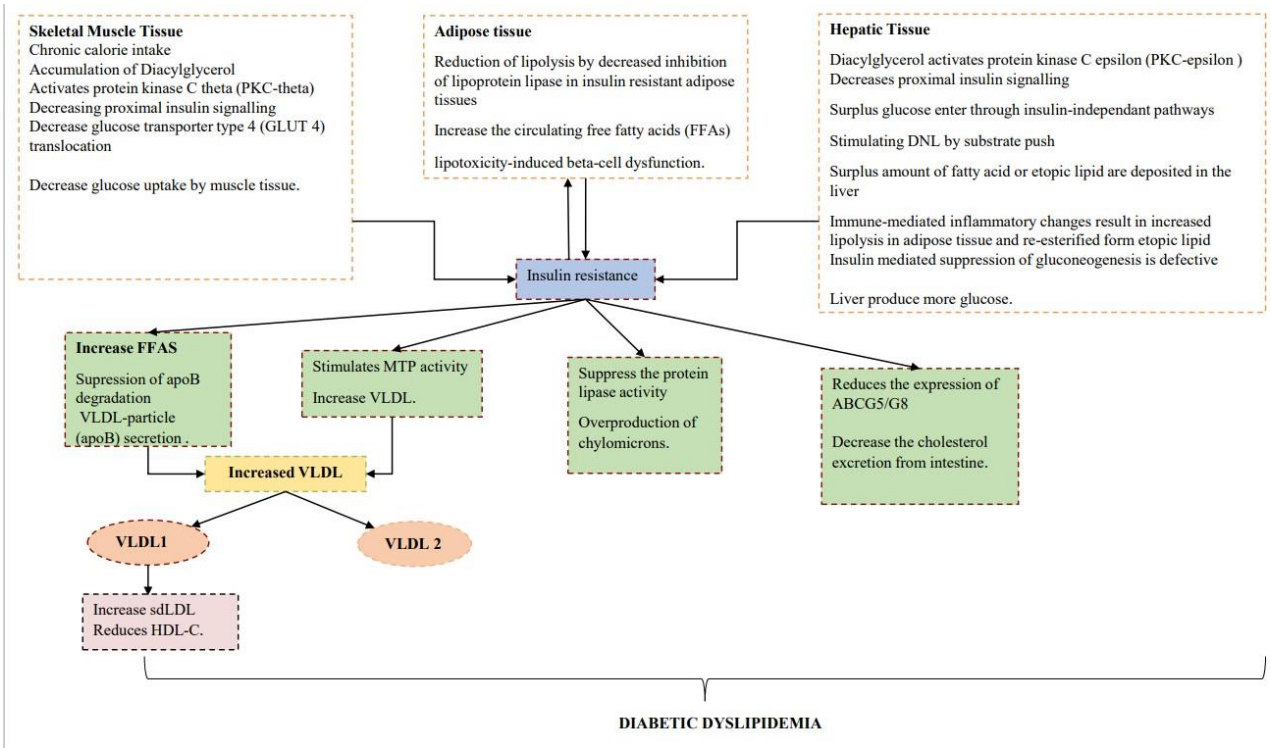

Figure 1: Three major sites of insulin resistance

Nuclear receptor PPARγ, also known as peroxisome proliferator-activated receptor gamma, isinvolved in metabolic regulation. The goal of PPARγ research is to comprehend how it contributes to insulin sensitivity. This interest was sparked by the finding that

Table 1: Glitazars

MOLECULE	COMPANY	COMMENTS
Muraglitazar	Bristol-Myers squibb (USA)	Approved and withdrawn from market in 2006 as a result of increase in cardiovascular problems (MI, TIA,Stroke, CHF) [14].
Tesoglitazar	AstraZeneca (UK)	Discontinued in phase III trials as a result of elevated creatinine levels along with decreased glomerular filtration [15].
Ragaglitazar	Novo Nordisk (Denmark)(Out licensed by Dr.Reddy's)	Discontinued 2002 as a result of bladder tumors inrodents [16].
Chiglitazar	Shenzhen Chipscreen, (china)	Completed phase III clinical trial in combination with metformin for treatment of diabetes mellitus [17].
Cevoglitazar	Novartis (Switzerland)	Discontinued in 2008 without giving a reason [18].
Aleglitazar	Hoffman-La-Roche (Swirtzerland)	Discontinued at phase III in 2013 as a result of GI bleeding, heart failure, renal dysfunction [19].
TAK-559	Takeda (Japan)	Discontinued in 2005 in phase III as a result of abnormalities in liver enzymes [20].
Naveglitazar	Eli Lilly (USA)	Discontinued in 2006 as a result of carcinogenic effectsin the urinary bladder or rodents with urothelial hypertrophy, inflammation and changes in urinary composition [21].
AVE-0847	Sanofi-Aventis (France)	Discontinued as a result of glitazar: repolarisation of product protofolia
Sipoglitazar	Takeda (Japan)	Discontinued in 2006 as a result of serious safety concerns [22].

