The Atorvastatin During Ischemic Stroke Study: A Pilot Randomized Controlled Trial

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Objectives: Statins have antioxidant, anti-inflammatory, anticoagulant, and profibrinolytic properties that might play a useful role in the acute phase of ischemic stroke. This pilot study assessed the possible neuroprotective action of high-dose atorvastatin administration during the first week after an ischemic stroke, to obtain data for planning a wider multicenter study.

Methods: Sixty-two patients with ischemic stroke, aged 75.3 (SD, ±11.9) years (68% women), were randomized into a placebo (n = 31) and an atorvastatin 80 mg/d (n = 31) group. The double-blind treatment lasted 7 days. The primary end point was a decrease of National Institutes of Health Stroke Scale score of 4 points or higher after 7 days. Infarct volume measured on computed tomographic scan after 3 days and a modified Rankin Scale of less than 2 at 3 months were secondary end points.

Results: There was no difference in the primary end point between the 2 groups (odds ratio, atorvastatin vs placebo, 0.74; 95% confidence interval, 0.26–2.17). Infarct volume also was similar in the 2 groups. Instead, there were more patients with modified Rankin Scale of less than 2 at 3 months in the atorvastatin than in the placebo group (adjusted odds ratio, 6.7; 95% confidence interval, 1.0–45.0; $P = 0.05$). This prevalence concerned only the subgroup with mild strokes (National Institutes of Health Stroke Scale, ≤10; 53.8% vs 15.4%, respectively; $P = 0.04$). Atorvastatin was well tolerated.

Conclusions: This pilot study was unable to show any short-term benefit of atorvastatin during the acute phase of ischemic stroke. However, it suggested a possible favorable functional effect at 3 months in the least severe strokes, which could be the primary end point for a future multicenter trial.

Key Words: atorvastatin, ischemic stroke, neuroprotection, pilot study, randomized controlled trial

(*Clin Neuropharm* 2011;34: 141–147)

The only approved therapy for acute ischemic stroke, systemic thrombolysis, can be applied to a minority of patients.[1,2] On the other hand, all attempts to provide neuroprotection with agents suitable for most patients have yielded disappointing results in the clinical setting.[3]

The inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase ("statins") have some effects, in addition to the cholesterol-lowering action, that might play a useful role in the acute phase of ischemic stroke. Among them, the upregulation of endothelial nitric oxide synthase[4]; the inhibition of nuclear factor κB with reduced synthesis of cytokines, chemokines, metalloproteinases, and adhesion molecules[5,6]; the decrease in plasminogen activator inhibitor-1[7]; and the lower production and activity of thromboxane A2 and tissue factor[8] are noteworthy.

Several experimental studies have shown a favorable effect of pretreatment or acute treatment with statins, generally at very high doses, on cerebral infarct size.[9–11] In man, a large randomized study demonstrated the efficacy of atorvastatin 80 mg/d in the secondary prevention of ischemic stroke or transient ischemic attack (TIA),[12] despite a greater incidence of new hemorrhagic strokes in the atorvastatin group.[13] Other studies showed that, in patients pretreated with statins, stroke was associated with a smaller size of cerebral lesions at magnetic resonance imaging,[14,15] a wider development of collaterals,[16] and a trend to a lower degree of disability at 3 months[17,18] with respect to nonpretreated patients, although the beneficial effects of statin pretreatment might mainly concern atherothrombotic and small vessel strokes.[19] Furthermore, the sudden withdrawal of statins during the acute phase of an ischemic stroke caused deleterious short- and medium-term rebound effects.[20]

Despite these premises, the clinical studies on statin effects during the acute phase of ischemic stroke have been scanty.[21–23] In particular, a randomized study[23] concerning 56 patients with ischemic stroke, who were treated with simvastatin 40 mg or placebo within 12 hours of the onset of symptoms, did not demonstrate any effect of simvastatin on markers of inflammation and on disability at 3 months, showing, however, an early lower neurological impairment in the simvastatin group. More recently, a nonrandomized retrospective study comparing the effects of atorvastatin 40 or 80 mg/d versus simvastatin at optimal dose in hyperlipidemic, simvastatin-pretreated patients with acute ischemic stroke showed a possible better neurological and functional outcome at 30 days in the atorvastatin groups.[24]

We report here on the first randomized controlled study assessing the short- and medium-term efficacy (reduction of neurological deficit, infarct size, and functional impairment) of atorvastatin 80 mg/d, a more powerful statin than simvastatin,[25] in patients with acute ischemic stroke not undergoing thrombolysis. The main goal of this pilot study was the collection of useful suggestions for planning a wider multicenter trial.

