Medicine
TEAM 437

MED437
KING SAUD UNIVERSITY

Rheumatoid Arthritis

Objectives :

- Recognize which patient is likely to have RA
- Know the different modes of presentation of RA
- Develop a plan of investigation and management of R

Done by :

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Resources :

Doctors slides+notes: Hussein Al Arfaj
Books: Kumar, Step Up
436 team

Rheumatoid Arthritis

Systemic* chronic inflammatory disease mainly affects synovial joints and tendons.

- Variable modes of presentation
- Prevalence about 3%
- Worldwide distribution
- Female:male ratio 3:1
- Peak age of onset: 25-50 years but could come at any age, even children.

A 30-year-old lady presented with multiple joint pain and swelling for three months, what is your DDx?

- Rheumatoid Arthritis
- Osteoarthritis
- Seronegative Psoriatic Arthritis
- SLE

*Systemic as it causes fatigue and it could also involve the lungs, heart, vessels, kidneys and the CNS.

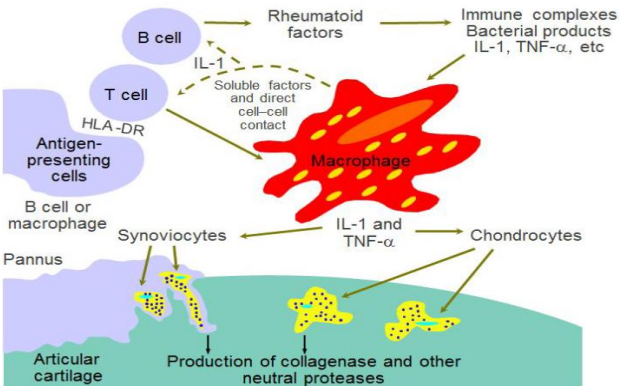
Etiology

- Unknown etiology (Genetics necessary associated with HLA-DR4*, Environmental such as smoking, Possible infectious component most likely viral) smoking is associated with positive RA serology
- Autoimmune disorder

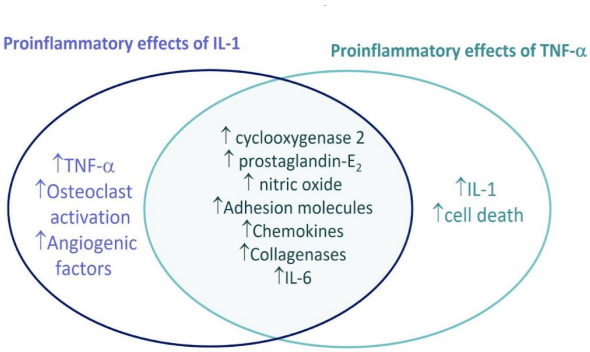
*Having HLA-DR4 increases the susceptibility for the development of RA and is associated with a poor prognosis.

Pathogenesis

Numerous cellular interaction drive the RA process:

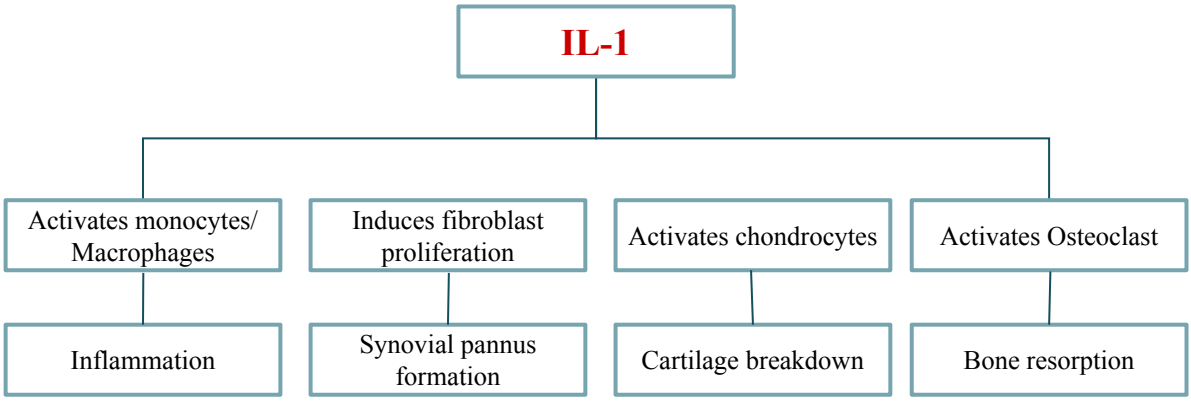


IL-1 and **TNF-a** Have a Number of Overlapping Proinflammatory Effects:



