Saroglitazar

Maria Talla[1]
MBChB, MRCP, Specialty Trainee

Gerry McKay[1]
BSc (Hons), FRCP, Consultant Physician

Miles Fisher[1]
MD, FRCP, Consultant Physician

[1]Glasgow Royal Infirmary, Glasgow UK

Correspondence to:
Dr Maria Talla, Department of Diabetes, Endocrinology & Clinical Pharmacology, Glasgow Royal Infirmary, 84 Castle Street, Glasgow G4 0SF, UK; email: mtalla@nhs.net

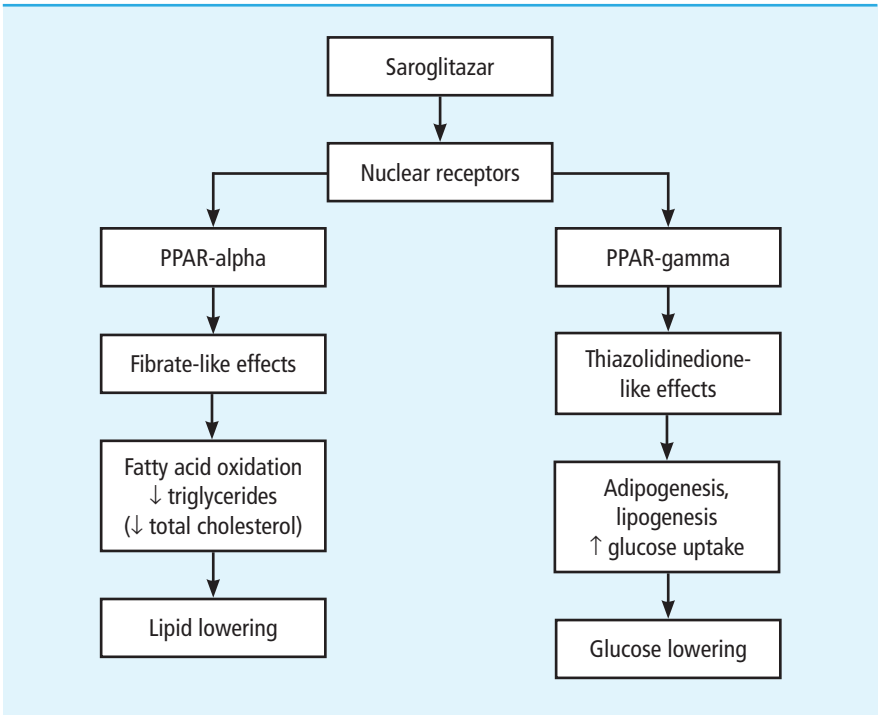

Figure 1. Saroglitazar has dual PPAR-alpha and PPAR-gamma activity, having effects on lipids and glucose respectively

Introduction

Pioglitazone, a thiazolidinedione, is a peroxisome proliferator-activated receptor (PPAR)-gamma agonist that improves glycaemic control in type 2 diabetes. A newer class of drugs, known as glitazars, has been developed with dual PPAR-alpha/gamma agonist activity. They improve dyslipidaemia through a mechanism similar to that of fibrates at the PPAR-alpha receptor, and improve glycaemic control in a manner comparable to the thiazolidinediones at the PPAR-gamma receptor.

The first glitazars were effective at reducing HbA_{1c} but did not reach clinical use because of serious side effects of heart failure (aleglitazar, muraglitazar) and decreased glomerular filtration rate (tesaglitazar). Saroglitazar is a new glitazar that has been approved in India for the treatment of diabetic dyslipidaemia.

Pharmacology

PPARs are transcription factors that belong to the superfamily of nuclear receptors. There are three isoforms – alpha, gamma and delta. Figure 1 outlines the pharmacological effect of saroglitazar through dual PPAR agonist activity. Saroglitazar activates PPAR-alpha, increasing hepatic oxidation of fatty acids and reducing formation and secretion of triglycerides.[1] Fatty acids are diverted from skeletal muscle and adipose tissue to the liver, which in turn decreases fatty acid synthesis and delivery of triglycerides to peripheral tissues.

Saroglitazar also increases lipolysis and elimination of triglyceride-rich particles from plasma by activating lipoprotein lipase and reducing the production of apolipoprotein C-III, an inhibitor of lipoprotein lipase activity.

Through modest effects on the PPAR-gamma receptor saroglitazar regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport and utilisation.

In healthy volunteers, peak plasma levels were attained at 1 hour post-dose with the absorption of the drug being unaffected by food. A maximum serum concentration of 337.1±91.0ng/ml (mean ± SD) was

achieved following a 4mg single dose of saroglitazar, with a mean plasma half-life of 2.9±0.9 hours. Saroglitazar is highly protein bound at approximately 96% in human plasma. It is excreted primarily via the hepatobiliary route. The recommended dose is 4mg daily.

Trials of efficacy

The effects on diabetic dyslipidaemia were studied in two small, short phase III trials.

The Prospective Randomised Efficacy and Safety study of Saroglitazar V (PRESS V) was a 26-week, multicentre, randomised, double-blind study to evaluate the safety and efficacy of saroglitazar 2mg and 4mg compared to pioglitazone 45mg in diabetic dyslipidaemia.[2] After a two-week run in period to allow lifestyle modification and to wash out previous medications that affect lipid levels, 122 patients were randomised to saroglitazar 2mg/day (n=41), saroglitazar 4mg/day (n=41), or pioglitazone 45mg/day (n=40). The primary end-point of the study was the change in serum triglyceride levels after a 24-week treatment period compared to baseline.

