Rheumatoid Arthritis:

A New Era in Understanding and Treatment

Blum Center Program
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CDC estimates that 23% (54 million) U.S. adults have arthritis.
Prevalence of common forms of arthritis in the US (in millions)\(^1,3-5\)

- **Osteoarthritis (OA)**: degenerative, occurs with aging. Does not respond to medications well, surgery may help.
- **Inflammatory** swelling, stiffness responds to medications.

**Legend:**
- JIA: juvenile idiopathic arthritis (juvenile rheumatoid arthritis)
- PMR: polymyalgia rheumatica
- RA: rheumatoid arthritis

**Numbers:**
- Osteoarthritis (OA): 26.9
- Gout: 6.1
- Rheumatoid arthritis (RA): 1.3
- Psoriatic arthritis: 0.52
- JIA: 0.3
- PMR: 0.7

RA: rheumatoid arthritis; JIA: juvenile idiopathic arthritis (juvenile rheumatoid arthritis); PMR: polymyalgia rheumatica.
Rheumatoid Arthritis (RA)

- Most common form of autoimmune arthritis, affects 1.3 million people
- Primarily involving joints, but may cause other symptoms
- Can lead to damage and destruction
- Typically affects the wrists and small joints of the hands and feet, but can affect many joints, including the spine
Who is affected by RA?

- Anyone, at any age
- Most common in middle age
- Women 2-3X more than men

![Annual Incidence of Rheumatoid Arthritis between 1995-2007, by sex and age group]

Note: This data is based upon the annual incidence of rheumatoid arthritis (per 100,000) in Olmstead County, Minnesota between 1995 and 2007.


![Rhematoid Arthritis among Gender]

Figure-1: Distribution of rheumatoid arthritis with respect to gender.
What are the signs of RA?

• Pain and swelling in multiple joints on both sides of the body (polyarthritis)
• >6 weeks in duration
• Typically worse in the morning
• Associated with stiffness (>30 min)
• Better with activity
• Systemic symptoms: fatigue, fever, loss of appetite, dry eyes/mouth (Sjogren’s)
Mechanisms/Causes of RA
Arthritic Joints
RA: mechanisms

[Diagram showing autoimmune mechanisms in RA: genetic and environmental triggers lead to joint damage through interactions between secondary lymphoid tissue, autoantibodies, and immune cells like dendritic cells, T cells, and B cells. Key mediators include TNF-alpha, IL-1, IL-6, IL-17, GM-CSF, and downstream mediators in the synovium and cartilage.]
Antibodies, asymptomatic

Clinical arthritis
Genes and RA

- RA Risk:
  - Identical twins: 15-30%
  - Fraternal twins: 5%
  - General population: 1%

- Genes important, but explain only small portion of RA

- Known genetic risk factors: HLA-DR alleles, PTPN-22
Environmental triggers of RA

• Not well understood, and likely many causes
• Smoking
• Obesity
• Live births, breastfeeding, alcohol: protective
• Viral and bacterial infections?
The trillions of microorganisms living on/in human body and their genetic material

- Majority live in the gut
- 10X more bacterial cells than human cells
- Correct balance of microbes helps with digestion, nutrient synthesis, immune system function
- Imbalance of good and bad bacteria (dysbiosis) can lead to disease
- Antibiotics, stress, diet can influence the microbiome
Microbial/Mucosal Triggers of RA

A. Periodontitis
   P. gingivalis
   PAD activity

B. Smoking
   Lung Disease
   PAD activity

C. Gut Microbiome
   Antibiotics

Rheumatoid Arthritis
**Periodontal Disease**

- Chronic inflammatory and infectious disease of tooth-supporting tissues
- Starts with mild gum inflammation (gingivitis)
- Can lead to tooth loss
- Has been linked to numerous health problems including heart disease, pregnancy complications, and RA
- Increased frequency and severity of periodontal disease in RA
RA patients have increased frequency and levels of antibodies to the periodontal pathogen \textit{P. gingivalis}
Pg-positive RA patients have greater disease activity

- Pg-positive RA patients tend to have greater disease activity at diagnosis and at 1 year of treatment
- There may be a role for evaluation and treatment of periodontitis in RA patients

Arvikar et al, Arthritis Research and Therapy, 2013
Evidence of the Immune Relevance of *Prevotella copri*, a Gut Microbe, in Patients With Rheumatoid Arthritis

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- RA patients had T cell and B cell responses to *Prevotella copri*, a gut microbe which was overexpanded in stool of RA patients
- These immune responses were specific for RA patients
- *P. copri* antibodies correlated with rheumatoid factor, CCP antibodies and inflammatory cytokines.
- *Prevotella copri* and other organisms in the gut microbiome may be a target for treatment or prevention of RA
How is RA diagnosed?
RA Diagnosis

- Clinical exam: swollen and tender joints
- Blood tests
- Joint fluid analysis
- X-rays: may be normal in early RA
- MRI and ultrasound: more sensitive for earlier detection of inflammation
Blood Tests in RA

- Rheumatoid factor (70% of patients, but less specific for RA)
- CCP antibodies (>95% specificity for RA)
- Up to 1/3 of patients may lack RF and CCP antibodies (seronegative RA)
- Inflammation tests: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), may be normal
- Anemia, blood count abnormalities
- Testing to rule out other diseases
Historical Perspective
Milestones in Treatment of Rheumatoid Arthritis

1900
Aspirin
First synthesized anti-inflammatory drug

1925
Gold salts
Forestier mistakes RA for tuberculosis

1950
Glucocorticoids
Rapid anti-inflammatory effects as well as qualities of DMARDs

1975
Methotrexate
Becomes gold standard

2000
Biologic DMARDs

1980’s 1990’s
Stages of RA

Early RA  Intermediate RA  Late RA

RA Treatment: The Earlier the Better!

