Review Article

Fenofibrate and diabetic retinopathy

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ABSTRACT

Background: Diabetic retinopathy (DR), a sight-threatening ocular complication of diabetes mellitus, is one of the main causes of blindness in the working-age population. Dyslipidemia is a potential risk factor for the development or worsening of DR, with conflicting evidence in epidemiological studies. Fenofibrate, an antihyperlipidemic agent, has lipid-modifying and pleiotropic (non-lipid) effects that may lessen the incidence of microvascular events.

Methods: Relevant studies were identified through a PubMed/MEDLINE search spanning the last 20 years, using the broad term "diabetic retinopathy" and specific terms "fenofibrate" and "dyslipidemia". References cited in these studies were further examined to compile this mini-review. These pivotal investigations underwent meticulous scrutiny and synthesis, focusing on methodological approaches and clinical outcomes. Furthermore, we provided the main findings of the seminal studies in a table to enhance comprehension and comparison.

Results: Growing evidence indicates that fenofibrate treatment slows DR advancement owing to its possible protective effects on the blood-retinal barrier. The protective attributes of fenofibrate against DR progression and development can be broadly classified into two categories: lipid-modifying effects and non-lipid-related (pleiotropic) effects. The lipid-modifying effect is mediated through peroxisome proliferator-activated receptor-α activation, while the pleiotropic effects involve the reduction in serum levels of C-reactive protein, fibrinogen, and pro-inflammatory markers, and improvement in flow-mediated dilatation. In patients with DR, the lipid-modifying effects of fenofibrate primarily involve a reduction in lipoprotein-associated phospholipase A2 levels and the upregulation of apolipoprotein A1 levels. These changes contribute to the anti-inflammatory and anti-angiogenic effects of fenofibrate. Fenofibrate elicits a diverse array of pleiotropic effects, including anti-apoptotic, antioxidant, anti-inflammatory, and anti-angiogenic properties, along with the indirect consequences of these effects. Two randomized controlled trials—the Fenofibrate Intervention and Event Lowering in Diabetes and Action to Control Cardiovascular Risk in Diabetes studies—noted that fenofibrate treatment protected against DR progression, independent of serum lipid levels.

Conclusions: Fenofibrate, an oral antihyperlipidemic agent that is effective in decreasing DR progression, may reduce the number of patients who develop vision-threatening complications and require invasive treatment. Despite its proven protection against DR progression, fenofibrate treatment has not yet gained wide clinical acceptance in DR management. Ongoing and future clinical trials may clarify the role of fenofibrate treatment in DR management.

KEYWORDS

type 2 diabetes mellitus, type 1 diabetes mellitus, diabetic retinopathies, dyslipidemia, phenofibrate, apo-fenofibrate, lipid regulating drugs, machine intelligence, computer vision system

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INTRODUCTION

Diabetic retinopathy (DR), a common ocular complication of types 1 and 2 diabetes mellitus (DM), is one of the main causes of blindness in the working-age population in both developed and developing countries [1]. DR is present in 27–40% of patients with DM; however, the prevalence is expected to rise owing to the increasing incidence of type 2 DM and longer life expectancy of patients with DR [1, 2].

DR pathogenesis is multifactorial and remarkably complex [3, 4]. Although hyperglycemia is the main pathological trigger, many biochemical pathways, including protein kinase C, nitric oxide, polyol, advanced glycation end-products, hexosamine, eicosanoid, reactive oxygen species, and the renin-angiotensin system, are responsible for DR pathogenesis [2-4]. Chronic low-grade inflammation mediated through these biochemical pathways induces retinal vascular dysfunction (retinal blood flow changes, basement membrane thickening, pericyte loss, breakdown of endothelial cell-cell junctions, and increased retinal vascular permeability), capillary loss, and ischemia, resulting in retinal changes that may cause permanent vision impairment and even blindness [2-4]. Vision impairment and blindness in patients with DR usually results from macular edema (ME), and less frequently, from proliferative DR (PDR). Leakage of fluid from the damaged capillaries leads to protein and lipid deposits, or hard exudates, which contribute to diabetic ME (DME) [5].

