PÉCSI TUDOMÁNYEGYETEM
ÁLTALÁNOS ORVOSTUDOMÁNYI KAR

Rheumatoid arthritis, SLE, szisztémás vaszkulitiszek új kezelési szempontjai

Kumánovics Gábor

PTE, KK, Reumatológiai és Immunológiai Klinika

Pécs

BELGYÓGYÁSZAT KÖTELEZŐ SZINTENTARTÓ TANFOLYAM

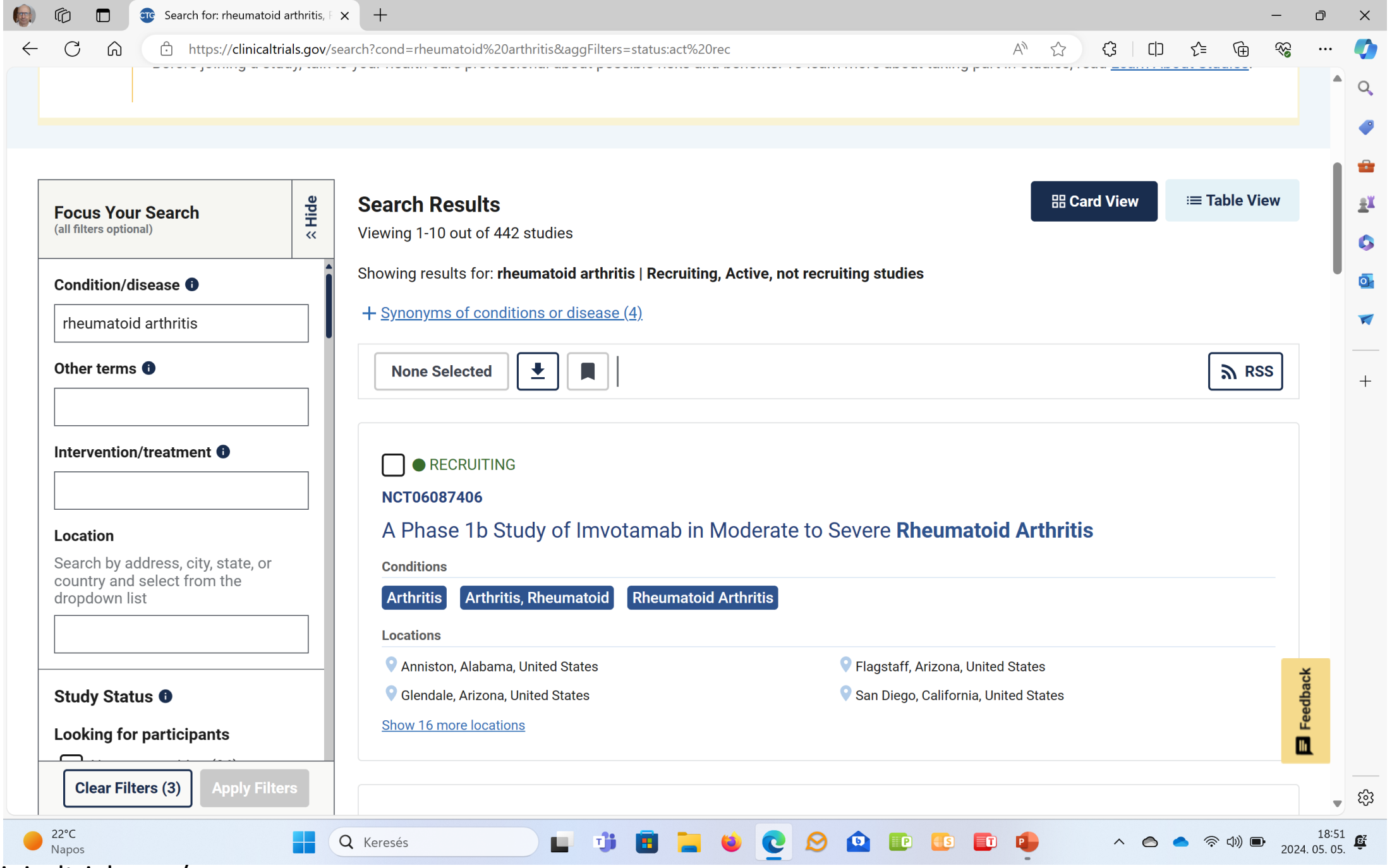
2024. október 10 - október 12.

PÉCS, Szentágothai János Kutatóközpont (Ifjúság útja 20.)

Előadás vázlata

- Új kezelési ajánlások
  - RA – 2022
    - D2T - 2021
  - SLE – 2023
  - Vasculitisek – 2022
  - ILD - 2024
- Új gyógyszerek és indikációk

- **Új gyógyszerek és indikációk**
  - **Előadás címével kapcsolatosak**
  - **Néhány másik is…**
- **Új kezelési ajánlások**
  - **RA – 2022**
    - **D2T - 2021**
  - **SLE – 2023**
  - **Vasculitisek – 2022**
  - **ILD - 2024**

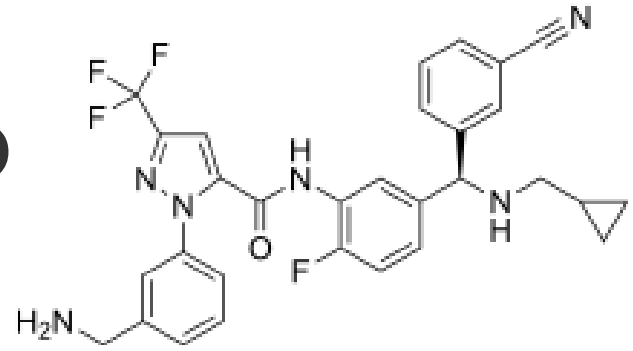


https://clinicaltrials.gov/

Új FDA indikációk 2020-2024.

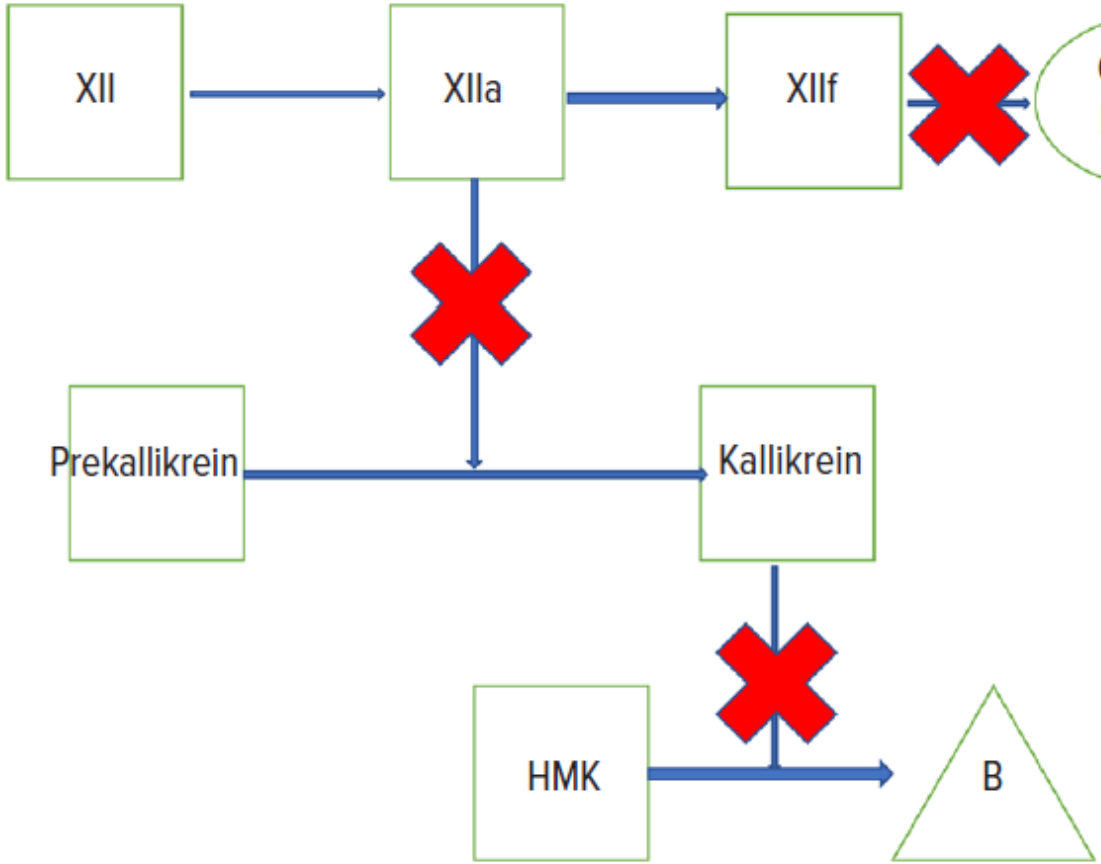
- 2020.
  - 53 gyógyszer
    - **Enspryng** (satralizumab) is used to treat neuromyelitis optica spectrum disorder (**NMOSD**) in adult patients with a particular antibody (who are anti-aquaporin-4 or AQP4 antibody positive). IL-6R-antagonist
    - **UPLIZNA** (inebilizumab) is used to treat neuromyelitis optica spectrum disorder (**NMOSD**) in adult patients with a particular antibody (who are anti-aquaporin-4 or AQP4 antibody positive). Anti-CD19 MAB
    - **Berotralstat** - patients with hereditary angioedema - plasma kallikrein inhibitor
    - **Ozanimod** – sclerosis multiplex - a sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Ozanimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. T
- 2021.
  - 51 gyógyszer
    - **Vyvgart** (efgartigimod) for the treatment of generalized myasthenia gravis (gMG) in adults who test positive for the anti-acetylcholine receptor (AChR) antibody. Antibody fragment to target the neonatal Fc receptor (FcRn).
    - **Tezspire** - tezepelumab-ekko - thymic stromal lymphopoietin (TSLP) blocker - asthma
- 2022.
  - 37 gyógyszer
- 2023.
  - 55 gyógyszer
    - **Sparsentan** is an endothelin and angiotensin II receptor antagonist indicated to reduce proteinuria in adults with **primary immunoglobulin A nephropathy** (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g
    - **Bimekizumab -** moderate to severe plaque psoriasis - interleukin-17A and F antagonist
    - **Zilucoplan** – C5-inhibítor - generalized myasthenia gravis
    - **Etrasimod** - sphingosine 1-phosphate receptor modulator - ulcerative colitis
    - **Sparsentan** - endothelin and angiotensin II receptor antagonist - primary immunoglobulin A nephropathy
- 2024
  - 15 gyógyszer
    - **Mavorixafor** - CXC chemokine receptor 4 antagonist - WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis)
    - **Sotatercept-csrk** - activin signaling inhibitor - treatment of adults with PAH, WHO Group 1
    - **Resmetirom** - thyroid hormone receptor-beta (THR-beta) agonist - noncirrhotic non-alcoholic steatohepatitis

2000 – berotralstat - Orladeyo

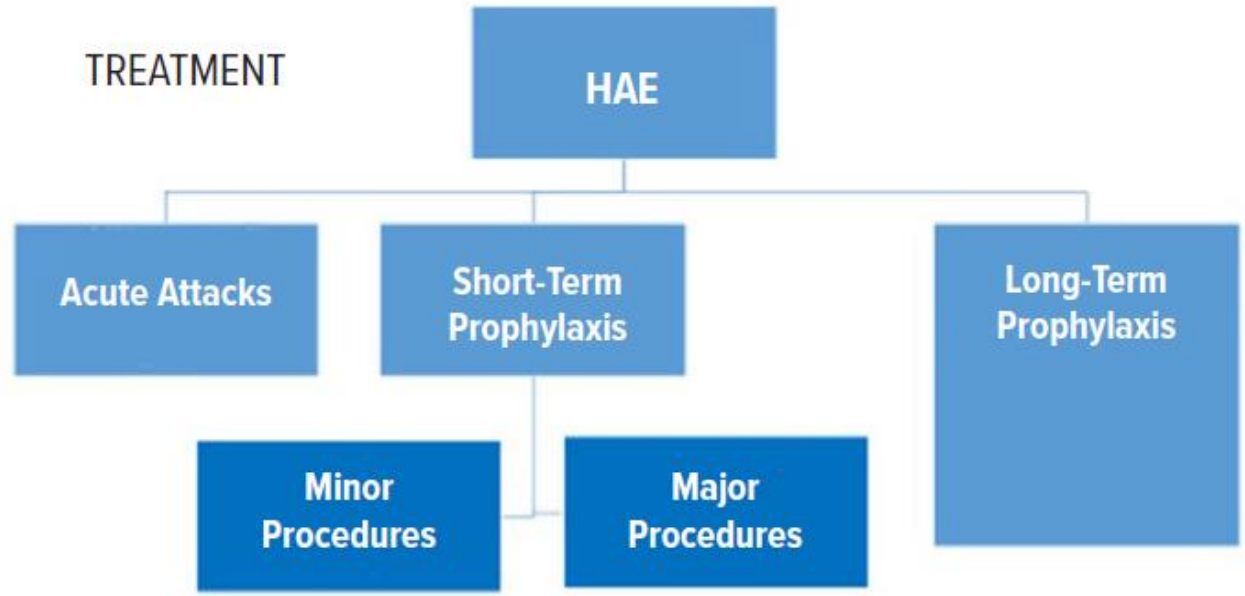


- The first targeted, oral administration of C1-INH-HAE prophylactic therapy has become available for clinical practice.
- The efficacy, safety and tolerability of the kallikrein inhibitor berotralstat have been demonstrated in multicentre placebo-controlled trials.
- Several doses of berotralstat have been shown to be safe in clinical trials, with a significant reduction in HAE attacks.
- The drug was well tolerated, with the most common adverse events being mild upper respiratory tract infections and gastrointestinal symptoms.

Expert Review of Clinical Immunology 19, 2023,
Henriette Farkas Zsuzsanna Balla



XII: Factor XII or Hagemann Factor
XII: Activated Factor XII
XIIf: Hageman Factor Fragment
HMK: High Molecular Weight Kininogen
B: Bradykinin
✖: Inhibited by C1 inhibitor

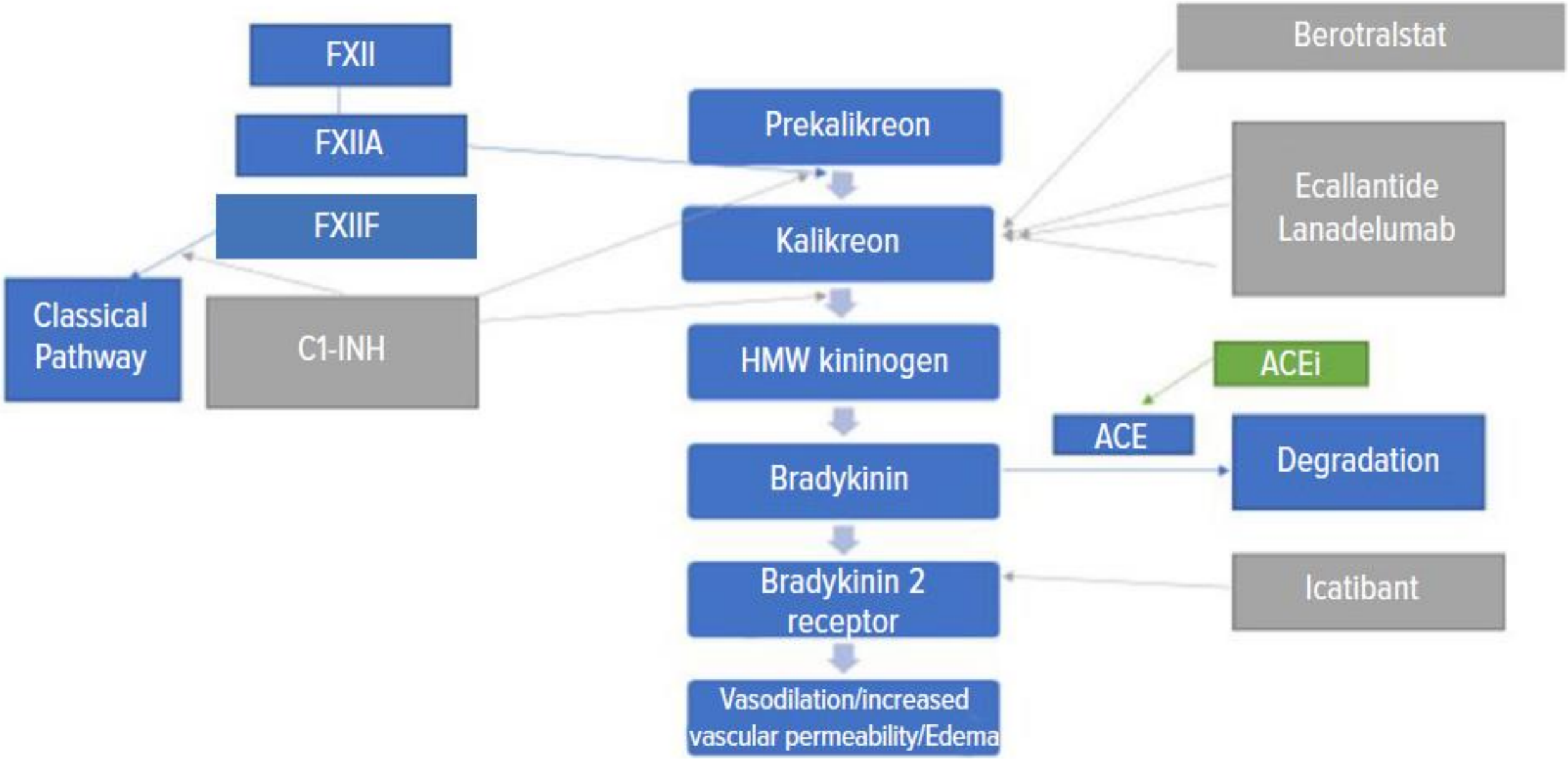


WMJ. 2022 Apr;121(1):48-53.

