



Review on Rosuvastatin and Fenofibrate

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ABSTRACT

This article is an examination of a review on Rosuvastatin and Fenofibrate. The scientific development and subsequent study of the effects that Rosuvastatin and Fenofibrate have, which taken individually and in combination, on various diseases, continues to influence the researchers all over the globe today. This article examines the research done and published by researchers and scientists. Consideration of current trends and data in scientific queries and demonstrates further aspects of Rosuvastatin and Fenofibrate. Additionally, this article explores the effect that rosuvastatin has on thromboinflammation, platelet volume and dyslipidaemia, the effects of Fenofibrate on diabetic retinopathy, non-alcoholic fatty liver disease and dyslipidaemia and finally the combined effects of rosuvastatin and fenofibrate on prostate cancer, Ischemic stroke and hypolipidemia.

Keywords: Rosuvastatin, Fenofibrate, Dyslipidaemia, Platelet, Stroke.

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INTRODUCTION

Combination drug therapy is a very useful tool which is being exploited nowadays to treat several diseases. This helps to lower the problems of drug resistance and also helps in identifying drugs having complementary effects which can help to significantly reduce the dose of the drug required to be administered. Additionally, this kind of therapy also helps to reduce the side effects of the drugs significantly.

Rosuvastatin is a type is stain medication that is an antagonist for the enzyme HMG-CoA reductase. It is typically employed clinically to lower the levels of cholesterol in the body, it has also been proven effective in treating heart and blood vessel diseases including stroke. The drawback of rosuvastatin is owed to its side effects which include lowering the levels of cq10 (ubiquinone) in the body. This often leads to muscle aches, tenderness and general weakness.

Fenofibrate belongs to the fibric acid derivatives class of drugs. Fenofibrate has also been used to lower the levels of Cholesterol in the body, it does do by increasing the breakdown and removal of bad cholesterol from the body.

It has also proven useful in treating diabetic retinopathy and preventing amputations of the foot. Its side effects include headaches, nausea and liver problems, to name a few.

Fenofibrate is less preferred to Rosuvastatin as it is not shown to decrease the risk of heart diseases, which is an important consideration while looking at drugs with cholesterol level lowering capacity. Additionally, it less effective at lowering the levels of LDL cholesterol. Therefore, by using the drugs in combination it will be beneficial, in order to overcome the side effects and drawbacks. The review aims to study and understand the roles of Rosuvastatin and Fenofibrate in various disorders, when use individually and in combination

METHODOLOGY

The study was conducted using four databases Google Scholars SAGE, DOAJ and PubMed. Selection of papers were done based on keywords and theme relevant to this review. Further the published papers from these databases were arranged in systematic order with respect to the year of publication.

RESULTS AND DISCUSSION

Rosuvastatin¹⁻¹⁰

Extra Lipid Effects of Rosuvastatin: Review

Statins apart from having beneficial lipid modulation effects, exert a variety of several “pleiotropic” actions that may result in clinical benefits. Rosuvastatin has proved remarkably potent in reducing low-density lipoprotein cholesterol levels. At present, no large-scale primary or



secondary prevention clinical trials document either its long-term safety or its effectiveness in preventing cardiovascular events. A substantial number of experimental and clinical studies have indicated positive effects of rosuvastatin on endothelial function, oxidized low-density lipoprotein, inflammation, plaque stability, vascular remodelling, haemostasis, cardiac muscle, and components of the nervous system. Available data regarding the effects of rosuvastatin on renal function and urine protein excretion do not seem to raise any safety concerns. Rosuvastatin reduces colonic inflammation and provides protection against intestinal ischemia. It reduces inflammatory cells infiltration of the kidneys and MMP-2 and MMP-9 activities in the kidneys. It provides protection against degenerative changes in podocytes, Reduction of the oxidative stress in epineurial arterioles and renal fibrosis. Regarding antioxidant properties, it reduces the ox-LDL plasma levels, vascular superoxide anion production and vascular ROS production. Multiple clinical trials have shown that treatment with rosuvastatin is associated with greater reductions in LDL-C than the other currently available statins and is considered safe. At present, no large-scale primary or secondary prevention clinical trials document either the long-term safety or the effectiveness of rosuvastatin in preventing coronary events. Rosuvastatin treatment may result in halting and regression of atherosclerosis in the carotid and coronary arteries. There is increasing evidence revealing favourable antiatherogenic and organ-protective actions of rosuvastatin beyond its lipid-lowering potential. Whether the lipid-lowering capacity and the beneficial extra-lipid effects of rosuvastatin may translate into reduced morbidity and mortality remains to be proved¹

Impact of Rosuvastatin on Thromboinflammation in case of Acute Coronary Syndrome (ACS): A clinical trial

The study was conducted to determine if early high dose administration of the HMG- CoA reductase inhibitor drug Rosuvastatin within the setting of ACS can be used for beneficial vascular effects by reducing and inhibiting biomarkers of thromboinflammation like platelet-monocyte, platelet-neutrophil interactions, and biomarkers of myocardial necrosis. Among the fifty- four patients, patients with normal cardiac necrosis when undergone biomarkers at randomisation rosuvastatin therapy had less myocardial damage as measured by troponin-I or CK-MB. Early administration of high-dose statin therapy in patients with ACS appeared to enhance biomarkers of inflammation within eight hours which may lead to fewer ischemic events. When neutrophil-platelets aggregates were analysed it was observed that there was a significant lowering in the rosuvastatin group on the first day. 31.7 ± 4.4 % of the neutrophils had attached platelets in the rosuvastatin group versus 23.1 ± 3.5 % in the placebo group. At 8-hour interval the percentage of circulating neutrophils with adherent platelet was less in the rosuvastatin group at 12.8 ± 2.1 (18.9 % absolute reduction) but only slightly lower in the placebo group at 18.6 ± 3.9 (4.5 % absolute reduction) ($P = 0.0029$ for the

difference between doses from baseline to eight hours). At eight hours and one day after rosuvastatin therapy, significant declines occurred in the total number of neutrophils–platelet aggregates per microlitre blood ($P = 0.0021$ and $P = 0.0052$ for eight hours and one day, respectively). The results of the clinical trial indicate that targeting pathways that link inflammation and thrombosis may be a beneficial strategy in patients with ACS. Although the sample size was too small to identify an effect on clinical outcomes, when considered with previously published work that demonstrated a reduction in ischemic and clinical events with early high dose statins that associated with reduced biomarkers of cardiac necrosis, these findings suggest that reducing monocyte–platelet and neutrophil–platelet interactions may contribute to the acute benefit that has been observed. If this is true, high-dose statin therapy should be administered rapidly, in patients presenting with ACS to maximize effects independent of LDL-cholesterol lowering.²

Effects of Rosuvastatin on Mean Platelet Volume (MPV) in Patients with Diabetes Mellitus: Clinical Study

Statins affect inflammation, plaque stabilization, endothelial function, and hemostasis. The study was conducted where the patients who were to be prescribed high-intensity rosuvastatin were enrolled according to their medical records. For 6 months, Baseline and biochemical tests, automated blood count, cell-volume analysis, and their cardiovascular risk factors were recorded. It was observed that Rosuvastatin significantly decreased the MPV as well as the cholesterol levels. The antiplatelet activation properties of high-dose rosuvastatin treatment in patients with Diabetes Mellitus who are not lipid dependent was concluded. Rosuvastatin treatment significantly decreased serum TC, TG, and LDL-C levels as well as MPV (from 8.6 [6.8-11.9] to 8.1 [6.8-12.7] fL) but did not change the platelet count. There was no correlation between LDL-C and the MPV before ($r = -.66$; $P = .383$) and after rosuvastatin treatment ($r = -.112$; $P = .135$). No correlation was found between DLDL-C and DMPV ($r = -0.155$; $P = .073$). No differences were found in terms of BMI, glucose, glycosylated haemoglobin, urea and creatinine, TC, TG, HDL-C, LDL-C, the percentages of those treated with renin-angiotensin system blockers, calcium channel blockers, beta-blockers, nitrates, aspirin, clopidogrel, oral antidiabetics, or insulin before and after rosuvastatin treatment. There was no correlation between the changes in MPV and plasma lipids after 40 mg/d of rosuvastatin for 6 months. These findings suggest that high-dose rosuvastatin treatment possesses significant antiplatelet activation as well as antilipidemic effects in diabetic patients. This study also had some limitations. First, it was a nonrandomized retrospective observational study. Second, the majority of the patients were on aspirin or clopidogrel. These drugs affect the MPV, but all of the study patients received all of their baseline medications during the 6-month study period, hence the changes in MPV to high-intensity rosuvastatin treatment. Third, there may be seasonal changes in MPV levels. But there was no



investigation of seasonal changes in the study. Finally, MPV was used as a single index of platelet function. If multiple markers for platelet function had been used, the results may have been more valid. In conclusion, high-dose rosuvastatin therapy decreases the MPV (an indicator of platelet activation), irrespective of the lipid-lowering effects.³

