AstraZeneca

NL950057

SUMMARY

ASTRAZENECA PHARMACEUTICALS

ACTIVE INGREDIENT: Rosuvastatin

Trial title (number): Evaluation of the efficacy of rosuvastatin in daily practice in untreated high risk patients and patients with a history of cardiac disease. (CHALLENGE)

Developmental phase: IV
First subject recruited: 17 September 2003
Last subject completed: 18 May 2005
Approval date: not applicable

OBJECTIVES

In an observational multi-centre study (CHALLENGE), the effects were assessed of starting treatment with low doses of rosuvastatin in statin naive patients with a history of coronary heart disease (CHD), peripheral vascular disease (PVD), cerebrovascular accident (CVA), transient ischemic attack (TIA) or diabetes (DM), on low-density lipoprotein cholesterol (LDL-C) goal achievement. Also proportional changes in LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG) and the ratio TC/HDL-C were studied.

METHODS

Study design & patients

The CHALLENGE study is an observational study conducted in 181 centres in the Netherlands. The centres consist of practices of specialists in internal medicine and cardiologists. All patients approved to place anonymous results at the disposal of AstraZeneca. In total 2,660 patients were included in the study. Patients eligible for the study were high-risk patients with a documented history of CHD, PVD, cerebrovascular atherosclerotic disease, DM II or DM I with microalbuminuria. LDL-C had to be $\geq$ 2.5 mmol/l and the patient did not use any cholesterol lowering medication during the last 3 months preceding inclusion. The specialist made the decision to start treatment with rosuvastatin irrespective of study participation. Exclusion criteria included patients familiar with muscular pain, myopathy or liver function disorders (inclusive elevation of serum transaminases), patients with familial dyslipideamia like familial hypercholesterolaemia and familial combined hyperlipideamia and/or patients with contra-indications for treatment with rosuvastatin. Patients were their own historical control. Patients were seen at 2 time points. The first visit took place when the specialist decided to start treatment

with rosuvastatin and the patient had LDL-C $\geq$ 2.5 mmol/l. Patient characteristics, medical history including myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass surgery (CABG), angina pectoris (AP), CVA, TIA, PVD, DM II, DM I with microalbuminuria, smoking behaviour, and if available TC, HDL-C and TG were obtained. The second visit took place when LDL-C was measured again to determine effectiveness of rosuvastatin treatment. Like in daily practice, the time between the two visits was variable. If measured, other lipids were also documented as well as serious adverse events, continuation with rosuvastatin and discontinuation as a result of (serious) adverse events (DAE).

Efficacy and safety parameters/assessments

The efficacy analysis was performed on intention-to-treat basis (ITT). Patients satisfying inclusion criteria and where at least LDL-C at visit 1 was measured, were included. The primary efficacy measure was the proportion of patients reaching LDL-C goal of < 2.5 mmol/l at visit 2. This goal has been recently formulated for high-risk patients by the Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice (2). Secondary efficacy measures included the proportional change from baseline of LDL-C, HDL-C, TC/HDL-C, TC and TG at visit 2. Additional analysis was carried out in order to increase insight in different subgroups of medical history and risk factors. In the first analysis, patients in specified groups had one risk factor and not a combination of different risk factors. The second analysis included subgroups of patients with a combination of different risk factors. In addition, absolute changes in LDL-C were determined.

Standard safety assessments included the registration of all SAE's and adverse events resulting in discontinuation (DAE) of rosuvastatin. All SAE's were to be documented and reported within 1 day to AstraZeneca. A SAE was defined as an AE leading to death, life-threatening situation, in-patient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity, a congenital abnormality/birth defect, or an important medical event. All patients satisfying the inclusion criterion of LDL $\geq$ 2.5 mmol/l and where visit 2 was performed, were evaluated for safety.

Statistical analysis

All data were analysed according to the intention-to-treat principle. Primary end point was the proportion of the ITT patients reaching LDL-goal of < 2.5 mmol/l at visit 2. Primary end point was also calculated for different subgroups of medical history and risk factors, with the corresponding 99% confidence intervals. Secondary end point was the proportional change (including 99% CI) from baseline of LDL-C, HDL-C, TC/HDL-C, TC and TG at visit 2. Changes were tested with a one-sample t-test. The overall P value indicating statistical significance was set at 0.01. Absolute changes from baseline to visit 2 for LDL-C were tested by a paired t-test.
Safety data were summarized by descriptive statistics.

