

# Rheumatoid arthritis

# DEFINITION

- Rheumatoid arthritis (RA) is a systemic, chronic, **immune-inflammatory** condition with unknown etiology and **autoimmune** pathogenesis, characterized by symmetrical joint involvement and progressive, deforming and **destructive evolution** as well as multiple **systemic manifestations**.

# EPIDEMIOLOGY

- RA accounts for approximately 10% of the rheumatic conditions.
- Its incidence reaches approximately 0.5/1000 in women and 0.2/1000 in men
- Prevalence reaches approximately 1.7% in women and 0.7% in men
- Usually affects young patients

# EPIDEMIOLOGY

- The female:male ratio is of 2.2-2.5:1
- In the middle aged (from 35 to 55 years old) it reaches 5:1
- In the elders (70 years)  
women = men

# Etiology

- The etiology is unknown
- It is considered that RA etiology is multifactorial, the predisposing factors being as follows:
  - **genetic**
  - **hormonal**
  - **infectious**
  - **autoimmunity**

# Predisposing factors: genetic factors

The genetic susceptibility is supported by:

- the studies of familial co-aggregation
- twin studies.
  
- Particularly, there was determined a strong association between RA and **class II HLA histocompatibility antigens**. The most frequently implied are **DR1 and DR4**.

# Predisposing factors:

## sex

- improvement of clinical symptoms in 90% of the patients during pregnancy and a dramatic exacerbation of RA activity in the postpartum period.
- It has been proven that women have a more elevated serum level of Igs of all classes, and particularly IgM
- Women are distinguished by an exaggerated immune response, with hyperactivity of the humoral immunity

# Predisposing factors: infections

- Many experimental arthritis' models in animals similar to RA have been induced by immunization with bacterial Ags.
- However, so far there are no convincing evidences of the role of any bacteria.
- A number of viruses were studied as potential etiological agents in RA, i.e. **Epstein-Barr virus**, **parvoviruses** (in some patients there was shown serologically confirmed B19 parvovirus infection), **lentiviruses**, **HTLV-1**, also without solid evidence.



# Predisposing factors: autoimmunity

- The main candidates for the auto-antigens mentioned by researchers are: type II collagen, proteoglycans, chondrocytes, immunoglobulins and heat shock proteins (hsp60).
- Special attention is given lately to the superantigens, viral or bacterial proteins that are able to activate an increased number of T-lymphocytes.

# Predisposing factors: autoimmunity

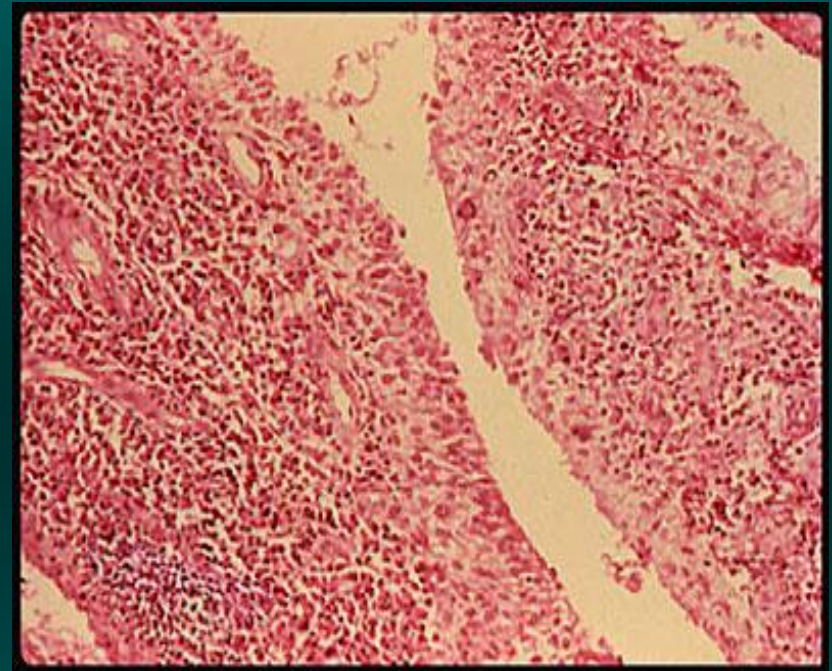
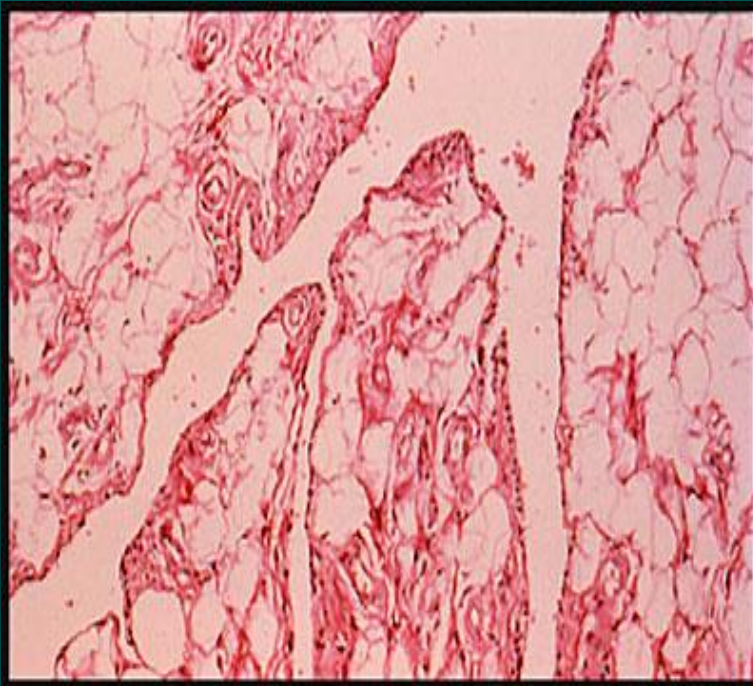
- *Heat shock proteins (PST)* – represent a family of proteins with average molecular weight (60-90 kD) produced by cells in response to stress.
- *Rheumatoid factors (RF)* - were the first evidence of autoimmunity in RA. RF activates complement and contributes to immune complexes, exacerbating synovitis and vasculitis. Thus, RF is currently considered a consequence, not a cause in the RA immunopathogeny.

# MORPHOPATHOLOGY

*The rheumatoid synovitis has 3 developmental stages:*

- The **exsudative stage** - the first weeks-months
- **The infiltrative-proliferative stage**, dominated by intima hyperplasia. The cells initially disposed in 1-2 layers form up to 10-20 layers. Additionally, a process of **angiogenesis** takes place, under the influence of numerous factors; VEGF (vascular endothelial growth-factor), TNF- $\alpha$ , IL-1, IL-8. This fact gives to rheumatoid synovitis features of tumoral type proliferation.

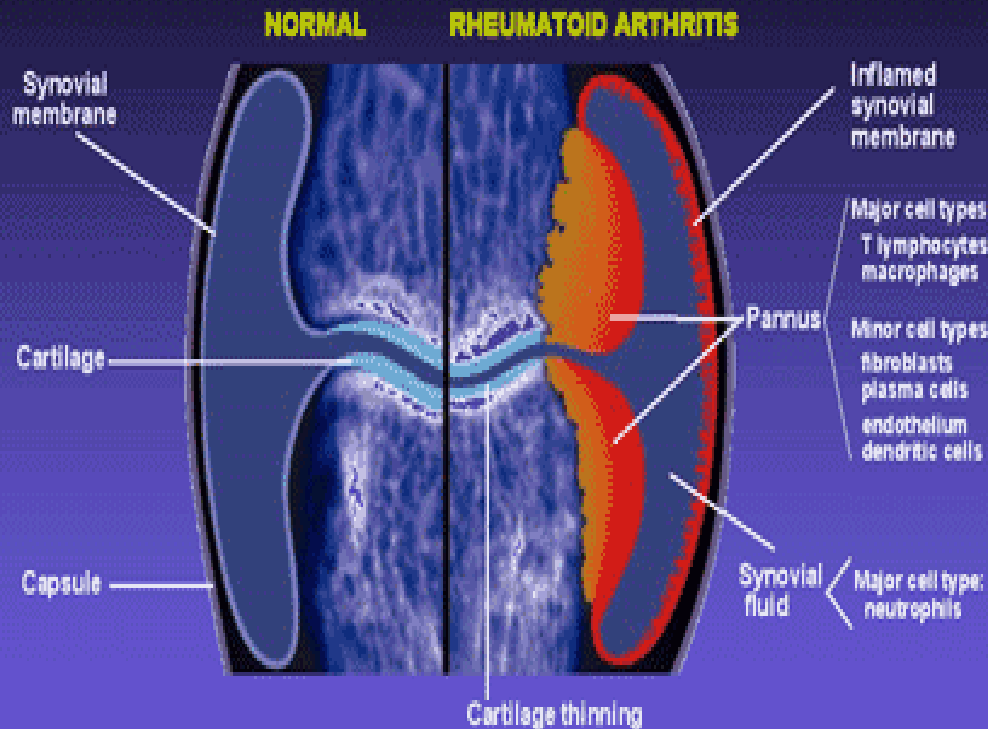
# MORPHOPATHOLOGY



- A – normal synovium
- B – rheumatoid synovium (hypertrophied with 8-10 layers)

# MORPHOPATHOLOGY

## The Pathogenesis of Rheumatoid Arthritis



Adapted from Feldmann M, et al. *Annu Rev Immunol*. 1996;14:397-440.

