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The influence of low dose atorvastatin on inflammatory marker levels in patients with acute coronary syndrome and its potential clinical value

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Abstract

Background: *High-dose statins are used in acute coronary syndromes (ACS) to reduce inflammation. The aim of the study was the evaluation of the influence of low-dose atorvastatin (20 mg) on selected inflammatory parameters and clinical outcomes after ACS.*

Methods: *Seventy eight patients (pts) with ACS were randomly divided into group A (39 pts) taking atorvastatin, and group NA (39 pts) not taking any statin for the following six weeks. C-reactive protein (CRP), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and tumour necrosis factor alpha (TNFα) levels were measured on the first and the fifth days and six weeks after ACS.*

Results: *There was no significant CRP and IL-6 level decrease in group A (CRP — 62%; IL-6 — 73%) or group NA (CRP — 44%; IL-6 — 62%). There was also no significant change in TNFα levels. The MCP-1 level finally reached the level of significant difference ($p < 0.04$). Cardiovascular events (MACE) and the restenosis rates did not differ between the groups.*

Conclusions: *Low-dose atorvastatin does not have a significant influence on cooling down inflammation in ACS, and MCP-1 can be used as an early indicator of statin anti-inflammatory activity. Furthermore, it does not reduce MACE or restenosis rates despite its influence on MCP-1 levels.* (Cardiol J 2008; 15: 357–364)

Key words: atorvastatin, acute coronary syndrome, inflammation, CRP, IL-6, MCP-1, TNFα, restenosis

Introduction

Inflammation, statins and acute coronary syndromes

One of most significant causes of plaque becoming "vulnerable" and the natural progression of the disease accelerating is the inflammatory state. Many publications, as well as clinical studies, have proven that increased levels of inflammatory markers are observed during acute coronary syndrome (ACS); moreover, this finding has been demonstrated to have a negative prognostic value.

C-reactive protein (CRP, measured using highly sensitive methods — hsCRP) is used as a predicative marker of clinical events (mostly cardiovascular). Various statins have the potential to lower the CRP, either related or not related to dose [1–4].

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The only completed randomized trial in which interleukin 6 (IL-6) level profiles were assessed during ACS was the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study. The authors suggested the reason for the lack of IL-6 reduction with atorvastatin use, despite CRP and SAA (serum amyloid A) reduction, might be the high diurnal variability, short half-life (2–4 h compared to 20 h for CRP) and/or very low serum concentration of this cytokine (about one thousand times lower than CRP) [5].

There has been no large study regarding the influence of statins administered during ACS on the tumour necrosis factor alpha (TNFα) level. Patients with a history of myocardial infarction had significantly higher levels of this cytokine compared to patients without infarction. Balbay et al. [6], in contrast, did not observe any difference in TNFα between stable and unstable patients.

Monocyte chemoattractant protein-1 (MCP-1) plays a direct role in facilitating monocytes to permeate into the atherosclerotic plaque (mostly through "rolling") as well as stimulating the inflammatory state and transforming monocytes into "foam cells" in the stable period of the disease. A relationship between intensified MCP-1 expression and rise of CPR activity has been observed, also during ACS [7]. It has been ascertained that the MCP-1 level is higher during ACS than stable coronary artery disease [8].

In the latest data obtained from the ARMYDA--CAMs study, attenuation of post-angioplasty increase of other inflammatory marker (adhesion molecules) levels was observed after 7-day pre-treatment with 40 mg of atorvastatin per day.

The treatment strategy for patients with ACS includes multidirectional striving for plaque stabilization. This has been tried using HMG-CoA inhibitors (statins) and their anti-inflammatory properties.

Most of the data on the modification of inflammation during ACS are included in the two big "statin" clinical trials: PROVE IT–TIMI-22 (PRavastatin and atOrVastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22) [9–11] and A to Z (Aggrastat to Zocor) [10, 12], along with *post hoc* analyses. The outcomes of these analyses gave rise to the hope that statin anti-inflammatory activity would be able to neutralize the independent disadvantageous impact of increased levels of CRP and also encourage further studies.

