
SCOR
The Art & Science of Risk

Painful Realities

Regina Rosace, M.D., FAAP, DBIM
VP, Medical Director
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rrosace@scor.com

A Joint Approach to Rheumatology

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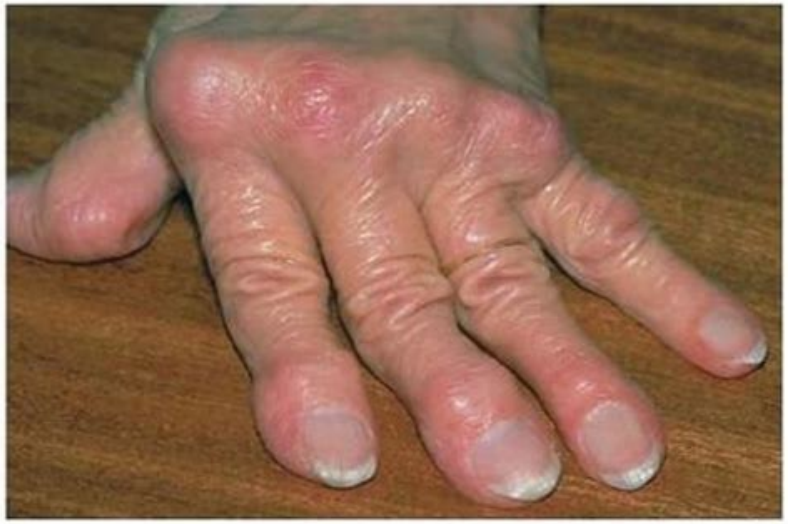
The Art & Science of Risk

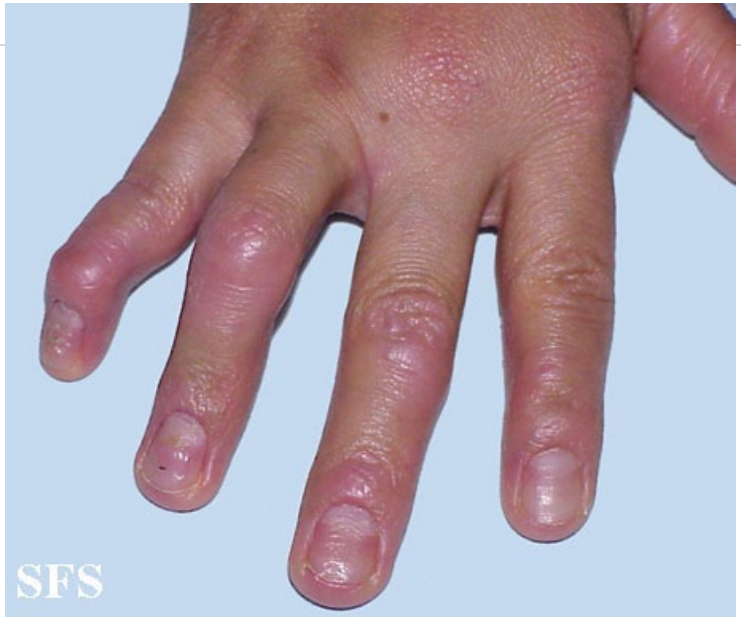
Rheumatology

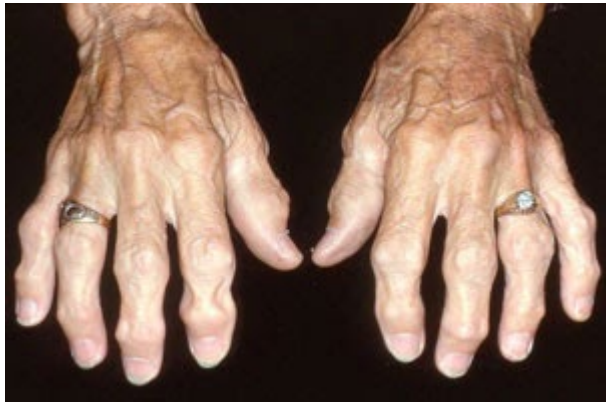
- Epidemiology
- Diseases
- DMARDS

Ready to go…?

