Tocilizumab Monotherapy Reduces Arterial Stiffness as Effectively as Etanercept or Adalimumab Monotherapy in Rheumatoid Arthritis: An Open-label Randomized Controlled Trial

KENSUKE KUME, KANZO AMANO, SUSUMU YAMADA, KAZUHIKO HATTA, HIROYUKI OHTA, and NORIKO KUWABA

**ABSTRACT.** Objective. To compare the respective effects of tocilizumab (TCZ) monotherapy, etanercept (ETN) monotherapy, and adalimumab (ADA) monotherapy on arterial stiffness in patients with rheumatoid arthritis (RA) in an open-label, randomized controlled trial. 

Methods. Patients with RA were eligible if they had active disease (28-joint Disease Activity Score > 3.2) and no prior treatment with methotrexate or biologics. All 64 patients had no history of cardiovascular disease or steroid treatment. Patients were randomly assigned to receive TCZ alone (n = 22), ETN alone (n = 21), or ADA alone (n = 21). Arterial stiffness was assessed with cardio-ankle vascular index (CAVI) and aortic augmentation index normalized to a fixed heart rate of 75 bpm (AIx@75) at baseline and 24 weeks’ followup. Clinical data were collected at regular visits.

Results. The characteristics of each group at baseline were not significantly different. In all groups there was significant attenuation from baseline to 24 weeks in CAVI (Week 0-Week 24, TCZ: 0.85 ± 0.15 m/s, p = 0.02; ETN: 0.81 ± 0.18 m/s, p = 0.03; ADA: 0.90 ± 0.21 m/s, p = 0.02) and in AIx@75. There were no significant differences among the groups in measures of CAVI or AIx@75. The 3 therapies made no difference to carotid intima-media thickness and carotid artery plaque. Only TCZ increased fasting serum total cholesterol from baseline to 24 weeks.

Conclusion. The 3 types of monotherapy limited arterial stiffness in patients with RA to a similar extent. (First Release Aug 1 2011; J Rheumatol 2011;38:2169–71; doi:10.3899/jrheum.110340)

Key Indexing Terms:

- ARTERIAL STIFFNESS
- ETANERCEPT
- RHEUMATOID ARTHRITIS
- TOCILIZUMAB
- ADALIMUMAB

We compared the effect of tocilizumab (TCZ) monotherapy with the effect of etanercept monotherapy (ETN) and adalimumab (ADA) monotherapy on arterial stiffness in patients with rheumatoid arthritis (RA).

MATERIALS AND METHODS

Patients with RA were eligible if they had active disease [28-joint disease activity score (DAS28)-erythrocyte sedimentation rate (ESR) > 3.2] and no prior treatment with methotrexate, steroids, or biologics. All patients had no history of cardiovascular disease or steroid treatment. Patients were randomly assigned to receive TCZ alone (n = 22), ETN alone (n = 21), or ADA alone (n = 21). Arterial stiffness was assessed with CAVI and AIx@75.

Results. The characteristics of each group at baseline were not significantly different. In all groups there was significant attenuation from baseline to 24 weeks in CAVI and AIx@75. There were no significant differences among the groups in measures of CAVI or AIx@75. The 3 therapies made no difference to carotid intima-media thickness and carotid artery plaque. Only TCZ increased fasting serum total cholesterol from baseline to 24 weeks.

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Measures of cardiovascular risk included the ankle-brachial index,3 the level of fasting serum total cholesterol (TC), and the ratio of TC to high-density lipoprotein cholesterol (HDL; T/H ratio)8. RA disease activity measurements included the Health Assessment Questionnaire (HAQ)9, DAS28-ESR1, and C-reactive protein (CRP). Each measurement was taken every 4 weeks.

Statistical analysis. It was estimated that for a 1:1:1 (TCZ: ETN: ADA) randomized controlled trial, ETN could show an improvement in CA VI in 10 patients with RA, meaning that a sample of 10 patients per group was required (a = 0.05, power = 0.80). Assuming a 30% dropout rate, we aimed to recruit 15 patients for each treatment.

Intention-to-treat analysis. Measures of arterial stiffness, and assessments of others at baseline and at 24 weeks, were compared between subjects within each treatment group by paired t test or chi-squared test.

The effects of treatment (∆; the change from baseline to 24 weeks) between each group were compared using 1-way ANOVA and a Bonferroni-corrected t test.

