A Double Blind, Placebo Controlled, Phase II, Randomized Study of Lovastatin Therapy in the Treatment of Mildly Active Rheumatoid Arthritis

C Aranow, J Cush, M Bolster, S Striebich, M Dall’Era, M Mackay, E Olech, T Frech, J Box, R Keating, M C Wasko, W St Clair, A Kivitz, K Boyle, B Welch, J Wedgewood, S Callahan, M Spychala, B Welch, J York, E Goldmuntz, B Diamond, A Davidson, Autoimmunity Centers of Excellence

Rationale

- Anti-inflammatory effects in animal models of acute inflammation
- Anti-inflammatory effects in humans with dyslipidemia
- Immunomodulatory effects:
  - ↓T cell mitogen and cytokine responsiveness
  - ↓IFNγ inducible Class II MHC expression on macrophages
  - ↓inflammatory cytokines and chemokines
- Effects on blood vessels
- Lovastatin has non-mevalonate effects
  - steric inhibition of the LFA-1: ICAM-1 interaction

Primary objective

- To determine the effect of lovastatin on levels of CRP in patients with RA

Specific aims

- To determine if lovastatin can reduce CRP in patients with RA (mean log CRP)
- To determine the effect of lovastatin on disease activity
  - DAS and DAS response
  - ACR 20 response
- To determine the effect of lovastatin on autoantibody titers in RA (RF, anti-CCP antibody)

TARA: Trial of Atorvastatin in Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Group</th>
<th>Δ DAS28</th>
<th>Δ log CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>-0.50 (-0.75 to -0.25)</td>
<td>-0.46 (~ 50%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.03 (-0.23 to 0.28)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

McCarey D et al Lancet 2004

Study design

Double-blind, randomized, placebo-controlled study:

lovastatin 80mg or placebo daily (1:1)

Baseline Randomization
Screening
Week 2 Safety check
Week 4
Week 6
Week 12
Study design
Key inclusion criteria:
- Mildly active RA
  - 2-8 tender joints
  - 1-6 swollen joints
- CRP > 5 mg/L (0.5 mg/dL)
- Stable background medication

Key exclusion criteria:
- Currently taking (or history of receiving within 12 weeks) a HMG-CoA reductase inhibitor (statin)
- Recent infection
- Safety:
  - History of an adverse reaction to a HMG-CoA reductase inhibitor (statin).
  - Myositis or an unexplained elevation in CPK.
  - Treatment with medications metabolized using the cytochrome P450 pathway.
  - Liver disease

132 assessed for eligibility
68 excluded:
54 exclusion criteria
14 other reasons
64 randomized
30 received placebo
5 discontinued treatment
2 subject decision
1 Investigator decision
1 adverse event
1 other: SGOT >3*ULN
25 analyzed for primary endpoint
Including 2 with dose reductions
34 received lovastatin
1 no baseline CRP
3 discontinued treatment
2 subject decision
1 Investigator decision
30 analyzed for primary endpoint
Including 1 with temporary discontinuation

Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Summary Statistic</th>
<th>Placebo (N=29)</th>
<th>Lovastatin (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean (SD)</td>
<td>52.6 (10.38)</td>
<td>55.8 (7.08)</td>
</tr>
<tr>
<td>Female</td>
<td>n (%)</td>
<td>28 (96.6)</td>
<td>32 (94.1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>n (%)</td>
<td>8 (27.6)</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Race: White</td>
<td>n (%)</td>
<td>20 (69.0)</td>
<td>26 (76.5)</td>
</tr>
<tr>
<td>Black</td>
<td>n (%)</td>
<td>5 (17.2)</td>
<td>6 (17.6)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>Mean (SD)</td>
<td>11.9 (12.63)</td>
<td>12.5 (9.56)</td>
</tr>
<tr>
<td>Biologic Use</td>
<td>n (%)</td>
<td>11 (37.9)</td>
<td>20 (58.8)</td>
</tr>
<tr>
<td>MTX Use</td>
<td>n (%)</td>
<td>16 (55.2)</td>
<td>20 (58.8)</td>
</tr>
<tr>
<td>Tender Joint Count</td>
<td>Mean (SD)</td>
<td>4.8 (2.10)</td>
<td>4.4 (2.53)</td>
</tr>
<tr>
<td>Swollen Joint Count</td>
<td>Mean (SD)</td>
<td>3.8 (1.57)</td>
<td>3.5 (1.44)</td>
</tr>
<tr>
<td>Patient Global Disease</td>
<td>Mean (SD)</td>
<td>4.5 (1.56)</td>
<td>3.5 (2.27)</td>
</tr>
<tr>
<td>Activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS-28 Score</td>
<td>Mean (SD)</td>
<td>3.59 (0.356)</td>
<td>3.46 (0.496)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>Mean (SD)</td>
<td>12.8 (16.43)</td>
<td>12.2 (11.42)</td>
</tr>
</tbody>
</table>

