Published in final edited form as:

Curr Opin Rheumatol. 2008 May ; 20(3): 327–333. doi:10.1097/BOR.0b013e3282fb03d8.

Biologics and heart failure in rheumatoid arthritis: are we any wiser?

Maria I. Danila^a, Nivedita M. Patkar^a, Jeffrey R. Curtis^a, Kenneth G. Saag^a, and Gim Gee Teng^b

^aDivision of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama, USA

^bDivision of Rheumatology, Department of Medicine, National University Hospital, Singapore, Singapore

Abstract

Purpose of review—To summarize the recent literature concerning the role of TNF- α in heart failure, epidemiology of heart failure in rheumatoid arthritis and risk of heart failure associated with biologic disease-modifying antirheumatic drugs in rheumatoid arthritis.

Recent findings—TNF- α has been implicated in the pathogenesis of heart failure. It has direct deleterious effects on the myocardium in the setting of acute injury or chronic heart failure. In animal models, TNF- α is important in cardiac remodeling, leading to cardiac dysfunction following acute injury. Both incident and worsening heart failure have been reported in patients with rheumatoid arthritis who are treated with anti-TNF- α therapy. Recent cohort studies, however, have shown no increased risk and, in some, a protective effect on the risk of heart failure. Certain traditional cardiovascular risk factors have a relatively lesser contribution to cardiovascular morbidity and mortality in patients with rheumatoid arthritis, suggesting that disease-related perturbations of the cytokine network may contribute to the excess risk of heart failure in these patients.

Summary—Overall mortality in rheumatoid arthritis has remained stagnant despite advances in rheumatoid arthritis and heart failure management and improved cardiovascular mortality in the general population. Heart failure prevalence is increased in patients with rheumatoid arthritis and leads to greater mortality. Despite current expert consensus contraindicating the use of anti-TNF- α agents in patients with moderate to severe heart failure, epidemiological studies in rheumatoid arthritis have not consistently substantiated this association.

Keywords

anti-TNF- α agents; biologic disease-modifying antirheumatic drugs; heart failure; rheumatoid arthritis

Introduction

Biologic response modifiers have expanded the therapeutic armamentarium for the treatment of rheumatoid arthritis (RA) over the last decade, but concerns remain regarding adverse effects such as heart failure. Tumor necrosis factor alpha (TNF- α) may play an important pathophysiologic role in mediating heart failure; however, clinical studies of TNF- α blockade in heart failure patients have not supported this hypothesis and were halted owing to the lack of efficacy or a trend towards worsening heart failure when higher doses of anti-TNF- α agents were administered [1,2]. Patients with inflammatory diseases such as RA have a higher risk for cardiovascular disease including heart failure compared with those without RA [3-7]. Population-based cohort studies have reported incidences of heart failure of 2–4% and nearly a two-fold risk of heart failure in RA patients compared with the general population [6,8]. Disease severity of RA, in addition to predicting premature mortality [9-11], is also interrelated to cardiovascular comorbidity. Relative to other RA-related risk factors, traditional cardiac risk factors may impart a lower risk of cardiovascular events in RA patients compared with those without RA [8,12,13]. Nevertheless, the extent to which the excess heart failure risk is related to systemic inflammation, seropositivity for rheumatoid factor, age-associated comorbidities or medications used to treat RA remains unclear [14-16].

To date, TNF- α antagonists randomized controlled trials (RCTs) in RA have not reported a significant increase in cardiovascular events including heart failure. These studies, however, were not statistically powered to detect increases in this adverse effect. Enrollees were generally a highly selected group of individuals without significant comorbidities. Moderate to severe established heart failure was a typical criterion for exclusion from enrollment. Postmarketing case reports of heart failure in patients who received TNF- α antagonists have raised concerns about its potential safety signal. This review summarizes data from the past year on heart failure associated with TNF- α antagonists in patients with RA and provides an evidence-based perspective that may be useful for clinical decision making.

