Connective tissue diseases

Rudolf Horváth, M.D., Ph.D.
Andrea Čaničová, M.D.
Dpt. of pediatric and adult rheumatology
Faculty Hospital Motol
Prague

Connective tissue diseases

- Rheumatoid arthritis (RA)
- Juvenile idiopathic arthritis (JIA)
- Systemic lupus erythematosus (SLE)
- Sjögren's syndrome (SjS)
- Systemic scleroderma (SSc)
- Polymyositis (PM), dermatomyositis (DM)
- Mixed connective tissue disease (MCTD)
- Overlap syndromes
- Vasculitides

Prevalence of some CTDs

Disease	Percentage	Czech republic
RA	1,0	100 000
SLE	0,1	10 000
SCL	0,018 - 0,04	1 800 – 4 000
SjS	0,6 – 2,7	60 000 – 270 000
PM/DM	0,01 ?	1 000 ?

Rheumatoid arthritis

Rheumatoid arthritis

- Is characterized by inflammatory polyarthritis
- Symmetric synovial proliferation and tenderness of multiple joints, particularly the small joints of the hands and feet.
- Joint stiffness for more than an hour in the morning.

Joint involvement

- Synovial tissues in rheumatoid arthritis (RA) are markedly expanded by the recruitment and retention of inflammatory cells, with the formation of **villous projections and the generation of pannus tissue** that invades and destroys cartilage and bone.

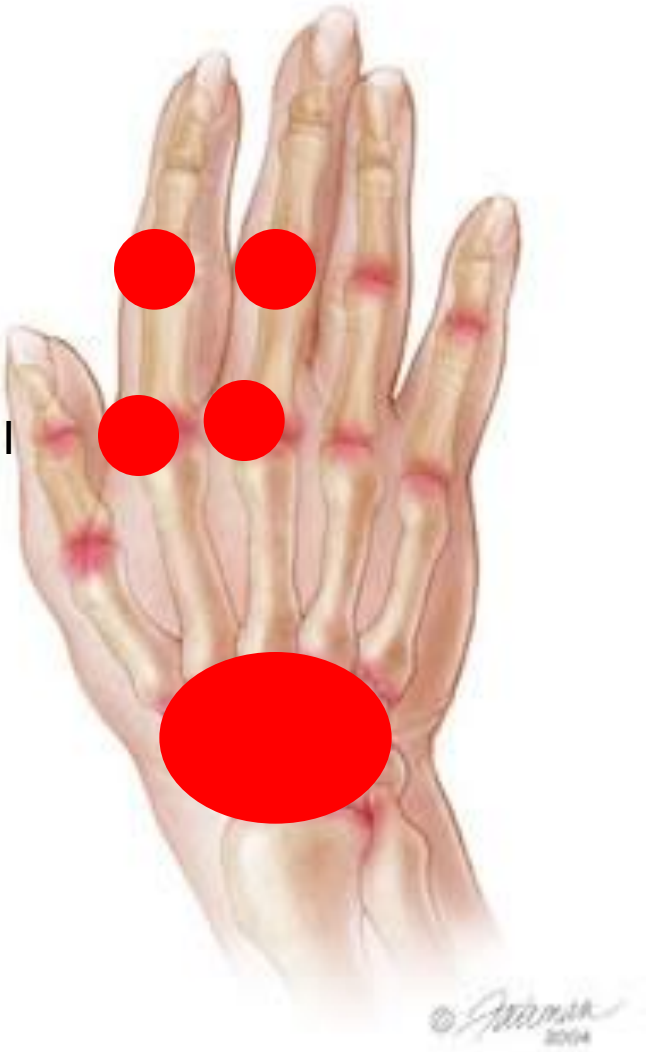
- Cartilage destruction results from the production of enzymes that destroy components of the cartilage extracellular matrix by cells within synovial tissues and by chondrocytes; osteoclasts contribute to destruction of articular bone.

