

Role of Glitazars in atherogenic dyslipidemia and diabetes: Two birds with one stone?

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ABSTRACT

A triad of high triglycerides, low high-density lipoprotein (HDL) cholesterol, and elevated small dense low-density lipoprotein particles occurring in a patient with type 2 diabetes is referred to atherogenic diabetic dyslipidemia (ADD). Despite statin therapy, a significant residual risk remains potentially attributable to increased triglyceride concentration and low HDL cholesterol, a characteristic hallmark of ADD. Current therapeutic options in reducing this residual risk include nicotinic acid, omega 3 fatty acids, and selective peroxisome proliferator-activated receptor-alpha (PPAR) agonists (fibrates). These drugs are limited in their potential either by lack of evidence to support their role in reducing cardiovascular events or due to their side effects. This review details their current status and also the role of new glitazar, saroglitazar dual PPAR α/γ agonist with predominant PPAR α activity in the management of ADD.

Key words: Atherogenesis, diabetic dyslipidemia, proliferator-activated receptor-alphas, saroglitazar

INTRODUCTION

A triad of high triglycerides, low high-density lipoprotein (HDL) cholesterol and elevated small dense low-density lipoprotein (LDL) particles occurring in a patient with type 2 diabetes is referred to atherogenic diabetic dyslipidemia (ADD). Insulin resistance at the level of adipocyte causing increased free fatty acid efflux is thought to be central to the pathogenesis of ADD. This results in increased very LDL (VLDL) cholesterol from the liver facilitated by increased synthesis of coprotein apo B.^[1] Subsequent actions mediated by cholesterol ester transferase protein in transferring triglycerides from VLDL particles to HDL and LDL result in increased apo A1 containing small dense HDL and apo B containing small dense LDL particles. The triglyceride-enriched HDL is subsequently

hydrolyzed by hepatic lipase or lipoprotein lipase resulting in low HDL; Apo A-I dissociates from the reduced-size HDL, which is filtered by the renal glomeruli and degraded in renal tubular cells^[2,3] [Figure 1].

Reducing LDL cholesterol (C) using statins is a proven strategy for primary as well as secondary prevention of cardiovascular events. Hence, statin therapy is accepted as a first line in management of dyslipidemia, diabetic, or otherwise. But, despite statin therapy, a significant residual risk remains potentially attributable to increased triglyceride concentration and low HDL cholesterol, a characteristic hallmark of ADD. A meta-analysis of 14 trials involving statins that included 18,686 people with diabetes proved that presence of low HDL and high triglyceride limits the efficacy of statin therapy alone in reducing the vascular events despite achieving target LDL-C levels.^[4] Similarly, a meta-analysis of 17 prospective studies showed that after adjusting for variables such as HDL-C, total cholesterol, and other risk factors, the relative risk for coronary heart disease with one mmol/L (1 mmol/L = 88.4956 mg/dL) increase in triglyceride was 1.14 [95% confidence interval (CI) 1.05-1.28] for men and 1.37 (95% CI 1.13-1.66) for women.^[5] This has led to renewed interest in treatments

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that could selectively target high triglycerides and low HDL thus, further reducing the cardiovascular risk. Omega 3 fatty acids, nicotinic acid, and fibrates are currently available drugs used to target such dyslipidemia.

ADD-THERAPEUTIC OPTIONS

Omega 3 fatty acids

A systematic review and meta-analysis of available evidence studying the merits of omega 3 fatty acid supplementation mainly, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have failed to show any cardiovascular benefit.^[6] Similarly, recently published randomized placebo controlled “ORIGIN trial (Outcome Reduction With Initial Glargine Intervention)” that included patients with dysglycemia (N: 12,536) showed no cardiovascular benefits in the study population exposed to omega 3 fatty acid compared to placebo during the study period of over 6 years. This is despite significant reduction ($P < 0.001$) in triglyceride concentration in study arm compared to placebo (23.5 +/- 3 mg/dL vs. 9 +/- 3 mg/dL). It is of interest though to note that baseline triglyceride value in both groups in this study was around 140 mg/dL.^[7] ASCEND (A Study of Cardiovascular Events in Diabetes) a large placebo-controlled randomized prospective trial involving about 15,000 patients with diabetes in currently underway looking at the efficacy of 1 g capsules containing 90% omega 3 fatty acids (0.4 g EPA, 0.3 g DHA) as a primary preventive measure against cardiovascular events in patients with diabetes mellitus (Clinicaltrials.gov: NCT00135226).