Various treatment modalities, such as standard laser photocoagulation, intravitreal steroid or anti-vascular endothelial growth factor (VEGF) administration, and surgical interventions, are implemented in DR [6]. Although laser therapy is waning in popularity for ME treatment, it remains the reference standard in PDR management and has been proven in clinical trials to eliminate retinal ischemia and leaky microaneurysms. Despite its success, pan-retinal photocoagulation is associated with visual field defects and various other ocular side effects. Intravitreal anti-VEGF and steroid implants are currently popular and frequently used as first- and second-line therapies for DME management. However, these intravitreal agents, which often require multiple administrations, confer a substantial economic burden, as well as a loss of productivity and income for the patient and family members [4-7]. In addition, treatment-related ocular and systemic side effects create marked inconveniences for clinicians and patients. Although intravitreal agents do not induce visual field loss, they are fraught with disadvantages, including the requirement for repeated administrations and serious ocular (e.g., cataract and endophthalmitis) and systemic (e.g., myocardial infarction and cerebrovascular event) side effects [4-7].

Until now, DR management comprised only the invasive methods described above. Newer non-invasive options for DR management reduce the frequency of intravitreal injections and/or laser therapy and may even delay the progression of retinopathy [6-10]. Preventing retinopathy progression will decrease the human and economic burden of treatment; therefore, researchers have focused on risk factors that may result in DR progression. Longer DM duration, uncontrolled hypertension, and greater degrees of hyperglycemia are among the well-identified risk factors. Although strict blood pressure and glycemic control decreases the incidence and deterioration of DR in most patients with DM, it is not fully effective in prevention. Other known potential risk factors include nephropathy, smoking, higher body mass index, and dyslipidemia [7-18].

Dyslipidemia effects on DR pathogenesis remains controversial. The results of previous studies on the association between the lipid profile and DR development or deterioration have been conflicting. Studies have reported that elevated serum triglyceride and low-density lipoprotein cholesterol (LDL-C) levels increased DR incidence, and elevated high-density lipoprotein cholesterol (HDL-C) levels demonstrated a protective effect [17-23]. In addition, several studies have demonstrated a link between increased serum lipid levels and DME development associated with hard exudate deposition [1, 5, 17].

Antihyperlipidemic agents are promising as new treatment options owing to the relationship between dyslipidemia and DME risk and/or DR progression [1, 5, 15]. However, uncertainty remains regarding the possible beneficial effects of antihyperlipidemic drugs in DR management, a subject investigated in previous observational studies [24-30].

Statins, which are commonly used antihyperlipidemic medications, inhibit 3-hydroxy-3-methyl-glutaryl coenzyme A reductase, thereby reducing serum LDL-C levels. They exhibit anti-angiogenic properties in retinal endothelial cells by suppressing VEGF phosphorylation [1]. In retinal pigment epithelium (RPE) cells, they ameliorate disruption of the blood-retina barrier by reducing the expression of matrix metalloproteinases. Furthermore, they impede VEGF upregulation and preserve the integrity of the blood-retina barrier through their antioxidant and anti-inflammatory effects. Additionally, statins induce endothelium-dependent nitric oxide-mediated vasodilation in retinal arterioles [1].

Although statins are beneficial to microvascular structure, their potential effects on DR development remain controversial. In a large cohort study (n = 62 716), Nielsen and Nordestgaard [24] observed that individuals with a history of statin use prior to DM diagnosis demonstrated a significantly reduced risk of DR development. However, observational studies by Klein et al. [20] and by Zhang and McGwin [25] did not support an association between statin use and the reduced risk of DR development. In addition, several studies with small sample sizes have suggested that statin use can lead to a reduction in hard exudates and fluorescein leakage or delayed DR progression [26-28]. However, despite the conflicting results from these observational studies and those with limited sample sizes, randomized placebo-controlled trials, such as the Collaborative Atorvastatin Diabetes Study [29] and Heart Protection Study [30], have demonstrated that statins did not have a significant impact on DR progression .

Fibrates represent another commonly used class of agents for treating dyslipidemia. The effect of fenofibrate on the necessity of laser treatment for DR (Fenofibrate Intervention and Event Lowering in Diabetes [FIELD] study) [5] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) eye study [15], two large randomized clinical trials, demonstrated that fenofibrate treatment was beneficial in decreasing DR progression [5, 15]. Previous reports also suggested that the beneficial effects of fenofibrate treatment might be independent of dyslipidemia improvement [1, 31].

