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Original article

Tumour necrosis factor antagonists and the risk of cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review

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Abstract

Objectives. RA is associated with early ischaemic heart disease. This appears to be driven largely by the presence of chronic inflammation. Studies suggest that treatment with disease-modifying drugs such as MTX may reduce the incidence of cardiovascular events in RA. Anti-TNF therapies significantly reduce inflammation in RA. However, the extent to which these agents also reduce cardiovascular disease (CVD) is uncertain. The purpose of this study was to explore the effect of anti-TNF agents on CVD in RA using a systematic literature review.

Methods. We searched for studies of adults with RA treated with TNF antagonists where cardiovascular outcomes were recorded using MEDLINE, EMBASE, Cochrane Database, Database of Abstracts and Reviews of Effects, Health Technology Appraisal, Science Citation Index and Clinical Evidence from 1989 to 2010. Conference proceedings for the British Society of Rheumatology, ACR and EULAR between 2005 and 2009 were hand searched. Two reviewers assessed abstracts for inclusion and then quality of selected papers was assessed.

Results. A total of 1840 abstracts were identified and 20 articles were suitable for inclusion. Information was obtained on the effect of TNF antagonists on overall CVD events, myocardial infarction, strokes and heart failure.

Conclusion. In many studies, TNF antagonists appear to reduce the likelihood of CVD in individuals with RA. Reassuringly, there does not appear to be an increased risk of cardiac failure. However, the reduction in CVD is not as consistently seen as with studies of MTX.

Key words: Rheumatoid Arthritis, Tumour necrosis factor antagonists, Cardiovascular Disease, Inflammation and Systematic Literature Review.

CLINICAL SCIENCE

Introduction

RA is an inflammatory polyarthritis that leads to joint destruction, deformity and loss of function [1, 2]. In addition, patients with RA have a reduced life expectancy, which is largely due to cardiovascular disease (CVD) [3–6]. CVD morbidity is also increased, and may be equal to the risk seen in type II diabetes [7]. The increased prevalence of CVD is probably due to an increase of both traditional risk factors for atherosclerosis and the presence of chronic inflammation [8]. Active systemic inflammation has multiple effects that accelerate atherosclerosis. These include changes to the endothelium by immune complexes, CRP and cytokines. Induction of secondary dyslipidaemia, altered glucose metabolism and creation

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of a hypercoagulable state due to platelet activation and increased production of clotting factors also play a role [9]. The importance of inflammation in the development of atherosclerosis is supported by the association of cardiovascular death with elevated levels of CRP in patients with inflammatory polyarthritis [10]. In the general population, raised levels of highly sensitive CRP (hsCRP) predict CVD events [11]. Given the importance of inflammation in the development of CVD, therapies aimed at reducing disease activity in RA may also have a positive impact on CVD risk by reducing the burden of systemic inflammation.

The link between inflammation and CVD is supported by the finding that a reduced CVD risk in RA is associated with the use of immunosuppressive therapies including MTX [12]. In the past decade, the treatment of RA has radically changed with the introduction of anti-TNF-α therapies, which are highly effective at reducing disease activity, disability and radiological damage in RA [13, 14]. TNF-α is implicated in all stages of atherosclerosis including endothelial dysfunction, plaque formation and rupture and promotion of a prothrombotic state [9]. In chronic settings, TNF-α can also induce insulin resistance and dyslipidaemia [15, 16]. It is therefore anticipated that TNF-α blockade may reduce the progression of atherosclerosis and ultimately the cardiovascular burden in patients with RA. Despite this, some studies have suggested detrimental affects of TNF antagonists in patients with heart failure and worsening of lipid profile [17, 18]. Therefore, we performed a systematic literature review to determine whether the use of TNF antagonists in patients with RA affects the likelihood of developing clinical CVD events.

Methods

We searched for studies that investigated the relationship between the use of TNF antagonists in patients with RA and clinical CVD outcomes. Studies were eligible for inclusion if they included adult patients, $\geqslant$18 years of age with RA. Children were excluded as CVD and RA are relatively rare in this age group and the commoner condition JIA is a distinct disease entity. To include the broadest range of studies patients did not have to fulfil specific diagnostic criteria for RA, but this was considered when assessing the study quality. Studies including patients with other inflammatory arthritis, e.g. PsA and AS, were excluded. Studies could be included if they examined data on the use of adalimumab, etanercept or infliximab used within the normal dosing range for RA.

Our review was intended to inform clinicians when deciding on individual treatment plans and also to identify areas of lack of evidence and promote research agendas. The clinical outcome measures selected were common clinical CVD outcomes (e.g. ischaemic heart disease, cerebrovascular disease and peripheral vascular disease). Table 1 shows a complete list of the outcomes we included.

Papers were included from 1989 onwards when the first studies demonstrating the efficacy of TNF antagonists in RA were published [13, 14]. Studies could be experimental (clinical or other controlled studies) or observational. Case reports and case series were excluded. Only English language papers were included.

Table 1 Outcomes measured

Death due to any cardiovascular disease
Myocardial infarction
Acute coronary syndrome
Angina
Ischaemic heart disease
Coronary artery disease
Heart failure
Chronic heart failure
Ischaemic cardiomyopathy
Stroke
Cerebrovascular disease
Transient ischaemic attack
Peripheral vascular disease
Aortic aneurysm
Abdominal aortic aneurysm
Thoracic aortic aneurysm

We searched MEDLINE, EMBASE, Cochrane database, Database of Abstracts and Reviews of Effects, Health Technology Appraisal, Science Citation Index and clinical evidence from 1989 to 2010. The bibliographies of all included papers were manually searched and the first authors of each paper were contacted for information on any other relevant studies or unpublished work. Conference proceedings for the British Society of Rheumatology, ACR and EULAR were hand searched from 2005 to 2009 to identify unpublished studies.

