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REVIEW **Open Access**

Therapeutic roles of PPARα activation in ocular ischemic diseases

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Summary. Ocular ischemia is one of the leading causes of blindness. It is related to various ocular diseases and disorders, including age-related macular degeneration, diabetic retinopathy, glaucoma, and corneal injury. Ocular ischemia occurs due to an abnormal supply of oxygen and nutrients to the eye, resulting in ocular metabolic dysfunction. These changes can be linked with pathologic conditions in the eye, such as inflammation, neovascularization, and cell death, ultimately leading to vision loss. The current treatment care for ocular ischemia is limited. Peroxisome proliferator-activated receptor α (PPARα) is a nuclear receptor protein functioning in regulating lipid metabolism, fatty acid oxidation, and glucose homeostasis. Recently, PPARα activation has been suggested as a useful therapeutic target in treating ocular ischemia. However, its applications have not been well summarized. In this review, we cover an overview of the therapeutic roles of PPARα activation in various ocular ischemic conditions with recent experimental evidence and further provide clinical implications of its therapeutic applications. Our review will enable more approaches to comprehensively understand the therapeutic roles of PPARα activation for preventing ocular ischemic diseases.

Key words: Peroxisome proliferator-activated receptor α (PPARα), Fibroblast growth factor 21 (FGF21), Ocular ischemia, Pemafibrate, Fenofibrate

Overall roles of PPARα

In the 1950s, it was found that the ester "phenylethyl acetate" in pesticides lowered cholesterol (Oliver, 2012). After that, studies showed that clofibrate reduced plasma lipid levels via very low-density lipoprotein (VLDL) and LDL, and it was the first lipid-lowering drug to be tested in humans. However, the mechanism of action of fibrates remained unclear for a long time. In the 1990s, a group discovered that fibrates could activate nuclear receptors called peroxisome proliferator-activated receptors (PPARs). Then, the elucidation of the structure of the PPARs revealed that PPARα might be involved in the transcription of high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) and thus be involved in the regulation of lipid metabolism (Katsiki et al., 2013). However, while activation of PPARα by fibrates showed improvements in lipid levels, various off-target effects were identified, including worsening liver and renal function tests. PPARα is a nuclear receptor that plays a significant role in metabolic regulation. It is activated by fatty acids as ligands and acts as a lipid sensor in the liver to regulate lipid metabolism, mainly fatty acid beta-oxidation (Kersten, 2014). PPARα binds to retinoid X receptors (RXRs) and goes into the nucleus (Daynes and Jones, 2002). These receptors bind to DNA as heterodimers and function as transcription factors, activating PPAR-mediated gene expression processes. Polyunsaturated fatty acids are thought to be endogenous PPAR ligands. In addition, a variety of lipids, including saturated butyrate, fatty acyl CoA species, prostaglandins, leukotrienes, oxidized butyrate, and oxidized phospholipids, are PPAR activators. Now, PPARα is widely known to be mainly expressed in the liver, regulate fatty acid oxidation, and control lipoprotein metabolism.

PPARα activation in ocular ischemic diseases

Ocular ischemia is a common cause of visual impairment and blindness. It occurs when the blood supply to the eye becomes abnormal, leading to metabolic dysfunction in the eye, including the cornea, retina, and other parts of the eye. Within a wide range, ocular ischemia can be divided into three categories (Campochiaro, 2013; Nicholas and Mysore, 2021): retinal ischemia, subretinal/choroidal ischemia, and

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corneal ischemia. Broadly, retinal diseases include diabetic retinopathy (DR) and glaucoma, while subretinal and corneal diseases include age-related macular degeneration (AMD) and corneal injury, respectively. This section introduces therapeutic evidence of PPARα activation against pathologic conditions in the above diseases (Fig. 1).

AMD

AMD is a degenerative disease of the aging retina. Early and intermediate AMD is indicated by the presence of drusen, while late AMD is defined by the presence of choroidal neovascularization (CNV) (Fleckenstein et al., 2021). Subretinal fibrosis can also be detected as one of the outcomes of wound healing responses that follow CNV in AMD (Ishikawa et al., 2016). As severe visual impairments are often associated with late AMD patients, research on suppressing the development of CNV has been mainly conducted with a pharmacologic and/or genetic strategy.