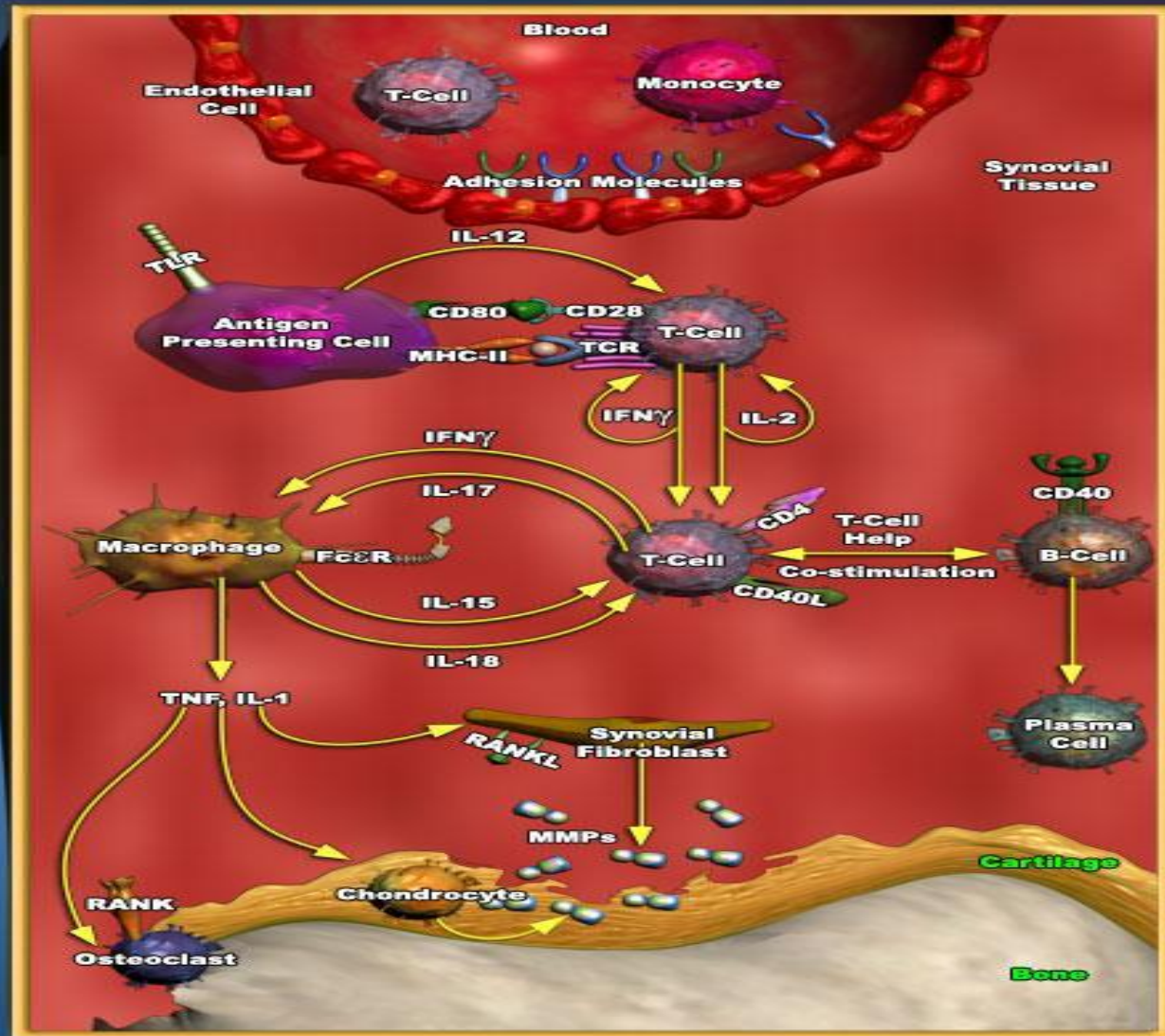
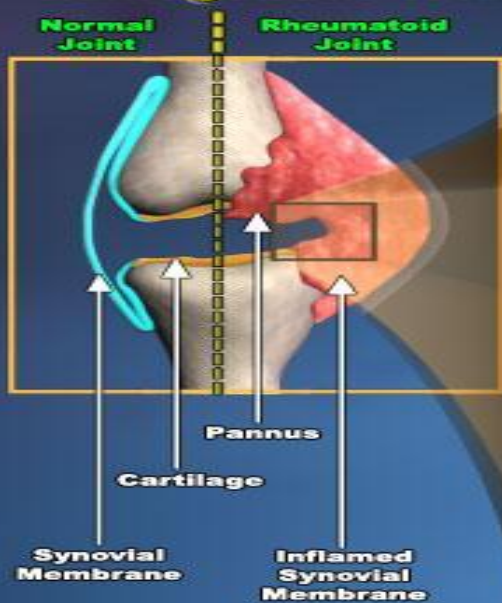
- *Granulomatous stage*, formation of hypertrophied and hypervascularised granulation tissue called **synovial pannus**, which may exceed 10 times the weight of the initial tissue.

# MORPHOPATHOLOGY

- **The pannus** has the capacity to become extremely invasive with respect to bone-cartilage interface.
- Pannus invasion is most prominent in the small joints, while in the hip either the knee there is a layer of fibroblasts which separates the pannus from the cartilage.

# RA PATHOGENESIS

## Pathogenesis of Rheumatoid Arthritis



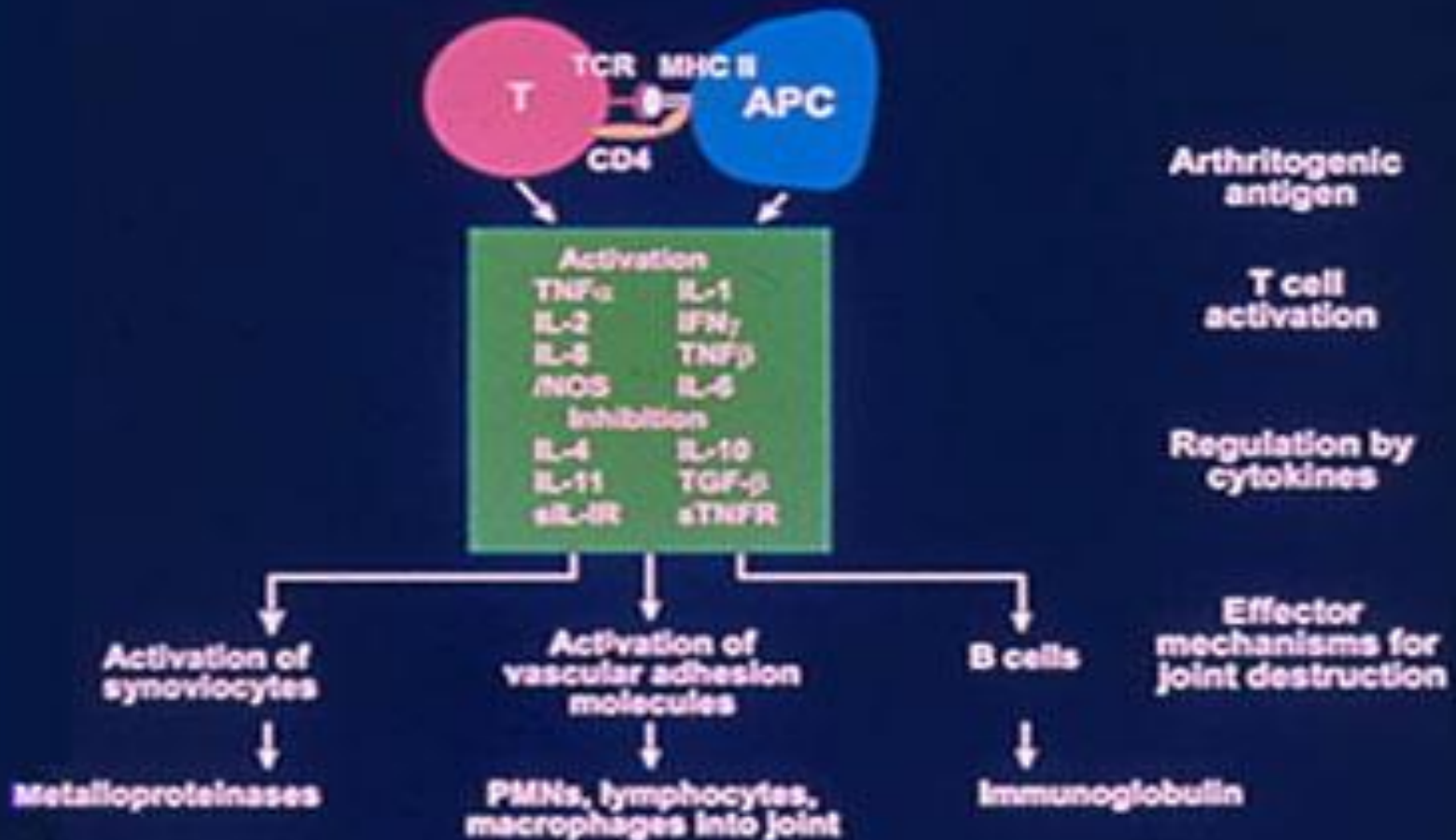
# RA PATHOGENESIS

- **Proliferative-infiltrative synovitis**
- The first event that occurs is *T lymphocyte activation*, probably by an Ag remained still unknown.
- This activation is followed by increased recruitment of T cells, their activation and proliferation (clonal expansion).
- Once triggered, the immune response escapes the normal mechanisms of suppression, becoming excessive and leading to inflammation.



