Rheumatoid Arthritis

Professor Omer Karadag, MD
Internal Medicine, Rheumatology

Hacettepe

Rheumatoid arthritis

- Rheumatoid arthritis (RA) is a chronic inflammatory arthritis
- RA primarily affects the small joints of the hands and feet
- If not treated early and aggressively, can be a major cause of
  - Work loss
    - Work disability: 30% in 3 years
    - Disability: 75% in 20 years
  - Decreased quality of life
  - Need for joint replacement surgery
  - early death

Prevalance & Incidence

- Rheumatoid arthritis is the most common inflammatory arthritis
- Prevalence
  - Worldwide 0.2-0.8%
  - Turkey 0.36%
- Onset usually 30-50 years
  - Prevalence rises with age
  - Female : Male = 3 : 1

Risk factors

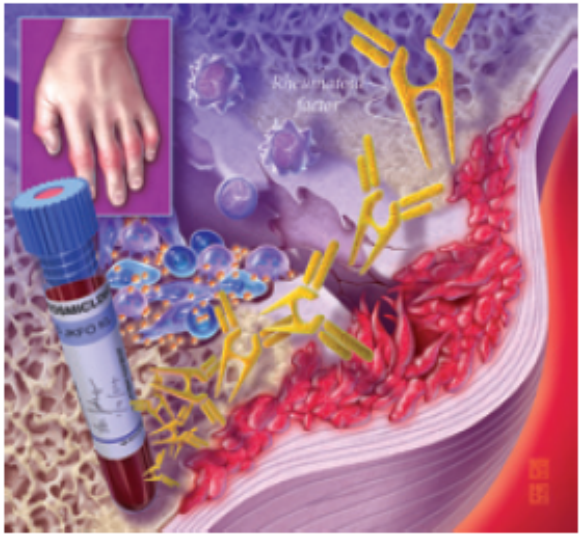
- Female sex
- A positive family history of RA (strong risk factor)
- Older age
- Silicate exposure
- Smoking

What's the role of a general practioner in RA management?

a) Make diagnosis

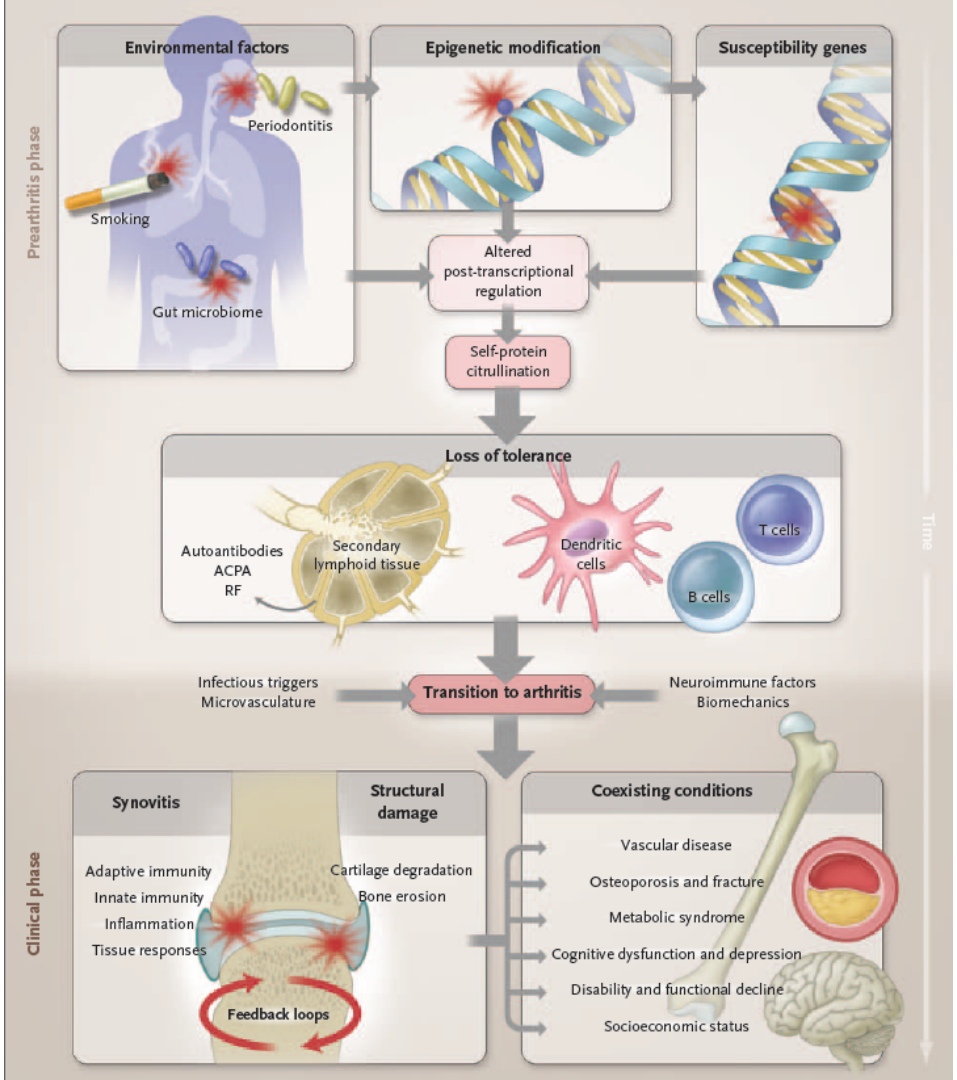
b) Make diagnosis and start treatment

c) Make diagnosis, start treatment on follow up patient



Role of Environment

Hypothetic Etiopathogenic and clinical course of Rheumatoid arthritis



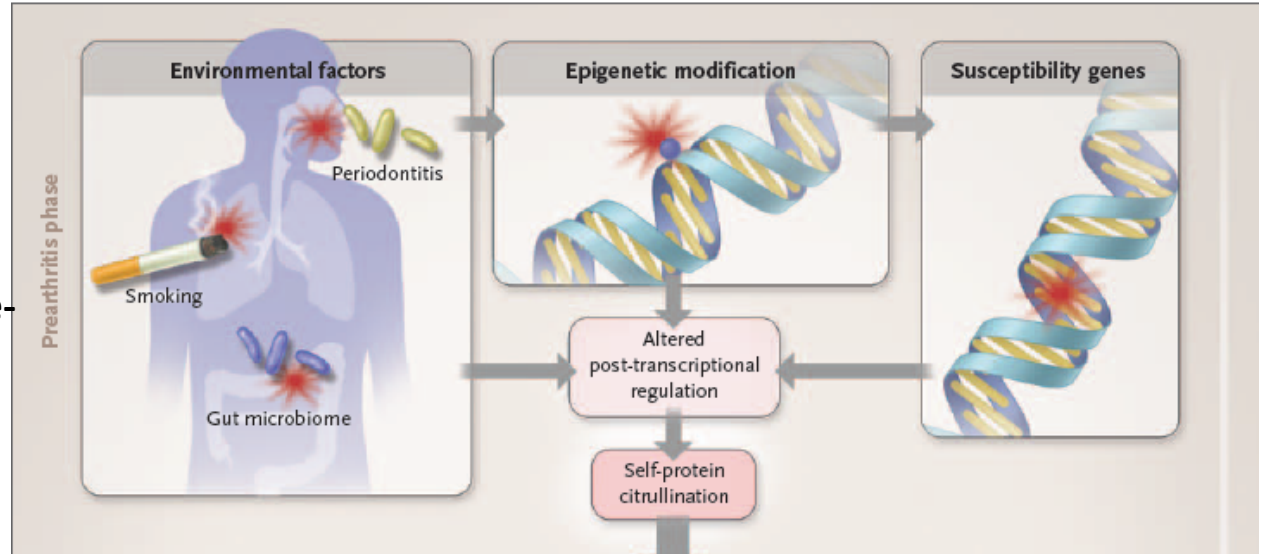
Genetics Shared epitope

Autoantibodies

Clinical Progression & Disease spectrum

Environment-gene interactions

- **Genes are not the sole influence-**
- **concordance rate for identical twins 12-15%**