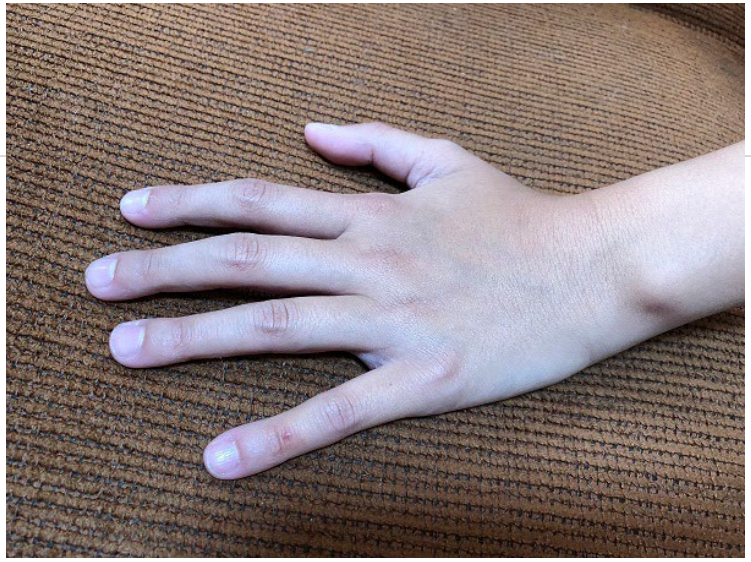
Rheumatology

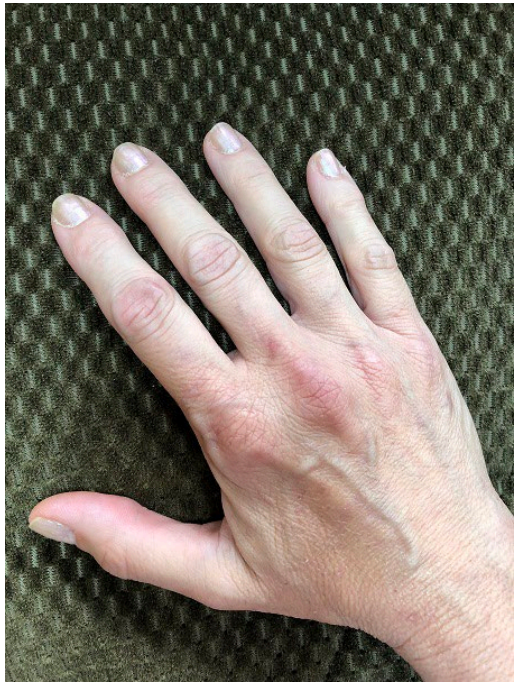




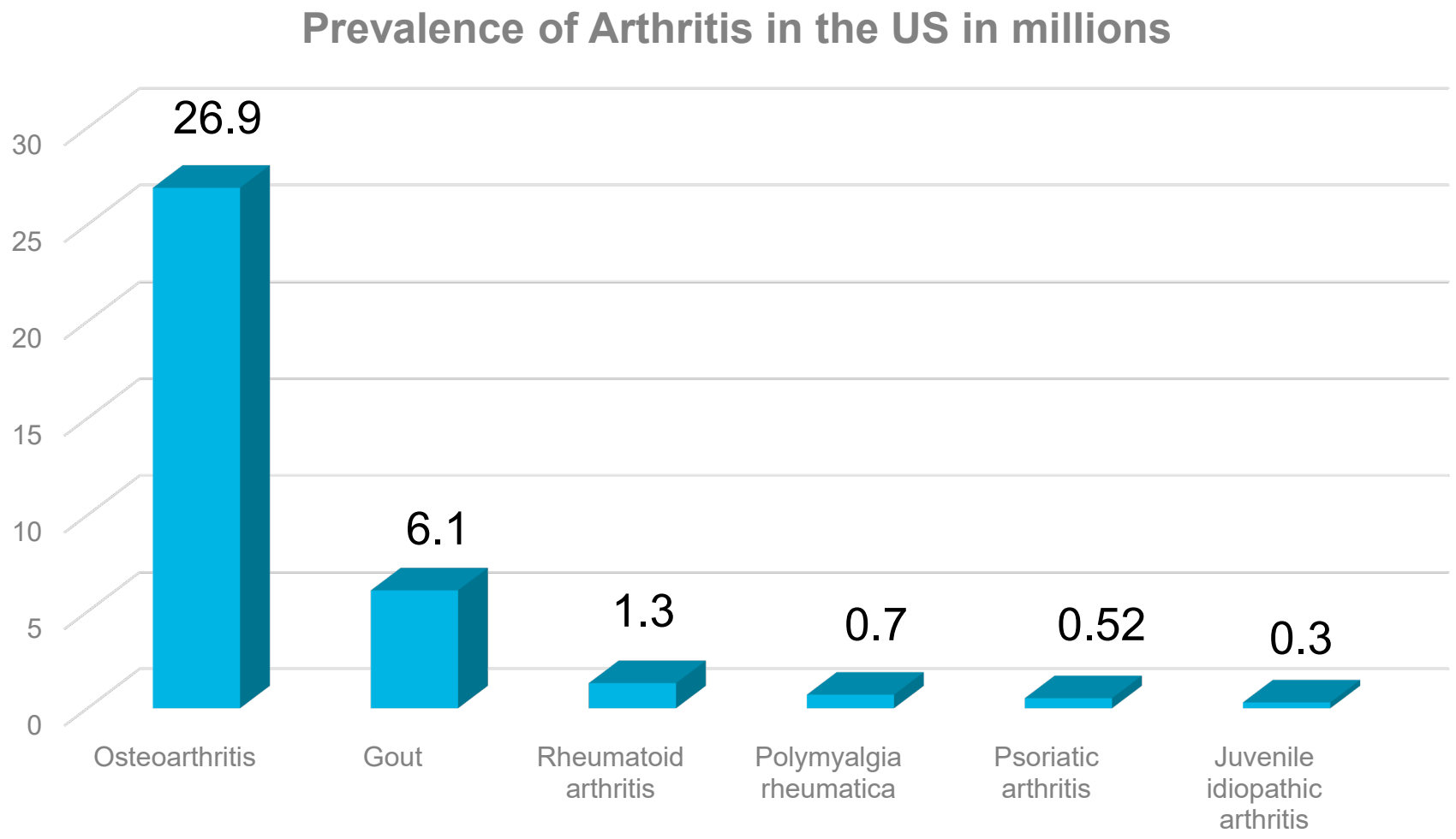


Rheumatology



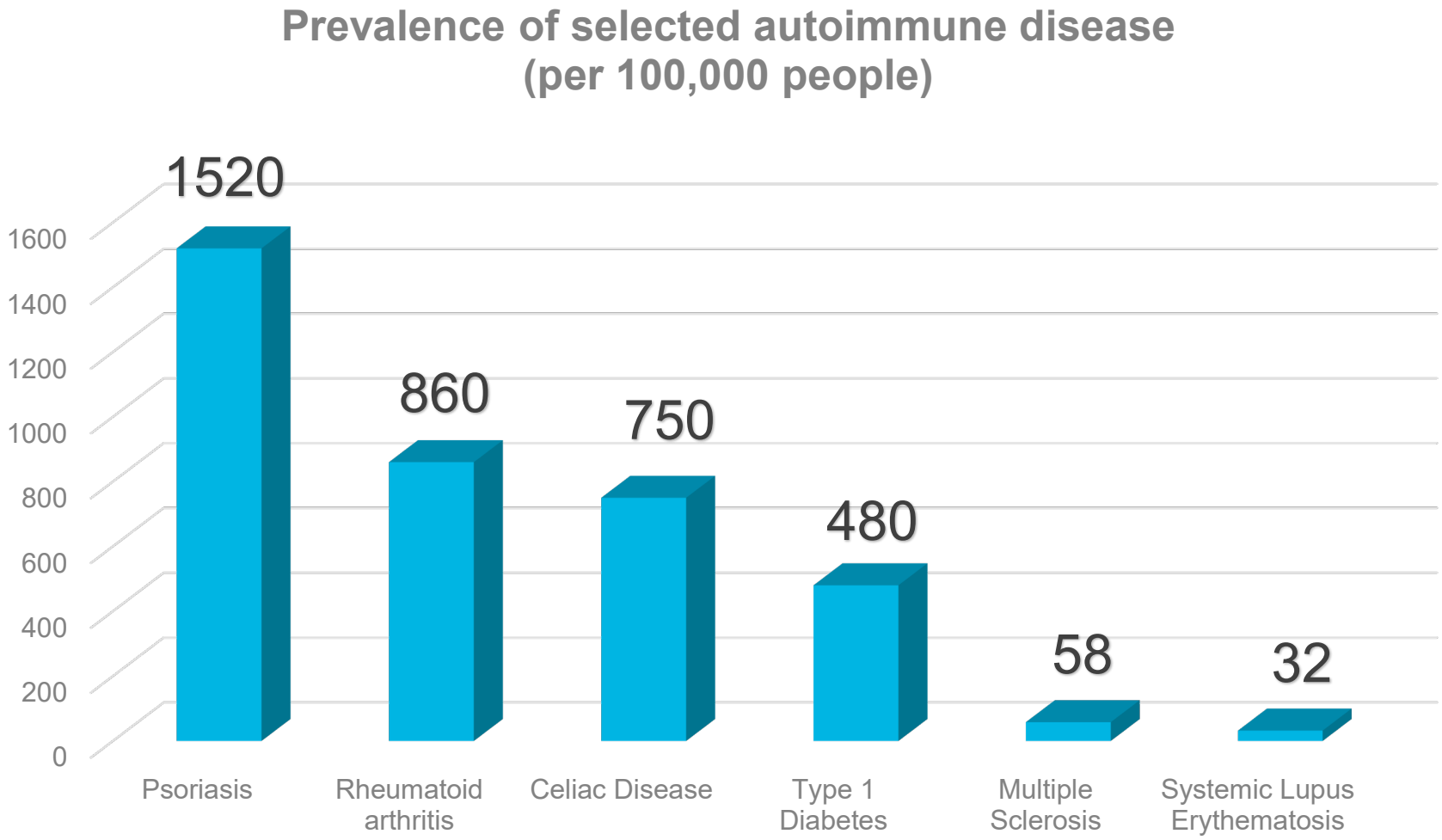


Prevalence of Arthritis in the US



rheumatoidarthritis.net/what-is-ra/ra-statistics/

Prevalence of Selected Autoimmune Diseases

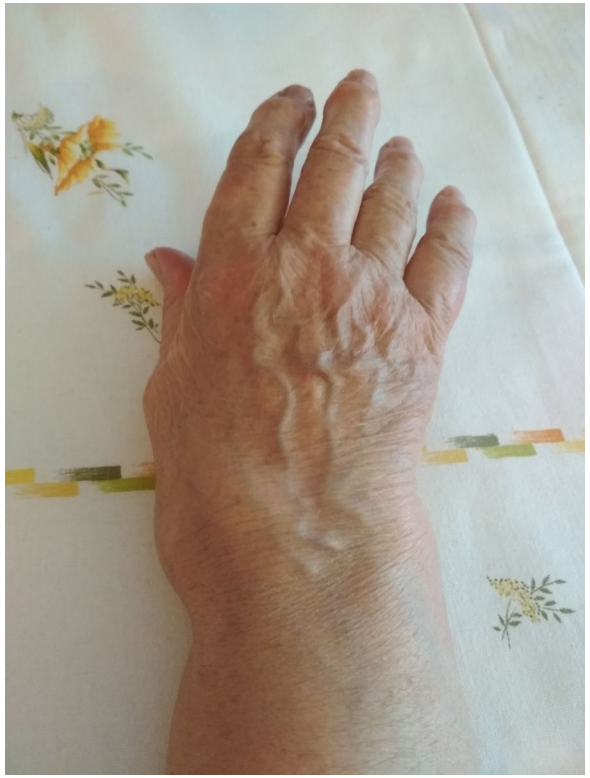


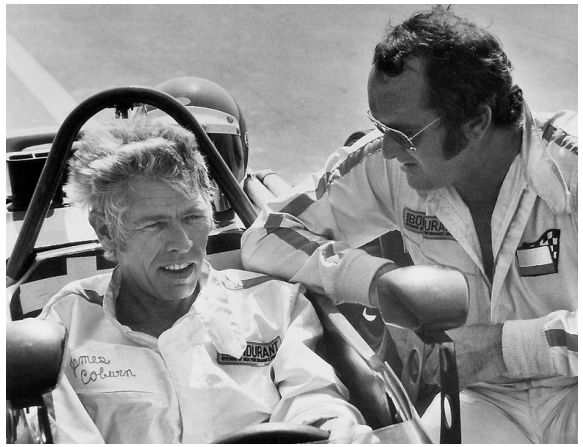
Hayter, Scott M., and Matthew C. Cook. "Updated assessment of the prevalence, spectrum and case definition of autoimmune disease." *Autoimmunity reviews* 11.10 (2012): 754-765.Gelfand, Joel M., et al. "Prevalence and treatment of psoriasis in the United Kingdom: a population-based study." *Archives of dermatology* 141.12 (2005): 1537-1541.

Diseases

- Rheumatoid Arthritis
- Systemic Lupus Erythematosus
- Psoriatic Arthritis
- Undifferentiated Connective Tissue Disease

Rheumatoid Arthritis (RA)





Google images, free to reuse, accessed 7/23/2018.

Rheumatoid Arthritis (RA)

- Systemic, inflammatory, peripheral polyarthritis of unknown etiology
- Multiple different factors (environmental, hormonal, genetic, infectious, etc) interact in genetically susceptible individuals to initiate polyarticular arthritis, which, once started, becomes self perpetuating.
- Leads to deformity through erosion of cartilage and bone
- If untreated or unresponsive to therapy, can lead to loss of physical function and inability to carryout tasks of daily living
- Often difficult to distinguish from other forms of inflammatory polyarthritis
- Distinctive signs of RA , i.e., joint erosions, rheumatoid nodules, are frequently absent on initial presentation.

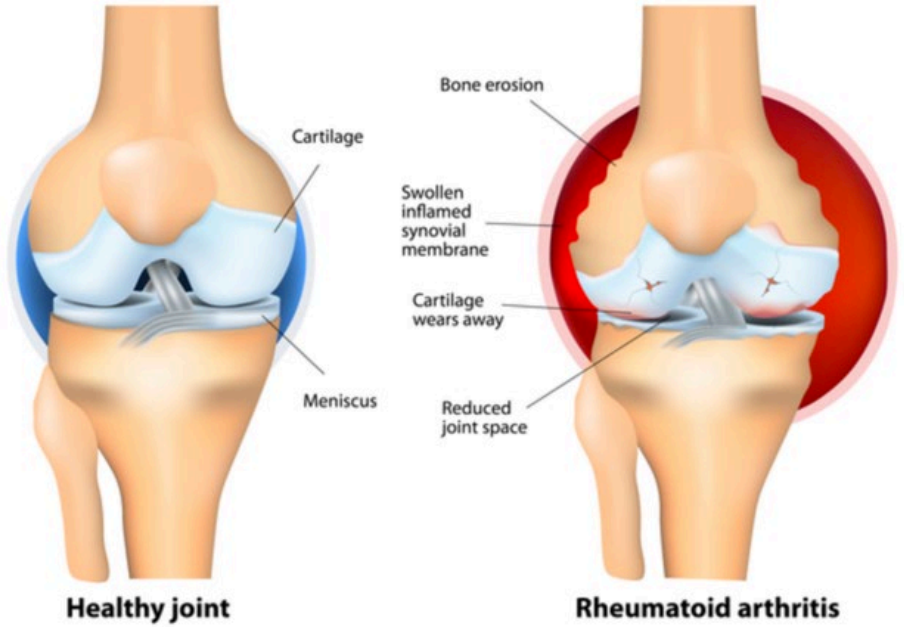
Rheumatoid Arthritis (RA) – Pathogenesis

Characteristics of RA synovitis:

- Hypertrophy of the synovial lining
- Neo-angiogenesis
- Infiltration of immune cells, all types
- Fibrin deposition on synovial surfaces (pannus)

Immune mediators:

- Interleukin (IL)1, 6, 8, 17
- Tumor necrosis factor (TNF) alpha
- COX-2
- Granulocyte-macrophage colony-stimulating factor (GM-CSF)



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Rheumatoid Arthritis (RA) – Epidemiology

- Annual incidence ~ 40 per 100,000
- Prevalence ~ 1% in Caucasians, varies between 0.1% - 5% in different populations
- Peak onset is between ages 50-75
- Lifetime risk of RA in adults 3.6% for women, 1.7% for men
- Women > Men ~ 2-3:1
  - ? Stimulatory effects of estrogen on immune system
  - Often remission in 3rd trimester of pregnancy with post partum flares
  - Males with lower testosterone and DHEA levels, and higher estradiol

www.uptodate.com

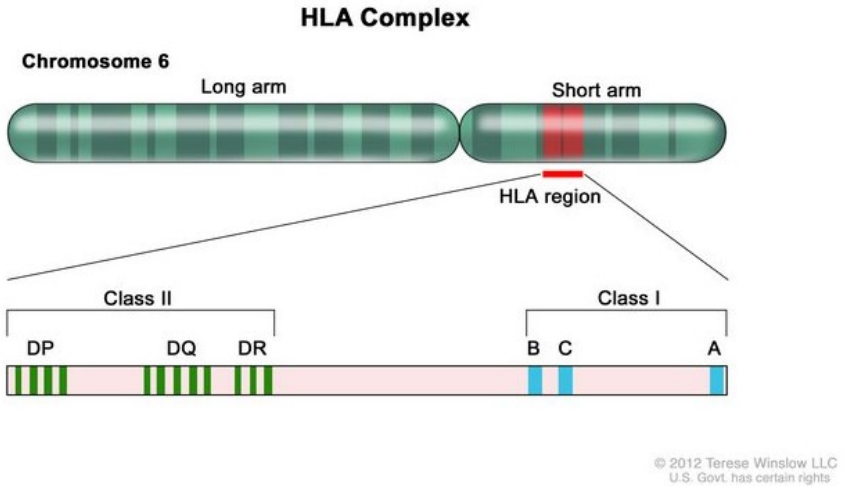
Rheumatoid Arthritis (RA) – Epidemiology

- Genetic susceptibility
  - Concordance for monozygotic 12-15%, vs dizygotic 3.5% twins
  - Standardized incidence ratio for RA in relatives
    - Affected parents → 3
    - Siblings → 4.6
    - Multiplex families → 9.3
    - Spouse → 1.2
- Environmental factors
  - Smoking, overweight, premenopausal status
- HLA and non-HLA susceptibility genes

www.uptodate.com; Frisell T, Saevarsdottir S, Askling J. Family history of rheumatoid arthritis: an old concept with new developments. Nat Rev Rheumatol. 2016 Jun;12(6):335-43.

Rheumatoid Arthritis (RA) – HLA

- Human leukocyte antigens (HLA)
  - Also known as human major histocompatibility complex (human MHC)
  - Gene products are expressed on the surface of white blood cells (WBCs) amongst other cells
  - HLA-DRB1 gene locus important in RA



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NIH National Cancer Institute Visuals Online
(www.cancer.gov)

Rheumatoid Arthritis (RA) – HLA

- HLA region of chromosome 6 contains over 200 genes that have immunologic relevance.
- (HLA)-DRB1 gene is major genetic susceptibility locus for RA
- Epitope = specific target against which an individual antibody binds
- Shared epitope - the portion of the DRB1 molecule (amino acids between 67-74) with a particular amino acid code - Highly associated with RA
  - Certain mutations at the same location are protective for RA
- Other individual amino acid sites (SNPs) within HLA-DRB1 affect risk susceptibility both positively and negatively
- Different HLA patterns are more prevalent in different populations

Rheumatoid Arthritis (RA) – HLA

- Most studies support a correlation between the presence of the shared epitope and the severity of RA, specifically erosive disease.
- In certain populations, specific risk categories and severity categories can be determined based on the amino acids present at locations 11, 13, 70 and 74 of HLA-DRB1.
- This association is highly correlated to ACPA status, which is a better predictor of erosions than HLA alleles or shared epitope status.
- Two copies of the shared epitope are associated with premature mortality and cardiovascular mortality, independent of ACPA status.

2010 ACR/EULAR Criteria

Requirements:

At least one swollen joint, not better explained by another disease, a score of 6 or higher.