PATIENTS AND METHODS

This was a monocenter, stratified (3 subgroups of initial National Institutes of Health Stroke Scale [NIHSS] score with balanced randomization), double-blind, placebo-controlled, parallel group study conducted in the stroke unit of the S.Orsola-Malpighi Hospital of Bologna, Italy.

The trial started on April 18, 2008, and the last patient was enrolled on December 12, 2009. During that period, 348 patients with suspected ischemic stroke (sudden and persistent focal neurological deficit without computed tomography (CT) signs of hemorrhage) were admitted to our hospital and were considered for possible inclusion in the study (Fig. 1).

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Conflicts of Interest and Source of Funding: This was an unsponsored self-financed study. No sources of funding have to be acknowledged.

DOI: 10.1097/WNF.0b013e3182206c2f

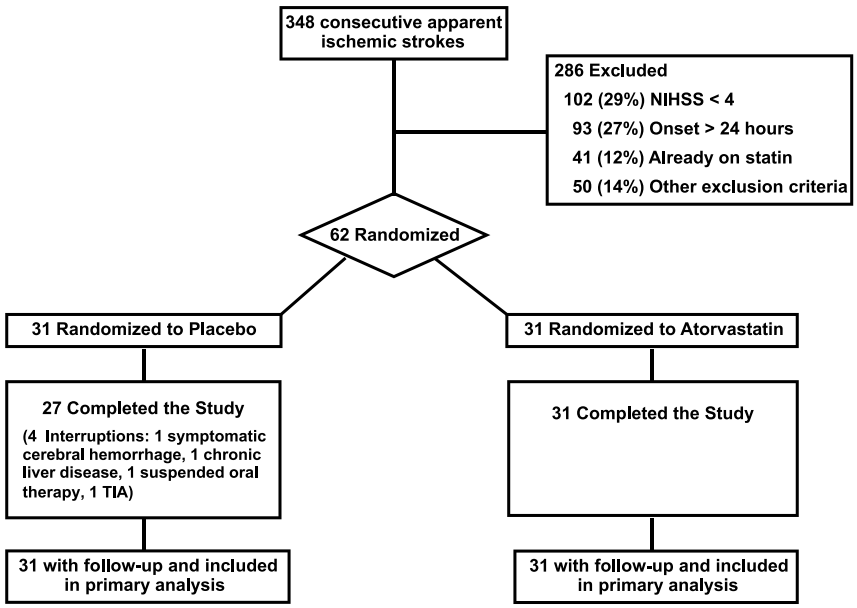

FIGURE 1. Flow chart of patients' selection and randomization. Percentages are referred to the total number of ischemic strokes (N = 348).

The present investigation adheres to the principles of the Declaration of Helsinki and was approved by the joint hospital-university ethics committee. All patients, or their relatives, provided an informed written consent to participate in the study.

Clinical trial registration: European (EMA) trial registry (EudraCT number 2008-000433-21).

Exclusion Criteria

Exclusion criteria were as follows: (1) initial NIHSS score of less than 4 points; (2) inability or refusal of the patient or relative to provide the informed consent; (3) patient already being treated with a statin; (4) known statin intolerance; (5) recent thrombolytic treatment; (6) delay of admission, after onset of symptoms, exceeding 24 hours (the initial limit of 12 hours was extended to 24 hours after 5 months because of the too low rate of enrollment); (7) previous modified Rankin Scale (mRS) of greater than 1; (8) malignant neoplasm; (9) cirrhosis of the liver, chronic hepatitis, or acute hepatic failure; (10) alcohol abuse; (11) concurrent therapy with cyclosporin, erythromycin, clarithromycin, itraconazole, ketoconazole, nefazodone, niacin, gemfibrozil, other derivatives of fibric acid, or inhibitors of human immunodeficiency virus proteases; and (12) aspartate aminotransferase (AST), alanine aminotransferase (ALT), or creatine kinase (CK) levels greater than 3 times the maximum normal value.

