THE USE OF ATROVASTATIN IN THE TREATMENT OF RHUMATIOD ARTHRITIS
AND IT'S EFFECTS ON DISEASE ACTIVITY
AND ACUTE PHASE REACTIONS

Sami Salman Shihab¹, Haidar Mahdi Jawad², Samer Shukur Mohammed²

¹Rheumatology unit, Dept. of Medicine,

²Dept. of Pharmacology, College of Medicine, University of Baghdad

Corresponding Author:

Prof. Sami Salman, Baghdad Teaching Hospital, Rheumatology Unit, Department of Medicine, Baghdad, Iraq

Email: ssshihab2@gmail.com
Abstract

Background
Rheumatoid arthritis (RA) is a common chronic inflammatory disorder characterized by synovitis, articular destruction, and many systemic extra-articular features. It is associated with a high rate of morbidity and mortality due to accelerated atherosclerosis and increased cardiovascular risk. Atorvastatin is a well-known anti dyslipidemic agent that might have valuable anti-inflammatory and immune modulatory functions in RA. Objectives The present study was performed to evaluate the anti-inflammatory effect of atorvastatin when used as adjuvant therapy to methotrexate (MTX) and etanercept in Iraqi patients with moderate to highly active RA.

Patients and Methods
A double blind randomized placebo - controlled clinical trial in which 100 patients, both males and females were included. All cases were with active RA who were on MTX and etanercept for at least one month. The cases were divided into two groups to receive either 20 mg atorvastatin or a placebo capsule for three consecutive months. Only 49 patients completed the three months trial, (25 in atorvastatin and 24 in placebo group).

All patients were clinically evaluated by measuring swollen joint count (SJC), tender joint count (TJC), visual analogue scale (VAS) and disease activity score (DAS28). Blood samples of RA patients were evaluated for erythrocyte sedimentation rate (ESR), C reactive protein (CRP) at baseline, monthly and at the end of the study.
**Results**

RA patients receiving 20mg atorvastatin showed a significant (p<0.05) reduction in CRP, SJC and TJC compared to those on placebo. In addition, atorvastatin helped to reduce ESR, VAS and DAS28 more than placebo but without achieving statistical significance (p>0.05).

**Conclusion**

Atorvastatin 20mg is a safe and well-tolerated drug that has a modest anti-inflammatory effect in patients with moderate to highly active RA.

**Key Words:** Rheumatoid Arthritis, disease activity index, atorvastatin

**Background**

Rheumatoid arthritis (RA) is a common chronic inflammatory disorder characterized by synovitis, articular destruction, and many systemic extra-articular features[1]. It usually presents with pain, swelling and stiffness affecting the small joints of the hands, feet and wrists[2]. The onset of disease can occur at any age, but the peak incidence occurs within the fourth and fifth decades of life. The average annual incidence of RA in the United States is 0.5 per 1000 persons per year [3]. It is associated with a high rate of morbidity and mortality due to accelerated atherosclerosis and increased cardiovascular risk [4]. Atorvastatin is well known anti dyslipidemic agent that mediates clinically significant cardiovascular risk reduction in patients without inflammatory disease by inhibiting 5- hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase enzyme. It has been found that atorvastatin can exert an anti-inflammatory effect in addition to its lipid-lowering actions in animal studies through inhibition of neutrophil infiltration and the local production of pro-inflammatory cytokines (tumor necrosis factor-a (TNF- α), interleukin-1 (IL-1) and interleukin-6 (IL-6)) and chemokines (CCL2 and CCL5) which significantly decrease tissue destruction [5]. Many clinical trials include usage of atorvastatin in rheumatoid arthritis patients as adjuvant therapy.
to disease modifying anti-rheumatic drugs (DMARDs), but most of these trials were performed on stable RA patients rather than those with active arthritis [6,7,8].

The present study was performed to evaluate the anti-inflammatory effect of atorvastatin when used as adjuvant therapy to methotrexate and etanercept in a group of Iraqi patients with moderate to highly active RA.

Patients and Methods

Study design

This was a 13-week randomized double blind placebo-controlled single center trial conducted at Rheumatology Unit, Baghdad Teaching Hospital, Baghdad, Iraq from 1st November 2012 until 1st June 2013. One hundred patients of both genders with active RA, who were on MTX and etanercept for at least one month, were divided into two groups to receive 20 mg atorvastatin tablet previously grinded and filled in capsules or capsules prefilled with starch as placebo orally for three consecutive months. The capsules were prepared and packed by a pharmacist who kept a log-book of the coding. The researchers had no way to know the content of the capsules.

