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Anti-TNF modulation reduces myocardial inflammation and improves cardiovascular function in systemic rheumatic diseases

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ABSTRACT

Background: Rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are common disorders associated with increased rates of cardiovascular disease (CVD), but the contribution of cytokine-induced inflammation to impaired cardiovascular function in these conditions remains poorly understood.
Objectives: We assessed the effect of anti-TNF therapy on myocardial and vascular function, myocardial tissue characteristics and perfusion in inflammatory arthropathy and systemic rheumatic disease (IASRD) patients, using cardiovascular magnetic resonance (CMR).
Methods: 20 RA patients, 7 AS patients, 5 PsA patients without previously known CVD scheduled to commence anti-TNF therapy and 8 RA patients on standard disease modifying antirheumatic drugs underwent CMR at 1.5 T, including cine, tagging, pulse wave velocity (PWV), T2-weighted, native and postcontrast T1 mapping, ECV quantification, rest and stress perfusion and late gadolinium enhancement (LGE) imaging.
Results: Following anti-TNF therapy, there was significant reversal of baseline subclinical cardiovascular dysfunction, as evidenced by improvement in peak systolic circumferential strain ($p < 0.001$), peak diastolic circumferential strain rate ($p < 0.001$), and total aortic PWV, ($p < 0.001$). This was accompanied by a reduction in myocardial inflammation, as assessed by T2-weighted imaging ($p = 0.005$), native T1 mapping ($p = 0.009$) and ECV quantification ($p = 0.001$), as well as in serum inflammatory markers like CRP ($p < 0.001$) and ESR ($p < 0.001$), and clinical measures of disease activity (DAS28-CRP, $p = 0.001$; BASDAI, $p < 0.001$). A trend towards improvement in myocardial perfusion was observed ($p = 0.07$). Focal myocardial fibrosis, as detected by LGE CMR was not altered by anti-TNF therapy ($p = 0.92$).
Conclusions: Anti-TNF therapy reduces subclinical myocardial inflammation and improves cardiovascular function in RA, AS and PsA. CMR may be used to track disease progression and response to therapy. Future CMR-based studies to demonstrate effect of anti-TNF therapy modulation of vascular structure and function on hard clinical events and outcomes would be useful.

1. Introduction

The inflammatory arthropathies and systemic rheumatic diseases (IASRD), including rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are common autoimmune disorders associated with progressive disability, multisystem complications, early death, substantial socioeconomic cost and psychological burden [1, 2]. These conditions are associated with increased rates of cardiovascular disease (CVD) in genetically predisposed individuals, with the propensity to affect every aspect of the cardiovascular tree, ultimately

Abbreviations: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CMR, cardiovascular magnetic resonance; CRP, C-reactive protein; DMARD, disease modifying antirheumatic drug; DAS28CRP, disease activity score with 28 tender and swollen joint count, incorporating C-reactive protein; ESR, erythrocyte sedimentation rate; ECV, extra-cellular volume; LGE, late gadolinium enhancement; PsA, psoriatic arthritis; ShMOLLI, Shortened Modified Look-Locker Inversion Recovery; RA, rheumatoid arthritis.

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leading to myocardial infarction, cerebrovascular events, arrhythmias, pulmonary hypertension and heart failure, typically in the young, even in the absence of traditional cardiovascular risk factors [3, 4]. About 50–80% of the excess mortality in patients with IASRD diseases is due to premature CVD [5].

The exact mechanisms underlying cardiovascular complications are poorly understood, and the true incidence and prevalence of cardiovascular involvement is probably underestimated as it usually remains clinically silent [6]. There is increasing evidence of the pathogenetic role of inflammation in myocardial dysfunction, plaque instability and subsequent coronary events [7] and the contribution of cytokine-induced inflammation at microvascular level involving myocardial structure and coronary arteries leading to dysfunction and heart failure in IASRD patients remains poorly understood.

Advances in molecular biology in the last 2 decades have resulted in the development of new treatment approaches for IASRD patients through the use of biological approaches that interfere with cytokine function, by inhibition of the second signal required for T-cell activation and depletion B cells [8]. TNF-α is a major pro-inflammatory cytokine involved in the pathogenesis of RA, AS and PsA [9]. When secreted by synovial macrophages, TNF-α stimulates synovial cells to proliferate and synthesise collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis [10]. TNF-α expression is associated with wide-ranging cardiovascular manifestations, including increasing the risk of atherosclerosis, endothelial dysfunction, myocardial infarction, heart failure and stroke [11]. To date, there are conflicting results on the efficacy of anti-TNF therapies in ameliorating CVD in IASRDs [12–25], and these concepts need further clarification.