RESULTS

Characteristics

A total number of 2,660 high-risk patients in 181 different centres were enrolled in the study by cardiologists and specialists in internal medicine. During the 3 months before enrolment in the study, patients were not treated with cholesterol lowering medication. The specialist made the decision to start treatment with rosuvastatin. This decision was made irrespective of study participation.

Of the 2,660 patients 55 (2.1%) did not meet the inclusion criterion of LDL-C≥ 2.5 mmol/l and 11 (0.4%) patients were not known with CHD, PVD, CVA, TIA, DM II or DM I with microalbuminuria. This resulted in an ITT population of 2,595 patients (one patient did not meet both criteria). The main baseline characteristics are depicted in Table 1 and are mainly based on these 2,595 patients. Year of birth was missing in 18 patients, smoking behaviour in 19 patients and the measurement of cholesterol was incomplete in 66 patients (2.5%). Therefore the number of patients may slightly vary between the different parameters. The daily starting dose of rosuvastatin was 10 or 20 mg. Most of the patients (88.6%) started with 10 mg a day, 11.1% started with 20 mg and in 0.3% of the patients starting dose was unknown. Baseline lipid levels in the 20 mg group were less favourable compared to the ITT group: LDL-C was 4.68 mmol/l, HDL-C was 1.28 mmol/l, TC was 6.90 mmol/l and TG was 2.34 mmol/l.

In all 2,595 patients some information was gathered about parameters of visit 2. But in a considerable amount of patients one or more items of visit 2 were missing. Measurement of cholesterol at visit 2 was incomplete in 223 patients (8.6%) and the date was missing in 117 patients (4.5%). In case LDL-C in visit 2 was unknown, these patients were evaluated as not reaching LDL-C goal. Secondary end point could not be determined in 161 patients for changes in LDL-C, 209 patients for changes in HDL-C, 177 patients for changes in TC, 229 for changes in TG and 212 for changes in the ratio of TC/HDL-C. Results of safety assessment are based on the total ITT population.

Table 1. Baseline characteristics

Characteristics	Numbers (%)
Number of patients	2,595
Male	1,525 (58.8)
Female	1,070 (41.2)
Age (years ± sd)	62.1 (11.4)
Male (years ± sd)	61.0 (11.3)
Female (years ± sd)	63.6 (11.5)
Medical History	
Myocardial infarction	616 (23.7)
PTCA and/or CABG	542 (20.9)
Angina pectoris	884 (34.1)
Ischemic CVA	174 (6.7)
TIA	170 (6.6)
PVD	393 (15.1)
Diabetes Mellitus type II	733 (28.2)

Diabetes Mellitus type I with microalbuminuria	47 (1.8)
Smoking behaviour	
Yes	676 (26.1)
No	1,900 (73.2)
Unknown*	19 (0.7)
Cholesterol (mmol/l ± sd)	
LDL-C (N = 2,595)	4.19 (0.97)
HDL-C (N = 2,551)	1.32 (0.46)
TC (N = 2,568)	6.31 (1.21)
TG (N= 2,534)	2.09 (1.27)

* *These data are not available. PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass surgery; CVA, cerebrovascular accident; TIA, transient ischemic attack; PVD, peripheral vascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.*

Cholesterol goal achievement

The mean time between visit 1 and 2 was 93.6 days with a standard deviation (sd) of ± 63.5. The range was wide because this observational multi-centre study represents daily practice of different specialists. Maximum effect of rosuvastatin is reached after 4 weeks of treatment. In 26 patients (1%) visit 2 took place before 4 weeks had passed.
At visit 2 LDL-C goal of < 2.5 mmol/l was reached in 62.7% (99% CI: 60.3-65.2) of the ITT population. Studying the group of patients starting with 10 mg rosuvastatin, LDL-C goal was reached in 63.0% (99% CI: 60.4-65.6). The goal was also determined for the following groups of medical history: CHD (MI, PTCA/CABG, AP), cerebrovascular atherosclerotic disease (CVA,TIA), PVD, DM II and DM I with microalbuminuria. Table 2 shows the proportion of patients achieving the goal of LDL-C < 2.5 mmol/l for above mentioned groups. Patients in specified groups of the first part of table 2 had one risk factor and not a combination of different risk factors. The patients with a combination of risk factors are omitted and therefore the total number of patients is less than 2,595. The proportion of patients reaching LDL-C goal in the DM II group was rather high compared to the other groups, whereas the groups DM I with microalbuminuria and PVD showed low proportions. In the second part of table 2 the proportion of patients reaching LDL-C goal for the same groups of medical history were determined. In contrast with previous analyses these groups were allowed to have a combination of different risk factors. The total number of patients therefore exceeds 2,595. Another important risk factor for CVD is smoking. 676 Patients were smokers and LDL-C goal in this group was reached in 58.6% of the patients (99% CI: 53.7-63.5). In the non-smoking group (N=1,900) this percentage was 64.3 (99% CI: 61.4 - 67.1) (Table 2). The difference was 5.7% (99% CI: 0.03-11.3).