SYMPTOM DURATION (AS REPORTED BY PATIENT)	POINTS
< 6 Weeks	0
> 6 Weeks	1

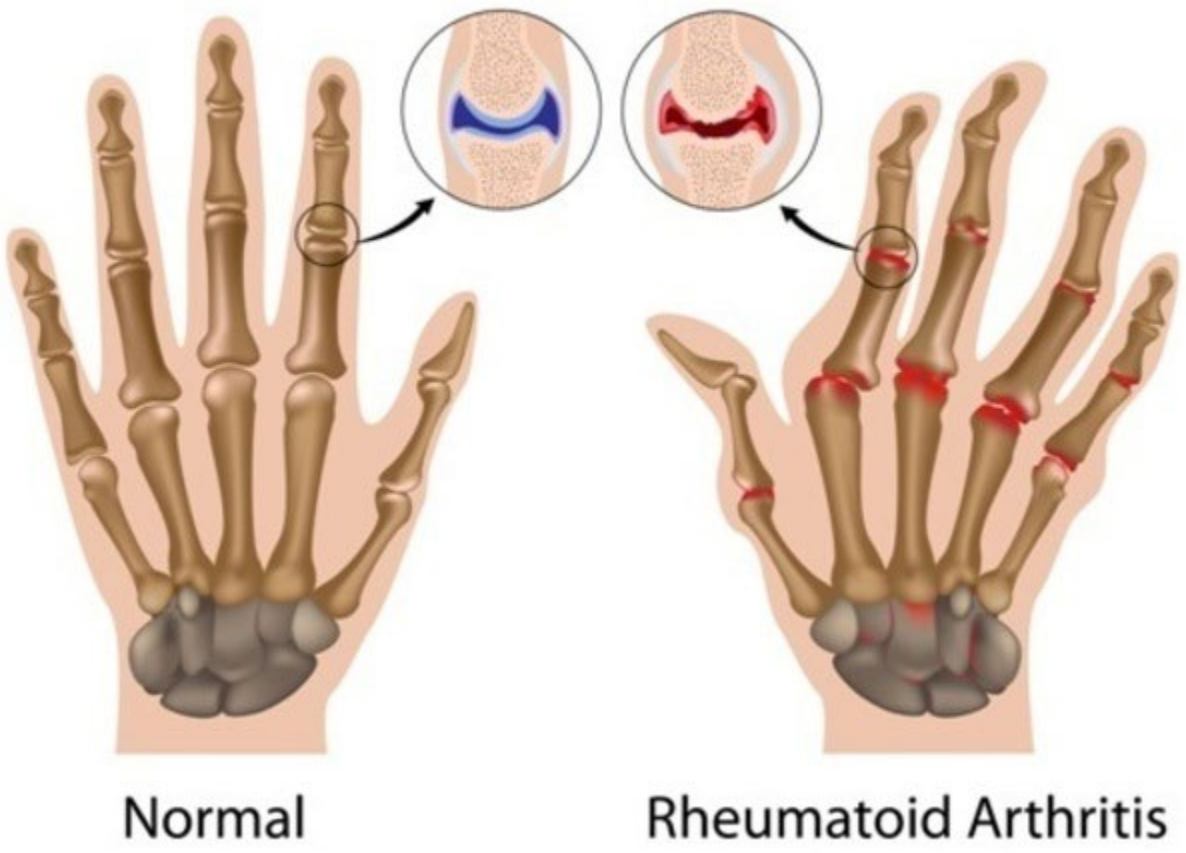
JOINT DISTRIBUTION	POINTS
1 large joint	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)	2
4-10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)	5

SEROLOGY	POINTS
RF- and CCP-	0
Low RF+ or CCP+	2
High RF+ or CCP+	3

ACUTE PHASE REACTANTS	POINTS
Normal ESR or CRP	0
Abnormal ESR or CRP	1

RF: rheumatoid factor. CCP: anti-citrullinated citric peptide. ESR: erythrocyte sedimentation rate. CRP: C-reactive protein. Low: < 3 x upper limit of normal (ULN). High: > 3 x ULN

Small Joint Involvement



Rheumatoid arthritis - Genetics Home ...
ghr.nlm.nih.gov

www.uptodate.com/contents/diagnosis-and-differential-diagnosis-of-rheumatoid-arthritis

Rheumatoid Arthritis (RA) – Differential Diagnosis

Diagnosis	Sex	Age	Lab tests	Comments
Undifferentiated seronegative polyarthritis	F>M	35-65	10-15% RF+	Up to 20% evolve into RA; nearly 50% will go into remission
Psoriatic arthritis	M=F	30-55	<20% RF+	Psoriasis evident in majority; 10% have an RA-like joint distribution
Gout	M>F F	25-70 M >45	95% RF- >95% ↑ serum urate	Intermittent inflammatory arthritis at onset; elevated serum urate and tophi
Erosive inflammatory OA	F>M	>60	RF- (or nl for age)	Chronic polyarthritis affecting PIP and DIP joints; erosions on xrays
Pseudogout	F=M	>60	5-10% RF+	5% with “rheumatoid-like” inflammatory arthritis lasting weeks to months
Reactive arthritis	M>F	16-50	95% RF-; 50-80% HLA B27+	See criteria for spondyloarthropathies; low back pain, ocular, GI and GU symptoms and enthesitis.
Enteropathic arthritis	M=F	All ages	95% RF-	~20% of IBD patients develop this; may have oral ulcers and spondyloarthropathy
SLE	F>M	15-40	10-15% RF+; usually ANA+	Chronic nondeforming inflammatory polyarthritis
Polymyositis/ dermatomyositis	F>M	30-60	95% RF-; 50%ANA+; 70% ↑ CK	Chronic inflammatory polyarthritis uncommonly occurs early in course
Scleroderma	F>M	30-50	95% RF-; >90% ANA+	Chronic inflammatory polyarthritis may predominate early in disease
Sarcoid arthritis	F>M	20-40	25% RF+	15% of those with sarcoidosis develop arthritis
Parvo B19 arthritis	F>M	Any age	<10% RF+; >80% B19 IgM Ab+	Adults with flu-like syndrome, seldom develop “slapped cheek”, arthralgias>arthritis, RA like distribution, <10% develop chronic arthritis
Polymyalgia rheumatica	F>M	>50	90% RF-; >95% ↑↑ ESR	Proximal girdle pain and stiffness without synovitis

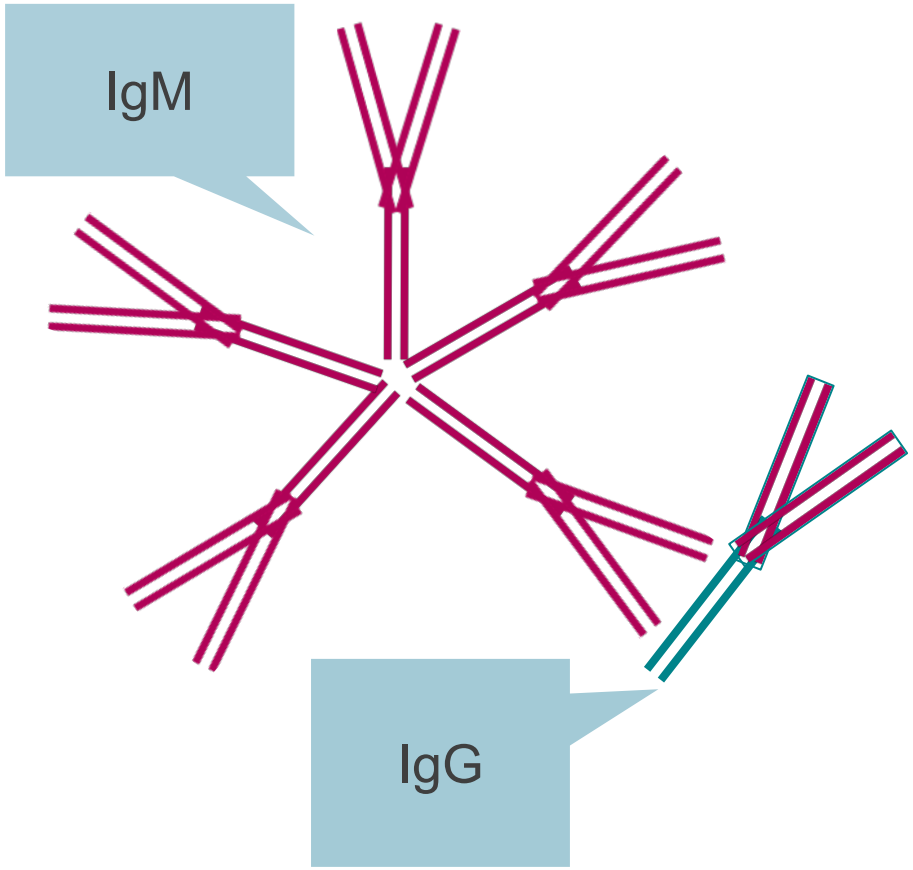
Rheumatoid Arthritis (RA) – Biomarkers

Definition: biologic characteristics that can be objectively measured and serve as indicators of normal or pathologic processes, as measures of the response to therapy, and degree of ongoing disease activity

- Rheumatoid Factors (RF)
- Antibodies to citrullinated peptides (ACPA)
- Acute phase reactants
  - ESR (indirect)
  - CRP (direct)
- Other antibodies and biomarkers may be tested, however there is limited information regarding usefulness.

Rheumatoid Arthritis (RA) – Rheumatoid Factors

- Rheumatoid Factors (RF)
- IgM autoantibodies directed against the Fc portion of IgG



Key points:

- High level, worse prognosis
- Predicts response to rituximab
- May take months to appear
- 20-30% of RA patients remain RF -
- Not specific for RA (other rheum disease, infections, aging)

Rheumatoid Arthritis (RA) – Citrullinated Proteins

- Citrullination or deamination is the conversion of the amino acid arginine in a protein into the amino acid citrulline.
- This occurs by an enzymatic reaction catalyzed by peptidyl arginine deiminase (PAD) enzymes.
  - Strongly activated by smoking
  - Neoantigens vs autoantigens
- Tests may be for ACPA, anti-CCP assay, anti-CCP2
- ACPA+ is ~90% specific for RA
- ACPA+ RA and ACPA- RA appear to be 2 different phenotypes
- ACPA+ : increased risk of radiographically progressive disease (erosions)

Rheumatoid Arthritis (RA) – Treatment Basics

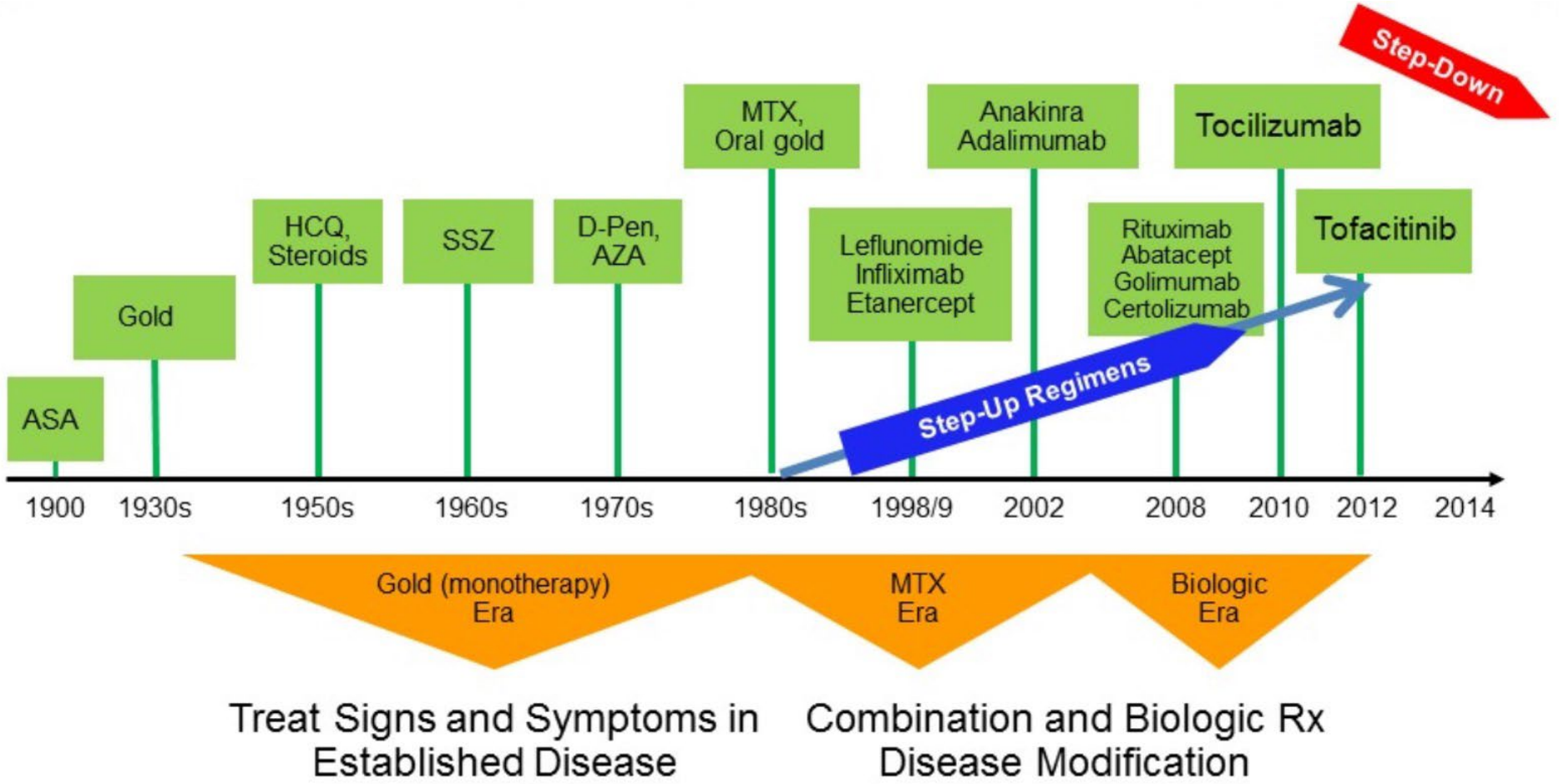
- Treatment by a rheumatologist
- Tight control of disease as early as possible
- Use of disease-modifying antirheumatic drug therapy (DMARD)
- Anti inflammatory meds (NSAIDS and steroids) to control symptoms until DMARDs take effect.
- Manage comorbidities
- Frequent evaluation
- Goal: lowest amount of medication to manage the disease

