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

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ABSTRACT. ***Objective.*** To study the influence of anti-tumor necrosis factor-α (TNF-α) treatment on echocardiographic measures and concentrations of endothelin 1 (ET-1), interleukin 6 (IL-6), and amino-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) in a cohort of 23 female patients with rheumatoid arthritis (RA).

Methods. We recruited 23 patients (mean age 51.3 ± 1.55 yrs) with RA resistant to treatment with disease-modifying antirheumatic drugs and average disease duration of 7.1 ± 1.0 years who had been selected to start treatment with the anti-TNF-α antagonist infliximab. Transthoracic echocardiographic examinations were performed before the first infusion and repeated after 1 year of treatment. Data for age, sex, RA disease activity by Disease Activity Score (DAS28) and echocardiographic data, NT-proBNP, IL-6, ET-1, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and other routine laboratory data were collected before treatment and after 1 year.

Results. Twelve months of treatment with infliximab resulted in reduction of RA activity (i.e., reduction of DAS and acute-phase reactants). There was increased left ventricle ejection fraction, from 58.5% before treatment to 63% after. Treatment with infliximab also resulted in significant reduction of ET-1 (1.26 fmol/ml before treatment vs 0.43 fmol/ml after), IL-6 (58.46 pg/ml vs 3.46 pg/ml), and NT-proBNP (43.06 fmol/ml vs 14.78 fmol/ml). These reductions were observed after just 4 months of treatment and remained significant until the termination of the study.

Conclusion. In patients with RA, treatment with infliximab contributed significantly to increase in left ventricular ejection fraction. Improvement of cardiac function was shown by conventional echocardiography; there was reduction of biochemical markers of heart failure. (First Release Feb 15 2012; J Rheumatol 2012;39:701–6; doi:10.3899/jrheum.110751)

Key Indexing Terms:
RHEUMATOID ARTHRITIS INFLIXIMAB HEART FAILURE
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Rheumatoid arthritis (RA) is a chronic inflammatory polyarthropathy with both systemic and articular manifestations[1]. Proinflammatory cytokines, mainly tumor necrosis factor-α (TNF-α) and interleukins (IL-1 and IL-6) are of special importance in RA and are responsible for driving the inflammation[2]. However, the role of TNF-α is not restricted to proinflammatory activities but also comprises a range of pathophysiological properties, including progression of

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atherosclerosis, regulation of immune response, endothelium dysfunction, and induction and progression of congestive heart failure (CHF)[3,4,5]. Anti-TNF-α antagonists (anti-TNF-α) have demonstrated high effectiveness in RA, and have dramatically improved the course of the disease and its prognosis[6]. On the other hand, rapid reduction of TNF-α level may have unexpected effects with possible risks to the patient. The use of anti-TNF-α inhibitors is associated with many adverse experiences such as infections, reactivation of tuberculosis, demyelination, and worsening of preexisting heart failure[7].

Introduction of TNF-α antagonists to treatment of RA brings some questions about their safety for the cardiovascular system. The concern about the toxic influence of TNF-α on the cardiovascular system seems at first to be paradoxical. TNF-α levels are markedly elevated in patients with CHF and this cytokine has a direct negative inotropic effect on heart function[8]. Thus any modality to reduce TNF-α should have a therapeutic effect. That was the theoretical background for interventional studies with TNF-α antagonists in patients with CHF, which were prematurely terminated due to the lack of efficacy or even worsening of cardiac function[9,10]. The underlying mechanism of this phenomenon remains unknown. It is speculated that interactions in the cytokine network may result in severe cytokine imbalances, leading to unexpected cardiovascular toxicity[11]. On the other hand, it is not clear to what extent data from anti-TNF-α studies in patients with CHF and animal models might be directly translated to treatment of patients with RA. The key is that a substantial portion of cases of heart failure occur in relatively healthy patients with RA who have no typical risk factors for CHF[12,13]. Thus, it is important to assess the influence of TNF-α blockade on heart function in patients with RA having normal heart function.