Recent data on epidemiology of heart failure in rheumatoid arthritis

Using data from the National Databank for Rheumatic Diseases, the frequency of heart failure, adjusted for demographic characteristics, was higher in RA patients [3.9% (95% CI: 3.4–4.3%)] than in osteoarthritis patients [2.3% (95% CI: 1.6–3.3%)] [6]. An RA inception cohort study reported a heart failure incidence rate of 2.0 per 100 person-years with a hazard ratio of 1.9 (95% CI: 1.5–2.4) compared with patients without RA, after adjusting for age, sex and presence of both ischemic heart disease and cardiovascular risk factors [8].

In a recent population-based inception cohort study of white patients with RA (n = 822) in Rochester, Minnesota, the overall mortality of RA patients remained relatively constant at 2.5 per 100 person-years over four decades, whereas the expected mortality rate of the general population declined, resulting in a widened mortality gap [17]. An earlier study [8] on the same cohort demonstrated a significantly higher cumulative incidence of heart failure (but not ischemic heart disease) in patients with RA compared with controls over 30 years (34 versus 25%, respectively, $P < 0.001$), but the risk of mortality from heart failure or

ischemic heart disease was similar between the groups. This result suggested that heart failure contributed to the excess mortality through increased incidence rather than an increased mortality associated with heart failure [5]. The same authors examined the relative contribution of cardiac risk factors and reported that male gender, smoking and personal cardiac history had a weaker association than the other traditional risk factors with cardiovascular events among the subjects with RA [18•], although results from this mainly white population could not be generalized to a more diverse population.

Despite normal left ventricle systolic function, diastolic dysfunction may occur in patients with RA who do not have clinical heart failure [19-21]. Although some previous work has shown a positive correlation of diastolic dysfunction with RA disease duration [22, 23], a recent study suggested an independent relationship [19]. It is well established that silent diastolic dysfunction predicts subsequent overt heart failure in patients without RA. Nevertheless, owing to a lack of longitudinal data and standardized diagnosis of diastolic dysfunction, currently no data are available on the factors that influence such a transition in RA. In summary, recent data support a greater risk of incident heart failure in patients with RA, related to the contribution of traditional risk factors, subclinical IHD and, possibly, diastolic dysfunction.

The association of TNF α with heart failure

TNF- α has been implicated in the pathogenesis of heart failure and cardiac cachexia. Studies have revealed negative inotropic and cardiac remodeling effects of TNF- α on the myocardium in various cardiac diseases [24 - 27]. TNF- α is not constitutively expressed in cardiac myocytes [28]. However, its synthesis in animal models can be induced by stress such as endotoxin stimulation [28], pressure overload [29] or myocardial infarction [30]. Circulating and cardiac TNF- α modulate intracellular pathways important for the stimulation of inflammation, cell growth and survival, and apoptosis [24].

Two recent studies [31•,32•] further illustrated that TNF- α contributed to adverse ventricular dysfunction by cardiac remodeling following acute injury. In a rat model of cardiac ischemia, the levels of TNF- α and other inflammatory cytokines peaked 8 days after coronary occlusion and reperfusion, in conjunction with infarct expansion and alteration in ventricular compliance [31•]. In another murine model of pressure overload induced by aortic banding, cardiac tissue expression of TNF- α , IL-6, MCP-1 and MIP-1 was significantly increased in the wild-type mice after aortic banding compared with TNF knockout mice [32•]. In the TNF knockout mice, cardiomyocyte apoptosis, hypertrophy, inflammatory response, fibrosis and cardiac matrix metalloproteinase-9 activity were attenuated and cardiac function was improved. Therefore, myocardial TNF- α seemed to mediate multiple processes important for cardiac remodeling after acute ischemia and pressure overload leading to cardiac dysfunction.

In chronic heart failure, the relative importance of TNF- α within the cytokine activation pattern might be different from that in acute cardiac injury. In dogs, TNF- α was shown to have a bimodal effect on inotropy, where initial increase in contractility was followed by marked systolic dysfunction [33,34]. In humans, serum TNF- α level is elevated in chronic

heart failure [25,35] and is a predictor of mortality in heart failure [36]. In a recent study [37•], the levels of proinflammatory markers (TNF- α , fibrinogen, sialic acid, C reactive protein) were elevated in 59 patients with stable heart failure compared with 59 healthy adults, irrespective of the cause of heart failure. In addition, levels of TNF- α and fibrinogen were associated with heart failure functional class, corroborating previous findings [26,38,39]. In contrast to serum TNF- α , myocardial TNF- α was not a useful prognostic marker for heart failure outcome in a small number of patients with chronic heart failure owing to dilated cardiomyopathy [40•].

