CLINICAL RESEARCH

Effects of rosuvastatin and atorvastatin on the apolipoprotein B/apolipoprotein A-1 ratio in patients with an acute coronary syndrome: The CENTAURUS trial design

Effet de la rosuvastatine et de l’atorvastatine sur l’ApoB/ApoA-1 chez les patients avec syndrome coronaire aigu (étude CENTAURUS)

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Summary
Background. — The mechanism underlying rapid, statin-induced event reduction in patients with an acute coronary syndrome (ACS) remains to be clarified.
Aim. — The primary objective is to compare the efficacy of rosuvastatin 20 mg/day and atorvastatin 80 mg/day in reducing the apolipoprotein B/apolipoprotein A-1 (apoB/apoA-1) ratio at three months, in ACS patients. Secondary objectives include a comparison of the effects of early-started rosuvastatin and placebo on inflammatory markers.

Methods. — This is a randomized, double-blind, parallel-group study. Patients with non-ST-segment elevation ACS, symptom onset less than 48 h before admission, and for whom a percutaneous coronary intervention is planned, are eligible for inclusion and are randomized into three groups (G1, G2 and G3). The study comprises two double-blind periods. Period 1 starts at hospital admission and lasts until Day 0 (discharge or less or equal to 6 days after admission); patients in G1 receive one tablet of rosuvastatin 20 mg/day and patients in G2 and G3 receive one matching placebo tablet per day. Period 2 starts at Day 0 and lasts for three months; patients in G1 continue to receive rosuvastatin 20 mg/day, patients in G2 receive rosuvastatin 20 mg/day and patients in G3 receive atorvastatin 80 mg/day. Recruitment of 1075 patients will ensure an 80 power to detect a 3% difference in percentage change in the apoB/apoA-1 ratio and a 20% difference in percentage change in high-sensitivity C-reactive protein.

Results. — Inclusion phase is complete; results will be reported at a later date.

Conclusion. — This is the first trial investigating the effect of statins on apolipoproteins in ACS patients.

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Introduction

The updated NCEP ATP III guidelines advocate the consideration of intensive statin therapy for all patients admitted to hospital with an acute coronary syndrome (ACS) — a recommendation that arises from the results of studies assessing the benefit of early statin treatment in this patient population [1—5]. The mechanism underlying the early effect of statin therapy is still unclear, but may involve both lipid-related effects and other purported pleiotropic effects [6], including effects on inflammatory markers such as CRP and thrombotic markers.

The elevated plasma levels of CRP detected in the first days of an ACS may reflect not only a high prevalence of myocardial necrosis [7], ischaemia-reperfusion damage or severe coronary atherosclerosis, but also an increased systemic inflammatory response, and have been associated with unfavourable short- and long-term prognoses [8—12].

The Myocardial ischemia reduction with acute cholesterol lowering (MIRACL) study showed that the early use of atorvastatin 80 mg/day potentiated the decline in inflammation in patients with ACS compared with placebo [13]. In another double-blind, placebo-controlled study in...
90 patients admitted within 48 h of ACS onset and with CRP concentration greater or equal to 1.4 mg/dL, a rapid decrease in CRP concentration was seen with the early use of atorvastatin 40 mg/day [14]. In both studies, CRP concentration decreased spontaneously in the placebo group.

Our CENTAURUS study is designed to compare the effects of early treatment with rosuvastatin 20 mg/day or atorvastatin 80 mg/day in patients with an ACS. Recent studies have shown that the apoB/apoA-1 ratio may be one of the strongest predictors of acute fatal MI [15,16]. Moreover, apolipoprotein concentration is unaffected by fasting status, unlike LDL-C concentration [17]. A maximal post-MI reduction in LDL-C concentration of 47% occurs at day 7 [18], and TG concentration increases after MI by about 58% [18]. Our study is the first to evaluate the change in apoB/apoA-1 ratio during the acute phase of ACS. In addition, we will investigate the early effects of rosuvastatin (started before PCI) on inflammatory markers.