Only patients who completed our study at 24 weeks were analyzed. SPSS v15.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Patient characteristics. Sixty-four patients were assigned randomly to receive TCZ (22), ETN (21), or ADA (21). Group characteristics at baseline were not significantly different (Table 1).

One patient taking ADA switched to ETN at 12 weeks. A total of 21 patients in the TCZ, 20 in the ETN, and 19 in the ADA group completed 24 weeks.

Outcome measures. CAVI was attenuated significantly by TCZ (Week 0–Week 24, 0.05 ± 0.18 m/s; p = 0.03), ETN (0.90 ± 0.21 m/s; p = 0.02), and ADA (3.54% ± 0.52%; p = 0.03). The ∆CAVI was not significantly different among TCZ, ETN, and ADA (p > 0.05; Figure 1).

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Alx@75 was attenuated significantly by TCZ (Week 0–Week 24, 3.59% ± 0.33%; p = 0.03), ETN (1.03% ± 0.44%; p = 0.03), and ADA (3.54% ± 0.52%; p = 0.03). The ∆Alx@75 was not significantly different among TCZ, ETN, and ADA (p > 0.05).

TCZ, ETN, and ADA did not significantly change CIMT (Week 0–Week 24, TCZ: 0.00 ± 0.13 mm; ETN: 0.00 ± 0.22 mm, ADA: –0.01 ± 0.13 mm; p > 0.05). They also did not produce significant changes in CAP (Week 0–Week 24, numbers of combined grade 0/1/2/3/4, TCZ: –1/1/0/0; ETN: 0/–2/0/0, ADA: –1/0/–1/0; p > 0.05).

There were no significant changes either within or between groups with respect to ankle-brachial index (Week 0–Week 24, TCZ: 0.03 ± 0.01; ETN: 0.09 ± 0.03; ADA: –0.03 ± 0.02) or fasting T/H ratio (Week 0–Week 24, TCZ: 0.09 ± 0.04; ETN: 0.09 ± 0.03; ADA: 0.07 ± 0.03; p > 0.05).

In the TCZ group, fasting serum total cholesterol was significantly increased (Week 0–Week 24, –18.0 ± 5.2 mg/dl; p = 0.03). There were no significant changes within the ETN or ADA groups in TC (ETN: –2.0 ± 0.6 mg/dl; ADA: –5.0 ± 1.8 mg/dl; p > 0.05). Delta TC levels of the TCZ group were significantly higher than those of the other groups (TCZ vs ETN, p = 0.024; TCZ vs ADA, p = 0.032).

HAQ score, DAS28-ESR score, and CRP improved significantly in all groups (Week 0–Week 24, HAQ score, TCZ: 0.70 ± 0.08, ETN: 0.68 ± 0.09, ADA: 0.69 ± 0.11; DAS28-ESR score, TCZ: 3.59 ± 0.33, ETN: 1.03 ± 0.44, ADA: 3.54 ± 0.52; p = 0.03). The ∆ESR was not significantly different among TCZ, ETN, and ADA (p > 0.05; Figure 1).