Assessment of heart function is usually done by echocardiography; recently, however, novel biochemical markers of heart function have been introduced to the cardiology clinic. Amino-terminal fragment of the pro-brain natriuretic peptide (NT-proBNP), endothelin 1 (ET-1), and IL-6 have been proven to aid assessment of the risk in CHF[14,15,16]. NT-proBNP belongs to the natriuretic peptide family and is considered to be a good marker of severity and prognosis of ischemic syndromes and CHF. It is also recognized as a diagnostic marker of left ventricular dysfunction[17,18]. The same is true for ET-1. ET-1 has been associated with CHF and patients with chronic CHF often present with elevated levels of vasoactive polypeptide[19]. The third agent, IL-6, has recently been identified as a useful diagnostic and prognostic marker in CHF. In patients with CHF, serum concentration of the cytokine correlates with impaired cardiomyocyte contractility, and a strong influence on ventricular remodeling and hypertrophy has been observed[20,21]. This indicates the usefulness of NT-proBNP, ET-1, and IL-6 as sensitive markers in assessment of cardiac function. The use of 3 independent cardiac biomarkers and echocardiography may result in better accuracy and sensitivity in assessment of the heart function.

The aim of our study was to evaluate the influence of anti-TNF-α treatment on cardiac function measured by the use of echocardiography and levels of cardiac markers in patients with RA who are free from cardiac disorders.

MATERIALS AND METHODS

Study design. We designed a prospective study in patients with disease-modifying antirheumatic drug (DMARD)-resistant RA who had been selected to start treatment with the anti-TNF-α antagonist infliximab. Average duration of disease before initiation of anti-TNF-α was 7.1 ± 1.0 years. All patients satisfied the 1987 American College of Rheumatology criteria for RA[22] and were characterized as having high disease activity despite treatment with methotrexate [i.e., with median Disease Activity Score in 28 joints (DAS28) 6.2 ± 0.28]. We excluded patients with uncontrolled hypertension, overt or latent heart failure [defined as left ventricle ejection fraction (LVEF) < 40% as assessed by conventional echocardiography], history of malignancy, renal function impairment, liver disease, or thyroid gland function disturbances. The study protocol was approved by the Ethics Committee at the Medical University of Silesia, Katowice, Poland, and informed consent was obtained in advance from all patients.

Assessment and treatment protocol. Patients received infliximab in a dose of 3 mg/kg body weight per infusion given every 8 weeks after the usual loading dose at Weeks 0, 2, and 6. Transthoracic echocardiographic examinations were performed using a Toshiba ultrasound machine, by the same cardiologist, who was not aware of the treatment status of the patient. Two-dimensional and color Doppler imaging were performed before the first infusion and repeated after 1 year of treatment. Left ventricular mass was calculated as follows: $1.04 \times [(IVSTd + PWTd + LVIDd)^3 - (LVIDd)^3] - 13.6$ g; where IVSTd is interventricular septal thickness at end-diastole, PWTd is posterior wall thickness at end-diastole, and LVIDd is left ventricular internal diameter at end-diastole[23]. Data were collected for age, sex, RA disease activity by DAS28, LVEF, blood pressure, and NT-proBNP, IL-6, ET-1, ESR, CRP, fasting glucose, creatinine, total cholesterol and triglyceride levels. We also measured body weight and height and body mass index (BMI), and recorded heart rate and blood pressure.

Fasting blood samples were collected between 8 and 9 AM from a peripheral vein after the patient had rested in supine position for at least 10 min. Samples were stored at –80°C for further analysis by appropriate techniques. Blood samples were obtained from patients before the study and repeated at Week 16 and after 1 year of the study.

Plasma cytokine levels. Plasma concentrations of NT-proBNP, IL-6, and ET-1 were assessed using a commercial ELISA (Biomedica Slovakia, DIAsource Belgium, and Enzo USA) and calculated using a standard curve generated with specific standards according to manufacturer's guidelines. The detection limit for NT-proBNP was 0 fmol/l ± 3 SD, with intraassay precision of 8% coefficient of variation (CV). For IL-6 the detection limit, defined as the apparent concentration 2 SD above the average OD at zero binding, was 2 pg/ml. Intraassay precision for IL-6 was established at 4.45% CV. The sensitivity of the ET-1 assay, defined as the concentration of ET-1 measured at 2 SD from the mean of 24 zeros along the standard curve, was determined to be 0.41 pg/ml and intraassay precision was 8.8% CV.

