EFFICACY AND SAFETY OF MICRONISED FENOFLIBRATE IN A RANDOMISED DOUBLE-BLIND STUDY COMPARING FOUR DOSES FROM 200 MG TO 400 MG DAILY WITH PLACEBO IN PATIENTS WITH HYPERCHOLESTEROLEMIA


SUMMARY
- The aim of this study was to evaluate the efficacy on LDL-cholesterol (LDL-C) of micronised fenofibrate given for three months at doses ranging from 200 to 400 mg once daily, compared with placebo. A double-blind, randomised, parallel-group, multi-centre trial was performed in four centres of France in 340 hypercholesterolemic patients (163M, 177F) aged 18-75 years. After a 2-3 month single-blind run-in period on placebo and diet, patients with LDL-C greater than or equal to 4.65 mmol/l (180 mg/dl) maintained on the same diet throughout the study were randomly allocated to placebo or to 200, 267, 340 or 400 mg micronised fenofibrate, given once daily with the evening meal for 3 months. LDL-C, total cholesterol (TC), total triglycerides (TG) and apolipoprotein B (Apo B) significantly decreased compared with placebo in all four fenofibrate groups. For all randomised patients, the decrease in the fenofibrate groups ranged from 31.6-38.8% for LDL-C, 24.5-31.9% for TC, 26.7-40.8% for TG, and 27.3-35.0% for Apo B. An increase in HDL-cholesterol of 4.1-8.2% was observed in the fenofibrate groups, but did not reach statistical significance. Lipid values in the placebo group remained unchanged. The therapeutic goal of LDL-C < 3.36 mmol/l (130 mg/dl) was reached in 27% in the 200 mg group and increased to 56% in the 300 mg group. There were no major clinical or biological adverse events in the dose interval from 200 mg to 400 mg of micronised fenofibrate per day. This study showed treatment for 3 months with micronised fenofibrate at doses up to 400 mg per day is effective and can reduce LDL-cholesterol up to 30% allowing further evaluation of these doses on longer trials.

Key-words: fenofibrate, dyslipidaemia, LDL-cholesterol.

RÉSUMÉ - Efficacité et tolérance du fénofibrate micronisé dans une étude randomisée en double insu comparant quatre doses allant de 200 mg à 400 mg par jour avec placebo chez des patients hypercholestérolémiiques

L’objectif de cette étude était d’évaluer l’efficacité sur le LDL-cholestérol (LDL-C) du fénofibrate micronisé administré pendant 3 mois à des doses de 200 à 400 mg/jour et comparé à un placebo. Un essai randomisé et contrôlé a été réalisé dans 4 centres français sur 340 patients hypercholestérolémiques (163 hommes et 177 femmes) âgés de 18 à 75 ans. Après 2 à 3 mois d’une période de pré-inclusion où les patients recevaient un régime adapté et un placebo, ceux ayant un LDL-cholestérol supérieur à 4,65 mmol/l (180 mg/dl) ont été maintenus sous le même régime durant l’étude et ont été randomisés en 4 groupes recevant respectivement: placebo, 200, 267, 340 et 400 mg de fénofibrate micronisé donné une fois par jour avant le dîner pendant 3 mois. Le LDL-cholestérol, le cholestérol total, les triglycérides et l’apolipoprotéine B ont été réduits significativement comparés au placebo dans les 4 groupes. Pour tous les patients randomisés, la diminution dans les groupes fénofibrate était comprise entre 31,6 et 38,8% pour le LDL-C, 24,5 à 31,9% pour le cholestérol total, 26,7 à 40,8% pour les triglycérides et 27,3 à 35% pour l’apo B. Une augmentation modérée du HDL-cholestérol de 4,1-8,2% a été observée dans les groupes traités par le fénofibrate mais n’a atteint pas une différence significative par rapport au groupe placebo dans lequel les paramètres lipidiques ne variaient pas. Un objectif thérapeutique de LDL-cholestérol < 3,36 mmol/l (130 mg/dl) était atteint pour 27-56% des patients recevant le fénofibrate. Il n’a pas été observé d’effets secondaires majeurs cliniques ou biologiques. En conclusion, cette étude montre qu’un traitement de 3 mois par fénofibrate micronisé jusqu’à 400 mg/jour est efficace pour réduire le LDL-C jusqu’à 30% de la valeur initiale, sans effets secondaires, permettant des évaluations ultérieures dans des essais thérapeutiques prolongés.

Mots-clés : fénofibrate, dyslipidémie, LDL-cholestérol.

