Indian Heart Journal xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original Article

Efficacy and safety of the intensive dose of rosuvastatin 40 mg/day in patients with acute coronary syndrome and at high risk of cardiovascular disease-ROSUVEES-2☆

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ARTICLE INFO

Article history:
Received 14 June 2016
Accepted 6 September 2016
Available online xxx

Keywords:
Rosuvastatin
Acute coronary syndrome
Pleiotropic
Statins
LDL-C

ABSTRACT

Background: Randomized clinical trials have established the benefits of statin therapy in acute coronary syndromes (ACS) via their pleiotropic effects.
Aim of the study: This was a 12-week, open-label, multicenter, postmarketing observational study evaluating the efficacy and safety of rosuvastatin 40 mg/day in very high-risk or high-risk Indian patients according to NCEP ATP III guidelines.
Methodology: One hundred and sixty two patients (age: 30 to 69 years) with evidence of coronary artery disease, hospitalized with chest pain with/without electrocardiogram changes and with non-ST segment elevation ACS and ST segment elevation ACS who received optimal reperfusion therapy were enrolled. The primary endpoint was the percent change from baseline in low-density lipoprotein cholesterol (LDL-C) levels at 6 and 12 weeks of treatment. Other lipid parameters, high sensitive C-reactive protein (hsCRP), glycosylated hemoglobin, and clinical biochemical parameters were also assessed.
Results: At 12 weeks, intensive therapy with rosuvastatin 40 mg/day significantly reduced LDL-C ($p < 0.001$), total cholesterol (TC) ($p < 0.001$), triglyceride ($p < 0.01$), TC/high density lipoprotein cholesterol (HDL-C) ratio ($p < 0.001$), non-HDL-C ($p < 0.001$), LDL-C/HDL-C ratio ($p < 0.001$), and hsCRP ($p = 0.034$) in very high-risk and high–risk patients with ACS. Overall, 54.5% (61/112) patients achieved LDL-C goal of <70 mg/dL. However, the change in HDL-C and very low density lipoprotein cholesterol (VLDL-C) were not significant. Few adverse events including myalgia were reported during the study.
Conclusion: Results of this study showed that 40 mg dose of rosuvastatin, initiated early and continued for 12 weeks, was effective in terms of reducing LDL cholesterol and was well tolerated.

1. Introduction

Acute coronary syndromes (ACS) result from acute obstruction of a coronary artery and may lead to consequences varying from unstable angina to sudden death.[1] Statins have emerged as the most effective lipid-lowering agents in preventing cardiovascular (CV) events in patients with established coronary heart disease (CHD).[2] Evidence accumulated over 20 years shows that statins can lower the long-term CV risk by reducing elevated low-density lipoprotein cholesterol (LDL-C), small-dense LDL-C, and C-reactive protein.[2,3]

The available evidence supports the beneficial effects of the regular use of statins in ACS, and highlights association between early initiation and reductions in recurrent coronary events and

☆ Registration number of clinical trials registry: CTRI/2014/01/004269 [Registered on: 01/01/2014].

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http://dx.doi.org/10.1016/j.ihj.2016.09.002

mortality.[4] Numerous pleiotropic effects of statins play a vital role in prevention of CV events.[5] Statins increase the release of endothelial nitric Oxide (NO) independent of cholesterol levels, thus increasing the NO production and reversing endothelial dysfunction.[1,2,6] Statins have been shown to modulate several mechanisms involved in the pathogenesis of ACS, such as stabilizing plaque and decreasing thrombogenicity and inflammation.[1,2]

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines recommend that intensive statin treatment should be used in patients admitted with ACS. As per guidelines, setting an 'optional' target of LDL-C goal <70 mg/dL for 'very high-risk' patients must be left as a therapeutic option on the basis of clinical trial evidence, whereas a LDL-C goal of <100 mg/dL can be retained as a strong recommendation for 'high-risk patients'.[7] Increasing evidence suggests that early administration of high dose statins in patients with ACS, aggressively lowers LDL-C and decreases morbidity and mortality.[8]

Randomized clinical trials evaluating statin therapy started early after ACS onset have clearly shown that administration of statins have beneficial effect on CV events at 6 months which persisted for 2 years of follow-up.[2] A meta-analysis of statin use in patients with ACS confirmed the benefits of early high-dose statin administration in decreasing recurrent myocardial ischemia and possibly coronary revascularization. A mortality benefit in patients with ACS was observed over the long term (24 months).[9] Additionally PRISM (The Platelet Receptor Inhibition in Ischemic Syndrome Management) study demonstrated that early withdrawal of statin treatment shortly after onset of ACS symptoms increases the risk of cardiac events.[6]

Intensive lipid-lowering statin regimen during ACS provides greater protection against death or major CV events, and rosuvastatin is the most potent statin currently available with the highest efficacy in decreasing LDL-C compared with other statins. Several studies have demonstrated the higher lipid-lowering efficacy of rosuvastatin over other statins. Compared with other potent statins, rosuvastatin has longer half-life of 20 hours with favorable safety profile in the dose range of 5 to 40 mg.[3,10] Rosuvastatin in the dose range of 5 to 40 mg has also shown reduction in LDL-C levels in range of 38.8–54.7 mg/dL.[10]

