



Comparative Study of Atorvastatin plus Fenofibrate versus Atorvastatin alone for its safety and efficacy in Hyperlipidemic patients

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ABSTRACT

The aim of this study was to compare the efficacy and safety of combination containing Atorvastatin plus Fenofibrate (ATO+FENO) and to determine whether combination of Fenofibrate had clinically significant benefit over Atorvastatin alone (ATO) in patients with Hyperlipidemia. This is a singlecentric, open labelled, prospectivestudy, involving 50 Hyperlipidemic patients of 18 years and older. Data of only Hyperlipidemic patients with Low Density Lipoprotein (LDL -C) ≥ 140 - < 250 mg/dl, High Density Lipoprotein (HDL-C) < 40 - > 60 mg/dl, Total Cholesterol (TC): 200-240 mg/dl and Triglyceride (TG): ≥ 165 - < 400 mg/dl and who were prescribed either Atorvastatin 10mg and Atorvastatin plus Fenofibrate 160mg were included in the study. Efficacy end points included the change in LDL-C, HDL-C, TC and TG at week 12 and the safety of the treatment was also evaluated based on adverse events. Total 50 patients were enrolled in the study but 1 patient lost to follow up in ATO Group and 2 patients in ATO+FENO Group. Therefore 24 patients in ATO and 23 patients in ATO+FENO group were completed study. A statistically significant reduction in LDL-C, TG and TC was seen in both the groups (Atorvastatin 10mg and Atorvastatin plus Fenofibrate 160mg). Similarly a statistically significant increase in HDL-C levels was observed in both the groups. ATO+FENO treatment showed a statistically significant reduction in TG at week 12 as compared to ATO alone. Decrease in LDL-C, TC, and TG were 24.86%, 24.81%, and 30.13% respectively and increasing HDL-C 42.37% in ATO+FENO group while the reduction was 21.1%, 21.31%, and 22.84% respectively and increasing HDL-C 38.2% in ATO alone group. The most common adverse events were headache, myalgia and nausea. ATO+FENO treatment showed a greater reduction in lipid parameters as compared to ATO alone (percentage change). Both treatments were well tolerated with similar incidence of adverse events. The result of this study demonstrated that combination treatment was more effective than Atorvastatin alone in reducing LDL-C, Total Cholesterol and Triglyceride. It was also better in increasing HDL-C as compared to Atorvastatin. Statin in combination of fenofibrate may have less adverse effects. Therefore Combination therapy seems to be a better treatment in patients having Hyperlipidemia.

KEY WORDS: Atorvastatin, Fenofibrate, Hyperlipidemia, Adverse effects

INTRODUCTION

High serum cholesterol and elevated low-density lipoprotein (LDL) cholesterol are important risk factors for coronary heart disease. Many patients on statin therapy have initial or recurrent coronary heart disease events despite reductions in LDL cholesterol (Sacks et al., 2000). Interestingly, fibrate therapy, which significantly decreases triglycerides and increases high-density lipoprotein (HDL) cholesterol without reducing LDL cholesterol, is associated with significant decreases in coronary events (Rubins et al., 1999). Moreover, combined therapy with statins and fibrates is more effective in controlling atherogenic dyslipidaemia in patients with combined Hyperlipidemia than the administration of either drug alone (Vega et al., 2003). Of concern is the fact that the combination of statins and fibrates is more likely to be accompanied by severe myopathy (Taher et al., 2002). This

limitation is not observed with fenofibrate, and no significant side effects have been reported with combined statin and fenofibrate treatment (Vega et al., 2003; Taher et al., 2002; Pan et al., 2000). Coronary heart disease frequently is associated with insulin resistance and metabolic disorders, such as obesity and combined Hyperlipidemia. Endothelial dysfunction associated with cardiovascular diseases may contribute to insulin resistance (Vincent et al., 2003). The effects of statins on insulin resistance are controversial (Paolisso et al., 2000; Ohrvall et al., 1995). Peroxisome proliferator-activated receptor- α activators improve insulin sensitivity in rodents (Guerre et al., 2000). The impact of atorvastatin and fenofibrate therapies on endothelial homeostasis and insulin resistance may differ because the mechanisms underlying the biological actions of these drugs are distinct. Therefore, we investigated whether combined

therapy has additive beneficial effects greater than atorvastatin or fenofibrate alone in patients with combined Hyperlipidemia.