Nicotinic acid

Nicotinic acid in extended release preparation (2 g/day) has been proven to increase HDL cholesterol by 20% and reduce triglyceride concentration by 25% in addition

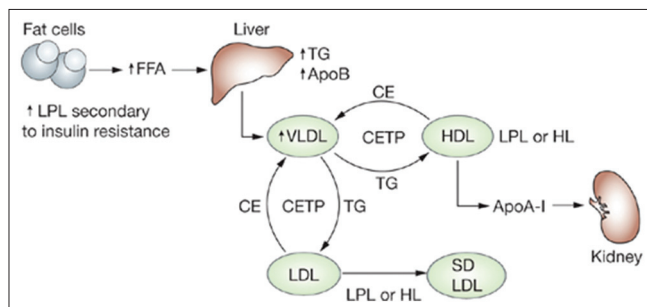


Figure 1: High concentration of VLDL-transported TG triggers CETP mediated transfer of LDL cholesteryl ester or HDL cholesteryl ester in exchange for TG. Triglyceride-rich HDL cholesterol or LDL cholesterol then undergoes hydrolysis by hepatic lipase or lipoprotein lipase. Abbreviations: ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; FFA, free fatty acid; HL, hepatic lipase; LPL, lipoprotein lipase; SD LDL, small dense LDL cholesterol; TG, triglyceride. Nature Clinical Practice Endocrinology and Metabolism (2009)5, 150-159

to lipid lowering by statin therapy.^[8] Clinical utility of nicotinic acid is primarily limited by significant side effects such as severe facial flushing and cutaneous rash that are thought to be mediated by prostaglandins. Liropiprant a prostaglandin receptor antagonist was designed as a codrug to minimize these unpleasant side effects.^[9] But, more recently “HPS2 THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events)” study done to assess the cardiovascular benefit of nicotinic acid/liropiprant combination in addition to statin +/- ezetimibe with a prestudy LDL cholesterol concentration of <130 mg/dL on over 40,000 patients across the globe showed highly significant four fold increased risk of myopathy in the study group compared to placebo and also double (0.9-0.4%) the incidence of diabetic complications (typically hyperglycemia)^[10] needing early termination of the study raising serious concerns about the safety of this approach.

Peroxisome proliferator-activated receptor agonists

Peroxisome proliferator-activated receptor-alpha (PPAR α), gamma (PPAR γ), and beta/delta (PPAR β/γ) agonists regulate gene transcription by binding to specific deoxyribonucleic acid response elements upon ligand activation and heterodimerization with 9-cis retinoic acid receptor. Depending on the activating ligand, different receptor conformations are adopted, leading to different coactivator recruitment and subsequent effects on gene expression. Even though all the PPAR agonists are from the same pharmaceutical class, their biological activity varies widely based on selective alpha or gamma modulation.^[11,12] PPAR α regulates expression of genes encoding enzymes and transport proteins controlling lipid metabolism and is expressed predominantly in tissues with a high capacity for fatty acid oxidation like liver, heart, skeletal muscle, brown fat, and kidney. PPAR γ not only promotes pre-adipocyte differentiation, but also induces adiponectin expression, which increases fatty acid oxidation by activation of the AMP-activated protein kinase pathway and down regulates the expression of genes encoding resistin and tumor necrosis factor together contributing to reduced insulin resistance.^[13-15] While PPAR γ agonism reduces insulin resistance, PPAR α agonism complements it by reducing the FFA load on peripheral tissues thereby augmenting glucose uptake.^[16] PPAR α and PPAR γ receptors have also been found in vascular endothelium, monocytes/macrophages, and smooth muscle cells of vascular lineage exerting specific anti-inflammatory and lipid modulating effects supporting their role in antiatherogenesis^[17] Figure 2.