Rheumatoid Arthritis (RA) – DMARDs

- Before using DMARDs
  - CBC, creatinine, LFTs, screen for Hep B, Hep C and TB
  - Vaccinations, CXR
- Methotrexate (MTX) – single weekly oral dose
  - Monitor for bone marrow, liver and lung toxicity
  - Folic acid supplements
  - Faster onset, comparable efficacy, better long-term tolerance
  - leflunomide (LEF), sulfasalazine (SSZ), hydrochloroquine (HCG)
    - Used singly or in combination
- Tumor necrosis factor (TNF) inhibitor
  - Etanercept (Enbrel)
  - Adalimumab (Humira)
  - Infliximab (Remicade)
  - Biosimilars – “highly similar” in structure and function with “no clinically meaningful differences”
- JAK inhibitor Tofacitinib (Xeljanz)
- Anti-interleukin (IL)-6 receptor Ab Tocilizumab (Actemra)

www.uptodate.com

Rheumatoid Arthritis (RA) – Treatments

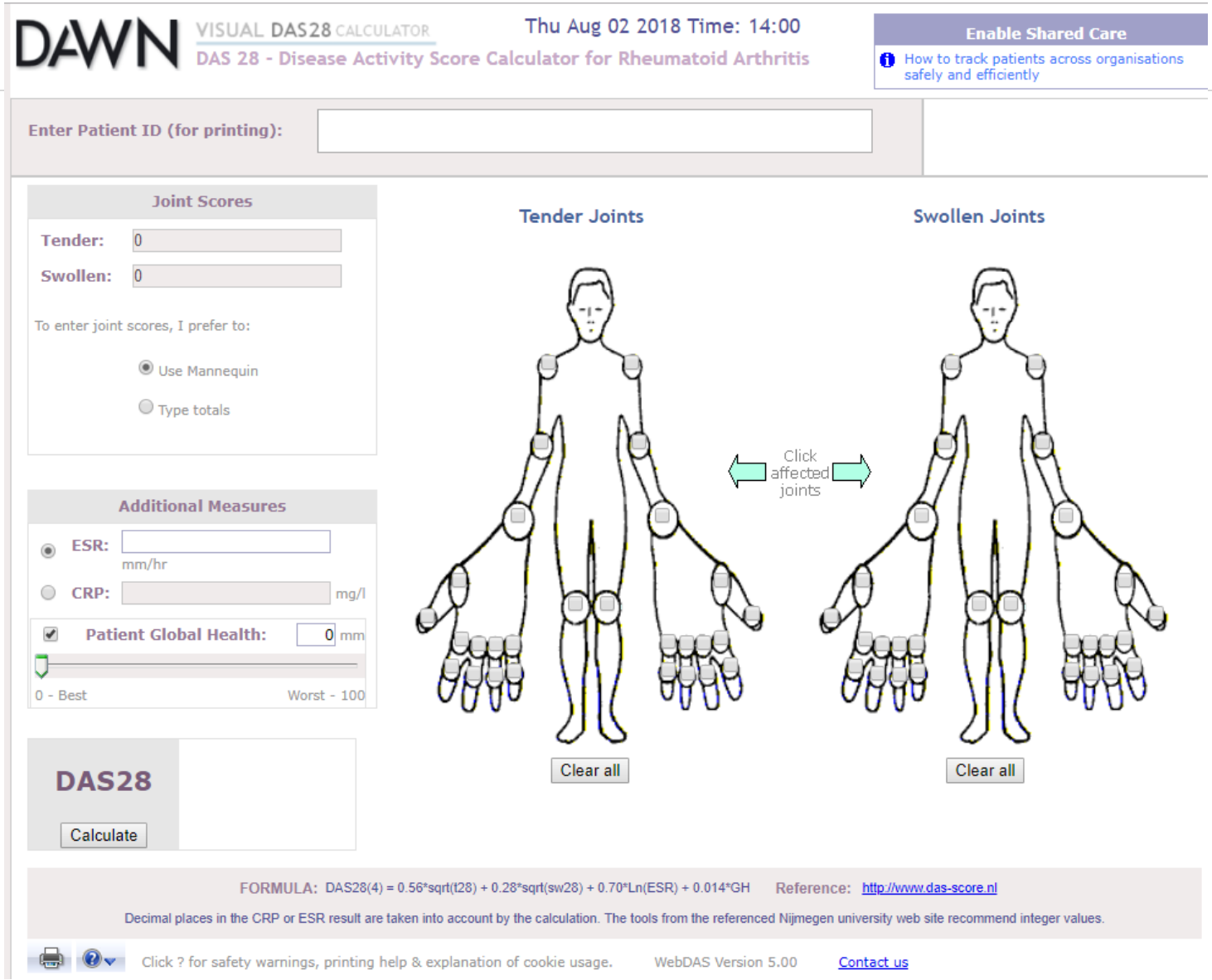


https://rheumnow.com/content/download/evolution-ra-treatment

Rheumatoid Arthritis (RA) – Assessment of Disease Activity

Physical function
- Pain
- Number of inflamed joints
- Extraarticular disease

Calculators
- Disease Activity Score derivative for 28 joints (DAS28)
- Simplified Disease Activity Index (SDAI)
- Clinical Disease Activity Index (CDAI)



www.4s-dawn.com/DAS28/

Rheumatoid Arthritis Clinical Disease Activity Index CDAI

CDAI = SJC + TJC + PGA + EGA

Input:

PGA [ ] [#]

EGA [ ] [#]

Result:

CDAI [ ] [score]

Decimal Precision [1]

Tender Joint Count

Shoulder	Shoulder
Elbow	Elbow
Wrist	Wrist
Right hand MCP 1-5 IP 1, PIP 2-5	Left hand MCP 1-5 IP 1, PIP 2-5
Knee	Knee

TJC [ ] Select All Clear All

Swollen Joint Count

Shoulder	Shoulder
Elbow	Elbow
Wrist	Wrist
Right hand MCP 1-5 IP 1, PIP 2-5	Left hand MCP 1-5 IP 1, PIP 2-5
Knee	Knee

SJC [ ] Select All Clear All

CDAI Interpretation

CDAI <= 2.8:	Remission
CDAI > 2.8 and <= 10:	Low Disease Activity
CDAI > 10 and <= 22:	Moderate Disease Activity
CDAI > 22:	High Disease Activity

www.merckmanuals.com/medical-calculators/RheumatoidArthritisCDAI.htm

Rheumatoid Arthritis (RA) – Morbidities

- Since there is a heterogenous response to treatment, it is clear that RA is a group of diseases with many pathways leading to autoreactivity
- ~15-20% of patients have intermittent disease with a relatively good prognosis
- Comorbidities
  - Affective disorders
  - Osteopenia with increased fracture risk
  - Muscle weakness
  - Skin disease (Rheumatoid nodules)
  - Eye involvement
  - Lung disease
  - Cardiac disease
  - Noncardiac vascular disease
  - Kidney disease
  - Other rheumatic diseases

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Rheumatoid Arthritis (RA) – Mortality

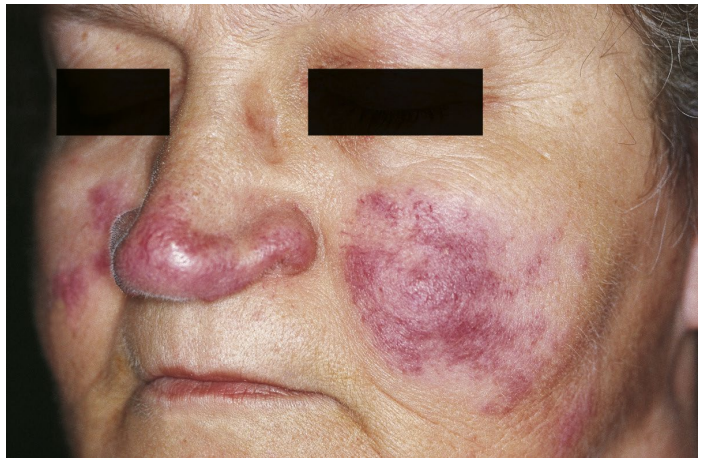
- Infection
- Lymphoproliferative disorders, both leukemia and lymphoma are present twice as often as the general population
- Cardiovascular disease
  - Largely responsible for increased mortality
  - Larger portion of clinically silent CAD
  - Mortality between 1.3-2.0 SMR, most due to CAD
  - Increase in respiratory disease mortality in the Nurses' Health Study

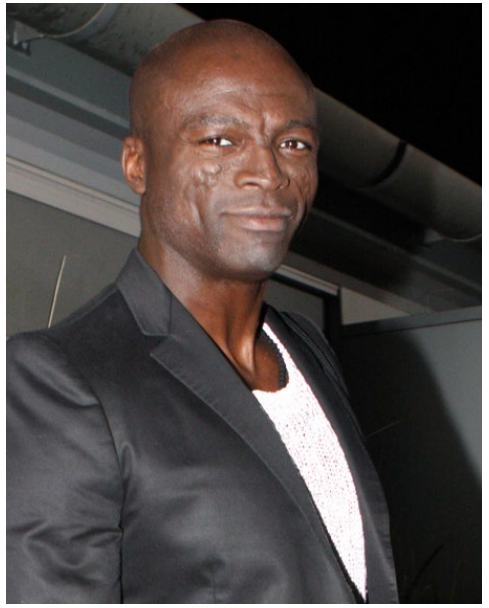
Aviña-Zubieta, J. Antonio, et al. "Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies." *Arthritis Care & Research* 59.12 (2008): 1690-1697.

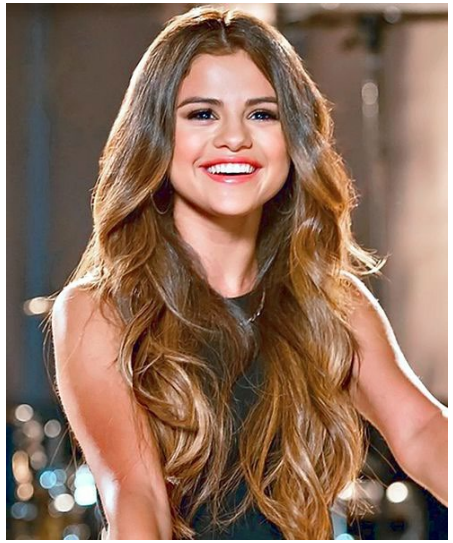
Meune, Christophe, et al. "Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies." *Rheumatology* 48.10 (2009): 1309-1313.

Sparks, Jeffrey A., et al. "Rheumatoid Arthritis and Mortality Among Women During 36 Years of Prospective Follow-Up: Results From the Nurses' Health Study." *Arthritis care & research* 68.6 (2016): 753-762.

Systemic Lupus Erythematosus







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Systemic Lupus Erythematosus (SLE) – Definition

- Chronic inflammatory disease of unknown cause that can affect any organ
- Immunologic abnormalities, especially antinuclear antibodies (ANA)
- Women > men
- Disease course marked by remissions and relapses
- Most common pattern involves constitutional symptoms, with skin, musculoskeletal, hematologic and serologic involvement

https://www.uptodate.com

Systemic Lupus Erythematosus (SLE)

- Constitutional Symptoms
- Arthritis and arthralgias
- Skin and mucus membrane involvement
- Vascular disease
- Renal Involvement
- Pulmonary disease
- Cardiac disease
- Neuropsychiatric involvement
- Ophthalmologic involvement
- Hematologic abnormalities

Mosca, M., et al. "European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies." *Annals of the rheumatic diseases* 69.7 (2010): 1269-1274..

