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

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
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<tbody>
<tr>
<td><strong>Acute viral polyarthritis</strong></td>
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<tr>
<td><strong>Connective Tissue Diseases – lupus, early scleroderma</strong></td>
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<tr>
<td><strong>Sarcoidosis</strong></td>
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<tr>
<td><strong>Psoriatic arthritis</strong></td>
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<tr>
<td><strong>Reactive arthritis</strong></td>
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<tr>
<td><strong>Crystal arthritis</strong></td>
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## RA - Differential Diagnosis

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<th>Differential Diagnosis</th>
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<tbody>
<tr>
<td><strong>Infectious arthritis</strong></td>
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<tr>
<td><strong>Osteoarthritis</strong></td>
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<tr>
<td><strong>Paraneoplastic disease</strong></td>
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<tr>
<td><strong>Multinodular reticulohistiocytosis</strong></td>
</tr>
<tr>
<td><strong>Hypermobility syndrome</strong></td>
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<tr>
<td><strong>Fibromyalgia</strong></td>
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</table>
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

### Pulmonary Rheumatoid Nodules
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
### 1987 ACR Classification Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Am stiffness – at least one hour</td>
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<tr>
<td>Arthritis in three or more joint areas</td>
</tr>
<tr>
<td>Arthritis of hand joints (&gt; 1 swollen joints)</td>
</tr>
<tr>
<td>Symmetric arthritis</td>
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<tr>
<td>Rheumatoid nodules</td>
</tr>
<tr>
<td>Serum RF</td>
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<tr>
<td>Radiographic changes - erosions</td>
</tr>
</tbody>
</table>

- Four of seven criteria must be present
- Criteria one through four must have been present for at least six weeks
- Sensitivity of 79% - 80% and specificity of 90% - 93% for established RA
- Sensitivity of 77% - 80% and specificity of 33% - 77% for early RA
### 1987 ACR Classification Criteria
- Based on average disease duration of 8 years
- Contains elements associated with disease severity – erosions, nodules, rather than disease development
- Distinguish RA patients from other joint diseases to enter clinical study
- Homogeneous patient group

### 2010 Classification Criteria
- Task force of Rheumatologists from USA and Europe
- American College of Rheumatology – ACR
- European League Against Rheumatism – EULAR
- Increased sensitivity and specificity to diagnose RA in an early phase of disease
### 2010 ACR/EULAR Criteria

- Target population – who should be tested
- 1 joint with synovitis or swelling
- Not better explained by another disease
- Score of > 6/10 for definite RA

### Joint Involvement

<table>
<thead>
<tr>
<th>Joint Involvement</th>
<th>Score</th>
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<tbody>
<tr>
<td>1 large joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>
## Serology

<table>
<thead>
<tr>
<th>Test</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Negative RF and negative anti-CCP</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF or low positive anti-CCP</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF or high pos anti-CCP</td>
<td>3</td>
</tr>
</tbody>
</table>

## Acute Phase Reactants

<table>
<thead>
<tr>
<th>Test</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td>1</td>
</tr>
</tbody>
</table>
Duration of Symptoms

<table>
<thead>
<tr>
<th>Duration</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

A score of > or = 6/10 is needed for classification of a patient with definite RA.

References

- Diagnosis and differential diagnosis of rheumatoid arthritis, UpToDate, 2010
- Clinical features of rheumatoid arthritis, UpToDate, 2010
- Overview of the systemic and nonarticular manifestations of rheumatoid arthritis, UpToDate, 2010
References


Management Of Rheumatoid Arthritis

Madhu Mehta, MD
Clinical Assistant Professor Of Medicine
Rheumatology
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## 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

### Analgesics

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

## Non biologic DMARDs

- Methotrexate
- Leflunomide/Arava
- Sulphasalazine
- Injectable Gold
- Hydroxychloroquine/Plaquinil
- Azathioprine/Imuran
- Cyclosporin
Methotrexate

- Oral, SQ, I/V, I/M routes, dose from 7.5-30 mgm weekly
- Adverse effects of Hepatotoxicity, Renal toxicity, Myelosuppression, Lymphoma, Pulmonary fibrosis
- Monitor for CBC, Cr, LFT-every one month initially, every 3 months on stable dose
- Screen for Hepatitis B & C

* Drug of choice unless C/I

Leflunomide

- Anti-inflammatory & Anti-proliferative action due to inhibition of Pyrimidine synthesis
- Dose of 10 to 20 mgm qd
- Monitor for CBC, LFT, Renal function and infections-monthly initially, every 3 months later
- Efficacy comparable to Methotrexate
- Screen for Hepatitis B & C
### Sulphasalazine

- Works by inhibiting Prostaglandin synthesis systemically
- Average dose of 1 gm - 2gm BID
- Folic acid supplementation
- Monitor for GI upset, CBC, LFT & Renal function
- Can cause reversible azoospermia in males

### Plaquenil

- Works by inhibiting chemotaxis & impairing complement mediated antigen antibody reactions
- Dose - 200 mgm bid or 6 mgm /kbw
- Check G6PD levels
- Monitor for CBC, Retinal toxicity & Myopathy. Baseline and yearly eye exams recommended
- Efficacy in early disease as mono therapy is limited
### Biologic DMARDS

#### TNF Antagonists
- Etanercept or Enbrel, soluble receptor antagonist
- Adalimumab or Humira, fully humanized monoclonal antibody
- Infliximab or Remicade, partially humanized monoclonal antibody
- Cetrolizumab 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 Tcell-B cell costimulatory molecules - Abatacept / Orenzia

#### 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, sulfasalazine 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.

### Recommendations

- 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!

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.
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

References

• Treatment of Rheumatoid Arthritis, Up-to-Date.com
• Smolen JS et al. Annals of Rheumatic Diseases. 2010; 69: 964-975