Rheumatoid Arthritis: Novel Strategies for an Old Problem

Assil Saleh, MD, MPH

Division of Rheumatology
The Johns Hopkins University School of Medicine
Objectives

- Recognize the public health impact of rheumatoid arthritis
- Recall the clinical characteristics, pathology, and pathogenesis of rheumatoid arthritis
- Discuss novel pharmacologic treatments
Greek "arthron" for joint and Latin "itis" for inflammation

Arthritic was used in English as an adjective and a noun from 1366
Arthritis in general

a massive public health problem

- The leading cause of disability in the US
- ~46 million (~20% of) U.S. adults have physician-diagnosed arthritis.
  - expected to reach ~60 million by 2020
- ~19 million U.S. adults / year report activity limitations due to arthritis.
- As the U.S. (and global) populations continue to age, these numbers will soar.
Rheumatoid Arthritis

Epidemiology
Self-reported chronic diseases in the U.S.

- Arthritis: 46 million
- Hypertension: 36.8 million
- Mental Disorders: 30.3 million
- Heart Disease: 19.2 million
- Diabetes: 13.7 million
- Cancers: 10.6 million
- Stroke: 2.4 million

Milken Institute. 2007. www.milkeninstitute.org
Arthritis: not just a disease of the elderly

- Nearly two thirds of people with arthritis are younger than 65.
- It affects children and adults of all racial and ethnic groups.
- More common among women and older adults.
Projected Number of Adults with Arthritis and Arthritis-Attributable Activity Limitations 2005–2030

Relative economic impact

- Cancers: $48B, $271B
- Hypertension: $33B, $280B
- Mental Disorders: $46B, $171B
- Heart Disease: $65B, $105B
- Pulmonary Conditions: $45B, $94B
- Diabetes: $27B, $105B
- Stroke: $22B, $14B

Total treatment expenditures = $277B
Total lost economic output = $1,047B

Milken Institute. 2007. www.milkeninstitute.org
“The Bone and Joint Decade”

- The years 2000-2010 as declared by the UN, WHO, and 37 countries
- A global initiative:
  - to improve the lives of those with musculoskeletal disorders
  - to advance knowledge and treatment through prevention, education and research
Rheumatoid Arthritis

_A systemic inflammatory disease_

- A chronic, progressive, systemic inflammatory disease
- Affects ~ 1% of total population
- Causes progressive, irreversible destruction of synovial joints →
  - Cartilage/bone loss
  - Ligament/tendon damage

MacLean CH et al. _JAMA_. 2000.
Rheumatoid Arthritis

A systemic inflammatory disease

- Classic features:
  - Joint pain, typically symmetric
  - Morning joint stiffness (≥ 1 hour)
  - Joint swelling
  - Constitutional symptoms (fever, fatigue, weight loss, etc.)
Rheumatoid Arthritis

A systemic inflammatory disease

- Mean age at onset: 40 – 60 years
- 2 – 3 fold more prevalent in women
- Genetic concordance in monozygotic twins: 15 - 21%
- Life expectancy ↓ by 5-15 years
- ↓ physical function, ↓ quality of life, disability and underemployment

MacLean CH, et al. JAMA. 2000
Rheumatoid Arthritis

Historical Perspective

- A new disease:
  - Emerged in the West ~16th - 17th centuries
- Possibly sparked by an infection/epidemic among medieval Europeans
- Sir Alfred Baring Garrod first coined the term 'rheumatoid arthritis' in 1859.
Renoir during a boat tour on the Seine in 1896. Swelling of the metacarpophalangeal and proximal interphalangeal joints is evident.
Despite these deformed hands, Renoir continued to roll his own cigarettes and completed more than 400 works of art. The bandages served to absorb the sweat to prevent maceration.

Boonen, A. *BMJ*. 1997
RA rendered Renoir wheelchair bound after 1912.
Rheumatoid Arthritis

Clinical Features
A 55-year old woman with:

- **6-months** of daily morning stiffness, joint tenderness, swelling, and difficulty with activities of daily living.
- On exam: swollen hands, wrists, elbows, knees, and feet
- Erythrocyte sedimentation rate: 85
- Rheumatoid factor: Positive
MCP and MTP Squeeze Test
Rheumatoid Arthritis

Clinical Characteristics
Rheumatoid Arthritis
Spectrum of Clinical Severity
Rheumatoid Arthritis

Complications, comorbidities and extra-articular manifestations
Rheumatoid Arthritis

Collateral Damage!!