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A n increased level of LDL-cholesterol is a well-recognised risk factor for the occurrence of coronary heart disease, and often requires drug treatment to achieve therapeutic goals [1]. Fenofibrate is a lipid-regulating agent which is well-established in the treatment of dyslipidaemias. It has a wide range of effects on cholesterol and triglyceride metabolism [2, 3].

The standard formulation of fenofibrate has been used at doses of 200 mg/day to 400 mg/day.

By co-micronisation, a new pharmaceutical formulation of fenofibrate was recently developed and provides an improved absorption of the active drug. A pharmacokinetic study has shown that 200 mg of micronised fenofibrate has an equivalent bioavailability as compared to 300 mg of standard fenofibrate [4], thus this formulation was progressively substituted to the standard formulation for therapeutic use.

The present study was designed to determine whether raising the dose of micronised fenofibrate from 200 mg/day to 400 mg/day produced an increase in the lipid-lowering effect with no side effects. Doses of 200 mg, 267 mg, 340 mg and 400 mg of micronised fenofibrate were compared with placebo in a double blind, randomised study over a three-month treatment period in patients with increased LDL-cholesterol.

The primary efficacy criterion was the percentage decrease in plasma concentrations of LDL-cholesterol (LDL-C) at three months in the five treatment groups. Plasma concentrations of other lipid parameters, including total cholesterol (TC), total triglycerides (TG), HDL-cholesterol (HDL-C), and apolipoprotein B (Apo B) were also measured, and laboratory and clinical safety data were monitored.

### PATIENTS AND METHODS

A double-blind, randomised, controlled, comparative, parallel-group, multi-centre trial was performed in four cities of France (Nantes, Angers, Dijon, Nice). The protocol was approved by an Ethical Committee (Comité Consultatif pour la Protection des Personnes se prêtant à une Recherche Biomédicale, Nantes, France). Each patient enrolled in the trial provided freely-given, informed written consent. The study was conducted according to the principles of Good Clinical Practice.

**Patients** — Male or female patients aged 18 to 75 years inclusive were sought for the study. Patients were to present hypercholesterolemia (LDL-C > 4.65 mmol/l). Use of any normolipidaemic agent was to be discontinued at the time of selection for the study and protocol was to have been discontinued for at least 6 months. Patients were to agree to follow a normocaloric, hypolipidaemic diet prescribed by the investigator for the entire duration of the study, and were not to modify their smoking habits.

Patients with obesity (body mass index [BMI] > 32.5 for men and 30.9 for women) were excluded from the study. Patients with a past medical history or concomitant illness of any of the following were also excluded: diabetes mellitus, pancreatitis, clinically diagnosed biliary lithiasis, hepatic function disorders (including cirrhosis, hepatitis and other chronic hepatopathies with ASAT or ALAT > 2 times the upper normal limit of the laboratory, or gamma-GT > 3 times normal), creatine phosphokinase > 2 times normal, renal disorders (creatinine > 1.5 times normal), unstable disorders of thyroid function, or known alcoholism. In the three months preceding the study, patients were not to have experienced myocardial infarction, cerebrovascular accident, cardiac surgery, unstable or newly diagnosed angina, or an active gastrointestinal ulcer.

None of the following types of medication was allowed during the study: oestroprogestative contraceptives with an exception for low dose oestroprogestative contraceptives (ethinyl oestriodiol combined with a norsteroid progestative), oral or percutaneous hormone replacement therapy for the menopause if they had been prescribed at a fixed dosage for at least 6 months, antihypertensive treatments by diuretics, corticoids (except dermocorticoids), retinoids, anorexiant and mucilages, anti-vitamin K and cyclosporin. Antihypertensive treatment other than diuretics, thyroid hormone treatment, H2 receptor antagonists were authorised if they had been prescribed at a fixed dosage for at least 6 months and this dosage did not vary during the study.

#### Study treatment and schedule —

The initial phase of the study was a single-blind run-in period of placebo (2 capsules per day with the evening meal), and a hypolipidaemic diet (American Heart Association Step 1 diet). The duration of this period was 2 months for patients receiving lipid-lowering treatment before the study and 3 months for newly diagnosed patients (one additional month of diet alone at the beginning).

