Tocilizumab Treatment Increases Left Ventricular Ejection Fraction and Decreases Left Ventricular Mass Index in Patients with Rheumatoid Arthritis without Cardiac Symptoms: Assessed Using 3.0 Tesla Cardiac Magnetic Resonance Imaging

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ABSTRACT. *Objective.* The aim of our pilot study was to prospectively evaluate the effect of inhibiting interleukin 6 on the left ventricular (LV) structure and function in patients with rheumatoid arthritis (RA) without cardiac symptoms, using cardiac magnetic resonance (CMR).

Methods. Female patients with RA with active disease and healthy controls were enrolled. Cardiac symptoms were absent in all subjects. Tocilizumab (TCZ; 8 mg/kg IV every 4 weeks) was prescribed for patients with RA with an inadequate clinical response to methotrexate. All subjects underwent baseline evaluation of LV function and structure measured by CMR. We compared measures of LV geometry and function between patients with RA and patients without RA controls at baseline, and changes in the same variables between baseline and after 52 weeks of treatment among the group with RA.

Results. Twenty women with RA were compared with 20 women without RA of similar mean age. In patients with RA at baseline, ejection fraction (EF) was significantly lower (–3.7%) and LV mass index (LVMI) significantly higher (+9.2%) compared with controls. TCZ treatment resulted in a significant decrease in the Simplified Disease Activity Index (SDAI) after 52 weeks of treatment, paralleling a significant increase in EF (+8.2%) and a significant decrease in LVMI (–24.4%) over the same period. The percentage change in LVMI correlated strongly with the percentage change in SDAI (r = –0.63, p = 0.0028). LV geometry in the group with RA at baseline showed eccentric hypertrophy compared with the group without RA, a condition that normalized after TCZ treatment.

Conclusion. TCZ treatment significantly increased EF and decreased LVMI associated with disease activity. (J Rheumatol First Release Aug 15 2014; doi:10.3899/jrheum.131540)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   LEFT VENTRICULAR FUNCTION AND STRUCTURE
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Individuals with rheumatoid arthritis (RA) have about a 2-fold higher risk of developing congestive heart failure (CHF) compared with the general population[1,2]. The prevalence of traditional risk factors for cardiovascular (CV) disease is not generally increased in RA, suggesting that RA itself is an important contributor to the development of CHF. Elevated serum levels of inflammatory cytokines, particularly interleukin 6 (IL-6), play a prominent role in the pathogenesis of both CHF[3] and RA[4]. Serum IL-6 level correlates with impaired cardiomyocyte contractility in patients with CHF, and has a strong influence on ventricular remodeling and hypertrophy[5,6]. The patterns of left ventricular (LV) remodeling and their associations with inflammatory markers have been described in large studies of the general population[7], and LV remodeling and hypertrophy predict CHF independent of traditional risk factors[8]. Widely variable, reported serum levels of IL-6 in patients with RA

are, on average, considerably higher than those in patients with CHF[3,9], raising the possibility of IL-6 as a contributor to abnormal LV remodeling in RA. However, the implications of these findings for patients with RA are uncertain.

Echocardiography and cardiac magnetic resonance (CMR) imaging have been successfully applied in the general population to identify early structural changes in the LV that predate the development of clinically overt CHF. Several studies have demonstrated that an increase in LV mass in asymptomatic individuals is a potent predictor of incident CHF, even in those who remain free of obstructive coronary artery disease at followup[10,11]. Although several noninvasive imaging modalities such as single-photon emission computed tomography and echocardiography may reveal functional abnormalities, spatial resolution is not of sufficient sensitivity, objectivity, or reproducibility to identify cardiac diseases compared with CMR[12,13].

Our study was undertaken to test the hypothesis that the powerful antiinflammatory effect of anti-IL-6 treatment [tocilizumab (TCZ)] might lead to a reduction in LV hypertrophy and dysfunction in patients with RA. In addition, we investigated LV geometric variables in patients with RA compared with patients without RA controls at baseline and after treatment.