# RA PATHOGENESIS

## T Cell Model for Synovitis in RA



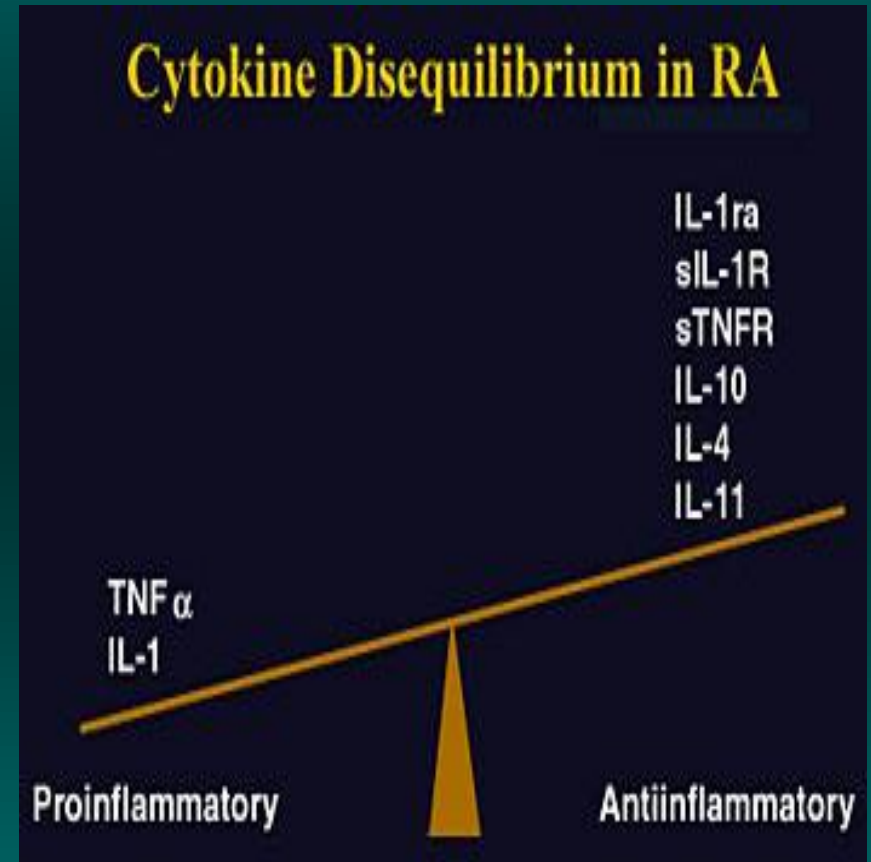
# RA PATHOGENESIS

The consequences of synovial infiltration with activated T lymphocytes are:

- the synovial and endothelial cells are activated and proliferate;
- additional pro-inflammatory cells are recruited from circulation and are activated;
- both type A (macrophage-like) and type B (fibroblast-like) synoviocytes increase the *production of cytokines*;
- The production of antibodies increases as a result of B cell activation, these cells infiltrate the synovium at a later stage.

# RA PATHOGENESIS

- The discovery of cytokines' role in RA is probably the most valuable advancement of the recent decade.
- The pathogenic role of cytokines consists in excessive production of some of them (specifically, pro-inflammatory ones) associated with an inadequate inhibition of the anti-inflammatory cytokines.



# RA PATHOGENESIS

- The main cytokine producers in RA are:
  - *macrophages*
  - *fibroblasts*
  - *endothelial cells*
  - *chondrocytes*
- The most important pro-inflammatory cytokines in RA are: IL-1, TNF- $\alpha$ , IL-6, and some growth factors.

# RA PATHOGENESIS

- **In conclusion**

From the onset until the final stages, the disease goes through the following steps mediated by different mechanisms :

- *Initial induction phase* of the disease is secondary to immune system activation in the genetically determined host. Synovial expression of this phase is represented by micro-vascular damage and proliferation of synovial cells;
- *Intermediate stage of induction* of inflammation is produced by the activation of self-reactive T cells (CD4 +) and pro-inflammatory cytokines intervention, plus the production of RF;
- *Final stage* of bone and cartilage destruction is mediated by pannus formation, osteoclast activation and formation of local bone and cartilage erosions.

# Clinical picture

- *An insidious onset* (primary chronic) is the most common, occurring in 60-65% of cases.
- *An acute or subacute onset* occurs in approximately 15-20% of cases.

# Joint Involvement

- **Joint damage** is of the **inflammatory type**:
  - **Pain and morning stiffness** are characteristic to all inflammatory arthropathies. Morning stiffness in RA usually lasts more than 1 hour.
  - **Swelling and local heat** are caused by: edema, inflammatory infiltrate, increased synovial fluid, synovial proliferation etc.
  - **Superjacent skin** redness is the only element of inflammation that is missing.
  - **Functional damage** develops gradually.

# Joint Involvement

The most Important characteristics of joint damage in RA are :

- *Symmetrical* - involvement a joint is followed by symmetrical joint damage within less than 3 months;
- *Additive* - another joint is affected before the previously involved joint has improved;
- *Progressive* - joint damage progresses to chronic erosions, deformities, ankylosis.





# Joint Involvement

The most commonly affected joints are the diarthrodial joints, especially small joints of the hand:

- **metacarpophalangeal (MCP)**, proximal **interphalangeal (PIP)** (91%)
- **radiocubitocarpal (RCC)** carpal (78%)
- distal interphalangeal (DIP) remain not involved



# Joint Involvement (hands)

- PIP joint swelling and lack of distal involvement produce the so called „fusiform digits“ (spindle-like).



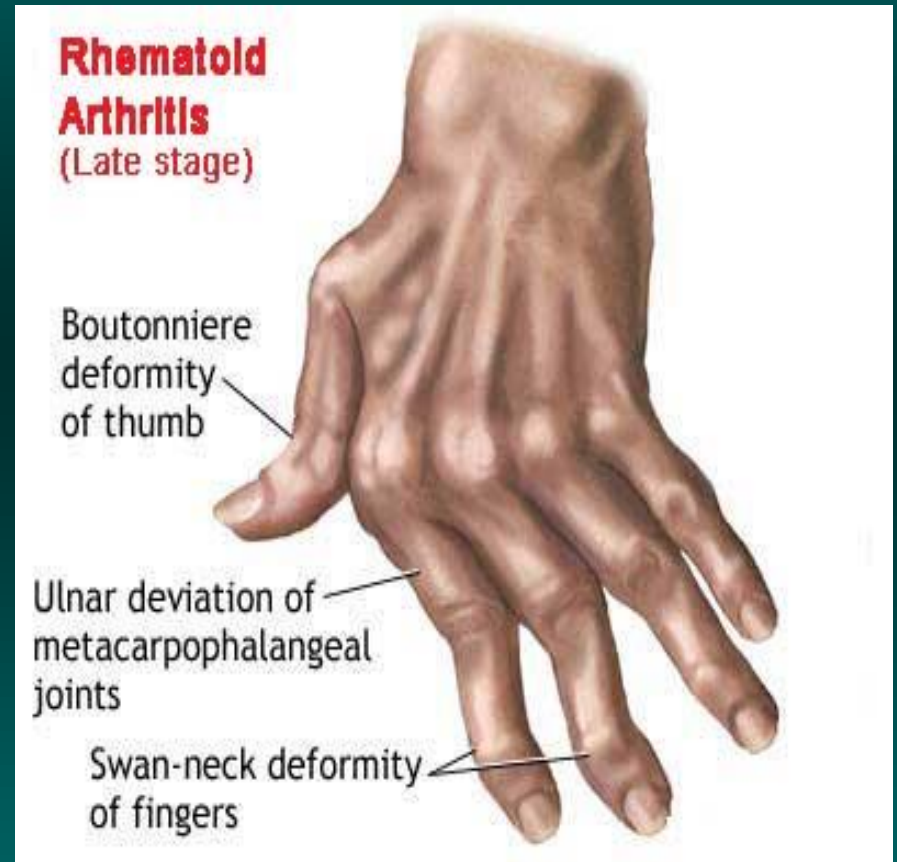
# Joint Involvement (hands)



- Swelling of the RCC and MCPs (II and III) associated with atrophy of interosseous muscles lead to a modification called "camel's back hand."

# Joint Involvement (hands)

- At the level of the fingers several changes may occur:
- **"Swan neck" deformity** - DIP flexion, hyperextension of the PIP, interosseous muscle shortening in time exercises traction on the extensors' tendons and produces PIP hyperextension
- **"Buttoniere" deformity** – the PIP is permanently bent toward the palm while the furthest joint (DIP) is bent back away ([PIP flexion](#) with [DIP hyperextension](#)).
- **Ulnar deviation** of MCF joints



# Joint Involvement (hands)



- Inflammation of the carpus and lack of elasticity of the transverse ligament of the carpus causing compression of the median nerve passing through the carpal tunnel, leads to "**carpal tunnel syndrome**", characterized by pain and numbness in median nerve territory (fingers I, II, III and IV half ), and atrophy may occur on the thenar eminence.

# Joint Involvement (hands)

- As the disease progresses, severe cartilage and bone destructions lead to important deformities, with bone resorption that can cause telescoping of fingers.

# Joint Involvement

- *Cervical spine* is the only spine segment interested in RA. The most commonly affected is the atlanto-axial joint.  
It manifests with pain irradiated upward to occiput, shoulders and arms, numbness occurring during the head movement, or in severe cases, slowly progressive spastic tetraparesis.  
The clinical examination reveals loss of occipital-cervical lordosis, and limited ROM
- *Temporo-mandibular joint* is commonly affected. Pain is exacerbated by chewing, impaired mobility (difficulty in closing the mouth), while computed tomography or magnetic resonance imaging reveals erosions.