	C1-INH Level	C1-INH Function	C4	C3	C1Q
HAE type 1	Low	Low	Low	Normal	Normal
HAE type 2	Normal-High	Low	Low	Normal	Normal
HAE-nC1-INH	Normal	Norman	Normal	Normal	Normal
Acq-AE	Low	Low	Low	Low-Normal	Low
ACEi-AE	Normal	Normal	Normal	Normal	Normal
IAE	Normal	Normal	Normal	Normal	Normal

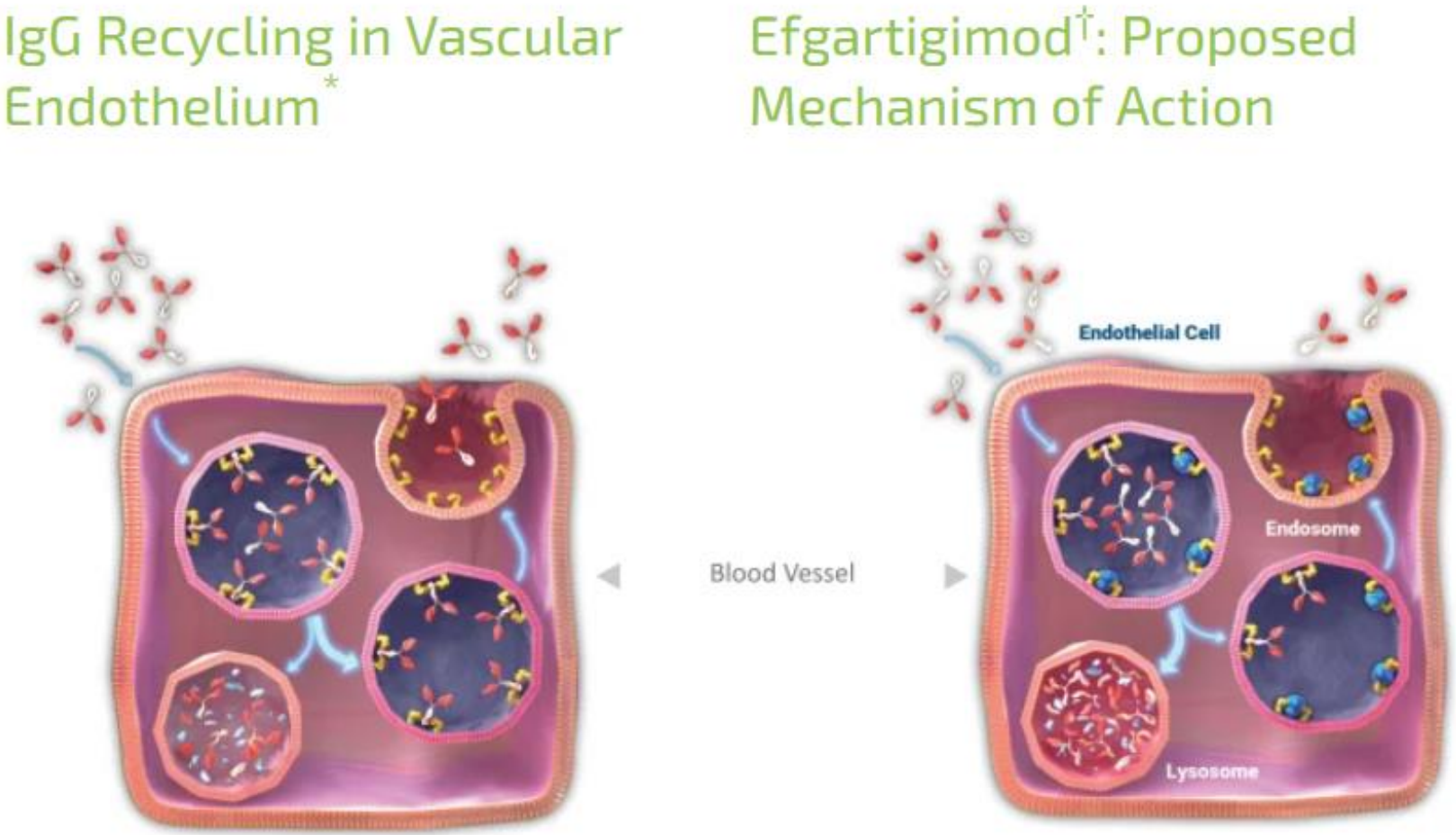
Abbreviations: CI-INH, C1 inhibitor; HAE, hereditary angioedema; HAE-nC1-INH, HAE with normal C1-INH; Acq-AE, acquired angioedema; ACEi-AE, ACE inhibitor angioedema; IAE, idiopathic angioedema.

WMJ. 2022 Apr;121(1):48-53.

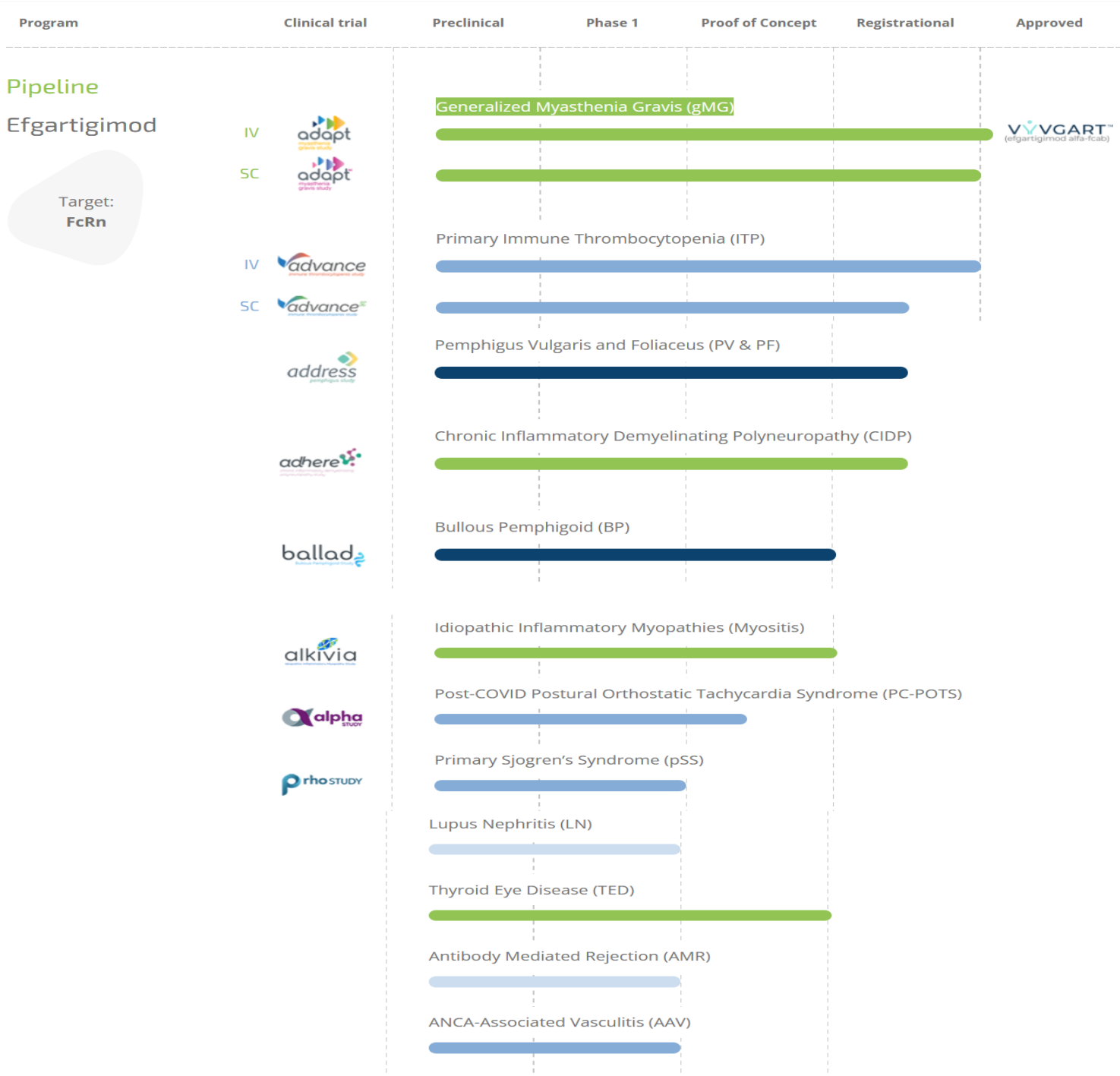


WMJ. 2022 Apr;121(1):48-53.

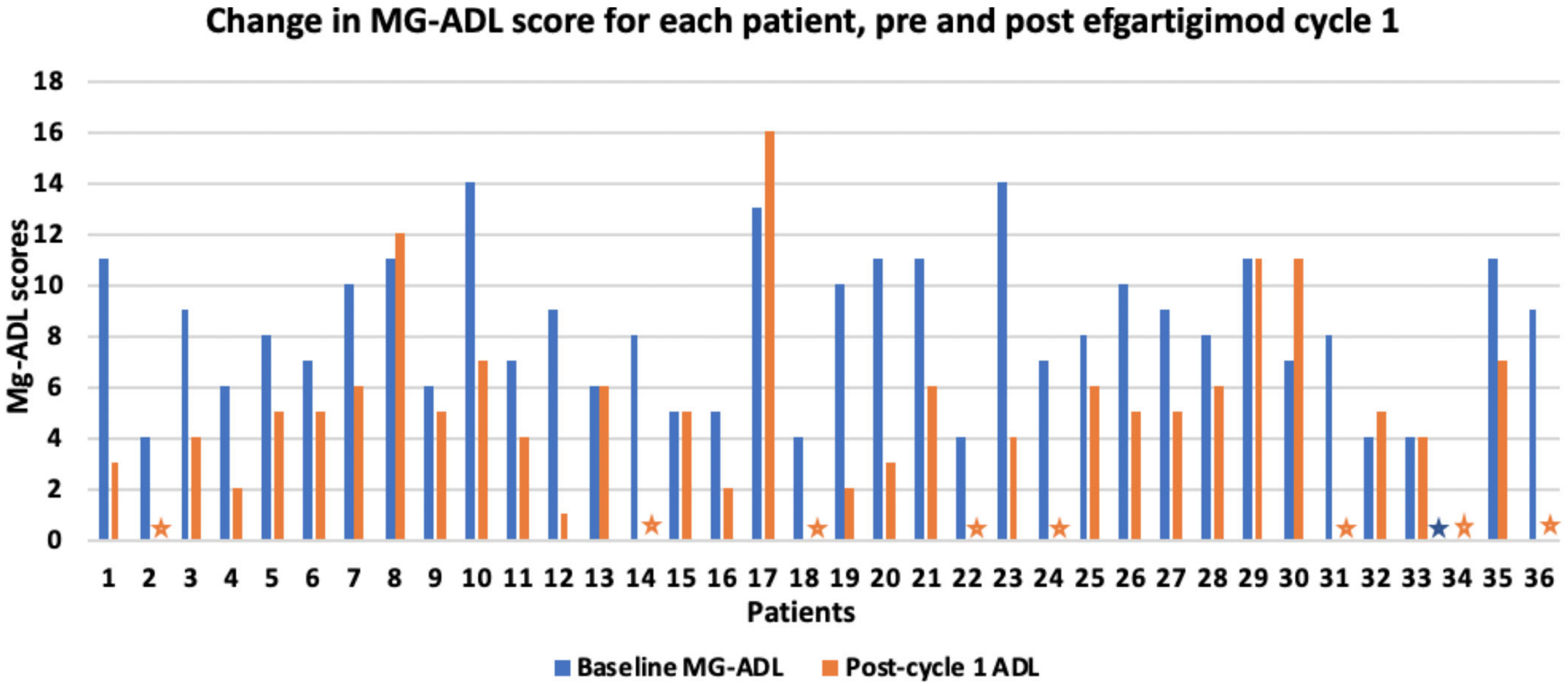
Efgartigimod, an IgG1 Fc fragment, is designed for increased affinity for FcRn. It competes with IgG to occupy FcRn and reduce overall IgG recycling: FcRn has been shown to bind IgGs and rescue them from lysosomal degradation, extending IgG half-life



https://www.argenx.com/pipeline/efgartigimod/mechanism-of-action-Efgartigimod


Program
Clinical trial
Preclinical
Phase 1
Proof of Concept
Registrational
Approved
Pipeline
Efgartigimod
Target:
FcRn
IV
SC
adapt
Generalized Myasthenia Gravis (gMG)
VYVGART
(efgartigimod alfa-fcab)
IV
SC
advance
Primary Immune Thrombocytopenia (ITP)
address
Pemphigus Vulgaris and Foliaceus (PV & PF)
adhere
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
ballad
Bullous Pemphigoid (BP)
alkivia
Idiopathic Inflammatory Myopathies (Myositis)
alpha study
Post-COVID Postural Orthostatic Tachycardia Syndrome (PC-POTS)
rho STUDY
Primary Sjogren's Syndrome (pSS)
Lupus Nephritis (LN)
Thyroid Eye Disease (TED)
Antibody Mediated Rejection (AMR)
ANCA-Associated Vasculitis (AAV)

2001 – Efgartigimod – real world evidence



Muscle & Nerve. 2023;68(5):758-762.

New Drug Approvals 2022

FDA New Approvals

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

Problems

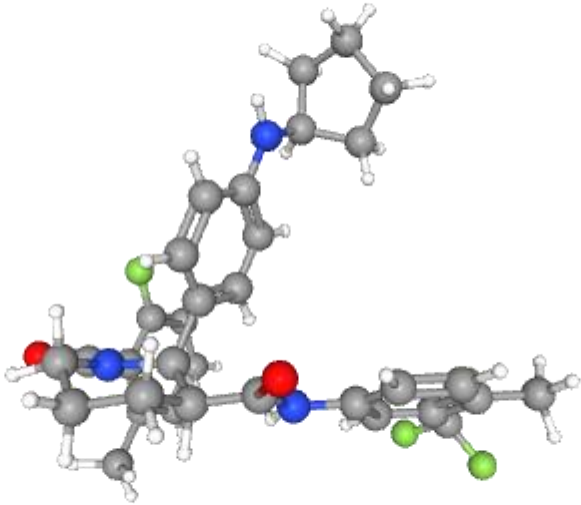
- Tanezumab denied
- Bimekizumab temp. delayed (resumed)

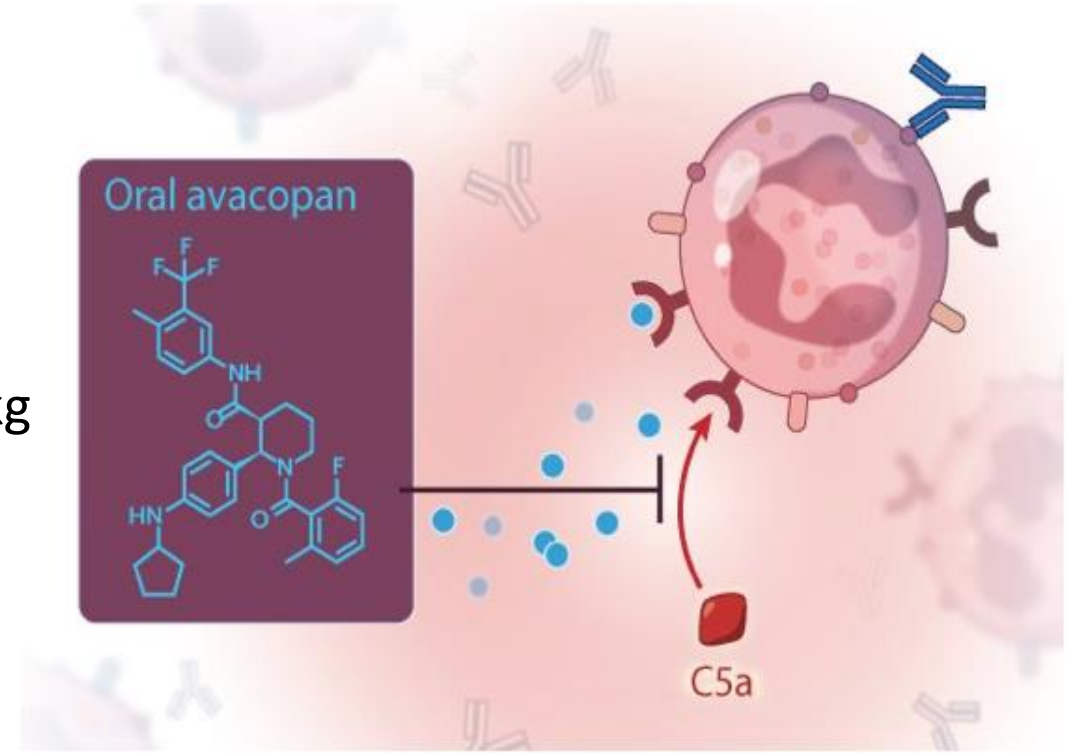
New Indications

- belimumab (lupus nephritis)
- tocilizumab (ILD of systemic sclerosis)
- IVIG (inflammatory myositis)
- secukinumab (juvenile PsA, ERA)
- tofacitinib (AS, atopic dermatitis)
- risakizumab (PsA, Crohns colitis)
- upadacitinib (PsA, AS, atopic dermatitis)
- baricitinib (COVID, alopecia areata)
- MTX + Pegloticase (gout)
- canakinumab (adult Still's disease)
- rilonacept (recurrent pericarditis),

Szteroid csökkentés

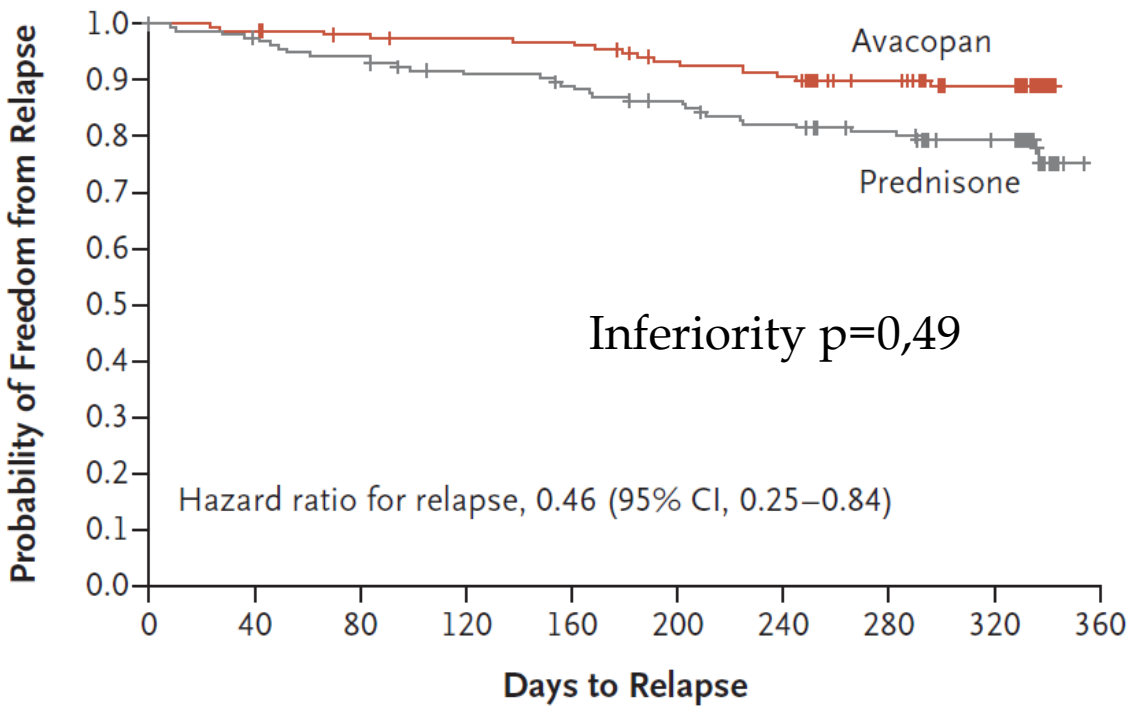
- **Avacopan**
  - C5a receptor antagonista
  - Kis molekula, p.o. szedhető
  - Neutrofil kemotaxist és aktivációt blokkolja
- Elfogadva
  - FDA 2021.10.
  - EMA 2022.01.
- Prednisolonnal szemben
  - Avacopan 2x30mg/die 52 hétig
  - Prednisolon 60mg, 21. hétre leépítve
- Báziskezelés
  - CYC 15mg/tskg iv. 2-3 hetente 6x, majd AZA 2mg/tskg
  - CYC 2mg/tskg p.o.
  - Rtx 375mg/m2/hét i.v. 4 héten át
- 331 beteg 143 centrumból