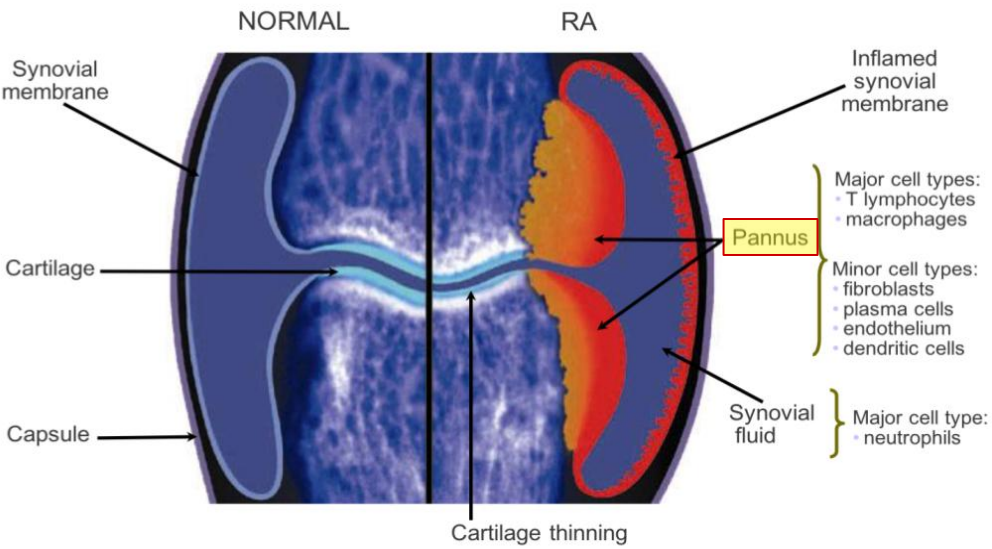
Pathogenesis cont.

IL-1 Plays a Pivotal Role in the Inflammatory and Destructive Processes of RA:



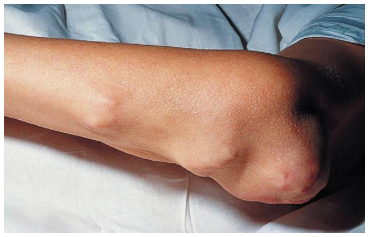
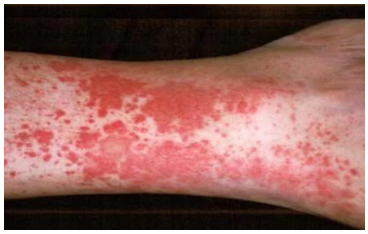
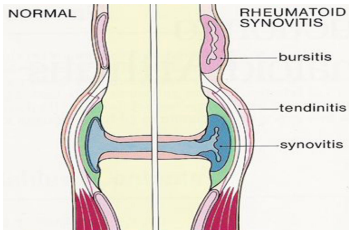
Comparison between healthy joint and Rheumatoid Arthritis:

RA Is Characterized by Synovitis with thickening of the synovial lining → infiltration by inflammatory cells → Synovium proliferates and grows out over the surface of cartilage → tumour-like mass called 'pannus' is produced → Pannus destroys the articular cartilage and subchondral bone → producing bony erosions.
→ joint destruction



A pannus is a hypertrophied synovium that invades bone and cartilage and leads to erosions that can be seen on x-ray.

The Pathology of RA

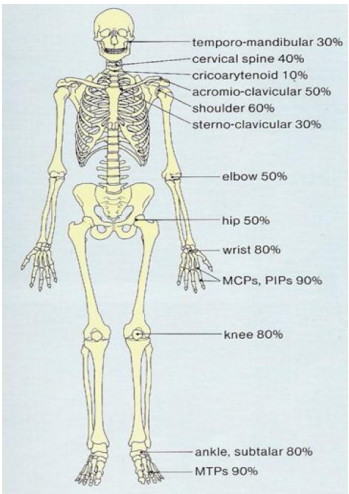
1- Subcutaneous Nodules	2- Vasculitis	3- Synovitis
		
Mostly at pressure areas		There is hypertrophy of the synovium, synovitis includes the capsule and tendons which invades the cartilage.