MATERIALS AND METHODS:-

Inclusion & Exclusion Criteria:

An Observational, Randomized, Prospective, Open labeled and Single centric study was conducted from November 2013 to April 2014 in patients with hyperlipidemia attending the out patients department of HCG multispecialty hospital, Ahmedabad. All patients provided written informed consent before enrolment. Eligible patients were men and women above 18 years of age with hyperlipidaemia and no coronary heart disease (CHD), and having the level of LDL-C : ≥ 140 - < 250 mg/dl, TG : ≥ 165 - < 400 mg/dl, TC : 200 - 240 mg/dl. Based on criteria laid down by National Cholesterol Education Program (NCEP Adult Treatment Panel III)^[15] guidelines were included in the study. Only newly diagnosed Hyperlipidemic patients were included in the study.

We excluded patients with liver disease, chronic renal failure, hypothyroidism, myopathy, diabetes type-1 & 2, hypertension, stroke, acute coronary events, evidence of alcohol abuse. Patients on concurrent therapy with beta blockers, thiazides, oral contraceptives pills, and cyclosporine, erythromycin and azole antifungals were excluded.

The Institutional Ethical Committee of HCG Multispecialty Hospitals, Ahmedabad approved the study protocol and informed consent was obtained from all patients before enrollment after detailed explanation of possible adverse effects of the drug combinations.

Patients who fulfilled the inclusion/exclusion criteria were randomly divided into two groups of 25 each by computer generated randomization. Patients also remained on the lipid-altering diet throughout the treatment period. Patients completing the 12 week base study

Study Design:

Study contains 2 group in which group 1 received atorvastatin 10 mg/day and Group 2 received combination of atorvastatin 10 mg/day and fenofibrate 160 mg/day for 12 weeks orally at night. All patients purchased the drugs from the hospital pharmacy as per prescription. Patients were assessed on 4th, 8th and 12th weeks and were asked to report immediately if they developed unusual muscle soreness or pain throughout the

study. Lipid profile was done at baseline, 4th, 8th and 12th weeks.

Sample Size Calculation and Statistical Analysis:

Sample size was calculated taking into consideration the mean values and standard deviation from the study done by Athyros et al. 2002. The data obtained were analyzed using descriptive statistics and paired and unpaired Student t-test to compare results within the group and between groups.

Efficacy endpoints:

The primary efficacy endpoint was percent change in LDL-C from baseline to study endpoint after treatment with FENO+ATO vs. ATO alone. The baseline value is defined as the average of the measurements obtained 1 week before randomization and the day of randomization. The endpoint value is defined as the last post-baseline measurement during the 12 week study.

Secondary efficacy endpoints included per cent change in other lipid and lipoprotein parameters like TC, TG and non-HDL-C from baseline to study endpoint. The proportion of patients shifting from a more atherogenic LDL size pattern to a less atherogenic LDL size pattern after treatment was tabulated for each treatment group.

Safety endpoints:

Safety and tolerability were assessed by clinical and statistical reviews of all safety parameters, including adverse experiences (AEs), laboratory values, and vital signs.

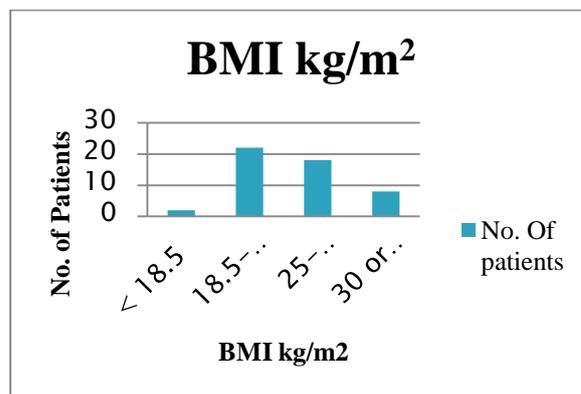
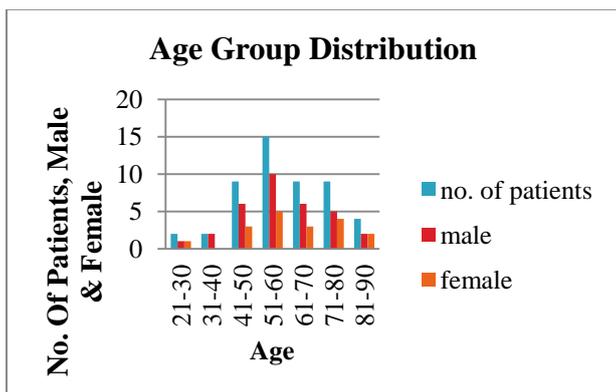
Result:

