Atorvastatin at high dosage before coronary stent implantation: effect on peri-procedure myocardial infarction

Protocol: ATORV/IMAPERIPROC

CE Approval: 04 Oct 2007

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Enrollment Start: 16 Jan 2008

Enrollment End: 12 Nov 2008

Screened Patients: 20

Enrolled Patients: 11

End of study Patients: 9

Drop-out Patients: 0

Study Closure: 13 Feb 2009

Investigators: Dr. A. Colombo, Dr. F. Airoldi, Dr. C. Briguori

Background. Stent implantations via percutaneous coronary intervention (PCI) are complicated by cardiac biomarkers (creatine kinase-myocardial isoenzyme [CK-MB] and troponin) augmented release in 5-40% of patients (1-5). Most of the times this complication is benign and asymptomatic, however several studies had already shown as even a small post-PCI cardiac enzymes increase could be associated to an augmented risk in cardiac events during the follow-up (1-6). Particularly, had been observed that CK-MB values exceeding normal limits (ULN) of 3, 5, and 8 times are associated to a long-term mortality increase, with a relative risk of 1.84 (3), 2.2 (7) and 5.91 (1) respectively. The American College of Cardiology and the American Heart Association consider CK-MB three times growing value as clinical relevant (6, 8).

Different factors are implicated in peri-procedural acute myocardial infarction onset: a) embolization b) prolonged spasm and dissection of the treated vessel c) vessel perforation d) secondary branches occlusion (4). Much more frequently, though, the peri-procedural damage is diagnosticated only in the hours following the uncomplicated intervention throughout the determination of cellular necrosis enzymes. In these instances, which represent the absolute majority (50-75%), the physiopathological process leading to the damage is given by microcirculation obstructive alterations (structural and partly functional) caused by atheromatous and thrombotic fragments embolization, neuro-hormonal activation and by inflammatory and oxidative stress injuries.

Actually, recommendations for periprocedural AMI prevention are: 1) dual antiplatelet therapy pretreatment (aspirin e thienopyridine) 2) heparin administration at the beginning of the procedure in order to obtain an activated coagulation time (ACT) >300 seconds; otherwise routine using of glycoprotein IIbIIIa inhibitors is not recommended. Despite the use of such strategies, there is still a 5-40% risk (dependent on the type of population treated) of developing a peri-procedural infarction (6, 8).

Statin and hydrossymetylglutaryl-coenzyme reductase (HMG-CoA reductase) inhibitors, in addition to their well-known cholesterol lowering property, own pleiotropic effects able to modify inflammatory response, plaque stability, endothelial function and thrombogenesis (9-12). Moreover, statin limit the activation of monolithic and macrophage system, reducing proteolytic enzymes release (metalloproteases). These drugs interact also with the T lymphocytic component, inhibiting its cytotoxic effect, reducing the Th-1 pro-inflammatory population and reinforcing Th-2 anti-inflammatory sub classes. Statin reduce synthesis and secretion of pro-inflammatory cytokines (IL-6, IL-8, TNF-alfa, CD40 ligand), reducing reactive protein C levels (CRP); where CRP exerts its effect on atherosclerosis progression, endothelial dysfunction and thrombosis. Hence statin are able to attenuate inflammation effects even through CRP modulation (13). Statin influence on pro-thrombotic factors had been evaluated for tissue factor (TF), platelet aggregation, fibrinogen, plasmatic viscosity, fibrinolytic factors (11-16). Platelet taken from high-level cholesterol patients were found to be more responsive to the stimulation with pro-aggregating substances. Cholesterol enrichment of the plasmatic membranes and high production of tromboxan A2 represented two hypothetical mechanisms behind the association between hyper-aggregability and hypercholesterolemia. At the endothelial level, statin improve healing processes, flown-dependent dilation, increase nitric oxide and adenosine bioavailability, limit the expression of surface proteins binding inflammatory cell receptors, platelet and coagulation factors.

Statin influence thrombosis by inhibiting platelet aggregation, coagulation factors, rheological and fibrinolytic factors (11-16); platelet aggregation is contrasted modifying the percentage of cholesterol contained within the plasmatic membrane, modulating membrane fluidity. Clinical studies had shown an association between hyperlipidemia and thrombogenicity (10). Statin reduce coagulation process acting on different level of the cascade, such as via tissue factor and thrombin activation (14) and promoting fibrinolysis through the alteration of fibrinogen tissue activator and the inhibition of plasminogen activator (16).