Inflammation and restenosis

The main reason for restenosis (especially after stent implantation) is the activation of an inflammatory state which induces neointimal hyperplasia [13, 14]. Certain data suggesting the main role of MCP-1 in stimulating restenosis seems of particular interest. Several authors reported a higher level of this chemokine in patients with restenosis than in *de novo* atherosclerosis or in the absence of restenosis [14, 15]. Thus, reducing the inflammatory mediator level should help achieve a reduction of the restenosis rate.

PROVE IT–TIMI 22 demonstrated that the best clinical outcomes occur in patients who had achieved very low (< 100 mg/dL or even < 70 mg/dL) LDL serum concentrations and CRP levels (< 2 mg/dL). However, these data, as well as others, revealed the anti-inflammatory activity of high-dose statin treatment (80 mg atorvastatin per day) during and after ACS. The lowest dose of atorvastatin that is effective in lowering CRP levels in ACS on 30-day follow-up is at present 40 mg [16]. Most physicians (according to data obtained from EUROASPIRE I and II survey [17]) do not use extremely high doses of statins, for many reasons. The purpose of our study was to determine whether a low dose of atorvastatin causes a lowering of inflammatory markers during the 6 week period after ACS.

Methods

Patients

The study group consisted of 78 patients with every kind of ACS included for study from 2003 until 2005. The diagnosis of ACS was based on the GRACE criteria published in May 2002. Patients older than 75 years old, with LDL levels > 130 mg/dL, diabetes, creatinine level > 2 mg/dL, liver dysfunction, hyper- or hypothyreosis, a chronic inflammatory state, or those undergoing treatment with steroids, non-steroid anti-inflammatory drugs or statins (in the month preceding ACS) were excluded. Hypertension was diagnosed previously and was one of the pre-existing conditions or was diagnosed based on the JNC-7. Lipid ranges were accepted from the NCEP ATP III guidelines. Every patient underwent urgent coronary angiography, and afterwards they were qualified to receive proper treatment. They were randomly divided into two groups, either taking or not taking atorvastatin at a dose of 20 mg per day. In this way, the groups (A — patients taking atorvastatin, NA — patients not taking any statin) consisted of 39 patients each. The patients did not differ between groups A and NA in clinical status, therapy or early outcome of treatment (Table 1). Blood samples were taken from the patients enrolled for the study on the first and fifth days of ACS and after 6 weeks (to measure hsCRP,

Table 1. Clinical characteristics of the group.

	Whole group	Atorvastatin group	Non-atorvastatin group
N	78	39	39
Female	12 (15.4%)	6 (15.4%)	6 (15.4%)
Male	66 (84.6%)	33 (84.6%)	33 (84.6%)
STEMI	62 (79.5%)	32 (82.1%)	30 (76.9%)
NSTEMI	12 (15.4%)	4 (10.3%)	8 (20.5%)
UA	4 (5.1%)	3 (7.7%)	1 (2.6%)
Follow-up (x ± SE; months)	15.8 ± 0.89	15.4 ± 1.29	16.3 ± 1.24
Age (x ± SE; years)	55 ± 1.03	54 ± 1.42	55 ± 1.51
Primary PCI	71 (91.0%)	36 (92.3%)	35 (89.8%)
Smokers	58 (74.4%)	27 (69.2%)	31 (79.5%)
SBP (x ± SE; mm Hg)	147 ± 7.7	146 ± 6.8	148 ± 5.6
DBP(x ± SE; mm Hg)	87 ± 5.1	85 ± 5.2	88 ± 5.1
Hypertension	40 (51.2%)	23 (59.0%)	17 (43.6%)
Prior myocardial infarction	7 (9.0%)	4 (10.3%)	3 (7.7%)
Coronary disease *de novo*	62 (79.5%)	33 (84.6%)	29 (74.4%)
Acetylsalicylic acid	77 (98.7%)	39 (100%)	38 (97.4%)
Clopidogrel	70 (89.7%)	35 (89.7%)	35 (89.7%)
Abciximab	15 (19.2%)	8 (20.5%)	7 (17.9%)
CK-MB max (x ± SE; u/L)	217 ± 20.01	211 ± 29.8	223 ± 27.01
LVEF (%); during ACS	46 ± 1.02	46 ± 1.66	46 ± 1.24

