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Fenofibrate and Diabetic Retinopathy

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Abstract

Diabetic retinopathy, a common and sight-threatening microvascular complication of diabetes mellitus, is a leading cause of blindness among working-aged adults. Medical therapies including intensive control of hyperglycemia and hypertension have been shown to reduce the incidence and progression of diabetic retinopathy. The association of dyslipidemia and treatment with statins with diabetic retinopathy is inconsistent in epidemiologic studies. However, two recent randomized clinical trials have demonstrated beneficial effects of systemic fenofibrate therapy in reducing the progression of diabetic retinopathy independently of serum lipid levels. These findings suggest that fenofibrate may be an effective strategy for reducing the progression of diabetic retinopathy, thus reducing the large and growing public health burden of treating the sight-threatening complications of diabetic retinopathy.

Keywords

Diabetic retinopathy; Diabetic macular edema; Fenofibrate

Introduction

Diabetic retinopathy is a common microvascular complication in persons with diabetes mellitus types 1 and 2 and is the leading cause of vision loss in working-aged adults globally [1]. The prevalence of diabetic retinopathy has been estimated at approximately 30 % of people with diabetes mellitus [1, 2]. Large population-based studies from three decades ago showed that nearly all people with type 1 and approximately 80 % with type 2 diabetes mellitus will develop some form of diabetic retinopathy after having the disease for 20 years [3, 4]. With earlier detection and improved systemic treatment of patients with diabetes

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Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest Jared E. Knickelbein, Akshar B. Abbott, and Emily Y. Chew declare that they have no conflict of interest.

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mellitus, the incidence and severity of diabetic retinopathy has declined in recent years [5–8]. Nonetheless, the overall number of people with diabetes and diabetic retinopathy is expected to triple over the coming decades presenting a significant public health burden [9, 10]. Moreover, the treatments for the vision-threatening diabetic retinopathy which includes diabetic macular edema and proliferative diabetic retinopathy have increasingly evolved to include injections of vascular endothelial growth factor (VEGF) inhibitors into the vitreous cavity [11, 12], with or without the previous standard laser photocoagulation [13–17]. The cost of each injection averages around $2000, and monthly injections are often required, thus increasing the cost of treatment markedly. These treatments require the expertise of specialized ophthalmologists who are not available in developing countries and even in the more rural areas of the USA. Both the patients and family members who accompany the patients for care may experience lost productivity and income. Thus, therapies that could prevent the progression of diabetic retinopathy would reduce the monetary and human cost of treatment. Known risk factors associated with progression of diabetic retinopathy, include duration of diabetes, degree of hyperglycemia, and hypertension, [1]. Large randomized clinical trials have established the benefit of glycemic [18, 19, 20••, 21] and blood pressure [22] control on reducing the progression of diabetic retinopathy. Dyslipidemia, another important cardiovascular risk factor, has also been associated with increased incidence and severity of diabetic retinopathy [23–25]. In population-based studies and observational data from clinical trials suggested that elevated levels of total cholesterol, triglycerides, and low-density lipoprotein (LDL) cholesterol doubled the risk of retinal hard exudate and macular edema compared to those with normal levels. Progression to proliferative diabetic retinopathy has not been consistently associated with dyslipidemia. Treatment with statin medications, which predominantly addresses dyslipidemia through reduction of LDL, does not appear to significantly alter the course of diabetic retinopathy [20••, 26]. Alternatively, fenofibrate, which is a peroxisome proliferator-activated receptor alpha (PPARα) agonist that reduces triglycerides in addition to LDL and increases high-density lipoprotein (HDL), has been shown in two large randomized clinical trials to have a beneficial effect on reducing the progression of diabetic retinopathy [20••, 27••]. Interestingly, the beneficial effect of fenofibrate may be independent of its effect on dyslipidemia. This review will focus on the current understanding of the role of fenofibrate in altering the course of diabetic retinopathy.