We followed the methods recommended by the Centre for Reviews and Dissemination [19] Two reviewers (S.W. and A.C.) independently assessed each title and abstract for potential relevance to the review. Full articles were retrieved if the title and abstract did not contain sufficient information and for papers fulfilling the inclusion criteria. Study quality was assessed using a tool based on the STrengthening the Reporting of Observational studies in Epidemiology (STROBE) for assessing the quality of observational studies and adapted from a tool used in a systematic literature review of infant growth and later obesity [20, 21] Studies were assessed on their use of an appropriate source population, measurement methods of exposure and outcome, methods to deal with design-specific issues such as bias and lost to follow-up, use of analytical methods and use of statistics for primary analysis of effect. Study quality was numerically assessed with a checklist of these domains and summarized with an overall assessment of the risk of bias as low, medium or high. The confounding factors we considered important were age, disease characteristics (duration, severity, level of function, RF positivity), serological measures of systemic inflammation (ESR, CRP), other drug treatments (NSAIDs, COX-2 inhibitors, other DMARDs and biologics)

and pre-existent CVD, risk factors for CVD and whether the report of CVD events was independently adjudicated. Consideration of these factors by the study authors was assessed when determining the study quality. In particular, as TNF antagonists are often started in patients with a poorer prognosis (confounding by indication) studies were considered to have a lower risk of bias if they adjusted for disease characteristics such as disease severity, erosive state and level of function. (See Tables 2–5 for individual studies level of bias and confounding factors controlled for.) Studies that provided data on all CVD outcomes and separate data on individual events [e.g. myocardial infarction (MI) or heart failure] were considered under both headings in the results section. Our approach to synthesis was mainly narrative but we explored the potential for meta-analysis according to standard procedures.

Results

A total of 1840 abstracts were identified. Twenty articles fulfilled the inclusion criteria [1 randomized controlled trial (RCT), 11 cohorts, 7 case– controls and 1 cross-sectional study]: 17 articles from the original search and 3 studies identified from poster abstracts [22–41].

TNF antagonists and all CVD comorbidity [27, 28]

The CVD morbidity outcomes considered were heterogeneous, but all studies included CVD and cerebrovascular disease. Most studies included heart failure. Seven studies: one RCT, four cohorts, one case– control and one cross-sectional were included [22–26] (Table 2). All studies had a medium risk of bias for our review. The RCT considered the risk of CVD in patients with pre-existing comorbidities treated with etanercept for 16 weeks. [22] CVD events occurred in 4.9% of patients treated with etanercept ($n = 266$) and 2.6% of controls ($n = 269$). The study was underpowered for detecting difference in CVD events and therefore no statistical analysis was performed. Three of the cohort studies included data from national biologics registers (Sweden, Spain and the USA) [23–25]. The control groups were TNF antagonist naïve patients from similar geographic locations treated with DMARDs. All studies demonstrated a statistically significant decrease in all CVD events with TNF antagonist use [rate ratio (RR) 5–7 for controls, relative risk reduction (RRR) 0.46 (95% CI 0.25, 0.85) and incident rate reduction (IRR) 0.724 ($P = 0.0491$)]. Two of the studies adjusted for markers of disease severity: one used the propensity score (the probability of being treated with biologics), which included baseline age, 28-joint DAS (DAS-28), disease duration and gender; the second adjusted for HAQ, visual analogue scale (VAS) patient global assessment, previous DMARD treatment, presently taking prednisolone, disease duration and comorbidities in separate analyses [23, 24], In the fourth cohort study (USA), retrospective analysis of a large pharmaceutical database demonstrated that use of biologic therapy in the year before the diagnosis of RA [patients fulfilled the international statistical classification of disease and health related problems-9 (ICD-9) criteria for RA, the ACR criteria was not used] did not reduce the risk of CVD in the 3.9 years follow-up [26]. No patient or biologic details were provided, including number of patients treated. In a USA study of elderly patients (mean age 81 years), the use of TNF antagonists ($n = 492$) did not alter the risk of MI or stroke when used as mono- or combination therapy compared with MTX monotherapy ($n = 1180$) [27]. This study adjusted for multiple confounders including prior MI, prior stroke, diabetes, race, number of physician visits, number of different medications, use of β-blockers, use of clopidogrel and no current use of immunosuppressive drugs. The final study [quantitative patient questionnaires in standard monitoring of patients with rheumatoid arthritis (QUEST-RA)], a large multinational study ($n = 4363$), demonstrated a 33% (95% CI 0.53, 0.85) reduction in the risk of all CVD events in patients treated for 1 year with TNF antagonists [28]. This study controlled for multiple confounders, including measures of disease severity and traditional CVD risk factors. However, there is a risk of selection bias in this study due to exclusion of patients with fatal CVD events. Ascertainment of outcomes relied on the reports of participating rheumatologists raising the possibility that reporting of outcome data may have been incomplete. Taken together, these studies suggest that TNF antagonist use is probably associated with a reduced risk of all CVD morbidity, although there may be no protective effect in elderly patients.

TNF antagonists and MI

Seven studies assessed the association between TNF antagonist use and MI: one cohort study, five case–control studies and one cross-sectional study [27–33] (Table 3). One study (cohort) had a low risk of bias for our review and the remaining six a medium risk. The study with the lowest risk of bias included patients from the UK biologics database and controls from a UK DMARD register [29]. There was no difference in the incidence of MI in TNF antagonist users compared with controls [IRR 1.13 (95% CI 0.65, 1.96)]. After controlling for multiple confounding factors, patients treated with TNF antagonists who achieved a good or moderate EULAR response (a reduction in the DAS-28 from baseline to 6 months of >1.2, or a reduction of >0.6 in addition to a DAS-28 score of $\leqslant 5.1$ at 6 months) at 6 months had a 64% (95% CI 0.19%, 0.69%) reduced risk of MI compared with EULAR non-responders. In four of the case–control studies there was no association between TNF antagonist use (mono- or combination therapy) and the risk of MI [27, 30, 31, 33]. In two of the studies, TNF antagonist use was compared with MTX monotherapy and in one to no DMARDS. Three of the studies controlled for multiple confounders and in the fourth TNF antagonist use was not a univariate predictor, and therefore no further analysis was done. In the fifth case–control study from a California database (abstract), current use of TNF antagonists combined with MTX reduced the risk of MI by 80% [RR 0.80 (95% CI 0.05, 0.88)] compared

