Rheumatoid Arthritis

Hala Eid, MD
Inflammatory polyarthritis of unknown etiology.

Disease prevalence is about 1% in Caucasians.

Women are affected 2-3 times more often than men.

Can occur at any age, peak onset is between 50-75.
Introduction

- Characterized by erosion of the cartilage and bone and irreversible joint destruction
- Untreated, RA can lead to loss of physical function.
- **Early diagnosis and treatment** is important in achieving control of disease and prevention of joint damage.
Natural History And prognosis of Rheumatoid Arthritis

• High degree of disability, early mortality and morbidity

• Mortality from severe RA is higher than 3-vessel CAD or stage IV Hodgkin lymphoma

• Joint damage can occur as early as the first 2 years of disease
Evaluation For Suspected RA

- History: joint pain, swelling, morning stiffness at least 30 minutes
- Duration of symptoms: more than 6 weeks
- Other symptoms suggesting alternative diagnosis such as psoriasis, IBD, SLE.
- Physical exam to assess for the presence of synovitis, limited range of motion, extra-articular disease (rheumatoid nodules)
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
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<tbody>
<tr>
<td>Morning stiffness</td>
<td>Morning stiffness in and around the joints, lasting at least one hour before maximal improvement.</td>
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<tr>
<td>Arthritis of three or more joint areas</td>
<td>At least three joint areas (out of 14 possible areas; right or left PIP, MCP, wrist, elbow, knee, ankle, MTP joints) simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) as observed by a physician.</td>
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<tr>
<td>Arthritis of hand joints</td>
<td>At least one area swollen (as defined above) in a wrist, MCP, or PIP joint.</td>
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<tr>
<td>Symmetric arthritis</td>
<td>Simultaneous involvement of the same joint areas (as defined above) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs, without absolute symmetry is acceptable).</td>
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<tr>
<td>Rheumatoid nodules</td>
<td>Subcutaneous nodules over bony prominences or extensor surfaces, or in juxta-articular regions as observed by a physician.</td>
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<tr>
<td>Serum rheumatoid factor</td>
<td>Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5 percent of normal control subjects.</td>
</tr>
<tr>
<td>Radiographic changes</td>
<td>Radiographic changes typical of rheumatoid arthritis on posteroanterior hand or wrist radiographs, which must include erosions or unequivocal bony decalcification localised in, or most marked adjacent to, the involved joints (osteoarthritis changes alone do not qualify).</td>
</tr>
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</table>

Note: For classification purposes, a patient has RA if at least four of these criteria are satisfied (the first four must have been present for at least six weeks).
2010 ACR/EULAR Criteria

- **Number and site of involved joints:**
  2 to 10 large joints (from among shoulders, elbows, hips, knees, and ankles) = 1 point
  1 to 3 small joints (from among the MCP, PIP, second through fifth MTP, thumb IP joints, and wrists) = 2 points
  4 to 10 small joints = 3 points
  Greater than 10 joints (including at least 1 small joint) = 5 points

- **Serological abnormality** (RF or anti-CCP)
  Low positive (above the upper limit of normal [ULN]) = 2 points
  High positive (greater than three times the ULN) = 3 points

- **Elevated acute phase response** (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]) above the ULN = 1 point

- **Symptom duration** at least six weeks = 1 point
Synovial thickening of the metacarpophalangeal joint

Bilateral swelling of the MCP joints is evident in this patient with rheumatoid arthritis. Note also the mild swan neck deformities present in several fingers, particularly the left middle and fifth fingers.

MCP: metacarpophalangeal.

Courtesy of Patrick J Venables, MD.
A woman with longstanding rheumatoid arthritis has soft tissue swelling and subluxation of the metacarpophalangeal joints. The right thumb shows hyperextension of the interphalangeal joint (a Z deformity). Both ring fingers have boutonniere deformities with flexion of the proximal and hyperextension of the distal interphalangeal joints.
Swelling of the metacarpophalangeal joints of the right hand in rheumatoid arthritis

Swelling of the MCP joints, moderate MCP flexion, and swan neck deformities are evident in this patient with rheumatoid arthritis.