Table 2 Proportion of patients reaching LDL-C < 2.5 for different subgroups.

	Only one risk-factor		**Combination of risk-factors**	
Risk factor	**N**	**Proportion (99% CI)**	**N**	**Proportion (99% CI)**
All risk factors (ITT)*	-	-	2,595	62.7 (60.3 – 65.2)
Coronary heart disease	1,275	60.4 (56.9 – 63.9)	1,657	62.5 (59.4 – 65.5)

CVA / TIA	175	62.9 (53.3 - 72.4)	332	65.7 (58.9 – 72.4)
PVD	198	51.5 (42.3 – 60.8)	393	59.3 (52.9 – 65.7)
DM type I + microalb.	26	53.9 (26.1 – 81.6)	47	66.0 (47.2 – 84.7)
DM type II	413	67.3 (61.3 – 73.3)	733	69.2 (64.8 – 73.6)
DM type I + II	439	66.5 (60.7 – 72.4)	780	69.0 (64.7 – 73.3)
Smoking*	-	-	676	58.6 (53.7 – 63.5)
Not smoking*	-	-	1,900	64.3 (61.4 – 67.1)

* All risk factors, smoking and not smoking group always had a combination of different risk factors.

To see the impact of rosuvastatin on secondary prevention, all patients with a history of cardiac disease but without DM were analysed. Patients with secondary prevention were defined as having a documented history of CHD, PVD and/or cerebrovascular atherosclerotic disease. This group included 2,156 patients and 61.9% of these patients (99% CI: 59.2-64.6) reached LDL-C goal of < 2.5 mmol/l.

Lipid changes

At visit 2 rosuvastatin reduced LDL-C by 44.3% (99% CI: 43.3-45.3), TC by 29.1% (99% CI: 27.2-31.1), TG by 14.1% (99% CI: 11.0-17.3) and the ratio TC/HDL-C by 27.3% (99% CI: 23.9-30.8). HDL-C increased by 3.6% (99% CI: 2.0-5.2). All changes were significant with a p-value < 0.0001.

Table 3 summarizes the baseline cholesterol values and proportional changes in cholesterols in the ITT group and all subgroups of medical history. For LDL-C also the absolute changes are shown. Patients in one category had only one risk-factor and not a combination of risk factors. For all groups the reduction in LDL-C, TC-C, TG-C and TC/HDL-C was highly significant ($p < 0.0001$), except the change in TG for the diabetic type I and II group. Changes in HDL-C were not significant for CVA/TIA, PVD and the diabetic group.

Table 3. Proportional lipid changes and absolute LDL-C changes from baseline to visit 2 for different groups of medical history.[#]

	ITT[2]	CHD[3]	CVA/TIA[3]	PVD[3]	DM I + II[3]
Numbers	2,595	1,275	175	198	439
LDL-C[1] baseline	4.19 (0.96)	4.25 (0.96)	4.12 (0.91)	4.50 (1.11)	4.05 (0.95)
% change	-44.3% *	-44.1% *	-43.0% *	-43.7% *	-44.8% *
Mean change in LDL-C	1.90 * (0.98)	1.93 * (0.99)	1.83 * (0.95)	2.01 * (1.04)	1.86 * (1.01)
HDL-C[1] baseline	1.32 (0.46)	1.33 (0.49)	1.39 (0.54)	1.37 (0.42)	1.30 (0.42)
% change	3.6% *	3.7% *	3.4% [ns]	3.1% [ns]	1.6% [ns]

TC[1] baseline	6.31 (1.20)	6.31 (1.24)	6.29 (1.18)	6.73 (1.14)	6.27 (1.24)
% change	-29.1% *	-27.6% *	-27.8% *	-32.2% *	-30.8% *
TG[1] baseline	2.09 (1.27)	2.03 (1.17)	2.13 (1.42)	2.05 (1.11)	2.26 (1.56)
% change	-14.1% *	-14.5% *	-19.4% *	-17.2% *	-8.0% [ns]
TC/HDL-C baseline	5.18 (1.86)	5.16 (1.63)	4.91 (1.53)	5.36 (2.03)	5.17 (1.55)
% change	-27.3% *	-25.4% *	-23.9% *	-32.9% *	-27.8% *

[#] Patients in specified subgroups (CHD, CVA/TIA, PVD and DM I+II) had one risk-factor and not a combination of different risk factors.The patients with a combination of risk factors are omitted and therefore the total number of patients is less than 2,595. CHD[2] group consists of MI, PTCA/CABG or AP.

