

The use of fenofibrate in the management of patients with diabetic retinopathy: an evidence-based review

Neil Sharma, Ju-Lee Ooi, Jong Ong, Douglas Newman

Background

Diabetic retinopathy is a significant cause of vision impairment, especially affecting those of working age. There are two large, randomised controlled trials examining the effect of fenofibrate on diabetic retinopathy.

Objective

We summarise their findings, and report on the available safety data.

Discussion

The FIELD study reported that patients treated with fenofibrate had a statistically significant relative risk reduction in the need for laser treatment for maculopathy and proliferative retinopathy. The ACCORD-Eye study reported a statistically significant reduction in diabetic retinopathy progression in patients treated with fenofibrate and statin combination therapy compared to statin therapy alone. There is firm evidence that fenofibrate slows the progression of diabetic retinopathy and the need for more invasive treatment modalities in patients with type 2 diabetes, especially those with pre-existing retinopathy. In October 2013, Australia became the first country in the world to approve the use of this medication for this specific indication.

Diabetic retinopathy is a significant cause of vision impairment and is predicted to become an increasingly large global public health problem. Diabetic retinopathy often affects those of working age and can have significant health, social and economic implications for the individual and the community. Diabetes has been described as the world's fastest growing chronic disease.¹ It has been estimated that over 800,000 Australians have diabetes and 96,200 Australians have a disability primarily caused by diabetes.² It has been estimated that every hour in Australia approximately 11 adults are diagnosed with diabetes.³

The management of diabetic retinopathy has advanced in recent years, especially with the advent of anti-vascular endothelial growth factor (anti-VEGF) injections for the management of diabetic macular oedema. Laser photocoagulation and vitrectomy surgery remain the main treatment options for proliferative diabetic retinopathy. These treatment modalities are invasive and can involve significant time and expense to the individual and to the healthcare system.

There is potentially a significant role for a medication that can slow the progression of diabetic retinopathy and reduce the need for more invasive treatment. There is now firm evidence from two prospective, multicentre, randomised, controlled trials that fibrate medications are beneficial in slowing the progression of diabetic retinopathy in patients with type 2 diabetes mellitus and pre-existing retinopathy. In October 2013, Australia became the first country in the world to approve the use of fenofibrate for this indication. It is possible that other countries will follow this lead in the coming years.

What is a fenofibrate?

Fenofibrate, a fibric acid derivative, is a peroxisome proliferator activated-receptor alpha (PPAR α) agonist. It has been available for clinical use since 1975 in other countries, but has only been registered for use in Australia since 2004.⁴ It is inexpensive, especially when compared with more invasive treatment options for diabetic retinopathy.

Through the activation of PPAR α , fenofibrate lowers free fatty acids by upregulating the synthesis of proteins responsible for fatty acid transport and β -oxidation, which inhibits the formation of triglycerides and very low density lipoproteins (VLDLs).⁵ The elimination of triglyceride-rich particles from the plasma is further achieved through upregulation of lipoprotein lipase synthesis and downregulation of Apo-CIII. Activation of PPAR α is thought to also induce an increase in the synthesis of apolipoproteins A-I and A-II, and of high-density lipoprotein (HDL)-cholesterol. Fibrates have been shown to be clinically effective in lowering triglyceride levels and improving HDL-cholesterol levels.⁶

Proposed mechanisms of action in diabetic retinopathy

The mechanism of action of fenofibrate in reducing diabetic retinopathy progression is thought to be more complex than the serum lipid-lowering effect. Several mechanisms have been proposed. Fenofibrate is known to increase the levels of circulating apolipoprotein A-I, which has recently been shown to be an independent

protective factor for diabetic retinopathy development.⁷ Fenofibrate may also be important in regulating intra-retinal lipid metabolism and reducing lipid deposition and lipotoxicity.⁸

Several other non-lipid mechanisms have also been reported to explain the mechanism of action of fenofibrate in diabetic retinopathy. These include anti-apoptotic, anti-oxidant, anti-inflammatory activity and anti-angiogenic activity, and protective effects on the blood-retinal barrier breakdown.⁹

The FIELD study

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study¹⁰ was a 5-year prospective, randomised controlled trial involving 63 centres in Australia, New Zealand and Finland. It enrolled 9795 patients aged 50–75 years who had type 2 diabetes. Patients were not taking statin therapy at the time of entry into the study. All individuals had an initial plasma total-cholesterol concentration of 3.0–6.5 mmol/L, plus either a total-cholesterol/HDL-cholesterol ratio of 4.0 or more or a plasma triglyceride concentration of 1.0–5.0 mmol/L. Patients were randomly allocated to a once daily micronised fenofibrate 200 mg or matching placebo capsules.