Qiu et al. demonstrated that intraperitoneal injections of fenofibric acid (one of the PPARα agonists) reduced laser-induced CNV volumes in rats and mice (Qiu et al., 2017). Using *Pparα*$^{-/-}$ mice, they further found that its therapeutic effect was PPARα dependent. Zhao et al. suggested that an injection of fenofibrate (another PPARα agonist, an ester of fenofibric acid) into the vitreous body of rats could inhibit CNV formation, explained with modulations of vascular endothelial growth factor-c *Vegfc* and *Vegfr3* expressions (Zhao et al., 2018). Recently, Qiu et al. showed the therapeutic effects of an intravitreal injection of fenofibrate-loaded biodegradable nanoparticles for suppressing CNV volumes in rats, as the systemic administrations may not be desired due to inefficient drug delivery to the eye (Qiu et al., 2019). Moreover, they suggested there was no toxicity of fenofibrate-loaded biodegradable nanoparticles to the eye, explained by assessing retinal structure and function after the treatment. When it comes to subretinal fibrosis, Chen et al. found that oral administrations of fenofibrate ameliorated subretinal fibrotic features in *Vldlr*$^{-/-}$ mice (one of the models for macular telangiectasia, retinal angiomatous proliferation, and subretinal fibrosis), explained with histologic and molecular analyses (Chen et al., 2020). The suggested mechanisms were that fenofibrate might inhibit subretinal fibrosis via suppressing TGF-β-Smad2/3 and Wnt signaling pathways important for the development of fibrosis (Walton et al., 2017; Xu et al., 2017; Tosi et al., 2018). Similar to this study, Mandala et al. demonstrated that fenofibrate treatment could prevent iron-induced activation of Wnt/β-catenin signaling by chelating the iron (Mandala et al., 2020). Taken together, various forms of PPARα agonists have shown promising therapeutic effects in experimental models of AMD.

