Peroxisome Proliferator-Activated Receptors and Their Agonists in Nonalcoholic Fatty Liver Disease

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Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases worldwide. In addition to the liver-related morbidity and mortality, NAFLD is now also associated with various extrahepatic diseases. Pathogenesis of NAFLD is multifactorial with limited pharmacotherapy options for the treatment of patients with NAFLD. Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that are involved in the transcriptional regulation of lipid metabolism, glucose homeostasis, energy balance, inflammation, and atherosclerosis. PPAR agonists are attractive options for treatment of NAFLD as they can act at multiple targets involved in the pathogenesis of NAFLD. We reviewed the available literature on the pathophysiological role of PPARs and use of PPAR agonists in the treatment of NAFLD. Original studies and review articles available on PubMed regarding the role of PPARs in the pathogenesis and utility of PPAR agonists in the treatment of NAFLD were included in this review article. ClinicalTrials.gov and Clinical Trials Registry-India sites were searched for ongoing studies on saroglitazar. The available literature suggests that PPARs play an important role in the pathogenesis of NAFLD. Use of PPAR gamma agonists is associated with histological improvement in NAFLD. Dual PPAR agonists with no or minimal PPAR gamma activity are being explored in the treatment of NAFLD. Because of the pathophysiological role of PPARs in NAFLD, PPAR agonists are attractive options for the treatment of patients with NAFLD. Dual PPAR agonists without significant gamma activity appear promising for the treatment of NAFLD. (J Clin Exp Hepatol 2019;9:731–739)

NAFLD

Peroxisome proliferator-activated receptors (PPARs) are a ligand-activated transcription factor belonging to a nuclear receptor subfamily that is involved in the transcriptional regulation of lipid metabolism, glucose homeostasis, energy balance, inflammation, and atherosclerosis. There are three PPAR isoforms, alpha (α), beta (β)/delta (δ), and gamma (γ), which are differentially expressed in various tissues.[1,2] PPARα is expressed ubiquitously but is largely present in the liver. PPARβ/δ is expressed mainly in skeletal muscles and to a lesser degree in adipose tissue and skin. PPARγ is highly expressed in adipose tissue (Table 1).[3–8]

Free fatty acids (FAs), eicosanoids, and various complex lipids are considered endogenous PPAR ligands. Exogenous ligands are environmental and pharmaceutical molecules that can activate various PPAR family receptors to varying degrees.[6–9] PPARs form a heterodimer with the retinoid X receptor (RXR) after binding to the ligand and bind to response elements that regulate the expression of genes encoding proteins involved in beta oxidation, FA uptake, adipogenesis, and adipocyte differentiation.[3,10–12] PPAR ligands have emerged as potential therapeutics for nonalcoholic fatty liver disease (NAFLD) (Table 1).

NAFLD has emerged as the most common liver disease in the world, including Asia Pacific, and is responsible for significant liver disease burden.[13,14] The spectrum of NAFLD ranges from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH), which has the propensity to progress on to cirrhosis of the liver and hepatocellular carcinoma.[15] NAFLD is characterized by presence of insulin resistance, dyslipidemia, and a proinflammatory state. The mainstay of current treatment of NAFLD is weight loss by lifestyle modification, which is difficult to achieve and sustain for most of the patients. There are limited pharmacotherapy options, and the focus of treatment has largely been on patients with progressive NASH.[15] PPARs affect glucose homeostasis (insulin-sensitizing properties), inflammation, and atherogenesis and control dyslipidemia. Thus, these agents should act at

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Abbreviations: CPT-1: Carnitine palmitoyltransferase-1; MPC: mitochondrial pyruvate carrier; NAFLD: nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; NF-κB: nuclear factor-kappa beta; OR: odds ratio; PPAR: Peroxisome proliferator-activated receptors; RXR: retinoid X receptor; TZDs: thiazolidinediones

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Table 1 Types and Actions of PPARs (Based on Grygiel-Górniak *et al*[3], Pawlak *et al*[4], Tailleux *et al*[5], Corton[6], Fisher *et al*[7], and Fisher *et al*[8]).

