


Rheumatic diseases

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Classification of arthritis and rheumatism I

- * Inflammatory arthritis
 - rheumatoid arthritis
 - spondyloarthropathy
 - psoriatic arthritis
- * Diffuse connective tissue diseases
 - SLE
 - systemic sclerosis
 - Sjogren syndrom
 - dermatomyositis/polymyositis
- Vasculitis, ANCA associated vasculitis
 - GPA – granulomatosis with polyangiitis
 - EGPA – eosinophilic granulomatosis with polyangiitis

Classification of arthritis and rheumatism II

- * Degenerative joint diseases – osteoarthritis
- * Rheumatic syndromes associated with infectious agents
 - reactive arthritis – postdysenteric, post-gonococcal, after other infections
 - direct infection arthritis
 - G+, G-, spirochete, Lyme disease?

Classification of arthritis and rheumatism III

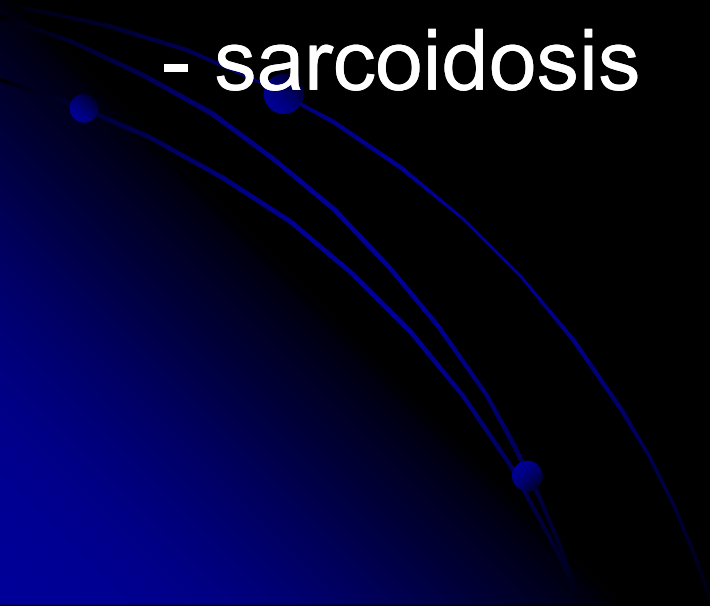
* Metabolic and endocrine diseases – crystal associated conditions

- gout
- CPPD chondrocalcinosis

* Bone and cartilage disorders

- osteoporosis
- osteomalacia
- Paget disease

Classification of arthritis and rheumatism IV

- * Extraarticular disorders
 - polymyalgia rheumatica
 - fibromyalgia
 - chronic fatigue syndrom
 - sarcoidosis
- 

Inflammatory arthritis

- rheumatoid arthritis

- spondyloarthropathy

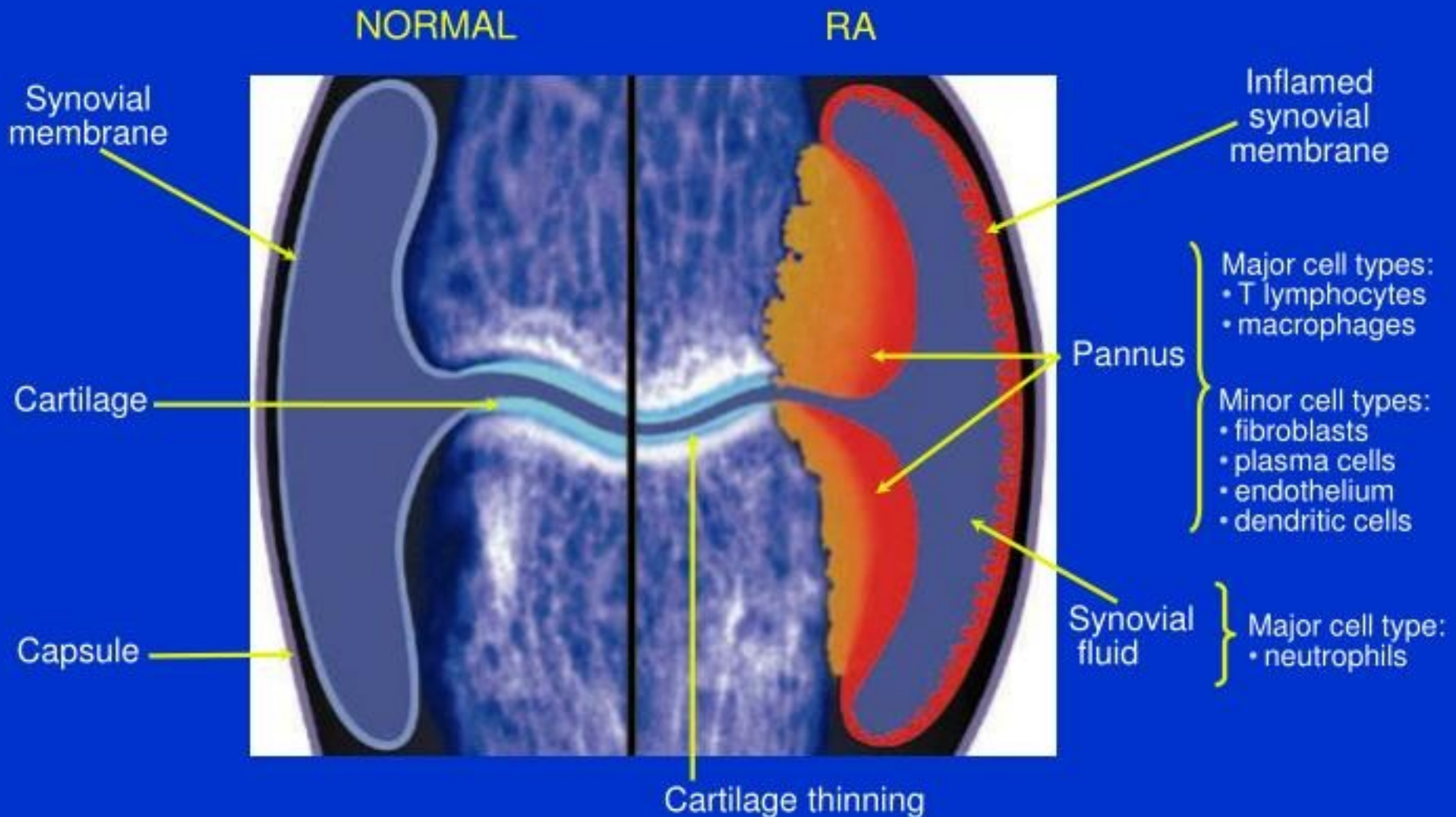
- psoriatic arthritis



Rheumatoid arthritis is
chronic, frequently
progressive and destructive,
systemic, inflammatory
disorders.

The main character of pathophysiology
is inflammation of synovial tissue,
membrane of joints, tendons and
bursitis

RA Is Characterised by Synovitis and Joint Destruction



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

JOINT INVOLVEMENT ON PRESENTATION OF RA

Polyarticular **75%**

Small joints
of hands and feet 60%

Large joints 30%

Large and
Small joints 10%

Monoarticular **25%**

Knee 50%

Shoulder }

Wrist }

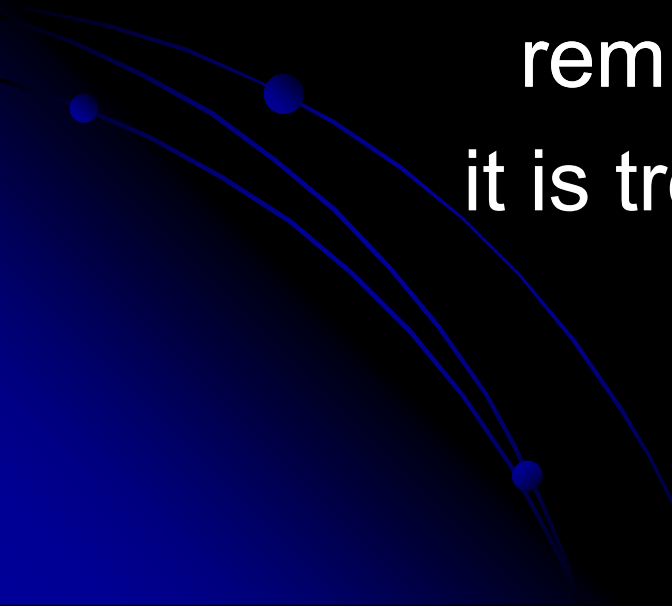
Hip }

Ankle }

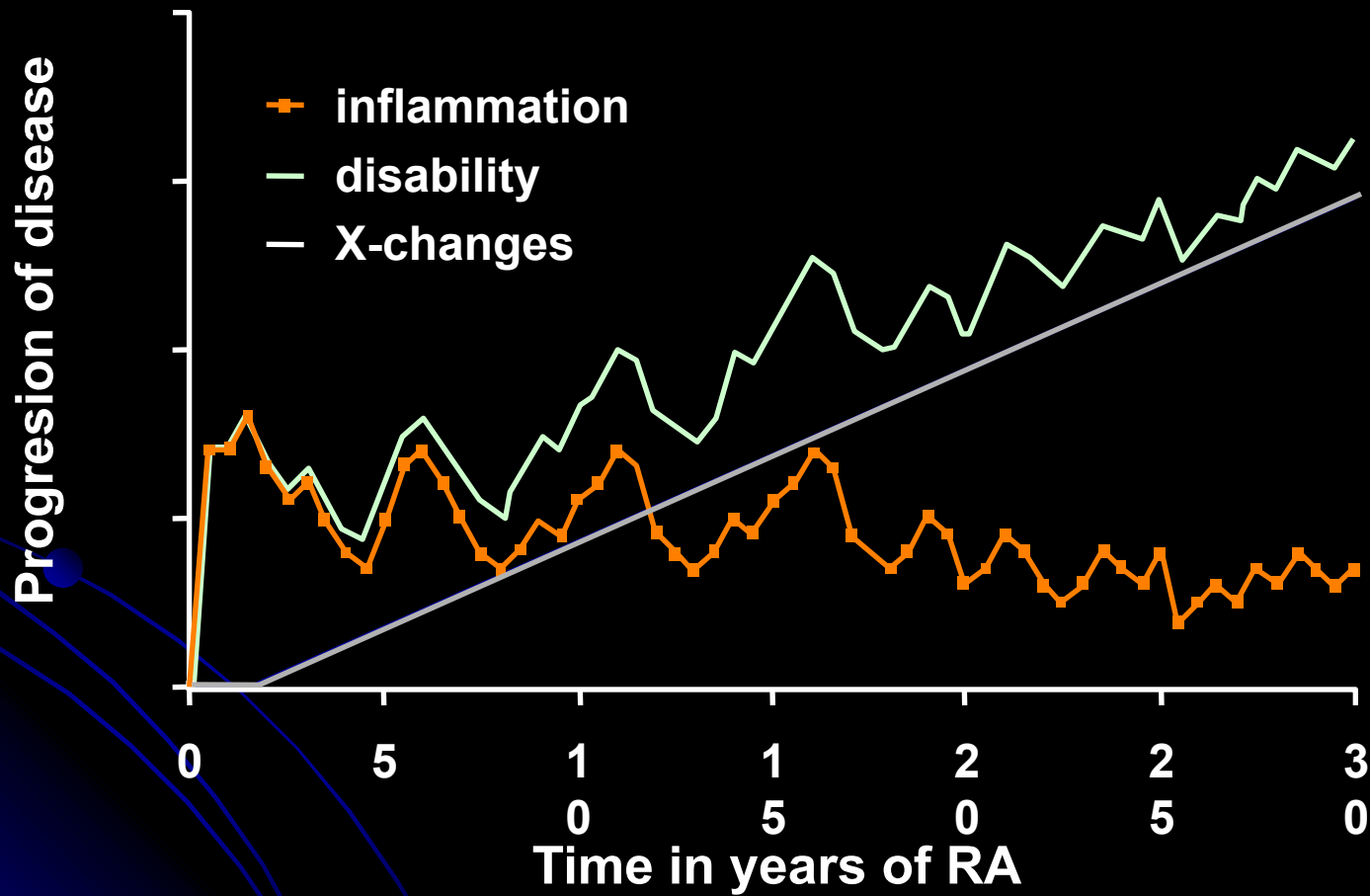
Elbow }

Rheumatoid arthritis is
chronic, systemic,
inflammatory disorders

Atacs of exacerbation and
remision, we can treat,
it is treatable but incurable



Course of RA: schematic model, RA is frequently progressive and destructive autoimmune disease



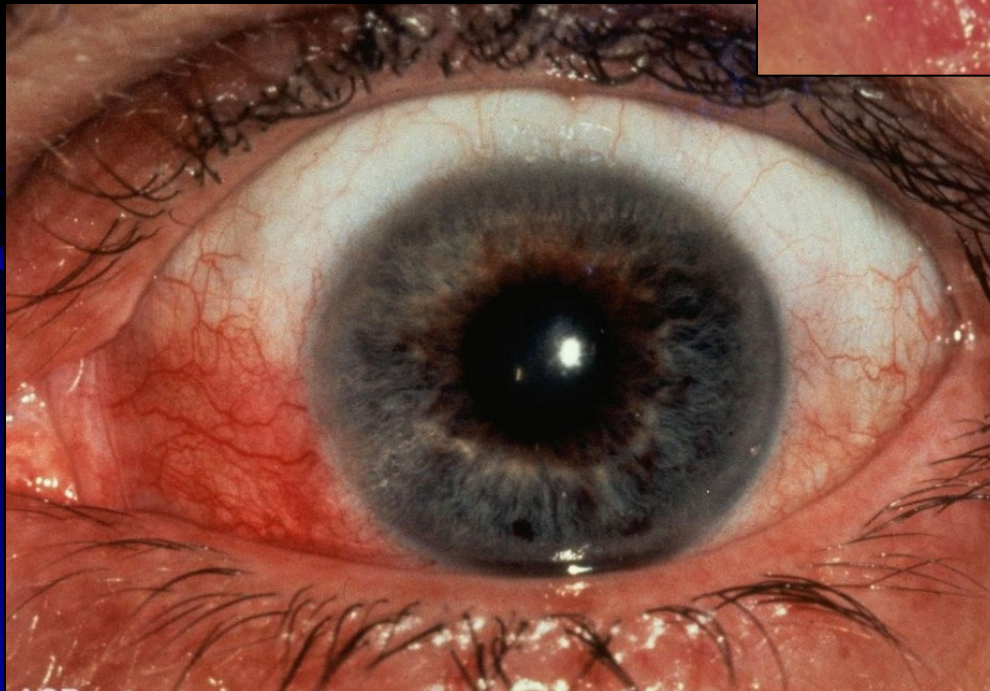
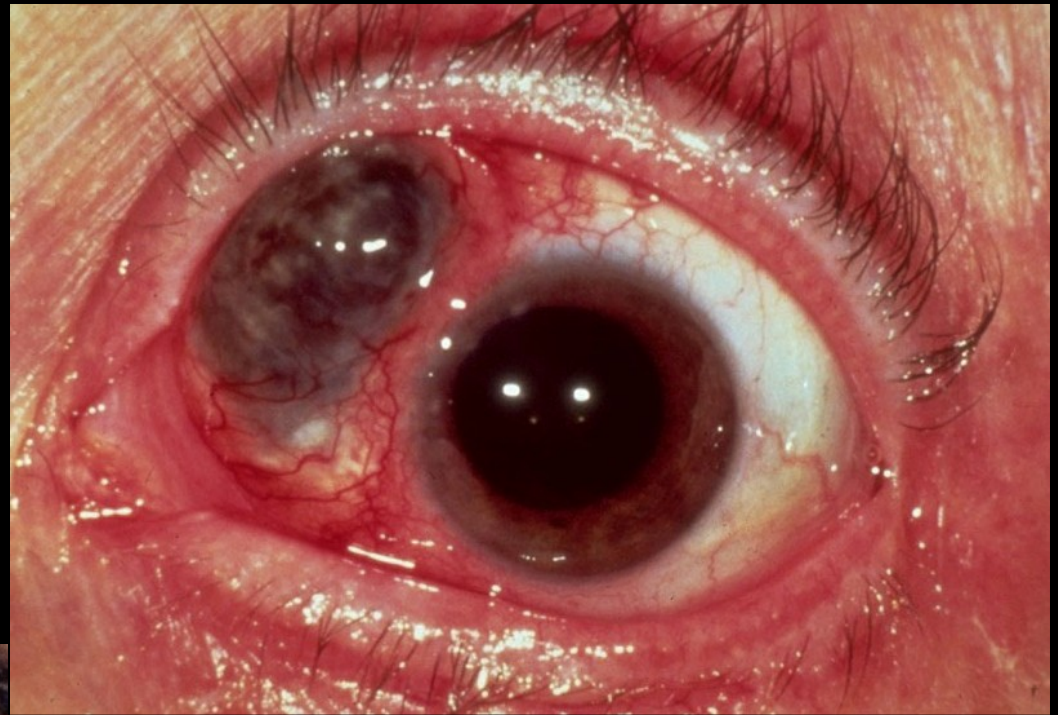
Rheumatoid arthritis is **chronic, systemic,** inflammatory disorders

