Effect of rosuvastatin as adjuvant therapy to methotrexate on hematological parameters in patients with moderately-highly active rheumatoid arthritis

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Abstract
Objective: Rheumatoid arthritis (RA) is a common inflammatory disease associated with many extra-articular features including anemia, leucocytosis and thrombocytosis. Rosuvastatin is an antidyshlipidemic agent with anti-inflammatory activity. The aim of the study was to evaluate the effect of rosuvastatin as adjuvant therapy to methotrexate on hematological parameters in Iraqi patients with moderately-highly active RA.

Methods: A single center randomized double-blind placebo-controlled trial of 8 weeks duration was performed. Disease activity was measured via calculating the disease activity score in 28 joints using erythrocyte sedimentation rate (DAS28-ESR). 40 Patients who were using methotrexate (MTX) intramuscularly were randomly allocated to receive each day either rosuvastatin 10 mg tablet or capsule prefilled with glucose as placebo and were evaluated at baseline and at week 8 for hematological parameters.

Results: Erythrocyte sedimentation rate (ESR) and platelet count were significantly more reduced in rosuvastatin group than placebo group after 8 weeks. Non significant changes were observed in the hemoglobin (Hb) amount and white blood cells (WBC) count between groups. No significant correlation was recorded between ESR and Hb in both groups.

Conclusion: Low dose rosuvastatin adjuvant to MTX seem to be an effective method to lower ESR and platelet count in rheumatoid arthritis patients.
Rheumatology Unit, Baghdad Teaching Hospital, Baghdad, Iraq from August 2011 till May 2012. Patients were randomly allocated to receive each day either rosuvastatin 10 mg tablet or capsules prefilled with glucose as placebo (PBO) orally in addition to their weekly intramuscular MTX dose. Rosuvastatin was bought from Unipharma Company, Damascus, Syria whereas glucose was bought from SDI, Samarra, Iraq. Patients were evaluated at baseline and at week 8.

Sample selection
Eligible patients had confirmed RA according to the 1987 American College of Rheumatology (ACR) criteria with moderate to highly active disease defined as disease activity score based on 28 joints and ESR (DAS28-ESR) greater than 3.2 at baseline. For inclusion, patients also were required to have taken methotrexate (MTX) intramuscularly and regularly for at least 3 previous consecutive months. The exclusion criteria included patients who were taking lipid-lowering therapy, had hypersensitivity to statin, pregnancy, breast feeding, renal and liver impairment, patients younger than 18 years old and those using high dose steroids. Additionally, 20 healthy age and sex matched individuals were considered as a control group.

Informed consent was obtained from all participants and this study was approved by the ethical committee of Baghdad University, College of Medicine - Medical Department.

Clinical and laboratory evaluation
Clinical evaluation of patients for tender and swelling joints was done by specialized rheumatologist who was blinded to treatment at zero time (baseline) and after 8 weeks. The RA disease activity was measured using DAS28-ESR which is a validated composite [9] and was calculated by the following equation:

\[
DAS28 = 0.56 \times (TJC)^{0.5} + 0.28 \times (SJC)^{0.5} + 0.70 \times \ln(ESR) + 0.014 \times VAS
\]

- TJC, tender joint count
- SJC, swollen joint counts
- ESR, erythrocyte sedimentation rate
- VAS, visual analogue scale

Blood specimen collection and laboratory analysis (at baseline and after 8 weeks) of WBCs count, platelets count, ESR and Hb was done by specialized laboratory researchers who did not participate in this study. WBCs count, platelets count and Hb were measured by a hematology auto-analyzer (Ruby-CELL-DYN 08H56-02, Abbott Company, Abbott Park, IL, USA). ESR was measured by Westergren method [10].

Statistical analysis
Statistical software (SPSS version 12, Chicago, IL, USA) was used for data input and analysis. Continuous variables were presented as mean ± standard deviation (SD) and discrete variables were presented as numbers and frequencies. Chi square test for independence was used to test the significance of association between discrete variables. Continuous variables were tested by the Shapiro Wilk test to determine if they were normally or abnormally distributed. ANOVA test was used to test the significance of difference in the mean of 3 independent samples in normally distributed continuous variables. Unpaired t-test was used to test the significance of difference in the mean of 2 independent samples in normally distributed continuous variables and Mann Whitney test for abnormally distributed data. Pearson correlation coefficient was used to assess the correlation between continuous variables. Findings with P value less than 0.05 were considered significant whereas P values less than 0.01 considered highly significant.