DR

DR is one of the diabetes complications which affect

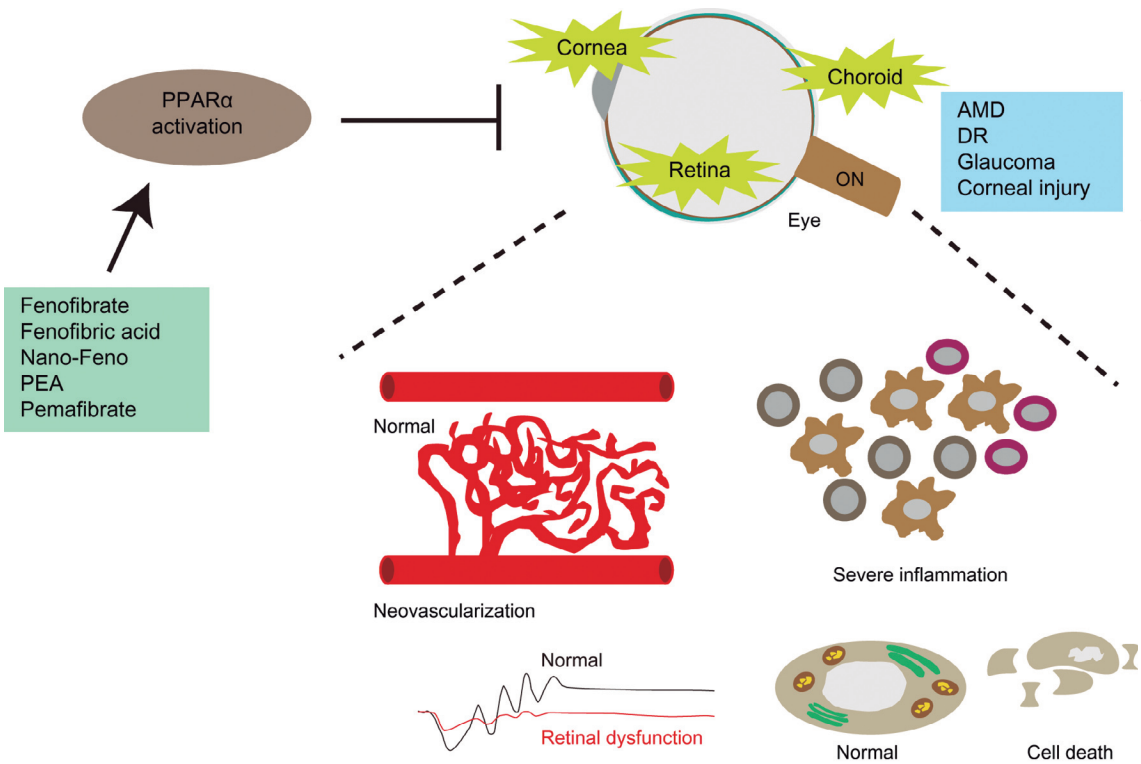

Fig. 1. Summary of therapeutic roles of PPARα activation in ocular ischemic diseases. PPARα activation induced by fenofibrate, fenofibric acid, fenofibrate nanoparticle (Nano-Feno), palmitoylethanolamide (PEA), or pemafibrate might exert therapeutic effects against various ocular diseases, including age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, or corneal injury. Suggested mechanisms include suppression of neovascularization, severe inflammation, retinal dysfunction (especially in DR and glaucoma), and cell death. ON, optic nerve.

the eyes, eventually leading to severe blindness. Pathogenic mechanisms of DR are enormously complex, including hyperglycemia-induced oxidative stress, ocular inflammation, production of advanced glycation end products, and activation of the protein kinase C pathway (Tomita et al., 2020b). Changes in pathological conditions include glial activation, angiopathy (including neovascularization of the retina), and neuronal disorders (Tomita et al., 2020b). As diabetes needs systemic and chronic managements, the therapeutic roles of systemic administrations of PPARα agonists have been mainly examined.

Wang et al. demonstrated that fenofibrate administrations exerted protective effects against streptozotocin-induced DR in rats by inhibiting the ANGPTL3 pathway (Wang et al., 2018), which might have associations with the vascular pathogenesis of DR (Yu et al., 2018; Harada et al., 2021). Li et al. suggested that fenofibrate administrations might ameliorate oxidative stress-induced retinal microvascular dysfunction in streptozotocin-induced DR in rats (Li et al., 2018). Fenofibrate administrations reduced increased retinal vascular permeability and reactive oxygen species levels. Enright et al. showed that oral administrations of fenofibrate reduced reactive gliosis and attenuated retinal dysfunction in *db/db* mice (Enright et al., 2020). According to a report from Pearsall et al. diabetes-induced visual dysfunction was worsened, and diabetes-induced oxidative stress markers were more upregulated in *Pparα*$^{-/-}$ mice (Pearsall et al., 2019). This group showed neuroprotective effects of PPARα activation in DR using fenofibrate and fenofibric acid, explained with optokinetic tracking and DNA fragmentation analyses. Along with the outcomes in vivo, antioxidant effects of PPARα activation were found using a 4-hydroxynonenal (4-HNE; an oxidative stress inducer)-stressed retinal R28 cell line. We recently found that oral administrations of pemafibrate (a novel selective PPARα modulator; SPPARMα) protected against retinal dysfunction in streptozotocin-induced DR mice (Tomita et al., 2020a). This outcome was explained by the perversion of oscillatory potentials (one of the most sensitive functional parameters in DR (Coupland, 1987; van der Torren and Mulder, 1993; Luu et al., 2010; Midena et al., 2021)) and the retinal expression of synaptophysin (one of the essential molecules for synapse formation (White and Stowell, 2021)). Shiono et al. also used experimental DR rats induced by streptozotocin injection and found that oral administrations of pemafibrate inhibited retinal inflammation and retinal vascular leukostasis and leakage (Shiono et al., 2020). We found preventive effects of oral administrations of pemafibrate or fenofibrate on inner retinal dysfunction in a mouse model of carotid artery occlusion-induced ocular ischemia via PPARα activation in the liver (Lee et al., 2021b,c). Taken together, treatments of PPARα agonists may have therapeutic roles against retinal dysfunction or oxidative stress under diabetic or ocular ischemic conditions.

Ye et al. found that intraperitoneal injections of palmitoylethanolamide (PEA; another PPARα agonist) reduced avascular areas in oxygen-induced retinopathy (OIR) mice, with reductions in the expressions of TNF-α, ICAM-1, and VEGF (Ye et al., 2020). Chen et al. demonstrated that an injection of fenofibrate into the vitreous of the eyes could attenuate retinal neovascularization in OIR rats (Chen et al., 2013). This outcome was supported by reductions in VEGF and HIF-1α expressions. On the other hand, we found that oral administrations of pemafibrate reduced retinal neovascularization in OIR mice, while those of fenofibrate had reducing tendencies without statistical significance (Tomita et al., 2019). This issue might be related to the injection method or the dose of fenofibrate. Oral administrations of pemafibrate reduced retinal *Vegfa* mRNA expression and HIF-1α immunoreactivity in OIR mice. Furthermore, we suggested that increased serum levels of fibroblast growth factor 21 (FGF21) by oral administration of pemafibrate may be involved in inhibiting HIF activity, using the HIF-reporter luciferase assay in a retinal 661W cell line with a long-acting FGF21 molecule (PF-05231023). Taken together, treatments of PPARα agonists may have therapeutic roles against retinal neovascularization.