[1]LDL-C, HDL-C, TC and TG are depicted in mmol/l (sd).

[2]ITT group includes all risk factors.

[3]CHD, coronary heart disease; CVA, cerebrovascular accident; TIA, transient ischemic attack; PVD, peripheral vascular disease; DM I + II, diabetes mellitus type I with microalbuminuria and type II.

[ns]: not significant, * $p < 0.0001$.

In Table 4 the analyses are repeated for subgroups of medical history allowing a combination of different risk-factors. This results in larger subgroups. The results are comparable to the results in Table 3.

Table 4. Proportional lipid changes and absolute LDL-C changes from baseline to visit 2 for different groups of medical history.[#]

	ITT[2]	CHD[3]	CVA/TIA[3]	PVD[3]	DM I + II[3]
Numbers	2,595	1,657	332	393	780
LDL-C[1] baseline	4.19 (0.96)	4.21 (0.96)	4.10 (0.95)	4.31 (1.04)	3.99 (0.89)
% change	-44.3% *	-44.4% *	-43.7% *	-44.3% *	-44.7% *
Mean change in LDL-C	1.90 * (0.98)	1.92 * (0.98)	1.86 * (0.96)	1.94 * (0.97)	1.83 * (0.96)
HDL-C[1] baseline	1.32 (0.46)	1.31 (0.47)	1.36 (0.47)	1.34 (0.42)	1.30 (0.41)
% change	3.6% *	4.3% *	2.8% [ns]	6.6% [ns]	2.0% [ns]
TC[1] baseline	6.31 (1.20)	6.28 (1.21)	6.21 (1.19)	6.52 (1.12)	6.20 (1.11)
% change	-29.1% *	-28.4% *	-28.2% *	-31.7% *	-31.1% *
TG[1] baseline	2.09 (1.27)	2.04 (1.16)	2.07 (1.35)	2.10 (1.16)	2.20 (1.43)
% change	-14.1% *	-14.7% *	-18.6% *	-15.5% *	-11.8 *
TC/HDL-C baseline	5.18 (1.86)	5.21 (1.96)	4.95 (1.54)	5.40 (2.95)	5.14 (1.52)
% change	-27.3% *	-26.7% *	-26.4% *	-32.9% *	-28.8% *

[#] Patients in specified subgroups (CHD, CVA/TIA, PVD and DM I+II) were allowed to have a combination of different risk-factors.The total number of patients therefore exceeds 2,595. CHD group consists of MI, PTCA/CABG or AP and might also have other risk factors.

[1]LDL-C, HDL-C, TC and TG are depicted in mmol/l (sd).

[2]ITT group includes all risk factors.

[3]CHD, coronary heart disease; CVA, cerebrovascular accident; TIA, transient ischemic attack; PVD, peripheral vascular disease; DM I + II, diabetes mellitus type I with microalbuminuria and type II.

[ns]: not significant, * $p < 0.0001$.

Safety

All patients of the ITT population (N=2,595) were included for safety assessment. SAE's were reported in 8 patients (0.3%). Three patients died due to cardiac failure and one patient died due to respiratory insufficiency (known COPD patient). The other reported SAE's were angina pectoris, muscle pain, decompensatio cordis and pneumonia.
Rosuvastatin was stopped during the study in 4.3% of the patients (N=112). The main reason to stop medication was because of an DAE or SAE (2.5%). 1.8% (N=46) Of all patients stopped medication for other reasons. They reported 80 DAE's. The most frequently reported DAE's are shown in Table 5.

Table 5. Most frequent adverse events leading to discontinuation of medication

Adverse event (DAE)	Frequency
Myalgia	16
Nausea	10
Headache	8
Diarrhoea	4
Itch	3
Rash	3

REFERENCE: None

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Crestor™ (rosuvastatin), Healthcare Professionals should view their specific country information.