Effects of Rosuvastatin in Metabolism and Proteomics of large and small dense LDL in combined Hyperlipidemia

Small dense LDL (sdLDL) has been reported to be more atherogenic than large buoyant LDL (IbLDL). The metabolism and protein composition of sdLDL and IbLDL in six subjects with combined hyperlipidemia on placebo and rosuvastatin 40 mg/day was observed. Proteomic analysis indicated that rosuvastatin decreased apoC-III and apoM content within the density range of IbLDL ($P < 0.05$). Through this study, it was concluded that sdLDL is more atherogenic than IbLDL because of its longer plasma residence time, potentially resulting in more particle oxidation, modification, and reduction in size, with increased arterial wall uptake. Rosuvastatin enhances the catabolism of apoB-100 in both IbLDL and sdLDL. Inhibition of HMG-CoA reductase with rosuvastatin 40 mg/day markedly lowered nonfasting plasma concentrations of TC (-37%, $P < 0.0001$), TGs (-32%, $P = 0.06$), LDL cholesterol (-52%, $P < 0.001$), and total apoB (-42%, $P < 0.0001$), as compared with placebo. Rosuvastatin also significantly ($P < 0.01$) reduced the concentrations of apoB and cholesterol within IbLDLs (apoB, -39%; cholesterol, -48%) and sdLDLs (apoB, -42%; cholesterol, -54%). Relative to placebo, rosuvastatin decreased the cholesterol content per particle from 940 ± 128 mol to 719 ± 66 mol (-19%, $P = 0.06$) in sdLDLs and from $5,536 \pm 518$ mol to $4,552 \pm 405$ mol (-14%, $P = 0.18$) in IbLDLs. However, the cholesterol:apoB molar ratio in sdLDLs, relative to IbLDLs, did not change significantly ($P = 0.55$). The concentration of sdLDL cholesterol was, on average, approximately 32% of total LDL cholesterol during both phases. Proteomic analysis of the IbLDL and sdLDL subfractions indicated the presence of the following apolipoproteins, in addition to apoB, in the density range of both subfractions: apoA-I, apoA-II, apoA-IV, apoC-I, apoC-II, apoC-III, apoCIV, apoD, apoE, apoF, and apoM. The importance of the findings is potentially limited by the small number of study subjects and relatively short duration of each kinetic study, the dyslipidemic phenotype of the subjects, and the feeding protocol used in the study, the data does indicate that a significant percentage of TRL apoB-100 (25% in this study) is catabolized directly; that the remaining TRL apoB-100 is converted directly and equally to both IbLDLs and sdLDLs, and that all IbLDL apoB-100 is converted to sdLDL apoB-100. These findings explain the elevated sdLDL concentrations observed in hypertriglyceridemic subjects, potentially due to the increased direct conversion of TRL apoB-100 to sdLDL apoB-100.⁴

Neuropathic Pain due to Statin: A Case Report

The most reported form of statin-induced pain is myalgia, sometimes peripheral neuropathy which is a rare side effect. In this case, it was reported that a patient who received rosuvastatin for hypercholesterolemia had experienced episodes of pain in both hands during the night. Rosuvastatin was stopped and atorvastatin was replaced. Re-introduction with another statin resulted in a more severe form of the similar adverse effect after four months. This is a rare adverse effect of an extensively prescribed class of drug. Physicians should be aware of the possibility of peripheral neuropathy symptoms in patients on statin therapy. The study described a 49-year-old female who developed neurotoxicity after the administration of hypolipidemic drugs; rosuvastatin and atorvastatin. The patient presented with neuropathic pain symptoms. The mechanism due to which statins lead to neuropathy is not fully known. The most stated hypothesis is that statins by inhibiting HMG-CoA reductase reduce the production of intermediates of farnesyl pyrophosphates, predominantly ubiquinones. When there is insufficient ubiquinone in our body it can affect neurons' energy consumption. Although neuropathy following the use of statins has been postulated in the literature, physicians may not consider this as a drug side effect due to its rare occurrence. Peripheral neuropathy should be suspected in patients taking statins and complain of severe pain with an abnormal sensation like stabbings pain, pins and needles, burning or cold or electric shocks sensation, numbness, and itching.⁵

Flexible lipid-based nanoparticles: Rosuvastatin nanocarrier system for improving Cytotoxicity

Rosuvastatin (RSV) is a poorly water-soluble drug that has an oral bioavailability of only 20%. This work aimed to prepare positively charged chitosan-coated flexible lipid-based vesicles (chitosomes) and compare their characteristics to the corresponding negatively charged flexible liposomal nanoparticles (NPs) to develop new rosuvastatin nanocarrier systems. Three formulation factors affecting the development of chitosomes nano-formulation were optimized for their effects on particle size, entrapment efficiency (EE), and zeta potential. The optimized flexible chitosomes and their corresponding liposomal nanoparticles were characterized for morphology, in vitro release, flexibility, and intestinal cell viability. The half-maximum inhibitory concentrations (IC₅₀) for both formulations were calculated. Based on the results it was observed that rosuvastatin loaded chitosomes nano-formulation could be considered as a promising nanocarrier system with a marked cytotoxic activity while rosuvastatin loaded liposomal nanoparticles are suitable nanocarrier to improve rosuvastatin activity in the treatment of cardiovascular disorders. The drug to lipid molar ratio, edge activator percent, and the chitosan concentration were significantly affecting the characteristics of nanoparticles. The optimized chitosomes nano-formulation exhibited a larger size, higher EE, and



greater zeta potential value when compared to the corresponding liposomal nanoparticles. Both formulations showed a spherical shape nanostructure with a marked outer shell for the chitosomes nano-formulation and exhibited anticancer activity in a time- and dose-dependent manner. Chitosomes nano-formulation is a promising nanocarrier for Rosuvastatin cytotoxicity while liposomal nanoparticles are an appropriate carrier to enhance rosuvastatin bioavailability in the treatment of hyperlipidemia⁶

Role of Rosuvastatin in Transduction of Natural Killer Cells

Adoptive natural killer (NK) cell therapy is attaining promising clinical outcomes in recent years, but improvements are needed. Genetic modification of NK cells with a tumor antigen-specific receptor on their surface coupled to intracellular signaling domains may lead to enhanced cytotoxicity against malignant cells. One of the most common approaches is lentivirus-mediated transduction. It was found that the transduction efficiency of VSV-G pseudotyped lentivirus is augmented by statins that induced higher LDLR expression. In both NK-92 cells and primary NK cells, the transduction efficiency increased after treatment with statins. Furthermore, statins have been reported to suppress NK cell cytotoxicity; however, the study showed that this can be completely reversed by adding geranylgeranyl-pyrophosphate (GGPP). Among the statins tested, it was found that the combination of rosuvastatin with GGPP most potently improved viral transduction without affecting the cytotoxic properties of the NK cells. In this study, the CD107a degranulation, granzyme B, FasL expression, and IFN- γ secretion after co-culture of NK cells with statins was investigated. It was observed that CD107a degranulation and FasL levels were reduced upon statin treatment. Interestingly, IFN- γ secretion was not altered. This could be due to cytokines and cell-cell contact with neighboring cells, which has been reported in earlier studies. These results could imply that the statin-induced inhibition of NK killing capacity might be due to changes in the degranulation process. Statins decreased NK cell cytotoxicity. However, this effect could be reversed completely by GGPP. GGPP is synthesized by HMG-CoA reductase and is independent of cholesterol metabolism. GGPP or mevalonate reversed the inhibitory effects of statins on HMG-CoA reductase. It was observed that GGPP or mevalonate was able to alter the cell cycle and DNA synthesis of NK cells, thus abrogating the negative effects of statins on NK cell proliferation. For future therapeutic applications, rosuvastatin plus GGPP currently is the most potent combination that increases VSV-G lentivirus transduction efficiency without a reduction of NK cell cytotoxicity. This finding is important for both scientists and clinicians, as it facilitates the transduction of NK cells that are known to be hard to transduce, but it holds important promise for cancer adoptive cell therapy.⁷

Effectiveness of Therapy with Rosuvastatin and Fenofibric Acid in Patients with mixed dyslipidemia