All patients received methotrexate once weekly in an average dose of 9.3 ± 0.53 mg/week (range 7.5–25 mg/wk) and folic acid 5 mg/day 6 days a week. All patients also received steroids, with an average dose of 5.3 mg prednisone per day. The dose of methotrexate and prednisolone were kept stable throughout the study.

Statistical analysis. Descriptive variables are presented as mean ± SD for data with normal distribution or as median with lower and upper quartile when data distribution was heavily skewed (non-normal). Plasma

NT-proBNP, IL-6, and ET-1 levels were non-normally distributed, thus decimal logarithmic transformations were used to normalize distribution prior to statistical analyses. Variable distribution was evaluated by the Shapiro-Wilk test. Homogeneity of variances was assessed by the Levene test. ANOVA for repeated measurements were carried out to assess time influence on changes of measures. Influence of changes of inflammatory variables for improvement of heart function at the end of study was assessed using general multivariable regression models. Correlations were measured with Spearman rank correlation coefficients. Calculations were performed using StatSoft (StatSoft Inc., 2008), version 8.0. All p values were 2-tailed and $p < 0.05$ was established as statistically significant.

RESULTS

We enrolled 23 female patients aged 51.3 ± 1.55 years with established diagnosis of RA who had failed previous treatment with classic DMARD. Demographic data, disease activity, blood pressure, and lipid measures are summarized in Table 1. Patients were characterized by normal heart function (ejection fraction > 50%) and routine physical examinations for cardiovascular disorders were unremarkable. Patients had normal kidney function (mean creatinine 69.4 ± 2.0 μmol/l), were normolipidemic (mean total cholesterol 4.9 ± 0.22 mmol/l; triglycerides 1.2 ± 0.16 mmol/l) and normotensive, and were characterized by normal BMI. We observed significant reduction of disease activity at the end of the study.

Twenty-one patients attained a clinical response; 8 (35%) had a good clinical response and 13 (57%) a mild or moderate response.

The echocardiographic examinations showed no valvular insufficiency, pulmonary hypertension, or segmental or global contractility disturbances. The median ejection fraction at the beginning of the study was 58.5% (25th and 75th percentiles 55.0% and 64.0%, respectively). Treatment with infliximab resulted in an increase of ejection fraction at 12 months (median value 63.0%; 25th and 75th percentiles 60.0% and 65.0%; $p < 0.05$). We also observed a statistically significant increase in the diameter of the right ventricle and reduction in left ventricular mass.

Treatment with infliximab resulted in marked reduction of IL-6 level ($p < 0.001$). The effect was observed after 4 months and the level of IL-6 remained suppressed until the end of the study. The level of NT-proBNP was significantly reduced at Month 4 ($p < 0.01$) and decreased further during the study. However, comparing the values at Month 4 and at 1 year, although levels were numerically lower, they were statistically nonsignificant. We observed a significant reduction of endothelin level at Month 4, which was further reduced at the end of the study. Differences between ET-1 levels before the study and at Month 4 were statistically significant ($p < 0.01$). The same result was observed between Month 4 and the end of the study ($p < 0.01$; Figure 1). All echocardiographic measures and laboratory results are presented in Table 2. Of all variables evaluated, the changes in NT-proBNP (before and after 12 months of treatment) correlated significantly with CRP ($r = 0.62$, $p < 0.05$) and inversely with IL-6 ($r = –0.62$, $p < 0.05$). We failed to show that changes of inflammatory variables, cytokines, and BNP predicted improvement of heart function, from observations in both treatment responders and nonresponders. We observed no statistically significant correlations between changes in NT-proBNP levels and E/A ratio, ejection fraction, and left ventricular mass. Moreover, the changes in IL-6, ET-1, and BNP levels did not differ between responders and nonresponders. Changes in ejection fraction and left ventricular mass did not differ significantly between the group with good clinical response and the group with moderate response [for ejection fraction, 1.12 ± 5.30 good response group vs 4.3 ± 6.2 moderate response group ($p = 0.24$); for left ventricular mass, –9.2 ± 24.3 good response group vs 12.6 ± 18.4 moderate response group ($p = 0.73$)]. Unfortunately, the very small number of patients with no clinical response (only 2 patients) did not allow detailed statistical analyses in this subgroup. In a multivariable regression model we observed no associations between changes in ejection fraction and reductions in each biomarker or changes in markers of inflammation (ESR, CRP, and DAS28). As for reductions of cardiac biomarkers, multivariable regression showed no associations between the reductions observed and changes in markers of inflammation.

