Review Article

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Saroglitazar In Nonalcoholic Fatty Liver Disease: A Comprehensive Review.

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) has emerged as one of the most common liver diseases worldwide, particularly affecting the Indian population. Despite the increasing prevalence, an effective pharmacological treatment for NAFLD remains inadequate. Saroglitazar, a dual PPAR-α/γ agonist, initially indicated for management of diabetic dyslipidemia, has also shown positive therapeutic activity for NAFLD and NASH. Various recent studies have shown that saroglitazar can improve both liver enzyme function and Insulin resistance, often associated with NAFLD and NASH. This review aims to explore the potential of saroglitazar as a novel treatment for NAFLD, discussing its mechanism of action, clinical efficacy, and the therapeutic benefit it offers to the increasing liver health problem.

Keywords: *Saroglitazar, Peroxisome proliferator activated receptor, PPAR- α/γ, NAFLD, NASH.*

INTRODUCTION

What is NAFLD?

Non-Alcoholic Fatty Liver Disease (NAFLD) is a condition characterized by the accumulation of excess fat in the liver due to metabolic dysfunction. It is part of the wide spectrum of liver diseases, ranging from non-alcoholic steatosis (fatty liver) to more severe stages such as non-alcoholic steatohepatitis (NASH), and eventually cirrhosis.[1]

NAFLD has become the leading cause of chronic liver disease (CLD), affecting approximately about 32% of the global population, and is projected to rise to 63% till 2030[2]. The disease is more prevalence among individuals who are overweight, obese, or diabetic. In patients with type 2 Diabetes Mellitus (T2DM), the prevalence is exhibited up to 75%, while it may be as high as 90% in those who are severely obese. [3] In India, NAFLD affects 9% to 32% [4] of the population, with higher rates observed in individuals with metabolic risk factors such as obesity and T2DM.

NAFLD is a manifestation of metabolic syndrome, often linked with obesity, type 2 diabetes (T2DM), and other metabolic disorders. It starts off as simple fatty liver, with fat accumulation in the liver devoid of inflammation, and can further progress to NASH, where inflammation and liver cell damage occur, eventually leading to fibrosis and cirrhosis. The growing rates of obesity, T2DM, and insulin resistance are driving the rise in NAFLD, increasing the risk of advanced liver disease and mortality.

Saroglitazar: Overview

Saroglitazar is a novel medication that is currently being investigated for its application in the treatment of non-alcoholic fatty liver disease (NAFLD). It acts as a potent dual PPAR-α/PPAR-γ agonist, exhibiting promising effects by improving liver function and lowering fat accumulation in liver cells. They influence the expression of genes involved in lipid metabolism and insulin sensitivity.

Saroglitazar originally was approved for the management of diabetic dyslipidemia but has also exhibited significant potential in the treatment of NAFLD. It has been approved in India since 2013 for dyslipidemia management. However, its approval for NAFLD treatment is still under review.[5][6]

Pharmacology of Saroglitazar

PPARs are a family of nuclear receptors associated with the peroxisome proliferation. These receptors exist in three different isoforms: PPAR- α, β/δ, and γ, with each isoforms having variable tissue distributions and function. However, the therapeutic activity is achieved by targeting majorly two subtypes of the PPAR receptor (PPAR-α/PPAR-γ). PPAR-α exhibits more predominant receptor activity, while PPAR-γ

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shows a more moderate level of activity. Saroglitazar exerts its effects by:

- PPAR-alpha and PPAR-gamma activation play key roles in regulating metabolic processes, particularly in the context of non-alcoholic fatty liver disease (NAFLD). PPAR-alpha receptors are primarily involved in lipid metabolism, whereby it promotes the oxidation of fatty acids in the liver, reducing the accumulation of lipids in liver cells, a hallmark of NAFLD. Moreover, saroglitazar helps lower triglyceride levels in the bloodstream, improving overall lipid profiles. And it also causes an increase in the HDL levels by enhancing the expression of HDL-regulating genes.[7]
- On the other hand, PPAR-gamma enhances Insulin sensitivity, which is essential for managing Insulin resistance and T2DM, often associated with NAFLD. Furthermore, PPAR-gamma is involved regulating the fat storage and its metabolism. Thus, these mechanisms highlight the agonistic therapeutic activity of PPAR-alpha and PPAR-gamma receptor targets for improving lipid profiles and managing metabolic conditions related to NAFLD.[8]