Ischemic heart disease is the leading cause of death in the world and is associated with dyslipidemia, high blood pressure, diabetes mellitus, and other factors. The study was conducted to determine the clinical effectiveness of the lipid profile of the rosuvastatin and fenofibric acid combination in Colombian patients with high cardiovascular risk and mixed dyslipidemia. It was a Longitudinal observational study in a random sample of patients with a diagnosis of mixed dyslipidemia and moderate, high, or very high cardiovascular risk who were treated with rosuvastatin and fenofibric acid. Anthropometric, clinical, laboratory, comorbidity, and pharmacological variables were identified and effectiveness on the lipid profile was determined. A total of 386 patients who started therapy with the combination of rosuvastatin and fenofibric acid during the observation period were analyzed. They had an average age of 60.8 \pm 11.4 years and 53.1% were women (n=205). The evaluation of the lipid profile at the beginning of the follow-up found a mean LDL-C of 138.4 \pm 67.1mg/dL (range: 20-477mg/dL) and triglycerides of 679.7 \pm 573.6 mg/dL (range: 124-5192mg/dL). At the end of follow-up, the values were reduced to an average LDL-C of 87.5 \pm 41.2mg/dL (range: 15-313mg/dL, reduction of 43.3%) and triglycerides of 243.5 \pm 170.5mg/dL (range: 47-1474mg/dL, reduction of 64.2%). The mean difference between the initial and final lipid profile values was statistically significant. The study has shown showed significant results in terms of the decrease in LDL-C and triglycerides, without reports of serious adverse events during the follow-up. This study has some limitations, such as the fact that it was a follow-up study in a single cohort without a comparison group, as well as that only a population of patients covered by insurance companies of the contributory regime were included. Therefore, the conclusions will be useful only for similar populations. The fixed-dose combination of rosuvastatin and fenofibric acid is an effective and safe option to lower lipid levels in patients with mixed dyslipidemia and high cardiovascular risk. Also, based on these results, there is a need to study this combination's cost-effectiveness, safety, and effectiveness in the long term especially in regards to cardiovascular outcomes.⁸

Role of Statins in Prevention of Proliferative Vitreoretinopathy: Clinical Pharmacokinetic Study

Proliferative vitreoretinopathy (PVR) with rhegmatogenous retinal detachment (RRD) is a complex inflammatory ocular disease. In this study, the efficacy of the drugs was tested in controlling postsurgical Proliferative vitreoretinopathy formation. Simvastatin (SIM), atorvastatin (ATV), or rosuvastatin (RSV) were added to cultures of human retinal pigment epithelial cells (ARPE-19) before exposure with the bacterial lipopolysaccharide (LPS), and the production of pro-inflammatory cytokines (IL-6, IL-8, MCP-1) was examined using an enzyme-linked immunosorbent assay.



Pharmacokinetic simulations of the intravitreal delivery of statins indicate that the measured clinical statin concentrations could be maintained with existing drug delivery technologies for months. The results suggest that intravitreal statin therapy can have the potential in alleviating the risk of post-surgical Proliferative vitreoretinopathy. ARPE-19 (Human retinal pigment epithelial cells) were exposed to three different statins at seven different concentrations ranging from 0.5 μM to 20 μM for 24 h. In the MTT (3-(4, 5-Dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) assay, rosuvastatin was well-tolerated Cell viability remained at 88% when compared to the DMSO control. The anti-inflammatory properties of rosuvastatin were tested in both DMSO and water. All these results support the concept of modulation of intraocular inflammation with statins especially rosuvastatin has clinical potential in reducing PVR development; for example, statins could be injected during surgery into the vitreous in a specialized drug delivery system.⁹

Anti- Atherosclerotic Effect of Rosuvastatin: Review

Atherosclerosis is a chronic vascular disease posing a great threat to public health. It was investigated whether rosuvastatin (RVS) could enhance autophagic activities to inhibit lipid accumulation and polarization conversion of macrophages and then attenuate atherosclerotic lesions. The potential mechanisms by which Rosuvastatin mediated atherosclerosis were explored by western blot, real-time PCR assay, and immunofluorescence staining in mice and RAW264.7 macrophages. The study showed that Rosuvastatin exhibits atheroprotective effects involving regulation lipid accumulation and polarization conversion by improving autophagy initiation and development via suppressing PI3K/Akt/mTOR axis and enhancing autophagic flux in macrophages. The data showed that Rosuvastatin treatment reduced plaque areas in the aorta inner surface and the aortic sinus of ApoE^{-/-} mice with a high-fat diet. Rosuvastatin improved lipid profiles and reduced the contents of inflammatory cytokines in the circulation. Then, results of Western blot showed that Rosuvastatin increased the ratio LC3II/I and level of Beclin 1 and decreased the expression of p62 in aortic tissues. Similarly, it was observed that Rosuvastatin decreased lipids contents and inflammatory factor expressions. These anti-atherosclerotic effects of Rosuvastatin were abolished by 3-methyladenine intervention. Moreover, Rosuvastatin could reverse the impaired autophagy flux in macrophages insulted by chloroquine. This study has indicated that Rosuvastatin intervention has inhibited atherosclerotic plaque development in ApoE^{-/-} mice induced by a high-fat diet. The results provided the evidence that Rosuvastatin was able to enhance autophagy activities via prohibiting activation of PI3K/Akt/mTOR pathway and increasing autophagic flux, thus leading to the anti-atherosclerotic effects involving suppression of lipid droplets accumulation and facilitation of anti-inflammatory M2 phenotype polarization, which thereby

provided new leads into the molecular mechanisms of Rosuvastatin against atherosclerosis development.¹⁰

Fenofibrate¹¹⁻²⁰

Fenofibrate- An overview of the pharmacological aspect

This study dated back to 1987 gives an overview of the human pharmacology of fenofibrate. The author has divided this paper into the pharmacokinetics of the drug, transport and turnover in plasma, excretion, tissue distribution and interaction with other hypolipidemic drugs. The unique chemical structure of the fenofibrate makes it insoluble in an aqueous solution with increased internal molecular mobility. The fenofibrate drug, when administered orally with the meal gets absorbed in the GI tract rapidly and in more quantity (90%) than without meal(50%). The primary metabolite of fenofibrate, fenofibric acid is formed due to the action of tissue and plasma esterases. The author compares plasma transport of the drug in healthy patients versus patients with renal dysfunction. In that, he talks about Plasma fenofibric acid concentrations versus time after administration. This was done by a gas chromatographic method and was found that "Administration of fenofibrate (300 mg per day) daily over 10 days to 10 healthy volunteers resulted in the establishment of an equilibrium state within two to three days, with a plasma level of 10 $\mu\text{g/ml}$ and an elimination half-life of 21.7 hours." In case of patients with renal inefficiency author notes that "significant accumulation of fenofibric acid occurs in renal insufficiency; this effect is more marked when repeated daily doses of fenofibrate are administered to such patients, and elimination half-lives may be as long as 10 to 15 days." The excretion of fenofibrate drug was investigated by measuring the radioactivity of 300 mg of ¹⁴C-labeled fenofibrate. It was established that urine secretes 60-80% of it and the entire drug is excreted in about 6 days. In experiments consisting of rats, it was found that the group of tissues with concentrations of [¹⁴C] superior to those of plasma include liver, kidney, and gut than lung, heart, and adrenals and then a third group (testis, spleen, skin, and epididymal fat) displayed still lower concentrations. Brain and eyes showed no concentration of the drug. When the pharmacokinetics of fenofibrate was investigated in the absence and in the presence of colestipol therapy in humans, it is found to be unmodified. Therefore, the author concludes that no interaction between these two hypolipidemic drugs occurs. The overall pharmacology of the experimental drug is thoroughly investigated through several studies performed.¹¹

An evaluation of several studies comparing the toxicity and reliability of fenofibrate along with other fibric acid derivatives.