Table 1. Clinical characteristics of patients at baseline and after 12 months of treatment. Data are mean ± SD.

Characteristic	Baseline	12 Months	p
Age, yrs	51.3 ± 1.55		
Body mass index, kg/m^2	26.0 ± 1.23	26.0 ± 1.29	0.57
Systolic blood pressure, mm Hg	125 ± 3.39	127.7 ± 4.43	0.22
Diastolic blood pressure, mm Hg	75.3 ± 3.12	79.0 ± 2.11	0.19
Heart rate, beats per min	76 ± 14	72 ± 12	0.46
Creatinine, μmol/l	69.4 ± 2.0	66.8 ± 2.22	0.86
Glucose, mmol/l	4.8 ± 0.22	4.9 ± 0.12	0.74
Total cholesterol, mmol/l	4.9 ± 0.22	5.1 ± 0.17	0.78
Triglyceride, mmol/l	1.2 ± 0.16	1.1 ± 0.08	0.45
DAS28	6.2 ± 0.28	3.2 ± 0.33	< 0.001

DAS28: 28-joint Disease Activity Score.

DISCUSSION

The results from our study showed no harmful effect of infliximab on cardiac function in patients with RA during 12 months' observation. Surprisingly, TNF-α neutralization increased the left ejection fraction as measured by conventional echocardiography, and this was observed in all patient groups. It also caused a reduction in levels of NT-proBNP, IL-6, and ET-1. As expected, treatment with infliximab resulted in better control of disease, and disease activity was reduced significantly.

Recently, reports have suggested that NT-proBNP is also a good marker of RA activity, with an association between NT-proBNP and CRP in patients with RA[24,25]. Peters, *et al*