Glitazars are the medications that agonise PPAR-αand PPAR-γ. That are used for treatment of diabetes and dislipidemia. Before approval of Saroglitazar few of the glitazars were discovered and withdrawn or discontinued due to adverse effects.

Basic Chemistry:

- Chemical name: [(S)-a-ethoxy-4-{2-[2-methyl-5-(4-methylthio)phenyl)]-1H-pyrrol-1-yl]- ethoxy})-benzenepropanoic acid magnesium salt [23]
- The molecular weight: 439.6 g/mol [23]
- Emperical formula: $[CH28NO4S]^2$ Mg [23]

Chemical structure of Saroglitazar [23]

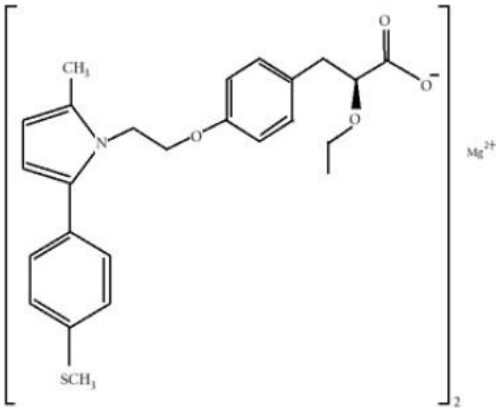

Figure 2: Chemical structure of Saroglitazar

Mechanism of action

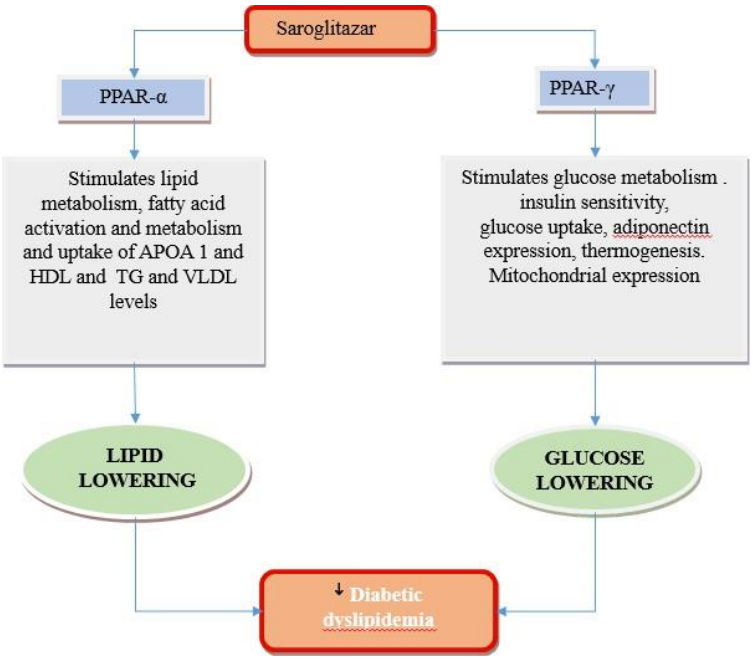

Figure 3: Mechanism of action of Saroglitazar

Cadila states that saroglitazar effectively targets both PPAR-γ and PPAR-α receptors**[25]**. This medication has been proven to provide favorable outcomes in terms of lipid and glycemic control while avoiding any adverse effects. It exhibits a moderate affinity for PPAR-γ and a higher affinity for the PPAR-α isoform. At a daily dosage of 4 mg, HDL-C levels were elevated and TG and LDL-C levels were reduced. Additionally, it reduces glycosylated hemoglobin and fasting plasma glucose levels **[26]**.

