Low dose rofecoxib, inflammation and prostacyclin synthesis in acute coronary syndromes

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Abstract

Purpose: To assess the influence of low dose rofecoxib on inflammatory mediators and prostacyclin synthesis in patients with acute coronary syndromes (ACS) in a short-term follow up.

Material and methods: Twenty nine patients with ACS without ST elevation were randomized to simvastatin alone or together with low dose rofecoxib. Serum levels of interleukin 6 (IL-6), 6-keto-PGF-1α – stable product of prostacyclin (PGI2) and hs-C-reactive protein (hs-CRP) were assessed on enrollment and after 30-day follow up.

Results: Combination of rofecoxib with statin significantly decreased levels of hs-CRP after one month therapy (5.21 mg/l ± 4.12 vs 2.11 mg/l ± 2.1; p=0.0092). This effect was not evident in a group on statin alone (3.95 mg/l ± 3.33 vs 2.48 mg/l ± 2.39; p=0.31). 6-keto-PGF-1α increased not significantly in both groups. IL-6 concentration has not changed during follow up.

Conclusions: Low dose of selective COX-2 inhibitor exerts significant anti-inflammatory effect and does not diminish PGI2 synthesis in study group of patients with ACS.

Key words: acute coronary syndromes (ACS), inflammation, simvastatin, cyclooxygenase-2 inhibitors, prostacyclin.

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Received 05.08.2005 Accepted 05.08.2005

Introduction

Cytokines involved in atherosclerosis together with hypoxia and tissue damage are the main factors to activate cyclooxygenase-2 (COX-2) [1]. COX-2 contributes to vascular prostacyclin (PGI2) synthesis, which prevents local thrombosis. Selective COX-2 inhibitors – coxibs, like rofecoxib, in opposite to nonspecific inhibitors (NSAIDs), reduce inflammation without significant gastrointestinal side effects [2]. HMG-CoA reductase inhibitors – statins have a strong lipid lowering effect and increase HDL levels. They also reduce C-reactive protein (CRP) levels [3]. Simvastatin in approved doses increases HDL-induced PGI2 release through COX-2 dependent mechanisms in vascular smooth muscle and endothelial cells [4]. This indicates their not only lipid-lowering and anti-inflammatory effect, but also endothelial protection.

Recent observations demonstrate that selective COX-2 inhibition via suppression of PGI2 biosynthesis shift the haemostatic balance toward a prothrombotic state [5,6]. At the end of September 2004, Merck Sharp & Dohme has withdrawn rofecoxib (Vioxx) from the market worldwide allegedly in response to the results of the APPROVe (Adenomatous Polyp Prevention On Vioxx) Trial [7]. In this placebo-controlled trial for colon cancer progression, its use in a dose of 25 mg/day after 18 months of therapy was associated with significant increased incidence of thromboembolic events. Whether this effect is dose-dependent remains an open question. At the time of Vioxx withdrawal some reports have shown that various doses of rofecoxib could have different effects on endothelial function, inflammatory cytokines and finally on cardiovascular events [8-10]. Besides it was postulated that rofecoxib added to statin may increase beneficial anti-inflammatory effect in patients after PCI [11].

We wanted to assess the anti-inflammatory effect of a low dose rofecoxib (12.5 mg/day) together with statin in a group of patients with ACS and the influence of the drugs combination on PGI2 synthesis, in short-term follow up.