N Engl J Med. 2021, 18;384(7):599-609

Avacopan



Inferiority p=0,49

No. at Risk										
Avacopan	158	153	149	146	145	133	129	115	92	0
Prednisone	157	151	146	137	133	126	119	111	90	0

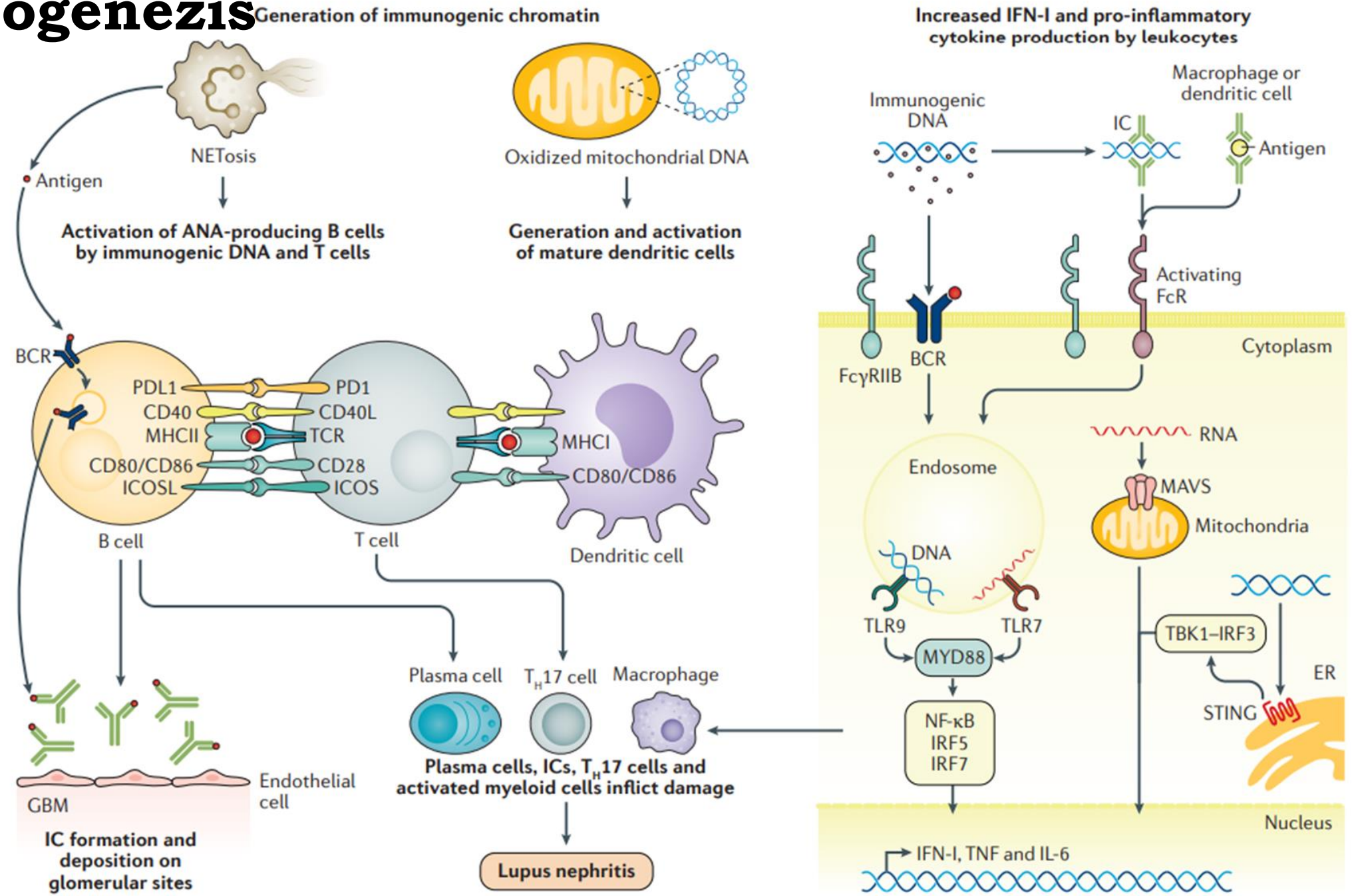
End Point	Avacopan (N = 166)	Prednisone (N = 164)	Difference (95% CI)
Primary end points			
Remission at wk 26 — no. (%)†	120 (72.3)	115 (70.1)	3.4 (–6.0 to 12.8)‡§
Sustained remission at wk 52 — no. (%)¶	109 (65.7)	90 (54.9)	12.5 (2.6 to 22.3)‡‖

Superiority p=0,007

Bármely súlyos, de nem az alapbetegség aktiválódásából származó AE:
33%-kal magasabb volt Prednizolon csoportban

N Engl J Med. 2021, 18;384(7):599-609

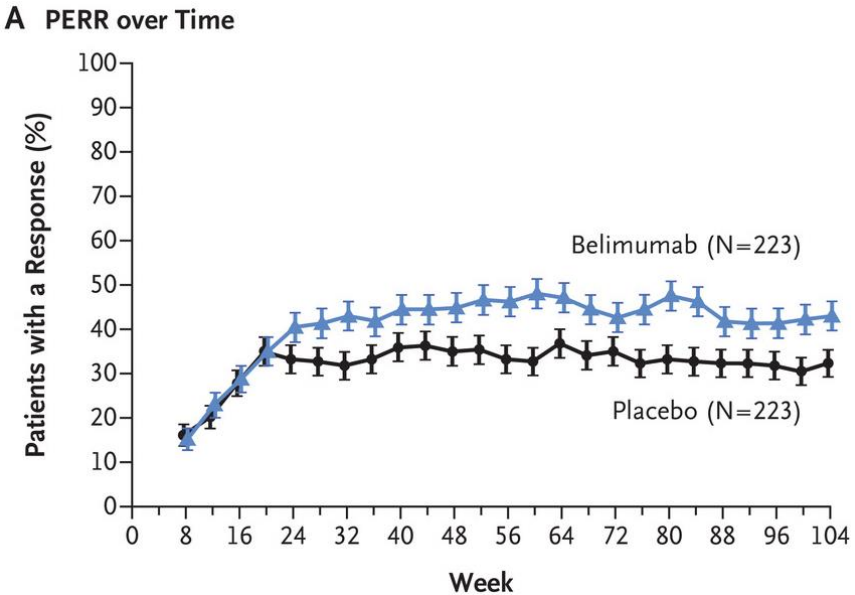
SLE – pathogenezis

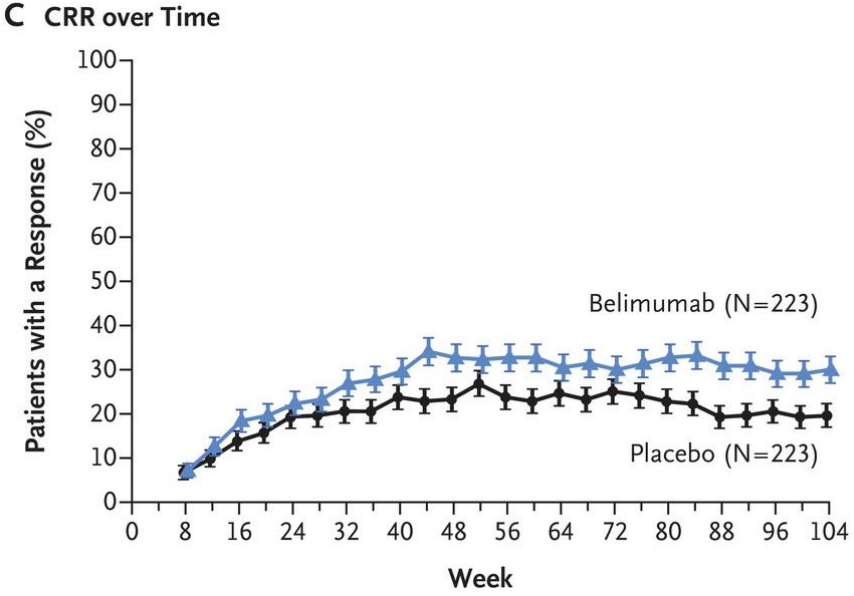


Anders H-Jet al. Nature Rewievs 2

SLE kezelése - belimumab

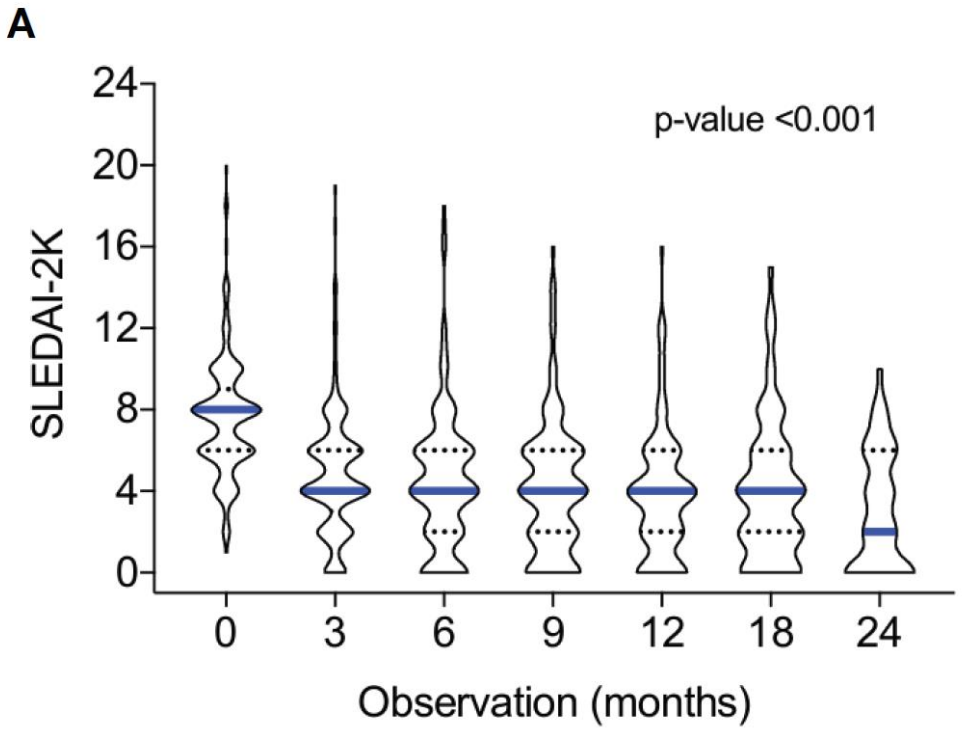
- PLUTO: 53% vs 44% SRI-4 válasz 5 év feletti gyerekeknél
- BLISS-LN: 448 SLE-s beteg 2 éven át CYC v MMF után
  - Veseparamétereket néztek – fehérje+vesefunkció
  - 43% vs 32% placebo, CR: 30 vs 20%
  - ha MMF-t kapott jó volt CR (indukció 3g, fenntartó 2g)
  - Ha CYC-ot kapott, akkor nem volt jó CR (fenntartó AZA mellett)
  - Veseeredetű szövődmények HR 0,51 placebohoz képest.
  - FDA 2020.12-ben elfogadta LN kezelésére

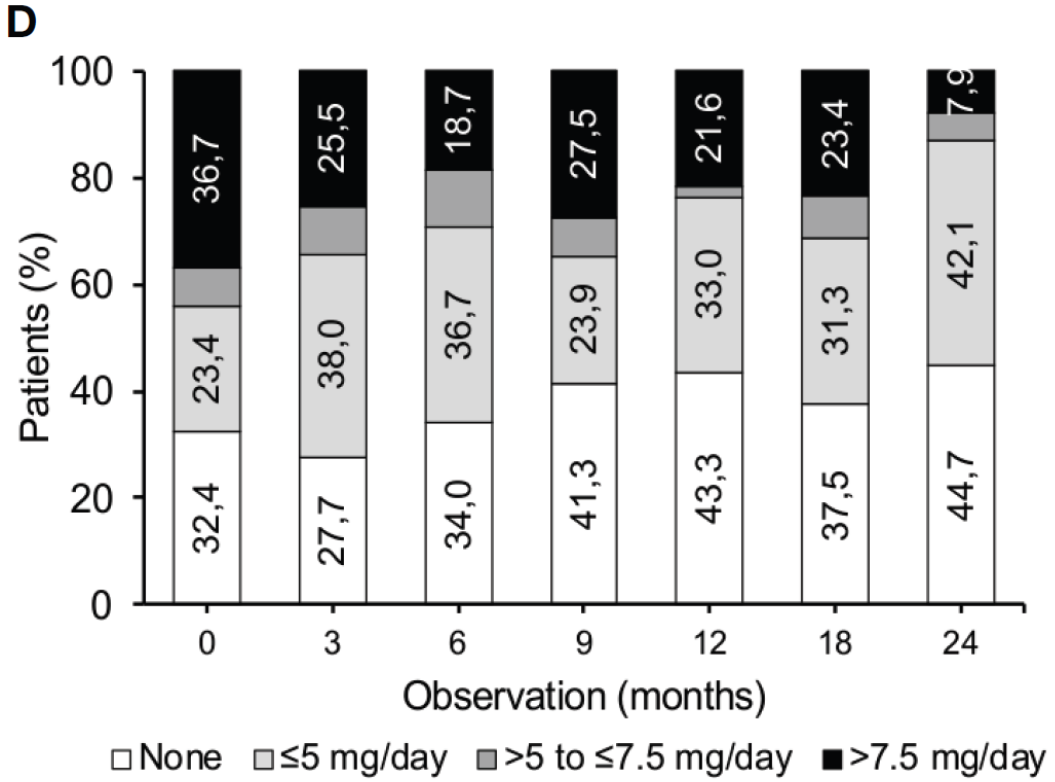




Real world evidence - belimumab

- 12/2014 - 08/2021
- Görög multicentrikus vizsgálat
- 188 beteg

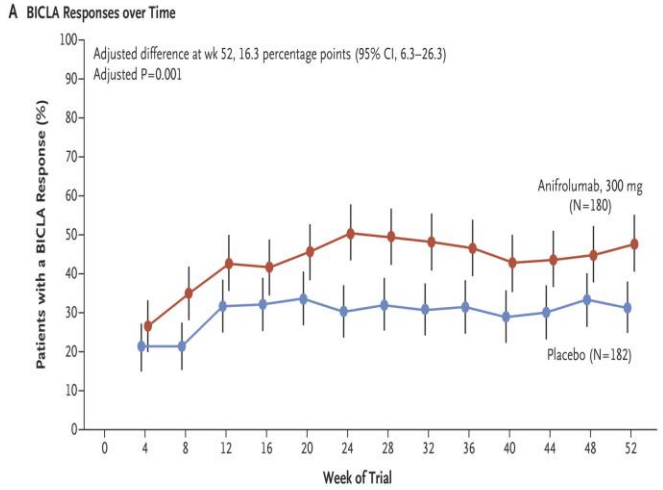


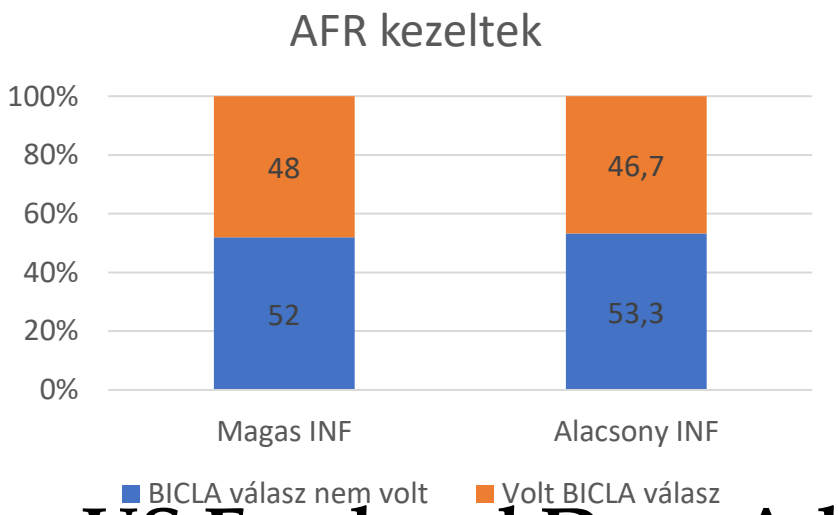


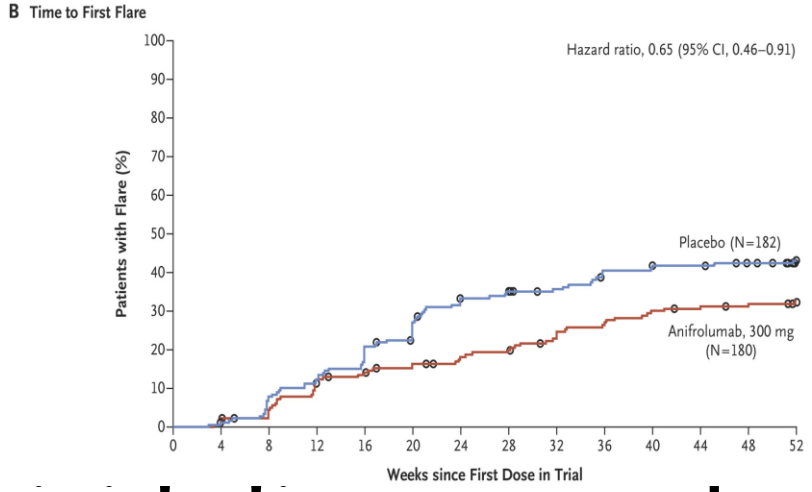
Front. Immunol. 2023. 13:1074044.

SLE kezelése – anifrolumab

- **Fázis-III: TULIP-2: 180 vs 182 placebo, 48 héten át 300mg/4 hetente iv., 52 hét**
  - **BICLA 47,8% vs.2 Placebo 31,5% - INF-gén aktivitás mértékétől függetlenül**
  - **Jó volt a bőrtünetek és a szteroid dózisának a csökkentésére is**







- **On July 30, 2021, the US Food and Drug Administration approved AstraZeneca's Saphnelo (anifrolumab-fnia) for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE) who are receiving standard therapy.**

N Engl J Med_2020;382:211-21.