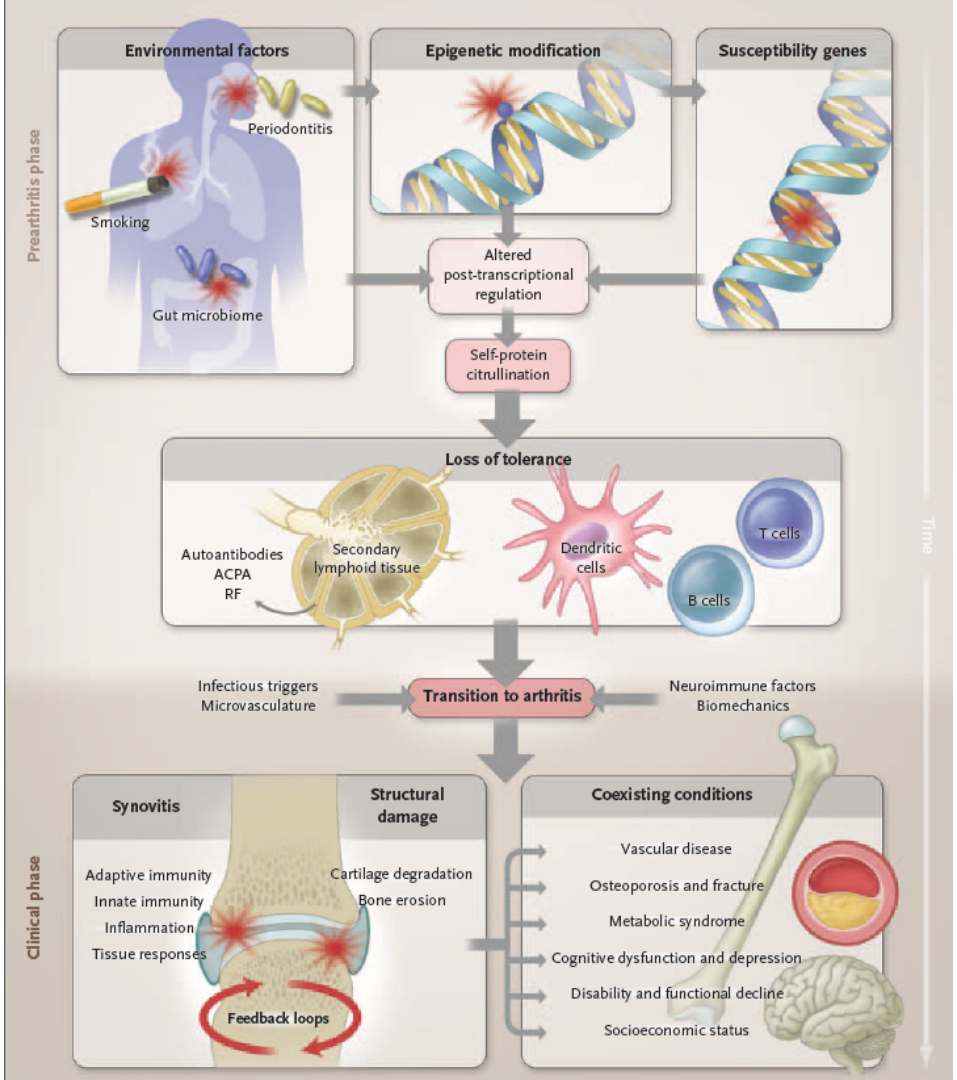


Major histocompatibility complex class II allele human leukocyte antigen (HLA), DRw4, is more common in patients with RA. (MHC-Class II)

These HLA alleles code for a shared amino acid sequence that has been named the shared epitope, which may be involved in the pathogenesis of RA

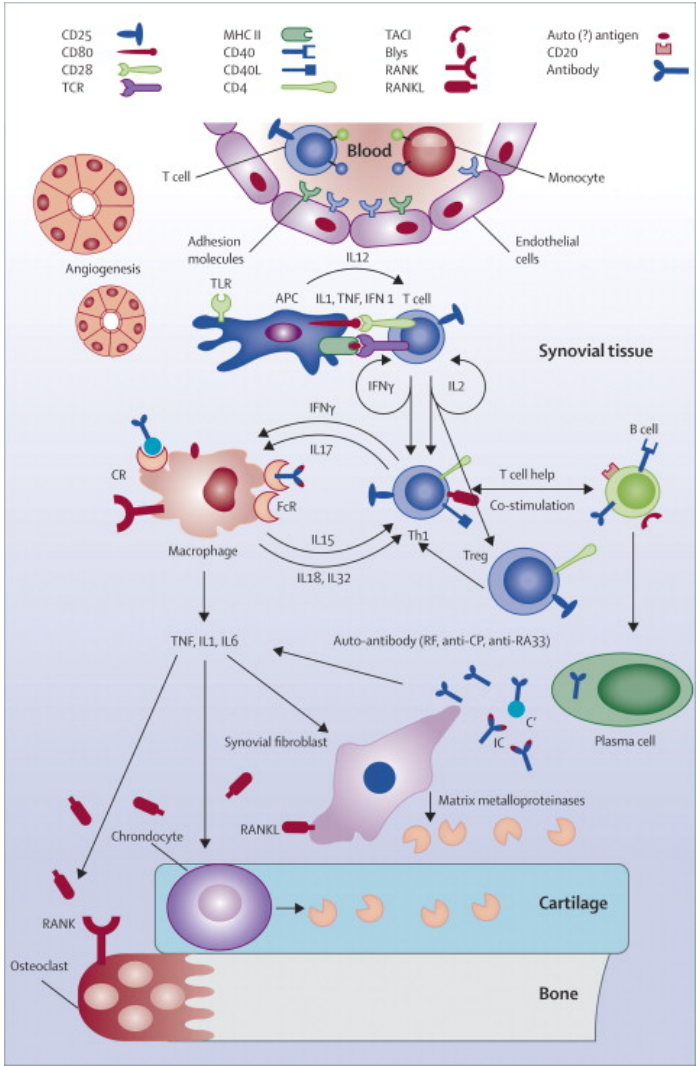
Environment–gene interactions promote loss of tolerance to self-proteins that contain a citrulline residue, which is generated by post-translational modification.

