Long-term evaluation of cardiac function in juvenile idiopathic arthritis under anti-TNF therapy

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Abstract

Objective

This paper aims to perform global assessment of long-term cardiac function in juvenile idiopathic arthritis (JIA) patients under TNF blockage therapy.

Methods

Twenty-five polyarticular-course JIA patients pre-anti-TNF and 22 healthy controls underwent conventional/tissue Doppler echocardiography and cardiac biomarkers measurements (N-terminal pro-brain natriuretic peptide [NT-pro-BNP] and troponin T) at baseline (BL). Twenty-one JIA patients completed six evaluations during two consecutive years. Clinical/laboratorial evaluations were assessed before and during TNF blockage therapy.

Results

JIA patients and controls were comparable regarding current age (p=0.898) and female gender (p=0.38). At BL isovolumetric relaxation time of left ventricle (p=0.03), ventricular septum (VS), E' wave (p=0.014) and VS S wave velocity (p=0.03) were significantly reduced in JIA patients compared to controls. Frequencies of elevated NT-pro-BNP and troponin T levels were similar in JIA and controls (p=0.297 and p=0.756) and levels remained within normal range throughout the study, except for one patient with mild troponin T elevation. During TNF blockage therapy, none of the 21 participants had heart failure, ejection fraction or other parameters alterations in conventional and tissue Doppler. Only one had mild pulmonary hypertension. Further analysis revealed that JIA patients with elevated levels of NT-pro-BNP at BL had significantly more active joints (p=0.025) and higher ESR (p=0.034).

Conclusion

Long-term TNF blockage safety was demonstrated in JIA patients in spite of the observed subclinical diastolic involvement. Elevated cardiac biomarker in these patients was associated with inflammatory parameters reinforcing the need for a careful interpretation of this finding in patients with active disease.

Key words

juvenile idiopathic arthritis, anti-TNF, cardiac function, safety, NT- pro-BNP, troponin T

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Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases that include chronic arthritis of unknown origin, which begins before 16 years of age (1-3). Extra-articular manifestations were described in 30% and may involve the cardiovascular system (2-5).

Cardiac involvement in JIA occurs in up to 30%, especially in systemic and polyarticular subtypes (5, 7). Pericarditis, the most common cardiac manifestation, was reported in up to 30% and it is generally asymptomatic. Diastolic dysfunction has been reported to be frequent in these patients (6-9). Myocarditis with congestive heart failure and endocarditis were described in 8% of this population (5).

In rheumatoid arthritis adult patients the use of biologic agents was associated with heart failure in retrospective studies (10). On the other hand, two large prospective evaluations showed an overall lower risk of cardiac dysfunction in those patients (11, 12). TNF blockage is also indicated in refractory JIA with polyarticular course (13-16), however there are no data regarding prospective echocardiography and cardiac biomarkers evaluations in JIA patients under these biologic therapies.

Therefore, the objective of this study was to perform a global assessment of the long-term cardiac function in JIA patients under TNF blockage therapy.

Patients and methods

During the enrolment period, from January 2008 to December 2012, 25 JIA patients were eligible for a two years prospective study. All of them fulfilled the International League Against Rheumatism criteria and were followed at the Paediatric Rheumatology Unit of Children's Institute of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. All of them were refractory to non-biologic disease-modifying anti-rheumatic drugs (DMARDs) and eligible for anti-TNF therapy. Twenty-two healthy subjects were included in the control group. None of the patients or controls had structural cardiac disease, symptoms of heart failure or arrhythmias.

All participants were evaluated at baseline for demographic data, echocardiography and cardiac biomarkers. Among the 25 JIA patients evaluated at baseline, one patient was excluded 4 months after the beginning of TNF blockage treatment for macrophage activation syndrome (17) and 3 others for poor adherence. Thereafter, 21 JIA patients were evaluated prospectively for cardiac function, clinical and laboratorial assessments, health related quality of life and treatment at baseline, and at 3, 6, 12, 18 and 24 months after anti-TNF treatment. None of them had symptoms of heart failure or arrhythmia.