Table 1. **Baseline clinical and biochemical characteristics of ACS patients**

	Simvastatin n=14	Simvastatin + rofecoxib n=15	p
Sex			
Male/ Female	9 (64.4)/ 5 (35.6)	5 (33.4)/ 10 (66.5)	0.1953
Age, years			
Mean	59	64	
Range	(50-74)	(49-78)	0.248
History			
IHD*	6 (42)	7 (46)	0.867
Smoking	7 (50)	4 (26)	0.3622
Hypertension	10 (71)	12 (80)	0.9165
Diabetes	3 (21)	4 (26)	0.9165
Dyslipidemia	5 (35)	2 (13)	0.3304
At admission:			
TIMI Risk Score (points)	3.4 (2-6)	3.3 (2-5)	0.965
Cholesterol (mg/dl)			
total	184±36.6	185±23.2	0.905
LDL	115±35.7	112±28.9	0.769
HDL	38±7.2	40±11.3	0.595
Triglicerides (mg/dl)	148±68.6	137±55.4	0.649
Troponin I (ng/ml) (range)	4.2 (0.0-45.0)	2.74 (0.01-10.9)	0.555

* previous: MI, angiographically proven IHD, PCI and/or CABG
Values are n (%) unless otherwise indicated

Table 2. **Pharmacological and invasive treatment in both groups of ACS patients**

	Simvastatin + rofecoxib group n=15	Simvastatin group n=14	p
Before admission:			
aspirin	6 (40)	7 (50)	1.0
β-blocker	4 (26)	4 (28)	0.763
ACE-I	4 (26)	5 (35)	0.908
At 30 day follow up:			
β-blocker	13 (86)	13 (92)	0.949
ACE-I	13 (86)	10 (71)	0.579
PCI (admission to 30 day follow up)	11 (73)	8 (57)	0.599
PCI in TIMI>4 points	6 (40)	4 (28)	0.79

Values are n (%) unless otherwise indicated

Material and methods

We have undertaken a study to investigate whether low dose of rofecoxib together with added *de novo* simvastatin has greater influence on inflammatory markers in patients with acute coronary syndromes (ACS) and what is the effect of both drugs on PGI2 synthesis. During this study we assessed the safety profile of the drugs.

The study had ethical committee agreement and written informed consent was obtained from each patient before enrollment. Study protocol was accomplished before rofecoxib withdrawal from the market worldwide.

Twenty-nine consecutive patients fulfilling the entry criteria (mean age 61.7±11.2 years) admitted to our Department because of ACS without ST segment elevation were included to the study. TIMI Risk Score was assessed in every patient at admission. Inclusion criteria were chest pain within previous month (IIB Braunwald class) or within the last 48 hours (IIIB Braunwald class) associated with ST segment depression (≥0.5 mm), T wave inversion or no ischemic changes in ECG. Exclusion criteria were persistent ST segment elevation, use of any cholesterol-lowering agent in the preceding month, acute myocardial infarction or revascularization procedures within the preceding month, any inflammatory disease or treatment with anti-inflammatory drugs, use of anticoagulant therapy, malignancy or contraindication to the study drugs.

The patients were randomized to simvastatin (20 mg daily) alone or together with rofecoxib (12.5 mg daily). All patients received acetylsalicylic acid (ASA; max 150 mg daily). Other medication was given according to acknowledged indications. Invasive treatment was preferred when TIMI Risk Score was over 4 points.

Medical history, lipid profile and serum levels of IL-6 (ELISA kits, Quantikine R&D Systems), hs-CRP (nephelometry, Dade Behring) and serum 6-keto-PGF-1α – a stable product of PGI2 (ELISA kits, R&D Systems) were assessed in both groups on enrollment and after 30-day follow up. We also controlled the renal, liver and skeletal muscle function (creatinine, transaminases, creatine kinase) in both groups during study.

Fasting blood samples were drawn, centrifuged (3000 rpm, 5 minutes). The serum was divided into aliquots and kept frozen at -20°C until analysis. According to the method, indomethacin (10 μg/ml) was added to samples in which 6-keto-PGF-1α was measured.

Data are expressed as mean ± standard deviation (SD). Categorical variables are presented as actual number of patients with relative frequencies given in brackets. These variables were assessed with Chi-square test. Mann-Whitney U test was used for comparison of non-categorical variables between groups and Wilcoxon matched pair test was used for comparison of two measurements within one group. A p value of less then 0.05 was considered as statistically significant.

