VIA MEDICA
ORIGINAL ARTICLE
Folia Cardiol.
2006, Vol. 13, No. 4, pp. 326–330

ISSN 1507–4145

High doses of simvastatin in ACS decrease serum PDGF levels without influencing immune activation

Katarzyna Mizia-Stec[1, 2], Zbigniew Gąsior[1], Barbara Zahorska-Markiewicz[2], Joanna Janowska[2], Magdalena Mizia[1], Piotr Pysz[1], Michał Holecki[2] and Grażyna Knauer-Janicka[1]

[1]Department of Cardiology, Silesian Medical University, Katowice, Poland
[2]Department of Pathophysiology, Silesian Medical University, Katowice, Poland

Abstract

Background: *The positive effects of statin therapy in acute coronary syndromes (ACS) may result from their anti-inflammatory and anti-thrombotic effects. The aim of the study was to compare the influence of standard and high-dose statin therapies in ACS on the serum markers of immune and platelet activation.*

Material and methods: *We examined 44 patients with ACS randomised into two groups: Group S(+) — 22 patients with ACS who were administered high doses of simvastatin (80mg per day) over a period of one month from a cardiac event; Group S(–) — 22 patients with ACS treated by standard doses of statins. In all patients successful percutaneous coronary interventions (PCI) were performed. Laboratory analyses were performed at the baseline on the 7th and 30th days from an ACS and involved the following: platelet-derived growth factor (PDGF), tumour necrosis factor (TNF) alpha, soluble forms of TNF receptor (sTNFR 1 and 2), Interleukin-2 (IL-2), and IL-10.*

Results: *During a one-month follow-up we found no difference between clinical data and the baseline levels of the assessed markers in the groups examined. There were no differences in the consecutive measurements of TNF-α, sTNFR1, sTNFR 2, IL-2, and IL-10 levels. Serum concentrations of PDGF were significantly lower on the 7th and 30th days in group S(+) (7th: 6111 ± 1834 pg/ml, p = 0.037; 30th: 5735 ± 1089 pg/ml, p = 0.016, respectively) in comparison to group S(–) (7th: 7292 ± 1952 pg/ml; 30th: 7034 ± 2008 pg/ml, respectively).*

Conclusions: *High doses of simvastatin administered over a period of one month following an acute coronary syndrome were associated with a significant decrease in serum PDGF levels without influence on the activation of serum immune markers.* (Folia Cardiol. 2006; 13: 326–330)

platelet-derived growth hormone, cytokines, acute coronary syndrome

Introduction

The question of high-dose statin administration in acute coronary syndromes (ACS) has been raised in the literature for several years. Analysis of clinical trials (MIRACL, PROVE-IT) suggests that the primary therapeutic objective is a reduction in the risk of cardiovascular incidents [1–3] and not solely

Address for correspondence:
Dr hab. med. Katarzyna Mizia-Stec
Department of Cardiology, Silesian Medical University
Ziołowa 45/47, 40–635 Katowice, Poland
Tel./fax: +48 32 252 74 07
e-mail: biboch@slam.katowice.pl; kmizia@op.pl
Received: 29.09.2005 Accepted: 7.04.2006

the normalisation of lipid markers. The early use of these medicines would seem, therefore, to be highly recommended, regardless of the initial serum lipid concentration.

Other than the lipid-related mechanisms, the beneficial effects of statins in ACS have not been fully explored. There are considerable data hinting at the influence of statins on the inflammatory processes, believed to be involved in the early stage of atherosclerosis development and its consequences [4]. Not only its early administration but also the dose administered seems to be of great significance [4]. Our observation suggests that the high-dose statins administered in ACS improve the endothelium function in the follow-up [7]. In this article we attempt to determine whether the high-dose statins, administered over a period of one month following an ACS, influence the immunological activation.

Material and methods

A total of 44 consecutive patients who had been diagnosed with an acute coronary syndrome were included in the study. The study group comprised 12 patients with unstable angina (Braunwald's III B class) and 32 patients with an acute myocardial infarction. In all subjects urgent successful percutaneous coronary interventions (PCI) were performed. They were hospitalised in the Cardiology Department of the Silesian University School of Medicine between June and October 2003.