This study was approved by the Local Ethics Committee of our University Hospital and an informed consent was obtained from all participants or their legal guardians.

Cardiac assessment – Echocardiography

Echocardiography was performed using a Toshiba Aplio 500 machine (Toshiba America Medical Systems, Tustin, CA, USA) with a 2.5-MHz or 7-MHz electronic transducer according to the subject's weight. A comprehensive echocardiographic study was performed, including bidimensional, M-mode, conventional and tissue Doppler imaging. All the subjects were evaluated in a supine position by the same examiner blinded for the clinical presentation.

The pattern of ventricular filling was assessed by the maximum velocity of blood flow through atrioventricular valves during early diastole (E wave), deceleration time of E wave and maximum velocity of blood flow through atrioventricular valves during atrial contraction (A wave). The two other Doppler parameters used were: Deceleration Time (DT), defined as the interval between the E wave peak and baseline; Isovolumetric Relaxation Time (IVRT), the time interval between closing of the aortic valve and the opening of the mitral valve.

E/A velocity ratio greater than 1.32 is indicative of normal filling pattern. Mild diastolic dysfunction is associated with IVRT prolongation, while IVRT shortening suggests severe dysfunction with reduced ventricular compliance (18, 19). Myocardial velocities were obtained

by tissue Doppler at the septum, right and left ventricles' free walls. E' and A' represent myocardial velocities during early and late diastole and S wave during systole. E' wave lower than 10 cm/s in the left ventricle free wall and 8 cm/s in the septum are related to mild diastolic dysfunction (20, 21).
Normal values of echocardiographic parameters according to age and weight were based on the American Society of Echocardiography Recommendations and Guidelines (20).

– Cardiac biomarkers
Cardiac biomarkers included dosage of N-terminal pro-brain natriuretic peptide (NT-pro-BNP, cut-off ≥125pg/mL for elevated values) and troponin T (cut-off >0.01μg/l for myocardial damage) by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Plasma samples were stored at -80°C until analysis. A blinded technician analysed all the samples in a single run on the same plate to minimise inter-assay variations. The coefficient of variation on batch intra-assay analyses was 1.4%.

Clinical and laboratorial assessments, disease scores and therapy of JIA patients
Clinical assessments of JIA patients included: number of active joints (swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness), number of limited joints, patient and physician global assessment of arthritis activity measured in cm on a 10 cm horizontal visual analogue scale (VAS), morning stiffness duration and validated Brazilian version of Childhood Health Assessment Questionnaire (CHAQ) (22). Laboratorial assessment included erythrocyte sedimentation rate (ESR) (Westergreen method) and C-reactive protein (CRP) (nephelometry). The Juvenile Arthritis Disease Activity Score with 27-joint reduced count (JADAS-27) (23), defined as the linear sum of the scores of 4 components (physician global assessment of disease activity, measured on a 10-cm VAS where 0 is no activity and 10 is maximum activity; parent/patient global assessment of well-being, measured on a 10-cm VAS where 0 is very well and 10 is very poor; number of active joints; and ESR) (range: 0–57 points), was calculated in all JIA patients. Current treatment with non-steroidal anti-inflammatory drugs (NSAIDs), prednisone, DMARDs (methotrexate and leflunomide), immunosuppressive drugs (cyclosporine) and anti-TNF agents (adalimumab and etanercept) were determined.

Table I. Demographic data, echocardiography parameters and cardiac biomarkers in juvenile idiopathic arthritis (JIA) patients before anti-TNF therapy and healthy controls.