At the end of the diet and placebo run-in phase, patients who presented plasma LDL-cholesterol levels > 4.65 mmol/l (180 mg/dl) and total triglycerides < 3.99 mmol/l (350 mg/dl) were randomly allocated to one of five parallel groups for a three-month double-blind treatment period. They received either placebo (2 capsules) or one of four doses of micronised fenofibrate (Lipanthyl®, Laboratoires Fournier S.A., Dijon, France): 200 mg/day (one 200 mg capsule and one placebo capsule), 267 mg/day (one 200 mg capsule and one 67 mg capsule), 340 mg/day (one 200 mg capsule and one 140 mg capsule), or 400 mg/day (two 200 mg capsules). Treatment was to be taken once daily with the evening meal.

Six visits at intervals of one month were scheduled (V-2, V-1, V0, V1, V2, V3). At each visit, a clinical examination was performed. Laboratory tests were performed a few days before each visit, and the results
on the safety parameters were given to the investigator (except uric acid and alkaline phosphatase at V1, V2 and V3, which would have broken the blind, since both measures are reduced by fenofibrate). Treatment was dispensed at each visit for the following month. At the inclusion visit (V0), patients who satisfied the inclusion criteria, and had shown satisfactory observance of the diet and placebo, were allocated to randomised treatment. Compliance to treatment was monitored by pill counting. Patients with a compliance less than 80% were not included in the study.

**Laboratory analyses** — Blood samples taken a few days before each study visit were analysed for safety parameters in a centralised laboratory in each city, and for lipid parameters in a national centralised laboratory (Pasteur Institut, Lille, France). LDL-cholesterol was calculated from the results for total cholesterol, HDL-cholesterol and total triglycerides using Friedewald’s formula if triglycerides levels were below 4 mmol/l [5]. Total cholesterol and glycerol free triglyceride were measured using enzymatic reactions (Beckman, Paris, France). HDL-cholesterol was determined after precipitation with Na phosphotungstate and Mg chloride (Beckman Paris, France). Apo B was measured by nephelometry (Behring, France).

**Statistical analysis** — The efficacy results were analysed both for all randomised patients and for patients assessable for efficacy. A quantitative safety analysis of changes in laboratory parameters was performed on all randomised patients.

Given the known efficacy of the lowest active dose of 200 mg micronised fenofibrate, the planned sample size of 50 assessable patients per treatment group was sufficient for all comparisons of an active dose versus placebo. A significance level of 5% and the null hypothesis of no difference between the different doses was used for all statistical tests. The homogeneity of the treatment groups at inclusion was tested using one-way analysis of variance for continuous variables. Categorical data were compared using the X²-test, or Fisher’s exact test if the former was not applicable.

The principal efficacy criterion was defined in the protocol as the value of LDL-cholesterol at the end (V3) expressed as the percentage change from baseline (V0). The percent changes of the four active doses were compared simultaneously to placebo using Dunnett’s two-sided test, thus controlling the overall experiment-wise error at 5%.

The secondary efficacy criteria (TG, TC, HDL-C, Apo B) were analysed in the same manner as the principal criterion. In addition, for all efficacy parameters two-by-two comparisons of the treatment groups were performed using Bonferroni-corrected t-tests.

For the quantitative safety analysis, the percent changes from baseline of the biological parameters were compared between the treatment groups as for the efficacy parameters.

Numerical results are presented as mean values with the standard deviation (SD) for all patients for whom data are available. The statistical analysis was performed using version 6.09 TS 044 of SAS® software (Cary, NC, USA) running on Digital DEC 3000-500 under Open VMS 6.2 as operating system.

### RESULTS

**Patient characteristics** — A total of 470 patients entered the dietary and placebo screening period, and 340 were randomised to double-blind treatment period.

The main baseline characteristics of the 340 randomised patients are shown in Table 1. There were no statistically significant differences between the treatment groups at baseline for sex, age, or body mass index. The type of dyslipidaemia (Table I) was classified as hypercholesterolaemia (LDL-C > 4.65 mmol/l and TG < 2.26 mmol/l), or combined hyperlipidemia.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Micronised fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg</td>
</tr>
<tr>
<td>n = 69</td>
<td>n = 69</td>
</tr>
<tr>
<td>Female/Male</td>
<td>41/28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.4</td>
</tr>
<tr>
<td>Body Mass Index (kg/m2)</td>
<td>24.3 (3.1)</td>
</tr>
<tr>
<td>Hypercholesterolemia (type IIa)</td>
<td>58 [84]</td>
</tr>
</tbody>
</table>

Numbers in parenthesis are SD and in brackets are %
(LDL-C > 4.65 mmol/l and mmol/l and TG > 2.26 mmol/l). The majority of patients in each treatment groups presented hypercholesterolemia. No statistical difference was observed regarding the type of dyslipidemia in all treatment groups. Since similar results were obtained for both randomized and evaluate patients, only the results on all randomised patients are presented.

