Rheumatic Disease, Inflammation, and the Heart

Faculty
Cheryl L. Lambing, MD, FAAFP
Clinical Professor
Department of Family Medicine
University of California, Los Angeles
Medical Director,
Ventura County Health Care Agency
Professional and Community Education and Outreach,
Ventura, California

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Learning Objectives
• Discuss the pathogenic mechanisms for cardiovascular risk in rheumatic disease
• Implement risk recognition and management strategies based on rheumatic disease activity and inflammation
• Apply clinical recommendations to improve cardiovascular outcomes for patients with common inflammatory joint disease and autoimmune conditions

Inflammatory Joint Disease and Autoimmune Conditions
Inflammatory joint disease and autoimmune conditions represent some of the most diverse, challenging, and controversial clinical disorders faced by physicians

Common inflammatory autoimmune RD: RA, SLE, PsA, AS, SS

Overall Lifetime Risk
• Risk of developing inflammatory autoimmune related-disease in US adults
  - 1 in 12 for women
  - 1 in 20 for men
• Greater than generally recognized
• Smaller than lifetime risks for other common diseases
• Autoimmune diseases fall in top 10 leading causes of death for women aged 15-64 years (usually 7th/8th) behind accidents, malignancies, CVD, CVA, chronic obstructive pulmonary disease, DM, and human immunodeficiency virus

CVD = cardiovascular disease; CVA = cerebrovascular accident; DM = diabetes mellitus
Autoimmune Diseases: Cardiovascular Events Are a Major Cause of Morbidity and Mortality

- Increased frequency in all autoimmune diseases (largest data set includes 110,000 patients with RA)
  - Autoimmune severity/disease activity
  - Corticosteroid therapy
  - Comorbid diseases (chronic kidney disease, congestive heart failure, insulin-dependent diabetes mellitus)
- Risk of CVD is 50% higher than the general population
- Risk of CVA is 52% higher than the general population
- Risk of mortality for ischemic heart disease is 59% higher than the general population

Risk of CVD

- Patients with rheumatic diseases are at increased risk of developing CVD
- Pathogenic mechanisms clinical expression of cardiovascular complications vary within rheumatic diseases
  - Rheumatic diseases are numerous
  - Risks vary in magnitude
  - Risks differ by age and sex
- Atherosclerosis is prominent in all inflammatory joint diseases, plus other non-ischemic cardiac conditions, heart failure, microvascular dysfunction, arrhythmias
- CVD model in RA most extensively studied

CVD

- CVD comorbidities/complications are most common
- Most significant impact on morbidity and mortality
- Only partially explained by traditional risk factors, medications, or both
- Rheumatic disease/inflammatory joint disease is an independent risk factor for CVD
  - Evidence disease activity impact on CVD risk
  - Cumulative disease activity/duration, number/duration of flares over time contribute to CV risk

Model of RA

- Increased risk of premature death compared with the general population (CVD)
- Cardiovascular risk increased two-fold
  - Same magnitude as patients with DM
- Early and accelerated atherosclerosis
- Increased risk of myocardial infarction

Model of RA (cont)

- Overall mortality rate decline over 1-2 decades
  - Gap between patients with RA and general population remains significant
  - In inflammatory joint disorder 10-year data, increased CV risk but CV-related mortality has not improved despite anti-rheumatic therapy
  - Non-optimized clinical management/risk reduction widespread; highlights need for education and better tools
  - Disease factors may have differential impacts on CV mortality vs all-cause mortality

Manufacturing Antibodies Directed to Body Cells

Complex Pathogenesis

- Genetics
- Epigenetics
- Auto-Antibodies
- Immunologic
- Hormonal Factors
- Environmental Triggers

Examples of Autoantibodies

**Rheumatoid Factor**
- Autoantibody to Fc IgG
- Fixes and activates complement
- Inflammatory cascade
  - Multi-organ involvement not uncommon
  - Systemic

**Anti-CCP Antibodies**
- Citrulline-amino acid derived from arginine
- Tightly binds to filamentous proteins, such as fibrin
- Citrullinated fibrin may be an important antigen in autoimmune process of RA
- 50% to 60% sensitivity; 95% to 98% specificity
- Predictive for active/erosive disease

**Clinical Syndromes Differing**
- Disease subsets
- Inflammatory cascades
- Patterns of progression

**Autoantibodies**

**Inflammation**

**Cytokines**

How Does This Occur?

**Cardiovascular Risk and Inflammatory Joint Disease**

**Cardiovascular Risk/CVD in Patients with Inflammatory Joint Disease**
- Unrecognized risk
- Underdiagnosed
- Undertreated
- Less preventative measures compared with those of the general population

**Cornerstone of Management**

**Cardiovascular Risk Management: Control of Disease Activity**
Management of Risk Factors

- Non-pharmacologic
  - Smoking cessation
  - Exercise
  - Healthy diet, including vitamin D intake
- Pharmacologic
  - Statins
  - Anti-hypertensives

Clinical Challenge

- Pathogenic mechanisms/clinical expression of CVD vary within rheumatic diseases
- Atherogenesis and atherosclerosis are a common pathway

Lipid Paradox

- Interpretation unclear; active inflammation results in reduction total cholesterol, LDL, HDL compared to the general population
- Altered predictive value; lipid-lowering interventions underutilized clinically
- Lowered lipids correlate with higher CV risk, altered lipids with pro-atherogenic effects
- Consider lipid measurements only during quiescence (controlled inflammation)
  - DAS28 (Disease Activity Score)

Clinical Assessment

Overactive Immune System
Mild Reactive Immune System

Vague Symptom Complex

Time

Vague Mild

Nonspecific Autoantibodies


Visual Analog Scale

Considering all the ways your arthritis affects you, how well are you doing?

