Rheumatoid Arthritis

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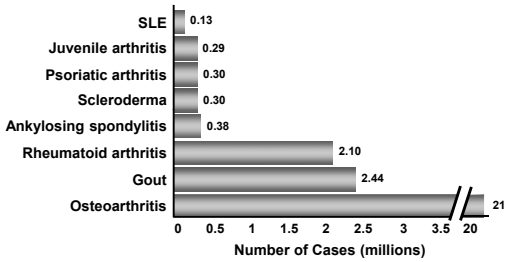
Overlook Medical Center
ATLANTIC HEALTH SYSTEM

Most Common Forms of Rheumatic Disease in the USA



In 2011 numbers, 75 million Americans have symptomatic rheumatic diseases

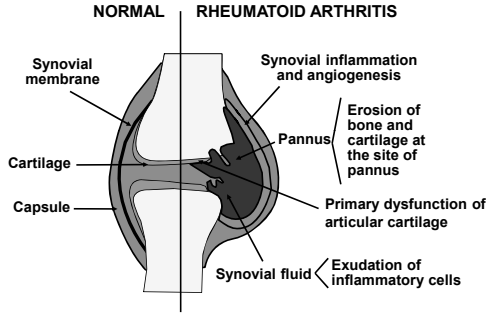
American College of Rheumatology. www.rheumatology.org/patients/factsheets.html 1996

RA

Characteristics of Rheumatoid Arthritis

- Chronic, progressive, systemic inflammatory disease of unknown etiology, demonstrating autoimmune pathogenesis
- Peak age of onset: 40-60 years (range, 20-80 years)
- 2-3 times more common in women
- Characterized by:
  - Progressive, symmetrical destruction of synovial joints with loss of cartilage and bone (erosions)
  - Damaged ligaments and tendons (deformities)
  - Loss of physical function and quality of life
  - Life expectancy reduced by 3-18 years

Pathogenesis of Rheumatoid Arthritis



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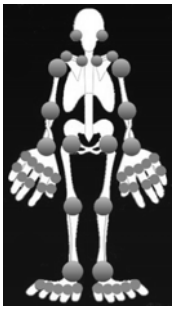
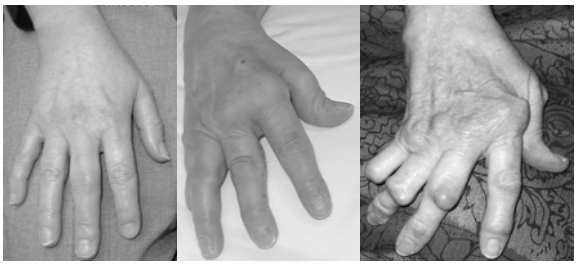
Clinical Presentation of RA: Key Presenting Signs and Symptoms

- Joint pain
- Symmetric swelling of small peripheral joints
- Morning joint stiffness of prolonged duration



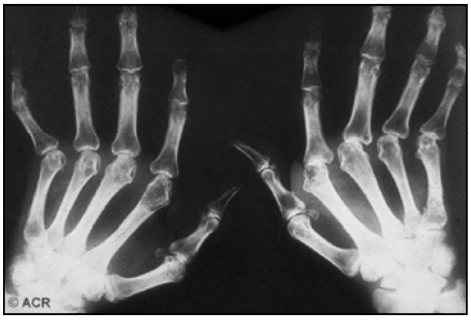
Stages of RA

Early | Intermediate | Late

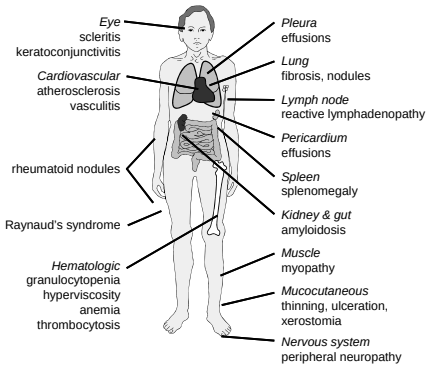


Courtesy of J. Cush, 2002.