**LDL-cholesterol**

Levels of LDL-cholesterol were statistically significantly reduced in all four fenofibrate groups compared with placebo (p < 0.05). Although there was no statistically significant difference between the four fenofibrate groups, the reduction in LDL-cholesterol levels ranged from 31.6 to 38.8% (Table II) and showed a trend to a dose relationship. The decrease in LDL-cholesterol (Fig. 1) was maximum after the first month of treatment, and persisted until the end of the treatment period. Although not significant compared to 200 mg fenofibrate, the highest dosages (340 and 400 mg) appeared to be more efficient. The percentage of patients with at least 15% reduction in LDL-cholesterol was 87.1% in the fenofibrate 200 mg group, 77.9% in the 267 mg group, 93.4% in the 340 mg group, and 77.9% in the 400 mg group.

**Table II.** Mean (SD) plasma concentrations of LDL-cholesterol, total cholesterol, HDL-cholesterol, triglycerides (mmol/l) and apolipoprotein B (g/l) at Visit 0, Visit 3 (3 months of treatment) and percentage changes (all randomised patients)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Micronised fenofibrate 200 mg</th>
<th>Micronised fenofibrate 267 mg</th>
<th>Micronised fenofibrate 340 mg</th>
<th>Micronised fenofibrate 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 0</td>
<td>69</td>
<td>69</td>
<td>69</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>Visit 3</td>
<td>66</td>
<td>63</td>
<td>66</td>
<td>61</td>
<td>63</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 0</td>
<td>5.89 (0.94)</td>
<td>5.80 (0.88)</td>
<td>5.78 (0.96)</td>
<td>5.80 (0.88)</td>
<td>5.83 (0.92)</td>
</tr>
<tr>
<td>Visit 3</td>
<td>5.89 (0.90)</td>
<td>3.94 (1.06)</td>
<td>3.86 (1.17)</td>
<td>3.59 (1.18)</td>
<td>3.69 (0.90)</td>
</tr>
<tr>
<td>% change</td>
<td>0.5 (14.2)</td>
<td>-31.6 (15.6)*</td>
<td>-32.5 (18.8)*</td>
<td>-38.8 (15.7)*</td>
<td>-36.0 (16.2)*</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Visit 0</td>
<td>8.09 (1.00)</td>
<td>7.87 (0.96)</td>
<td>7.84 (1.04)</td>
<td>7.94 (1.03)</td>
<td>7.87 (1.02)</td>
</tr>
<tr>
<td>Visit 3</td>
<td>8.12 (0.99)</td>
<td>5.92 (1.18)</td>
<td>5.67 (1.17)</td>
<td>5.42 (1.19)</td>
<td>5.53 (0.88)</td>
</tr>
<tr>
<td>% change</td>
<td>0.5 (11.0)</td>
<td>-24.5 (11.9)*</td>
<td>-26.9 (14.8)*</td>
<td>-31.9 (12.2)*</td>
<td>-29.2 (12.2)*</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td></td>
<td></td>
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<tr>
<td>Visit 0</td>
<td>1.50 (0.43)</td>
<td>1.44 (0.38)</td>
<td>1.30 (0.37)</td>
<td>1.40 (0.41)</td>
<td>1.33 (0.34)</td>
</tr>
<tr>
<td>Visit 3</td>
<td>1.49 (0.39)</td>
<td>1.55 (0.42)</td>
<td>1.37 (0.35)</td>
<td>1.42 (0.38)</td>
<td>1.36 (0.44)</td>
</tr>
<tr>
<td>% change</td>
<td>1.3 (14.9)</td>
<td>8.0 (20.0)</td>
<td>8.2 (23.1)</td>
<td>5.8 (25.2)</td>
<td>4.1 (24.7)</td>
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<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 0</td>
<td>1.53 (0.70)</td>
<td>1.36 (0.64)</td>
<td>1.66 (0.84)</td>
<td>1.63 (0.78)</td>
<td>1.59 (0.70)</td>
</tr>
<tr>
<td>Visit 3</td>
<td>1.55 (0.79)</td>
<td>0.97 (0.78)</td>
<td>0.97 (0.52)</td>
<td>0.92 (0.46)</td>
<td>1.04 (0.48)</td>
</tr>
<tr>
<td>% change</td>
<td>3.5 (33.9)</td>
<td>-26.7 (37.2)*</td>
<td>-35.3 (25.6)*</td>
<td>-40.8 (19.2)*</td>
<td>-29.3 (32.5)*</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 0</td>
<td>1.76 (0.28)</td>
<td>1.70 (0.29)</td>
<td>1.75 (0.29)</td>
<td>1.73 (0.31)</td>
<td>1.75 (0.26)</td>
</tr>
<tr>
<td>Month 3</td>
<td>1.79 (0.28)</td>
<td>1.22 (0.35)</td>
<td>1.25 (0.35)</td>
<td>1.14 (0.33)</td>
<td>1.22 (0.29)</td>
</tr>
<tr>
<td>% change</td>
<td>2.0 (13.1)</td>
<td>-27.3 (19.9)*</td>
<td>-27.8 (18.4)*</td>
<td>-35.0 (14.0)*</td>
<td>-30.8 (14.4)*</td>
</tr>
</tbody>
</table>

