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

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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. (J Rheumatol First Release Aug 1 2011; doi:10.3899/jrheum.110340)

Key Indexing Terms:
ARTERIAL STIFFNESS RHEUMATOID ARTHRITIS TOCILIZUMAB
ETANERCEPT 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 (DAS)28-erythrocyte sedimentation rate (ESR)[1] > 3.2][2] and no prior treatment with methotrexate, steroids, or biologics. The dosage of all disease-modifying antirheumatic drugs had to be stable for at least 8 weeks prior to enrollment.

Patients were assigned randomly to receive TCZ, ETN, or ADA monotherapy. TCZ (8 mg/kg) was administered every 4 weeks subcutaneously, ETN (25 mg) twice a week subcutaneously, and ADA (40 mg) every 2 weeks, subcutaneously. All patients with worsening disease activity as measured by DAS28-ESR at Week 12, defined by change of DAS28-ESR from baseline > 1.2, or DAS 28-ESR > 5.1, were allowed to leave the group (by clinician's judgment). The primary outcome was change in the cardio-ankle vascular index (CAVI)[3]. Secondary outcomes were changes in augmentation index[4] corrected to a heart rate of 75 bpm (AIx@75), and vascular ultrasound assessments from baseline to 24 weeks. Other outcome measures were cardiovascular risk factors and RA disease activity.

CAVI and AIx@75 were measured at baseline and at 24 weeks by using a CAVI system (Vasera VS-1500N; Fukuda Denshi, Tokyo, Japan).

Brachial ankle pulse wave velocity (PWV) has been used as a therapeutic endpoint in studies of treatments for RA[5].

CAVI was calculated by the following formula[3]:

$$CAVI = 2\rho/dP \times \ln(Ps/Pd)PWV2$$

Ps is systolic blood pressure, Pd is diastolic blood pressure, dP is Ps minus Pd, and p is blood density.

CAVI measures arterial stiffness independently of blood pressure and is superior to PWV as an index of arterial stiffness[3].

Carotid intima-media thickness (CIMT) and carotid artery plaque (CAP) were measured at baseline and 24 weeks. CIMT was examined and measured on both common carotid arteries 1.5 cm proximal to the carotid sinus[6]. We evaluated the average of the measurements.

CAP was measured from 0 to 4.5 cm proximal to the carotid sinus. A grade of 0 was assigned for no plaque, 1 for minimal, and 2 for extensive. Each individual subject was given a score of 0 to 4, comprising the sum of the scores for both arteries.

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Measures of cardiovascular risk included the ankle-brachial index[7], 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-ESR[1], 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 CAVI 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 (Δ; 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, 0.85 ± 0.15 m/s; $p = 0.02$), ETN (0.81 ± 0.18 m/s; $p = 0.03$), and ADA (0.90 ± 0.21 m/s; $p = 0.02$). The ΔCAVI was not significantly different among TCZ, ETN, and ADA ($p > 0.05$; Figure 1).

AIx@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%; $p = 0.02$). The ΔAIx@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 ± 0.02; 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-

Table 1. Patient characteristics at baseline.

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

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.