# Joint Involvement



- The legs are interested in more than one third of patients with RA.  
More frequently: - MTPs  
- talocrural
- Lateral deviation of the fingers and the PIP joint flexion ("the hammer" finger), and hallux valgus may occur in advanced stages.
- The non-physiological distribution of tasks on the foot surface can lead to painful thickening of the plantar skin



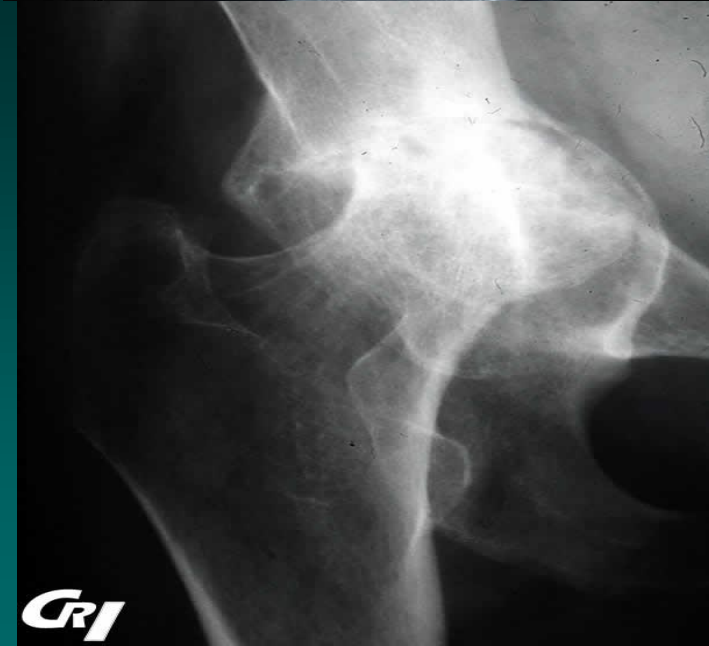
# Joint Involvement

- *Knees* are commonly affected:
  - in the initial stages, in addition to pain, swelling and patella shock occurs (expression of synovial accumulation of fluid);
  - Increased intra-articular pressure can lead to pushing fluid to the joint posterior compartment, where it cannot be returned (via a valve mechanism), thus forming a popliteal cyst called the Baker's cyst. Limitation in flexion, extension and fixation may also be present.
- *Hip* – in time, arthritis of the hip may occur, associated with limited internal rotation or with trochanteric bursitis.

# Joint Involvement



- Large joints (knee, hip, elbows, shoulders) are usually affected later, they remain asymptomatic for longer.



- The joints without synovium (manubrio-sternal, pubic symphysis, disco-vertebral) are not interested in RA.

# ***Extra-articular Involvement***

- The extra-articular manifestations of RA are very **different** in their expression and severity.
- The number and severity of extra-articular manifestations depend on the **duration** and **severity** of disease.
- They are caused by **vasculitic infiltrates** and usually occur in patients with high titers of RF, low serum complement, high concentrations of circulating immune complexes and cryoglobulines.

# ***Extra-articular Involvement***

***Rheumatoid nodules*** are the most common extra-articular manifestation.

- Subcutaneous rheumatoid nodules have a variable consistency (from soft to elastic) can be mobile or adherent to the periosteum or tendons
- They have varying sizes (from few mm to several centimeters) and may be multiple. Sometimes can get infected or fistulise.

# *Extra-articular Involvement*

- They occur in 20-35% of RA patients and are located most commonly on the extensor surfaces (olecranon, proximal ulna), on tendons and near the affected joints
- Sometimes they can have other sites: the larynx, heart, lungs, pleura, kidneys, and extremely rare the leptomeninges or vertebral body.
- Patients with rheumatoid nodules nearly always have RF in their serum.



# ***Extra-articular Involvement***

***Vasculitis*** - inflammation of vessels from different territories can be expressed in several ways :

- ***Distal arteriitis*** with erosions, ulcers or even gangrene areas;
- ***Skin ulcers***;
- ***Palpable purpura***;
- ***Peripheral neuropathy*** (*vasa nervorum vasculitis*);
- ***Visceral arteritis*** (heart, lung, digestive system, kidney, liver etc).

# *Extra-articular Involvement*



Histologically, rheumatoid vasculitis is a panarteritis with inflammatory infiltrates and fibrinoid necrosis seen in active lesions.

This complication occurs more frequently in men with high titers of RF, in severe erosive forms, with other associated extra-articular events.

# ***Extra-articular Involvement***

**Lung damage** can occur in several ways:

- **Pleurisy** is rarely diagnosed clinically, being more frequently established during autopsy.
- **Interstitial fibrosis** is probably due to excessively reactive mesenchymal cells and may be secondary to methotrexate (MTX) therapy;
- **Caplan's syndrome** is the association between RA and pneumoconiosis;
- **Lung nodules** may be single or multiple, differential diagnosis requires their biopsy;
- **Pneumothorax** may be caused by lung nodules with subpleural location, which can cause rupture of the pleura;
- **Bronchiolitis** can lead to severe respiratory failure;
- **Pulmonary vessels arteritis** with development of pulmonary hypertension;
- **Upper respiratory obstruction** caused by affected cricoarytenoid joints .



# *Extra-articular Involvement*

## Heart disease

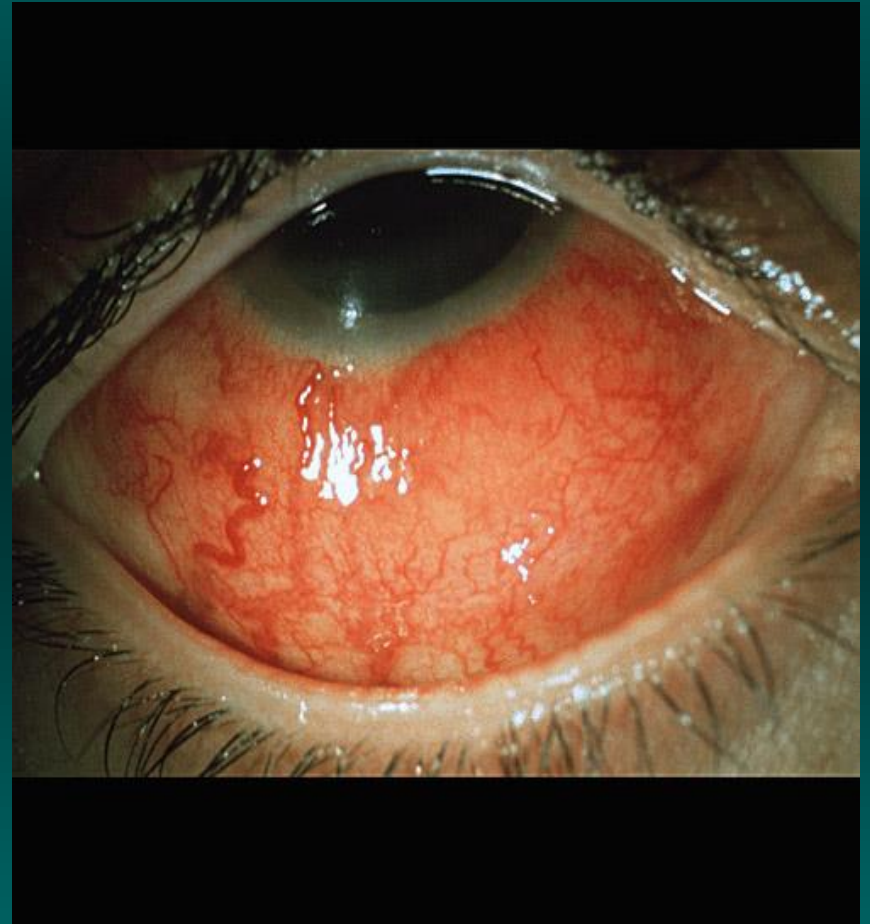
- **Pericarditis** is seen in 50% of cases at necropsy, as clinically evidenced cases are rare. Constrictive pericarditis is extremely rare;
- **Interstitial granulomatous myocarditis** can develop. Rheumatoid nodules located in the myocardium can generate arrhythmias;
- **Endocarditis** is a consequence of rheumatoid nodules located in the valves and may cause stenosis or insufficiency (especially of the aortic valve);
- **Coronary vasculitis** can lead to angina or myocardial infarction.
- As in all chronic inflammatory processes, **atherosclerosis** is more severe and earlier.

# *Extra-articular Involvement*

- **Renal disease**, although rare, may occur as **vasculitis**, due to the presence of **rheumatoid nodules** in the renal parenchyma and especially as a **result of treatment** (NSAIDs, Gold salts, D-penicillamine, cyclosporine). However, RA is the most important cause of secondary **amyloidosis**, which may occur especially in severe forms, with long-standing course and is most commonly manifested as nephrotic syndrome.
- **Neurological damage** can occur as vasculitis of vasa nervorum (sensorial and motor **polyneuritis** expressed as paresthesia, paralysis, areflexia, and amyotrophy), **compression processes** (carpal tunnel syndrome, cord compression due to atlanto-axial subluxation) or as infiltration of meninges.

# *Extra-articular Involvement*

- **Eye involvement** is more common in women and may present with: episcleritis, scleritis, scleromalacia perforans as a result of location of rheumatoid nodules in sclera, keratoconjunctivitis sicca in Sjögren's syndrome and uveitis.
- Eye damage may be a consequence of treatment with hydroxychloroquine.



# *Extra-articular Involvement*

- **Digestive impairment** is most commonly the result of therapy with NSAIDs and cortisone. MTX, lefiunomide, cyclosporine can cause liver damage. Mesenteric vasculitis may occur rarely, equally as hepatomegaly.
- **Felty's syndrome** is a redoubtable complication that occurs in long-standing and progressive forms of RA associated with splenomegaly, neutropenia (+ / - anemia, trombopenia, hepatomegaly, adenopathy).
- **RA and bone damage:** juxtaarticular osteopenia, subchondral erosions (marginal or focal) and generalized osteoporosis, all are responsible for pain, joint deformity and functional impairment and increased risk of fractures.
- **Muscle damage is represented by:** muscle atrophy, non-specific inflammatory myositis.

# Paraclinical investigations

## Haematologic changes:

- **Anemia** is normochromic, normocytic, characteristic of all chronic inflammatory conditions produced by blocking iron in macrophages. Autoimmune hemolytic anemia is a rare manifestation of RA.
- WBC is usually normal, **leukopenia** may occur in Felty's syndrome or may be due to immunosuppressive therapy.
- **Thrombocytosis** can be found in very active forms of the disease.

