Clin Rheumatol (2013) 32:61–66
DOI 10.1007/s10067-012-2091-4

ORIGINAL ARTICLE

Acute and long-term effect of infliximab on humoral and echocardiographic parameters in patients with chronic inflammatory diseases

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Received: 5 February 2012 / Revised: 31 August 2012 / Accepted: 11 September 2012 / Published online: 26 September 2012

Abstract Tumor necrosis factor alpha (TNF-alpha) plays an important role in the pathogenesis of chronic inflammatory diseases, i.e., rheumatoid arthritis (RA), ankylosing spondylitis (AS), Crohn's disease (CD), and ulcerative colitis (UC). Anti-TNF-alpha strategies are successfully used in their treatment. However, their effect on heart function is still uncertain. The objectives of the study were to examine the acute and long-term effect of infliximab on the heart morphology and function in patients with chronic inflammatory disorders. Thirty-one patients (21 men and 10 women) were included. Ten percent of them were diagnosed with RA, 22.5 % with AS, 22.5 % with CD, and 45 % with UC, respectively. N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) was measured before and immediately after infliximab administration at the beginning of the study and in the sixth and 12th months. Echocardiography was performed at baseline and in the sixth and 12th months. There was a significant increase in NT-proBNP after the first infliximab infusion (88.40±14.09 vs. 95.24±14.28 pg/ml, p=0.0046) and similar response was detected after each infusion in the sixth and 12th months. Plasma NT-proBNP slightly but not significantly decreased (88.40±14.09 vs. 81.74±23.14 pg/ml, p=0.583, and 88.40±14.09 vs. 56.83±17.77 pg/ml, p=0.0576, in the sixth and 12th months, respectively). There were no significant changes in echocardiographic structural and functional parameters of the left ventricle during follow-up. Plasma NT-proBNP mildly but significantly increases immediately after infliximab infusion. However, long-term infliximab administration does not deteriorate both cardiac morphology and function.

Keywords Chronic inflammatory diseases · Echocardiography · Infliximab · NT-proBNP

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Introduction

Chronic inflammatory diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis and psoriatic arthritis (PA), Crohn's disease (CD), and ulcerative colitis (UC) are associated with increased cardiovascular morbidity and mortality which was clearly documented in RA studies and one study of CD [1–4]. Among various pathogenic mechanisms, chronic inflammation is assumed to play an important role in the increased risk of premature atherosclerosis, coronary heart disease, and heart failure (HF). Inflammatory cytokines including tumor necrosis factor alpha (TNF-alpha) participate in this cardiovascular involvement and contribute to the progression of heart failure [5]. Anti-TNF-alpha strategies have been successfully used for at least 10 years in the treatment of chronic inflammatory rheumatic and intestinal disorders to prevent joints and bowel damage and to reduce chronic inflammation [6–9]. However, clinical trials of TNF-alpha blockade in patients with heart failure have demonstrated little benefit or even harm and had to be halted prematurely [10–12].

Therefore, it may be assumed that treatment of chronic inflammatory disorders with TNF-alpha blocking agents

may lead to worsening of cardiac function, which can be altered subclinically by preexisting inflammatory disease. However, clinical data on the effect of TNF-alpha blockers on heart morphology and function are poor in the current literature. Despite some papers reporting cases of cardiac arrhythmias or worsening of myocardial function or other cardiac events after administration of biologics, randomized control trials or other prospective studies are missing. Some studies showed that HF was not significantly more common among patients with RA or CD exposed to TNF-alpha antagonists [13–15]. Nevertheless, these studies examined predominantly the long-term effect of biologics on cardiac function, and there is no prospective trial assessing the acute effect of TNF-alpha blockers on the heart function. Moreover, methods of evaluation of cardiac function are different in the studies mentioned above. Majority of them used only clinical data and echocardiography [13–17]. Only one study used measurement of plasma N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) as a marker of cardiac function showing that TNF-alpha blockers decreased NT-proBNP levels in RA patients by about 18 % [17].

Based on these data, it is still not known whether anti-TNF therapy, which is being used increasingly in the treatment of various chronic inflammatory diseases, affects the risk of HF in these patients. Objectives of this study were to assess the acute and long-term effect of infliximab on the heart morphology and function by using echocardiography and plasma NT-proBNP evaluation in patients with chronic inflammatory disorders.