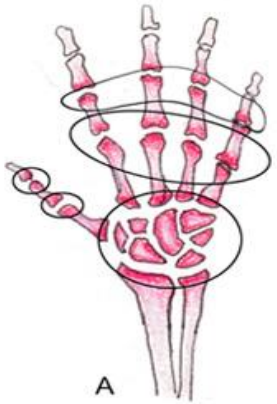
Distribution of joint involvement

PIP II, III

MCP II, III

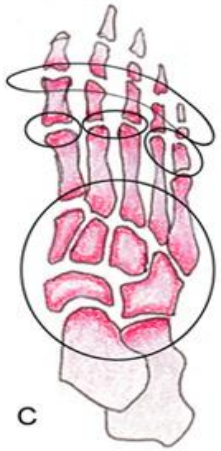
RC





A

Rheumatoid Arthritis



C

Rheumatoid Arthritis

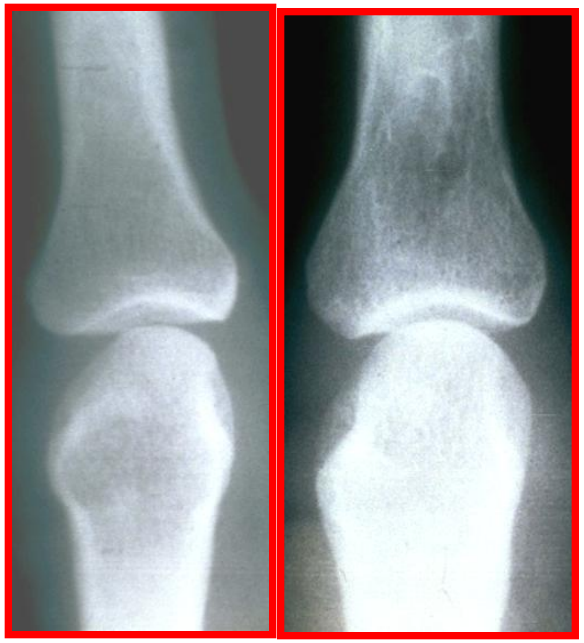
Frequency of mostly affected joints

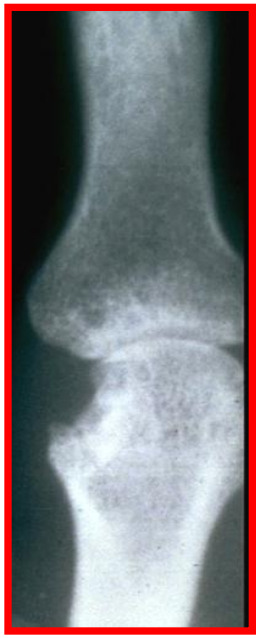
Joints	A (%)	B (%)
Metacarpophalangeal (MCP)	52	87
Radiocarpal (RC)	48	82
Proximal interphalangeal (PIP)	45	63
Metatarsophalangeal (MTP)	43	48
Shoulder	30	47
Knee	24	56
Ankle	18	53
Elbow	14	21

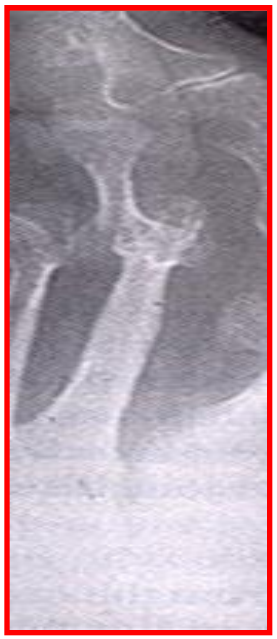
A = affected joints early RA
B = affected joints chronic RA