PRECLINICAL DEVELOPMENT:

Saroglitazar has undergone extensive preclinical studies using various animal modelsto evaluate its effects on T2DM and dyslipidemia. These studies demonstrate that saroglitazarhas the dual benefits of lowering lipids and reducing hyperglycemia. In a hyperinsulinemic- euglycemic clamp study, saroglitazar significantly improved the rate of glucose infusion, indicating its ability to enhance insulin sensitivity. In rats with high cholesterol levels, saroglitazar effectively reduced total serum cholesterol, LDL-C, and TG levels by up to 77 %, 67%, and 90 %, respectively. Moreover, it increased the lipid clearance by as much as 68%. In a diabetic model, saroglitazar improved oral glucose tolerance by 59% and lowered serum glucose levels by up to 65%. Additionally, it decreased the FFA and fasting insulin levels in Zucker fa/fa rats and db/db mice. Safety pharmacology research has demonstrated that saroglitazar, even when administered at significantly higher doses than those prescribed for therapeutic use, does not affect the functioning of the gastrointestinal (GI), respiratory (RS), cardiovascular (CVS), or central nervous systems (CNS). Additionally, extensivecomparative mechanistic studies utilizing molecular biomarkers in both rats and non-human primates have provided evidence that there is no potential risk of cancer associated with saroglitazar in humans [27].

CLINICAL DEVELOPMENT: [27]

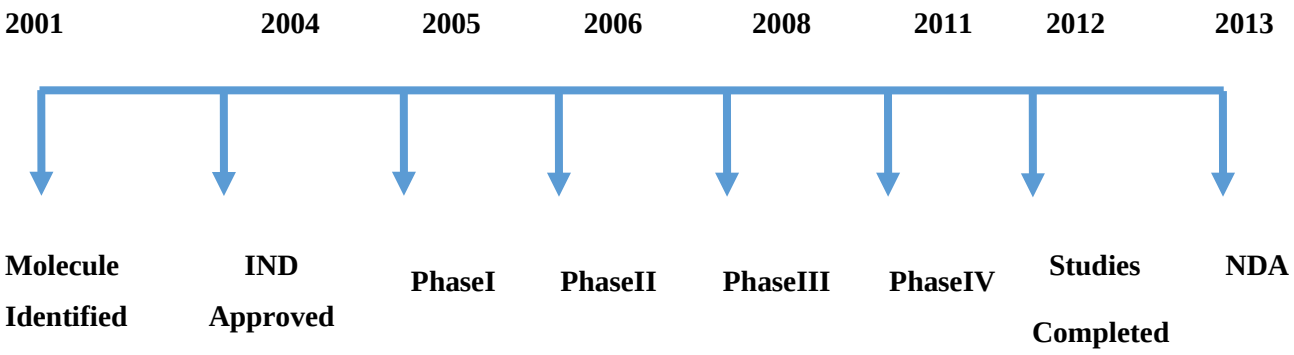

Figure 4: Clinical development of saroglitazar

The comprehensive clinical development program spanned over eight years and encompassed rigorous Phase I, Phase II, and Phase III clinical trials.

- **Phase I**: This prospective, randomized, double-blind, placebo-controlled, single- centred trial involved 136 healthy individuals to evaluate the safety, tolerability, and pharmacokinetics of saroglitazar **[27].**

- **Phase II:** A prospective randomized study was conducted to assess the safety and efficacy of saroglitazar in 222 participants. The study included four programs for dose determination and proof of concept, with participants receiving 0.5, 1, 2, or 4 mg saroglitazar once daily over a 12-week period.**[27]**
- **Phase III**: Two phase III programs comprised of phase III investigations. In the first phase III trial, the 4 mg dose of saroglitazar demonstrated a significant decrease in TG, LDL-C, fasting plasma glucose, and glycosylated hemoglobin (HbA1c), while also showing an increase in HDL-C, when compared to a program involving diabetic patients treated with pioglitazone. These findings support the favourable effects of thisdrug on lipid and glycemic control in patients with diabetes. During the second Phase III trial, Saroglitazar was evaluated in individuals with diabetes mellitus who had uncontrolled blood sugar levels despite traditional statin therapy. The results of this study indicated a notable enhancement in both the glycemic and lipid profiles for eachparticipant **[27]**.