MATERIALS AND METHODS

Study population. All patients with RA were recruited at our center from December 2010 to May 2012. All patients met the 2010 American College of Rheumatology/European League Against Rheumatism criteria for RA[14]. Healthy volunteers were recruited as a control group based on age and sex, to match the patients with RA. Patients with moderate to severe active RA [Disease Activity Score based on 28-joint counts (DAS28) > 3.2] receiving methotrexate (MTX) without prior use of any biologic were included in our study. Participants were excluded if they had prior self-reported, physician-diagnosed CV events or procedures, such as myocardial infarction, angioplasty, and CHF. Additional exclusions were diabetes (glycosylated hemoglobin > 6.1), hypertension [systolic blood pressure (BP) > 140 mmHg and/or diastolic BP > 90 mmHg], and dyslipidemia [low-density lipoprotein (LDL) cholesterol levels > 140 mg/dl, a high-density lipoprotein (HDL) cholesterol level < 40 mg/dl, or a triglyceride level > 150 mg/dl]. Because the mechanism of developing LV hypertrophy may differ between men and women, and RA is more common in women, we decided to include only women in our study. Our study was approved by the local ethics committee (Itabashi Chuo Medical Center, Japan), and informed consent was obtained from each patient in accordance with the Helsinki Declaration of 1975 (revised in 1983).

Treatment and scanning protocol. Treatment with intravenous TCZ at a dose of 8 mg/kg every 4 weeks was prescribed after baseline evaluation using noncontrasted CMR on a 3.0 T scanner. CMR evaluation was repeated after 52 weeks of TCZ therapy. Doses of MTX and glucocorticoids were kept stable throughout our study.

All the magnetic resonance imaging (MRI) sequences have been scanned under breath-holding and electrocardiographic gating (ECG). An average individual can breath-hold for 15 to 25 s. ECG gating techniques use an electrical impulse based on the R wave from an ECG to accept, reject, or reorder data in K-space contributing to an image.

Assessment protocol of cardiac MRI. The following variables were measured: global LV function [LV ejection fraction (EF), end-systolic volume, end-diastolic volume (EDV), stroke volume (SV), cardiac output (CO)]; and LV hypertrophy [absolute LV mass (LVM), LV mass index (LVMI; mass/body surface area)]. Based on LV mass index (LVMI) and Mass/EDV of healthy volunteers, "mean + 2 SD" of each measure was defined as the values for elevated LVMI and LVM/EDV (66.6 and 1.02, respectively). LV geometry was classified as (1) concentric remodeling: LVMI < 66.6 and Mass/EDV > 1.02; (2) concentric hypertrophy: LVMI > 66.6 and Mass/EDV > 1.0; (3) eccentric hypertrophy: LVMI > 66.6 and Mass/EDV < 1.02; and (4) normal geometry: LVMI < 66.6 and Mass/EDV < 1.02.

RA-specific evaluation. All patients were clinically evaluated at baseline and at 52 weeks by the same observer. The DAS28, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) were calculated from standardized joint counts.

Clinical and laboratory assessment. Fasting samples of serum and plasma were separated by centrifugation and stored at –70°C.

All assays were performed at our institute using our internal quality control procedures. At the time of our study visit, all subjects underwent routine laboratory investigations and basic screening for traditional atherosclerotic disease risk factors, including history of cigarette smoking, serum cholesterol, triglycerides, HDL, LDL, fasting blood glucose concentration, chest radiograph, 12-lead electrocardiogram, rheumatoid factor (RF), and anticitrullinated protein antibodies (ACPA). Clinical values of BP were obtained 2 times from each patient using a digital monitor. While measuring BP, the participant remained seated with the arm comfortably placed at heart level. BP was considered as the mean of the 2 readings.