Methods

Trial design

CENTAURUS is an international, multicentre, randomized, double-blind, parallel-group study comparing the efficacy and safety of rosuvastatin 20 mg/day versus atorvastatin 80 mg/day in patients with an ACS. Patients are being recruited from Belgium, Canada, Estonia, France, Greece, Hungary, Ireland, Italy, Portugal, Spain and Tunisia.

The study is being conducted in accordance with the Declaration of Helsinki and under the principles of good clinical practice, as laid out in the International conference on harmonisation document “Good clinical practice: Consolidated guidance” [19].

Study population

The inclusion criteria are:

- age greater than or equal to 18 years;
- diagnosed with NSTE-ACS;
- admitted to hospital less than 48 h after the onset of symptoms;
- evidence of coronary artery disease in addition to ischaemic symptoms;
- a PCI planned or anticipated within four days for treatment of the index event, in accordance with local or European guidelines for PCI [20].

Patients with NSTE-ACS include those with unstable angina and NSTEMI [21,22].

The exclusion criteria are:

- STEMI;
- cholesterol-lowering medication in the preceding month;
- contraindication for statin treatment;
- homozygous familial hypercholesterolemia;
- CK concentration greater than three times ULN and CK-MB concentration less than two times ULN at visit 1 (if CK-MB unavailable, cardiac troponin I or T concentration = 0 at visit 1);
- planned coronary revascularization other than primary PCI during the current hospitalization;
- coronary artery bypass graft or PCI in the three months before visit 1;
- occurrence of ventricular fibrillation, sustained ventricular tachycardia, complete heart block, new onset atrial fibrillation with uncontrolled ventricular rate (greater than 100 beats per minute), or paced ventricular rhythm in the four weeks before visit 1;
- stroke, sepsis, acute pericarditis, or any evidence of systemic or pulmonary embolus in the preceding four weeks;
- pregnancy;
- initiation of hormone-replacement or oral contraceptive therapy (in women) in the three months before visit 1.

Randomization

The study is divided into two double-blind periods with randomization at the beginning of the first period (Fig. 1). Period 1 starts at the hospital admission of the patient for an ACS and lasts until hospital discharge (or for a maximum of six days). Period 2 starts at Day 0 (i.e., at hospital discharge or six days after admission) and lasts for three months.

After validation of eligibility, patients are randomized into one of three treatment groups (G1, G2 and G3; Fig. 1) in a ratio of 1:2:2, by means of a telephone call to an interactive voice response system, as soon as possible after informed consent is obtained. Informed consent must be obtained before any study-related examination or drug administration. Participation in a pharmacogenomic substudy is optional, and requires completion of a separate written consent form.

Intervention

In Period 1, patients receive treatment with either one tablet of rosuvastatin 20 mg/day (G1) or one matching tablet of rosuvastatin 20 mg/day (G1) or one matching
placebo tablet per day (G2 and G3). The first dose should be taken within 48 h of symptom onset, and as soon as possible after randomization (ideally within 2 h of randomization). Two doses of study medication are strongly recommended before the PCI. If the PCI is planned earlier, just after hospital admission, the first dose of study treatment should be taken after randomization and the second dose as soon as possible after the PCI. A minimum time period of 12 h is recommended between the first two doses.

After Period 1 and throughout Period 2, patients in G1 continue to receive rosuvastatin 20 mg/day, patients in G2 also receive rosuvastatin 20 mg/day and patients in G3 receive atorvastatin 80 mg/day, in accordance with the original randomization. To ensure blinding, patients are instructed to take one tablet and two capsules with water once daily, at any time of the day. Each tablet contains rosuvastatin 20 mg or matching placebo and each capsule contains atorvastatin 40 mg or matching placebo. The first Period 2 dose takes place on the day after the last Period 1 dose. The final dose is administered three months later, on the day of visit 4. Investigators provide general diet counselling to patients at the following visits.
Assessments

Efficacy assessments comprise measurement of the concentrations of inflammatory markers (hs-CRP, soluble CD40, interleukin-10 and interleukin-18) and evaluation of the lipid profile (total cholesterol, LDL-C, high-density lipoprotein cholesterol, TG, apoB and apoA-1).