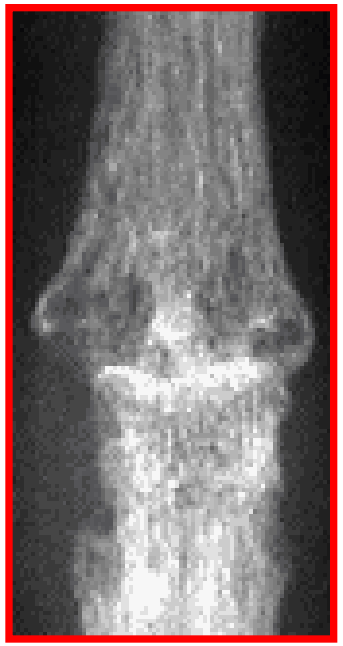
Pavelka et. al, Revmatologie, 2013

Evolution of x-ray destructions staging of RA









Swelling of soft tissues

Narrowing of joint space

Erosions, narrowing of joint space

Erosions, narrowing of joint space, deformities

Ankylosis

Stage I

Stage II

Stage III

Stage IV

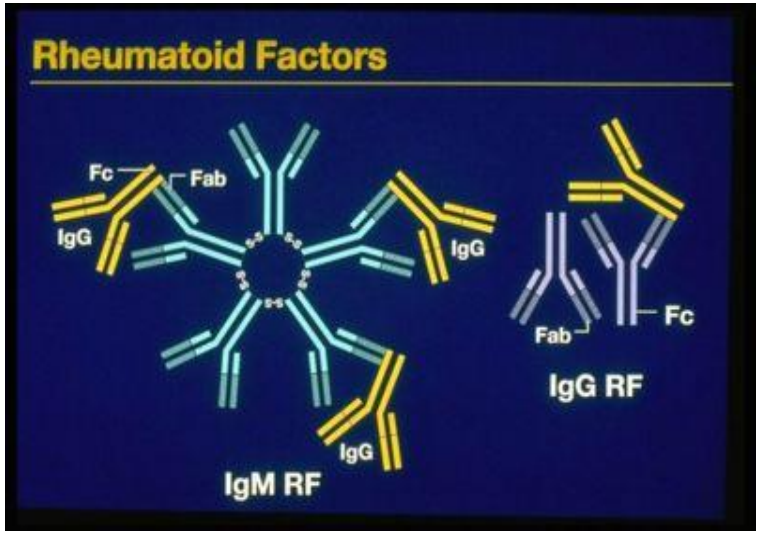
Extra articular manifestations

Skin	Rheumatoid nodules - subcutaneous nodules typically in RF+ patients.
Hematologic abnormalities	Anemia, thrombocytosis, lymphadenopathy.
Felty syndrome	RA in combination with splenomegaly, leukopenia, thrombocytopenia.
Hepatic involvement	Elevated liver tests
Pulmonary involvement	Pleural disease - usually asymptomatic. Parenchymal pulmonary nodules. Pulmonary nodulosis +pneumoconiosis + RA (Caplan syndrome) exposure to coal dust. Interstitial lung disease (ILD)
Cardiac involvement	Pericarditis, accelerated atherosclerosis, valvulitis - rare
Ocular involvement	Keratoconjunctivitis sicca, episcleritis, scleritis
Neurological involvement	Peripheral entrapment neuropathy /nerve is compressed by the inflamed synovium against a fixed structure/ atlantoaxial subluxation - caused by erosion of the odontoid process or the transverse ligament of C1 may allow the odontoid process to slip posteriorly and cause a cervical myelopathy.
Muscles	Atrophy, myositis – rare
Renal involvement	low-grade membranous nephropathy, glomerulitis, vasculitis, and nephrotic syndrome due to secondary reactive amyloidosis have all been described.
Vascular	Rheumatoid vasculitis

Pavelka et. al, Revmatologie, 2013

Rheumatoid factors

- Rheumatoid factors are auto-antibodies that recognize antigenic determinants on the Fc portion of IgG
- Specificity 78 %, sensitivity 74 %