In addition to TNF- α , other cytokines and soluble cytokine receptors may also exhibit cardiodepressor effects. A recent study [41•] using human right atrial tissue derived from clinically stable NYHA class I–II patients demonstrated that exogenous administration of clinically relevant doses of proinflammatory cytokines TNF- α and IL-1 β decreased the cardiac muscle contractility immediately. Moreover, both cytokines increased activity-specific oxygen consumption during electrical stimulation, but not basal oxygen consumption, suggesting the existence of an impaired cardiac chemo-mechanical energy transduction in human atrial myocardium. Nevertheless, results from short-term administration of these cytokines cannot be extrapolated to chronic cytokine stimulation. In addition, the properties of ventricular myocardium may be different from that of atrial tissue. The effects of TNF- α could have been mediated through IL-1 β , as IL-1 β is arguably functionally downstream of TNF- α in the cytokine network, extrapolating from our understanding of the rheumatoid synovium.

The anti-inflammatory cytokine, IL-10 downregulates the expression of several proinflammatory cytokines such as TNF- α [42]. A recent study on rats [43] evaluated the association between TNF- α -to-IL-10 ratio and myocardial depression in heart failure. As in previous studies, the levels of membrane-bound and circulating TNF- α were initially elevated after MI, but later declined towards baseline levels. In contrast, although the levels of membrane-bound IL-10 decreased over time, the levels of soluble IL-10 did not change over the 16 weeks follow-up period. An important finding of this study was that the depression in cardiac function correlated with the ratio of IL-10 and TNF- α rather than with TNF- α levels alone. By exposing rat myocardium to different concentration of IL-10 and TNF- α alone or in combination, the same authors demonstrated that the ratio between IL-10 and TNF- α , rather than each alone, was more important in mediating cardiac injury [44]. Taken together, these findings, in turn, may explain the futility of TNF- α blockade in advanced heart failure clinical trials.

In summary, the effects of TNF- α on the myocardium are complex and still not completely understood. TNF- α may mediate cardiac myocyte hypertrophy and other pathways involved in cardiac remodeling culminating in cardiac dysfunction. TNF- α may have time-dependent opposing effects and other cytokines (i.e. IL-1 β , IL-10, etc.) may also carry independent pathophysiologic importance in heart failure. The same cytokines (TNF- α , IL-1 β , IL-6) produced in abundance in the inflamed synovium of rheumatoid joints are implicated in the pathogenesis of heart failure. At present, the direct effects of inflammatory cytokines (and RA therapies) on the myocardia of patients with RA and consequential excess risk for heart failure in RA are unknown.

Heart failure with use of anti-TNF- α in rheumatoid arthritis interventional and observational studies

Randomized clinical trials are designed to establish the general safety, tolerability and efficacy of drugs and are usually not powered to evaluate the risk of rare adverse events. Therefore, it is not so surprising that no heart failure concern signals have arisen from RA RCTs of TNF- α antagonists. Recognizing that the events are reported by an investigator and have no standardized definition of heart failure applicable universally, few studies have reported heart failure as an adverse event, with frequency ranging from 0.11% in the extension phase of an adalimumab trial [45] to 0.3% in the infliximab- treated groups [46,47].

Spontaneous reporting systems such as the FDA Med- watch program and other postmarketing surveillance studies are helpful in suggesting possible safety signals of rare but serious adverse events after introduction of new agents into the market. These approaches, however, often have the limitations of underreporting, duplicate reporting, lack of denominators to determine event rates and diagnostic misclassification. A series of 38 incident cases of heart failure and nine heart failure exacerbations in patients (38 had RA) receiving etanercept or infliximab reported to the FDA MedWatch program was published in 2003 [48]. Interestingly, in this study, half of the patients that experienced new onset heart failure had no identifiable traditional risk factor for heart failure (previous myocardial infarction, coronary artery disease, hypertension or diabetes mellitus), 10 were 50 years or younger and the median interval from the first anti- TNF- α dose to diagnosis of incident heart failure was 3.5 months (range 1 day to 2 years) [48].