Statistical analysis. The distributions of all variables were examined. Mean SD were calculated for normally distributed continuous variables and compared using t tests. Median and interquartile ranges were calculated for non-normally distributed continuous variables and compared using Wilcoxon signed-rank test and the Steel test. Counts and proportions were calculated for categorical variables and compared using Fisher's exact test. Spearman's rank correlation coefficient was used to assess the correlation between the percent change of LVMI, EDV, EF, and other patient characteristics. Multivariable linear regression model was used to evaluate the association of the percentage change in SDAI with the percentage change in LVMI. Statistical calculations were performed using JMP 9 (SAS Institute Inc.). In all tests, a 2-tailed α of 0.05 was defined as the level of statistical significance.

RESULTS

Baseline characteristics for the group with RA and the control group are summarized in Table 1. There were no major differences among the baseline characteristics in terms of age, CV risk factors, and smoking status. Both the group with RA and the control group were, on average, normolipidemic and normotensive, and had no diabetes or reported smoking. The median baseline disease duration was 30 months. All patients with RA received TCZ treatment for 52 weeks without any adverse events. All patients with RA were prescribed concomitant MTX with an average dose of 8.3 ± 0.53 mg/week (range 6.0–10.0 mg/week) and folic acid 5 mg/day. Five patients received steroids with an average dose of 2.4 mg/day. The characteristics of RA disease activity at baseline and after 52 weeks of TCZ treatment are summarized in Table 2. The patients with RA had high disease activity on average, as reflected by a mean DAS28 score above 5.0, a mean SDAI of 24, and a mean CDAI of 21.1. After 52 weeks of TCZ treatment, all disease activity measures were significantly lower on average (Table 2). We found no changes in BP, body mass

Table 1. Baseline characteristics between control group and patients receiving TCZ. Data are median (range) unless otherwise indicated.

Median (IQR)	Control, n = 20	Patients with RA, n = 20	p
Demographics			
Age, yrs*	54.5 (50–57.5)	56.5 (42.8–60)	0.912
Female, n (%)**	20 (100)	20 (100)	0.532
Cardiovascular risk factors			
Diabetes, n (%)**	0 (0)	0 (0)	1.000
Systolic BP, mmHg*	122.5 (118.3–125)	121.5 (110–127.8)	0.741
Diastolic BP, mmHg*	70 (66.8–78.0)	68 (62.5–72)	0.389
Total cholesterol, mg/dl*	175 (161.3–194)	174 (163.3–186)	0.982
LDL cholesterol, mg/dl*	88 (84–95.5)	95 (80.3–103)	0.567
HDL cholesterol, mg/dl*	59 (53–71)	61 (54.3–67.8)	0.895
Triglycerides, mg/dl	116 (104.8–142.5)	121.5 (106–138)	0.982
HbA1c, %*	5.6 (5.3–6.0)	5.7 (5.4–6.0)	0.535
Smoking status			
Current smoker, n (%)**	0 (0)	0 (0)	1.000

*Wilcoxon rank sum test. **Fisher's exact test. TCZ: tocilizumab; IQR: interquartile range; RA: rheumatoid arthritis; BP: blood pressure; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HbA1c: glyco-sylated hemoglobin.

Table 2. RA characteristics between baseline and after 52 weeks (Wilcoxon signed-rank test).

Characteristics	TCZ at Baseline	TCZ After 52 Weeks	p
Tender joint count	6.25 ± 4.87	1.15 ± 1.76	< 0.0001
Swelling joint count	5.20 ± 2.38	1.55 ± 2.11	< 0.0001
PtGAS	55.00 ± 17.92	17.00 ± 15.25	< 0.0001
PGA	57.25 ± 24.25	12.00 ± 12.81	< 0.0001
DAS28	5.18 ± 1.03	2.08 ± 0.73	< 0.0001
SDAI	23.55 ± 6.76	5.67 ± 5.07	< 0.0001
CDAI	21.90 ± 6.69	5.55 ± 5.06	< 0.0001
mHAQ	0.57 ± 0.52	0.36 ± 0.48	0.0430
CRP	2.28 ± 2.74	0.05 ± 0.11	< 0.0001
ESR	48.75 ± 30.61	5.85 ± 3.44	< 0.0001
MMP-3	314.66 ± 386.25	151.07 ± 237.53	< 0.0001