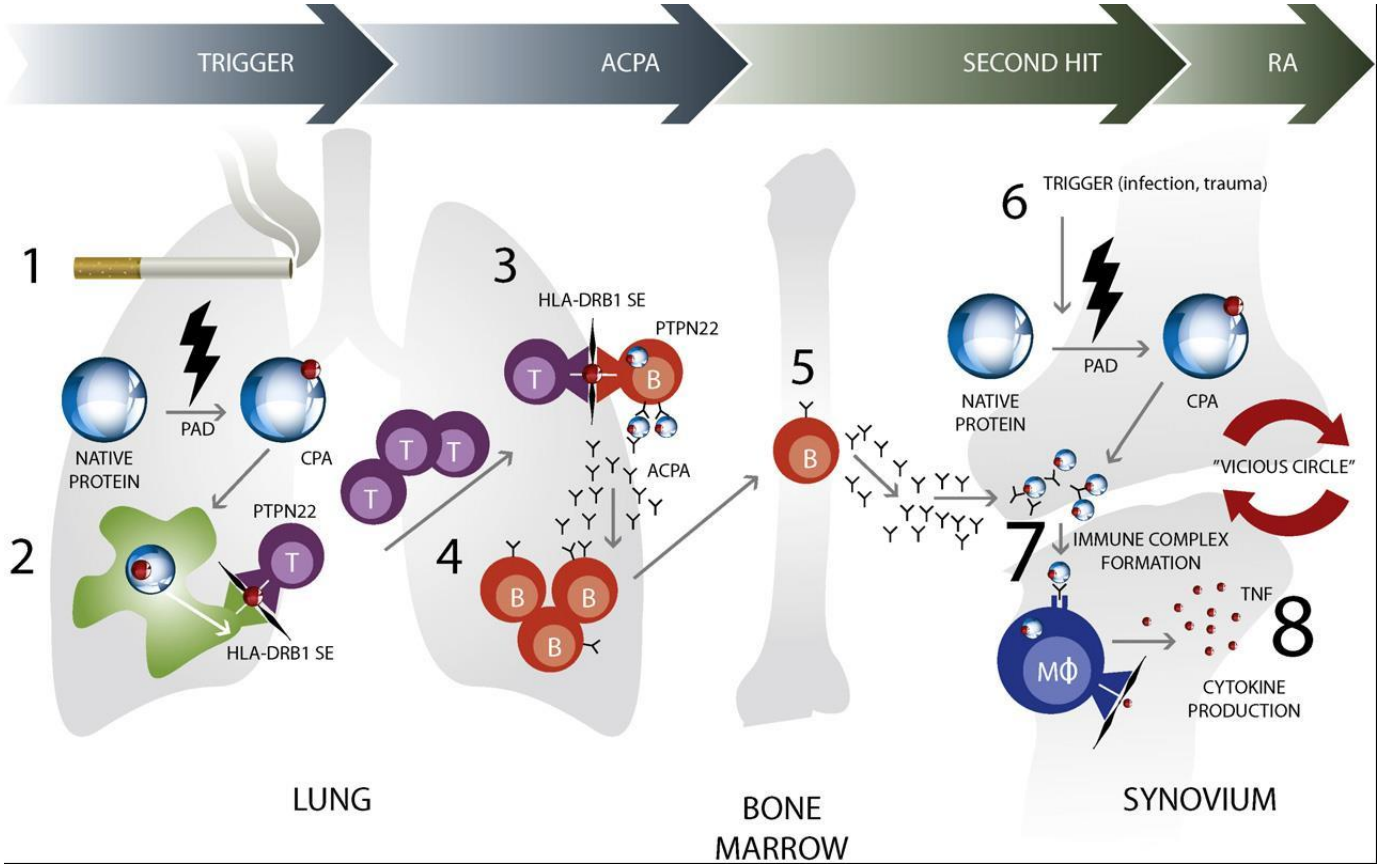


	Frequency (%)
Systemic autoimmune diseases	
Rheumatoid arthritis	75-90
Sjögren syndrome	52-62
Systemic lupus erythematosus	10-27
Systemic sclerosis	8-44
Mixed connective tissue disease	~ 70
Polymyositis/Dermatomyositis	~ 18
Juvenile idiopathic arthritis	< 5
Other diseases	
Osteoarthrosis	~ 25
Reactive arthritis	~ 10
Mixed cryoglobulinemia	10-60
Sarcoidosis	38-64
Primary biliary cirrhosis	~ 70
Infection	
HIV infection (IgA RF)	~ 50
Hepatitis B	11-15
Hepatitis C	11-53
Active TBC	~ 62
Subcutaneous bacterial endocarditis	36-72
EBV	~ 30
Tumors	
Chronic lymphoid leukemia	< 60
Tumors gastrointestinal tract	~19
Healthy population	
Younger 60 years	under 3
Older 60 years	5-6

Pavelka et. al, Revmatologie, 2013

Autoantibodies to Citrullinated Antigens

- Arginyl residues can be post-translationally deaminated by the enzyme peptidyl arginine deiminase (PAD), leading to the generation of citrullinated proteins. Therefore, autoantibodies recognizing citrullinated epitopes are now generally named anti-citrullinated protein antibodies (ACPAs).
- Specificity 97 %, sensitivity 77%



Klareskog, Seminars in Immunology, 2011

2010 ACR/EULAR criteria for RA

2010 ACR/EULAR Classification Criteria for RA

JOINT DISTRIBUTION (0-5)	
1 large joint	0
2-10 large joints	1
1-3 small joints (large joints not counted)	2
4-10 small joints (large joints not counted)	3
>10 joints (at least one small joint)	5
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
SYMPTOM DURATION (0-1)	
<6 weeks	0
≥6 weeks	1
ACUTE PHASE REACTANTS (0-1)	
Normal CRP AND normal ESR	0
Abnormal CRP OR abnormal ESR	1

≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria…

→ **Prospectively** over time (cumulatively)

→ **Retrospectively** if data on all four domains have been adequately recorded in the past