PHARMACOKINETIC STUDIES

Absorption

In a pharmacokinetic study involving a single dose, saroglitazar was efficiently absorbed at all doses at a rapid pace. When taken on an empty stomach, it reaches its highest concentration in the bloodstream (Tmax) in less than an hour, with a range of

0.63 to 1 h. The maximum concentration of saroglitazar in the plasma (Cmax) varied between 3.98 and 7,461 ng/mL across the dose range of 4 mg to 128 mg. Furthermore,the area under the plasma concentration-time curve (AUC) increased in a dose-dependent manner. Multiple dose studies in humans have demonstrated that when saroglitazar is administered once daily for ten days, there is no build-up or accumulationof the drug [27].

Distribution

Saroglitazar typically has a terminal half-life of 5.6 hours. Following the administrationof a 4 mg tablet, the average apparent oral volume of distribution (Vd/F) of saroglitazarwas 20.14 ± 6.92 L. Saroglitazar was found to be 96% protein bound in human plasmain vitro. The mean plasma half-life (t1/2) of saroglitazar after a single 4 mg tablet doseis 2.9 ± 0.9 hours [27].

Metabolism

The observed oral clearance (CL/F) of saroglitazar 4 mg in healthy individuals was 4.8

± 0.93 L/hr. In vitro studies using depleted human liver microsomes have demonstratedthat saroglitazar exhibits consistent metabolism. Saroglitazar (4 mg) metabolism resulted in the production of three minor oxidative metabolites. The predominant oxidative metabolite accounted for less than 10% of overall saroglitazar exposure [27].

Elimintaion

Saroglitazar is primarily eliminated through the hepatobiliary system rather than through the renal route, as indicated by preclinical studies[28].The sex of the individualsdid not have an impact on the pharmacokinetics of saroglitazar, except for the terminalhalf-life, which was significantly shorter in females compared to males. The effect of food on pharmacokinetics differed slightly between males and females. Saroglitazar was well tolerated when administered orally once at a maximum dose of 128 mg. The data obtained from the well-established human Caco-2 cell model for intestinal absorption and the high transepithelial permeability of saroglitazar (162 nm/s) are consistent with these findings [28].

INDICATIONS AND USAGE

Saroglitazar is recommended for the management of diabetic dyslipidemia and hyperglycemia in type 2 diabetes patients who do not respond to statin therapy. Studies haveindicated that it can increase HDL-C levels and reduce TG, LDL-C, VLDL-C, and non-HDL-cholesterol levels. Moreover, it has shown positive effects on glycemic control by lowering fasting plasma glucose and glycosylated hemoglobin levels in diabetic individuals. It is suggested to take a 4 mg dose orally once daily before breakfast [27].

SAFETY AND TOLERABILITY

Saroglitazar's clinical laboratory investigations, physical examinations, vital signs, and ECGs did not reveal any noteworthy findings. Over the duration of the study, 22 adverseeffects (AE) were documented in 11 participants. These adverse effects included symptoms such as fever, malaise, giddiness, dyspepsia, diarrhea, rash/itching, abdominal pain, nausea, cough, cold, headache, backache, body pain, and calf pain. It is worth noting that none of these adverse effects requires medical intervention for resolution [28].

A comprehensive investigation employing molecular biomarkers in non-human primates substantiated the absence of any indications of potential carcinogenic risk to humans.Multiple genetic toxicology assessments, including the mouse micronucleus assay, chromosomal aberration assay utilizing peripheral human blood lymphocytes, and Ameis mutagenicity test, have demonstrated that saroglitazar does not possess mutagenic or neurotoxic properties [29].

INTERACTION

Saroglitazar at a concentration of 10μM, did not exhibit notable inhibition of CYP1A2,2C9, 2C19, 2D6, or 3A4. Similarly, in HepG2 cells that were transiently transfected, saroglitazar showed no signs of inducing CYP3A4 enzyme when tested in a luciferase-basedreporter assay at concentrations up to 100 μM [28].

SAROGLITAZAR VS CURRENT THERAPIES

1) Statins

Patients diagnosed with atherogenic diabetic dyslipidemia (ADD) are believed to derive the greatest benefit from statins as the primary treatment for lowering LDL-C levels. These drugs not only enhance HDL-C and TG levels but also reduce LDL-C levels by as muchas 50%. Nevertheless, the most common concern associated with statin

use is its impact on muscle function, which can manifest as myositis and myalgia. Furthermore, statin use is known to affect hepatic function. Moreover, prolonged statin therapy, especially at high dosages, worsens glycemic control and triggers the development of type 2 diabetes [30].