Sensitivity and Specificity

Formula	Definition
Sensitivity Sen = TP / (TP + FN) = TP / Diseased	❖ Percentage of patients with the disease that receive a positive result ❖ Probability of a positive test within a group of patients who have the disease
Specificity Spec = TN / (TN + FP) = TN / Not Diseased	❖ Percentage of patients without the disease that receive a negative result ❖ Probability of a negative test within a group of patients who do NOT have the disease

Utility of Common Rheumatic Tests

Test	Sensitivity	Specificity	in Dx-ing
RF	70%	85	RA
ACPA	65%	98%	RA
ANA	98%	57%	SLE
dsDNA	57%	97%	SLE
Sm	30%	97%	SLE
Uric Acid	63%	96%	Gout
HLA-B27	80-95%	94%	AS
ESR/CRP	50-60%	<40%	RA

http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/rheumatology/laboratory-evaluation-rheumatic-diseases/

Systemic Lupus Erythematosus (SLE) – Lab Tests

- CBC
- Creatinine
- Urinalysis
- ANA
- Antiphospholipid antibodies
- C3 and C4
- ESR/CRP
- Urine protein to creatinine ratio

- Anti-dsDNA
- Anti-Sm antibodies

- Anti-Ro/SSA
- Anti-La/SSB

- Anti-U1 RNP antibodies

May reveal leukopenia, mild anemia or thrombocytopenia. Elevated creatinine or abnormal UA may suggest renal involvement. The last 5 tests support the diagnosis of SLE if abnormal: +ANA, low C3, C4, elevated ESR/CRP, elevated protein/creatinine ratio

Dilution of ANA	1:40	1:80	1:160	1:320
% of healthy individuals	31.7%	13.3%	5.0%	3.3%

Both highly specific for SLE. Anti-Sm Abs lack sensitivity

Present in 20-30% of patients with SLE, but more commonly associated with Sjogren's syndrome.

Present in 25% of patients with SLE, but highly associated with mixed connective tissue disease (MCTD).

Mosca, M., et al. "European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies." *Annals of the rheumatic diseases* 69.7 (2010): 1269-1274..
Tan, E. M., et al. "Range of antinuclear antibodies in "healthy" individuals." *Arthritis & Rheumatism* 40.9 (1997): 1601-1611.

Systemic Lupus Erythematosus (SLE) – Imaging and Biopsy

- Not routine but may be clinically appropriate
  - CXR
  - Xrays of joints
  - US of joints or kidneys
  - ECHO
  - CT
  - MRI
- Biopsy of involved organ

Systemic Lupus Erythematosus (SLE) – Criteria

2012 SLICC SLE CRITERIA

Criteria are cumulative and need not be present concurrently. See notes below.

SLICC† Classification Criteria for Systemic Lupus Erythematosus

RheumTutor.com

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

Clinical Criteria

1. Acute Cutaneous Lupus*
2. Chronic Cutaneous Lupus*
3. Oral or nasal ulcers *
4. Non-scarring alopecia
5. Arthritis *
6. Serositis *
7. Renal *
8. Neurologic *
9. Hemolytic anemia
10. Leukopenia *
11. Thrombocytopenia (<100,000/mm^3)

Immunologic Criteria

1. ANA
2. Anti-DNA
3. Anti-Sm
4. Antiphospholipid Ab *
5. Low complement (C3, C4, CH50)
6. Direct Coombs' test (do not count in the presence of hemolytic anemia)

†SLICC: Systemic Lupus International Collaborating Clinics
* See notes for criteria details

Petri M, et al. Arthritis and Rheumatism. Aug 2012

2019 ACR/EULAR criteria

New ACR and EULAR criteria for classification of SLE

All patients classified as having systemic lupus erythematosus must have a serum titer of antinuclear antibody of at least 1:80 on human epithelial-2-positive cells or an equivalent positive test. In addition, a patient must tally at least 10 points from these criteria. A criterion is not counted if it has a more likely explanation than SLE. Occurrence of the criterion only once is sufficient to tally the relevant points, and the time when a patient is positive for one criterion need not overlap with the time when the patient is positive for other criteria. SLE classification requires points from at least one clinical domain, and if a patient is positive for more than one criterion in a domain only the criterion with the highest point value counts:

Clinical domains	Points
Constitutional domain	
Fever	2
Cutaneous domain	
Nonscarring alopecia	2
Oral ulcers	2
Subacute cutaneous or discoid lupus	4
Acute cutaneous lupus	6
Arthritis domain	
Synovitis in at least two joints or tenderness in at least two joints, and at least 30 min of morning stiffness	6
Neurologic domain	
Delirium	2
Psychosis	3
Seizure	5
Serositis domain	
Pleural or pericardial effusion	5
Acute pericarditis	6
Hematologic domain	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Renal domain	
Proteinuria >0.5g/24 hr	4
Class II or V lupus nephritis	8
Class III or IV lupus nephritis	10

Immunologic domains	Points
Antiphospholipid antibody domain	
Anticardiolipin IgG >40 GPL or anti-β2GP1 IgG >40 units or lupus anticoagulant	2
Complement proteins domain	
Low C3 or low C4	3
Low C3 and low C4	4
Highly specific antibodies domain	
Anti-dsDNA antibody	6
Anti-Smith antibody	6

MDedge News

Source: Dr. Johnson

https://www.mdedge.com/rheumatology/article/168702/lupus-connective-tissue-diseases/new-sle-classification-criteria-reset

Systemic Lupus Erythematosus (SLE) – Treatment

- Frequent monitoring to assess for flares and progression
- Predicting flares: ↑ serum titer of anti-dsDNA Ab, ↓ complement levels
- Sun protection
- Diet and nutrition, including Vitamin D supplementation
- Exercise
- Smoking cessation
- Immunizations
- Treating comorbid conditions
  - Cardiovascular disease
  - Antiphospholipid syndrome
  - Osteoporosis
- Avoidance of sulfonamides and minocycline
- Pregnancy counseling
- Hydroxychloroquine (Plaquenil) or chloroquine (Aralen)
- Prednisone
- Other meds, including: methotrexate, azathioprine, cyclophosphamide, rituximab, belimumab, etc.

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Systemic Lupus Erythematosus (SLE) – Prognosis

- Renal disease
- Hypertension
- Male
- Low socioeconomic status
- Antiphospholipid antibodies
- High disease activity

Systemic Lupus Erythematosus (SLE) – Mortality

- Overall increased SMR ~ 3
- ↑ death due to cardiovascular disease, infection and renal disease
- No ↑ in mortality from malignancies overall, but increased incidence of non-Hodgkin lymphoma
  - Often aggressive diffuse large B-cell lymphoma
- Highest mortality risk is in those with renal disease (SMR 7.9)

Yurkovich, Marko, et al. "Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies." *Arthritis care & research*66.4 (2014): 608-616.

Psoriatic Arthritis (PsA)

www.enbrel.com/psoriatic-arthritis/phil-mickelsons-story

Psoriatic Arthritis (PsA) – Definition

- Inflammatory arthritis associated with psoriasis
- Initially thought to be a variant of RA, but now considered a distinct clinical entity
- Usually seronegative for rheumatoid factor (RF)
- Pain and stiffness in affected joints, accentuated with prolonged immobility and relieved with motion
- ~70% of patients have previous history of psoriasis
- Men = women
- ~31% of patients with psoriasis have PsA after 30 years
- Prevalence between 14-30% of patients with psoriasis
- Present with joint pain and morning stiffness
- Often asymmetric distribution
- Joints less tender than with RA

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Psoriatic Arthritis (PsA) – Classic Patterns

- Distal arthritis – DIP joint involvement
- Asymmetric oligoarthritis – less than 5 small or large joints
- Symmetric polyarthritis – difficult to distinguish from RA
- Arthritis mutilans – deforming and destructive arthritis
- Spondyloarthritis (SpA) – includes both sacroiliitis and spondylitis

Rheum Dis Clin North Am. 2015 November ; 41(4): 545–568

Psoriatic Arthritis (PsA) – Current Descriptions

- Peripheral arthritis
- Axial disease
- Enthesitis – inflammation at the insertion site of tendons, ligaments or synovium
- Tenosynovitis
- Dactylitis – sausage digit
- Nail lesions – occur in 80-90% of patients with PsA
- Ocular involvement – 7-10% of patients with PsA

Rheum Dis Clin North Am. 2015 November ; 41(4): 545–568

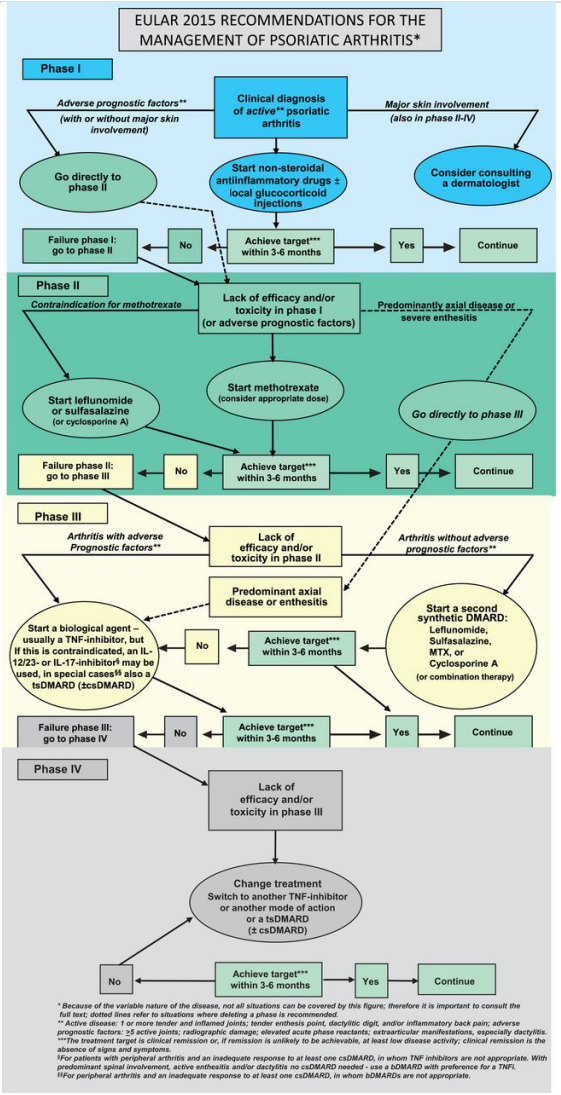
Psoriatic Arthritis (PsA) – Lab and Imaging Findings

- No characteristic lab values/findings and no characteristic HLA types
- Radiographic findings:
  - Erosive changes and new bone formation
  - Lysis of terminal phalanges
  - Fluffy periostitis at the site of enthesitis
  - Gross destruction with “pencil in cup” appearance
  - MRI can often be helpful
- Diagnostic criteria nor criteria for remission not well defined:
  - Psoriasis
  - Inflammatory arthritis in a typical pattern
  - Not better explained by another diagnosis

Psoriatic Arthritis (PsA) – Non-topical Treatments

The EULAR 2015 algorithm for treatment of PsA with pharmacological non-topical treatments.

- bDMARD, biological DMARD
- csDMARDs, conventional synthetic DMARD
- DMARD, disease-modifying antirheumatic drug
- EULAR, European League Against Rheumatism
- IL, interleukin
- MTX, methotrexate
- PsA, psoriatic arthritis
- TNFi, tumour necrosis factor inhibitor
- tsDMARD, targeted synthetic DMARD



L Gossec et al. Ann Rheum Dis doi:10.1136/annrheumdis-2015-208337

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Psoriatic Arthritis (PsA) – Treatment