These criteria led to the exclusion of 286 patients, that is, 82% of the 348 patients with ischemic stroke (Fig. 1). Most exclusions (29% of the ischemic strokes) were due to a low initial NIHSS score. Other important causes of exclusion were an admission delay exceeding 24 hours (27%) and being on statin treatment (12%). Refusal to participate in the study, thrombolytic treatment, malignancies, and elevated basal levels of transaminases or CK were less frequent causes of exclusion (2%–5% for each category).

Reasons for Discontinuing the Study

The reasons were as follows: (1) voluntary withdrawal; (2) supervened impossibility to take the therapy by mouth or nasogastric tube; (3) complete disappearance of symptoms within 24 hours (diagnosis of TIA); (4) AST, ALT, or CK increase greater than 3 times the maximum normal value; and (5) symptomatic hemorrhagic transformation of cerebral infarct.

End Points

The primary end point was a reduction of NIHSS score of 4 points or greater [23] 7 days after enrollment. Secondary end points were cerebral infarct volume at 3 days (measured on brain CT scan) and an mRS of less than 2 at 3 months.

Main Phases of the Study and Treatment

The first NIHSS score was obtained on admission, and a blood sample was drawn to detect possible exclusion factors. All NIHSS assessments were performed by certified physicians, and for each patient, both baseline and seventh day assessment were performed by the same physician, who also enrolled the patient and assigned him/her to the random treatment. This was a new numbered package from the box corresponding to the NIHSS subgroup of the patient.

The randomization sequence was computer generated using a fixed block size of 6 and was stratified into 3 subgroups of initial NIHSS score (NIHSS $\leq$ 10, NIHSS between 11 and 18, and NIHSS $\geq$ 19).

Treatment started immediately after admission. It consisted of the oral administration of a white powder mixed with jelly or with water in case of administration through nasogastric tube, once a day at any time (corresponding to the time of enrollment) for 7 days. In the atorvastatin group, the powder was a triturated tablet of atorvastatin 80 mg, whereas in the placebo group, the powder was rice starch.

In the morning after the admission, a fasting blood sample was drawn for baseline determinations, including complete blood count, serum lipids, creatinine, C-reactive protein, transaminases, and CK (Table 5). The same blood measurements and NIHSS assessment were repeated on the seventh day.

The first brain CT scan was performed immediately on admission to ascertain the ischemic nature of the stroke, and a second CT scan was performed on the third day to assess site and size of the infarct. Mainly because of the transient presence of vasogenic edema, early measurements may often overestimate infarct size.[26] Nevertheless, we preferred not to use a late measurement to avoid

the loss of data caused by possible unavailability or death of the patient. However, a linear association between the volume measured 3 to 6 days after the stroke and the one measured after 30 to 45 days has recently been shown with magnetic resonance imaging[27]; in addition, randomization should have ensured an equal distribution of the overestimation between the 2 groups.

The same operator measured the infarct size of all patients. In particular, optimal visualization of cerebral tissue was preset in the radiological software, with automatic adjustment and standardization of contrast. In each CT slice, the ischemic area, possibly consisting of multiple separate areas, was manually outlined and then measured by the radiological software. All areas were summed up and then multiplied by the mean slice thickness (which was calculated for each scan), with resulting estimation of the infarct volume in milliliters.

After 3 months, by a telephone interview with the patient or care giver, an operator unaware of group allocation and not involved in the enrollment and management of patients obtained an mRS score for all participants using a standardized set of questions, as well as the list of the drugs currently being assumed by the patient.