Type	Tissue distribution[a]	Gene targets	Natural ligand	Synthetic agonists	Effect
PPARα	**Liver** **Muscle** Heart Kidney	B oxidation Fatty acid transport protein Fatty acid translocase Lipoprotein lipase Apolipoprotein A-I and A-II Sterol 12-hydroxylase	Unsaturated fatty acids Leukotriene B4 8-Hydroxyeicosatetraenoic acid	Gemfibrozil Fenofibrate Clofibrate	Fatty acid oxidation Anti-inflammatory
PPARβ/δ	Ubiquitous, muscle, gastrointestinal, adipose tissue Macrophages Heart	Genes involved in lipid uptake, metabolism, and efflux (repressed by PPARs)	Unsaturated fatty acids Carbaprostacyclin Components of VLDL	GW501516 GW0742 MBX-8025	Glucose homeostasis, insulin sensitivity
PPARγ	**Adipose tissue** Liver, kidney, intestine	Fatty acid–binding protein (aP2) Fatty acid transport protein Fatty acid translocase	Unsaturated fatty acids, 15-hydroxyeicosatetraenoic acid, 9- and 13- hydroxyoctadecadienoic acid, 15-deoxy-12,14-prostaglandin J2, prostaglandin PGJ2	Thiazolidinediones	Adipogenesis Insulin sensitization, glucose homeostasis Fatty acid oxidation

PPAR, peroxisome proliferator-activated receptor; VLDL, very low-density lipoprotein.
[b]All tissues not shown.
[a]Tissues in bold fonts indicate main tissue expression.

multiple levels in NAFLD pathogenesis, which makes them an attractive target for drug development.

PPARα AND ITS AGONISTS

PPARα is expressed in many mammalian cells and tissues such as the liver, kidney, heart, muscle, adipose tissue, and others including immune cells (e.g., macrophages).[16] PPARα plays a role in multiple regulatory functions. In the liver, it plays a crucial role in FA oxidation, which provides energy for peripheral tissues, and has a potential role in the oxidant/antioxidant pathway.[17] PPARα also has anti-inflammatory effects through complex regulation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).[18] The activation of PPARα occurs after dimerization with the RXR, resulting in formation of a multiprotein complex with protein coactivators. After activation, PPARα binds to responsive elements in DNA, resulting in the transcription of various anti-inflammatory proteins, such as the kB-α inhibitor.[19] Carnitine palmitoyltransferase 1 (CPT-1) is a pivotal enzyme that allows the FA to go through the inner mitochondrial membrane and reach the mitochondrial matrix for further metabolism.[20] Reduction of PPARα expression in the liver causes impairment of the transcription of its target gene CPT-1, and excessive FAs tend to accumulate in the form of triglycerides.[21,22]

PPARα acts as a nutritional sensor, which allows adaptation of the rates of FA oxidation, lipogenesis, and ketone body synthesis, in response to feeding and fasting.[23] During excessive dietary intake of lipids, hepatic PPARα expression decreases.[24,25] Studies in mice with genetic deletion of PPARα (PPARα−/−) and high-fat diet resulted in accumulation of more hepatic triglycerides with a significantly higher NAFLD activity score (NAS) compared with wild-type (WT) controls.[26,27] Mice with the PPARα gene knockout, fed with a high-fat diet, also showed increased markers of oxidative stress, inflammation, and cell death.[28]

Natural agonists of PPARs include FAs, eicosanoids, and phospholipids derived from cellular FA metabolism or from dietary lipids. The synthetic ligands include fibrates, thiazolidinediones (TZDs), glitazars, elafibranor, and several others.[29] In the mice model, the PPARα agonist Wy-14643 prevented methionine and choline deficient (MCD) diet-induced hepatic triglyceride accumulation in WT mice, but it had no effect on PPARα−/− mice.[30]