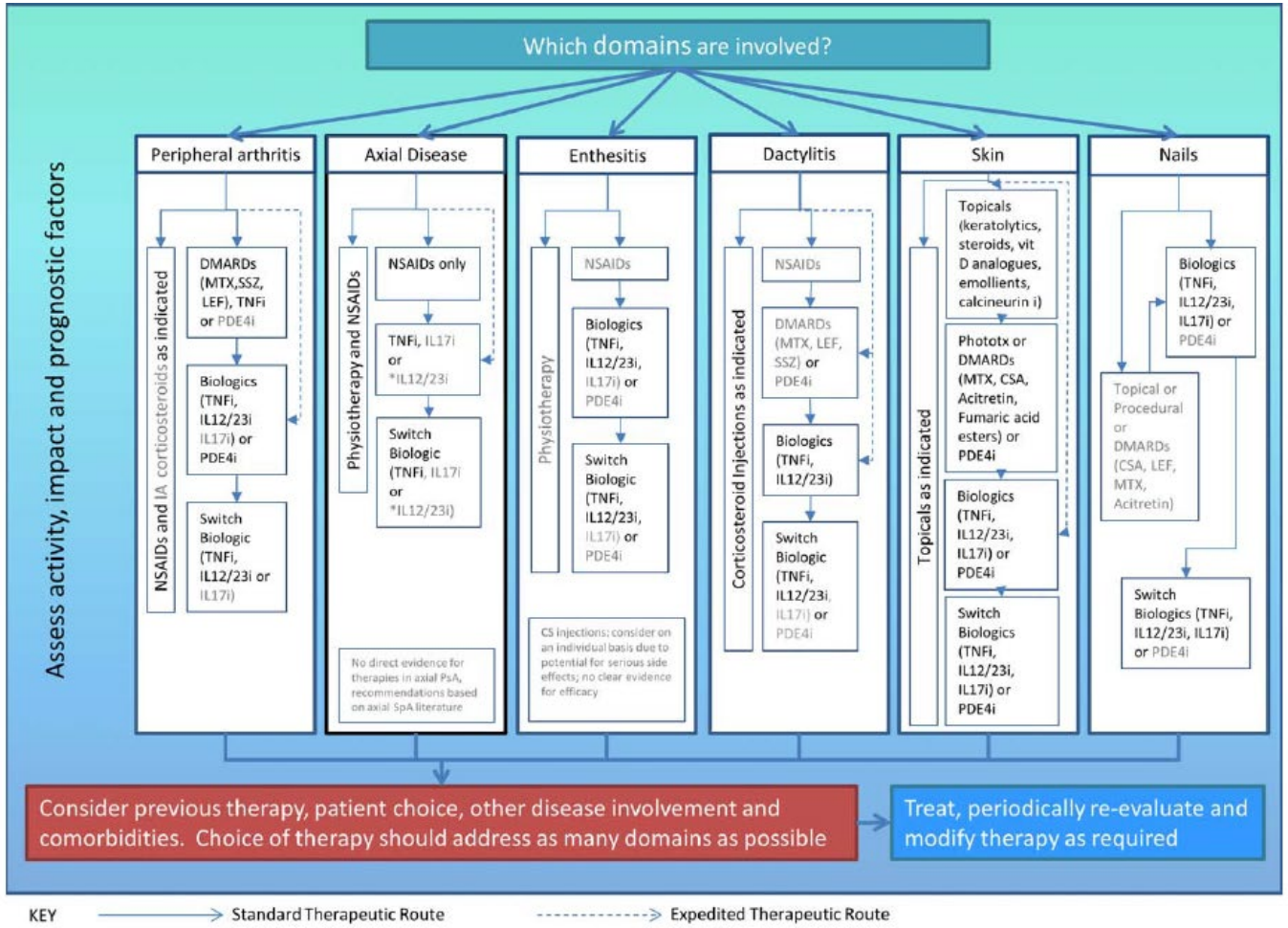

Figure 1. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis treatment schema for active psoriatic arthritis (PsA). Light text identifies conditional recommendations for drugs that do not currently have regulatory approvals or for which recommendations are based on abstract data only. NSAIDs = nonsteroidal antiinflammatory drugs; IA = intraarticular; DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide; TNFi = tumor necrosis factor inhibitor; PDE-4i = phosphodiesterase 4 inhibitor (apremilast); IL-12/23i = interleukin-12/23 inhibitor; SpA = spondyloarthritis; CS = corticosteroid; vit = vitamin; phototx = phototherapy; CSA = cyclosporin A.

Coates, Laura C., et al. "Group for research and assessment of psoriasis and psoriatic arthritis 2015 treatment recommendations for psoriatic arthritis." *Arthritis & rheumatology* 68.5 (2016): 1060-1071

Undifferentiated Connective Tissue Disease (UCTD) – Definition

Undifferentiated rheumatic diseases and overlap syndromes

Name	Synonyms
Mixed connective tissue disease	
Lupus-scleroderma-polymyositis-rheumatoid arthritis	
Undifferentiated systemic rheumatic disease	(Early) undifferentiated connective tissue, collagen vascular, or autoimmune disease
Nonclassic systemic lupus erythematosus	Lupus-like, lupus variant, or near, borderline, latent, incipient, incomplete, possible, or probable lupus[1,2]
Nonclassic rheumatoid arthritis	Palindromic rheumatism[3], pre-rheumatoid arthritis, early rheumatoid arthritis
Nonclassic scleroderma	Prescleroderma[4]
Overlap syndromes	
Rheumatoid arthritis-lupus	Rhupus
Scleroderma-polymyositis/dermatomyositis	
Scleroderma-lupus	
Scleroderma-rheumatoid arthritis	
Other scleroderma overlaps	
Polymyositis overlaps	
Juvenile idiopathic arthritis-lupus	
Sjögren's syndrome overlaps	
Other	
Undifferentiated polyarthritis syndrome	
Undifferentiated spondyloarthritis	

References:

1. Greer JM, Panush RS. Incomplete lupus erythematosus. Arch Intern Med 1989; 149:2473.
2. Lambers WM, Westra J, Jonkman MF, et al. Incomplete lupus erythematosus: What remains after application of the American College of Rheumatology and systemic lupus international collaborating clinics criteria? Arthritis Care Res 2020; 72:607.
3. Ellingwood I, Schieir O, Valois MF, et al. Palindromic rheumatism frequently precedes early rheumatoid arthritis. Results from an incident cohort. ACR Open Rheumatology 2019; 1:614.
4. Valentini G, Pope JE. Undifferentiated connective tissue disease at risk for systemic sclerosis: Which patients might be labeled prescleroderma? Autoimmunity Rev 2020; 19:102659.

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Undifferentiated Connective Tissue Disease (UCTD)

- Account for 15-25% of tertiary rheumatology referrals
- Present with incompletely expressed rheumatic disease and nonspecific autoantibodies
- If differentiation is to occur, usually within 5-10 years of presentation
- Although studies show various numbers:
  - ~30% evolve to a well-defined syndrome
  - ~ 10-15% resolve
  - Remaining continue as UCTD
  - ~ 20% that remain will have pulmonary involvement

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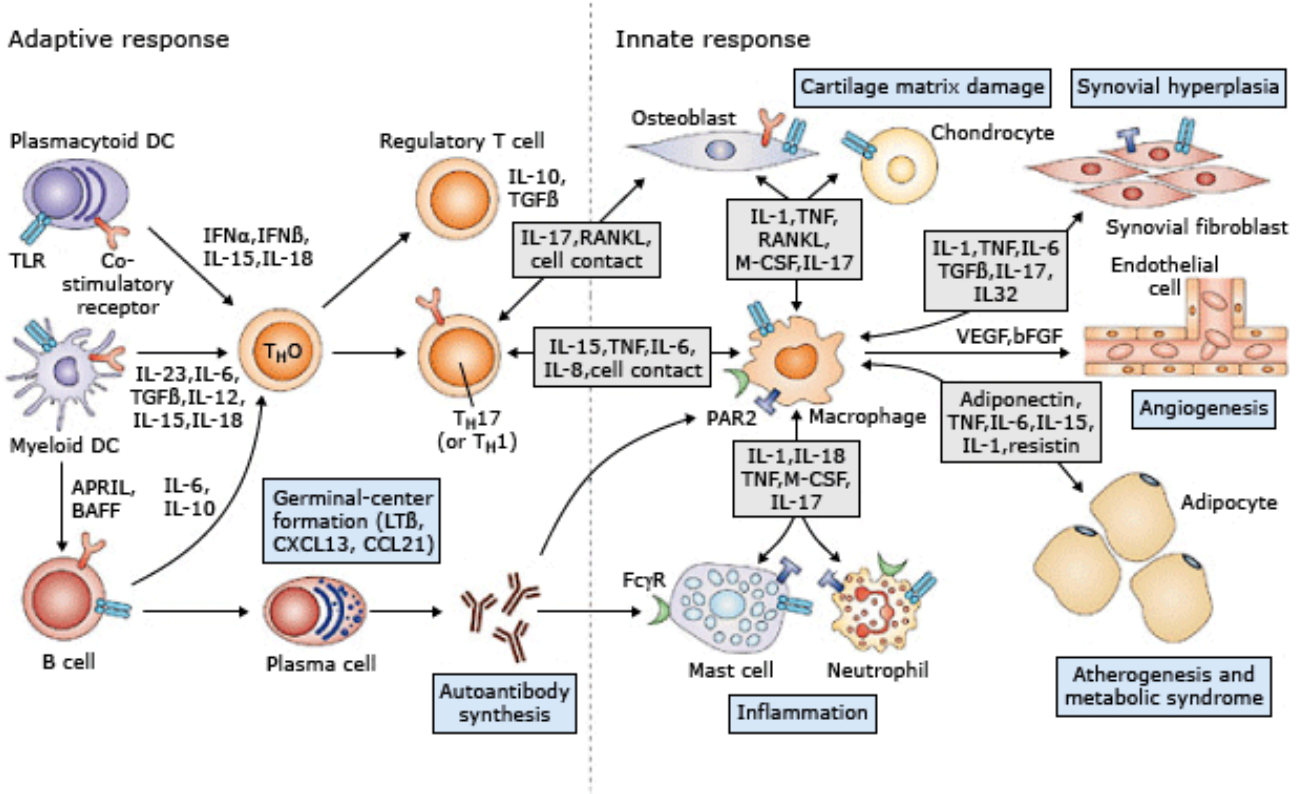
Cytokines

- Proteins that regulate the immune system and participate in intercellular communications
- Immune mediated diseases involve the abnormal regulation of cytokines

An overview of the cytokine-mediated regulation of synovial interactions



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Cytokines

- T cell cytokines
  - Interferon-gamma (IFN-γ)
  - Granulocyte macrophage colony-stimulating factor (GM-CSF)
- Macrophage and fibroblast cytokines
  - Interleukin-1 (IL-1)
  - Tumor necrosis factor-alpha (TNF-α)
  - Interleukin-6 (IL-6)
- SLE
  - Low TNF-α
  - High IFN-α, most is acid labile
  - IL-2
  - IL-6

Big players in RA

Disease-Modifying Antirheumatic Drugs (DMARDS)

- Methotrexate
- Hydrochloroquine
- Sulfasalazine
- Leflunomide
- Glucocorticoids
- Cyclophosphamide
- Azathioprine
- Cyclosporine
- Belimumab - monoclonal Ab that inhibits B lymphocyte stimulator for SLE
- Anti TNF products
  - Adalimumab - Humira
  - Infliximab – Remicade, Inflectra, Remsima, Flixabi
  - Etanercept – Enbrel, Benepali
  - Golimumab - Simponi
  - Certolizumab – Cimzia
- Anakinra – recombinant human interleukin-1 receptor antagonist
- Tocilizumab – Interleukin-6 receptor antagonist

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Disease-Modifying Antirheumatic Drugs (DMARDS)

Relationship between mechanism of action and licensed indication: current systemic therapies licensed for psoriasis, psoriatic arthritis, or rheumatoid arthritis in the European Union

Category	Molecule	Mechanism of action	Indication		
			Psoriasis	Psoriatic arthritis	Rheumatoid arthritis
Synthetic DMARDs/other	Methotrexate	Anti-metabolite [106]	X	X	X
	Leflunomide	Anti-metabolite [106]		X	X
	Corticosteroids	Direct and indirect immune mechanisms [107]		X	X
	Hydroxychloroquinine	Interference with antigen processing [108]			X
	Sulfasalazine	Anti-inflammatory and antimicrobial [109]			X
	Minocycline	Metalloproteinase inhibitor [110]			X
	Cyclosporine	T-cell-activation inhibitor [111]	X		X
	Acitretin	Activates retinoid acid receptor subtypes [112]	X		
	Fumaric acid	Modulator of intracellular glutathione [113]	X		
	Apremilast	PDE4 inhibitor [114]	X	X	
Biologics	Etanercept	Recombinant human TNF-receptor fusion protein [31]	X	X	X
	Infliximab	Humanized chimeric anti-TNF-α monoclonal antibody [31]	X	X	X
	Adalimumab	Human monoclonal anti-TNF-α antibody [31]	X	X	X
	Golimumab	TNF-α blocker [31]		X	X
	Certolizumab	TNF-α blocker [31]		X	X
	Ustekinumab	Anti-IL-12/IL-23p40 monoclonal antibody [31]	X	X	
	Anakinra	IL-1-receptor antagonist [31]			X
	Abatacept	T-cell-activation inhibitor [31]			X
	Rituximab	CD20 inhibitor [31]			X
	Tocilizumab	IL-6-receptor inhibitor [31]			X
	Secukinumab	IL-17A antagonist [115]	X	X	

CD, cluster of differentiation; DMARD, disease-modifying anti-rheumatic drug; IL, interleukin; TNF, tumor necrosis factor.

Coates, Laura C., et al. "Psoriasis, psoriatic arthritis, and rheumatoid arthritis: is all inflammation the same?." *Seminars in arthritis and rheumatism*. Vol. 46. No. 3. WB Saunders, 2016.