Sample Size

In the only previous study concerning the effects of a statin (simvastatin 40 mg) on acute ischemic stroke,[22] a reduction of NIHSS score of 4 points or greater was obtained, after 3 days, by 46.4% (13/28) of the statin-treated patients and 17.9% (5/28) of the placebo patients. Hypothesizing that, after 7 days, 50% of atorvastatin patients and 25% of placebo patients reached the primary end point, we estimated that, to obtain a significant result ($\alpha = 0.05$) with a power of 80% ($\beta = 0.2$), each group should consist of 58 patients. We planned to reach this sample size within a year. Unfortunately, the rate of enrollment was much slower than expected. We were able to prolong the study by 8 further months (up to the end of 2009), with an overall enrollment of 62 patients, who were randomized into the atorvastatin (n = 31) and the placebo (n = 31) groups.

Statistical Analysis

The statistical analysis concerning the primary and secondary end points was performed according to intention to treat. Therefore, all randomized patients were included in the analysis, although 4 patients of the placebo group did not complete the 7 days of study (Fig. 1).

The continuous variables were described with mean and SD in case of normal distribution and with median and interquartile range in case of non-Gaussian distribution. Accordingly, the differences between groups were tested using Student *t* for unpaired data or by Mann-Whitney *U* test. The differences between percentages were assessed using χ^2 test.

The comparison of laboratory parameter changes between the 2 study groups was performed using variance analysis for repeated measures (group × treatment interaction), whereas the changes within each group between baseline and seventh day were tested using Student *t* for paired data or Wilcoxon test.

Unadjusted and adjusted odds ratios and 95% confidence intervals were obtained using multiple logistic regression.

Two-tailed tests were used throughout, and $P < 0.05$ was considered significant.

RESULTS

Sample Description

The baseline characteristics of the 2 groups of patients are illustrated in Table 1. Randomization ensured a substantial equivalence, with only a greater prevalence (of borderline significance) of former smokers in the placebo group. In general, mean age was 75.3 ± 11.9 years, and there were more women (67.7%) than men. The median initial NIHSS score was 12.5, with preponderance of total and partial syndromes of the anterior circulation. Of the 3 subgroups of neurological severity, the most numerous one concerned the patients with an NIHSS score of 10 or lower (n = 26, 41.9%, 13 atorvastatin and 13 placebo). The median delay between onset of symptoms and first treatment administration was of 7 hours. Seventeen patients (27.4%) were hypercholesterolemic (total cholesterol, ≥200 mg/dL). Eight patients (12.9%) had had a previous stroke.

TABLE 1. Baseline Characteristics of the 2 Groups of Patients

	Placebo (n = 31)	Atorvastatin (n = 31)	*P*
Age (yr)	75.6 ± 12.2	74.9 ± 11.8	0.82
Male sex	12 (38.7)	8 (25.8)	0.28
OCSP classification*			
LACS	5 (16.1)	3 (9.7)	0.45
PACS	10 (32.3)	12 (38.7)	0.60
TACS	13 (41.9)	13 (41.9)	1.00
POCS	2 (6.5)	3 (9.7)	0.64
TOAST classification*			
Large artery	6 (19.4)	6 (19.4)	1.00
Cardioembolism	10 (32.3)	10 (32.3)	1.00
Small artery	6 (19.4)	5 (16.1)	0.74
Other cause	1 (3.2)	0	0.31
Undefined cause	7 (22.6)	10 (32.3)	0.39
Preadmission mRS = 1	10 (32.3)	9 (29.0)	0.78
NIHSS score (first assessment)	12 (8–21)	13 (7–21)	0.98
NIHSS ≤ 10 (n = 13 + 13)	7 (5–8)	6 (5–8)	0.78
NIHSS > 10 and ≤ 18 (n = 8 + 8)	15.5 (12–16.5)	16 (12.5–17.5)	0.60
NIHSS > 18 (n = 10 + 10)	22.5 (21–24)	22.5 (21–24)	0.97
Delay of treatment (h)	7 (5.5–16.3)	7.5 (5.0–15.0)	0.93
Diabetes	5 (16.1)	8 (25.8)	0.35
Hypertension	30 (96.8)	27 (87.1)	0.16
Hypercholesterolemia	8 (25.8)	9 (29.0)	0.78
Hypertriglyceridemia	3 (9.7)	2 (6.5)	0.64
Current smoker	6 (19.4)	4 (12.9)	0.49
Ex–smoker	9 (29.0)	3 (9.7)	0.054
Previous stroke	3 (9.7)	5 (16.1)	0.45
Previous TIA	2 (6.5)	0	0.15
Previous myocardial infarction	2 (6.5)	2 (6.5)	1.00

Values are number (percentage), or mean ± SD, or median (interquartile range).