Variables	JIA patients (n=25)	Controls (n=22)	*p*-value
Demographic data			
Female gender, n (%)	14 (56)	9 (40.9)	0.385
Current age, years	10.3 (2.2–17.8)	9.5 (6–17)	0.898
Disease duration, years	2.7 (0.4–9.9)		
Echocardiography parameters			
Conventional Doppler			
E wave, m/s	1 (0.6–1.43)	1.01 (0.77–1.33)	0.974
A wave, m/s	0.55 (0.35–0.7)	0.53 (0.34–0.76)	0.272
DT	176 (129–275)	177.5 (129–222)	0.806
IVRT	76 (56–89)	81.5 (71–96)	0.030
Tissue Doppler			
Left ventricular free wall			
E´ wave, m/s	0.17 (0.14–0.25)	0.18 (0.13–0.28)	0.153
A´ wave, m/s	0.07 (0.05–0.12)	0.07 (0.05–0.1)	0.677
S wave, m/s	0.1 (0.06–0.15)	0.1 (0.07–0.15)	0.482
Ventricular septum			
E´ wave, m/s	0.12 (0.1–0.16)	0.14 (0.12–0.16)	0.014
A´ wave, m/s	0.06 (0.04–0.1)	0.07 (0.04–0.08)	0.79
S wave, m/s	0.08 (0.06–0.11)	0.08 (0.07–0.12)	0.03
Right ventricular free wall			
E´ wave, m/s	0.16 (0.11–0.23)	0.15 (0.12–0.2)	0.579
A´ wave, m/s	0.1 (0.06–0.17)	0.1 (0.07–0.13)	0.983
S wave, m/s	0.14 (0.08–0.17)	0.14 (0.09–0.17)	0.296
Chamber diameter and EF			
LVED, mm	40.9 (26–51.2)	41 (32.2–48)	0.749
LVSD, mm	24.1 (15–33)	24 (20–32)	0.782
RVED, mm	15 (9.1–21.4)	15.6 (13.4–21)	0.258
S, mm	6.3 (3.7–8.1)	6 (5–8)	0.536
PW, mm	6.3 (4–9)	6.2 (4.6–7.8)	0.662
EF, %	70 (60–78)	70.8 (57.7–79)	0.631
Cardiac biomarkers			
Troponin T	0.003 (0.003–0.01)	0.003 (0.003–0.005)	0.756
NT-pro-BNP, pg/mL	73 (7–1107)	42.5 (9–213)	0.156
Elevated Pro-BNP > 125 pg/mL	7 (28)	3 (13.6)	0.297

Data are expressed as n (%) and median (range); DT: decelaration time; IVRT: isovolumetric relaxation time; EF: ejection fraction; LVED: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; RVED: right ventricular diastolic diameter; S: ventricular septum; PW: posterior wall.

Statistical analysis
Categorical variables were compared using Fisher's exact test. Continuous variables were presented as mean±standard deviation or median (range) and compared using a two-sided Student's *t*-test or Mann-Whitney U-test. The prospective analysis of echocardiography parameters was performed by Friedman repeated measures analysis of variance (ANOVA) on ranks, followed by a *post-hoc* analysis to determine where the difference occurred between the groups. Correlations between NT-pro-BNP levels and JIA parameters and echocardiography measurements were analysed by Spearman's rank correlation coefficient. The statistical significance was set at p-value <0.05.

Results

JIA patients at baseline and healthy controls
Demographic data, echocardiographic parameters and cardiac biomarkers in 25 JIA patients before anti-TNF therapy and 22 healthy controls are included in Table I. The median of current age and frequency of female gender were

Table II. Demographic data, disease parameters and treatment in juvenile idiopathic arthritis patients with high and normal N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels at baseline.