Advanced cardiovascular imaging techniques such as cardiovascular magnetic resonance (CMR) may be of great utility in the early identification of patients with cardiovascular involvement from IASRD. CMR offers high spatial and temporal resolution, yielding accurate functional and morphological data, in the absence of ionizing radiation and enabling a detailed characterization of the cardiovascular phenotype in rheumatic diseases. CMR is the single imaging modality capable of assessing non-invasively global and regional cardiac function, fibrosis (both regional and diffuse), perfusion (both at rest and stress), vascular function, and inflammatory edema. We have previously demonstrated that subclinical cardiovascular disease is frequent in RA, including focal and diffuse myocardial fibrosis and inflammation, which are associated with impaired strain and RA disease activity [26]. In this study, we hypothesized that anti-TNF therapy would result in an improvement in myocardial and vascular characteristics in patients with IASRDs. Therefore, we aimed to assess the effect of anti-TNF therapy on myocardial and vascular function, myocardial tissue characteristics and perfusion using CMR in IASRD patients without known CVD or symptoms.

2. Methods

2.1. Study design and population

The study was designed as a prospective, cohort study. The population consisted of 20 RA, 7 AS and 5 PsA patients without known CVD or symptoms assessed before commencement of anti-TNF therapy and at 3–6 months after commencement of anti-TNF therapy, and thus served as their own controls. 8 RA patients who were not receiving anti-TNF therapy were also scanned at these same time points, and served as positive controls. The choice of anti-TNF agent was at the discretion of the clinical team.

2.2. Study recruitment

Patients were recruited from 6 hospitals in the Thames Valley, United Kingdom. Patients included into the study were between 18 and 70 years of age, and had a confirmed diagnosis of RA based on the 1987 American College of Rheumatology criteria (modified in 2010), AS based on the modified New York Criteria for the diagnosis of AS, PsA based on the modified Moll and Wright criteria for the classification of PsA. All patients were assessed by clinical consultant rheumatologists, and had been stable on disease modifying antirheumatic drugs (DMARDs) for at least 12 weeks. Patient identification and assessment of suitability for the study took place before obtaining informed consent. All subjects gave written informed consent to participate in the study. Ethical approval was granted for all study procedures by the Oxford Research Ethics Committee.

Exclusion criteria included inability to tolerate CMR, contraindications to CMR, non-sinus rhythm, known heart disease (previous myocardial infarction, prior abnormal coronary angiography, previous myocarditis on history, heart failure, arrhythmia on 12-lead electrocardiography [ECG] or other chronic cardiac condition), significant renal impairment (estimated glomerular filtration rate < 30 ml/min), impaired liver function (alanine aminotransferase > twice the upper limit of normal), a female who was pregnant, lactating or planning a pregnancy, and known hypersensitivity to gadolinium. As is the standard for patients receiving anti-TNF therapy, all patients with pre-existing blood dyscrasias (such as significant marrow hypoplasia, leukopenia, thrombocytopenia or anaemia), malignancy, hepatitis B and C viral infection, tuberculosis or other severe infection (sepsis, abscess, opportunistic infections or recurrent systemic infections), moderate to severe heart failure and known hypersensitivity to infliximab, etanercept, adalimumab, golimumab, certolizumab or other murine proteins, or to any excipients were excluded from the study. 8 RA patients used as positive controls, who were matched for age, sex and ethnicity had no cardiac history, were not on cardiovascular medications and had a normal ECG.