Percentages were compared using χ^2 test; mean values were compared using Student *t* test; median values were compared using Mann-Whitney *U* test.

*One patient in the placebo group was not classified as ischemic stroke (TIA).

LACS indicates lacunar anterior circulation syndrome; OCSP, Oxfordshire Community Stroke Project; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; TACS, total anterior circulation syndrome; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

TABLE 2. NIHSS Change After 7 Days According to Treatment Group

	Δ NIHSS ≥ 4 (No. Patients)			Δ NIHSS (Absolute Value)		
	Placebo	Atorvastatin	*P*	Placebo	Atorvastatin	*P*
All	11 (35.5)	9 (29.0)	0.59	2 (−3 to 4)	2 (−1 to 4)	0.98
NIHSS ≤ 10	7 (53.8)	4 (30.8)	0.23	4 (1–5)	2 (1–4)	0.61
NIHSS > 10 and ≤ 18	2 (25.0)	4 (50.0)	0.30	−0.5 (−3.5 to 3.5)	2.5 (−2.5 to 7.5)	0.34
NIHSS > 18	2 (20.0)	1 (10.0)	0.53	0.5 (−4 to 2)	−0.5 (−3 to 1)	0.62

Values are number (percentage) or median (interquartile range).

Percentages were compared using χ^2 test; median values were compared using Mann-Whitney *U* test.

ΔNIHSS = NIHSS score on admission – NIHSS score after 7 days.

Efficacy of Treatment

This study did not show any difference between the 2 groups in relation to the change of NIHSS score between admission and seventh day, both as number of patients with ΔNIHSS of 4 or greater (odds ratio, atorvastatin vs placebo, 0.74; 95% CI, 0.26–2.17) and as absolute value (Table 2). Similarly, the infarct volume was equivalent in the 2 groups (Table 3). Nonsignificant results also were obtained considering separately the 3 subgroups of neurological severity and the patients enrolled before or after the median delay of 7 hours.

At follow-up, 9 patients (14.5%) displayed an optimal functional outcome (mRS, <2) (Table 4). Seven of them had been treated with atorvastatin and 2 with placebo (unadjusted odds ratio, atorvastatin vs placebo, 4.2; 95% CI, 0.8–22.3; after adjustment for initial NIHSS score, the odds ratio was 6.7; 95% CI, 1.0–45.0; $P = 0.05$). All the 9 patients with an mRS of less than 2 at 3 months belonged to the subgroup with an initial NIHSS score of 10 or lower. Considering only this subgroup, 53.8% of the patients treated with atorvastatin, versus 15.4% of the patients treated with placebo, had an mRS of less than 2 ($P = 0.04$, number needed to treat = 3). This corresponded to a median mRS of 1 in the atorvastatin group, versus 3 in the placebo group ($P = 0.17$; Table 4).

Forty-five patients (21 from the atorvastatin group and 24 from the placebo group) reported the therapy they were currently taking at the time of follow-up (of the remaining 17 patients, 14 had died, and 3 refused or were unable to provide this information). Nine (42.9%) of the atorvastatin group versus 6 (25%) of the placebo group were taking atorvastatin ($P = 0.20$). Similarly, at the time of follow-up, there were no significant differences concerning the other main classes of drugs.

Table 5 reports the changes in the main laboratory parameters during the week of treatment. The only significant difference between the changes in the 2 groups concerned total cholesterol levels, which decreased more markedly in the atorvastatin group than in the placebo group (-29.8% and –12.0%, respectively; $P = 0.0002$). However, the decrease of cholesterol levels in the placebo group also was significant. Moreover, there was a significant reduction of high-density lipoprotein (HDL) cholesterol in both groups, whereas triglycerides and C-reactive protein increased significantly only in the placebo group. A significant increase of transaminases and gamma-GT was found in both groups, whereas platelets increased only in the atorvastatin group.