2) Fibrates

Their impact on LDL-C is minimal, but they reduce TG levels and increase HDL-C levels [19]. Nevertheless, it is worth noting that gastrointestinal problems including nausea andabdominal pain, are prevalent side effects affecting approximately 5% of individuals. In addition, the use of fibrates can lead to myopathy. It is advisable to avoid prescribing fibratesto patients with renal dysfunction as they are at a higher risk of developing myopathy. Furthermore, it is important to highlight that gemfibrozil has a lesser impact on serum creatinine levels compared to Fenofibrate [30].

3) TZDS

The impact of TZDs on HDL and LDL levels may lead to an increase, but the lastingconsequences of such alterations remain unclear [31]. Raising HDL cholesterol levels in diabetic patients poses a significant challenge because of the general contraindication of niacin, the most potent agent, in this patient population [32].The incorporation of saroglitazar in individuals already taking anti-diabetic medications resulted in a notable decrease of 0.9%in HbA1c levels and a substantial enhancement in fasting and postprandial plasma glucose.

SAROGLITAZAR 2MG VERSES 4MG

In general, 4 mg of saroglitazar has produced better outcomes than 2
mg Saroglitazar, when compared to the control and 2 mg saroglitazar, 4 mg of saroglitazar has demonstrated the ability to significantly reduce glycaemic-related outcome markers likeFPG [33]. Saroglitazar 4 mg has been shown to effectively reduce triglycerides and LDL-C levels, although it may lead to a slight increase in body weight compared to a placebo [33].

SAROGLITAZAR AS ADD ON THERAPY WITH METFORMIN ANDFENOFIBRATES

Compared to add-on therapy of fenofibrate with metformin, add-on therapy of saroglitazar with metformin substantially lowered FPG and PPPG levels when analyzedbetween-group data shown at every follow-up visit [35].

SAROGLITAZAR AS ADD-ON THERAPY WITH ROSUVASTATIN INPATIENTS WITH DIABETIC DYSLIPIDEMIA

Saroglitazar, when used in conjunction with Rosuvastatin, resulted in decreased levels of triglyceride, total cholesterol, LDL, and VLDL, while also enhancing HDL levels and improving glycemic index in individuals with type 2 diabetes, all without any notable adverse effects. Therefore, the combination of Saroglitazar and Rosuvastatin proved to be asafer and more efficient treatment option compared to Rosuvastatin therapy alone [36].

CONCLUSION

By reviewing the articles, saroglitazar was found to be effective and safe for diabetic dyslipidemia and significantly improved glycemic parameters, cholesterol, and triglyceride levels without causing any serious ADR.

REFERENCES

1. Shetty SR, Kumar S, Mathur RP, Sharma KH, Jaiswal AD. Observationalstudy to evaluate the safety and efficacy of saroglitazar in Indian diabeticdyslipidemia patients. *Indian Heart Journal*. 2015;67(1):23-26. doi:https://doi.org/10.1016/j.ihj.2015.02.007
2. Feingold KR. Dyslipidemia in Patients with Diabetes [Internet]. NCBI Bookshelf.2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305900/
3. Management of diabetic dyslipidemia in Indians: Expert consensus statement from theLipid Association of India. Journal of Clinical Lipidology. 17(2):e1–14.
4. Prevalence and pattern of diabetic dyslipidemia in Indian type 2 diabetic patients.Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 4(1):10–2.
5. Krishnappa, M., Patil, K., Parmar, K., Trivedi, P., Mody, N., Shah, C., Faldu, K., Maroo, S., &Parmar, D. (2020). Effect of saroglitazar 2 mg and 4 mg on glycemic control, lipid profile and cardiovascular disease risk in patients with type 2 diabetes mellitus: A 56-week, randomized, double blind, phase 3 study (PRESS XII study). Cardiovascular Diabetology, 19(1), 1–13. https://doi.org/10.1186/s12933-020-01073-w.
6. Joshi, S. R. (2015). Saroglitazar for the treatment of dyslipidemia in diabetic patients.*Expert Opinion on Pharmacotherapy*, *16*(4), 597–606. https://doi.org/10.1517/14656566.2015.1009894
7. Plutzky J. Emerging concepts in metabolic abnormalities associated with coronaryArtery disease. CurrOpinCardiol 2000; 15:416-21
8. Freeman AM, Pennings N. Insulin Resistance. nih.gov. Published 2023. https://www.ncbi.nlm.nih.gov/books/NBK507839/
9. Touyz RM, Schiffrin EL. Peroxisome proliferator-activated receptors in vascular biology-molecular mechanisms and clinical implications. *Vascular Pharmacology*.2006;45(1):19-28. doi:https://doi.org/10.1016/j.vph.2005.11.014
10. Pawlak M, Lefèbvre P, Staels B. Molecular mechanism of PPARα action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. *Journal of Hepatology*. 2015;62(3):720-733. doi:10.1016/j.jhep.2014.10.039
11. Gervois P, Kleemann R, Pilon A, et al. Global Suppression of IL-6-induced Acute Phase Response Gene Expression after Chronic in Vivo Treatment with the Peroxisome Proliferator-activated Receptor-α Activator Fenofibrate. *Journal of Biological Chemistry/˜ the œJournal of Biological Chemistry*. 2004;279(16):16154-16160. doi:10.1074/jbc.m400346200
12. Ip E, Farrell FRACPGC, Robertson G, De La M Hall P, Kirsch R, Leclercq I. Centralrole of PPARα-dependent hepatic lipid turnover in dietary steatohepatitis in mice. *Hepatology*. 2003;38(1):123-132. doi:10.1053/jhep.2003.50307