Disease-Modifying Antirheumatic Drugs (DMARDS)

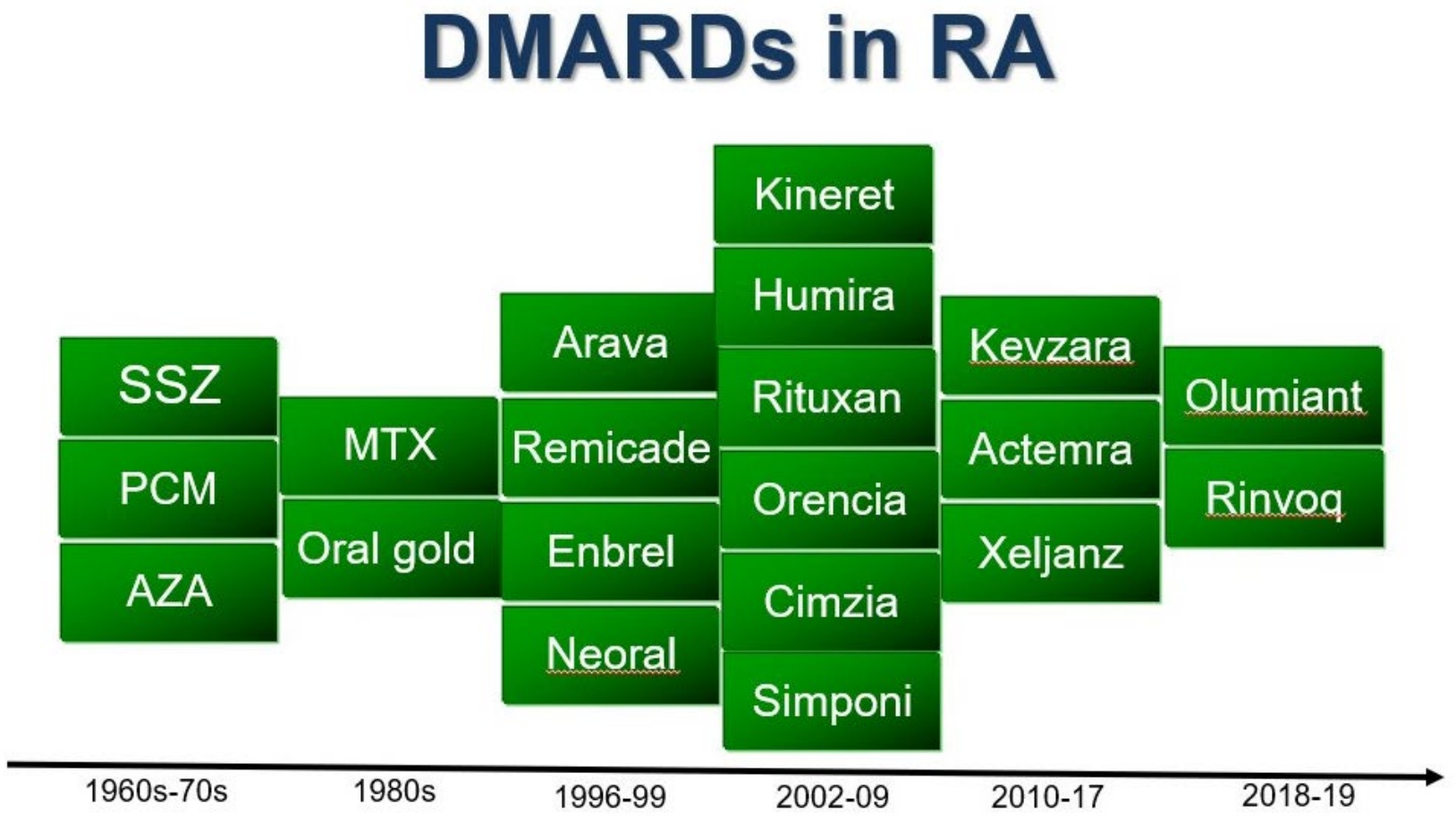
Selected novel non-biologic agents approved in the USA and in development for the treatment of psoriasis, psoriatic arthritis, and rheumatoid arthritis

Molecule	Target/mechanism of action	Indication (FDA approved) or clinical phase		
		Psoriasis	Psoriatic arthritis	Rheumatoid arthritis
Tofacitinib	JAK-1/3 inhibitor	Phase 3	Phase 3	X
Apremilast	PDE4 inhibitor	X	X	–
Baricitinib	JAK 1/JAK 2 inhibitor	–	–	Phase 3
Ixekizumab		Phase 3	Phase 3	Phase 2
CF101	A3 adenosine receptor agonist	Phase 2/3	–	Phase 2
AN2728 (topical)	PDE4 inhibitor	Phase 2	–	–
ASP-015K	JAK inhibitor	Phase 2	–	Phase 3
ACT-128800	S1P receptor agonist	Phase 2	–	–
VB-201	TLR-2/TLR-4 antagonist	Phase 2	–	–
GLPG0634	JAK-1 inhibitor	–	–	Phase 2
CCX354-C	CCR1 antagonist	–	–	Phase 2

This table is not intended to be an exhaustive list of all novel non-biologic molecules in rheumatoid arthritis, psoriatic arthritis and psoriasis.
CCR, chemokine receptor; FDA, Food and Drug Administration; JAK, Janus kinase; PDE4, phosphodiesterase type 4; TLR, toll-like receptor improve efficacy.

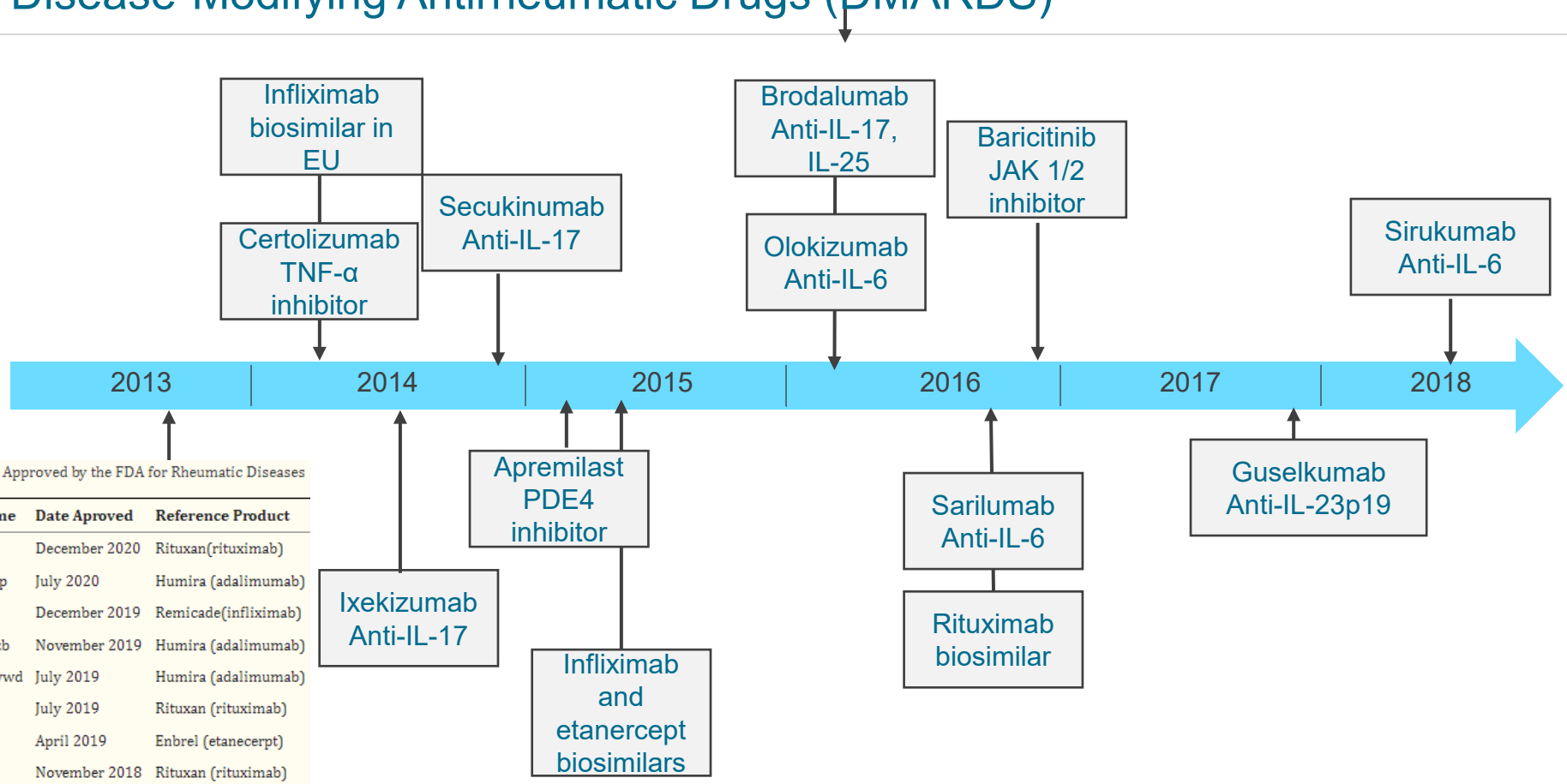
Coates, Laura C., et al. "Psoriasis, psoriatic arthritis, and rheumatoid arthritis: is all inflammation the same?." *Seminars in arthritis and rheumatism*. Vol. 46. No. 3. WB Saunders, 2016.

Disease-Modifying Antirheumatic Drugs (DMARDS)



https://rheumnow.com/news/cost-effective-use-biological-and-targeted-synthetic-dmards?utm_content=buffer1cb40&utm_medium=social&utm_source=twitter.com&utm_campaign=buffer

Disease-Modifying Antirheumatic Drugs (DMARDS)



Up to Date 15 Biosimilars Have Been Approved by the FDA for Rheumatic Diseases

Comercial Name	Compound Name	Date Aproved	Reference Product
Iabni	Rituximab-arx	December 2020	Rituxan(rituximab)
Hulio	Adalimumab-fkjp	July 2020	Humira (adalimumab)
Avsola	Infliximab-axxq	December 2019	Remicade(infliximab)
Abrilada	Adalimumab-afzb	November 2019	Humira (adalimumab)
Hadlima	Adalimumab-bwwd	July 2019	Humira (adalimumab)
Ruxience	Rituximab-pvvr	July 2019	Rituxan (rituximab)
Eticovo	Etanecerpt-ykro	April 2019	Enbrel (etanecerpt)
Truxima	Rituximab-abbs	November 2018	Rituxan (rituximab)
Hyrimoz	Adalimumab-adaz	October 2018	Humira (adalimumab)
Ixifi	Infliximab-qbtx	December 2017	Remicade (infliximab)
Cyltezo	Adalimumab-adbm	December2017	Humira (adalimumab)
Renflexis	Infliximab-abda	Mayo2017	Remicade (infliximab)
Amjevita	Adalimumab-atto	September 2016	Humira (adalimumab)
Erelzi	Etanecerpt-szzi	August 2016	Enbrel (etanecerpt)
Inflectra	Infliximab-dyyb	April 2016	Remicade (infliximab)

Mysler E, Caubet M, Lizarraga A. Current and Emerging DMARDs for the Treatment of Rheumatoid Arthritis. *Open Access Rheumatol*. 2021;13:139-152. Published 2021 Jun 1. doi:10.2147/OARRR.S282627

Coates, Laura C., et al. "Psoriasis, psoriatic arthritis, and rheumatoid arthritis: is all inflammation the same?." *Seminars in arthritis and rheumatism*. Vol. 46. No. 3. WB Saunders, 2016.

