

The Relationship Between Rheumatoid Arthritis and Heart Failure

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Summary

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting approximately 1 percent of the adult general population. Cardiovascular disease is recognized as the leading cause of death in RA patients, accounting for nearly 50 percent of their mortality. Patients with RA are at an increased risk for myocardial infarction, stroke, and heart failure. Some medications for RA may also worsen or precipitate heart failure. Optimal management of the RA patient requires attention to not only management of RA but also prevention of cardiovascular disease.

Key Points

- The risk of myocardial infarction, stroke, and heart failure is higher in patients with RA than those without.
- Cardiovascular damage begins at the time the disease process of RA begins and accumulates over time.
- The inflammatory process of this disease appears to be the cause for increased risk of cardiovascular morbidity and mortality.
- Patients with RA who develop HF have fewer typical presenting signs and symptoms.
- Tumor necrosis factor inhibitors should be avoided in patients with moderate to severe HF.
- Control of inflammation with tumor necrosis factor inhibitors appears to reduce risk of cardiovascular disease.

RHEUMATOID ARTHRITIS IS AN AUTOIMMUNE disease that affects 1.3 million adults in the United States.¹ Of these, about 75 percent are women. Disease onset generally occurs between 30 and 50 years of age. Disease hallmarks are synovial inflammation, progressive bone erosion, joint mal-alignment and destruction, and subsequent weakness of surrounding tissues and muscles. Systemic manifestations also occur. Presentations range from mild to severe, although the typical patient has a progressive course leading to functional limitations.

Therapies commonly used include anti-inflammatory agents [corticosteroids and nonsteroidal anti-inflammatory agents (NSAIDs)], nonbiologic disease-modifying antirheumatic drugs (DMARDs) [hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine], and biologic DMARDs [abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab] (Exhibit 1). The biologic DMARDs are also known as biologic response modifiers. The DMARDs are used to inhibit or halt the underlying

immune process and prevent long-term damage.

The era of biologic response modifiers revolutionized treatment of RA by directly targeting specific underlying immune system abnormalities. Tumor necrosis factor alpha (TNF-alpha) is one of the most important cytokines involved in the cascade of inflammatory reactions in RA. TNF-alpha inhibitors (TNFIs) bind to TNF-alpha, rendering it inactive, and interfering with inflammatory activity, ultimately decreasing joint damage. Etanercept (Enbrel[®]), the first TNFI, was FDA-approved in late 1998. Infliximab (Remicade[®]) followed in 1999 and Adalimumab (Humira[®]) in 2002. Anakinra (Kineret[®]) is a selective blocker of interleukin one (IL-1), an inflammatory protein found in excess in rheumatoid arthritis patients. By blocking IL-1, anakinra inhibits inflammation and pain associated with rheumatoid arthritis. It appears to be less effective compared with the TNFIs and is used in less than five percent of patients. Abatacept (Orencia[®]) is the first T-cell co-stimulation modulator approved for

Exhibit 1. Available Disease Modifying Antirheumatic Drugs

Commonly used nonbiologic DMARDs:

- Antimalarial medications [hydroxychloroquine (Plaquenil®) or chloroquine (Aralen®)]
- Leflunomide (Arava®)
- Methotrexate (Rheumatrex®)
- Sulfasalazine (Azulfidine®)

Less commonly used nonbiologic DMARDs:

- Azathioprine (Imuran®)
- Cyclophosphamide (Cytoxan®, Neosar®)
- Cyclosporine (Neoral®, Sandimmune®)
- Gold salts (Ridaura®, Aurolate®)
- Minocycline (Minocin®)
- Penicillamine (Cuprimine®)

Biologic DMARDs:

- Abatacept (Orencia®)
- Adalimumab (Humira®)
- Anakinra (Kineret®)
- Etanercept (Enbrel®)
- Infliximab (Remicade®)
- Rituximab (Rituxan®)

Exhibit 2^o: Hazard ratios for developing heart failure among RA subjects compared with non-RA subjects

Models	Overall RA vs non-RA	RF - RA (n=201) vs non-RA	RF + RA (n=374) vs non-RA
Age and sex	1.96	1.43	2.49
Age, sex, and ischemic heart disease (IHD)	1.95	1.27	2.83
Age, sex, and CV risk factors	1.82	1.34	2.29
Age, sex, CV risk factors, and IHD	1.87	1.28	2.59

RF-, rheumatoid factor negative; RF+, rheumatoid factor positive

the treatment of rheumatoid arthritis. Rituximab (Rituxan®), a widely used cancer medication, was FDA-approved in 2005 to be used in combination with the drug methotrexate to treat RA by reducing the signs and symptoms in adult patients who have moderately-to-severely active rheumatoid arthritis and have failed one or more anti-TNF drugs.

