Rheumatoid Arthritis

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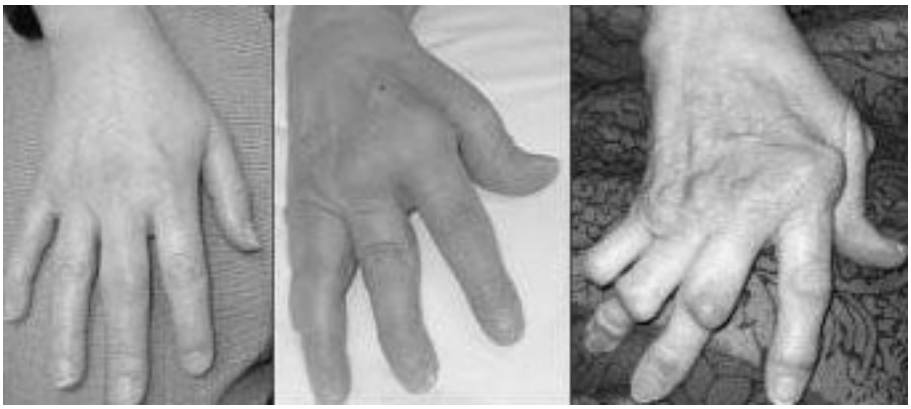
RA Introduction

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



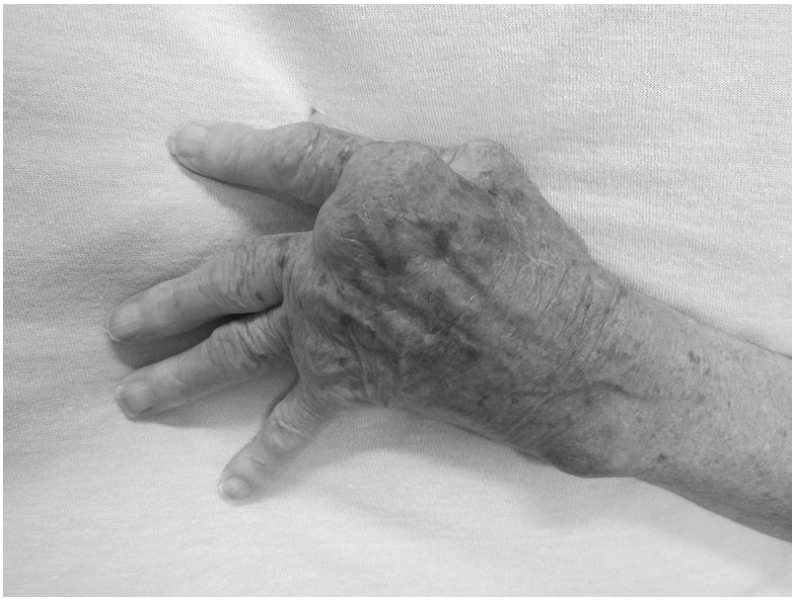


Photo by James Heilman, MD

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

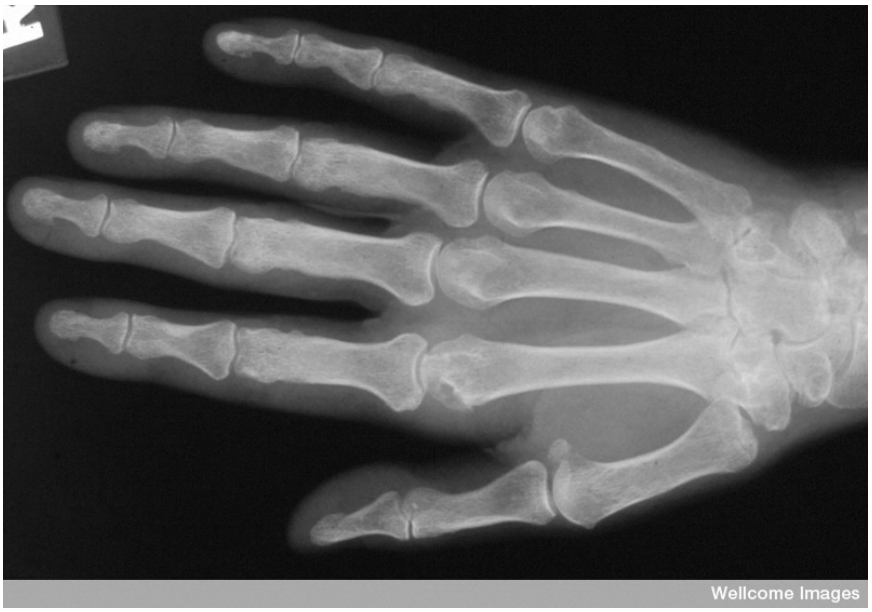
- Acute viral polyarthritis
- Connective Tissue Diseases – lupus, early scleroderma
- Sarcoidosis
- Psoriatic arthritis
- Reactive arthritis
- Crystal arthritis