Fibrates are considered PPARα agonists, although less potent than the PPARα agonist Wy-14643. Several studies have shown improvement of biochemical or histological parameters with fibrates in patients with NAFLD.[31–33] Fibrates, however, have limited clinical efficacy because they are weak PPARα agonists and have significant adverse events. Fernandez-Miranda *et al* used 200 mg/day fenofibrate for 48 weeks in a series of 16 patients with NAFLD. The authors noted a significant decrease in levels of triglycerides, glucose, and gamma-glutamyl transpeptidase and proportion of patients with raised transaminases or metabolic syndrome and a trend of decreasing insulin resistance. The repeat biopsy at the end of the study showed decreased ballooning, but other histologic parameters did not improve significantly.[31] El-Haggar *et al* compared fenofibrate with fenofibrate plus

pentoxifylline for 24 weeks. The addition of pentoxifylline to fenofibrate did not improve lipid parameters, but a beneficial effect on indirect markers of hepatic fibrosis, inflammation, insulin resistance, and liver stiffness was present.[33] Laurin *et al*[34] compared clofibrate with ursodeoxycholic acid in a 1-year study. The authors could not find any advantage of clofibrate in patients with NAFLD. Newer selective PPARα-specific agonists, known as selective PPARα modulators, are in different phases of development.[35,36]

PPARβ/δ AND ITS AGONISTS

PPARβ/δ is the least studied among all the PPAR isotypes, although it has significant expression in tissues controlling lipid metabolism, such as adipocytes, heart, skeletal muscle, liver, and macrophages.[37] In the liver, PPARβ/δ is well expressed in hepatocytes but is also expressed in Kupffer cells and hepatic stellate cells, suggesting a potential role in inflammation and fibrosis.[38] The PPARβ/δ agonist, GW501516, has been shown to ameliorate obesity and insulin resistance in rats.[39] In a small 2-week pilot trial on six subjects, it was found by magnetic resonance imaging that GW501516 resulted in reduction of liver fat along with reduction in serum triglycerides and low-density lipoprotein cholesterol.[40] However, clinical development of GW501516 was abandoned owing to development of cancer in preclinical models.[41] Another PPARβ/δ agonist, GW0742, improved insulin signaling and reduced hepatic steatosis in a rat model.[42]

In a study using GW0742, the activation of PPARβ/δ was found to inhibit CCl4-induced liver toxicity through the PPARβ/δ-dependent downregulation of proinflammatory signaling through interactions between PPARβ/δ and NF-κB.[43] A novel PPARβ/δ agonist, MBX-8025, was evaluated in a randomized, double-blind, placebo-controlled study. The study included overweight subjects with dyslipidemia and found that treatment with MBX-8025 (seladelpar) resulted in favorable lipid profiles and decreased liver enzymes.[44] In a randomized study of MBX-8025 versus vehicle (1% methylcellulose), MBX-8025 normalized hyperglycemia, hyperinsulinemia, and glucose disposal in foz/foz mice. MBX-8025 reduced alanine aminotransferase and normalized serum lipids. There was significantly less steatosis, inflammation, ballooning, apoptosis, and fibrosis in the MBX-8025 arm.[45]

At this time, data regarding effectiveness of PPARβ/δ in treatment of NAFLD are limited to derive any conclusion.

PPARγ AND ITS AGONISTS

PPARγ is most highly expressed in adipose tissue, where it serves an important role in the regulation of adipocyte differentiation, adipogenesis, and lipid metabolism.[46] In an animal model of NASH, Zhong and Liu[47] showed that the activation of PPARγ regulates the polarization of the macrophages to M2 subtype. Kupffer cells have proinflammatory (M1) and anti-inflammatory (M2) subtypes; thus, change toward the M2 subtype may prevent development of NAFLD.[47]

TZDs are the most widely investigated PPARγ agonists. TZDs represent a class of clinically used insulin-sensitizing drugs, which currently include rosiglitazone and pioglitazone. TZDs promote the uptake and storage of FAs in adipose tissue, increasing adipose tissue mass while sparing the skeletal muscle and the liver.[48] In an animal model of NASH induced with a choline–methionine–deficient diet, rosiglitazone prevented the development of NASH.[49] In another animal model, Deng *et al*[50] demonstrated that pioglitazone has anti-inflammatory and antifibrotic effects by repressing the expression level of platelet-derived growth factor and tissue inhibitor of metalloproteinase-2.