- Not only joints, but also others organs
- Systemic changes (lung, cor, kidney)
- RA is associated with comorbidities
- RA is associated with reduction of life expectancy appr. 5 -10 years

Rheumatoid vasculitis

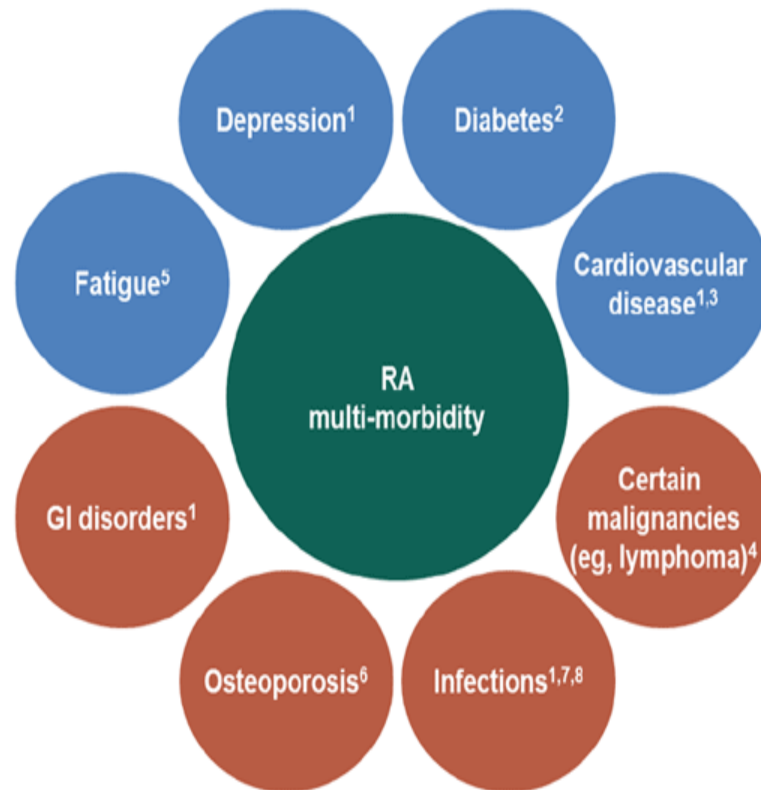


Scleromalacia



Episcleritis

RA Systemic Manifestations and Comorbidities



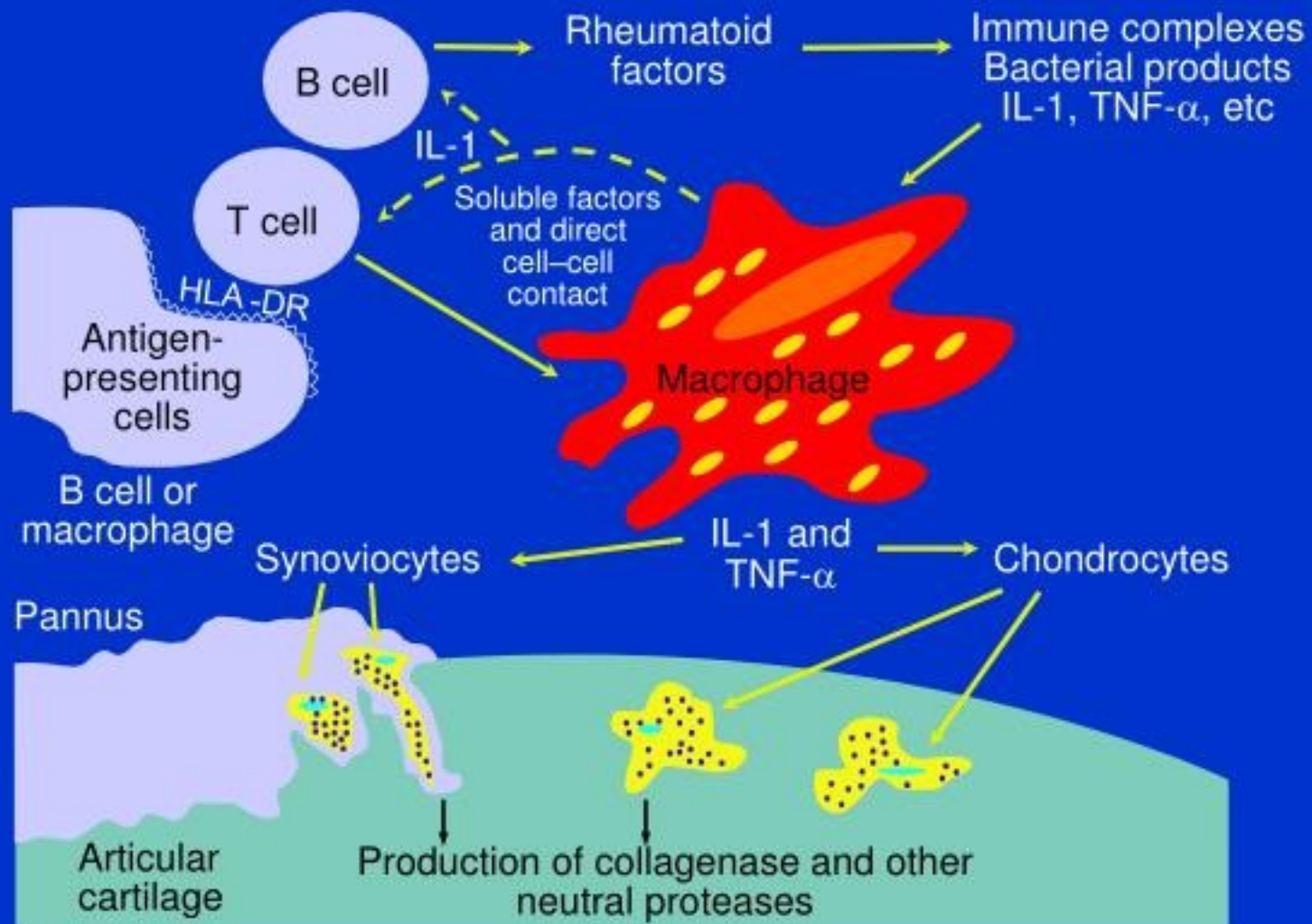
GI: gastrointestinal.

1. Dougados M et al. *Ann Rheum Dis*. 2014;73:62-68. 2. Albrecht K et al. *Rheumatology (Oxford)*. 2018;57:329-336. 3. van Halm VP et al. *Ann Rheum Dis*. 2009;68:1395-1400. 4. Simon TA et al. *Arthritis Res Ther*. 2015;17:212. 5. Pollard LC et al. *Rheumatology (Oxford)*. 2006;45:885-889. 6. Hauser B et al. *Rheumatology (Oxford)*. 2014;53:1759-1766. 7. Shaw M et al. *Eur Respir Rev*. 2015;24:1-16. 8. Listing J et al. *Rheumatology (Oxford)*. 2013;52:53-61.

Rheumatoid arthritis is
chronic, systemic,
inflammatory disorders

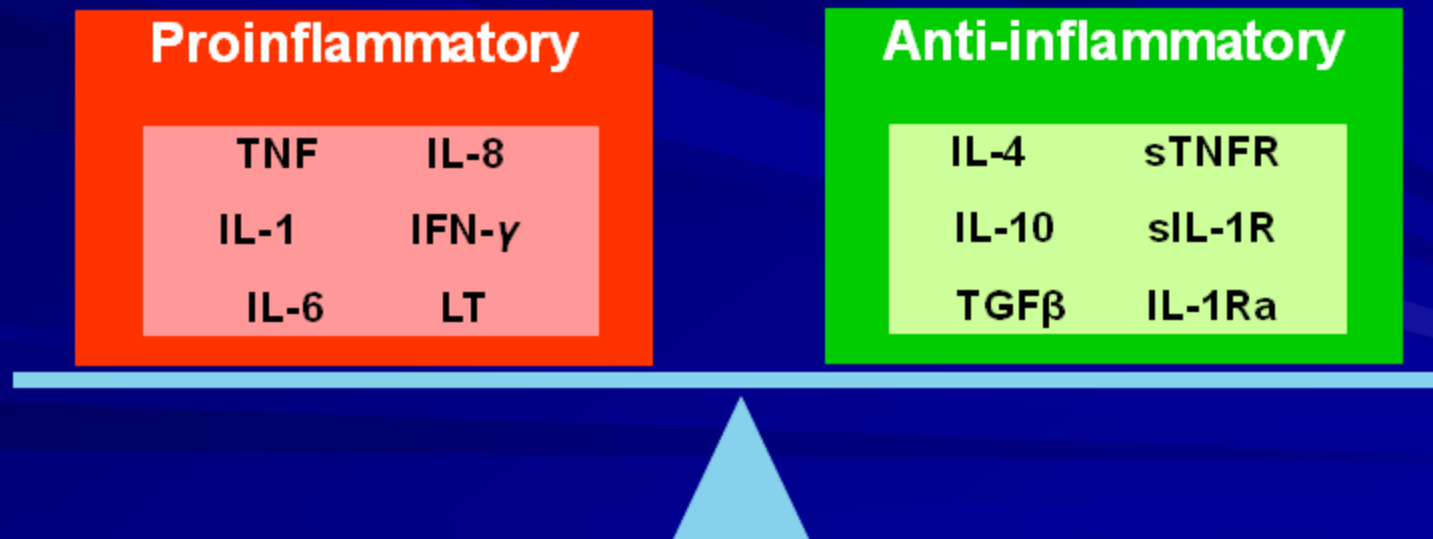
The main character of pathophysiology is inflammation in synovial tissue, infiltration of pro inflammatory cytokines (Interleukines - 1,6, TNF)

Numerous Cellular Interactions Drive the RA Process



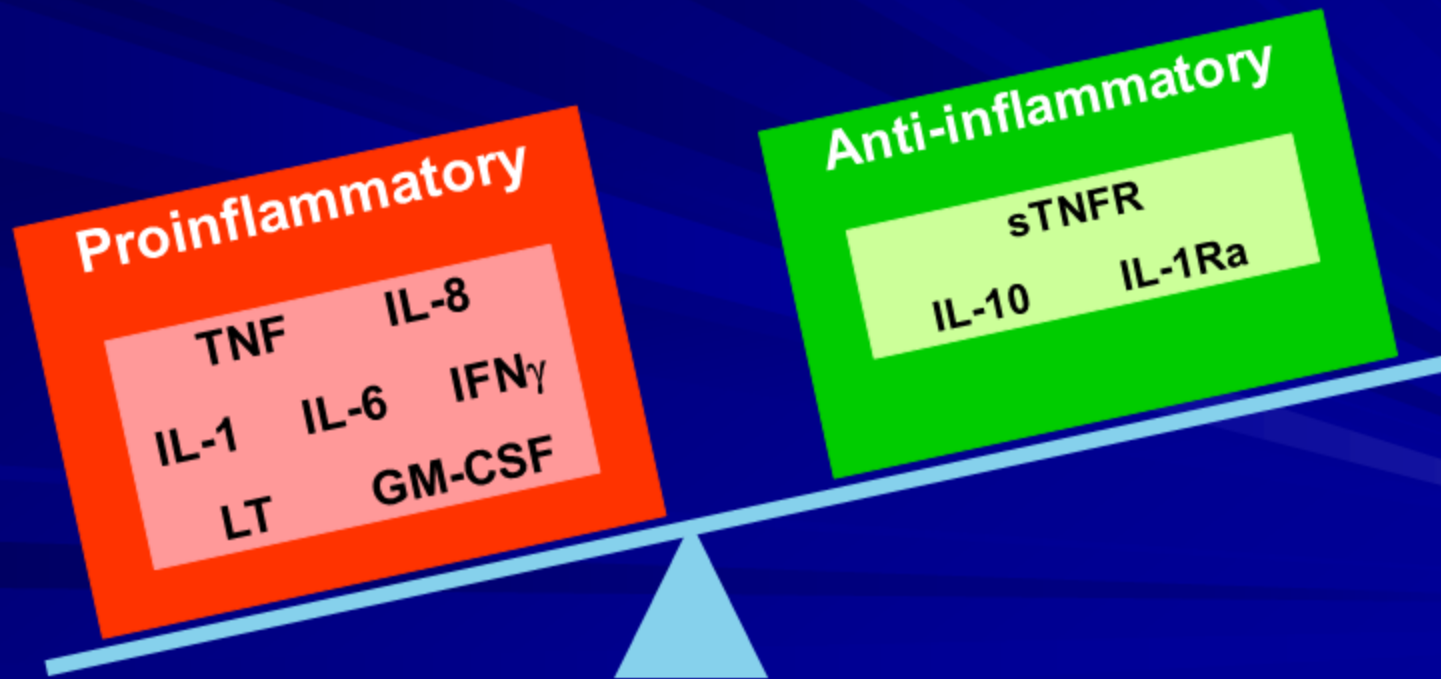
TNF α in the Cytokine Balance

- In a healthy system there is an equilibrium between cytokines that activate inflammation and those that inhibit inflammation

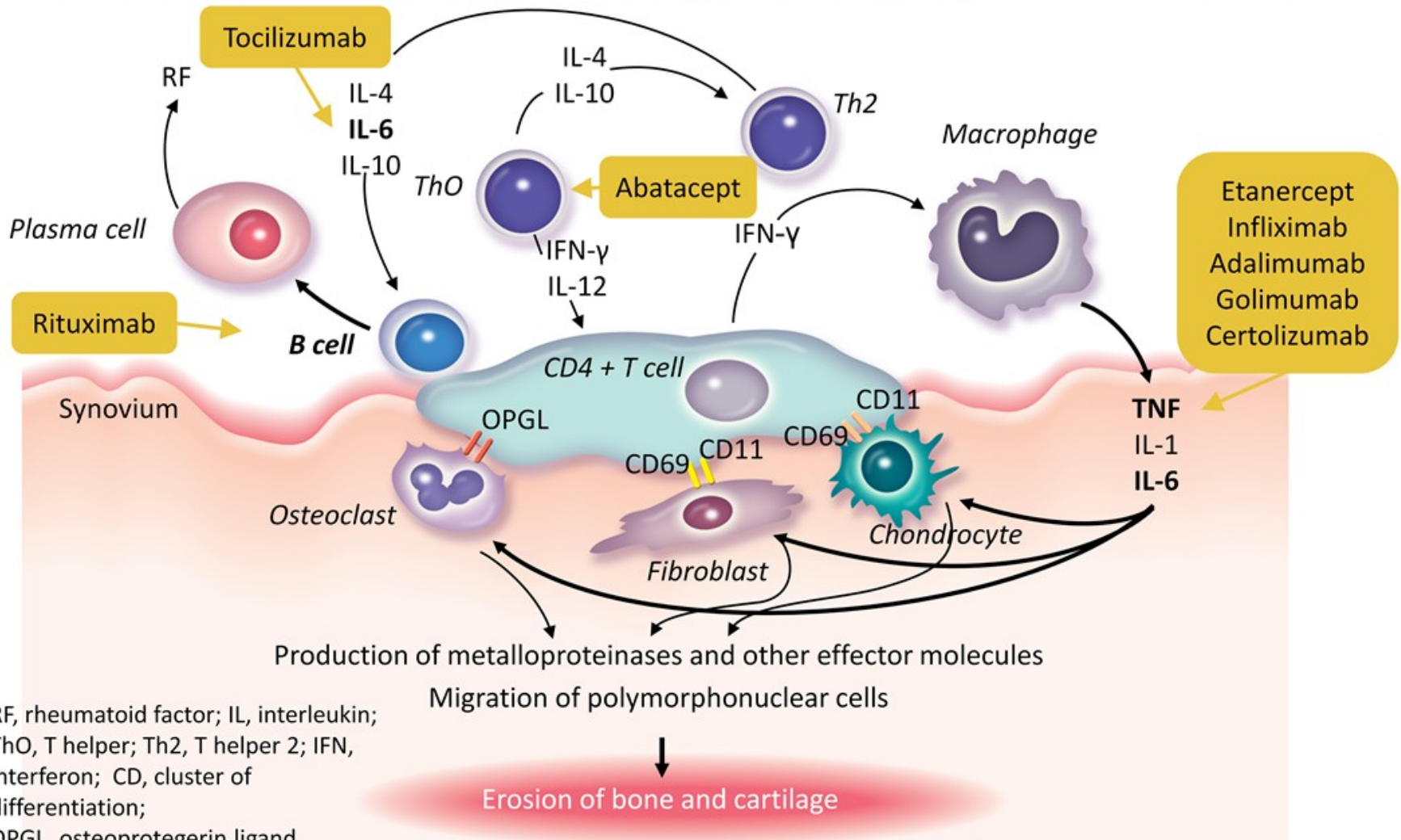


TNF α in the Cytokine Balance

- Activated macrophages and T cells release proinflammatory cytokines that go on to stimulate further proinflammatory cytokine production, tipping the cytokine balance^{1,2}