	NT-Pro-BNP ≥125pg/mL (n=7)	NT-Pro-BNP <125pg/mL (n=18)	*p*-value
Demographic data			
Female gender, n (%)	2 (28.6)	9 (50)	0.407
Current age, years	7.8 (4.3–17.8)	10.5 (2.2–17.3)	0.785
Age at diagnosis, years	4.2 (3.2–14.1)	6.9 (1.5–13.3)	0.976
Disease duration, years	3.2 (0.4–9.2)	2.5 (0.4–9.9)	0.976
JIA parameters			
Morning stiffness, min	5 (0–60)	2.8 (0–180)	0.92
Number of active joints, n (%)	8 (2–20)	3 (0–26)	0.025
Number of limited joints, n (%)	8 (1–24)	7 (0–31)	0.856
ESR, mm/1st h	55 (25–65)	29 (4–61)	0.034
CRP, mg/L	49.9 (0.8–332.9)	11.1 (0.2–150)	0.102
Patient's VAS, cm	4 (0–10)	2.5 (0–8)	0.607
Physician's VAS, cm	4 (3–7)	3 (0–8)	0.079
JADAS-27	23 (12.7–29.5)	11 (3–30.5)	0.014
CHAQ	0.625 (0–2.375)	0.563 (0–2.125)	0.88
Treatment			
NSAID	7 (100)	17 (94.4)	1.0
Glucocorticoids	2 (28.6)	6 (33.3)	1.0
Methotrexate	6 (85.7)	17 (94.4)	0.49
Leflunomide	2 (28.6)	3 (16.7)	0.597
Cyclosporine	2 (28.6)	5 (27.8)	1.0

Data are expressed as n (%) and median (range); ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analogue scale; JADAS-27: Juvenile Arthritis Disease Activity Score with 27-joint reduced count; CHAQ: Childhood Health Assessment Questionnaire; NSAID: non-steroidal anti-inflammatory drug.

similar in both groups (10.3 *vs*. 9.5, p=0.898; 56% *vs*. 40.9%, p=0.385; respectively) (Table I).

Regarding the echocardiographic parameters at baseline, the median of IVRT by conventional Doppler (76 [56–89] *vs*. 81.5 [71–96] ms, p=0.03), the ventricular septum (VS) E' (0.12 [0.1–0.16] *vs*. 0.14 [0.12–0.16] m/s, p=0.014) and VS S waves by tissue Doppler were significantly lower in JIA patients *vs*. controls (0.08 [0.06–0.11] *vs*. 0.08 [0.07–0.12], p=0.03) (Table I).

The medians of troponin T and NT-pro-BNP cardiac biomarkers were similar in both groups at BL. Likewise, the frequency of elevated NT-pro-BNP levels was comparable in JIA (28%) *vs*. health controls (13.6%), (p=0.297) (Table I).

Further comparison of JIA patients with elevated and normal NT-pro-BNP levels at baseline showed a significantly higher number of active joints (8 *vs*. 3, p=0.025), ESR (55 *vs*. 29 mm/1st hour, p=0.034) and JADAS-27 (23 *vs*. 11, p=0.014) in the former group. No association was observed between elevated and normal NT-pro-BNP levels and demographic data, other JIA parameters and concomitant treatment (Table II). Moreover at baseline, positive correlations were observed between NT-pro-BNP levels and number of active joints (r=+0.59, p=0.002) and between NT-pro-BNP levels and ESR (r=+0.51, p=0.009). With regard to JADAS, at baseline there was a positive correlation solely with NT-pro-BNP levels (r=+0.69, p<0.0001) and not with echocardiography (p>0.05). After 24 months of anti-TNF therapy, no correlation was observed between JADAS and serum biomarkers or echocardiographic parameters (p>0.05).

Only 3 healthy controls had NT-pro-BNP higher than 125 pg/mL, without any evidence of infectious disease.

Prospective evaluation of JIA patients under TNF blockage

Table III shows a prospective analysis of conventional and tissue Doppler echocardiography in 21 JIA patients before and during anti-TNF therapy. The median of septum A' wave increased slightly at 18 and 24 months (p=0.026) and the median of septum S' wave had a mild decrease at 3 and 6 months, and a mild increase at 12, 18 and 24 months (p=0.007). Of note, all values remained within normal range (Table III). Mild pulmonary hypertension was observed in only one (4.7%) of 21 JIA patients after 12 month of anti-TNF therapy (estimated systolic pulmonary artery pressure=40 mmHg).