Signs and Symptoms:

1. **Joint inflammation:** can involve every joint in the body except the DIP
   - Warm swollen and tender joints
   - Symmetrical pattern Classical presentation
2. **Pain**
   a. Insidious onset of pain
   b. Not relieved by rest
   c. Relieved by movement
3. **morning stiffness** >30 mins **of joints**
4. **Symptoms in other parts of the body.**
   a. (Subcutaneous nodules, anemia, fatigue, occasional fever, malaise)

Joint Involvement On Presentation Of RA:

- **Polyarticular 75%** (more than one joint involved)
  - %60:
    - Only small joints of hand & feet involved
  - 30%:
    - Only large joints involvement, and
  - 10%:
    - BOTH small & large joint involvement.
- **Monoarticular 25%:** Sometimes, if they present early it could be monoarticular and then becomes symmetrical polyarticular.
- 50%
  - Knee involvement only.
  - 50%:
    - shoulder, wrist, hip, ankle, or elbow involvement.
- It's very important to rule out septic arthritis (infection) whether acute, as it presents similarly (monoarticular joint pain, with redness and swelling) if you give those patients autoimmune medications such as steroids/immunosuppressive, their condition will get worse..



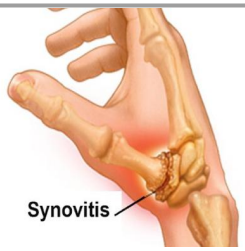
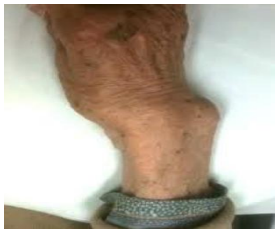
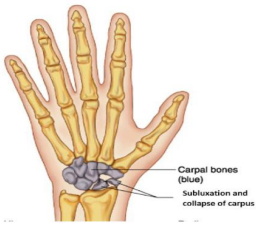
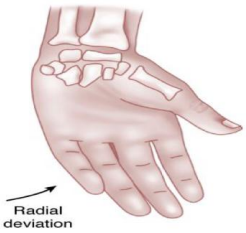
The temporomandibular could go missed, don't forget it.

Articular features seen in the Rheumatoid Hand:

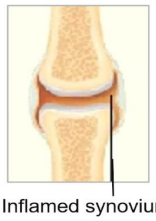
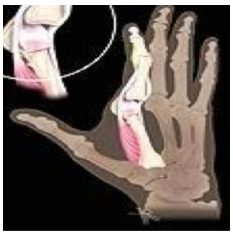
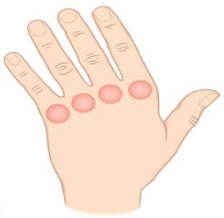
Pictures are extra for understanding

In RA, deformities are due to ligaments destruction and bone erosions

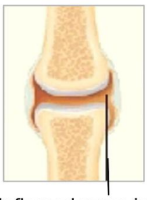
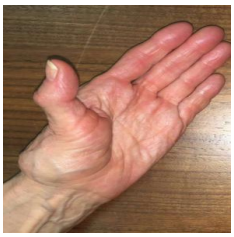
Wrist

Synovitis	Prominent ulnar styloid Because ligaments that hold it in place are destroyed	Subluxation and collapse of carpus	Radial deviation
			

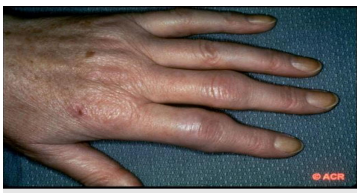
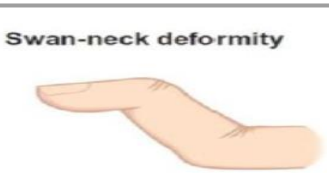
Metacarpophalangeal Joints (MCPs)

Synovitis	Subluxation	Ulnar deviation
		

Thumbs

Synovitis	Z deformity
	

Proximal Interphalangeal Joints (PIPs)

Synovitis	Fixed flexion (boutonniere deformity)	Fixed extension (Swan neck)
		

Swelling confined to joints and it cause "spindling", a spindle shaped finger (not dactylitis which is mainly with seronegative).

