Keynote Address

Heart Disease in Rheumatoid Arthritis: Changing the Paradigm of Systemic Inflammatory Disorders

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting about 1% of the adult general population[1]. A growing body of evidence supporting an inflammatory basis for atherosclerosis[2,3] has led to a reexamination of the relationship between systemic inflammatory conditions such as RA and cardiovascular (CV) disease.

CV disease is the leading underlying cause of mortality among patients with RA[4]. Indeed, persons with RA appear to have a higher risk of CV morbidity and mortality, with a standardized mortality ratio that ranges from 1.3 to 2.4 in most studies[5-7]. However, the magnitude of these excess risks, the contribution of risk factors toward these risks, and the clinical implications of these findings are not fully understood. We review these key topics, highlighting emerging knowledge in each.

CARDIOVASCULAR DEATH

Survival among persons with RA is significantly poorer than survival in the general population[8,9]. Much of the observed excess mortality appears to be driven by an increased risk of CV deaths[5,7,9,10]. Notably, there is no evidence that this worsening survival has improved. In fact, recent data suggest that the mortality gap between persons with RA and those in the general population has actually widened, suggesting that persons with RA have not experienced the same improvements in survival (Figure 1).

ISCHEMIC HEART DISEASE

Several controlled studies of the risk of ischemic heart disease in RA demonstrate relative risk estimates between 1.47 and 3.96[5,11-14]. Our own studies examining the prevalence of ischemic heart disease in RA subjects and matched non-RA controls show an increased risk of hospitalized myocardial infarction (MI) of 3.17 (95% CI 1.16, 8.68) and of silent MI odds ratio of 5.86 (95% CI 1.29, 26.64). The risk of reported angina pectoris was significantly lower among RA patients, with an odds ratio of 0.58 (95% CI 0.34, 0.99). A longitudinal analysis over the course of the disease demonstrated that the cumulative incidence of silent MI increases over time. After 30 years of followup, adjusted for competing risk of death, the risk for silent MI in RA subjects was about 6%, while the risk of silent MI in the non-RA cohort was only 3.7% ($p = 0.05$; Figure 2).

Similarly, the cumulative incidence of sudden death after 30 years of followup, adjusted for the competing risk of death by other causes, was 6.7% in the RA and 3.8% in the non-RA cohort ($p = 0.05$; Figure 3).

Histological examination of a series of 41 autopsied RA subjects and 82 age/sex matched controls has demonstrated evidence of more coronary artery inflammation in the RA subjects ($p = 0.005$ and $p = 0.024$ in the left circumflex and left anterior descending coronary arteries, respectively). Notably, among those RA subjects with preexisting CV disease, there was less histological evidence of multiple vessel disease ($p = 0.011$), less extensive coronary artery atherosclerosis ($p = 0.011$), and a lower overall grade of stenosis ($p = 0.023$ and $p = 0.029$ in the left main and left circumflex coronary arteries, respectively). However, RA subjects had more unstable plaque in their coronary arteries, 42% versus 22% ($p = 0.018$ in the left anterior descending coronary artery).

Thus, histologically, CV disease in persons with RA appears to be characterized by increased evidence of inflammation and increased frequency of unstable plaque, but less severe coronary artery atherosclerosis with fewer affected vessels, lesser extensive atherosclerosis, and lesser grade of stenosis compared to non-RA subjects.

HEART FAILURE IN RHEUMATOID ARTHRITIS

Fewer studies have addressed the risk of heart failure in persons with RA. Wolfe and Michaud reported that heart failure was more common in persons with RA compared to those without RA (3.9% vs 2.3%), and that individuals with RA appeared to have a risk factor profile similar to that of patients with osteoarthritis[15]. Population-based analyses from our group have shown that the cumulative incidence of heart failure is statistically significantly higher in RA subjects compared to controls[4].

Even after adjusting for the competing risk of death, the cumulative incidence of heart failure in the RA incidence cohort was statistically significantly greater than in non-RA ($p < 0.001$), a difference that persisted throughout the followup period (Figure 4).

