Rofecoxib, a COX-2 Inhibitor, Lowers C-Reactive Protein and Interleukin-6 Levels in Patients With Acute Coronary Syndromes*

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**Background:** Patients with acute coronary syndromes (ACS) have high levels of inflammatory mediators such as C-reactive protein (CRP) and interleukin (IL)-6.

**Aim:** To evaluate whether patients with ACS treated with rofecoxib, a COX-2 inhibitor, will have reduced CRP, IL-6, and soluble tumor necrotic factor receptor-1 (sTNF-R1) levels and improved endothelial function.

**Methods and results:** Thirty-four patients hospitalized with ACS were randomized to receive rofecoxib, 25 mg/d plus aspirin 100 mg/d, or placebo plus aspirin, 100 mg/d, for a period of 3 months. Blood samples for CRP, IL-6, and sTNF-R1 levels were drawn prior to randomization, and after 1 month and 3 months. CRP levels in the rofecoxib group (n = 18) were significantly lower both at 1 month and 3 months compared to the baseline levels (p < 0.02). IL-6 levels were significantly lower at 1 month (p < 0.02) in the rofecoxib group, but not at 3 months. There was no change in endothelial function or sTNF-R1 levels.

**Conclusion:** Patients recovering from ACS had lower levels of CRP and IL-6 at 1 month and lower CRP levels at 3 months when treated with rofecoxib plus aspirin. Suppression of inflammatory processes may lead to retardation of coronary atherosclerosis and coronary events.

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**Key words:** acute coronary syndromes; COX-2 inhibitor; C-reactive protein; endothelial function; interleukin-6; rofecoxib

**Abbreviations:** ACS = acute coronary syndromes; CAD = coronary artery disease; CRP = C-reactive protein; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; IL = interleukin; LDL = low-density lipoprotein; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drug; sTNF-R1 = soluble tumor necrosis factor receptor-1; TNF = tumor necrosis factor

High levels of inflammatory mediators such as interleukin (IL)-6, serum amyloid A, and especially C-reactive protein (CRP) were found in patients with coronary artery disease (CAD), and their presence was predictive of cardiovascular events in patients with stable and unstable angina, as well as in healthy men and women. Data suggest that CRP may play a direct role in the progression and activation of atherosclerosis. This effect may be due to its ability to enhance macrophage uptake of low-density lipoprotein (LDL) cholesterol and formation of foam cells, inducing the expression of adhesion molecules in human endothe-
congestive heart failure; however, treatment with predictor for mortality in a study of patients with receptor 1 (sTNFR-1) was found to be the best as oxidized LDL. Soluble tumor necrosis factor was associated with reduction in CRP levels as well celecoxib, 200 mg bid, for 2 weeks. This treatment patients with stable CAD treated with aspirin plus prevention trials, suggesting that they possess anti-inflammatory properties in addition to their antiplatelet (aspirin) or lipid-lowering effect (statins). This may contribute to retardation of atherosclerosis and reduction in frequency of cardiac events.

Endothelial dysfunction is well documented in patients with CAD, and has been associated with high CRP levels. Recently, improvement in endothelial function was reported by Chenevard et al in patients with stable CAD treated with aspirin plus celecoxib, 200 mg bid, for 2 weeks. This treatment was associated with reduction in CRP levels as well as oxidized LDL. Soluble tumor necrosis factor receptor 1 (sTNF-R1) was found to be the best predictor for mortality in a study of patients with congestive heart failure, however, treatment with tumor necrosis factor (TNF) antagonists showed no benefit. TNF-α has less variability than other inflammatory markers, reflecting a more chronic inflammatory process. Although elevated levels of soluble TNF receptor 2 were found in patients with documented CAD, the level of TNF receptor 1 in patients with ACS is not yet known.