Extra-articular manifestations:

General	Fever low grade with active flares, lymphadenopathy, weight loss, fatigue Anemia
Dermatologic	Palmar erythema, nodules nodules are usually subcutaneous, but could deposit anywhere., vasculitis usually small vessels (infarcts).
Ocular	episcleritis/scleritis, scleromalacia perforans, choroid and retinal nodules
Cardiac	pericarditis, myocarditis, coronary vasculitis, nodules on valves. RA is a risk factor for IHD just like DM.
Neuromuscular	entrapment neuropathy eg. carpal tunnel syndrome, peripheral neuropathy, monoarthritis multiplex this condition affects one neuron and it's due to **vasculitis.**
Hematologic	Anemia of chronic disease (normochromic, normocytic). Thrombocytosis due to inflammation. felty's syndrome a triad of RA + Neutropenia + Splenomegaly large granular lymphocyte syndrome, lymphomas
Pulmonary	pleuritis, nodules they could present as cavities and can be mistaken for TB, interstitial lung disease, bronchiolitis obliterans, arteritis, effusions
Others	sjogren's syndrome, amyloidosis if someone with RA presents with proteinuria, its due to amyloidosis deposition NOT glomerulonephritis "GN is with SLE".

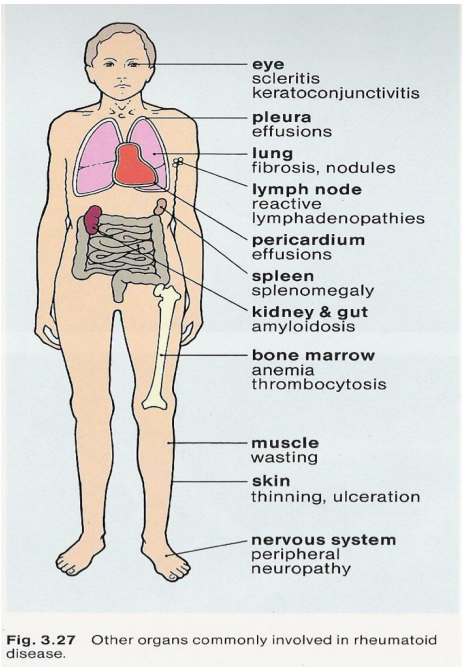
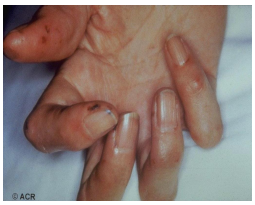
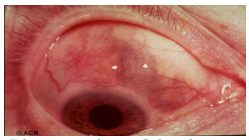


Fig. 3.27 Other organs commonly involved in rheumatoid disease.

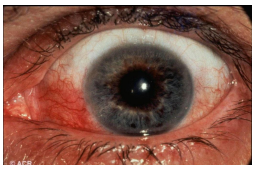
Summary of extra articular manifestations:



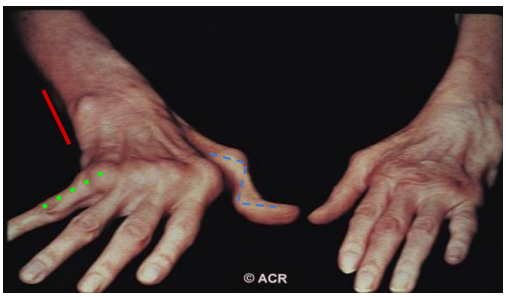
Small vessel vasculitis



Pigmentation of the deep layer due to thinning of the sclera



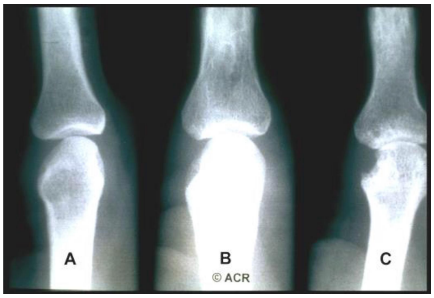
Scleritis is very painful, while in episcleritis comes with minimal eye pain.