Komedikáció

- TULIP-1

	Placebo (n=184)	Anifrolumab 150 mg (n=93)	Anifrolumab 300 mg (n=180)
Oral corticosteroid (prednisone or equivalent)	153 (83%)	78 (84%)	150 (83%)
Antimalarials	134 (73%)	76 (82%)	124 (69%)
Azathioprine	34 (18%)	16 (17%)	32 (18%)
Methotrexate	38 (21%)	14 (15%)	22 (12%)
Mycophenolate	22 (12%)	9 (10%)	31 (17%)

- TULIP-2

Glucocorticoid	151 (83.0)		141 (78.3)
Antimalarial agent	133 (73.1)		119 (66.1)
Immunosuppressant agent††	86 (47.3)		88 (48.9)

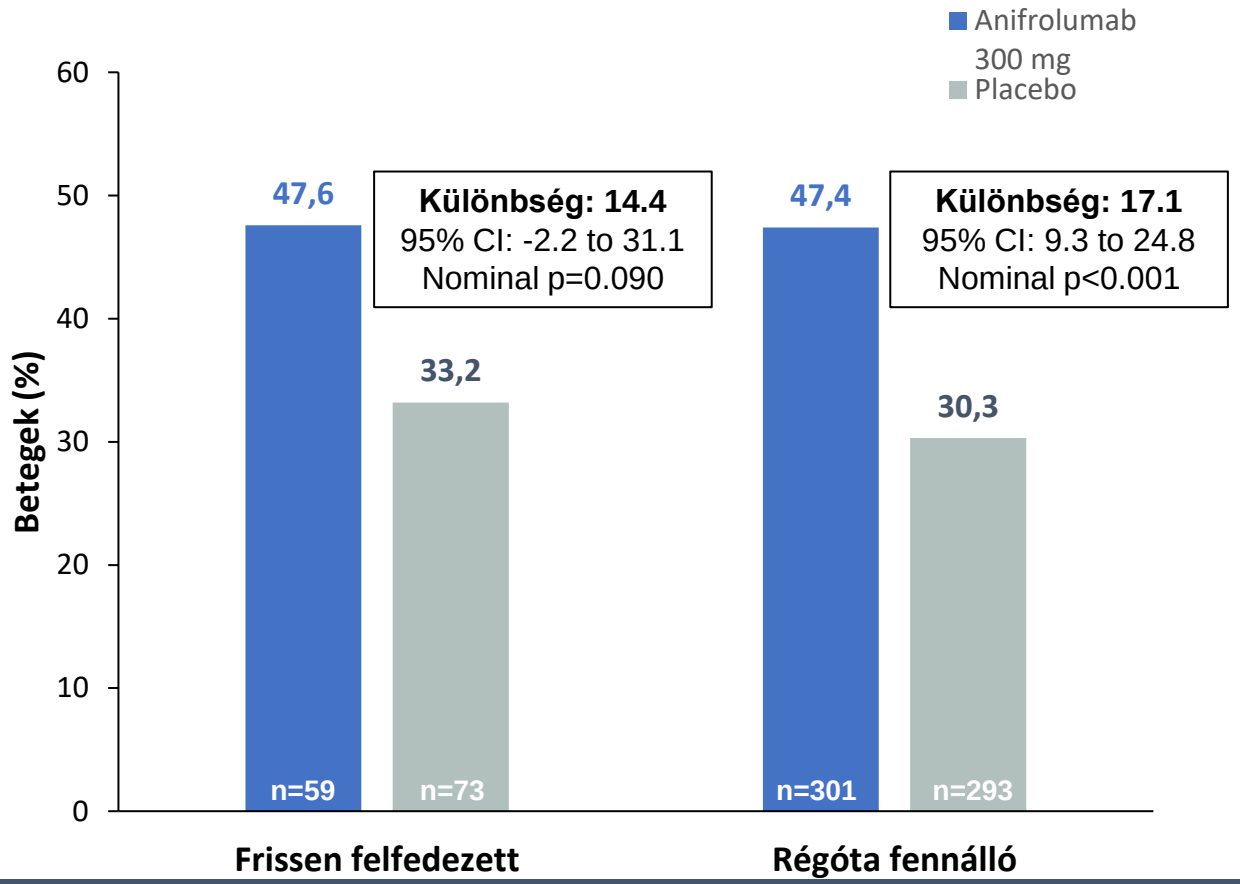
- TULIP-LN

		Anifrolumab combined (n=96)	Anifrolumab BR (n=45)	Anifrolumab IR (n=51)	Placebo (n=49)
Oral glucocorticoids**	Yes, n (%)	94 (97.9)	43 (95.6)	51 (100)	48 (98.0)
MMF before randomisation	Yes, n (%)	72 (75.0)	36 (80.0)	36 (70.6)	33 (67.3)

Jelentős arányú volt az immunmodulans kezelések aránya!

Lancet Rheumatol 2019 Ann Rheum Dis 2022;81:496–506. N Engl J Med_2020;382:211-21.

Az anifrolumab kezelés mellett mutatkozott BICLA válasz mind a frissen felfedezett, mind a régóta fennálló betegség esetén megfigyelhető volt



A BICLA reszponderek aránya hasonló volt a frissen felfedezett és a régóta fennálló SLE betegség esetén SLE

Leíró eredmények.

A betegeket frissen felfedezett (≤2 év) vagy régóta fennálló (>2 év) csoportba sorolták az első SLE diagnózis ideje alapján a randomizációkor.

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Kalunian, KC et al. Presented at: American College of Rheumatology Annual Meeting (All-Virtual); November 3–10, 2021

BICLA válasz a szerológiai státusz szerint az 52. héten

TULIP-1 és TULIP-2 vizsgálatok összegzett eredményei

Alcsoport		Anifrolumab 300 mg n/N (%)	Placebo n/N (%)	Kezelések közti különbség, % (95% CI)
Összes beteg[1]		171/360 (47.5)	112/366 (30.8)	9.7 **16.6** 23.6
Complement (C3 or C4)	Alacsony (C3 vagy C4)	81/153 (53.0)	40/158 (25.4)	17.0 **27.6** 38.2
	Normál (nem alacsony C3 és C4)	90/207 (43.0)	72/208 (35.0)	−1.3 **8.0** 17.3
Anti-dsDNA antitest	Pozitív	82/167 (49.2)	47/155 (30.4)	8.2 **18.8** 29.4
	Negatív	89/193 (46.2)	65/211 (30.2)	6.6 **16.0** 25.4
Alacsony complement (C3 vagy C4) és pozitív anti-dsDNA		51/98 (52.0)	29/104 (27.9)	10.9 **24.1** 37.3
Normál complement (nem alacsony C3 és C4) vagy negatív anti-dsDNA		120/262 (45.8)	83/262 (31.6)	5.9 **14.2** 22.4
Alacsony complement (C3 vagy C4) vagy pozitív anti-dsDNA		112/222 (50.5)	58/209 (27.4)	14.1 **23.1** 32.1
Normál complement (nem alacsony C3 és C4) és negatív anti-dsDNA		59/138 (42.4)	54/157 (33.9)	−2.7 **8.5** 19.7

Minden szerológiai csoportban kedvezőbb eredményeket találunk az anifolumab csoportban a placebohoz képest

Leírós eredmények.

Reprinted from ACR Convergence held November 3–10, 2021. The American College of Rheumatology does not guarantee, warrant, or endorse any commercial products or services. Reprinted by AstraZeneca. The response rates, treatment differences, and associated 95% CIs were calculated using a stratified Cochran–Mantel–Haenszel method with stratification factors of Systemic Lupus Erythematosus Disease Activity Index-2000 score at screening, glucocorticoid dosage at baseline, type I interferon gene signature status at screening, and trial (TULIP-1 and TULIP-2).

Bruce IN, et al. Corrected Version. Presented at: American College of Rheumatology Annual Meeting (All-Virtual); November 3–10, 2021.

SLE kezelése - voclosporin

- AURORA PHASE 3
  - 357 beteg
    - WHO –III / IV / V LN
    - 1:1 randomizáció – voclosporin+MMF vs placebo+MMF
    - 2x24mg voclosporin vs placebo
  - 52 hét
  - CRR
    - UPCR of 0.5 mg/mg or less,
    - eGFR of 60 ml/min or more or no change of 20% or more from baseline,
    - no receipt of rescue medication for LN
    - no use of 10 mg prednisone for 3 days or more or for 7 days or more in total during Week 44 through Week 52
  - CRR: 41% v 23%
  - sAE: 37/179 vs 38/178
    - Fele infekció –tüdőgyulladás
    - Elhalálozás: 1/179 vs 5/178
- January 22, 2021, the U.S. Food and Drug Association (FDA) approved voclosporin (Lupkynis)

SLE kezelése - voclosporin

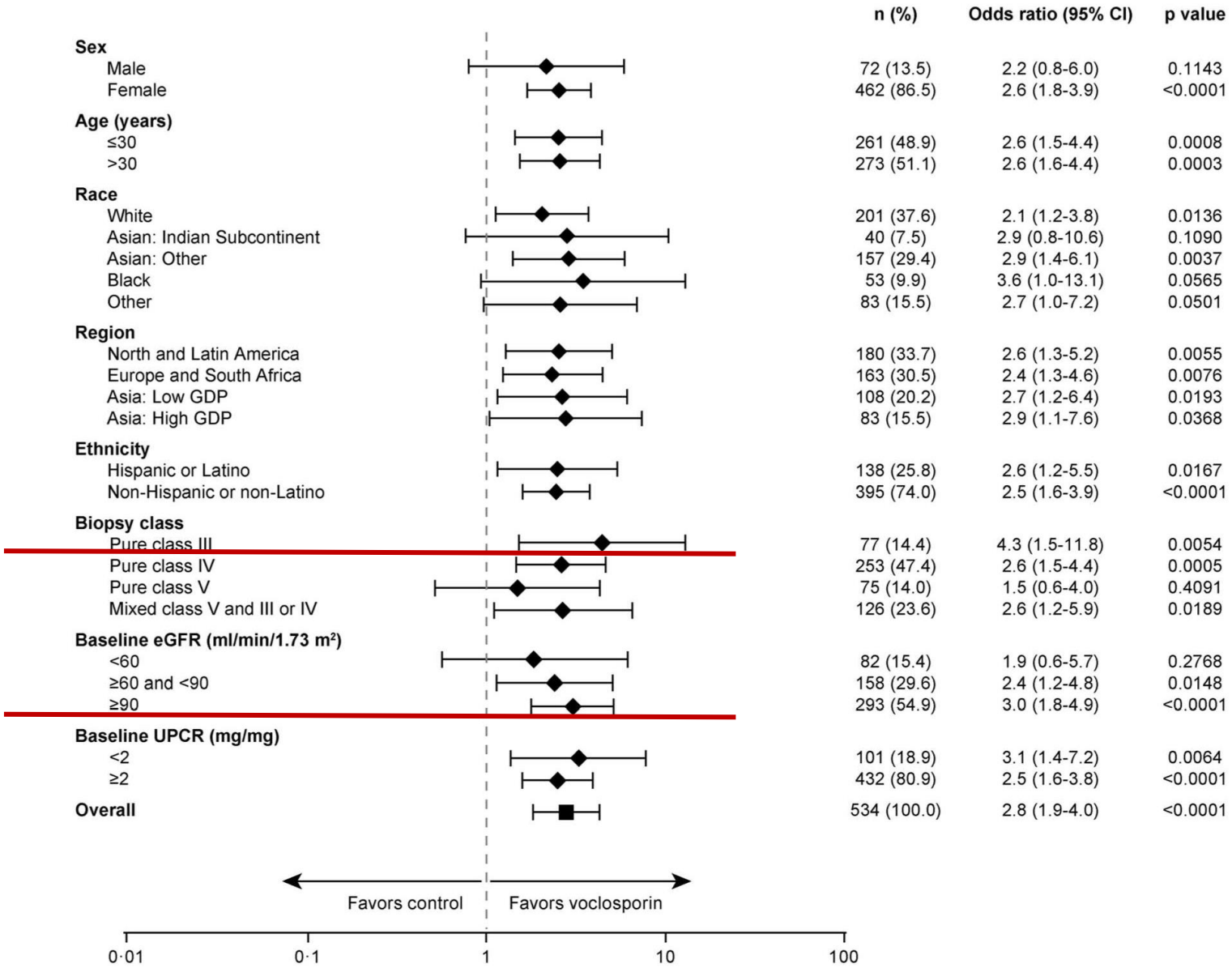
Dózis:

p.o. MMF mellé
napi 3 kapszula 2 részletben
fix adag
nincs szérumszint mérés

Ne adjuk együtt (CYP3A):

itraconazole, ketoconazole

SLE kezelés - voclosporin



Arthritis Care Res. 2023, 1-10.

SLE kezelés - voclosporin

Table 2. Summary of adverse events*

Event	Voclosporin (n = 267)	Control (n = 266)
AE	244 (91.4)	232 (87.2)
SAE	61 (22.8)	50 (18.8)
SAE of infections and infestations	27 (10.1)	27 (10.2)
Treatment-related SAE	12 (4.5)	9 (3.4)
AE leading to study drug discontinuation	36 (13.5)	35 (13.2)
Death	11 (4.1)	6 (2.3)
Treatment-related AE leading to death	0	0
AEs of interest		
Glomerular filtration rate decreased	70 (26.2)	25 (9.4)
Hypertension	51 (19.1)	23 (8.6)
Anemia	33 (12.4)	16 (6.0)
Alopecia	17 (6.4)	7 (2.6)
Tremor	9 (3.4)	2 (0.8)
Seizure/convulsion	3 (1.1)	0
Hyperglycemia	2 (0.7)	4 (1.5)
QTc prolongation	2 (0.8)	2 (0.8)
Posterior reversible encephalopathy	1 (0.4)	0
Pure red cell aplasia	0	0

Bangladesh, Sri Lanka, Philippines

súlyosabb betegek

több volt közülük az aktív karban

mint a placebóban

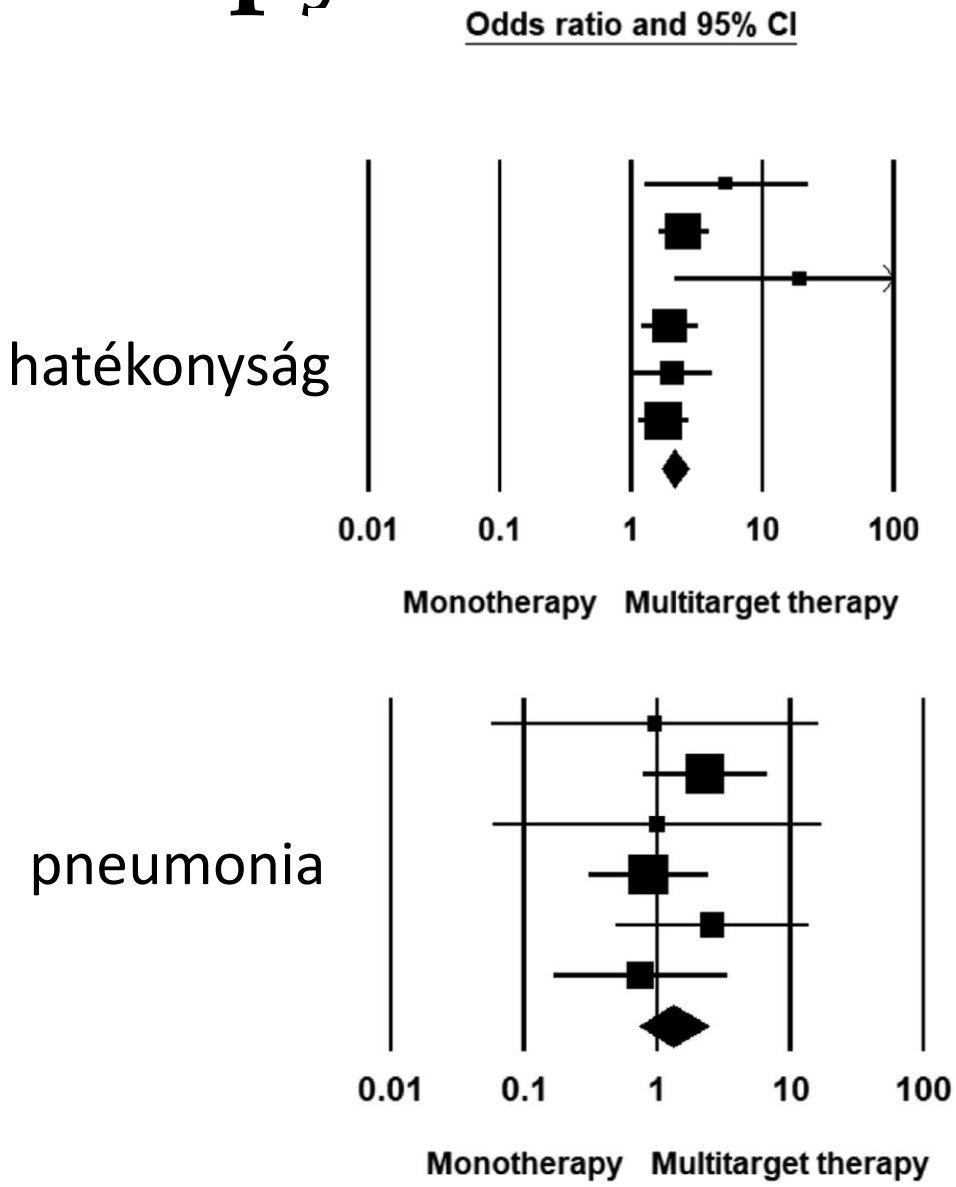
Arthritis Care Res. 2023, 1-10.

SLE kezelés – multitarget therapy

6 RCTs, 1437 participants
MMF / CYC + Voclosp / Tacrol / Belimumab

Multi vs Mono

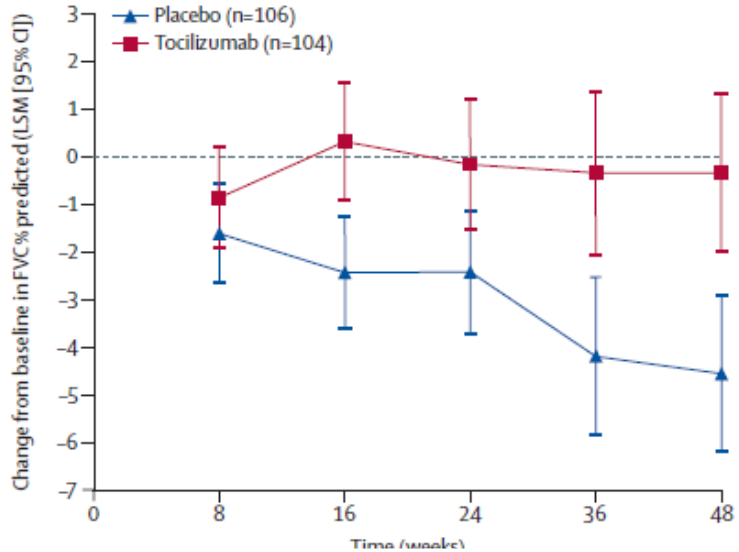
- komplett remisszió OR: 2,15
- nincs eltérés AE gyakoriságában
- de
  - több hypertonia
  - több menstruációs zavar
  - több pneumonia

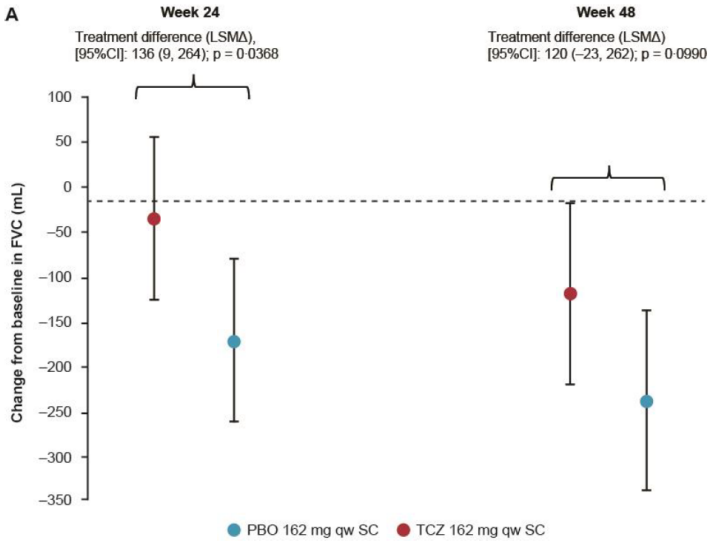


Lupus 2022 Oct;31(12):1468-1476.