Very Well

Very Poor


Application for Diagnosing RA and Measuring Disease Activity

Active Synovitis Correlates with Inflammation and Atherosclerosis

• Patients with RA are more likely to demonstrate coronary plaques, plaque rupture, high risk of infarction with poor outcomes, hypercoagulable states
• Immune and coagulable systems are activated by inflammatory mediators
• SLE confers higher risk due to contribution of hypercoagulable mediators


RD (RA Model), Insulin Resistance, and DM

• Strong correlation
• Inflammation and insulin resistance correlate; increased inflammation, higher level of disease activity predicts degree of insulin resistance
• Anti-rheumatic treatment (anti-TNF, MTX, hydroxychloroquine) appears to reverse insulin resistance

TNF = tumor necrosis factor; MTX = methotrexate.

Organ System Inflammation

Antibodies → Cytokines → Organ Dysfunction

Progressive Accumulation of Autoantibodies (SLE)

- Increased organ system involvement or symptoms
- ANA, Antiphos SSA/SSB dsDNA Sm, RNP

Length of Symptoms (Time Since Presentation)

SLE

- Highest CV risk, multifactorial
  - Traditional risk factors, inflammation, endothelial alteration, pro-thrombotic microenvironment, anti-phospholipids, anti-cardiolipins, corticosteroids
  - Complex alteration in lipid metabolism; autoantibodies impact lipoproteins involved in atherogenesis, foam cells, plaque formation
  - Advanced atherosclerosis

Survival 20 Years Ago

- Poor prognostic features
- Survival
  - 50% over 5 years

Current Survival Estimates in Autoimmune Disease

- Improved overall survival unless poor prognostic factors present
  - More antibodies and more organ systems affected
  - Improvements continue with medical advances (eg, SLE)

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<th>All Patients</th>
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<tr>
<td>5 years</td>
<td>96%</td>
<td>90%</td>
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<tr>
<td>10 years</td>
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<td>85%</td>
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<td>15 years</td>
<td>76%</td>
<td>65%</td>
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Clinical Application

- Limitation to cardiovascular risk tools
- Using routine tools, rheumatic patients appear to have reduced risk
- Risk underestimated, especially in women
- Clinical application
  - EULAR clinical recommendations
EULAR Clinical Recommendations

- Calculation using established CV risk assessment tools
- Multiply by cofactor for disease >10 years, positive RF or CCP, presence of anti-cardiolipin or anti-phospholipids or extra-articular manifestations
- Other potential assessments have been studied in small studies, not tested adequately (carotid duplex for plaque or biomarkers)

Clinical Recommendations for Cardiovascular Risk Management for Inflammatory Rheumatic Conditions

- Low threshold for identification of rheumatic patients (RA/IJD) as high risk of CV disease
- Control of inflammatory disease to reduce CV risk

Clinical Recommendations (cont)

- Apply CV risk stratification and intervention using established guidelines, reassess annually and with change in disease activity/treatment
- 1.5 multiplication factor applied to risk assessment models
- Limited utility of lipid profile
  - Best option total cholesterol/high-density lipoprotein ratio most stable marker for CV risk
- CV risk interventions; use established guidelines, including preferred agents (statins, angiotensin-converting enzyme inhibitor)

Clinical Recommendations (cont)

- Caution use of NSAIDs in the presence of CV risk
- Lowest effective dose, shortest duration of corticosteroids
- Smoking cessation

Clinical Pearls

- Medically complex diseases that impact multiple organ systems
- Cannot change genetics, gender, or even environmental exposures
- Recommend healthy lifestyles and control of environmental factors that are controllable, such as smoking, blood pressure, dietary intake, weight gain, DM (impact on the immune system), and early atherosclerosis
- Recommend early identification (for intervention or surveillance) before increased antibody load, antibody localization, inflammatory cytokines
- Making an early diagnosis is complex but critical in improving CV outcomes

Prognosis of RD

- CV Complications
  - Mild
  - Severe or Multi-organ

RF = rheumatoid factor.
Take-Away Points

- Cardiovascular events are a major cause of morbidity and mortality in patients with RD (cardiovascular burden)
- Smoking cessation/avoidance is a critical intervention for individuals at risk for RD and especially for RA
- Disease activity, duration of disease, presence of flares, and other poor prognostic features correlate with chronic inflammation, which is closely linked to atherosclerosis
- Early diagnosis, early treatment, and control of inflammation represent the mainstay for management
- Assess all patients with RD regularly using CV tools/cofactor
- Ensure guideline-recommended CV-preventive measures are implemented

Questions?