Premature CV Disease 10 Years Earlier

2 X ↑ Malignancy

↓ Life Expectancy 10 yr women, 4 yr men

6-9 X ↑ Serious Infections

↑ Pulmonary Disease

↑ GI Bleeding

Joint

Pain

Disability

Destruction

Deane K. J Musculoskel Med. 2006
Rheumatoid Arthritis
The Aftermath
**Clinical Features**
- Female > Male
- *Morning stiffness >1 hour*
- Fatigue

**Musculoskeletal Characteristics**
- Symmetrical
- Polyarticular (>3 joints)
- MCP/PIP/Wrist/MTP
- Cervical spine
- Spares thoracolumbar spine

**Laboratory features**
- *Rheumatoid factor*
- Anti-CCP Antibody
- ESR/CRP
- Anemia

**Extra-Articular Manifestations**
- Cardiovascular disease
- *Nodules*
- Vasculitis
- Iritis
- Pulmonary fibrosis

**Radiographic Characteristics**
- *Erosions*
- *Periarticular osteopenia*
- Joint space loss

**ACR Classification Criteria:**
≥ 4 criteria with symptoms for ≥ 6 wks
Rheumatoid Arthritis

Laboratory Testing

- Rheumatoid factor (RF)
  - <50% positive in first 6 months
  - 85% of established disease are RF positive
  - Not specific for RA (infection, malignancy, etc.)

- Anti-Cyclic Citrullinated Peptide Antibody (Anti-CCP)
  - Increased sensitivity and specificity for RA
  - May be present before RF
  - Found in up to 40% of RF-negative patients
  - Predictive of erosive disease and joint damage
Rheumatoid Arthritis

Clinical Course

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

Rheumatoid Arthritis

Radiographic Changes

Periarticular Osteopenia

Cartilage loss

Erosion
Rheumatoid Arthritis

Radiographic Changes
Rheumatoid Arthritis

Disease Progression

- Rate of progression: 1\textsuperscript{st} year >> 2\textsuperscript{nd} and 3\textsuperscript{rd} years
- 67\% have joint space narrowing/erosions in first 2 years
- Progression continues

Wolfe F, Sharp J. \textit{Arthritis Rheum}. 1998
Rheumatoid Arthritis

Early Disease Detection

Normal Plain Radiograph

Erosion on MRI
Rheumatoid Arthritis

*Early Disease Detection*

MRI

Ultrasound

Rheumatoid Arthritis

Pathology and Pathogenesis
Autoimmunity 
at the core of rheumatologic diseases
Autoimmunity

Multifactorial

- Genetic susceptibility:
  - HLA DR4 with Rheumatoid Arthritis, type I diabetes
  - HLA DR2 with lupus
- Gender:
  - Females >> Males (Role for Sex steroids?)
- Environmental Factors:
  - Infections
  - Overexposure to pesticides and toxins
  - Stress
"My doctor told me to avoid any unnecessary stress, so I didn't open his bill."
Rheumatoid Arthritis

Pathogenesis

Initiation

Susceptibility

Accelerants

Triggers

Immune Responses

Inflammation

Amplification

Damage/ Destruction
Rheumatoid Arthritis

Pathology

RA Synovium

Normal Synovium

Pathogenesis of RA

Integrated Immune Response

Antigen-presenting cells:
- B cells
- Dendritic cells
- Macrophages

**T cell**
- IL-2
- IFN\(\gamma\)
- IL-17

**MΦ**
- TNF-\(\alpha\), IL-1, IL-6, Metalloproteinases
- RANKL

**B cell**
- IL-6, TNF-\(\alpha\), IFN\(\gamma\), Lymphotoxin

**Plasma cell**
- Rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies

**Osteoclast**
- Erosion of bone and cartilage

**Synoviocytes**
- Migration of polymorphonuclear cells

**Chondrocytes**
- Production of metalloproteinases, prostaglandins, other effector molecules

**Articular cartilage**

Adapted from:
Rheumatoid Arthritis

Management
A 55-year old woman with:

- **6-months** of daily morning stiffness, joint tenderness, swelling, and difficulty with activities of daily living.
- On exam: swollen hands, wrists, elbows, knees, and feet
- Erythrocyte sedimentation rate: 85
- Rheumatoid factor: Positive

What would you do?
“When a patient with Rheumatoid Arthritis walks through the front door, I run out the back door.”