13. Picard F, Auwerx J. PPARΓANDGLUCOSEHOMEOSTASIS. *Annual Review ofNutrition*. 2002;22(1):167-197. doi:10.1146/annurev.nutr.22.010402.102808
14. Nissen SE. Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus. *JAMA*.2005;294(20):2581. doi:https://doi.org/10.1001/jama.294.20.joc50147
15. .Hamrén B, Öhman KP, Svensson MK, Karlsson MO. Pharmacokinetic- Pharmacodynamic Assessment of the Interrelationships Between TesaglitazarExposure and Renal Function in Patients With Type 2 Diabetes Mellitus. *TheJournal of Clinical Pharmacology*. 2012;52(9):1317-1327. doi:https://doi.org/10.1177/0091270011416937
16. Hong F, Xu P, Zhai Y. The Opportunities and Challenges of Peroxisome Proliferator-Activated Receptors Ligands in Clinical Drug Discovery and Development. *International Journal of Molecular Sciences*. 2018;19(8):2189.doi:https://doi.org/10.3390/ijms19082189
17. Positive results from Phase II clinical trial (CGZ203 study) of Chiglitazarmonotherapy for non-alcoholic steatohepatitis. Yahoo Finance. PublishedMarch 18, 2024. Accessed May 7, 2024. https://finance.yahoo.com/news/positive- results-phase-ii-clinical-112500760.html?fr=yhssrp_catchall
18. Colca JR. Discontinued drugs in 2008: endocrine and metabolic. *ExpertOpinion on Investigational Drugs*. 2009;18(9):1243-1255. doi:https://doi.org/10.1517/13543780903132673
19. A. Michael Lincoff, Tardif JC, Schwartz GG, et al. Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients WithType 2 Diabetes Mellitus. *JAMA*. 2014;311(15):1515-1515. doi:https://doi.org/10.1001/jama.2014.3321
20. Sakamoto J, Kimura H, Moriyama S, et al. A novel oxyiminoalkanoic acid derivative, TAK-559, activates human peroxisome proliferator-activated receptor subtypes. *European Journal of Pharmacology*. 2004;495(1):17-26.doi:https://doi.org/10.1016/j.ejphar.2004.05.020
21. Long GG, Reynolds VL, Lopez-Martinez A, Ryan TE, White S, Eldridge SR.Urothelial Carcinogenesis in the Urinary Bladder of Rats Treated with Naveglitazar, a γ-dominant PPAR α/γ Agonist: Lack of Evidence for Urolithiasis as an Inciting Event. *Toxicologic Pathology*. 2008;36(2):218-231. doi:10.1177/0192623307311757
22. Nishihara M, Sudo M, Kamiguchi H, et al. Metabolic Fate of Sipoglitazar a Novel Oral PPAR Agonist with Activities for PPAR-γ, -α and -δ, in Rats and Monkeys andComparison with Humans In Vitro. *Drug Metabolism and Pharmacokinetics*. 2012;27(2):223-231. doi:10.2133/dmpk.dmpk-11-rg-061
23. PubChem. Saroglitazar. pubchem.ncbi.nlm.nih.gov. Accessed December 15, 2022. https://pubchem.ncbi.nlm.nih.gov/compound/Saroglitazar
24. SannappaGowda NG 1, Shiragannavar VD 1, Puttahanumantharayappa LD 1, Vamadevaiah RM 2, Santhekadur PK 1. *Therapeutic Role of Saroglitazar in NAFLDand Metabolic Syndrome*. Vol 6–6. Nov Appro Drug Des Dev; 2022:001-002. doi:10.19080/NAPDD.2022.06.555689
25. Jain MR, Giri SR, Bhoi B, et al. Dual PPARα/γ agonist saroglitazar improves liver histopathology and biochemistry in experimental NASH models. *Liver International: Official Journal of the International Association for the Study of the Liver*. 2018;38(6):1084-1094. doi:https://doi.org/10.1111/liv.13634