Delivering drugs non-invasively and targeting a specific site of interest has been considered a promising therapeutic approach in many diseases (Anselmo et al., 2019; Kim and Woo, 2021). Hanaguri et al. recently applied topical administrations of fenofibrate nano-eye drops to DR treatment (Hanaguri et al., 2022). Impairments of retinal blood flow regulation in response to systemic hyperoxia or flicker stimulation in *db/db* mice were improved by fenofibrate nano-eye drops. Furthermore, the activation of VEGF and GFAP expressions was also prevented. Huang et al. also demonstrated that fenofibrate nano-emulsion eye drops could increase PPARα expression and reduce retinal inflammation in streptozotocin-induced DR rats (Huang et al., 2021). Its administration had no toxicity to the cornea and retina in rats and mice. Even though more studies are needed, non-invasive targeting of the diabetic retina by fenofibrate nano-eye drops could be an alternative therapeutic strategy.

Glaucoma and retinal ganglion cell loss

Glaucoma is a condition that damages the optic nerve. It is also one of the leading causes of blindness worldwide (Sun et al., 2022). Retinal ganglion cell (RGC) loss is a feature of optic neuropathies (You et al., 2013). RGC loss can be experimentally induced in various murine models of retinal ischemia/reperfusion (I/R) injury, optic nerve injury, N-methyl-D-aspartate (NMDA)-induced excitotoxicity, and carotid artery occlusions (Evangelho et al., 2019; Lee et al., 2021a). Research on RGC loss models has been conducted using RGC protection with PPARα activation.

Yao et al. used fenofibric acid to examine RGC protection in a rat model of retinal I/R injury and an oxygen-glucose deprived (OGD) retinal R28 cell line (Yao et al., 2021). This group considered that PPARα seemed to participate in one of the pathological mechanisms of retinal I/R injury or OGD induction in that PPARα expression in the retina and retinal cell line decreased after retinal I/R injury or OGD induction. Fenofibric acid treatment increased PPARα expression in vitro and in vivo, finally leading to RGC protection functionally and histologically. We also have examined the therapeutic roles of pemafibrate in a mouse model of retinal I/R injury (Lee et al., 2022). We found that oral administrations of pemafibrate protected against RGC loss in multiple therapeutic ways, such as inhibiting the HIF/VEGF signaling, suppressing inflammation (especially microglial activation), and increasing the anti-oxidant pathway (NRF2/HO-1). Fujita et al. demonstrated that oral administration of pemafibrate prevented RGC loss against NMDA-induced excitotoxicity in rats by inhibiting phosphorylated c-Jun expression (Fujita et al., 2021), in that the c-Jun pathway is involved in retinal cell death (Bossy-Wetzel et al., 1997; Herzog et al., 1999). Taken together, PPARα activation may exert protective and preventive actions in various experimental glaucoma models.

Corneal injury

Corneal injury, especially corneal neovascularization, is also one of the sight-threatening conditions in the eye. It can be characterized by forming new vascular capillaries into the avascular corneal regions, extending from the limbus to various areas of the cornea (Sharif and Sharif, 2019). Research on suppressing this pathologic condition has also been conducted with PPARα activation.