Baseline characteristics:

From the initial 25 patients in Group A+F, 2 patients terminated the study for personal reasons.. Thus, 23 patients completed the study while in Group A, 1 patient had left study so total 24 patients in Group A has completed this study. They received atorvastatin (n = 24) and combination of atorvastatin and fenofibrate (n = 23) for a period of 3 months. These patients tolerated both study medications well and completed the study. No significant adverse events were recorded during the study

No significant differences among baseline values before each treatment period or carryover effects were noted (Fig. 1)

Fig. 1: Patient demographic and Baseline characteristics



➤ **Effects on lipids:**

Fenofibrate in combined therapy with Atorvastatin significantly lowered triglycerides and increased HDL cholesterol level when compared with atorvastatin alone (Fig. 2).

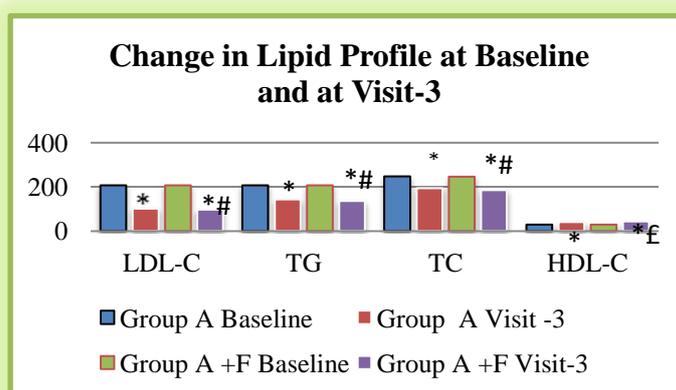
Changes in the Lipid Profile:

Changes from baseline to visit 3 in both treatment groups in the various lipid parameters are shown in Fig. 2. Patients in ATO (Group-I) showed reduction in LDL-C from 206.97 ± 27.55 at baseline to 101.2 ± 6.12 at 12 week, HDL-C from 29 ± 3.22 at baseline to 40.95 ± 1.83 at 12 week, TGs from 205.98 ± 30.81 at baseline to

142.45 ± 2.88 at 12 week and TC from 245.96 ± 21.92 at baseline to 193.54 ± 5.91 at 12 week.

While in ATO+FENO (Group-II) showed Reduction in LDL-C from 206.32 ± 28.52 at baseline to 96.13 ± 3.18 at 12 week, HDL-C from 29.08 ± 3.26 at baseline to 43.73 ± 3.13 at 12 week, TGs from 205.88 ± 30.34 at baseline to 135.6 ± 2.83 at 12 week and TC from 245.6 ± 20.79 at baseline to 184.65 ± 4.85 at 12 week. Mean reductions in trough LDL-C, HDL-C, TG and TC from baseline were statistically significantly with ATO+FENO compared with ATO treated group ($p < 0.0001$)

Fig. 2: Comparison of changes in the lipid profile between both treatment group at Baseline and Visit 3.



* p value < 0.0001 (at week 12 compared to Baseline), paired t-test.

p value < 0.0001 (at week 12 compared to week 12), unpaired t-test.

£ p value = 0.0005 (at week 12 compared to week 12), unpaired t-test.

LDL=Low Density Lipoprotein, HDL-C=High Density Lipoprotein Cholesterol

TC= Total Cholesterol, TG=Triglyceride.

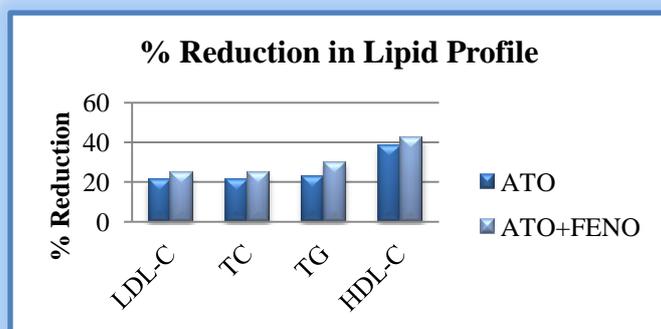
So, above all reported data ATO+FENO showed a better reduction in all other lipid parameter as

compared to ATO alone at week 12.