This review analyses studies across Europe and the USA, both clinical and experimental categories. The author then compares the results and draws inferences about the toxicity and safety of the drug fenofibrate. The prolonged hepatomegaly and perturbed peroxisomal enzymatic



activity at high dose levels result in hepatocellular carcinomas with all fibrates. Long term studies have shown that fenofibrate alone appears to be effective in reducing the elevated total cholesterol and low-density lipoprotein-cholesterol levels of patients with normal triglycerides levels, it has been used in combination with the resins cholestyramine, colestipol and with nicotinic acid with remarkable effect. In shorter-term studies, six to 12 months, fenofibrate increased high density lipoprotein-cholesterol levels about 10 percent, whereas cholestyramine had less effect. The five studies that were analysed indicated lithogenicity of bile has increased significantly. The author discusses the data from individual European trials, which show that 'total plasma cholesterol levels were reduced by approximately 20-25%. The mean total cholesterol reduction after one month of treatment was 24% (for 345 patients, more than 261 mg/dl).' There was no significant difference found between fenofibrate and placebo treatments in all except the dermatologic category. The clinical side effects seen were skin problems such as rash, hives, and urticarial, fatigue and decreased libido. There has been no evidence of a significant rise in the incidence of cholelithiasis in the clinical trials completed to the date of the study. Mean serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels change little during long-term use of fenofibrate, there is evidence that approximately 9% of patients will have a transaminase value above the normal laboratory mean. As noted 'The Lipid Research Clinics/Coronary Primary Prevention Trial cholestyramine study published in 1984 proved that lowering low-density lipoprotein-cholesterol levels in asymptomatic men can diminish the incidence of coronary heart disease morbidity and mortality. Thus, the author promotes the use of fenofibrate over other fibric acid derivative drugs.¹²

Metabolic and Pleiotropic effects of widely used fibric acid derivative - fenofibrate.

The widely used fenofibrate is hydrolyzed by tissue and plasma esterases to the active metabolite form fenofibric acid. The dissolution of micronised fenofibrate is enhanced by the development of a modified release tablet. The current study claims, 'this new tablet formulation has the potential to replace the micronised fenofibrate capsules. These drugs mainly exert their actions via the activation of specific nuclear receptors called peroxisome proliferator-activated receptors a (PPARa)'. In this review, the author summarizes the evidence suggesting that fenofibrate, exerts several other antiatherogenic actions. Based on published studies, fenofibrate is a useful option for patients with primary or secondary combined dyslipidaemias, refractory dyslipidaemia and the combination of fenofibrate with statins is a therapeutic option. It is found that 'The availability of the micronised fenofibrate form is around 30% greater than that of the unmodified form. Micronised fenofibrate (200 mg once daily) administered to dyslipidaemic patients significantly reduced serum uric acid levels by 27.9% by increasing uric acid excretion.' It is shown in the study that, 'the changes

induced by ciprofibrate, bezafibrate and fenofibrate were significantly greater than those seen after gemfibrozil ($p < 0.0001$, for all comparisons).' There were significant reductions (40%) in progression in minimum lumen diameter and progression in percentage diameter stenosis. Associations were observed between means in treatment concentrations of total cholesterol, LDL-C, HDLC and triglycerides and angiographic changes but the correlation coefficients were small. This wide angle review study focuses on many important parameters like the effect of fenofibrate on blood pressure, uric acid, plasma, renal function, liver enzymes. These assessments of pleiotropic and metabolic effects of fenofibrate resurface many key findings. Fenofibrate monotherapy not only represents the treatment of choice in patients with primary combined dyslipidaemia but also patients with specific forms of secondary dyslipidaemias like diabetic dyslipidaemia and dyslipidaemias associated with infections such as MetS and HIV. Fenofibrate may diminish the hyperuricaemia of concurrently used medications.¹³

The effect of the use of fenofibrate in conditions like dyslipidemia.

It is well established that fenofibrate is used for the treatment of hypertriglyceridaemia and mixed dyslipidaemia. The activation of 'peroxisome proliferator-activated receptor- α ' mediates the lipid-modifying effects of fenofibrate. Whereas, pleiotropic effects of Fenofibrate, like reducing levels of fibrinogen, C-reactive protein and various pro-inflammatory markers, and improving flow-mediated dilatation may contribute to its clinical efficacy, in improving microvascular outcomes. This paper concludes, 'Compared with statin monotherapy, fenofibrate monotherapy tends to improve TG and HDL-C levels to a significantly greater extent, whereas statins improve low-density lipoprotein-cholesterol (LDL-C) and total cholesterol levels to a significantly greater extent.' Cardiovascular diseases are the third leading cause of death worldwide. Thus, this review paper thoroughly investigates the properties of fenofibrate and the experimental trials that took place like ACCORD and FIELD with Diabetes type 2 patients. Elevated low-density lipoprotein-cholesterol (LDL-C) levels are a major predictor of CVD, and LDL-C continues to be the primary target of cholesterol-lowering therapy, but the aim of cholesterol-lowering treatment varies as per the risk of a CHD event. A subsequent analysis found that the relative reduction in the risk of total CHD events improved from 11% to 16%, and the relative reduction in the risk of total CVD events improved from 11% to 15% with fenofibrate versus placebo. The concentrations of ciclosporin in the blood were significantly reduced in heart transplant patients receiving concomitant fenofibrate, and serum creatinine levels were significantly increased. The incidence of CVD events after a silent MI was significantly lower with fenofibrate than with placebo (8.9% vs 34.5%). Another substudy revealed that in the overall population, the proportion of patients experiencing 2-step progression of retinopathy grade did not significantly differ between



fenofibrate and placebo recipients (9.6% vs 12.3%); however, among patients with pre-existing retinopathy, fenofibrate recipients were significantly less likely than placebo recipients to experience 2-step progression. In the ACCORD Eye trial, patients receiving fenofibrate plus simvastatin were 40% less likely than those receiving placebo plus simvastatin. According to results of randomized, double-blind trials that primarily evaluated lipid profiles, TG levels were consistently reduced from baseline to a significantly greater extent with fenofibrate than with placebo in patients with dyslipidaemia. The article concludes that fenofibrate improves the lipid profile in patients with dyslipidaemia. In the paradigm-shifting studies like FIELD and ACCORD Lipid trials in patients with type 2 diabetes, fenofibrate monotherapy did not reduce the risk of CHD events to a greater extent than placebo, also fenofibrate plus simvastatin failed to reduce the risk of major CV events to a greater extent than simvastatin plus placebo. These studies show that the risk of some nonfatal macrovascular events and certain microvascular outcomes was reduced significantly more with fenofibrate than with placebo. In these trials, patients receiving fenofibrate plus simvastatin were less likely to experience progression of diabetic retinopathy than those receiving simvastatin plus placebo. Thus the author suggests that fenofibrate is of the greatest benefit in decreasing cardiovascular events in patients with atherogenic dyslipidaemia. This drug is well tolerated when administered alone or in combination with a statin. Hence, making fenofibrate a potential treatment drug against the mentioned clinical problems.¹⁴

PPAR α plays a role in the pathogenesis of Non-alcoholic fatty liver disease by regulating lipid and glucose metabolic pathways.

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disorders associated with hepatic lipid accumulation in the absence of viral hepatitis or alcohol abuse, steatosis to non-alcoholic steatohepatitis (NASH). In NASH, not only lipid accumulation but also necroinflammation and fibrosis exist. Final-stage liver disease and hepatocellular carcinoma are liver-specific endpoints of NAFLD. Increased bodyweight considerably increases the risk of this abnormality. Considering the current obesity epidemic, it is expected that NAFLD prevalence will rise. On this background, the current study brings the novel concept that 'the activation of the PPAR α subunit may protect from liver steatosis. Fenofibrate, by activating PPAR α , effectively improves the atherogenic lipid profile associated with type 2 diabetes mellitus and metabolic syndrome.' The evidence from the study suggested fenofibrate related PPAR α activation may enhance the expression of genes promoting hepatic FA β -oxidation and, fenofibrate reduces hepatic insulin resistance. Eventually, fenofibrate can limit hepatic macrophage infiltration. The limitations possessed by this study were a small sample size, use of fenofibrate as a part of the multifactorial approach, absent histological data. The use of fenofibrate resulted in inhibition of the expression of inflammatory

mediators involved in non-alcoholic steatohepatitis pathogenesis. Among patients with abnormal liver function tests those who received a statin experienced a greater reduction of CV events compared with those who did not receive a statin. Moreover, among statin-treated patients, those with abnormal liver function tests had fewer CV events compared with those with normal liver function. NAFLD is a common health problem associated with increased liver-specific morbidity and mortality. Impaired fibric acid turnover, often associated with insulin resistance, is its pathophysiological hallmark of this syndrome. It is well established that in the presence of inflammation hepatic steatosis can progress to NASH and concomitantly to cirrhosis. The novel concept reported in this article is that PPAR α activation acts as protective and therapeutic against NAFLD. The given experimental data suggested such a role of fenofibrate in the setting of high fat diet, obesity, insulin resistance and T2DM. Genes promoting FA β -oxidation result in anti-inflammatory with anti-oxidant actions, which prevent NASH-related necroinflammation, apoptosis and fibrosis. As mentioned, 'These are attributed to inhibited expression of inflammatory mediators, including TNF- α , MCP-1, VCAM-1 and ICAM-1, together with reduced lipid peroxidation and reactive oxygen species formation.' All these effects are PPAR α -dependent and the advantage of it is, fenofibrate increases the expression and plasma levels of adiponectin while preserving its liver-active receptor. The report claims, this adipokine enhances FA hepatic β -oxidation and exerts various anti-inflammatory and anti-fibrotic effects on the liver. The current study having many limitations but shades light on the possible metabolic pathway and promotes a basis for large prospective studies, including proper control groups and full assessment of liver histology.¹⁵

The fenofibrate may influence multiple pathways, including several key pathways involved in the pathogenesis of diabetic retinopathy.