p = NS (atorvastatin *vs*. non-atorvastatin group), PCI — percutaneous coronary intervention, ACS — acute coronary syndrome, UA — unstable angina, NSTEMI — non-ST elevation myocardial infarction, STEMI — ST elevation myocardial infarction, NSTACS — non-ST elevation acute coronary syndrome (= NSTEMI + UA), x — mean value, SE — standard error, LVEF — left ventricle ejection fraction, SBP — systolic blood pressure, DBP — diastolic blood pressure

IL-6, TNFα, MCP-1, lipids and aminotransferases). After 6 weeks most patients (35 patients, 89%) from the NA group commenced treatment with atorvastatin (20–40 mg/day) and all of the A group continued therapy with atorvastatin at a modified dose (20–40 mg/day).

The study was approved by the local Bioethical Committee and all patients gave their informed consent.

Clinical follow-up

Clinical follow-up was performed in all 78 patients (100%). The mean period of observation was 15.8 months (±SE = 0.89).

Angiographic follow-up

Angiographic follow-up was carried out at least 6 months after ACS in 68 (87%) patients. Sixty two of them were treated during ACS with primary percutaneous coronary intervention (PCI) with no difference between the A and NA groups. The rest of the investigated population did not agree to undergo repeated angiography. Restenosis was identified when 50% of the coronary lumen diameter was narrowed in the vessel previously treated with PCI.

Statistical analysis

Due to the lack of a normal distribution of data confirmed in the Shapiro-Wilk test, in most cases we used non-parametric methods for comparing particular values. Mean values were compared using the Mann-Whitney U-test. In the case of comparing variables for recurrent parameters, we used Wilcoxon's test for paired variables. Quality variables were examined in independent tests for multi-divided scoreboards: χ^2 Pearson test (in the case of a low expected number we used the Yates' update) and, in the case of a general number lower than 40 for 2 × 2 scoreboards 0151, the exact Fisher's test. A statistical significance level of $p = 0.05$ was accepted.

Results

Lipid and blood pressure measurements

Initially there were no significant differences in lipids between the A and NA groups. Significant differences between the A and NA groups were observed after 6 weeks in total cholesterol, LDL-cholesterol ($p < 0.01$) and triglyceride levels. After 6 weeks the therapeutic goal (LDL level below

Table 2. Lipid level changes.

	Group A (mean ±SE)			Group NA (mean ±SE)			Statistical significance between the groups A and NA (p)	Statistical significance throughout the study (p)
	1 day (a)	6 weeks (b)	Follow-up (c)	1 day (d)	6 weeks (e)	Follow-up (f)		
TCh [mg/dL]	196 ± 4.44	171 ± 6.75	174 ± 6.45	204 ± 6.52	236 ± 7.17	186 ± 6.85	$NS^{1,3}$ $p < 0.01^{2}$	$p < 0.01^{(a-b),\ (a-c),\ (d-e),\ (e-f)}$ $p < 0.03^{(d-f)}$
LDL [mg/dL]	109 ± 2.45	83 ± 4.17	89 ± 4.52	106 ± 2.99	131 ± 5.14	98 ± 5.81	$NS^{1,3}$ $p < 0.01^{2}$	$p < 0.01^{(a-b),\ (a-c),\ (d-e),\ (e-f)}$ NS
HDL [mg/dL]	54 ± 1.94	57 ± 2.42	56 ± 3.13	54 ± 2.36	51 ± 1.87	53 ± 3.43	$NS^{1,2,3}$	
TG [mg/dL]	131 ± 11.56	138 ± 16.01	135 ± 12.78	156 ± 18.3	187 ± 12.6	144 ± 11.3	$NS^{1,3}$ $p < 0.01^{2}$	$p < 0.01^{(e-f)}$

SE — standard error, A — atorvastatin group, NA — non-atorvastatin group, TCh — total cholesterol, HDL — HDL-cholesterol, LDL — LDL-cholesterol, TG — triglycerides; [1]group A *vs.* group NA on first day; [2]group A *vs.* group NA after 6 weeks; [3]group A *vs.* group NA in follow-up

Table 3. Level of inflammatory markers.