MCP: metacarpophalangeal.

Courtesy of Patrick J Venables, MD.
Chronic inflammation at the metatarsophalangeal (MTP) joints causes damage resulting in subluxation of the toes upwards. With the MTP joints displaced, weightbearing is not shared through the toes, but falls directly on the prominent metatarsal heads. This painful condition results in pain on weightbearing and difficulty in walking, and can cause the metatarsal to erode through the skin on the sole of the foot. Treatment in the early stages includes appropriate shoes and fitting of an orthotic that will support weight away from the painful metatarsal heads. Late-stage treatment may involve surgical excision of the prominent metatarsal heads.

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Rheumatoid nodules are firm, nontender lesions that typically occur in areas of trauma in individuals with rheumatoid arthritis. Nodules are present near the elbows in this patient. Reproduced with permission from: www.visualdx.com. Copyright Logical Images, Inc.
Episcleritis in a patient with rheumatoid arthritis characterized by a patch of intense injection without scleral edema.

Courtesy of Reza Dana, MD, MSc, MPH.
Chest x-ray demonstrating a cavitating rheumatoid nodule. The patient presented with pleuritic chest pain.

*Courtesy of Fiona R Lake, MD.*
Plain radiograph of rheumatoid arthritis proximal interphalangeal joint erosions

The plain x-ray of the right hand magnified at the proximal interphalangeal joints shows soft tissue swelling (arrows) and mild erosive changes (arrowheads).

Courtesy of Richard Waite, MD.
Plain radiograph of metatarsophalangeal joint space narrowing and erosions in rheumatoid arthritis

The radiograph of the left foot in the AP projection demonstrates an erosion in the periarticular, marginal "bare" area of the joint of the 5th MTP joint and more subtle erosions at the 1st, 2nd, 3rd, and 4th MTPs (arrows), characteristic of rheumatoid arthritis. Also present is joint space narrowing of the 1st and 2nd MTP joints (arrowheads).

AP: anteroposterior; MTP: metatarsophalangeal.

Courtesy of Richard Waite, MD.
Evaluation For Suspected RA

1- Laboratory tests:
   • RF, CCP, ANA, Lyme
   • ESR, CRP, CBCD

2- Synovial fluid analysis

3- Radiographs of the hands, wrists and feet

4- MRI or ultrasound
Biologic markers in the diagnosis of rheumatoid arthritis

- Rheumatoid factor (RF)
- Antibodies to citrullinated peptides (ACPA)
- The presence of RF or ACPA predicts poorer prognosis
Rheumatoid Factors (RF)

- RF are autoantibodies directed against the Fc portion of IgG
- Present in 75-80% of RA patients
- High titer predicts a severe disease course, extra-articular manifestations such as ILD and vasculitis.
- Moderate specificity for RA, can be present in lupus, primary Sjogren, hepatitis C and other infections
Rheumatoid factor

- IgM against the Fc portion of IgG
- IgA and IgG against Fc portion of IgG
- Origin not completely understood
- Normal human lymphoid tissue possesses B lymphocytes with RF expression on cell surface
- However RF is not routinely detectable in the circulation in the absence of an antigenic stimulus
RF