Table 2 Summary of studies of TNF antagonist use and all-cause CVD morbidity

Study	Study type	Number of subjects	Exposure—TNF antagonist and comparator	CVD outcome	Analysis	Confounding factors controlled for	Size of effect	Conclusion (risk of bias)
[22]	RCT	All participants had a comorbidity (DM, COPD, pneumonia or recurrent infections) 266 cases (TNF) with a mean age of 60.6 years, 72.2% female, mean disease duration 9.4 years. 269 controls (placebo +/− MTX), mean age 59.3 years, 78.1% female, mean disease duration 10.1 years.	Etanercept s.c. 25 mg twice weekly for 16 weeks or s.c. injections of placebo.	Serious cardiovascular events (heart failure, CAD, MI and cerebrovascular disease).	Post-marketing analysis (no other details given). Recruitment was slow and therefore the study was underpowered.	RCT with similar baseline demographics.	In cases, 4.9% patients had serious CVD events compared with 2.6% of controls. This was not statistically significant.	No significant difference in the risk of CVD events between patients treated with etanercept and placebo (± MTX) in patients with significant pre-existent comorbidities. Medium.
[23]	Cohort	531 cases (TNF) from a Swedish database. Median age 58 years, 78% female, mean disease duration 12 years. 543 controls. Median age 61 years, 75% female, mean disease duration 12 years. Both databases covered 90% of the population.	Treatment with etanercept and infliximab.	CVD events retrieved from the Swedish National Hospital Discharge Register (nationwide coverage from 1987) and the Causes of Death Register.	Incidence/1000 rate for CVD events was calculated.	Age, gender and one marker of disease severity (disease duration, HAQ, VAS pain, VAS patient global assessment).	After adjusting for age and gender the incidence/1000 for all CVD events was 14.0 (95% CI 5.7, 22.4) for cases and 35.4 (95% CI 16.5, 54.4) for controls. The risk reduction with TNF antagonists was 0.48 for the period 1 February 1999 to 30 June 2000 and 0.32 for the period 1 July 2000 to 31 December 2001.	Use of etanercept and infliximab is associated with a decreased risk (>50%) of all CVD events. Medium.
[24]	Cohort	789 cases from the BIOBADASER database. Mean age 59 years, 79% female. 789 controls from the EMECAR (DMARDs) database. Mean age 61 years, 72% female. Mean disease duration not given.	Use of etanercept, infliximab or adalimumab.	Incidence of CVD events—IHD, HF, stroke and CVD mortality. Date of death and cause of death were obtained from charts, patients' families and regional death registries. Data on other CVD events were registered by the treating centre under AE according to the WHO	The incidence rate (IR) for CVD events was calculated. It was adjusted for the propensity score (probability of being treated with TNF antagonists) The RR compared CVD mortality between cases and controls.	Baseline age, DAS-28, disease duration and gender.	IR of IHD in cases *vs* controls = 140 (95% CI 53, 373) *vs* 881 (95% CI 569, 1366). IR for HF 175 (95% CI 73, 420) *vs* 1234 (95% CI 852, 1787). IR for stroke 105 (95% CI 34, 326) *vs* 617 (95% CI 365, 1042). All statistically significant (no *P*-value given). Mortality RR 0.58 (95% CI 0.24, 1.41).	Patients treated with etanercept, infliximab and adalimumab have a decreased risk of CVD events compared with TNF antagonist naïve patients. (Need to R/W mortality data.) Medium.
[25]	Cohort	4837 cases (TNF) from the CORRONA database and 5858 controls (no TNF). No demographics given. Median follow-up 3 years.	Current use of TNF antagonist. 2112 etanercept, 1070 adalimumab, 2254 infliximab.	Coronary artery disease, MI, congestive heart failure and stroke. Probably recorded by ICD-9 codes.	CVD events rates and IRRs were analysed using mixed Poisson regression models (unadjusted).	TNF antagonist use was only assessed in unadjusted univariate analysis.	IRR for TNF antagonist *vs* no TNF antagonist 0.724 ($P = 0.0491$). IRR for etanercept *vs* no TNF antagonist 0.577 ($P = 0.0256$).	TNF antagonist use is associated with a decreased risk of all CVD events. Medium.

(continued)