Indeed, RA subjects reach the same cumulative incidence of heart failure as subjects without RA in about half the time. For example, after 10 years of followup, an RA patient has the

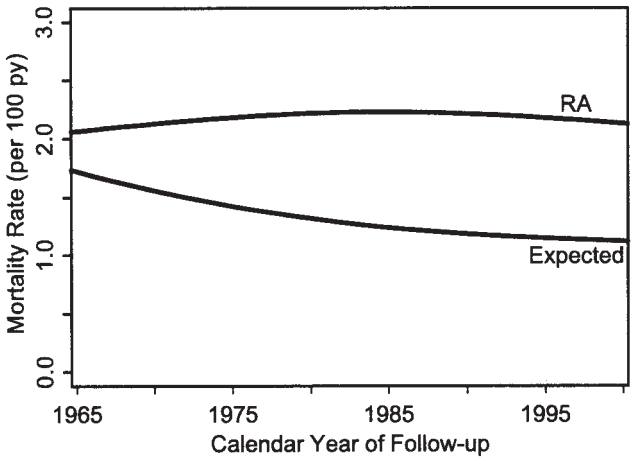

Figure 1. Trends in mortality among Rochester, MN, USA, residents with RA first diagnosed January 1, 1955, to January 1, 1995, with followup until January 1, 2005, as compared to the expected mortality among Minnesota residents over the same time period.

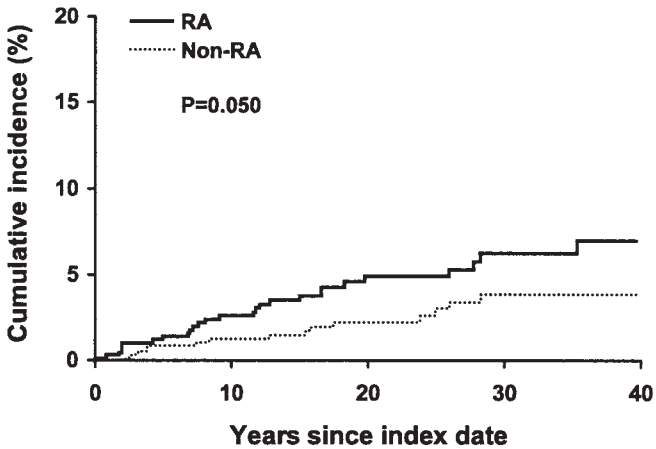

Figure 2. Cumulative incidence of silent myocardial infarction in a population-based incidence cohort of subjects with RA compared to matched non-RA subjects.

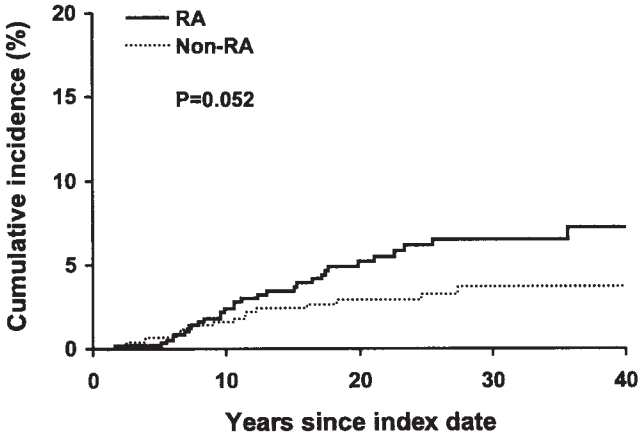

Figure 3. Cumulative incidence of sudden death in a population-based incidence cohort of RA subjects compared to matched non-RA subjects.

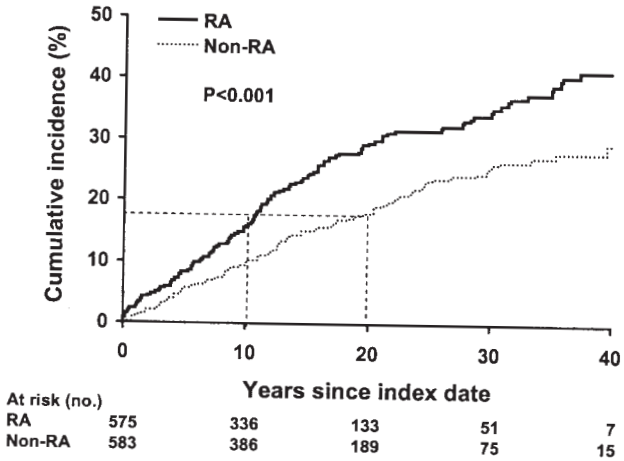

Figure 4. Cumulative incidence of heart failure in a population-based incidence cohort of RA subjects compared to matched non-RA subjects.

same probability of developing heart failure as an age and sex matched individual without RA after a full 20 years of followup (Figure 4). These differences in risk of heart failure become apparent around 45 years of age and appear to be constant across ages, i.e., at any particular age, the incidence of heart failure in RA subjects is about twice that in non-RA subjects.