- Sensitivity for the diagnosis of RA: 69%
- Moderate specificity: 85%
- Prevalence of RF in a healthy population is 5% usually at a low titer
- RF can be present in other rheumatic diseases such as Sjogren, lupus
- RF commonly occur in the setting of chronic infections and malignancy
# The major nonrheumatic diseases associated with rheumatoid factor (RF)-positivity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency of RF, percent</th>
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<tbody>
<tr>
<td><strong>Aging (≥ age 60)</strong></td>
<td>5 to 25</td>
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<tr>
<td><strong>Infection</strong></td>
<td></td>
</tr>
<tr>
<td>Bacterial endocarditis*</td>
<td>25 to 50</td>
</tr>
<tr>
<td>Hepatitis B or hepatitis C*</td>
<td>20 to 75</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>8</td>
</tr>
<tr>
<td>Syphilis*</td>
<td>Up to 13</td>
</tr>
<tr>
<td>Parasitic diseases</td>
<td>20 to 90</td>
</tr>
<tr>
<td>Leprosy*</td>
<td>5 to 58</td>
</tr>
<tr>
<td>Other viral infection*</td>
<td>15 to 65</td>
</tr>
<tr>
<td><strong>Pulmonary disease</strong></td>
<td></td>
</tr>
<tr>
<td>Sarcoidosis*</td>
<td>3 to 33</td>
</tr>
<tr>
<td>Interstitial pulmonary fibrosis</td>
<td>10 to 50</td>
</tr>
<tr>
<td>Silicosis</td>
<td>30 to 50</td>
</tr>
<tr>
<td>Asbestosis</td>
<td>30</td>
</tr>
<tr>
<td><strong>Miscellaneous diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Primary biliary cholangitis*</td>
<td>45 to 70</td>
</tr>
<tr>
<td>Malignancy*</td>
<td>5 to 25</td>
</tr>
<tr>
<td>After multiple immunizations</td>
<td>10 to 15</td>
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</tbody>
</table>

* Refers to disorders that may cause symptoms suggestive of rheumatoid arthritis. The best-documented examples of viral infection (in addition to hepatitis B and C) are rubella, mumps, influenza, and HIV. Chagas’ disease, Leishmaniasis, onchocerciasis, and schistosomiasis are major parasitic diseases. B cell neoplasms are the most common malignancies.
Prognostic value of RF

• RF-positive patients with RA may experience more aggressive and erosive disease and extraarticular manifestations

• Cigarette smoking is a risk factor for more severe RA and is associated with an increased prevalence of RF
Anti-Citrullinated Peptide Antibodies (ACPA)

- Citrullination is a posttranslational modification of arginine to citrulline by the enzyme peptidyl arginine deiminase (PAD)
- This process occurs during inflammation
- Several citrullinated proteins are present in RA synovium and are the targets of highly RA-specific autoantibodies
Anti-citrullinated peptide antibodies (ACPA)

- Anti-CCP (anti-cyclic citrullinated peptides)
- Anti-MCV (anti-mutated citrullinated vimentin)
- Sensitivity: 50-70%, specificity: 90-96%
- Increased risk for progressive joint damage
- Reported in other autoimmune conditions: psoriatic arthritis, SLE, Sjogren, Scleroderma
- Positive ACPA in active tuberculosis
14-3-3eta

- Isoform of the 14-3-3 family of intracellular chaperone protein
- Has similar sensitivity and specificity to RF and ACPA
- An assay is commercially available
- More studies needed to justify the role of the assay in clinical practice
Disease activity and prognosis

- ESR and CRP are the main clinically useful markers to assess disease activity and to predict radiographic outcome.

- Radiologic damage is significantly more likely to progress when CRP and ESR are elevated.
Multibiomarker disease activity

- Combined use of multiple markers offers an advantage over the use of a single lab test for predicting disease activity and progression.
- The commercially available test for RA is Vectra DA, which uses 12 biomarkers to generate an MBDA score between 1-100.
- High MBDA scores are good predictors of joint damage.
Pathogenesis of RA

• Complex interaction between genes and environment
• Leading to breakdown in immune tolerance and synovial inflammation
• RA is not a single disease, many pathways can lead to autoreactivity.
Pathogenesis of Rheumatoid Arthritis

Current Treatment Targets

B cell

T cell

HLA-DR

Antigen-presenting cells

B cell or macrophage

Synoviocytes

Pannus

Articular cartilage

Production of collagenases and other neutral proteases

Bone

Rheumatoid Factors, anti-CCP

Immune complexes

Complement

Neutrophil

Mast cell

Macrophage

IFN-γ & other cytokines

TNFα, IL-1

Chondrocytes

Osteoclast

Adapted from Arend WP, Dayer JM. Arthritis Rheum. 1990;33:305–15
Inflammation and the Pathogenesis of RA