This mini-review examines the efficacy and safety profile of fenofibrate and summarizes the outcomes of fenofibrate treatment in the literature.

METHODS

A PubMed/MEDLINE search spanning the last 20 years, between January 1, 2003 and November 30, 2023, using the general term “diabetic retinopathy” and specific terms “fenofibrate” and “dyslipidemia” was performed to compile all related studies. The references cited in these articles were also evaluated and included, if relevant, to create this mini-review.

RESULTS

In total, 55 articles were examined in detail, including articles identified through focused keyword searches and those obtained from their reference lists. These articles were utilized to explore various features of fenofibrate, including its pharmacokinetic properties, mechanisms of action, and role in DR treatment. Central to the review were seminal studies investigating the effectiveness of fenofibrate treatment in attenuating DR advancement. These pivotal investigations underwent meticulous scrutiny and synthesis, with particular attention to methodological approaches and clinical outcomes. A summary of the key findings of these seminal studies [5, 15, 32-34] is provided in Table 1 to enhance comprehension and comparison.

DISCUSSION

Mechanism of action, indications, pharmacokinetics, adverse reactions, and fenofibrate drug interactions

Fenofibrate, a derivative of fibric acid, is an antihyperlipidemic drug generally used for mixed dyslipidemia and severe hypertriglyceridemia in patients who are unresponsive to non-pharmacological treatments. Following oral intake, fenofibrate is metabolized to fenofibric acid, the active form of fenofibrate, by plasma and tissue esterases. Fenofibric acid is a potent agonist of peroxisome proliferator-activated receptor-α (PPAR-α), an important transcription factor in the expression of genes that have a regulatory role in lipid metabolism. Fenofibrate treatment improves the lipid profile by reducing the serum levels of triglycerides, LDL-C, and apolipoprotein B, reducing low-density lipoprotein particle density, and increasing HDL-C levels [1, 31, 35, 36]. Numerous mechanisms illustrating the protective attributes of fenofibrate against DR progression and development have been proposed. These mechanisms can be broadly classified into two categories: lipid-modifying effects and non-lipid-related (pleiotropic) effects. The lipid-modifying effect is mediated through PPAR-α activation, while the pleiotropic effects involve the reduction in serum levels of C-reactive protein, fibrinogen, and pro-inflammatory markers, and improvement in flow-mediated dilatation [31, 35, 36]. In patients with DR, the lipid-modifying effects of fenofibrate primarily involve reduction in lipoprotein-associated phospholipase A2 (PLA2) levels and the upregulation of apolipoprotein A1 (ApoA1) levels. Lipoprotein-associated PLA2 is well known for its potent inflammatory potential, as it releases arachidonic acid, which serves as a substrate for prostaglandin production. Prostaglandins, in turn, exhibit pro-angiogenic effects by inducing VEGF production. Therefore, PLA2 inhibition reduces pro-angiogenic prostaglandin production, consequently mitigating retinal neovascularization; thus, contributing to the anti-inflammatory and anti-angiogenic effects of fenofibrate in the context of DR [36-38].

Table 1. Key findings of the main studies investigating the role of fenofibrate treatment in diabetic retinopathy