26. Sharma A, S A, Kushwah DS, S R. Saroglitazar, a novel cardiometabolic agent for diabetic dyslipidemia - A Review. *Journal of Young Pharmacists*. 2014;7(1):2-6. doi:https://doi.org/10.5530/jyp.2015.1.2
27. Jani R, Joshi S, Patel P, et al. *Saroglitazar 2 and 4 Mg Compared to Pioglitazone 45Mg in Diabetic Dyslipidemia (PRESS v) a Multicenter, Prospective, Randomized,Double-Blind Study to Evaluate the Safety and Efficacy of on Behalf Of: DiabetesTechnology Society Can Be Found At: Journal of Diabetes Science and TechnologyAdditional Services and Information For*.; 2014. Accessed April 21, 2024.https://www.lipaglyn.com/downloads/Lipaglyn%20Saroglitazar%20Phase%20III%20Press%20V%20Trial%20Publication%20J%20Diabetes%20Sci%20Technol-2014- Pai-1932296813518680.pdf.
28. Jani RH, Kansagra K, Jain MR, Patel H. Pharmacokinetics, Safety, and Tolerability ofSaroglitazar (ZYH1), a Predominantly PPARα Agonist with Moderate PPARγ AgonistActivity in Healthy Human Subjects. *Clinical Drug Investigation*. 2013;33(11):809- 816. doi:https://doi.org/10.1007/s40261-013-0128-3
29. AravindSosale S, Saboo B, Sosale B. Saroglitazar for the treatment of hypertriglyceridemia in patients with type 2 diabetes: current evidence. *Diabetes,Metabolic Syndrome and Obesity: Targets and Therapy*. Published online April 2015:189. doi:https://doi.org/10.2147/dmso.s49592
30. Singh G, Correa R. Fibrate Medications. PubMed. Published 2020. https://www.ncbi.nlm.nih.gov/books/NBK547756/
31. Farrer S. Beyond Statins: Emerging Evidence for HDL-Increasing Therapies and Diet in Treating Cardiovascular Disease. *Advances in Preventive Medicine*. 2018;2018:1-9. doi:https://doi.org/10.1155/2018/6024747
32. Haffner SM. Management of Dyslipidemia in Adults With Diabetes. *Diabetes Care*. 1998;21(1):160-178. doi:https://doi.org/10.2337/diacare.21.1.160
33. Chhabra M, Vidyasagar K, Gudi SK, Sharma J, Sharma R, Rashid M. Efficacyand safety of saroglitazar for the management of dyslipidemia: A systematic review and meta-analysis of interventional studies. Zhao JV, ed. *PLOS ONE*. 2022;17(7):e0269531. doi:https://doi.org/10.1371/journal.pone.0269531
34. Oliveira VM, Oliveira IC, Antonio. Abstract 16336: Efficacy and Safety ofSaroglitazar in the Management of Atherogenic Dyslipidemia: An UpdatedMeta-Analysis of Randomized Clinical Trials. *Circulation*. 2023;148(Suppl_1). doi:https://doi.org/10.1161/circ.148.suppl_1.16336
35. Ghosh A. Comparison of Effectiveness and Safety of Add-on Therapy of Saroglitazar and Fenofibrate with Metformin in Indian Patients with DiabeticDyslipidaemia. *JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH*. Published online 2016. doi:https://doi.org/10.7860/jcdr/2016/16908.7362
36. Anil Batta, Sumesh Prasad Sah. Impact of Saroglitazar as an add-on therapy torosuvastatin in patients with diabetic dyslipidemia: A prospective, single centre, observational study in Indian patients. *Open Access Research Journal of Science and Technology*. 2024;10(1):001-009. doi:https://doi.org/10.53022/oarjst.2024.10.1.0080