Saroglitazar 2mg and 4mg significantly reduced mean plasma triglyceride from baseline by 26.4% and 45%, respectively, as compared to 15.5% for pioglitazone after 24 weeks ($p<0.001$). The maximum effect of saroglitazar was achieved by week 12 and sustained at week 24. Other lipid effects were also demonstrated, particularly with the 4mg dose (decrease in low-density lipoprotein [5%], very low-density lipoprotein [45.5%], total cholesterol [7.7%] and apolipoprotein B [10.9%]).

HbA_{1c} levels were slightly reduced at 24 weeks in all three treatment groups. This was significant when compared to baseline, but with no significant difference between saroglitazar 2mg, saroglitazar 4mg and pioglitazone 45mg (HbA_{1c} -0.3%, -0.3% and -0.4%, respectively).

The Prospective Randomised Efficacy and Safety study of Saroglitazar VI (PRESS VI) was a 16-week, multicentre, prospective, randomised, double-blind study to evaluate the safety and efficacy of saroglitazar 2mg and 4mg, compared to placebo, in type 2 diabetes with hypertriglyceridaemia not controlled with atorvastatin therapy.[3] A total of 302 subjects were randomised to saroglitazar 2mg (n=101), saroglitazar 4mg (n=99), or matching placebo (n=102). There was a four-week run in period where other anti-dyslipidaemic drugs other than atorvastatin 10mg were discontinued. The primary end-point was the reduction in serum triglyceride level after a 12-week double-blind treatment period.

Saroglitazar 2mg and 4mg significantly reduced mean triglycerides by 45.5% and 46.7% respectively at 12 weeks ($p<0.001$). These reductions were statistically significant when compared to baseline and placebo. Both saroglitazar doses showed a significant increase in HDL-C compared to placebo.

There was a statistically significant decrease in fasting plasma glucose levels in both the saroglitazar 2mg and 4mg arms compared to placebo, but the decrease in HbA_{1c} was not statistically significant compared to placebo (-0.3% and -0.2% for saroglitazar 2mg and 4mg respectively).

Evidence for safety

In PRESS V saroglitazar did not alter body weight, while there was a mean increase of 1.6kg in the pioglitazone arm. Seven of 41 patients in the saroglitazar 2mg arm, seven of 41 in the saroglitazar 4mg arm and 11 of 40 patients in the pioglitazone 45mg arm reported adverse events. Most of these events were considered to be unrelated to treatment and mild in severity. There were no serious adverse events reported in either of the saroglitazar groups.

Similarly, in PRESS VI both doses of saroglitazar were well tolerated with similar numbers of adverse events in all treatment arms. Most adverse events were not related to treatment and were mild to moderate in severity. There were two reports of serious adverse events during the study, both due to chest pain, which were adjudicated and considered unrelated to the study drug.

No significant changes in renal function were reported in either study.

In terms of cardiovascular safety, 2D Echo, ECG and ultrasonography were carried out two weeks prior to the start of the study, at the start of the study and at week 24 in the PRESS V trial. During the PRESS VI study, patients 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.

Key points

- Glitazars combine clinical features of fibrates and thiazolidinediones to improve lipids and reduce HbA_{1c}
- Saroglitazar has been approved for use in India, and improves lipids with only minor effects on glycaemia
- Much more safety data are required for saroglitazar, particularly effects on cardiovascular and renal end-points

Discussion

Saroglitazar is now approved and used in India for use in treatment of dyslipidaemia and hypertriglyceridaemia in type 2 diabetes. The evidence for its use in terms of efficacy and safety is limited. It appears to produce significant improvements in lipid parameters with only minimal, if any, improvement in HbA_{1c}. Further larger studies are required to evaluate its safety, efficacy and role in managing diabetic dyslipidaemia, particularly given that all the previous drugs in this class have been withdrawn from development because of adverse effects.

Both phase III studies of saroglitazar had short durations of follow up and small numbers of patients, therefore no meaningful data on cardiovascular safety outcome can be implied. Long-term cardiovascular safety studies would be required to satisfy criteria for licensing in the United States or European Union.[4]

Declaration of interests

Professor Fisher has received honoraria for lectures and advisory boards from Takeda, GlaxoSmithKline, AstraZeneca and Roche. Professor McKay has received honoraria for lectures for AstraZeneca.

References

References are available in *Practical Diabetes* online at www.practicaldiabetes.com.

References

1. Joshi SR. Saroglitazar for the treatment of dyslipidaemia in diabetic patients. *Expert Opin Pharmacother* 2015;16(4):597–606.
2. Pai V, *et al*. A multicenter, prospective, randomized, double-blind study to evaluate the safety and efficacy of saroglitazar 2 and 4 mg compared to pioglitazone 45 mg in diabetic dyslipidemia (PRESS V). *J Diabetes Sci Technol* 2014;8(1):132–41.
3. Jani RH, *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.
4. Llano A, *et al*. Drug development and licensing in diabetes. *Pract Diabetes* 2016;33(2):60–64.