Safety assessments include chemistry tests (creatinine, alanine transaminase, CK and CK-MB), measurement of the concentrations of cardiac troponin (I or T), thyroid-stimulating hormone and haemoglobin A1c and adverse events.

Pharmacogenomic substudy

Blood samples are taken for the central determination of the concentrations of inflammatory markers and cardiac troponin T, and for analysis of potential new markers of cardiovascular disease.

Study outcomes

The primary efficacy outcome is percentage change in the apoB/apoA-1 ratio from Day 0 to three months. The secondary outcomes are as follows:

- percentage change in lipid concentrations from Day 0 to one month and three months;
- percentage change in inflammatory marker concentrations from randomization to one month and three months;
- percentage changes in lipid, cardiac troponin and inflammatory marker concentrations from randomization to Day 0;
- percentage of patients reaching their established 2003 European LDL-C concentration target of 2.58 mmol/L (100 mg/dL) [23] at three months;
- percentage of patients reaching their updated 2004 NCEP ATP III LDL-C concentration target of 1.81 mmol/L (70 mg/dL) [3] at three months;
- percentage change in hs-CRP concentration from randomization to Day 0 (area under the curve [AUC] of hs-CRP) and to one month and three months;
- incidence and severity of adverse events and abnormal laboratory values during the study;
- incidence of major adverse clinical events (death, non-fatal MI, non-fatal stroke, documented unstable angina requiring hospitalization and repeat coronary revascularization) during the study.

Secondary efficacy outcomes

Considering a non-inferiority margin of 3%, an S.D. of 14% and a 2-sided significance level of 5%, 343 evaluable patients per group will give 80% power to demonstrate non-inferiority in LDL-C concentration reduction from the beginning of Period 2 between rosuvastatin 20 mg/day (G2) and atorvastatin 80 mg/day (G3). The upper limit of the two-sided 95% CI has to be less than 3% to conclude non-inferiority. A 3% non-inferiority margin has been chosen as it corresponds to less than half of the effect of a dose doubling (statins generally produce an extra 6% reduction in LDL-C concentration for every doubling of dose) [25].

To compare the effect of rosuvastatin 20 mg/day and placebo on the concentration of hs-CRP and other inflammatory markers at the end of Period 1, 686 placebo-treated patients (G2 plus G3) and 172 rosuvastatin-treated patients (G1) will give approximately 80% power to detect an absolute difference of 20% in hs-CRP percentage change in concentration from baseline, assuming an S.D. of 70% for hs-CRP percentage change in concentration from baseline and a 20% adjustment for the use of a non-parametric method in the analysis.

Taking all these calculations into consideration, and assuming a 20% drop-out rate, 1075 patients will have to be included.

Statistical analysis

The statistical analysis of Period 2 data will include all patients who have taken greater than or equal to one dose of study medication, have a baseline lipid measurement at Day 0 and have greater than or equal to one post-baseline measurement of one lipid variable. The analyses will be done using the last observation carried forward method.

The statistical analysis of Period 1 data will comprise secondary endpoints only and will include all patients who have taken greater than or equal to one dose of study medication, have greater than or equal to one lipid variable or inflammatory marker measurement at admission and greater than or equal to one lipid variable or inflammatory marker measurement post-admission. Analyses will use observed data.

The safety population will consist of all randomized patients who have taken greater than or equal to one dose of study medication. A per-protocol population will also be defined, to provide for the occurrence of an unforeseen event that requires a sensitivity analysis.

Percentage change in the apoB/apoA-1 ratio from Day 0 to three months will be compared between G2 and G3 using an analysis of variance, with treatment and country included in the model. The hypothesis of superiority of rosuvastatin compared with atorvastatin will be tested by an upper limit of 95% CI for the difference between treatments being less than zero. Data from G1 will be summarized only.