	A (n = 39) x±SE	NA (n = 39) x±SE	p
CRP [mg/L] — 1 day	10.06 ± 3.5	10.55 ± 3.25	< 0.03
CRP [mg/L] — 5 day	18.81 ± 4.4	19.01 ± 2.96	NS
CRP [mg/L] — 6 weeks	3.95 ± 0.66	5.90 ± 0.76	< 0.02
IL-6 [pg/mL] — 1 day	10.07 ± 2.0	9.72 ± 1.95	NS
IL-6 [pg/mL] — 5 day	7.27 ± 1.45	7.04 ± 1.03	NS
IL-6 [pg/mL] — 6 weeks	2.65 ± 0.34	3.69 ± 0.86	NS
TNFα [pg/mL] — 1 day	3.61 ± 0.46	4.09 ± 0.72	NS
TNFα [pg/mL] — 5 day	4.18 ± 0.48	5.01 ± 0.68	NS
TNFα [pg/mL] — 6 weeks	4.89 ± 0.78	5.07 ± 0.66	NS
MCP-1 [pg/mL] — 1 day	363 ± 29.93	315 ± 20.99	NS
MCP-1 [pg/mL] — 5 day	313 ± 17.26	329 ± 24.70	NS
MCP-1 [pg/mL] — 6 weeks	361 ± 20.16	422 ± 23.60	< 0.04

x – mean value, SE – standard error; p (A *vs.* NA), A — atorvastatin group, NA — non-atorvastatin group

100 mg/dL) was achieved in 31 patients (79.5%) from the A group and in 7 patients (17.9%) from the NA group ($p < 0.01$). The influence on the HDL-cholesterol level was not significant. In group A there was a significant 13% reduction of total cholesterol level, a 24% reduction of LDL-cholesterol level after 6 weeks of treatment with atorvastatin and an insignificant 5% increase of HDL-cholesterol level. In group NA there was a 23% increase of LDL-cholesterol level and 5% decrease of HDL-cholesterol level. The triglyceride level increased only by 5% in group A but by 20% in group NA. These were non-significant changes, but after 6 weeks the difference between the investigated groups was significant (Table 2).

The blood pressure did not differ between the investigated groups throughout the study (p = NS). After 6 weeks of the study the systolic blood pressure was 137 ± 5.8 mm Hg (group A) and 138 ± ± 5.7 mm Hg (group NA).

Level of inflammatory markers

The levels of particular inflammatory markers and their changes in the subgroups are shown in Table 3 and Figures 1–3.

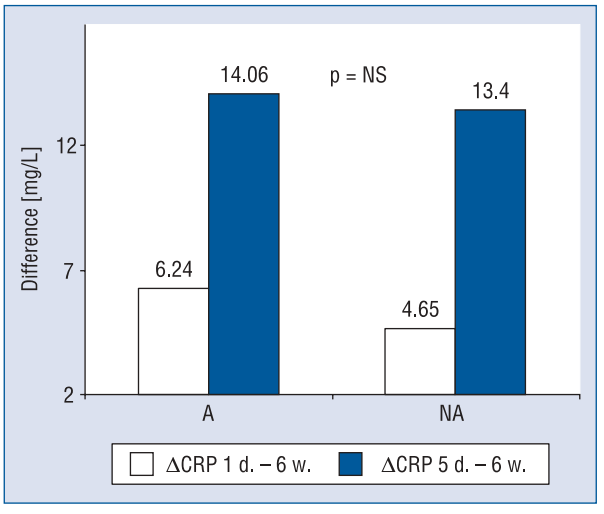

Figure 1. C-reactive protein (CRP) level decrease during 6 weeks (atorvastatin group [A] and non-atorvastatin group [NA]); p (A *vs*. NA); ΔCRP 1 d. – 6 w. — CRP decrease between 1 day and 6 week after ACS (A — 62%, NA — 44%); ΔCRP 5. d. – 6. w. — CRP decrease between 5 days and 6 weeks after ACS (A — 75%, NA — 70%).