Atorvastatin was bought from Micro Company, India under trade name (Avas® 20mg). Patients were evaluated at baseline, monthly and at week 12.

Sample selection

Eligible patients had confirmed RA according to the 1987 American College of Rheumatology (ACR) criteria [12] 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) and etanercept regularly for at least one month. The exclusion criteria included patients who were taking lipid-lowering therapy, had hypersensitivity to statin, pregnancy, breast feeding, renal and liver impairment and patients younger than 18 years old.
Informed consent was obtained from all participants and the ethical committee of Baghdad University, College of Medicine – Medical Department, approved this study. **Clinical and laboratory evaluation**

Clinical evaluation of patients for tender and swollen joints was done by a specialized rheumatologist who was blinded to the treatment at the beginning, monthly and after 12 weeks of treatment. The RA disease activity was measured using DAS28-ESR, which is a validated composite [9] and was calculated by the following equation:

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

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

Blood specimens were collected and laboratory analyzed (at baseline, monthly and after 12 weeks) for the measurement of ESR and CRP. ESR was measured by Westergren method [10] while C-RP was measured by slide agglutination test [11].

**Statistical analysis**

Statistical software (SPSS version 20) 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. Mann Whitney test was performed to test the significance of difference in the mean of two samples in abnormally distributed continuous variables. Findings with P value less than 0.05 were considered significant whereas P values less than 0.01 considered highly significant.
Results

In this randomized double blind study, 100 patients were included in the study and randomly assigned to receive atorvastatin or placebo. Half of them received atorvastatin and the other half received placebo. Ten patients in the atorvastatin group and five patients in the placebo group withdrew within the first month of the trial and those patients were excluded from the study. Twenty five patients in the atorvastatin group and 26 of patients in the placebo group did not complete the three month treatment course. Patients in the two groups had similar demographic and baseline characteristics. Patients were predominantly middle-aged women (80.25% of the atorvastatin group vs 80% of controls) with disease duration more than eight years. Most of them have positive rheumatoid factor (57.5% of the atorvastatin group vs 68.9% of controls). C-RP is nearly similar between the two groups. Most of the patients in the two groups are non smokers (87.5% of the atorvastatin group vs 88.9% of controls). Table 1 shows the mean value of the indices used to evaluate the progress of the patients in the two study groups. It shows a significant difference at pre-treatment ESR level between atorvastatin and placebo group (p=0.017). There was a progressive and highly significant decrease in ESR level in atorvastatin groups during the first, second and third month of treatment compared to pretreatment level. While in the placebo group, the only significant decrease in ESR level was seen after completing three months of treatment. However, there was no significant difference (p=0.58) between the ESR levels of the atorvastatin and placebo at the end of the study.

The CRP levels for patients taking atorvastatin was significantly lower compared to patients receiving placebo after one month of treatment (p=0.008).

The SJC of patients receiving atorvastatin for three months was significantly lower compared to patients receiving placebo (p=0.028).

The TJC in patients receiving atorvastatin was significantly lower compared to patients receiving placebo after two months of treatment (p=0.041). There was a non-significant difference (p=0.115) in the VAS between the atorvastatin and placebo groups during three
months of treatment. A non-significant difference (p=0.23) in DAS28 between the atorvastatin and placebo groups during three months of treatment.

Table 1 Mean ± s.d. of Indices Used in the Effect of atorvastatin and placebo Groups

