USING PPAR AGONISTS TO TREAT DR


This class of drugs warrants further investigation of its potential to mitigate microvascular damage and improve patient outcomes.

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Diabetic retinopathy (DR) is primarily driven by chronic hyperglycemia, which progressively damages retinal capillaries, resulting in vascular leakage, increased permeability, tissue edema, and structural injury. Several interlinked biochemical pathways are implicated in the pathogenesis of DR, including the polyol pathway, hexosamine pathway, and activation of protein kinase C, each of which exacerbates oxidative stress and inflammation. In addition, excessive extracellular matrix deposition leads to basement membrane thickening, pericyte loss, and endothelial dysfunction. These changes promote the development of microaneurysms and increase the likelihood of vascular occlusion and ischemia. As a compensatory mechanism, abnormal neovascularization occurs; however, these newly formed vessels are fragile and prone to rupture, resulting in hemorrhage and further retinal damage.[1-4] Hypertension and hyperlipidemia also contribute to the development of DR.[5,6]

Management options for DR include vitreoretinal surgery, intravitreal injection of anti-VEGF agents and/or corticosteroids, and laser photocoagulation. These therapies are invasive, may have serious negative effects, and are primarily appropriate for advanced stages of DR.[7-9]

Strong evidence indicates that strict control of blood pressure and glucose can significantly reduce or delay the onset and progression of DR.[10] However, even with optimal management, elevated cholesterol, particularly low-density lipoprotein, has been linked to the development of hard exudates, as well as increased retinal thickness and volume.[11,12] In this context, oral medications offer several advantages, including pain reduction, ease of administration, safety, and high patient compliance.[13] Notably, research supports the potential benefits of oral peroxisome proliferator-activated receptor (PPAR) agonists in preventing the development and progression of DR.[14]

PPAR AGONISTS: MECHANISMS AND THERAPEUTIC POTENTIAL

PPARs belong to the nuclear hormone receptor superfamily and function as ligand-activated transcription factors. When bound by specific ligands, they interact with co-activator complexes and bind to peroxisome proliferator response elements within target gene promoters, thereby regulating gene transcription. In the absence of ligands, PPARs associate with co-repressor complexes, suppressing gene expression.[15] PPARs are categorized into three subtypes: PPARα, PPARγ, and PPARβ/δ, each with distinct but overlapping metabolic functions. Collectively, these receptors play a critical role in maintaining energy balance and metabolic homeostasis. PPARα activation reduces triglyceride levels and enhances lipid metabolism, PPARβ/δ promotes fatty acid oxidation, and PPARγ improves insulin sensitivity while facilitating glucose metabolism.[16]

PPARα

PPARα is highly expressed throughout the body, including in the liver; enterocytes; non-neuronal cells such as microglia and astroglia; vasculature and immunologic cell types such as monocytes/macrophages; lymphocytes; endothelial cells; and smooth muscle cells. PPARα also presents in cells of skeletal muscles, intestinal mucosa, adrenal glands, brown adipose tissue, the heart, and the retina.[17,18]

In response to fasting, PPARα is a potent regulator of lipid metabolism and plays a role in maintaining glucose homeostasis equilibrium. A well-known PPARα agonist, fenofibrate, is used to treat hyperlipidemia by raising levels of high-density lipoprotein cholesterol and decreasing triglyceride level.[19,20] Fenofibrate has been investigated for the prevention of DR due to its therapeutic effects on the control of lipid metabolism.[21]

Selective PPARα modulators exert protective effects in DR through both systemic and local mechanisms. Activation of PPARα in the liver stimulates fibroblast growth factor 21 (FGF21) production, which circulates to the retina and retinal endothelial cells. This leads to improved lipid and glucose metabolism, reflected by reductions in triglyceride and blood glucose levels. In the retina, FGF21 suppresses hypoxia-inducible factor activity, thereby inhibiting pathological neovascularization, while also enhancing synaptophysin expression to support neuronal function. In retinal endothelial cells, PPARα activation increases thrombomodulin expression, reducing

