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ORIGINAL ARTICLE

Rationale and design of assessment of lipophilic vs. hydrophilic statin therapy in acute myocardial infarction (the ALPS-AMI) study

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Summary
Background: Statins reduce the incidence of cardiovascular events in patients with acute myocardial infarction (AMI). Although all statins are equally effective in secondary prevention, there might be certain differences in the effects of lipophilic and hydrophilic statins. Therefore, our aim is to compare the effectiveness of lipophilic atorvastatin and hydrophilic pravastatin in secondary prevention after AMI.
Methods and results: This study is a prospective, randomized, open-label, multicenter study of 500 patients with AMI. Patients that have undergone successful percutaneous coronary intervention will be randomly allocated to receive either atorvastatin or pravastatin with the treatment goal of lowering their low-density lipoprotein-cholesterol level below 100 mg/dl for 2 years. The primary endpoint will be death due to any cause, nonfatal MI, nonfatal stroke, unstable angina, or congestive heart failure requiring hospital admission, or any type of coronary revascularization.
Conclusion: This is the first multicenter trial to compare the effects and safety of lipophilic and hydrophilic statin therapy in Japanese patients with AMI. It addresses an important issue and could influence the use of statin treatment in the secondary prevention of coronary artery disease.

Introduction

Cardiovascular incidents are the second leading cause of death in Japan. Many large-scale clinical

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trials in Western countries have shown that statins reduce the incidence of cardiovascular events in patients with acute myocardial infarction (AMI) [1]. Recently, several studies on the beneficial effects of early statin therapy for Japanese patients with AMI have been reported [2,3]. The OACIS-LIPID study of Japanese patients with AMI revealed that early treatment with pravastatin reduces the recurrence of major adverse cardiac events; there was a 44% relative reduction in the primary combined endpoint of death, nonfatal MI, unstable angina, stroke, revascularization, and other cardiovascular diseases [4]. In the MUSASHI-AMI study of Japanese patients with AMI, a lipid-lowering strategy with statins decreased subsequent cardiovascular events, particularly, congestive heart failure and unstable angina [5]. In the ESTABLISH study of Japanese patients with acute coronary syndromes, early aggressive lipid-lowering therapy with atorvastatin for 6 months significantly decreased the plaque volume in the coronary arteries, as measured by serial intravascular ultrasound [6].

Different statins are equally effective in secondary prevention after AMI. However, based on studies in which experimental animal models were used, it has been reported that each statin has a different effect depending on its water solubility [7,8]. For example, in comparison with hydrophilic pravastatin, lipophilic statins enhance myocardial stunning in association with adenosine triphosphate reduction after ischemia—reperfusion injury in dogs. This suggests that hydrophilic statins might be more cardioprotective than lipophilic statins, particularly in patients undergoing reperfusion therapy for AMI. Indeed, in a subanalysis of the MUSASHI-AMI study, hydrophilic pravastatin was found to be superior to lipophilic statins in preventing new Q-wave appearance and reducing cardiovascular events [9]; however, this was a retrospective reanalysis of the MUSASHI-AMI study in which patients were randomized to any available statin or control (no statin) [5]. It has been reported that clopidogrel is less effective in inhibiting platelet aggregation when coadministered with atorvastatin, while its effectiveness was not altered by pravastatin. This is because atorvastatin could competitively inhibit the activation of hepatic CYP3A4, which metabolizes clopidogrel to its pharmacologically active form [10]. On the other hand, lipophilic statins may be superior to hydrophilic statins in preventing cardiovascular events because of their potent pleiotropic effects such as the inhibition of pro-inflammatory cytokine production or matrix metalloproteinase expression [11,12].