<table>
<thead>
<tr>
<th>Test</th>
<th>Group</th>
<th>Pre treatment</th>
<th>After treatment for</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1 month</td>
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<tr>
<td>ESR</td>
<td>Atorvastin</td>
<td>58.35±22.9</td>
<td>41.88±20.33</td>
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<td></td>
<td>(n=40)</td>
<td></td>
<td>(p&lt;0.01)</td>
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<td></td>
<td>Placebo</td>
<td>48.69±29.75</td>
<td>44.38±25.37</td>
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<td></td>
<td>(n=40)</td>
<td></td>
<td>(p&lt;0.01)</td>
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<tr>
<td>CPR</td>
<td>Atorvastin</td>
<td>38.8±20.17</td>
<td>23.55±16.77</td>
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<td></td>
<td>(n=45)</td>
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<td>(p&lt;0.01)</td>
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<td></td>
<td>Placebo</td>
<td>40.8±30.74</td>
<td>33.42±28.37</td>
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<tr>
<td></td>
<td>(n=45)</td>
<td></td>
<td>(p&lt;0.01)</td>
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<tr>
<td>SJC</td>
<td>Atorvastin</td>
<td>4.95±4.26</td>
<td>3.13±3.87</td>
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<td></td>
<td>(n=45)</td>
<td></td>
<td>(p&lt;0.01)</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>5.31±4.15</td>
<td>4.02±3.65</td>
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<tr>
<td></td>
<td>(n=45)</td>
<td></td>
<td>(p&lt;0.01)</td>
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<tr>
<td>TJC</td>
<td>Atorvastin</td>
<td>8.68±5.27</td>
<td>5.43±4.34</td>
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<td></td>
<td>(n=40)</td>
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<td>(p&lt;0.01)</td>
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<td></td>
<td>Placebo</td>
<td>6.87±5.26</td>
<td>5.98±5.09</td>
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<td></td>
<td>(n=45)</td>
<td></td>
<td>(p&lt;0.01)</td>
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<tr>
<td>VAS</td>
<td>Atorvastin</td>
<td>6.63±1.9</td>
<td>4.93±1.91</td>
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<td></td>
<td>(n=40)</td>
<td></td>
<td>(p&lt;0.01)</td>
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<tr>
<td></td>
<td>placebo</td>
<td>6.04±1.93</td>
<td>5.16±1.87</td>
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<tr>
<td></td>
<td>(n=45)</td>
<td></td>
<td>(p&lt;0.01)</td>
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<tr>
<td>DAS 28</td>
<td>Atorvastin</td>
<td>5.80±1.07</td>
<td>4.70±1.16</td>
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<td></td>
<td>(n=40)</td>
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<tr>
<td></td>
<td>placebo</td>
<td>5.33±1.17</td>
<td>4.91±1.33</td>
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<td></td>
<td>(n=45)</td>
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<td>(p&lt;0.01)</td>
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Note: values shown as mean± standard deviation, * significantly different compared to pretreatment within the same group (p<0.05); ** highly significant difference compared to pretreatment within the same group (P<0.01), ♦ significant difference of the effect of atorvastatin compared to placebo within same month (P<0.05).
Discussion

This study was designed as a double blind randomized clinical trial, which is compatible with a high rate of agreement and decreases the possibility of bias [13]. Because it is ethically unaccepted to use atorvastatin alone as a separate arm in the trial, adjuvant therapy to methotrexate and etanercept pattern is implemented. Moreover, atorvastatin was not compared alone versus placebo to avoid the unacceptable risks in patients who remain untreated for the required duration of the trial [14].

A high dropout rate was observed in the present study in patients randomized to atorvastatin or placebo but there was non-significant difference between the two treatment groups in this aspect. In the country of Iraq, where the security situation is still volatile, and patient education is low, it is always expected to have a high dropout rate with an impossible task of tracing the patients.

Only 49% of patients completed the three month trial. The other non-completers showed no evidence for the reasons of withdrawal. However, withdrawal may be due to poor compliance, adverse effects of treatment, lack of efficacy, cultural factors or other reasons. Acute phase reactants ESR and CRP provide reliable means for discrimination between drugs that provide symptomatic relief only and others with a more profound effect in RA [15].

The ESR is sensitive for most types of inflammation, but cannot distinguish if the underlying cause is infectious, inflammatory, or paraneoplastic [16]. The results of this study showed that ESR level in RA patients with active disease was significantly reduced by using 20mg atorvastatin (but less in placebo) over three months of treatment, but with no significant difference between atorvastatin and placebo at the end of the study. Similar result was found in a trial using 80mg atorvastatin for 12 weeks versus placebo [17]. The same finding was reported when 10mg rosuvastatin was used for 38 patients for 8 weeks [18]. Many other studies showed that atorvastatin has the ability to reduce ESR significantly when compared to placebo [19-21]. The different results of those trials from the present findings may be attributed to that this study use 20mg atorvastatin in contrast to 40mg used in
other studies. In addition, this study was performed for a shorter duration (3 months) compared to 6 months duration in the other studies. One study showed that 20mg simvastatin decrease ESR level significantly when used for 6 weeks [22], which may be attributed to different anti-inflammatory properties of statins [23]. Serum CRP level is the best biochemical indicator of disease activity in RA patients [24]. Serum CRP level changes more quickly than ESR. With sufficient stimulus, CRP can be increased within 4 to 6 hours and normalized within a week [25]. In addition, CRP elevation is directly correlated with RA disease activity [24]. Serum CRP level in the current study decreased significantly by atorvastatin (less with placebo) with a significant difference between the two groups only in the first month. This finding may be due to the decrease in the number of patients in the second and third month. But this result was compatible with many studies using 40mg atorvastatin in RA patients [19-21], and the same result was found after using 20mg simvastatin [22]. In the METEOR study, 40mg rusovastatin reduced CRP level significantly when compared to placebo [26]. While using 10mg rusovastatin for 12 months [27] or 80mg atorvastatin for 12 weeks for 11 RA patients [8] showed no significant improvement in CRP.

