Current Therapeutic Research 89 (2018) 1–6

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

Effects of Treatment with Adalimumab on Blood Lipid Levels and Atherosclerosis in Patients with Rheumatoid Arthritis ☆

Ulf Bergström, MD, PhD[1,2], Stefan Jovinge, MD, PhD[3,4], Jerker Persson, MD, PhD[5], Lennart T.H. Jacobsson, MD, PhD[6], Carl Turesson, MD, PhD[1,2,*]

[1] Department of Clinical Sciences, Malmö, Lund University, Malmö, Sweden
[2] Department of Rheumatology, Skåne University Hospital, Malmö, Sweden
[3] Fred and Lena Meijer Heart and Vascular Institute, Spectrum Health, Grand Rapids, Michigan
[4] Van Andel Institute, Grand Rapids, Michigan
[5] Department of Medicine, Sahlgrenska University Hospital, Mölndal, Sweden
[6] Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden

ARTICLE INFO

Article history:
Received 19 May 2018
Revised 15 July 2018
Accepted 17 July 2018

Key words:
Atherosclerosis
Lipids
Rheumatoid arthritis
TNF inhibitors

ABSTRACT

Background: Treatment with tumor necrosis factor inhibitors for rheumatoid arthritis has been associated with a decreased risk of cardiovascular disease in observational studies. There are conflicting data on the influence of tumor necrosis factor inhibitors on lipid levels.

Objectives: To evaluate the effect of treatment with adalimumab on blood lipid levels, lipoproteins, and atherosclerosis of the carotid artery.

Methods: Fourteen patients with active rheumatoid arthritis (11 women and 3 men; mean age 63.7 years; median disease duration 9.0 years; and 78% rheumatoid factor positive) were treated with adalimumab 40 mg subcutaneously every 2 weeks and followed for 3 months. The patients had not been treated with adalimumab previously and had not received other tumor necrosis factor inhibitors within the past 3 months or moderate/high dose corticosteroids within the past 2 weeks. The intima-media thickness of the common carotid artery was assessed using B mode ultrasonography. Triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol levels were analyzed in fresh fasting blood samples, whereas apolipoprotein B and apolipoprotein A1 (apoA1) levels were determined in thawed plasma samples using standard turbidimetric immunoassays.

Results: Total cholesterol (mean = 5.36 vs 5.96 mmol/L; $P = 0.005$), LDL cholesterol (mean = 3.33 vs 3.77 mmol/L; $P = .005$), HDL cholesterol (mean = 1.43 vs 1.55 mmol/L; $P = 0.048$), apolipoprotein B (mean = 1.04 vs 1.13 g/L; $P = .012$), and apoA1 (mean = 1.42 vs 1.58 g/L; $P = 0.005$) all increased, but there were no major changes in the LDL to HDL cholesterol ratio (median = 2.56 vs 2.35; $P = 0.27$) or the apolipoprotein B to apoA1 ratio (mean = 0.76 vs 0.74; $P = 0.46$). There was no change in triglyceride levels ($P = 0.55$). Disease activity decreased significantly from baseline to the 3-month evaluation (disease activity score based on 28 joints mean = 5.6 vs 4.1; $P = 0.007$). An increase in apoA1 correlated with decreases in the patient global assessment of disease severity ($r = 0.79$; $P = 0.001$) and C-reactive protein level ($r = 0.74$; $P = 0.003$). Changes in the apoliprotein B to apoA1 ratio correlated with changes in erythrocyte sedimentation rate ($r = 0.54$; $P = 0.046$). There was no major change in the common carotid artery intima-media thickness (mean = 0.78 vs 0.80 mm; $P = 0.48$).

Conclusions: Although these results suggest that control of inflammation could have a beneficial effect on the lipid profile through an increase in HDL cholesterol levels, the observed protective effect on cardiovascular disease events by tumor necrosis factor blockers is likely to be explained by other mechanisms than changes in lipid levels or short-term effects on atherosclerosis of the carotid artery.

☆ ClinicalTrials.gov identifier: NCT01270087.