Glitazones

Predominant PPAR γ agonists recognized as “Glitazones” proven to improve insulin resistance have been used

as antidiabetic agents for a few years now. Ciglitazone was first of this kind synthesized in 1982. Pioglitazone, englitazone, troglitazone, rosiglitazone, and darglitazone were synthesized later and among these, Troglitazone, Pioglitazone, and Rosiglitazone were evaluated in clinical studies.^[18] Troglitazone was approved for clinical use 1997 but were subsequently withdrawn within 3 years because of idiosyncratic liver toxicity.^[19] Rosiglitazone was withdrawn from Indian market in 2010 secondary to cardiovascular concerns.^[20] Pioglitazone although is still available to be prescribed, but concern regarding increased risk of bladder cancer on cumulative exposure^[21] and risk of osteoporosis in women^[22] has limited its potential for widespread use. Because of predominant PPAR γ agonism, these agents have minimal influence if any on ADD.

Fibrates

Predominant PPAR α agonists, “fibrates” as they are known, are proven to influence lipid profile but their role in ADD is extensively debated. Meta-analysis of several trials involving fibrates by Sacks *et al.*,^[23] (ACCORD, FIELD, BIP, HHS, VA-HIT) showed that fibrates are very likely to be beneficial as an add on therapy in subgroup of patients characterized by high triglycerides and low HDL cholesterol despite statin usage. Similar systematic review on usefulness of fibrate therapy by Jun *et al.*,^[24] demonstrated that those patients with a high mean triglyceride concentration obtained greater reduction in cardiovascular outcomes. All fibrates (except gemfibrozil) have shown reversible elevation of creatinine (up to 30%) of unknown significance.^[25] In another meta-analysis, combination therapy with statin and fibrate was shown to be safe with no increased risk of serious myopathy or rhabdomyolysis.^[26] Despite lack of any significant influence on PPAR γ receptors, fibrates were shown to have some positive influence on glucose metabolism probably secondary to their influence on insulin resistance^[27] but clinical outcome study proving their usefulness in improving glycemic control in addition to dyslipidemia is lacking.

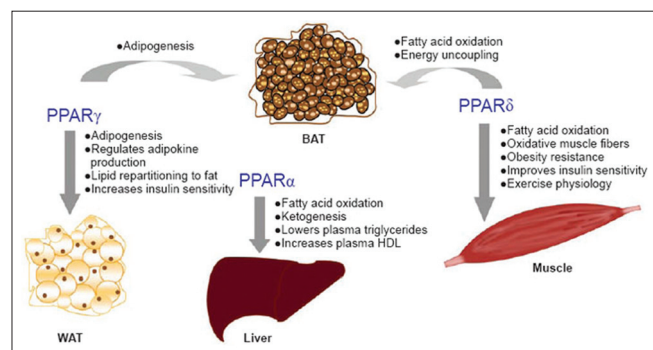


Figure 2: An overview of the physiological and/or pharmacological roles of the PPARs in energy metabolism. Data summarized from PPAR knockout and ligand studies. *Cell Research* 2010; 20:124-137

Glitazars

A combined PPAR α/γ agonist should ideally be a suitable drug in treatment of type 2 diabetic patients on statin therapy who have residual cardiovascular risk secondary to elevated triglyceride concentration. This molecule would not only target the dyslipidemia but also contribute to improved glycemic control. Given these benefits of dual PPAR α/γ agonism, several pharmaceutical agents with such action commonly named as “glitazars” have been developed.