Cytokine Signalling Pathways Involved in RA^{1,2}



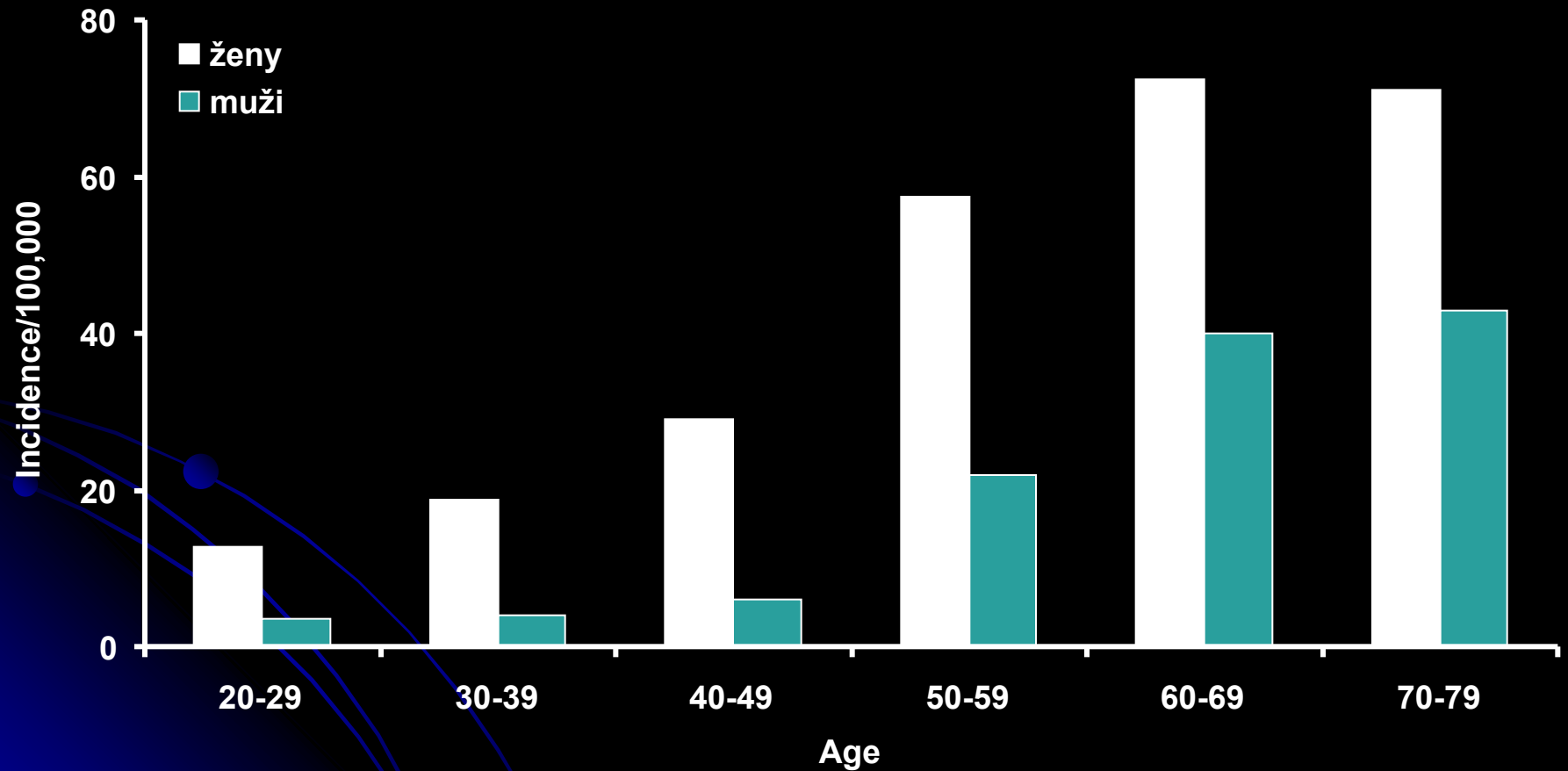
RF, rheumatoid factor; IL, interleukin; Th0, T helper; Th2, T helper 2; IFN, interferon; CD, cluster of differentiation; OPG, osteoprotegerin ligand.

1. Adapted from Choy EH, Panayi GS. *N Engl J Med*. 2001;344:907-916. 2. Tak P, et al. *Arthritis Res Ther*. 2011;13:S5.

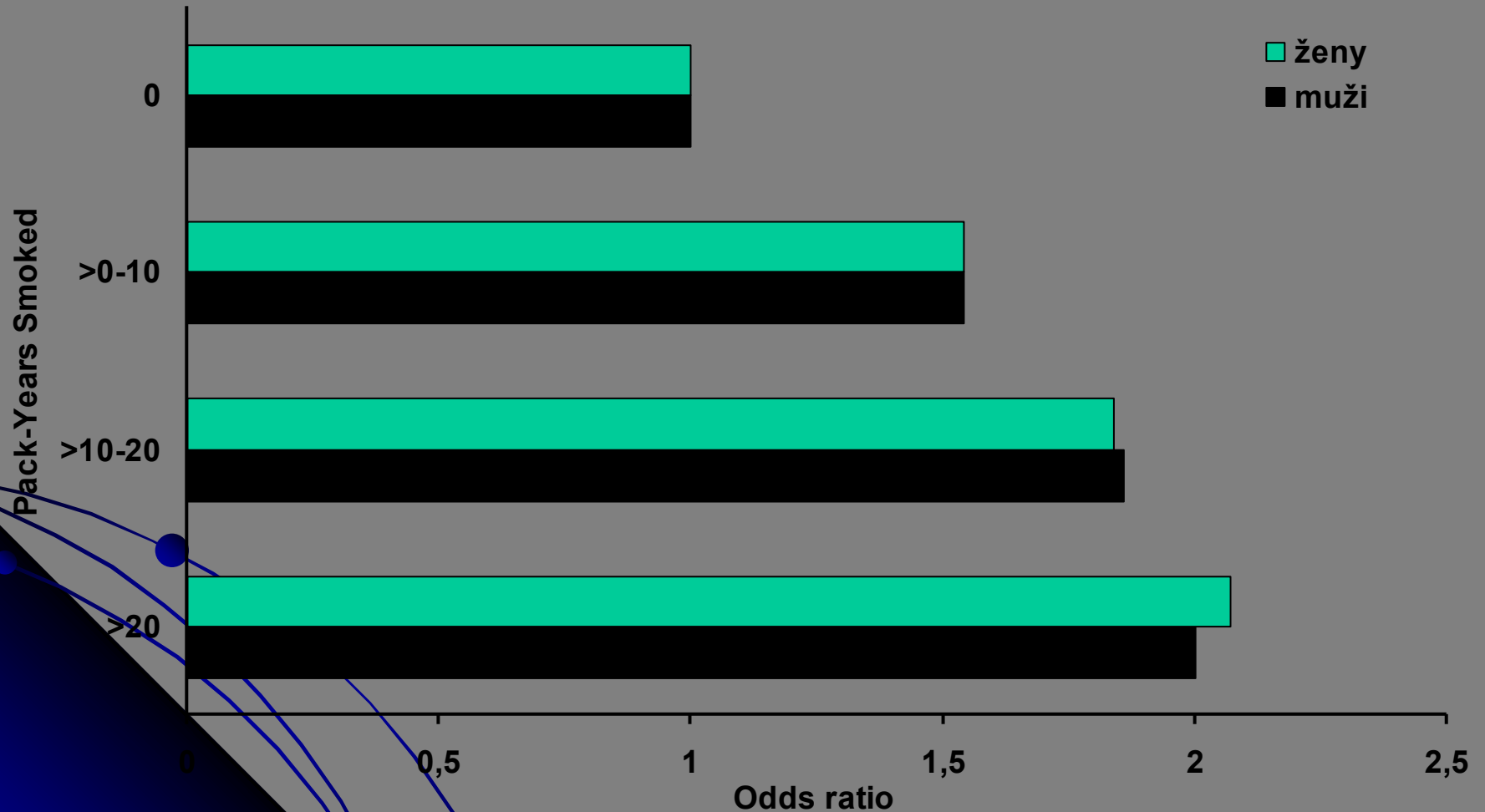
Signs & Symptoms of RA

- Fatigue.
- Stiffness, especially in early morning and after sitting a long period of time.
- Not relieved by pain
- Low Grade Fever, Weakness.
- Muscle pain and pain with prolonged sitting.
- Symmetrical, affects joints on both sides of the body.
- Rheumatoid nodules.
- Deformity of your joints over time.
- Raynauds phenomenon.
- Pain

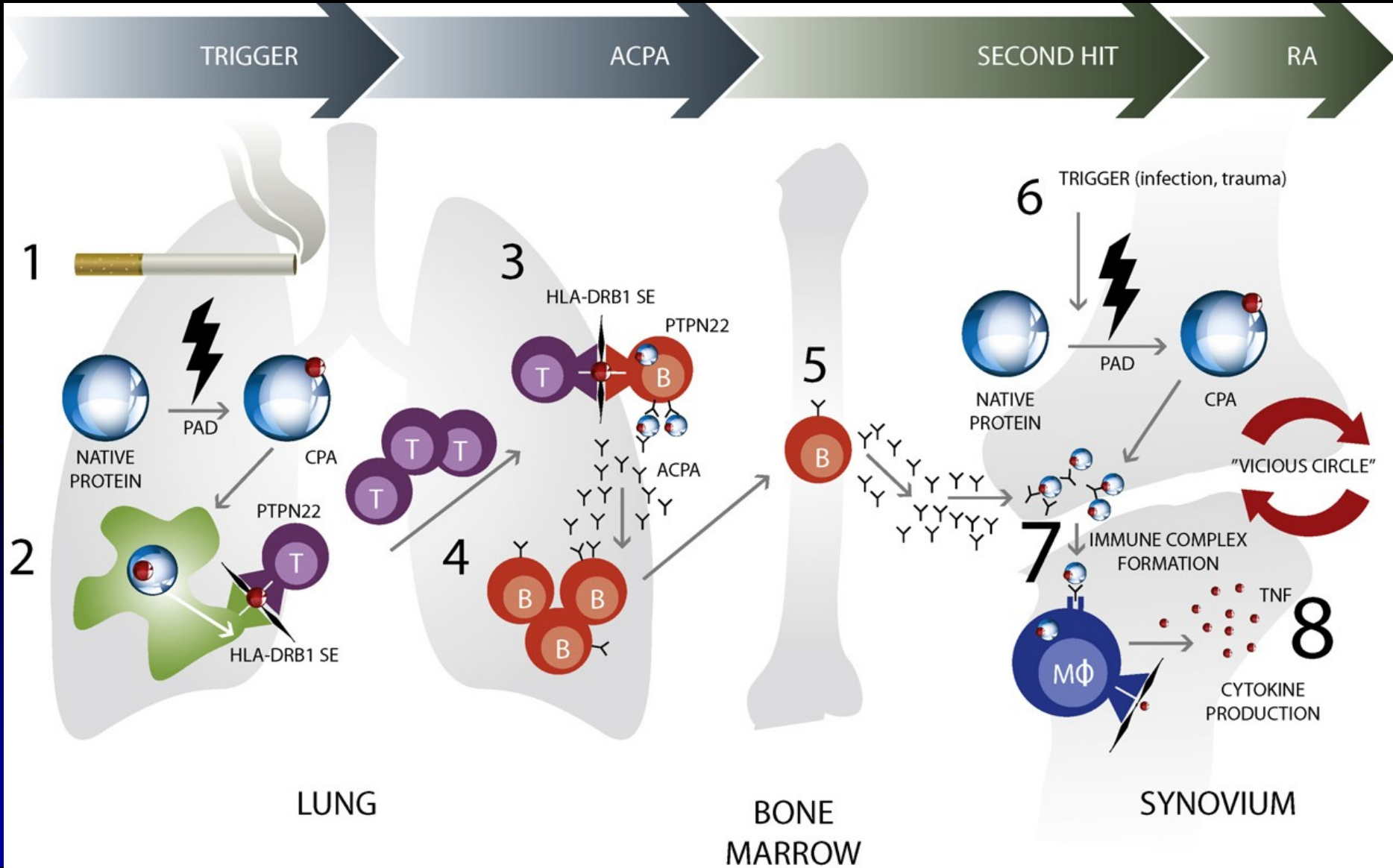
Incidence RA is higher in women



Smoke and risc of RA



Hypothesis of pathophysiology of RA



American College of Rheumatology / European League Against Rheumatism (ACR/EULAR) 2010 Classification Criteria for RA

Factor		Points
Joint involvement	1 large joint (shoulder, elbow, hip, knee, ankle)	0
	2-10 large joints	1
	1-3 small joints (metacarpophalangeal, proximal interphalangeal, 2 nd through 5 th metatarsophalangeal joints, and wrist)	2
	4-10 small joints	3
	> 10 joints (at least 1 small joint required)	5
Serology*	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
Acute-phase reactants*	Normal CRP and normal ESR	0
	Elevated CRP or elevated ESR	1
Duration of symptoms	<6 weeks	0
	≥6 weeks	1

Criteria to be classified as RA = At least 1 swollen joint (unexplained by another disease) and a total of ≥6 points

* at least 1 laboratory test result is needed for classification

Legend: CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, RF= rheumatoid factor, ACPA = anti-citrullinated protein antibody

Aletaha D, et al. *Arthritis Rheum*. 2010;62:2569-2581.

Revmatoidní artritida- otok PIP kloubů





Pokročilé změny u RA



RA



Revmatoidní artritida

teleskopické prsty



**Arthritis
mutilans**





**Pokročilé degenerativní změny
ulnární deviace,**

Revmatoidní artritida



subperiostální novotvorba
kosti

zúžení štěrbiny

eroze



protruze acetabula



Rheumatoid nodule

Indexis for measure activity RA

Objective Disease Measures

DAS28^[a]

- TJC28, SJC28, ESR, **patient global (VAS-GH)**

CDAI^[b]

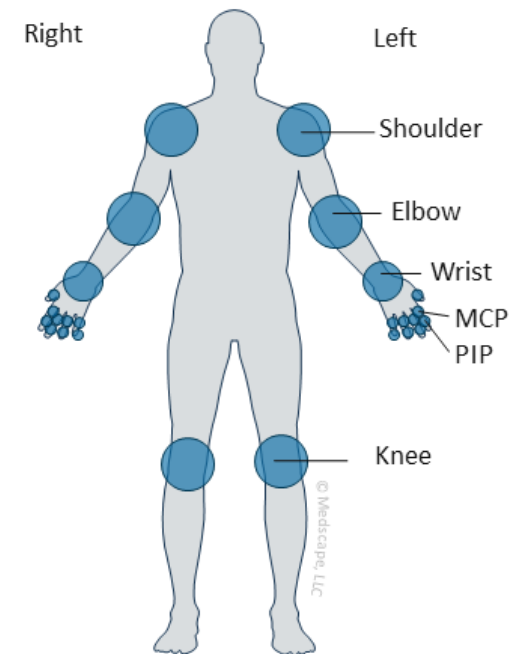
- TJC28, SJC28, **patient global**, provider global

SDAI^[b]

- TJC28, SJC28, CRP, **patient global**, provider global

The ACR response criteria measure improvements in tender or swollen joint counts and 3 of the 5 following parameters:^[c]

- **Patient global**, provider global assessment, patient pain scale, physical function questionnaire, acute phase reactant



The joints, which are depicted as circles, are measured for the TJC and SJC

The Burden of RA



- ▶ RA is associated with serious comorbidities such as heart disease, infection, and malignancies, with a reduction in life expectancy of 5–10 years^{1,2}
- ▶ Higher than expected mortality rates have been reported in most rheumatic conditions, in especially inflammatory rheumatic diseases³
- ▶ RA is associated with a reduced QoL compared with patients with other serious conditions⁴
- ▶ RA carries a considerable economic burden⁴

Figure from Harris ED, Firestein GS. In: *Kelley's Textbook of Rheumatology*. 8th ed. Philadelphia: Elsevier Saunders; 2008;2:1094; RA, rheumatoid arthritis; QoL, quality of life