* Address correspondence to: Carl Turesson, MD, Department of Rheumatology, Skåne University Hospital, Jan Waldenströms gata 1B, S-205 02 Malmö, Sweden.
E-mail address: Carl.Turesson@med.lu.se (C. Turesson).

https://doi.org/10.1016/j.curtheres.2018.07.001

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by chronic polyarthritis, with progressive, erosive joint damage and extensive disability. Patients with RA also have an increased mortality compared with the general population, in particular from cardiovascular disease (CVD).[1] This excess risk is not explained by traditional risk factors for CVD.[1] A large number of studies have demonstrated an increased rate of cardiovascular events in patients with RA.[2] Predictors of CVD in patients with RA include disease severity measures such as elevated serum markers of inflammation,[3] severe disability,[4] and systemic extra-articular disease manifestations.[5] Although overall rates of CVD have decreased in many countries, including Sweden, in recent years, the extent of the excess risk in patients with RA has been demonstrated to be stable over time.[6,7]

Treatment with tumor necrosis factor (TNF) inhibitors has been shown to be effective in RA.[8–11] TNF inhibitors are currently recommended for the treatment of patients with active disease despite monotherapy with conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs),[12,13] in particular those with prognostically unfavorable factors.[12] In the era of more effective treatment of RA, quality of life has improved in many patients.[14,15]

Active antirheumatic treatment may also contribute to reduced risk of CVD. An observational study demonstrated reduced CVD-related mortality in patients with RA treated with methotrexate (MTX).[16] An association between lower CVD risk and anti-TNF treatment has also been found in a number of observational studies.[17,18] In particular, patients with an adequate clinical response to TNF inhibitors have been shown to have a reduced risk of CVD,[19,20] suggesting that control of inflammation may prevent RA-related cardiovascular events. However, the mechanisms underlying such associations are not completely understood.

In observational studies, an increase of serum lipid levels in patients treated with TNF inhibitors has consistently been demonstrated.[21–23] This has been attributed to reversal of the catabolic effect of inflammation, which is known to affect serum lipid levels in RA.[24] By contrast, in a meta-analysis of randomized controlled trials (RCTs), the risk of hyperlipidemia was not significantly increased in patients treated with TNF inhibitors compared with control RA patients.[25] Differences in case selection between RCTs and observational studies may explain such discrepancies.

Treatment with tocilizumab, a monoclonal antibody directed against the interleukin-6 receptor, has also been shown to increase lipid levels in patients with RA.[26] In a direct comparison, increases in serum cholesterol levels were greater in RA patients treated with tocilizumab compared with those receiving adalimumab.[27] Treatment with janus kinase (JAK) inhibitors has also been reported to increase lipid levels.[28] The clinical relevance of these effects is unclear.

A number of studies have evaluated markers of atherosclerotic vascular disease in patients with RA treated with TNF inhibitors. In such studies, intima-media thickness (IMT) of the carotid artery, which is a validated and reproducible measure of early atherosclerosis,[29] has been reported to be improved,[30,31] or to have a reduced rate of progression compared with control RA patients.[32,33] These reports included patients treated with a mix of different TNF inhibitors, and did not differentiate between individual drugs. Whether TNF inhibitors differ in their effect on the risk of CVD is unknown. There is limited information on changes in IMT during treatment with adalimumab.

The aim of this study was to investigate the effect of treatment with the adalimumab, a fully human, monoclonal anti-TNF antibody, on blood lipid levels, lipoproteins, and atherosclerosis in a Phase IV clinical trial of patients with RA.

Subjects and Methods

Study design

This was a single-center, open label, Phase IV clinical trial of adalimumab for the treatment of RA. The purpose was to evaluate the effect of adalimumab on vascular markers and blood lipid levels after 3 months of treatment. The trial was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). All participating patients gave their written informed consent to participate. The study was approved by the Regional Ethical Review Board for southern Sweden (Lund, Sweden), and also approved as a clinical trial by the Swedish Medical Products Agency. The study was monitored according to a standard protocol by an independent agent. This study is registered with ClinicalTrials.gov (identifier No. NCT01270087). Results from evaluation of vascular endothelial markers in skeletal muscle[34] and serum cytokine profiles[35] from this study have been published previously.

Inclusion and exclusion criteria

Consecutive patients with a clinical diagnosis of RA fulfilling the 1987 American College of Rheumatology classification criteria for RA[36] for whom treatment with adalimumab was indicated according to a rheumatologist, were included. They had to have been nonresponders to at least 1 DMARD. Additional inclusion criteria were at least 6 swollen joints in the 28-joint index,[37] and a C-reactive protein (CRP) level >8 mg/L at ≥ 1 occasion within the past 3 months.

Patients were excluded if they had been treated with anti-TNF drugs during the 3 months before inclusion, received intravenous corticosteroids within 14 days before inclusion, and if they had ongoing treatment with oral moderate to high-dose corticosteroids (equivalent to ≥ 20 mg prednisolone daily) or had completed such treatment <15 days before inclusion.