The FIELD study found that treatment with fenofibrate did not significantly reduce the primary outcome of coronary events. It did reduce total cardiovascular events (mainly due to fewer non-fatal myocardial infarctions) but there was no overall mortality benefit. In Australia the FIELD results did not change the

previous recommendations that statins should be first-line lipid-modifying therapy, even in patients with diabetes. The primary indication for fenofibrate was as first-line treatment (after lifestyle modification) in hypertriglyceridaemia or in mixed dyslipidaemia where an elevated triglyceride level was the primary abnormality.⁴

The FIELD study did, however, produce important findings in relation to diabetic retinopathy. Information was collected from all patients regarding any history of retinopathy at baseline, and instances of laser photocoagulation were then recorded routinely at every visit and supporting documentation requested subsequently. Furthermore, in a sub-study population, 1012 patients underwent standardised retinal photography and were graded according to the standardised Early Treatment of Diabetic Retinopathy Study (ETDRS) grading scheme.¹¹ The grading ophthalmologists were blinded to the patients' treatment assignment.

The FIELD study showed that there were 535 courses of laser treatment given to patients on placebo, and 337 to patients on fenofibrate (relative reduction with fenofibrate 37%, $P = 0.0003$). There was a relative reduction in the need for laser treatment of 36% ($P = 0.003$) with fenofibrate treatment in those with any maculopathy, and of 38% ($P = 0.009$) in those with proliferative retinopathy. These results are shown in *Table 1*. There was also a relative reduction in the need for first laser with fenofibrate for maculopathy of 31% ($P = 0.002$), corresponding to an absolute risk reduction of 1.1%

Table 1. FIELD retinopathy results, showing reduced need for laser treatments in fenofibrate group

	Placebo (n = 4900)	Fenofibrate (n = 4895)	Hazard ratio (95% CI)	P value
First laser for any maculopathy	167	115	0.69 (0.54–0.87)	0.002
First laser for proliferative retinopathy	108	75	0.70 (0.52–0.93)	0.015
All laser treatments for any maculopathy	342	218	0.64 (0.48–0.86)	0.003
All laser treatments for proliferative retinopathy	193	119	0.62 (0.43–0.89)	0.009
All laser treatments for all patients	535	337	0.63 (0.49–0.81)	0.0003

(95% confidence intervals [CI] 0.4–1.7). For proliferative retinopathy there was a risk reduction of 30% ($P = 0.015$), corresponding to an absolute risk reduction of 0.7% (CI 0.1–1.2). Interestingly, there was a reported apparent relatively rapid onset of benefit of fenofibrate treatment, with divergence in the need for laser treatment evident within 8 months of treatment allocation.

The use of fenofibrate reduced the need for any first laser treatment, especially in those with pre-existing retinopathy. The FIELD study reported that, if treated with fenofibrate, there would have been 1.1 fewer first laser treatments performed per 100 patients in those without pre-existing retinopathy (number needed to treat [NNT] 90). However, in those with a history of diabetic retinopathy, there would have been 5.8 fewer first laser treatments needed per 100 patients treated (NNT 17).

In the FIELD ophthalmology sub-study, the primary endpoint of two-step progression of retinopathy grade did not differ significantly between the two groups. However, in patients with pre-existing retinopathy, significantly fewer patients taking fenofibrate had two-step retinopathy progression than did those on placebo (3.1% patients on fenofibrate versus 14.6% on placebo; $P = 0.004$). By contrast, the number of patients without pre-existing retinopathy who had a two-step progression was much the same in the two groups (11.4% versus 11.7%; $P = 0.87$).

The ACCORD study

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was a large, multicentre, prospective, randomised, controlled trial that was supported by

the US National Heart, Lung and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Eye Institute and the Centers for Disease Control and Prevention.¹² In total, it enrolled 10,251 patients with type 2 diabetes, to test the effects of three medical strategies to reduce cardiovascular disease morbidity and mortality. The details of the Glycaemia and Blood Pressure trials are outside the scope of this paper. The Lipid Trial was a double-blinded study of 5518 patients that showed no benefit of fenofibrate addition to statin therapy for the primary endpoint of cardiovascular event reduction, or any secondary outcome.¹³

The ACCORD-Eye was a sub-study of 2856 patients to assess the effect of these treatment strategies on the progression of diabetic retinopathy or the need for retinal laser or vitrectomy surgery.¹⁴ 1593 patients were enrolled in the Lipid control component of the ACCORD-Eye study. A comprehensive, standardised eye examination was conducted by a study ophthalmologist or optometrist, along with fundus photography of seven standard stereoscopic fields, at baseline and year 4 of follow-up. The fundus photographs were evaluated by trained graders, who were unaware of the treatment assignments, at a single grading centre. Information was also collected at the annual visits in the main ACCORD trial, to determine whether retinal laser or vitrectomy had been performed during the previous year.