Caldwell *et al* reported data of troglitazone treatment in 10 female patients with histological NASH including 3 with compensated cirrhosis. Troglitazone was given for ≤6 months. A repeat biopsy in responders (normal alanine aminotransferase (ALT) at the end of treatment) showed persistence of NASH in all; four patients had one-point improvement of necroinflammation.[51] Troglitazone was associated with serious hepatotoxicity and was banned later.[52] Ratziu *et al*[53] studied the role of rosiglitazone in a randomized controlled trial (RCT) called the FLIRT trial. Thirty-two patients on rosiglitazone were compared with 31 patients on placebo. The rosiglitazone arm had improved steatosis (47% vs 16%) and transminases (38% vs 7%) at the end of 1 year as compared with the placebo arm. There was no improvement in fibrosis and the NAFLD activity score. Weight gain happened significantly in the rosiglitazone arm, and dose reduction/discontinuation happened in some patients owing to painful swollen legs.[53]

In the PIVENS trial involving patients with NASH randomized to receive pioglitazone, vitamin E, or a placebo for 96 weeks, pioglitazone demonstrated a reduction in hepatic steatosis, lobular inflammation, and hepatic enzymes aspartate aminotransferase (AST) and ALT.[54] A meta-analysis evaluated randomized placebo-controlled trials using TZDs in the treatment of patients with NASH. In the identified four high-quality randomized trials, treatment with TZDs resulted in significant decrease in serum ALT along with improvement in steatosis, inflammation, and hepatocyte ballooning, but the change in fibrosis was not statistically significant.[55] But when three studies evaluating the effectiveness of pioglitazone were included, the improvement in fibrosis became statistically significant, suggesting that pioglitazone has superior effects on reversing hepatic fibrosis compared with rosiglitazone.[55]

The use of PPARγ agonists is associated with pedal edema, weight gain, cardiac adverse events, and risk of bladder cancer. A recent meta-analysis of 26 studies

Table 2 Summary of Studies of PPAR Agonists in NAFLD.