Percentage change in LDL-C concentration from Day 0 to one month and three months will be compared between G2 and G3 using the same method as for the primary efficacy outcome. Percentage change in other lipid concentrations from Day 0 to one month and three months will be summarized.

Percentage change in hs-CRP concentration from randomization to Day 0 will be compared between G1 and G2.
The effect of early, intensive statin therapy on acute coronary syndrome.

**Table 1** The effect of early, intensive statin therapy on acute coronary syndrome.

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A meta-analysis of randomised controlled trials [26] investigating the effect of early, intensive statin therapy on patients with an acute coronary syndrome [32].

The percentage change in hs-CRP concentration from Day 0 to one month and three months, and all the percentage changes in the concentrations of other inflammatory markers and cardiac troponin will be summarized descriptively.

The data relating to hs-CRP from randomization to Day 0 will also be explored using plots and AUC (assuming that more than three measurements are available between randomization and Day 0).

The percentage of patients reaching the 2003 European LDL-C concentration target [23] and updated 2004 NCEP ATP III LDL-C concentration target [3] will be presented, with 95% CI in each group.

**Interim analysis and timelines**

No interim analysis is planned. The final version of the protocol was approved by the local ethics committees in December 2005. The first patient was enrolled in January 2006 and by June 2007, 1120 patients had been enrolled.

**Discussion**

Some new data have been published since the design and start of the CENTAURUS trial. In the A to Z trial, the hs-CRP concentrations achieved 30 days and four months after ACS were found to be associated independently with long-term survival [26]. In another study, atorvastatin 40 mg/day was shown to reduce CRP concentration rapidly in patients admitted within 48 h of onset of ACS and with CRP concentration greater than or equal to 1.4 mg/dL [14]. In CENTAURUS, the hs-CRP concentration will be estimated at 30 days and three months.

More recently, a meta-analysis was published on 13 randomized controlled trials in patients with ACS [1,4,27–38]. Time to initiation of treatment ranged from one day to 14 days, with a median duration of four days. In CENTAURUS, statin treatment will start less than or equal to six days after hospitalization. The meta-analysis provides evidence that early, intensive statin therapy is associated with a reduction in adverse cardiovascular outcomes, particularly cardiovascular death, unstable angina and revascularization, when prescribed within 14 days of hospitalization for ACS. These benefits took more than four months to begin to accrue and were sustained for two years (Table 1). There was no significant evidence that reduction in LDL-C concentration influenced these results [32].

The atorvastatin for reduction of myocardial damage during angioplasty acute coronary syndromes (ARMYDA-ACS) study in patients with NSTE-ACS [39] undergoing early coronary angiography (<48 h) and PCI was published after the meta-analysis. Patients were randomized to pretreatment with atorvastatin (80 mg, 12 h before PCI, with a further 40 mg preprocedure \( N = 86 \)) or placebo \( N = 85 \). Patients already receiving statin therapy were excluded. Short-term pretreatment with atorvastatin reduced the incidence of cardiac events compared with placebo, with the difference being driven essentially by a significant reduction in periprocedural MI.

To date, no data have been published on the effect of statins on apoB or apoA-1 in patients with ACS.

**Conclusion**

CENTAURUS will provide important information on the anti-inflammatory effects of early treatment with rosuvastatin 20 mg/day, and will be the first trial to compare the effects of rosuvastatin 20 mg/day and atorvastatin 80 mg/day on lipid profiles and to explore the change in the apoB/apoA-1 ratio, in patients with an ACS.
Funding

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Conflict of interest

None declared.

Acknowledgements

The CENTAURUS Steering Committee initiated the trial, and will review the data independently, confirm all statistical analyses independently, and support the preparation of all manuscripts for publication. The Steering Committee comprises: J.-M. Lablanche, France; J.-C. Tardif, Canada; J. Alonso, Spain; P. Crean, Ireland; A. Leone, Belgium; J. Morais, Portugal; and M. Santini, Italy. The Endpoint Adjudication Committee comprises: P. Gueret, France; I. Mahet, France; and M. White, Canada.

References