Table 2 Continued

Study	Study type	Number of subjects	Exposure—TNF antagonist and comparator	CVD outcome	Analysis	Confounding factors controlled for	Size of effect	Conclusion (risk of bias)
[26]	Cohort	16 752 cases with incident RA from an insurance database. Mean age at diagnosis 59.8 years. 72% female. Mean follow-up 3.9 years.	TNF antagonist use in the year before fulfilment of the ICD-9 criteria for RA.	History of pericarditis, retinal vasculitis, other vasculitis, ischaemic heart disease, heart failure, cerebrovasuclar disease or atherosclerosis recorded by ICD-9 code.	Cox proportional hazards model.	Gender, age, payer type, region, Charlston comorbidity index, chronic disease score, a baseline history of COPD or diabetes and a baseline use of MTX, other DMARDs, biologics, CSs and NSAIDs. The HR for CVD events was calculated using Cox proportional hazards model for use of TNF antagonists *vs* never use.	HR 0.99 (95% CI 0.83, 1.18).	TNF antagonist use before the diagnosis of RA is not associated with a decreased risk of CVD disease. Medium.
[27]	Case–control	946 cases from a USA insurance database with a CVD event. Mean age 81 years, 89% female, median disease duration 24 months. 9460 controls with no CVD event. Mean age 80 years and 92% female, median disease duration 22 months.	Use of etanercept, infliximab, adalimumab or anakinra within 90 days of the index event compared with MTX monotherapy.	Hospitalization with MI or stroke.	Logistic regression with control for multiple confounding factors to determine the OR.	Age, gender, race, hospitalization, nursing home residence, number of physician visits, number of medications, orthopaedic surgery, inflammation markers, joint aspiration/injection, RA visits, extra-articular disease, prior CVD, heart failure, DM, angina, statin use, folate use, naproxen use, non-naproxen NSAID use, COXIB use, clopidogrel use and β-blocker use.	OR of CVD with TNF monotherapy was 1.0 (95% CI 0.5, 1.9) TNF and MTX OR 0.8 (95% CI 0.3, 2.0) TNF and other DMARD OR 1.2 (95% CI 0.7, 2.2).	There is no alteration in the risk of CVD events in patients with early RA treated with TNF antagonists compared with MTX monotherapy. Medium.
[28]	Cross-sectional	4363 patients with RA from 15 countries. 78% female. 90% Caucasian. Mean age 57 years. Mean disease duration 11 years.	Years of exposure to TNF antagonists.	History of MI, angina, coronary disease, coronary bypass surgery and stroke were verified by a detailed record review and patient history.	Time of exposure to TNF antagonists was calculated in years. The HR for CVD events by years of exposure to TNF antagonists were analysed using an independent Cox regression model.	Each DMARD was analysed independently in Cox regression model first unadjusted and then adjusted for confounders. Age, gender, RF, extra-articular disease, hypertension, hyperlipidaemia, diabetes, smoking, obesity, DAS-28 and HAQ.	Adjusted HR for all CVD events 0.64 (95% CI 0.49, 0.83) MI 0.42 (95% CI 0.21, 0.81) Stroke 0.64 (95% CI 0.39, 1.05) (i.e. 1 year of MTX treatment reduces CVD events by 36% and MI by 58%).	TNF antagonist use is associated with a decreased risk of all CVD events and MI. Medium.

COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; BIOBADASER: base de datos de productos biologics de la sociedad espanola de reumatologia; EMECAR: the estudio de la morbilidad y expression clinica de la arthritis reumatoide; IHD: ischaemic heart disease; HF: heart failure; AE: adverse event; CORRONA: consortium of rheumatology researchers of North America; OR: odds ratio; COXIB: cyclooxygenase 2 inhibitor.

Table 3 Summary of studies of TNF antagonist use and MI

Study	Study type	Number of subjects	Exposure—TNF antagonist use	CVD outcome	Analysis	Confounding factors controlled for	Size of effect	Conclusion (risk of bias)
[29]	Cohort	8659 cases from the UK biologics register. Mean age 56 years, 76% female, median disease duration 12 years. 2170 controls from a DMARD register. Mean age 60 years, 72% female, median disease duration 7 years.	3844 cases treated with etanercept, 2944 infliximab and 1871 adalimumab. All cases treated for $\geqslant$6 months.	Incidence of first MI from rheumatologists and patients questionnaires and confirmed by discharge summaries or death certificate.	IRRs to compare cases with controls and TNF responders at 6 months (EULAR response) with TNF non-responders.	Age, gender, RA disease severity (DAS-28, HAQ and disease duration), BMI, social deprivation, CVD comorbidity, DM, smoking and baseline use of steroids, NSAIDs, lipid-lowering drugs and anti-platelet drugs.	The age- and sex-adjusted IRR for cases was 1.13 (95% CI 0.65, 1.96). In multivariate analysis the IRR for responders *vs* non-responders was 0.36 (95% CI 0.19, 0.69).	TNF antagonists do not reduce the risk of MI compared with treatment with DMARDs. Responders to TNF at 6 months have a significantly reduced risk of MI compared with non-responders. Low.
[27]	Case–control	438 cases (MI) Mean age 81 years, 89% female. 9460 (no MI). Mean age 80 years and 92% female.	Use of etanercept, infliximab, adalimumab or anakinra within 90 days of the index event compared with MTX monotherapy.	Hospitalization with MI.	Logistic regression with control for multiple confounding factors to determine the OR. The reference group was MTX monotherapy.	Age, gender, race, hospitalization, nursing home residence, number of physician visits, number of medications, orthopaedic surgery, inflammation markers, joint aspiration/injection, RA visits, extra-articular disease, prior CVD, heart failure, DM, angina, statin use, folate use, naproxen use, non-naproxen NSAID use, COXIB use, clopidogrel use and β-blocker use.	OR of MI with TNF monotherapy 1.7 (95% CI 0.5, 5.7) TNF and MTX OR 1.8 (95% CI 0.5, 6.8) TNF and other DMARD OR 1.5 (95% CI 0.7, 3.7).	There is no alteration in the risk of MI in patients with early RA treated with TNF antagonists compared with MTX monotherapy. Medium.
[30]	Case–control	558 cases with AMI and 5580 controls without AMI. Mean age 65 years and 55% female. No information of disease duration given.	Current exposure to infliximab, etanercept or anakinra compared with no current DMARD.	Acute MI requiring hospitalization recorded by ICD-9 code.	Conditional logistic regression was used to estimate the RR of AMI.	Age, NSAID, steroid use and comorbidity (IHD, heart failure, stroke, peripheral arterial disease, other CVDs, hypertension, diabetes mellitus, hypercholesterolaemia, respiratory disease and cancer).	RR 1.30 (95% CI 0.92, 1.83).	Infliximab, etanercept and anakinra use is associated with a non-statistically significant increase in the risk of MI. Medium.
[33]	Case–control	17 738 patients with RA. Mean age 41 years, 78% female. 283 patients with MI were compared with	The use and cumulative dose of etanercept (mean dose 50 mg/ week), adalimumab (mean dose 88 mg/	All and first MI from study questionnaires, hospital records, physician reports and death certificates.	Conditional logistic regression was used to derive OR (multiple confounders were controlled for).	College education, ethnicity, smoking status, diabetes, aerobic exercise, hypertension, comorbidity index, low-dose aspirin, BMI,	TNF monotherapy ever OR 1.1 (95% CI 0.8, 1.6) TNF monotherapy currently OR 1.3 (95% CI 0.9, 1.8)	There was no association between the use of TNF antagonists and the risk of MI. Medium.