Author	N, treatment duration	Results	
		Biochemical response	Histological response
Fernandez-Miranda *et al*[31]	16, fenofibrate for 48 weeks, no comparative group	Significant decrease in triglyceride, glucose, liver enzymes, MS	Decreased ballooning, grade steatosis, inflammation/fibrosis—no change
Laurin *et al*[34]	16 clofibrate arm, 24 UDCA arm, 1 year	No change in the clofibrate arm other than decreased ALP	No change in the clofibrate arm
Neuschwander-Tetri *et al*[60]	N = 30, 22 had paired biopsies, rosiglitazone for 48 weeks, no comparative group	Decreased AST, ALT, and GGT	Improved steatosis and ballooning, weight gain occurred in 67% of patients, and the median weight increase was 7.3%. Within 6 months of completing treatment, liver enzyme levels had increased to near-pretreatment levels
Ratziu *et al*[53]	RCT, 32 rosiglitazone 31 placebo	Normalized transaminase levels (38% vs 7%, *P* = .005)	Improved steatosis (47% vs 16%; *P* = .014), although only half of the patients responded, no change of other histologic parameters, weight gain in rosiglitazone
Torres *et al*[61]	RCT, n = 137, rosiglitazone and metformin versus rosiglitazone and losartan versus rosiglitazone alone, 48 weeks	Decreased transaminases in all groups	108 completed the study, overall improvement of all histologic parameters, no added benefit of metformin (did not prevent weight gain) or losartan
Belfort *et al*[62]	RCT, 6 months of low-calorie diet with pioglitazone (n = 26) or diet and placebo (n = 21)	Decreased transaminases in pioglitazone arm	Improved steatosis, inflammation, and ballooning, no change of fibrosis, weight gain despite low-calorie diet in the pioglitazone arm
Aithal *et al*[63]	RCT, 12 months of diet, exercise, and either placebo or pioglitazone, 30 in placebo and 31 in the pioglitazone arm had paired biopsies	Improvement of ALT and GGT	Hepatocellular injury (*P* = .005), Mallory–Denk bodies (*P* = .004), and fibrosis (*P* = .05) were reduced in patients treated with pioglitazone, weight gain
Sanyal *et al*[54]	RCT, pioglitazone (n = 80), vitamin E (n = 83), placebo (n = 84), 96 weeks	Improvement of transaminases in the vitamin E and pioglitazone arm	Improvement in NASH as compared with placebo (vitamin E, *P* = .001), with (pioglitazone *P* = .04), both vitamin E and pioglitazone associated with significant reductions in steatosis, lobular inflammation. Improvement in fibrosis, weight gain in pioglitazone
Cusi *et al*[64]	RCT, 18 months, followed by an 18-month open-label phase with pioglitazone (n = 50) or placebo (n = 51)	More normalization in the pioglitazome arm	Pioglitazone is associated with a better NAS reduction and resolution of NASH, steatosis, inflammation, ballooning, no improvement in fibrosis, weight gain
Ratziu *et al*[68]	Elafibranor 120 mg, elafibranor 80 mg, and placebo	Liver enzymes, lipids, glucose profiles, and markers of systemic inflammation significantly reduced in the elafibranor 120-mg group	Elafibranor 120 mg superior to placebo, NASH resolution without worsening of fibrosis in 19% versus 12% in the placebo group (*P* = .045), based on a *post hoc* analysis for the modified definition

PPAR, peroxisome proliferator-activated receptor; NAFLD, nonalcoholic fatty liver disease; RCT, randomized controlled trial; NASH, nonalcoholic steatohepatitis; NAS, NAFLD activity score; MS, metabolic syndrome; AST, aspartate aminotransferase; ALT, alanine aminotransferase; UDCA, Ursodeoxycholic Acid; GGT, gamma-glutamyl transferase.

including 15,332 patients with type 2 diabetes mellitus (T2DM) showed that the odds ratio (OR) for edema with TZDs was 2.26 (95% confidence interval [CI], 2.02–2.53).[55] TZDs are also associated with risk of cardiac adverse events. A meta-analysis of 3 RCTs showed an OR of 2.1, and 4 observation studies showed an OR of 1.55 for heart failure with TZDs.[56] Rosiglitazone is associated with more cardiac adverse events than pioglitazone.[57] The use of pioglitazone was found to be associated with risk of bladder cancer in RCTs (OR, 1.84; 95% CI, 0.99–3.42) and in observational studies (OR, 1.13; 95% CI, 1.03–1.25). The risk of bladder cancer with pioglitazone increased in a dose- and time-dependent manner.[58]

Table 2 summarizes histology-based studies of PPAR agonists in patients with NAFLD.[31,34,50–64,68]

The mitochondrial target of TZD modulators bind and modulate activity of the mitochondrial pyruvate carrier (MPC). MSDC-0602 is the next-generation TZD, which has diminished ability to activate PPARγ.[65] Improved insulin sensitivity by these compounds decreases lipolysis from adipose tissue and *de novo* lipogenesis. In addition, blocking pyruvate entry into the mitochondria should normalize the tricarboxylic acid cycle, which is increased in NAFLD. This normalization of the tricarboxylic acid cycle leads to decreased reactive oxygen species and cell damage signals, which should reduce inflammation and stellate cell activation.[66] Genetic (selective knockout) or pharmacologic targeting of the MPC by MSDC-0602K has been shown to increase insulin sensitivity and to prevent or reverse NASH pathology in a mouse model.[67]