RA: rheumatoid arthritis; PtGAS: patient global assessment; PGA: physician's global assessment; DAS28: 28-joint Disease Activity Score; SDAI: Simple Disease Activity Index; CDAI: Clinical Disease Activity Index; mHAQ: modified Health Assessment Questionnaire; CRP: C–reactive protein; ESR: erythrocyte sedimentation rate; MMP-3: matrix metalloproteinase 3.

index (BMI), level of LDL cholesterol, or triglyceride level in our study (data not shown).

LV structure and function measures between patients with RA and controls. Baseline measures of LV structure and function for the group with RA and the control group, as well as the results after 52 weeks of TCZ treatment, are depicted in Figure 1. The baseline value of pre-LVMI showed a mild correlation with the disease duration (r = 0.39). At baseline compared with the control group without RA, patients with RA had a higher median LVMI by 9.2% (p = 0.029; Figure 1a), lower median EF by 3.7% (p = 0.048; Figure 1b), and higher median EDV by 3.7% (p = 0.057; Figure 1c). The ratio of LV mass to EDV did not significantly differ by RA status (Figure 1d), as the median SV, EDV, and CO have revealed (data not shown).

When we evaluate the normal range of LVMI and Mass/EDV (i.e., mean ± 2 SD), 16 patients (80%) of the population with RA were in the normal range, and 4 patients (20%) showed eccentric hypertrophy. The baseline values of the population with RA before treatment showed statistically higher values of LVMI compared to the control group; however, there were no significant differences in the mean Mass/EDV. Four patients who showed eccentric hypertrophy before treatment improved to the normal range after treatment.