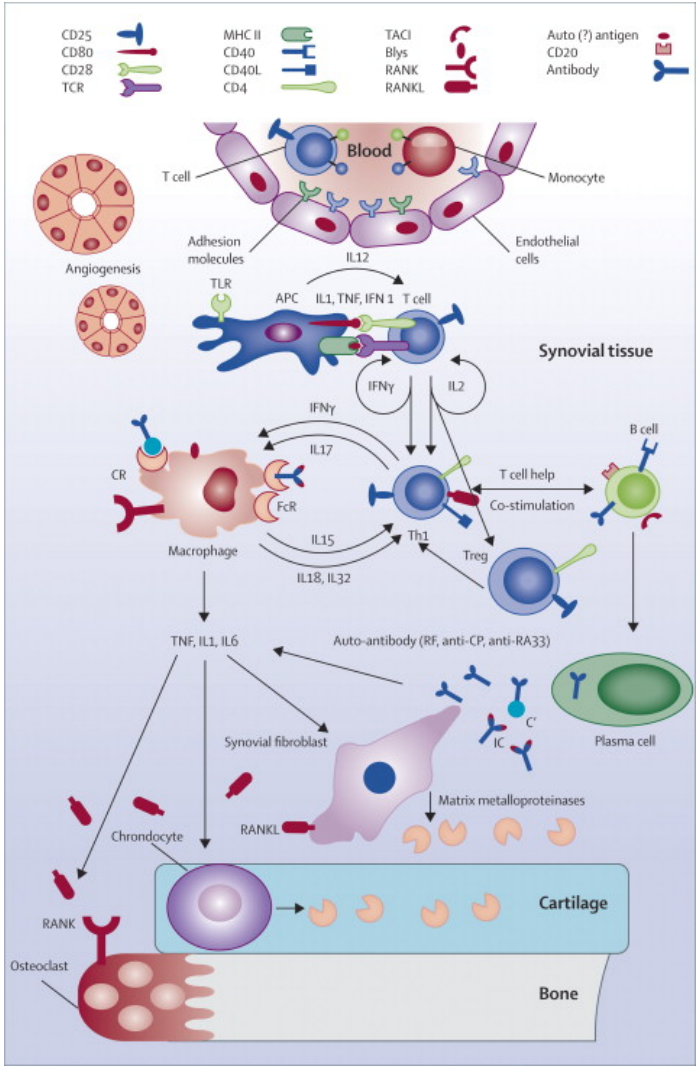
This anticitrulline response can be detected in T-cell and B-cell compartments and is probably initiated in secondary lymphoid tissues or bone marrow.



patients commonly have serologic markers (rheumatoid factor, anticyclic citrullinated peptide [anti-CCP] antibodies) years before they develop the disease

Schematic representation of RA pathogenesis





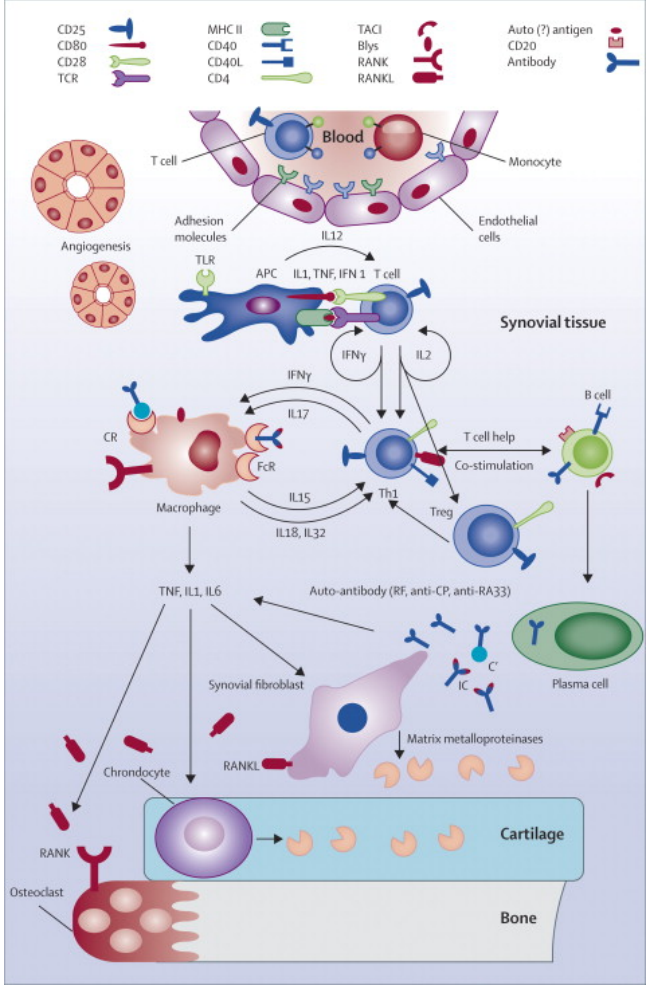
Inflamed synovium is central to the pathogenesis.

The synovium shows

- increased angiogenesis
- Cellular hyperplasia
- influx of inflammatory cells
- changes in the expression of cell surface adhesion molecules, and many cytokines.

Angiogenesis leads to new blood vessels proliferating to provide for the hypertrophic synovium.

Tumor necrosis factor (TNF), interleukin 1, and interleukin 6: seem to be the most abundant in the joint.



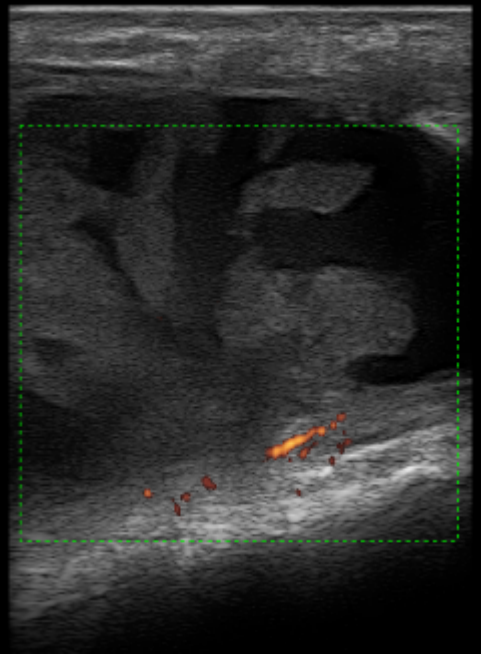
Both TNF and interleukins

- promote proliferation
- metalloproteinase expression
- adhesion molecule expression
- further secretion of other cytokines

High levels of matrix metalloproteinase activity are thought to contribute to joint destruction.

This very inflammatory setting, when not treated, leads to the eventual destruction of the involved joint.

Ultrasonography of knee arthritis



Normal US image

The synovial lining becomes hyperplastic
This formation of locally invasive synovial tissue is characteristic (PANNUS in pathologic specimen)
it is involved in causing the erosions seen in RA.

Differential diagnosis of a patient with arthritis looks like solving a puzzle

You need to put more pieces together to get correct diagnosis

Index case

- A 42-year-old woman presents with a 2-month history of bilateral hand and wrist pain, and swelling in her fingers.
- She has also recently noted similar pain at her feet.
- She finds it hard to get going in the morning and feels stiff for hours after waking up.
- She also complains of increasing fatigue and is unable to turn on and off faucets or use a keyboard at work without a significant amount of pain in her hands.
- She denies any infections before or since her symptoms started.

Swelling of 3rd , 4th Proximal interphalangeal joint
Difficulties in making a fist

A middle-aged female with arthritis at small joints

What do to next?