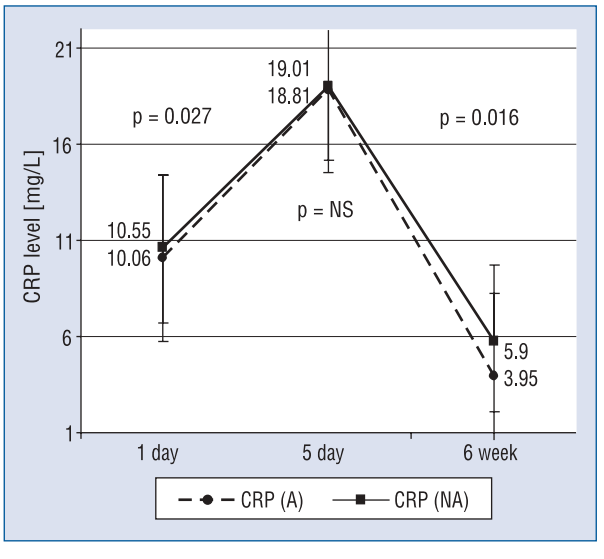

Figure 2. Changes of C-reactive protein (CRP) level; A — atorvastatin group, NA — non-atorvastatin group.

Initially there was a significant difference in the CRP levels ($p < 0.03$) between groups A and NA. There were no significant differences regading IL-6, TNFα or MCP-1 levels. On the fifth day there were still no significant differences between the groups. After 6 weeks there was a 62% (6.24 mg/L) CRP reduction in group A and 44% (4.65 mg/L) reduction in group NA (a 33% difference between the A and NA groups). Similarly, there was a 73%

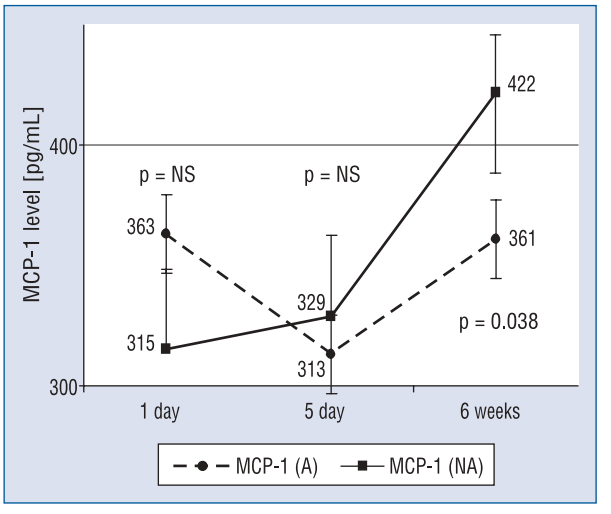

Figure 3. Changes of monocyte chemoattractant protein-1 (MCP-1) level; A — atorvastatin group, NA — non-atorvastatin group.

(7.42 pg/mL) IL-6 reduction in group A and 62% (6.03 pg/mL) reduction in group NA (a 28% difference between the A and NA groups). In both cases the difference was visible but not statistically significant. After 6 weeks there was a 35% increase of the TNFα level in group A and 24% increase in group NA (p = NS). There was almost no change in the MCP-1 level in group A (2 pg/mL) and a 34% (107 pg/mL) increase in group NA. The difference between groups A and NA reached 17% and was statistically significant ($p < 0.04$). Thus, after 6 weeks a significant influence on MCP-1 was observed and this effect (although not originally significant) was observed since the fifth day of ACS.