Results

Fourteen patients were enrolled to simvastatin group and fifteen received both simvastatin and rofecoxib. There were neither clinical nor biochemical baseline differences of the patients in both groups (*Tab. 1*). Mean TIMI Risk Score for the whole group was 3.4 points-intermediate risk group.

During whole study all patients received ASA – max 150 mg daily. There were no significant treatment differences in both groups with regard to pharmacological and invasive treatment (*Tab. 2*).

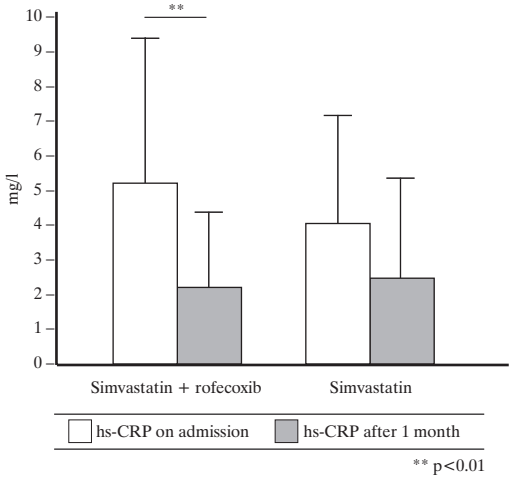
There were no differences in IL-6 levels on admission and its change during follow-up in both groups (Wilcoxon and Mann-Whitney tests) (*Tab. 3*).

Table 3. **IL-6 and 6-keto-PGF-1α values in both groups**

	Interleukin 6 on enrollment (pg/ml)	Interleukin 6 after follow up (pg/ml)	p	6-ketoPGF-1α on enrollment (pg/ml)	6-ketoPGF-1α after follow up (pg/ml)	p
Simvastatin	8.33 (1.3-9.6)	7.6 (3.8-9.2)	0.972	279.1 (209.1-342.1)	329.4 (93.8-1040)	0.345
Simvastatin+ rofecoxib	10.8 (1.2-14.9)	9.5 (7.5-10.4)	0.975	356.2 (207.4-768.3)	603.9 (294.7-1604)	0.109

Data are given as median value and interquartile range. Wilcoxon matched pair test was used for statistical analysis

Figure 1. **The effect of combination of low dose rofecoxib with simvastatin or simvastatin alone on serum concentration of CRP in ACS patients. Data are presented as mean ± standard deviation**



Admission levels of 6-keto-PGF-1α did not differ between groups. Although not significant, the levels similarly increased during therapy (*Tab. 3*).

There were no differences in hs-CRP concentrations at admission in both groups (3.95 mg/l ± 3.33 vs 5.21 mg/l ± 4.12; p=0.369). This result was confirmed in Mann-Whitney test. Rofecoxib with statin significantly decreased levels of hs-CRP during one month follow up. Such trend was not statistically significant in patients who took statin alone. (*Fig. 1*)

There were neither differences in side effects, nor in biochemical markers of renal, liver and sceletal muscle function between groups (data not shown).

Discussion

This is one of few studies to demonstrate that a selective COX-2 inhibitor together with standard therapy with added *de novo* statin reduces markers of inflammation.

High levels of inflammatory mediators, like IL-6 and CRP are found in patients with ACS [12]. It has been shown that high CRP levels are associated with endothelial dysfunction [13]. Treatment with statins reduces levels of inflammatory mediators indicating their anti-inflammatory effect [3]. Besides this, they are capable of modulating cell signaling and vascular function [4,14]. Recently it has been reported that simvastatin induces PGI2 release through COX-2-dependent mechanisms in vascular smooth muscle cells (VSMC) and endothelial cells. This indicates another effect of statins – improvement of endothelial function [4].

