Using cardiovascular magnetic resonance to define mechanisms of comorbidity and to measure the effect of biological therapy: the CADERA observational study

Sven Plein,[1] Bara Erhayiem,[1] Graham Fent,[1] Jacqueline Andrews,[2] John Greenwood,[1] Paul Baxter,[3] Elizabeth M Hensor,[2,4] Sue Pavitt[5] and Maya H Buch[2,6,7]*

[1]Department of Biomedical Imaging Science, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
[2]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[3]Department of Specialist Science Education, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
[4]National Institute for Health Research Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[5]Dental Translational Clinical Research Unit, School of Dentistry, University of Leeds, Leeds, UK
[6]Centre for Musculoskeletal Research, Division of Musculoskeletal & Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine & Health, University of Manchester, Manchester, UK
[7]NIHR Manchester Biomedical Research Centre, Manchester, UK

*Corresponding author maya.buch@manchester.ac.uk

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Scientific summary

The CADERA observational study

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Scientific summary

Background

Rheumatoid arthritis is a chronic, systemic, inflammatory arthritis affecting over 400,000 (0.8%) of the UK population. Rheumatoid arthritis has considerable health and socioeconomic impacts. The life expectancy of patients with rheumatoid arthritis is reduced and the mortality rate is increased up to threefold compared with the general population. This is largely because of the increased frequency of premature cardiovascular disease, which accounts for up to 40% of mortality in rheumatoid arthritis patients and is independent of and incremental to traditional cardiovascular disease risk factors.

According to current guidelines, patients with newly diagnosed rheumatoid arthritis should be treated with conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) therapy in combination with short-term glucocorticoids in a 'treat-to-target' (with the target of remission) approach. Biologic disease-modifying anti-rheumatic drug (bDMARD) therapy, including tumour necrosis factor inhibitor therapy, is recommended in patients with inadequate disease control with csDMARDs [in the UK, National Institute for Health and Care Excellence guidelines permit bDMARD after failure of at least after two conventional agents, including methotrexate and in the presence of high disease activity].

Treatment of rheumatoid arthritis with methotrexate and tumour necrosis factor inhibitors has been shown to have beneficial effects on cardiovascular disease in epidemiological studies, with relative risks in the range of 0.72 and 0.46–0.70, respectively, in patients with established rheumatoid arthritis. It is not clearly known if patients with a new diagnosis of very early rheumatoid arthritis already have signs of cardiovascular disease, if disease-modifying anti-rheumatic drug (DMARD) therapy confers benefits in this patient group and if DMARD therapy reduces the incidence of cardiovascular disease, including whether or not bDMARD therapy has additional benefits over csDMARDs.

The VEDERA (Very Early vs. Delayed Etanercept in early Rheumatoid Arthritis) study was a phase IV, pragmatic, single-centre, open-label randomised controlled trial with the aim of determining the effect of bDMARD therapy with tumour necrosis factor inhibitor in patients with new-onset, treatment-naive early rheumatoid arthritis compared with standard methotrexate ± additional csDMARD therapy in a treat-to-target approach (with escalation to tumour necrosis factor inhibitor if clinical remission was not achieved). Participants were randomised to one of two first-line therapeutic strategies: (1) group 1 – immediate tumour necrosis factor inhibitor (etanercept) and methotrexate or (2) group 2: methotrexate ± additional csDMARD therapy in a treat-to-target approach, with switch to delayed etanercept and methotrexate in the event of failure to achieve clinical remission at 6 months. The primary end point of the VEDERA trial was a comparison of the proportion of patients in each treatment arm achieving Disease Activity Score-28 remission at 1 year. Secondary end points included evaluation of the response to first-line etanercept compared with delayed etanercept (following methotrexate).

The CADERA (Coronary Artery Disease Evaluation in Rheumatoid Arthritis) study was a bolt-on study to the VEDERA trial in which patients randomised in the VEDERA trial underwent additional multiparametric cardiovascular magnetic resonance imaging to assess cardiovascular disease at baseline and after initiation of either of the two treatment strategies.

Objectives

Primary objectives

- To determine if cardiovascular abnormalities, as assessed by cardiovascular magnetic resonance imaging, are present in a treatment-naive inception cohort of early rheumatoid arthritis patients compared with control subjects.

- To establish whether or not (any) rheumatoid arthritis DMARD strategy is associated with improvement in cardiovascular abnormalities, as measured by cardiovascular magnetic resonance imaging, in a treatment-naive inception cohort of early rheumatoid arthritis patients over a 1-year period.
- To establish whether or not tumour necrosis factor inhibitor therapy confers a quantitative difference in cardiovascular disease, as measured by cardiovascular magnetic resonance imaging, compared with standard therapy in a treatment-naive inception cohort of early rheumatoid arthritis patients over a 1-year period.