New Drug Approvals 2021-22

FDA New Approvals

- Voclosporin (Lupkynis) for lupus nephritis
- Anifrolumab (Saphnelo) for mod-severe SLE
- Avacopan, (Tavneos) for AAV
- Efgartigimod (Vyvgart), for myasthenia gravis
- Deucravacitinib (Sotyktu) for Psoriasis

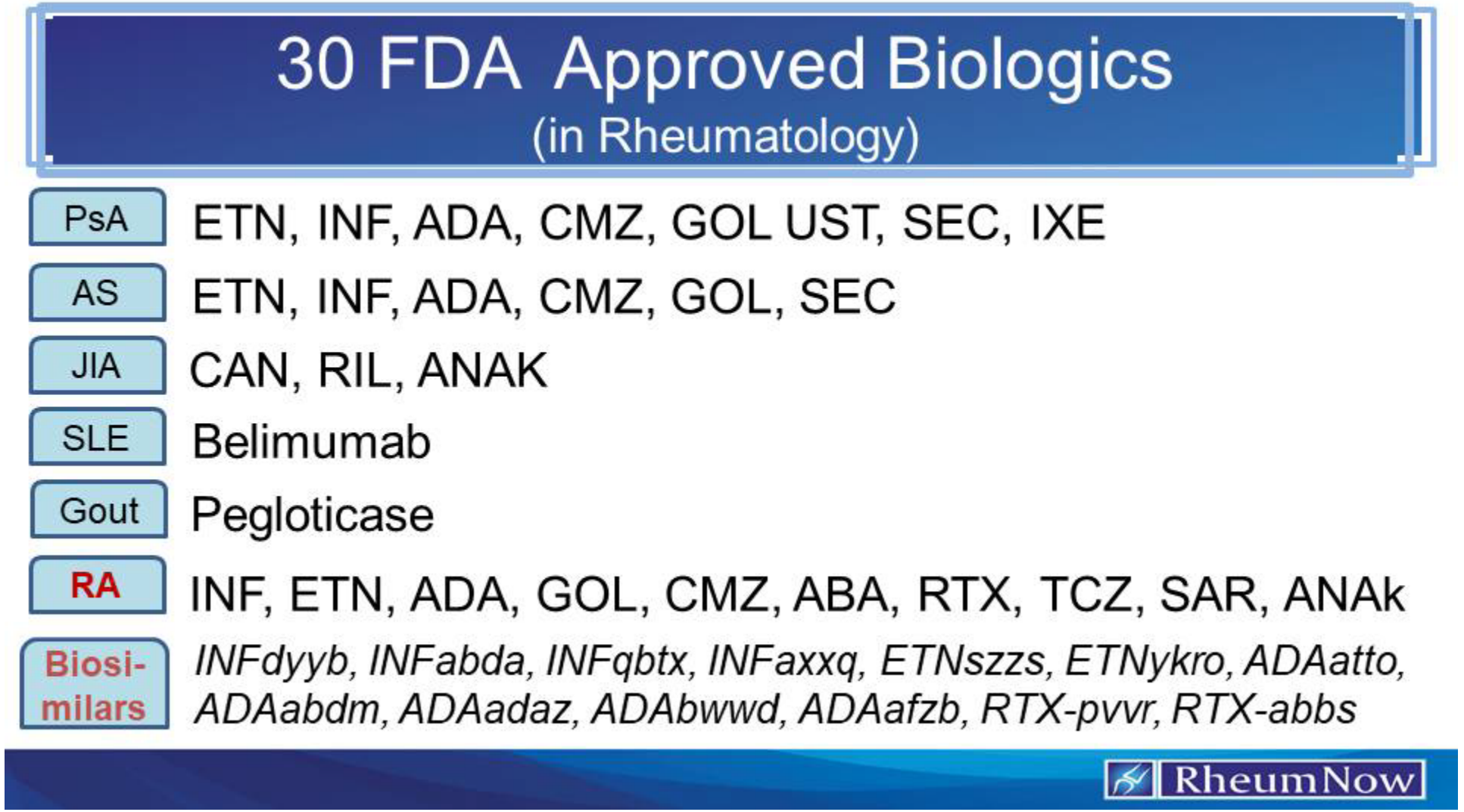
Problems

- Tanezumab denied
- Bimekizumab delayed

FDA Indications

- belimumab (lupus nephritis)
- apremilast (mild-moderate psoriasis)
- tocilizumab (ILD of systemic sclerosis)
- rilonacept (Recurrent pericarditis),
- IVIG (inflammatory myositis)
- secukinumab (jPsA, ERA)
- tofacitinib in AS, atopic dermatitis
- upadacitinib PsA, AS, atopic dermatitis
- baricitinib (COVID, alopecia areata)
- MTX + Pegloticase (gout)
- canakinumab in Adult Stills Dz
- risakizumab in PsA and Crohns colitis

Conclusions



Conclusions

Can be difficult to diagnose

Similar and overlapping presentations and labs

Relapsing and remitting

ACPA+ and high level RF
Worse RA prognosis

Renal disease portends high mortality in SLE

EARLY CAD in RA and SLE

New treatments!

Questions?

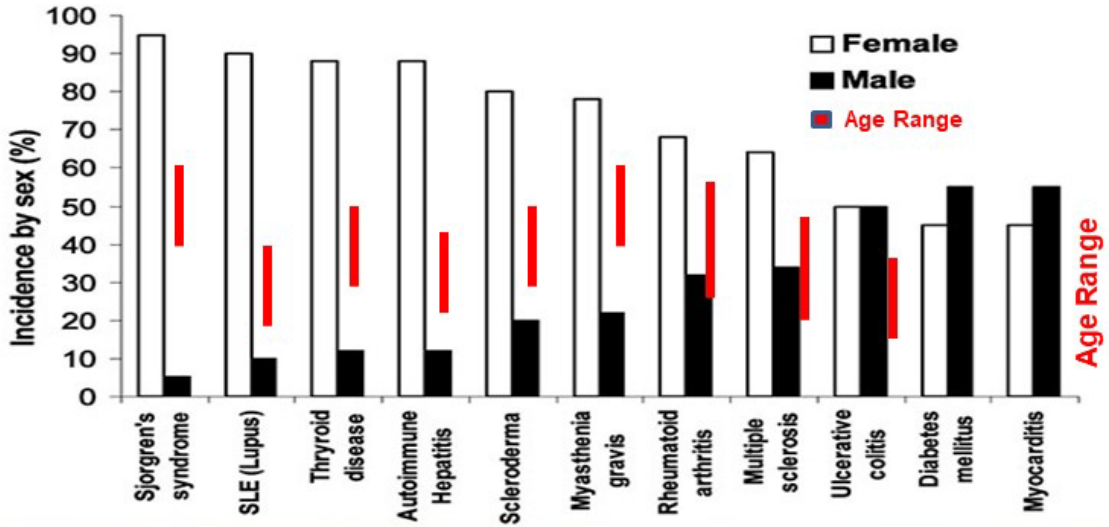
Conclusions

Autoimmune Disease in the USA

Graves disease
Thyroiditis
Systemic sclerosis
Myositis
SLE (lupus)
Sjögren's syndrome
Rheumatoid arthritis
Psoriasis
Psoriatic arthritis
Ankylosing spond
Spondyloarthritis
Reactive arthritis
Crohns disease
Ulcerative colitis
Juvenile arthrtitis
Juvenile diabetes
Autoimmune hepatitis
Hemolytic anemia/ITP
Multiple sclerosis
Myasthenia gravis
Uveitis
Vasculitis

- USA: 8% (78%♀) have Autoimmune diseases (AID)
- 1997: 8,511,845 (1/31) have AID
- 2005: 23.5 million (1/12♀ and 1/20♂ have AID)

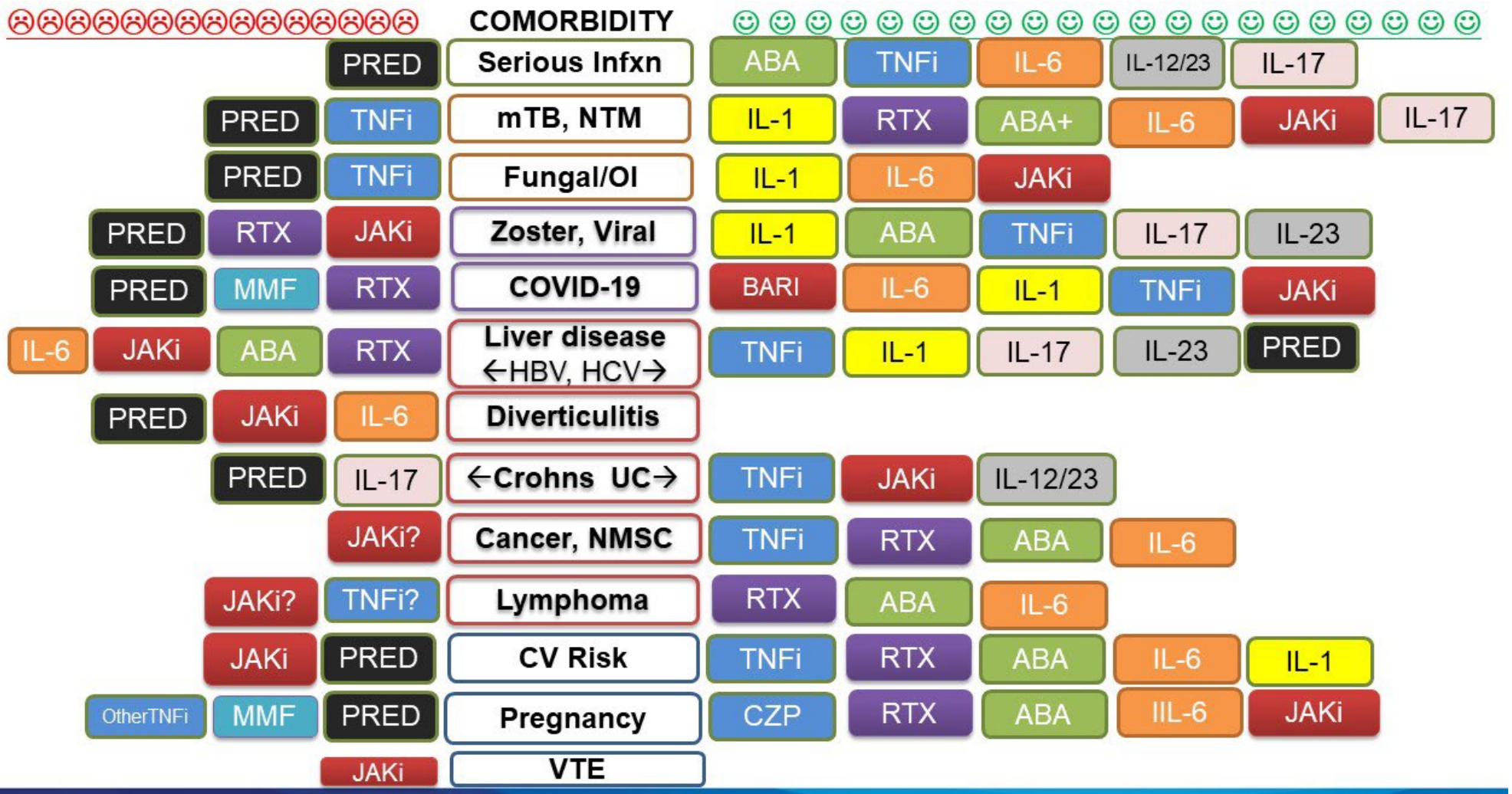
Autoimmune Dz by Age & Sex



J Autoimmun. 2009 Nov–Dec; 33(3-4): 197–207 Emerg Infect Dis 2004.

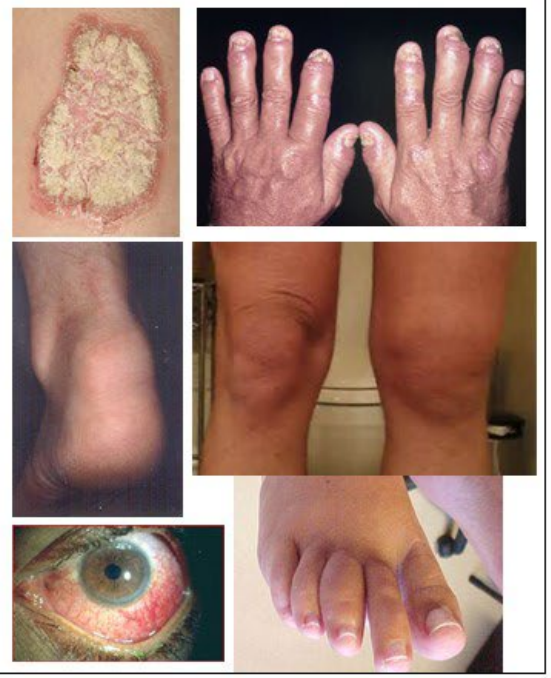
RheumNow

Conclusions

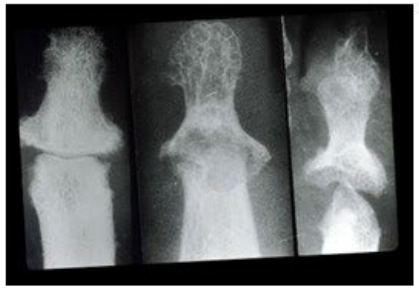


Psoriatic Arthritis: A Multifaceted Disease

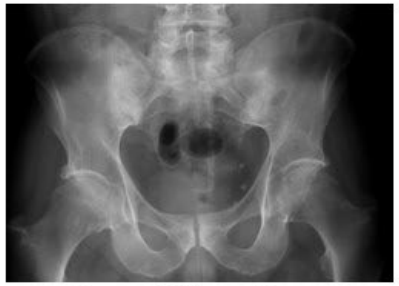
Joint & Skin Features



Imaging



Pencil in cup deformity



Sacrolilitis – X-ray

Seronegative

Comorbidity