(continued)

Table 3 Continued

Study	Study type	Number of subjects	Exposure—TNF antagonist use	CVD outcome	Analysis	Confounding factors controlled for	Size of effect	Conclusion (risk of bias)
		5660 patients without MI. The average disease duration was 9-10 years.	fortnightly) and infliximab			baseline MI status, PAS score, total joint replacement and RA duration.	TNF and MTX OR 0.7 (95% CI 0.5, 1.2) TNF, MTX and prednisolone OR 1.5 (95% CI 1.0, 2.3). No association with duration of TNF use	
[31]	Case–control	41 cases (MI) and 181 controls (no MI). Mean age of cases 67.5 years, controls 56 years. 51.2% cases male and 30.9% controls male. Disease duration <1 year in all patients.	Percentage use of TNF antagonists (drugs not stated).	First episode of MI or unstable angina diagnosed by a cardiologist.	Univariate logistic regression analysis with time-average disease activity as dependent variable.	None. TNF antagonist use was not the main focus of the paper.	TNF antagonist use: cases 4.9% ($n=2$), controls 9.4% ($n=17$) ($P=0.279$).	TNF antagonist use early in RA is not associated with an altered risk of MI. Medium.
[32]	Case–control	441 cases (MI) and 1764 controls (no MI). Mean age for entire population 54.7 years, 79.4% female. Disease duration not stated.	Current use of TNF antagonists (not stated which) defined as a filled prescription within the 60 days before the index event compared with MTX monotherapy.	Acute myocardial infarction. No other data given.	Multivariate adjusted relative risk.	38 confounding factors, including surrogate variables for smoking and dyslipidaemia, concomitant aspirin and NSAIDs. None other stated.	TNF-inhibitor combined with MTX significantly reduced the risk of MI compared with MTX monotherapy, RR 0.20 (95% CI 0.05, 0.88, $P<0.03$). There was no reduction in risk with TNF inhibitor monotherapy [RR 1.17 (95% CI 0.50, 2.75)] or in combination with another DMARD (RR 0.80 95%).	TNF inhibitors combined with MTX, but not TNF inhibitor monotherapy reduces the risk of acute MI. Medium.
[28]	Cross-sectional	4363 patients with RA from 15 countries. 78% female. 90% Caucasian. Mean age 57 years. Mean disease duration 11 years.	Years of exposure to TNF antagonist.	History of MI, verified by a detailed record review and patient history.	Time of exposure to TNF was calculated in years. The HR for CVD events by years of exposure to TNF was analysed using an independent Cox regression model.	Each DMARD was analysed independently in Cox regression model first unadjusted and then adjusted for confounders. Age, gender, RF, extra-articular disease, hypertension.	Adjusted HR forMI 0.42 (95% CI 0.21, 0.81).	The prolonged use of TNF antagonists reduce the risk of MI. Medium.

COXIB: cyclooxygenase 2 inhibitor; AMI: acute myocardial infarction; PAS: patient activity scale.

Table 4 Summary of studies of TNF antagonist use and stroke

Study	Study type	Number of subjects	Exposure—TNF antagonist use	CVD outcome	Analysis	Confounding factors adjusted for	Size of effect	Conclusion (risk of bias)
[34]	Cohort	8073 cases treated with TNF antagonists and 1807 controls treated with DMARDs from UK cohorts. No demographics given.	Use of etanercept (3782), infliximab (2812) and adalimumab (1479).	Hospitalization of death from CVA identified by patient and medical questionnaires and from death certificates.	Adjusted IRR.	Age, gender, disease duration and severity, baseline CVD and CVD risk factors.	Adjusted IRR for cases *vs* controls 0.51 (95% CI 0.27, 0.95). In the first 6/12 treated IRR 0.67 (95% CI 0.28, 1.61).	TNF antagonists are associated with a decreased risk of CVA after 6/12 of therapy. Medium.
[28]	Cross-sectional	4363 patients with RA from 15 countries. 78% female. 90% Caucasian. Mean age 57 years. Mean disease duration 11 years.	Years of exposure to TNF antagonists.	History of stroke verified by a detailed record review and patient history.	Time of exposure to TNF antagonists was calculated in years. The HR for CVD events by years of exposure to TNF antagonists were analysed using an independent Cox regression model.	Each DMARD was analysed independently in Cox regression model first unadjusted and then adjusted for confounders. Age, gender, RF, extra-articular disease, hypertension, hyperlipidaemia, diabetes, smoking, obesity, DAS-28 and HAQ.	Adjusted HR for Stroke 0.64 (95% CI 0.39, 1.05).	TNF antagonist use is associated with a non-statistically significant reduction in the risk of stroke. Medium.
[27]	Case–control	639 cases (CVA) Mean age 81 years, 89% female, median disease duration 24 months. 9460 (no CVA). Mean age 80 years and 92% female, median disease duration 22 months.	Use of etanercept, infliximab, adalimumab or anakinra within 90 days of the index event compared with MTX monotherapy.	Hospitalization with MI.	Logistic regression with control for multiple confounding factors to determine the OR. The reference group was MTX monotherapy.	Age, gender, race, hospitalization, nursing home residence, number of physician visits, number of medications, orthopaedic surgery, inflammation markers, joint aspiration/injection, RA visits, extra-articular disease, prior CVD, heart failure, DM, angina, statin use, folate use, naproxen use, non-naproxen NSAID use, COXIB use, clopidogrel use and β- blocker use.	OR of CVA with TNF monotherapy 1.5 (95% CI 0.6, 4.1) TNF and MTX OR 1.3 (95% CI 0.4, 4.0) TNF and other DMARD OR 1.2 (95% CI 0.6, 2.5).	There is no alteration in the risk of CVA in patients with early RA treated with TNF antagonists compared with MTX monotherapy. Medium.
[35]	Case–control	59 cases of RA and ischaemic stroke and 1180 RA controls. Average disease duration was 15.9 years.	Exposure to etanercept, infliximab or adalimumab any time before stroke.	Strokes confirmed by medical review and death certificates.	Conditional logistic regression to determine RR (adjusted for multiple confounders).	Prior CVD (use of low-dose aspirin), comorbidity, RA severity (total joint replacements and HAQ) and treatment variables (prednisolone, NSAIDs and DMARDs).	OR 0.79 (95% CI 0.34, 3.84) $P = 0.584$.	TNF antagonists did not alter the risk of ischaemic stroke. Medium.