Secondary objectives

- To determine cardiovascular changes, as assessed by cardiovascular magnetic resonance imaging, in a treatment-naive inception cohort of early rheumatoid arthritis patients over a 2-year period.
- In additional analysis (in line with the VEDERA parent study), following a protocol amendment, to evaluate the response relative to Disease Activity Score-28 control (Disease Activity Score-28 category of remission-defined clinical response/non-response status) and therapeutic intervention (tumour necrosis factor inhibitor/methotrexate and csDMARD including methotrexate).

Methods

Design

The CADERA study was a bolt-on study to the VEDERA parent randomised controlled trial. Patients recruited to the VEDERA trial and randomised to the csDMARD or bDMARD treatment group underwent cardiovascular resonance imaging at baseline and at 1 year and 2 years following initiation of therapy.

Setting

Participants were recruited from a single tertiary centre, an early rheumatoid arthritis rheumatology outpatient clinic (Chapel Allerton Hospital, Leeds, UK), and underwent cardiovascular magnetic resonance imaging at the Multidisciplinary Cardiovascular Research Centre (MCRC) at the Leeds Institute of Cardiovascular and Metabolic Medicine.

Participants

The methods used in the VEDERA and CADERA studies have been published previously. Patients were recruited between February 2012 and November 2015. Consecutive patients diagnosed with new-onset rheumatoid arthritis according to American College of Rheumatology/European League Against Rheumatism 2010 criteria were invited to enrol into the VEDERA randomised controlled trial and parallel CADERA substudy. Thirty control subjects (free of cardiovascular disease) were recruited through advertisements, e-mail and word of mouth and were approximately individually matched by age and sex to the first 30 CADERA patients.

Outcome measures

The primary outcome measure was difference in aortic distensibility between patients and control subjects at baseline and in patients from baseline to 1 year of follow-up.

Secondary outcome measures were myocardial perfusion reserve, left ventricular strain and twist, left ventricular ejection fraction and left ventricular mass.

The exploratory outcome measure was myocardial extracellular volume.

Sample size

The sample size estimation for the primary end point aortic distensibility was based on previous published studies showing improved aortic distensibilty in rheumatoid arthritis patients in response to interleukin-1-directed therapy. Thirty-three patients in each treatment group would equate to 80% power to detect a difference in aortic distensibility between the two treatment groups at a 5% significance level.

Interventions

All recruited patients were randomised into two groups according to the VEDERA protocol.

1. Group 1: experimental treatment arm – etanercept group: immediate etanercept and methotrexate treatment.
2. Group 2: control treatment arm – standard treatment group: initial myocardial extracellular volume monotherapy with treat-to-target regimen; escalation to combination DMARD therapy at or after 8 weeks (up to week 24) if failing to meet the predefined target at 4-weekly assessments, and if failing to meet the predefined target of clinical remission at week 24, step up to bDMARD, etanerceptand methotrexate.

Etanercept (Enbrel®, Pfizer Inc. New York, NY, USA) is a human tumour necrosis factor receptor p75Fc fusion protein produced by recombinant deoxyribonucleic acid (DNA) technology. Methotrexate and/or additional csDMARDs include sulfasalazine and hydroxychloroquine.

Study procedures

All patients underwent screening within the 4 weeks prior to the baseline visit for the VEDERA trial. At the baseline visit eligibility for the study was confirmed, patients were randomised to one of the treatment groups and study treatment was initiated. Further visits, which included assessment of disease activity, took place at weeks 4, 12 and every 12 weeks thereafter, up to week 96, for both treatment arms, with additional visits (for group 2) at week 8, 16 and 20 for safety and efficacy within a treat-to-target protocol.

At baseline and at 1 and 2 years following initiation of therapy, patients recruited to the CADERA study were invited for cardiovascular magnetic resonance imaging. The cardiovascular magnetic resonance imaging protocol included aortic cine imaging, cine imaging in left ventricular short- and long-axis orientations, myocardial tissue tagging, adenosine stress and rest first-pass perfusion imaging using a dual-bolus technique, with intravenous infusion of 0.01 and 0.1 mmol/kg gadopentetate dimeglumine (Magnevist®, Bayer, Berlin, Germany), myocardial T1 mapping pre and post contrast and late gadolinium enhancement imaging.

Analysis

All post-processing analysis of cardiovascular magnetic resonance scans was performed by experienced blinded assessors using CVI 42 software (Circle Cardiovascular Imaging, Calgary, Canada). Aortic distensibility was calculated from aortic cine images according to previously described methods. Left ventricular contours were drawn manually at both end-diastole and end-systole on the left ventricular short-axis cine stack and left ventricular volumes and mass derived. Left ventricular strain and peak left ventricular twist were derived from tissue tagging images and myocardial extracellular volume was derived from pre- and post-contrast T1 mapping.