Essential step is questioning of patients regarding other rheumatic findings

We need to put pieces together to get correct diagnosis

Questioning for rheumatic signs

- Fever
- Fatigue/ Malasia
- Weight loss
- Night sweats
- Raynaud's phenomenon
- Back pain
- Morning stiffness
- Neurologic findings
- Abortus

- Abdominal pain
- Diarrhea
- Oral ulcer
- Genital ulcer
- Skin and nail changes
- Photosensitivity/malar rash

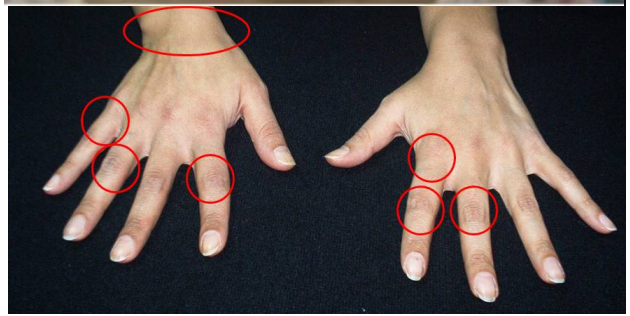
- Dry mouth
- Dysphagia
- Eye findings (Dry eyes-uveitis)

If the patient has

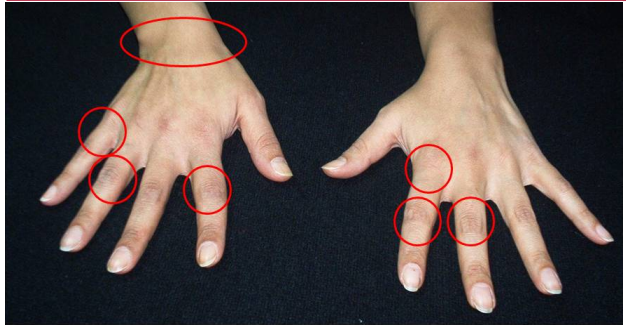
- **malar rash**

- **+** arthritis at small joints →

- **Systemic Lupus Eryhthematosus**

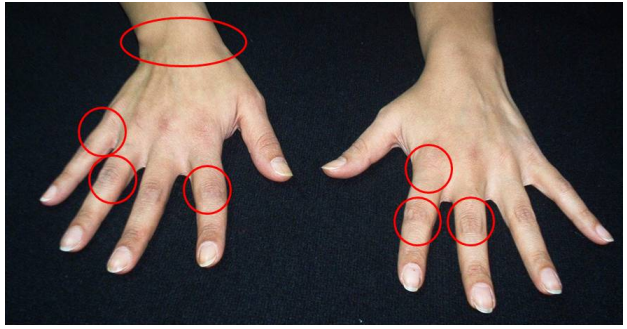


- **Tophus at auricula of ear**
- **+** arthritis at small joints →
- **Gout**



- **Skin and nail changes**
- **+** arthritis at small joints →

- **Psoriatic arthritis**



Differential Diagnosis of Rheumatoid Arthritis

Connective tissue diseases (Lupus, Sjogren)	Non erosive arthritis
Polyarticular gout	Joints often erythematous; podagra commonly found; gout and rheumatoid arthritis rarely coexist
Seronegative spondyloarthropathies	Tend to be more asymmetric than rheumatoid arthritis. More commonly lower limd oligoarthritis and the spine. Evaluate for history of psoriasis, Reiter's comorbidities, inflammatory bowel disease.
Still's disease	Tends to present with fever, leukocytosis with left shift, sore throat, splenomegaly, liver dysfunction, and/or rash.
Hemochromatosis	Iron studies and skin coloration changes may guide diagnosis
Infectious endocarditis	Rule out murmurs, high fever, and history of intravenous drug use
Reactive arthritis	can be postinfective, sexually acquired, or related to gastrointestinal disorders.
Viral arthritis	Consider parvovirus, hepatitis B.
Polymyalgia rheumatica	Rheumatoid arthritis, unlike polymyalgia rheumatica, rarely presents with pain in the proximal
Sarcoidosis	Granulomas likely, as are hypercalcemia and chest film findings

Romatoid arthritis; Disease onset

- Slow and insidious (65-70%) (months)
- Subacute (15-20%) (weeks)
- Acute (8-15%) (days)
- Rarely
  - Palindromic
  - Mono, oligoarticular
  - Polymyalgia, polyarthralgia (esp. elderly)
  - Tenosynovitis, subcutaneous nodule

Joint involvement pattern

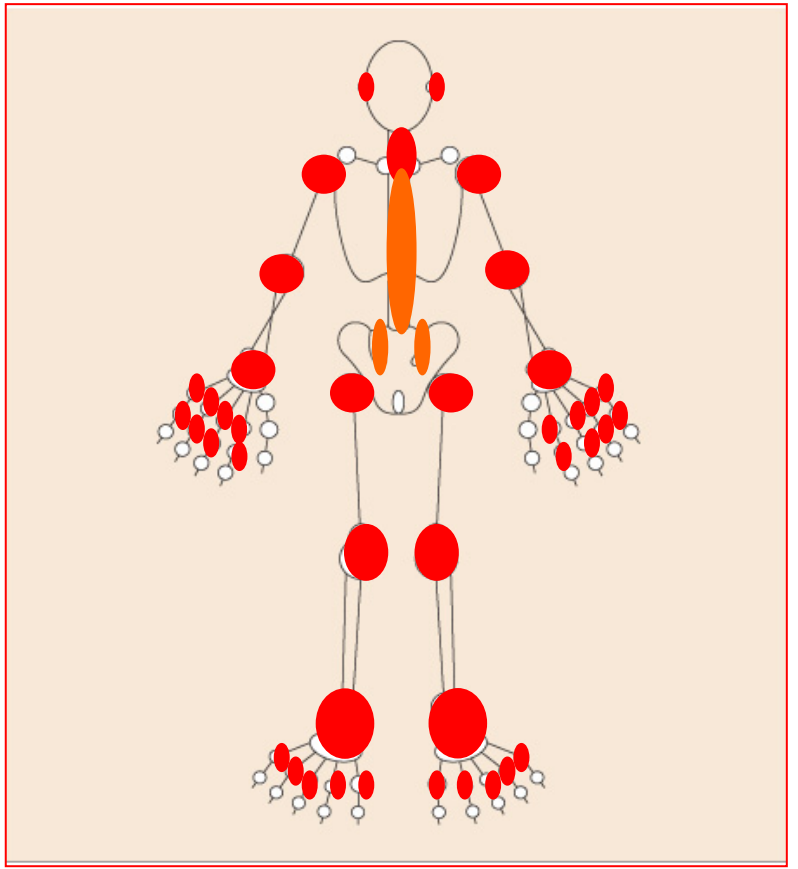
- ❑ **Hand**

(MCP, PIF, Wrist)

- ❑ **Foot**

(Ankle, MTP, subtalar, talonavicular, tibiotalar)

- ❑ **Knee**
- ❑ **Wrist**
- ❑ **Hip**
- ❑ **Shoulder**
- ❑ **Atlantoaxial**
- ❑ **Temporomandibular**
- ❑ **Cricoarythrenoid**



- The distal interphalangeal (DIF) joints and sacroiliac joints tend not to be affected
- Morning stiffness lasting at least 60 minutes after initiating movement is common.

Clinical presentation

Patients usually present with a history of bilateral, symmetric pain
swelling of the small joints of the hands and feet that has lasted for more than 6 weeks.
Morning stiffness lasting over 1 hour is commonly reported but can also be seen in other inflammatory conditions.

RA - Deformities

Z deformity
Buttonnoire
Swan neck
Mallet finger

Swan neck deformity: seen in advanced RA with damage to the ligaments and joints; proximal interphalangeal (PIP) hyperextension with distal interphalangeal (DIP) hyper flexion

Boutonniere deformity: PIP flexion with DIP hyperextension.