CVA: cerebrovascular accident; COXIB: cyclooxygenase 2 inhibitor.

Table 5 Summary of studies of TNF antagonist use and heart failure

Study	Study type	Number of subjects	Exposure—TNF antagonist use	CVD outcome	Analysis	Confounding factors adjusted for	Size of effect	Conclusion (risk of bias)
[36]	Cohort	2757 cases treated with TNF (mean age 53.7 years, 78.1% female, mean disease duration 9 years) and 1491 controls treated with DMARDs (mean age 56.1 years, 78.9% female, mean disease duration 6 years) from German cohorts.	TNF use (etanercept, infliximab and adalimumab) within the last 6 months.	Heart failure, acute heart failure, congestive heart failure or ventricular failure diagnosed by a rheumatologist.	Cox proportional hazards model with time-dependent covariates applied to calculate the HR.	Age, sex, BMI and comorbid conditions, disease duration, RF, functional capacity, rheumatoid nodules, erosive disease and propensity score.	Adjusted HR 1.66 (95% CI 0.67, 4.1), $P = 0.28$.	Compared with patients treated with DMARDs recent use of TNF antagonists was not associated with an altered risk of stroke. Low.
[37]	Cohort	Cases $n = 1138$. 330 infliximab, mean age 40 years, 70% female; 808 etanercept, mean age 38 years, 75% female. Controls $n = 983$. TNF unexposed, on MTX. Mean age 39 years, 75% female. No disease duration given.	Use of infliximab or etanercept within the last 9 months.	Inpatient or outpatient diagnosis of HF by ICD-9 code.	Cumulative incidence ratios (CIRs) to compare the relative risk	None. The number of cases was too small to do multivariate analysis.	Etanercept CIR 5.0 (95% CI 1.3, 12.6), RR 4.9 and infliximab CIR 3.0 (95% CI 0.1, 16.8), RR 3.0. Number needed to harm 294.	The incidence of HF in patients <50 years is low. There is a non-significant increased risk of HF in patients treated with etanercept and infliximab compared with MTX. Medium.
[38]	Cohort	USA Veterans affairs. Cases (TNF) $n = 103$. Mean age 59 years, 8% female. Controls $n = 100$, (TNF unexposed). Mean age 68 years, 7% female. No disease duration given.	Treated with at least one dose of infliximab, etanercept or adalimumab.	New or worsening heart failure by ICD-9 code.	Pearson chi square analysis and Fisher's exact test to determine differences between the groups in CHF, CHF exacerbation and mortality.	None.	No difference in HF admissions between cases and controls ($P = 0.940$).	Compared with TNF naïve patients there was no increased risk of HF in patients treated with TNF antagonists. Medium.
[39]	Cohort	USA database. Cases $n = 5832$ (TNF). Mean age 60 years, 78% female, mean disease duration 14 years. Controls $n = 7339$ (no TNF). Mean age 61.5 years, 76% female, mean disease duration 15 years.	Current use of infliximab or etanercept.	Incident or prevalent HF.	Adjusted rates of heart failure between cases and controls.	Propensity score, HAQ, global severity, pain, prednisolone use, age, age squared and sex.	All HF the adjusted frequency in cases 2.8 *vs* 3.9% in controls ($P = 0.03$). Incident HF in both cases and controls 0.2% ($P = 0.68$).	Current treatment with etanercept or infliximab is associated with a decreased risk of HF compared with non-current use. Medium.
[40]	Cohort	Cases, $n = 1002$ (TNF). Mean age 72–73 years, 78–79% female. Controls (MTX), $n = 4591$. Mean age 74–77 years, 74–79% female. No disease duration given.	Current use of etanercept of infliximab compared with current use of MTX. Median duration of use 1.2 years, 55%, >2 years.	Hospitalization with HF.	Cox proportional hazards regression to determine the HR, with adjustment for the multiple confounders and the propensity score.	Demographic variables, risk factors for CVD, previous heart failure hospitalizations, factors associated with severity of RA (oral steroids, NSAIDs and other DMARDs) and other major comorbid conditions.	HR with TNF use 1.70 (95% CI 1.07, 2.69).	In elderly patients current treatment with etanercept or infliximab is associated with a significantly increased risk of HF compared with current treatment with MTX. Medium.
[41]	Case–control	520 cases and 5200 controls from and insurance database. Mean age of cases 67 years, and controls 65 years. 67% of cases were female and 75% of controls. No disease duration given.	Current use of infliximab or etanercept compared with non-current use of a DMARD.	First occurrence of congestive heart failure requiring hospitalization defined by ICD-9 code.	Conditional logistic regression to estimate the RR of hospitalization for CHF with use of infliximab or etanercept.	Age, gender, duration of time in the cohort, comorbidity, NSAIDs, COX-2 inhibitors and other DMARDs.	RR 0.5 (95% CI 0.2, 0.9).	Compared with no current DMARD use, current use of infliximab or etanercept (but not MTX, LEF or other DMARDs) is associated with a significantly decreased risk of CHF. Medium.

CHF: chronic heart failure.

with MTX monotherapy [32]. No reduction was seen with TNF antagonist monotherapy [RR 1.17 (95% CI 0.50, 2.75)] or TNF antagonists combined with other DMARDs [RR 0.88 (95% CI 0.60, 1.31)]. The analysis was controlled for 38 confounding factors, but these are not stated in the abstract. In a large multi-centre study (see above), 1 year of exposure to TNF antagonists reduced the risk of MI by 58% compared with non-use [28]. These studies suggest that TNF antagonists are not associated with an increased risk of MI in patients with RA. Responders to TNF antagonists may have a significantly decreased risk of MI compared with non-responders.