Patients were compared with control subjects for the primary outcome, aortic distensibility, using matched pairs analysis and regression analysis. The objective was to determine if a significant difference ($p < 0.05$) existed between patients and control subjects and to estimate the magnitude of this difference as a 95% confidence interval. The patients as a whole group and the two randomised treatment groups were compared at baseline to 1 year with primary outcome aortic distensibility and aforementioned secondary outcomes on 1-year follow-up.

Myocardial perfusion analysis is not included in this report.

Following a protocol amendment, further analyses were conducted for patients stratified as responders or non-responders to therapy according to Disease Activity Score-28 remission status.

All analyses were adjusted for baseline aortic distensibility, age, sex, systolic blood pressure and pack-years smoking (± baseline Disease Activity Score-28-erythrocyte sedimentation rate as applicable). All analyses were performed on 81 patients, with imputation of missing baseline and follow-up outcomes.

Results

A total of 82 patients were enrolled into the CADERA study and underwent baseline cardiovascular magnetic resonance imaging. In one participant no aortic distensibility data could be acquired. Of the remaining 81 patients at baseline, 71 underwent a 1-year cardiovascular magnetic resonance scan. A total of four patients were withdrawn from the study during the first year of follow-up, one because of treatment non-compliance and the other three because of serious adverse events relating to treatment. The reasons for the remaining six patients not undergoing a 1-year cardiovascular magnetic resonance scan were refusal or claustrophobia (five patients) and moved away and not able to attend a repeat scan (one patient). In total, 56 patients attended for a 2-year cardiovascular magnetic resonance scan.

Early rheumatoid arthritis patients and control subjects were of similar median [interquartile range] age [51 (21) and 54 (23) years, respectively] and systolic blood pressure [121 (26) mmHg and 121 (14) mmHg, respectively]. Median (interquartile range) erythrocyte sedimentation rate, C-reactive protein and Disease Activity Score-28 in early rheumatoid arthritis patients were 30 (30) mm/hour, 8 (23) mg/l and 5.3 (1.4), respectively. In total, 64 (84%) and 57 (75%) patients were anti-citrullinated peptide antibody and rheumatoid factor positive, respectively. A total of 17 (22%), 25 (33%) and 34 (45%) patients in the rheumatoid arthritis group were current, former and never smokers, respectively, and 4 (13%), 5 (17%) and 21 (70%) patients in the control group were current, former and never smokers, respectively.

Primary objectives

Primary outcome

The primary outcome measure aortic distensibility [geometric mean (95% confidence interval)] was significantly reduced in patients ($n = 81$) compared with control subjects ($n = 30$) [3.0×10^{-3}/mmHg (2.7×10^{-3}/mmHg to 3.3×10^{-3}/mmHg) vs. 4.4×10^{-3}/mmHg (3.7×10^{-3}/mmHg to 5.2×10^{-3}/mmHg), respectively; $p < 0.01$]. Aortic distensibility improved significantly from baseline to 1 year across the whole patient cohort [3.0×10^{-3}/mmHg (2.7×10^{-3}/mmHg to 3.4×10^{-3}/mmHg) vs. 3.6×10^{-3}/mmHg (3.1×10^{-3}/mmHg to 4.1×10^{-3}/mmHg), respectively; $p < 0.01$].

All differences remained significant when adjusted for age, sex, systolic blood pressure and pack-years smoked.

Secondary outcomes

Of the secondary outcome measures, left ventricular mass [geometric mean (95% confidence interval)] was significantly lower in patients ($n = 81$) than in control subjects ($n = 30$) [78.2 g (74.0 to 82.7 g) vs. 92.9 g (84.8 to 101.7 g), respectively; $p < 0.01$]. Left ventricular mass in patients increased from baseline to 1 year, from 78.2 g (95% confidence interval 73.7 to 83.0 g) to 81.4 g (95% confidence interval 76.3 to 86.9 g; $p = 0.01$). All differences remained significant when adjusted for age, sex, systolic blood pressure and pack-years smoked.

Myocardial extracellular volume [geometric mean (95% confidence interval)] was significantly increased at baseline in patients ($n = 78$) compared with control subjects ($n = 30$) [27.1% (26.4% to 27.9%) vs. 24.9% (23.8% to 26.1%), respectively; $p < 0.01$]. This difference remained significant when adjusted for age, sex, systolic blood pressure and pack-years smoked. Myocardial extracellular volume in patients ($n = 81$) decreased from baseline to 1 year [geometric mean (95% confidence interval)], from 27.2% (26.4% to 28.1%) to 26.4% (25.6% to 27.3%), but this difference was not statistically significant ($p = 0.06$).