1. Harris ED, Firestein GS. In: *Kelley's Textbook of Rheumatology*. 8th ed. Philadelphia: Elsevier Saunders; 2008;2:1087–1118; 2. Kvien TK. *Pharmacoeconomics*. 2004;22:1–12; 3. Callahan LF, Pincus T. *Arthritis Care Res*. 1995;8:229–241; 4. Lundkvist J, et al. *Eur J Health Econ*. 2008;8:S49–S60

DMARDs – disease modifying antirheumatic drugs

- csDMARDs - conventional synthetic DMARDs
- boDMARDs – biologic originator DMARDs
- bbDMARDs – biosimilar DMARDs
- smDMARDs – small molecule DMARDs

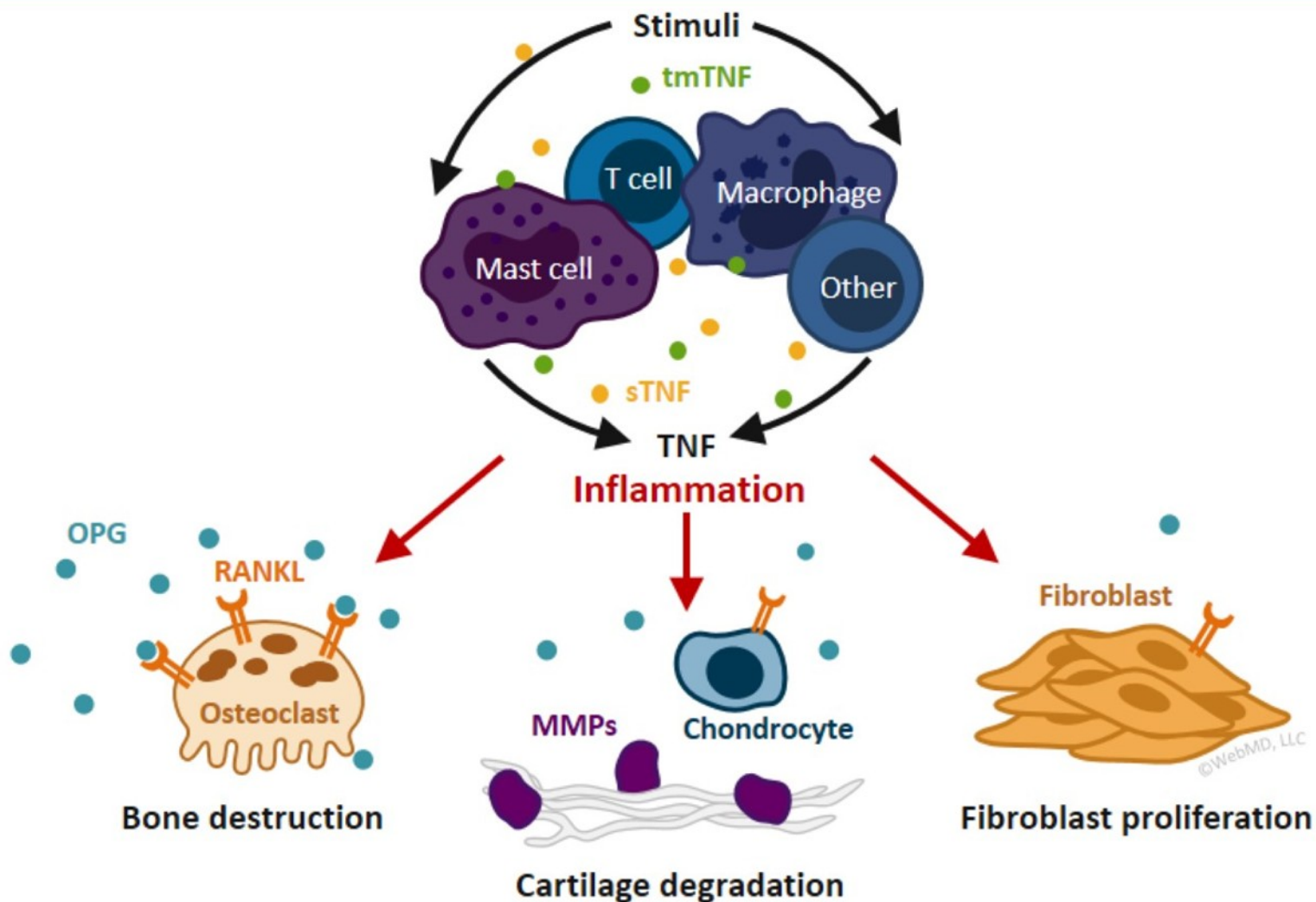
Conventional syntetic DMARDs

Agent	Time to benefit	Potential for toxicity	Toxicities to monitor
Methotrexate	1–2 months	Moderate	Myelosuppression, hepatic fibrosis and cirrhosis, pulmonary infiltrates
Hydroxychloroquine	2–6 months	Low	Macular damage
Leflunomide	4–12 weeks	Low	Diarrhea, alopecia, rash, headache, risk of immunosuppression infection
Sulfasalazine	1–3 months	Low	Myelosuppression
Cyclosporine	4–8 weeks	High	Renal insufficiency, hypertension
Gold, oral	4–6 months	Low	Myelosuppression, proteinuria
Gold, parenteral	3–6 months	Moderate	Myelosuppression, proteinuria
Azathioprine	2–3 months	Moderate	Myelosuppression, hepatotoxicity, lymphoproliferative disorders
Minocycline*	1–3 months	Low	Hyperpigmentation, dizziness, vaginal yeast infections, lupus

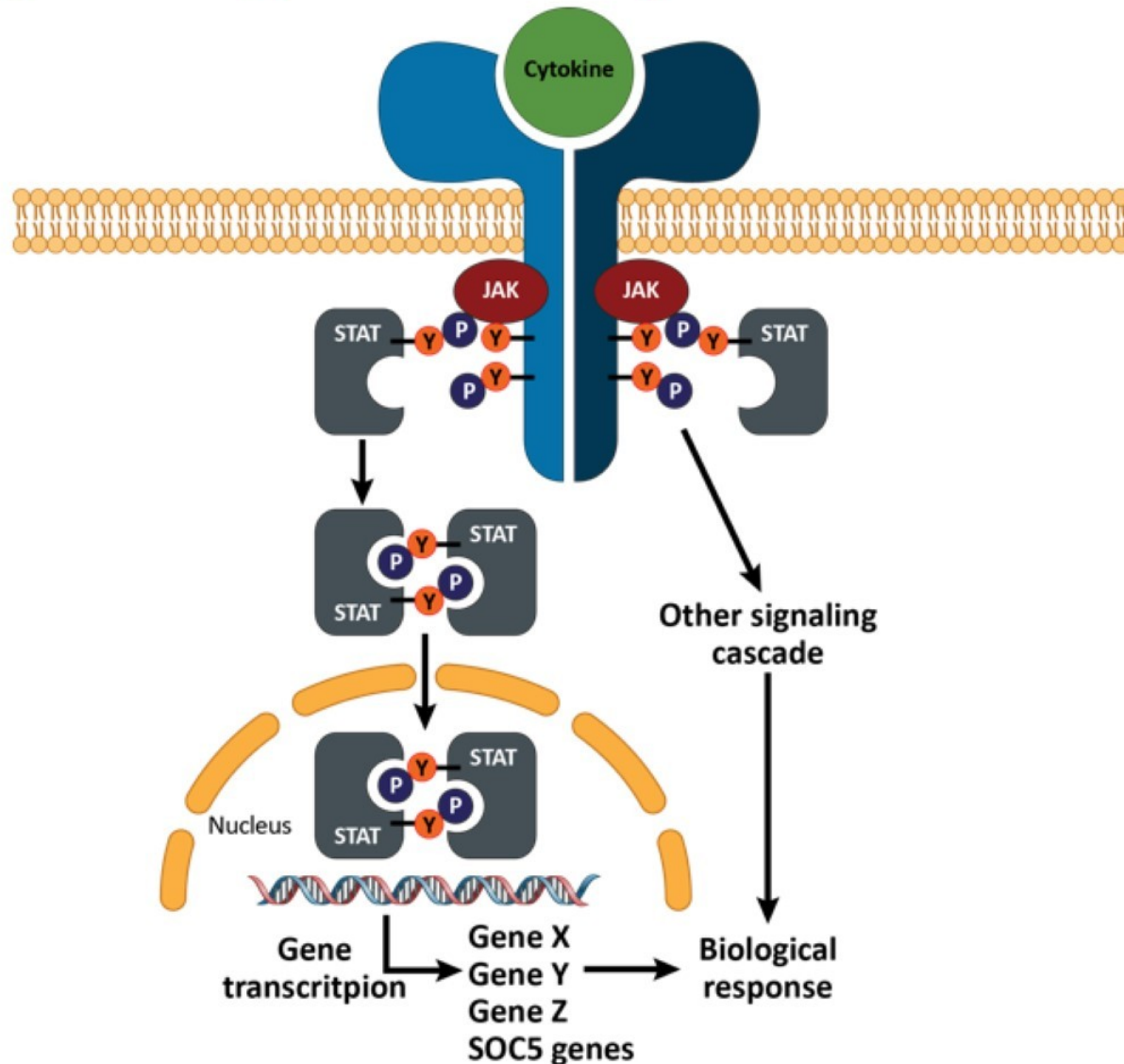
* Not approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis.

SOURCE: ACR 2002

Tumor Necrosis Factor and the Pathogenesis of RA



JAK Signaling Pathway

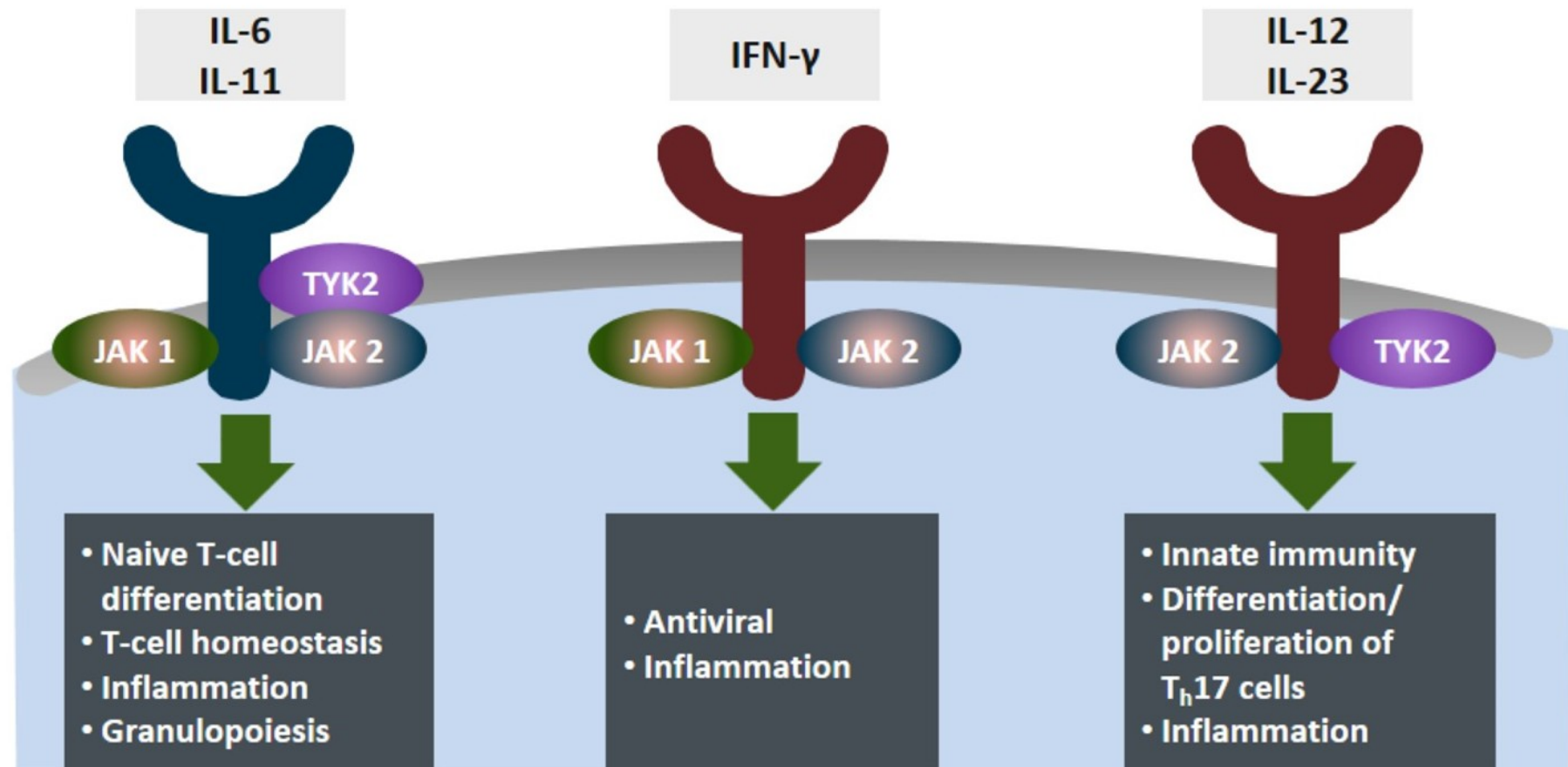


Shuai K, et al. *Nat Rev Immunol.* 2003;3:900-911.

Alexander WS. *Nat Rev Immunol.* 2002;2:410-416.

The Biological Significance of Signaling Through Different JAK Combinations

Multiple Pathophysiologic Targets^[a-d]








a. O'Sullivan LA, et al. *Mol Immunol*. 2007;44:2497-2506; b. Ghoreschi K, et al. *Immunol Rev*. 2009;228:273-287; c. Vijayakrishnan L, et al. *Trends Pharmacol Sci*. 2011;32:25-34; d. Sanjabi S, et al. *Curr Opin Pharmacol*. 2009;9:447-453.

Benefits of Blocking the TNF Pathway in Controlling Inflammation

- ▶ TNF contributes to bone destruction¹⁻⁵
- ▶ TNF-i's prevent radiographic damage beyond inflammation, whereas DMARDs do not^{6,7}
- ▶ TNF-i's have been reported to improve lipid and arthrogenic profiles, reduce arterial stiffness, and decrease insulin resistance in comparison with controls⁸
- ▶ TNF-i's have been shown to decrease cardiovascular comorbidities in RA^{9,10}

1. Lam J, et al. *J Clin Invest*. 2000;106:1481-1488. 2. Li P, et al. *Arth Rheum*. 2004;50:265-276. 3. Gilbert L, et al. *Endocrinology*. 2000;141:3956-3964. 4. Abbas S, et al. *Cytokine*. 2003;22:33-41. 5. Almedia M, et al. *J Biol Chem*. 2011;286:44326-44335. 6. Alehata D, et al. *Ann Rheum Dis*. 2011;70:1975-1980. 7. Smolen J, et al. *Ann Rheum Dis*. 2009;68:823-827. 8. Furst DE, et al. *Ann Rheum Dis*. 2011;70:i2-i36. 9. Wijbrants CA, et al. *Ann Rheum Dis*. 2009;68:1316-1321. 10. Popa C, et al. *Ann Rheum Dis*. 2009;68:868-872.