TABLE. CLINICAL STUDIES OF PPAR AGONISTS

Study	Drug/Class	Dose	Population/Design	Primary Retinal Outcome	Key Finding(s)
FIELD[23]	Fenofibrate (PPARα agonist)	200 mg/day	Randomized, placebo-controlled study of 9,795 patients with type 2 diabetes	Requirement for first retinal laser treatment (Prespecified tertiary endpoint)	Fenofibrate reduced the need for first laser treatment (HR, 0.69; absolute risk reduction 1.5%) and composite endpoints of retinopathy progression in some subgroups.
ACCORD-Eye[24]	Fenofibrate + statin versus statin alone (lipid trial arm)	Fenofibrate (typical trial dose 160-200 mg/day) + simvastatin	Sub-study of ACCORD; approximately 2,856 participants followed prospectively for retinopathy	3-step or greater progression (ETDRS scale) over 4 years	Addition of fenofibrate (in the lipid arm) was associated with a lower rate of retinopathy progression compared with statin alone; intensive glycemic control also reduced progression.
Retrospective cohorts/claims analyses[27]	Fenofibrate	Typical clinical doses	Large retrospective cohorts/claims datasets	Progression to VTDR, PDR, treatment events	Several real-world analyses reported lower rates of progression or reduced risk of VTDR/PDR among fenofibrate users after adjusting for confounders.
Observational/meta-analytic data on PPARγ agonists[28-30]	Thiazolidinediones (PPARγ agonists)	Typical therapeutic doses for type 2 diabetes (pioglitazone 15-45 mg/day)	Observational cohorts, cross-sectional, and meta-analyses	DME/worsening of macular edema	Evidence is mixed; some observational studies reported an association between TZD exposure and increased risk of DME while other large cross-sectional analyses and meta-analyses found no clear association or inconsistent results.

Abbreviations: DME, diabetic macular edema; ETDRS, Early Treatment of Diabetic Retinopathy Study; HR, hazard ratio; PDR, proliferative diabetic retinopathy; PPAR, peroxisome proliferator-activated receptor; TZD, thiazolidinediones; VTDR, vision-threatening DR.

vascular leakage, leukostasis, and inflammation (Figure 1). Together, these actions help preserve retinal structure and function, mitigating the progression of DR.[22]

PPARγ

In DR, chronic hyperglycemia induces an upregulation of VEGF and intercellular adhesion molecule-1 (ICAM-1) within the retinal vasculature. Elevated ICAM-1 facilitates leukocyte adhesion (ie, leukostasis) to the capillary endothelium, thereby compromising vascular integrity and enhancing retinal vascular permeability, which contributes to the development of macular edema.

Activation of PPARγ by agonists, such as rosiglitazone (Avandia, GlaxoSmithKline), can downregulate ICAM-1 expression, thereby reducing leukostasis and maintaining endothelial function. This cascade of events leads to decreased vascular leakage and offers a potential mechanism through which PPARγ confers protection against microvascular injury in DR (Figure 2).[23]

Dual PPAR Agonists

Dual PPAR agonists that activate PPARα and PPARγ represent a potential synergistic therapy for DR in which PPARα activation improves lipid metabolism and reduces vascular inflammation, while PPARγ enhances insulin sensitivity and protects endothelial function. Preclinical studies with aleglitazar (Roche) suggest this class of drug can improve glucose and lipid homeostasis while reducing retinal microvascular inflammation, effects that were more pronounced compared with a single PPAR agonist.[24] Despite these encouraging findings, the clinical progress of several early agents has been stalled due to

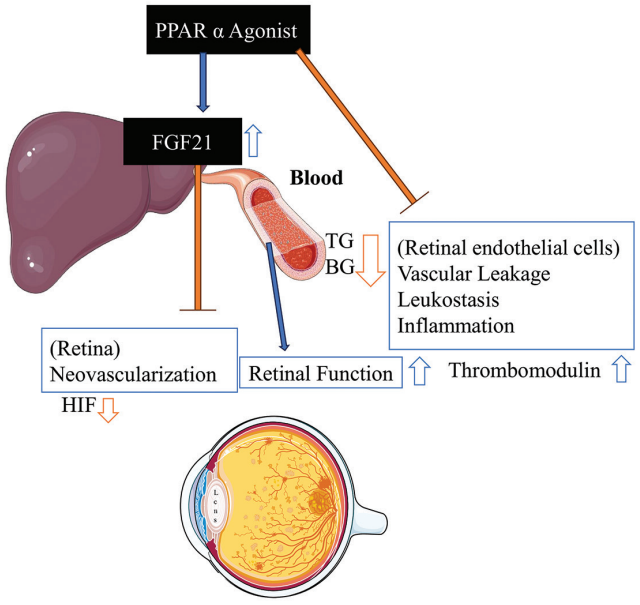

Figure 1. Mechanisms of PPARα activation in the prevention of DR.

cardiovascular safety concerns.[25,26]