Matched pairs analyses corroborated the significant differences between the control group and the rheumatoid arthritis group for aortic distensibility, myocardial extracellular volume and left ventricular mass (with left ventricular mass showing a consistent magnitude of change).

No significant differences were seen in the other secondary outcome measures between patients and control subjects at baseline or in patients between baseline and 1 year of follow-up.

Secondary objectives

At the 2-year follow-up time point, differences in the primary end point of aortic distensibility and in the secondary end point of left ventricular mass were maintained. In addition, peak left ventricular twist significantly increased from baseline to the 2-year follow-up, from a geometric mean of 14.9° (95% confidence interval 14.0° to 15.9°) to a geometric mean of 16.6° (95% confidence interval 15.5° to 17.8°; $p = 0.02$).

As part of the additional analyses (following the protocol amendment), no significant differences in aortic distensibility improvement were seen in the following comparisons (geometric means):

- group 1 ($n = 40$ at baseline) versus group 2 ($n = 41$ at baseline): 3.8×10^{-3}/mmHg versus 3.4×10^{-3}/mmHg; $p = 0.49$
- combined group 1 and 2 non-responders ($n = 38$) versus combined group 1 and 2 responders ($n = 43$): 3.5×10^{-3}/mmHg versus 3.6×10^{-3}/mmHg; $p = 0.87$
- group 1 non-responders ($n = 17$) versus group 1 responders ($n = 23$): 3.6×10^{-3}/mmHg versus 3.9×10^{-3}/mmHg; $p = 0.73$.

There was a trend towards a 10–30% difference between treatment strategies comparing group 1 responders ($n = 23$) with group 2 responders ($n = 13$): geometric mean 3.9×10^{-3}/mmHg versus 2.8×10^{-3}/mmHg; ratio 0.7 (95% confidence interval 0.4 to 1.2; $p = 0.19$); ratio adjusted for baseline aortic distensibility 0.8 (95% confidence interval 0.5 to 1.2; $p = 0.29$); ratio fully adjusted for baseline characteristics 0.9 (95% confidence interval 0.6 to 1.4; $p = 0.56$).

Discussion

The CADERA study presents the first evidence from a randomised controlled trial of the effects of DMARD therapy on cardiovascular magnetic resonance imaging markers of cardiovascular disease in patients with early, treatment-naive rheumatoid arthritis. The CADERA study has demonstrated that aortic distensibility, a measure of aortic stiffness and a surrogate marker of cardiovascular disease risk, is lower in patients with new-onset early rheumatoid arthritis than in control subjects. This finding suggests that cardiovascular disease abnormalities are an early manifestation of rheumatoid arthritis, with potential implications for the routine care of these patients.

The CADERA study has further shown that aortic distensibility improves at the 1- and 2-year follow-ups after the initiation of DMARD therapy. Although there was no significant difference between the two treatment regimes, first-line etanercept/methotrexate responders had a higher aortic distensibility at 1 year than first-line methotrexate/csDMARD responders. This finding suggests that, in those patients who respond well to first-line therapy, bDMARD treatment may be of further benefit. However, these preliminary findings are based on modest patient numbers and require corroboration in future prospective studies.

Among the other cardiovascular magnetic resonance measures, we have demonstrated elevated myocardial extracellular volume in patients compared with control subjects, which shows a trend towards improvement after therapy. Myocardial extracellular volume is a marker of diffuse interstitial fibrosis and the elevated values may relate to myocardial inflammation in early rheumatoid arthritis.

We have also observed lower baseline left ventricular mass in patients compared with control subjects and an increase in left ventricular mass in patients from baseline to the 1- and 2-year follow-ups. This observation may relate to the phenomenon of 'rheumatoid cachexia' caused by the reduced physical activity in rheumatoid arthritis patients prior to the initiation of therapy.

Conclusion

These randomised controlled trial data show changes in vascular function and myocardial composition in treatment-naive early rheumatoid arthritis of < 12 months' symptom duration compared with control subjects. Optimal DMARD therapy (whether csDMARDs or bDMARDs) to control rheumatoid arthritis disease activity is associated with significant improvements in aortic distensibility at 1 year. However, aortic distensibility improvement appears not to be associated with response status per se (whether within a treatment arm strategy or not). Exploratory evaluation suggests greater aortic distensibility improvement with etanercept/methotrexate than with methotrexate (when controlling for response status).

Trial registration

This trial is registered as ISRCTN89222125 and ClinicalTrials.gov NCT01295151.

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