Baseline log CRP
2.22 (.68)                   2.14 (.91)

Day 84 log CRP
1.96 (.89)                   1.82 (.88)

Δ log CRP*
-0.23 (.62)                  -0.23 (.66)

*p = 0.735

Primary endpoint

Mean CRP
Baseline to Day 84

ITT population with available data
**Percentage of subjects achieving a 20% CRP Response**

ITT Population with available data

**Percentage of subjects achieving a non-elevated CRP**

ITT Population with available data

**Das28 from Baseline to Day 84**

ITT Population with available data

**Clinical response at Day 84**

ITT Population with available data

**RF titer did not change significantly from Baseline to Day 84**

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<tr>
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<th>Placebo</th>
<th>Lovastatin</th>
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<tr>
<td>Δ RF mean (SD) Baseline to day 84</td>
<td>0.37 (33.21)</td>
<td>-3.44 (9.38)</td>
</tr>
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</table>

ITT with available data

**Anti-CCP antibody titer did not change significantly from Baseline to Day 84**

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<tr>
<td>Δ CCP mean (SD) Baseline to day 84</td>
<td>0.89 (58.05)</td>
<td>16.25 (72.94)</td>
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</table>

ITT with available data
Change in Lipid Profile from Baseline to Day 84 by Treatment Group

Post-hoc analysis: Biologic use

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<th>Lovastatin</th>
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<tbody>
<tr>
<td>Overall</td>
<td>N= 29</td>
<td>N=34</td>
</tr>
<tr>
<td>Biologic Use</td>
<td>N=11 (37.9%)</td>
<td>N=20 (58.8%)</td>
</tr>
</tbody>
</table>

ITT Population with available data

Primary and Secondary Endpoints in subjects using biologic therapy vs non-biologic users

- Δ CRP-- Baseline to Day 84
  - Non-biologic users: -4.75 (10.37) Lovastatin: -2.00 (6.47) placebo
  - Biologic therapy: -1.21 (4.26) Lovastatin: -2.38 (2.82) placebo
- Achievement of non-elevated CRP at Day 84
  - Non-biologic users: 25% Lovastatin: 13% placebo
  - Biologic therapy: 32% Lovastatin: 50% placebo
- DAS28 Response at Day 84
  - Non-biologic users: 41.7% Lovastatin: 40% placebo
  - Biologic therapy: 42.1% Lovastatin: 40% placebo
- ACR 20 at Day 84
  - Non-biologic users: 33.3% Lovastatin: 40% placebo
  - Biologic therapy: 26.3% Lovastatin: 40% placebo

Safety

- Well tolerated
- No SAEs related to study drug
- No myositis observed
  - CK elevations:
    - 4 subjects receiving lovastatin (1 grade 2)
    - 3 subjects receiving placebo
- No hepatic toxicity
  - Transaminase elevations:
    - 6 subjects receiving lovastatin (1 w grade 2 AST)
    - 5 subjects receiving placebo (1 w grade 2 AST)
- 36 Musculoskeletal adverse events
  - Arthralgia: 6 subjects (2 placebo, 4 lovastatin)
  - Myalgia: 2 subjects (1 placebo, 1 lovastatin)

Conclusions:

- A 12 week treatment with a statin showed
  - No significant effect on CRP
  - No significant effect upon clinical disease activity
  - No significant effect upon autoantibody titers
- Post-hoc analyses in a subset of patients not receiving biologic therapy suggested that lovastatin may have a potential but modest effect on CRP reduction
- Lovastatin was well tolerated with an adequate safety profile
Study design

• Primary endpoint:
  – Reduction in CRP (mean log CRP)

• Secondary endpoints:
  – Disease activity
    • DAS and DAS response
    • ACR 20 response
  – RF titers
  – Anti-CCP titers

Study design:  
Sample size determinations

TARA
Mean baseline log CRP 2.5 (1.2)
6 months: Statin: Δ log CRP -0.46 (~ ↓ 50%)
Placebo: Δ log CRP 0.17
ARA 02 assumptions:
12 weeks: Statin: 50% reduction in CRP
Placebo: no change
If n=34 subjects/arm, then 80% power
If n=46 subjects/arm, then 90% power

Sample size of 40 subjects/arm

Percent of subjects achieving a non-elevated CRP at Day 84 in subjects using biologic therapy vs non-biologic users

ITT Population with available data
Conclusions

- No significant anti-inflammatory or clinical effects were observed after treatment with lovastatin vs placebo
- Lovastatin may have a modest anti-inflammatory effect in patients not using biologic therapy
- Well tolerated with no safety concerns