Rheumatoid Arthritis

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Diarthroidal Joint

Diarthroidal Joint in Rheumatoid Arthritis

Normal Synovium

Synovium in Rheumatoid Arthritis

Synovium in Rheumatoid Arthritis
Cartilage-Pannus Interface

Pannus composed of macrophages and mesenchymal cells which erode into cartilage and bone

Cellular Components of Synovial Inflammation in RA

- T cells
  - CD4 TH1 phenotype (IFN-γ, IL-2)
- Macrophages
  - TNF and IL-1
- B cells
  - Rheumatoid Factor
  - Anti-Cyclic Citrullinated Peptide Ab (anti-CCP Ab)

Emerging Cytokine Targets in RA

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Activity</th>
<th>Molecule</th>
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<tbody>
<tr>
<td>IL-1</td>
<td>Produces IL-6</td>
<td>IL-15</td>
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M, Ly, Fibr, M, Syn, Endo

TH17 cells

M, Ly

TLR-like; activates NF-κB
Induces IL-17; stimulates bone resorption

IL-2-like; stimulates TH1 polarization

Induces TNF, IL-1, RANKL

TLR-like; activates NF-κB

IL-12 family member; induces IL-17

Induces TNF, IL-1, IL-6, and chemokines

Epidemiology of Rheumatoid Arthritis

- Prevalence of 1% in most populations
- Age of onset: 30-50 yrs
- Sex: F:M 3:1

Risk Factors for Rheumatoid Arthritis

- Sex
  - F:M 3:1
- Family History:
  - Monozygotic twins: RR = 8
    - Concordance rate: 30%
  - Dizygotic twins: RR = 2-3.4
  - First degree relative: RR = 1.5

Genetics of Rheumatoid Arthritis

- MHC association accounts for 40% genetic risk
  - Alleles of the DRβ1 locus are responsible for increased risk to RA
  - Alleles of DRβ1 chain that confer increased risk exhibit a "shared epitope" of amino acid sequence in the third hypervariable region from amino acids 70-74
e.g., DRβ1*0401, DRβ1*0404, DRβ1*0101
- In some populations >95% of patients with RA exhibit this “shared epitope”
**Genetics of Rheumatoid Arthritis**

- "Shared Epitope" Third Hypervariable Region Sequence:
  - glutamine-lysine-arginine-arginine-alanine-alanine-
  - 70 71 72 73 74

**Rheumatoid Factor**

IgM antibody with specificity for the Fc region of IgG

**Diseases associated with Rheumatoid Factor**
- Rheumatic Diseases
  - SLE, Sjogren’s syndrome
- Viral Infections
  - HCV, HIV
- Bacterial Infections
  - SBE, TB, syphilis, leprosy
- Neoplasms
  - Lymphoproliferative diseases

- Present in 3% general population

**Rheumatoid Factor in RA**

- Sensitivity: 70%
- Specificity: 60%

**Anti-Cyclic Citrullinated Peptide Antibodies**

- Post-translational modification of arginine as a consequence of cell death and inflammation, i.e., oxidative stress

  - Arginine → Citrulline

- Proteins derived from synovial tissue in RA exhibit enhanced citrullination
- Patients with RA have high titers of autoantibodies directed against proteins with citrulline residues
  - e.g., anti-CCP Assay (ELISA assay)
Anti-Cyclic Citrullinated Peptide Antibodies

- Sensitivity: 70%
- Specificity: 95%

Diagnostic Criteria for Rheumatoid Arthritis*

- Morning stiffness (> 1 hour)
- Arthritis of 3 or more joint areas (polyarticular)
- Arthritis of hand joints
- Symmetric arthritis
- Rheumatoid nodules
- Rheumatoid Factor in serum
- Radiographic changes:
  - Periarticular demineralization of bone (early)
  - Marginal erosions (later)

4 of 7 criteria should be present to diagnose Rheumatoid Arthritis

*1987 American College of Rheumatology Revised Criteria for the Classification of RA

Joint involvement in Rheumatoid Arthritis

- Polyarticular
- Arthritis of hand joints most common
  - Metacarpophalangeal joints (MCPs)
  - Proximal interphalangeal joints (PIPs)
  - Never Distal interphalangeal joints (DIPs)
  - Symmetric arthritis

Clinical Features of Rheumatoid Arthritis

- Less commonly involves:
  - Toes, wrists, knees
- Least commonly involves:
  - Shoulders, hips
New Therapies in Rheumatoid Arthritis

**Anatomy of the Hand**

**PIP Involvement**

**MCP Involvement**

**Ulnar Deviation**

**Boutonierre's Deformity**

**Swan neck deformity**
Radiographic Changes in Rheumatoid Arthritis

- Early changes
  - No abnormalities
- Initial changes
  - Periarticular osteopenia secondary to cytokine-induced bone loss
- Later changes
  - Marginal erosions at periphery of joint (cartilage-pannus interface)
- Advanced changes
  - Joint space narrowing, subluxation

Extra-articular Manifestations of Rheumatoid Arthritis

- Extra-articular manifestations of RA are generally found in those patients who have relatively severe articular disease
- Extra-articular disease is associated with increased morbidity and mortality
Rheumatoid Nodules

Rheumatoid Nodule Histopathology

Scleritis

Pulmonary Nodules

“Rheumatoid Lung”

Interstitial infiltration of macrophages and T cells resulting in pulmonary fibrosis

Rheumatoid Vasculitis
Felty's Syndrome

- Rheumatoid Arthritis
- Neutropenia
- Splenomegaly

Felty's Syndrome

- 1-2% Rheumatoid Arthritis patients
- 1/3 have expansion of CD3+CD8+ Large Granular Lymphocytes in peripheral smear
- Increased risk for infections and non-Hodgkins lymphoma

Goals of Therapy

- Reduce or eliminate pain
- Prevent or retard joint destruction
- Maintain musculoskeletal functional status
- Prevent or retard development of extra-articular manifestations of disease

Evidence of Early Radiographic Change

- Joint-space narrowing and erosion are seen in 67% of patients within the first 2 yrs of disease
- Joint-space narrowing and erosion are seen in 77% of patients within the first 5 yrs of disease
- Progression is most rapid during the first 5 yrs of disease

Current Guidelines for the Management of Rheumatoid Arthritis

“The majority of patients with newly diagnosed RA should be started on Disease-Modifying Anti-Rheumatic Drug (DMARD) therapy within 3 months of diagnosis.”