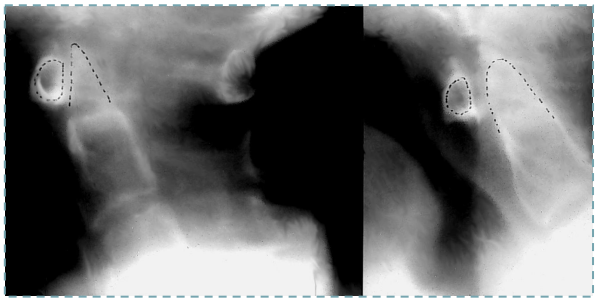
1) Radial deviation at wrist marked by wrist angle loss "straight line"
2) Ulnar deviation at MCP joints. "Dotted line"
3) Z deformity at thumb "Dashed line"
4) Muscle wasting, another important manifestation of RA.

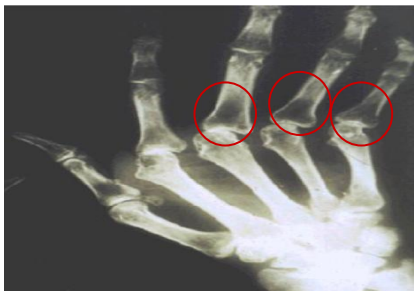
Investigations:

- **Hematology**:
  - CBC Start with CBC, to get baseline for use of meds and also to check for anemia.
    - Normochromic, normocytic anemia, Thrombocytosis
  - ESR + CRP
    - Elevated with activation of the disease
- **Biochemistry**:
  - LFT, Renal profile
- **Serology**:
  - RF
    - Present In 70% of patient and not specific for RA
    - neither confirmatory nor excluding, but a high titer is associated with increased risk of extra-articular manifestations.
  - Anti-CCP/ ACPA
    - High specificity and sensitivity. "Hallmark of RA"
    - Adds more value to the diagnosis than RF
    - **High titers** are associated with **increased risk** of complications + worse prognosis.
- **Radiography**:
  - Joints, Spines, Chest
  - X-Ray OF CERVICAL SPINE Prior to ANY SURGERY or endoscopy to detect possible instability in vertebrae. It's essential because the endotracheal intubation could cause hyperextension of the neck subluxation of the atlantoaxial joint **compressing the cord leading to quadriplegia**. Usually it's **C1-C2 subluxation**, could be **C3-C4** but this is seen more in **juvenile** RA.



Joint destruction due to invasion of the pannus, with periarticular osteoporosis
A: Early
C: Advanced stage



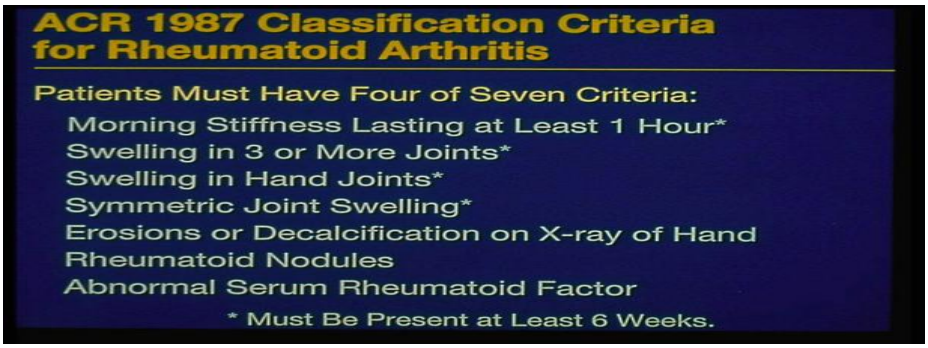


Periarticular osteoporosis, narrowing of joint space, bony erosion = RA

Classification criteria for rheumatoid arthritis:

Diagnosis is mostly clinical

Don't memorize criteria



The 2010 ACR /EULAR

Target population (who should be tested?)
Patients:

1. Who have at least 1 joint with definite clinical synovitis (Swelling)
2. with the synovitis not better explained by another disease.