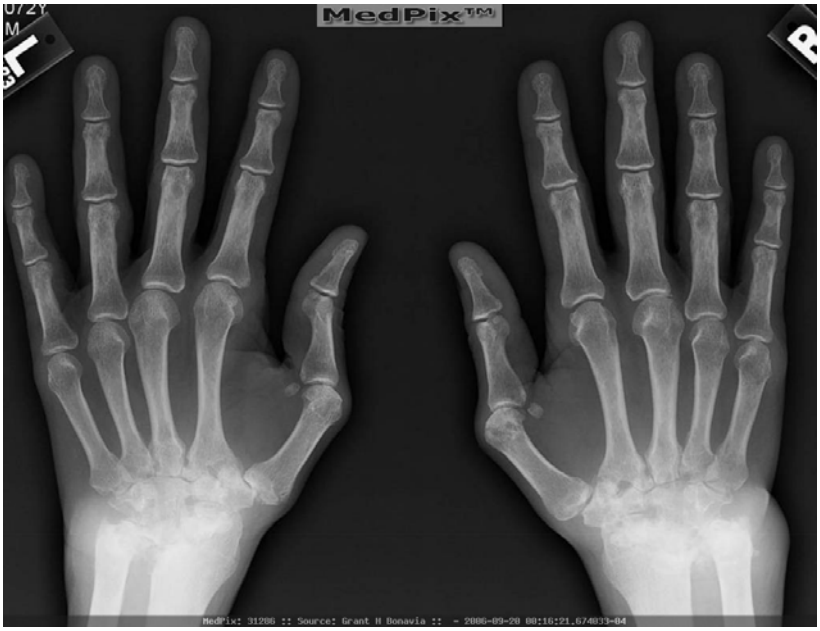
RA - Differential Diagnosis

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

RA - Imaging

- **Plain films**
- **Ultrasonography**
- **MR imaging**

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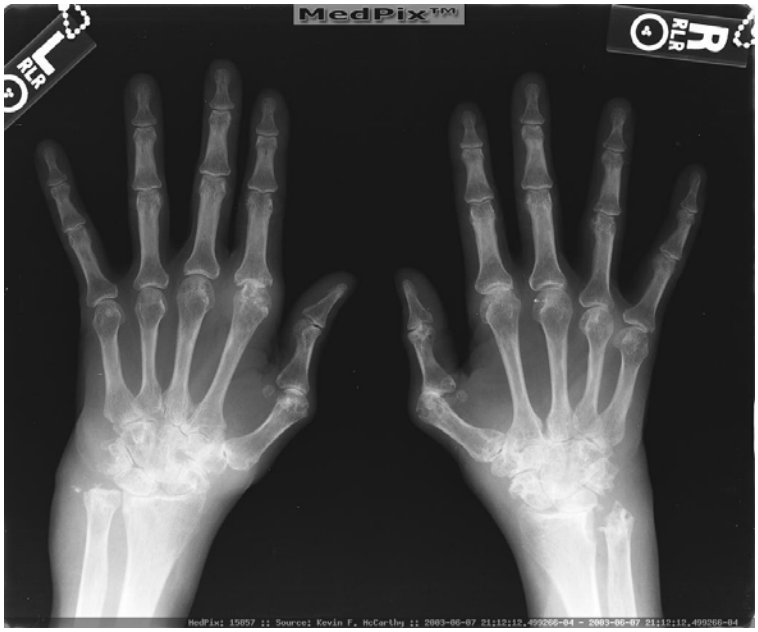