Changes in clinical and biological variables after 52 weeks of TCZ treatment. Among the group with RA, TCZ treatment was associated with an average decrease in LVMI of 24.4% (p < 0.001; Figure 1a), resulting in values that on average no longer differed from baseline levels for the
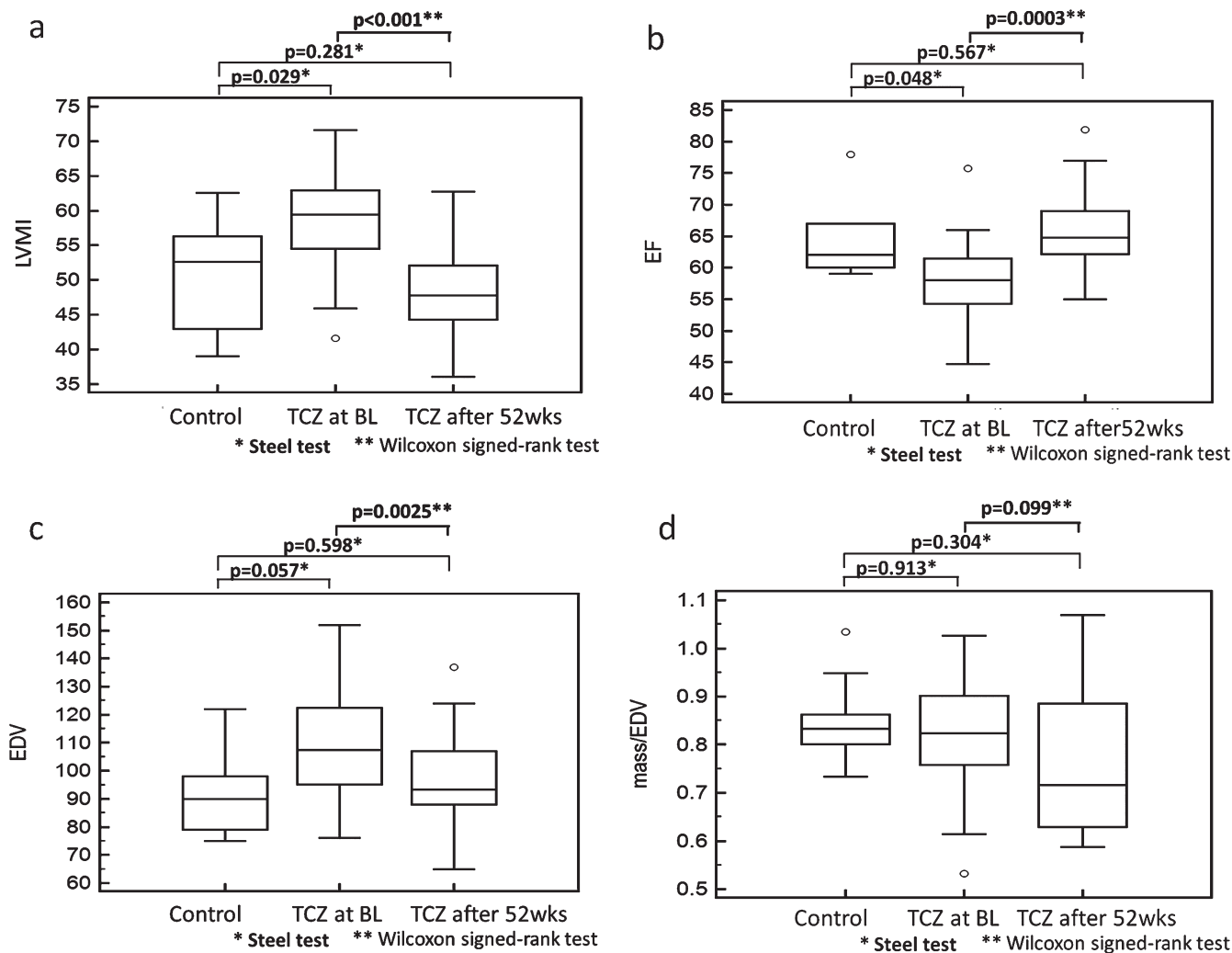
Figure 1. LV structure and function measures between patients with RA and controls. Baseline measures of LV structure and function for the group with RA and control group without RA, and for the group with RA after treatment with TCZ for 52 weeks are depicted. At baseline compared with the control group, patients with RA had a higher median LVMI by 9.2% (p = 0.029; Figure 1a), lower median EF by 3.7% (p = 0.048; Figure 1b), and higher median EDV by 3.7% (p = 0.057; Figure 1c). The ratio of LVMI did not significantly differ by RA status (Figure 1d). LV: left ventricular; RA: rheumatoid arthritis; TCZ: tocilizumab; LVMI: LV mass index; EF: ejection fraction; EDV: end-diastolic volume; BL: baseline.

Table 3. Correlations between the percentage change in myocardial measures according to participant characteristics. Correlation coefficients ρ are Spearman correlation coefficients.

Characteristic	% Change in LVMI		% Change in EDV		% Change in EF	
	ρ	p	ρ	p	ρ	p
% change in ESR	0.006	0.98	0.561	0.010	0.201	0.40
% change in CRP	0.191	0.42	0.034	0.89	–0.043	0.86
% change in SDAI	–0.616	0.004	–0.150	0.53	0.047	0.84
% change in CDAI	–0.580	0.007	–0.338	0.15	0.145	0.54
Baseline age	0.537	0.015	0.029	0.89	–0.306	0.19
ACPA titer	–0.121	0.61	0.190	0.42	0.017	0.94
RF titer	0.050	0.83	0.126	0.60	–0.023	0.92
Baseline RA duration	0.186	0.43	–0.076	0.75	0.078	0.74

LVMI: left ventricular mass index; EDV: end-diastolic volume; EF: ejection fraction; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; ACPA: anticitrullinated protein antibodies; RF: rheumatoid factor; RA: rheumatoid arthritis.

control group without RA. Similar normalization to levels congruent with the control group without RA was also observed in EF, which increased by 8.2% with TCZ treatment (p < 0.0003; Figure 1b), and EDV, which decreased by 15.2% with TCZ treatment (p = 0.0025; Figure 1c). LVMI in the group with RA with TCZ treatment was < 66.6 and Mass/EDV was < 1.02, indicating a normalization of LV geometry.