Study/Author (Year)	Sample size and study design	Key findings
FIELD trial, Keech et al. (2007) [5]	In total, 9795 patients (placebo: n = 4900, fenofibrate: n = 4895). Ophthalmological sub-study: 1012 patients (placebo: n = 500, fenofibrate: n = 512). Multicenter randomized clinical study.	Significant reduction in the need for first laser therapy in all patients over an average of 5 years: placebo (n = 238, 4.9%) versus fenofibrate (n = 164, 3.4%) group (P = 0.0002). No significant difference between the placebo (n = 57, 12.3%) and fenofibrate (n = 46, 9.6%) groups regarding the rate of the two-step DR progression grade (P = 0.19). In the patients with pre-existing DR sub-group, a significantly lower rate of a two-step DR progression grade was determined in the fenofibrate group (n = 3, 3.1%) compared to the placebo (n = 14, 14.6%) group (P = 0.004). No significant difference in the incidence of new DR between the fenofibrate and placebo groups (P > 0.05). Significantly lower incidence of retinal pathology (rate of progression in DR grade, DME, or the need for laser treatment) observed in the fenofibrate group (n = 53, 11.1%) compared to the placebo (n = 75, 16.1%) group (P = 0.022). Reduction in the need for laser therapy, independent of lipid level, with fenofibrate therapy.
ACCORD study, Chew et al. (2014) [15]	In total, 10 251 patients → ACCORD eye study; n = 3472 patients → Results of 2856 patients with 4-year data. Randomized controlled clinical study.	Fenofibrate yielded a significant reduction in DR progression (≥ three-step, photocoagulation, or vitrectomy) (fenofibrate group: 52/806 versus placebo group: 80/787, OR: 0.60, P = 0.0056). The least progression of retinopathy in the fenofibrate group was observed in patients at the early stage of DR. In this subgroup, the fenofibrate group exhibited significantly less progression compared to the placebo group (8/264 versus 26/258, OR: 0.27, P = 0.0009). No evidence of benefit was observed for the patients with no DR (OR: 1.12, P = 0.72), mild-to-moderate NPDR (OR: 0.41, P = 0.09), moderate-to-moderately severe NPDR (OR: 0.44, P = 0.21), and severe NPDR or PDR. An additive effect on DR progression was observed with strict glycemic control combined with antihyperlipidemic treatment.
ACCORDION eye study, Chew et al. (2016) [32]	In total, 1310 patients of the ACCORDION eye study → Lipid sub-study; n = 762 patients Randomized controlled clinical study.	Continued reduction in DR progression with prior strict glycemic control despite similar glycated hemoglobin levels 4 years after the ACCORD trial. Rate of DR progression: Strict glycemic therapy, 5.8%; standard therapy, 12.7% (OR: 0.42, P < 0.0001). The beneficial effects of fenofibrate discontinued after the study ended. Rates of DR progression at year 4 after the cessation of the ACCORD eye trial: fenofibrate group, 11.8%; placebo group, 10.2% (OR: 1.13, P = 0.60). Strict blood pressure control had no effect on DR progression.
Morgan et al. (2013) [33]	In total, 5038 patients and 3176 controls. Retrospective cohort study.	Significant decrease in the rate of newly diagnosed DR in patients using fibrates (P = 0.002). Rate of newly developing DR: fibrate group, 15.4% (n = 468); control group, 17.9% (n = 569).
Meer et al. (2022) [34]	In total, 150 252 participants (5835 fenofibrate users and 144 417 non-users). Multicenter retrospective cohort study.	Rate of DR progression: vision-threatening DR 18.2%, PDR 2.71%, and DME 15.1%. Fenofibrate treatment reduced the risk of PDR (HR: 0.76; P = 0.001) and vision-threatening DR (HR: 0.92; P = 0.01), but not DME (HR: 0.96; P = 0.27).

Abbreviations: FIELD, fenofibrate intervention and event lowering in diabetes; n, number of participants; %, percentage; P, P-value; DR, diabetic retinopathy; DME, diabetic macular edema; ACCORD, Action to Control Cardiovascular Risk in Diabetes; OR, odds ratio; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; ACCORDION, ACCORD Follow-on; HR, hazard ratio.

The upregulation of ApoA1 can independently serve as a protective factor in DR. ApoA1 is distributed in various retinal locations, including the neural retina and RPE. ApoA1 prevents the accumulation of oxidized lipids in the retina and acts as a potent scavenger of reactive oxygen species. Hence, ApoA1 protects the retina against oxidative stress and the detrimental effects of lipotoxicity [36, 39, 40].

Fenofibrate elicits a diverse array of pleiotropic effects, including anti-apoptotic, antioxidant, anti-inflammatory, and anti-angiogenic properties, along with the indirect consequences of these effects. The protective impact of fenofibrate on human retinal endothelial cells against apoptosis is mediated through mechanisms that are both PPAR-α-independent and adenosine monophosphate-activated protein kinase-dependent pathways. Furthermore, fenofibrate induces survival pathways within RPE cells while concurrently downregulating stress-mediated signaling [36, 41, 42]. The antioxidant and anti-inflammatory qualities of fenofibrate in DR are associated with various distinct processes. Specifically, the anti-inflammatory effects in DME are evident through nuclear factor-kappa B activity inhibition and a significant reduction in the expression of proinflammatory cytokines. The ability of fenofibrate to increase adipocytokine levels in individuals with elevated serum triglyceride levels may also contribute to some of its anti-inflammatory benefits [36, 43].