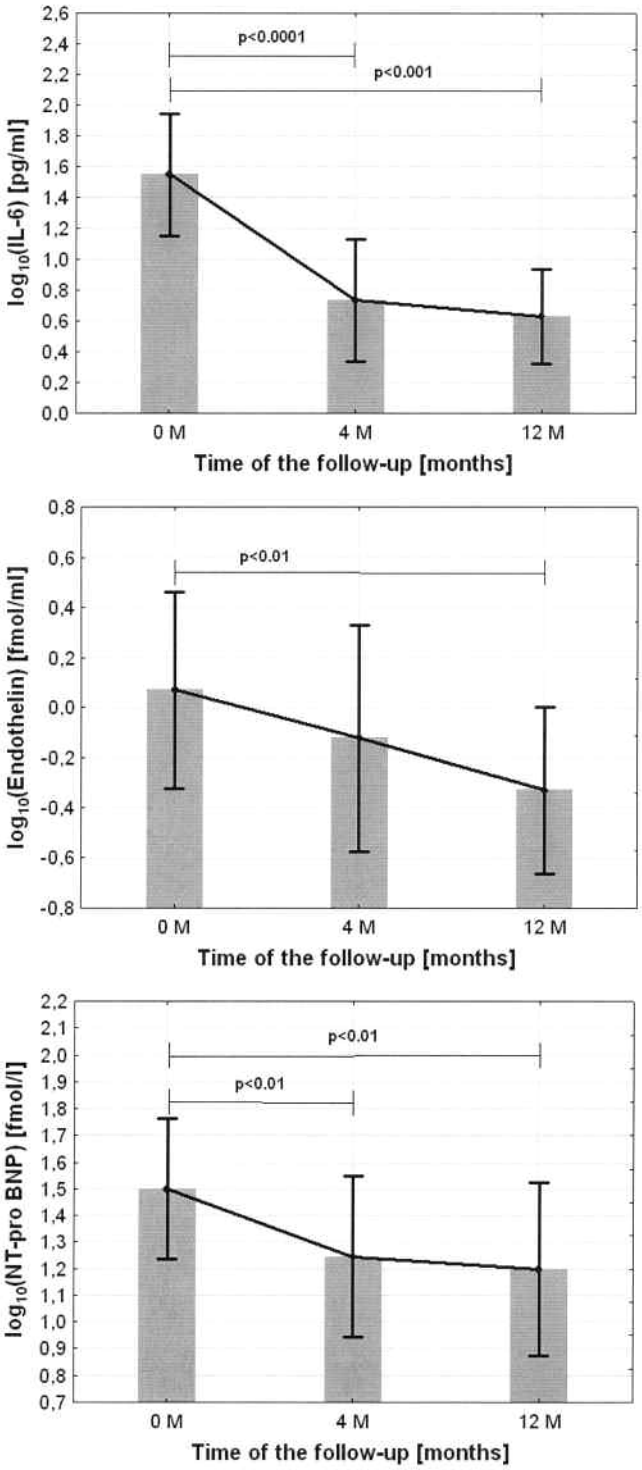

Figure 1. Changes of heart biomarkers in patients with rheumatoid arthritis treated with infliximab. IL-6: interleukin 6; NT-proBNP: amino-terminal fragment of the pro-brain natriuretic peptide.

demonstrated reduction of NT-proBNP levels in patients with RA after 4 months of treatment with adalimumab[26]. This is in agreement with our results, where marked suppression of NT-proBNP, ET-1, and IL-6, together with reduction of disease activity, was observed at Week 16. Moreover, reduction of markers remained significant until the termination of the study at Week 52. This provides additional information that prolonged suppression of TNF-α does not exert a toxic effect on the cardiovascular system.

The role of NT-proBNP as a sensitive marker of heart failure is well recognized. Less is known about ET-1 and IL-6 in this regard. However, Jug, *et al* recently demonstrated that IL-6 is a strong predictor of outcome in patients with stable chronic heart failure and is associated with an increased risk of heart failure-related death or hospitalizations, even allowing for known prognostic factors such as NT-proBNP, LVEF, and New York Heart Association class[27].

ET-1 is a polypeptide released from activated endothelium. It has been associated with the CHF syndromes and patients with chronic CHF often present with elevated levels of this polypeptide. ET-1 is not directly involved in the inflammatory response in RA, although laboratory data suggest that ET-1 stimulates IL-6 production in osteoblast cells[28]. It is likely that this is a local phenomenon and probably does not contribute to systemic changes in IL-6 concentration in serum.

Assessment of NT-proBNP alone is not, unfortunately, free of bias. As it is established that NT-proBNP is a marker of both systemic inflammation and heart function, it might be difficult to differentiate what mechanism is responsible for NT-proBNP changes observed in patients with RA treated with an anti-TNF-α agent. To overcome this issue we used 4 independent methods — 3 laboratory heart markers (NT-proBNP, ET-1, and IL-6) and echocardiographic examination — which give precise insight into heart function. We observed significant reduction of all laboratory markers associated with increment of systolic function.

Patients with RA had increased left ventricular mass prior to the infliximab treatment. To date only a few studies have addressed left ventricular mass in patients with RA and results are conflicting. Our data support the results of Rudominer, *et al*, who reported incremental of left ventricular mass in patients with RA and good systolic heart function[29]. Surprisingly, we observed marked reduction of left ventricular mass as the result of infliximab treatment. To our knowledge this is the first report indicating the influence of TNF-α blockade on left ventricular mass in patients with RA over time. We may speculate that left ventricular mass may be increased in patients with RA as a result of inflammation-induced endothelium dysfunction, a common finding in patients with RA[30,31]. In a general population the strong association between left ventricular mass and impaired endothelial function has been observed[32]. TNF–α antagonists restore endothelial function in patients with RA, which in turn reduces left ventricular mass, as observed in our study[33,34].

We also observed a surprising inverse correlation

Table 2. Echocardiographic measures and biochemical and cytokine data in study patients.