Effects of Fenofibrate on Diabetic Retinopathy: Results from Randomized Clinical Trials

FIELD Study—The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was a multi-center randomized placebo-controlled clinical trial investigating the effect of fenofibrate 200 mg/day on microvascular and macrovascular complications in 9795 adult patients with diabetes mellitus type 2 [27••, 28]. Per patient report, 8.3 % of patients had a history of diabetic retinopathy at study entry. The incidence of laser treatment for diabetic retinopathy, either for macular edema or proliferative disease, was a pre-specified tertiary endpoint of the study. A substudy of 1012 patients who had standardized retinal photographs that were graded according to Early Treatment of Diabetic Retinopathy Study (ETDRS) criteria was conducted to determine the incidence and progression of diabetic retinopathy.

In the entire FIELD study population, the rate of first laser treatments for diabetic retinopathy was significantly reduced in patients in the fenofibrate group compared to the control group over an average of 5 years (3.4 and 4.9 %, respectively; HR: 0.69) [27••]. The majority of laser treatments were performed for macular edema, yet an approximately 30% relative risk reduction was observed for either macular edema or proliferative retinopathy in the fenofibrate group compared to placebo. Beneficial effects of fenofibrate in terms of reducing the requirement of laser treatment for either macular edema or proliferative retinopathy were apparent at 8 months of therapy with progressively greater benefits accumulating with time. Interestingly, levels of total, LDL, and HDL cholesterol as well as triglycerides were not different between patients requiring laser treatment and those who did not.

In the substudy of patients who had graded retinal photographs, there was no difference in the proportion of patients with a two-step progression in diabetic retinopathy according to ETDRS grading criteria between patients in the fenofibrate and control groups (9.6 vs. 12.3 %; $p = 0.19$) [27••]. However, in the subgroup of patients with pre-existing diabetic retinopathy, significantly fewer patients in the fenofibrate group experienced a two-step progression compared to those in the placebo group (3.1 vs. 14.6 %; $p = 0.004$). When a composite endpoint of two-step progression in the level of diabetic retinopathy, development of macular edema, or laser photocoagulation was assessed, significantly fewer participants met this endpoint in the fenofibrate group compared to the placebo group (HR 0.66, 95 % CI: 0.47 to 0.94, $p = 0.022$). The incidence of new diabetic retinopathy was not different between the fenofibrate and placebo groups.

The major limitations of the FIELD study include patient's self-reporting of outcomes (e.g., laser therapy), and only a small subgroup had fundus photography for grading. Furthermore, this study was conducted prior to the routine use of optical coherence tomography for diagnosis and monitoring of macular edema and of intravitreal anti-VEGF agents for the treatment of diabetic macular edema. How fenofibrate may have affected these outcomes requires further study.

ACCORD Eye Study—The Action to Control Cardiac Risk in Diabetes (ACCORD) Eye study evaluated a subgroup of the overall ACCORD trial. This study was a randomized controlled clinical trial of 10,251 participants that evaluated the effects of specific management strategies for hyperglycemia, hypertension, and hyperlipidemia on cardiovascular outcomes in persons with type II diabetes and increased cardiovascular risk [20••, 29]. Participants were all randomized to either intensive or standard glycemic control (target glycosylated hemoglobin <6.0 or 7.0–7.9 %, respectively). There were two additional studies with one group randomized to intensive blood pressure control (target systolic blood pressure control <120 or <140 mmHg) and the other group to lipid management (160 mg daily fenofibrate plus simvastatin or placebo plus simvastatin). For the ACCORD Eye study, a subgroup of 2856 participants was evaluated for the effects of these interventions on the progression of diabetic retinopathy at 4 years [30•]. Progression was determined by analysis of seven standardized stereoscopic fundus photographs for the progression of diabetic retinopathy by three or more steps on the ETDRS severity scale or by the development of diabetic retinopathy requiring laser photocoagulation or vitrectomy.