Mar 4, 2021 - Approval Genentech's Actemra Becomes the First Biologic Therapy Approved by the FDA for Slowing the Rate of Decline in Pulmonary Function in Adults With SSc-ILD

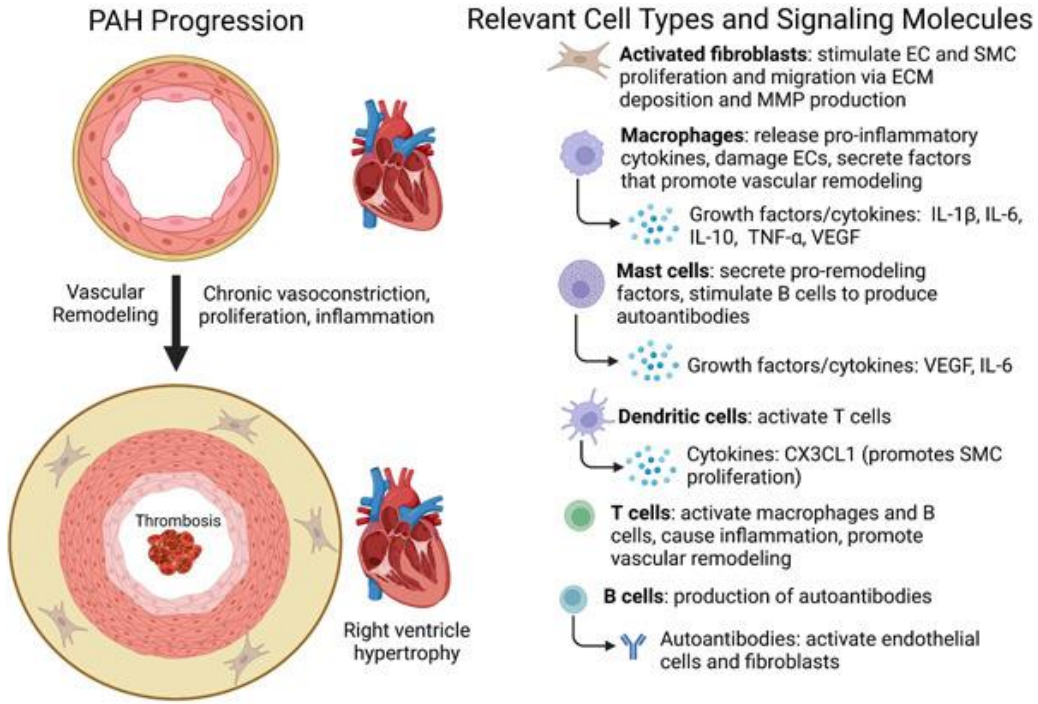
- Tocilizumab
  - legmagasabb IL-6 szérum szint a korai (3 év alatti), ill. a diffúz bőreltérésekkel és tüdőérintettséggel járó betegeknél mérhető
  - focuSSced
    - 212 beteg, 48 hét, 1:1 tocilizumab vs placebo, 65% és 64% ILD-vel, DD<5 év
    - mRSS csökkenés nem volt szignifikáns tcz -5,88 vs placebo -3,77
    - FVC csökkenés tocilizumab 0.07% vs. Placebo -6.4% (14 ml vs 255 ml)
  - faSScinate
    - 87 beteg, 48 hét, DD<5 év, 1:1 tocilizumab vs placebo
    - mRSS: -3,92 vs -1,22 (nem szign)
    - FVC csökkenése lassult: tcz -34ml vs placebo 171ml
    - Súlyos fertőzés tcz 16% vs placebo 5%

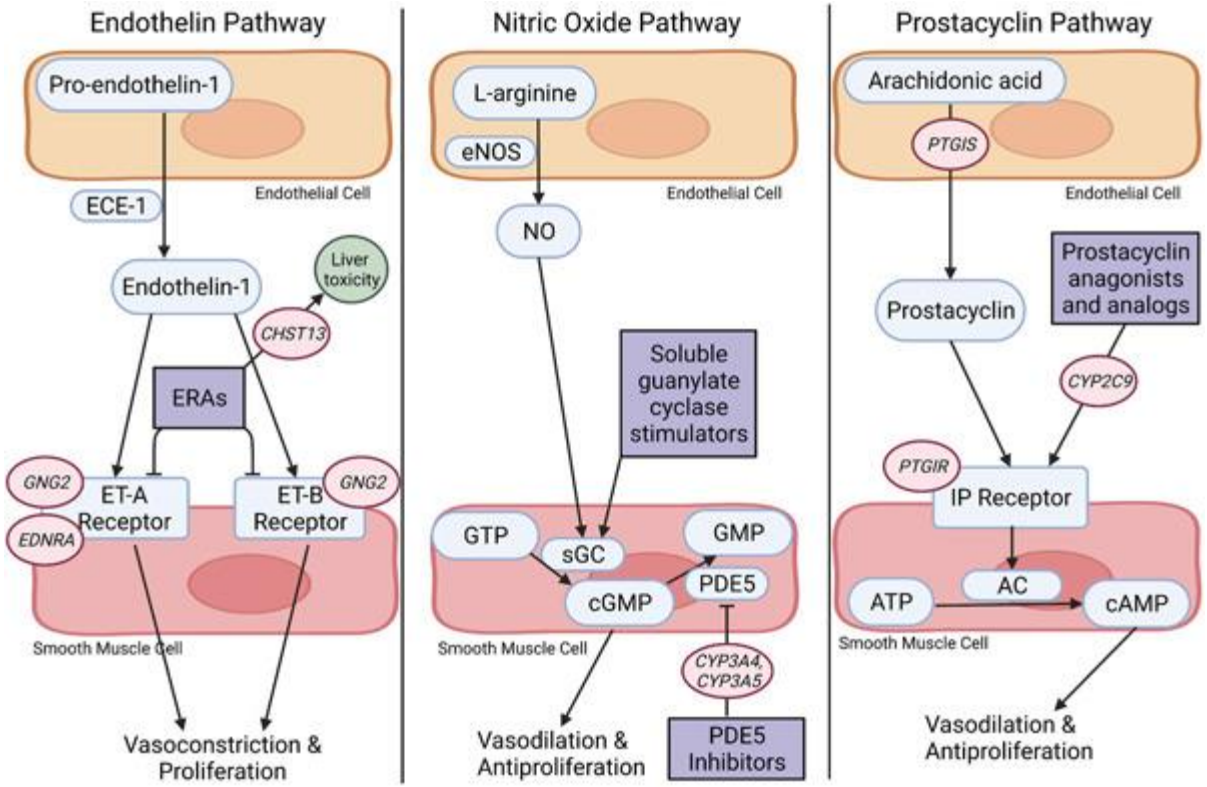




2024. – Sotatercept – PAH

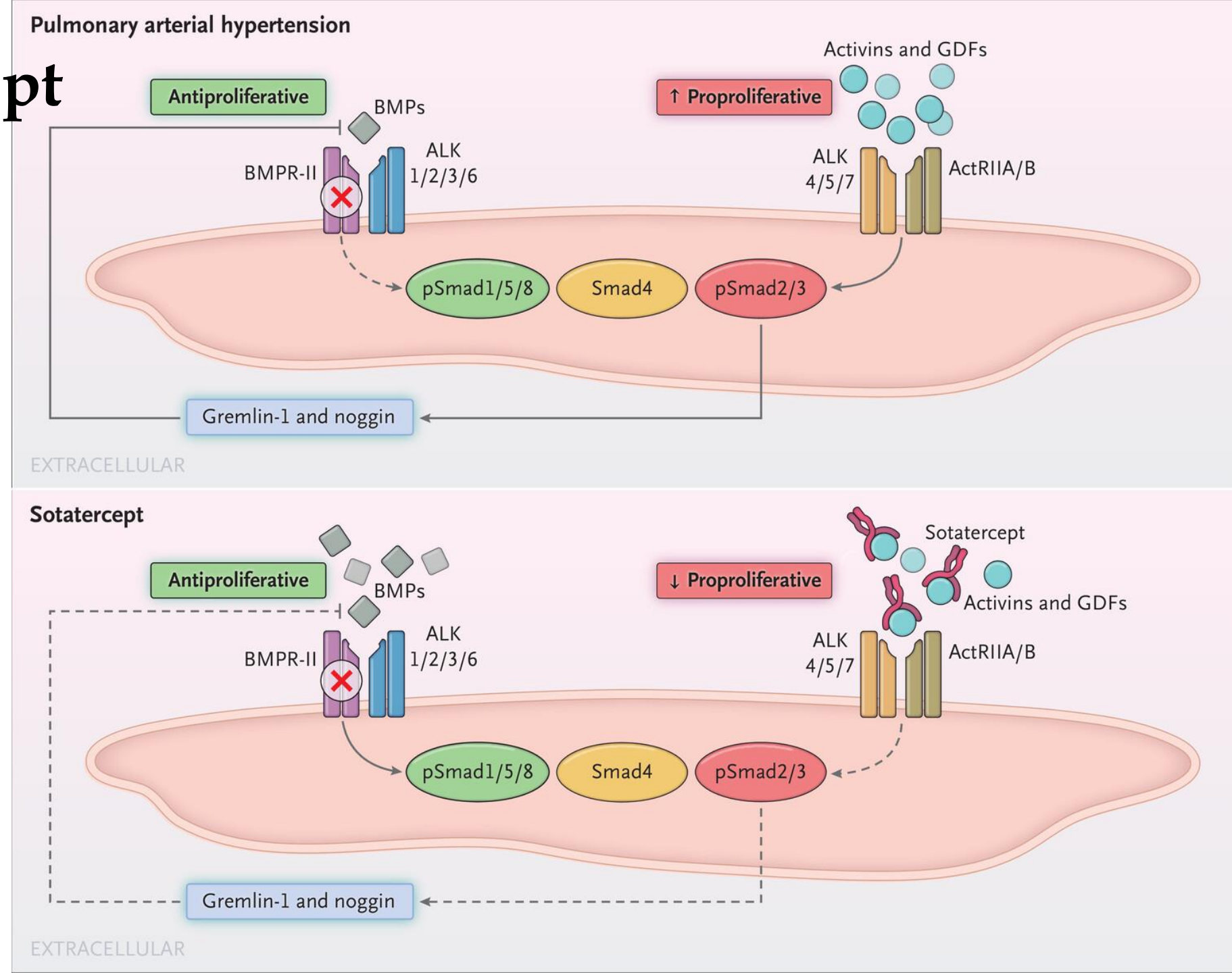
- activin signaling inhibitor
- recombinant fusion protein
  - extracellular domain of the activin type 2 receptor
  - immunoglobulin Fc domain
- rebalance pulmonary vascular homeostasis toward growth-inhibiting and proapoptotic signaling





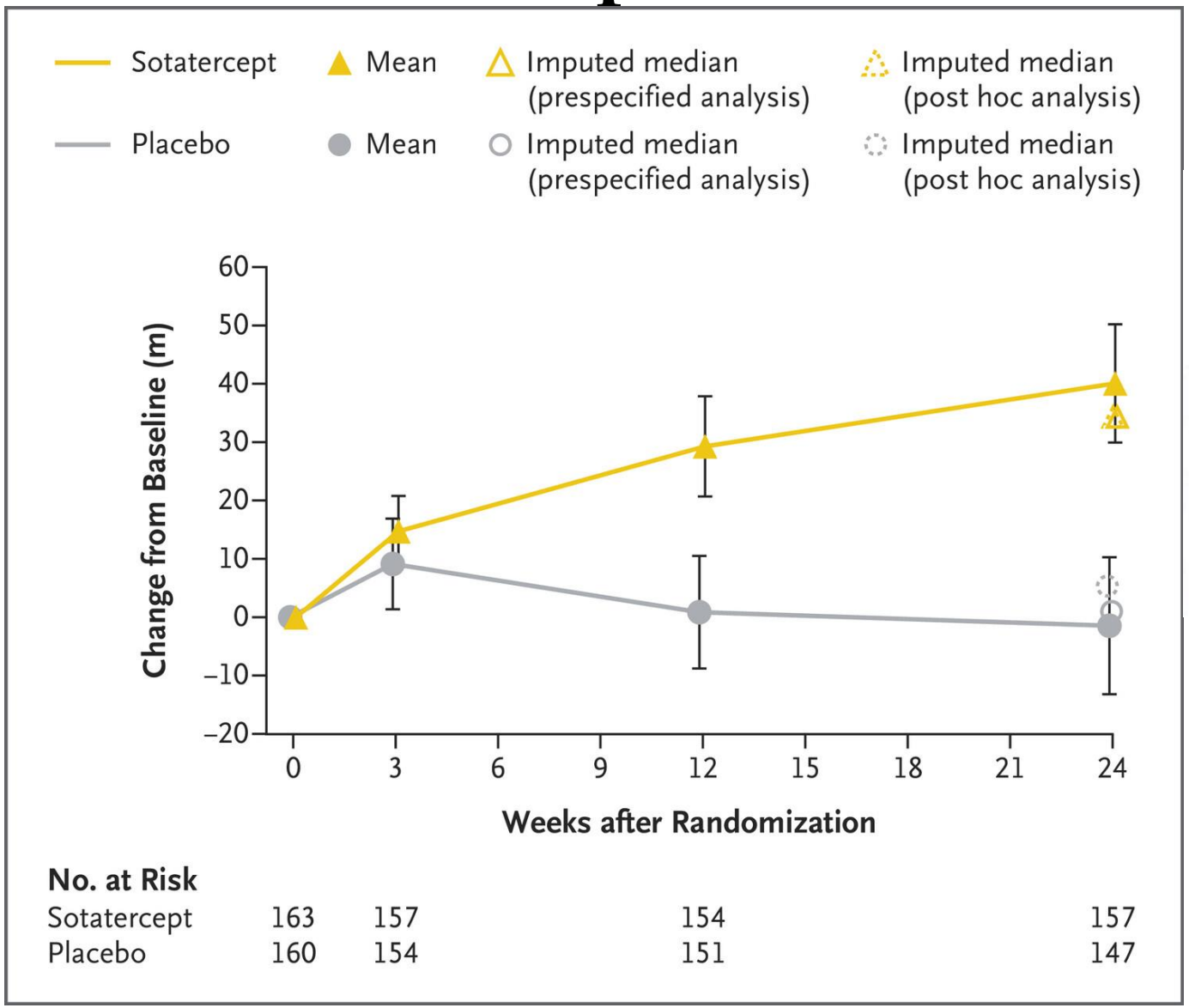
. 2023 Apr 20;388(16):1478-1490

2024. – Sotatercept



N Engl J Med 2021;384:1204-1215

2024. – Sotatercept – PAH

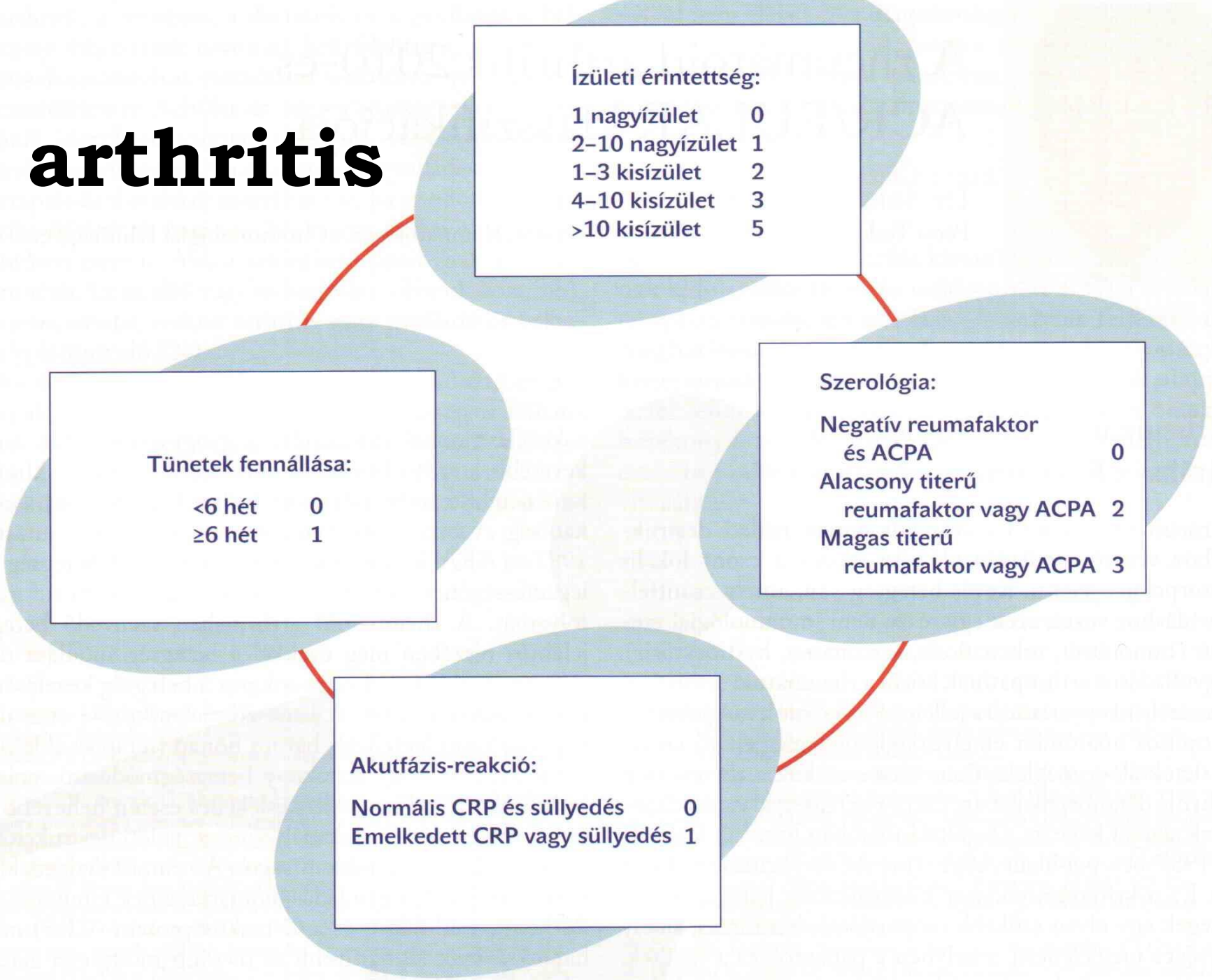


Adverse Events of Interest or Special Interest

	Sotatercept (N=163)	Placebo (N=160)
	no. of patients (%)	
Increased hemoglobin	9 (5.5)	0
Thrombocytopenia	10 (6.1)	4 (2.5)
Bleeding events	35 (21.5)	20 (12.5)
Increased blood pressure	6 (3.7)	1 (0.6)
Telangiectasia	17 (10.4)	5 (3.1)