Don't memorize criteria

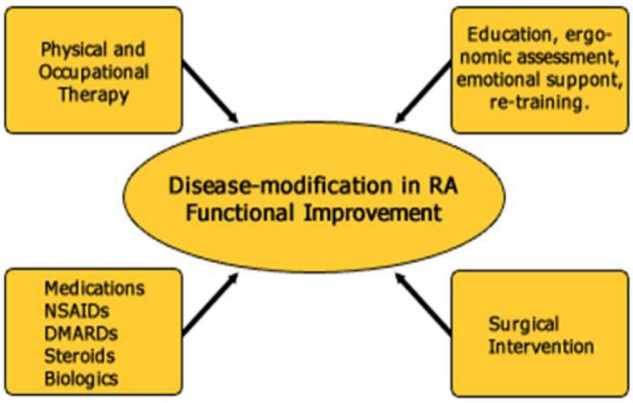
Add **A–D**; a score of 6/10 is needed to classify patient as having definite RA

A. Joint involvement	
1 large joint.	**0**
2-10 large joints	**1**
1-3 small joints (with or without involvement of large joints)	**2**
4-10 small joints (with or without involvement of large joints)	**3**
3-10 joints (at least 1 small joint)	**5**
B. Serology (at least 1 test result is needed for classification)	
Negative RF *and negative ACPA*	***0***
Low-positive RF *or low-positive ACPA*	***2***
High-positive RF *or high-positive ACPA*	***3***
C. Acute-phase reactants (1 test result is needed for classification)	
Normal CRP *and normal ESR*	***0***
Abnormal CRP *or abnormal ESR*	***1***
D. Duration of symptoms	
6 weeks	**0**
>6 weeks	**1**

Treatment

Goals:

- Relieve pain
- Reduce inflammation
- Prevent/slow joint damage
- Improve functioning and quality of life



Approaches:

- Lifestyle modification ex: stop smoking.
- Rest any inflamed joint should be rested, but not prolonged to prevent the occurrence of muscle dystrophy and contractures.
- Physical and occupational therapy
- Medications
- Surgery

Rationale for the Early Treatment of RA:

- Erosions develop **early** in the disease course
- Destruction is **irreversible**.
- Disease **activity** is strongly associated with **joint destruction** later in the disease course.
- Early treatment can slow down radiographic progress
- Disease activity must be suppressed maximally in its **early** stages to prevent destruction and preserve function.

Medications:

The only drugs to **stop the progression** of the disease are DMARDs and biologic modifiers.

Nonsteroidal Anti-Inflammatory Drugs NSAIDs 1st line:

- **Traditional** NSAIDS
  - (**Diclofenac**, Ibuprofen, Ketoprofen, Naproxen)
- **COX-2 Inhibitors**
  - (Celecoxib, Etoricoxib) these are selective, so less side effects on GIT

- To relieve pain and inflammation
- Do not slow the disease progression!!
- Use in combination with DMARD
- **Gastrointestinal side effects** Might develop iron deficiency anemia.

Disease-Modifying Antirheumatic Drugs DMARDs 2nd line:

- Hydroxychloroquine (eye exam) for retinal toxicity
- Sulfasalazine (CBC, LFTs)
- **Methotrexate** (CBC, LFTs) Best initial, gold standard drug in RA
- Leflunomide (CBC, LFTs)
- Azathioprine (CBC, LFTs)
- You monitor CBC count bc all of them could lead to **bone marrow suppression**

- Control symptoms
- No immediate analgesic effects
- Can delay progression of the disease (prevent/slow joint and cartilage damage and destruction)
- Effects generally not seen until a few weeks to months usually takes 4 weeks, and may reach up to 8 weeks. Here use steroids as a bridge until DMARDs work then taper the steroids down until you take it off.

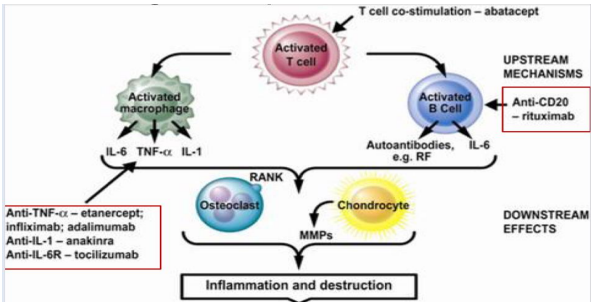
Methotrexate:
- Most commonly used DMARD
- **Teratogenic**, so women should take oral contraceptives while using it and stop methotrexate at least 3 months before pregnancy.

Sulfasalazine:
- For mild to moderate disease
- Can be used in pregnancy

Hydroxychloroquine is a mild anti-rheumatic that could be used for females in reproductive age (pregnancy), but an eye exam should be done every 6-8 months to exclude retinal side effects.

Biologic Response Modifiers: used when DMARDs fail.