The PROVE-I trial, which was a head-to-head comparison of lipid-lowering therapy with atorvastatin and pravastatin, showed that lipid lowering with lipophilic atorvastatin at 80 mg/day provided greater protection against death and cardiovascular events than lipid lowering with hydrophilic pravastatin at 40 mg/day in patients with acute coronary syndrome [13]; however, the results reflected the difference in the low-density lipoprotein-cholesterol (LDL-C) levels achieved during follow-up (95 mg/dl vs. 62 mg/dl) rather than the difference in the water solubility of the statins. In addition, the doses of statins used in this trial exceeded the clinical doses administered in Japan. Therefore, prospective studies of lipophilic vs. hydrophilic statins at their most clinically effective doses and at equal LDL-C levels are required to identify differences between the cardioprotective effects of lipophilic and hydrophilic statins in Japanese patients with AMI.

To achieve equal LDL-C levels with both lipophilic and hydrophilic statins, we added ezetimibe to the statin therapy when the target LDL-C level of <100 mg/dl was not achieved. In comparison with the use of statins alone, the combination of statins and ezetimibe inhibits both cholesterol synthesis and intestinal cholesterol absorption, resulting in approximately 20% greater reduction in the LDL-C level [14,15]. However, it is not known whether the additional LDL-C-lowering effect achieved by ezetimibe addition to statin therapy will lead to clinical benefits.

Methods

Objective

The assessment of lipophilic vs. hydrophilic statin therapy in acute myocardial infarction (ALPS-AMI) study is a head-to-head comparison of the efficacy of lipophilic atorvastatin vs. hydrophilic pravastatin at clinical doses in Japan in secondary prevention after AMI. Based on a retrospective reanalysis of the MUSASHI-AMI study [9], we hypothesize that pravastatin will reduce the incidence of the composite endpoint of cardiovascular death, nonfatal MI, rehospitalization for unstable angina, coronary revascularization, or stroke over at least 2 years of follow-up relative to atorvastatin therapy.

Study population

The ALPS-AMI study is a prospective, randomized, open-label, blinded endpoint study. In this trial, we are enrolling men and women who have been

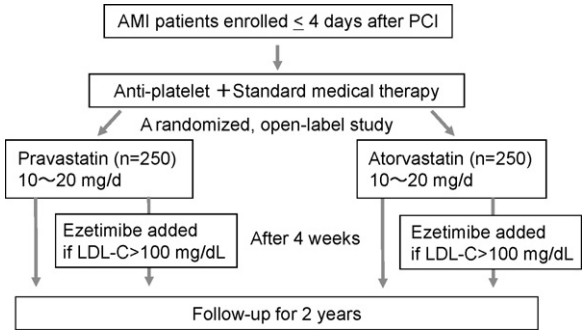

Figure 1 ALPS-AMI study design. AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; LDL-C, low-density lipoprotein-cholesterol.

hospitalized for both ST-segment elevation and non-ST-segment elevation MI. Patients with AMI who satisfy all criteria for inclusion will be enrolled within 96 h of receiving successful percutaneous coronary intervention (PCI). Such patients will provide written informed consent and be randomly allocated to receive 10 mg of either atorvastatin or pravastatin once daily (Fig. 1). Patients with prior lipid-lowering therapy will also be randomized to the atorvastatin or pravastatin groups. Their dose will be increased to 20 mg, and the treatment goal is to reduce the LDL-C level below 100 mg/dl. If the subject's LDL-C level is elevated, i.e., >100 mg/dl after 4 weeks of statin treatment, 10 mg ezetimibe will be added. Coronary angiography (CAG) will be performed at baseline and at 6—9 months after PCI. Safety monitoring includes blood tests for liver function and creatine kinase (CK) (Fig. 2).

Major exclusion criteria include the presence of hemodynamic events (hypotension, congestive heart failure, acute mitral regurgitation, or acute ventricular septal defect) and serious arrhythmic

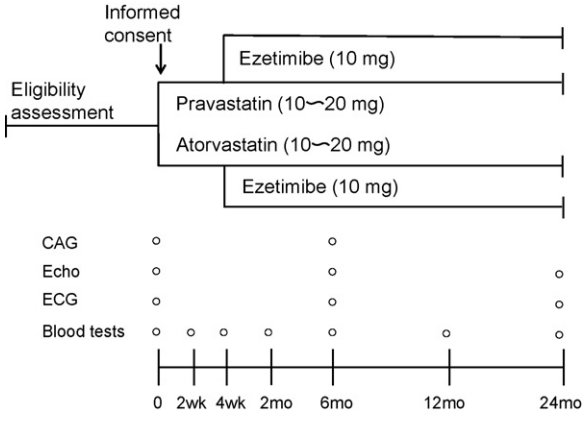

Figure 2 Flowchart showing the study timeline. CAG, coronary angiography; echo, echocardiography; ECG, electrocardiography.