Methods

Patients

The study participants were residents of East Slovakia region scheduled to treatment with infliximab due to chronic inflammatory rheumatic and intestinal diseases from January 2007 to December 2009. The cohort consisted of 31 patients (21 men and ten women) with mean age of 37.5±9.7 years (median 39 years, range 19–53 years). Mean duration of the disease was 7.1±6.2 years (median 5 years, range 1–23 years). Three (10 %) patients were diagnosed with RA, seven (22.5 %) with AS, seven (22.5 %) with CD, and 14 (45 %) with UC. The indication for treatment with infliximab was the failure of the previous pharmacologic treatment. The treatment, except for lowering of corticosteroid dose in some patients, was not changed. None of these patients was treated with TNF-alpha antagonists before the beginning of this study.

Exclusion criteria were as follows: age over 65 years, severe renal insuficiency, history of cardiac disease especially coronary heart disease, cardiomyopathy, valvular disorders, arrhythmias and heart failure. The study protocol was approved by the Ethics Committee of University Hospital of Louis Pasteur, Košice, Slovakia. All patients provided written informed consent prior to participation in accordance with the Declaration of Helsinki.

Study design

All patients underwent the echocardiographic evaluation before the beginning of the treatment with infliximab. Infliximab was administered in accordance with general recommended schemes. The dose for RA was 3 mg/kg and for other diseases, 5 mg/kg. The carrier solution was 250 ml of 0.9 % saline solution. Immediatelly before and after administration of infliximab (time gap 2–3 h), the blood sample was drawn from the antecubital vein while in the lying position. It was immediatelly transferred to the laboratory for analysis of NT-proBNP, plasma renin activity (PRA), and plasma aldosterone (PA). Plasma samples for TNF-alpha evaluation were after blood centrifugation stored by −70 °C till analysis. The blood samples were taken repeatedly during the sixth and 12th months of infliximab treatment, and echocardiographic evaluation was performed in the same time. Body mass index (BMI) was calculated and recorded during the follow-up period.

Echocardiography

Transthoracic echocardiography was performed with Esaote Technos MPX machine using 2.5–3.5 MHz transducer by registered cardiac sonographer. Two-dimensional and Doppler echocardiograms were used to measure the following parameters: interventricular septum wall thickness (IVST), posterior left ventricular (LV) wall thickness (PWT), LV end-diastolic diameter index (LVEDD-i), LV ejection fraction calculated by Simpson's rule, and LV mass index (LVM-i). Indexes (LVEDD-i and LVM-i) were calculated by adjustment for body surface area. Aditionally, deceleration time (DT), peak velocity of filling in early diastole (E), and in atrial systole (A) and their ratio (E/A) were evaluated as the expression of the diastolic function.

Laboratory investigations

NT-proBNP was examined by the electrochemilluminiscent immunoassay using Elecsys analyzer kit from Roche Germany on. PRA and PA were evaluated radioimmunoanalytically using kits from Immunotech France. TNF-alpha was measured by enzyme-linked immunosorbent assay using kits from Thermo Scientific USA.

Statistical analysis

Values are expressed as means ± standard error of mean (means ± SEM). Differences between measured humoral

and echocardiographic parameters before and after infliximab administration were analyzed using paired *t* test. Analysis of variance for repeated measurements was used to assess the influence of infliximab after 6 and 12 months. Linear regression analysis with determination of Pearson's correlation coefficients (*r*) was used to detect relationship between variables. A level of $p<0.05$ was considered to be statistically significant.

Results

Acute effect of infliximab on humoral markers

Mean values of measured humoral parameters and TNF-alpha before and after first infliximab administration are shown in the Table 1. There was a significant increase in NT-proBNP levels in patients after first infliximab infusion. Simultaneously, a significant decrease in PRA and PA was detected. There was no significant change in TNF-alpha levels after infliximab infusion.

A significant increase in NT-proBNP levels immediately after infliximab administration in the sixth and 12th months of treatment was detected (81.74±23.14 vs. 84.86±20.45 pg/ml, $p=0.012$ after 6 months and 56.83±17.77 vs. 60.48±17.80 pg/ml, $p=0.0344$ after 12 months, as shown in Fig. 1).

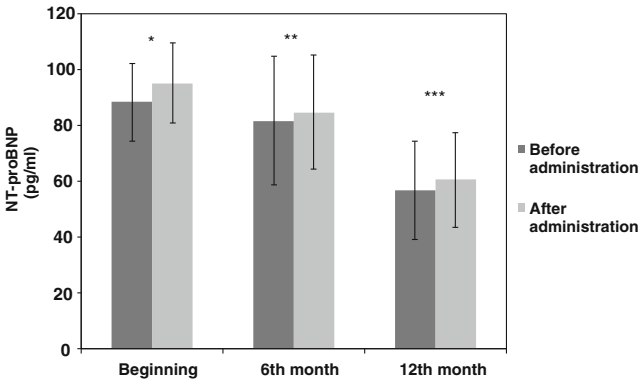

Fig. 1 Mean values of NT-proBNP before and after acute infliximab administration at the beginning (*single asterisk* $p=0.0046$), after 6 months (*double asterisks* $p=0.012$), and 12 months (*triple asterisks* $p=0.0344$) of treatment