Antigen-presenting cells (APCs)
- B cells
- Dendritic cells
- Macrophages

IL-4
IL-6
IL-10

TNF-α
IL-2
IFN-γ
IL-17
RANKL

IL-6, TNF-α, IFN-γ, lymphotoxin

RF, anti-CCP antibodies

Immune complexes
Complement fixation
Attract inflammatory cell infiltrates

TNF-α, IL-1, IL-6, metalloproteinases

Osteoclast
Synoviocytes
Chondrocytes
Pannus
Articular cartilage

Production of metalloproteinases and other effector molecules
Migration of polymorphonuclear cells
Erosion of bone and cartilage

General principles of management of RA

• Early diagnosis

• Early use of DMARDs to prevent progression and joint damage: 80% of patients with RA of less than 2 years duration had JSN on X-rays while 2/3 had erosions

• Tight control, using a treat-to-target strategy
Treat-To-Target

• Initiate DMARDS as soon as the diagnosis is made

• Achieve low disease activity

• Frequent assessments off the efficacy and safety of the treatment
Choice of therapy

• Level of disease activity
• Presence of comorbid conditions
• Regulatory restrictions (health insurance coverage)
• Patient preferences
Pretreatment Evaluation

- CBCD, serum creatinine, LFTS, ESR and CRP
- Hepatitis B and C
- PPD or Quantiferon-TB
Non Biologic DMARDs

- Methotrexate
- Sulfasalazine
- Hydroxychloroquine
- Leflunomide
Biologic Agents

• Interfere with cytokine function and production
• Inhibit the “second signal” required for T-cell activation.
• Deplete B cells
• Small molecule kinase inhibitors
Anticytokines

- **Cept**: refers to fusion of a receptor to the FC portion of human IgG1: Etanercept
- **Mab**: indicates a monoclonal antibody: Adalimumab, Certolizumab, Golimumab.
- **Ximab**: a chimeric Monoclonal Ab: Infliximab
- **Zumab**: humanized monoclonal Ab: Tocilizumab
<table>
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<tr>
<th>Agent</th>
<th>Class</th>
<th>Target</th>
<th>Structure</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Cytokine inhibitor</td>
<td>TNF-α</td>
<td>Human monoclonal antibody</td>
<td>TNF-α blockers were the first biologic agents approved for the treatment of rheumatoid arthritis; TNF-α blockade has become a central strategy of targeted antiinflammatory therapy in the disease.</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Cytokine inhibitor</td>
<td>TNF-α</td>
<td>Pegylated humanized Fab’ fragment of an anti-TNF-α monoclonal antibody</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>Cytokine inhibitor</td>
<td>TNF-α</td>
<td>TNF-α receptor–Fc fusion</td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td>Cytokine inhibitor</td>
<td>TNF-α</td>
<td>Human monoclonal antibody</td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Cytokine inhibitor</td>
<td>TNF-α</td>
<td>Chimereric monoclonal antibody</td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Cytokine inhibitor</td>
<td>Interleukin-6 receptor</td>
<td>Humanized monoclonal antibody</td>
<td>This agent is considered the second major advance in cytokine blockade in rheumatoid arthritis; it has profound effects on systemic features, acute-phase response, and synovitis.</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Cytokine inhibitor</td>
<td>Interleukin-1</td>
<td>Interleukin-1 receptor antagonist</td>
<td>Despite good antiinflammatory activity in inflammasome-driven disease (e.g., the Muckle-Wells syndrome, Still’s disease, and gout), this agent has had only limited efficacy in rheumatoid arthritis.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Cell-depleting agent</td>
<td>CD20</td>
<td>Chimeric monoclonal antibody</td>
<td>This is the only approved cell-depleting agent for rheumatoid arthritis; its use has reinforced the role of adaptive immunity, particularly humoral immune responses, in the disease.</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Costimulation blocker</td>
<td>CD80 and CD86</td>
<td>CTLA4–Ig fusion protein</td>
<td>This agent disrupts the interaction of antigen-presenting cells with T cells, an effect that confirms the link between innate and adaptive immune responses in rheumatoid arthritis.</td>
</tr>
</tbody>
</table>