The percentage change in LVMI in the group with RA was significantly correlated with the percentage change in SDAI (p = –0.62, p = 0.004; Table 3). Also, the percentage change in EDV in the group with RA was significantly correlated with the percentage change in erythrocyte sedimentation rate (ESR; p = 0.56, p = 0.01; Table 3). RF seropositivity, increase in RF titer, or ACPA was not associated with decreases in measures of cardiac structure (results not shown). We have stratified the patients with RA treated with TCZ by short versus long disease duration to assess whether the effect of TCZ on LVMI differed between these 2 groups. Percentage change of LVMI did not differ between short and long disease duration (p = 0.517). Likewise, other current or cumulative use of glucocorticoids was not significantly associated with the mean values of LV structure (data not shown). Adjustment for the percentage change in ESR and C-reactive protein did not affect the association of the percentage change in CDAI with the percentage change in LVMI (Table 4). The percentage change in CDAI accounted for almost 35% of the total variability in the percentage change in LVMI ($R^2 = 0.34$).

DISCUSSION

We studied the longterm effect (52 weeks) of treatment with an IL-6 inhibitor, TCZ, in women with established RA to assess LV morphological features and the predictors of TCZ-induced variation in LVM. First, we observed that a 52-week course of TCZ significantly increased EF, decreased LVMI, and normalized several LV morphological features. Secondly, these findings were correlated with the

Table 4. Crude and adjusted association of the percent change in CDAI with LVMI. Multivariable linear regression. Adjustment for the percentage change in ESR and CRP did not modify the association of the percentage change in CDAI with the percentage change in LVMI. The percentage change in CDAI accounted for almost 35% of the total variability in the percentage change in LVMI ($R^2 = 0.34$).

	Model 1		Model 2		Model 3	
	β	p	β	p	β	p
% change CDAI	–0.298	< 0.001	–0.293	0.011	–0.324	0.006
% change CRP			0.117	0.815		
% change ESR					–0.138	0.393
R2	0.336		0.338		0.365	

CDAI: Clinical Disease Activity Index; LVMI: left ventricular mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CDAI: Clinical Disease Activity Index.

amelioration of SDAI. Lastly, LV geometry in the group with RA at baseline showed eccentric hypertrophy compared with the control group, which also normalized after TCZ treatment. To our knowledge, there are no published reports using CMR for the investigation of the effect of anti-IL-6 therapy on LV structure and function in RA.

The etiology of the increased prevalence of CHF in RA is uncertain. Crowson, *et al*[15] showed higher rates of CHF in patients with RA compared with controls even after controlling for clinical ischemic heart disease, suggesting that causes other than infarction may play a role. Proinflammatory cytokines, especially IL-6, are known to play an important part in the pathogenesis of RA and might explain the augmentation of LVMI in this disease. IL-6 is increased in various CV diseases, including myocarditis, myocardial infarction, and congestive heart failure. For these reasons, therapies that reduce inflammation (i.e., anti-IL-6 therapy) may delay the onset and/or slow the progression of LV hypertrophy and dysfunction. Recently, Kotyla, *et al*[16] and Daïen, *et al*[17] reported a significant decrease in LVMI with medium or longterm treatment with tumor necrosis factor-α (TNF-α) inhibitors. Their results may suggest that TNF-α might also be an important contributor to LV hypertrophy. These results were in line with other reports. Giles, *et al*[18] also reported that treatment with biologic agents was associated with a lower LV mass in patients with RA. However, few studies have been done to assess the effect of TCZ treatment on LV structure and function.