Estimated Sample Size for a Future Confirmatory Study

The only significant difference shown by our study concerned the subgroup with NIHSS score of 10 or lower, in which 53.8% of the patients treated with atorvastatin, versus 15.4% of the patients treated with placebo, had an optimal functional outcome at 3 months. Thus, an mRS of less than 2 at 3 months could be the primary end point for a future confirmatory study. Hypothesizing that 45% of the atorvastatin patients and 25% of the placebo patients reached this end point, each group should consist of 89 patients to obtain a significant result with a power of 80%. In our study, the patients with NIHSS score of 10 or lower were 42% of those enrolled who, in turn, were 18% of all ischemic strokes. From this, it can be estimated that 2543 ischemic strokes (corresponding to nearly 7 centers like ours) should be screened to obtain the wanted sample size, with the same exclusion criteria of the present study, in 20 months.

Safety of Treatment

During the stay in stroke unit, 4 patients died (6.5%), 2 in the atorvastatin group and 2 in the placebo group. All had an initial NIHSS score of 23 or higher and were older than 76 years. During the follow-up period, 10 further patients died, again equally distributed in the 2 groups (5 atorvastatin and 5 placebo). Only 1 patient (atorvastatin group) had a new ischemic stroke during the follow-up period.

The second brain CT scan, performed on the third day, showed a hemorrhagic transformation in 13 cases (21.0%), 6 of which had been treated with atorvastatin and 7 with placebo. In 1 case only, belonging to the placebo group, the hemorrhage was symptomatic (appearance of stupor), and the patient was withdrawn from the study.

Eleven patients had fever, 3 in the atorvastatin group and 8 in the placebo group. On the seventh day, there were no transaminase or CK values exceeding 3 times the maximum normal value; thus, there were no discontinuations for that reason.

TABLE 3. Cerebral Infarction Volume According to Treatment Group

	Cerebral Infarction Volume (mL)		
	Placebo	Atorvastatin	*P*
All	16.2 (0.8–70.5)	30.4 (2.2–76.7)	0.33
NIHSS ≤ 10	1.6 (0.4–3.1)	1.3 (0.5–28.4)	0.70
NIHSS > 10 and ≤ 18	23.4 (6.6–79.7)	23.0 (6.9–47.9)	0.91
NIHSS > 18	61.2 (38.8–118.2)	163.0 (30.9–226.6)	0.13

Cerebral infarction volume obtained from second CT scan.

Values are median (interquartile range). Median values were compared using Mann-Whitney *U* test.

TABLE 4. Modified Rankin Scale at 3 Months According to Treatment Group

	mRS <2 (No. Patients)			mRS (Absolute Value)		
	Placebo	**Atorvastatin**	***P***	**Placebo**	**Atorvastatin**	***P***
All	2 (6.5)	7 (22.6)	0.07	4 (3–5)	4 (2–5)	0.79
NIHSS ≤ 10	2 (15.4)	7 (53.8)	0.04	3 (2–3)	1 (1–3)	0.17
NIHSS > 10 and ≤ 18	0	0	—	4.5 (3.5–5)	5 (4–6)	0.27
NIHSS > 18	0	0	—	5.5 (5–6)	5 (5–6)	0.73

Values are number (percentage) or median (interquartile range).

Percentages were compared using χ^2 test; median values were compared using Mann-Whitney *U* test.

However, in 9 patients, the ALT concentration exceeded 3 times the baseline value (6 atorvastatin and 3 placebo). Similarly, in 3 cases (2 atorvastatin and 1 placebo), the triple of the AST baseline value was exceeded.

Finally, there were no significant differences between the 2 groups in the few subjective complaints occurring during hospitalization and in the 3 months of follow-up (nausea, vomiting, constipation, diarrhea, cough, asthma, rash, itching, and abdominal pain). Seven patients referred muscular pain, mainly during the follow-up period (5 atorvastatin and 2 placebo, $P = 0.23$).