In recent safety analyses of adalimumab use in patients with RA [49], 0.3% had new onset heart failure, 7% had worsening heart failure. This led to an overall rate of heart failure of 0.28 events per 100 patient-years in all RCTs and subsequent open-label extensions compared with a much lower rate of 0.06 events per 100 patient-years in the postmarketing surveillance [49]. In a nationwide comprehensive monitoring system for RA patients in Sweden treated with etanercept, the reported rate of heart failure (reported as serious events) was 0.04 per 100 patient-years [50]. The difference between these rates may be explained by different methods of reporting and variable strategies to calculate the patient-year exposure to anti-TNF- α therapy.

Observational studies provide a valuable study design for addressing the epidemiology of adverse events in a 'real-world' context, but they need to be carefully conducted to have adequate internal validity and generalizability. Beyond the major challenge of addressing channeling bias in these studies (confounding by indication), another limitation is the recurring theme of misclassification of heart failure cases. Recent studies attempted to overcome this major limitation of imprecise heart failure diagnosis.

In a study of the National Databank for Rheumatic Diseases, heart failure was reported by a patient and was considered valid if supported by medical records, physician contact or documentation that it was diagnosed by a physician [6]. The validity of heart failure cases was reported to be greater than 90%. Infliximab and etanercept users had significantly less

heart failure (3.1%) than non anti-TNF- α users (3.8%), even after adjusting for important covariates using propensity scores [6]. In this cohort, the rate of incident heart failure in patients with RA without a history of cardiovascular disease was 0.4% and was not related to anti TNF- α therapy, although the number of cases was small. In patients younger than 50 years of age, no incident cases of heart failure were noted in the anti-TNF- α group. A limitation of the study is that patients who were started on anti-TNF- α therapy were less likely to have known heart failure, although adjusting for the history of heart failure did not alter the results [6].

A small case-control study of Veteran's Affairs patients with RA (n = 103) evaluated the rate of new and worsening heart failure after receiving at least one dose of etanercept, infliximab and/or adalimumab [51]. A RA control group from rheumatology clinic (n = 100) who did not receive TNF- α antagonists and a non-RA control group from a VA primary care clinic (n = 100) were used for comparisons. Heart failure was determined using the ICD-9 code for systolic heart failure coupled with medical record review. History of heart failure was present in 13% patients in all the groups. There were no significant differences between the groups with regards to hospital admissions for heart failure or all-cause mortality. Only one out of seven patients in the anti- TNF- α group had incident heart failure. The study was limited by the small sample size, a large range in the follow-up durations between the three anti-TNF- α agents, and a sensitivity of the ICD-9 codes which may be inadequate for case finding. Confounding by selection of younger patients with fewer comorbidities is also a potential concern.

The risk of hospitalization for heart failure associated with the use of disease-modifying antirheumatic drugs (DMARDs) in RA was evaluated using administrative claims data within a cohort of 41 885 patients with RA who were dispensed a DMARD between September 1998 and December 2001 [52]. The authors discussed the very high positive predictive value of the single ICD- 9 code for heart failure from previous work in Canada, which may not be generalizable. Over approximately 1 year mean follow-up, the incidence of heart failure was 1.0 event per 100 person-years. In this nested case-control study, infliximab and etanercept were shown to be associated with a lower risk for developing heart failure with a RR of 0.5 (95% CI: 0.2–0.9) relative to non-DMARD therapy, after adjustment for a variety of potentially confounding factors including use of nonsteroidal anti-inflammatory drugs and glucocorticoids [52]. The protective effect was consistent with any DMARD groups, particularly methotrexate monotherapy (RR 0.8, 95% CI: 0.6–1.0). This result suggests that the benefit was related to the control of inflammation by any disease-modifying agent and was not unique to anti-TNF- α agents alone. Potential confounding due to channeling bias was partially addressed by excluding patients with a history of heart failure. There was no increase risk of cardiovascular events even after discontinuation of DMARDs, stopping of drugs just before the event due to deteriorating health or patients becoming at risk, could potentially confer a false protective effect of the drugs.