Adiponectin, through the modulation of inflammatory responses, particularly those involving tumor necrosis factor-α, protects against retinal vascular injury in experimental animal models [44]. Moreover, the anti-angiogenic effect of fenofibrate is associated with its inhibition of the upregulation of VEGF production in RPE cells. Furthermore, fenofibrate prevents the disorganization of tight junction proteins in RPE cells and consequent hyperpermeability. Fenofibrate also downregulates basement membrane components, specifically fibronectin and collagen type IV. These actions may reduce leakage of the outer blood-retinal barrier associated with DR [36, 43].

Fenofibrate is administered orally, once daily, with or without food, and is well absorbed (approximately 60%). It reaches its maximum plasma concentration in 4–8 h, has an approximate half-life of 20–23 h, and is excreted in the urine (60%) or feces (25%) [31, 35, 36, 45]. Flu-like symptoms, dizziness, headache, joint pain, back pain, diarrhea, constipation, nasopharyngitis, asthenia, nausea, indigestion, and cough are among the common side effects associated with fibrate use. Severe adverse effects that may require drug discontinuation or dose adjustment are rare and include myocardial infarction, arrhythmia, pulmonary embolism, pancreatitis, cholelithiasis, agranulocytosis, and elevations in liver enzyme levels. Clinicians must be aware of drugs that interact with fenofibrate, such as ciprofibrate, cyclosporine, warfarin, vitamin K antagonists, and bile acid sequestrants [45-48].

Major clinical studies on fenofibrate treatment in DR

FIELD trial

This multicenter, randomized clinical study [5] assessed whether long-term fenofibrate treatment could decrease DR progression and the need for laser photocoagulation in patients with type 2 DM. The study comprised 9795 patients aged 50–75 years with type 2 DM, and the patients were randomly allocated to a fenofibrate or placebo group. The proportion of patients with DR at study initiation was 8.3% (n = 412). During follow-up, 4.1% (n = 402) of patients received laser treatment to treat DR. Most of the first laser treatments were administered for the treatment of ME alone or related to PDR (61%), and the remainder were for PDR without ME (39%). An ophthalmological sub-study included 1012 patients. These patients were allocated to either a placebo or fenofibrate group. A history of DR was present in 24 patients in the fenofibrate group and 22 patients in the placebo group at sub-study initiation. Standardized fundus photographs were obtained, and retinopathy severity was graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria to determine the cumulative incidence of DR. Laser therapy was required more frequently in patients with poor blood pressure or glycemic control, owing to the increased clinical burden of microvascular disease. However, plasma lipid concentrations did not affect the need for laser treatment. Over an average of 5 years, the need for first laser therapy in all patients was significantly higher in the placebo group than in the fenofibrate group. No significant difference was found between groups regarding two-step progression in DR grade [5] (Table 1). On evaluating the combined endpoint of a two-step progression in DR grade, DME, or laser treatment, significantly fewer participants in the fenofibrate group met this endpoint compared with the placebo group. However, no significant difference in the incidence of new DR was found between groups. The authors suggested that fenofibrate reduced the need for laser therapy; thus, this effect was independent of plasma lipid concentrations [5].

ACCORD eye study

The ACCORD study [15] comprised three randomized controlled clinical trials evaluating the effect of strict treatment of hypertension, hyperglycemia, and dyslipidemia on DR development and progression in patients with type 2 DM and known cardiovascular risk factors. The main ACCORD trial included 10 251 participants. Of those, 3472 participants were included in the ACCORD eye study, and the 4-year data of 2856 patients were analyzed (Table 1). Patients with PDR who had previously undergone laser therapy and/or vitrectomy were excluded. The modified ETDRS severity scale was used to document DR progression. The severity scale comprises 17 steps from *no DR* to *high-risk PDR* [49]. Similarly, the ETDRS DME severity scale was utilized to evaluate DME development on stereoscopic fundus photographs of the macula [50]. At study initiation, the mean patient age was 62 years, and DM duration was 10 years. At baseline, 48% of participants had no DR, 21% had only microaneurysms, 20% had non-proliferative DR (NPDR), and the remaining 11% had moderate-to-severe NPDR or mild PDR. In contrast, DME was present in <10% of the patients (mild: 5.7%, moderate: 1.6%, and severe: 0.5%). In the ACCORD eye study, patients who had moderate dyslipidemia were randomly allocated to one of two arms in a sub-study to receive a combination of either fenofibrate and a statin or placebo and a statin. Fundus photographs were captured in all participants at study initiation and year 4, and the photographs were graded based on ME and DR severity using the ETDRS method [49, 50].