DUAL AND PAN-PPAR AGONISTS

Combining the role of PPARs can result in multiple actions useful to treat NAFLD. If a compound holds desired potency for different PPARs, it can be maximally beneficial with minimal undesired effects. Thus, dual or pan-PPAR agonists can produce antihyperlipidemic (PPARα) effect with insulin sensitization (PPARγ) and increase β-oxidation in the liver and skeletal muscle (α and β/δ) while limiting side effects of singular agonists such as weight gain/cardiac events with TZDs or improving limited clinical efficacy of fibrates. However, development of several agents has been terminated owing to safety concerns, and only few are in later phases of development.[29]

a) PPARα/δ and their agonists

In recent years, agonists of PPARs have arisen with affinity for binding to multiple isoforms owing to relatively nonselective ligand-binding pockets, known as dual agonists, and represent interesting therapeutic targets. A novel dual PPARα/δ agonist, GFT505, also known as elafibranor, has been studied in treating NASH. Using various rodent models of NASH, treatment with GFT505 (elafibranor) demonstrated improvement in histologic features of NASH and decreased hepatic triglyceride content, along with reduced expression of inflammatory cytokines and fibrosis markers.[69]

Elafibranor is an agonist of PPARα and PPARδ. Thus, it works on insulin sensitivity, glucose homeostasis, and lipid metabolism. The RCT by Ratziu *et al*[68] (GOLDEN trial) included the following arms: elafibranor 80 mg (n = 93), elafibranor 120 mg (n = 91), and placebo (n = 92). The study was conducted in Europe and the United States, and the study duration was 52 weeks. The primary outcome was resolution of NASH without worsening of fibrosis. While there was no difference between elafibranor and placebo groups in the primary outcome in intention-to-treat analysis, NASH resolved without worsening of fibrosis in a higher proportion of patients in the 120-mg elafibranor group (19%) versus the placebo group (12%, $P = .045$), based on a *post hoc* analysis for the modified definition. The modified definition defined resolution of NASH as disappearance of ballooning with either disappearance of lobular inflammation or persistence of mild inflammation only. Thus, the modified target was pathologic diagnosis of steatosis alone or steatosis with mild inflammation only. The authors found improvement in the histological score after removing patients with mild steatohepatitis from analysis. The outcomes in the 80-mg dose arm were not better than those of placebo. In addition, liver enzymes, lipids, glucose profiles, and markers of systemic inflammation were significantly reduced in the elafibranor 120-mg group versus the placebo group. Elafibranor was well tolerated and did not result in weight gain or cardiac events, the authors noted a mild and reversible increase in serum creatinine (4.31 ± 1.19 mmol/L).[68] A phase III study (RESOLVE-IT) is presently recruiting a large number of patients with NASH to study the efficacy of elafibranor in comparison with placebo (ClinicalTrials.gov. NCT02704403).

b) PPARα/γ and their agonists

Compounds working as PPARα/γ agonists are called glitazars. These compounds improve dyslipidemia, which is α-action, and glycemic parameters/insulin sensitivity, which is γ-action. Thus, theoretically, these compounds address 2 important issues of NAFLD, dyslipidemia and insulin resistance and thus are the area of interest. Several glitazars were initially tried, but their clinical development was stopped later owing to adverse events. Tesaglitazar was the first dual PPARα/γ agonist; a large dose was needed owing to weak action, and clinical development was stopped owing to nephrotoxicity.[70] Muraglitazar produced better lipid changes, but increase in cardiovascular events was observed.[71,72] AleCardio was a phase 3 multicenter randomized placebo-controlled trial that was conducted across 26 countries. A total of 7226 patients hospitalized for myocardial infarction or unstable angina with type 2

diabetes received either aleglitazar 150 μg or placebo. The trial was terminated after an interim analysis owing to serious adverse events that included statistically significant gastrointestinal hemorrhages and renal dysfunction in the aleglitazar arm.[73] Most of these glitazar compounds had significant PPARγ action (than PPARα), which contributes to adverse events. Saroglitazar is the first glitazar class compound approved as a therapeutic agent. Saroglitazar has a different structure from glitazones, other glitazars, and fibrates. It is an aryl alkoxy propionic acid class molecule, which contains a unique pyrol moiety and lacks the glitazone ring. Saroglitazar was designed as a dual PPAR agonist having predominant PPARα effect with moderate PPARγ effect; thus, it provides antilipid effect with insulin sensitization, without being associated with typical glitazone side effects.[74,75] Although the data on the use of saroglitazar in NAFLD are still evolving, based on the results of various studies (PRESSV, VI), Drug Controller General of India has already approved use of saroglitazar for patients with diabetic dyslipidemia, uncontrolled by statins.[76–79]