ESR, mm/h, mean (SD) 38 (9) 39 (8) 37 (8) 0.69

CRP, mg/l, mean (SD) 27.8 (11.2) 26.7 (10.8) 26.1 (10.5) 0.68

Table 1. Patient characteristics at baseline.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Tocilizumab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients (female/male, n)</td>
<td>22 (19/3)</td>
<td>21 (18/3)</td>
<td>21 (18/3)</td>
<td>0.79</td>
</tr>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>62 (16)</td>
<td>61 (15)</td>
<td>63 (17)</td>
<td>0.77</td>
</tr>
<tr>
<td>Disease duration, mo, mean (SD)</td>
<td>10 (6)</td>
<td>11 (5)</td>
<td>9 (5)</td>
<td>0.79</td>
</tr>
<tr>
<td>RF-positive, %</td>
<td>89.2</td>
<td>88.6</td>
<td>85.8</td>
<td>0.61</td>
</tr>
<tr>
<td>ACPA-positive, %</td>
<td>71.2</td>
<td>68.2</td>
<td>69.2</td>
<td>0.79</td>
</tr>
<tr>
<td>ESR, mm/h, mean (SD)</td>
<td>38 (9)</td>
<td>39 (8)</td>
<td>37 (8)</td>
<td>0.69</td>
</tr>
<tr>
<td>CRP, mg/l, mean (SD)</td>
<td>27.8 (11.2)</td>
<td>26.7 (10.8)</td>
<td>26.1 (10.5)</td>
<td>0.68</td>
</tr>
<tr>
<td>HAQ, mean (SD)</td>
<td>1.38 (0.32)</td>
<td>1.35 (0.31)</td>
<td>1.37 (0.34)</td>
<td>0.78</td>
</tr>
<tr>
<td>DAS28, mean (SD)</td>
<td>5.22 (1.6)</td>
<td>5.17 (1.5)</td>
<td>5.34 (1.4)</td>
<td>0.57</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>22</td>
<td>16</td>
<td>19</td>
<td>0.25</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>18.2 (5.3)</td>
<td>20.1 (4.9)</td>
<td>19.5 (5.1)</td>
<td>0.76</td>
</tr>
<tr>
<td>Systolic BP, mmHg, mean (SD)</td>
<td>127.9 (21)</td>
<td>125.5 (18)</td>
<td>128.3 (20)</td>
<td>0.59</td>
</tr>
<tr>
<td>Diastolic BP, mmHg, mean (SD)</td>
<td>68.8 (13.3)</td>
<td>65.5 (14.3)</td>
<td>70.9 (14.4)</td>
<td>0.59</td>
</tr>
<tr>
<td>Heart rate bpm, mean (SD)</td>
<td>68.2 (18)</td>
<td>72.2 (19)</td>
<td>72.2 (18)</td>
<td>0.81</td>
</tr>
<tr>
<td>ABI, mean (SD)</td>
<td>1.12 (0.21)</td>
<td>1.21 (0.22)</td>
<td>1.15 (0.16)</td>
<td>0.62</td>
</tr>
<tr>
<td>T/H ratio</td>
<td>4.51</td>
<td>4.52</td>
<td>4.32</td>
<td>0.68</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>221 (31.2)</td>
<td>217 (26.2)</td>
<td>216 (25.4)</td>
<td>0.78</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>49 (5.2)</td>
<td>48 (4.9)</td>
<td>50 (5.1)</td>
<td>0.89</td>
</tr>
<tr>
<td>CAVI, mean (SD)</td>
<td>10.72 (1.22)</td>
<td>10.69 (1.33)</td>
<td>10.66 (1.43)</td>
<td>0.89</td>
</tr>
<tr>
<td>Alx@75 (%), mean (SD)</td>
<td>38.1 (5.4)</td>
<td>37.7 (6.2)</td>
<td>37.9 (4.3)</td>
<td>0.82</td>
</tr>
<tr>
<td>CIMT, mm, mean (SD)</td>
<td>1.1 (0.1)</td>
<td>1.1 (0.1)</td>
<td>1.1 (0.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>CAP, (number with each combined grade 0/1/2/3/4)</td>
<td>9/10/2/1/0</td>
<td>7/7/5/1/1</td>
<td>10/8/2/1/0</td>
<td>0.57</td>
</tr>
</tbody>
</table>

RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; DAS: Disease Activity Score; BMI: body mass index; BP: blood pressure; ABI: ankle-brachial index; TC: total cholesterol; HDL: high-density lipoprotein cholesterol; T/H: ratio of fasting serum to TC to HDL; CAVI: cardio-ankle vascular index; AIx: augmentation index; CIMT: carotid intima-media thickness; CAP: carotid artery plaque.
DAS28-ESR score, TCZ: $-2.10 \pm 0.35$, ETN: $-2.84 \pm 0.42$, ADA: $-2.12 \pm 0.38$; CRP, TCZ: $24.3 \pm 3.2$ mg/l, ETN: $19.0 \pm 2.31$ mg/l, ADA: $20.7 \pm 2.11$ mg/l; $p < 0.05$). There were no significant differences among the groups.

**DISCUSSION**

CA VI and Alx@75 improved after 24 weeks of TCZ, ETN, and ADA. The improvement in CA VI measures was remarkable. The observed difference of 1 m/s was equivalent to the difference previously seen between 1- and 2-stenosis vessel disease$^{10}$. CIMT and CAP did not change over the course of our study, and this may reflect an error, the limited size of the patient groups, or the short followup$^{11}$.

TCZ could possibly play a role in upregulating levels of serum cholesterol$^{12}$. Hypercholesterolemia can induce cardiovascular disease$^{13}$. Our study confirmed that TCZ reduced arterial stiffness but increased levels of TC. This might be because TC rises together with HDL, such that the T/H ratio did not change. T/H ratio is a more important predictor of cardiovascular disease than TC$^{14}$.

**REFERENCES**