DISCUSSION

This pilot study provides the first data concerning the short-medium term effects of the administration of high-dose atorvastatin, compared with placebo, during the acute phase of ischemic stroke. It was mainly aimed at providing suggestions for planning a wider multicenter study, as we were aware that a small monocenter trial would unlikely yield a definitive information on this subject. However, although our sample could not reach the size needed to confer a power of 80% to the study, the data concerning NIHSS changes at 7 days and cerebral infarct volume at 3 days were so far from significance (even apparently favoring the placebo group) that their use as end points in a new similar study would not seem reasonable.

On the other hand, the follow-up at 3 months suggested a more frequent optimal functional outcome (mRS, <2) in the patients treated with atorvastatin than in those treated with placebo, an effect that seemed to concern exclusively the least severe strokes (NIHSS, ≤10; 42% of our sample). If a more numerous series will confirm our percentages of optimal outcome among the least severe strokes (53.8% in the atorvastatin group vs 15.4% in the placebo group), approximately 1 in 3 of such patients could benefit of the treatment.

Overall, these data seem plausible, considering that also the only approved therapy for acute ischemic stroke, that is, systemic thrombolysis with r-tPA, provides more significant results at 3 months than short-term,[28] and the benefits mainly concern the less severe strokes with distal, rather than proximal, arterial occlusion.[29] Similar favorable outcomes at 3 months after an ischemic stroke also were obtained in patients pretreated with statins.[17] Thus, it seems possible that the antioxidant,[4] anti-inflammatory,[5] and fibrinolytic[7] actions of atorvastatin, as well as the development of new collaterals,[16] do not cause any visible effects immediately but that they may predispose to a subsequent better functional recovery (this can only be hypothesized, as our study

TABLE 5. Changes of Laboratory Parameters According to Treatment Group

	Placebo			Atorvastatin			
	Baseline	**After 1 Wk**	***P****	**Baseline**	**After 1 Wk**	***P****	***P*†**
Total cholesterol (mg/dL)	177.7 ± 33.5	156.3 ± 24.5	0.002	180.1 ± 35.4	126.5 ± 26.8	<0.0001	0.0002
HDL cholesterol (mg/dL)	49.5 ± 12.0	34.4 ± 12.1	<0.0001	53.0 ± 14.7	41.6 ± 12.8	<0.0001	0.53
Triglycerides (mg/dL)	92.5 (83.0–107.5)	112.5 (95.5–138.0)	0.01	90.0 (67.0–126.0)	96.5 (85.0–117.0)	0.30	0.48
C–reactive protein (mg/dL)	0.96 (0.54–2.05)	3.7 (2.07–11.65)	0.001	1.71 (0.41–5.27)	2.47 (0.59–6.98)	0.21	0.09
CK (U/L)	66.5 (54–92)	51 (34–78)	0.06	91.5 (51–185)	84 (49–144)	0.18	0.91
AST (U/L)	19.5 (16.5–22)	24.5 (20–32.5)	0.001	18 (15–23.5)	27.5 (23–42.5)	0.005	0.46
ALT (U/L)	14 (11.5–22)	23 (16–36)	0.002	15.5 (11.5–24)	32 (19–48.5)	0.0004	0.15
Gamma–GT (U/L)	20 (13–40)	25 (16–60)	0.004	23 (14–38)	29.5 (18–71)	0.004	0.37
INR	1.06 (1.01–1.17)	1.09 (1.02–1.20)	0.75	1.08 (1.03–1.16)	1.05 (1.02–1.17)	0.28	0.74
Hemoglobin (g/dL)	13.5 ± 1.8	13.1 ± 1.5	0.06	13.4 ± 1.7	13.4 ± 1.6	0.61	0.31
Leukocytes (n/1000/mmc)	9.49 (8.44–11.95)	9.23 (6.81–11.07)	0.05	10.66 (8.35–13.28)	10.67 (8.36–13.48)	0.29	0.57
Platelets (n/1000/mmc)	252 (203–317)	268.5 (212–331)	0.69	290 (245.5–352)	310.5 (278–340)	0.009	0.12
Creatinine (mg/dL)	0.92 (0.86–1.05)	0.83 (0.78–1.13)	0.38	0.92 (0.89–1.15)	0.87 (0.73–1.13)	0.87	0.26

Values are mean ± SD or median (interquartile range).