The patients were randomised into two groups:

— group S(+) — 22 patients with ACS to whom high doses of simvastatin were administered (80 mg per day) over a period of one month from the cardiac event;
— group S(–) — 22 patients with ACS treated by standard doses of statins (previous statin therapy was continued without serum lipids analysis at a mean of 20 mg simvastatin per day, or 20 mg simvastatin were administered). The statin had been administered to 10 patients before hospital admission.

The exclusion criteria included: 1) previous myocardial infarction within the preceding six months; 2) infectious diseases and malignant diseases confirmed by clinical, laboratory analyses and, in some cases, by specialist consultations; 3) ECG abnormalities that would hamper ST-T segment analysis.

The clinical characteristics of the patients were drawn up on the basis of the following:

— the medical history of the patients with special attention drawn to smoking status (whether they were non-smokers, ex-smokers or current smokers) and to concomitant diseases (such as hypertension and diabetes mellitus);
— results of physical examination;
— laboratory analyses: serum lipids (total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), serum immune marker concentrations: platelet-derived growth factor (PDGF), tumour necrosis factor alpha (TNF-α), soluble TNF receptor 1 and 2 (sTNFR 1 and 2), Interleukin 2 (IL-2), IL-10;
— ECG — diagnostic criterion;
— echocardiography — left ventricular ejection fraction (LVEF), wall motion score index (WSMI), left ventricular mass (LVM) and left vetricular mass index (LVMI) were all assessed;
— coronary angiography — a division into one, two and three-vessel disease was used.

The complex assessment of the study group was performed at the baseline on the 7^{th} and 30^{th} days from the ACS.

The study was approved by the local ethics committee. All subjects gave their informed consent to the study.

Statistical analysis

All statistical analyses were carried out using Excel v. 2000 Microsoft Company. The results are expressed as mean ± SEM and some data as median values. Student's t-test was used for normally distributed continuous variables. In the case of abnormal distribution the Mann-Whitney test was used. Discontinuous variables were tested by a contingency χ^2 with the Yates correction. $P < 0.05$ was considered statistically significant.

Results

We included 44 patients with ACS: 12 patients with unstable angina (mean age: 51.8 ± 8.5 years; angina symptom history: 2 days – 16 years) and 32 patients who had been diagnosed with AMI (mean age: 51.7 ± 10.6 years; angina symptom history: 2 h – 11 years).

The following values characterised the group with AMI: a mean time from the onset of chest pain of 5.6 ± 1 h; a mean value of the highest MB level of 2329.7 ± 55.8 UI/l; mean values of the highest CKMB level of 452 ± 16.8 IU/l; maximal ST elevation of 5.1 ± 0.7 mm.

The PCI procedures (31 patients underwent PCI with stent implantation) were performed urgently. The results of PCI obtained in the TIMI scale were as follows: TIMI 3 — 37 patients (88.6%);

Table 1. Clinical characteristics of the examined patients: the inclusion data

	Group S(+) N = 22	Group S(–) N = 22
MI	15 (68.2%)	17 (77.3%)
UA	7 (31.8%)	5 (22.7%)
Age (years)	49.4 ± 10.5	54.3 ± 10.5
BMI [kg/m^2]	27.6 ± 4.0	26.6 ± 5.2
TC [mg/dl]	231.6 ± 67.4	227.1 ± 54.0
HDL-cholesterol [mg/dl]	47.4 ± 2.5	49.4 ± 1.3
LDL-cholesterol [mg/dl]	140.6 ± 57.4	140.9 ± 40.9
TG [mg/dl	188.3 ± 121.9	153.6 ± 70.6
LVMI [g/m^2]	141.4 ± 39.0	159.1 ± 42.7
EF (%)	49.0 ± 6.7	45.0 ± 8.2
Motion score index	1.349 ± 0.24	1.526 ± 0.39
Coronary angiography:		
1-vessel CAD	8 (36.4%)	7 (31.8%)
2-vessel CAD	2 (9.1%)	4 (18.2%)
3-vessel CAD	12 (54.5%)	11 (50.0%)
Smoking status:		
active smoker	11 (50.0%)	12 (54.5%)
ex-smoker	4 (18.2%)	4 (18.2%)
never smoked	7 (31.8%)	5 (22.7%)
Concomitant diseases:		
SH	11 (50.0%)	13 (59.1%)
DM	3 (13.6%)	5 (22.7%)

There were no significant differences between groups in all tested parameters, MI — myocardial infarction, UA — unstable angina, CAD — coronary artery disease, SH — systemic hypertension, DM — diabetes mellitus TG — triglycerides, TC — total cholesterol, BMI — body mass index, LVMI — left ventricular mass index, EF — ejection fraction

TIMI 2 — 5 patients (11.4%) — 2 from group S(+), 3 from group S(–). For analysis of the clinical parameters see Table 1.