These deformities are no longer common, as most patients are treated with DMARDs at an early stage.

Extra-articular findings in Rheumatoid arthritis

- Nodules
- Pulmonary
  - Pulmonary nodules
  - Pleural effusion
  - Fibrosing alveolitis
- Ocular
  - Keratoconjunctivitis sicca
  - Episcleritis
  - Scleritis
- Vasculitis
  - Nail fold
  - Systemic
- Amyloidosis
- Cardiac
  - Pericarditis
  - Pericardial effusion
- Neurological
  - Nerve entrapment
  - Cervical myelopathy
  - Peripheral neuropathy
- Cutaneous
  - Vasculitic rashes
  - Leg ulcers

Extra-articular involvement

- Lung

- Romatoid nodules
- Vasculitis
- Eye

Romatoid Nodules

Once a clinical diagnosis is made, several laboratory tests help to determine prognosis.

- Rheumatoid factor (RF) positivity: 60-70%
  - not required for diagnosis but is helpful if present
  - It should be tested at presentation and does not need to be repeated if positive
  - The higher the values, the worse the prognosis and the greater the need for aggressive treatment
- Anticyclic citrullinated peptide antibody (anti-CCP), a prognostic marker: positive in 70% of patients with RA.
  - can be positive when RF is negative, and it seems to play more of a pathogenic role in the development of RA
  - Anti-CCP does not need to be serially measured
- Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels are also usually obtained because they reflect the level of inflammation (up to 40% of patients with RA may have normal levels)

IgM RF is produced in many chronic inflammatory conditions

- Long-standing infections
  - Bacterial endocarditis
  - Hepatitis B and C
  - Tuberculosis
- Chronic bronchitis
- Silicosis
- Primary biliary cirrhosis
- Chronic autoimmune hepatitis

RF is not specific for a particular rheumatic disease such as RA

Imaging

- Baseline radiographs of the hands and feet are obtained to help with diagnosis and in determining disease severity.
- **Most of erosions occur in first 2 years of RA, late findings**
- Patients with erosions at baseline who fulfill one of the classification criteria for RA are at risk for severe disease.

Typical changes in posteroanterior hand and wrist radiographs; must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.

Periarticular osteoporosis

Marginal erosion

Radiological changes, RA

Periarticular osteoporosis (early)

Joint cavity narrowing (moderate)

Erosion (early)

Late changes

How to confirm diagnosis of Rheumatoid arthritis?

Classification Criteria for RA, American College of Rheumatology,1987

- Morning stiffness > 1 hour
- Arthritis of ≥ 3 joint areas
- Arthritis of hand joints (MCPs, PIPs, wrists)
- Symmetric swelling (arthritis)
- Serum rheumatoid factor
- Rheumatoid nodules
- Radiographic changes

- Four or more of the criteria must be present
- First four criteria must be present for ≥6 weeks

Do we need new criteria for RA?

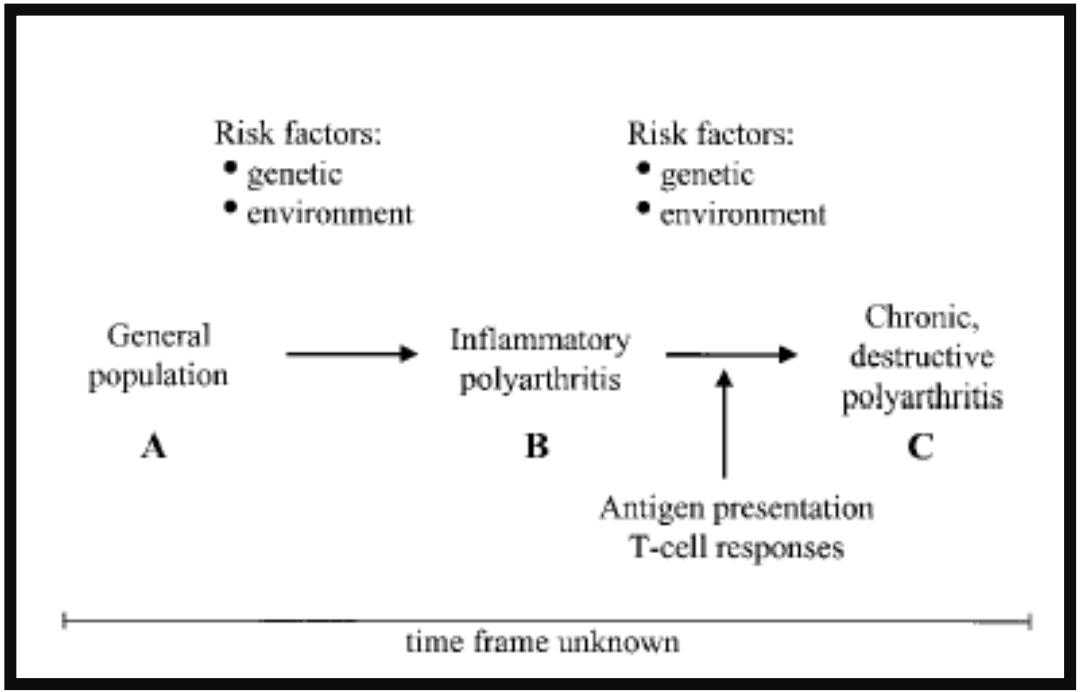
ACR 1987 criteria

1. Morning stiffness (at least 1h)
2. Arthritis of three or more joint areas
3. Arthritis of hand joints (≥1 swollen joints)
4. Symmetrical arthritis
5. Rheumatoid nodules
6. Serum rheumatoid factor
7. Radiographic changes (erosions)

Late findings

- **Yes!**
- **We need new criteria set**

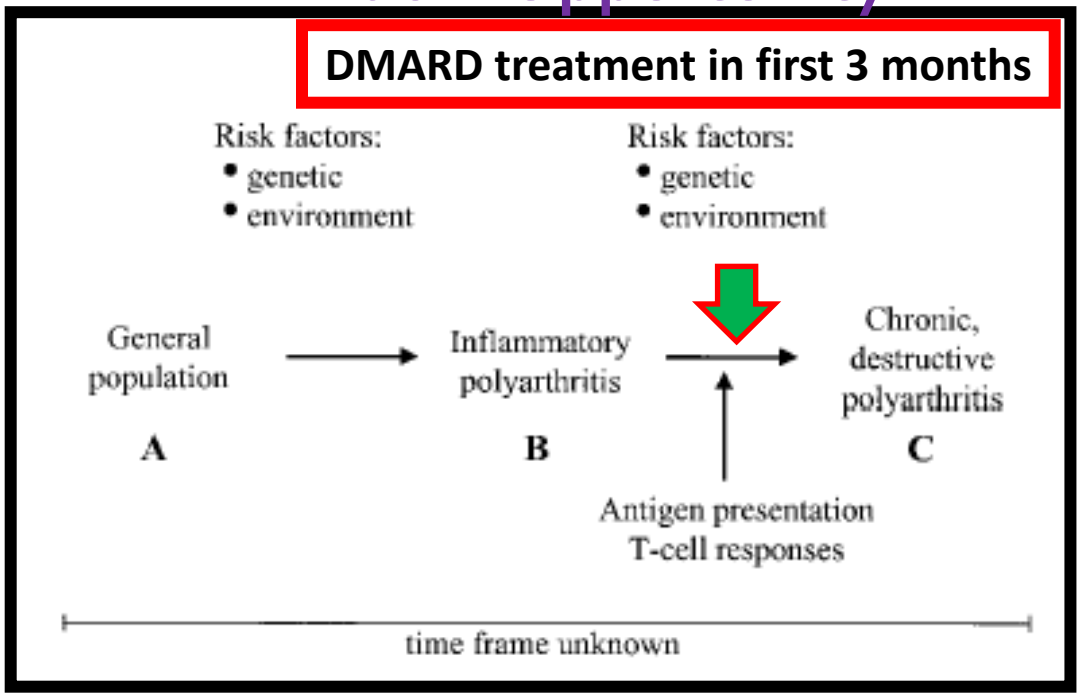
Romatoid Arthritis



Huizinga TMJ. ve ark Arthritis Rheum 2002

Romatoid Arthritis
Window Oppurtunity

To prevent deformities and complications Our aim is to diagnose and start treatment early