Overview of TNF-i Biologics

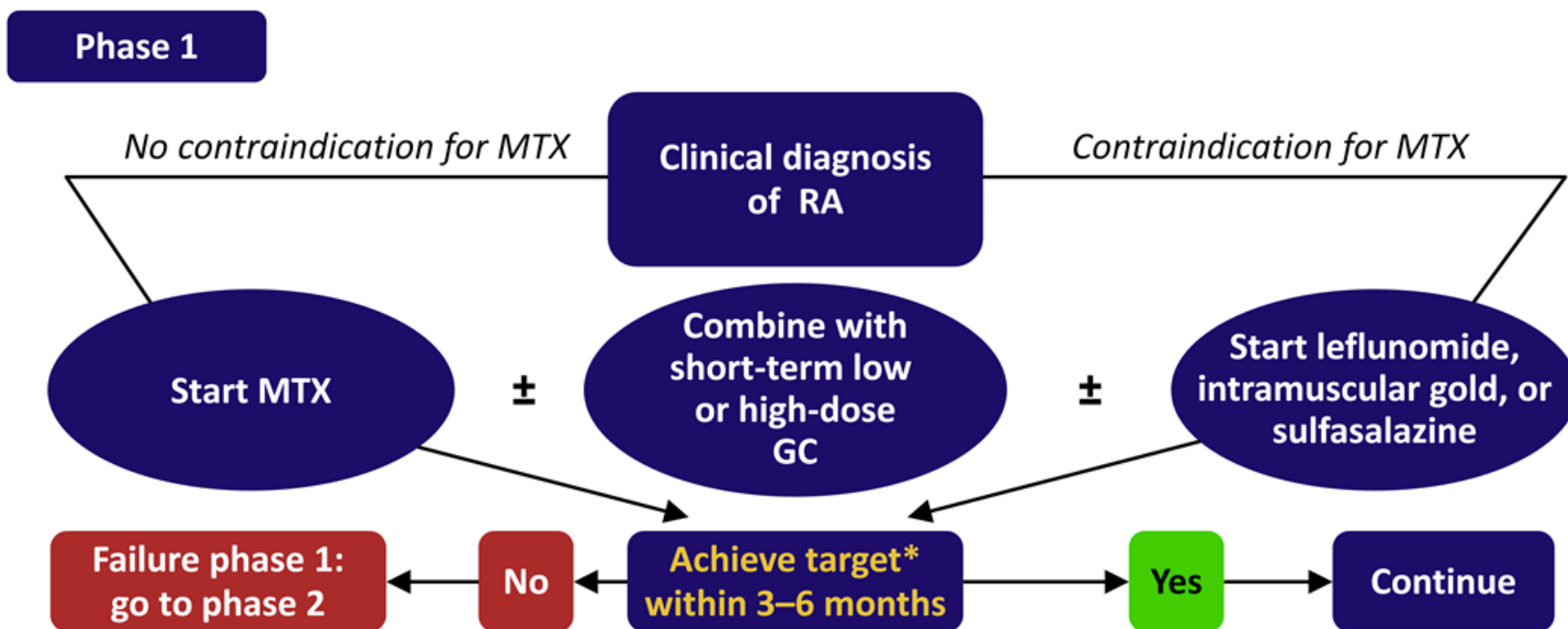
	Infliximab ¹	Adalimumab ²	Golimumab ³	Certolizumab pegol ⁴	Etanercept ⁵
Class	Chimeric mAb	Human mAb	Human mAb	Humanized Fab' fragment conjugated to PEG	Human soluble receptor TNF-i
					
Construct	Chimeric mAb	Recombinant human mAb	Recombinant human mAb	Recombinant fusion protein	Recombinant fusion protein
Binding target	TNF- α	TNF- α	TNF- α	TNF- α	TNF- α and LT- α
Half-life	8.0-9.5 days	14 days	12 \pm 3 days	14 days	70 hours
Antibodies that affect efficacy	Yes	Yes	Yes	Yes	No
Neutralizing Antibody	Yes	Yes	Yes	Yes	No

mAb, monoclonal antibody; Fab', fragment antigen-binding; PEG, polyethylene glycol; LT- α , lymphotoxin- α .

1. Remicade EU SmPC. 2. Humira EU SmPC. 3. Simponi EU SmPC. 4. Cimzia EU SmPC. 5. Enbrel EU SmPC.

EULAR RA Treatment Algorithm: Regular Monitoring (Every 3–6 Months) Is Critical to Optimizing Outcomes

Phase 1 of EULAR RA treatment algorithm



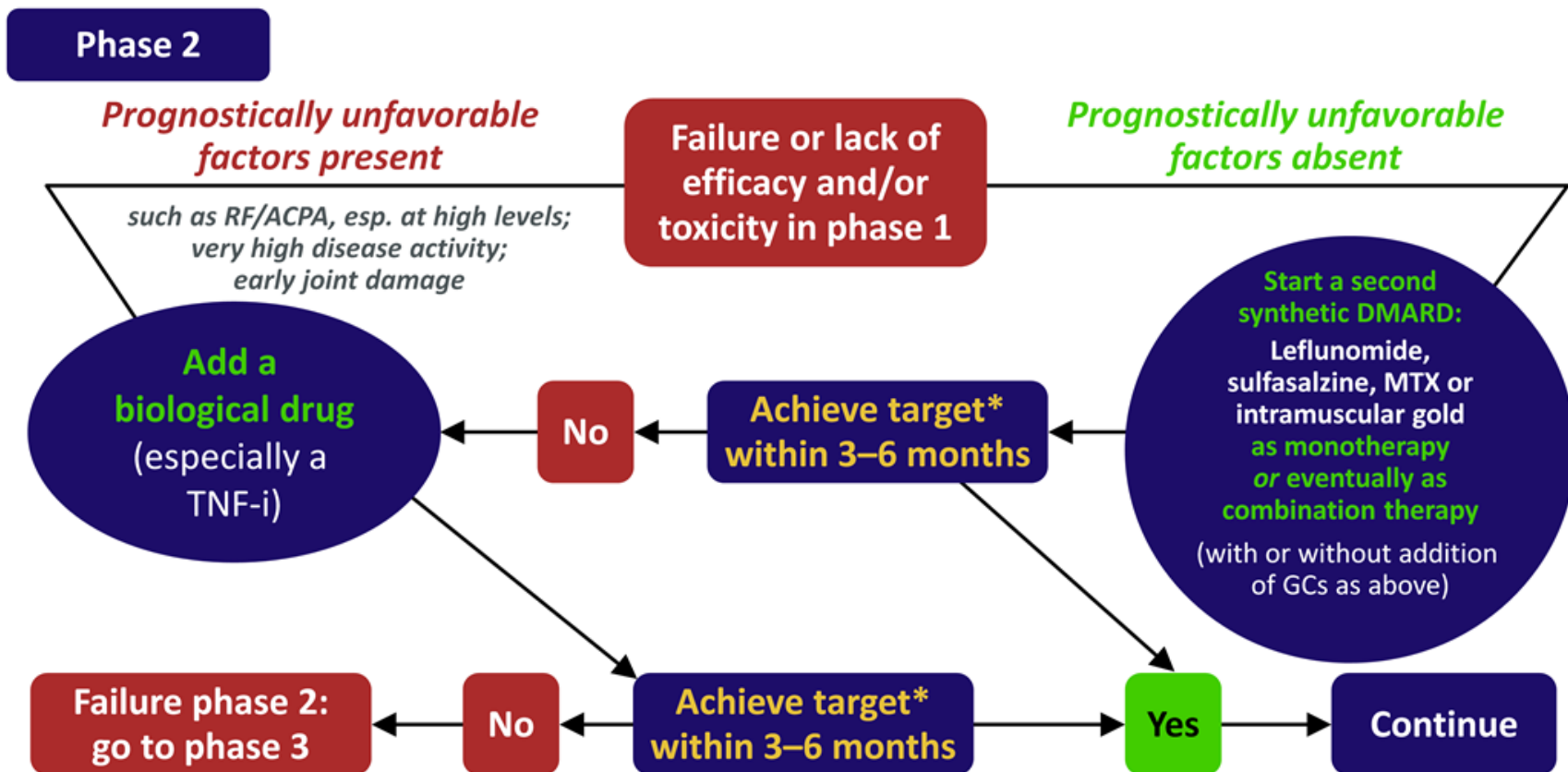
*The treatment target is clinical remission or, if remission is unlikely to be achieved, at least LDA

EULAR, European League Against Rheumatism; GC, glucocorticoids; LDA, low disease activity.

Smolen JS, et al. *Ann Rheum Dis.* 2010;69:964-975.

EULAR RA Treatment Algorithm: Regular Monitoring (Every 3–6 Months) Is Critical to Optimizing Outcomes

Phase 2 of EULAR RA treatment algorithm



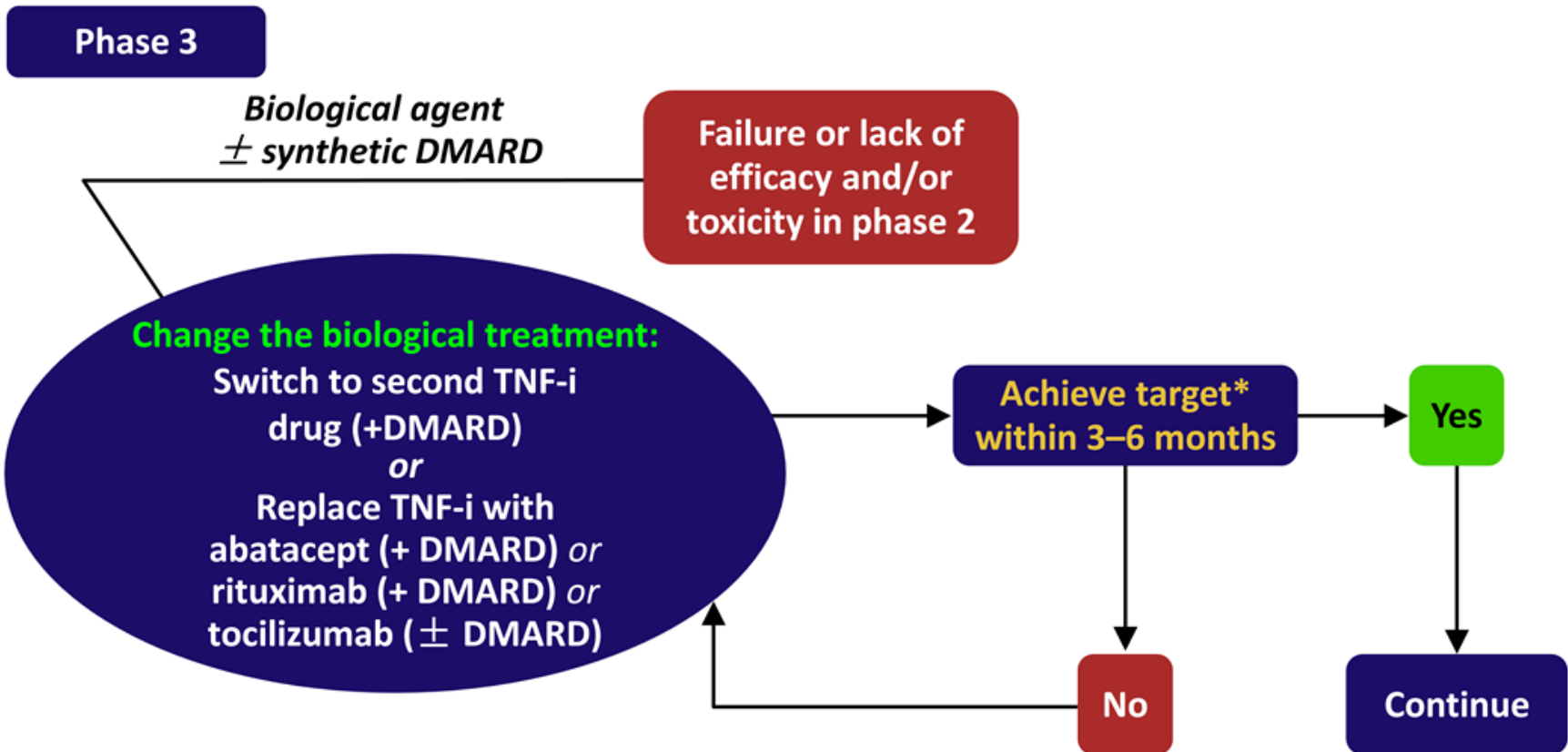
*The treatment target is clinical remission or, if remission is unlikely to be achieved, at least LDA

EULAR, European League Against Rheumatism; RF, rheumatoid factor; ACPA, anti-cyclic peptides antibodies; TNF-i, tumor necrosis factor inhibitor; GC, glucocorticoid; LDA, low disease activity.

Smolen JS, et al. *Ann Rheum Dis.* 2010;69:964-975.

EULAR RA Treatment Algorithm: Regular Monitoring (Every 3–6 Months) Is Critical to Optimizing Outcomes

Phase 3 of EULAR RA treatment algorithm

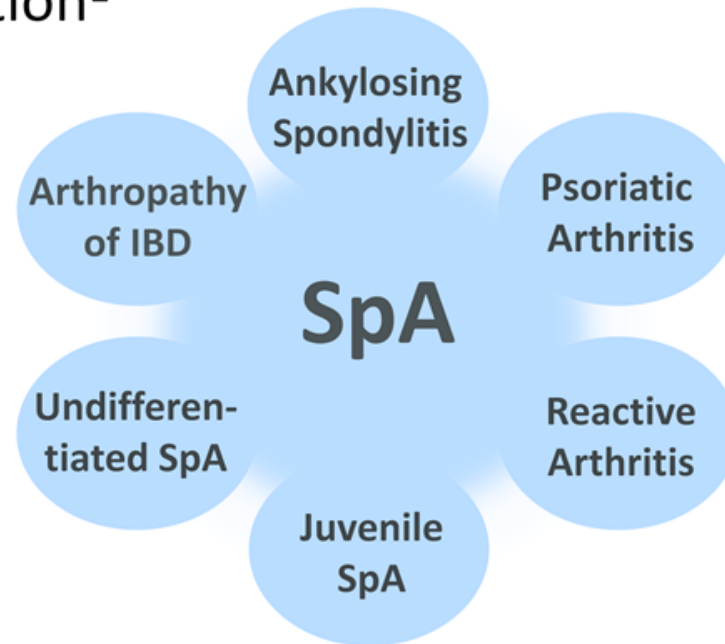


*The treatment target is clinical remission or, if remission is unlikely to be achieved, at least LDA
EULAR, European League Against Rheumatism; TNF, tumor necrosis factor; LDA, low disease activity.

Smolen JS, et al. *Ann Rheum Dis*. 2010;69:964-975.

Spondyloarthritis (SpA)

- ▶ Spectrum of SpA disorders: distinct clinical features, common genetic predisposition¹



- ▶ SpA disorders are associated with the HLA-B27 gene²
- ▶ They may be categorized as axial or peripheral, based on their predominant clinical manifestations²

IBD, inflammatory bowel disease; HLA-B27 gene, human leukocyte antigen B27 gene

1. Zeidler H, et al. *Ann Rheum Dis.* 2011;70:1-3; 2. Philipose J, et al. *J Musculoskel Med* 2011; 28:1-5

Spondylartropatie ... hlavní charakteristiky



Okno

Uveitida

Kůže

Psoriáza



Axiální postižení

Sacroiliitida, spondylitida



Močový trakt

Urogenitální reaktivní arthritida



Periferní postižení

Arthritida, enthesitida, daktylitida



Zánětlivá choroba střevní

Enterogenní reaktivní arthritida

Associations with HLA-B27

Rheumatic diseases

Ankylosing spondylitis

Reiter's syndrome/reactive arthritis

IBD related arthritis

Psoriatic arthritis

Degree of associations

>90%

>80%

~75%

~50%

Normal Associations

Native Americans

Caucasians

Blacks

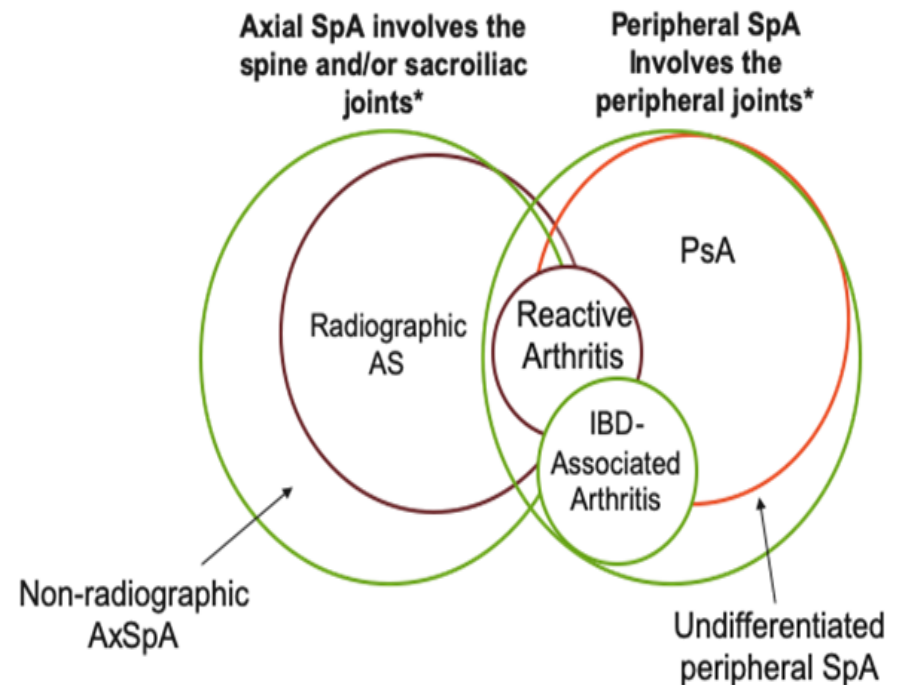
13%

8%

4%

Introduction to the SpA Spectrum of Diseases

- SpA family divided into axial SpA (both radiographic and non-radiographic) and peripheral SpA^[a]
 - Undifferentiated peripheral SpA: patients who do not fit any of these categories^[a]
- Symptoms may overlap and progress into one another^[a]



Axial and Peripheral SpA

SpA Classification¹

Predominant Axial

Early non-radiographic SpA
Ankylosing spondylitis

Predominant Peripheral

Reactive arthritis
Psoriatic arthritis
Arthritis with IBD
Undifferentiated SpA

Axial SpA Criteria^{1,2}

Sacroiliitis by MRI* or radiographs[†]
+ one SpA clinical criterion

OR

HLA-B27
+ two SpA clinical criteria

SpA clinical criteria

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)

- Uveitis
- Dactylitis
- Psoriasis
- IBD

- Good response to NSAIDs
- Family history of SpA
- Positive HLA-B27
- Positive C reactive protein

*Active inflammation compatible with sacroiliitis; †According to the modified New York Criteria

MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; SpA, spondyloarthritis

1. Sieper J, et al. 2011; Springer-Verlag London Limited;
2. Rudwaleit M, et al. *Ann Rheum Dis* 2009;68:770–776

The Prevalence of Extra-Axial Features



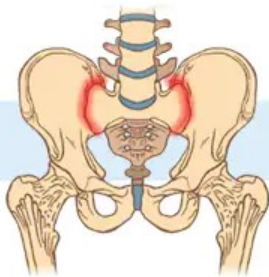
AS, ankylosing spondylitis.

a. Robinson PC, et al. Nat Rev Rheumatol. 2021;17:109-118; b. de Winter JJ, et al. Arthritis Res Ther. 2016;18:196.