2.3. Study assessments

2.3.1. CMR image acquisition

CMR studies were performed using a single 1.5 T MR system (Avanto, Siemens Healthcare, Germany) using standard and previously published methods [26]. A complete stack of short axis (SA) images were obtained during breath-hold and cardiac gating for cine, precontrast T1 mapping, T2-weighted and LGE imaging. T1-mapping was performed using the ShMOLLI (Shortened Modified Look-Locker Inversion Recovery) sequence, and T2-weighted CMR was performed with the black-blood short-Tau inversion recovery (STIR) sequence. Three SA (basal, midventricular and apical) scans and a single long axis (horizontal) scan were obtained for cine tagging. CMR based aortic pulse wave velocity (PWV) was measured using ECG-gated, spoiled gradient echo sequences (with velocity-encoding gradient for phase contrast applied to assess through-plane flow) cine images in the ascending (AA) and proximal descending aorta (PDA) at the level of the main pulmonary artery as well as in the distal descending aorta (DDA) 12 cm vertically down, just below the diaphragm, perpendicular to the vessel. Native T1-maps, T2-weighted, cine tagged and velocity-encoded images were acquired before administration of gadolinium contrast. Perfusion imaging was performed every cardiac cycle using a T1-weighted fast (spoiled) gradient echo sequence during the first pass of an intravenous (IV) bolus of gadolinium-based contrast agent (0.03 mmol/kg Gadoterate meglumine (Gadoteric Acid), Dotarem, Guerbet LLC, France). Three short axis images (base, midventricular and apical) were chosen from the short axis stack for perfusion imaging, taking care to avoid the LV outflow in systole. A second IV bolus of 0.03 mmol/kg gadolinium contrast was given for rest perfusion imaging 20 min after completion of stress. LGE imaging was performed with a T1-weighted phase-sensitive inversion recovery sequence 8–12 min after a top-up dose of 0.09 mmol/kg gadolinium contrast (total Dotarem dose 0.15 mmol/kg). A single midventricular SA slice was acquired for post contrast T1 maps at 20 min after the last administration of contrast. Typical imaging parameters for the sequences used were as previously published [26].

2.3.2. CMR image analysis

All CMR images and maps were analyzed offline and in a blinded fashion.

2.3.2.1. Cine images. Analysis of left ventricular ejection fraction (LVEF) was performed using Argus software (Version VB17, Siemens Healthcare). LV SA epicardial and endocardial borders were manually contoured at end-diastole and end-systole. For more details, see Online Supplement.

2.3.2.2. Tagged cine images. Postprocessing and semiautomated analysis was performed using Cardiac Image Modeler software (CIMTag2D, Auckland, New Zealand) by aligning a grid to the myocardial tagging planes in end-diastole. For more details, see Online Supplement.

2.3.2.3. STIR images. Semiquantitative analysis was performed by comparing the LV myocardium in the SA against a region of interest (ROI) drawn in nearby skeletal muscle in the same slice, verified on a corresponding SSFP image. The T2 signal intensity (SI) ratio was calculated as T2 SImyocardium:skeletal = SImyocardium / SIskeletal muscle. Myocardial edema was diagnosed when myocardial T2 SI ratio is >1.9. For more details, see Online Supplement.

2.3.2.4. Aortic PWV images. Image analysis was performed using Argus (Siemens Medical Solutions, Erlangen, Germany). Flow images were manually contoured throughout the cardiac cycle and all the frames of the sequence were then integrated over the cardiac cycle. For more details, see Online Supplement.

2.3.2.5. Perfusion images. For analysis of myocardial perfusion, SI over time curves were generated by tracing *endo-* and epicardial contours (QMass software, version 6.2.3, Medis, Leiden, Netherlands) after manual correction for displacement during breathing. A ROI was drawn in the LV blood pool, avoiding any papillary muscles therein, to permit the derivation of an arterial input function. The myocardium was divided into equiangular segments on the basis of the American Heart Association (AHA) segmentation model. Rest and stress myocardial perfusion up-slopes were calculated using 5-point linear fit model

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of SI versus time and normalized to the LV blood pool upslope. Myocardial perfusion reserve index (MPRI) was derived for each of the 16 segments, defined as the ratio of stress to rest normalized myocardial perfusion upslopes. For more details, see Online Supplement.

2.3.2.6. LGE images. Images were evaluated qualitatively for the presence or absence, pattern (subendocardial, midwall, subepicardial, transmural) and regional distribution of LGE areas by three observers, each with at least 4 years of CMR experience. The detection of LGE was made by consensus of all 3 observers. In addition, lesion fractions of LGE were calculated as the ratio of contiguous >40 mm^2 area of the myocardium with the SI ≥ 2.0 standard deviations above the mean SI of normal myocardium (dedicated MC-ROI software, SKP, Interactive Data Language, version 6.1, Exelis Visual Information Solutions, Boulder, Colorado, USA) [25].