*Significant (p < 0.05) difference compared with the placebo group
‡Significant (p < 0.05) difference between treatment groups (200 mg vs 340 mg)
mg group and 92.1% in the 400 mg group, compared with only 7.6% in the placebo group. The percentage of patients whose levels of LDL-cholesterol were < 3.36 mmol/l (130 mg/dl), and those whose levels were above 3.36 mmol/l, but less than 4.14 mmol/l (160 mg/dl), after three months of treatment are shown in Figure 2. None of the patients in the placebo group had LDL-cholesterol levels < 3.36 mmol/l at Visit 3, and only one patient (1.5%) reached a level lower than 4.14 mmol/l. In the four fenofibrate groups, the total percentage of patients whose LDL-cholesterol levels were reduced after three months of treatment to < 4.14 mmol/l increased significantly with the treatment dose (Fig. 2). The percentage of patients with LDL-cholesterol < 3.36 mmol/l was significantly higher in the all treatment groups (p<0.001) compared to placebo.

Total cholesterol — The plasma concentrations of total cholesterol over the three-month treatment period are shown in Table II. The reduction in total cholesterol in patients treated with fenofibrate was maximal, or close to maximal, after one month of treatment, and remained stable until the end of the study as observed on LDL-cholesterol.

The decrease in the four fenofibrate groups ranged from 24.5 to 31.9% (Table II), and all were significantly different from placebo. Moreover, there was a statistically significant difference between the decrease in the 200 mg fenofibrate group and the larger decrease in the 340 mg fenofibrate group.

Triglycerides — Total triglycerides decreased significantly from V0 to V3 in all four fenofibrate groups compared with placebo (Table II). A near-maximal effect was reached after one month of treatment. Although the percentage reduction in triglycerides in the four fenofibrate groups varied from 26.7 to 40.8% (Table II), the differences between the groups were not statistically significant.
**HDL-cholesterol** — Plasma concentrations of HDL-cholesterol increased by 4.1-8.2% in the fenofibrate groups (Table II). However, these increases were not statistically significantly different from the placebo group, or from each other.

**Apolipoprotein B** — Plasma levels of apolipoprotein B decreased in all four fenofibrate groups by 27.3-35.0% between V0 and V3 (Table II) and paralleled the changes in LDL-cholesterol. These decreases were all statistically significant compared with placebo.

**Safety** — A total of 21 patients discontinued double-blind treatment. Only 3 patients discontinued placebo treatment, 6 patients in fenofibrate 200 mg, 3 patients in fenofibrate 267, 5 patients in fenofibrate 340 and 4 patients in fenofibrate 400 group. There was no statistically significant difference between the treatment groups in the total number of patients who discontinued treatment prematurely. The biological adverse events leading to discontinuation were elevation of transaminases and gamma-GT. The clinical adverse events involved gastrointestinal symptoms (including nausea, vomiting and diarrhoea) in five cases.

Overall, the percentage of patients presenting adverse events during double-blind treatment ranged from 37.7-54.0% across the treatment groups (Table III). The percentage of patients whose liver enzyme levels rose above normal limits tended to increase with the two higher doses of fenofibrate. Of the total of 12 patients with increase of one or more liver enzymes (ASAT, ALAT or gamma-GT) to over three times normal after normal determinations at baseline, six were discontinued from treatment. Of the remaining six patients, two normalised with continued treatment and four presented the maximum value at the end of the treatment period (Month 3). When follow-up was performed after discontinuation of treatment, a normalisation of liver enzymes was observed within a 2-4 week period.