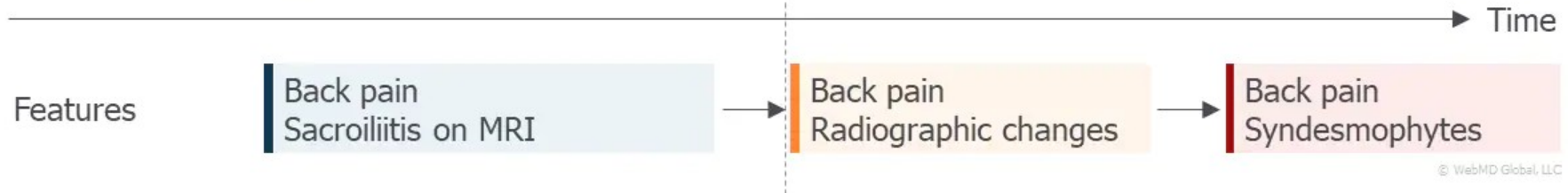
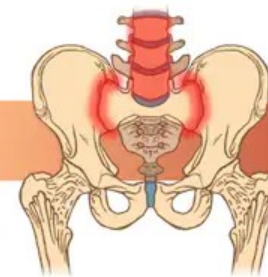
AxSpA Is a Continuum of Disease

The concept of axSpA has expanded from ankylosing spondylitis with evidence of erosions to a spectrum of disease encompassing non-radiographic axSpA and radiographic axSpA^[a]

Non-radiographic axial spondyloarthritis



Radiographic axial spondyloarthritis (ankylosing spondylitis)



© WebMD Global, LLC

axSpA, axial spondyloarthritis; MRI., magnetic resonance imaging.
a. Robinson PC, et al. Nat Rev Rheumatol. 2021;17:109-118.

Progression of Non-radiographic Axial SpA to AS: Data from GESPIC*

Non-radiographic axial SpA



**12%
in 2 years**

**Main predictor:
elevated CRP****

Ankylosing spondylitis



no definite radiographic sacroiliitis (grade 0 at the right side, grade 1 – possible subchondral sclerosis – at the left side)

definite radiographic sacroiliitis (grade 2 bilaterally) fulfilling the radiographic criterion of the modified New York criteria

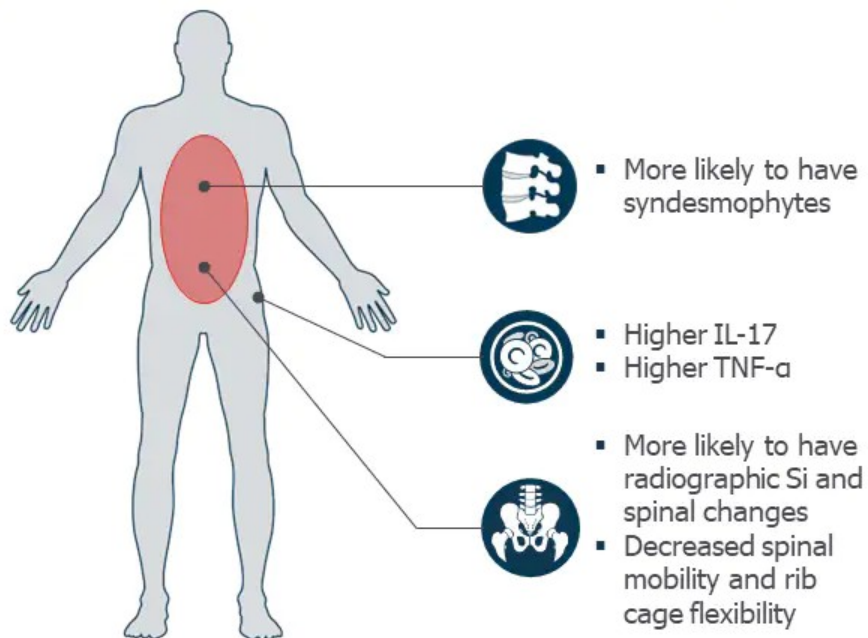
*GESPIC = GERman Spodyloarthritis Inception Cohort

**Odds ratio for progression in patients with elevated serum C-reactive protein level (>6 mg/l) was: 4.11 (95% CI 1.13-14.95).

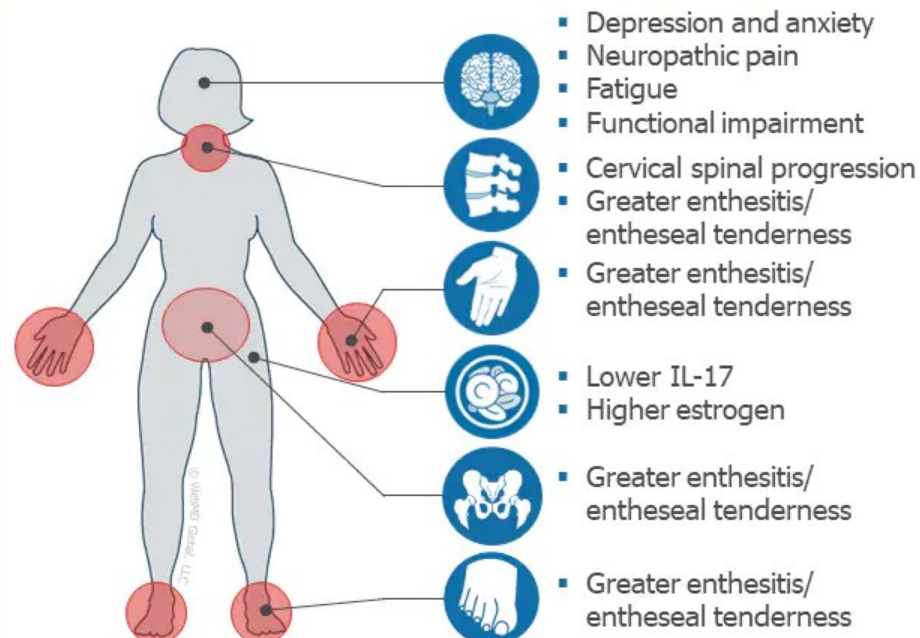
Gender Differences in AxSpA

Emerging evidence suggests that women and men experience axSpA differently, with women presenting later and with prolonged diagnostic delay vs men (8.8 vs 6.5 y, respectively, $P = .01$)

Greater axial involvement

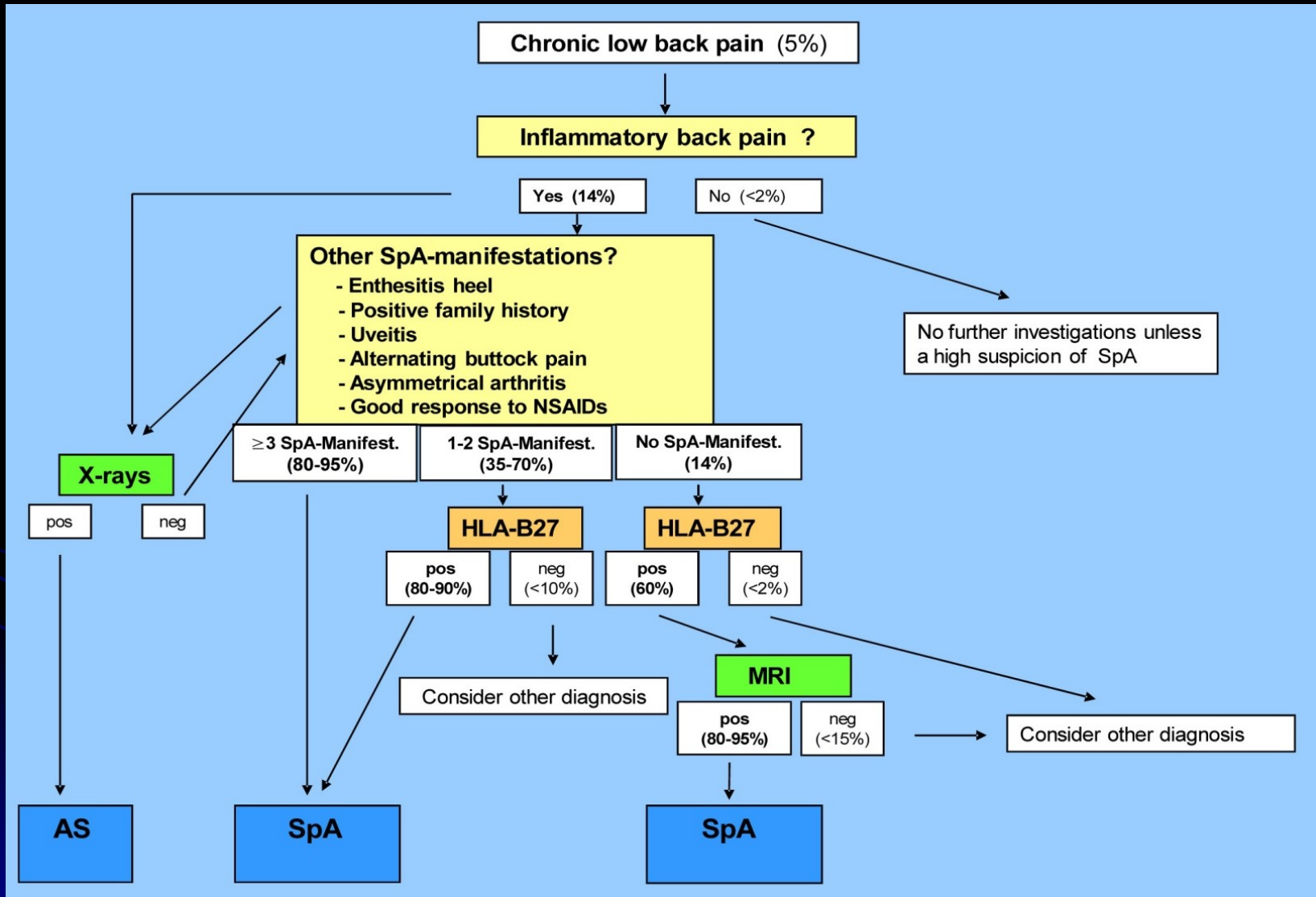


Greater peripheral and upper axial involvement



IL-17, interleukin 17; TNF- α , tumor necrosis factor alpha.
Wright GC, et al. Semin Arthritis Rheum. 2020;50:687-694.

Diagnosis of axSpA: Diagnosis



Inflammatory Back Pain

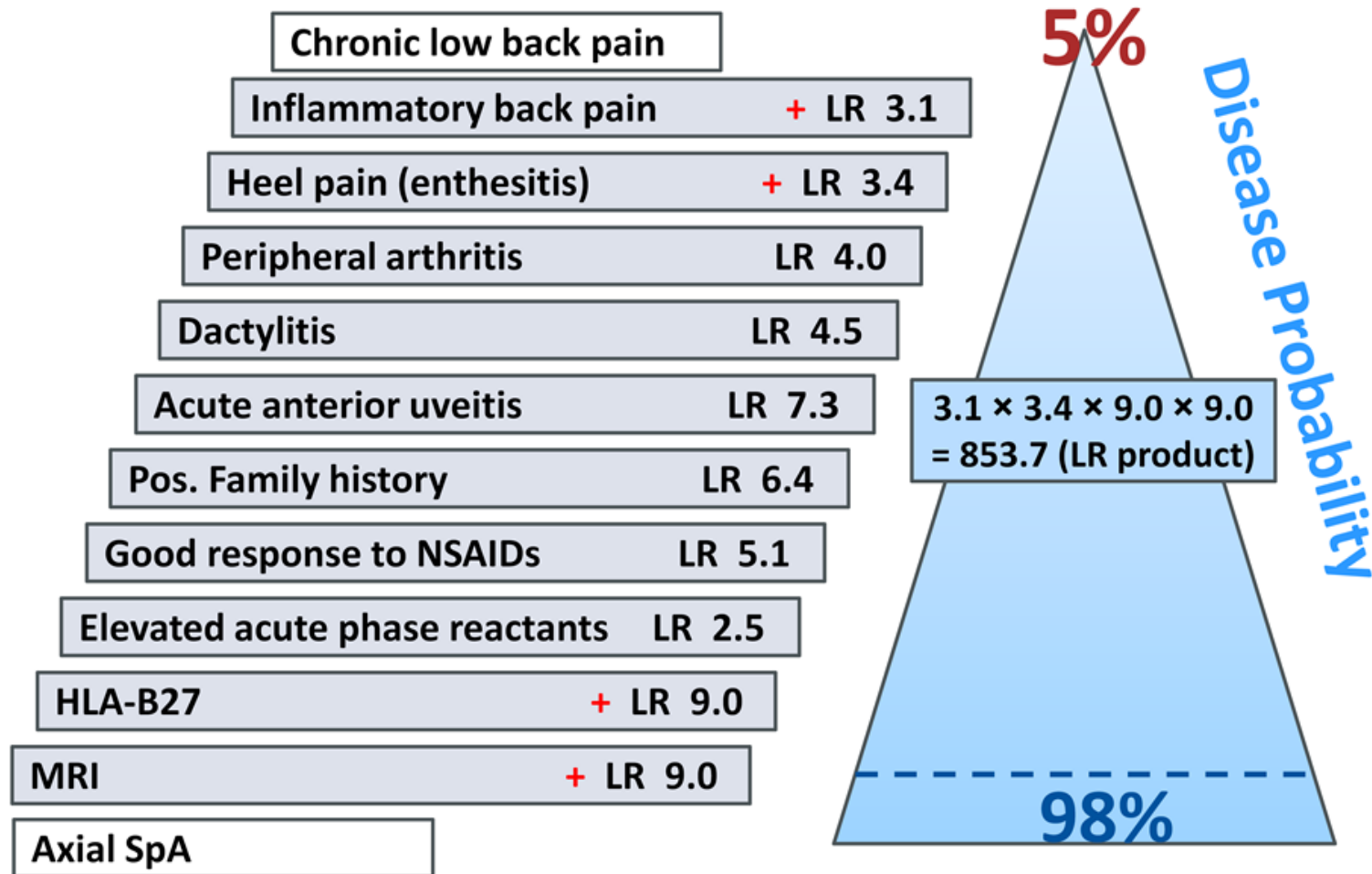
- ⦿ Worse in the late night and early morning
- ⦿ Pain interferes with sleep to the point that the patient gets up to walk in the middle of the night
- ⦿ The discomfort can be characterized by alternating buttock pain.
- ⦿ prolonged morning stiffness of greater than 30 minutes.