Rituximab selectively targets CD20-positive B-cells (B-lymphocytes). Most commonly these agents are used in combination with methotrexate.

RA is a systemic disease that actually results in a decrease in life expectancy. The median life expectancy of persons with RA is shortened by three-to-seven years.¹ Patients with RA have a higher risk of several serious comorbid conditions and they tend to experience worse outcomes after the occurrence of these illnesses. Second, patients with RA do not appear to receive optimal primary or secondary preventive care. And third, the systemic inflammation and immune dysfunction associated with RA appears to promote and accelerate comorbidity and mortality.²

There is substantial evidence of excess cardiovascular morbidity and mortality in RA patients. Recent studies have shown that the risk of myocardial infarction (MI), heart failure (HF) and stroke is higher in patients with RA.³⁻⁵ Cardiovascular disease mortality is increased by approximately 50 percent in RA patients compared with the general population.⁶

Interestingly, cardiovascular disease related to RA can manifest before the diagnosis of RA. In one study that reviewed all medical records for patients for approximately 27 years before and 15 years after the diagnosis of RA, RA subjects were significantly more likely to have been hospitalized for acute MI (odds ratio 3.17) or to have experienced unrecognized MIs (OR 5.86) compared with non-RA subjects in the two years before diagnosis.⁷ After the diagnosis of RA, patients with RA were twice as likely to suffer unrecognized MIs (hazard ratio 2.13) and sudden deaths (HR 1.94) and less likely to undergo coronary artery bypass grafting (HR 0.36) compared with non-RA subjects. Adjustment for traditional CHD risk factors did not substantially change these risk estimates. It appears that cardiovascular damage begins at the time the disease process of RA begins and accumulates over time.

Heart failure appears to be an important contributor to the excess overall mortality among patients with RA. Heart failure contributes to this excess mortality primarily through the increased incidence of HF in RA, rather than increased mortality associated with HF in patients with RA compared with non-RA subjects.⁸ People with RA have twice the risk of developing HF and this excess risk is not explained by traditional risk factors and/or clinical ischemic heart disease.⁹ Additionally, the presentation and outcome of heart failure in patients with rheumatoid arthritis differs from that in the general population.¹⁰

In a cohort study of newly diagnosed patients followed for 30 years, the cumulative incidence of HF was 34 percent in RA patients and 25 percent in non-RA subjects (p<0.01).⁹ RA conferred a sig-

Exhibit 3²⁰: Established risk factors and associative markers for the development of heart failure

Associated with CHF risk in the general population	Shown to be comparatively over-represented in rheumatoid arthritis
Clinical risk factors	
Systemic hypertension	+/-
Coronary atherosclerosis/myocardial infarction	+++
Valvular heart disease	+
Smoking	+
Obesity	+
Echocardiographic predictors	
Asymptomatic left ventricular enlargement	+
Increased left ventricular mass	+
Asymptomatic left ventricular systolic dysfunction	+/-
Left ventricular diastolic dysfunction	+++
Biochemical risk markers	
Cardiac natriuretic hormones	+
Hyperhomocysteinemia	+
Inflammatory cytokines	+++
Medications	
Non-steroidal anti-inflammatory drugs	++
Rare causes of HF in the general population	
Myocardial nodules	+
Restrictive pericarditis	++
Coronary arteritis	+

HF, heart failure. + evidence for increased prevalence; -, no evidence for increased prevalence; +/-, evidence equivocal for increased prevalence

nificant excess risk of HF even after adjusting for demographics, ischemic heart disease, and cardiovascular risk factors. Rheumatoid-factor (RF) status discriminated two groups of RA subjects at different risks of heart failure, with those who were RF positive having a higher risk than RF-negative patients (Exhibit 2).⁹ The higher risk among RF-negative patients seemed to be largely explained by clinical ischemic heart disease and/or cardiovascular risk factors, but this was not the case for RF-positive patients. The researchers noted little difference between rates of heart failure in men and women with rheumatoid arthritis, which is quite different from the situation in the general population, where rates of HF are significantly higher among men than among women. This suggests that whatever protects women from HF compared with men in the general population is not the same in patients with rheumatoid arthritis. Additionally, medications did not appear to be a contributing factor in the risk for HF. The higher risk of HF in those with RA did not change between 1995 and 2001 which was a period marked by major changes in RA therapy (i.e., the introduction of biologic DMARDs).

