Clinical Neurology and Neurosurgery 120 (2014) 6–13

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

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

Efficacy and safety of intensive statin therapy in Chinese patients with atherosclerotic intracranial arterial stenosis: A single-center, randomized, single-blind, parallel-group study with one-year follow-up

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ARTICLE INFO

Article history:
Received 21 December 2013
Received in revised form 11 January 2014
Accepted 2 February 2014
Available online 10 February 2014

Keywords:
Intensive statin therapy
Atorvastatin
Atherosclerotic intracranial arterial stenosis
Computed tomography angiography
Computed tomography perfusion

ABSTRACT

Objectives: The purpose of this study is to validate the efficacy of intensive statin therapy for patients with atherosclerotic intracranial arterial stenosis (AICAS).
Methods: In this study, we performed a single-center, randomized, single-blind, parallel-group clinical trial. A total of 120 Chinese patients with AICAS were enrolled and randomly divided into three groups [low-dose atorvastatin therapy (LAT, 10 mg/day), standard-dose atorvastatin therapy (SAT, 20 mg/day), and intensive-dose atorvastatin therapy (IAT, 40 mg/day) groups] in a 1:1:1 ratio. Evaluation variables, including changes in serum lipid profiles, degree of stenosis, and perfusion-related parameters derived from computed tomography perfusion (CTP) imaging from baseline to weeks 26 and 52, as well as the occurrence of cerebrovascular events during the study period, were used to compare the benefits of these three statin therapies.
Results: After 52 weeks of treatment, improvement of serum lipid profiles, degree of stenosis, and perfusion-related parameters were all significantly better in the IAT group. In addition, the cumulative probability of cerebrovascular events at 52 weeks was significantly lower in the IAT group than in the LAT group, although there was no statistical difference between the IAT group and the SAT group. The proportion of patients experiencing any adverse event was similar among the three treatment groups. Adverse events caused by IAT were generally mild; no serious adverse events occurred throughout the entire period of study.
Conclusion: In conclusion, long-term use of IAT appears to be a safe and effective treatment at least for Chinese patients with AICAS.

1. Introduction

Atherosclerotic intracranial arterial stenosis (AICAS) corresponds to luminal narrowing of the major intracranial arteries, which is most often attributed to primary atherosclerosis [1]. It is one of the most common causes of stroke around the world [2,3] and highly associated with the risk of stroke recurrence, especially in Hispanics, Asians, and Blacks [4,5]. According to previous reports, for patients with a recent transient ischemic attack (TIA) or stroke and severe stenosis (70–99% of the diameter of a major intracranial artery), the risk of recurrent stroke in the territory of the stenotic artery was approximately 23% per year, even though these patients received standard management of vascular risk factors and aspirin therapy [6,7]. Therefore, the treatment and management of patients with AICAS poses a significant challenge to neurologists and alternative therapies are urgently needed by this population.

Several vascular risk factors including hypertension and dyslipidemia have been identified to be closely associated with symptomatic AICAS [8,9]. Currently, it has been widely accepted that general guidelines for primary and secondary prevention of stroke should also apply to AICAS; in particular, those concerning aggressive control of vascular risk factors [1,10,11]. Statins have been demonstrated to slow progression of atherosclerosis and reduce the incidence of cerebrovascular events in stroke patients through their effective lipid-lowering capabilities [12,13].

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http://dx.doi.org/10.1016/j.clineuro.2014.02.001

However, current challenges have led professionals to focus on an intensive statin therapy approach as well as on benefits that statins may possess other than lipid lowering [14]. Findings from a multicenter SAMMPRIS trial involving patients with intracranial large artery stenosis suggest that the lower than expected rate of stroke in the aggressive medical arm of the group may be a result of intensive lipid management aimed at bringing LDL-C levels down below 1.81 mmol/l (70 mg/dl) in addition to aggressive management of hypertension and anti-platelet therapy [15]. In a single-arm, prospective, observational study, 6-month intensive atorvastatin therapy (40 mg/day) induced less progression of AICAS in the enrolled participants [16]. Despite these published results, there is still a lack of evidence from a randomized, parallel-group clinical trial to support the efficacy of intensive statin therapy in reducing the progression of AICAS. Therefore, in the current study, we designed a single-center, randomized, single-blind, parallel-group clinical trial. The aim of our study was to validate the effects of intensive statin therapy on AICAS.

2. Patients and methods

2.1. Study design

A single-center, prospective, randomized, single-blind, parallel-group clinical trial was conducted in this study. A total of 158 patients with ischemic stroke or TIA were assessed for eligibility by the Department of Neurology of the Affiliated Xiangyang Hospital of Hubei University of Medicine from January 2010 to October 2012. The study protocol was approved by the institutional ethics committee and all participants provided informed written consent.