TNF antagonists and stroke

Four studies assessed the association between TNF antagonist use and stroke: one cohort, one case–control and two cross-sectional study [27, 28, 34, 35] (Table 4). All studies had a medium risk of bias for our review. Data from the UK biologics register (abstract) demonstrated a reduced risk of stroke in TNF antagonist users compared with non-users [IRR 0.51 (95% CI 0.27, 0.95)] [34]. In the UK, patients not achieving a good or moderate EULAR response at 6 months stop TNF antagonist therapy. The reduction in risk of stroke was only seen in patients treated for >6 months, suggesting that only responders to TNF antagonists have a decreased risk of stroke. In a USA case–control study, 41 RA patients with ischaemic stroke were compared with 791 RA controls [35]. After adjusting for multiple confounding factors (prior CVD, comorbidities, RA severity and treatment variables), TNF antagonist use before the stroke was associated with no alteration in risk [odds ratio (OR) 0.79 (95% CI 0.34, 3.84), $P = 0.584$]. Similar results were found in a study of elderly patients with RA [27]. Compared with MTX monotherapy, patients recently treated with TNF antagonists (as monotherapy, in combination with MTX or another DMARD) had the same risk of stroke. In a large, multi-centred cross-sectional study (see above), 1 year exposure to TNF antagonists was associated with a non-statistically significant trend towards a decreased risk of stroke [hazards ratio (HR) 0.64 (95% CI 0.39, 1.05)] [28]. In most of the studies, TNF antagonists were not associated with an alteration in the risk of stroke. In responders to TNF antagonists at 6 months the risk of stroke may be reduced.

TNF antagonists and heart failure

Six studies assessed the association between TNF antagonist use and heart failure: five cohort and one case–control study [36–41] (Table 5). One study had a low risk of bias for our review and five a medium risk. The study with the lowest risk of bias included patients from the rheumatoid arthritis observation of biologics therapy (Germany biologics register) [33] (RABBIT) [36]. After adjusting for multiple demographic, CVD- and RA-related risk factors, the risk of developing *de novo* or worsening heart failure was no different between patients treated with TNF antagonists and DMARDs, adjusted HR 1.49 (95% CI 0.70, 3.18; $P = 0.31$). A similar result was found in a small cohort study of Veterans ($n = 203$) [38]. This included predominantly male patients (92.5%) and demonstrated no difference in admissions to hospital with heart failure between those treated and not treated with TNF antagonists. A study from the USA including patients <50 years of age demonstrated a non-statistically significant increase in the risk of heart failure with TNF antagonists compared with MTX treatment, with the number needed to harm being 294 [37]. In total, however, there were only 9 cases of heart failure among 4018 patients and due to the low event rate no multivariate analysis adjusting for confounding factors was conducted. In a large cohort of elderly RA patients (mean age 73–77 years), current use of TNF antagonists compared with use of MTX was associated with a significant increase risk of hospitalization with heart failure, adjusted HR 1.70 (95% CI 1.07, 2.6) [40]. This was after adjustment for demographic variables, risk factors for CVD, previous heart failure hospitalizations, factors associated with severity of RA and other comorbid factors. One cohort and case–control study demonstrated that TNF antagonist use was associated with a significant decrease in the risk of heart failure [39, 41]. In the large ($n = 13\,171$) USA cohort study, the risk of heart failure (incident and prevalent) was statistically significantly lower in patients currently treated with infliximab or etanercept compared with patients treated with DMARDs or no DMARDs and biologics (adjusted frequency 2.8% in TNF antagonist users and 3.9% in non-users, $P = 0.03$) after adjustment for the propensity score (HAQ, pain, global severity, prednisolone use, age and gender) [39]. In patients with no history of heart failure and no use of CVD medications, the frequency of heart failure was low (0.2%), with no difference between TNF users and non-users and no increased risk in TNF users <50 years of age. In a USA insurance database case–control study, data were collected before the food and drug administration (FDA) warning on the increased risk of heart failure with TNF antagonist use [41]. After adjustment for multiple confounders, but not disease severity, current use of infliximab or etanercept compared with no DMARD use was associated with a decreased risk of first hospitalization with heart failure [RR 0.5 (95% CI 0.2, 0.9)]. The results of these studies are conflicting and therefore no definite conclusion can be drawn, particularly when comparing TNF antagonist users with DMARD users. Compared with non-DMARD users there may be a decreased risk of heart failure in TNF antagonist users. In elderly patients, the use of TNF antagonists may be associated with an increased risk of heart failure. The number of events in patients <50 years of age is too small to draw any definite conclusions.

Further analysis

We could not carry out a meta-analysis on the relation between TNF antagonist use and CVD outcomes because of the heterogeneity in study design, participants, definition of TNF antagonist use and CVD outcomes in the studies.

Discussion

Our review suggests that use of TNF antagonists may be associated with a decreased risk of all CVD comorbidity in RA. No definite association was seen with the risk of the individual events of MI, stroke and heart failure. However, overall, the number of individual events is smaller and therefore less likely to achieve statistical significance, which may explain this finding. There is a suggestion from three of the studies that the response to TNF antagonists may be important, with TNF responders having a significantly lower risk of CVD events compared with non-responders [29, 34, 36]. This suggests that the mechanism of effect is through a reduction in systemic inflammation. No firm conclusion can be drawn on the association between TNF antagonist use and heart failure as the evidence is conflicting. It is perhaps reassuring that most of the studies demonstrated no relationship between TNF antagonist use and incident heart failure as earlier studies in patients with severe heart failure demonstrated a significant worsening of heart failure with TNF antagonists [17, 42]. However, most of the studies in our review were undertaken after the FDA warning following these heart failure studies, and therefore in the majority of studies patients with pre-existent heart failure were not included. In addition, the finding that elderly patients potentially have an increased of heart failure should lead to ongoing caution in this group.