The primary outcome of this study was progression of three or more steps on the ETDRS person scale, or retinopathy that required photocoagulation, or vitrectomy in either eye. The secondary outcomes were retinopathy development in participants without pre-existing retinopathy and changes in visual acuity and ME features. In the dyslipidemia subgroup, fenofibrate treatment significantly reduced the original total with DR progression (≥ three-steps, photocoagulation, or vitrectomy) compared to the placebo (Table 1). In contrast, when the DR subgroups were examined according to the ETDRS severity scale, the DR stage with the least progression in the fenofibrate group, compared to the placebo group, were steps 2–4 (microaneurysms or mild DR in one eye, no DR or microaneurysms only in the other eye) (Table 1). However, there was no evidence of beneficial effects for the patients in step 1 (no DR), steps 5–6 (mild-to-moderate NPDR), steps 7–9 (moderate-to-moderately-severe NPDR), and steps 10–17 (severe NPDR or PDR) (Table 1). The authors reported that intensive glycemic control might have an additive effect on DR progression when combined with lipid treatment. Four-year rates of ETDRS progression of ≥ three-steps or photocoagulation, according to the randomization group, were lower in the strict treatment group (fenofibrate, n = 19/400 patients; 4.8% versus placebo, n = 27/406 patients; 6.7%) than in the standard group (fenofibrate, n = 30/406 patients; 7.4% versus placebo, n = 50/381 patients; 13.1%) [15].

The ACCORD Follow-on (ACCORDION) eye study

The ACCORDION eye study [32] was conducted to determine whether the reduction in DR progression associated with combined fenofibrate treatment and strict glycemic control, reported in the ACCORD study [15], persisted beyond the study's completion. Participants in the ACCORD eye study were reassessed 4 years after the study. The primary outcome measure was ≥ three-steps in DR progression on the ETDRS severity scale. Of the 1310 participants in the ACCORDION eye study, 762 were included in the lipid sub-study. At the end of the ACCORDION study, the authors observed a continued reduction in DR progression with prior strict glycemic control, despite similar glycated hemoglobin levels 4 years after the ACCORD trial. DR progression rate decreased significantly using strict glycemic therapy than when using standard therapy (Table 1) [32]. However, the beneficial effects of fenofibrate were discontinued, and strict blood pressure control had no effect on DR progression. DR progression rates 4 years after the ACCORD eye trial were comparable in the fenofibrate and placebo groups. The authors posited that the discontinuation of fenofibrate treatment after the ACCORD eye trial was responsible for the absence of these beneficial effects, thus, emphasizing that fenofibrate treatment should be maintained [32].

Retrospective cohort studies

A retrospective cohort study by Morgan et al. [33] compared DR progression in patients with type 2 DM who received and did not receive fibrate treatment. The researchers identified 5038 participants with type 2 DM who had a history of fibrate treatment and no evidence of DR. Of these participants, 3176 were matched to a control. The rates of newly developing DR were 15.4% in the fibrate treatment group (n = 468) and 17.9% in the control group (n = 569). This study demonstrated a reduction in newly diagnosed DR in patients using fibrates compared to the matched control group (33.4 and 40.4 events per 1000 person-years, respectively; $P = 0.002$).

A recent multicenter retrospective cohort study by Meer et al. [34] investigated the influence of fenofibrate treatment on NPDR progression to vision-threatening DR. The study included 352 779 patients with NPDR, and patients with pre-existing PDR, or DME diagnoses, or treatment for sight-threatening DR were excluded. Ultimately, 150 252 participants (5835 fenofibrate users and 144 417 non-users) were included in the analysis. During follow-up, 18.2% of the patients progressed to vision-threatening DR; 2.71% progressed to PDR; and 15.1% progressed to DME. A Cox model controlling for all covariates revealed that fenofibrate treatment significantly reduced the risk of PDR and vision-threatening DR, but not the risk of DME (Table 1). The authors suggested that although fenofibrate treatment did not reduce the risk of DME alone, it might decrease the risk of PDR progression and vision-threatening DR [34]. In a commentary by Frank [51] pertaining to the study of Meer et al. [34], the author stated that the beneficial effect of an oral antihyperlipidemic drug was "an unexpected yet exciting advancement" in preventing DR progression. Additionally, Frank [51] emphasized that fenofibrate is not used globally, and that only approximately 4% of patients received fenofibrate treatment in Meer et al.'s study. [34], and that this drug might be prescribed as a new agent in DR management following the growing evidence and ongoing studies [51].