Sir William Osler
The father of modern medicine
A History of RA Therapy:  
*from gold to whiskey*

- 1920s: some believed RA was linked to TB
  - Jacques Forestier introduced **gold** to treat RA
- Many early therapies now considered absurd & even harmful:
  - Bed rest
  - Consuming **whiskey** or gin with evening meals
- Quinine therapy emerged early in the 20th century and is still used in the form of hydroxychloroquine.
Milestones in RA Therapy

1900: Aspirin - First synthesized anti-inflammatory drug
1925: Gold Salts - Forestier mistakes RA for TB
1950s: Steroids - Rapid anti-inflammatory effects & qualities of DMARDs
1975: Methotrexate - Becomes the standard of care
2000s: Biologic DMARDs

DMARDs: Disease-modifying anti-rheumatic drugs
Rheumatoid Arthritis

The Old Treatment Pyramid

- NSAIDS
- Steroids
- Hydroxychloroquine
- Sulfasalazine
- Methotrexate (lower dose)

Initial Rx (Gold)
Rheumatoid Arthritis

Goals of therapy

- Improvement
- Remission
- Cure
Rheumatoid Arthritis

*Therapy is a race against time!*

“Time = Joint”
25-year old woman with 4 months of pain, stiffness in hands & feet. Normal XRay. RF negative. Anti-CCP positive.

MCP #5 Erosion with Active Synovitis
Rheumatoid Arthritis

The modern treatment paradigm

- Prompt DMARDs treatment really works:
  - Orthopedic surgery for RA now less common
  - RA manifestations of a prior era no longer seen (e.g., subcutaneous nodules, RA vasculitis, RA eye disease)
  - Decreased atherosclerosis
  - Prolonged survival
  - Remission now a true possibility
Rheumatoid Arthritis

Therapy in 2009

- NSAIDS/Coxibs
  - Adjunctive treatment
- Glucocorticoids
  - Combined with DMARDs
  - Bridge to DMARDs
- Traditional DMARDs
  - Mono- or Combination therapy
    - Methotrexate
    - Sulfasalazine
    - Leflunomide
  - Biologic DMARDs
    - TNF antagonists
      - Adalimumab
      - Etanercept
      - Infliximab
    - IL-1 antagonist
      - Anakinra
    - Costimulation modulation
      - Abatacept
    - B-cell depletion
      - Rituximab

DMARDs = disease-modifying antirheumatic drugs; TNF = tumor necrosis factor; IL = interleukin
Rheumatoid Arthritis

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Rheumatoid Arthritis

**Therapy**

*Methotrexate (Rheumatrex®)*

- First used in 1951
  - *Widespread use in RA by late 1970’s*
- Its cellular action has been identified (a purine antagonist), but the mechanism by which it improves RA is not yet known.
Methotrexate (Rheumatrex®)

- The “Gold Standard” DMARD for RA
- Indicated at all stages of disease
- Administered PO or SQ once per week
- Aggressive rather than step-wise approach to dosing
- Must use with folic acid or leucovorin to prevent hematological, other SE’s
Adverse Effects: Methotrexate (Rheumatrex®)

Well recognized toxicities:
- Headache, Fatigue, Oral Ulcers, Alopecia, Nausea
- Anemia, Leukopenia, Thrombocytopenia
- Liver toxicity (increased with alcohol)
- Pulmonary fibrosis and Pneumonitis
- Cutaneous Nodulosis

Appropriate monitoring is critical:
- Baseline chest x-ray
- Hepatitis serologies before use
- Alcohol avoidance
- Complete blood count, liver function tests q4-12 weeks
Rheumatoid Arthritis

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Rheumatoid Arthritis

Therapy

Leflunomide (Arava®)