These findings contrast with our previous work that more strongly suggests a significantly decreased risk of CVD mortality and all CVD events in MTX users [12]. Interestingly, in the current review, when considering all CVD comorbidities, the studies that compared TNF antagonists with all other DMARD treatments demonstrated a reduction in the risk of CVD events, whereas those compared with MTX monotherapy demonstrated no alteration in risk. Only one study in our review demonstrated a reduced CVD risk with TNF antagonists compared with MTX monotherapy and this was only when TNF antagonists were used in combination with MTX [32]. For heart failure, only one study compared TNF antagonist use with MTX monotherapy and this demonstrated an increased risk in the TNF antagonist users [40]. These findings may suggest that TNF antagonists have no additional benefit over MTX treatment for reducing CVD but some benefit over other DMARDs.

The increased risk of CVD in RA is likely to be multi-factorial (drugs use, inactivity, etc.) but a significant contribution is thought to be due to systemic inflammation. Chronically elevated levels of cytokines, including TNF, can induce changes in the vasculature that accelerates the process of atherosclerosis including endothelial dysfunction, secondary dyslipidaemia and activation of the coagulation cascade [9]. Therefore, it would be anticipated that inhibiting TNF would significantly reduce the development of atherosclerosis and subsequently CVD. Reasons why this may not be completely evident in our review include: the possible adverse effects of TNF antagonist on lipid and glucose profiles [15, 16]; longer disease duration and therefore cumulative damage in patients treated with TNF antagonists; selection bias, as patients treated with TNF antagonists usually have the severest disease; and the short duration of the studies, the development of atherosclerosis and subsequent CVD events takes many years.

Disease duration and severity

Studies in patients with early RA have demonstrated increased intima/media wall thickness early in the disease, suggesting that accelerated atherosclerosis starts very early in the disease process [43]. Indeed, an increased risk of MI is seen soon after disease onset (personal correspondence: C.J. Edwards). Therefore, it would be anticipated that measures to decrease the risk of CVD are most effective when started early. TNF antagonist use, outside of clinical trials, is predominantly in patients with long-standing disease who are unresponsive to DMARD therapies. Indeed, most of the studies in our review included patients with a long disease duration and potentially significant cumulative damage. This contrasts with the use of DMARDs, particularly MTX, which are often used at disease onset. Despite this two studies, the review did include patients with early RA ($<$2 years duration) but demonstrated no change in risk of CVD with TNF antagonist use [26, 27]. The best way of determining whether patients with early RA have a reduced risk of CVD when treated with TNF antagonists is through RCTs. Unfortunately, to date, most of these studies have not published data on clinical CVD outcomes.

Short study durations

Clinical CVD events are often the result of many years of endothelial activation and the accumulation of atherosclerosis. Drug therapies that potentially halt or reverse this process are likely to be slow acting and require significant periods of time to be effective. Most of the studies in our review did not consider the impact of treatment length with TNF antagonists on CVD outcomes. Indeed, most of the studies did not include data on length of treatment with TNF antagonists and some only considered current or recent exposure. Interestingly, in the Quest RA study, which calculated events per year of exposure to TNF antagonists a significant reduction in the risk of all CVD events and MI was demonstrated [28]. It is therefore possible that longer treatment duration may be more important than current or recent exposure to TNF antagonists. This may also be supported by the finding that responders to TNF antagonists, who are likely to remain on treatment longer, have a reduced risk of CVD events compared with non-responders in whom therapy is stopped [23, 29].

Strengths and limitations

Our review used rigorous and standard methods: an extensive literature search was conducted; two reviewers independently assessed the relevance of abstracts for the

review; grey literature was included in an attempt to overcome publishing bias; and authors of all included papers were contacted. The main limitation of our review is interpreting the evidence of observational studies, most of which had at least a medium risk of bias. A particular potential source of bias is confounding by indication: severe RA is associated with a higher risk of CVD. TNF antagonists are more frequently used in patients with severe disease. Therefore, patients with the highest risk of CVD are more likely to be treated with TNF antagonists. Most of the studies in our review adjusted for some measure of disease severity reducing the risk of confounding by indication. The other main potential confounder is from the concurrent use of MTX. Very few of the studies presented separate data for the use of TNF antagonist monotherapy, TNF antagonists and MTX and TNF antagonists and other DMARDs. MTX use is associated with a decreased risk of all CVD events and it is therefore not possible to determine from the studies in our review whether the decreased risk of all CVD morbidities relates the use of TNF antagonists, MTX or both [12]. Our review included only patients with RA and not other inflammatory arthritides. This was because there is a strong body of evidence that RA is associated with an increased risk of CVD and the greatest amount of published information is available in RA patients. Therefore, it is not possible in this review to determine whether our findings are generalizable to other inflammatory rheumatic conditions treated with TNF antagonists or whether this is a disease-specific effect. Future reviews could consider other inflammatory arthritides as more information becomes available. Finally, it was our intention to study the effect of individual TNF antagonists on CVD outcomes. However, this was made difficult by the fact that most of the authors published information on the whole group of TNF antagonist therapies. In addition, subdivision would produce smaller numbers and reduce the relevance of our findings. Given the finding of similar efficacy of all TNF antagonists, it seems unlikely that major differences would exist on the effects of individual TNF antagonists on CVD. Further reports from national registries may help to define differences if they exist.

Conclusion

The current literature suggests that TNF antagonists are associated with a decreased risk of all CVD events and reassuringly in the majority of patients are not associated with an increased risk of heart failure. Importantly, for normal clinical practice responders to TNF antagonists, and therefore those patients who are likely to have more prolonged treatment, may have an even greater benefit. What is perhaps most striking from our review is the lack of evidence from RCTs, despite the multitude published on TNF antagonists in RA. As disease control continues to improve in RA more attention needs to direct towards reducing the risk of CVD, the leading cause of death. All future studies of new treatments in RA should collect and publish data on the impact of CVD.

Rheumatology key messages

- TNF antagonists may reduce the number of cardiovascular events in individuals with RA.
- The effect of TNF antagonists in reducing cardiovascular events does not seem as large as with MTX.

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