2.3.2.7. T1-maps. T1 maps were manually contoured using MC-ROI to outline the endocardium and epicardium, and then divided into 6 segments per slice using the anterior right ventricular-left ventricular insertion point as reference for comparing segments amongst sequences. Consistent with prior reports on ECV estimation [27], we measured precontrast and postcontrast myocardial and blood T1 values and the estimation of ECV and lambda (λ) was based on multipoint regression [28]. For more details, see Online Supplement.

2.3.2.8. Fractions of myocardial involvement by STIR and native T1 mapping. On dark-blood T2W images, edema was diagnosed when myocardial T2 SI was >1.9× that of remote skeletal muscle. On T1 maps, acute myocardial injury was diagnosed when T1 was >990 ms. For all quantitative analyses of T2W and T1 mapping images, only regions of myocardium with a contiguous area of ≥40 mm^2 above the specified thresholds were considered relevant, to reduce the detection of noise as positive findings. For more details, see Online Supplement.

2.3.3. Disease activity and duration

Disease activity in RA was assessed using the DAS28-CRP, a disease activity score, which incorporates a 28-tender joint and swollen joint count, in addition to a measure of general health, together with the serum C-reactive protein level. Disease activity is AS and PsA was assessed using the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), which is a well-validated tool based on 6 questions from the history: degree of fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, morning stiffness duration and morning stiffness severity.

2.4. Statistical analysis

Normally distributed data are presented as mean ± standard deviation (SD) or, where highly skewed, as median (interquartile range); ratios are presented as percentages. The chi-square test or Fischer's exact test was used to compare dichotomous data. The paired Student *t*-test was used to compare continuous variables between patients from the first to the second visits. Bivariate correlations were assessed using the Pearson "R" or Spearman "RS" coefficient, as appropriate. Any segmental analysis was averaged on a per-subject basis before any interindividual and group comparisons to control for clustering of segments within each subject. To determine the presence of significant differences in subject groups when using multiple CMR methodologies, analysis of variance was performed with Bonferroni-corrected post hoc comparisons for parametric data; for nonparametric data, the Kruskal-Wallis 1-way analysis of variance was performed with post hoc pairwise comparisons. To compare the extent of myocardial injury measured by 2 different CMR tissue characterization sequences (LGE and T1 mapping) within the same patient subgroup, the Wilcoxon test was used for nonparametric data with post hoc comparisons. The Fisher exact test was used for comparison of categorical data. All statistical tests were two-tailed and a p-value of <0.05 was considered statistically significant. All analysis was performed using SPSS version 20 (IBM, Armonk, New York, USA).

3. Results

3.1. Baseline characteristics of patients receiving anti-TNF therapy

20 RA patients, 7 AS patients and 5 PsA were successfully enrolled into the study. Table 1 depicts the baseline characteristics of the study cohort, including demographics, comorbidities, DMARD and disease activity and chronicity indices. As expected, patients scheduled to commence anti-TNF therapy had high levels of disease activity despite frequent use of antiinflammatory therapies.

3.2. Anti-TNF therapy and response

The types of anti-TNF therapies prescribed for study participants are shown in Fig. 1. Overall, adalimumab (59%) was the most frequently prescribed anti-TNF agent. All of the AS and PsA patients responded well to TNF antagonism with demonstrable serological and clinical improvement. Of the RA patients enrolled, 3 patients had to discontinue therapy (one for development of a large pericardial effusion with tamponade, another due to recurrent respiratory infections, and another after being diagnosed with cervical cancer) and 1 patient was a true non-responder who failed on adalimumab, golimumab and abatacept and showed partial response to rituximab. All the other RA patients studied showed good response to anti-TNF therapy.

3.3. Clinical and serological measures and disease activity in patients receiving anti-TNF therapy

As expected, overall there were significant improvements in the serum ESR ($p < 0.001$) and CRP ($p < 0.001$), as well as in the disease activity indices: DAS28-CRP ($p = 0.001$) and BASDAI ($p < 0.001$), as shown in Table 2. These improvements were also associated with improvements in clinical signs and symptoms, including marked decline in joint pain, joint swelling and morning stiffness, and striking functional improvement.

3.4. Effect of anti-TNF therapy on myocardial and vascular function

Following anti-TNF therapy, there was improvement in myocardial systolic strain ($p < 0.001$), diastolic strain rate ($p < 0.001$) and total aortic PWV ($p < 0.001$). There was no difference in LV volumes and global systolic function before and after anti-TNF therapy (Table 2). While there was a mild reduction in LV mass, likely reflecting reduction in myocardial edema, this trend did not reach statistical significance.