Inflammatory Back Pain

- ⦿ Exercise alleviates the pain rest makes it worse.
- ⦿ Affects younger patients
- ⦿ Peaking during the mid-20s
- ⦿ onset before the age of 40

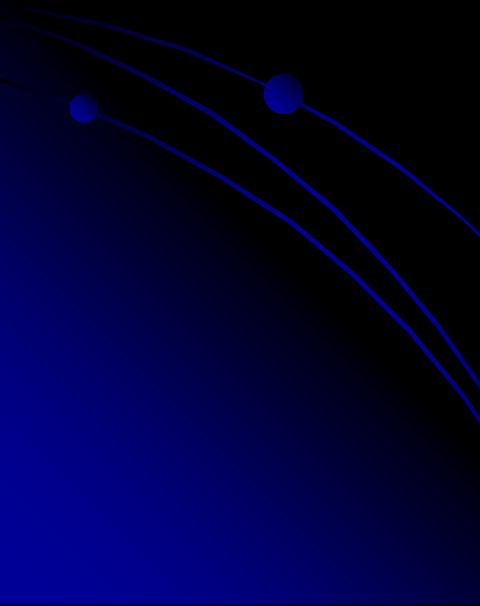


Diagnostic Pyramid for Axial Spondyloarthritis

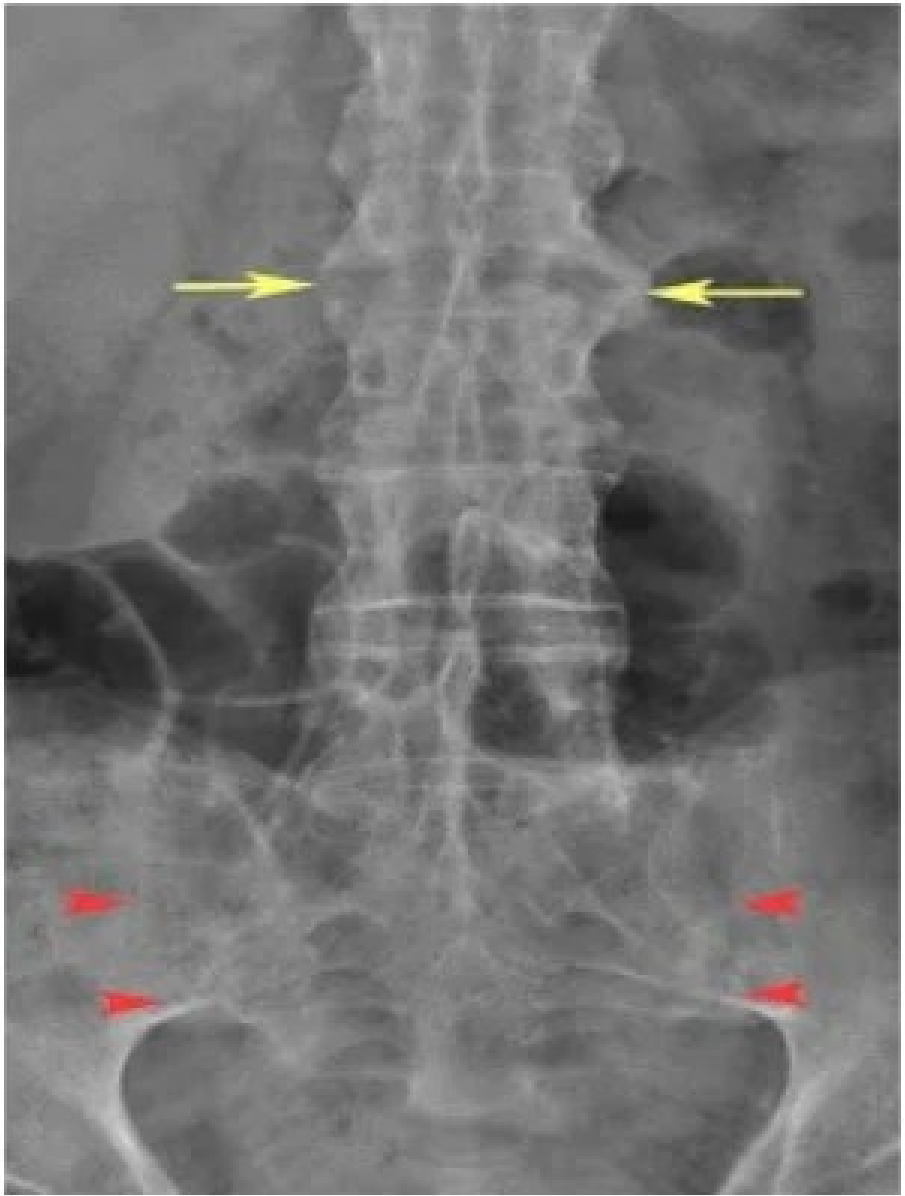


LR, likelihood ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; HLA-B27 gene, human leukocyte antigen B27 gene; MRI, magnetic resonance imaging; SpA, spondyloarthritis

Rudwaleit M, et al. *Arthritis Rheum* 2005;52:1000–1008



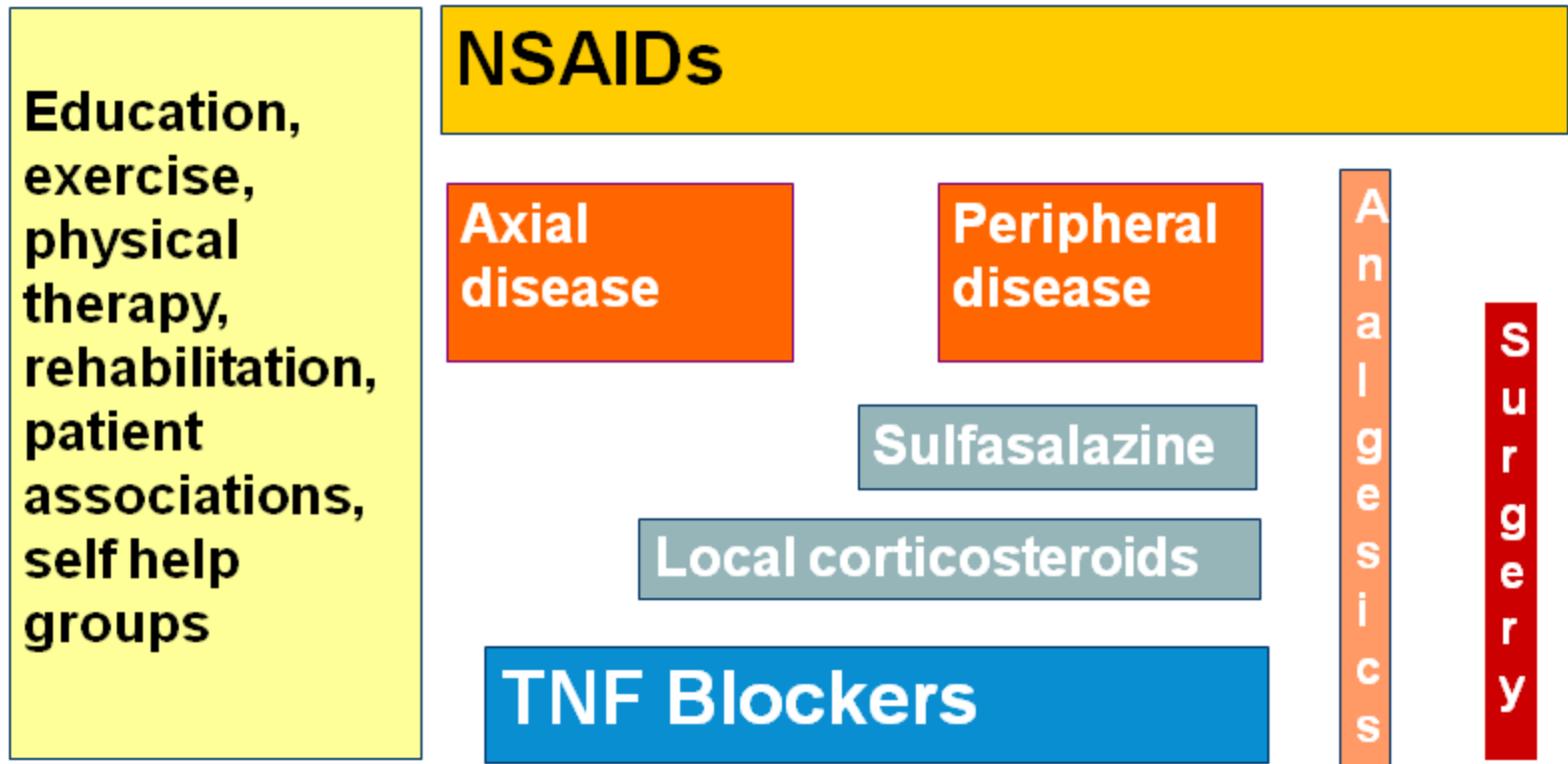




Ocular Manifestations

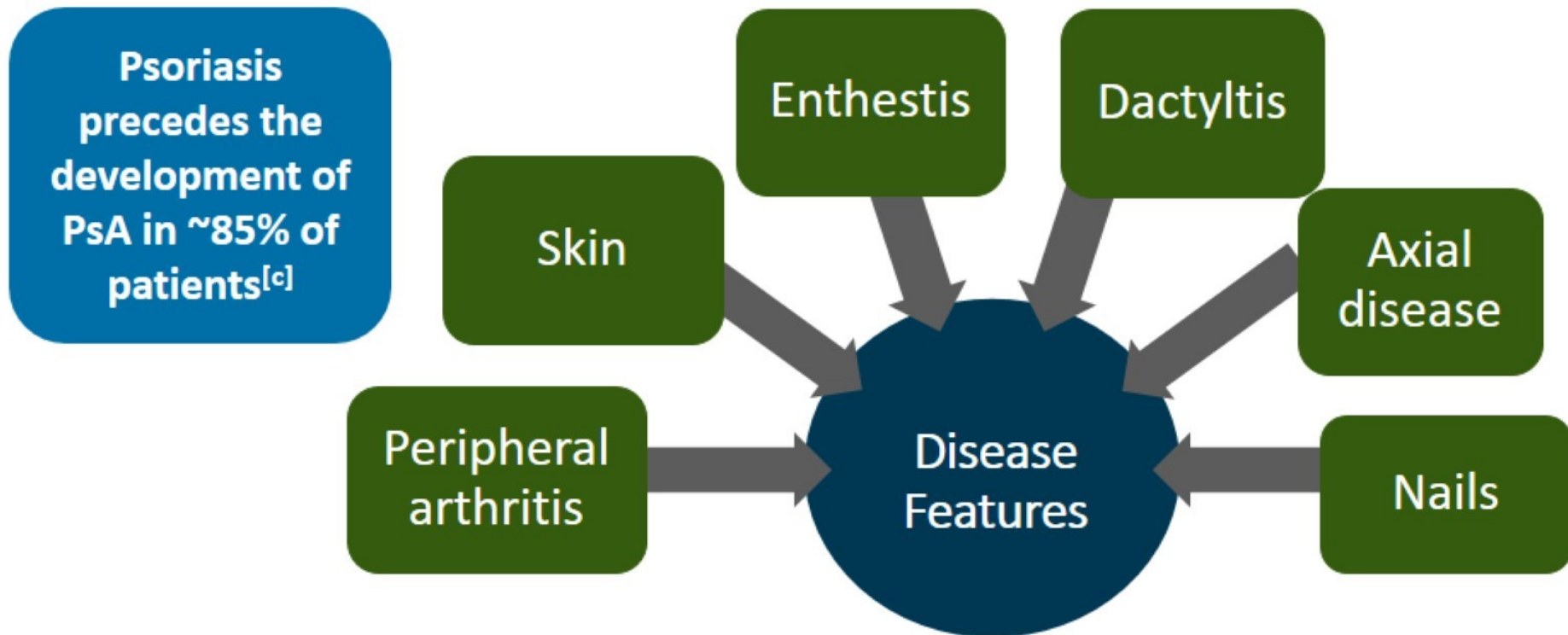
- ① Uveitis is one of the most common
- ② occurring in 25% to 40% of patients.
- ③ there appears to be no correlation between the course of inflammatory eye disease and that of the arthritis.

ASAS/EULAR Recommendations for the Management of Ankylosing Spondylitis



Psoriatic Arthritis

- Heterogeneous disease with numerous musculoskeletal and dermatological manifestations^[a,b]



Classical Description of PsA Using the Diagnostic Criteria of Moll and Wright

□ Including 5 clinical patterns:

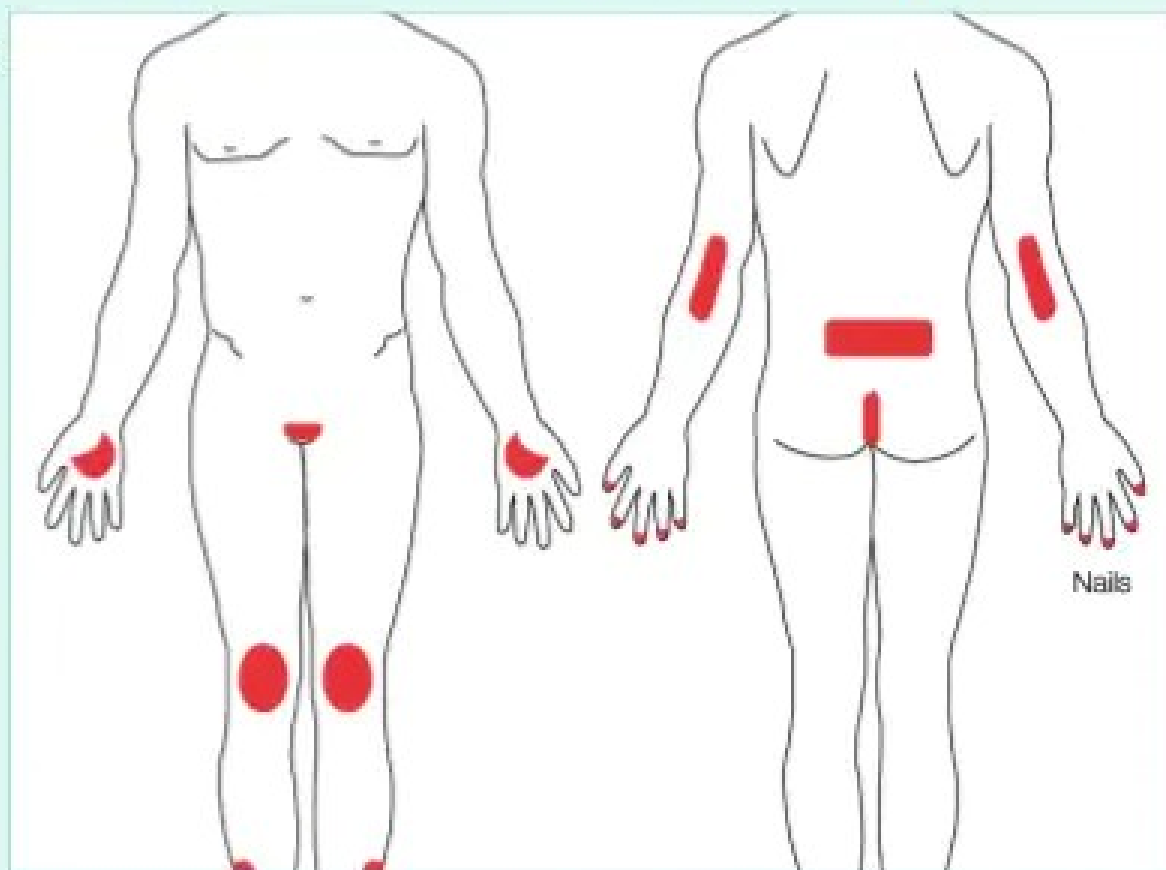
- × Asymmetric mono-/oligoarthritis (~30% [range 12-70%])¹⁴
- × Symmetric polyarthritis (~45% [range 15-65%])¹⁴
- × Distal interphalangeal (DIP) joint involvement (~5%)¹
- × Axial (spondylitis and Sacroiliitis) (HLA-B27) (~5%)^{1,3}
- × Arthritis Mutilans (<5%)^{1,3}



- **However patterns may change over time and are therefore not useful for classification** ⁵

COMMON SITES AFFECTED BY PSORIASIS

- Can affect any part of the body – typically scalp, elbow, knees and sacrum
- Extent of disease varies



ASYMMETRICAL OLIGOARTICULAR ARTHRITIS

- ✘ MC type (70%)
- ✘ Asymmetrical similar to low grade gout.
- ✘ Sausage like swelling of one or more digit (dactylitis).
- ✘ A large joint, such as the knee, is also commonly involved.
- ✘ Usually, <5 joints are affected at any one time.
- ✘ Enthesitis
- ✘ Flexor sheath synovitis



Dactylitis in PsA

- Inflammation of an entire digit^[a]
- Reported in 40% to 50% of patients^[b]
- Most prevalent in the third and fourth toes but may also involve the fingers^[b]
- Can be either acute (swelling, redness of the skin, and pain) or chronic (swelling without inflammation)^[a]
- Often associated with severe disease that is characterized by polyarthritis, bone erosion, and new bone formation^[a]



Republished with permission of Dove Medical Press, from Optimal management of dactylitis in patients with psoriatic arthritis, Toshiyuki Yamamoto, 2015, 2015; permission conveyed through Copyright Clearance Center, Inc.^[c]

Enthesitis in PsA

- Inflammation of connective tissue between tendon or ligament and bone
- Prevalence of enthesitis in patients with PsA:
 - 30% to 50% based on clinical exam
 - 70% based on imaging
- Commonly involves the plantar fascia and Achilles' tendon



SYMMETRICAL POLYARTHRITIS

- ✗ Rheumatoid like pattern.
- ✗ 15%
- ✗ Hands, wrists, ankles, and feet may be involved.
- ✗ D/D from RA by
 - DIP joint involvement,
 - Morning stiffness
 - Fusiform deformity
 - Wind swept deformity
 - Relative asymmetry,
 - Subcutaneous nodules absent.
 - RF negative.
 - Milder, with less deformity.