In NAFLD, saroglitazar has been shown to be more effective for reduction of the histological NAS than pioglitazone and fenofibrate in a mice model.[80] C57BL/6 mice that were maintained on choline-deficient, L-amino acid–defined, high-fat diet for 8 weeks were treated with saroglitazar (3 mg/kg), fenofibrate (100 mg/kg), pioglitazone (30 mg/kg), or vehicle for 12 weeks. Saroglitazar reduced hepatic steatosis, inflammation, and ballooning and prevented development of fibrosis. It also reduced serum ALT and AST levels and expression of inflammatory and fibrosis biomarkers. Pioglitazone and fenofibrate did not show any improvement in steatosis but partially improved inflammation and liver function. In the same study, antifibrotic effect of saroglitazar (4 mg/kg) was also observed in the carbon tetrachloride–induced fibrosis model.[80] Use of saroglitazar in patients with type 2 diabetes mellitus and dyslipidemia or those with type 2 diabetes mellitus and without dyslipidemia has been shown to improve serum transaminase levels.[81,82]

A phase II study has also evaluated the improvement in serum ALT levels with saroglitazar in patients with biopsy-proven NASH (CTRI/2010/091/000108).[83] Another phase II study in the USA is evaluating the efficacy of saroglitazar in improving serum liver enzymes and other serum biomarkers of inflammation and fibrosis with improvement in hepatic steatosis on MR imaging-estimated proton density fat fraction (MR-PDFF) in patients with NAFLD/NASH diagnosed on imaging or histology (NCT03061721).[84] In addition, a recent phase III study in India is evaluating the histological efficacy of saroglitazar in comparison with placebo in patients with biopsy-proven NASH (CTRI/2015/10/006236).[85] The results of these studies would clarify the role of saroglitazar in patients with NAFLD.

c) Pan-PPAR agonists

Several pan-PPAR agonists are in various phases of development, with many studies reported in animal models.[26,86–90] Bezafibrate has predominantly alpha action and has been shown to improve glycated hemoglobin in patients with diabetes mellitus.[91,92] Bezafibrate has also been shown to improve atherogenic dyslipidemia and insulin resistance without causing overweight.[91–93] Although human studies are lacking, bezafibrate has been shown to improve NAFLD and diabetes in mice models.[94,95] Lanifibranor (IV1337) is another pan-PPAR agonist, which in addition to improving insulin sensitivity, has been shown to have antilipid, anti-inflammatory, and antifibrosis properties.[96–98] In animal models, lanifibranor has been shown to improve insulin sensitivity and decrease hepatic steatosis, inflammation, ballooning, and fibrosis in liver tissue.[96] An ongoing study is evaluating the efficacy of lanifibranor in patients with diabetes and NAFLD (ClinicalTrials.gov: NCT03459079).

PPAR agonists are attractive targets for the treatment of patients with NAFLD, given multiple actions of the PPAR on lipid metabolism, oxidation of FAs, glucose homeostasis, and inflammation. This becomes all the more important in absence of any recommended pharmacotherapy for these patients. Of all the PPAR agonists, the PPARγ agonist pioglitazone is the most extensively evaluated and has been found to be useful in patients with NAFLD but is limited by its side effect profile. Emerging data of dual PPAR agonists and pan-PPAR agonists appear encouraging and may hold promise for patients with NAFLD.

CONFLICTS OF INTEREST

The authors have none to declare.

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