Another recently published study [53•] evaluated the risk of incident heart failure among younger adults with RA and Crohn's disease (≥ 50 years old) exposed to etanercept or infliximab compared with those who received nonbiologic immunosuppressives. Heart

failure was initially identified by diagnosis codes for heart failure on any claims within 9 months of most recent exposure to a study drug. Subjects with heart failure prior to index date were excluded. Medical records were then reviewed for elements of the modified Framingham criteria for heart failure and ejection fraction. Among 2121 patients with RA and 1897 with Crohn's disease followed for a mean duration of 18 months, heart failure was confirmed in nine cases (0.2%). The relative risk of heart failure trended towards an increased risk at 4.3 for patients with RA who were treated with TNF- α antagonist and 1.2 for those with Crohn's disease, although neither estimate was statistically significant [53•]. Had the risk estimate been significant, the resultant numbers needed to harm would have been 294 and 3333 for RA and Crohn's disease, respectively. The selection of a younger population allowed for evaluation of incidence of new onset heart failure in those with a low prevalence of cardiovascular comorbidities. Despite being a large cohort of patients with reasonable follow-up, the small number of events limited the power of the study and the ability to control for potential confounding by indication.

A recent study evaluated the mortality from Spanish nationwide cohorts with RA treated with TNF- α antagonists from Spanish Society of Rheumatology Data- base on Biologic Products (BIOBADASER) and those not treated with TNF- α antagonist from the Morbidity and Clinical Expression of Rheumatoid Arthritis (EMECAR) registry [54•]. Causes of death were obtained from charts, patients' families and death registries. The patients had similar cardiovascular risk profile, but the EMECAR patients were older with lower disease activity and more prevalent smoking history. The age-stratified incidence rates of heart failure were significantly lower in the BIOBADASER cohort [0.4 (95% CI: 0.2–0.9)/100 person-years] compared with EMECAR cohort [1.9 (95% CI: 1.3–2.7)/100 person-years]. The mortality rate ratios (BIOBADASER/EMECAR) due to all-causes and cardiovascular diseases were decreased at 0.3 (95% CI: 0.02–0.5) and 0.6 (95% CI: 0.2–1.4), respectively, although there was significant increase in rate of infection. There was adjustment for the systematic differences expected between the two cohorts using propensity scores [54•].

In summary, albeit widely variable and imperfect definitions of heart failure, clinical studies have not shown an increased risk of new onset or worsening of clinical heart failure associated with anti-TNF- α therapies in patients with RA.

Other biological agents and heart failure in rheumatoid arthritis

Beyond anti-TNF- α therapy, there is even less data on the association of anakinra, abatacept or rituximab with cardiovascular adverse effects. There were no heart failure adverse events in anakinra RCTs [55-57] and no difference in cardiac events including heart failure in abatacept RCTs [45,58,59]. Rituximab carries a black box warning for fatal infusion reactions that may mimic or could potentially lead to heart failure, as severe infusion reactions may include hypoxia, pulmonary infiltrates, acute respiratory distress, myocardial infarction, ventricular fibrillation or cardiogenic shock [60,61]. Nevertheless, there are no published data, to our knowledge, that report associations of rituximab with heart failure.

Conclusion

Despite animal and human studies highlighting the importance of TNF- α in pathogenesis of heart failure, RCTs have shown a lack of efficacy of anti-TNF- α agents in patients with advanced heart failure. The exact role and interaction of the various cytokines implicated in the pathogenesis of heart failure remains to be elucidated.

Rheumatoid arthritis patients have a higher risk of heart failure than the general population. This increased risk can only partially be attributed to traditional cardio-vascular risk factors. Other factors such as silent IHD and diastolic dysfunction may be important. To date, there are no compelling data that TNF- α antagonist therapy in RA may worsen heart failure. If anything, the anti-inflammatory action of TNF- α antagonist therapies in RA may overall ameliorate the deleterious effects of circulating TNF- α on the heart. Until diagnostic criteria of heart failure and diastolic dysfunction are standardized and more studies performed, it is hard to refute the current recommendation to avoid use of anti-TNF- α agents in patients with heart failure, especially in those with worse functional classes.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 367).

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