The percentage decreased in lipid parameter like LDL-C, TC and TG were 21.1%, 21.31% and 22.84% respectively in ATO group as compared to 24.86%, 24.81% and 30.13% respectively in ATO+FENO group. The increase in HDL-C level was 42.37% in

ATO+FENO group as compared to 38.2% in ATO group. These data indicate that combination therapy is able to reduce the lipid parameter to a greater extent as compared to Atorvastatin alone.

Fig. 3: % Reduction in Lipid Profile at Baseline and at 12 weeks



➤ **Safety and adverse effect:**

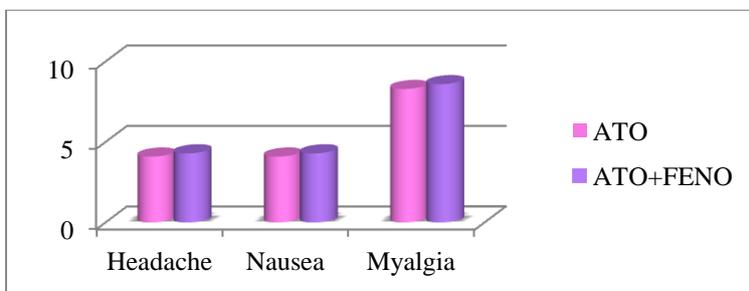
No patients were withdrawn from the study because of serious adverse effects.

Elevations in gastrointestinal upset, nausea, and headache were mainly transient and resolved spontaneously after patients finished the study. So, we

can say that present treatment therapy is safe & well tolerated.

Both treatments were well tolerated with only a few incidences of mild adverse events. The common adverse events reported in both group were headache, nausea and myalgia as shown in Fig. 4.

Fig. 4: Adverse Events related to different treatments



Discussion:

The study reported here addressed the efficacy and tolerability of the combination therapy in patients with hyperlipidaemia, defined as elevated LDL-C (>130 mg/dL) and elevated TG (≥150 and ≤500 mg/dL) independent of HDL-C levels. The 160-mg dose of fenofibrate plus 10 mg of Atorvastatin in the combination therapy and 10 mg dose of Atorvastatin as monotherapy were used in this study. One of the objectives was to evaluate whether the combination would confer the same or better lipid lowering than atorvastatin monotherapy. It is reported that, atorvastatin and fenofibrate therapy alone changed the lipoprotein profiles (Harfindal et al., 2006) in

Hyperlipidemic patients, so it may be possible that they have additional benefits with combined fibrate/statin therapy.

The result of this study shows % reduction in LDL-C, TG and TC 21.1 %, 22.84 % and 21.31 % respectively and increasing HDL-C 38.2% in ATO group, while 24.86%, 30.13 % and 24.81 % respectively and increasing HDL-C 42.37 % in ATO+FENO group. In present study ATO+FENO was associated with a TG reduction of 30.13 %/mg (atorvastatin 10 mg + fenofibrate 160 mg for 12 weeks), whereas previously reported studies found a decrease in TG of -0.31%/mg (atorvastatin 40 mg + fenofibrate 135 mg for 12 weeks),

(Goldberg et al., 2009) $-0.25\%/mg$ (atorvastatin 20 mg + fenofibrate 200 mg for 24 weeks), (Athyros et al. 2002) and $-0.29\%/mg$ (atorvastatin 10 mg + fenofibrate 200 mg for 8 weeks). (Koh et al., 2005)

The findings of this 12-week prospective study suggest that the Combination therapy provided effective management of lipids then monotherapy in Hyperlipidemic patients. Decreases in TC, LDL-C, TG and increases in HDL-C with Combination therapy were significantly greater than atorvastatin monotherapy. Our findings are also supported by previously reported research by Michael et al; (2009) they found combination had either comparable or significantly greater improvements in lipid variables (Davidson et al., 2009).