3.5. Effect of anti-TNF therapy on myocardial tissue characteristics and perfusion

At baseline, focal fibrosis, detected by LGE CMR, was common (44%), accounting for approximately 4% of the myocardial volume and was not altered following biological therapy. Following anti-TNF therapy, there was reduction in measures of myocardial inflammation (Fig. 2 – also see Online Supplement) as assessed by global myocardial T2 SI ratio ($p = 0.005$), area of myocardial edema ($p = 0.002$), mean native T1 ($p = 0.009$) and area of myocardium with T1 > 990 ms ($p = 0.006$). The ECV also decreased following anti-TNF therapy ($p < 0.001$), likely reflecting a decline in systemic inflammatory response and in myocardial inflammatory burden. There was a modest improvement in the myocardial perfusion reserve index (Table 2), a proxy for microcirculatory dysfunction, though this showed only a trend towards statistical significance ($p = 0.07$).

3.6. Progression of vascular and myocardial disease in RA patients not receiving anti-TNF therapy

In RA patients not receiving anti-TNF therapy, there was no significant change in CMR parameters during the period of follow-up (6 months) – see Online Supplement. This observation makes it highly likely that the vascular and myocardial changes noted in patients receiving anti-TNF therapy are driven by these powerful antiinflammatory treatments and do not merely reflect natural history of the disease.

4. Discussion

We have demonstrated that advanced CMR imaging can both detect subclinical cardiovascular involvement and track response to anti-TNF therapy in asymptomatic RA, AS and PsA patients without known CVD but with high levels of disease activity despite optimal antiinflammatory treatment. Specifically, the use of adjunct anti-TNF therapies is associated with improvements in: [1] peak systolic circumferential strain and peak diastolic circumferential strain rates, [2] aortic stiffness, as assessed by PWV, and [3] myocardial edema, as assessed by T2-weighted imaging, native T1 mapping and ECV quantification. While a trend towards improvement in myocardial perfusion was observed, this did not reach

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Table 1
Baseline characteristics of patients.

	RA patients prior to anti-TNF therapy N = 20	AS patients prior to anti-TNF therapy N = 7	PsA patients prior to anti-TNF therapy N = 5	RA patients not on anti-TNF therapy N = 8
Demographic and clinical features and co-morbidity				
Female sex, n (%)	14 (70)	1 (14)	0	4 (50)
Age, years	48 ± 12	38 ± 9	44 ± 13	44 ± 10
Current smokers, n (%)	5 (25)	2 (29)	0	1 (13)
Hypertension, n (%)	2 (10)	0	1 (20)	1 (13)
Diabetes, n (%)	1 (5)	0	0	0
Hyperlipidaemia, n (%)	1 (5)	0	0	0
Obesity, n (%)	1 (5)	0	1 (20)	0
BMI, kg/m^2	25 ± 4	23 ± 3	28 ± 4	26 ± 4
Medical therapy				
Methotrexate, n (%)	15 (75)	1 (14)	4 (80)	6 (75)
Sulfasalazine, n (%)	7 (32)	1 (14)	1 (20)	1 (13)
Chloroquine, n (%)	6 (27)	0	1 (20)	5 (63)
Leflunomide, n (%)	4 (18)	0	0	2 (25)
Prednisolone, n (%)	2 (9)	0	1 (20)	1 (13)
NSAID use, n (%)	14 (70)	6 (86)	3 (60)	1 (13)
Duration of DMARDs, years (median, IQR)	5 (3–7)	1 (0–1)	2 (2–3)	4 (3–6)
Disease activity and chronicity indices				
DAS28-CRP	6 ± 1	7 ± 1	6 ± 1	4 ± 1
CRP, mg/L (median, IQR)	8 (4–12)	5 (3−12)	6 (4–9)	3 (1–5)
ESR, mm/h (median, IQR)	14 (6–29)	13 (9–14)	12 (8–12)	7 (3–8)
Duration of disease, years (median, IQR)	7 (3–12)	8 (1–17)	18 (11−20)	7 (5–8)

Continuous data are mean ± SD unless otherwise indicated.
BMI, body mass index; CRP, C-reactive protein; DSA28-CRP, rheumatoid arthritis disease activity score incorporating 28 swollen and tender joint count as well as serum C-reactive protein; DMARD, disease modifying anti-rheumatic drug(s); ESR, erythrocyte sedimentation rate; NSAID, nonsteroidal anti-inflammatory drug.

statistical significance. These novel observations were further supported by parallel improvements in serum inflammatory parameters like CRP and ESR, as well as in clinical measures of disease activity. Focal myocardial fibrosis, detected by LGE CMR was not altered by anti-TNF therapy. Importantly, no significant changes were observed in vascular and myocardial function of RA patients not receiving anti-TNF therapy, suggesting that the observed improvements following anti-TNF therapy indicate a mechanistic role of TNF inhibition in modulating cardiovascular inflammation in IASRD.