2023 Apr 20;388(16):1478-1490

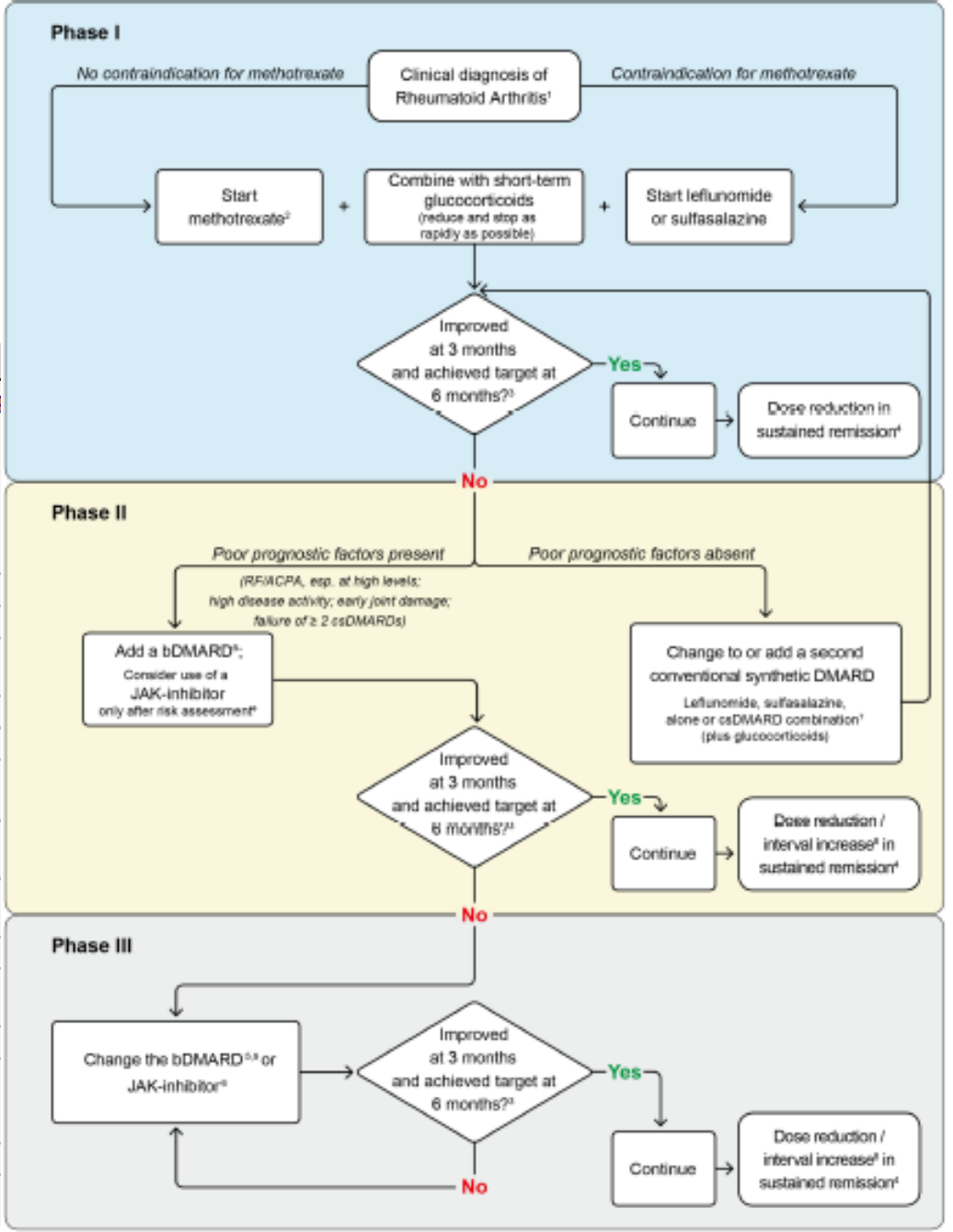
Rheumatoid arthritis



Rheumatoid arthritis EULAR 2022.

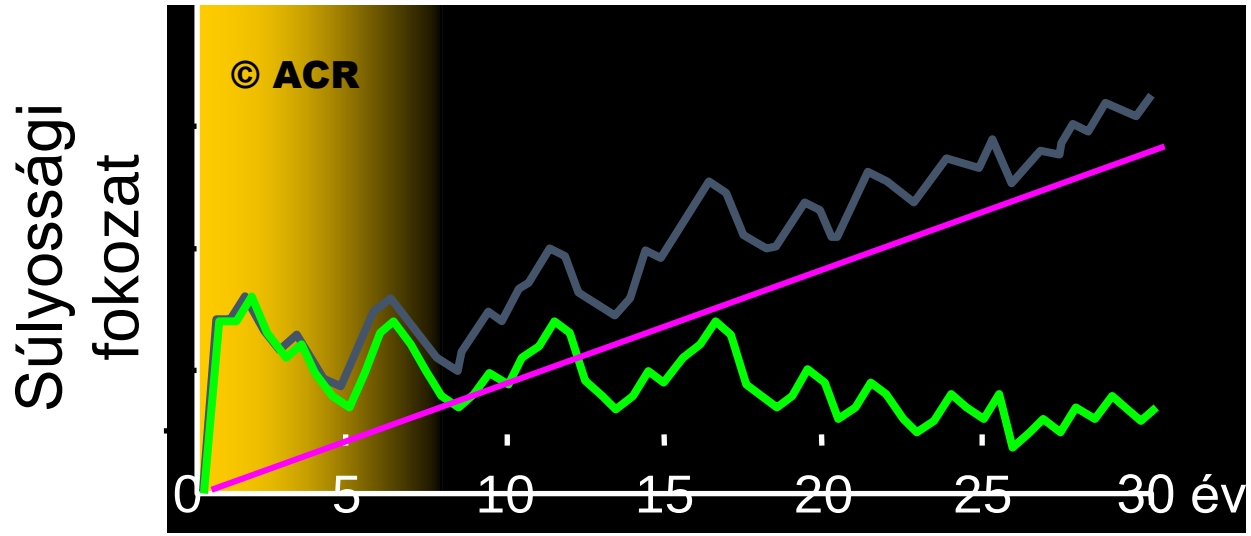
Term	Definition	
Poor prognostic factors	► Persistently moderate or high disease activity (after csDMARD therapy) according to composite measures including joint counts despite csDMARD therapy ► High acute phase reactant levels ► High swollen joint count ► Presence of RF and/or ACPA, especially at high levels ► Presence of early erosions ► Failure of 2 or more csDMARDs	
Low dose glucocorticoids	► ≤7.5 mg/day prednisone equivalent	
Short-term	► Up to 3 months	
Tapering	► Reduction of drug dose or increase of the interval between doses ► May include cessation (tapering to 0), but then only after slow reduction	
Discontinuation, cessation, stopping	Stopping of a particular drug	
Disease activity states		
Remission	ACR-EULAR remission definition (Boolean or index-based); sustained remission: ACR-EULAR-defined remission for ≥6 months	
Low disease activity	Low disease activity state according to validated composite disease activity measures that include joint counts, performed by a HCP; sustained low disease activity: low disease activity for ≥6 months	
Moderate, high disease activity	Respective disease activity state according to validated composite disease activity measures that include joint counts by a HCP	
DMARD nomenclature		
Synthetic DMARDs	► Conventional synthetic DMARDs	For example, methotrexate, leflunomide, sulfasalazine, hydroxychloroquine
	► Targeted synthetic DMARDs	For example, baricitinib, filgotinib, tofacitinib, upadacitinib
Biological DMARDs	► Biological originator DMARDs	TNFi: adalimumab, certolizumab, etanercept, golimumab, infliximab; IL-6Ri: sarilumab, tocilizumab; Co-stimulation-i: abatacept; anti-B-cell (CD20): rituximab
	► Biosimilar DMARDs	Currently for adalimumab, etanercept, infliximab, rituximab

ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HCP, healthcare professional; RF, rheumatoid factor.



Ann Rheum Dis 2023;82:3–18.

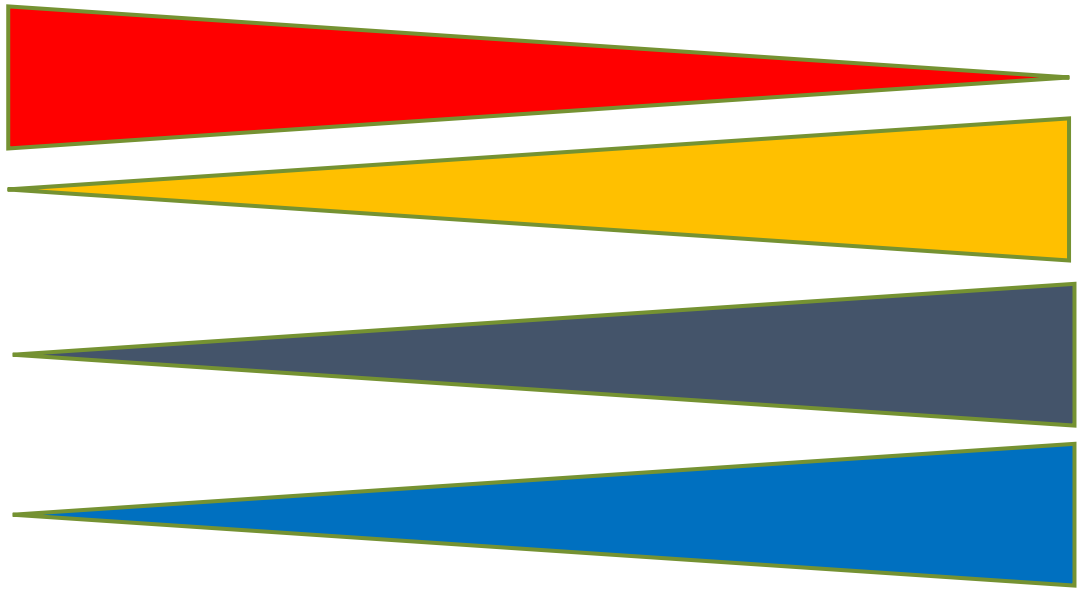
De nem csak a gyulladás a fontos!



Gyulladás

Mozgáskorlátozottság

Radiológiai elváltozás



Gyulladás

Ízületi károsodás: destructio sec. degeneratív eltérések

Neurogén fájdalmak

Psychés eltérések

Grafika: adaptálva a Kirwan JR, J Rheumatol, 2001;28: 881-886.

Általános szempontok

- A beteg kezelése során fontos a rendszeres ellenőrzés:
  - betegség aktivitás
  - súlyosság meghatározás
  - terápia hatásossága:
    - **Célértékre történő kezelés (Treat to Target T2T) – a terápia megkezdésekor kitűzött célhoz igazítom a kezelést, amíg a célt el nem érem**
      - **Teljes remisszió (korai RA ill. jó válasz az első DMARD-ra)**
      - **vagy alacsony betegség aktivitás (késői RA vagy rossz válasz az első DMARD-ra)**
  - Terápia mellékhatása
  - Komorbiditások

Rheumatoid Arthritis - prognózis

dohányzás
genotípus (HLA-DRB1 shared epitope)
idősebb kor
női nem
hirtelen kezdet, kezdeti nagy aktivitás
tartósan nagy aktivitás
korai magas titerű RF, CRP

rossz terápiás válasz a kezdeti DMARD kezelésre

korán megjelenő eróziók
extraarticularis tünetek (neuropathia, vasculitis, scleritis, pericarditis, stb.)
reumatoid csomók
nyaki gerinc érintettség
súlyos kísérő tünetek
rossz funkcionális állapot (HAQ)

Általános szempontok

- **Kezelési sorrend**
  - **Diagnóziskor DMARD**
    - **Jó prognózis esetén - Mtx adása**
    - **Rossz prognózis esetén – kombinált csDMARD**
  - **Ha nem érjük el a célt, akkor kombinált kezelés:**
    - **kémiai (+ kémiai)**
    - **Kémiai + biológiai terápia**
  - **Ha nem érjük el a célt:**
    - **kémiai (dózis növelés / váltás) + másik biológiai terápia**
  - **Ha nem érjük el a célt**
    - **dózis növelés / váltás**
    - **többszörös kombináció**

TNFα-gátló szerek

Infliximab (Remicade)	Monoclonalis chimerikus TNF-α human-rágcsáló antitest
Etanercept (Remicade)	Chimerikus solubilis TNF-α receptor (egér p75 fehérje + human FcIgG1)
Golimumab (Simponi)	Monoclonalis humanizált TNF-α antitest
Certolizumab pegol (Cimzia)	Humanizált antitest Fab' fragmentum + PEG
Adalimumab (Humira)	Monoclonalis humanizált TNF-α antitest

Más típusú biológiai kezelések

	Típus	Célmolekula	Mechanizmus	Alkalmazhatóság
Rituximab	Humán/egér kimerikus Mab	B lymphocyta CD20	B sejt depléció	NHML RA – TNFα gátlás hatástalansága
Abatacept	Rekombináns fúziós fehérje CTLA4 + human IgGFc	CD80/86	T sejt kostimuláció gátlás	RA – DMARD és TNFα gátlás elégtelensége esetén
Tocilizumab	Humanizált Mab	IL-6 receptor α lánca	T, B sejt, macrophag és osteoclast aktiváció gátlása	RA

Targeted synthetic DMARDs

- Janus-Kinase-gátlók
  - Gyógyszerek
    - tofacitinib (Xeljanz) – 2x5mg
      - vesebetegnek is adható (GFR<30: 1x5mg, akár dialízis kezelteknek is)
      - enyhe májbetegnél is már óvatosan
    - baricitinib (Olumiant) – 1x4mg
      - nem súlyos májbetegnek is adható
      - vesebetegeknek óvatosan (GFR 30-60: 2mg)
    - upadacitinib (Rinvoq) – 15mg
      - nem súlyos máj-, ill. nem súlyos vesebetegnek is adható
  - Hatékonyság
    - ≈ TNFi, vagy jobb
  - Mellékhatások
    - Hányinger / hasi panaszok
    - Felső légúti fertőzések
    - Trombembolia
    - LDL-koleszterin szint emelkedése
    - Teratogenitás?

D2T

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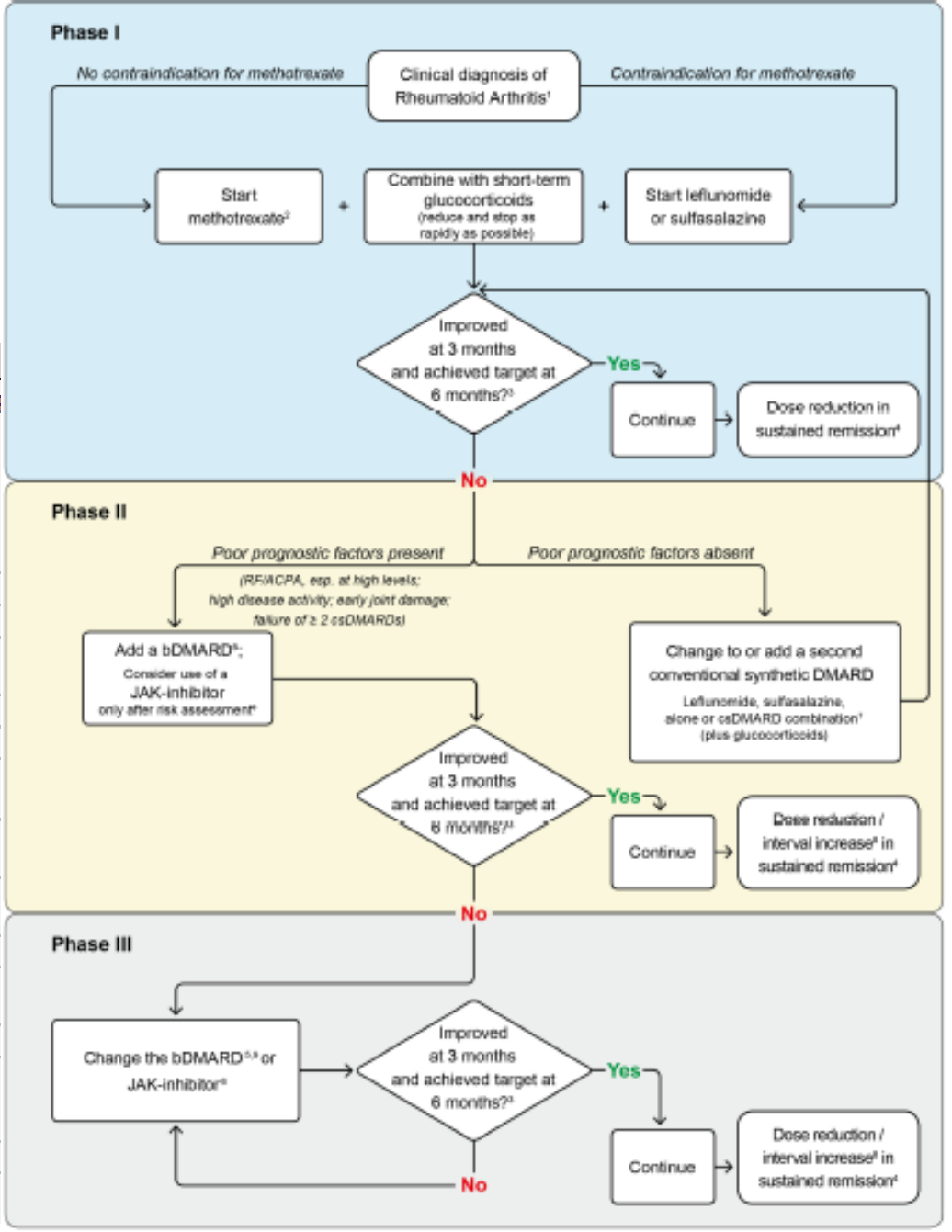
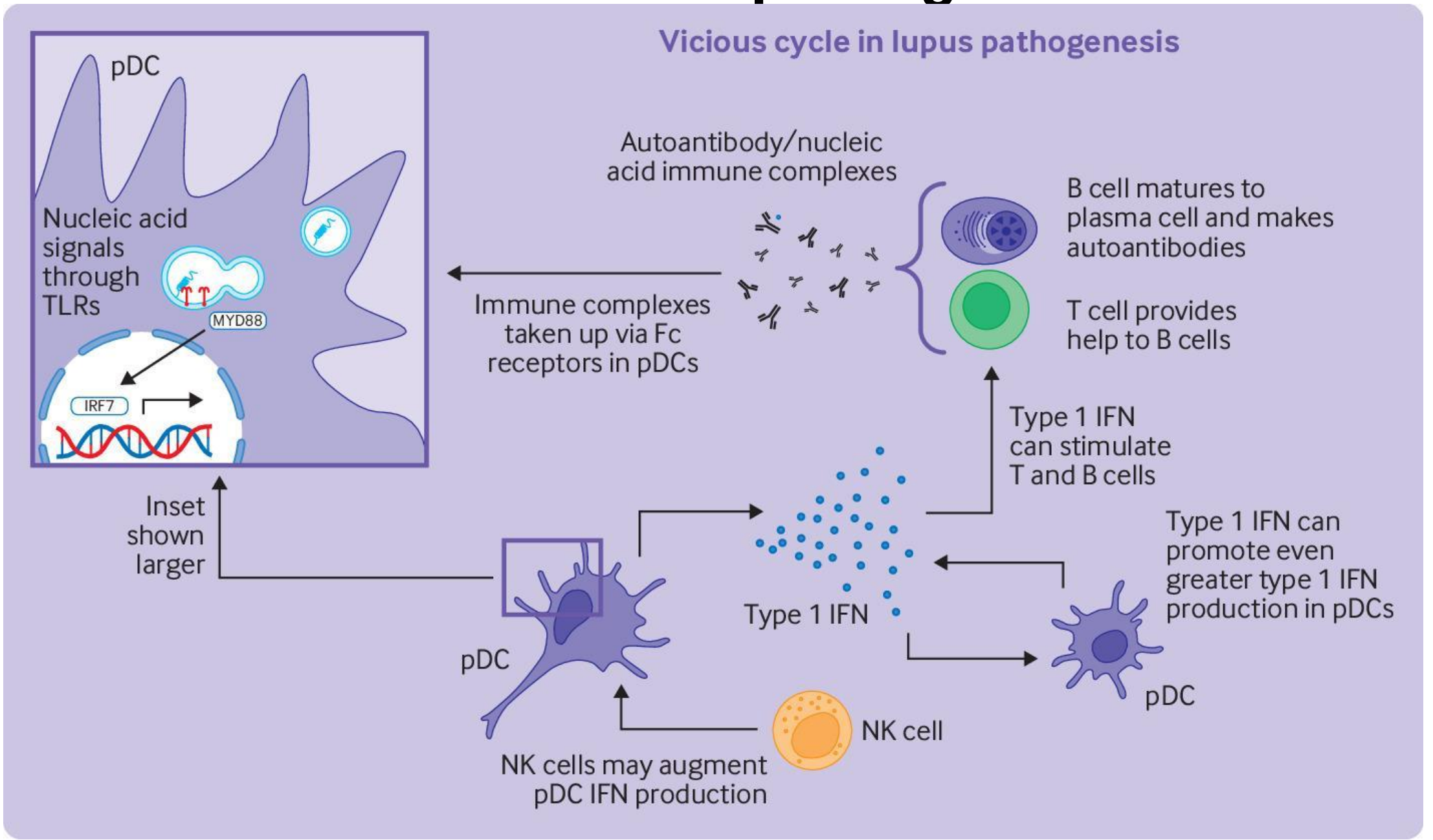