Accordingly, we observed marked reduction of the LVMI as a result of TCZ treatment. Because there were no changes in blood pressure, BMI, level of LDL cholesterol, or triglyceride level after 52 weeks of TCZ treatment, these variables may not explain the LVMI changes in RA. Further, EF after TCZ treatment significantly increased compared to baseline figures. It is possible that the reason for improvement of EF was a beneficial effect of reducing LVMI (i.e., hypertrophy). Interestingly, we observed that the pattern of eccentric hypertrophy in RA at baseline normalized after 52 weeks of TCZ treatment, suggesting also that IL-6 may be an important determinant of LV structure and function. Recently, Myasoedova, *et al* reported that RA was associated with LV concentric remodeling in a cross-sectional study using echocardiography[19]. In echocardiography, the LV geometry is evaluated by examining the cross section of the short axis image and not by its volume. In MRI, the entire LV volume is evaluated by measuring the LV mass and the volume of the cardiac chamber, hence MRI might be a better option to precisely measure the LV geometry. When we compare our results with previous publications of echocardiography, our results differ in terms of LV geometry. We speculate that this is attributable to the different modality used to measure the LV geometry. We believe it is necessary to further investigate this matter with more patients.

We may speculate that improvements in global contractility over 52 weeks correlate with reductions in measures of RA disease activity. Given this, control of disease activity with TCZ may explain part of the decrease in LVMI.

Cardiac MRI is now considered the gold standard for the assessment of LV dimensions, mass, and function. Using spin-echo techniques, MRI is superior to echocardiography in the assessment of LV mass and volume[20], with an accuracy of about 98%[21]. Thus, MRI provides a highly accurate and sensitive method for evaluating changes in both global and regional ventricular function. This is particularly important for the proposed studies because IL-6 antagonists may affect global LV function and structure attributable to RA.

Our study had some limitations. This was a pilot study with a relatively small sample size; however, given the magnitude of effects and sensitivity of the imaging method, it was more than adequate to observe highly significant changes in LV function. We did not perform T2-weighted MR images and delayed enhancement MRI, which are used to assess myocarditis and myocardial fibrosis. Nevertheless, our preliminary data lend support for a high prevalence of LV global dysfunction and eccentric hypertrophy in patients with RA with higher levels of disease activity, and for a modulating effect on the LV by IL-6 antagonist treatment. It is critically important, therefore, to separate the effects of the disease from the effects of anticytokine treatment on LV structure and function, because this distinction may have important implications for the longterm management of patients with RA.

TCZ treatment significantly increased LVEF and decreased LV mass among patients with RA with active disease treated for 52 weeks. Further, we found a significant relationship between disease activity and measures of LV function and structure. TCZ may reduce progression of LV dysfunction and improve LV structure in association with the reduction in disease activity. It can be presumed that RA itself may be an important contributor to the development of myocardial abnormalities.