The median of LVED, LVSD and RVED increased significantly during the 24 months (p<0.05) although in the normal range. The median of troponin T levels increased significantly at 18 and 24 months (p=0.014), probably due to the slight elevation (0.02 μg/l) observed in one patient (Table III). The median of echocardiographic parameters of the right ventricular free wall (E´, A´ and S waves), as well as ventricular septum and posterior wall thickness were similar during the 24 months (p>0.05).

Discussion

To our knowledge, this was the first study to assess prospectively cardiac function in JIA patients under TNF blockage therapy, and clearly showed long-term cardiovascular safety.

The strength of our study was the homogenous group of polyarticular course JIA refractory to DMARDs (1) and inclusion of an age-matched healthy control group since the heart growth occurs at childhood and reference values change according to age (20). The prospective design using echocardiographic concomitantly with laboratorial parameters and the rigorous exclusion criteria applied gave an unique opportunity to a more accurate determination of the cardiovascular safety of the TNF-blockage therapy in JIA patients. One limitation of this study was the small sample size. We also have not evaluated time intervals using TDI derived measurements, such as the IVRT, since this parameter was not standardised for pediatric population at our initial enrollment. Due to the prospective nature of this study, we had to maintain the same assessment with TDI wave velocities for all patients in order to sustain homogeneity of data collection.

Cardiac involvement is common in active JIA patients and includes pericarditis, myocarditis and valvulitis (5) with a wide range of clinical manifestations

Table III. Prospective analysis of conventional and tissue Doppler echocardiography in 21 juvenile idiopathic arthritis patients before and during anti-TNF therapy.

Variables	Baseline	3M	6M	12M	18M	24M	*p*-value
Conventional Doppler-Mitral inflow•							
E wave, m/s	1.05 (0.6–1.43)	1.01 (0.79–1.25)	0.99 (0.62–1.47)	1.0 (0.68–1.5)	1.0 (0.68–1.4)	1.03 (0.7–1.4)	0.765
A wave, m/s	0.55 (0.35–0.7)	0.55 (0.35–1.6)	0.58 (0.34–1.0)	0.49 (0.4–0.77)	0.56 (0.3–0.81)	0.5 (0.34–0.7)	0.703
DT	176 (129–275)	172 (125–249)	183 (103–230)	192 (117–242)	188 (131–258)	183 (131–242)	0.855
IVRT	76 (56–89)	72 (58–97)	76 (55–92)	76.5 (53–97)	72 (53–97)	79 (63–89)	0.751
Tissue Doppler•							
Left ventricular free wall							
E´ wave, m/s	0.17 (0.14–0.25)	0.17 (0.15–0.26)	0.17 (0.14–0.22)	0.16 (0.12–0.22)	0.15 (0.12–0.22)	0.17 (0.1–0.24)	0.051
A´ wave, m/s	0.07 (0.05–0.1)	0.07 (0.04–0.11)	0.07 (0.05–0.13)	0.07 (0.06–0.13)	0.08 (0.05–0.1)	0.07 (0.05–0.11)	0.521
S wave, m/s	0.1 (0.06–0.15)	0.09 (0.05–0.17)	0.1 (0.06–0.18)	0.1 (0.06–0.18)	0.1 (0.07–0.15)	0.09 (0.07–0.15)	0.655
Ventricular septum							
E´ wave, m/s	0.12 (0.1–0.16)	0.12 (0.1–0.16)	0.13 (0.09–0.16)	0.13 (0.08–0.17)	0.13 (0.08–0.18)	0.13 (0.08–0.17)	0.273
A´ wave, m/s	0.06 (0.04–0.08)	0.06 (0.04–0.08)	0.06 (0.04–0.08)	0.06 (0.04–0.1)	0.07 (0.04-0.11)	0.07 (0.05–0.1)	0.026
S wave, m/s	0.08 (0.06–0.11)	0.07 (0.05–0.09)	0.07 (0.04–0.09)	0.08 (0.05–0.1)	0.08 (0.05–0.1)	0.08 (0.07–0.1)	0.007
Chamber diameter and EF•							
LVED, mm	40.9 (26–51.2)	40 (29–49.2)	41 (30–51)	42 (30–54)	42 (27.7–52)	43 (32.8–52)	<0.001
LVSD, mm	24.2 (15-33)	25 (17–34.7)	25 (17–33)	24 (17–35)	25 (18–33)	25.6 (18–33)	0.033
RVED, mm	15.1 (9.1–21.4)	15.2 (10–22)	15 (10.23)	15 (10–21.4)	17 (12–21)	17.8 (12–26)	0.026
EF, %	70 (60–78)	70 (56–78)	69 (60–78)	72 (62.5–77)	68.6 (61.5–81)	69.6 (62.2–81)	0.153
Cardiac biomarkers							
Troponina T, >0.01µg/l	0.003 (0.003–0.01)	0.003 (0.003–0.01)	0.003 (0.003–0.01)	0.003 (0.003–0.005)	0.003 (0.003–0.018)	0.003 (0.003–0.02)	0.014
NT pro-BNP, >125pg/mL	73 (9–1107)	52 (5–537)	38 (8–226)	87 (15–711)	38 (6–163)	36 (12–126)	0.585