Assessment of tender points is considered as the cornerstone during evaluation and treatment decision making in RA [28]. In the present study, TJC was significantly decreased by atorvastatin (-66.16%) compared to pretreatment, while placebo showed non-significant decrease in TJC. Moreover, there was a significant difference between the effect of atorvastatin and placebo at the second month of treatment with no difference at the end of the study which may be due to decreased number of patients at the third month. A similar finding was reported in El-Barbary and co-workers (2011), where 40mg atorvastatin produced a significant decrease in TJC compared to placebo. Two other studies on simvastatin and statins respectively showed a significant decrease in TJC compared to placebo [22,29]. Other trials showed non-significant decrease in TJC when atorvastatin was used compared to placebo. The difference from our findings may be due to the inclusion of mild RA patients [19] or due to low number of patients [8].
Swelling of joints are considered as the best single variable that detects response to drug therapy in RA patients [30]. In the present study, SJC was significantly reduced by atorvastatin compared to placebo. This finding was confirmed by several trials when atorvastatin as adjuvant therapy was used for six months in rheumatoid arthritis patients [19, 21]. In addition, another large cohort study about using statins in RA patients showed decreased number of swollen joint [29]. Another study using 80mg atorvastatin for 3 months showed non-significance improvement in SJC [17], and this finding may be attributed to small number of RA patient in this study (n=11). One other study where 20mg simvastatin was used showed non-significant decrease in SJC [22]. A similar finding was observed when 10mg rusovastatin was used for 12 months [27] and those different findings may be attributed to different anti-inflammatory potency of statins. Visual analogue scale (VAS) was shown to be a valid measure of pain intensity in RA patients [31]. In the current study, VAS was significantly reduced by both atorvastatin and placebo, though atorvastatin showed a greater percent of reduction, with no significance difference between them. Several studies confirmed this finding when 40mg atorvastatin was used for RA patients for six months [19, 21] and 80mg atorvastatin for 3 months [8]. While in another cohort which used statin showed a significant difference between the effect of statins and placebo, and this different finding could be due to inclusion of different statins rather than specific one which lead to different anti-inflammatory properties [23].

DAS28 remains the most extensively validated activity index for RA patients [32] to observe the clinical response of the patients to the treatment. Results of the present study showed that both atorvastatin and placebo produced significant improvement in DAS28 scores after 12 weeks of therapy, though atorvastatin produced a greater percent of the reduction, with no clinical significance between the two groups. Similar results were reported for using atorvastatin 40mg in moderately active RA patients, at which atorvastatin and placebo improved DAS28 but the level of significance was higher in atorvastatin arm [20]. Another large cohort study demonstrated that there is no statically significant difference between placebo and statin on RA disease activity [29]. A third double blind study showed a
comparable effect of 80mg atorvastatin and placebo on DAS28 when used for 12 weeks [8]. Two other studies [19,21] reported a significant improvement in atorvastatin group compared to the placebo group. The difference in the results in those trials from the current study may be due to many reasons: The dose dependent pleiotropic effect of statins [33] may be responsible for our finding of no more benefit of atorvastatin than placebo because of the use of low dose atorvastatin (20mg) in the current study whereas in other studies a higher dose of atorvastatin 40mg was used. Moreover, the shorter period of follow up and smaller sample size in the current study may be a potential reason for such difference compared to the two other trials.

Conclusions
It can be concluded that 20mg atorvastatin is a safe and well-tolerated drug that has modest anti-inflammatory effect in patients with moderate to highly active RA. It also has the ability to reduce C-RP level, SJC and TJC but with less effect on ESR, VAS and DAS28 when compared to placebo.

Recommendation
Larger scale multicenter clinical trials are required to support the reported data. In addition, evaluation of the effect of higher doses of atorvastatin in patients with moderate to highly active RA should be taken. Longer period of follow up are required to evaluate long-term benefit of atorvastatin on RA disease activity.

References:


33. . Aletaha, D., & Smolen, J. S. 2007; The simplified disease activity index (SDAI) and clinical disease activity index (CDAI) to monitor patients in standard clinical care. Best practice & research Clinical rheumatology; 21(4), 663-675.