No significant differences were found between baseline values.

*Significance of change tested with paired *t* test or Wilcoxon test.

†Significance of difference between changes tested with repeated–measures analysis of variance (interaction term).

Gamma-GT indicates gamma-glutamyltransferase; INR, international normalized ratio.

was not designed to investigate the possible mechanisms involved). Furthermore, although the treatment delay of this study could appear excessive for a neuroprotectant (half of our patients received the first atorvastatin dose between 7 and 24 hours after the onset of symptoms), in rats, atorvastatin treatment initiated 1 day after stroke was able to induce brain plasticity, with increased angiogenesis, neurogenesis, and synaptogenesis.[30]

All this would be in contrast with the good early results on NIHSS score and the absence of effects on mRS at 3 months, obtained by Montaner et al[23] with simvastatin 40 mg/d in a sample similar to ours in size, mean stroke severity, and age of patients. However, their sample differed from ours for a series of other factors, such as the exclusion of lacunar strokes, an earlier treatment, and the type of statin used. Moreover, Lampl et al,[24] in their retrospective study, found that atorvastatin-treated stroke patients had a better mRS score at 30 days than simvastatin-treated patients. Also, in patients with TIA or minor stroke, simvastatin treatment (40 mg/d) started within 24 hours of symptom onset was unable to reduce stroke occurrence during the subsequent 3 months.[31]

As far as the changes of laboratory data are concerned, as expected, the main difference between the 2 groups was the greater reduction of cholesterol levels in the atorvastatin than in the placebo group. However, a cholesterol reduction also was observed in the placebo group, in relation to the dietary restrictions occurring in acute stroke patients. The other (borderline significant) difference concerned the lack of increment of C-reactive protein in the atorvastatin group, compared with the significant increase in the placebo group. This difference was likely due to the anti-inflammatory effect of atorvastatin,[5] which also was shown by the similar behavior of triglycerides.

Our study did not show any relevant adverse events associated with the treatment with atorvastatin 80 mg/d during the acute phase of ischemic stroke. Although previous studies reported a possible greater incidence of hemorrhagic transformation,[13] the only case of symptomatic (and fatal) hemorrhagic transformation occurred in the placebo group.

Also, the finding of a greater number of infections in simvastatin-treated patients[22] was not confirmed by this study on atorvastatin, in which fever was instead more frequent in the placebo group. In no case, an increase in transaminases or CK was large enough to cause withdrawal from the study.

CONCLUSIONS

Further randomized adequately powered clinical trials will be required to ascertain the impact of acute atorvastatin treatment on stroke outcome (if any) and clarify the potential mechanisms of action.

With the limitation of the small sample size, this pilot study was unable to show any short-term benefit of atorvastatin administration during the acute phase of ischemic stroke, suggesting, however, that a future larger trial should rather focus on medium-term outcome in the least severe patients.

This study did not show any significant risk associated with the administration of atorvastatin 80 mg/d to patients with acute ischemic stroke.

ACKNOWLEDGMENTS

The authors thank Drs A. Bonfiglioli, N. Castaldini, S. De Pascalis, S. Flori, C. Giannoni, R. Giuzio, A. Lucicesare, C. Ludovico, C. Napoli, V. Olivelli, L. Pierpaoli, N. Pisacane, C. Tiani, and L. Vizioli, for assistance in patients' selection and data collection, and R. Chianese (Department of Internal Medicine, Aging and Nephrological Diseases, University of Bologna), for the technical support. The authors also thank Dr P. Juric, for supervising the study protocol and generating the randomization lists, and S. Sasdelli, for assistance in patients' management (S.Orsola-Malpighi Hospital, Bologna). Finally, the authors also thank Dr A. Stancari (Pharmacy of the S.Orsola-Malpighi Hospital, Bologna), for preparing the study treatments, and Pfizer Italia S.R.L., for providing the drug for the atorvastatin group.

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