At 4 years, the rate of progression of diabetic retinopathy was significantly less with intensive compared to standard glycemic control (7.3 and 10.4 %, respectively; OR: 0.67; 95 % CI: 0.51–0.87) [20••]. The rates of diabetic retinopathy progression were also significantly less in participants receiving fenofibrate plus simvastatin compared to those receiving placebo plus simvastatin for lipid management (6.5 and 10.2 %, respectively; OR: 0.60; 95 % CI, 0.42–0.84). The rates of retinopathy progression were not statistically different in the alternative hypertension management groups.

The beneficial effect of fenofibrate therapy was driven primarily by the reduction in progression for participants with mild non-proliferative diabetic retinopathy (microaneurysms or mild diabetic retinopathy in one eye and no diabetic retinopathy or only microaneurysms in the other), as there were no significant differences in progression for participants without diabetic retinopathy or in those with moderate or severe non-proliferative disease [30]. There were also no differences in the development or progression of macular edema, as assessed by fundus photography, between participants receiving fenofibrate and not. As with the FIELD study [27••], the ACCORD Eye study was conducted prior to the routine use of optical coherence tomography for diagnosis and monitoring of macular edema. Another major limitation is only one time point in follow-up at 4 years.

Recent results from the ACCORD Follow-On (ACCORDION) Eye study demonstrated that the beneficial effects of strict glycemic control on reducing the progression of diabetic retinopathy persisted at 4 years after the end of the original ACCORD, despite similar glycosylated hemoglobin levels between participants who previously underwent strict or standard hyperglycemic control [31•]. This phenomenon of sustained beneficial effects after a period of improved glycemic control has been referred to as metabolic memory or legacy effect [32]. This effect was not demonstrated in the ACCORD participants treated with fenofibrate, as the rates of progression of diabetic retinopathy were equivalent in participants regardless of fenofibrate treatment 4 years after the end of the ACCORD trial [31•].

Safety of Systemic Fenofibrate Therapy

Fenofibrate was approved by the US Food and Drug Administration in 1993 and has been used for decades in the management of hyperlipidemia and is generally well-tolerated. The most commonly reported adverse effects include elevated liver enzymes, increased creatinine phosphokinase (CPK), and rhinitis [33]. In both the FIELD and ACCORD studies, increases in serum creatinine were observed during active fenofibrate treatment with return to baseline levels within 6–8 weeks of discontinuing therapy [28, 34]. Rhabdomyolysis has also been rarely reported [33]. The risk of rhabdomyolysis may be increased in elderly patients and patients with diabetes, renal failure, or hypothyroidism. Paradoxical reductions in HDL may also occur [35]. Adverse events do not appear to be increased when fenofibrate is co-administered with a statin [36].

Potential Mechanisms of Fenofibrate in Reducing Diabetic Retinopathy

Following oral administration, fenofibrate is rapidly metabolized to its active form, fenofibric acid, by tissue and plasma esterases [37]. Fenofibric acid is a potent agonist of

peroxisome proliferator-activated receptor-α (PPARα), a transcription factor important for the expression of genes regulating lipid metabolism. Fenofibrate is particularly effective in reducing TG levels and increasing levels of HDL. In both the FIELD and ACCORD Eye studies, fenofibrate-associated reductions in diabetic retinopathy progression were observed independent of serum lipid levels, suggesting mechanisms other than systemic lipid lowering are responsible for the beneficial effect on the retina. Fenofibrate also reduces apolipoprotein B levels and LDL particle density, which may have physiologic effects beyond absolute serum levels of LDL particles [38].