Huizinga TMJ. ve ark Arthritis Rheum 2002

Advances in RA diagnosis; 2000's

Introduction of higher quality imaging

+

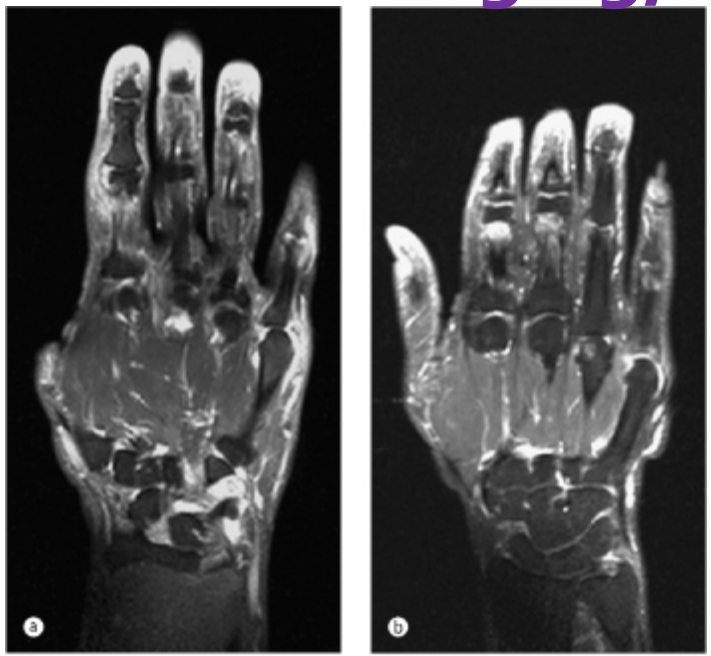
better understanding of disease pathogenesis and

additional autoantibody

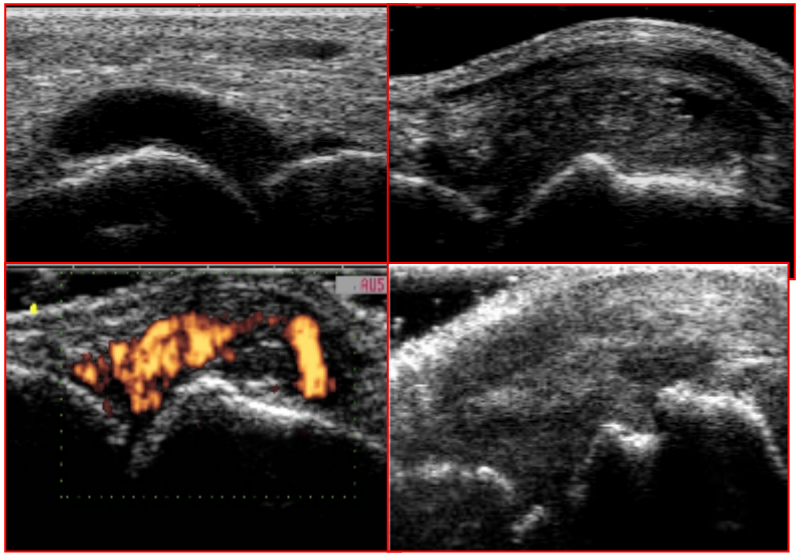
- Early inflammatory arthritis
- Early rheumatoid arthritis
  - <3months

Anti CCP antibody
MR
USG

Imaging, Romatoid Arthritis



MRI: Radiologist opinion dependent



Musculoskeletal US

Clinicians can perform Ultrasound and it is a reproducible method to detect synovitis in the wrist and fingers, and may be considered in the diagnosis of RA

Clues of early inflammatory arthritis

- Greater than or equal to 3 swollen joints
- Positive compression (Gaenslen's squeeze) test on MCPs –hands or MTPs-feet
- Morning stiffness of more than 30 minutes
- Autoantibody (RF, CCP) positivity

ACR/EULAR 2010 criteria

1. Joint involvement (0–5)
   - One medium-to-large joint (0)
   - Two to ten medium-to-large joints (1)
   - One to three small joints (large joints not counted) (2)
   - Four to ten small joints (large joints not counted) (3)
   - More than ten joints (at least one small joint) (5)
2. Serology (0–3)
   - Negative RF *and* negative ACPA (0)
   - Low positive RF *or* low positive ACPA (2)
   - High positive RF *or* high positive ACPA (3)
3. Acute-phase reactants (0–1)
   - Normal CRP *and* normal ESR (0)
   - Abnormal CRP *or* abnormal ESR (1)
4. Duration of symptoms (0–1)
   - Less than 6 weeks (0)
   - 6 weeks or more (1)