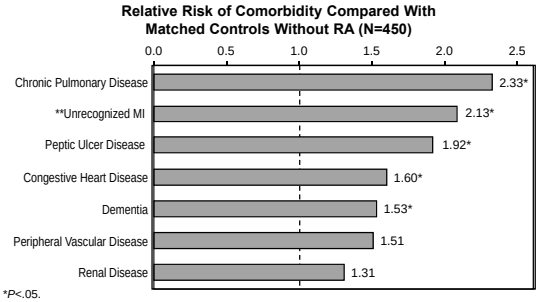
Advanced RA



RA: Multisystem Disease



Increased Risk of Comorbidities in RA Patients

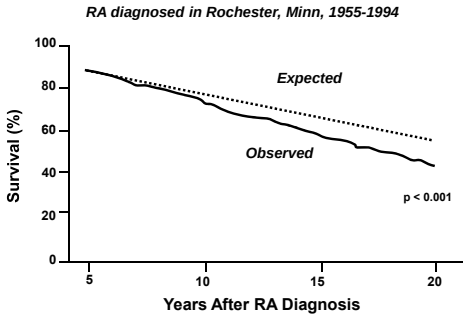


*P<.05.

**Cohort of 603 patients. Maradit-Kremers H, et al. *Arthritis Rheum*. 2005;52:402-411.

Gabriel SE, et al. *J Rheumatol.* 1999;26:2475-2479.

Mortality Rate Higher in RA Patients



Gabriel SE et al. *Arthritis Rheum.* 2002;48:51-58.

Earlier RA Diagnosis Allows Earlier Treatment

American College of Rheumatology guidelines[5] recommend initiation of therapy within 3 months of symptom onset

- Radiographic damage[1]
- Functional decline and work disability[2]
- Psychosocial dysfunction[3]
- Premature death[4]

1. van der Heijde DM, et al. *Br J Rheumatol.* 1995;34(suppl 2):74-78. 2. Sokka T. *Clin Exp Rheumatol.* 2003;21(suppl 31):S71-S74. 3. Dickens C, et al. *Psychosomatics.* 2003;44:209-215. 4. Gabriel SE, et al. *Arthritis Rheum.* 2003;48:54-58. 5. American College of Rheumatology Subcommittee on Rheumatoid Arthritis. *Arthritis Rheum.* 2002;46:328-346.

Treatment Options in RA

- **Nonpharmacologic treatment**
  - Patient education, occupational and physical therapy, exercise programs, joint range of motion/strengthening exercises, and programs to improve psychological well-being
- **Pharmacologic treatment**
  - Nonsteroidal anti-inflammatory drugs (NSAIDs)*, nonselective and selective
  - Traditional DMARDs, e.g., MTX, leflunomide, hydroxychloroquine, sulfasalazine, cyclosporine, injectable gold
  - Biologic treatments – abatacept, adalimumab, anakinra, etanercept, infliximab, rituximab
- **Surgery**
  - Carpal tunnel release, synovectomy, resection of metatarsal heads, total joint arthroplasty, joint fusion

DMARD= disease-modifying anti-rheumatic drug

*NSAIDs should not be used as sole treatment for RA, because they do not alter disease course or prevent joint destruction.

American College of Rheumatology Subcommittee on Rheumatoid Arthritis. Guidelines for the management of rheumatoid arthritis:2002 update. *Arthritis Rheum.* 2002;46:328-346.

Rheumatoid Arthritis:
Non-Steroidal Anti-inflammatory Drugs

- **NSAIDs (including COX-2 specific inhibitors) are anti-inflammatory and analgesic**
- **Do not modify the disease course**
- **GI side effects are common**
- **Monitor older patients closely (hypertension, congestive heart failure, and renal insufficiency)**
- **Tendency to cardiovascular thrombosis (?)**
- **Consider traditional NSAIDs, if not at risk for NSAID-induced GI side effects, or non-acetylated salicylates, COX-2 inhibitors or co-administration of PPI**

Rheumatoid Arthritis:
Glucocorticoids

- **A low oral dose (prednisone <10 mg) effective for management of arthritis symptoms**
- **Long-term effects on erosions controversial (?DMARD)**
- **Toxicity issues, especially osteoporosis, complicate chronic use—use anti-osteoclastic drugs to avoid bone toxicity (bisphosphonates)**
- **Intra-articular administration effective for monoarticular synovitis**