Several studies reported a correlation between the COX-2 enzyme activity and atherosclerotic plaques. Overexpression of functionally coupled cyclooxygenase-2 and prostaglandin-E synthase was found in carotid artery atherosclerotic plaques of patients with recent transient ischemic attack or stroke. The author concludes that, "the current available COX-2 inhibitors might provide a novel form of therapy for plaque stabilization of patients with atherosclerotic disease and prevention of acute ischemic syndromes." In a study by Altman et al, the use of aspirin plus meloxicam, a COX-2 inhibitor, for 30 days in patients with ACS without ST-segment elevation was associated with lower rate of recurrent angina, myocardial infarction (MI), or death. An interesting experiment by Saito et al showed better cardiac function in rats that received a selective COX-2 inhibitor after ligation of the left coronary artery in contrast to the control group. Recently, a concern was raised regarding the safety of the COX-2 inhibitors. In the Vioxx Gastrointestinal Outcomes Research study, the rate of MI was higher in patients with rheumatoid arthritis treated with rofecoxib as compared to those treated with naproxen. This was primarily seen in the population with the highest risk for MI that had indication for antiplatelet therapy. However, in that study no aspirin was administered. In a retrospective cohort study, Ray et al found that users of high-dose rofecoxib (50 mg/d) were 1.7 times more likely than nonusers to have coronary heart disease, while no increased risk was observed in users of rofecoxib at doses of ≤ 25 mg. In an analysis of 23 studies with > 28,000 patients, there was no excess of cardiovascular events in patients treated with rofecoxib compared to placebo or non-naproxen nonsteroidal anti-inflammatory drugs (NSAIDs). The differences observed with naproxen were most likely due to its antiplatelet effect. Rofecoxib, which is a specific inhibitor of the COX-2 enzyme, has less GI side effects than the nonselective NSAIDs; therefore, we considered it to be safe for our study population.

The purpose of our study was to prospectively evaluate the influence of a COX-2 inhibitor (rofecoxib) on levels of inflammatory markers (CRP, IL-6, sTNF-R1), and on endothelial function in patients recovering from non-ST-segment elevation ACS.

Materials and Methods

This was a prospective, randomized, double-blind, placebo-controlled study. Patients hospitalized for non-ST-segment elevation ACS were randomized to receive either rofecoxib, 25 mg/d, plus 100 mg of aspirin, or placebo plus 100 mg of aspirin for a period of 3 months. Regarding the randomization of the patients, a tablet of rofecoxib, 25 mg, or a placebo tablet was put into a nontransparent capsule. The hospital pharmacist distributed the medications in separate dark boxes. The boxes were distributed to the patients by the research coordinator of the study, without knowing the content of the boxes. Patients were randomized into two equiprobable groups via a common pseudorandom number generator. In this specific case, a discrete uniform distribution of the 10 digits (0–9) was used, with odd numbers allocating patients to group A, and even numbers allocating patients to group B. A Fisher exact test was used as a quality control tool for verifying that the observed allocation follows the above-mentioned distribution. Compliance was monitored by tablet counts.

Patients hospitalized for a non-ST-segment elevation ACS were included in the study. This was defined as rest angina with ST-T abnormalities in the presence or absence of elevated creatine phosphokinase or troponins. ST-segment elevation on
hospital admission, infectious or other inflammatory disease, serum creatinine > 1.5 mg/dL, active peptic ulcer, history of GI bleeding, uncontrolled hypertension, asthma, allergy to NSAIDs, and congestive heart failure were considered exclusion criteria. The study was approved by the hospital ethics committee, and written informed consent was obtained from each patient prior to enrollment.

**Laboratory Tests**

Blood samples of inflammatory markers, biochemistry, and lipid profile were drawn at hospital admission and again at 1 month and 3 months. The baseline samples were obtained prior to any invasive procedure, at an average of 24 h after the index anginal episode. CRP levels were determined by nephelometry, using a high-sensitivity assay (Dade Behring Marburg GmbH; Marburg, Germany), and IL-6 and sTNF-R1 by enzyme-linked immunosorbent assay (R&D Systems; Minneapolis, MN). Endothelial function was evaluated noninvasively using high-frequency ultrasound of the brachial artery, assessing blood flow response to hyperemia (endothelium-dependent vasodilatation) and nitroglycerin spray (endothelium-independent vasodilatation).48

**Statistical Analysis**

Statistical analysis of CRP, IL-6, sTNF-R1 levels and endothelial function was performed by the Wilcoxon test, comparing the 1-month and 3-month results to the baseline values of each group.