This risk changed minimally even after accounting for the presence of ischemic heart disease and other risk factors with regression modeling. Moreover, the excess risk appeared to be largely confined to rheumatoid factor (RF)-positive RA cases. Indeed, RF-positive RA subjects had a risk of developing heart failure that was 2.5 times greater than in non-RA subjects. This is similar to the excess risk of heart failure experienced by persons with diabetes mellitus[16].

Thus, patients with RA appear to be at increased risk of heart failure. Since heart failure is a highly fatal disorder, this excess risk likely explains a proportion of the excess mortality in persons with RA[17].

CARDIOVASCULAR RISK FACTORS IN RHEUMATOID ARTHRITIS

Several factors can modulate CV risk in persons with RA. These can be categorized into traditional CV risk factors (e.g., smoking), markers of inflammation and RA disease (e.g., RF), and medications used to treat RA (e.g., methotrexate). The role these risk factors play in promoting CV disease in RA is unclear. The central question is whether persons with RA have an increased incidence of CV risk factors, whether the risk of CV disease imparted by these factors is greater in persons with RA compared to those without the disease, or whether the excess risk is independent of known risk factors, i.e., due

to an unknown or unmeasured factor. Our group and others have examined this question and observed that the incidence of CV risk factors [i.e., rates of hypertension, dyslipidemia, high body mass index (BMI), and diabetes mellitus] among persons with RA does not appear to differ from those in the general population[18]. The impact of traditional CV risk factors on CV disease (defined as the combined endpoint of MI, heart failure, and CV death) was also examined. These analyses clearly showed that the risk imparted by traditional CV risk factors (i.e., smoking, personal history of ischemic heart disease, family history of ischemic heart disease, hypertension, dyslipidemia, BMI $\geq$ 30 kg/m^2, and diabetes mellitus) on the CV outcome is not higher in RA compared to non-RA subjects[9,19].

An examination of the independent contribution of RA disease characteristics and inflammatory indicators, and RF all demonstrate that these characteristics are significantly associated with increased CV morbidity and mortality, after adjusting for other CV risk factors and comorbidities[9,20,21-23]. Together these data indicate that markers of inflammation and RA characteristics are risk factors for CV morbidity and mortality, and underscore the importance of additional research focused on more clearly explicating the biological mechanisms underlying CV disease in persons with RA.

The role of RA medications in CV disease risk is somewhat more controversial. Our own data suggest that corticosteroids may attenuate the risk of CV death in patients with RA who have a history of ischemic heart disease[9]. The effect of other agents on RA mortality has been somewhat controversial. For example, with respect to methotrexate, there has been one publication demonstrating that methotrexate may have a survival benefit, largely by reducing CV mortality[24], while another concluded that methotrexate significantly increases CV morbidity and mortality in RA subjects, perhaps by increasing serum homocysteine[25]. More recently, Suissa and colleagues showed that disease modifying antirheumatic drug use, including methotrexate, is associated with a reduction in MI risk in patients with RA[26].

In summary, a number of significant risk factors have been identified that may modulate the risk of CV morbidity and mortality in persons with RA. These include traditional CV risk factors, such as history of ischemic heart disease, smoking, hypertension, and diabetes mellitus; and RA characteristics such as joint swelling, rheumatoid vasculitis, and RA lung disease; as well as markers of inflammation and immune dysregulation such as elevated erythrocyte sedimentation rate and positive RF. The role of RA medications in CV risk is somewhat more controversial, but emerging evidence suggests that use of disease modifying antirheumatic drugs may, in fact, reduce CV risk in persons with RA.

CONCLUSIONS

The mortality gap between persons with RA and the general population appears to be widening. RA patients experience a higher risk of CV death, ischemic heart disease (especially silent MI), sudden cardiac death, and heart failure. These CV risks occur early in the disease and may be silent and without warning. Traditional CV risk factors are important, but are only one piece of a very complicated puzzle leading to the excess CV risk in persons with RA. RA characteristics such as erythrocyte sedimentation rate, RF positivity, large joint swelling, vasculitis, rheumatoid lung, and the presence of autoantibodies are also highly significant predictors of CV morbidity and mortality in persons with RA. Together, these findings suggest that the systemic inflammation and immune dysfunction that characterize RA appear, in themselves, to promote CV disease and CV death, and that effective, even optimal control of traditional risk factors alone will be inadequate in reducing the excess risk of CV disease and CV death in persons with RA.

From a clinical perspective, these results underscore the importance of vigilance with preventive care and a high index of suspicion for CV disease. However, it is also evident that more research is needed to clearly define the disease mechanisms leading to the excess risk of CV morbidity and mortality in RA, and to identify high risk groups in whom preventive intervention should be targeted.

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