Rheumatoid Arthritis

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RA Introduction

- Chronic, systemic, inflammatory
- Unknown etiology
- Primarily involves joints
- Extra-articular manifestations
- 1% of world’s population
- Women 3 times more than men
Onset of RA

- Insidious
- Pain, stiffness, joint swelling
- MCPs, PIPs, thumb IP, wrist, ulnar styloid
- MTPs feet
- Elbow, shoulder, ankle, knee

RA Diagnosis

- Symmetrical peripheral polyarthritis
- Morning stiffness
- Rheumatoid nodules
- Laboratory features
- Radiographic bone erosions

RA - Differential Diagnosis

- Acute viral polyarthritis
- Connective Tissue Diseases – lupus, early scleroderma
- Sarcoidosis
- Psoriatic arthritis
- Reactive arthritis
- Crystal arthritis

RA - Differential Diagnosis

- Infectious arthritis
- Osteoarthritis
- Paraneoplastic disease
- Multinodular reticulohistiocytosis
- Hypermobility syndrome
- Fibromyalgia
RA - Imaging

- Plain films
- Ultrasonography
- MR imaging
RA – Nonarticular Manifestations

- Osteopenia
- Myositis
- Vasculitis
- Skin involvement
- Eye involvement
- Lung disease
RA – Nonarticular Manifestations

- Cardiac involvement
- Peripheral artery disease
- Sjogren’s syndrome
- Nervous system involvement
- Hematologic involvement

Pathophysiology of RA

- Genetic link with HLA-DR4
- Abnormal B cell – T cell interaction
- Autoantibodies – RF and anti-CCP
- Synovial cell proliferation
- Fibrosis and pannus formation
- Cartilage and bone erosion
- Proinflammatory cytokines – IL-1, TNF-a

Pulmonary Rheumatoid Nodules
<table>
<thead>
<tr>
<th>1987 ACR Classification Criteria</th>
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<tr>
<td>• Am stiffness – at least one hour</td>
<td>• Based on average disease duration of 8 years</td>
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<tr>
<td>• Arthritis in three or more joint areas</td>
<td>• Contains elements associated with disease severity – erosions, nodules, rather than disease development</td>
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<tr>
<td>• Arthritis of hand joints (&gt; 1 swollen joints)</td>
<td>• Distinguish RA patients from other joint diseases to enter clinical study</td>
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<tr>
<td>• Symmetric arthritis</td>
<td>• Homogeneous patient group</td>
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<tr>
<td>• Rheumatoid nodules</td>
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<tr>
<td>• Serum RF</td>
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<tr>
<td>• Radiographic changes - erosions</td>
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<thead>
<tr>
<th>1987 ACR Classification Criteria</th>
<th>2010 Classification Criteria</th>
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<tbody>
<tr>
<td>• Four of seven criteria must be present</td>
<td>• Task force of Rheumatologists from USA and Europe</td>
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<tr>
<td>• Criteria one through four must have been present for at least six weeks</td>
<td>• American College of Rheumatology – ACR</td>
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<tr>
<td>• Sensitivity of 79% - 80% and specificity of 90% - 93% for established RA</td>
<td>• European League Against Rheumatism – EULAR</td>
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<tr>
<td>• Sensitivity of 77% - 80% and specificity of 33% - 77% for early RA</td>
<td>• Increased sensitivity and specificity to diagnose RA in an early phase of disease</td>
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### 2010 ACR/EULAR Criteria

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<th>Target population – who should be tested</th>
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<tr>
<td>1 joint with synovitis or swelling</td>
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<tr>
<td>Not better explained by another disease</td>
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<tr>
<td>Score of &gt; 6/10 for definite RA</td>
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### Serology

| Negative RF and negative anti-CCP         | 0 |
| Low positive RF or low positive anti-CCP  | 2 |
| High positive RF or high pos anti-CCP     | 3 |

### Joint Involvement

| 1 large joint | 0 |
| 2-10 large joints | 1 |
| 1-3 small joints | 2 |
| 4-10 small joints | 3 |
| > 10 joints (at least one small joint) | 5 |

### Acute Phase Reactants

| Normal CRP and normal ESR | 0 |
| Abnormal CRP or abnormal ESR | 1 |
## Duration of Symptoms

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<thead>
<tr>
<th>Duration</th>
<th>Score</th>
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<tr>
<td>&lt; 6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 6 weeks</td>
<td>1</td>
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A score of ≥ 6/10 is needed for classification of a patient with definite RA.