- Approved in the US in 1998
- Pyrimidine antagonist
- Interferes with multiple components of the immune-inflammatory response
- As effective as methotrexate

Adverse Effects: Leflunomide (Arava®)

- Diarrhea and nausea (in up to 15%)
- Transaminitis (in up to 15%)
- Hypertension (especially when in combination with NSAIDs)
- Rare Leukopenia
- More toxicities when combined with other DMARDs
Rheumatoid Arthritis

Therapy in 2009

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  - Adjunctive treatment
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- Biologic DMARDS
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The Biologic Revolution

Prof. Marc Feldmann and Sir Ravinder Maini
Pathogenesis of RA

Integrated Immune Response

Antigen-presenting cells:  
- B cells  
- Dendritic cells  
- Macrophages

IL-4  
IL-6  
IL-10

B cell  
IL-6, TNF-α, IFNγ, Lymphotoxin

MΦ  
IL-2  
IFNγ  
IL-17  
RANKL

TNF-α, IL-1, IL-6, Metalloproteinases

Osteoclast  
Synoviocytes  
Chondrocytes

Articular cartilage

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

Rheumatoid factor (RF), anti–cyclic citrullinated peptide (anti-CCP) antibodies

Immune complexes  
Complement fixation  
Attract inflammatory cell infiltrates

Adapted from:  
Currently Approved TNF Antagonists

**Infliximab**
*Remicade®*
(Binding site for TNF)

**Human (IgG1)**

**Etanercept**
*Enbrel®*

**Adalimumab**
*Humira®*

- Currently Approved TNF Antagonists
- **Fc region of human IgG1**
- **Extracellular domain of human p75 TNF receptor**
Combination Therapy: MTX + TNF Antagonist in RA

Infliximab 10mg/kg/q8w
D2E7 40 q2w
Etanercept 25 mg biw

Patients %

- ACR20 Drug+MTX
- ACR20 PBO+MTX
- ACR50 Drug+MTX
- ACR50 PBO+MTX
- ACR70 Drug+MTX
- ACR70 PBO+MTX

Lipsky
NEJM 2000
52 weeks

Weinblatt
A & R 2003
24 weeks

Weinblatt
NEJM 1999
24 weeks
**TNF Antagonists in Early RA**

**ACR50 Responses at 1 Year**

- **Etanercept**
  - TEMPO (N=682)\(^1\)
  - Disease duration: ~0.7 y
  - 43 patients (%)

- **Infliximab**
  - ASPIRE (N=1004)\(^2\)
  - 32 patients (%)

- **Adalimumab**
  - PREMIER (N=799)\(^3\)
  - 46 patients (%)

**Notes:**

Rheumatoid Arthritis

Therapy in 2009

- **Biologic DMARDs**
  - TNF antagonists
    - Adalimumab
    - Etanercept
    - Infliximab
  - IL-1 antagonist
    - Anakinra
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    - Abatacept
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- **NSAIDS/Coxibs**
  - Adjunctive treatment

- **Glucocorticoids**
  - Combined with DMARDs
  - Bridge to DMARDs

- **Traditional DMARDs**
  - Mono- or Combination therapy
    - Methotrexate
    - Sulfasalazine
    - Leflunomide

DMARDs = disease-modifying antirheumatic drugs; TNF = tumor necrosis factor; IL = interleukin
Abatacept (Orencia®)  
Inhibiting T Cell Co-stimulation

Without Abatacept

With Abatacept

T Cell Activation Blocked

Without Abatacept:
- DC bound to T cell
- CD80/86 and CD28
- Activated T cell

With Abatacept:
- DC bound to T cell
- T cell activation blocked by Abatacept
Abatacept + Background DMARDs in TNF Inadequate Responders (ATTAIN) Responses at 6 months


<table>
<thead>
<tr>
<th></th>
<th>ACR20</th>
<th>ACR50</th>
<th>ACR70</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>19.5</td>
<td>3.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Abatacept 10mg/kg q 4wks</td>
<td>20.2</td>
<td></td>
<td>10.2</td>
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All patients on background DMARDS
Rheumatoid Arthritis

Therapy in 2009

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Rituximab
Targeting B Cells

- Antigen
- CD20
- IL-10
- other cytokines
- B Cell
- T Cell
- Costimulation
- Antigen Presentation
- Antibodies
- Inflammation
- TNF
- IL-1
- IL-15