Efficacy of Saroglitazar in NAFLD

Saroglitazar has shown promising efficacy in the management of non-alcoholic fatty liver disease (NAFLD). Studies have shown a significant reduction in liver enzymes, specifically ALT and AST, indicating its potential for improvement in liver function. Furthermore, saroglitazar has also shown reduction in liver fat content, as measured by advanced imaging techniques such as MRI-PDFF, suggesting an improvement in liver inflammation and fibrosis.[1][9]

Additionally, saroglitazar also impacts the lipid metabolism and glucose homeostasis. It has been associated with lower triglyceride levels and increase HDL cholesterol, offering benefits to NAFLD patients. Moreover, saroglitazar enhances insulin sensitivity, causing a reduction in fasting glucose and HbA1c levels, which may be advantageous for individuals with both NAFLD and type 2 diabetes dyslipidemia.[1][10]

Supporting clinical evidence

Multiple clinical studies have been conducted to evaluate the effects associated with saroglitazar in NAFLD patients. Various studies conducted particularly from India, have focused on biochemical improvements, specifically on liver enzyme levels and lipid profile parameters. Liver enzymes, including ALT (alanine aminotransferase) and AST (aspartate aminotransferase), have long been used as key indicators to assess the extent of liver injury in NAFLD. Thus, a significant reduction in the level of these enzymes in response to saroglitazar treatment are suggestive of a potential improvement in liver function and reduction in liver damage. Additionally, improvements in lipid profile parameters, such as lowered triglycerides and increased HDL cholesterol have been noted as supporting evidence for saroglitazar in NAFLD management.

Recent studies have demonstrated the benefits of saroglitazar on liver enzymes in patients with NAFLD. Jain N et al. highlighted reduction in dyslipidemic changes and improves insulin resistance by reducing glucolipotoxicity and by activating the agonistic effect of PPARγ pathway.[10]

Supporting these findings, Jaiswal et al. observed a significant reduction in liver enzymes, including ALT and AST that reduced to 58.51% and 58.43% respectively, after 24 weeks of saroglitazar therapy.[11] The Liver stiffness measurements (LSM) and Controlled attentauted parameters (CAP) also showed 10.71% reduction. These results are aligning with the results of other studies, such as those by Goyal O et al. Similarly, Kaul U et al. reported a notable reduction in ALT after 12 to 58 weeks of saroglitazar treatment.[12]

Furthermore, an animal model study demonstrated a 60% reduction in ALT and a 43% reduction in AST following 12 weeks of saroglitazar administration, reinforcing its potential as an effective therapy for managing liver enzyme levels and improving metabolic dysfunctions in diabetes-related conditions.[9]

Safety and Tolerability

Saroglitazar is generally well-tolerated at a dose of 3 -4 mg/kg, with mild adverse effects such as gastrointestinal disturbances being the most reported. However, long-term safety data is still limited, and further research is needed to understand the long-term benefits and risks associated with saroglitazar in treatment of NAFLD.

Future Perspective

Clinical trials are ongoing to assess the long-term benefits and risk of saroglitazar in treating NAFLD. These studies have focused on the impact on histological improvements (liver biopsy outcomes) and overall liver function parameters. Although early results are promising, but long-term data on safety and efficacy are necessary to fully understand the role of saroglitazar in managing NAFLD. Most of the current research have been conducted on specific populations, mainly in India, and hence a more diverse clinical trials across various populations are needed to assess the benefits.

Researchers are also investigating the potential of combining saroglitazar with other drugs, such as GLP-1 agonists, to enhance the therapeutic outcomes in treating NAFLD.

CONCLUSION

Saroglitazar appears as a promising treatment option for NAFLD individuals. In particular, for improving liver fat

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reduction, enhancing insulin sensitivity, and addressing metabolic dysfunctions. However, more robust long-term studies are essential to assess the safety and risk in the management of these liver diseases.

Abbreviation

1. NAFLD - Non-alcoholic fatty liver disease
2. NASH – Non-alcoholic steatohepatitis
3. PPAR – Peroxisome Proliferator activated receptor
4. T2DM – Type II Diabetes Mellitus
5. MRI- PDFF – Magnetic Resonance Imaging- proton density fat fraction.

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