# Paraclinical investigations

## Non-specific inflammatory syndrome

- ESR acceleration
- C-reactive protein
- Fibrinogen
- Gamma-globulins

# Paraclinical investigations

## Immunologic changes:

- **RF** is positive in 65-80% of RA patients. RF titers correlate with disease activity and extra-articular manifestations occur only in seropositive cases.
- Recently, **Abs against citrullinated peptides** have been described; they have the highest specificity in RA (approximately 95%) and a sensitivity comparable to RF. They appear early in RA and are found in higher titers in more severe cases.

# Paraclinical investigations

## Synovial fluid examination

- Seropositive citrine slightly opalescent fluid or character of exsudate
  - protein concentration may reach 6 g / mm<sup>3</sup>
  - rich cellularity with predominance of neutrophils up to 75%.
  - Sometimes PMN phagocytic immune complexes may be seen (composed of RF, complement-cells called ragocytes)
  - RF is always present
  - complement concentration is low
- **Synovial biopsy** may be necessary in case of mono-  
either oligoarticular forms to allow for the differential  
diagnosis with other inflammatory artropathies.



# Imaging

## X-ray

- In the first months, the X-ray images of the involved joints may appear normal. Subsequently, the following changes may be seen:
- *Swelling of the soft periarticular tissue*, particularly around PIPs, RCCs, knees, which shows soft tissue oedema, increased quantity of synovial fluid, and synovium inflammatory changes.
- *Juxta-articular osteoporosis*, initially involving epiphysis but lately diffuse is produced by a number of mechanisms: activation of osteoclasts, long-term immobilization, some drugs, and post-menopause.
- *Narrowing of joint space* is produced gradually and is the consequence of joint cartilage destruction. In time, the joint spaces are completely compromised.

# Imaging

## X-ray



- *Marginal erosions, geodes and microgeodes* occur in advanced stages. Erosions may be seen at the bone-cartilage interface, are poorly delimited and may have variable dimensions.
- Geodes and microgeodes are bone lysis areas located in the subchondral bone, which unlike bone cysts that occur in osteoarthritis are not bounded by a sclerotic margin.

# Imaging

Normal  
hand



Rheumatoid  
arthritis

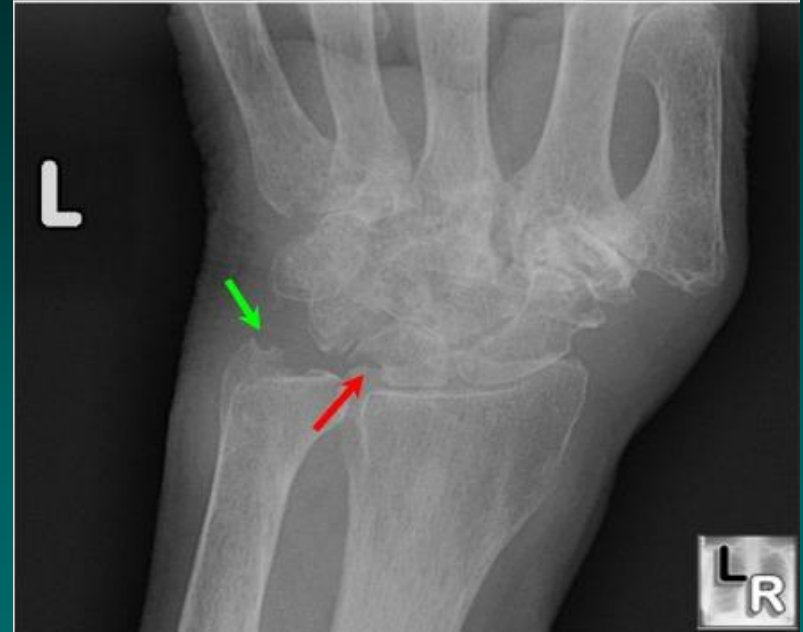
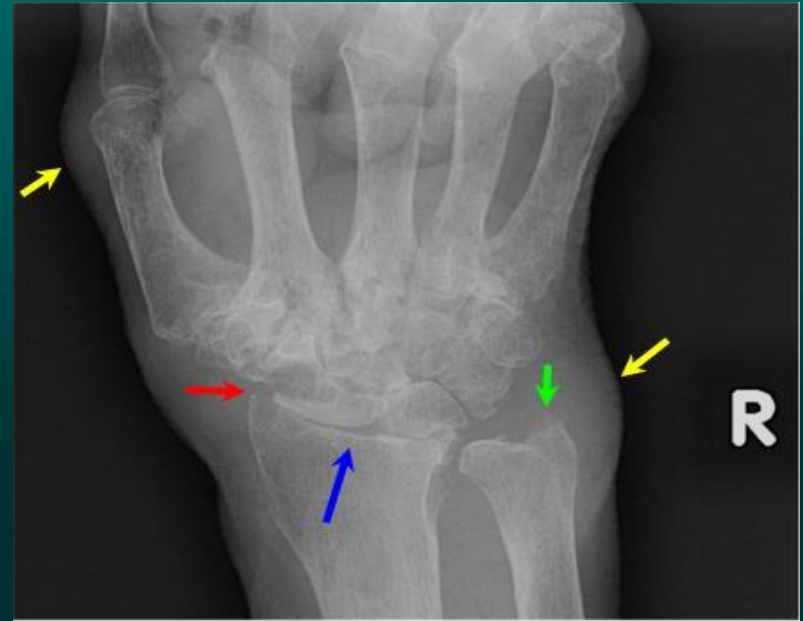
Bone  
erosion

Bone  
displacement



# Imaging

- **Ankyloses** represent the consequence of totally compromised osteo-articular areas and occur specifically in the carpal, MCPs, PIPs and tarsal area.



# Imaging



## X-ray

- In the large joints such as knees or coxo-femoral joints, the radiographic changes appear at a later stage and consist mainly of joint space narrowing and rarely of marginal erosions.

# Imaging

- **Joint ultrasound** puts out early the synovial fluid, inflammation of tendons and synovium and the presence of synovial cysts and pannus. Ultrasound of the popliteal region allows differential diagnosis between Baker's cyst rupture and deep vein thrombosis.
- **Nuclear magnetic resonance (NMR)** is an imaging method that shows early erosions, bone subchondral bone cysts, altered articular cartilage, synovium hypertrophy, and the state of the periarticular structures



# Diagnostic criteria developed by the American Rheumatism Association (ARA) 1987 (reviewed)

- **Morning stiffness** – articular or periarticular lasting at least 1 hour
- **Arthritis of 3 and more joint areas**, with soft tissue swelling, observed by the doctor
- **Hand arthritis:**
  - Arthritis involving proximal interphalangeal joints (PIPs), metacarpophalangeal joints (MCPs) or radiocarpal joints (RC)
- **Symmetric arthritis:**
  - Concomitant involvement of similar bilateral joint areas
- **Rheumatoid nodules:**
  - Subcutaneous nodules localized on the bony prominences on the extensor surface either in the joints' proximity
- **Rheumatoid factor** in serum
- **Radiologic changes:**
  - Juxta-articular osteoporosis and /or erosions in the affected joints

RA diagnosis is considered established in the presence of at least 4 out the 7 above mentioned criteria. Criteria 1 to 4 must persist for at least 6 weeks.

# ACR classification criteria (2010)

- **A. Joint involvement**
  - One large joint 0 points
  - 2-10 large joints 1 points
  - 1-3 small joints (with or without large joint involvement) 2 points
  - 4-10 small joints (with or without large joint involvement) 3 points
  - > 10 joints (at least 1 small joint) 5 points
- **B. Serology(at least 1 test result is necessary)**
  - RF negative and anti-CCP negative 0 points
  - RF mildly positive or anti-CCP mildly positive 2 points
  - RF highly positive or anti-CCP highly positive 3 points
- **C. Acute phase reactants (at least 1 test result is necessary)**
  - Normal CRP and ESR 0 points
  - Elevated CRP or ESR 1 points
- **D. Duration of symptoms**
  - <6 weeks 0 points
  - ≥ 6 weeks 1 points

**Positive diagnosis is confirmed in case of ≥6 points**



# Classification

The evolution of the disease is classified according to the ARA criteria, as follows:

- **Slowly-progressive evolution:** moderate joint deformity, 2-3 joints involved, radiological stage I-II, functional class I, grade 1-2 disease and lack of activity and no systemic symptoms
- **Rapidly-progressive evolution:** severe joint deformity, involvement of 3 or more joints in the rheumatoid process, radiological stage has a two-stage progression within one year, functional class II-III, 2-3 rheumatoid process activity, the presence of extraarticular damage.

Depending on the detection of rheumatoid factor in serum of patients, RA is classified as:

- **Seropositive**
- **Seronegative**



# Classification

Classification of structural damage to joints radiographically detected, was done according to generally accepted criteria proposed by Steinbrocker O.:

## Stage I (early)

- No radiological signs of destruction
- The incipient osteoporosis may be present

## Stage II (moderate)

- Osteoporosis with or without cartilage or bone damage
- The absence of deformation (mobility limitation may be present)
- Neighborhood muscular atrophy
- Periarticular lesions, nodules or possible presence of tenosynovitis

## Stage III (severe):

- Cartilage or bone destructions
- Axial deformation
- Extensive muscular atrophy
- Periarticular lesions, nodules or possible presence of tenosynovitis

## Stage IV (terminal)

1. Fibrous or bony ankylosis
2. + Stage III criteria

# Classification

## Clinical and functional classification :

- Class I: normal physical activity, unaltered capacity to perform all daily activities;
- Class II: daily activities can be performed, but with pain and reduced joint mobility;
- Class III: self-care capacity maintained;
- Class IV: immobilization in bed or wheelchair, self-care disability.