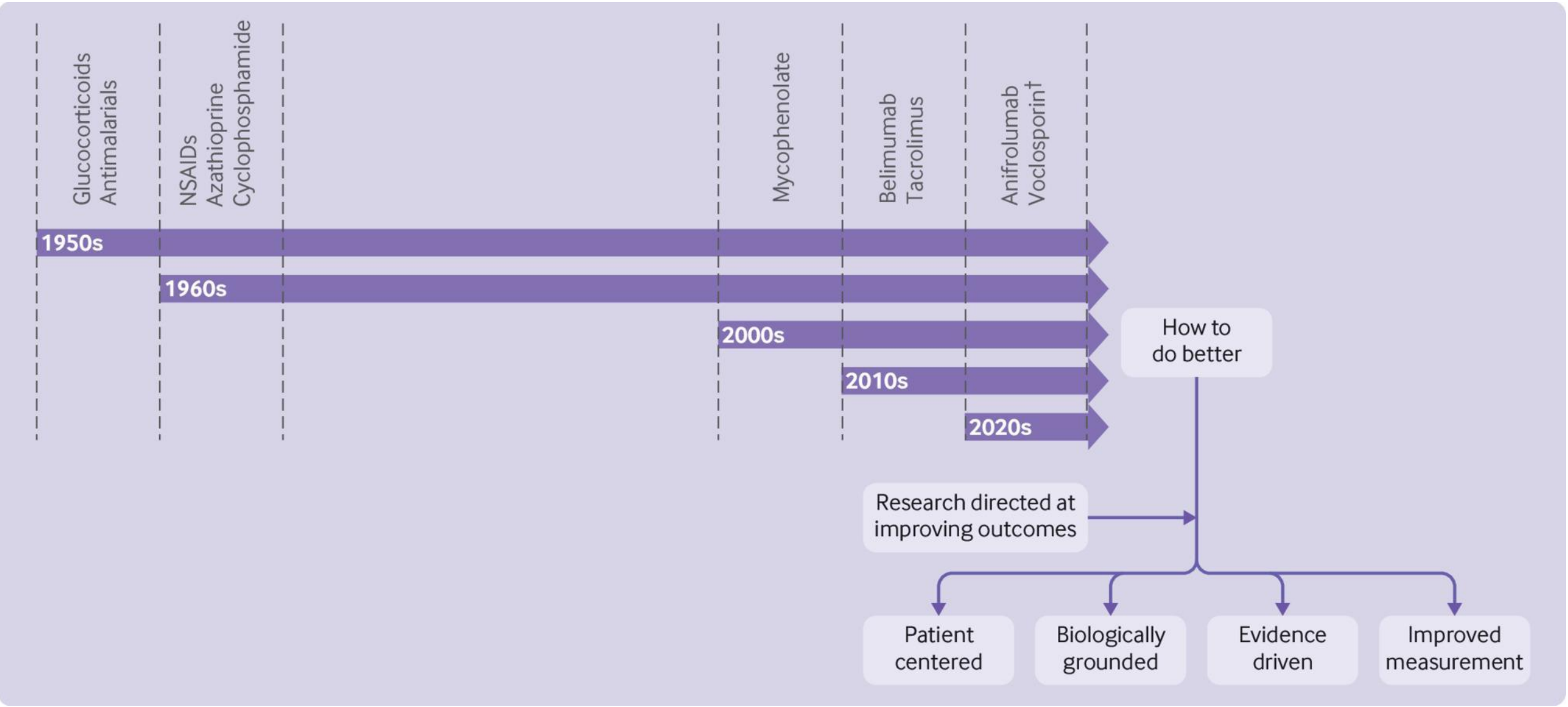
Ann Rheum Dis 2022;81:20–33.

Cellular and molecular pathogenesis in SLE



Eric F Morand et al. BMJ 2023;383:bmj-2022-073980

Timeline of treatments for SLE, and a roadmap for future progress.



Eric F Morand et al. BMJ 2023;383:bmj-2022-073980

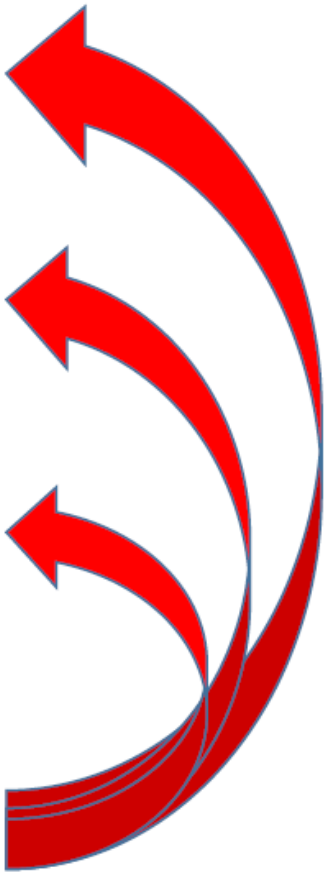
A terápia célja

- **Az autoimmun jelenségek gátlása**

- A súlyos szervkárosodások (vese, központi idegrendszer)
  - **kialakulásának megakadályozása**
  - **Időben történő kezelése**

- **Megnyújtani az inaktív szakaszt**

- A tünetek befolyásolása
- Az élettartam meghosszabbítása
- Jobb életminőség biztosítása



A betegség aktivitására ható „általános” DMARD kezelés

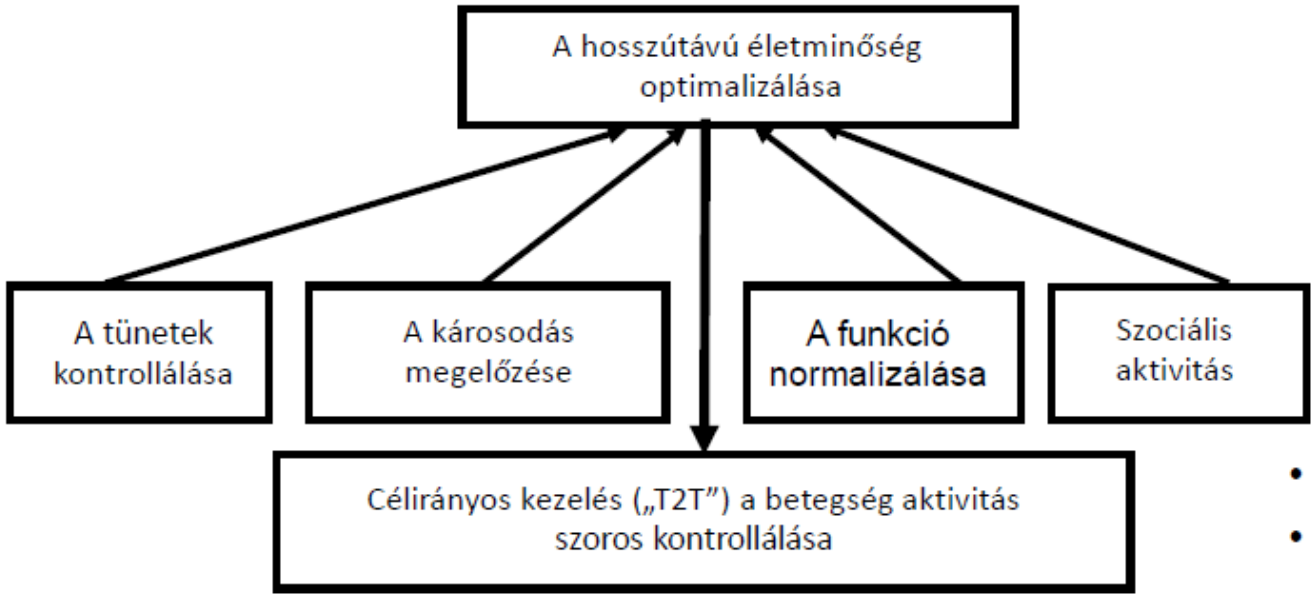
Szervspecifikus kezelés

A betegség aktivitás komplex értékelése nehéz
A jövő:

remisszió-alacsony betegség aktivitás értékelése
szervhez kapcsolódó aktivitás értékelése

Czirják László anyagából

Célirányos kezelés SLE-ben(„T2T”)



- Betegség-aktivitás csökkentése
- Irreverzibilis károsodás megelőzése
  - Betegség-aktivitás okozta
  - Gyógyszer- (glükokortikoid) okozta
- Életminőség javítása

- Alacsony betegség aktivitás: kisebb kockázat a további károsodás kialakulására
- A **már jelenlévő károsodás** a legjobb prediktora a **további károsodások** kialakulásának (!)
- Már **rövid ideig tartó remisszió is** csökkenti a további károsodás kockázatát

Czirják László anyagából

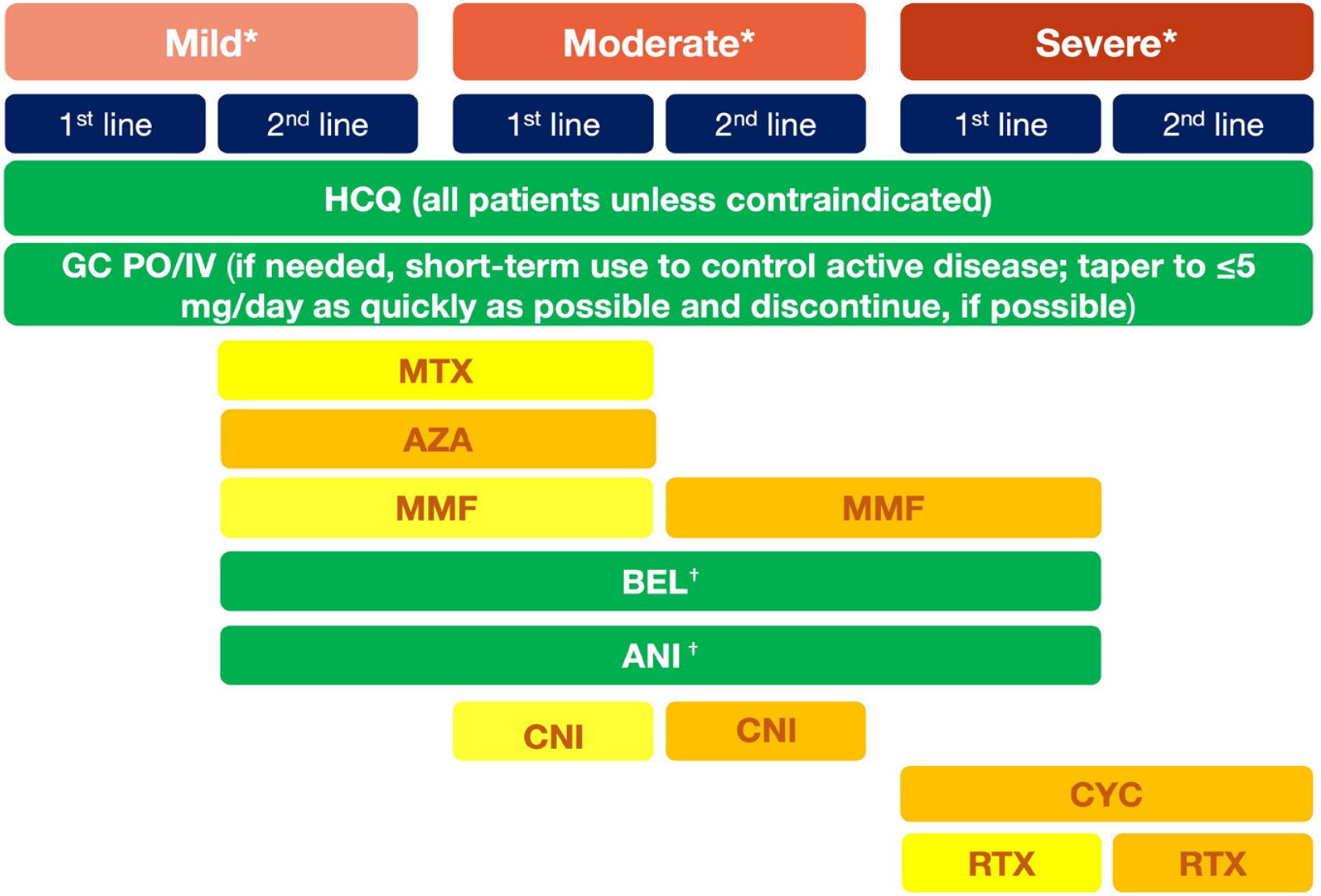
Treatment of Non-Renal Systemic Lupus Erythematosus

General measures

Sun protection
Exercise
No smoking
Balanced diet
Vaccinations
Normal body weight
Blood pressure, lipid, glucose control

Acetylsalicylic acid, VKA
(in aPL+/APS)

Assess adherence to treatment



Target

Remission
Clinical SLEDAI=0
HCQ
GC ≤ 5 mg/day

or

Low disease activity
SLEDAI ≤4
HCQ
GC ≤ 5 mg/day

Immunosuppressive or biological agents at stable, tolerated dose

Ann Rheum Dis 2024;83:15–29

Treatment of Lupus Nephritis

	Initial	Subsequent
Adjunct treatment for kidney protection# *ACEi/ARBs* *Consider SGLT2i (if decreased eGFR)* *VKA, heparin (if concomitant APS nephropathy)*	**HCQ (all patients unless contraindicated)**	
	GC PO/IV (consider pulse IV MP, then 0.3-0.5 mg/kg/day depending on severity; taper to ≤ 5 mg/day as quickly as possible)	
	MMF	
	Low-dose CYC	**AZA/MMF**
	MMF/low-dose CYC + BEL§	**MMF/AZA + BEL§**
	MMF + CNI (esp. VOC, TAC)^	**Any of the above–mentioned unless contraindicated^**
	High-dose CYC *,¶	
Assess adherence to treatment	**RTX †**	

Targets

3 months
≥25% reduction in UPr

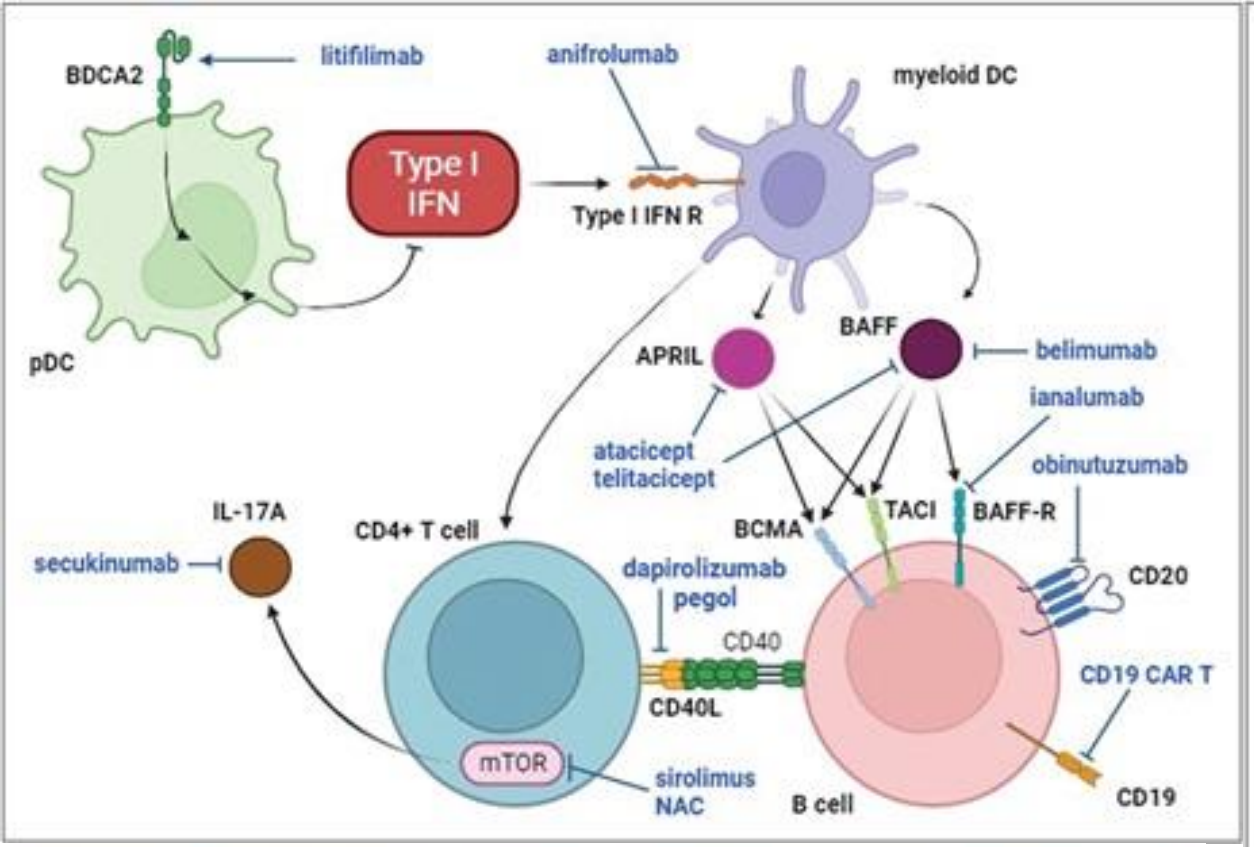
6 months
≥50% reduction in UPr to <3 gr/day

