

UPDATE ARTICLE

Improving Diabetic Retinopathy Outcomes: FIELD Fenofibrate

Sanjay Kalra¹, Rakesh Sahay²**Abstract**

This brief communication describes evidence which proves the beneficial effects of fenofibrate on the retinal vasculature in type 2 diabetes, acting via both lipid lowering and non-lipid lowering mechanisms. It discusses data from FIELD and other trials to support the use of fenofibrate as a secondary preventive therapy for diabetic retinopathy. These data contrast with the lack of retinal benefit shown in major cardiovascular outcome trials of other blood pressure lowering and glucose lowering agents such as empagliflozin, liraglutide, perindopril + indapamide, and ramipril.

Introduction

With the diabetes juggernaut moving from epidemic to endemic status, pharmaceutical researchers are working to develop newer and better drugs for this condition. The process of drug development has become more and more challenging, and introduction of novel molecules has become difficult. At the same time, there are greater expectations from pharmaceutical products, which are required to provide pleiotropic benefits beyond their primary mode of action.¹ The clinically most relevant benefits pertain to long term or vascular outcomes, which affect quality as well as duration of life.²

Difficulty in developing newer, and pluri-beneficial drugs has also spurred interest in older, existing molecules, which can be exapted for multiple uses.³ Within the diabetes care arena, it has encouraged reassessment of such entities with modern methods of analysis. A classic example is metformin, a six decade old chemical, which continues to unravel new secrets, and exude maiden charm.⁴ We focus on fenofibrate, a well-known lipid lowering drug, which has not received due respect. We discuss the results of seminal trials on fenofibrate and explain their significance, in the light of limitations of more modern metabolic drugs, as revealed by recent mega-trials.

The FIELD Trial

The Fenofibrate Intervention and

Event Lowering in Diabetes (FIELD) study included 9795 statin-naïve participants aged 50-75 years with type 2 diabetes (T2DM), and randomized them to micronized fenofibrate 200 mg once daily or placebo for 5 years. The fenofibrate cohort experienced a relative reduction of 11% in coronary events, 24% reduction in non-fatal myocardial infarction, and non-significant increase in coronary heart disease mortality. Total cardiovascular disease events reduced significantly by 11% including a 21% reduction in coronary revascularization. Fenofibrate use was associated with less albuminuria progression and less requirement for laser treatment.⁵

In spite of excellent results in microvascular outcomes and a significant reduction in CV events, the authors concluded with a surprisingly weak interpretation. It must be noted that FIELD was conducted at a time when there was relatively lesser interest in outcomes research, and the significance of these results was not appreciated. Later analysis showed that the absolute benefits of fenofibrate were most marked in patients with severe hypertriglyceridemia. A 27% relative risk reduction ($p=0.005$; number needed to treat=23) was noted in participants with elevated serum triglycerides (>2.3 mmol/l and low HDL cholesterol).⁶

When attention was focused on the retinal effects of fenofibrate, a much more optimistic picture emerged. FIELD study design included gathering of information concerning laser treatment for diabetic retinopathy at every clinic visit. Expert ophthalmologists who were blinded to study drug/placebo allocation adjudicated events of laser treatment for macular edema, proliferative retinopathy, or other eye conditions. In a sub study of 1012 participants, standardized retinal photographs were graded by Early Treatment Diabetic Retinopathy Study (ETDRS) criteria to determine cumulative incidence of diabetic retinopathy.⁷

Laser treatment was required more frequently by patients with poorer glucose or blood pressure control, and by patients with a greater burden of microvascular complications. There was no impact of plasma lipid levels on need for laser. Necessity of first laser therapy was significantly lower in the fenofibrate group (3.4% vs 4.9%; hazard ratio 0.69; $p=0.0002$). In the ophthalmology study fewer patients with pre-existing retinopathy on fenofibrate experienced a 2 step progression than those on placebo (3.1% vs 14.6%; $p=0.004$). However, no such difference was noted in the overall group or in the sub group without pre-existing retinopathy. Analysis of a composite endpoint including 2-step progression of grade of retinopathy, macular edema, or laser treatments revealed a lower incidence in the fenofibrate group than in the placebo group (hazard ratio 0.66; $p=0.022$).