RESULTS
Of a total of 74 patients who were randomized in this double-blind study, 40 completed the 8 weeks of treatment (20 from the rosuvastatin group and 20 from the placebo) (Fig.1). The two groups did not differ significantly in baseline characteristics (Tables 1 & 2).

Baseline hematological parameters showed that Hb level was significantly lower in patients with active RA than healthy control subjects whereas ESR, WBC count and platelet count were significantly higher in patients with active RA than those in control group (P < 0.001, Table 3).

After 8 weeks of starting adjuvant treatment with either rosuvastatin or placebo, ESR and platelet count decreased significantly by rosuvastatin (P < 0.05) while other parameters showed no any difference between the effect of rosuvastatin and placebo (P > 0.05, Table 4)

On the other hand, no significant correlation was recorded between ESR and Hb (P > 0.05, Table 5).
The results of this study showed that Hb level in RA patients was significantly less than control subjects, this finding was proved by many other studies showing that anemia was a common extra articular manifestation of RA patients [1, 4]. The cause of anemia in RA patients is multifactorial and includes anemia of chronic disease which is mostly related to the use of DMARDs [14], RA disease activity and degree of inflammation, and iron deficiency anemia that is related mostly to gastrointestinal tract (GIT) blood loss due to NSAIDs usage [15]. This study also showed that neither rosuvastatin nor placebo improve Hb level, which was consistent with another study that found no difference between rosuvastatin and placebo in patients with anemia and low grade inflammation [16].

Although rosuvastatin significantly reduced inflammation by reducing ESR values as shown by this study, it failed to improve Hb level; this finding is likely due to the reason that patients who participated in that study having low initial ESR level since they have just mildly active RA disease [8] whereas the present excluded any patient with mild or inactive RA disease.

**DISCUSSION**

The results of this study showed that ESR level in RA patients with active disease were significantly higher than healthy control subjects, which was similar to the finding of other studies [11]. This finding was expected in patients with inflammatory disease such as RA.

More importantly was that rosuvastatin but not placebo significantly reduced ESR level. Two other studies showed that 40 mg atorvastatin have the ability to reduce ESR significantly [12, 13], but a study regarding the effect of 10 mg rosuvastatin showed no any benefit to lower ESR; this difference from the current study can be due to the reason that patients who participated in that study having low initial ESR level since they have just mildly active RA disease [8] whereas the present excluded any patient with mild or inactive RA disease.

### Table 1. Baseline demographic data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rosuvastatin (n = 20)</th>
<th>Placebo (n = 20)</th>
<th>Control (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>43.35 ± 9.96</td>
<td>44.4 ± 13.53</td>
<td>42.95 ± 10.39</td>
<td>0.917</td>
</tr>
<tr>
<td>Female:Male [n (%)]</td>
<td>14:6 (70%)</td>
<td>16:4 (80%)</td>
<td>15:5 (75%)</td>
<td>0.766</td>
</tr>
<tr>
<td>Smoking [n (%)]</td>
<td>3 (15%)</td>
<td>2 (10%)</td>
<td>5 (25%)</td>
<td>0.432</td>
</tr>
</tbody>
</table>

### Table 2. Baseline disease, drugs, clinical and laboratory data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rosuvastatin (n = 20)</th>
<th>Placebo (n = 20)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of disease in years (mean ± SD)</td>
<td>7.55 ± 5.38</td>
<td>6.65 ± 4.96</td>
<td>0.586</td>
</tr>
<tr>
<td>Family history of rheumatoid arthritis [n (%)]</td>
<td>2 (10%)</td>
<td>7 (35%)</td>
<td>0.058</td>
</tr>
<tr>
<td>Dose of methotrexate(mean ± SD)</td>
<td>13.88 ± 4.4</td>
<td>13.25 ± 3.54</td>
<td>0.624</td>
</tr>
<tr>
<td>Disease activity score of 28 joints (mean ± SD)</td>
<td>6.19 ± 1.21</td>
<td>6.01 ± 1.17</td>
<td>0.631</td>
</tr>
<tr>
<td>Subcutaneous nodules</td>
<td>2</td>
<td>0</td>
<td>0.147</td>
</tr>
<tr>
<td>Positive Rheumatoid factor [n (%)]</td>
<td>13 (65%)</td>
<td>12 (60%)</td>
<td>0.743</td>
</tr>
</tbody>
</table>