**RESULTS**

Thirty-four patients participated in the study, and all completed at least 1 month of treatment; 18 patients received rofecoxib, and 16 patients received placebo. Of the 23 patients who completed 3 months of treatment, 12 patients received rofecoxib and 11 patients received placebo. Most of the patients who did not complete the 3-month follow-up were excluded, mainly due to the development of infections and inflammatory conditions that could potentially elevate the inflammatory markers studied. There were no significant differences in baseline clinical characteristics between the two groups (Table 1). All patients in the rofecoxib group and 14 of the 16 patients in the placebo group were treated with aspirin prior to hospitalization, and most were receiving HMG-CoA reductase inhibitors. Most patients had proven CAD either by angiography or having a history of MI. There were no significant differences in baseline laboratory values between the groups (Table 2).

Baseline CRP levels in the rofecoxib group ranged from 0.06 to 3.14 mg/dL (mean, 0.64 ± 0.76 mg/dL). In an intention-to-treat analysis, CRP levels were significantly reduced at 1 month by 0.84 mg/dL in the rofecoxib group compared to its baseline values and by 1.3 mg/dL after 3 months (p < 0.02; Fig 1). No significant change of CRP level was detected in the placebo group. After excluding the poorly compliant patients (n = 3) from the analysis, a more significant reduction in CRP levels both at 1 month and 3 months was noted (p < 0.004 and p < 0.02, respectively). CRP reduction was also significant (p < 0.03 at 1 month and 3 months) after excluding

**Table 1—Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rofecoxib (n = 18)</th>
<th>Placebo (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62.4</td>
<td>61.7</td>
</tr>
<tr>
<td>Male gender</td>
<td>14 (78)</td>
<td>15 (94)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.3</td>
<td>78.6</td>
</tr>
<tr>
<td>Medical history</td>
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</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>14 (78)</td>
<td>14 (78)</td>
</tr>
<tr>
<td>Diabettes</td>
<td>8 (44)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (55)</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1 (5.5)</td>
<td>3 (19)</td>
</tr>
<tr>
<td>MI</td>
<td>8 (44)</td>
<td>12 (75)</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>10 (55)</td>
<td>13 (81)</td>
</tr>
<tr>
<td>CABG</td>
<td>5 (28)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>18 (100)</td>
<td>14 (57)</td>
</tr>
<tr>
<td>Statins</td>
<td>12 (67)</td>
<td>10 (62)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>13 (72)</td>
<td>11 (69)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>7 (39)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>15 (77)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>11 (54)</td>
<td>6 (37)</td>
</tr>
<tr>
<td>Gplla/vlla</td>
<td>5 (28)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Discharge diagnosis UA-NQMI</td>
<td>14:03</td>
<td>12:02</td>
</tr>
<tr>
<td>Hospitalization, d</td>
<td>5.3</td>
<td>5.6</td>
</tr>
</tbody>
</table>

*Data are presented as mean or No. (%) unless otherwise indicated. CAGB = coronary artery bypass grafting; ACE = angiotensin-converting enzyme; UA-NQMI = unstable angina-non-Q wave myocardial infarction.

<table>
<thead>
<tr>
<th>Results</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib</td>
<td>Placebo</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>141.72 (1.77)</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>4.11 (0.2)</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>134.11 (64.66)</td>
</tr>
<tr>
<td>BUN, mg/dL</td>
<td>16.89 (5.46)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.96 (0.28)</td>
</tr>
<tr>
<td>Hemooglobin, g/dL</td>
<td>14.13 (1.52)</td>
</tr>
<tr>
<td>WBC, 10³/µL</td>
<td>7.83 (1.73)</td>
</tr>
<tr>
<td>Platelets, 10⁹/µL</td>
<td>234,646 (83,853)</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>459.2 (146.6)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>212.56 (32.45)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>129.23 (30.56)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol, mg/dL</td>
<td>45.06 (9.05)</td>
</tr>
<tr>
<td>Cholesterol/high-density lipoprotein ratio</td>
<td>4.82 (1.16)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD).
one patient with a very high baseline CRP level (13.6 mg/dL) in the rofecoxib group (n = 17 and n = 11 at 1 month and 3 months, respectively).

