Rheumatoid Arthritis: Key Features

- Symptoms >6 weeks’ duration
  - Often lasts the remainder of the patient’s life
- Inflammatory synovitis
  - Palpable synovial swelling
  - Morning stiffness >1 hour, fatigue
- Symmetrical and polyarticular (>3 joints)
  - Typically involves wrists, MCP, and PIP joints
  - Typically spares certain joints
    - Thoracolumbar spine
    - DIPs of the fingers and IPs of the toes
**Demographics**

- **Prevalence:** 1% of adults worldwide \(^1\)
- **Annual incidence:** three in 10,000 adults \(^1\)
- **Gender:** two to three times more women affected \(^1\)
- **Age:** peak onset 30 to 50; most patients under 65 \(^2,3\)

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**Incidence of RA in U.S. Population by Age Group** \(^3\)

- 65 AND OVER: 30%
- 55 TO 64: 22%
- 45 TO 54: 22%
- 35 TO 44: 16%
- 25 TO 34: 7%
- 15 TO 24: 3%

Adapted from Hecht et al, 1997.\(^3\)

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**References:**
The Etiology of Rheumatoid Arthritis is Unknown

There is an established role for:

- autoimmunity
- genetic components

There is a suspected role for:

- infectious agents

Biology of Cytokines

Cytokines are Intercellular Messenger Molecules

- Mediate effect by binding to cell-associated receptors on target cells, leading to intracellular signaling and activating gene transcription

- Produced in small amounts

- Act principally in the local cellular environment

Disequilibrium of Cytokines in Joints of Patients with Rheumatoid Arthritis

Rheumatoid Arthritis: Key Features (cont’d)

- May have nodules: subcutaneous or periosteal at pressure points
- Rheumatoid factor
  - 45% positive in first 6 months
  - 85% positive with established disease
  - Not specific for RA, high titer early is a bad sign
- Marginal erosions and joint space narrowing on x-ray

The Pathology of Rheumatoid Arthritis

Scientific Rationale

Rheumatoid Arthritis: PIP Swelling

- Swelling is confined to the area of the joint capsule
- Synovial thickening feels like a firm sponge
DETECTING SYNOVIAL EFFUSION: DEMONSTRATING FLUCTUATION

Four-finger technique

Two-thumb technique

© www.rheumtext.com - Hochberg et al (eds)
Rheumatoid Arthritis: Ulnar Deviation and MCP Swelling

- An across-the-room diagnosis
- Prominent ulnar deviation in the right hand
- MCP and PIP swelling in both hands
- Synovitis of left wrist
Clinical Course of RA

Type 1 = Self-limited—5% to 20%
Type 2 = Minimally progressive—5% to 20%
Type 3 = Progressive—60% to 90%

RHEUMATOID ARTHRITIS

Presenting Signs and Symptoms

- Symmetric joint pain
- Swelling of small peripheral joints
- Morning joint stiffness of variable duration
- Other diffuse aching
- Fatigue, malaise, and depression
  may precede other symptoms by weeks or months

RHEUMATOID ARTHRITIS
Pathology and Clinical Manifestations

- Pathologic alterations
  - Synovial hyperplasia
  - Inflammatory infiltrate
  - Increased vascularity
  - Pannus formation

RHEUMATOID ARTHRITIS

Radiologic Features

- **Early stage**
  - Soft tissue swelling
- **Intermediate stage**
  - Mild juxtaarticular osteoporosis
  - Narrowing of joint space and bone erosions
- **Late stage**
  - Large erosions, ankylosis, deformities

RHEUMATOID ARTHRITIS

Laboratory Findings

- Rheumatoid factor positive in up to 80% of patients
- Antinuclear antibody positive in 80% of patients
- Acute phase reactants (ESR, CRP) ↑ in almost all patients at some point
- Chemistries normal, except slight ↓ in albumin, ↑ total protein, and ↓ iron
- Hematologic findings
  - Mild anemia in 25% to 35% of patients
  - Normal or slight ↑ in white cell count
  - Thrombocytosis

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

RHEUMATOID ARTHRITIS

Complications

- Rheumatoid nodules
- Cardiovascular: vasculitis, pericarditis
- Pulmonary: pulmonary nodules, interstitial fibrosis, pleuritis
- Ocular: scleritis, conjunctivitis
- Neurologic: compression neuropathy, vasculitis
- Skin: distal leg ulcers, palmar erythema
- Hematologic: granulocytopenia (Felty’s syndrome), hyperviscosity
- Renal/hepatic: amyloidosis, ↑ liver enzymes

Rheumatoid Arthritis: Typical Course

- Damage occurs early in most patients
  - 50% show joint space narrowing or erosions in the first 2 years
  - By 10 years, 50% of young working patients are disabled
- Death comes early
  - Multiple causes
  - Compared to general population
    - Women lose 10 years, men lose 4 years
Spondylarthropathies
Osteoarthritis
Rheumatoid Arthritis

Key points:

- The sicker they are and the faster they get that way, the worse the future will be
- Early intervention can make a difference
- Essential to establish a treatment plan early in the disease
TREATMENT OF RHEUMATOID ARTHRITIS

Disease Activity Score (DAS)

Assessment of Improvement or Response

\[ \text{DAS} = 0.54 \times \sqrt{\text{RAI}} + 0.065 \times \text{sw} + 0.33 \times \ln(\text{ESR}) + 0.0072 \times \text{GH} \]