### Table 3. Baseline hematological parameters of the patients and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rosuvastatin (n = 20)</th>
<th>Placebo (n = 20)</th>
<th>Control (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>48.95 ± 31.1</td>
<td>38.25 ± 19</td>
<td>11.7 ± 3.85</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>12.64 ± 1</td>
<td>12.14 ± 0.93</td>
<td>14.06 ± 1.07</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>White blood cells count</td>
<td>8.58 ± 2.31</td>
<td>9.59 ± 3.29</td>
<td>5.84 ± 0.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelet count</td>
<td>326.45 ± 94.49</td>
<td>315.4 ± 68.38</td>
<td>241.85 ± 37.75</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table 4. Changes in hematological parameters after 8 weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rosuvastatin (n = 20)</th>
<th>Placebo (n = 20)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte sedimentation rate</td>
<td>-16.85± 28.66</td>
<td>-0.55± 17.72</td>
<td>0.012</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>-0.09±0.99</td>
<td>-0.2±0.95</td>
<td>0.72</td>
</tr>
<tr>
<td>White blood cells count</td>
<td>0.06±2.24</td>
<td>-0.8±2.29</td>
<td>0.357</td>
</tr>
<tr>
<td>Platelet count</td>
<td>-52.65±54.76</td>
<td>1.25±48.97</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Table 5. Correlation between Erythrocyte sedimentation rate and hemoglobin

<table>
<thead>
<tr>
<th>Group</th>
<th>At baseline (r)</th>
<th>P-value</th>
<th>After 8 weeks (r)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>-0.17</td>
<td>0.482</td>
<td>-0.29</td>
<td>0.215</td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.31</td>
<td>0.191</td>
<td>-0.31</td>
<td>0.179</td>
</tr>
</tbody>
</table>

*r = Pearson correlation coefficient*
strengthened by the absence of significant correlation between ESR as a measure of inflammation [17] and Hb level in patients participated in this study. This may mean that inflammation is less likely to be the cause of anemia in those patients than other causes like the use of MTX, NSAIDs and GIT blood. Anyhow, whatever the cause of anemia in RA patients, rosuvastatin is less likely to improve it.

Regarding WBC count, this study indicated that the number of WBCs was significantly higher in RA patients than control subjects; this finding was consistent with another clinical trial that showed a high level of WBC count in RA patients [18] while some other studies found a correlation between inflammation and WBC count [19]. The present results also showed that rosuvastatin was not more effective than placebo to decrease WBC count; similarly 10 mg rosuvastatin failed to reduce WBC count in patients with mildly active RA [8]. Moreover, simvastatin 20 mg also failed to reduce WBC count in patients with coronary disease and diabetes mellitus [20].

Rosuvastatin has anti-inflammatory effect which is mainly related to increase in the level of the anti-inflammatory cytokine interleukin (IL)-10 [21]. Since the peak of IL-10 levels were significantly correlated with WBC counts [22], it can be postulated that rosuvastatin cannot decrease WBC count despite its anti-inflammatory effect.

The present study showed that platelet count in active RA patients was significantly higher than those in control group, which was consistent with the report of Selroos [23] who noted that many patients with RA had a high platelets count, whereas Farr et al [24] found that platelets count were higher in patients with more active disease. Recently, it was found that thrombocytosis is one of the most common extra-articular features of RA [4], and that mild to moderate thrombocytosis is frequent in RA patients [25]. This study showed that rosuvastatin was more effective than placebo and significantly reduced platelet count; however up to date there is no published study regarding the effect of statins on platelet count in RA patients and, to our knowledge, the present study publishes this finding for the 1st time.

It was reported that platelets count has a significant positive correlation with ESR [26]. Since rosuvastatin significantly reduced ESR in this study, the finding of platelet reduction seems to be highly acceptable. So it can be concluded that rosuvastatin is effective in improving platelet count in patients with active RA. Moreover, there was no evidence that statins can adversely cause thrombocytopenia [27]. Hence, low dose rosuvastatin adjuvant to MTX was found to be effective in lowering ESR and platelet count in active RA patients.

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REFERENCES


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