Saroglitazar (Lipaglyn, Zydus Lifesciences), a newer generation dual PPARα/γ agonist, has demonstrated promising results in experimental models of DR; in streptozotocin-induced diabetic rats, it reduced retinal expression of VEGF, tumor necrosis factor-α, ICAM-1, and vascular-CAM-1. In oxygen-induced retinopathy models, saroglitazar effectively suppressed pathological neovascularization, which suggests potent antiinflammatory, antiangiogenic, and vasoprotective actions with a more favorable safety profile than earlier compounds. As such, saroglitazar may be a promising candidate for clinical development in DR.[27]

FUTURE DIRECTIONS

Future studies should prioritize large-scale randomized controlled trials to validate the beneficial retinal outcomes observed in animal models and small clinical studies.[28-31] In particular, selective PPAR modulators, such as pemafibrate (Parmodia, Kowa Pharmaceuticals), and dual agonists, such as saroglitazar, have shown potent antiinflammatory, antiangiogenic, and neuroprotective effects in experimental models. However, their efficacy and long-term safety require confirmation in a diverse population with diabetes.[27,32] Mechanistic studies are warranted to further delineate how PPAR activation modulates pathways involving VEGF, ICAM-1, oxidative stress, and neurovascular coupling in DR.[23,32,33]

Combination strategies incorporating PPAR modulators with anti-VEGF therapy or use of corticosteroids may provide synergistic benefits, especially in advanced DR.[7-9] Integration of randomized trial data with real-world evidence will be crucial to determine the effect of PPAR-targeted therapies in routine clinical practice.[34] ■

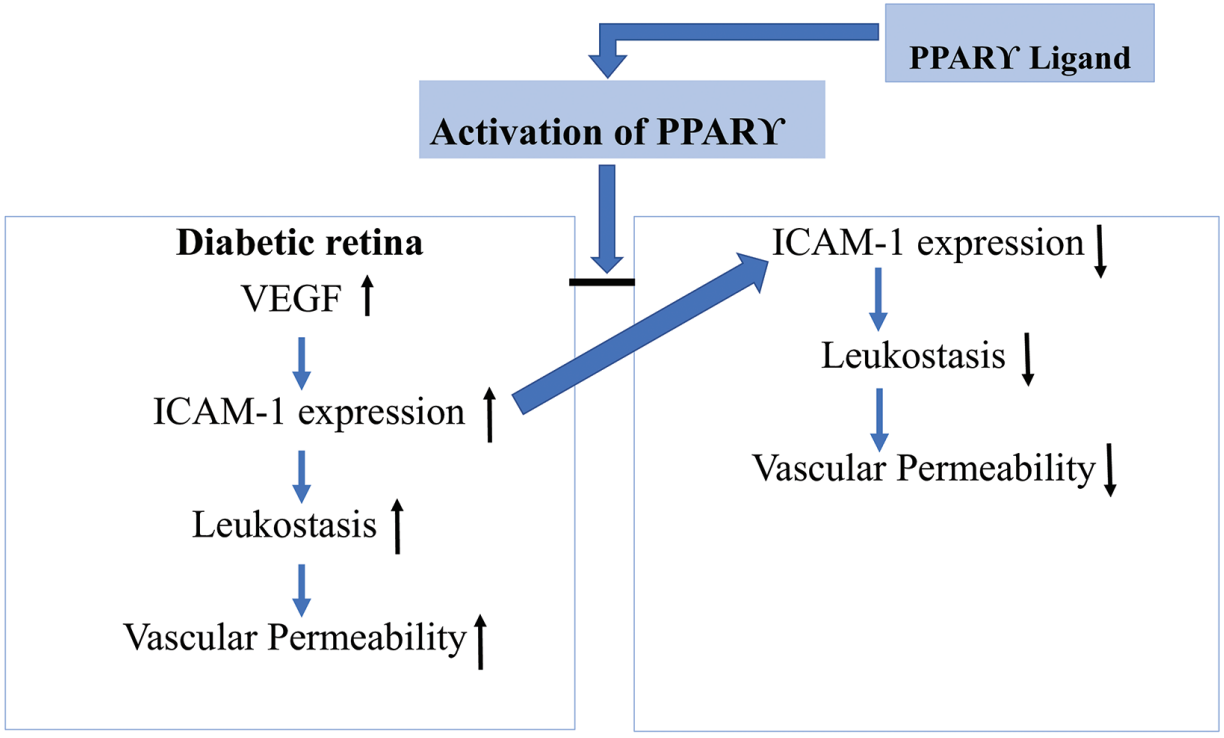

Figure 2. This diagram shows the mechanistic role of PPARγ activation in DR: suppression of ICAM-1 expression, reduced leukostasis, and decreased vascular leakage.

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