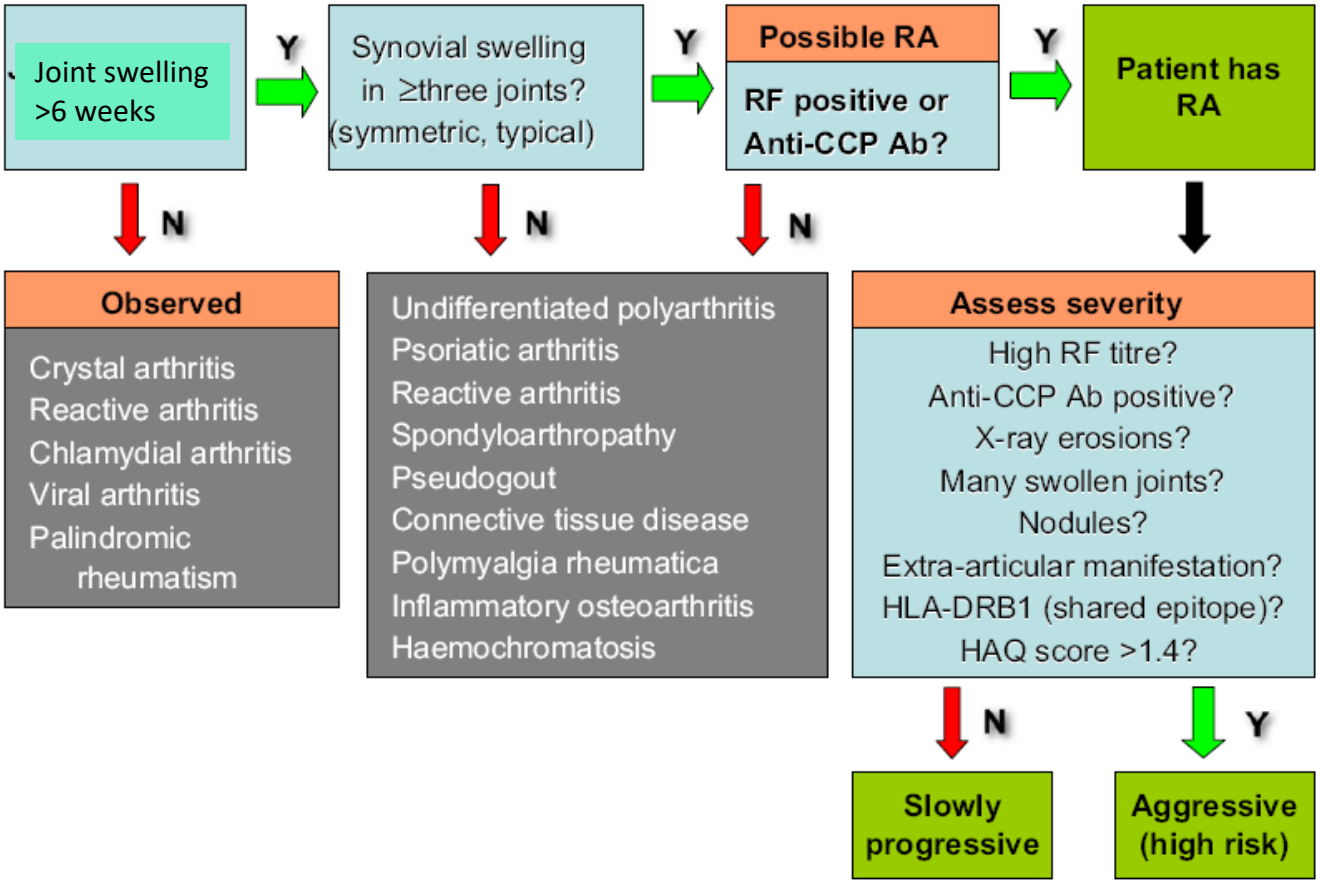
Diagnostic criteria for RA

Diagnosis is obtained with total score of ≥6

Assessment of disease activity

- *Core assessments*
  - Joint counts (tender and swollen joint counts)
  - Global assessment (doctor and patient) and pain score
  - Laboratory (erythrocyte sedimentation rate and C-reactive protein)
- *Additional assessment*
  - Radiological damage
- *Combined status indices*
  - Disease activity score (DAS)
  - ACR20, ACR50, and ACR70 responders
  - Functional status measured by a health assessment questionnaire (HAQ)

Early RA


Joint swelling >6 weeks
Y
Synovial swelling in ≥three joints? (symmetric, typical)
Y
Possible RA
RF positive or Anti-CCP Ab?
Y
Patient has RA
N
N
N
Observed
Crystal arthritis
Reactive arthritis
Chlamydial arthritis
Viral arthritis
Palindromic rheumatism
Undifferentiated polyarthritis
Psoriatic arthritis
Reactive arthritis
Spondyloarthropathy
Pseudogout
Connective tissue disease
Polymyalgia rheumatica
Inflammatory osteoarthritis
Haemochromatosis
Assess severity
High RF titre?
Anti-CCP Ab positive?
X-ray erosions?
Many swollen joints?
Nodules?
Extra-articular manifestation?
HLA-DRB1 (shared epitope)?
HAQ score >1.4?
N
Y
Slowly progressive
Aggressive (high risk)

Treatment

- Joint destruction in rheumatoid arthritis begins within a few weeks of symptom onset; early treatment decreases the rate of disease progression

Therapeutic goals include
- preservation of function and quality of life
- minimization of pain and inflammation
- joint protection
- control of systemic complications

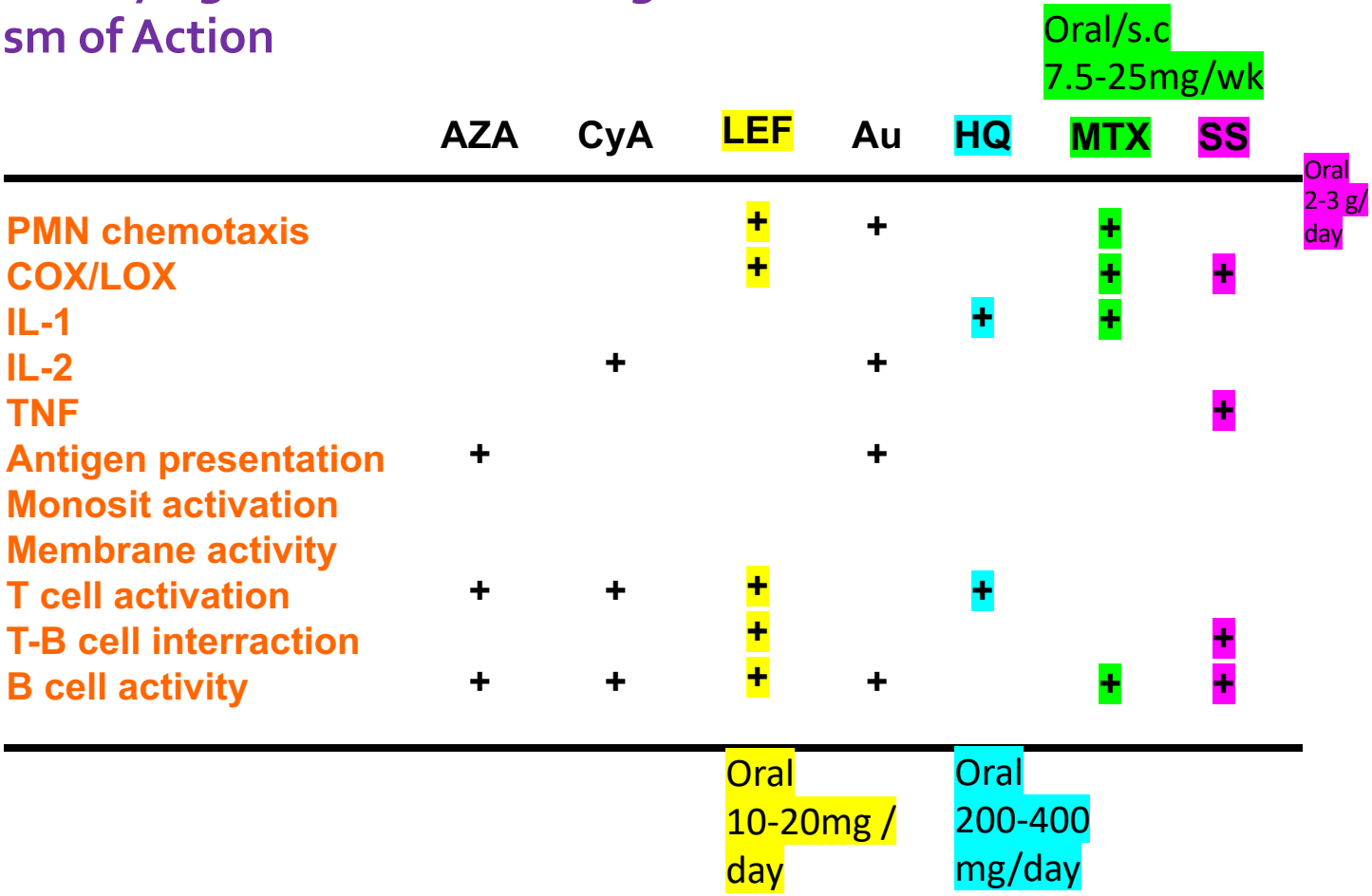
Informing the patient and partner of the patient
- Regarding disease
- treatment plan
- possible adverse effects of agents
- Contraception for some agents

Disease-modifying antirheumatic drugs(DMARDs)

- Metotrexate
- Sulphasalazine
- Hidroxychloroquine
- Leflunomide

- A heterogeneous collection of agents grouped together by use and convention
- They are the mainstay of treatment
- Their diverse mechanisms of action are incompletely understood.
- Their effect on disease findings occurs slowly. We should inform the patient for this action.
- They reduce joint swelling and pain, decrease acute-phase markers, limit progressive joint damage, and improve function.