The exact reason why patients with RA are at higher risk for various cardiovascular diseases is not known. It is speculated that the underlying inflammatory processes of the disease contributes to increased risk and an accelerated process of atherosclerosis. We now understand that inflammation plays a crucial role in the onset and perpetuation of atherosclerosis. An injury to the blood vessel endothelium triggers an immune response, sending immune system cells rushing to repair the damage. But in chronic inflammatory states such as RA, the immune response does not shut off after the injury heals. The accumulating immune system cells along with deposits of cholesterol, blood platelets, cellular debris, and calcium clump together within the blood vessel wall to form plaque. Coronary artery tissue from autopsied RA patients has increased evidence of inflammation and an increased proportion of unstable plaques.^{11,12}

Pathogenic mechanisms appear to include pro-oxidative dyslipidemia, insulin resistance, prothrombotic state, hyperhomocysteinemia, and immune mechanisms such as T-cell activation that subsequently lead to endothelial dysfunction, a decrease

Exhibit 4²⁹:
**Incidence rates of verified first MI in
 nonresponders and responders to TNFI**

	Nonresponders (n=1,638)	Responders (n=5,877)
Person-years	1,815	9,886
No. of reported MIs	17	35
Rate of MIs per 1,000 person-years (95% CI)	9.4 (5.5-15.0)	3.5 (2.5-4.9)

in endothelial progenitor cells, and arterial stiffness, which are the congeners of accelerated atherosclerosis observed in RA patients. Anti-cyclic citrullinated peptide antibodies, which precede the onset of RA, are independently associated with the development of ischemic heart disease.¹³ Autoantibodies recognizing oxidized low-density lipoprotein strongly related with the degree of inflammation and may predispose to a higher risk for CVD, as they were independently associated with subclinical atherosclerosis in patients with RA.¹⁴ Interleukin six and TNF-alpha levels in RA patients have been shown to correlate with insulin resistance, another promoter of atherosclerosis.¹⁵

Medications used in the treatment of RA may also be a contributor to cardiovascular risk. Corticosteroids are one class which have been linked to increased heart attack risk by increasing the likelihood of high blood pressure, diabetes and high cholesterol.³ NSAIDs are also linked to increased risk of cardiovascular disease and are frequently used in RA treatment.¹⁶ Some studies examining increased CV risk in RA have eliminated medications as a reason for the differences compared to the general population whereas others have not examined the impact of medications.

A higher rate of some traditional cardiovascular risk factors (type II diabetes, hyperlipidemia, and hypertension) have been found in RA and other autoimmune disease populations.¹⁷ In a 15 year follow-up of patients with RA (73 percent female; mean age 58 years) ending in 2001, male gender, smoking, and personal cardiac history had weaker associations with CV events among RA subjects, compared to non-RA subjects.¹⁸ There was no significant difference between RA and non-RA subjects in the risk imparted with respect to the other CV risk factors

(i.e., family cardiac history, hypertension, dyslipidemia, body mass index, or diabetes mellitus). In assessing a patient's risk for cardiovascular disease, the contribution of underlying inflammation should be considered along with the traditional risk factors to gain a complete picture.

In addition to the reasons already discussed for increased CV risk, there appears to be some common pathophysiology with RA and HF. Pathological conditions contributing to myocardial dysfunction such as high serum levels of IL-6, C-reactive protein (CRP) and TNF alpha are present in both RA and HF patients. The most common pathological mechanism leading to the development of heart failure is left ventricular (LV) diastolic dysfunction, which remains clinically asymptomatic for a long time. Rheumatoid arthritis is associated with increased left ventricular (LV) mass.¹⁹ Disease duration is independently related to increased LV mass, suggesting a pathophysiologic link between chronic inflammation and LV hypertrophy. In contrast, LV systolic function is typically preserved in RA patients, indicating that systolic dysfunction is not an intrinsic feature of RA. Exhibit 3 shows the various risk factors for HF which are over-represented in RA populations.²⁰

Initial signs and symptoms of heart failure in patients with RA are less obvious than those in patients without RA. In one study, patients with rheumatoid arthritis were less likely to present with symptoms of paroxysmal nocturnal dyspnea (16 percent vs. 23 percent, $P < 0.05$), hepatjugular reflux (11 percent vs. 20 percent, $P < 0.05$), dyspnea on exertion (67 percent vs. 76 percent), orthopnea (21 percent vs. 34 percent, $P < 0.05$), and elevations in systolic or diastolic blood pressure ($P < 0.05$ for both); however, they were more likely to present with rales on physical examination (92 percent vs. 84 percent, $P < 0.05$).¹⁰ In this particular study, patients with RA had a higher frequency of preserved ejection fraction (EF 50 percent vs. 43 percent, $P = 0.007$). This suggests that diastolic dysfunction may play an important role in heart failure in RA patients. In patients without RA, preserved ejection fraction is thought to be associated with lower death rates in heart failure patients. Although myocardial function was usually better preserved in RA patients in this study, mortality was higher. The 1-year mortality after heart failure diagnosis in RA patients was 35 percent, significantly higher than the 19 percent noted in non-RA patients.¹⁰ Unfortunately, this study did not adjust for factors that may have modified the outcome such as RA disease severity, RA medications (particularly corticosteroids), comorbidities, or smoking.