Comparison of data such as age, body mass index (BMI), serum lipid levels, ejection fraction, mass of the left ventricular and coronary angiography and the results for PCI, smoking status and concomitant diseases did not reveal any significant differences between the study groups.

The pharmacotherapy used (aspirin, ticlopidin, β-blockers, ACE-I, nitrates) was also comparable in groups S(+) and S(–). The statin dose was the only parameter that differentiated the groups examined. For analysis of the serum immune markers see Table 2.

Mean concentrations of immune activation markers were measured at the baseline, on the 7th, and 30th days from the ACS.

On consecutive observation days a decrease in PDGF concentrations was observed in group S(+), in contrast to group S(–), in which PDGF levels increased. In group S(–) a significant increase in PDGF serum level was observed on the 30th day from the ACS in comparison to the baseline value ($p = 0.017$). The analysis of serum PDGF levels on the 7th and 30th days of observation showed significant differences. The mean PDGF concentrations on the 7th and 30th days were significantly lower in group S(+) than those observed in group S(–) ($p = 0.037$, $p = 0.016$, respectively).

The analyses of TNF-α and sTNFR 1 concentrations revealed their highest levels in the period of the ACS event in both study groups, becoming lower over the observation period. The main differences were found in group S(–), in which TNF-α and sTNFR levels were significantly lower on the 7th day of observation than at the baseline. On the 30th day of observation there were no significant differences, while TNF-α concentrations showed a large individual variation. In group S(+) the mean serum sTNFR 2 concentration was significantly lower on the 30th day of therapy in comparison with the baseline levels.

Mean TNF alpha and sTNFR 1 and 2 concentrations were comparable between the study groups.

There were no differences between mean IL-2 and IL-10 serum levels either in the results obtained from a comparison of the study groups or in the findings of consecutive days of observation.

Discussion

The literature data indicate long-lasting immune activation following the ACS [8, 9]. The above analysis confirms these observations. Relatively high serum concentrations of TNF-α, sTNFR 1, as well as IL-2 and IL-10 have been revealed after the ACS. It was clear that the high-dose statin administration did not significantly modify the serum concentrations of 1) TNF-α — a cytokine of crucial pleiotropic pro-inflammatory influence, 2) TNF receptors — reciprocally modifying the serum TNF activity and 3) interleukins — neither the pro-inflammatory IL-2, nor the anti-inflammatory IL-10. The analysis of the dynamics of the change in levels of PDGF (platelet derived growth factor — a factor produced by the endothelium and thrombocytes, which takes part in the activation of the inflammatory and aggregation/coagulation processes), however, proved remarkable. The serum concentration of PDGF in group S(+), originally even slightly

Table 2. Mean serum concentrations of immune activation markers in patients with acute coronary syndrome: consecutive results

	Group S (+), High dose	Group S (–), Low dose
PDGF [pg/ml]	0) 6202 ± 2450 7) 6111 ± 1834$^{\$}$ 30) 5735 ± 1089$^{\$}$	0) 5884 ± 1185* 7) 7292 ± 1952 30) 7034 ± 2008
TNF-α [pg/ml]	0) 22.0 ± 3.1 7) 18.2 ± 8.8 30) 18.6 ± 19.2 (Median: 12.5)	0) 22.0 ± 3.1$^{\#}$ 7) 15.9 ± 7.4 30) 26.3 ± 34.6 (Median: 14.2)
sTNFR 1 [pg/ml]	0) 1715 ± 546 7) 1613 ± 588 30) 1493 ± 590	0) 1664 ± 394$^{\#}$ 7) 1177 ± 391 30) 1445 ± 636
sTNFR 2 [pg/ml]	0) 2103 ± 607* 7) 1852 ± 380 30) 1721 ± 688	0) 2063 ± 634 7) 2082 ± 651 30) 2064 ± 690
IL-10 [pg/ml]	0) 19.0 ± 3.6 7) 18.5 ± 4.6 30) 17.1 ± 3.2	0) 19.3 ± 4.9 7) 17.8 ± 2.9 30) 16.1 ± 5.5
IL-2 [pg/ml]	0) 89.7 ± 12.7 7) 88.8 ± 10.6 30) 95.9 ± 36.7	0) 86.0 ± 28.4 7) 82.9 ± 25.2 30) 81.6 ± 37.3