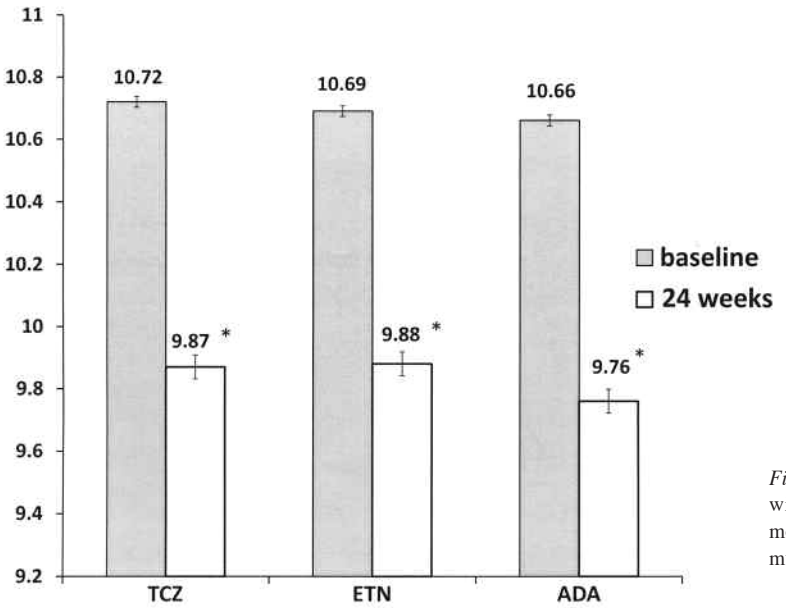

Figure 1. Cardio-ankle vascular index at baseline compared with 24 weeks of treatment with tocilizumab (TCZ) monotherapy, etanercept (ETN) monotherapy, and adalimumab (ADA) monotherapy. *p < 0.05.

ESR score, TCZ: –2.10 ± 0.35, ETN: –2.84 ± 0.42, ADA: –2.12 ± 0.38; CRP, TCZ: 24.3 ± 3.2 mg/l, ETN: 19.0 ± 2.31 mg/l, ADA: 20.7 ± 2.11 mg/l; $p < 0.05$). There were no significant differences among the groups.

DISCUSSION

CAVI and AIx@75 improved after 24 weeks of TCZ, ETN, and ADA. The improvement in CAVI 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

1. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
2. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism criteria. Arthritis Rheum 1996;39:34-40.
3. Shirai K, Utino J, Otsuka K, Takata M. A novel blood pressure-independent arterial wall stiffness parameter; cardio-ankle vascular index (CAVI). J Atheroscler Thromb 2006;13:101-7.
4. Avalos I, Chung CP, Oeser A, Gebretsadik T, Shintani A, Kurnik D, et al. Increased augmentation index in rheumatoid arthritis and its relationship to coronary artery atherosclerosis. J Rheumatol 2007;34:2388-94.
5. Wong M, Oakley SP, Young L, Jiang BY, Wierzbicki A, Panayi G, et al. Infliximab improves vascular stiffness in patients with rheumatoid arthritis. Ann Rheum Dis 2009;68:1277-84.
6. Kumeda Y, Inaba M, Goto H, Nagata M, Henmi Y, Furumitsu Y, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. Arthritis Rheum 2002;46:1489-97.
7. Paraskevas KI, Kotsikoris I, Koupidis SA, Giannoukas AD, Mikhalidis DP. Ankle-brachial index: a marker of both peripheral arterial disease and systemic atherosclerosis as well as a predictor of vascular events. Angiology 2010;61:521-3.
8. Malaspina JP, Bussière H, Le Calve G. The total cholesterol/HDL cholesterol ratio: a suitable atherogenesis index. Atherosclerosis 1981;40:373-5.
9. Matsuda Y, Singh G, Yamanaka H, Tanaka E, Urano W, Taniguchi A, et al. Validation of a Japanese version of the Stanford Health Assessment Questionnaire in 3763 patients with rheumatoid arthritis. Arthritis Rheum 2003;49:784-8.
10. Nakamura K, Tomaru T, Yamamura S, Miyashita Y, Shirai K, Noike H. Cardio-ankle vascular index is a candidate predictor of coronary atherosclerosis. Circ J 2008;72:598-604.
11. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, Garcia-Porrua C, Llorca J, Gonzalez-Gay MA. Active but transient improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti-tumor necrosis factor alpha antibody. Arthritis Rheum 2004;51:447-50.
12. Kawashiri SY, Kawakami A, Yamasaki S, Imazato T, Imamoto N, Fujikawa K, et al. Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. Rheumatol Int 2011;31:451-6.
13. Wilkinson IB, Prasad K, Hall IR, Thomas A, MacCallum H, Webb DJ, et al. Increased central pulse pressure and augmentation index in subjects with hypercholesterolemia. J Am Coll Cardiol 2002;39:1005-11.
14. Lemieux I, Lamarche B, Couillard C, Pascot A, Cantin B, Bergeron J, et al. Total cholesterol/HDL cholesterol ratio vs LDL cholesterol/HDL cholesterol ratio as indices of ischemic heart disease risk in men: the Quebec Cardiovascular Study. Arch Intern Med 2001;161:2685-92.