Diabetes is one of the prevailed health challenges in the world; as a result, the prevalence of one of its major complications, diabetic retinopathy (DR), is expected to escalate. The evidence from two major trials, the Fenofibrate Intervention and Event Lowering in Diabetes study and the Action to Control Cardiovascular Risk in Diabetes Eye study, the sample of 11,388 people with type-2 diabetes concludes that fenofibrate reduces the risk of development and progression of DR. While there are well-established modalities that target the more severe vision-threatening stages of DR, including laser photocoagulation and newer therapies that inhibit vascular endothelial growth factor (VEGF), such options are resource-intensive, costly, and invasive. Thus this study reviews the several putative therapeutic mechanisms for fenofibrate, both dependent and independent of lipids, but concludes that a deeper understanding of the mode of action of fenofibrate will further help to define the usage of fenofibrate clinically as an adjunct to the management of DR. In the Renin-Angiotensin System Study (RASS), treatment with either



enalapril or losartan reduced DR progression by 65% and 70% respectively. DR progression, defined by 2-steps of the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, the primary endpoint of the sub-study, was significantly reduced with fenofibrate versus placebo in patients with prior DR, but not in the patients who were not suffering from DR. Fenofibrate treatment was associated with a 40% decrease in DR progression over 4 years. Data from the FIELD and ACCORD-Eye studies provide a relative reduction of DR progression of 30-40% over 4-5 years. Consistent findings were reported by the ACCORD-Eye trial. DR remains the most common cause of visual impairment in working age individuals globally. The current thinking is that fenofibrate may influence multiple pathways, including several key pathways involved in the pathogenesis of DR. Potential mechanisms of interest include both lipid dependent and independent effects and involve systemic and ocular pathways such as antioxidants, anti-inflammatory, anti-apoptotic, antiangiogenic and neuroprotective actions. Because DR is recognized as a multifactorial and multi-pathway complication, this broad therapeutic action of fenofibrate may be especially advantageous in early-stage disease. A clearer understanding of the mechanistic basis of DR, addressing pathophysiological areas, is needed. This includes further research efforts to develop an appropriate animal model for studying the underlying mechanisms involved in the pathogenesis of DR. Further studies aimed at unraveling the mode of action of fenofibrate will be useful in the design of clinical strategies for its use in preventing or arresting DR.¹⁶

Fenofibrate increased serum Cr levels in patients with chronic diseases such as diabetes, hypertension, and chronic renal failure.

Diabetes and obesity are closely related to hypertriglyceridemia, high low-density lipoprotein (LDL) cholesterol, and low high-density lipoprotein (HDL) cholesterol. Recent research shows that high serum triglyceride (TG) levels are a significant risk factor for arteriosclerosis. The current study aimed to assess the effects of fibrates on renal function in relatively healthy adult subjects with no cardiovascular diseases. The retrospective approach of this study included 558 outpatients. Some were given 160 mg fenofibrate (fenofibrate group) and the other, 10 mg atorvastatin (control group). Serum creatinine levels and estimated glomerular filtration rates prior to and after treatment were compared between these two groups. The experimental drug treated group resulted in increased serum creatinine levels and reduced estimated glomerular filtration rates in a primary care setting. When the two groups are compared, the fenofibrate group showed greater changes in serum creatinine levels than in the control. Furthermore, 55.1% of patients in the fenofibrate group, but only 6.1% of those in the control group, exhibited a serum creatinine level increase of 0.1 mg/dL. The fenofibrate group showed significantly greater declines in the estimated glomerular filtration rate than

the control group. There were significant differences in gender, BMI, smoking status, alcohol intake, and eGFR between CG and FG patients. The present study investigated the effects of months of fenofibrate treatment in patients with hypertriglyceridemia who did not have a history of cardiovascular disease. Broeders et al study defined nephrotoxicity as a serum Cr level increase of 0.2 mg/dL. These results showed that the mean serum Cr level increased by 40%. The results of the present study imply that an increase of serum Cr levels was reported in subjects with normal renal function, but that the elevations were less marked than in previous studies. This was a retrospective study, which used PSM to identify groups that were adjusted for age, chronic diseases, and lifestyle, to reduce the limitations, however, one limitation of the present study is that it would be challenging to generalize the results because the subjects were outpatients at the family medicine department of the only one hospital in Gunposi. Considering patient compliance, a fenofibrate treatment effect was defined as a serum TG reduction >90 mg/dL. In hyperlipidemia management, lifestyle modifications such as diet and exercise are as important as medication. Finally, the present study could not determine whether a normal renal function was restored after fenofibrate administration had stopped.¹⁷

Fenofibrate properties exert anticancer effects via a variety of pathways involved in apoptosis, cell-cycle arrest, invasion, and migration.

The new-age disease, cancer has increased the fatality rate over the period because of the lack of options for treatment drugs. However, recent research promoted that fenofibrate inhibits the proliferation of cell lines derived from breast and oral tumors, melanoma, lung carcinoma, glioblastoma, and fibrosarcoma in mouse models. Hence this review paper aims to focus on recent developments in the anticancer actions of fenofibrate. The author has mentioned some studies in this review that have further confirmed the possibility and efficacy of fenofibrate anticancer in xenograft mouse models. In the last part of this review, the author also discusses the potential mechanisms of action of fenofibrate based on the available information. Overall, the author repurposes fenofibrate as an anticancer drug in cancer treatment. After investigating several papers, the author has noted the following results- 1) Fenofibrate induced apoptosis along with NF- κ B pathway activation and induced cell cycle arrest independent at G0/G1 phase by up-regulating p21, p27/Kip and down-regulating Cyclin D1 and Cdk4. 2) Fenofibrate inhibited the semaphorin 6B protein expression that can prompt tumor invasion and metastasis. (PPAR- α dependent). 3) Fenofibrate induced necrotic cell death by increasing ROS and intracellular calcium, decreasing GSH level, and impairing mitochondrial function. 4) Fenofibrate induced G1 arrest and G2/M arrest through up-regulating CTMP-mediated AKT phosphorylation inhibition (PPAR- α independent). The in vivo experimental results discussed confirm that fenofibrate exerts positive effects against various tumor



types, only its application in high doses (200 mg/kg or 0.3%) inhibited the tumor growth. Thus author regards fenofibrate as an adjuvant drug in cancer treatment, which can be used in combination with chemotherapy or targeted molecular drugs in future research.¹⁸

Chronic fenofibrate administration normalizes endothelial function by balancing endothelial-dependent relaxation and constriction in diabetic mice.

The characteristics of vascular endothelial dysfunction are reduced activity of endothelial nitric oxide synthase, decreased generation of nitric oxide (NO) and increased generation of reactive oxygen species (ROS). The imbalance between endothelial-dependent vascular relaxation and constriction triggers pathologies associated with vascular disease. The experiment had four groups: vehicle-treated control group, fenofibrate-treated control group, vehicle-treated diabetic group and fenofibrate-treated diabetic group. The hypothesis which was tested was that 'fenofibrate improves vascular endothelial dysfunction by balancing endothelium-dependent relaxation and contractility of the aorta in diabetes mellitus (DM)'. This experiment showed the following results, "In streptozotocin-induced diabetic mice, improved endothelium-dependent relaxation in the macro and microvessels, increased nitric oxide (NO) levels, reduced renal damage markers and effects of the vasoconstrictor prostaglandin were seen. Thus authors concluded that 'fenofibrate treatment in diabetic mice normalizes endothelial function by balancing vascular reactivity via increasing NO production and suppressing the vasoconstrictor prostaglandin, suggesting a mechanism of action of fenofibrate in mediating diabetic vascular complications.' In diabetic mice, fenofibrate administration ameliorates renal dysfunction and reduces blood lipids. The study showed that fenofibrate treatment reduced renal damage markers and plasma triglyceride levels, while there was no significant change in blood glucose and body weight between vehicle and fenofibrate-treated diabetic mice (DM). The aorta vasodilation by fenofibrate treatment was reversed by a peroxisome proliferator-activated receptors α (PPAR α) and by an AMPK α inhibitor. Western blot results showed that fenofibrate treatment elevated PPAR α expression. The present study was designed to assess the effects of fenofibrate on endothelial function in diabetes and explores possible signaling mechanisms involved. The vascular relaxation effect of fenofibrate most likely is through modulation of the PPAR/LKB1/AMPK/ eNOS pathway to increase production of NO and suppress oxidative stress. The vascular contractility effect of fenofibrate is believed to be via inhibition of the NF κ B/COX-2 pathway to reduce vasoconstrictor prostaglandin. These findings give further insights into the mechanisms underlying the vascular protective effect of fenofibrate in diabetic endothelial function, suggesting a potential advantage of intervention with fenofibrate as a therapeutic approach to diabetes-related vascular complications.¹⁹

The number of nanotechnology-based techniques and literature reports demonstrate tremendous progress in the process of improved solubility, dissolution, bioavailability, and control delivery of Fenofibrate.