**MANAGEMENT**

# Groups of drugs

- **SMARDs** (symptom modifying antirheumatic drugs) which include:
  - nonsteroidal anti-inflammatory drugs (NSAIDs)
  - corticosteroids
- **DMARDs** (disease-modifying antirheumatic drugs) which include :
  - Methotrexate
  - Leflunomide
  - Gold salts
  - Synthetic antimalarials
  - Sulfasalazine
  - Cyclophosphamide
  - Azathioprine
- **Biologic therapy**

# Nonsteroidal anti-inflammatory drugs (NSAIDs)

- reduce pain and inflammation,
- do not control the progression of joint erosions
- do not influence the extra-articular symptoms
- act purely symptomatically and their effect lasts only for the time of the treatment

# NSAIDs

## COX-1 selective inhibitors

- Acetylsalicylic acid in small doses

## COX-1, COX-2 non-selective inhibitors

- Diclofenac
- Ibuprofen
- Indomethacin
- Naproxen

## COX-2 selective inhibitors

- Meloxicam
- Etodolac
- Nimesulide

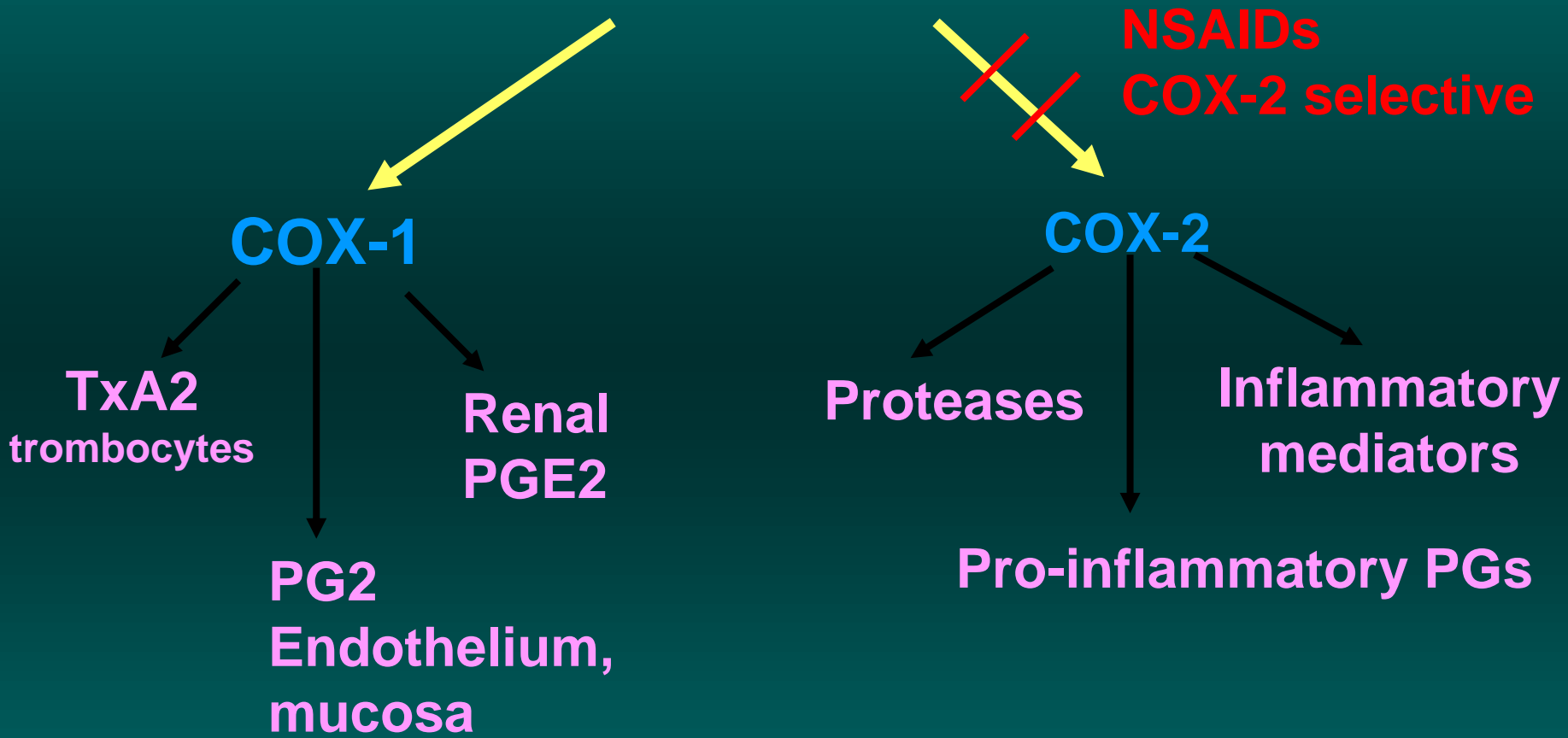
## Ultra-selective COX-2 inhibitors (coxibs)

- Celecoxib
- Rofecoxib
- Valdecoxib



# INFLAMMATION

## ARACHIDONIC ACID



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Physiological function

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INFLAMMATION

# NSAIDs

## COX-1, COX-2 non-selective inhibitors

- Diclofenac 75-150 mg/24h
- Ibuprofen 1200 mg/24h

## COX-2 selective inhibitors

- Meloxicam 15-7,5 mg/24h, once a day
- Nimesulide 100 mg bid /24h
- **D. Ultra-selective COX-2 inhibitors (Coxibs)**
- Celecoxib 100 -200 mg/24h, once a day

# Corticosteroids

- *Local* – are very effective in relieving symptoms, but their use should be judicious
- *Systemic* – has a rapid symptomatic effect
  - can be administered short term in high doses, in case of drug toxicity
  - in case of vasculitis or other systemic manifestations of disease, pulse-therapy is preferred;
  - are indicated in severe progressive disease flare-ups or severe forms;
  - May be indicated alone, if necessary, during pregnancy;
  - Administration of low doses and for short term, until the onset of disease modifying therapy ("bridge therapy").

# Systemic Corticosteroids

Systemic corticosteroid side effects often limit their use; and are dose-dependent. The most common side effects are:

- Moon face with acne
- Hirsutism
- Trunk obesity
- Flatulence and other gastrointestinal symptoms
- Fluid retention with hypo-K-emia
- Hypertension
- Recurrent infections
- Amenorrhea

# Systemic Corticosteroids

## Adverse Events

- steroid diabetes
- gastroduodenal ulceration and bleeding
- osteoporosis
- aseptic osteonecrosis
- myopathy
- subcapsular cataract
- mental disorders
- can stop growth in children.

# ***Disease modifying therapy (DMARD)***

Has the potential to maintain the integrity and functionality of osteo-articular apparatus!

# Methotrexate

- Methotrexate (MTX) the most widely used, the "gold standard" in RA treatment
- The therapeutic effects of MTX are determined by its cytostatic, immunosuppressive and anti-inflammatory actions of the.
- MTX is administered (orally or parenterally) on a weekly basis.
- The whole dose may be given once or may be spaced within 24 hours.
- Maintenance dose is between 7.5-25 mg/week. The co-administration of 1 mg/day (min 5 mg/week) of folic acid reduces toxicity without reducing its effectiveness.

# Methotrexate

- The therapeutic effect of MTX occurs after 4-6 weeks of treatment. It is effective in approximately 80% of patients and is indicated in patients with mild, moderate or very active disease, as well as in drug combinations.
- **Absolute contraindications:** hypersensitivity to MTX, pregnancy, lactation, severe bone marrow depression, and the **relative** ones are pre-existing liver disease, kidney failure, severe lung disease. Therapy should be interrupted in case of acute infection or major surgery.



# Leflunomide (LF)

- Is a therapeutic alternative for patients not responding or no longer tolerating MTX treatment.
- LF is administered at a dose of 100 mg / day for 3 days followed by a maintenance dose of 20 mg / day.
- Therapeutic response is quick, in 4 weeks (the starting dose of 100 mg / day for 3 days probably contributes to this rapid response).

# Hydroxychloroquine

- Hydroxychloroquine has a place in RA therapy especially in mild forms of disease, as part of therapeutic combinations.
- There are no data to prove that hydroxychloroquine has an effect on the rate of progression of joint destructive lesions.
- Regimens using doses up to 400 mg / day are associated with a low rate of side effects (eye, hematologic, renal).