Arima et al. demonstrated that fenofibrate treatment suppressed corneal neovascularization in a rat corneal alkali burn model (Arima et al., 2017). PPARα activation was observed in the fenofibrate-treated cornea. Moreover, fenofibrate treatment suppressed various markers for neutrophils and macrophages, which is associated with the development of corneal neovascularization (Moore and Sholley, 1985; Gong and Koh, 2010; Hadrian et al., 2021). Nakano et al. used a combination therapy of PPARα and PPARγ agonists (fenofibrate and pioglitazone) to prevent corneal neovascularization in a rat alkali burn model (Nakano et al., 2020). Treatment of both PPARα and PPARγ agonists increased both *Pparα* and *Pparγ* mRNA expressions and suppressed ocular inflammation at the acute stage of the alkali burn. Along with these outcomes, corneal neovascularization was suppressed by treatment of both PPARα and PPARγ agonists via reductions in *Vegfa* and *Ang-2* expressions. Matlock et al. found a decrease in PPARα expression in the human and rat diabetic cornea and showed a reduction in corneal nerve fiber loss by fenofibrate treatment in streptozotocin-induced diabetic rats (Matlock et al., 2020). Furthermore, they suggested that PPARα ablation could increase the incidence of corneal lesions using *Pparα*$^{-/-}$ mice. Taken together, PPARα activation could also be a promising target for treating the corneal injury.

Clinical implications of fibrate

In two previous randomized clinical trials, the Fenofibrate Intervention in Event Lowering in Diabetes (FIELD) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials, fenofibrate reduced the risk of laser treatment and DR progression (Keech et al., 2005; Group et al., 2010). Many studies have been conducted using fenofibrate for multiple diseases. We introduce recent studies or ongoing clinical trials.

Clinical trial for fenofibrate

Systemic effect

A FIELD sub-study analyzed the relationship between proteinase 3 (PR3) and neutrophil elastase (NE), and risk factors and chronic complications of type 2 diabetes (Ong et al., 2021). In conclusion, plasma NE and PR3 levels in patients with type 2 diabetes were associated with vascular risk factors and total microvascular diseases at baseline but not with complications during the study in rigorous analysis. However, those levels were not altered by fenofibrate treatment.

Michielsen et al. showed that dietary fish oils and fenofibrate were able to effectively lower TG in the serum (Michielsen et al., 2022). These reductions were associated with decreasing the risk of cardiovascular disease (CVD) development/progression. Interestingly, ingestion of fish oil could increase some unsaturated lipids, which are also related to reducing the risk of CVD development/progression. This indicates that fish oil may beneficially alter the metabolic system of plasma lipids.

Despite prior statin monotherapy, the residual reduction in cardiovascular risk with fenofibrate in patients with high serum TG levels had not been thoroughly evaluated. A multicenter, randomized, double-blind, comparative study (Phase IV) aimed to assess the efficacy and safety of the combination therapy of fenofibrate and statins in patients who had previously received statin monotherapy but had poor control of TG levels (ClinicalTrials.gov identifier: NCT03874260). The results suggested that combination therapy with fenofibrate and a statin effectively controlled serum TG levels and may be well tolerated in patients with high TG levels despite statin administration (Park et al., 2021).

Another group conducted a randomized controlled trial to evaluate the efficacy and safety of adding fenofibrate to phototherapy to treat morbid jaundice in full-term infants (ClinicalTrials.gov identifier:

NCT04418180). In conclusion, fenofibrate to phototherapy for full-term neonates with morbid jaundice is well tolerated as adjunctive therapy, with both single and double doses without significant side effects, and is associated with lower serum bilirubin levels, shorter hospital stays, shorter phototherapy duration, and increases frequency of exclusive breastfeeding (Awad et al., 2021).

Effect on eyes

Several studies have shown the relationship between fenofibrate therapy and eye diseases. For developing commonly available and convenient treatments to reduce the risk of progression of DR and maculopathy, randomized trials must be conducted primarily to examine the efficacy of diabetic eye diseases. Recently, Preiss et al. conducted a meta-analysis of randomized controlled trials of fenofibrate therapy for laser treatment of DR (Preiss et al., 2022). They concluded that fenofibrate therapy might reduce the need for retinal laser therapy by more than 20% compared to placebo in an integrated analysis of the large cardiovascular trials conducted to date.

Meer et al. evaluated fenofibrate therapy on 150,252 patients aged 18 years and older with NPDR and without sight-threatening conditions, collected between 2002 and 2019 (Frank, 2022; Meer et al., 2022). At baseline, five thousand eight hundred thirty-five had been prescribed fenofibrate as a lipid-lowering agent. This is 3.9% (5,835 of 150,252 patients were taking fenofibrate). The results showed fenofibrate may be associated with reductions in a risk factor of vision-threatening DR (hazard ratio [HR], 0.92; 95% CI, 0.870.98; P=0.01) and proliferative DR (PDR, HR, 0.76; 95% CI, 0.64-0.90; P=0.001), but not diabetic macular edema (DME, hazard ratio, 0.96 [95%CI, 0.90-1.03]; P=0.27). These results might support the need for further clinical trials to determine whether there is a causal link between the use of fenofibrate and the reduction in a risk factor of PDR or vision-threatening DR (VTDR).