- **TNF inhibitors:**
  - etanercept, infliximab, adalimumab
- **IL6 receptor inhibitors:**
  - tocilizumab
- **T cell costimulation modulator:**
  - Abatacept
- **Anti- CD20:**
  - rituximab



Corticosteroid: not used for maintenance (long time), only used as a bridge to wait for DMARDs to work

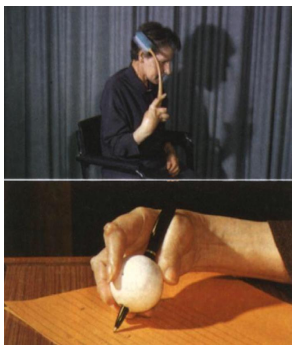
- (low dose) use these if NSAIDs do not provide adequate **pain relief.**
- Short-term treatment may be appropriate but avoid long-term use.

Physiotherapy: to prevent contractures and muscle atrophy.

- Effective in maintaining the range of motion
- Strengthening of muscles
- Prevent contractures
- Prevent deformities
- Maintain activities of daily living

Occupational Therapy:

- Education of patients in the use of daily living activities
- Prevention of joint contractures and deformities



Summary:

Rheumatoid Arthritis

RA is Systemic chronic inflammatory disease Mainly affects synovial joints, It is a systemic disease that has many extra-articular manifestations.

Etiology	Unknown could be : 1. Genetic 2. infectious 3. environmental 4.Autoimmune	
Clinical presentation	Joint inflammation: ● symmetrical. ● polyarticular. ● warm swollen joints. ● morning stiffness. Constitutional symptoms: ● Low-grade fever. ● weight loss. ● Fatigue.	Articular feature: Wrist : synovitis, radial deviation , subluxation and collapse of carpus prominent ulnar styloid. MCP: synovitis , ulnar deviation, subluxation. Thumbs: synovitis, Z deformity. PIP: synovitis, swan neck, boutonniere deformity.
	Extra-articular manifestations: ● palmar erythema. ● nodules. ● vasculitis. ● dry eyes (Sjögren's syndrome) ● pericarditis + IHD ● peripheral neuropathy ● Felty's syndrome.its a triad ;RA +neutropenia +splenomegaly ● Pleural effusions ● Amyloidosis	
Investigation	1. hematology: CBC, ESR 2. Biochemistry: LFT, Renal profile 3. Serology: RF, Anti-CCP 4. Radiology: joints, spines, chest	
Treatment	Treatment approaches: (lifestyle modifications, rest, physical and occupational therapy, medication, surgery) Medication: 1. DMARDs: eg. methotrexate (Best initial, gold standard' drug in RA) 2. NSAIDS: To relieve pain and inflammation, Use in combination with a DMARD. 3. Corticosteroids: only in active phase, avoid long-term use. 4. Biologic Response Modifiers: a. TNF Inhib: etanercept, infliximab, Adalimumab b. IL6 receptor inhib: tocilizumab c. T Cell costimulation modulator: abatacept d. Anti-CD20 (B cell): rituximab "very effective" e. IL1 inhibitor: anakinra	

Questions:

1- what would be the drug of choice to quickly control RA symptoms?
A. Corticosteroids
B. Sulfasalazine
C. Methotrexate
D. NSAIDs

2- What is the gene that is highly linked to pathogenesis of rheumatoid arthritis?
A. HLA-DR4
B. HLA-b27
C. HLA-DR3
D. HLA-DR5

3- A 50 years old lady presented to your clinic and you are suspecting rheumatoid arthritis, upon hand inspection: all of the following can be present in metacarpophalangeal joints EXCEPT:
A. Ulnar deviation
B. z deformity
C. Subluxation
D. Synovitis

4- A 67 years old man has a long history of symmetrical small joint arthritis with deformities. He now develops shortness of breath on exertion with a dry cough, but no sputum or chest discomfort. His heart sounds have a loud P2, and the lungs have fine bibasilar crackles. Which one of the following is the most likely diagnosis:
A. pericarditis
B. caviating lung lesions.
C. Pneumonia
D. Interstitial fibrosis

5- A 20 years old presented to the rheumatology clinic complaining of joints pain has been diagnosed with rheumatoid arthritis, what would you Initially prescribe to slow the progression of the disease?
A. NSAIDs
B. Methotrexate
C. Corticosteroids
D. sulfasalazine

Answer key:
1(D) 2(A) 3(B) 4(D) 5(B)