0) at the baseline; 7) on the 7th day; 30) on the 30th day from the enrolment; *$p < 0.05$ *vs.* result observed on the 30th day; $^{\#}p < 0.01$ *vs.* result observed on the 7th day; $^{\$}p < 0.05$ *vs.* group S(–)

higher than in group S(–), decreased gradually. A statistically significant difference was shown on the 7th day of hospitalisation, and this had increased by day 30. In group S(–) the serum concentrations of PDGF, higher than on admission, remained unaffected on day 30. Limited data on a similar PDGF--release inhibiting influence of simvastatin has also been found by other authors [10].

The significance of our results should be reflected upon in view of the available data on PDGF. The PDGF influence on atherosclerosis development has not been unambiguously determined. Some authors suggest that it has a cardioprotective effect. Firstly, PDGF is supposed to stimulate the angiogenesis in the post-infarct myocardium [12, 13]. This effect however, declines with age [12, 13]. In rodents PDGF encourages the formation of angiogenesis stimulators (angiopoietin, vessel-derived growth factor VDGF) in young specimens, without having this effect on adults [14]. In experimental *in vitro* models endothelium cells intensify the release of PDGF in the presence of cardiomyocytes [15] and PDGF alone enhances stem cell differentiation into cardiomyocytes [16].

Nevertheless, the data on a positive correlation between worse outcomes of invasive procedures in coronary artery disease and a higher expression of inflammatory markers, including PDGF, prevails. The elevated serum concentration of PDGF, while inducing the migration and proliferation of smooth muscle cells and hyperplasia of the intima, particularly in concurrence with lowered fibrinolytic activity of the serum, is considered a major risk factor for restenosis [17]. The use of a number of methods to lower PDGF activity correlates with a significant reduction in restenosis occurrence after percutaneous angioplasty and stenting. Those described in the literature, mostly in animal models, include: 1) the use of a specific inhibitor of the PDGF-receptor tyrosine kinase, which restrains the proliferation and migration of SMCs [18]; 2) decorin — a proteoglycan-binding PDGF; 3) PDGF-specific A-chimeric DNA-RNA ribozymes hindering post-angioplasty intima proliferation with simultaneously applied PDGF A and B antibodies to induce the atrophy of hyperplastic intima [19, 20].

In one of the randomised clinical trials a PDGF antagonist, trapidil, with ticlopidine has proven as effective in preventing restenosis after stenting as acetylosalicic acid with ticlopidine [21].

We are not aware of the remote effects of invasive treatment in our group. The administration of high-dose simvastatin, while efficiently decreasing the serum concentration of PDGF, may enhance the above-described beneficial effect of PDGF inhibition after coronary angioplasty. The lowering of PDGF serum concentration may influence both restenosis occurrence and early intra-stent thrombosis.

Conclusions

High-dose simvastatin, administered over a period of one month following an ACS, has

proven to significantly decrease PDGF serum concentration, while having no remarkable impact on the concentration of other well-established immune activation markers.