On the other hand, a group from India showed the efficiency of fenofibrate reducing the central macular thickness in DME (Srinivasan et al., 2018). This group evaluated the benefit of adding fenofibrate to the DME patients and quantitatively assessed the effects of DME on macular thickness and visual function. They randomized 43 eyes of 50 patients into treatment group A (fenofibrate 160 mg/day) and control groups (Group B). The improvement in visual acuity at six months was 0.15 for Group A and 0.11 for Group B (P=0.186). Therefore, more studies are desired in this aspect.

Several preclinical studies have examined the effect of fenofibrate on hematopoietic stem cells (HSPCs), however their opinions are controversial (Wang et al., 2014; Shao et al., 2019). Meanwhile, Bonora et al. conducted a randomized clinical trial to show whether fenofibrate may increase circulating HSPCs in a patient with DR or not (Bonora et al., 2021). They randomized 41 participants with DR (20 in the placebo group and 21 in the fenofibrate group). They showed that fenofibrate increased circulating HSPCs levels in participants with DR. It may additionally support the suppressive effects of fenofibrate on the progression of retinopathy.

Table 1. Clinical studies of fibrate for eye diseases.

Therapeutic agent	Molecular target	Study design (subject / treatment / measurement)	Clinical trial	Sponsor or collaborator
Fenofibrate	PPARα	Type 1 and 2 DM, mild to moderately severe NPDR and no CI-DME at baseline. Fenofibrate 160 mg or 54 mg, 4 years, 910 participants to evaluate worsening of DR. Randomized, double-masked, placebo-controlled, Protocol AF (DRCR.net, NCT04661358)	Phase 3	Jaeb Center for Health Research; National Institutes of Health (NIH); National Eye Institute (NEI); Juvenile Diabetes Research Foundation; Roche Pharma AG; The Leona M. and Harry B. Helmsley Charitable Trust
Fenofibrate	PPARα	Type 1 DM, NPDR. Fenofibrate 145 mg, 3 years, 450 participants, to evaluate occurrence of clinical significant retinopathy progression. Randomized, multicenter, double-masked, placebo-controlled, The Fenofibrate And Microvascular Events in Type 1 Diabetes Eye (FAME 1 EYE, NCT01320345)	Phase 3	University of Sydney; National Health and Medical Research Council, Australia; Juvenile Diabetes Research Foundation Australia; Mylan Pharmaceuticals
Fenofibrate	PPARα	Type 1 and 2 DM, NPDR. Fenofibrate 145 mg, 4 years, 1,150 participants, to evaluate progression to clinically significant diabetic retinopathy/maculopathy. Randomized, placebo controlled, Lowering Events in Non-proliferative Retinopathy in Scotland (LENS, NCT03439345)	Phase 4	University of Oxford; National Institute for Health Research, United Kingdom; University of Glasgow; University of Aberdeen; University of Dundee; University of Edinburgh; NHS Scotland Diabetic Retinopathy Screening Collaborative
Fenofibrate, Serine	PPARα	MacTel Type 2. Fenofibrate 200 mg, Serine 200 or 400 mg, 60 patients, to check serum deoxysphingolipid levels, safety assessment. Randomized, placebo-controlled trial, Serine and Fenofibrate Study in Patients With MacTel Type 2 (SAFE, NCT04907084)	Phase 2a	The Lowy Medical Research Institute Limited

DM, Diabetes mellitus; nPDR, non-proliferative diabetic retinopathy; CI- DME, central-involved diabetic macular edema; MacTel, macular telangiectasia.

Currently, four clinical trials of fenofibrate for eye disease are underway (Table 1). The first, Protocol AF is a newly conducted randomized clinical trial evaluating fenofibrate for preventing DR worsening (910 people with type 1 or type 2 diabetes, ClinicalTrials.gov identifier: NCT04661358). This clinical trial compares the effect of fenofibrate to placebo in preventing DR worsening in eyes with mild to moderate NPDR and no central-involved DME at baseline over a 4-year follow-up. The subjects are patients aged 18 to 80 years with mild to moderate DR measured on the Early Treatment Diabetic Retinopathy Test (ETDRS) scale, without DME, neovascularization, or renal impairment. The study endpoints are worsening of retinopathy by two or more levels as measured by the ETDRS photographic severity scale.