Since elevated levels of TNF-alpha have been

shown in HF patients, TNFIs have been investigated as a treatment for HF. In animal models and small-scale clinical trials, anti-TNF therapy showed some promise in treating chronic heart failure, whereas larger, multicenter, randomized, placebo-controlled clinical trials failed to show a statistically significant difference in composite clinical function score for anti-TNF therapy versus placebo.²¹ In an infliximab trial, higher rates of hospitalizations and all-cause mortality were seen in patients treated with the highest dose (10 mg/kg) of infliximab compared to placebo.²² Data on the effects of other biologic response modifiers in heart failure have not been published.

Interestingly, the treatment of RA can unmask heart failure in some patients. In elderly patients with rheumatoid arthritis, treatment with TNFIs may increase their risk of new-onset heart failure and exacerbate pre-existing heart failure. In one study, anti-TNF treatment quadrupled the risk of mortality due to established heart failure compared with methotrexate treatment in RA patients over 65.²³ A study in a Veteran's Administration population showed no difference in either HF exacerbation or mortality in patients receiving TNFIs compared with an RA population not on these medications and a non-RA group.²⁴ In an examination of claims from RA and Crohn's disease patients less than 50 years old, only a small number of presumed HF cases (n = 9, or 0.2 percent) were found in a large population of relatively young patients.²⁵ Although there was an increased relative risk, HF risk was not statistically significantly different among those exposed to TNFIs compared to those unexposed. The American College of Rheumatology guidelines for use of TNF- α agents indicate they are contraindicated in moderate or severe heart failure (New York Heart Association class III-IV with reduced ejection).²⁶ Thus, despite current expert consensus contraindicating the use of TNFIs in patients with moderate to severe heart failure, epidemiological studies in a wide age range of patients have not consistently substantiated this association.²⁷

Because TNFIs are usually prescribed to patients with more active or severe RA, adverse outcomes may be incorrectly ascribed to the therapy rather than the disease. This concept, known as confounding by indication, can make it difficult to parse out helpful versus harmful effects of therapeutics in non-randomized (i.e. cohort/case-control) studies. Long standing RA or other risk factors may have contributed to the development of HF rather than TNFIs.

Although the TNFIs were not successful in treating long standing HF, there is speculation that treatment of RA with the newer biologic agents may reduce the long term risk of heart failure in younger

patients with rheumatoid arthritis by significantly reducing the inflammatory response. A study of RA patients 18 to 75 indicated that TNFI treatment that effectively reduces the inflammatory activity of RA is more likely to be beneficial than harmful with regard to the risk of heart failure, especially if there is no concomitant therapy with glucocorticoids or cyclooxygenase 2 inhibitors.²⁸ At least one study examining rates of heart failure in patients with RA or osteoarthritis found that those patients with RA who were treated with a TNFI has slightly lower rates of HF (3.1 percent versus 3.8 percent, $p < 0.5$). (Am J Med 2004;116:305-311.

There are also data that TNFIs reduce the rate of MI in patients with RA (Exhibit 4).²⁹ Other studies of TNFI use in RA have shown reduced or unchanged cardiovascular related mortality.^{30,31} Additionally, studies of methotrexate use have shown modest reduction in cardiovascular outcomes compared with other nonbiologic DMARDs. As more patients are treated earlier in the disease process, the cardiovascular outcomes of RA are likely to be improved.

Controlling traditional cardiovascular risk factors may also reduce the rate of adverse cardiovascular outcomes in RA patients. Some therapies for hypertension and lipid disorders have been shown to have impact on various markers of inflammation. These include statins and angiotension converting enzyme inhibitors. Novel targeted therapies in development may also have a major impact on future coronary heart disease risk in RA and other autoimmune diseases.³²

Conclusion

Because cardiovascular damage begins when the inflammatory process of RA begins, early diagnosis of RA is important along with the recognition of increased risk of cardiovascular disease. The contribution of inflammatory biomarkers should be considered along with the status of traditional CAD risk factors to gain a complete picture of patient's risk. Control of inflammation with TNFIs appears to reduce risk of cardiovascular disease. Although the data are inconclusive at this time, treatment of RA with TNFIs should be avoided in patients with moderate to severe HF. **JMCM**

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