Our results have important implications for the care of patients with IASRD: first, CMR is clearly an important tool for early detection of subclinical CVD; second, vascular and myocardial dysfunction is common even in the context of lack of cardiovascular symptoms and preserved LV ejection fraction; and, third, potent antiinflammatory agents like anti-TNF therapies reduce not only joint inflammation, but also cardiovascular inflammation and may reverse some of the adverse cardiovascular manifestations observed. Furthermore, we demonstrate that CMR is a useful tool to track response to therapy in these patients, without the need for LGE (which was not altered over time in this study). While focal fibrosis may still develop with increasing disease duration, it is possible that a gadolinium-free protocol may be employed in the follow-up imaging of these patients in assessing response to therapy.

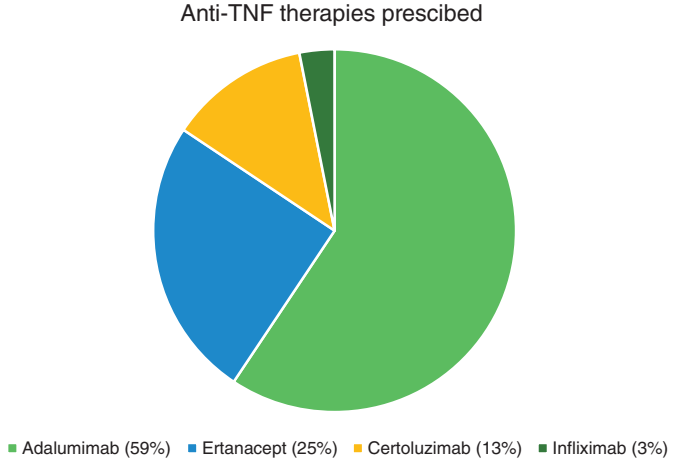

Fig. 1. Anti-TNF therapies prescribed.

Table 2
Clinical and serological measures, disease activity and CMR parameters before and after anti-TNF therapy.

	Baseline visit N = 32	Visit 2 N = 32	p value
Clinical, serological and disease activity measures			
Systolic BP, mm Hg	130 ± 15	127 ± 16	0.09
Diastolic BP, mm Hg	73 ± 13	72 ± 10	0.41
Heart rate, bpm	70 ± 12	66 ± 8	0.44
BMI, kg/m^2	25 ± 4	25 ± 4	0.23
ESR, mm/h (median, IQR)	12 (8–16)	6 (2–9)	<0.001
CRP, mg/L (median, IQR)	6 (4–11)	2 (1–4)	<0.001
DAS28-CRP	6 ± 1	4 ± 1	0.001
BASDAI	6 ± 1	3 ± 1	<0.001
CMR measures of cardiac function and cardiovascular inflammatory activity			
LVEDV indexed to BSA, ml/m^2	76 ± 15	74 ± 14	0.78
LVESV indexed to BSA, ml/m^2	21 ± 5	20 ± 6	0.67
LVEF, %	72 ± 4	72 ± 5	0.56
LV mass indexed to BSA, g/m^2	54 ± 14	51 ± 13	0.12
LA size, mm	32 ± 4	32 ± 4	0.38
Mid SA circumferential strain	−14.9 ± 0.8	−17.3 ± 0.4	<0.001
Peak diastolic circumferential strain rate (s^{-1})	69 ± 19	93 ± 22	<0.001
Total aortic PWV (m/s)	7 ± 2.3	4.4 ± 1.5	0.002
Presence of LGE (%)	14 (44)	14 (44)	0.92
Volume fraction of LGE > 2SD (%)	4.1 ± 0.1	4.0 ± 0.1	0.78
Global myocardial T2 SI ratio	1.9 ± 0.3	1.6 ± 0.2	0.005
Volume fraction of oedema by T2 (%)	27 (13–41)	8 (3–19)	0.002
Native myocardial T1, ms	990 ± 29	975 ± 26	0.009
Volume fraction of T1 > 990 ms (%)	30 (15–39)	19 (8–29)	0.006
ECV (%)	37.2 ± 5.5	33.1 ± 4.0	<0.001
MPRI	1.6 ± 0.3	1.8 ± 0.3	0.07

Continuous data are mean ± SD unless otherwise indicated.
BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; ECV, extracellular volume; ESR, erythrocyte sedimentation rate; LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle/ventricular; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MPRI, myocardial perfusion reserve index; PWV, pulse wave velocity; SI, signal intensity.