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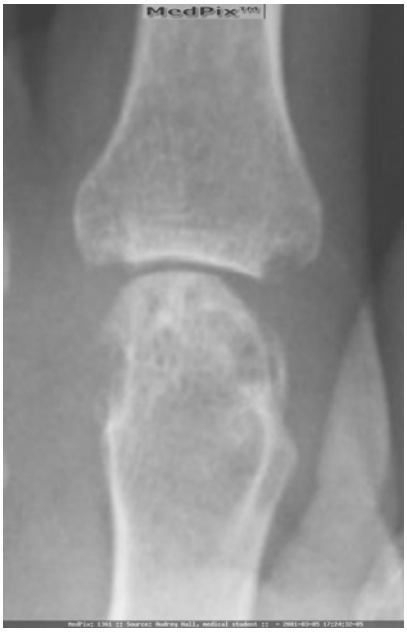
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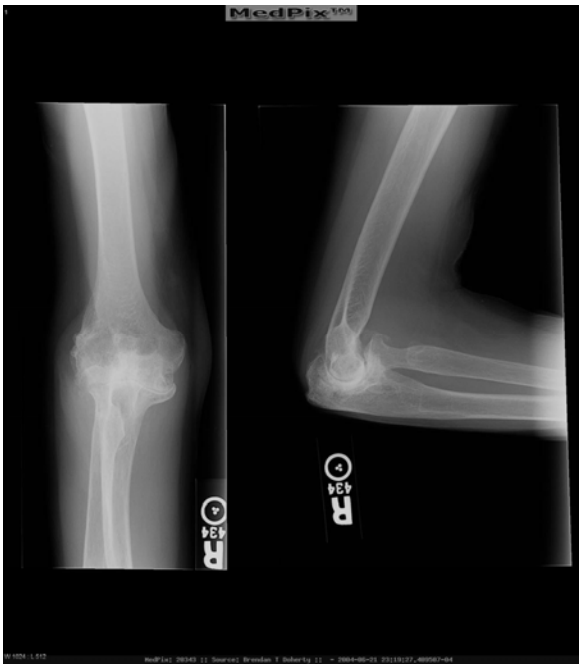
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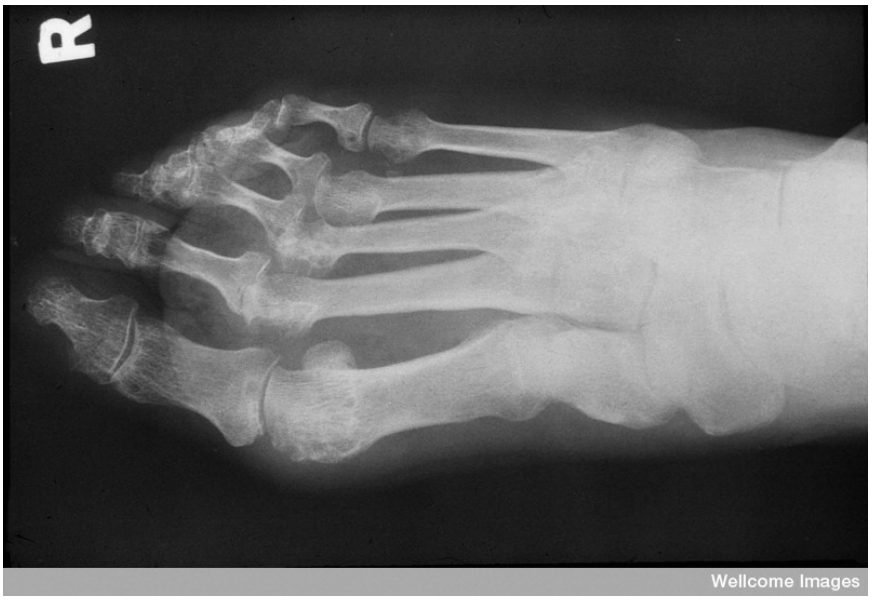