# Sulfasalazine (SSZ)

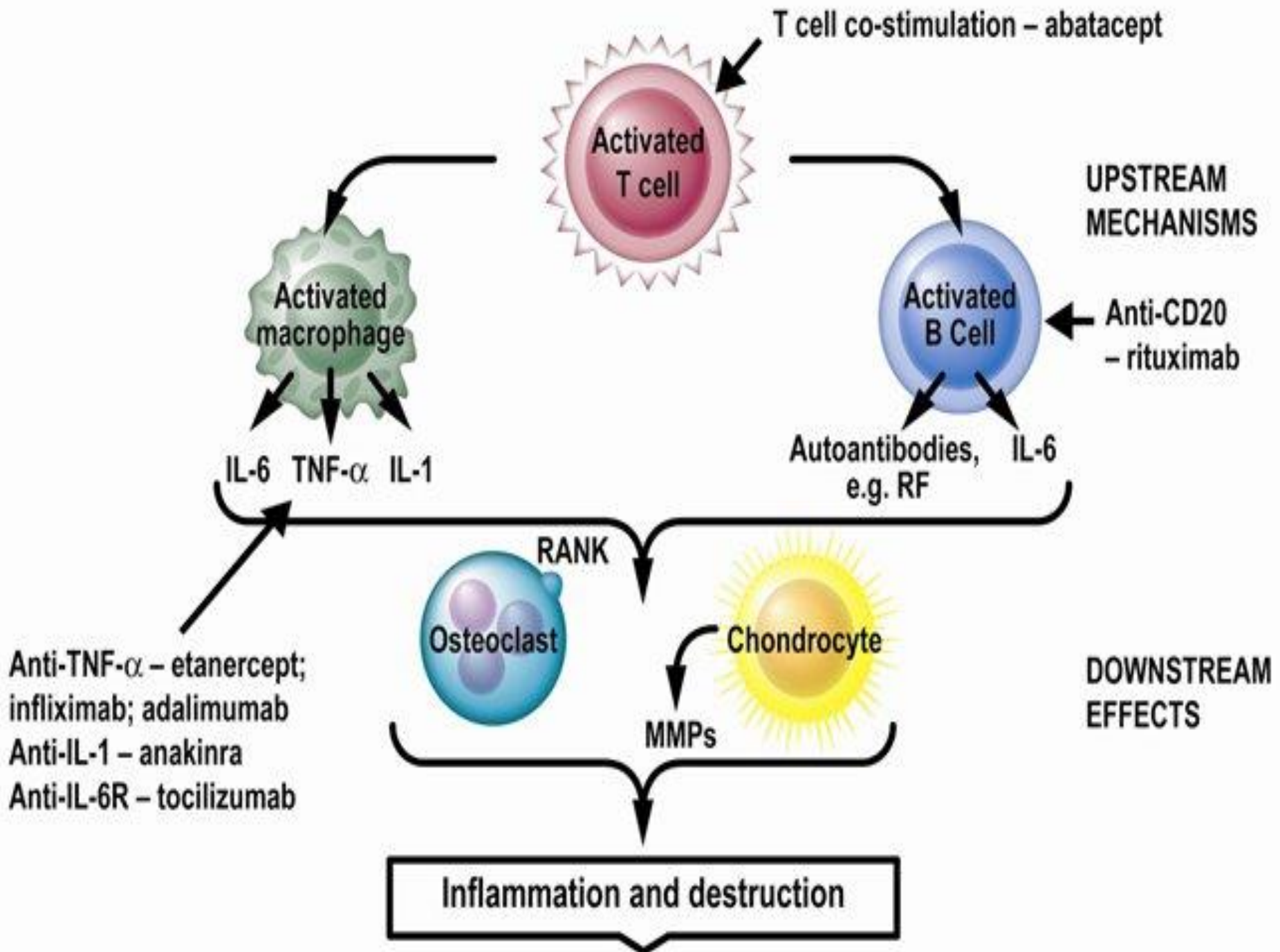
- SSZ acts as a anti-inflammatory (by acid 5-aminosalicylates), antibacterial (by sulfapyridine) and immunomodulating agent.
- Currently used doses (2000-3000 mg/day)
- SSZ is indicated in patients with mild or moderate disease, when MTX is contraindicated or in combination with MTX, LF or hydroxychloroquine.
- The most common SSZ side effects are: digestive (nausea, vomiting, abdominal pain, diarrhea), skin (rash, itching), hematologic (leukopenia with neutropenia, anemia macrocytic, aplastic anemia), liver (elevated transaminases), neuropsychiatric (depression).

# Cyclophosphamide

- Cyclophosphamide is an alkylating agent acting by nucleic acid synthesis inhibition and thereby depressing both T and B lymphocyte
- Is indicated as pulse therapy at a dose of 1g monthly until the total dose of 10 g, usually associated with a corticosteroid in severe life-threatening, highly active, forms of disease with extra-articular involvement.

# ***Biologic therapy in RA***

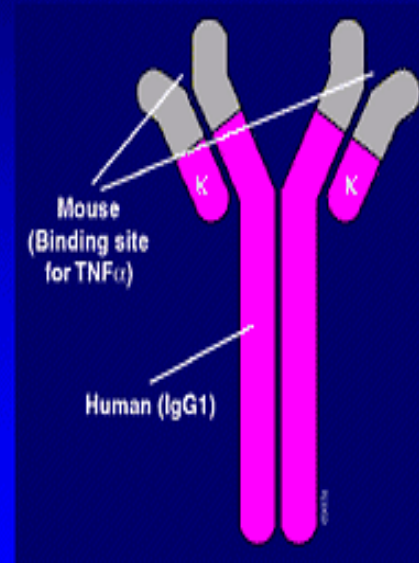
- Biological agents are substances that have the ability to interact with specific components of inflammation, as evidenced following groups:
  - **monoclonal antibodies (MAB)**
  - **receptor antagonists**
  - **soluble receptors**



# Infliximab

- Is a chimeric monoclonal antibody (murine-human) of IgG1 type that binds to TNF and blocks its activity. The murine portion binds to TNF- $\alpha$ , and the human origin is responsible for the effector functions.

## Remicade® (Infliximab)



- Chimeric IgG1 monoclonal antibody
- High affinity binding to TNF $\alpha$  ( $K_a = 10^{10}M^{-1}$ )
- Neutralizes only TNF $\alpha$
- Highly stable complexes
- Selective lysis of activated TNF $\alpha$  expressing cells

# Adalimumab

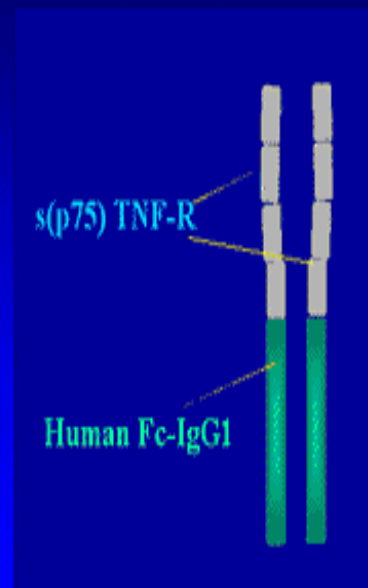
- A completely humanized IgG1 monoclonal anti-TNF- $\alpha$  antibody.
- Exerts its effect by blocking TNF- $\alpha$  and preventing its binding to specific cell receptors.
- Being completely humanized, adalimumab is less immunogenic, and therefore does not require compulsory administration with another immunosuppressive agent (eg. MTX).
- The usual dose is 40 mg s.c. once in 2 weeks.



# Etanercept

- The soluble receptors for TNF- $\alpha$  are a fusion protein produced by genetic engineering, formed by a combination of two identical chains of recombinant TNF- $\alpha$  receptors (p75-type II) with Fc-IgG1 fragment.

## Enbrel<sup>®</sup> (Etanercept)



- Human s(p75) TNF-R linked to Fc $\gamma$ 1
- Dimer binding affinity to TNF $\alpha$  and Lt $\alpha$  :  $K_a = 10^{10}$
- Dissociation of TNF-complexes in the presence of free TNF or receptor
- No cell lysis

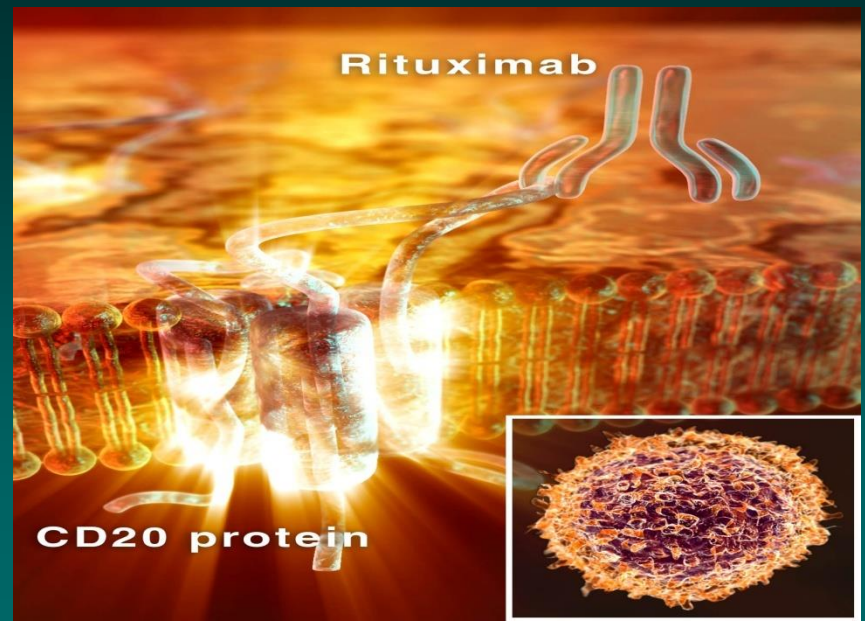
# Etanercept

- It was used both as monotherapy in patients with RA, with beneficial effects and in combination with MTX. The product is administered 25 mg s.c. 2 times / week.
- Favorable effects are obtained in 71% of patients and appear after the first two weeks.
- Minor adverse reactions (injection site irritation and upper respiratory tract infections) and generally resolved without discontinuation of therapy. Most side effects occur in the first month of treatment.
- Serious infections occurred in 2.9% of patients, 16% developed Ab against soluble receptor and in 15% antinuclear or anti-dsDNA Ab appeared. There were no reported cases of SLE or lymphoproliferative disease.