References

1. Schwartz GG, Olsson AG, Ezekowitz MD et al. Myocardial ischemia reduction with aggressive cholesterol lowering (MIRACL) study investigators: effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA, 2001; 285: 1711–1718.
2. Ridker PM, Morrow DA, Rose LM, Rifai N, Cannon CP, Braunwald E. Relative efficacy of atorvastatin 80 mg and pravastatin 40 mg in achieving the dual goals of low-density lipoprotein cholesterol < 70 mg/dl and C-reactive protein < 2 mg/l: an analysis of the PROVE-IT TIMI-22 trial. J Am Coll Cardiol, 2005; 45: 1644–1648.
3. Ong HT. The statin studies: from targeting hypercholesterolaemia to targeting the high-risk patient. QJM, 2005; 98: 599–614.
4. Braunwald E, Zipes DP, Libby P. Heart disease. W.B. Saunders Company, Philadelphia 2001; 1070–1081.
5. Auer J, Weber T, Eber B. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med, 2004; 351: 714–717.
6. Patel M, McGuire DK. How aggressive should lipid lowering be among patients with acute coronary syndromes? Curr Cardiol Rep, 2005; 7: 283–287.
7. Mizia-Stec K, Gąsior Z, Zahorska-Markiewicz B, Jastrzębska-Maj E, Gomułka Sz, Mizia M. Duże dawki simwastatyny stosowane w ostrych zespołach wieńcowych a dopplerowskie wskaźniki funkcji śródbłonka w obserwacji odległej. Folia Cardiol, 2004; 6: 425–432.
8. Mizia-Stec K, Mandecki T, Zahorska-Markiewicz B et al. Selected cytokines and soluble forms of cytokines receptors in patients with coronary artery disease. Eur J Inter Med, 2002; 13: 115–122.
9. Zhou Y, Liu X, She M. Molecular basis for the effect of lipid lowering drugs on growth factors after de-endothelialization. Chin Med J, 2001; 114: 976–982.
10. Hao X, Mansson-Broberg A, Gustafsson T et al. Angiogenic effects of dual gene transfer of bFGF and PDGF-BB after myocardial infarction. Biochem Biophys Res Commun, 2004; 315: 1058–1063.
11. Edelberg JM, Cai D, Xaymardan M. Translation of PDGF cardioprotective pathways. Cardiovasc Toxicol, 2003; 3: 27–35.
12. Cai D, Xaymardan M, Holm JM, Zheng J, Kizer JR, Edelberg JM. Age-associated impairment in TNF-α cardioprotection from myocardial infarction. Am J Physiol Heart Circ Physiol, 2003; 285: H463–H469.
13. Xaymardan M, Zheng J, Duignan I et al. Senescent impairment in synergistic cytokine pathways that provide rapid cardioprotection in the rat heart. J Exp Med, 2004; 199: 797–804.
14. Edelberg JM, Lee S, Kaur M et al. Platelet-derived growth factor-AB limits the extent of myocardial infarction in a rat model: feasibility of restoring impaired angiogenic capacity in the aging heart. Circulation, 2002; 105: 608–613.
15. Xaymardan M, Tang L, Zagreda L et al. Platelet-derived growth factor-AB promotes the generation of adult bone marrow-derived cardiac myocytes. Circ Res, 2004; 94: E39–E45.
16. Fornitz GG, Nielsen P, Amtorp O et al. Impaired fibrinolysis determines the outcome of percutaneus transluminal coronary angioplasty (PTCA). Eur J Clin Invest, 2001; 31: 586–592.
17. Bilder G, Amin D, Morgan L et al. Stent-induced restenosis in the swine coronary artery is inhibited by a platelet-derived growth factor receptor tyrosine kinase inhibitor, TKI963. J Cardiovasc Pharmacol, 2003; 41: 817–829.
18. Kotani M, Fukuda N, Ando H et al. Chimeric DNA-RNA hammerhead ribozyme targeting PDGF A-chain mRNA specifically inhibits neointima formation in rat carotid artery after balloon injury. Cardiovasc Res, 2003; 57: 265–276.
19. Nili N, Cheema AN, Giordano FJ et al. Decorin inhibition of PDGF-stimulated vascular smooth muscle cell function: potential mechanism for inhibition of intimal hyperplasia after balloon angioplasty. Am J Pathol, 2003; 163: 869–878.
20. Englesbe MJ, Hawkins SM, Hsieh PC, Daum G, Kenagy RD, Clowes AW. Concomitant blockade of platelet-derived growth factor receptors alpha and beta induces intimal atrophy in baboon PTFE grafts. J Vasc Surg, 2004; 39: 440–446.
21. Galassi AR, Tamburino C, Nicosia A et al. A randomized comparison of trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, versus aspirin in prevention of angiographic restenosis after coronary artery Palmaz-Schatz stent implantation. Catheter Cardiovasc Interv, 1999; 46: 162–168.