The protocol for the study included a muscle biopsy at baseline and at the 3-month evaluation. Details on these procedures and tissue evaluation studies, and the results of these analyses, have been described in a separate report.[34] Patients with contraindications to muscle biopsy, such as severe bleeding disorder, extensive or refractory leg ulcers, or severe peripheral vascular disease, were also excluded from the study.

Treatment

All patients were started on adalimumab, administered as subcutaneous injections of 40 mg every 14 days. Current treatment with DMARDs, glucocorticosteroids, and nonsteroidal anti-inflammatory drugs was continued. No change in the doses of these medications was allowed during the study period.

Clinical evaluation

Patients were evaluated at baseline and after 3 months for RA disease activity, using standard clinical measures (ie, number of swollen joints and number of tender joints, using the 28-joint index[37]) and patient reported outcomes (health assessment questionnaire [HAQ] disability index[38]), patient's assessment of pain (visual analog scale of 0-100), and patient's global assessment of disease activity (visual analog scale of 0-100). The composite Disease Activity Score based on 28 joints (DAS28) was calculated, as previously described.[37] Changes in disease activity (DAS28) from baseline to the 3-month follow-up were categorized according to

the European League Against Rheumatism response criteria.[39] Clinical remission was defined as DAS28 < 2.6.[37]

In addition, a standard general physical examination was performed, and data on medications and cardiovascular risk factors such as smoking, current hypertension, and history of cardiovascular events were recorded through a structured clinical interview. Blood pressure was measured with a mercury sphygomanometer to the nearest 5 mm Hg with the patient supine, after 10 minutes of rest.

Laboratory investigations

Fasting blood samples were drawn on the same day as the clinical evaluation, at inclusion and after 3 months of treatment. Serum and plasma was stored at −70 °C.

Antibodies to cyclic citrullinated peptides were detected with ELISA second generation test (Eurodiagnostica, Malmö, Sweden), whereas rheumatoid factor and CRP were quantified using nephelometry (Beckman Image; Beckman Coulter, Fullerton, California). The erythrocyte sedimentation rate (ESR) was determined using the Westergren method.

Triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol levels were analyzed in fresh serum samples, using standard methods at the Department of Clinical Chemistry, Malmö University Hospital. Apolipoprotein B (apoB) and apolipoprotein A1 (apoA1) levels were determined in thawed plasma samples, at a single time point after study completion, using standard turbidimetric immunoassays, at the Department of Clinical Chemistry, Malmö University Hospital.

Ultrasonography

On the same day as the clinical evaluation, the IMT of the common carotid artery (CCA) was assessed using B mode ultrasonography. For this investigation, an Acuson128 Computed Sonography System (Acuson, Mountain View, California), with a 7 MHz transducer, was used. The examination procedure and the image analysis system have been described previously.[29,40,41] In brief, using a standardized procedure, longitudinal images showing the intima-media complex along at least 1 cm of the CCA proximal to the bifurcation were recorded for offline analysis. The images were captured in end-diastole by R-trigging in an electrocardiogram recording. Images were analyzed offline by the sonographer according to a strict protocol and by means of a computerized image-analysis system.[40] Leading edges of wall layer echoes were outlined on the frozen video image by using a digitizer. The computer calculated IMT as the mean thickness along a 1-cm portion of the far wall of the vessel. Repeated examinations were performed without knowledge of the results of previous examinations. The identity of all patients, and the timing of the investigation (baseline vs end of study), were coded to minimize the possibility of observer bias. Mean values of 3 examinations of the left and the right CCA were calculated, and the average CCA-IMT values for each patient were determined.

Most previous studies of changes in CCA-IMT have used a longer follow-up than 3 months. However, several studies investigating effect of antidiabetes treatment using pioglitazone[42] or dipeptidyl peptidase-4 inhibitors[43] have demonstrated meaningful changes in CCA-IMT already after 3 months.

Statistical analyses

Normality of distribution for parameters at baseline and at follow-up, and for changes over time, was examined using the Shapiro-Wilk test. For comparison of findings at baseline and after 3 months treatment, the paired *t* test was used for parameters with a change demonstrating a normal distribution (eg, apoB to apoA1 ratio and CCA-IMT). For parameters without a normal distribution of the change (eg, CRP level and LDL to HDL cholesterol ratio), the Wilcoxon sign-rank test was used. Pairwise correlations between changes in different parameters from baseline to 3 months were assessed using Pearson test and Spearman test, as appropriate.

Table 1
Baseline characteristics of the included patients with rheumatoid arthritis.