Arthritis & Rheumatism, 46(2), 328-46, 2002
Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

- Prostaglandin inhibitors that exhibit analgesic and anti-inflammatory effects
  - e.g., aspirin, ibuprofen, naproxen

- NSAIDs do not inhibit or retard the progression of articular destruction in Rheumatoid Arthritis

- Useful for symptom management only

Initial DMARD Therapy in Rheumatoid Arthritis

- Methotrexate: Folic acid analog that inhibits dihydrofolate reductase, an enzyme active in nucleic acid synthesis

Methotrexate

- Cytostatic agent that inhibits nucleic acid synthesis and therefore the proliferation of immune cells that mediate inflammation.

- Inhibits pathways of purine metabolism which results in increased production of adenosine which mediates immunosuppressive and anti-inflammatory effects.

Efficacy of Methotrexate in RA

- Definitely improves symptoms and function, and retards joint destruction in a significant percentage of patients.

- However, < 50% of patients experience a sustained remission on methotrexate alone

Biologic Agents in RA Therapy

- Anti-cytokine agents
  - Anti-TNF agents
    - Etanercept (Enbrel)
    - Infliximab (Remicade)
    - Adalimumab (Humira)
  - Anti-IL 1
    - Anakinra (Kineret)

- B cell depleting agent
  - Anti-CD20
    - Rituximab (Rituxan)

- Costimulatory inhibitor
  - Anti-B7 (CD80)
    - Abatacept (Orencia)
**TNF-α**

- Proinflammatory 17 kD protein that is composed of three identical subunits
- Produced primarily by activated macrophages
- TNF binds to 2 distinct receptors: TNFR1 (p55) and TNFR2 (p75)
- Activates fibroblasts, chondrocytes, and osteoclasts
- Promotes secretion of other pro-inflammatory cytokines, (e.g., IL-1 and IL-6) and matrix metalloproteinases

**Etanercept**

- Etanercept binds to TNF
- Antagonizes TNF receptor activation
- Dimeric structure of etanercept allows it to be 1000% times more efficient than the monomeric structure in neutralizing TNF
- Addition of Fc IgG1 portion markedly prolongs the half-life

**Etanercept Administration**

- Subcutaneous Injection:
  - 50 mg q. week
- Half-life of 4 days
- Generally administered in addition to methotrexate

**Infliximab**

- Chimeric (mouse/human) IgG1 monoclonal antibody
- Binds to TNFα with high specificity, high affinity, and high avidity

**Infliximab Administration**

- Intravenous Infusion of 3 mg/kg every 8 weeks
- Development of anti-chimeric antibodies to the murine region of the molecule is partially inhibited by the maintenance of methotrexate therapy
Adalimumab (Humira)

- IgG1 fully “humanized” monoclonal antibody generated through application of phage display library technology
- Avoids generation of anti-chimeric antibodies

Adalimumab Administration

- Subcutaneous Injection:
  - 40 mg q. 2 wks
- Half-life: 2 weeks
- In addition to methotrexate maintenance therapy

Anti-TNF Inhibitors

- Rapid onset of action (1-2 weeks)
- Sustained clinical response
- Retards (arrests/reverses?) joint destruction
- Well tolerated

Adverse Effects of TNF Inhibitors

- Reactivation of Latent Tuberculosis
  - TNF is an important cytokine in the immune response to *Mycobacterium tuberculosis*
  - All patients need to be screened for previous exposure to *M. tuberculosis* before initiating therapy with any anti-TNF agent
  - Those that exhibit a positive response to PPD (purified protein derivative) need to be treated with antituberculous therapy

Anti-IL 1 Therapy

- IL 1 receptor antagonist (IL-1 Ra)
  - Naturally occurring protein produced by macrophages at sites of inflammation that inhibits IL-1 induced activation
- Anakinra (Kineret)
  - Human recombinant form of IL-1 Ra produced *in vitro*

Anakinra Administration

- Subcutaneous injection
  - 100 mg per day
- Half-life: 6 hours
- Very modest efficacy
**B Cell Depletion Therapy**

**Rituximab (Rituxan)**
- Chimeric human-murine monoclonal antibody targeting CD20 expressed on B cells
- CD20 is a 35 kD B cell lineage specific cell surface molecule expressed from pre-B cells to mature B cells (not expressed on plasma cells)
- Cytolytic effect mediated by:
  - Complement activation
  - ADCC

**Mechanism of action in RA?**
- Does not interfere with autoantibody production (e.g., RF or anti-CCP Ab) since it does not target plasma cells
- Hypothesis: Rituximab reduces the role of B cells that function as antigen presenting cells in presenting self-peptides to T cells in RA

**Rituximab Administration**
- Intravenous infusion of 1000 mg every 6 months
- Half-life: 2-3 weeks
- B cell depletion lasts 4-6 months

**Costimulatory Blockade**

**Abatacept (Orencia)**
Extracellular CTLA-4 + IgG1 Constant Region
Costimulatory Blockade

Abatacept (Orencia)
- Administration: Intravenous infusion of 10 mg/kg per month
- Half-life: 15 days

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