# Rituximab (Mabthera)

Monoclonal antibodies designed to act on the CD20 positive B lymphocytes

- Fix region of human origin
- Variable region of murine origin
- The murine region binds to the surface of B-lymphocytes by the CD20 antigen
- Constant region of human origin activates cellular mechanisms that induce B cell depletion

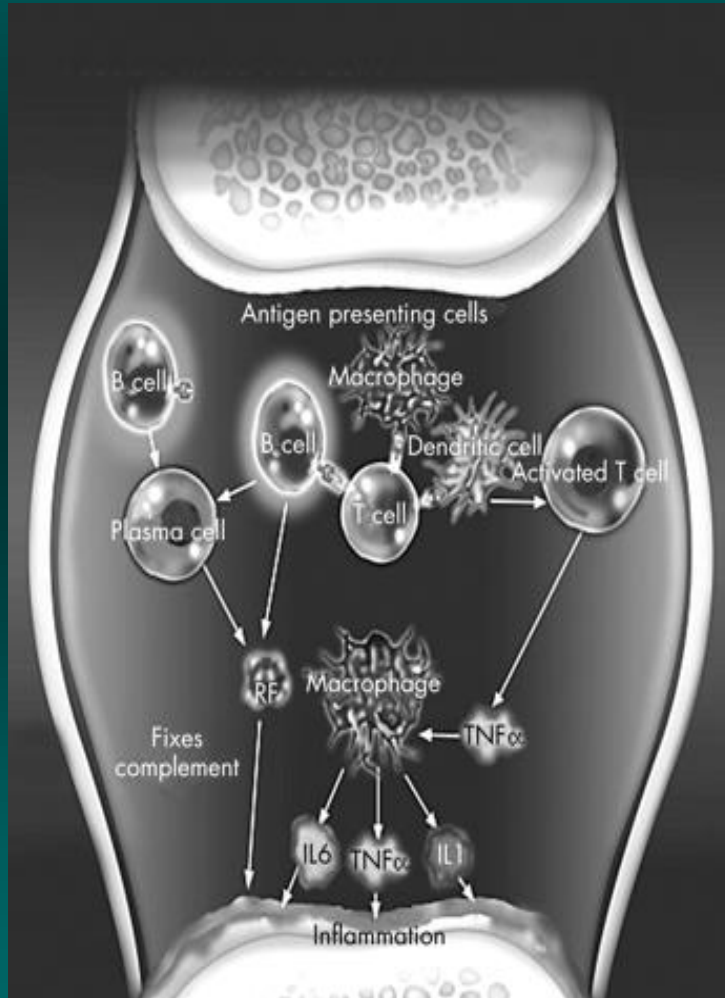


# Rituximab (Mabthera)

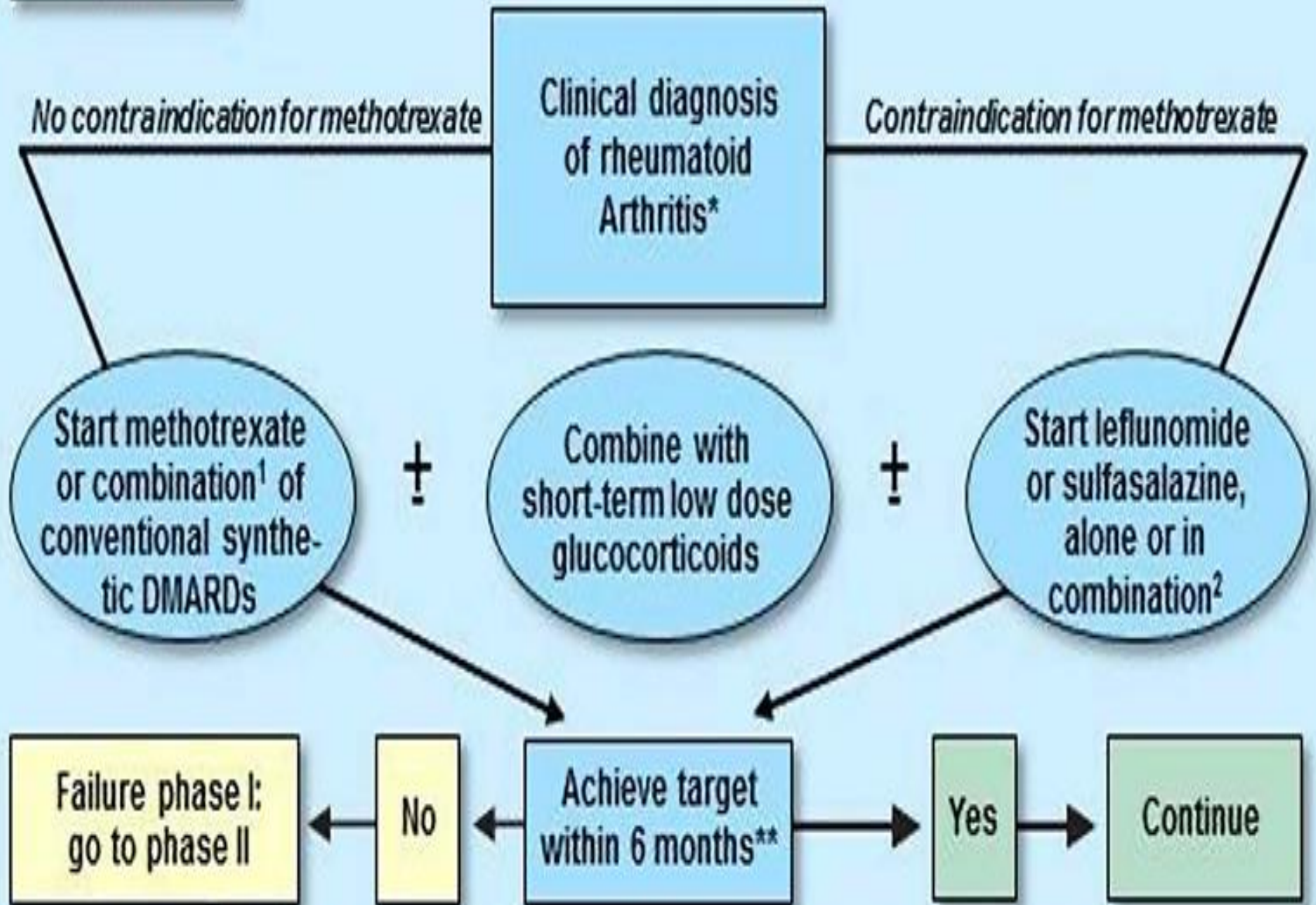
- B lymphocytes can function as antigen-presenting cells
- In the synovial joint B-lymphocytes can secrete pro-inflammatory cytokines such as TNF- $\alpha$  and chemokines
- Are producing auto-Ab (RF)
- B lymphocyte depletion mechanisms are achieved by:

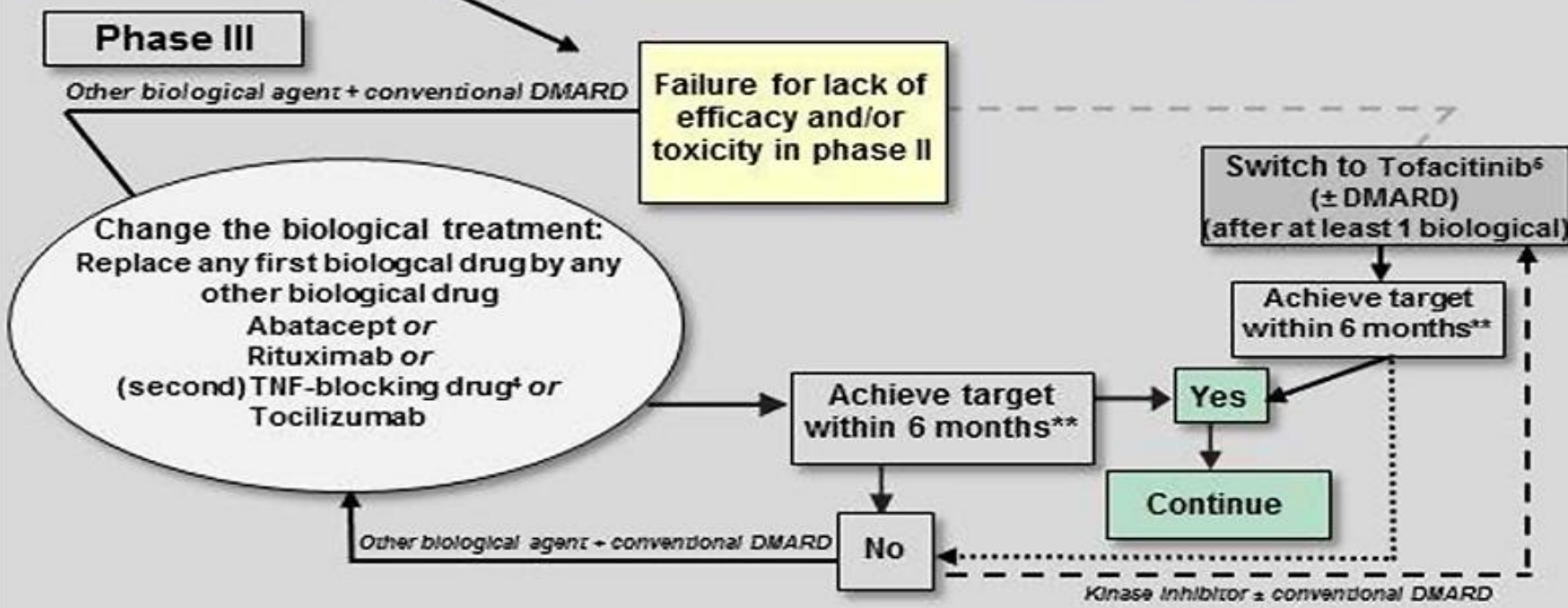
- Complement-mediated cytotoxicity
- Cell-mediated cytotoxicity
- Apoptosis

- is given as two infusions i / v 1,000 mg daily 1:15 infusions of 3-4 hours duration. Patients concurrently are administered steroids to minimize post-infusional reactions.



# Phase I





# Surgery

- In the early stages one could perform a synovectomy (if a joint effusion is resistant to drug therapy), interventions for carpal tunnel syndrome, tendon rupture, atlanto-axial subluxation, or Baker's cyst rupture.
- In late stages, when it was ankylosis, arthroplasty with total joint prosthesis is the only therapeutic method that can improve the patient's functional status.

# Rehabilitation

- Physical spa treatment should be applied with caution in patients with RA and should be reserved for only the periods of remission of the disease (otherwise could extend the flare-ups).
- The program includes particularly kinetic and hydrotherapy, which may:
  - relieve pain
  - strengthen muscles
  - prevent osteoporosis
  - prevent muscle atrophy.



**THANK YOU FOR  
ATTENTION!**