Rituximab Bind B Cells and CD20, leading to
Antigen Presentation to T Cells and
Costimulation through cytokines like IL-10.
All patients received approximately 1000 mg corticosteroids
**Response in TNF Failures (REFLEX)**

Patients With Inadequate Response to ≥1 TNF Inhibitors

All patients on background MTX & all received ~1000 mg corticosteroids

- Placebo: 18 patients
  - ACR20: 5
  - ACR50: 1
  - ACR70: 1

- Rituximab 1000 mg: 51 patients
  - ACR20: 27
  - ACR50: 12
  - ACR70: 12

Cohen SB. Arthritis Rheum. 2006
RA Therapy
Balancing the Risks

Risks
Cardiovascular
Gastrointestinal
Infection
Bone loss
Malignancy
Disability
Pain
Joint Destruction

Benefits
Pain Relief
Symptom Control
Return of Physical Function
Maintaining Employment
Safety Concerns

Biological DMARDs

- Infectious complications
  - **Serious bacterial infections** *(hold with infection)*
  - **TB** -- TNF Antagonists *(PPD and CXR before use)*
  - **Opportunistic** *(coccidiomycosis, histoplasmosis, etc.)*
  - **Viral reactivation** *(Zoster, CMV, Hepatitis B and C)*

- Impaired immunization responses, Avoid Live Virus Vaccines
  - e.g., **Yellow fever, rabies, zoster, mumps/measles/rubella, typhus**
TNF Antagonist Therapy

May Cause Tuberculosis to Disseminate

TNF

Granuloma

Dissemination
“Window of Opportunity” in RA

DMARDs associated with decrease in radiographic disease progression

No DMARD

DMARD

Weisman M. Ann Rheum Dis. 2002
Powerful Therapies for RA

The Dark Side

All agents (corticosteroids, NSAIDS, COX-2 inhibitors, DMARDs, biologics) have side effects.

Guidelines for appropriate monitoring are available:

www.rheumatology.org

When to Refer Early Arthritis:

- When there is a clinical suspicion
- Persistence of symptoms > 6 weeks
- >3 swollen joints
- MTP/MCP “squeeze test”
- Morning stiffness > 30 minutes
- Positive Rheumatoid factor
- Positive Anti-CCP antibody
- Elevated ESR or CRP

Cush JJ, J Rheumatol 2005
Early diagnosis is critical to improve RA outcomes.

Expectations of treatment have grown significantly.

Early DMARD therapy improves outcomes, decreases disability, and prevents damage.

Biologics have expanded treatment options and improved outcomes.

Recognizing potential adverse effects of DMARDs and biologics is important.

- These therapies should only be initiated by practitioners familiar with their toxicities.

Optimal care for RA patients is achieved through partnerships between primary care providers and rheumatologists.
RA Challenges in the Arab World

- RA in Arab patients is mild and nondestructive – *A myth!*
- Delayed diagnosis
  - lag time between symptom onset to diagnosis: 1.2 yrs
  - lag time to first DMARD: 18 months.
- Anti-TNF use still not widespread
  - locally: 5%
  - in contrast to 40% in the USA (and up to 54% in France)
Alarm Bells in the RA Patient

Urgent Rheumatologist Discussion

- Infections: particularly in patients on steroids, anti-TNF therapy, other biologics
  - Fever
  - Isolated monoarthritis when all other joints stable
  - Swelling / tenderness in a joint replacement

- Cord compression from Rheumatoid: Neck disease: C1-C2 subluxation
  - Neck pain with focal motor neurologic signs

RA patients may not mount febrile response and the WBC may not be elevated
**Alarm Bells in the RA Patient**

*Urgent Rheumatologist Discussion*

- **Rheumatoid eye disease**
  - Painful red eye
  - Usually not photosensitive
  - Scleritis/episcleritis: refer to ophthalmologist

- **Drug-induced lung disease**
  - Dyspnea and cough in a patient on MTX: could be MTX pneumonitis
Acupuncture is superior to sham (or placebo) for treating chronic knee pain

A. White et al, Rheumatology 2007