Rheumatoid Arthritis:
Disease-Modifying Anti-Rheumatic Drugs

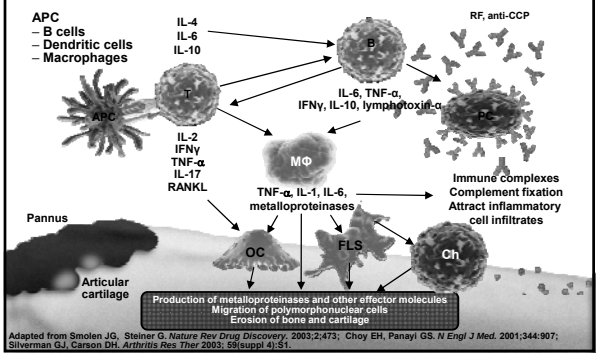
- DMARDs can alter the progression of RA
- Should be used before joints are damaged
- Should be initiated within the first 3 months of diagnosis in addition to treatment with NSAIDS
- Rheumatologist should be consulted whenever corticosteroids or DMARDs are used
- Reassess status often to determine need for DMARD regimen adjustment

Traditional Nonbiologic DMARDs

DMARD	Benefits	Considerations
Methotrexate	• Cornerstone of most treatment regimens for RA • Well-tolerated once-weekly medication • Slows radiographic damage	• Contraindicated in potentially child-bearing women • Administered with folic acid
Hydroxychloroquine	• Effective for active disease and in combination with methotrexate	• Takes 3-6 months to become effective • No evidence of halting radiographic progression
Sulfasalazine	• Effective for active disease • May be used in combination with other agents • Slows radiographic damage	• Contraindicated in patients who have sulfa allergies
Leflunomide	• For moderate-to-severe disease • Slows radiographic progression	• Greater cost • Long half-life • Contraindicated in potentially child-bearing women

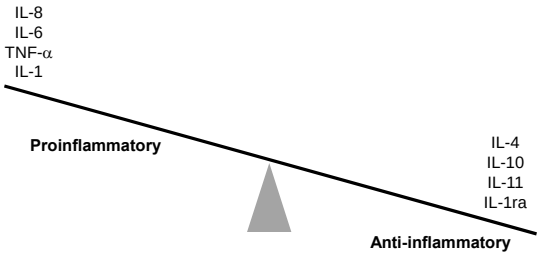
Bykerk VP, et al. *J Musculoskelet Med.* 2004;21:133-146.
O'Dell JR. *N Engl J Med.* 2004;350:2591-2602.
Bingham CO, et al. *J Fam Pract.* 2007;59(suppl 10):S1-S8.

Integrated Immune Response and Pathogenesis of RA



Adapted from Smolen JG, Steiner G. *Nature Rev Drug Discovery.* 2003;2;473; Choy EH, Panayi GS. *N Engl J Med.* 2001;344:907; Silverman GJ, Carson DH. *Arthritis Res Ther* 2003; 59(suppl 4):S1.

Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation



IL1-ra = interleukin IL-1 receptor antagonist

Arend WP. *Arthritis Rheum.* 2001;45:101-106. Cohen MD, Fox DA. Medscape. Available at: http://www.medscape.com/viewprogram/1941_pnt. Accessed July 22, 2005.

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Major Changes in DMARD Therapy of RA over the Past 30 Years

1980s Options

- Hydroxychloroquine
- Injectable gold salts
- D-penicillamine
- Azathioprine
- Sulfasalazine
- Cyclophosphamide

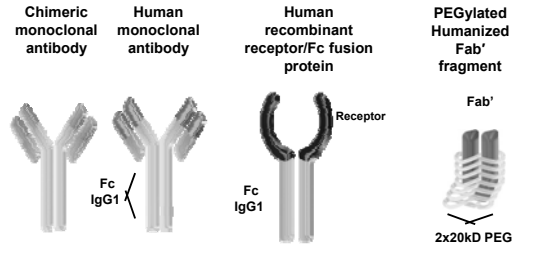
Current Options

- Methotrexate
- Leflunomide
- Sulfasalazine
- Hydroxychloroquine
- Cyclosporine
- Minocycline*
- Etanercept
- Infliximab
- Adalimumab
- Anakinra
- Abatacept
- Rituximab
- Golimumab
- Certolizumab
- Tocilizumab