Clinical follow-up

There was no death in the investigated population during follow-up. 11 (14.1%) major adverse cardiovascular events (MACE, i.e.: ACS, stroke, other significant vascular complications) were observed in the entire group. The total number of ACS was 7 (group A — 4, group NA — 3) in the entire examined population. There were no significant differences between groups A and NA concerning MACEs during the follow-up. There was no myopathy, rhabdomyolysis or liver dysfunction (aminotransferase increase) observed in either group.

Angiographic follow-up

Significant restenosis was observed in 18 patients (29%) who were treated with PCI and accepted repeated angiography. There were no significant differences between groups A (8 patients, 25%)

and NA (10 patients, 33%) although restenosis was observed a little more frequently in patients who did not take any statin during the first 6 weeks after ACS.

Discussion

We observed a significant reduction in the total cholesterol and LDL-cholesterol levels in group A. This is consistent with a moderate dose, and the 24% reduction of the LDL-cholesterol level is less than reported in trials with high-dose atorvastatin treatment. In PROVE IT (80 mg atorvastatin per day) there was a 51% LDL-cholesterol level reduction and in MIRACL (also 80 mg atorvastatin per day) there was a 40% LDL-cholesterol level reduction. It is comparable to the reduction in the LDL-cholesterol level obtained with 40 mg per day of pravastatin (PROVE IT 22%, REVERSAL trial 26%) [9]. The influence on the HDL-cholesterol level is basically consistent with data obtained from multicentre trials with atorvastatin (2% MIRACL study, 6.5% PROVE IT study). The triglyceride level change was not significant throughout our study, which was also the case in the multicentre trials.

On the basis of the obtained results, we can say that early usage of low-dose atorvastatin apparently caused the limited CRP increase after the onset ACS, but it did not achieve a statistically significant reduction. The CRP level obtained was comparable with levels observed in earlier published trials. When analyzing CRP changes over time (Fig. 1, 2) there appears to be a characteristic curve to the CRP level which exemplifies a "natural" course of inflammation (group NA) compared to the "modified" course found with statin therapy (group A). The first analysis of the effects of atorvastatin usage during ACS in a randomized, multicentre trial was in the MIRACL study [5]. After 16 weeks of treatment with 80 mg of atorvastatin and 40 mg of pravastatin there was a 30% difference between the groups, and at the end of follow-up (2.5 years) a 38% difference between the CRP levels was observed ($p < 0.001$). In the A to Z trial the significant CRP level reduction occurred in the subgroup with aggressive statin treatment (80 mg *vs*. 20 mg simvastatin per day; $p < 0.001$). The difference between the groups was 17%. It is vital to point out two differences between these two big trials. In PROVE IT the CRP level difference in the investigated groups was 38% and in A to Z only 17%. In our own study the difference achieved was 33% (but it was not statistically significant). In the A to Z trial the CRP level did not decrease until after 4 months of treatment with simvastatin, and even then with a maximal dose. In our own study this effect could be seen earlier (after 6 weeks) but was not statistically significant. As mentioned above, the lowest dose of atorvastatin that was efficient in lowering CRP levels in ACS in 30-day follow-up, for the time being, is 40 mg [16].

Despite the fact that a reasonably marked distinction between IL-6 levels in groups A and NA in our own study was indeed observed (28% after 6 weeks), it was not significant. A stable decreasing trend of the IL-6 level (measured on the first and fifth days and six weeks after ACS) may testify that the peak level is before the fifth day of ACS and then lowers rapidly until it reaches a point lower than at the start of observation. This might be due to the relatively short half-life of the cytokine. Similar conclusions were reached in the MIRACL, in which, after 16 weeks, there was no significant reduction of IL-6 concentration in any of the subgroups [5]. Interesting facts regarding these findings may be brought to light when FACS trial is completed [18].

