Short-term effects of atorvastatin on C-reactive protein

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\textbf{Aim} To study the short-term effect of atorvastatin on C-reactive protein (CRP) in patients with or at risk for coronary heart disease.

\textbf{Methods and Results} One hundred and fifty-five randomly selected patients from the SWiss Intervention Trial for lowering CHolesterol (SWITCH) were assessed for high sensitivity CRP, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides at baseline, and after 1 and 3 months of treatment with atorvastatin at various doses to reach pre-defined lipid target values. The median decrease of cholesterol was 28\% after 1 month and 35\% after 3 months. LDL-cholesterol was decreased by 37\% and 45\%, HDL-cholesterol was increased by 7\% and 8\%, respectively. Patients with a low CRP baseline concentration (lowest quartile <1.34 mg l\textsuperscript{-1}) displayed no significant change, whereas patients in the other quartiles showed a significant decrease, of 22\% to 40\% (\textit{P}-value <0.05 to <0.001) at 1 month and of 32\% to 36\% after 3 months compared to baseline. The decrease in CRP lowering was thus fully established by 1 month and this response was independent of lipid and lipoprotein changes as well as atorvastatin doses.

\textbf{Conclusion} Atorvastatin significantly decreases CRP concentrations after 4 weeks of therapy. These results may be important with respect to the early benefit of statin therapy. (\textit{Eur Heart J}, 2002; 23: 794–799, doi:10.1053/euhj.2001.2967) © 2001 The European Society of Cardiology. Published by Elsevier Science Ltd. All rights reserved.

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short-term effects of such drugs. We report results on high sensitivity CRP measurements after 1 and 3 months of treatment with atorvastatin within the SWITCH (Swiss Intervention Trial for Lowering Cholesterol) trial[14].

Patients and methods

The study was approved by the local ethics committees and patients gave their informed consent.

Inclusion criteria for the SWITCH study were:
(i) Stable coronary heart disease, cholesterol >5·2 mmol·l⁻¹ and cholesterol/HDL-cholesterol >5
(ii) Two risk factors for coronary heart disease, cholesterol >6·5 mmol·l⁻¹ and cholesterol/HDL-cholesterol >5
(iii) Cholesterol >8·0 mmol·l⁻¹ and cholesterol/HDL-cholesterol >6·5

Exclusion criteria were as follows: triglycerides >10 mmol·l⁻¹; creatine kinase, alanine aminotransferase >3 times upper limit of normal, creatinine >130 μmol·l⁻¹; myopathy, nephrotic syndrome, diabetes (fasting glucose >8 mmol·l⁻¹) pancreatitis; acute coronary event within the past 3 months; initial high sensitivity CRP <8·4 mg·l⁻¹ and a marked increase after 1 month (>25 mg·l⁻¹, suggesting the possibility of an acute infection).

After a pre- or wash-out phase with a defined dietary intervention during a 2–4 week period, baseline laboratory parameters were determined and treatment with atorvastatin 10 mg per day was started. Patients with total cholesterol ‘greater than’ 7·5 mmol·l⁻¹ and a cholesterol/HDL-cholesterol ratio >6·5 were started on 20 mg of atorvastatin per day. Patients were treated for 3 months and laboratory tests were performed every 4 weeks. The dosage of atorvastatin could be doubled at any follow-up visit until target levels (cholesterol <5·2, cholesterol/HDL-cholesterol <5) were reached (maximal dose: 80 mg·day⁻¹).

One hundred and fifty-five patients (99 males, 56 females) were randomly selected from all patients included into the SWITCH study (877 patients).

Methods and statistics

Cholesterol, LDL-, HDL-cholesterol and triglycerides were measured on a HITACHI 917 autoanalyser using reagents from Roche Diagnostics (Rotkreuz, Switzerland). HDL-cholesterol was determined by a direct homogeneous enzymatic test (LDL-C plus, Roche)[15]. The coefficient of variation from day to day of this method was smaller than 2·5% at 1·0 mmol·l⁻¹.

The coe cient of variation from day to day of this method was smaller than 3·0% at 3·0 mmol·l⁻¹.

The dosage of atorvastatin could be doubled at any follow-up visit until target levels (cholesterol <5·2, cholesterol/HDL-cholesterol <5) were reached (maximal dose: 80 mg·day⁻¹).

One hundred and fifty-five patients (99 males, 56 females) were randomly selected from all patients included into the SWITCH study (877 patients).