Long-term effect of infliximab on humoral and echocardiographic parameters

Mean values of BMI and humoral parameters at the beginning and in the sixth and 12th months of infliximab administration are documented in the Table 2. As expected, there was a significant decrease in serum TNF-alpha in the sixth as well as in the 12th month of treatment. Plasma NT-proBNP decreased after 6 and 12 months of infliximab treatment; however, the changes did not reach the statistical significance ($p=0.4219$). There were no significant changes in BMI, PRA, and PA after long-term infliximab administration (Table 2).

Mean values of measured echocardiographic parameters of the left ventricle structure and function after 6 and 12 months of treatment are shown in the Table 3. There were no significant changes in structural and functional parameters of the left ventricle, i.e., EF, LVEDD-i, IVST, PWT, LVM-i, E/A, and DT after infliximab treatment. Inflammatory activity expressed as TNF-alpha levels was not in correlation with humoral and echocardiographic parameters.

Table 1 Mean values of NT-proBNP, PRA, PA, and TNF-alpha before and after first infliximab administration

Parameter	Before infliximab	After infliximab	Significance (*p*)
NT-proBNP (pg/ml)	88.40±14.09	95.24±14.28	0.0046
PRA (ng/ml/h)	1.32±0.38	0.59±0.12	0.0104
PA (pg/ml)	54.28±10.83	36.42±4.43	0.0241
TNF-alpha (pg/ml)	147.23±28.64	116.03±20.57	0.1166

NT-proBNP N-terminal fragment of pro-brain natriuretic peptide, *PRA* plasma renin activity, *PA* plasma aldosterone, *TNF-alpha* tumor necrosis factor alpha

Discussion

To the best our knowledge, this is the first study demonstrating both acute and chronic effect of TNF-alpha antagonist infliximab on the heart morphology and function in patients with chronic inflammatory disorders, namely RA, AS, CD, and UC. Moreover, this study is the first one to assess the cardiac function after infliximab therapy in relation to humoral and echocardiographic parameters.

The current prospective trial presents two interesting findings. The first one is an acute increase in NT-proBNP after each administration of infliximab independently of duration of the treatment. On the other hand, neither NT-proBNP levels nor echocardiographic parameters have been changed after long-term treatment, although there was a tendency for NT-proBNP values to lower after 12 months.

Evidence shows that chronic inflammatory disorders especially RA, AS, and CD are associated with an increased risk of cardiovascular morbidity and mortality [18–20]. Some studies found that aberrant systemic immune responsiveness is associated with advanced myocardial dysfunction in patients [21–24]. In agreement with these authors,

Table 2 Mean values of BMI and humoral parameters at the beginning and after 6 and 12 months of infliximab treatment

Parameter	Beginning	6th month	12th month	Significance (p)
BMI (kg/m^2)	24.44±0.62	24.57±0.63	25.13±0.69	0.7344
NT-proBNP (pg/ml)	88.40±14.09	81.74±23.14	56.83±17.77	0.4219
PRA (ng/ml/h)	1.32±0.38	1.68±0.66	1.20±0.24	0.7701
PA (pg/ml)	54.28±10.83	62.69±9.29	64.79±13.09	0.7686
TNF-alpha (pg/ml)	147.23±28.64	73.31±15.19	52.12±12.04	0.0066

BMI body mass index, *NT-proBNP* N-terminal fragment of pro-brain natriuretic peptide, *PRA* plasma renin activity, *PA* plasma aldosterone, *TNF-alpha* tumor necrosis factor alpha

NT-proBNP is considered to be a good prognostic marker in RA patients. Reports on the significance of NT-proBNP in the assessment of cardiac dysfunction in patients with AS, CD, or UC are poor, although some authors demonstrated higher frequency of diastolic dysfunction in AS and subclinical cardiac impairment in CD patients [19, 20].