- RAI = number of tender joints (t) calculated using Ritchie Articular Index
- Number of swollen joints (sw)
- Erythrocyte sedimentation rate (ESR, mm/hour)
- General health status (GH) using a 100-mm visual analog scale (VAS)

High disease activity \( >3.7 \), low disease activity \( \leq 2.4 \), remission \( <1.6 \)
Rheumatoid Arthritis: Treatment Principles

- Confirm the diagnosis
- Determine where the patient stands in the spectrum of disease
- When damage begins early, start aggressive treatment early
- Use the safest treatment plan that matches the aggressiveness of the disease
- Monitor treatment for adverse effects
- Monitor disease activity, revise Rx as needed
Critical Elements of a Treatment Plan: Assessment

- Assess current activity
  - Morning stiffness, synovitis, fatigue, ESR
- Document the degree of damage
  - ROM and deformities
  - Joint space narrowing and erosions on x-ray
  - Functional status
- Document extra-articular manifestations
  - Nodules, pulmonary fibrosis, vasculitis
- Assess prior Rx responses and side effects
Critical Elements of a Treatment Plan: Therapy

- Education
  - Build a cooperative long-term relationship
  - Use materials from the Arthritis Foundation and the ACR
  - Assistive devices

- Exercise
  - ROM, conditioning, and strengthening exercises

- Medications
  - Analgesic and/or anti-inflammatory
  - Immunosuppressive, cytotoxic, and biologic
  - Balance efficacy and safety with activity
Rheumatoid Arthritis: Drug Treatment Options

- NSAIDs
  - Symptomatic relief, improved function
  - No change in disease progression
- Low-dose prednisone ($\leq 10$ mg qd)
  - May substitute for NSAID
  - Used as bridge therapy
  - If used long term, consider prophylactic treatment for osteoporosis
- Intra-articular steroids
  - Useful for flares

Rheumatoid Arthritis: Treatment Options

- Disease modifying drugs (DMARDs)
  - Minocycline
    - Modest effect, may work best early
  - Sulfasalazine, hydroxychloroquine
    - Moderate effect, low cost
  - Intramuscular gold
    - Slow onset, decreases progression, rare remission
    - Requires close monitoring

Rheumatoid Arthritis: Treatment Options (cont’d)

- Immunosuppressive drugs
  - Methotrexate
    - Most effective single DMARD
    - Good benefit-to-risk ratio
  - Azathioprine
    - Slow onset, reasonably effective
  - Cyclophosphamide
    - Effective for vasculitis, less so for arthritis
  - Cyclosporine
    - Superior to placebo, renal toxicity

Rheumatoid Arthritis: Treatment New Options—Combinations

- Methotrexate, hydroxychloroquine, and sulfasalazine
- Superior to any one or two alone for ACR 50% improvement response and maintenance of the response
- Side effects no greater

2-Year Outcome

Percent With 50% ACR Response

- Triple RX
- SSZ+ HCQ
- MTX
Rheumatoid Arthritis: Treatment New Options—Combinations (cont’d)

- Step-down prednisone with sulfasalazine and low-dose methotrexate*
  - Superior to sulfasalazine in early disease*
- Methotrexate + hydroxychloroquine or methotrexate + cyclosporine†
  - May have additive beneficial effects†

Rheumatoid Arthritis: Treatment Options—New DMARDs

- Leflunomide
  - Pyrimididine inhibitor
  - Effect and side effects similar to those of MTX

- Etanercept
  - Soluble TNF receptor, blocks TNF
  - Rapid onset, quite effective in refractory patients in short-term trials and in combination with MTX
  - Injection site reactions, long-term effects unknown, expensive

Rheumatoid Arthritis: Monitoring Treatment With DMARDs

- These drugs need frequent monitoring
- Blood, liver, lung, and kidney are frequent sites of adverse effects
- Interval of laboratory testing varies with the drug
  - 4- to 8-week intervals are commonly needed
- Most patients need to be seen 3 to 6 times a year
# Rheumatoid Arthritis: Adverse Effects of DMARDs

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*Long-term data not available.

Felty's Syndrome

Seropositive Rheumatoid Arthritis
Splenomegaly
Granulocytopenia
Rheumatoid Arthritis: Case 2 (cont’d)

- Early erosion at the tip of the ulnar styloid
Rheumatoid Arthritis: Case 2 (cont’d)

How fast is joint damage progressing?

A. Soft-tissue swelling, no erosions

B. Thinning of the cortex on the radial side and minimal joint space narrowing

C. Marginal erosion at the radial side of the metacarpal head with joint space narrowing
Scientific Rationale

Central Role of TNFα in RA

Kirwan JR, J Rheumatol. 1999; 7:720-725
Generations of TNFα Antibodies

1st Murine

2nd Chimeric

3rd Humanized

Fully-Human (No Mouse Protein)

10% Mouse Protein

100% Mouse Protein

100% Mouse Protein

Infliximab

Adalimumab (D2E7)
juvenile chronic arthritis

- **Definition**
  - A heterogeneous group of systemic inflammatory disorders affecting children below the age of 16 years
  - Major subsets, defined on the basis of clinical features at onset, have been described and appear to differ in genetic associations and prognosis

- **Clinical features**
  - Pauciarticular onset (fewer than four joints involved) may be of several types - most common are early childhood with antinuclear antibodies positivity and risk of ocular disease, and late childhood with risk of spondyloarthropathy
  - Polyarticular onset are at greatest risk for chronic, severe arthritis
  - Systemic onset with fever, rash and arthritis may be associated with serious morbidity and mortality