Characteristic	Result
Sample size	14
Sex	11 female / 3 male
Age at inclusion, y*	63.7 (8.9)
Disease duration, y†	9.0 (2.6-11.6)
Rheumatoid factor positive‡	11 (78)
Positive for antibodies to cyclic citrullinated peptides‡	13 (93)
Methotrexate treatment at inclusion‡	8 (57)
Prednisolone treatment at inclusion‡	9 (64)
Current smoker‡	7 (50)
Systolic blood pressure, mm Hg*	134 (14)
Diastolic blood pressure, mm Hg*	77 (12)

* Values are presented as mean (SD).
† Value is presented as median (interquartile range).
‡ Values are presented as n (%).

Results

Clinical baseline characteristics

A total of 14 patients (79% women) with active RA were included (Table 1). Of these, 8 were taking MTX, with a mean dose of 18.75 mg/wk (range = 10–25 mg/wk). The other 6 had previously been treated with MTX. Nine patients were taking prednisolone (median dosage = 5 mg/d, range = 5–10 mg). Two patients had been treated with anti-TNF drugs in the past. One patient had stopped her only previous anti-TNF treatment just more than 3 months before the start of the study. The other had received 2 previous TNF inhibitors, the last of which was stopped more than 18 months before inclusion. Both these patients had discontinued anti-TNF treatment due to adverse events. No patient had been treated with other biologic DMARDs than TNF inhibitors, or with JAK inhibitors. Ten patients had previously been treated with 1 or more other conventional synthetic DMARDs, mainly sulphasalazine (n = 7) and antimalarial agents (n = 5).

The majority of patients were rheumatoid factor and/or positive for antibodies to cyclic citrullinated peptides (Table 1). Four patients had extra-articular involvement in the form of rheumatoid nodules at inclusion, but no current vasculitis or other severe manifestations were recorded. One patient had a history of systemic rheumatoid vasculitis.

At inclusion, all patients had active, severe RA, as demonstrated by high levels of DAS28 and HAQ-DI (Table 2).

Cardiovascular risk profile

Seven patients were current smokers, 3 were former smokers, and 4 had never smoked. Two patients reported a history of cardiovascular events, and another 2 had been diagnosed with hypertension. Although the mean systolic and diastolic blood pressures were within the normal range (Table 1), 6 patients had a blood pressure above 140/80 mm Hg at inclusion. Three patients used antihypertensive drugs. Diabetes or hyperlipidemia had not been diagnosed in any patient. None were treated with statins or other lipid-lowering drugs.

Table 2
Disease characteristics, blood lipid levels and CCA-IMT at baseline (before starting adalimumab) and after 3 months of treatment.*

Characteristic	Baseline	Follow-up at 3 mo	*P* value
DAS28	5.6 (1.3)	4.0 (1.4)	0.007†
HAQ-DI	1.48 (0.73)	1.30 (0.81)	0.22†
Patient global assessment‡	55 (25)	42 (29)	0.17†
CRP, mg/L	22 (9-39)	8 (2-22)	0.055§
ESR, mm/h	30 (18-47)	18 (9-31)	0.096§
Cholesterol, mmol/L	5.36 (0.98)	5.96 (1.10)	0.005†
LDL, mmol/L	3.33 (1.00)	3.77 (1.14)	0.005†
HDL, mmol/L	1.43 (0.43)	1.55 (0.48)	0.048†
LDL to HDL ratio	2.56 (1.50-3.50)	2.35 (1.54-4.05)	0.27§
Triglycerides, mmol/L	1.38 (0.70)	1.40 (0.93)	0.55§
Apolipoprotein B, g/L	1.04 (0.27)	1.13 (0.28)	0.012†
Apolipoprotein A1, g/L	1.42 (0.24)	1.58 (0.21)	0.005†
Apolipoprotein B to apolipoprotein A1 ratio	0.76 (0.25)	0.74 (0.26)	0.46†
CCA-IMT, mm	0.78 (0.16)	0.80 (0.16)	0.48†

CCA-IMT = common carotid artery-intima-media thickness; CRP = C-reactive protein; DAS28 = disease activity score based on 28-joint count scores; ESR = erythrocyte sedimentation rate; HAQ-DI = health assessment questionnaire disability index.
* Values are presented as mean (SD), except CRP, ESR, and LDL to HDL ratio, which are presented a median (interquartile range).
† Paired *t* test.
‡ Based on visual analog scale of 0 to 100.
§ Wilcoxon signed-rank test.