In addition to its lipid-modulating effects, fenofibrate has been shown to have vasodilatory, anti-inflammatory, and anti-apoptotic properties that may be beneficial in diabetic retinopathy. For instance, fenofibrate was shown to cause vasodilation in a nitric oxide-dependent manner in an ex vivo model of porcine retinal arterioles [39]. Fenofibrate also reduced the expression of the inflammatory protein COX-2 and decreased permeability in rate retinal endothelial cells cultured in hyperglycemic conditions [40]. Additionally, in human RPE cells, fenofibrate inhibited NF-kB-mediated inflammatory cytokine expression and blocked IL-1β-mediated RPE disruption, suggesting a beneficial effect in preserving the outer blood-retinal barrier [41]. Furthermore, treatment with fenofibrate significantly reduced human retinal endothelial cell apoptosis in vitro [42] as well as retinal capillary acellularity and pericyte loss in streptozotocin-induced diabetic mice [43]. Many, but not all, of these effects were dependent on PPARα. The exact mechanism of how fenofibrate reduces the progression of diabetic retinopathy remains to be determined.

Conclusions

Two large clinical trials have demonstrated the ability of systemic fenofibrate to reduce the rate of progression of diabetic retinopathy in patients with type 2 diabetes mellitus [20••, 22]. Based on the results of these trials, regulatory agencies in Australia approved the use of fenofibrate to slow the progression of existing diabetic retinopathy in patients with type 2 diabetes in 2013 [44]. Despite an increased number of fenofibrate prescriptions in the USA over recent years [45], fenofibrate is still not routinely used for its beneficial effects on diabetic retinopathy.

Many questions still remain regarding the use of fenofibrate to treat diabetic retinopathy. While the FIELD study showed a reduced incidence of laser therapy for diabetic macular edema in patients treated with fenofibrate, the ACCORD Eye study did not detect any difference in the incidence of photographically demonstrable diabetic macular edema in patients treated or not with fenofibrate. However, the ACORD Eye study may have been under-powered to detect a difference in macular edema, since only 10 % of participants had macular edema and most were considered mild. Neither of these studies assessed macular edema utilizing OCT, which is now standard, and the effects of fenofibrate on potentially lowering the burden of intravitreal anti-VEGF treatment in diabetic patients with macular edema have yet to be investigated.

Furthermore, beneficial effects of fenofibrate therapy in both the FIELD and ACCORD Eye study were only seen in patients with pre-existing retinopathy, and in the ACCORD Eye

study, benefits were restricted to those with mild diabetic retinopathy. Why diabetic patients without retinopathy or patients with more severe retinopathy do not appear to benefit from fenofibrate therapy requires further investigation.

Diabetes mellitus and its microvascular complications, such as diabetic retinopathy, present a tremendous burden on patients and the health care system. In the USA, intravitreal anti-VEGF agents used to treat neovascular age-related macular degeneration and macular edema associated with retinal vein occlusion in addition to that associated with diabetes, account for approximately one sixth of the Medicare Part B drug budget [46]. While adverse events are very rare with intravitreal anti-VEGF injections, blinding infectious endophthalmitis can occur. PRP laser treatment is very effective at regressing retinal neovascularization in proliferative diabetic retinopathy; however, retinal ablation causes a reduction in visual field. Therefore, a therapy that is safe, can effectively reduce the progression of diabetic retinopathy, and limit the need for additional treatment of macular edema or proliferative disease would be extremely beneficial. Fenofibrate may be one such medication. A limitation for using the fenofibrate for the treatment of diabetic retinopathy is its lack of efficacy for reducing cardiovascular events resulting in fewer medical physicians prescribing it for dyslipidemia or for reduction of diabetic retinopathy. Ophthalmologists are less inclined to prescribe drugs for other organs because of the discomfort in monitoring the systemic side effects. Furthermore, the two clinical trials of fenofibrate previously described are perceived as subgroup analyses. Further treatment trials with a focus on the primary outcome of diabetic retinopathy progression are warranted prior to the general acceptance of fenofibrate for the treatment of diabetic retinopathy, especially for those who are already affected with diabetic retinopathy. Such studies are currently underway. If these studies replicate the beneficial effect of fenofibrate found in the previous studies, it would be important to find ways of implementing this therapy that could potentially have a large public health impact and reduce the cost of treatment for diabetic retinopathy dramatically.

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