The second is a randomized phase 3 trial to evaluate the efficacy of fenofibrate in retinopathy and the safety of fenofibrate in adult patients with type 1 DM. This is an Australian and international multicenter, double-blind, placebo-controlled trial called Fenofibrate and Microvascular Events in Type 1 Diabetes Eye (FAME 1 Eye) trial (450 participants with type 1 diabetes, ClinicalTrials.gov identifier: NCT01320345). This study aims to evaluate the potential usefulness of fenofibrate 145 mg/day in adult patients with type 1 diabetes and pre-existing NPDR for 36 months.

The third is the LENS (Lowering Events in Non-proliferative Retinopathy in Scotland) study (1,150 patients, ClinicalTrials.gov identifier: NCT03439345) in patients with type 1 or type 2 diabetes. LENS is a multicenter, randomized, placebo-controlled study examining the effect of fenofibrate treatment on the progression of DR. The study aims to recruit approximately 1,060 participants and treat them for at least 4 years. The primary objective of LENS is to investigate the effect of fenofibrate treatment on the progression to clinically significant DR.

The fourth is a serine and fenofibrate study in patients with macular telangiectasia (MacTel) Type 2 (SAFE). This phase 2a study contains 60 patients and evaluates the effects of serine supplementation and fenofibrate administration on serum deoxysphingolipid levels in patients with type 2 MacTel, a late-onset macular degeneration. Patients are randomly assigned to either regimen or no treatment (control group). The safety is evaluated with the serum deoxysphingolipid concentration as the primary endpoint. Participants will be screened, visited at weeks 0, 3, 6, and 10, and followed up for 10 weeks. Positive outcomes are highly desired as there have been no efficient treatments for the disease (ClinicalTrials.gov Identifier: NCT04907084).

Clinical trial for pemafibrate

Pemafibrate has stronger selectivity for PPARα than fenofibrate (Ginsberg et al., 2022). The researchers evaluated the safety, tolerability, and efficacy of pemafibrate in European hypertriglyceridemia patients receiving statin treatment. This phase II, randomized, double-blind, placebo-controlled trial enrolled 408 adults receiving statin treatment. They randomly assigned participants to either placebo or one of the six pemafibrate regimens. The primary endpoint was a decrease in non-HDL-C and TG levels at week 12. In this study, pemafibrate reduced TG and increased HDL-cholesterol levels. Pemafibrate is safe and well tolerated, with only slight increases in serum homocysteine and creatinine levels. The researchers concluded that pemafibrate is effective and safe for lowering TG in Europeans with hypertriglyceridemia despite statin treatment.

Wang et al. compared the efficacy of pemafibrate and fenofibrate in treating dyslipidemia (Wang et al., 2019). A comprehensive search for relevant randomized controlled trials (RCTs), comparing pemafibrate and fenofibrate treatment effects on lipid parameters in dyslipidemic patients, was conducted in public databases. Three RCTs were included, involving 744 patients (pemafibrate=547 and fenofibrate=197 patients). Compared to the fenofibrate group (100 mg/day), the pemafibrate group (0.05-0.4 mg/day) was superior in reducing levels of VLDL cholesterol, TG, residual lipoprotein cholesterol, ApoCIII, and apolipoprotein B48. LDL-C increased slightly in the pemafibrate group, while HDL-C and ApoAI levels increased significantly. However, the two groups had no significant differences in total cholesterol levels, non-HDL-C, ApoB, and ApoAII. The incidence of total adverse events and side effects was lower in the pemafibrate group than in the fenofibrate group. The investigators concluded that pemafibrate is more effective than fenofibrate in the suppression of dyslipidemia.

In another study, Yokote et al. investigated the detailed effects of pemafibrate on glucose metabolism and liver function in hypertriglyceridemia patients in randomized, double-blind, placebo-controlled phase 2 and phase 3 studies (Yokote et al., 2021). In this study, about 1,253 participants were randomly assigned to placebo (n=298), pemafibrate 0.1 mg/day (n=127), 0.2 mg/day (n=584), or 0.4 mg/day (n=244). Fasting blood glucose, insulin, and HOMA-IR were significantly lower in all pemafibrate groups compared to placebo. ALT, γ-GT, ALP, and total bilirubin were significantly lower in all pemafibrate groups compared to placebo. FGF21 significantly increased at all pemafibrate doses. The rate of adverse events was similar in all groups, including placebo. The researchers concluded that pemafibrate might improve glucose metabolism and liver function and increase FGF21 levels in patients with hypertriglyceridemia without increasing the risk of adverse events.