Fenofibrate is a slow water-soluble lipid-regulating drug, which is used to control triglyceride and cholesterol levels in blood plasma. This poor aqueous solubility of the fenofibrate declines its therapeutic effectiveness. New nanotechnology research approaches have been developed to enhance the water solubility, dissolution, bioavailability, and control release of the drug. However, lesser of these innovative formulations have reached the stage of clinical trials and fewer have commercialized. In this current systematic review of the techniques, the author has included milling, antisolvent precipitation, sonication, supercritical fluid techniques, electrospray, self-emulsifying drug delivery, lipid-based nanoparticle, and silica nanostructure-based formulation are evaluated for the enhancement of bioavailability of Fenofibrate. This paper has reviewed the progress in fenofibrate nanoformulations, commercial products, and future challenges. SDP release more than 80 % of the drug in 60 min, SMEDDS showed drug release as 25 % FF nanoparticles processed through bead milling showed dissolution kinetics similar to commercial product Lipidil. 61 % of oral bioavailability in beagle dogs was observed for FF nanoparticles with size 400 nm formulated through milling technique DBD and DTD methods are feasible for high solid loading but semi continuous techniques. From the literature reports it is concluded that most of the techniques successfully achieved nanoparticles of FF with size less than 500 nm. These techniques can also be used for other APIs as well as cancer drugs, which are deemed failures because of lack of solubility. In top-down processes, milling is widely employed for particle size reduction of FF. A freeze-drying method based on FF amorphous solid dispersion nanoparticles with size 300 nm and stability for 6 months showed an ability to control the fatty liver and serum lipid levels in hyperlipidemic rabbits. Fewer formulations have shown improved bioavailability compared to existing products. Reduction of particle size enhanced solubility in water due to enhance surface to volume ratio. Further studies need to conduct to perform nanocrystallization in a continuous flow through different channels of the microfluidic chip and continuous nanocrystallization inside the microfluidic channel by generating the stable droplet.²⁰

Rosuvastatin and Fenofibrate^{18,19,21-29}

Effect of Rosuvastatin and Fenofibrate Monotherapy and Combination Therapy in Type 2 Diabetes Patients with Combined Hyperlipidemia

In this study, Effects of rosuvastatin and fenofibrate alone and in combination in type 2 diabetes associated with combined hyperlipidaemia were determined in this study. Triglyceride reduction in the rosuvastatin 10 mg/fenofibrate group (47.1%) was considerably greater



than in the placebo/rosuvastatin group ($P = 0.001$), with no significant differences in other lipid measures found between these two groups. All treatments were well tolerated. Results showed that rosuvastatin produce significant reductions in triglycerides and LDL cholesterol when used alone or in combination with fenofibrate in type 2 diabetes patients with elevated cholesterol and triglyceride levels and may be used as a good treatment option in the diabetic population. In this study, Results in fixed-dose phase showed Percentage changes in lipid measures over 6 weeks with rosuvastatin 5 and 10mg, compared with the combined placebo group. Triglyceride levels were lowered by 24.5% with rosuvastatin 5 mg and 29.5% with rosuvastatin 10 mg (both $P < 0.001$ versus placebo). LDL cholesterol was reduced by more than 40% and HDL cholesterol was increased by approximately 10% in both rosuvastatin groups ($P < 0.001$). Both rosuvastatin doses were associated with significant reductions in total cholesterol, apoB, VLDL cholesterol and all lipoprotein ratios (all $P < 0.001$). Rosuvastatin 10 mg was also associated with a significant increase in apoAI ($P = 0.011$). At week 6, 77.4% of patients receiving rosuvastatin 10 mg reached the American Diabetes Association LDL-C goal of < 100 mg/dl, compared with 8.3% of patients in the combined placebo group. This Case study suggested that large extra reductions in triglycerides can be achieved with the combination of a low dose of rosuvastatin and dose-titrated fenofibrate, compared with dose-titrated fenofibrate alone. The combination of rosuvastatin and fenofibrate was well tolerated and associated with no particular safety concerns in this small, short-term study. Therefore, combination of rosuvastatin and fenofibrate in comparison to rosuvastatin and fenofibrate monotherapy may be considered as a good drug of choice in diabetic patients with significant elevated triglyceride levels or hyperlipidemia.²¹

Effect of Rosuvastatin & Fenofibrate on Lipoprotein-Associated Phospholipase A2.

Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) can be used to determine risk of atherosclerotic diseases. In this article effect of hypolipidemic drugs (Rosuvastatin & Fenofibrate) that worked on different mechanisms on plasma & Lp-PLA2 activity and mass was explored. Lp-PLA2 is mainly associated with apoB-containing lipoproteins, mainly atherogenic low density lipoproteins (LDL) and small portion of high density lipoprotein (HDL). Fenofibrate and Rosuvastatin both reduces plasma Lp-PLA2 activity and mass which was associated mainly with apoB containing LDL (LDL5) . Fenofibrate also increased activity of HDL associated Lp-PLA2 which is found to be helpful in reducing risk of Cardiovascular diseases (CVDs). Effect of Hypolipidemic Therapy on Serum Lipid Profile and on Lipoprotein Subclasses showed that Rosuvastatin remarkably decreased serum triglycerides, total cholesterol, LDL-cholesterol, non-HDL-cholesterol, and apoB levels and Fenofibrate remarkably decreased serum levels of triglycerides, total cholesterol, LDL-cholesterol, non-HDL-cholesterol, and apoB and reduced the mass of

all apoB-containing lipoprotein subclasses However, not affected sdLDL proportion and mean LDL size. Fenofibrate also induced a significant increase in the serum levels of HDL-cholesterol and apoA-I, mean LDL size and reduced VLDL-cholesterol, sdLDL- cholesterol levels. but it did not affect LDL-cholesterol or buoyant LDL-cholesterol levels. Type IV dyslipidemic patients had I levels of HDL-2 and HDL-3 subclasses at baseline compared with type IIA patients. Both drugs reduce Lp-PLA2 activity and mass associated with the atherogenic apoB-containing lipoproteins. Some clinical studies had shown an independent association between plasma levels of Lp-PLA2 mass or activity and CVD. Fenofibrate reduces Lp-PLA2 activity and mass associated with apoB-containing lipoproteins in type IV dyslipidemia patients and increases the HDL-Lp-PLA2 activity and mass. However the role of the HDL-Lp-PLA2 in humans has not been established yet, data from in vitro experiments as well as in vivo studies in animal models suggest that it may significantly contribute to the antiatherogenic effects of HDL". This increase of HDL-Lp-PLA2 induced by fenofibrate represents an important antiatherogenic effect, that needs further investigation to be proved in humans.²²

Combined Use of Rosuvastatin and Fenofibrate Can Cause Acute Renal Failure

Statins and fibrates are most commonly used lipid-lowering drugs and are considered relatively safe. To treat patients with extremely high cholesterol and triglycerides levels, we need to use combination of lipid-lowering drugs but they can cause adverse side effects. In this study, an unusual case of acute renal failure (ARF) in a patient who had been prescribed both a statin (rosuvastatin) and a fibrate (fenofibrate) is reported. In this case study, patient was taking low dose of rosuvastatin (10mg) & fenofibrate. Even this low dose of statin drug in combination of fenofibrate resulted in severe rhabdomyolysis and was responsible for acute renal failure, suggesting severe synergistic adverse interactions. Statin therapy are associated with myopathic syndromes. Susceptibility to myopathy is substantially increased in statin using patients receiving concurrent therapy with a number of drugs that inhibit CYP3A. Statin drug, rosuvastatin cause least myopathy risk as it is not extensively metabolised by CYP3A. In one large study it was observed that relative to statin monotherapy, the rate of hospitalisation was approximately 10 folds higher when fibrates and statins were combined. Fenofibrate is considered to have very low potential for myopathy and is the preferred drug when some combination with a statin is needed, but in this case study ARF occurred due to combined use of fenofibrate & rosuvastatin. This case study gives a fair idea that even safe drugs in combination may cause unexpected adverse effects. So physician prescribing combination regimen of drugs should closely monitor patients for adverse events.²³