***Not approved by FDA for treatment of RA**

Biologic DMARDs: Anti–TNF-α Therapies

Monoclonal Antibodies, Fusion Protein and Fab′ Fragment



Weir et al. Therapy 2006;3(4):535-545

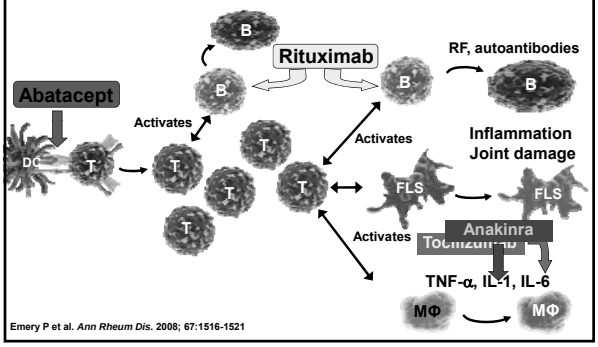
Biologic DMARDs: Anti–TNF-α Therapies

DMARD	Benefits	Considerations
Infliximab (recombinant chimeric mAb)	***All 5 shown to be:*** • **Effective for moderate-to-severe disease** • **Effective at slowing radiographic damage**	• High cost • Administered with methotrexate • Infused every 4-8 weeks after loading doses
Etanercept (recombinant fusion protein)		• High cost • Subcutaneous injection weekly
Adalimumab **Golimumab** (recombinant human mAb)		• High cost • Subcutaneous injections • bi-weekly or weekly (ADA) • Monthly (GOL)
Certolizumab (recombinant human Fab')		• High cost • Subcutaneous injections bi-weekly or monthly

- **These medications are most effective when used in combination with methotrexate**
- **Prior to initiation of therapy, perform tests for HIV, PPD, hepatitis B and C, as well as appropriate immunizations***

Bykerk VP, et al. *J Musculoskelet Med.* 2004;21:133-146.
O'Dell JR. *N Engl J Med.* 2004;350:2591-2602.
Bingham CO, et al. *J Fam Pract.* 2007;59(suppl 10):S1-S8. * Expert opinion

Biologic Therapies: Other Targets



Emery P et al. *Ann Rheum Dis.* 2008; 67:1516-1521

RA: Other Biologic DMARDs

DMARD	Benefits	Considerations
Abatacept (recombinant fusion protein)	• Effective in patients who are nonresponsive to methotrexate and in patients who have failed TNF antagonists • Slows radiographic damage	• High cost • Administered as 30-minute infusions every 4 weeks
Rituximab (monoclonal antibody)	• Effective in long-standing, active RA with inadequate response to TNF antagonist therapy, used in combination with MTX • Efficacy may persist many months after infusion • Slows radiographic damage	• High cost • Administered as 2 separate 3-4 hour infusions 2 weeks apart • Administration of IV corticosteroids before infusion to prevent serious reaction • Delay in clinical response
Tocilizumab (monoclonal antibody)	• Effective in patients with inadequate response to TNF antagonist therapy • Slows radiographic damage	• High cost • Administered as 60-minute infusions every 4 weeks
Anakinra (recombinant human IL-1 receptor antagonist)	• Effective in subsets of patients with RA • Slows radiographic damage	• High cost • Daily subcutaneous injections • Less effective than TNF antagonists at symptom relief and slowing radiographic progression

Bykerk VP, et al. *J Musculoskelet Med.* 2004;21:133-146. O'Dell JR. *N Engl J Med.* 2004;350:2591-2602.
Bingham CO, et al. *J Fam Pract.* 2007;59(suppl 10):S1-S8. Visentini M, et al. *Clin Immunol.* 2007;125:30-33.

Emerging Therapies for RA*

Anti-TNF-α – *TACE inhibitors*	**Anti-IL-12/23** – *Ustekinumab*
Anti-interleukin-1 – *IL-1 TRAP (Rilonacept)* – *sIL-1RI:Fc fusion protein* – *mAb to IL-1 (Canakinumab)*	**Anti-IL-15, -IL-17, IL-18, -IL-33**
B-cell inhibitors – *Belimumab (anti-BLyS)* – *Ocrelizumab* – *Ofatumumab*	**Signal transduction inhibitors** – *JAK-3 inhibitor* – *Syk kinase inhibitor* – *p38 MAP kinase inhibitors*
RANK-RANK-L inhibition – *Denosumab*	**Other small molecules** – *Apremilast*

*** Therapies listed are not approved by FDA at current time**

Obstacles to Diagnosis and Treatment of Chronic Arthritides

- **Patients delay seeking medical care**
- **Limited access to specialty care**
- **The utility of non-pharmacologic therapies unrecognized, unavailable or under-utilized**
- **Under-utilization of local and intra-articular therapies**
- **Over-emphasis on systemic drug therapy in OA, with under-utilization of DMARD therapies in RA and biologics in particular in PsA and AS**