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Editorial

From 'Make in India' to 'Made in India': The saroglitazar story

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Indian pharmaceutical industry is successfully following the 'make in India' theme, much before it became a buzz word in governance. India has dominated the manufacturing of generic and bio-similar drugs. A few of the Indian companies have made anti-tubercular, anti-retroviral and anti-cancer drugs available to the vast majority of the world population at a fraction of the cost of their patented counterparts. Make in India theme has helped the Indian pharmaceutical industry to forge ahead even in difficult economic times clocking an annual growth of >10% for over a decade. It may appear fragmented with around 24,000 estimated players; but it has around 350 companies in the organized sector and nearly one third of the market is dominated by the top ten companies. In terms of volumes, Indian pharmaceutical industry is the third largest in the world. However, Indian share is a meager 1–2% of the global market share and is ranked a distant 10th in terms of value.[1] India entered the global scene mainly through its engineered generic drugs and active pharmaceutical ingredients. For instance, India has 74 US FDA-approved manufacturing units, highest in any country outside the US.[2] Indian industries presence in the patented drugs club is nearly non-existent.

After success in the generic market and it (generic market) getting competitive and highly regulated, a few Indian pharmaceutical companies have ventured into the field of new molecule development and have accordingly increased their research and development expenses. Most of the efforts have gone into making innovative processing for existing molecules, making different combination and/or formulations of existing drugs and making bio-similar agents. Some of the most successful combinations that have crossed Indian boundaries include the various poly-pills developed by Indian industries.[3,4] However, as of date, only a very few new molecules have been developed in India (one of them is the newer anti-malarial – Synriam).[5] In this context, saroglitazar, a novel dual peroxisome proliferator activated receptor (PPAR)-α/γ agonist, is a novel first in class drug and is the first indigenously developed new clinical entity by any Indian pharmaceutical company, ever![6]

In this issue of Indian heart journal, Shetty SR et al.,[7] describe the encouraging results of a post marketing surveillance report on the safety and efficacy of saroglitazar in Indian diabetic dyslipidemia patients. Saroglitazar is a dual PPAR-α/γ agonist, with predominant PPARα and moderate PPARγ activity.[8] The mechanism of action and the resultant effects are summarized in the Fig. 1. PPAR are transcription factors; a group of nuclear receptor proteins that regulate the expression of various genes. PPAR have been shown to play a key role in a wide variety of cellular events including cellular development and differentiation, carbohydrate, lipid and protein metabolism, and tumorigenesis. Currently, 3 types of PPARs have been identified: alpha, gamma, and delta (beta). PPAR-alpha is expressed in liver, kidney, heart, muscle, and adipose tissue. PPAR-alpha is a key regulator of hepatic lipid metabolism. PPAR-alpha promotes fatty acid utilization. In energy deprivation, PPAR-alpha is activated that stimulates ketogenesis. PPAR β/δ is markedly expressed in brain and also in adipose tissue, and skin. PPAR γ is expressed in three forms: γ1 – expressed in virtually all tissues, γ2 – expressed mainly in adipose tissue and γ3. PPARG regulates glucose metabolism and storage of fatty acid.[9] A few existing molecules are PPAR agonists; fibrates activate PPARα, and the anti diabetic thiazolidinediones activate PPARγ. Combined activation of PPAR α and γ would result in anti diabetic and anti-dyslipidemic effects. For instance, the antidiabetic properties of pomegranate flower are suggested to be due to dual PPAR-alpha/-gamma activator properties.[10] Saroglitazar is another novel dual PPAR-alpha/-gamma activator.

In the limited literature available, saroglitazar has shown good efficacy and acceptable safety profile.[6–8] In the double blind