REFERENCES

1. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, Ballman KV, et al. The risk of congestive heart failure in rheumatoid arthritis: a population-based study over 46 years. Arthritis Rheum 2005;52:412–20.
2. Nicola PJ, Crowson CS, Maradit-Kremers H, Ballman KV, Roger VL, Jacobsen SJ, et al. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. Arthritis Rheum 2006;54:60–7.
3. Dibbs Z, Thornby J, White BG, Mann DL. Natural variability of circulating levels of cytokines and cytokine receptors in patients with heart failure: implications for clinical trials. J Am Coll Cardiol 1999;33:1935–42.
4. Dayer JM, Choy E. Therapeutic targets in rheumatoid arthritis: the interleukin-6 receptor. Rheumatology 2010;49:15–24.
5. Raymond RJ, Dehmer GJ, Theoharides TC, Deliargyris EN. Elevated interleukin-6 levels in patients with asymptomatic left ventricular systolic dysfunction. Am Heart J 2001;141:435–8.
6. Wollert KC, Drexler H. The role of interleukin-6 in the failing heart. Heart Fail Rev 2001;6:95–103.
7. Masiha S, Sundstrom J, Lind L. Inflammatory markers are associated with left ventricular hypertrophy and diastolic dysfunction in a population-based sample of elderly men and women. J Hum Hypertens 2013;27:13–7.
8. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. J Am Coll Cardiol 2008;52:2148–55.
9. Klimiuk PA, Sierakowski S, Latosiewicz R, Cylwik JP, Cylwik B, Skowronski J, et al. Circulating tumour necrosis factor alpha and soluble tumour necrosis factor receptors in patients with different patterns of rheumatoid synovitis. Ann Rheum Dis 2003;62:472–5.
10. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561–6.
11. Gardin JM, McClelland R, Kitzman D, Lima JA, Bommer W, Klopfenstein HS, et al. M-mode echocardiographic predictors of six- to seven-year incidence of coronary heart disease, stroke, congestive heart failure, and mortality in an elderly cohort (the Cardiovascular Health Study). Am J Cardiol 2001;87:1051–7.
12. Maksimović R, Seferović PM, Ristić AD, Vujisić-Tesić B, Simeunović DS, Radovanović G, et al. Cardiac imaging in rheumatic diseases. Rheumatology 2006;45 Suppl 4:26–31.
13. Mavrogeni S, Vassilopoulos D. Is there a place for cardiovascular magnetic resonance imaging in the evaluation of cardiovascular involvement in rheumatic diseases? Semin Arthritis Rheum 2011;41:488–96.
14. van der Linden MP, Knevel R, Huizinga TW, van der Helm-van Mil AH. Classification of rheumatoid arthritis: comparison of the 1987 American College of Rheumatology criteria and the 2010 American College of Rheumatology/European League Against Rheumatism criteria. Arthritis Rheum 2011;63:37–42.
15. Crowson CS, Nicola PJ, Kremers HM, O'Fallon WM, Therneau TM, Jacobsen SJ, et al. How much of the increased incidence of heart failure in rheumatoid arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? Arthritis Rheum 2005;52:3039–44.
16. Kotyla PJ, Owczarek A, Rakoczy J, Lewicki M, Kucharz EJ, Emery P. Infliximab treatment increases left ventricular ejection fraction in patients with rheumatoid arthritis: assessment of heart function by echocardiography, endothelin 1, interleukin 6, and NT-pro brain natriuretic peptide. J Rheumatol 2012;39:701–6.
17. Daïen CI, Fesler P, du Cailar G, Daïen V, Mura T, Dupuy AM, et al. Etanercept normalises left ventricular mass in patients with rheumatoid arthritis. Ann Rheum Dis 2013;72:881–7.
18. Giles JT, Malayeri AA, Fernandes V, Wendy P, Blumenthal RS, Bluemke D, et al. Left ventricular structure and function in patients with rheumatoid arthritis, as assessed by cardiac magnetic resonance imaging. Arthritis Rheum 2010;62:940–51.
19. Myasoedova E, Davis JM 3rd, Crowson CS, Roger VL, Karon BL, Borgeson DD, et al. Rheumatoid arthritis is associated with left ventricular concentric remodeling: results of a population-based cross-sectional study. Arthritis Rheum 2013;65:1713–8.
20. Møgelvang J, Stokholm KH, Saunamäki K, Reimer A, Stubgaard M, Thomsen C, et al. Assessment of left ventricular volumes by magnetic resonance in comparison with radionuclide angiography, contrast angiography and echocardiography. Eur Heart J 1992;13:1677–83.
21. Longmore DB, Klipstein RH, Underwood SR, Firmin DN, Rees RS. Dimensional accuracy of magnetic resonance in studies of the heart. Lancet 1985;1:1360–2.