In the light of the physiophatological mechanisms involved in peri-procedural AMI and of the hypocolesterolemic-independent effects of statin, retrospective studies had shown as pre-procedure statin therapy reduces non-Q wave myocardial infarction incidence and improve long-term outcomes (17-18). Randomized studies have confirmed statin positive effect on peri-procedural AMI: in Briguori et al. study (19) 451 patients had been hospitalized for an elective PCI; all patients were not assuming statin. Patients were randomized in 2 treatment groups: *Statin Group,* patients receiving HMG-CoA reductase inhibitor at least 3 days before procedure (in media 17±8 days prior the procedure) and *Control Group,* patients who did not receive any statin before the procedure. The incidence of peri-procedural infarction with CK-MB and troponin I values 5 times beyond the normal limit were 15.6% for the Control Group and 8% for the Statin Group (P=0.012 and P=0.043 respectively).

In the ARMYDA study (20) 135 patients electively hospitalized for stable chronic angina and not assuming statin were randomized on patients taking atorvastatin (40 mg/die) during the 7 days prior PCI vs patients taking placebo. Pre-treatment with statin reduced peri-procedural myocardial damage: both the number of peri-procedural AMI cases and peak values reached by CK-MB (12% vs 35%, P=0.001, 2.9±3.0 vs 7.5±1.8 ng/mL, p=0.007 respectively), troponin I (20% vs 48%, P=0.0004, 0.09±0.2 vs 0.47±1.3 ng/mL, p=0.0008) and myoglobin (22 vs 51%, P=0.0005, 58±36 vs 81±49 ng/mL, p=0.0002), in fact, had proven to be significant lower in patients group treated with atorvastatin. In both the studies above-mentioned atorvastatin was administrated at least 3 days before the procedure, which represents a relevant problem for the normal clinical practice of patients not assuming atorvastatin. Mensah et al. (21) used an experimental model to demonstrate that the assumption of atorvastatin (20 mg/kg die) within 3 days before the procedure reduced infarction extension; conversely cardioprotective effect was lower if the assumption occurred 1-2 weeks before. For chronic statin assumption patients, instead, cardioprotective effect can be preserved even taking atorvastatin (40 mg /Kg) 3-4 hours pre-procedure. According to the authors, the difference between acute and chronic administration can be explained in relation to the phosphokinase B (PKB) phosphorylation status within PKB/Akt pathway (22-23). Statin acute administration, in fact, appears to induce PKB/Akt complex phosphorylation, increasing nitric oxide and adenosine bioavailability and promoting endothelial progenitor cells proliferation. On the contrary, chronic atorvastatin administration in mice has shown to up-regulate PTEN phosphatase expression, consequently inducing PKB/Akt complex inhibition. Effectiveness of high-dose atorvastatin administration the day before the procedure in reducing peri-procedural AMI risk is

still unknown at the moment.

Aim of the research

To evaluate the efficacy of acute high-dose atorvastatin (80 mg) administration the day before the procedure in preventing peri-procedural AMI.

Expected outcomes

To evaluate the reduction of the incidence of peri-procedural AMI in patients treated with high-dose of atorvastatin the day before the procedure.

Study design

Monocentric, randomized, open study not placebo controlled. About 700 patients would have been be enrolled.

Enrollment: All consecutive patients not assuming statin and hospitalized for an elective PCI on de novo lesions in coronary native vessels were randomize in 2 groups: 1) *Atorvastatin Group*: patients pre-treated with atorvastatin; 2) *Control Group*: patients not pre-treated with atorvastatin. *Atorvastatin Group* patients were treated with 80 mg dose atorvastatin the day before the procedure and 20 mg/die in the following days. *Control Group* patients did not assume any statin neither before the procedure nor during the hospitalization.
Nevertheless, all patients were discharged with atorvastatin 20 mg/die. Randomization 1:1 has been performed according to a numerical allocation system randomly created by a computer.

Randomization: each patient who met inclusion and exclusion criteria and who had signed informed consent was randomized in one of the 2 groups of treatment: 1) *Atorvastatin Group* and 2) *Control Group.*

Method of administration and planned dosage:

- ***Atorvastatin Group*** treated with 80 mg of atorvastatin the day prior the procedure and with 20 mg/die during the following days.
- ***Control Group*** did not assume any statin neither before the procedure nor during the hospitalization. These patients were discharged with atorvastatin 20 mg/die.

Sample estimation. We considered a peri-procedural AMI incidence (CKMB >3 times compared to ULN) of 18% for the *Control Group* (19-20) and of 10% for the *Atorvastatin Group*. Therefore, 322 patients would have been necessary for each group in order to demonstrate a statistically significant difference ($\alpha = 0.80$; $p<0.05$). To cover possible and predictable loss of data 700 patients (350 for each group) would have been enrolled.