American College of Rheumatology

eular

Pharmacotherapy of RA

I. Nonsteroidal anti-inflammatory drugs (NSAIDs)

II. Disease modifying anti-rheumatic drugs („DMARDs“)

III. Glucocorticoids

IV. Biological therapy

Disease modifying anti-rheumatic drugs („DMARDs“)

- Chemically heterogeneous group of medicaments
- immunosuppressive / immunomodulatory effect
- Don’t influence the synovitis immediately
- Don’t have direct analgestic effect

- Act with time retardation of 3-6 months.
- Decrease disease activity in the majority of pats.
- If administrated early, the may induce remission
- Slow x-ray progression

Row of toxic effects

(oculotoxicity, hepatotoxicity, nefrotoxicity, disturbances of haematopoesis, teratogenic, oncogenic potential)

DMARDs

methotrexate

leflunomide

sulfasalazine

antimalarial drugs

azathioprin

cyclosporin

cyclofosfamide

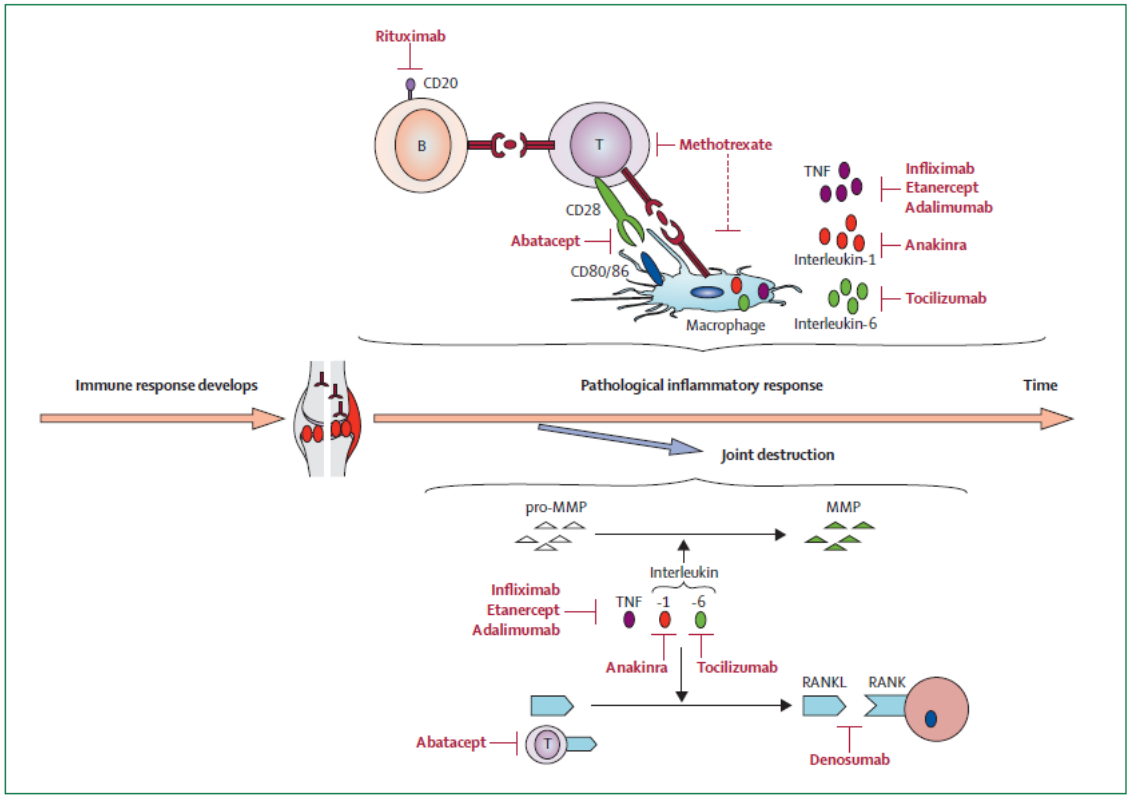
gold salts

Combinations:

- SSZ + MTX + AM
- MTX + CsA
- MTX + leflunomide

Biological therapy of RA

- **Anticytokines**
  - Anti-TNF
    - infliximab, adalimumab, etanercept, certolizumab, golimumab
  - Anti-IL-6
    - tocilizumab
- **Inhibition of co-stimulatory molecules**
  - abatacept
- **Blockade of B-lymphocytes (anti-CD20)**
  - rituximab
- **Small molecules**
  - inhibition of JAK kinase (tofacitinib)



Klareskog, Lancet, 2009