Rosuvastatin as a Suppressor of Growth of Prostate Cancer, Studied in Zebrafish Chemical Genetic Screen for Antiangiogenic Compounds

Cell based assay is commonly used strategy for drug discovery but has limited ability in biologically complex in-vivo systems. This limitation is overcome by the use of Zebrafish as a model organism. Embryonic development of Zebrafish includes the formation of intersegmental vessels from dorsal aorta through angiogenesis. Various methods were followed to identify the small molecules which inhibit Zebrafish angiogenesis. A transgenic line of Zebrafish, Tg(flk1:EGFP), were treated and visually inspected. Seven antiangiogenic compounds were identified having different optimal concentrations. These lead compounds were classified into three groups based on their bioactivities: rotenoids (isorotenone and dihydromunduletone), statins (simvastatin, mevastatin, lovastatin and rosuvastatin) and aristolochic acid. Their inhibitory effect followed a dose-dependent trend. HUVEC proliferation, capillary like tube formation and migration were inhibited by rosuvastatin in dose dependent manner. Using flow cytometry, it was observed that rosuvastatin can induce apoptosis and can cause HUVEC G1 arrest. Rosuvastatin suppresses the growth of PPC-1 in vitro and its xenograft in mice. Immunohistochemical CD31 assay showed the inhibition of tumor angiogenesis by rosuvastatin. Furthermore, TUNEL Assay showed the significant increase in apoptotic index. In this study, seven antiangiogenic compounds have been identified and classified into three groups. Except from simvastatin and lovastatin, there is no published evidence that the other five hits antiangiogenic and antitumor effects. In this study, isorotenone and dihydromuduletone were firstly identified as antiangiogenic compound. Aristolochic acid is a nephrotoxic and can cause Balkan nephropathy and associated urothelial cancer. Statins are a group of HMG-CoA reductase inhibitors which help in Prostate Cancer prevention and treatment. Out of four, Rosuvastatin is the latest and the most potent and it decreases the VEGF levels in patients. This study has given a preclinical evidence that Rosuvastatin is therapeutically potential for the treatment of prostate cancer.²⁴

HPLC Method for Simultaneous Estimation of Rosuvastatin Calcium and Fenofibrate in Combined Tablet Dosage Form

Rosuvastatin Calcium is a HMG-CoA reductase inhibitor. Fenofibrate shows lipid modifying effects in humans, by activation of peroxisome proliferator activated receptor type alpha (PPAR α). Treatment with fenofibric acid plus Rosuvastatin, increased HDL (high density lipoprotein) and decreased triglyceride levels significantly better than statin monotherapy and decreased LDL levels better than fenofibric acid monotherapy. For the simultaneous determination of Rosuvastatin Calcium and Fenofibrate, a simple, fast and precise reverse phase high performance liquid chromatographic method is developed. This method was found to be accurate, precise and rapid for

simultaneous determination of Rosuvastatin Calcium and Fenofibrate. It can be used for routine analysis of this drug combination. The HPLC method used for this analysis was validated based on ICH guidelines with validation parameters like specificity, Linearity, range, accuracy, precision, limit of detection and limit of quantitation. This method by using reverse phase high performance liquid chromatography (HPLC) was found to be simple, precise, accurate and rapid for simultaneous determination of Rosuvastatin Calcium and Fenofibrate from bulk and in pharmaceutical dosage forms. The sample recoveries in all formulations were good and accurate and that suggested non-interference of formulation excipients in the estimation. Spectrophotometric and chromatographic methods have been reported for determination of Rosuvastatin Calcium and Fenofibrate in pharmaceutical dosage forms in combination with other drugs. In previous HPLC methods Rt for Fenofibrate was reported to be 20.5min. But in this work, Fenofibrate Retention time is reduced to 8.5min. Hence, this method can be used for routine analysis of Rosuvastatin Calcium and Fenofibrate in combined dosage forms.²⁵

Comparative Study to Achieve Lipid Goals using Fenofibrate & Rosuvastatin Combination Therapy versus Increased Rosuvastatin Dose in Patients with Diabetes or Atherosclerosis with Metabolic Syndrome

This study aims to test the hypothesis that whether increased rosuvastatin dose is non-inferior to combined administration of fenofibrate and rosuvastatin in patients with diabetes or atherosclerosis with metabolic syndrome. 112 patients were chosen and initially treated with 5mg/day of rosuvastatin for 12 weeks. They were then randomly assigned to two groups A and B, with one receiving 10mg rosuvastatin /day (Group A) and the other receiving 5mg/day supplemented with 80mg/day fenofibrate for a period of 12 weeks again. Lipid profiles [Total Cholesterol (TC), HDL-C and TG], liver and muscle enzymes, and eGFR levels were assessed for each group after the initial run-in period and at the end of 12 weeks of randomized treatment. After the treatment, the lipid profiles of both groups were comparable and both therapies provided almost equal results. After the end of run-in period, serum ALT, AST, CPK, TC and HDL-C levels were similar. The group B had higher Creatinine and TG levels and lower eGFR and LDL-C level. After Randomised open-label treatment period for 12 weeks, TC and LDL-C levels were lower and TG level & eGFR were higher in group A. Following ATP-III treatment guidelines, 39.47% of group A and 36.11% of groups B achieved their TC treatment goal (< 160 mg/dl) (p = 0.70); 41.37% of group A and 38.69% of groups B achieved their LDL-C treatment goal (< 100 mg/dl) (p = 0.79); 57.89% of group A and 50.0% of groups B achieved their HDL-C treatment goal (40 mg/dl) (p = 0.45); 37.26% of group A and 42.31% of groups B achieved their TG treatment goal (< 150 mg/dl) (p = 0.53); 40.86% of group A and 36.45% of groups B achieved their non-HDL-C treatment goal (< 130 mg/dl) (p = 0.58). The result demonstrated that there was no significant



difference on the TC, TG, non HDL-C and HDL-C; and CPK, AST and ALT levels between the 2 groups. Group A with increased statin dose, however showed further decrease in LDL-C from initial levels. Group B with combination therapy had higher creatinine level and lower eGFR. It is believed that fibrate reduces TG levels better than statins, but there was no significant difference for the two groups in our case. It may be due to the potency of statin to reduce TG along with LDL-C; and the possible lowered efficiency of fibrate due to 80mg dose. This study showed, both therapies are safe and feasible. While combination therapy can reduced the cost, the increased dose of rosuvastatin tended to achieve more LDL-C and non HDL-C goal.²⁶

A Repurposing Use of Fenofibrate in Cancer as Anticancer drug

Treatment of cancer is challenging because of its metastatic property. We use various drugs and therapies to treat cancer but their therapeutic efficacy and safety is point of concern as they are not very specific in nature and may have various side effects. Fenofibrate is a hypolipidemic drug. Recently, several studies showed efficacy of fenofibrate in treatment of cancer, as it regulate variety of pathways involved in apoptosis, cell cycle arrest, invasion and migration. These studies showed that fenofibrate has anticancer effects in several human cancer cell lines, such as breast, liver, prostate, pancreas, lungs cancer. We still need further study and investigation to explore the real potential of fenofibrate in treatment of cancer. Fenofibrate stimulates peroxisome proliferator-activated receptor α (PPAR α), this is believed to be the reason of its lipid lowering effect. In recent studies, PPAR α specific agonists were reported to have anticancer effect in a large number of human cancer types such as leukaemia, liver, ovary, breast, skin and lung cancer. In mouse models, fenofibrate inhibited the proliferation of cell lines derived from breast, oral tumours, melanoma, lung carcinoma, glioblastoma & fibrosarcoma. In vitro studies showed that fenofibrate has anticancer properties in PPAR α dependent or independent manner. Fenofibrate was found to inhibit the proliferation of breast cancer MDA-MB-231 cell lines by inducing apoptosis & cell cycle arrest. In liver cancer, fenofibrate induces necrotic cell death by increasing ROS. In vivo studies in animal models like mice model also showed potential anticancer effects of fenofibrate. Fenofibrate showed potential anticancer effects by induction of apoptosis, cell cycle arrest and inhibition of tumour invasion & migration. There are various complex pathways through which fenofibrate showed its anticancer properties, like by acting as PPAR α agonist, by activating AMPK in oral cancer, by inducing ROS accumulation in neuroblastoma, by decreasing AKT activity in prostate cancer, by reducing phosphorylation of ERK in lung cancer. It had bidirectional modulatory effect on NF-kB activity in different cancers, these varying interactions might be due to direct interaction between fenofibrate and NF-kB. Above studies showed that fenofibrate can be used as potential anticancer drug in future. As high dose (200 mg/kg) of fenofibrate is needed to inhibit tumour

growth. So, we can use it as an adjuvant in combination with chemotherapy or targeted molecular drug therapies in future. Further studies are needed to explore full potential of fenofibrate as an anticancer drug.¹⁸