Myocardial enzymes dosage. CK-MB (mass concentration) and troponin I (cTnI) values were evaluated before the procedure and 6 and 12 hours after. Additional blood sampling were performed in case of myocardial ischemia. CK-MB mass upper limit of normal values are ≤3.5 (range 0.6-3.5) ng/ml, cTnI upper limit of normal values are ≤0.10 (range 0.00-0.10) ng/ml. CK-MB and/or cTnI elevated basal level were considered as study enrollment exclusion criteria.

Percutaneous myocardial revascularization procedure. PCI with stent implantation have been performed according to standard techniques. All patients were treated with heparin (70 UI/kg) at the beginning of the procedure, in order to get an ACT >300 seconds. The type of stent to be implanted and the implantation technique (with/without pre and/or post-dilatation) were chosen by the operator, as well as the use of directional or rotational atherectomy and that of glycoprotein IIbIIIa inhibitors. The final stenosis <20% procedures were considered successful. Intra-procedural complications taken into account were: vessel acute occlusion, acute thrombosis, prolonged spasm, flow/no-flow limiting dissection, slow/no-flow, distal embolization, secondary branches impairment, temporary/permanent occlusion, vessel break. We experienced 3 adverse events: 3 target vessel revascularizations (2 on target lesion); these events were expected, not associated to the experimental treatment. Any AMI occurred.

Patients enrollment method.

All consecutive patients not assuming statin and hospitalized for an elective PCI on de novo lesions in native coronary vessels were enrolled according to the following criteria:

Inclusion criteria

1) age ≥18 years
2) any ongoing treatment with statin
3) *de novo* stenosis in a native vessel

Exclusion criteria

1) pregnant women
2) acute pulmonary edema
3) AMI and/or acute coronary syndrome
4) elevated basal values of cardiac enzymes (CKMB and/or troponin)
5) recent (≤2 days) acute coronary syndrome and/or AMI
6) patients enrolled in other ongoing studies
7) ongoing treatment with statin
8) dialysis treatment for chronic kidney disease
9) history of statin intolerance
10) aspirin and/or thienopyridine (ticlopidine or clopidogrel)
11) glycoprotein IIbIIIa inhibitors ongoing treatment

Side effects evaluation.

Side effects risk associated to a single high-dose (80 mg) of atorvastatin is extremely low. Literature data showed good tolerability and absence of significant side effects even in case of long-term assumption (24-28). Side effects incidence, in fact, was shown to be comparable with 10 mg/die dose (24). Nausea and intestinal disorders occurr rarely. As with all statin, there might be an increase in CK serum levels. In extremely rare cases (0.04%) muscle damage occur (rabdomyolysis), in most of the cases side effects are transitory and are resolved with the withdrawal of the drug.

Endpoints reached

Primary Endpoint: increase of CK-MB value beyond the upper limit of normality (>3) in association or not with the identification of ST and T waves alteration in ECG.

Secondary Endpoint: 1) Increase of troponin I value beyond the upper limit of normality (>3) 2) endpoint which gathers all the in-hospital events including myocardial infarction, new revascularization, death

Eleven statin-naive patients were randomly assigned the day before the elective PCI to receive atorvastatin 80 mg (atorvastatin group; n=7) or no statin treatment (control group; n=4). Creatine kinase myocardial isoenzyme (CK-MB) (upper limit of normal [ULN] 3.5 ng/ml) and cardiac troponin I (ULN 0.10 ng/ml) were assessed before and 6 and 12 h after the intervention. Periprocedural MI was defined as a CK-MB elevation >3 x ULN alone or associated with chest pain or ST-segment or T-wave abnormalities.

In both groups no periprocedural MI was detected, as defined by CK-MB elevation >3 x ULN. Median Tn-I peak after PCI was 0.15 ng/ml (interquartile range 0.04 to 0.56 ng/ml) in the atorvastatin group and 0.17 ng/ml (interquartile range 0.06 to 0.22 ng/l) in the control group (p=0.172). The incidence of cardiac troponin I elevation >3 x ULN was 42.9% in the atorvastatin group and 75% in the control group (odds ratio: 0.25; 95% confidence interval: 0.26 to 60.32; p=0.317).

Considering the early interruption of the study discussed in the following paragraph we cannot drive any conclusions based on the preliminary study results .

Study closing

In view of the difficulties in enrolling a number of patients able to cover the sample size established by the protocol (few patients meeting inclusion/exclusion criteria), study PI decided to interrupt prematurely the study. This decision was communicated to local EC.

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