• **NSAIDs** (Ibuprofen, Naproxen)
• **Steroids** (prednisone, injections), usually short term
• **Disease-modifying antirheumatic drugs (DMARDs)**: medications that slow the progression of joint damage:
  -- **Conventional/Synthetic**: methotrexate, hydroxychloroquine, sulfasalazine, lefluonomide
  -- **Biologic Medications**
How is RA Treated?

**Biologics**

- TNF inhibitors:
  - Etanercept (Enbrel)
  - Adalimumab (Humira)
  - Infliximab (Remicade)
  - Certolizumab (Cimzia)
  - Golimumab (Simponi)
- Abatacept (Orencia)
- Tocilizumab (Actemra)
- Rituximab (Rituxan)
- Anakinra (Kineret)
- Tofacitinib (Xeljanz) oral
Treatment Side Effects

• Infections
• Osteoporosis, diabetes (steroids)
• Pregnancy concerns (especially methotrexate)
• Liver and blood count abnormalities (methotrexate)
• Injection site reactions, rashes
• Non-melanoma skin cancers
Minimizing Side Effects of RA Treatment

• **Laboratory tests** (especially for methotrexate and leflunomide, need every 3 month lab checks)

• **Hold medications** for infections and surgical procedures

• **Routine vaccinations** (except “live” vaccinations if on biologic)
  – influenza
  – pneumonia
  – Zoster/shingles, if over 50: *cannot do if on biologic*
Adjunctive Treatments

- Physical and Occupational Therapy, exercises, splinting
- Aerobic exercise, low-impact
- Healthy lifestyle, weight loss, smoking cessation
- Supplements: Fish Oil, Turmeric, Curcumin, Vitamin D
- Regular follow-up with rheumatology
- Monitoring with labs/Xrays
Surgical Treatment in RA

- RA can damage joints, and accelerate osteoarthritis
- Surgery can improve pain and function
- Total joint replacement for end-stage arthritis in knees, hips, shoulders
- Arthroscopic synovectomy can remove inflamed tissue
- Joint fusions or implants for small joints, tendon release, carpal tunnel surgery
- Infections and cervical spine disease can be particular concerns in RA patients
- Pre-op cervical spine Xrays and plan for RA medications is important
Unmet Needs in RA

• Need earlier methods for diagnosis
• Treatment can be trial-and-error
• Need biomarkers to identify best treatment for a patient among the many available choices
• More oral medications may be desirable
• Still no cure for RA
• Medications often needed in the long-term
• Some patients do not completely respond to treatment
• Non-medication approaches such as dietary interventions need further development
Complications of RA
Outside the Joints

• Skin (nodules)
• Inflammatory eye disease (scleritis, uveitis)
• Lung disease (interstitial lung disease)
• Neuropathy and ulcers (vasculitis)
• Hematologic (enlarged spleen and neutropenia, Felty’s syndrome), lymphoma
• Cardiac (pericarditis, cardiovascular disease)
RA equals diabetes as an independent risk factor for CV disease - 3 year study

HR in diabetic patients - 2.0 (95% CI 1.1–3.7)
HR in nondiabetic patients with RA - 2.2 (95% CI 1.3–3.6).

Cardiovascular Disease in RA

- RA patients have 50% >risk for cardiovascular mortality
- 2X higher risk for heart attack
- Inflammation contributes to risk, increases plaque in arteries (atherosclerosis)
- Lipid levels may be less reliable in RA patients
- Need to control inflammation, and modify cardiovascular risk factors
Studies
MGH Early RA Cohort Study

• An observational study assessing causes of RA
• Focusing on newly diagnosed RA patients, but also enrolling later RA patients
• Involves blood draws, questionnaire at entry, 3, 6, and 12 months
• Referral for free dental exam at Harvard-Affiliate Forsyth Institute
• Will be collecting stool samples soon
• Contact MGH Rheumatology Clinic for more information
Rheumatoid Arthritis
Clinical Trials at MGH

• 3 trials investigating heart health and how it changes when taking medications used to treat RA:
  
  TARGET  
  LiiRA  
  ActemRA

• All studies are currently recruiting patients who are changing medications

• What you get for participation:
  – Free medications
  – Reimbursement for your time
  – Information about your cardiovascular health

Grab our handouts, ask your rheumatologist, or call Ethan Lam at (617) 732-8169 for more information.
Conclusions

• RA is the most common form of autoimmune arthritis
• Primarily affects joints but may have systemic manifestations
• Many treatment options now available to manage the disease and prevent complications
• Ongoing studies aim to identify causes and biomarkers, future treatments in development may target the microbiome
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Rheumatology Research Foundation
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Arthritis Foundation
www.arthritis.org
• Yawkey, 2nd Floor, Suite 2C
• Contact: 617-726-7938
Resources for Patients

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  https://www.rheumatology.org/
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