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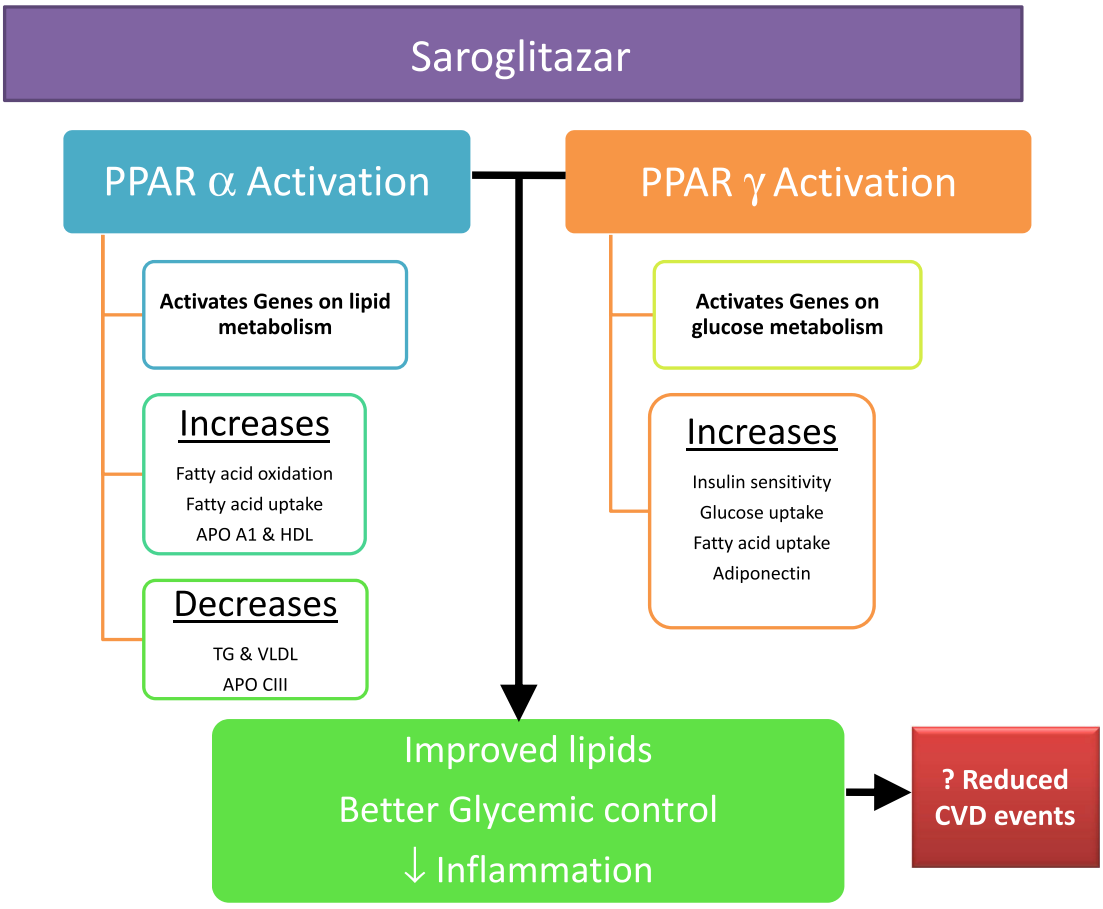

Fig. 1 – Mechanism of action of saroglitazar.

PRESS V and Press VI studies,[11,12] saroglitazar has demonstrated excellent anti-glycemic and anti-lipid effects in patients with diabetic dyslipidemia as compared to placebo or Pioglitazone. Based on these evidences, saroglitazar is approved for clinical use in India. In this issue of IHJ, data on the post marketing surveillance of the use of saroglitazar 4 mg in 3133 diabetic dyslipidemic patients over a 3 months period is presented.[7] There was 35.8% reduction in triglycerides, 16.4% reduction in LDL cholesterol, 19% reduction in total cholesterol and 23.4% reduction in non-HDL cholesterol. In addition, the use of saroglitazar showed an impressive 0.9% absolute reduction in HbA1c. Unlike the fibrates and niacin, the drug is well tolerated. No serious adverse events including edema and weight gain are reported; two common side effects known to occur with drugs having a similar mechanism of action. The better tolerability and absence of significant side effects could be due to the absence of thiazolidinedione (TZD) ring in saroglitazar molecule.

The data presented is of post marking surveillance. Lack of consistent inclusion criteria and the differing data quality are the major drawbacks of such a survey. Under-reporting of complications and inadequate denominator data (i.e., number of persons received the drug) are the other shortcomings of such post marking surveillance. However, combined with previous clinical trials, the data arguers well for the routine use of saroglitazar in diabetic dyslipidemia not controlled with statin. However, further development and global launch of saroglitazar molecule is challenging for a variety of reasons. Definitely the sponsor need to organize a large multi-centric, randomized controlled trial (RCT) with FDA monitoring using clinically meaningful hard end points. Majority of similar agents in the field of lipidology have failed to prove their absolute need over and above good doses of statins, including fibrates and niacin.[13,14] Even though it is known that low HDL and high TG are risk factors for CVD, there is no proven therapy that reverses these risks and produces clinical benefit.[15] In the field of anti-diabetic medication also cardiovascular risk reduction is rarely shown in a clinical trial. Organizing mega multicentric trials are extremely expensive and are risky. New molecule development is also time consuming; saroglitazar was also discovered in 2001, but was approved for the treatment of Type II diabetes by the Drug Controller General of India only in June 2013. A failed RCT could create havoc for the finances of the company, but a positive trial could truly create the first 'Indian global molecule' and a true Indian multinational pharmaceutical company. Only then it can claim the status of 'made in India'.

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