The effect of TNF-alpha antagonists on cardiac function has been studied in few trials although NT-proBNP was measured in only one of them. In this study, a significant decrease in NT-proBNP levels after 16 weeks of adalimumab administration was demonstrated (p=0.004) [17]. However, there is no published study evaluating the acute effect of TNF-alpha antagonists on plasma NT-proBNP levels. Our results showed slight but significant increase of NT-proBNP levels immediately after infliximab administration. This increase was detectable not only after the first dose but also after infusion of infliximab in the sixth and 12th months. These results could indicate an acute deleterious effect of infliximab on the heart. The cytotoxic effect of infliximab is considered to be a possible explanation of this finding, as being documented previously [23, 24]. On the other hand, extra-infliximab effects should be considered, because an intravenous administration of saline infusion (a carrier solution for infliximab) as well as supine position of the patient during drug administration may lead to an increased blood flow to the heart and slight volume overload, which is a potent stimulus for BNP release from the heart. This fact is supported by significant decrease in PRA and PA levels as a response to supine position and volume increase. However, supine position or saline administration in the dose of 250 ml invoke only low or no response of NT-proBNP, which was demonstrated by some authors [25, 26]. Nevertheless, our findings suggest a potential harmful acute effect of infliximab administration on the heart which could be supported by some case reports of acute HF or arrythmias in patients receiving anti-TNF-alpha agents [27–29].

In this study, we did not demonstrate a significant decrease in NT-proBNP levels in the sixth and 12th months of infliximab treatment, although there was a clear tendency that levels of this hormone lower after treatment. This finding is partly in agreement with the previous study of Peters et al. documenting a mild but significant decrease in circulating NT-proBNP after adalimumab treatment [17]. Based on this study and our results, TNF-alpha blockers do not seem to induce deterioration of cardiac function and a possible cardiovascular long-term risk.

We also did not demonstrate significant changes in echocardiographic parameters of cardiac morphology and function in the sixth and 12th months of infliximab treatment, supporting the previous findings of mild decrease in NT-proBNP. One recent study found a reduction of systolic function after infliximab infusion in patiens without cardiac

Table 3 Mean values of echocardiographic parameters of the left ventricle structure and function at the beginning and after 6 and 12 months

Parameter	Beginning	6th month	12th month	Significance (p value)
EF (%)	65.52±1.33	66.11±1.82	66.00±1.48	0.9548
LVEDD-i (cm/m^2)	2.69±0.04	2.73±0.07	2.71±0.06	0.8822
IVST (cm/m^2)	0.98±0.03	1.00±0.03	0.98±0.03	0.8475
PWT (cm/m^2)	0.98±0.03	1.00±0.03	0.99±0.03	0.8981
LVM-i (g/m^2)	114.00±5.42	119.26±6.33	116.58±7.59	0.8439
E/A	1.42±0.09	1.48±0.10	1.44±0.12	0.9005
DT (ms)	181.05±12.11	169.47±12.76	179.53±9.66	0.7620

EF ejection fraction, *LVEDD-i* Left ventricular enddiastolic diameter index, *IVST* interventricular septum wall thickness, *PWT* posterior left ventricular wall thickness, *LVM-i* left ventricular mass index, *E/A* ratio of peak velocity of filling in early diastole (E) and in atrial systole (A), *DT* deceleration time

pathologies [30]. On the other hand, some other studies did not confirm a significantly higher occurrence of HF in patients with RA and CD exposed to TNF-alpha antagonists compared to those unexposed [14, 15]. Moreover, others showed that HF was significantly less common in anti-TNF-treated patients than in those without treatment. In the absence of preexisting cardiovascular disease, the risk of HF was low and was not related to anti-TNF therapy [13]. In the retrospective study of Cole et al., patients receiving TNF-alpha blockers appeared to have a trend towards a lower mortality as compared to the control groups [16]. Similar results were demonstrated by others, and this fact was supported also by a recently published metaanalysis in Cochrane Database systematic review. The rate of serious adverse events including congestive HF was not significantly different between biologics and other treatment options [15, 31]. All these data are in accordance with our results. However, many of these studies did not use the measurement of both humoral factors and echocardiographic parameters for assessment of cardiac function.

The main limitation of this study is relatively small: heterogenous cohort of patients with possible different overall effects of infliximab in various inflammatory diseases due to different cytokine networks involved in heart impairment. The second limitation is the fact that the study is not blinded and controlled, and we used some methods of limited value, i.e., E/A ratio to assess diastolic dysfunction. However, this is the first pilot study on the acute and long-term effects of infliximab, and some recently published studies used similar ultrasound parameters for the evaluation of heart function in patients with systemic disorders.

We can conclude that because of slight acute increase in NT-proBNP as well as due to some cases reported on HF, a careful observation on the patient during infliximab administration is necessary. On the other hand, long-term treatment with infliximab does not deteriorate the cardiac morphology and function, and the development of HF may not be a real adverse drug event. Further prospective studies on larger cohorts of patients are warranted.

Acknowledgments The study was funded by the Ministry of Health, Slovak Republic (2007/4-UPJS-01).

Disclosures None

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