Lipids

All patients completed the study. Total cholesterol (mean change = 0.59 mmol/L), LDL cholesterol (mean change = 0.44 mmol/L), and HDL cholesterol (mean change = 0.12 mmol/L) levels all increased significantly, but there were no major changes in the LDL to HDL cholesterol ratio (median change = 0.06) (Table 2). There was no change in triglyceride levels (median change = –0.05 mmol/L) (Table 2).

Plasma levels of apoB (mean = 1.04 g/L vs 1.13 g/L; $P = 0.012$) and apoA1 (mean = 1.42 g/L vs 1.58 g/L; $P = 0.005$) both increased during the first 3 months on adalimumab treatment (Table 2). The mean changes in apoB and apoA1 were 0.09 g/L (95% CI, 0.02–0.15) and 0.16 g/L (95% CI, 0.05–0.25), respectively. However, the average apoB/apoA1 ratio was stable over time (mean = 0.76 at inclusion vs 0.74 at 3 months; $P = 0.46$) (Table 2).

An increase in apoA1 correlated with decreases in the patient global assessment of disease severity ($r = 0.79$; $P = 0.001$) and CRP ($r = 0.74$; $P = 0.003$). Changes in the apoB to apoA1 ratio correlated with changes in ESR ($r = 0.54$; $P = 0.046$); that is, patients with a major reduction in ESR after initiation of adalimumab were more likely to have a reduced apoB to apoA1 ratio. The correlation between changes in CRP and changes in the apoB to apoA1 ratio did not reach statistical significance ($r = 0.53$; $P = 0.052$).

CCA-IMT

The average CCA-IMT at inclusion was 0.78 mm and 0.80 mm at 3 months ($P = 0.48$) (Table 2). The mean change in CCA-IMT between inclusion and the 3-month follow-up was 0.02 mm (95% CI, –0.03 to 0.06).

Clinical outcomes

Disease activity decreased from baseline to the 3-month evaluation (DAS28 mean = 5.6 vs 4.1; $P = 0.007$). A good or moderate European League Against Rheumatism response was seen in 8 out of 14 patients. Disability measured by the HAQ-DI, and inflammation measured by CRP and ESR, were also reduced after 3 months, but the differences from baseline did not reach statistical significance (Table 2). Two patients achieved clinical remission (DAS28 < 2.6) at the follow-up at 3 months.

Discussion

In this study of patients initiating adalimumab for RA, lipid levels and apolipoproteins increased significantly, but there were no major changes in the LDL to HDL cholesterol ratio or the apoB to apoA1 ratio. Reduced inflammation was associated with an increase in apoA1, and an improved apoB to apoA1 ratio, although larger studies are needed to further assess the nature of these associations. Atherosclerosis, measured as CCA-IMT, did not change significantly during 3 months of treatment with adalimumab. There was an estimated increase in CCA-IMT of 0.02 mm, which did not reach statistical significance. For comparison, previous surveys of patients with RA not treated with TNF inhibitors have demonstrated increases of CCA-IMT of approximately 0.02 mm/y.[31,32] Given the short follow-up and the small sample size, the relevance of the estimated increase in the present study is unclear.

Most previous studies of lipid changes in RA patients treated with TNF inhibitors have mainly included patients treated with infliximab or etanercept.[21] Most observational studies have reported an increase in both total cholesterol and HDL cholesterol levels, with unchanged atherosclerotic indices (LDL to HDL ratio or total cholesterol to HDL ratio).[21] However, changes in serum lipid levels have also been evaluated in patients treated with adalimumab or tocilizumab in the ADalimumab ACTemrA (ADACTA) RCT.[27] In that study, total cholesterol, LDL cholesterol, and HDL cholesterol levels all increased significantly more in patients who were treated with tocilizumab. There was a significant increase in the total cholesterol to HDL cholesterol ratio in the tocilizumab group, but not in the adalimumab group.[27] This suggests that, although control of inflammation in general leads to increased lipid levels in patients with RA, the effects of inhibition of TNF and interleukin-6 in this context are different.

In contrast to most observational studies,[21] and to a meta-analysis of RCTs,[25] we found a significant increase in LDL cholesterol levels. The increase in total cholesterol levels in the present study was also greater than in most observational studies (mean = 0.59 mmol/L compared with an estimated average of 0.27 mmol/L in meta-analysis).[21] The magnitude of these changes suggest that they may be clinically meaningful. On the other hand, there was also a substantial increase in HDL cholesterol levels, which is in concordance with previous findings.[21]

HDL cholesterol and its main apolipoprotein, apoA1, have several putative atheroprotective functions.[44] The increase in apoA1 in this study is in accordance with a previous report on patients treated with adalimumab.[45] We cannot rule out that long-term control of inflammation may lead to improved atherogenic indices and reduce atherosclerosis, and that this could translate into a reduction of CVD events.