Normal range values of echocardiographic parameters according to age and weight were based on the American Society of Echocardiography Recommendations and Guidelines (18); DT: decelaration time; IVRT: isovolumetric relaxation time; EF: ejection fraction; LVED: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; RVED: right ventricular diastolic diameter; S: ventricular septum.

varying from heart failure to asymptomatic diastolic dysfunction.

Diastolic evaluation is a complex process in adults, requiring a group of altered parameters. In children and adolescents, some of these findings may not appear, and specific findings may not be present until they become symptomatic. Our data, at baseline, do not reveal an overt diastolic dysfunction, however, the reduced velocity of the septum E wave and shortening of the IVRT may indicate involvement of some diastolic components, particularly compliance and relaxation (19, 21). In contrast, Oguz *et al*. (7), reported serious abnormalities in diastolic function whereas others also observed mild alterations in JIA (6, 8, 9) and adults with rheumatoid arthritis (23). Additionally, systolic function was normal in JIA patients, as observed by other authors (7, 26).

The role of concomitant treatments (steroids, NSAIDs and immunosuppressive agents) in cardiac function is not clear in the pediatric population, although there are some evidences of elevated blood pressure in JIA patients related to steroid therapy and NSAIDs intake, leading to salt and water retention (9). In adult patients with RA, oral glucocorticoids as well as other immunosuppressive agents such as azathioprine, cyclosporine, and leflunomide were associated with an increased cardiovascular risk, in contrast to MTX (27, 28).

Importantly, the long-term use of TNF blockage did not hamper heart function of JIA patients, as described in a prospective study in RA adult patients (25). The significant increase observed in left and right ventricle diameters are consistent with children's growth.

We extended previous studies of cardiac function in JIA (6-9, 26) and further demonstrated using serum cardiac biomarkers that anti-TNF therapy does not seem to have a deleterious effect in cardiac function since NT-pro-BNP is an excellent predictor for systolic heart failure in the general population and high-risk cardiovascular groups (29).

Of note, this marker was associated with disease activity parameters with no other evidence of cardiovascular disease, as also reported by our group in adults with active ankylosing spondylitis receiving TNF blockers (30). This correlation is still poorly known in pediatric population and further studies are necessary.

In fact, there is some evidence that pro-inflammatory cytokines, such as TNF and interleukin-1, could stimulate BNP production in the absence of left ventricular function impairment (31).

Conclusion

In conclusion, long-term anti-TNF cardiovascular safety was demonstrated in JIA patients in spite of the observed mild subclinical diastolic involvement. Elevated cardiac biomarker in these patients was associated with inflammatory parameters reinforcing the need for a careful interpretation of this finding in patients with active disease.

Key messages

- Long-term TNF blockage is safe in terms of cardiovascular aspect in JIA patients in spite of subclinical diastolic involvement;
- Elevated cardiac biomarker in JIA patients may be associated with inflammatory parameters.

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