Results

The cumulative frequency of CRP levels in 158 tested patients is shown in Fig. 1. It can be seen that 10% of all patients had levels below 0·7 mg·l⁻¹ (which represents no risk for coronary heart disease) 25% below 1·34 mg·l⁻¹ and 10% above 8·4 mg·l⁻¹. The usual cut-off for the diagnosis of potential acute infections is 8·0 mg·l⁻¹. Three patients with initial CRP levels <8·4 mg·l⁻¹ and a marked increase after 1 month (CRP >25 mg·l⁻¹), indicative of acute viral or bacterial infection, were excluded from the statistical analysis.

The median lipid, lipoprotein and CRP levels during the initial visit, after 1 month and after 3 months of treatment with atorvastatin are displayed in Table 1.

The median decrease for cholesterol was 28% after 1 month and 35% after 3 months of treatment.
Triglycerides decreased by 20% and 35%, respectively. The decrease in LDL-cholesterol was 37% and 45%, while HDL-cholesterol increased by 7% and 8%, respectively. The median decrease in CRP was already fully established after 4 weeks, no additional significant decrease occurs at 3 months (Table 3). A comparison of the effects of atorvastatin, simvastatin and pravastatin in one study showed no significant differences in concentrations before and after 3 months of treatment.[20] In addition, de Maat et al.[21] found that pravastatin therapy did not affect CRP in patients with familial hypercholesterolaemia for a period of up to 12 months. They concluded that the effect of statins on CRP occur preferably in patients with an increased inflammatory state.[22] Our data point to a similar assumption since median CRP levels in the lowest quartile (<1.34 mg . l⁻¹) did not change while levels in the three upper quartiles were significantly decreased (P<0.0001). Such differences

Statin therapy has been shown not only to affect lipid and lipoprotein levels but also haemostatic and inflammatory molecules.[16]. Beyond lipids, these molecules are thought to be important risk markers of atherosclerotic disease. CRP especially has been shown to be an important independent risk factor, which is additive to the cholesterol/HDL-cholesterol related risk[17] and it is also a strong prognostic marker for 90-day outcome in acute coronary syndrome[9]. Measures to decrease CRP are therefore promising interventions to decrease cardiovascular risk.

Ridker et al. have shown that 5 years of therapy with pravastatin decreases CRP levels significantly and improves clinical outcome as compared to a placebo group where CRP levels tended to increase[6]. Our data show that atorvastatin induces a significant and extensive decrease in CRP levels within the first 4 weeks of therapy but with no further decrease after 3 months. It was reported recently that therapy with atorvastatin and simvastatin (for 4 months in hyperlipidaemic patients with stable coronary heart disease[18]) or cerivastatin (after 2 months[19]) significantly decreases CRP concentrations. In contrast, a comparison of the effects of atorvastatin, simvastatin and pravastatin in one study showed no significant differences in concentrations before and after 3 months of treatment[20]. In addition, de Maat et al.[21] found that pravastatin therapy did not affect CRP in patients with familial hypercholesterolaemia for a period of up to 12 months. They concluded that the effect of statins on CRP occur preferably in patients with an increased inflammatory state[22]. Our data point to a similar assumption since median CRP levels in the lowest quartile (<1.34 mg . l⁻¹) did not change while levels in the three upper quartiles were significantly decreased (P<0.0001). Such differences

### Table 1 Lipid and CRP levels (median, 50% range)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Initial visit</th>
<th>1 month</th>
<th>3 months</th>
<th>Friedman Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol . l⁻¹)</td>
<td>7.7 (7.1–8.9)</td>
<td>5.7 (5.1–6.4)</td>
<td>5.0 (4.5–5.7)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides (mmol . l⁻¹)</td>
<td>2.8 (1.9–4.1)</td>
<td>2.2 (1.5–3.0)</td>
<td>2.9 (1.3–2.6)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>LDL-C (mmol . l⁻¹)</td>
<td>5.3 (4.6–6.0)</td>
<td>3.3 (2.9–4.1)</td>
<td>2.9 (2.4–3.5)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>HDL-C (mmol . l⁻¹)</td>
<td>1.1 (1.0–1.3)</td>
<td>1.2 (1.0–1.4)</td>
<td>1.2 (1.1–1.4)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>CRP (mg . l⁻¹)</td>
<td>2.25 (1.32–5.04)</td>
<td>2.12 (0.85–4.48)</td>
<td>1.83 (0.81–4.27)</td>
<td>P&lt;0.0005</td>
</tr>
</tbody>
</table>