* CTLA-4–Ig denotes cytotoxic T-lymphocyte–associated antigen 4 and the Fc fragment of IgG1.
Biologic DMARDs

- TNF-alpha inhibitors:
  1. Etanercept (Enbrel)
  2. Infliximab (Remicade)
  3. Adalimumab (Humira)
  4. Golimumab (Simponi)
  5. Certolizumab pegol (Cimzia)
Anti-TNF-α Protein-Engineered Antibodies And Fusion Proteins

Chimeric Monoclonal Antibody
Humanized Monoclonal Antibody
Human Recombinant Antibody
Humanized Fab’ Fragment
Human Recombinant Receptor/Fc Fusion Protein

Infliximab
CDP571
Adalimumab
Etanercept

Certolizumab Pegol

CDR = complementarity-determining region.
PEG = polyethylene glycol.

IL-6 Inhibition

- IL6 has proinflammatory effects: activates T cells, B cells, macrophages and osteoclasts
- Tocilizumab (Actemra) Anti-IL6-receptor antibody
- Sarilumab (Kevzara); anti-IL6 receptor antagonist
Biologic DMARDs

- T cell costimulation blocker:
  Abatacept (Orencia)

- Monoclonal antibody against CD20 B cell:
  Rituximab (Rituxan)
Abatacept modulates the immune response by bonding to CD80/CD86 on an antigen-presenting cell (APC), such as a dendritic cell, thus preventing costimulatory binding of CD28 on naïve T cells and attenuating T-cell activation.
Site of Action of Rituximab - Rituxan®

Joint Fluid

B Cell

Rheumatoid Factors, anti-CLP

immune complexes

Complement

Neutrophil

IFN-γ; other cytokines

T Cell

Antigen-presenting Cell

Macrophage

TNFα and IL1

Cartilage Surface

Pannus

Osteoclast

Bone

Chondrocyte

Production of collagenase and other neutral proteases

Adapted from Arend WP, Dayer JM. Arthritis Rheum. 1990;33:305–15
Rituximab in RA

Rituximab: anti-CD-20

CD-20

B-Cell
Kinase Inhibitors

• The Janus Kinases are cytoplasmic protein tyrosine kinases that mediate signaling from multiple cytokines to the nucleus

• Tofacitinib (Xeljanz) orally administered, inhibits JAK-1 and JAK-3
Targeted Synthetic DMADS

• Kinase inhibitors:

Tofacitinib (Xeljnaz): oral small molecule DMARD, that inhibits cytokine and growth factor signaling through interference with Janus kinases
Comorbidities

- Serious infections
- Hepatitis B reactivation; patient with hx of natural immunity to hepatitis B should be monitored with viral loads every 6 months to detect reactivation
- Tuberculosis: if latent TB is diagnosed, at least 1 month of therapy should be completed prior to initiation of biologic DMARDs
Malignancy

- Non melanoma skin cancer: use if conventional DMARDs over biologic DMARDs
- Melanoma skin cancer: Conventional DMARDs preferred
- HX of lymphoproliferative disorder: Non biologic DMARDs and or rituximab
- Solid organ malignancy:
  - < 5 years: Conventional DMARD or rituximab
  - > 5 years: RA treatment is no different
Cardiovascular disease

- Active RA is associated with an increase risk of CVD
- Glucocorticoids and NSAIDS increase risk of CVD
- Tight control reduced the risk CVD
- TNF inhibitors should be avoided in patients with moderate or severe heart failure
Other Comorbidities

• Demyelinating diseases: avoid TNF inhibitors

• Diabetes: patients treated with hydroxychloroquine or TNF inhibitors have lower risk for diabetes

• Renal disease: usually secondary to NSAIDS
Vaccinations

- Influenza vaccine to all patients who are going to be or already treated with immunosuppressive drugs
- Pneumococcal vaccine should be given to all RA and a single revaccination is recommended if > 5 years since the last vaccination
- Hepatitis B should be given before immunosuppressive medications
• Live vaccines should not be given to patients on high dose prednisone (20 mg) or on immunosuppressive therapy.

• There should be a month hiatus between the Zoster vaccine and the immunosuppressive treatment.