## References

### General Principles

- Early accurate diagnosis- first 3-6 months critical
- Early Referral to Rheumatologist
- Risk stratification & Prognostication
- Emphasis on both non pharmacological vs pharmacological treatment
- Assessment of comorbidities

### Poor Prognostic Factors

- Presence of anti-cyclic citrullinated peptide antibody
- Presence of markedly elevated rheumatoid factor
- High disease activity with marked elevations in ESR and or C-reactive protein, poor functional status
- Extra articular disease with rheumatoid nodules, lung disease etc.
- Presence of erosions and or joint space narrowing by x-ray ultrasound or MRI
- Delayed diagnoses and treatment

### Non Pharmacological

- Patient Education
- Rest
- Exercise
- Physical Therapy
- Occupational Therapy
- Dietary Modification
- Vaccinations/Bone Health/Cardiovascular health

### Pharmacological

- NSAIDS
- Analgesics
- Glucocorticoids
- Non Biologic/Synthetic DMARDS
- Biologic DMARDS

*Goal is Remission/Low disease activity without toxicity*
### NSAIDS
- Analgesics & Anti-inflammatory
- Do not alter disease outcome
- Use in RA is not evidence based & is not part of management algorithm

### Glucocorticoids
- Prednisone or Prednisolone
- Oral, Intraarticular, Parenteral routes
- Doses less than 7.5 mgm qd recommended for short periods of time, higher doses recommended only for early aggressive disease
- Reduce pain & inflammation and also prevent disease progression
- Poor Toxicity profile especially infections
- Attention to Osteoporosis prophylaxis

### Analgesics
- Darvocet, Tramadol, Percocet, Vicodin etc.
- No effect on disease outcome, but frequently used for pain management

### Non biologic DMARDS
- Methotrexate
- Leflunomide/Arava
- Sulphasalazine
- Injectable Gold
- Hydroxychloroquine/Plaquenil
- Azathioprine/ Imuran
- Cyclosporin
<table>
<thead>
<tr>
<th>Methotrexate</th>
<th>Sulphasalazine</th>
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<tr>
<td>• Oral, SQ, I/V, I/M routes, dose from 7.5-30 mgm weekly</td>
<td>• Works by inhibiting Prostaglandin synthesis systemically</td>
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<tr>
<td>• Adverse effects of Hepatotoxicity, Renal toxicity, Myelosuppression, Lymphoma, Pulmonary fibrosis</td>
<td>• Average dose of 1 gm - 2gm BID</td>
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<tr>
<td>• Monitor for CBC, Cr, LFT-every one month initially, every 3 months on stable dose</td>
<td>• Folic acid supplementation</td>
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<tr>
<td>• Screen for Hepatitis B &amp; C</td>
<td>• Monitor for GI upset, CBC, LFT &amp; Renal function</td>
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<tr>
<td>* Drug of choice unless C/I</td>
<td>• Can cause reversible azoospermia in males</td>
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<tr>
<th>Leflunomide</th>
<th>Plaquenil</th>
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<td>• Anti-inflammatory &amp; Anti-proliferative action due to inhibition of Pyrimidine synthesis</td>
<td>• Works by inhibiting chemotaxis &amp; impairing complement mediated antigen antibody reactions</td>
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<tr>
<td>• Dose of 10 to 20 mgm qd</td>
<td>• Dose - 200 mgm bid or 6 mgm /kbw</td>
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<tr>
<td>• Monitor for CBC, LFT, Renal function and infections-monthly initially, every 3 months later</td>
<td>• Check G6PD levels</td>
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<tr>
<td>• Efficacy comparable to Methotrexate</td>
<td>• Monitor for CBC, Retinal toxicity &amp; Myopathy. Baseline and yearly eye exams recommended</td>
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<tr>
<td>• Screen for Hepatitis B &amp; C</td>
<td>• Efficacy in early disease as mono therapy is limited</td>
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### Biologic DMARDS