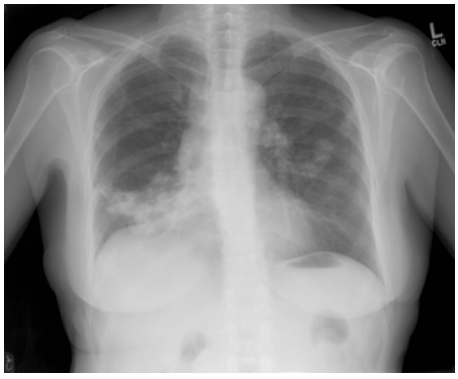
RA – Nonarticular Manifestations

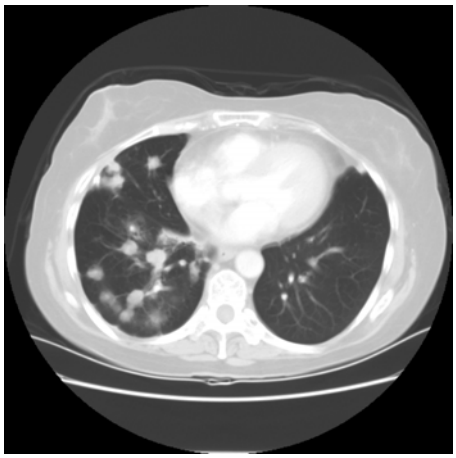
- Osteopenia
- Myositis
- Vasculitis
- Skin involvement
- Eye involvement
- Lung disease

RA – Nonarticular Manifestations

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

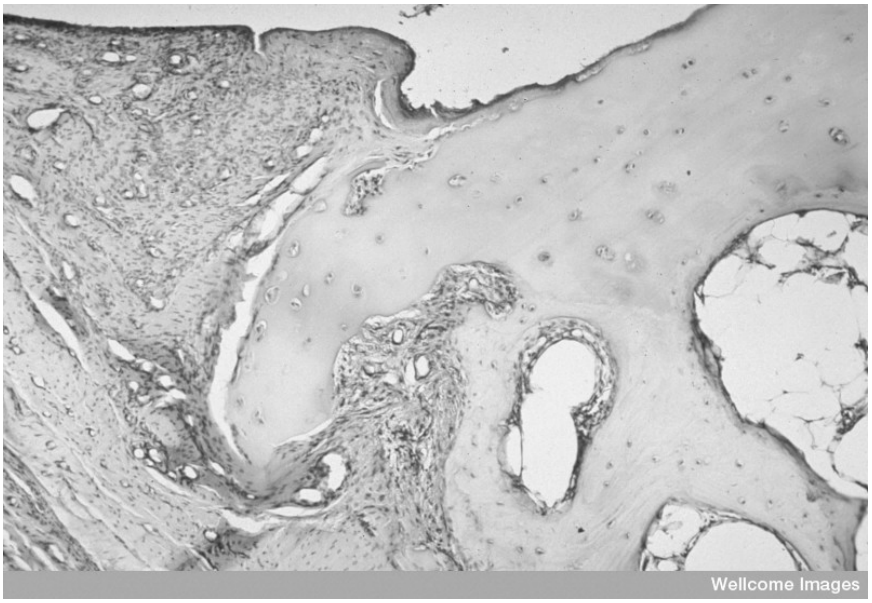
Pulmonary Rheumatoid Nodules





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

- Am stiffness – at least one hour
- Arthritis in three or more joint areas
- Arthritis of hand joints (> 1 swollen joints)
- Symmetric arthritis
- Rheumatoid nodules
- Serum RF
- Radiographic changes - erosions

1987 ACR Classification Criteria

- 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

• 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

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**

Acute Phase Reactants

- **Normal CRP and normal ESR** **0**
- **Abnormal CRP or abnormal ESR** **1**

Duration of Symptoms

- **< 6 weeks** **0**
- **> 6 weeks** **1**
- **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

- Henkel G, Debut New RA Classification Criteria in August, The Rheumatologist, Vol 4, No. 8, Aug 2010.
- Van der Helm-van Mil AH and Huizinga TWJ, The Key to Early Rheumatoloid Arthritis, The Rheumatologist, Vol 4, No. 9, Sept 2010.

Management Of Rheumatoid Arthritis

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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/Plaquenil
- Azathioprine/ Imuran
- Cyclosporin

Methotrexate

- **Oral, SQ, I/V, I/M routes, dose from 7.5- 30 mgm weekly**
- **Adverse effects of Hepatotoxicity, Renal toxicity, Myelosupppression, Lymhoma, 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 Prostagalndin 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**

Biologic DMARDS

- **IL-1 Receptor antagonists - Anakinra**
- **IL-6 Receptor antagonists - Tocilizumab or Actemra**
- **Inhibitors of Tcell-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, 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