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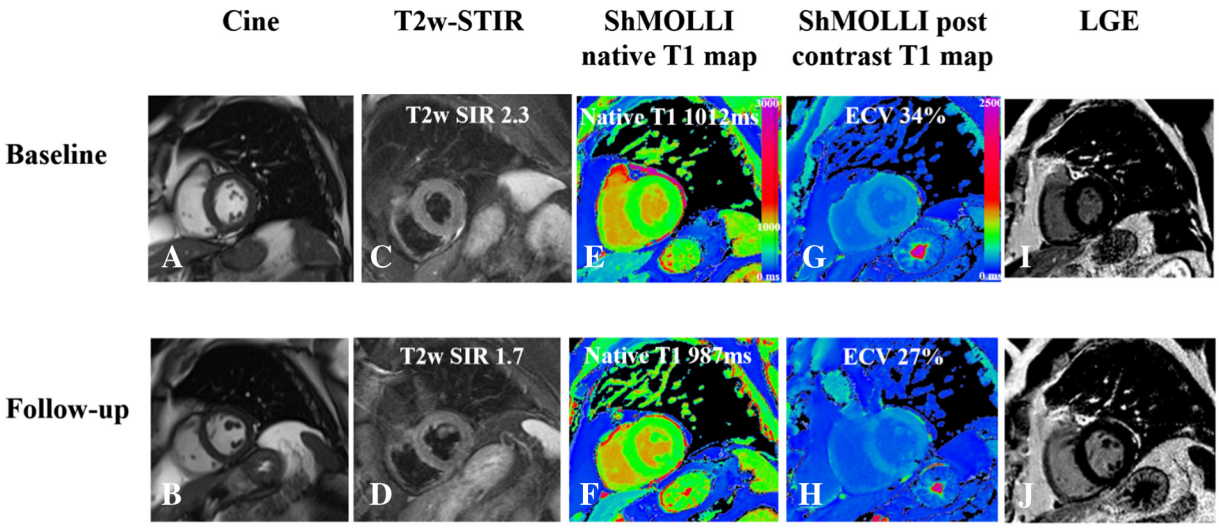

Fig. 2. Effect of anti-TNF therapy on myocardial tissue characteristics. Cine image before (A) and after (B) anti-TNF therapy. T2-weighted images before (C) and after (D) anti-TNF therapy. The T2 SIR improved from 2.3 to 1.7 following anti-TNF administration. Native T1 image before (E) and after (F) anti-TNF therapy. Mean native T1 values improved from 1012 ms to 987 ms following anti-TNF administration. Postcontrast T1 image before (G) and after (H) anti-TNF therapy. Mean postcontrast T1 values increased from 367 ms (ECV 34%) to 422 ms (ECV 27%). LGE image before (I) and after (J) anti-TNF therapy.

We comprehensively show for the first time that anti-TNF therapy results in improvement in myocardial inflammation as assessed by a variety of CMR indices such as T2-weighted imaging, native T1 and ECV. Although ECV is often thought to be an imaging marker that reflects diffuse myocardial fibrosis, we show that anti-TNF therapy also decreases the ECV fraction, indicating that inflammation also contributes to expanded ECV. Taken together, these data indicate that there is substantial myocardial inflammation in patients with IASRD with high disease activity, supported by other biomarkers of inflammation, which can be downregulated through administration of potent inhibitors of the inflammatory cascade. It also worthwhile to highlight that the ECV can be modulated by antiinflammatory therapy.