We wanted to check what would be the effect of low dose (12.5 mg daily) rofecoxib together with de novo added simvastatin not only on inflammatory cytokines, but also on PGI2 synthesis. We showed that simvastatin alone does not significantly lower inflammatory biomarker profiles (hs-CRP, IL-6) during one month treatment. Although not significantly simvastatin still increases PGI2 synthesis, which is consistent with its endothelial protection.

Coxibs, selective blockers of COX-2 isoform, have two main effects: lowering cellular-derived eicosanoides, which indicate their anti-inflammatory effect and decrease PGI2 synthesis-thus could impair endothelial function and disorder a thrombotic balance [5,15]. There are some data regarding the use of coxibs in patients with atherosclerosis. Their effect depends not only on the type of coxib used, but also, especially according to rofecoxib, seems to be dose-dependent. The dose of 25 mg daily used in APPROVe Trial was the one who lead Merck to withdraw rofecoxib from the market. According to APPROVe Trial rofecoxib in a dose of 25 mg daily, after 18 months of therapy doubled the risk of a myocardial infarction compared with placebo [7]. Ray et al. [8] in a meta-analysis (almost 400 thousand patients) showed that users of high dose rofecoxib, >25 mg daily (lowest approved daily dose is 12.5 mg), were 1.7 times more likely to have cardiac events (acute myocardial infarction and/or cardiac death) than non-users; among new users this rate increased to 1.93. There was no evidence of raised events risk rate among users of rofecoxib at doses of 25 mg daily or less or among users of other NSAIDs (including celecoxib). In another study rofecoxib in a dose of 25 mg/day had no favorable and adverse effects not only on endothelial function, but also on vascular inflammation (measured as hs-CRP, soluble intercellular adhesion molecule-1 and soluble IL-6 receptor levels) in patients with angiographically proven coronary artery disease (CAD) [10]. Solomon et al. showed that rofecoxib in doses >25 mg was associated with higher risk of acute myocardial infarction than dosages ≤25 mg [9].

The aim of our study was to test the low dose of rofecoxib in ACS patients. The completion of a statin-free study group was

difficult and was stopped in the moment of rofecoxib withdrawal from the market worldwide. Our data suggest that a low dose rofecoxib added to simvastatin does not decrease PGI2 levels during therapy. Perhaps the explanation is not only a dose of rofecoxib added to simvastatin, but also the finding that COX-2 blockade still allows COX-1 to produce PGI2 [16]. Still because of rofecoxib withdrawal we could not continue our study. Our small study pilot group did not allow us to evaluate clinical effects of the drugs. However we showed that the combination of the drugs has an important influence on hs-CRP levels and does not change IL-6 levels. Although Monakier et al. [17] showed that rofecoxib in a dose of 25 mg per day lowers both CRP and IL-6 levels, after three months of therapy the effect persisted only for CRP, but not for IL-6. This reveals the new point of activity of selective COX-2 inhibitors and their possible greater role in inhibiting liver CRP synthesis than in inflammatory cells-derived cytokines. Similar effect was observed in patients receiving statins, which lowered CRP levels and did not changed IL-6 [18]. On the other hand in REVERSAL Trial intensive lipid-lowering treatment with atorvastatin reduced progression of atherosclerosis, which was compliant with the greater reduction in C-reactive protein, independently of atherogenic lipoproteins [19].

Conclusions

Our study supports the hypothesis that low dose of selective COX-2 inhibitor added to standard therapy with statin in ACS patients has a significant anti-inflammatory effect and does not diminish prostacyclin synthesis.

Acknowledgement

This paper was financed by grant from Medical University in Białystok, Poland, No 3-53845. Preliminary data were published on ESC Congress in Munich, 2004.

Special thanks to Irena Słomińska and Elżbieta Kulikowska for excellent technical assistance and to Lucyna Traciecka who was involved in patient sampling. The authors are grateful to Jolanta Tobolczyk MSc PhD, from Department of Paediatric Allergology Medical University in Białystok for laboratory work.

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