The results from SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin) showed that change in primary efficacy end point percent atheroma volume (PAV), was comparable between atorvastatin and rosuvastatin. However, effect on normalized total atheroma volume (TAV), a secondary end point, was significantly more with rosuvastatin as compared to atorvastatin.[11] The CENTAURUS (Comparison of the Effects Noted in The ApoB:ApoA-1 ratio Using Rosuvastatin or Atorvastatin in Patients with Acute Coronary Syndrome) study demonstrated that rosuvastatin 20 mg produced similar changes in ApoB:ApoA-1 ratio at 3 months when compared with atorvastatin 80 mg. The study showed that rosuvastatin 20 mg is as effective as atorvastatin 80 mg in intensive statin treatment.[12]

There is dearth of data on effect of high dose rosuvastatin in Indian 'high' risk and 'very high' risk patients. This study was undertaken to explore the efficacy and safety of the intensive dose of rosuvastatin 40 mg/day, initiated early and continued for 12 weeks, in 'very high' or 'high' risk Indian patients, identified as per NCEP ATP III guidelines.

2. Methods

2.1. Trial design

This was a 12-week, open-label, multicenter study (CTRI/2014/01/004269) evaluating the efficacy and safety of the intensive dose of rosuvastatin, 40 mg/day, initiated early and continued for 12-weeks, in a very high risk or high risk Indian patients, according to NCEP ATP III guidelines. Study was conducted in 12 centers spread across 6 cities in India.

Enrolled patients were prescribed and advised to self-administer commercially available rosuvastatin 40 mg orally once daily (OD) for the period of 12 weeks as per discretion of treating physicians. During the 2nd visit (after 6 weeks of treatment) and 3rd visit (after 12 weeks of treatment), patients were evaluated if he/she could tolerate rosuvastatin 40 mg and assessed history of myalgia/myopathy with increased creatine phosphokinase (CPK) enzyme levels. At the end of 12 weeks of treatment with rosuvastatin 40 mg, all patients were titrated to rosuvastatin 20 mg and continued at the discretion of the investigator. Patients, whose dose titration to rosuvastatin 20 mg was made at 2nd visit or 3rd visit, were to continue with the same dosage of rosuvastatin 20 mg at the discretion of the investigator. In addition to rosuvastatin treatment, patients were advised for therapeutic lifestyle changes (diet, exercise). All concomitant medications taken by the patient were noted in the case report form. This study did not interfere with any therapeutic or diagnostic measures taken by the treating physicians and patients were recruited regardless of past or present therapeutic regimens.

The study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines. Written informed consent was obtained from all study participants before being examined for eligibility criteria. The study protocol and the informed consent form were reviewed and approved by relevant Institutional Review Board before initiation of study.

2.2. Patients

Men and non-pregnant women aged ≥30 to ≤69 years, with evidence of coronary artery disease, who were hospitalized with recent chest pain (ischemic symptoms) with or without ECG changes; or with non-ST segment elevation acute coronary syndrome (ACS) and ST segment elevation ACS were eligible for enrollment in study.

Main exclusion criteria were: patients receiving intensive lipid-lowering therapy of rosuvastatin 40 mg for >3 months before admission; alanine aminotransferase (ALT) levels >3× upper limit of normal (ULN); unexplained serum creatine kinase (CK) level >3× ULN; serum creatinine >2 mg/dL; and history of hypersensitivity to statins.

2.3. Endpoints

The primary endpoint was the percent change from baseline in LDL-C levels after 6 and 12 weeks of treatment. The secondary endpoints included the percent change from baseline in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-HDL-C, apolipoprotein A-I (ApoA1-I), apolipoprotein B (ApoB), LDL-C/HDL-C ratio, TC/HDL-C ratio, non-HDL-C/HDL-C ratio, and ApoB/ApoA-I ratio, after 6 and 12 weeks of treatment; and the percent change from baseline in the levels of high sensitive C-reactive protein (hsCRP), an inflammatory marker, after 6 and 12 weeks of treatment. Non-HDL-C was calculated as total cholesterol from whole plasma minus HDL cholesterol.

The safety and tolerability of rosuvastatin were assessed by evaluating the incidence and severity of adverse events (AEs), serious AEs (SAEs), and abnormal laboratory values through 12 weeks of treatment.

Compliance was assessed; patients were considered non-compliant if they missed their medication for more than 5 days.

Please cite this article in press as: Shah CP, et al. Efficacy and safety of the intensive dose of rosuvastatin 40 mg/day in patients with acute coronary syndrome and at high risk of cardiovascular disease-ROSUVEES-2, *Indian Heart J.* (2016), http://dx.doi.org/10.1016/j.ihj.2016.09.002