It is curious that anti-TNF therapies reduce systemic and myocardial inflammation, and thereby improve many cardiovascular indices. It is logical to assume that these effects are due to the antiinflammatory properties of anti-TNF therapy. However, there is emerging evidence that anti-TNF agents may have a pleiotropic role in disease modulation and may have mechanisms other than reduction of inflammation by which they improve cardiovascular function. Evidence of the pleiotropic role of TNF-antagonists is supported by improvements in endothelial function [14], post-ischaemic reconditioning [29], left atrial function [30], heart failure and LV function in septic shock [31], and improving coronary artery function [32]. The latter is interesting, and we expected to demonstrate improvements in myocardial perfusion. However, in our study, likely due to small sample size, our observations on perfusion did not reach statistical significance. A positron emission tomography study in patients with RA found impaired coronary flow reserve (CFR), which correlated with disease duration [33]; and concluded that reduced CFR, in the absence of significant coronary artery disease, is suggestive of coronary microvascular dysfunction, likely a consequence of prolonged systemic inflammation, which may precede and contribute to premature coronary artery disease. An additional mechanism by which anti-TNF agents provide cardioprotection may be through improvement in coronary microvascular function.

While we show for the first time clear evidence of myocardial inflammation that is modulated by anti-TNF therapy, improvements in serum inflammatory markers, disease activity and myocardial strain have been reported by various authors following TNF antagonism [22, 23, 34–39], similar to our findings. TNF-α has extensive metabolic effects and functional pleiotropy which results in increased cardiac and vascular risk. As shown in this study, subclinical myocardial inflammation likely plays a significant role in contributing to this risk, and anti-TNF can at least partially modulate this via the reduction of inflammation, in addition to other downstream effects such as adipose tissue lipolysis, insulin resistance, increased hepatic production of CRP and fibrinogen, increased serum levels of triglycerides and low density lipoproteins, endothelial activation and increased oxidative stress [38]. The reversal of some of these processes is likely to result in improvement in myocardial function. We also show, in line with other studies [21, 22, 39–44], that TNF antagonism improves vascular stiffness in patients with RA, AS and PsA. In our study, these improvements are pronounced in the first 3 to 6 months.

This study is limited by the small sample size and heterogeneous patient populations included. Nonetheless, significant differences are observed in many of the CMR parameters measures when comparing patients before and after anti-TNF therapy. This study highlights the utility of CMR as a robust and powerful imaging modality for the study of disease mechanisms in IASRD.

5. Conclusions

In patients with IASRD with high disease activity, there is subclinical cardiovascular involvement, and anti-TNF therapy results in improvements in myocardial inflammation, functional strain parameters, and aortic stiffness. These changes were associated with improvements in serum inflammatory biomarkers and improved measures of disease activity. Focal myocardial fibrosis was not altered by anti-TNF therapy. Anti-TNF therapy has a significant role in improving myocardial and vascular inflammation and in modulating cardiovascular inflammation in IASRD, which can be tracked on CMR, and clinical disease activity indices, without the need for gadolinium contrast. In the future, it will be imperative for CMR-based studies to demonstrate the effect of anti-TNF therapy modulation of vascular structure and function on hard clinical events and outcomes.

Declarations

- **Ethics approval and consent to participate**: All subjects gave written informed consent to participate in the study. Ethical approval was granted for all study procedures by the Oxford Research Ethics Committee (REC Reference: 10/H0606/32).
- **Consent for publication**: All subjects gave written informed consent to participate in the study including the publication of its findings.

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- **Availability of data and material**: All data generated or analyzed during this study are included in this published article [and its Supplementary information files].
- **Authors' contributions**: NABN had substantial contribution to conception and design of study, acquisition, analysis and interpretation of the data and major contributor in writing the manuscript. JMF acquired and interpreted the data, SKP analyzed data and provided intellectual input. VMF contributed to writing and provided intellectual input. PMM involved in the design of study and provided intellectual input. MDR provided intellectual input, PBW involved in the design of study, interpreted the data and provided intellectual input, SN interpreted the data, provided intellectual input and contributed to writing. TDK had substantial contribution to conception and design of study, interpretation of data and revision of the manuscript. All authors read and approved the final manuscript.

Conflicts of interest

None.

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Relationship with industry

US patent pending 61/387,591: SKP, MDR. Systems and methods for shortened look locker inversion recovery (ShMOLLI) cardiac gated mapping of T1. September 29, 2010. All rights sold exclusively to Siemens Medical Solutions. US patent pending 61/689,067: SKP, MDR. Color map design method for immediate assessment of the deviation from established normal population statistics and its application to cardiovascular T1 mapping images.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.06.099.

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