Disease-modifying antirheumatic drugs(DMARDs)
Mechanism of Action



DMARDs

- DMARDs are sometimes combined, and several combinations of DMARDs have proven effi cacy
- An example is methotrexate, sulfasalazine, and hyroxychloroquine—termed triple therapy.

- Minor (eg, nausea) and serious (eg, hepatotoxicity, blood dyscrasias, and interstitial lung disease)
- Monitoring of adverse effects requires
  - pretreatment screening and
  - subsequent safety recording of blood counts and liver function tests

Treatment of symptoms
Bridging therapy

- Glucocorticoids can be especially useful
  - Short-term use during flare-ups in disease can lead to rapid improvement and allow other treatments

- Analgesics
- Non-steroidal antiinflammatory drugs (NSAIDs) lessen pain and stiffness

- proton-pump inhibitors for gastroprotection
- administered for short periods to minimise risks

Corticosteroids

- Treatment usually involves low-dose daily oral prednisone; doses >10 mg/day are rarely required.
- High-dose corticosteroids may be required for the treatment of severe extraarticular involvement, such as vasculitis or eye involvement
- Occasionally, intra-articular corticosteroid injections are used to control individually inflamed joints in acute flares of disease activity.

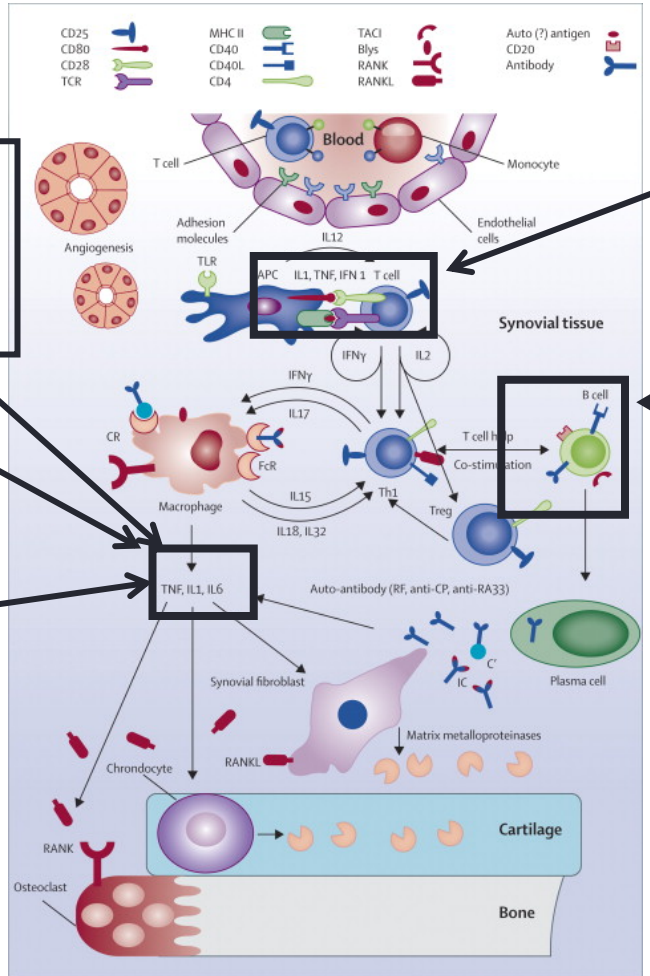
Follow up

- Laboratory monitoring for CBC and LFT abnormalities is done every 4 to 8 weeks at the start of treatment.
- When the patient is on a stable dose, they should be checked every 3 to 4 months
- Disease activity and response to therapy is monitored by any of the composite scores available. disease activity score (DAS) and its derivatives, health assessment questionnaire (HAQ)

Failure to reach low disease activity/remission after 3-6 months of therapy→

Modification of therapy

Biologic agents



Anti TNF:
Infliximab, Etanercept, Adalimumab, Golimumab*, Certolizumab*

Anti IL 1:
Anakinra

Anti IL 6:
Tocilizumab*

T cell modulator:
Abatacept

Anti CD20:
Rituximab

Targeted synthetic DMARD
Tofacitinib

Biologic agents

- Pretreatment questioning and screening
  - latent tuberculosis
  - Demyelinated diseases (multiple sclerosis)
  - Malignancy
  - Herpes zoster
  - Diverculitis

- Highly effective
- Combined conventionally with methotrexate or leflunomide
- Expensive

Be careful and keep in mind
- Increase in frequency of infections
- Allergic reactions
  - Injection/Infusion reactions
  - Systemic
- Antibody – autoimmune disease

Reactivation of latent tuberculosis can be observed after initiation of biologic agents or targeted synthetic DMARDS

- Patients candidate for biologic agents/targeted synthetic DMARDS should be screened for

Latent tuberculosis with purified protein derivative (PPD) or Quantiferon-TB test for patients

Positive patients use prophylactic INH for 9 months

Comorbidities in RA

- *Cardiovascular*
  - Myocardial infarction
  - Stroke
  - Peripheral vascular disease
  - Hypertension
- *Cancer*
  - Lymphoma and lymphoproliferative diseases
- *Infection*
  - General
  - Bacterial
- Depression
- Gastrointestinal disease
- Osteoporosis
- Renal disease

Management of comorbidities

- Annual reviews to detect and treat comorbidities is recommended
- Systemic complications such as Sjogren's syndrome, lung disease, and vasculitis, need specific treatments, which range from eye drops to cytotoxic drugs.
- Surgical treatment, particularly joint replacement surgery, is vital to maintain function when joints fail, and collaboration with orthopedic specialists is required.

Prognosis of RA

- Patients treated aggressively and early → have a good prognosis
- A delay in treatment initiation or the disease remains untreated→ many patients are disabled within 10 years
- Untreated RA associated with increased premature mortality, most commonly from coronary artery disease.
- Flares of disease are common, even in patients well controlled with disease-modifying antirheumatic drugs (DMARDs). Temporary measures, such as oral corticosteroids, are usually adequate.

Take home messages

- RA; chronic, erosive arthritis→ early diagnosis and aggressive treatment
- Diagnosed clinically ; laboratory and radiographic testing provide prognostic information
- Disease-modifying antirheumatic drugs are the mainstay of management.
  - Methotrexate is commonly used first line; various other agents, including biologic agents and small molecule drugs, can be prescribed concomitantly.
- Follow up, treatment modification, patient informing
- Swollen and tender joint count, patient global assessment and disease activity scores (e.g., 28-joint count version of disease activity score [DAS28] are examples of items to monitor disease activity.

Happy to get your comments & answering your questions

Prof. Dr. Omer Karadag
omerk@hacettepe.edu.tr
omerkaradag@ymail.com

For the patients
www.romatizmatv.org