However, given the lack of significant changes in apoB to apoA1 ratio and in CCA-IMT in the present study, it is likely that other mechanisms may contribute to a reduced risk of CVD in patients treated with TNF inhibitors. We have previously reported decreased expression of markers of vascular endothelial activation after 3 months of adalimumab treatment in the present study sample.[34] Moreover, initiation of adalimumab in RA patients previously refractory to another TNF inhibitor (ie, infliximab) has been associated with improved endothelial function.[46] Such vascular changes may be more relevant to short-term effects of anti-TNF treatment on CVD.

Guidelines for the management of cardiovascular risk in patients with RA and other rheumatic disorders recommend the use of risk assessment algorithms based on traditional CVD risk factors, including serum lipid levels.[47] Such algorithms have been shown to be useful in patients with RA.[48] However, the importance of adequate control of inflammation through antirheumatic treatment for prevention of CVD is also underlined in current recommendations.[47]

Limitations of this study are mainly related to the small sample size, the lack of a control group of RA patients not treated with TNF inhibitors, and the relatively short follow-up. Three months may be too short to detect a change in CCA-IMT, and the findings for this outcome are therefore not unexpected. Compared with previous studies of changes in CCA-IMT during anti-TNF treatment in RA,[30–33] the participants in the present study were older, with higher proportions of smokers and more patients treated with glucocorticosteroids.

Strengths include the thorough evaluation of consecutive patients using standardized methods. Patients with previous cardiovascular events or systemic disease were not excluded. This may partly explain the differences in results on lipid changes in the present study, compared with RCTs of highly selected patients.[25] The participants in the study are representative for patients treated with adalimumab for RA in clinical practice, but were also subjected to structured follow-up using a prespecified protocol. The study therefore adds information to previous RCTs and cohort studies.

Conclusions

In patients with severe RA initiating treatment with adalimumab, serum lipid and apolipoprotein levels increased without major changes to the atherogenic profile or to CCA-IMT within 3 months. Although reduced inflammation correlated with increase of the potentially beneficial apoA1, other mechanisms may explain the negative associations between anti-TNF treatment and CVD events in observational studies.

Acknowledgments

Dr Ulf Bergström contributed to the study design, performed the major part of the data collection, contributed to the statistical analyses and the analysis and interpretation of data, and the revision of the manuscript. Dr Stefan Jovinge contributed to the analysis and interpretation of data, and the revision of the manuscript. Dr Jerker Persson contributed to the data collection, the analysis and interpretation of data, and the revision of the manuscript. Dr Lennart Jacobsson contributed to the study design, the analysis and interpretation of data, and the revision of the manuscript. Dr Carl Turesson contributed to the study design, data collection, statistical analysis and interpretation of data, and drafted the manuscript.

This study was supported by an unrestricted grant from Abbvie (see below). In addition, the study was supported by Lund University (grant No. ALFSKANE-446501 to Dr. Carl Turesson), the Swedish Rheumatism Association (grant No. R-481821 to Dr. Carl Turesson), and the Swedish Research Council (grant No. 2015-02228 to Dr. Carl Turesson).

The datasets generated and/or analyzed during the current study are not publicly available due to Swedish legislation (the Personal Data Act), but a limited and fully anonymized dataset containing the individual patient data that support the main analyses is available from the corresponding author on reasonable request.

The authors thank Gerd Östling and Birgitta Frid for their work with the ultrasonography assessments, Käth Nilsson for her work on collecting samples and clinical data, Dr. Lida Marsal for providing valuable aid in the patient recruitment, and Dr. Göran Berglund for providing valuable advice on the study.

Conflicts of Interest

Dr. Lennart T.H. Jacobsson has received consultancy fees and/or speaker honoraria from Abbvie, MSD, Pfizer, and UCB. Dr. Carl Turesson has received consultancy fees and/or speaker honoraria from Abbvie, Bristol-Myers Squibb, Janssen, MSD, Pfizer, Roche, and UCB, and unrestricted research grants from Abbvie, Pfizer, and Roche.

This study was funded by an unrestricted grant from AbbVie. AbbVie was not involved in the conduct of the study, the data analysis, manuscript preparation, or the decision to submit the manuscript. Before submission, AbbVie had the opportunity to comment on the manuscript.

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2018.07.001.