events. Patients in whom coronary artery bypass grafting (CABG) is planned are excluded. Other exclusion criteria include age <18 years, pregnancy, active liver or renal disease, and subjects with LDL-C levels <70 mg/dl without statin therapy.

Participants will be recruited at 20 participating sites in Nagano and Niigata Prefectures of Japan. The protocol has been reviewed and approved by each participating site's ethics committee, and written informed consent will be obtained. During follow-up, no specific recommendations are made with respect to the diagnostic and therapeutic strategy, with the exception that other lipid-lowering drugs should not be administered after randomization until day 28. All management decisions are left to the discretion of each patient's treating physician. Study medication is discontinued when there are concerns for the patient's safety such as the development of hepatic dysfunction or myopathy.

Patients were enrolled from July 2008, and enrollment will continue until June 2010. The study has been registered at the University Hospital Medical Information Network (UMIN) (ID 000001521).

Study endpoints

The primary endpoint is the occurrence of one of the following: death due to any cause, nonfatal MI, nonfatal stroke, unstable angina or congestive heart failure requiring hospital admission, or any type of coronary revascularization occurring at least 28 days after randomization.

The secondary endpoints include changes in the minimal lumen diameter (MLD) and % stenosis at the site of PCI, changes in left ventricular function evaluated by echocardiography, changes in the levels of serum high-sensitivity C-reactive protein and brain natriuretic peptide, the percentage of patients who achieve the target LDL-C level of <100 mg/dl, and any adverse incidents including changes in laboratory values such as those in the liver function tests and CK levels.

Sample size

The trial has been designed based on the information available up until Spring 2008. An initial sample size of 500 patients was selected to afford 80% power to detect a relative risk reduction in the primary endpoint by a two-sided two-sample *t*-test at a significance level of 0.05. The sample size was based on anticipated event rates at 1 year (9.9% in the lipophilic statin group and 3.6% in the hydrophilic statin group) [9].

Conclusion

The ALPS-AMI trial is the first multicenter trial to compare the effects and safety of lipophilic atorvastatin and hydrophilic pravastatin therapy in Japanese patients with AMI. This study addresses the important issue of the performance of lipophilic vs. hydrophilic statins in secondary prevention after AMI. It could influence the treatment of many hundreds of thousands of patients.

Appendix A.

A.1. Investigators

Uichi Ikeda, Shinshu University Hospital; *Mitsuru Kagoshima*, Joetsu General Hospital; *Noboru Watanabe*, Hokushin General Hospital; *Jiro Yoshioka*, Nagano Red Cross Hospital; *Takahisa Maruyama*, Nagano Municipal Hospital; *Takuo Misawa*, Nagano Matsushiro General Hospital; *Hiroaki Yamamoto*, Nagano Chuo Hospital; *Kazuo Hoshino*, Shinonoi General Hospital; *Osamu Kinoshita*, Azumino Red Cross Hospital; *Shunpei Sakurai*, Aizawa Hospital; *Kyohei Yamazaki*, Matsumoto Kyoritsu Hospital; *Susumu Takahashi*, Nagano National Hospital; *Kenichi Itoh*, Komoro Kosei General Hospital; *Yasuaki Takenaka*, Yodakubo Hospital; *Issei Takagi*, Saku General Hospital; *Mafumi Owa*, Suwa Red Cross Hospital; *Miki Horigome*, Nagano Prefectural Kiso Hospital; *Hiroshi Kitabayashi*, Ina Central Hospital; *Masanobu Makiuchi*, Kenwakai Hospital; *Kazuya Yamamoto*, Iida Municipal Hospital.

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