Efficacy and Safety of Fluvastatin in Women with Primary Hypercholesterolaemia

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Summary

Women with primary hypercholesterolaemia are often considered for lipid-lowering drug therapy at a later age than men. With regard to the prevention of cardiovascular morbidity, women can expect to receive the same benefits from lipid-lowering treatment as men. Thus, it is of interest to evaluate the efficacy, safety and tolerability of the new lipid-lowering agent fluvastatin in women.

A retrospective analysis was made on the basis of data from controlled clinical trials in which 1815 patients were treated with fluvastatin at a daily dose of ≥ 20mg, and 783 patients received placebo. 782 of the fluvastatin-treated patients (43.1%) and 315 patients on placebo (40.2%) were women. Within these groups, 577 patients (73.8%) treated with fluvastatin and 183 patients receiving placebo (78.4%) were at least 50 years of age.

The effect of fluvastatin 40 mg/day on low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol was more favourable in women than in men. In women, the change from baseline was -26.7% for LDL cholesterol and 5.3% for HDL cholesterol. In men, the equivalent changes from baseline were -23.8% and 4.0%, respectively. All changes from baseline were highly significant (p < 0.001). Fluvastatin lowered triglycerides to a similar extent in women and men (7.1% vs 6.9%, respectively).

More women than men experienced a confirmed increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) when receiving fluvastatin. Such increases were observed for AST in 3 women (0.4%) but no men, and for ALT in 10 women (1.3%) and 2 men (0.2%). In placebo-treated patients, no such increases in AST were observed (irrespective of gender) but increases in ALT were noted in one male patient (0.2%) and one female patient (0.3%). No notable increases in creatine phosphokinase of > 10 times the upper limit of normal were observed in women. The tolerability of fluvastatin, as assessed by an analysis of adverse events, was not consistently influenced by gender.

In conclusion, an exploratory analysis of the efficacy and safety of fluvastatin suggests that it is effective, safe and well tolerated, irrespective of gender. The observed tendency to enhanced efficacy in women should be further evaluated by use of data from prospective studies in female patients.
Lipid-lowering drug therapy for primary hypercholesterolaemia is often considered at a later age for women than it is for men. This may occur because men are considered to be at higher risk of coronary heart disease (CHD) than women, irrespective of age. Indeed, in premenopausal women the risk of CHD is approximately 10 years behind that in men of similar age (Expert Panel 1993). However, after menopause the risk of CHD and cardiovascular morbidity in women approaches that in men. CHD still accounts for approximately 37% of all hospital stays for women aged 55 years and above. On average, women live longer than men, and their annual death rate from CHD is actually greater (Moreno et al. 1993).

Premenopausal women have lower levels of low density lipoprotein (LDL) cholesterol (Grundy 1990) and higher levels of high density lipoprotein (HDL) cholesterol than men (Bush et al. 1988). However, after menopause there is a trend for HDL cholesterol levels to decline (Kannel 1987). In addition, the decrease in endogenous estrogen postmenopausally may be a contributing factor to the increase in LDL cholesterol in older women (Gotto et al. 1990). Women also have lower triglyceride (TG) levels, but these increase and eventually exceed those of men after 60 years of age (Heyden et al. 1980). These changes may contribute to the markedly increased risk of developing CHD that occurs in postmenopausal women (Gotto 1990).

Using data from the second and third US National Health and Nutrition Examination Surveys (NHANES II and III), Sempos et al. (1993) showed that, overall, 32% of men and 27% of women may require dietary intervention to control blood lipid levels. This difference between the sexes is most pronounced in those under 55 years of age; between 55 and 64 years of age the requirement for dietary intervention is approximately equal, and after 75 years of age it is reversed. However, dietary treatment may fail to control hypercholesterolaemia, in which case drug treatment may be the only option. There has been increasing interest in the use of hormone replacement therapy (HRT) in postmenopausal women, but clinical evidence concerning its risk: benefit ratio is still lacking (Goldberg 1993).

With regard to the prevention of cardiovascular morbidity, women can be expected to receive the same benefits from lipid-lowering treatment as men. There have been a large number of clinical studies investigating the efficacy and safety of such drugs, but very few have sought to establish these parameters specifically in women.

The newest lipid-lowering agents are the statins, which are 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors; one of the most recent additions to this group is fluvastatin. In contrast to the existing agents such as lovastatin, simvastatin and pravastatin, which are derived from fungal metabolites, fluvastatin is an entirely synthetic molecule. It has undergone extensive investigations in clinical trials to establish its efficacy, safety and tolerability in patients with primary hypercholesterolaemia whose LDL cholesterol levels were not adequately controlled after at least 8 weeks on a sustained lipid-lowering diet. Data from these studies have been included in an international database.

The purpose of this study was to determine the influence of gender on the efficacy, safety and tolerability of fluvastatin by analysing pooled data from controlled clinical studies.

1. Methods

Studies with fluvastatin have been conducted in North America, Europe and Israel, and the international database includes more than 2600 patients. The present analysis includes all patients who participated in randomised double-blind controlled clinical trials and who received fluvastatin dosages of $\geq 20$ mg/day or placebo. The data include the patients' demographic details and other baseline characteristics; details of efficacy in terms of response to treatment based on plasma levels of LDL cholesterol, HDL cholesterol and TG; and major safety data based on plasma levels of the transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and creatine...