DISTAL INTERPHALANGEAL ARTHROPATHY

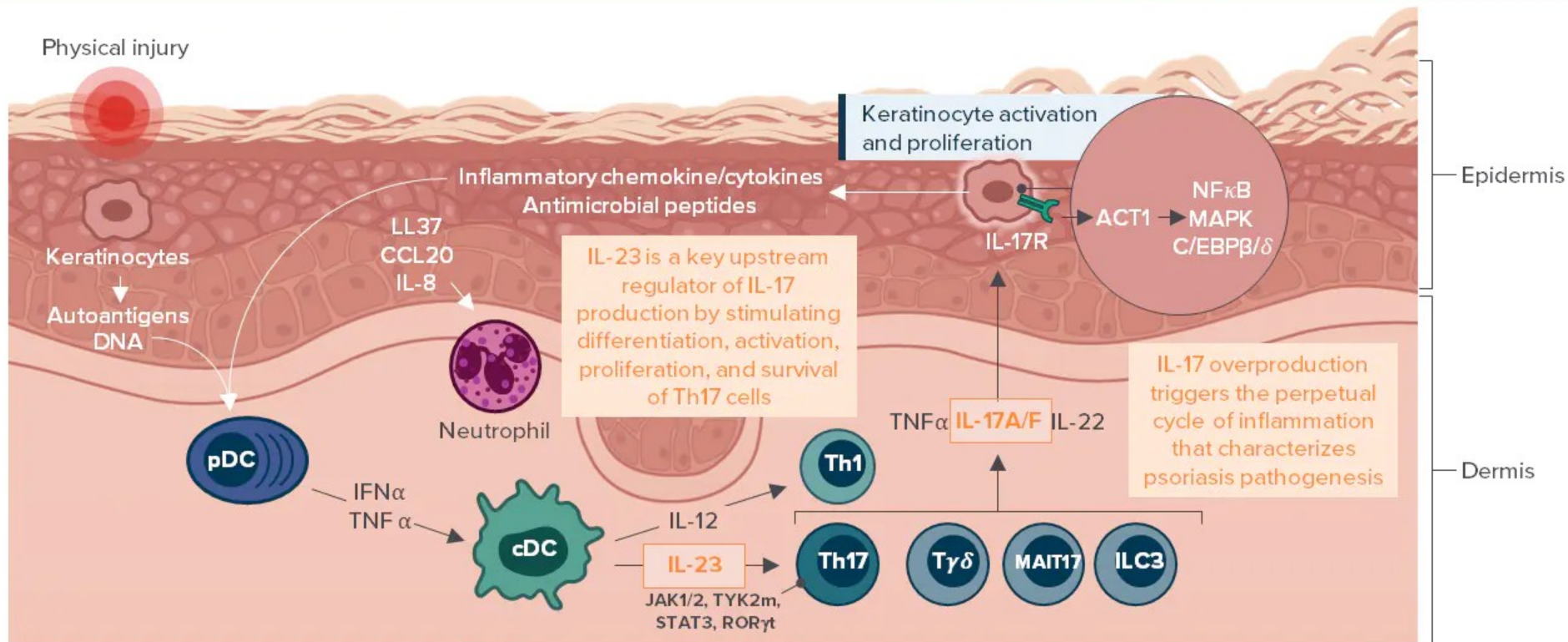
- ✘ Classical form
- ✘ Less common 16%
- ✘ Involvement of the nail with significant inflammation of the paronychia and swelling of the digital tuft may be prominent,
- ✘ 30 pits with inflammatory arthritis of DIP joints considered diagnostic.

Crumbling nail/DIP joint involvement

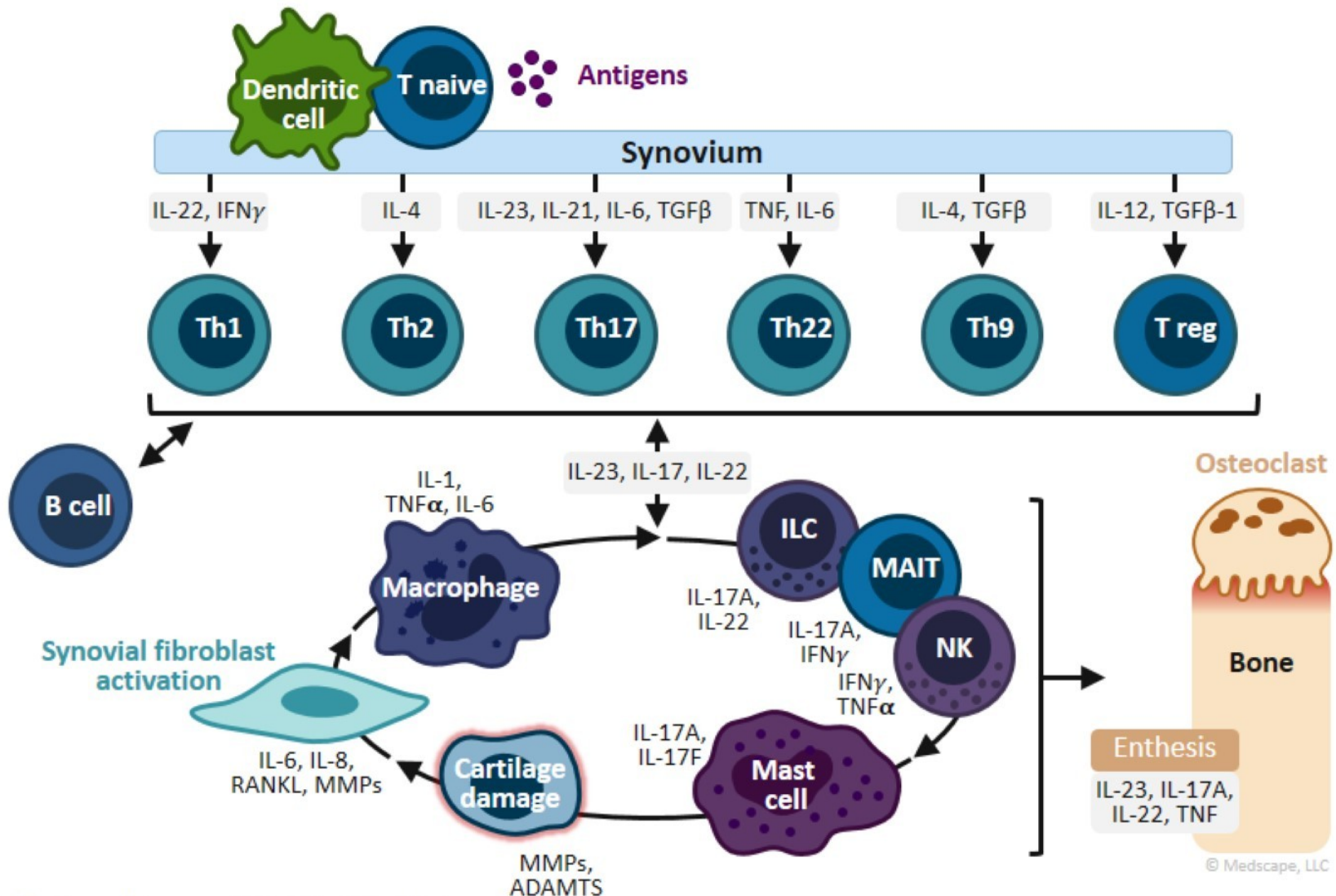


Key Cytokines Involved in Psoriasis Pathogenesis

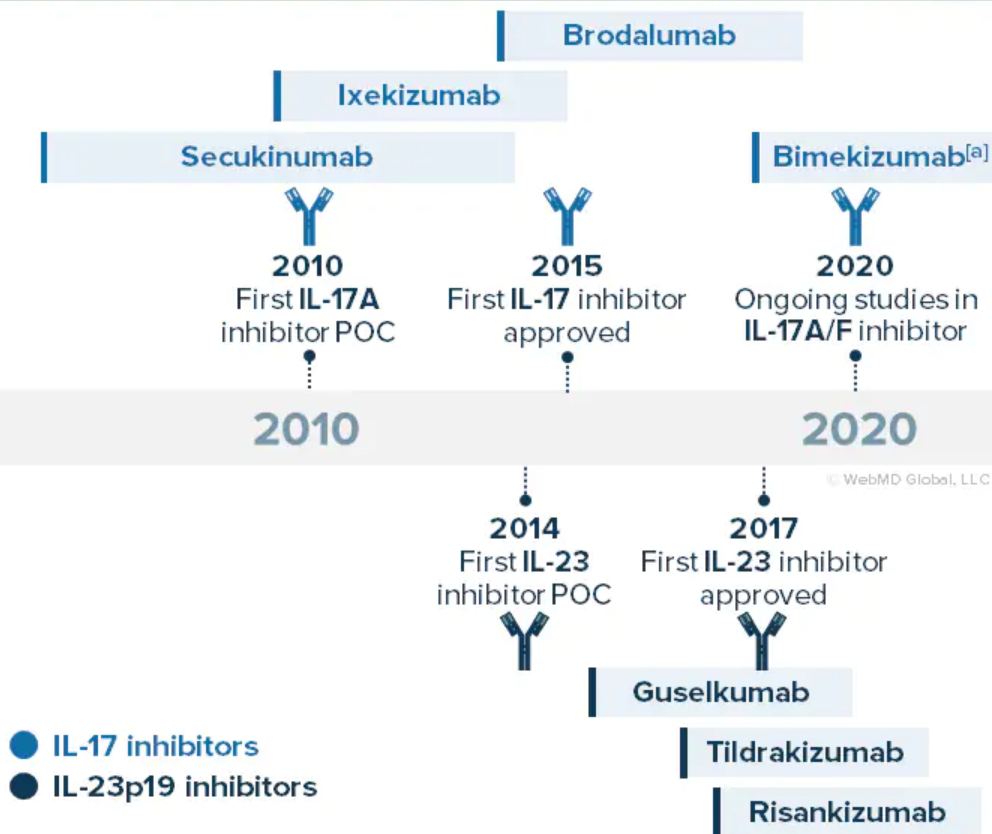
IL-23 and IL-17 Are Central to the Pathogenesis of Psoriasis



Key Cell Types and Activated Pathways in Psoriatic Arthritis



IL-23p19 and IL-17 Inhibitors for Psoriasis

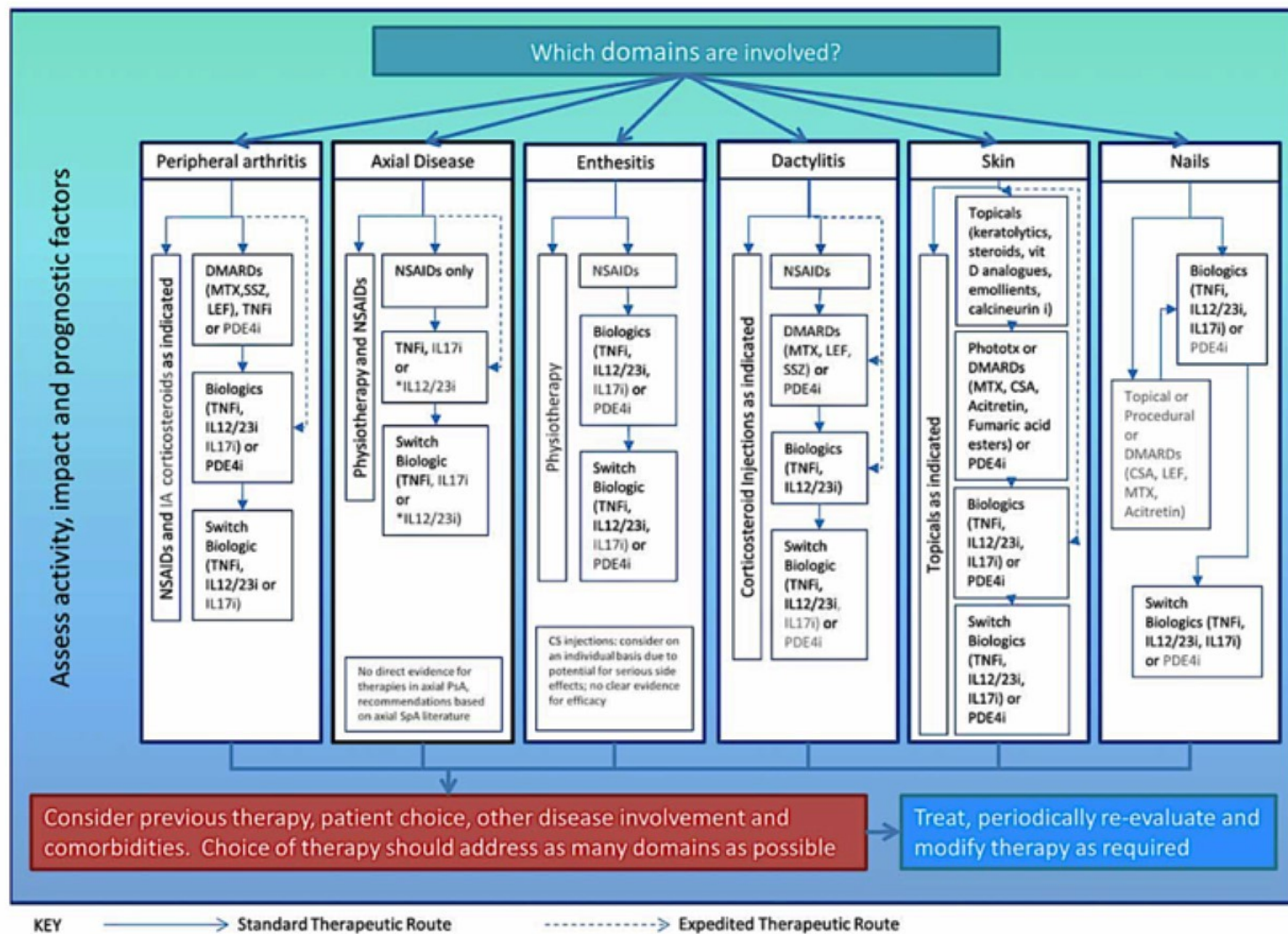


IL-23p19 and **IL-17** inhibitors appear more efficacious compared with TNF- α and IL-12/IL-23 dual inhibitors^[b]

POC, proof-of-concept.

Gooderham MJ, et al. J Eur Acad Dermatol Venereol. 2018;32:1111-1119; a. Bimekizumab [PI]. Approved August 2021; b. Armstrong AW, et al. Dermatol Ther (Heidelb). 2021;11:885-905.

GRAPPA Treatment Scheme



PsA



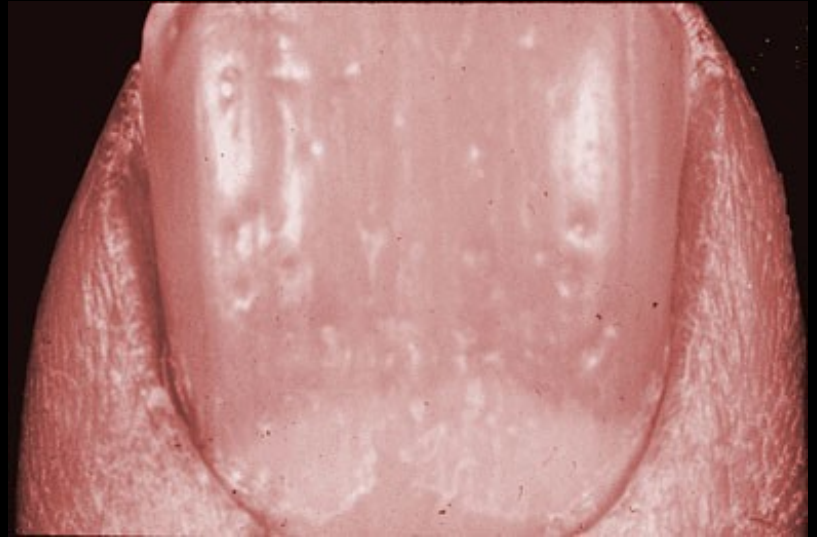
PsA



Postižení nehtů u PsA



**Postižení DIP kloubů s
onycholýzou**



„Olejové skvrny“

RTG nálezy u psoriatické artritídy



Kloubní postižení u PsA



Párkovitý prst



Postižení DIP kloubů



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