In present study, the lowering of TG by the Combination therapy relative to the sum of the lowering by the individual monotherapy (atorvastatin alone) supports the concept of pharmacokinetic/pharmacodynamics interactions between the drugs and a resulting influence on lipid pathways (Davidson et al., 2009). The monotherapy (ATO) lowers 22.84% TG, whereas the Combination (ATO+FENO) was associated with a change of 30.13% in TG. This conceptual pharmacokinetic/pharmacodynamics interaction was evident in other statin/fenofibrate studies that compared monotherapy with the respective co-administration regimens (Goldberg et al. 2009; Davidson et al., 2009; Athyros et al., 2002). An interaction between statin and fibrate for the TG and LDL-C pathways was clearly evident in previous trials. (Goldberg et al. 2009; Davidson et al., 2009; Athyros et al., 2002; Koh et al., 2005). The present study found an improved efficiency of lipid lowering similarly to the previously studies (Davidson et al., 2009; Guerin et al., 2000; Murdock et al., 1999; Pierce et al., 1990; Guerin et al., 2000; Jones et al., 1998; Dart et al., 1997; Staels et al., 1998) reported with hyperlipidaemia patients.

The two Hypolipidemic drugs used in the present study have complementary modes of action. Atorvastatin is a potent inhibitor of hydroxymethylglutaryl-CoA reductase, which decreases LDL cholesterol in plasma by up regulating LDL receptor activity (Davidson et al.,

2009). It has been shown that atorvastatin significantly reduced circulating levels of all major LDL subspecies: light, intermediate, and dense (Guerin et al., 2000); the latter is believed to be responsible for the TG-lowering effect of atorvastatin and has profound effects at higher doses. (Jones et al., 1998; Dart et al., 1997)

Fenofibrate activates peroxisome proliferator-activated receptors (Staels et al., 1998), which induce an increase in LP lipase activity and a reduction in cholesterol ester transfer protein activity. These result in TG level reduction, redistribution of LDL particle size, and an HDL cholesterol increase. The significant reduction of TG, and increase in HDL cholesterol, seen in this study with atorvastatin and fenofibrate combination is indicative of a beneficial increase in LDL particle size (Pierce et al., 1990).

Importantly, no patients were withdrawn from our study as the result of serious adverse effects. The primary risk of using statins in combination with fibrates is believed to be hepatotoxicity and myopathy. In most studies combination therapy was no more hepatotoxic than the statin itself (Murdock et al., 1999). The use of statin/fibrate combination therapy in clinical practice has raised concerns about the increased risk of muscle-associated AEs, such as myositis, myalgia, and Rhabdomyolysis (Davidson et al., 2009). Use of lower-dose statins and fibrates is recommended to avoid muscle related as well as liver and renal toxicities (Guerin et al., 2000). In the present study, the Combination therapy was not associated with any cases of myositis or Rhabdomyolysis, whereas 4.1 % of patients reported headache, 4.1 % of patients reported nausea and 8.3 % of patients reported myalgia (Goldberg et al., 2009). In general, the Combination treatment was associated with a lower number of total AEs, compared with fenofibrate or atorvastatin alone.

Limitation of this study:

Limitations to consider when evaluating the clinical applicability of this study should include the constraints of the inclusion and exclusion criteria, which limit the extrapolation of these results to the general population. Other possible limitations are the dyslipidaemia criteria for patient eligibility, the population size of each

treatment arm and the short duration of the study. Hence, further studies in a large number of patients and for longer duration are necessary to assess the long-term safety of this combination.

In summary, present study suggests that combined atorvastatin/fenofibrate therapy is comparatively safe and has beneficial additive effects on all lipid parameters and it is a very effective therapeutic approach of patients with Hyperlipidemia supporting the updated National Cholesterol Education Program Adult Treatment Panel III guidelines [15]. These properties reduce CAD risk, expand the spectrum of therapeutic choices, and enhance the individualization of hypolipidemic treatment in patients with Hyperlipidemia (Athyros et al., 2002)

Conclusion:

In this 12-week prospective study, patients with hyperlipidaemia treated with the atorvastatin/fenofibrate 10/160-mg had a significantly greater reduction in TG, also decreases in non-HDL-C, LDL-C, TC and increases in HDL-C than those treated with atorvastatin 10 mg alone. The combination therapy also shows less adverse effects than atorvastatin monotherapy.

Monotherapy with statins is considered the gold standard for treatment of mixed Hyperlipidemia, but greater benefits were observed with combination therapy hence, monotherapy may not effectively control all lipid abnormalities whereas, long term Fenofibrate plus Atorvastatin combination therapy is efficacious, safe and well tolerated.

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