Nakajima et al. evaluated the efficacy and safety of pemafibrate in patients with high-risk nonalcoholic fatty liver disease (NAFLD) (Nakajima et al., 2021). This was a multicenter, randomized, double-blind, placebo-controlled study in which 118 patients were assigned to receive pemafibrate 0.2 mg twice daily or a placebo

orally for 72 weeks. They did not see a significant difference between the two groups in the change from baseline to the 24 weeks of the primary endpoint, MRI-PDFF (magnetic resonance imaging-estimated proton density fat fraction). However, MRE (magnetic resonance elastography)-based liver hardness was significantly lower than placebo at 48 weeks, maintained at 72 weeks, and ALT and LDL-C were substantially lower. Adverse events were similar between treatment groups (ClinicalTrials.gov identifier: NCT03350165).

The Phase 3 PROMINENT trial examined the effect of pemafibrate on the risk of CV events in high-risk patients with T2DM, low HDL-C, and mild to moderate hypertriglyceridemia who were on statins. The primary endpoint was a composite of non-fatal MI, non-fatal ischemic stroke, coronary reperfusion, and CV death. Unfortunately, it will be stopped early because although there were no notable safety concerns, the interim analysis concluded that it did not reach the primary endpoint which would be met. However, promising data in new therapeutic areas such as NAFLD and non-alcoholic steatohepatitis (NASH) have been obtained, and analysis will be continued to investigate (ClinicalTrials.gov identifier: NCT03071692). The PROMINENT-Eye Ancillary Study has been conducted to investigate the inhibition of DR progression. However, it was terminated because the number of subjects did not meet the study criteria (ClinicalTrials.gov identifier: NCT03345901).

A phase 3, multicenter, placebo and activity control, randomized, double-blind study evaluating the efficacy and safety of pemafibrate in Chinese patients with low HDL-C and high TG is currently underway. Three hundred fifty hyperlipidemic patients are assigned to pemafibrate (0.1 mg), fenofibrate (200 mg), and control groups. The primary endpoints are baseline to baseline and baseline to control. The primary endpoints are the percent change in fasting TG versus placebo or fenofibrate from baseline (ClinicalTrials.gov identifier: NCT04998981).

There is also an active clinical trial examining the efficacy and safety of pemafibrate extended release (ER) once daily in the morning or evening for 52 weeks for dyslipidemia. This is a multicenter, randomized, open-label, parallel-group, Phase III long-term study of pemafibrate ER tablets in patients with dyslipidemia associated with high TG. One hundred and ten dyslipidemia patients received pemafibrate ER 0.2 mg/day morning and pemafibrate ER 0.2 mg/day evening dosing. The study has been completed, and it is expected for a positive outcome (ClinicalTrials.gov identifier: NCT 04716595).

Future directions and conclusions

The current treatment for various eye diseases has mainly focused on anti-VEGF therapy (Osaadon et al., 2014; Tomita et al., 2021; Wallsh and Gallemore, 2021). However, anti-VEGF therapy is invasive and has several side effects (Nagai et al., 2016; Yang et al., 2016; Wallsh and Gallemore, 2021). It can directly affect ocular homeostasis, and clinical cases have shown that some patients are resistant to anti-VEGF therapy. Furthermore, its therapy is only available at the late stage of disease states. In this regard, developing additional treatments for anti-VEGF therapy is highly desired. Although there is growing evidence that PPARα agonist can slow the progression of DR, it has not yet become a widely accepted treatment. If these trials above demonstrate that PPARα agonist effectively inhibits the progression of DR, it could be adopted as a new treatment for the disease. Using effective medications inhibiting the worsening of DR could reduce the number of patients who undergo more invasive treatments and thus are at risk of side effects that negatively affect visual function.

Based on our current summary, PPARα activation could resolve these issues above; non-invasiveness, usefulness at the acute and chronic stages as demonstrated in the publications above. Our review will enable more preclinical and clinical approaches to understand the therapeutic roles of PPARα activation in preventing various ocular ischemic diseases.

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