### Table 2 Frequency of CRP changes according to baseline levels

<table>
<thead>
<tr>
<th>Changes in CRP-levels</th>
<th>Percentiles</th>
<th>Decrease</th>
<th>Increase</th>
<th>No significant change</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 1 month (vs baseline)</td>
<td>&lt;25th %</td>
<td>49%</td>
<td>43%</td>
<td>8%</td>
</tr>
<tr>
<td>25–75th %</td>
<td>61%</td>
<td>29%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>&gt;75th %</td>
<td>73%</td>
<td>15%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>After 3 months (vs baseline)</td>
<td>&lt;25th %</td>
<td>39%</td>
<td>46%</td>
<td>15%</td>
</tr>
<tr>
<td>25–75th %</td>
<td>65%</td>
<td>29%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>&gt;75th %</td>
<td>67%</td>
<td>28%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>After 3 months (vs 1 month)</td>
<td>&lt;25th %</td>
<td>42%</td>
<td>42%</td>
<td>17%</td>
</tr>
<tr>
<td>25–75th %</td>
<td>44%</td>
<td>44%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>&gt;75th %</td>
<td>46%</td>
<td>48%</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3 The course of CRP levels during atorvastatin therapy with regard to the distribution at baseline

<table>
<thead>
<tr>
<th></th>
<th>&lt;25th percentile (g . l⁻¹)</th>
<th>26th–75th percentile (g . l⁻¹)</th>
<th>&gt;75th percentile (g . l⁻¹)</th>
<th>All (g . l⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 baseline</td>
<td>0.70</td>
<td>2.44</td>
<td>7.82</td>
<td>2.35</td>
</tr>
<tr>
<td>P (1 vs 2)</td>
<td>0.623</td>
<td>0.0222</td>
<td>&lt;0.0003</td>
<td>0.0003</td>
</tr>
<tr>
<td>2 1 month</td>
<td>0.65</td>
<td>2.10</td>
<td>5.02</td>
<td>2.12</td>
</tr>
<tr>
<td>P (2 vs 3)</td>
<td>0.739</td>
<td>0.628</td>
<td>0.862</td>
<td>0.932</td>
</tr>
<tr>
<td>3 3 months</td>
<td>0.59</td>
<td>2.03</td>
<td>4.96</td>
<td>1.83</td>
</tr>
<tr>
<td>P (3 vs 1)</td>
<td>0.639</td>
<td>0.0066</td>
<td>0.0077</td>
<td>0.0005</td>
</tr>
</tbody>
</table>
were also observed by de Maat et al. with simvastatin[21] and by Ridker et al. with cerivastatin[19]. However, a decrease did not occur in each patient. In some patients, especially those with low initial CRP levels, even a slight increase could been seen. This finding suggests that the effect of the statin is not a direct effect on CRP synthesis. This is in line with data of Jialal et al.[23], who observed that statins had no effect on IL-6 levels.

Atherosclerosis is a disease of high complexity, involving inflammatory as well as other factors. CRP levels are only a rough measure of inflammatory activity. It is therefore difficult to assess the mechanisms by which
statins reduce CRP concentrations and accordingly their antiinflammatory effects. Theoretically, it cannot be completely ruled out that our findings represent a regression to the mean since our study lacked a placebo control group, which is due to ethical considerations (see inclusion criteria). However, it is most unlikely that regression to the mean plays an important role in our patient group given that 75% of all patients displayed a decrease in CRP compared to baseline. In addition, the CRP levels at 3 months are different within the three different percentile groups. Also, the intra-individual variation of CRP concentration could potentially interfere with a correct interpretation of the data. However, in a recent study it was shown that the relative variation for high sensitivity CRP and total cholesterol was comparable. Moreover, we did not observe extreme variations; there were, in particular, few changes between 1 and 3 months of treatment.

In this study, as well as in others, the changes in CRP were independent of lipid changes with the exception of triglycerides after 3 months of treatment; this might be fortuitous given that there was no association at all at 1 month. A significant correlation between a reduction in HDL-cholesterol and apo A-I. In their study, the change in HDL-cholesterol explained 20% of the change in CRP, which is in line with the notion that HDL has antiinflammatory properties. Despite these findings the reason for the antiinflammatory effect of statins remains to be elucidated.

The observation that CRP levels are extensively reduced through treatment with atorvastatin at 4 weeks may be of particular interest in view of new data on early intervention with statins in acute coronary syndromes. These data show a significant benefit for early statin treatment as compared to controls with conventional, non-invasive therapy. Whether this clinical benefit is due to an improvement of endothelial function or plaque stabilization, either via lowering of lipids or via reduction of inflammatory processes remains, to be elucidated.

Since recent data indicate that endothelial dysfunction can be improved through statin therapy within days, it is conceivable that chronic inflammation can consecutively be improved within a short period.

References