**IL-6**

Baseline IL-6 levels in the rofecoxib group ranged from 0.96 to 6.7 pg/dL (mean, 3.57 ± 2.07 pg/dL); in the placebo group, baseline IL-6 levels ranged from 0.12 to 6.7 mg/dL (mean, 3.02 ± 2.10 pg/dL). In an intention-to-treat analysis, IL-6 levels were significantly reduced at 1 month in the rofecoxib group (p = 0.01) but not at 3 months (p = 0.13) when compared to baseline. There were no significant changes in IL-6 levels in the placebo group (Fig 2). When poorly compliant patients were excluded from analysis in the rofecoxib group, there was a very significant reduction of IL-6 level at 1 month (p < 0.002) and a borderline reduction at 3 months (p = 0.067).

**sTNF-R1**

Analysis of sTNF-R1 serum levels showed no significant change from baseline to 1-month and 3-month values in the rofecoxib or the placebo groups. Results were within normal range (820 to 990 pg/mL) in all but one patient.

**Endothelial Function**

Assessment of endothelial function was performed on 22 patients who were nonsmokers: 12 patients in the rofecoxib group, and 10 patients in the placebo group. No change in brachial artery vascular reactivity was detected between baseline measurements and those at 1 month or 3 months in the rofecoxib or the placebo groups.

**Safety and Tolerability**

During the 3 months of treatment, there were no significant side effects. One placebo-treated patient had a suspected allergic reaction. Three patients had acute MIs: two patients in the placebo group, and one patient in the rofecoxib group. Two further patients were hospitalized for unstable angina, both from the placebo group. Three patients underwent revascularization, all in the rofecoxib group.

**DISCUSSION**

The main findings of this study were that treatment with rofecoxib, a COX-2 inhibitor, in patients hospitalized for ACS was associated with significant reduction of CRP and IL-6 levels. The reduction in both CRP and IL-6 levels was observed after 1 month of treatment and persisted for 3 months. The treatment was well tolerated. The reduction in CRP and IL-6 was observed in patients already receiving medical treatment, as all patients were treated with aspirin and most were receiving HMG-CoA reductase inhibitors.

Biasucci et al[49] showed that 49% of patients who were hospitalized for unstable angina had high CRP levels at discharge, and 42% of them had persistence of elevated CRP levels for ≥ 3 months. Patients with elevation of CRP on hospital discharge had an increased incidence of recurrence of instability or MI compared to those with lower CRP levels at discharge.

Data suggest that CRP may be not only a marker, but may have a direct role in the process of atherosclerosis. Zwaka et al[10] demonstrated that CRP mediated the uptake of LDL cholesterol by macrophages, and Pasceri et al[17] demonstrated a direct proinflammatory effect of CRP, inducing the expression of adhesion molecules in human endothelial cells. Therefore, therapy that reduces CRP levels in patients with ACS may directly suppress the atherosclerotic process and reduce event rates.

In our study, as previously noted, all patients were
additionally treated with 100 mg of aspirin, as COX-2 inhibitors have no antiplatelet effect. No change in sTNF-R1 levels was observed during the study. In both groups, levels were within normal range, and there were no significant changes noted between baseline, 1 month, and 3 months in either group. Therefore, sTNF-R1 levels, unlike TNF-α and soluble TNF receptor 2, probably do not reflect the inflammatory process in patients with non-ST-segment elevation ACS.

Endothelial function did not change during the course of this study in either group. This is in contrast to a previous study in which patients with CAD and high levels of CRP had impaired endothelial function, while reduction in CRP was associated with improvement in function. The lack of improvement in endothelial function in patients treated with rofecoxib in spite of reduction in CRP may be due to the small number of patients in each group and the short follow-up period.

The major limitations of the study are the small number of patients studied, and the high dropout rate at the 3-month follow-up (six patients in the rofecoxib group, and five patients in the placebo group). Patients were excluded because of various reasons: rehospitalization because of acute MI (n = 3), unstable angina (n = 2), and infection or inflammatory conditions requiring anti-inflammatory treatment (n = 6). In spite of the relatively small number of patients studied, even the intention-to-treatment analysis showed a significant reduction of CRP and IL-6 in the rofecoxib group after 1 month and 3 months of treatment, and there was no significant change in the placebo group.

We conclude that in patients hospitalized for non-ST-segment elevation ACS, treatment with a COX-2 inhibitor NSAID in combination with aspirin is associated with lower levels of CRP and IL-6 at 1-month and 3-month follow-up periods. The reduced level of inflammatory markers may translate into reduction of acute coronary events. This has to be evaluated in large-scale studies and for a longer follow-up period.

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