Although, during the entire time of observation, TNFα levels were lower in group A (treated with atorvastatin) than in group NA (without any statin in treatment), there is an observable, continuously growing tendency in both groups, and the increase in the level was higher (although not significantly) in the group treated with atorvastatin than in the group with no statin therapy. Brueckmann [19] noticed that the TNFα level was still elevated 120 days after ACS. In contrast, Fahim et al. [20] did not observe a higher TNFα level 48 hours after ACS. In Halawa's study, observations [21] showed a transient peak of this cytokine on the third day after myocardial infarction. Balbay et al. [22], in turn, did not report any differences between the TNFα levels in patients with stable coronary artery disease or with infarction. Vasa et al. [23] published an article in which they observed no significant influence of atorvastatin on the level of this inflammatory marker, which is similar to what we formally report in this study. In summary, it can only fairly be said that to date the obtained data are still ambiguous and discrepant, and attempts at explaining the reasons for this state of affairs (i.e., low serum concentrations, putatively short half-life and the involvement of many pathologic processes) are essentially incomplete and need clarification by further investigation.

Comparing MCP-1 levels (Fig. 3), there was a significant difference between the groups after 6 weeks of follow-up ($p = 0.038$), ultimately reaching 61 pg/mL (17%). This marker was not analysed in any of the main randomized trials concer-

ning ACS. In the study by Mazzone et al. [8] the MCP-1 mean level measured in 29 patients during the first hours of unstable angina was 267 pg/mL. Kobusiak-Prokopowicz et al. [24] observed changes of MCP-1 concentration in the acute phase of ST-elevation myocardial infarction (STEMI). By comparing these results to our own results, it can be ascertained that the initial peak of MCP-1 (observed in the mentioned study 3 hours after myocardial pain started) was not directly detected in our investigation. A possible reason for this is the fact that we took blood samples only once during the first day of ACS. However, the significant difference between the A and NA groups after 6 weeks of observation should be linked with the anti-inflammatory activity of atorvastatin. Such activity has also been described by other authors [25]. It may be (concerning such changes of inflammatory markers) that MCP-1 can be used as an earlier and more efficient indicator than CRP and IL-6 of low-dose statin anti-inflammatory activity during ACS.

The most recent data [26] suggest that also other molecules, such as ICAM-1 and E-selectin, may be influenced by atorvastatin earlier, and more significantly, than CRP. The mentioned study was conducted on a group of 76 patients with stable angina, and it was observed that the CRP level did not change significantly despite the use of atorvastatin, whilst attenuation of post-PCI increase of adhesion molecule levels was observed.

Extensive clinical studies have shown [5, 9, 10] some clinical benefit (reduction of MACEs) in patients treated with a high dose of statins (simvastatin, atorvastatin) during and after ACS. In our group we did not observe a significant reduction of adverse events during clinical follow-up. These data are consistent with the rather surprising results of the last large meta-analysis concerning the role of statin therapy in ACS [27].

Because we observed a significant influence on MCP-1 levels in the group treated with atorvastatin, we continued our investigation in order to determine whether there was a significant relationship with the reduction of the restenosis rate. At present there is no oral treatment available which is able to reduce both inflammation (especially MCP-1) and restenosis after stent implantation. Unfortunately, we observed only a non-significant trend in reducing restenosis rates in group A (25% *vs*. 33.3% in group NA; p = NS), despite a significant influence on MCP-1 levels. Perhaps higher doses of atorvastatin could yet play a positive role in reducing the restenosis rate, although there are as yet no reliable data to support this hypothesis.

Limitations of the study

The significance of some of our results could be limited by the small number of patients in the investigated groups as well as the relatively short period of follow-up. Another limitation is that patients from the non-atorvastatin group started to take statins after 6 weeks of observation. This may particularly limit the clinical outcome of the study, which is why the conclusions are focused only on inflammatory markers, although some clinical observations have been made. Of particular interest is the observation that low-dose atorvastatin does not significantly reduce the restenosis rate despite its influence on the MCP-1 level.

Conclusions

In conclusion, we were able to ascertain that low-dose atorvastatin produces a beneficial but weak (not significant) influence on cooling down inflammation in ACS. MCP-1 may serve as an earlier and more efficient indicator than CRP and IL-6 of low-dose statin anti-inflammatory activity during ACS.

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