Ongoing studies

A new randomized clinical trial, known as Protocol AF, including 560 individuals with type 1 or 2 DM aged between 18–80 years, has been conducted since 2021 by the DRCR Retina Network (Clinical Trial ID: NCT04661358) [52]. The participants were randomly assigned (1:1) to a fenofibrate or placebo group.

The trial aims to determine whether fenofibrate is effective in preventing DR progression via a 6-year follow-up in eyes with mildly-to-moderately severe baseline NPDR, but without DME. Other inclusion criteria comprises ≥74 letters of ETDRS visual acuity score and the other eye having at least a microaneurysm if only one eye is eligible [52]. The exclusion criteria include DME according to the central subfield thickness (CST) on optical coherence tomography (Heidelberg Spectralis, CST ≥320 μm in men and ≥305 μm in women; Zeiss Cirrus, ≥305 μm in men and ≥290 μm in women) or clinical examination, intraocular steroid, or anti-VEGF therapy within the previous year, any treatment other than focal/grid laser for DME or DM (if patients have < 12 months history of focal/grid laser), and renal dysfunction requiring dialysis [52]. The primary efficacy outcome of this study is DR exacerbation within 6 years determined using the following criteria: a) ≥ two-step worsening of DR on the ETDRS photographic severity scale, b) presence of retinal neovascularization within seven-modified ETDRS fields and by fundus fluorescein angiography, or c) the need for invasive approaches such as pan-retinal photocoagulation, intraocular anti-VEGF and/or steroid injections, and/or vitrectomy. Protocol AF is expected to provide important data regarding the effect of fenofibrate therapy on DR progression [52].

Herein, literature on fenofibrate treatment-induced reduction in DR progression possibly due to its protective effects on the blood-retinal barrier is summarized. Previous studies remark on the protective effects of fenofibrate treatment against DR worsening independent of serum lipid levels. However, our method did not include a systematic review and meta-analytic search strategy, increasing the likelihood that some relevant studies were omitted. Furthermore, real-world evidence is necessary to clarify the efficacy of fenofibrate administration in preventing or reducing DR or DME progression in patients with other comorbidities. Further longitudinal studies using artificial intelligence-based software in patients with DM taking fenofibrate may assist in monitoring the progression of DR and DME by tracking lesional changes, such as hemorrhages and exudates, on color fundus photographs [53, 54] or optical coherence tomography patterns [55]. This may provide robust evidence on the preventive or therapeutic efficacy of fenofibrate in this potentially blinding yet preventable ocular condition.

CONCLUSIONS

Fenofibrate, an oral antihyperlipidemic agent that is effective in decreasing DR progression, may reduce the number of patients who develop vision-threatening complications and require invasive treatment. However, this treatment has not received wide acceptance by clinicians. In the ACCORD and FIELD studies, fenofibrate treatment appeared more effective in eyes with mild NPDR as a baseline. The extended ACCORDION study showed that the beneficial effects did not persist when fenofibrate treatment was discontinued. Although the underlying mechanism of the beneficial effects of fenofibrate therapy remains unclear, the substance achieves this beneficial effect in a manner different from that of its target purpose. The use of fenofibrate has declined since statins started being used. However, the use of fenofibrate may increase owing to its growing fame in the treatment of patients with DR. The results of ongoing or future clinical trials will clarify the role of fenofibrate in the treatment of patients with DM. A multidisciplinary consensus is needed regarding the initiation of fenofibrate therapy in patients with DM, and at what stage of DR fenofibrate therapy is recommended.

ETHICAL DECLARATIONS

Ethical approval: This was a narrative review and no ethical approval was required.

Conflict of interest: None.

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