Comparison with Newer Trials

In the decade following the publication of FIELD results, major changes took place in the field of diabetology. Cardiovascular outcome trials (CVOT), which hitherto had

¹Consultant, Endocrinology, Bharti Hospital, Karnal, Haryana; ²Professor and HOD, Endocrinology, Osmania medical College, Hyderabad, Telangana

Received: 26.08.2016; Revised: 05.01.2017; Accepted: 28.03.2018

been thought to be necessary only for cardio active drugs, were made mandatory for glucose-lowering drugs as well.⁸ This led to a series of CVOT of newly-introduced drugs, and renewed interest in older trials which reported cardiovascular outcomes. Over the past few years, results of CVOTs have improved. Newer drugs such as empagliflozin, canagliflozin and liraglutide^{9,10} have reported cardiovascular benefit, as opposed to cardiovascular safety demonstrated by earlier drugs like sitagliptin, saxagliptin and lixisenatide.⁸

A surprising similarity is noted when results of the most positive CVOTs are analysed. A cardio-cerebral discordance is noted in the benefits reported with not only empagliflozin and liraglutide, but perindopril + indapamide and ramipril as well. The improvement in cardiac outcomes is much more pronounced than that seen in cerebrovascular outcomes. An even more pronounced reno-retinal discordance is noted when nephrologic and ophthalmic outcomes are compared. The ADVANCE, EMPA-REG, HOPE and LEADER trials all report significantly improved microvascular outcomes, which are driven by a reduction in renal events.^{9,12} However, this benefit does not extend to the retinal vasculature.

Fenofibrate and the Retina

These data suggest that different pathogenetic factors are at play in the renal and retinal vascular beds. They also imply that unique strategies apart from glycemic control and blood pressure management, will be required to prevent and control retinal damage.

Fenofibrate is one such evidence-based strategy. It is surprising that while the use of this drug is being exapted to novel indications, such as primary biliary cirrhosis,¹³ we have not been able to utilize it fully in diabetology. FIELD results show that fenofibrate is effective in secondary prevention of diabetic retinopathy, as it reduces progression of retinopathy, and lessens requirement of laser treatment. Similar results are reported by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study.¹⁴

At the same time, fenofibrate is also able to improve renal outcomes^{15,16} and reduce minor amputations, especially in persons without major

vessel disease.¹⁷ This suggests that an endothelial protective effect may be at play in all micro vascular beds. In an in vitro study conducted on cultured retinal epithelial cells, fenofibric acid prevented monolayer disruption, and the consequent hyper permeability induced by IL-1 β , through inhibition of NF- κ B activity. This effect was due to PPAR α activation and was associated with a significant down regulation of the expression of proinflammatory cytokines. These findings suggest that the anti-inflammatory effects of FA through inhibition of NF- κ B activity play a key role in the beneficial effect of fenofibrate for treating diabetic macular edema.¹⁸ It must be noted, however, that the beneficial effects of fenofibrate did not persist after completion of trial in the ACCORD Eye Study.¹⁹

Fenofibrate and the Lipids

This effect is in addition to the proven efficacy of fenofibrate in improving lipid parameters. Fenofibrate has been shown to decrease serum triglycerides and remnant like particle cholesterol. This is achieved by reduction in activity of lipoprotein associated phospholipase A2.²⁰ At the same time, serum high density lipoprotein (HDL) cholesterol is increased, with a rise in concentration of similar, less antiatherogenic a3 and a 4 HDL-C particles. These results have been maintained for an average duration of 39.6 months. At the same time there was no change in total LDL, small dense LDL (sdLDL), serum insulin or adiponectin.²¹ In both normo- and hyper-cholesterolemic subjects, it reduces alimentary lipemia following a fat load. Concomitant increase in plasma HDL of 10% is also noted. Fenofibrate acts by increasing lipoprotein lipase activity by 37% (p<0.001) to improve chylomicron catabolism.²² The case for fenofibrate is strengthened by evidence which supports the fact that fenofibrate treatment reduces the angiographic progression of coronary artery disease in type 2 diabetes.²³ This effect is partly related to the correction of lipoprotein abnormalities. This is achieved without increasing weight (as opposed to rosiglitazone, which lowers triglycerides but causes weight gain).²⁴ Within the retina, fenofibrate is thought to inhibit cytochrome P450 Epoxygenase 2C activity, and thus suppress pathological angiogenesis.²⁵

Caution

These data encourage the more widespread use of fenofibrate, not only for lipid modification, but also for improvement of vascular outcomes in diabetes. All patients with or at risk of vascular complications should benefit from fenofibrate use. Patients with retinopathy or at high risk of amputations are robust candidates for its use.

A word of caution is necessary, however. One must be aware of contraindications, drug interactions and potential side effects of the drug before prescribing it. The decision to prescribe should be based on informed and shared decision making, including a realistic cost: benefit ratio analysis. Regular monitoring must be done to ensure safety and tolerability. Newer formulations of fenofibrate,^{26,27} which have better bioavailability and enhanced tolerability, should be preferred.

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