The reduction in uric acid levels in the four fenofibrate groups ranged from 22.7 to 37.1%, all changes being significantly different from placebo.

**DISCUSSION**

This three-month, double-blind, placebo-controlled study was designed to evaluate the efficacy of four doses of micronised fenofibrate in lowering LDL-cholesterol and total cholesterol in patients with dyslipidaemia.

The three-month duration of the active treatment period was sufficient to assess the full effects of micronised fenofibrate, as indicated by the maximal efficacy at one month. Lipid parameters were unchanged in patients in the placebo group, showing both that the dietary run-in phase was of sufficient length, and that compliance to the diet during the treatment phase was good. Further evidence of compliance to diet was supported by the stable weight of the patients (data not shown). The efficacy results of the study can therefore be evaluated as representing the effects of micronised fenofibrate in this dyslipidaemic population.

A significant reduction in LDL-cholesterol, total cholesterol, total triglycerides and apolipoprotein B was observed with all tested doses of fenofibrate compared with placebo. The decrease in plasma levels of LDL-cholesterol ranged from 32-39% across treat-
ment groups. In addition, the therapeutic goal defined by LDL-cholesterol less than 3.36 mmol/l (130 mg/dl) was reached in 27-56% of the patients receiving micronised fenofibrate, despite high initial levels of LDL-cholesterol. None of the patients in the placebo group reached this target. Total cholesterol levels decreased by 25-32% in the four fenofibrate groups. Total triglycerides were also substantially reduced (27-41%) in the fenofibrate treated patients. HDL-C levels slightly rose in all four fenofibrate groups and the increases did not achieve statistical significance. The percentage decreases in apolipoprotein B were of a similar magnitude to the percentage decreases in LDL-cholesterol. The reductions in LDL-cholesterol, total cholesterol and total triglycerides were close to maximal after the first month of treatment, and remained stable until the end of the study.

The effect of micronised fenofibrate on lowering plasma levels of LDL-cholesterol showed a modest dose-proportionality in the overall population and appeared to be maximal at the dose of 340 mg and in the same response range for the 400 mg dose. This was more pronounced for total cholesterol, which showed a statistically significant difference between the decreases in the 200 mg group (~25%) and the 340 mg group (~32%). The percentage of LDL-C decrease for this latter dose treatment was in the same range than those previously reported with other drugs used at low or usual recommended doses [6, 7]. For example in comparison studies between 200 mg micronised fenofibrate and HMG-CoA reductase inhibitors [8-11], it was shown that LDL-C reduction was about 20% with fenofibrate and was ~35% with 20 mg/d simvastatin and ~17% with 20 mg/d pravastatin. With fluvastatin, a reduction of 23 to 28% was reported with 40 mg/d [12] but comparisons with high dose of fluvastatin or in controlled studies with fenofibrate are not yet available. Finally, a significantly greater reduction of LDL-C was observed with 10 mg/d atorvastatin compared to 200 mg/d micronised fenofibrate in combined dyslipidemia [13]. However the magnitude of the reduction of LDL-C observed with 10 mg atorvastatin was in the same range we have observed with 340 mg/d of fenofibrate although the patient populations were different. It has to be also pointed out that almost 70% in the two highest dose groups were in the NCEP recommendations for patients with less than two risk factors (<160 mg/dl) and 50% of the patients in the 340 mg group met the criteria for two or more risk factors (<130 mg/dl). Again, these results are in the same range than those recently reported with low or usual doses of statins [14, 15].

The study treatment was well tolerated, with fewer than 5% of any treatment group discontinuing due to adverse events. The main clinical adverse events leading to withdrawal involved gastro-intestinal symptoms (including nausea, vomiting and diarrhoea). The main biological adverse events leading to withdrawal were elevation of transaminases and gamma-GT. These adverse events are all well-documented side-effects of fenofibrate [2]. There were no unexpected clinical or biological adverse events in the dose interval from 200 mg to 400 mg micronised fenofibrate per day.

In conclusion, both 200 mg and 267 mg doses of micronised fenofibrate were both highly effective in lowering LDL-cholesterol, total cholesterol and total triglycerides in dyslipidaemic patients, and were well tolerated. The two higher doses of 340 mg and 400 mg were significantly more effective although they appeared to lead to larger concomitant increases in transaminases. Then these higher doses could be used for treatment of some particular patients but with a careful survey of safety parameters. Long-term studies using higher dosages than the recommended dose of 200 mg of micronised fenofibrate per day are needed to further establish their efficacy and safety profile.

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REFERENCES