Depending on their molecular structure, these molecules exert dual action with varying degrees of PPAR α and PPAR γ activism. Faglitazar, the first glitazar to be tested, was dropped very early on in development phase secondary to significant edema.^[28] Similarly, ragaglitazar was also dropped early on due to its carcinogenic potential on urothelial cells in rodent models.^[29] Muraglitazar,^[30] although proved successful in improving insulin sensitivity and treating diabetic dyslipidemia, was suspended in 2006 due to significant cardiovascular side effects. Tesaglitazar^[31] showing similar promise was withdrawn secondary to its bone marrow and renal toxicities. Although these tested molecules resulted in adverse events, these have been compound specific and of diverse origin, that is, urothelial, renal, and cardiac rising hopes of a potential drug that could mitigate these side effects and yet have a positive influence on insulin sensitivity and dyslipidaemia dominated by high triglycerides, small dense LDL and low HDL cholesterol Figure 3.

Saroglitazar, also a dual PPAR α/γ agonist with predominant PPAR α activity, is considered novel and unique as it was conceptualized to deliver antidyslipidemic and antihyperglycemic effects without any of the adverse events of its predecessor molecules.^[32] In a phase 1 study designed to evaluate pharmacokinetics, safety and tolerability of the drug, healthy volunteers were subject to varying doses of saroglitazar (0.25-128 mg/day). The drug was confirmed

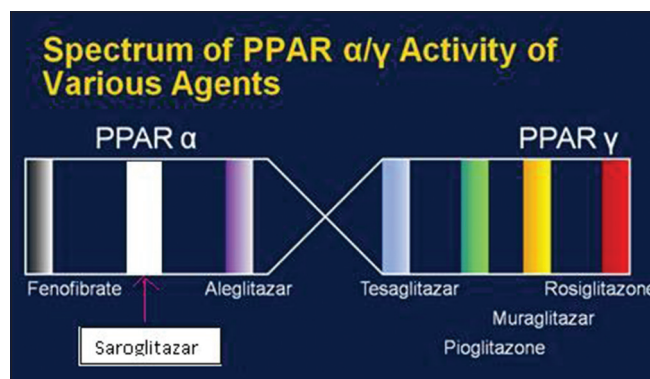


Figure 3: Graphic representation of various PPARs based on their relative affinity to α/γ agonism. <http://www.theheart.org/documents/sitestructure/en/content/programs/1228135/1228135.html>

to have hepatobiliary excretion as a predominant route. All doses were very well-tolerated with no serious adverse events (renal/hepatic/cardiac) reported in the study group.^[33] Similarly in a 16-week (4 week wash out phase) multicenter, randomized, placebo-controlled, phase 3 trial of diabetic patients on treatment with atorvastatin 10 mg and with residual dyslipidemia consisting of triglycerides of >200 and <500, subjects were put to 12-week therapy with 2 and 4 mg of saroglitazar. At the end of 12 weeks, the results showed statistically significant reduction in triglyceride concentration (-45.5 mg/dL +/- 3.03%) with 2mg/d of saroglitazar + atorvastatin and similar reduction (-46 mg/dL mg/dL +/- 3.02%) in those on 4 mg/day of saroglitazar + atorvastatin compared with those on placebo + atorvastatin.^[34] Although non significant in statistical terms, patients in study group reduced glycated hemoglobin levels by 0.3+/- 0.08% with 2 mg/day and 0.2+/- 0.07% with 4 mg/day dosage. At the end of 24 weeks, study group reported no significant renal, hepatic, and cardiac adverse events.

For now as observed in phase 1 and phase 3 trails, saroglitazar appears safe and has not shown any of the adverse effects that are commonly recognized with its class of molecules (e.g. Muraglitazar-cardiovascular and Tesaglitazar-renal and bone marrow). But given historical concerns, proof of long-term safety remains paramount and is yet to be proven. Although, it has shown positive results in improving glycemic and lipid parameters in patients with ADD in short term, a longer term clinical trial proving its efficacy in improving cardiovascular outcome is currently nonexistent but much desired. Until such time given recent approval of saroglitazar by Indian authorities permitting its clinical use in treatment of ADD, both the pharmaceutical industry and medical profession should exercise close pharmacovigilance and report any adverse events as soon as observed.

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