- **TNF Antagonists**
  - Etanercept or Enbrel, soluble receptor antagonist
  - Adalimumab or Humira, fully humanized monoclonal antibody
  - Infliximab or Remicade, partially humanized monoclonal antibody
  - Cetuxizumab or Cimzia, pegylated soluble receptor antagonist
  - Golimumab or Simponi, fully humanized monoclonal antibody

- **IL-1 Receptor antagonists** - Anakinra
- **IL-6 Receptor antagonists** - Tocilizumab or Actemra
- **Inhibitors of T-cell-B cell costimulatory molecules** - Abatacept / Orencia
- **Monoclonal antibodies against B cells** - Rituximab/Rituxan

*Combination of biologics from 2 different groups is not recommended as it does not increase efficacy but increases toxicity*

### Precautions with Biologic DMARDS

- Infections - Bacterial, opportunistic, Viral
- Screen for Hepatitis B & C, T.B., Attention to vaccinations
- Precipitation of other autoimmune diseases like lupus
- Demyelinating diseases like multiple sclerosis
- Malignancies especially lymphomas
- Multifocal Leucoencephalopathy especially with Rituxan

### Optimal Treatment of Rheumatoid Arthritis

- **EULAR/ACR Recommendations**
  - Three overarching principles
  - 15 recommendations

  **EULAR**
  - European League Against Rheumatism

  **ACR**
  - American College of Rheumatology
Overarching Principles

• Rheumatologists to be the primary caretakers
• Treatment should aim at best care and should be a shared decision between patient and the rheumatologist
• Medical and productivity costs should be considered by the treating rheumatologist

Recommendations from EULAR and ACR

• Initiate treatment with nonbiological DMARDs as early as possible
• Treatment should be to a target of remission or low disease activity as early as possible and should be adjusted frequently, every one to 3 months till achieved
• Methotrexate should be part of the first treatment strategy in active RA
• If methotrexate contraindicated or poorly tolerated, Arava, sulphasalazine or injectable Gold should be the next choice

Recommendations

• In DMARD naïve patients, synthetic mono therapy rather than synthetic combination therapy should be considered
• Glucocorticoids in short courses recommended in combination with synthetic DMARDs in early disease
• If treatment target not achieved with first DMARD strategy, switch to biologic if poor prognostic factors, and switch to another synthetic DMARD in the absence of these factors

• If target not achieved with combination of methotrexate and another synthetic DMARD, with or without glucocorticoids, add a TNF inhibitor
• If first TNF inhibitor fails, change to another TNF inhibitor, Abatacept, rituximab or Tocilizumab
• In refractory severe rheumatoid arthritis or if biologics contraindicated, consider treatment with Azathioprine, Cyclosporin as monotherapy or as combination therapy
**Recommendations**

- Intensive medication strategies with frequent monitoring should be considered in every patient, especially those with poor prognostic factors
- If patient in persistent remission, first taper glucocorticoids, then taper biological DMARDs especially if patient on combination therapy with synthetic DMARDs
- In cases of sustained long-term remission, very cautious titration of synthetic DMARD could be considered, flares are common!

**Conclusions**

- Interesting and promising times for treatment of rheumatoid arthritis
- Financial constraints brought by progress to be considered
- Anchor drugs like methotrexate and glucocorticoids beneficial for many patients so risk stratification and prognostication important
- Move towards early aggressive induction regimens followed by tapering (synonymous to treatment for cancers) - as best chance of remission appears to be with this approach

**Recommendations**

- DMARD naïve patients with poor prognostic factors might be considered for combination of methotrexate plus a biological agent at the outset
- Adjusting treatment should take into account not only disease activity but factors such as progression of structural damage, comorbidities and toxicities

**References**

- Treatment of Rheumatoid Arthritis, Up-to-Date.com