Inclusion criteria were as follows: (1) age between 30 and 80 years old; (2) recent (within 3 months) ischemic stroke or TIA according to the World Health Organization (WHO) criteria; (3) having large artery atherosclerosis according to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria [17] and symptomatic stenosis in the middle cerebral artery (MCA) or basilar artery (BA); (4) having angiographically verified 50–99 percent stenosis; (5) ischemic stroke or TIA attributed to high grade intracranial stenosis; (6) serum total cholesterol (TC) > 5.2 mmol/l or low density lipoprotein cholesterol (LDL-C) > 3.6 mmol/l with normal liver function.

Exclusion criteria were: (1) cerebral embolism or recent (within 6 weeks) intracranial hemorrhage or hemorrhagic cerebral infarction; (2) extracranial carotid stenosis (>50%) ipsilateral to the symptomatic intracranial stenosis; (3) presence of chronic devastating diseases, multiple organ failure, or psychiatric disorders; (4) nonatherosclerotic vasculopathy, such as dissection, vasculitis, vasospasm, dissecting aneurysm, radiation-induced vasculopathy, or Moya Moya disease; (5) having any contraindications to statins and contrast agents; (6) allergic to statins and contrast agents; (7) using medications that may increase the toxicity of statins or alter lipid profiles; (8) having severe neurological deficits that render the patient incapable of living independently.

2.2. Randomization and study interventions

Patients who met the inclusion criteria were randomly assigned to the three treatment groups [low-dose atorvastatin therapy (LAT), standard-dose atorvastatin therapy (SAT), and intensive-dose atorvastatin therapy (IAT) groups] in a 1:1:1 ratio using a computer-generated stochastic system. Patients were blinded to intervention assignment. Prior to randomization, all patients entered a washout phase lasting one week, during which use of any previous cholesterol-lowering agents was stopped. Baseline clinical characteristics, including serum lipid levels [TC, LDL-C, high density lipoprotein cholesterol (HDL-C), and triglyceride (TG)], degree of stenosis (percentage of stenosis), and perfusion-related parameters [relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), and relative time to bolus peak (rTTP)], were then measured using standard laboratory methods, computed tomography angiography (CTA), and computed tomography perfusion (CTP) imaging. Measurement of the percentage of stenosis by CTA was performed in accordance with the method described previously [18]. Measurements of rCBF, rCBV, and rTTP were carried out based on procedures described by Koenig et al. [19].

Following randomization, patients in the three groups were given 10 mg/day, 20 mg/day, and 40 mg/day of atorvastatin (Lipitor®, Pfizer, New York, NY, USA), respectively, for at least 52 weeks. All patients were also given 75 mg/day clopidogrel and 100 mg/day aspirin in the first month, followed by aspirin therapy (100 mg/day) alone throughout the rest of the study period. Furthermore, blood pressure (BP) was controlled at less than 140/90 mm Hg in patients overall (<130/80 mm Hg in the case of patients with diabetes). Clinic and home BP monitoring (morning and evening measurements) was performed to verify BP control during the period of study. Aggressive glucose control was conducted in diabetic patients, with a target glycosylated hemoglobin (HbA1c) level of less than 7%.

2.3. Follow-up and assessment of clinical outcomes

The primary endpoint in our study was the change in the degree of stenosis from baseline to 26 and 52 weeks. Secondary endpoints included changes in CTP parameters from baseline to 26 and 52 weeks, as well as the occurrence of cerebrovascular events during the study period. At weeks 26 and 52, serum lipid levels, percentage of stenosis, and CTP parameters were measured by investigators who were blinded to randomization and all clinical information. Cerebrovascular events were defined as cerebrovascular death and/or recurrent TIA and ischemic stroke requiring hospitalization. Patients had monthly follow-up examinations to determine whether any such events had occurred.

2.4. Evaluation of safety

The safety profile of the study interventions was assessed using adverse event monitoring, routine clinical laboratory testing, and vital sign assessment. An adverse reaction (ADR) was defined as any undesired, noxious, or pathological change indicated by signs, symptoms, and/or changes in laboratory findings either reported by a patient or noted by an investigator during the period of study, regardless of its suspected cause. Each adverse event was recorded by investigators, noting its severity and whether or not they considered it related to the study interventions.

2.5. Statistical analysis

The sample size was calculated using PASS 2008 software (NCSS LLC, Kaysville, UT, USA) based on the results of a pilot study. In this study, the means and standard deviations (SD) of the change in degree of stenosis from baseline to week 52 in the LAT, SAT, and IAT groups was -1.6 ± 1.3, -2.0 ± 1.7, and -6.8 ± 2.1, respectively. This required at least 7 subjects per group with 99% power $(1 - \beta)$ at the 0.05 significance level (α) for statistical analysis. In this study, we decided to consider 40 subjects per group in order to ensure sufficient statistical power.

All statistical analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). For continuous variables, normality was tested using the Kolmogorov–Smirnov test. Data with normal distribution are presented as mean ± SD. Data with skewed distribution are presented as median and interquartile ranges (IQR,