References

1. Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum.* 2005;52(3):722–732.
2. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis.* 2012;71(9):1524–1529.
3. Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. *J Rheumatol.* 1999;26(12):2562–2571.
4. Young A, Koduri G, Batley M, Kulinskaya E, Gough A, Norton S, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. *Rheumatology (Oxford).* 2007;46(2):350–357.
5. Turesson C, Jacobsson L, Bergstrom U. Extra-articular rheumatoid arthritis: prevalence and mortality. *Rheumatology (Oxford).* 1999;38(7):668–674.
6. Bergstrom U, Jacobsson LT, Turesson C. Cardiovascular morbidity and mortality remain similar in two cohorts of patients with long-standing rheumatoid arthritis seen in 1978 and 1995 in Malmo, Sweden. *Rheumatology (Oxford).* 2009;48(12):1600–1605.
7. Holmqvist M, Ljung L, Askling J. Acute coronary syndrome in new-onset rheumatoid arthritis: a population-based nationwide cohort study of time trends in risks and excess risks. *Ann Rheum Dis.* 2017;76(10):1642–1647.
8. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. *Ann Intern Med.* 1999;130(6):478–486.
9. Lipsky PE, van der Heijde DM, St Clair EW, Furst DE, Breedveld FC, Kalden JR, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med.* 2000;343(22):1594–1602.

10. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum*. 2003;48(1):35–45.
11. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum*. 2006;54(1):26–37.
12. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. 2017;76(6):960-77.
13. Singh JA, Saag KG, Bridges Jr SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol.* 2016;68(1):1–26.
14. Hekmat K, Jacobsson LT, Nilsson JA, Lindroth Y, Turesson C. Changes and sex differences in patient reported outcomes in rheumatoid factor positive RA-results from a community based study. *BMC Musculoskelet Disord*. 2014;15:44.
15. Austad C, Kvien TK, Olsen IC, Uhlig T. Health status has improved more in women than in men with rheumatoid arthritis from 1994 to 2009: results from the Oslo rheumatoid arthritis register. *Ann Rheum Dis*. 2015;74(1):148–155.
16. Choi HK, Hernan MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet*. 2002;359(9313):1173–1177.
17. Jacobsson LT, Turesson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. *J Rheumatol*. 2005;32(7):1213–1218.
18. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis*. 2015;74(3):480–489.
19. Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum.* 2007;56(9):2905–2912.
20. Ljung L, Rantapaa-Dahlqvist S, Jacobsson LT, Askling J. Response to biological treatment and subsequent risk of coronary events in rheumatoid arthritis. *Ann Rheum Dis.* 2016;75(12):2087–2094.
21. Daien CI, Duny Y, Barnetche T, Daures JP, Combe B, Morel J. Effect of TNF inhibitors on lipid profile in rheumatoid arthritis: a systematic review with meta–analysis. *Ann Rheum Dis.* 2012;71(6):862–868.
22. Curtis JR, John A, Baser O. Dyslipidemia and changes in lipid profiles associated with rheumatoid arthritis and initiation of anti-tumor necrosis factor therapy. *Arthritis Care Res (Hoboken)*. 2012;64(9):1282–1291.
23. Hassan S, Milman U, Feld J, Eder L, Lavi I, Cohen S, et al. Effects of anti-TNF-alpha treatment on lipid profile in rheumatic diseases: an analytical cohort study. *Arthritis Res Ther*. 2016;18(1):261.
24. Myasoedova E, Crowson CS, Kremers HM, Roger VL, Fitz-Gibbon PD, Therneau TM, et al. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. *Ann Rheum Dis*. 2011;70(3):482–487.
25. Souto A, Salgado E, Maneiro JR, Mera A, Carmona L, Gomez-Reino JJ. Lipid profile changes in patients with chronic inflammatory arthritis treated with biologic agents and tofacitinib in randomized clinical trials: a systematic review and meta-analysis. *Arthritis Rheumatol.* 2015;67(1):117–127.
26. McInnes IB, Thompson L, Giles JT, Bathon JM, Salmon JE, Beaulieu AD, et al. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. *Ann Rheum Dis*. 2015;74(4):694–702.
27. Gabay C, McInnes IB, Kavanaugh A, Tuckwell K, Klearman M, Pulley J, et al. Comparison of lipid and lipid-associated cardiovascular risk marker changes after treatment with tocilizumab or adalimumab in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2016;75(10):1806–1812.
28. Wolk R, Armstrong EJ, Hansen PR, Thiers B, Lan S, Tallman AM, et al. Effect of tofacitinib on lipid levels and lipid-related parameters in patients with moderate to severe psoriasis. *J Clin Lipidol*. 2017;11(5):1243–1256.
29. Persson J, Stavenow L, Wikstrand J, Israelsson B, Formgren J, Berglund G. Noninvasive quantification of atherosclerotic lesions. Reproducibility of ultrasonographic measurement of arterial wall thickness and plaque size. *Arterioscler Thromb.* 1992;12(2):261–266.
30. Ferrante A, Giardina AR, Ciccia F, Parrinello G, Licata G, Avellone G, et al. Long-term anti-tumour necrosis factor therapy reverses the progression of carotid intima-media thickness in female patients with active rheumatoid arthritis. *Rheumatol Int*. 2009;30(2):193–198.
31. Del Porto F, Lagana B, Lai S, Nofroni I, Tinti F, Vitale M, et al. Response to anti-tumour necrosis factor alpha blockade is associated with reduction of carotid intima-media thickness in patients with active rheumatoid arthritis. *Rheumatology (Oxford)*. 2007;46(7):1111–1115.
32. Giles JT, Post WS, Blumenthal RS, Polak J, Petri M, Gelber AC, et al. Longitudinal predictors of progression of carotid atherosclerosis in rheumatoid arthritis. *Arthritis Rheum*. 2011;63(11):3216–3225.
33. Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Gomez-Acebo I, Testa A, Garcia-Porrua C, et al. Anti-TNF-alpha-adalimumab therapy is associated with persistent improvement of endothelial function without progression of carotid intima-media wall thickness in patients with rheumatoid arthritis refractory to conventional therapy. *Mediators Inflamm*. 2012;2012.
34. Bergstrom U, Grundtman C, Lundberg IE, Jacobsson LT, Nilsson K, Turesson C. Effects of adalimumab treatment on endothelial cell activation markers in the skeletal muscle of patients with rheumatoid arthritis. *Clin Exp Rheumatol.* 2014;32(6):883–890.
35. Olsson P, Theander E, Bergstrom U, Jovinge S, Jacobsson L, Turesson C. Multiplex cytokine analyses in patients with rheumatoid arthritis require use of agents blocking heterophilic antibody activity. *Scand J Rheumatol.* 2017;46(1):1–10.
36. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*. 1988;31(3):315–324.
37. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum*. 1995;38(1):44–48.
38. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum.* 1980;23(2):137–145.
39. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum*. 1996;39(1):34–40.
40. Wendelhag I, Gustavsson T, Suurkula M, Berglund G, Wikstrand J. Ultrasound measurement of wall thickness in the carotid artery: fundamental principles and description of a computerized analysing system. *Clin Physiol.* 1991;11(6):565–577.
41. Persson J, Israelsson B, Stavenow L, Holmstrom E, Berglund G. Progression of atherosclerosis in middle-aged men: effects of multifactorial intervention. *J Intern Med*. 1996;239(5):425–433.
42. Koshiyama H, Shimono D, Kuwamura N, Minamikawa J, Nakamura Y. Rapid communication: inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab*. 2001;86(7):3452–3456.
43. Barbieri M, Rizzo MR, Marfella R, Boccardi V, Esposito A, Pansini A, et al. Decreased carotid atherosclerotic process by control of daily acute glucose fluctuations in diabetic patients treated by DPP-IV inhibitors. *Atherosclerosis*. 2013;227(2):349–354.
44. Tuteja S, Rader DJ. High-density lipoproteins in the prevention of cardiovascular disease: changing the paradigm. *Clin Pharmacol Ther.* 2014;96(1):48–56.
45. Wijbrandts CA, van Leuven SI, Boom HD, Gerlag DM, Stroes EG, Kastelein JJ, et al. Sustained changes in lipid profile and macrophage migration inhibitory factor levels after anti-tumour necrosis factor therapy in rheumatoid arthritis. *Ann Rheum Dis*. 2009;68(8):1316–1321.
46. Gonzalez-Juanatey C, Llorca J, Sanchez-Andrade A, Garcia-Porrua C, Martin J, Gonzalez-Gay MA. Short-term adalimumab therapy improves endo-thelial function in patients with rheumatoid arthritis refractory to infliximab. *Clin Exp Rheumatol.* 2006;24(3):309–312.
47. Agca R, Heslinga SC. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. 2017;76(1):17-28.
48. Breunig M, Kleinert S, Lehmann S, Kneitz C, Feuchtenberger M, Tony HP, et al. Simple screening tools predict death and cardiovascular events in patients with rheumatic disease. *Scand J Rheumatol*. 2017:1–8.