Benefits of Using Rosuvastatin in Blood- Brain Barrier Damage following Experimental Ischemic Stroke

Haemorrhage transformation and it is associated with recombinant tissue plasminogen activator (rt-PA)-induced blood-brain barrier (BBB) damage is considered as Most challenging preventable complication in thrombolytic therapy. The integrity of the BBB was increased by normal and high doses of rosuvastatin as determined from Evans blue staining, ultrastructure assessments and immunochemistry at 24 hrs after reperfusion. The levels of TJ proteins were preserved. Rosuvastatin significantly lowers rt-PA therapy-associated BBB permeability by PDGFR- α - and LRP1-k associated MAPK pathways to reduce the mortality of mice, and a normal dose of rosuvastatin exerted greater preventative effects on reducing BBB damage than high dose of rosuvastatin. In this study CBF is monitored at three time points, i.e., before MCAO, after ischemia and at 24 h after rt-PA reperfusion, using a two-dimensional laser speckle imaging technique. Mice subjected to MCAO (with rosuvastatin) demonstrated similar extents of recovery from ischemia as exhibited by mice in the MR group (MCAO mice treated with rt-PA). Rosuvastatin Decreased BBB Permeability at 24 h Following rt-PA Reperfusion After Brain Ischemia, Upregulated the levels of Tight Junctions (TJs) and Adherence Junctions (AJs) in the Peri-Infarct Region Following rt-PA Reperfusion, it also Reduced MMP Expression and Increased TIMP Expression in Peri-Infarct Regions. Rosuvastatin-Mediated Reduction in the BBB Damage Induced by rt-PA Reperfusion After MCAO was associated with the expression of PDGFR- α and LRP-1 and was also associated With MAPK Pathways. A much higher dose of about 10-fold of rt-PA is used than the dose used in clinical therapy and both induce HT after reperfusion in the ischemic brain. rt-PA linked MMP activation occurred in the ischemic brain tissue and induced BBB permeability. Noticeably, a reduction in permeability will promote a decrease in occurrence of haemorrhage. In this study, we hypothesised that a single statin treatment would decrease BBB permeability by inhibiting MMPs and activating TIMPs through LRP1 and PDGFR- α . These benefits might be linked with the inactivation of pJNK and p38 and the activation of pERK, further inhibiting the expression of MMPs and activating TIMP-1. As, Normal dose of rosuvastatin exerted greater preventative effects on reducing BBB damage than high dose of rosuvastatin, therefore normal dose should be used for better results.²⁷

A Comparative Study on Efficacy and Safety of Fixed Dose Combination Therapy of Rosuvastatin and Choline Fenofibrate Versus Rosuvastatin and Fenofibrate in Patients of Mixed Dyslipidemia in Indian Population

Comparison of safety and efficacy of fixed dose combination (FDC) of rosuvastatin and choline fenofibrate



to FDC of rosuvastatin and fenofibrate among Indian population with mixed dyslipidemia was evaluated by this study. A randomised, open-label, multicentre clinical trial was conducted at 12 centres spread all across India. Mixed dyslipidemia patients aged between 18-70 years were randomly given FDC therapy of rosuvastatin (10mg/day) & choline fenofibrate (135mg/day), named as RCF group and FDC therapy of rosuvastatin (10mg/day) & fenofibrate (160mg/day), named as RF group. They are treated for 180 days. This study showed that FDC of rosuvastatin & choline fenofibrate is more safe and effective as it has certain advantages like better bioavailability & no interaction with food, so patients can take it anytime. Patients from both RCF & RF groups had similar baseline characteristics and are chosen randomly and divided in 1:1 ratio (120 patients in each group) to receive one dose treatment, daily for 180 days. There was remarkable reduction in primary end point, serum triglycerides level noticed in both groups (-37.7% in RCF group & 37.8% in RF group) while in secondary endpoints like HDL-C, LDL-C, VLDL-C & total cholesterol, there was significant reduction in LDL-C, VLDL-C & total cholesterol levels but remarkable rise in HDL-C levels seen in both groups (17.8% in RCF & 14.9% in RF). Difference in all parameters between both groups was not statistically significant. Some mild adverse effects like asthenia, headache, dizziness and very few serious adverse events were also reported in this study. Fenofibrate is poorly water soluble, so it's not absorbed properly from the intestine and its bioavailability is less. While, Choline fenofibrate is water soluble and does not have interaction with food. It is rapidly dissociates in intestine and release fenofibric acid (active moiety) which is well absorbed throughout all the gastrointestinal regions so bioavailability of it is good. Results showed that both combinations provide remarkable reduction in the serum triglycerides levels (37.7% vs. 37.8%, respectively). Also, increase in HDL-C and reduction in LDL-C, VLDL-C, and total cholesterol was also statistically similar in both the groups. Results of above study showed that FDC of rosuvastatin and choline fenofibrate is as safe and effective as rosuvastatin and micronized fenofibrate combination in Indian patients with mixed dyslipidemia. The FDC of rosuvastatin and choline fenofibrate offers a better alternative to patients with mixed dyslipidemia due to better bioavailability and no interaction with food.²⁸

Propensity Matched Cohort Study on the Use of Fenofibrate on cardiovascular outcomes in Statin Users with Metabolic Syndrome

Use of Statin and hypolipidemic drugs was considered as the primary treatment for metabolic syndromes, as various clinical trials showed that statin treatment alone was not completely effective in these cases. Fenofibrate, a receptor α -antagonist had shown effects on the hypertriglyceridemia and low HDL concentration and showed reduction in cardiovascular events in people with atherogenic dyslipidemia. This study was conducted to evaluate the effect of fenofibrate in the most susceptible population of East Asian Origin. 514866 Koreans of age

group 40-79 were selected through NHIS-HEALS cohort. A database was created recording various information required. Patients were selected on the basis of different categories and Propensity score matching was done for those who were on combined statin-fenofibrate treatment and the statin-only treatment. The propensity score model was derived from multiple logistic regression along with the cutoff points for HDL cholesterol and triglycerides concentration. Finally, the index date for propensity score matching was set and statistical analysis was performed using SAS Software, version 9.4. In each treatment group, changes were observed in the serum lipid profiles. In the combined treatment group, initially, triglycerides concentration was higher but along with time the group showed greater reduction in its concentration. Also, the risk of cardiovascular events and the composite cardiovascular events in the subgroups were non-significantly lowered. In this propensity matched cohort study, Some Parameters that are needed to be noticed for better results are immortal and time lag biases that are problematic in pharmacoepidemiologic studies and to exclude such biases, index date is set for propensity score matching to be the same as the date for starting fenofibrate treatment in participants and their matched control. They also analysed the outcomes only during the fenofibrate treatment period in participants and matched controls and found that the statistically significant reduction in cardiovascular diseases with combined treatment was achieved. Other possible errors might arise as some variables (β blocker use, diuretic use, and triglycerides concentrations) were not balanced at baseline even after matching. Therefore these variables should be adjusted for further analyses. Overall, combination of fenofibrate to statin treatment in reduced cardiovascular risk in adults with metabolic syndrome. So it is a good choice to use combination therapy instead of monotherapy of statins.²⁹

CONCLUSION

This research review's purpose is to help the reader understand different aspects posed by the research on the Rosuvastatin and Fenofibrate. This is significant because it gives insights about the individual and combined effect of these two drugs. There has been much research and discussion conducted on these opinions of them. Most of the research found was on the effect that rosuvastatin has on thromboinflammation, platelet volume and dyslipidaemia, the effects of Fenofibrate on diabetic retinopathy, non-alcoholic fatty liver disease and dyslipidaemia and finally the combined effects of rosuvastatin and fenofibrate on prostate cancer, Ischemic stroke and hypolipidemia. More research and testing is required to gain a better understanding of Rosuvastatin and Fenofibrate individually and in combination.

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HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

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The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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