	Before Treatment	After 4 Months	After 12 Months	p
ESR, mm/h*	39.7 ± 6.4	23.4 ± 3.6	25.2 ± 4.6	< 0.001
CRP, mg/l*	34.3 ± 7.3	18.2 ± 7.7	15.0 ± 4.8	< 0.001
Platelets, g/l*	350.1 ± 22.8	266.9 ± 13.8	236.8 ± 14.1	< 0.05
Right ventricle, mm*	20.8 ± 2.1		23.0 ± 2.8	< 0.001
LVEF, %†	55.0/58.5/64.0		60.0/63.0/65.0	< 0.05
Left ventricle mass, g*	193.7 ± 44.0		182.3 ± 35.4	< 0.05
V_e*	0.88 ± 0.17		0.90 ± 0.32	0.21
V_a*	0.78 ± 0.19		0.83 ± 0.28	0.82
IL-6, pg/ml†	7.22 (58.46/104.85)	1.18 (3.62/29.40)	1.18 (3.46/16.05)	< 0.001
Endothelin, fmol/ml†	0.29 (1.26/4.34)	0.33 (0.56/48.90)	0.24 (0.43/3.28)	< 0.01
NT-proBNP, fmol/ml†	23.04 (43.06/62.72)	16.74 (26.73/36.74)	12.8 (14.78/30.22)	< 0.01

* Mean ± SD. † Median (upper/lower quartiles). ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LVEF: left ventricular ejection fraction; IL-6: interleukin 6; NT-proBNP: amino-terminal fragment of the bone natriuretic peptide.

between IL-6 and BNP. The most probable reason for this unusual finding is statistical bias due to the small group of patients. However, there are no data in the literature regarding the relationship between BNP and IL-6 in patients treated with anti-TNF-α, so this relationship should be addressed in a larger cohort of patients.

TNF-α is a pluripotent inflammatory cytokine that is a key agent in the inflammatory cascade in RA, and is also deeply involved in the pathogenesis of CHF. TNF-α levels as well as other inflammatory cytokines and neurohormones play significant roles in the development and progression of CHF. Taking into account the action of TNF–α upon the heart, we are not surprised that reduction of TNF-α effected by anti-TNF-α agents in patients with RA contributes to increased LVEF. That is in agreement with the study by Wolfe and Michaud, who described protective effects of anti-TNF–α treatment on development of heart failure in patients with RA[35]. Recently, Listing and colleagues confirmed that treatment with anti-TNF-α is relatively safe and the ratio of cardiac side effects in an RA group treated with anti-TNF-α was similar to that of the group that was anti-TNF-α-free[36]. This trend was supported in our study, where improvement of heart function as the result of anti-TNF-α treatment was observed. Moreover, the increment of LVEF, although numerically low (5%), was statistically significant, and marked a positive trend toward improvement of the heart function. It also goes together with reduction of 3 independent markers of inflammation and heart function: ET-1, NT-proBNP, and IL-6. Reduction of the IL-6 and NT-proBNP, however, should be interpreted with caution, since reduction of cytokine levels is caused at least partly by suppression of TNF-α. In our study we found no changes in levels of markers between responders and nonresponders; however, only 2 patients were nonresponders, and this did not allow detailed statistical analysis.

What is perhaps more important is that values for ET-1, the level of which is currently not linked to RA activity, but which reflects endothelial damage, were also reduced significantly, suggesting direct improvement of endothelium and heart functions[37]. As it has been shown that ET-1 levels are reduced as the result of anti-TNF-α treatment, we may speculate that increases of LVEF at the end of our study might be at least partly mediated by restoration of endothelium function, with subsequent reduction of ET-1, a marker of its dysfunction[38]. On the other hand, we were unable to show that changes of inflammatory measures and heart biomarkers at the end of our study were associated with improvement of heart function. The reason for this was the relatively small group of patients observed and weak statistical power. This question should be addressed in future studies.

Patients with RA, but without heart failure, benefit from anti-TNF-α treatment with respect to heart function. Our results also demonstrate the usefulness of 3 independent markers of heart failure (IL-6, ET-1, and NT-proBNP) in the assessment of heart function in patients with RA undergoing anti-TNF-α treatment.

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