After 4 years, the proportion of patients who progressed three or more steps on the ETDRS severity scale for diabetic retinopathy or required laser photocoagulation or vitrectomy was 6.5% in the fenofibrate plus statin group versus 10.2% in the statin alone group (adjusted

odds ratio 0.60; 95%CI 0.42 to 0.87; $P = 0.006$). There was no statistically significant difference between the two groups regarding the percentage of patients with moderate vision loss. These results are shown in *Table 2*.

Safety

Fenofibrate is a generally well-tolerated medication.⁴ The most common side effects are gastrointestinal, such as nausea, diarrhoea and abdominal pain. Serum transaminase levels may also be elevated. Skin rashes, pruritus and urticaria are other common side effects.

Myopathy is a rare potential complication, and this may be of particular concern with the use of statins. A recent systematic review of the literature was performed aiming to examine the safety of using fenofibrate in conjunction with a statin.¹⁵ Discontinuation attributed to any adverse events (4.5% versus 3.1%, $P = 0.20$), and serious adverse events (2.0% versus 1.5%, $P = 0.71$) were not significantly different in the two arms. The incidence of transaminase elevations greater than three times the upper limit of normal was significantly higher in the combination group than the statin monotherapy arm (3.1% versus 0.2%, $P = 0.0009$). There were no reported cases of myopathy or rhabdomyolysis in either group. Nevertheless, patients prescribed fenofibrate who complain of muscle pain, tenderness or weakness should have prompt medical evaluation.¹⁶

There have been reports of raised serum creatinine levels following the use of fenofibrate therapy. It is recommended that serum creatinine be checked at baseline and within 3 months of therapy commencement, and then monitored periodically thereafter.¹⁶

Table 2. ACCORD-Eye study results

	Simvastatin plus placebo	Simvastatin plus fenofibrate	Adjusted odds ratio (95%CI)	P value
Progression of diabetic retinopathy	10.2%	6.5%	0.60 (0.42–0.87)	0.006
Moderate vision loss	24.5%	23.7%	0.95 (0.79–1.14)	0.57

Limitations of the studies

Despite the firm evidence of benefit, there are a few limitations of both the FIELD and ACCORD-Eye studies. First, when interpreting the findings and clinical implications, it is important to remember that diabetic retinopathy was not a primary endpoint by design in either study. Second, neither the FIELD nor ACCORD-Eye studies showed an improvement in visual acuity outcomes, despite showing a reduction in diabetic retinopathy progression. Third, neither study used a quantitative measurement of diabetic macular oedema, such as optical coherence tomography, which is now routinely used in clinical practice.

On-label prescription

In October 2013, Australia became the first country in the world to add diabetic retinopathy as an indication for fenofibrate. It is approved for reducing the progression of diabetic retinopathy in patients with type 2 diabetes and existing diabetic retinopathy. Importantly, fenofibrate does not replace appropriate control of blood pressure, blood glucose and blood lipids in reducing the progression of diabetic retinopathy.¹⁶

Dosing

The majority of clinical trials have been conducted with a micronised fenofibrate 200 mg capsule formulation. The micronised fenofibrate 200 mg capsule, three tablets of 48 mg and the 145 mg tablet have reportedly been demonstrated to be bioequivalent under fed conditions.¹⁶

Key points

- There is firm evidence that fenofibrate slows the progression of diabetic retinopathy and reduces the need for laser photocoagulation and vitrectomy surgery.
- Fenofibrate is now indicated in Australia for the reduction of diabetic retinopathy progression in patients with type 2 diabetes and existing retinopathy.
- Fenofibrate does not replace the need to maintain appropriate control of serum

glucose and blood pressure to reduce the progression of diabetic retinopathy.

- Serum creatinine and liver transaminases need to be monitored while a patient is on fenofibrate therapy.
- Myopathy and rhabdomyolysis are very rare complications, but patients should be aware that they should seek prompt medical attention if any symptoms of muscle pain, tenderness or weakness develop.

Conclusion

This new indication for fenofibrate may have significant public health benefits in reducing the progression of diabetic retinopathy and the need for more expensive and invasive treatment modalities.

Authors

Neil Sharma MBBS (Hons), MPH, FRANZCO, Ophthalmologist, Eye and Retina Specialists, Sydney, Cambridge University Hospitals NHS Trust, UK and Department of Ophthalmology, Westmead Hospital, Sydney, NSW. neilsss@hotmail.com

Ju-Lee Ooi MBBS MPH FRANZCO, Ophthalmologist, Eye and Retina Specialists, Sydney, and Clinical Lecturer, University of Sydney and University of New South Wales.

Jong Ong MBBS MRCP FRCOphth, Ophthalmologist, Cambridge University Hospitals NHS Trust, Cambridge UK

Douglas Newman MA FRCOphth, Ophthalmologist, Cambridge University Hospitals NHS Trust, Cambridge UK

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correspondence afp@racgp.org.au