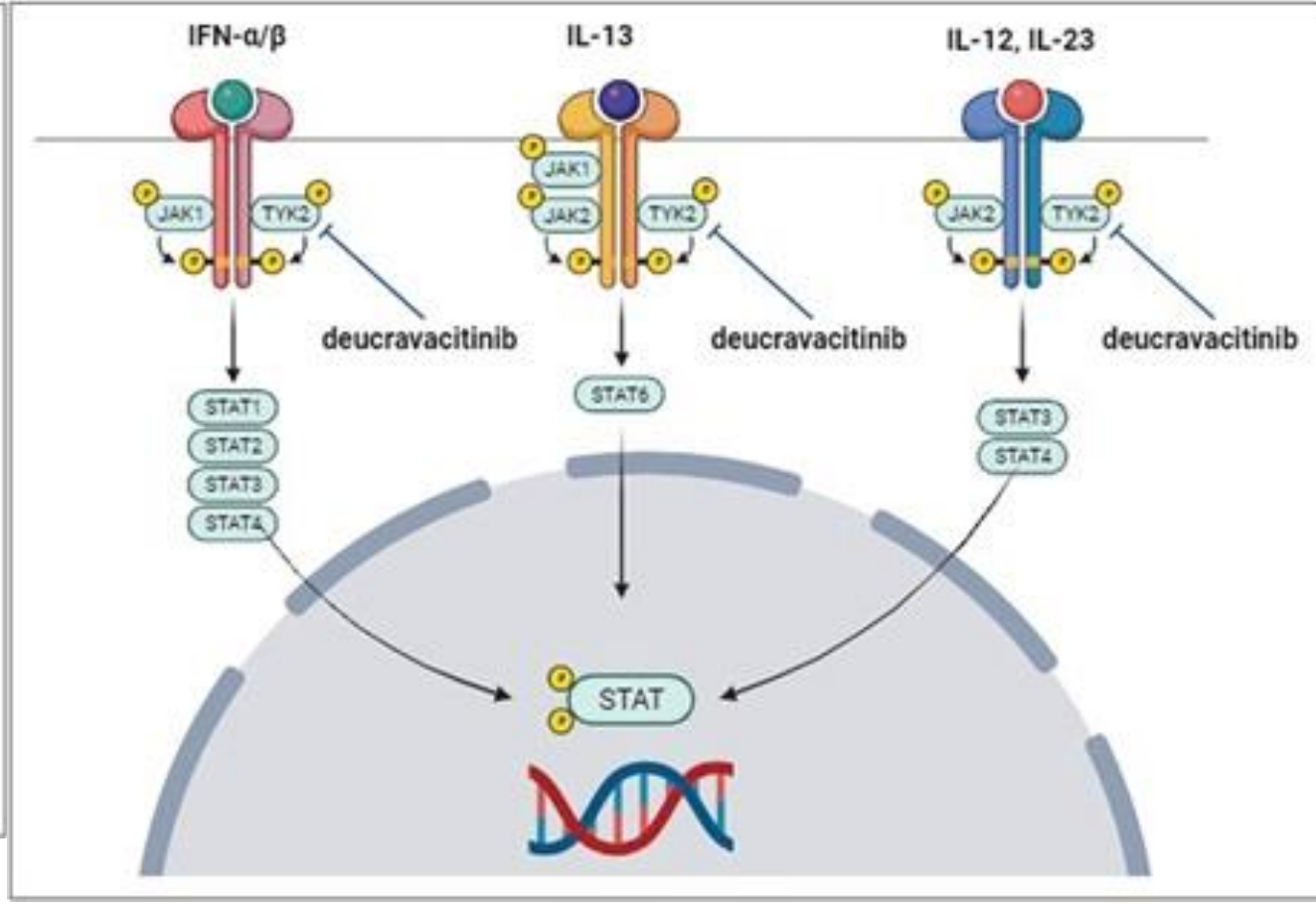
12 to 24 months
UPr <0.5-0.7 gr/day

(all with eGFR within 10% from baseline)

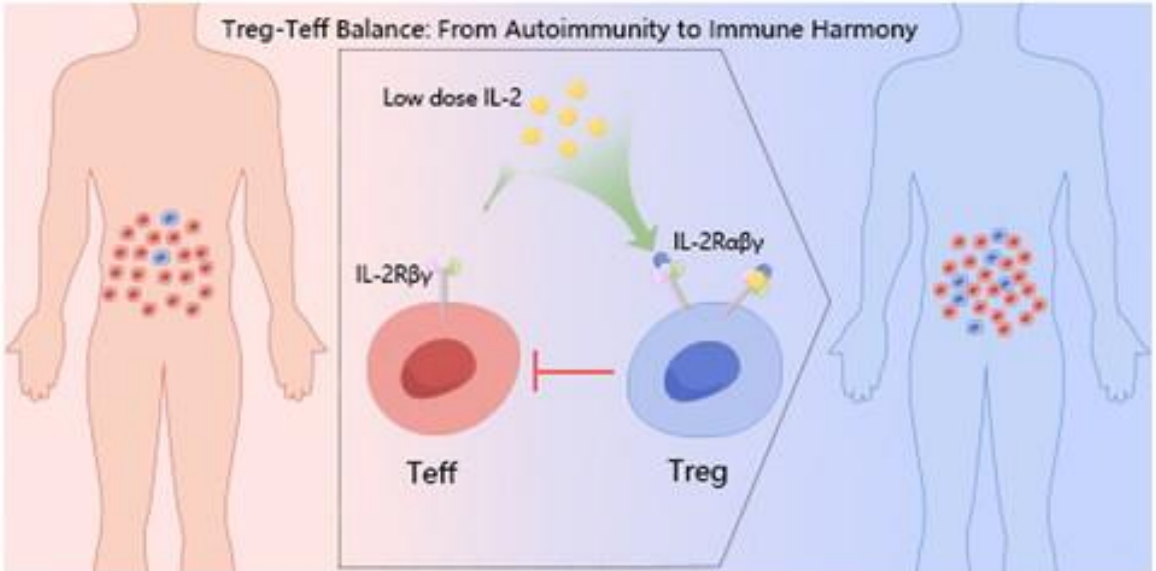
Grade A Grade B Grade C Grade D

Ann Rheum Dis 2024;83:15–29



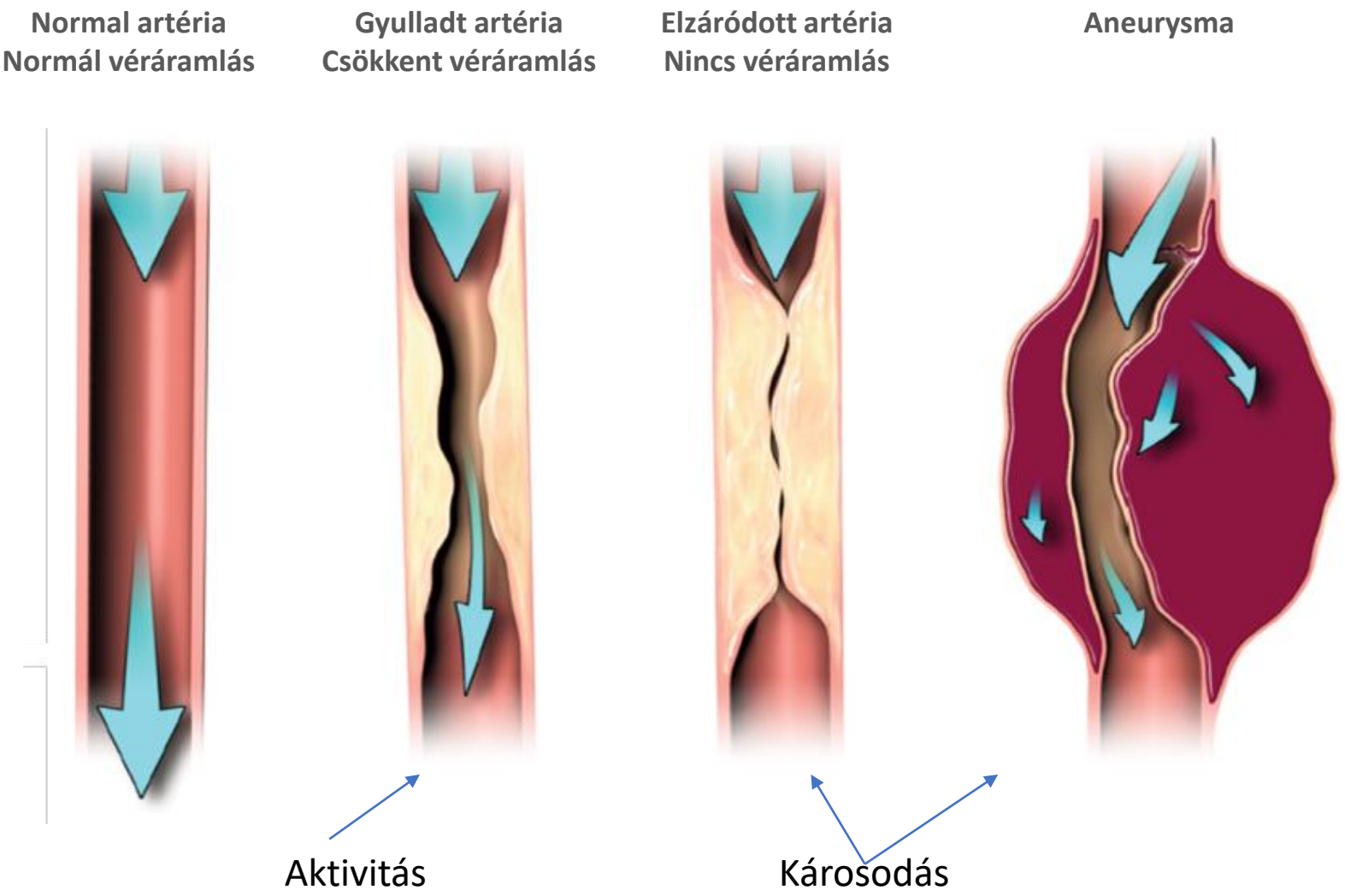


Current Opinion in Rheumatology 36(3):p 169-175, May 2024.



Int Rev Immunol. 2024 May;43(3):113-137

Vasculitis:
az erek falának gyulladásos infiltrációja



Langford 2010;. Gómez-Puerta & Bosch 2009;. Jennette et al. 1994

Vasculitis alakulhat ki

- Malignus tumorokban
- Infectiókban
- Autoimmun kórképekben
- Gyógyszer-vegyszer hatás következtében

Large vessel vasculitis:

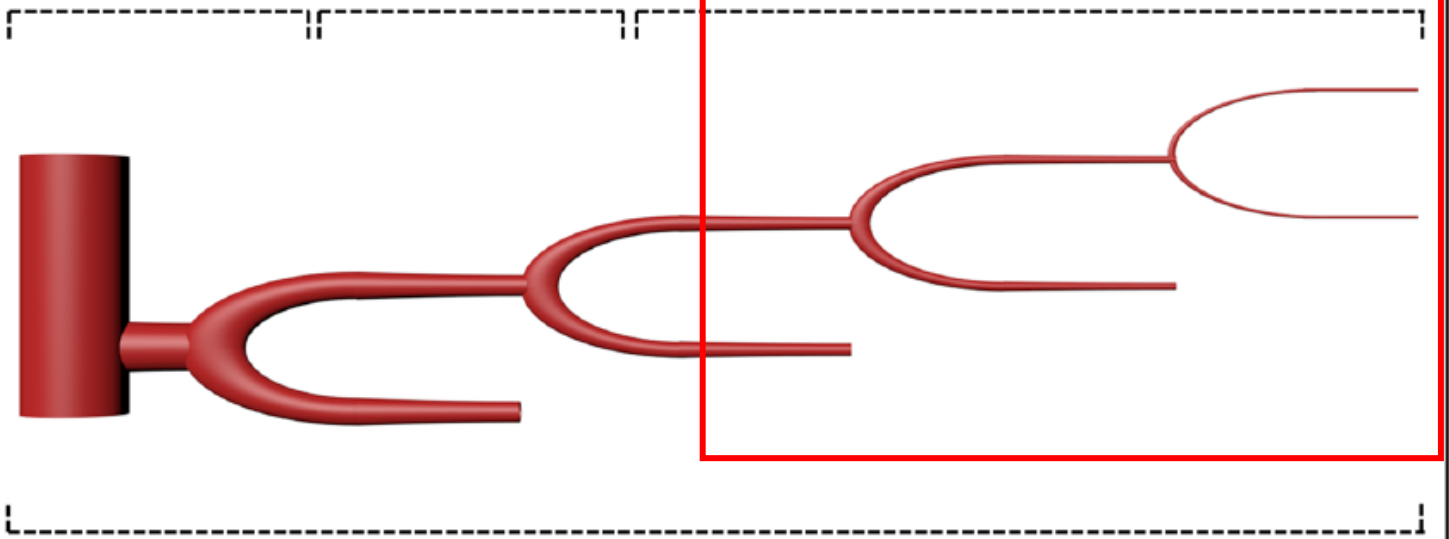
- **Takayasu arteritis**
- **Giant cell arteritis**

Medium vessel vasculitis:

- **Polyarthritis nodosa**
- **Kawasaki disease**

Small vessel vasculitis:

- **ANCA-associated vasculitis:**
  - Microscopic polyangiitis
  - Granulomatosis with polyangiitis
  - Eosinophilic granulomatosis with polyangiitis
- **Immune complex vasculitis**
  - Anti-glomerular basement membrane
  - Cryoglobulinemic vasculitis
  - IgA vasculitis
  - Hypocomplementemia urticarial vasculitis



Variable vessel vasculitis:

- **Behçet disease**
- **Cogan's syndrome**

Other types of vasculitis:

- **Single-organ vasculitis**
  - Cutaneous leukocytoclastic angiitis
  - Cutaneous arteritis
  - Primary central nervous system vasculitis
  - Isolated aortitis
  - Others
- **Vasculitis associated with systemic disease**
  - Lupus vasculitis
  - Rheumatoid vasculitis
  - Sarcoid vasculitis
  - Others
- **Vasculitis associated with probable etiology**
  - Hepatitis C virus–associated cryoglobulinemic vasculitis
  - Hepatitis B virus–associated vasculitis
  - Syphilis-associated aortitis
  - Drug-associated immune complex vasculitis
  - Drug-associated ANCA-associated vasculitis
  - Cancer-associated vasculitis
  - Others

Fig. 1 Diagram of various types of vasculitis based on the size of the affected vessel and etiology

Amouei *et al. Insights into Imaging (2022) 13:143*

ANCA asszociál vasculitis prevalencia: 48-184 eset / millió

Feature	GPA	MPA	Eosinophilic GPA
Incidence	0.4–11.9 cases per 1 million person-years	0.5–24.0 cases per 1 million person-years	0.5–2.3 cases per 1 million person-years
Prevalence	2.3–146.0 cases per 1 million persons	9.0–94.0 cases per 1 million persons	2.0–22.3 cases per 1 million persons
Typical age of onset (years)	45–65	55–75	38–54
Male: female ratio	1:1	1:1	1:1
2012 revised CHCC definition[145]	Necrotizing granulomatous inflammation, usually involving the upper and lower respiratory tract; necrotizing vasculitis affecting predominantly small-to-medium vessels (such as capillaries, venules, arterioles, arteries and veins); necrotizing glomerulonephritis is common	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels (such as capillaries, venules or arterioles); necrotizing arteritis involving small and medium arteries may be present; necrotizing glomerulonephritis is very common; pulmonary capillaritis often occurs; granulomatous inflammation is absent	Eosinophil-rich and necrotizing granulomatous inflammation, often involving the respiratory tract; necrotizing vasculitis predominantly affecting small-to-medium vessels; associated with asthma and eosinophilia; ANCA$^+$ is more frequent when glomerulonephritis is present
Frequency of ANCA	PR3-ANCA$^+$: 65–75% MPO-ANCA$^+$: 20–30% ANCA$^-$: 5%	PR3-ANCA$^+$: 20–30% MPO-ANCA$^+$: 55–65% ANCA$^-$: 5–10%	PR3-ANCA$^+$: <5% MPO-ANCA$^+$: 30–40% ANCA$^-$: 55–65%
Key innate immune cell	Neutrophil	Neutrophil	Eosinophil
Relapse rate	Higher than MPA (or MPO-AAV)	Lower than GPA (or PR3-AAV)	Relapse is frequent

AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; CHCC, Chapel Hill Consensus Conference; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, leukocyte proteinase 3.

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CLASSIFICATION CRITERIA FOR **GRANULOMATOSIS WITH POLYANGIITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify a patient as having granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage, or septal defect / perforation	+3
Cartilaginous involvement (inflammation of ear or nose cartilage, hoarse voice or stridor, endobronchial involvement, or saddle nose deformity)	+2
Conductive or sensorineural hearing loss	+1

LABORATORY, IMAGING, AND BIOPSY CRITERIA

Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	+5
Pulmonary nodules, mass, or cavitation on chest imaging	+2
Granuloma, extravascular granulomatous inflammation, or giant cells on biopsy	+2
Inflammation, consolidation, or effusion of the nasal/paranasal sinuses, or mastoiditis on imaging	+1
Pauci-immune glomerulonephritis on biopsy	+1
Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies	-1
Blood eosinophil count ≥ 1 x10^9/liter	-4

Sum the scores for 10 items, if present. A score of ≥ 5 is needed for classification of GRANULOMATOSIS WITH POLYANGIITIS.

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CLASSIFICATION CRITERIA FOR **MICROSCOPIC POLYANGIITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify a patient as having microscopic polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CLINICAL CRITERIA

Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage or septal defect / perforation	-3

LABORATORY, IMAGING, AND BIOPSY CRITERIA

Positive test for perinuclear antineutrophil cytoplasmic antibodies (pANCA) or antimyeloperoxidase (anti-MPO) antibodies ANCA positive	+6
Fibrosis or interstitial lung disease on chest imaging	+3
Pauci-immune glomerulonephritis on biopsy	+3
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-1
Blood eosinophil count $\geq 1 \times 10^9$/liter	-4

Sum the scores for 6 items, if present. A score of ≥ 5 is needed for classification of MICROSCOPIC POLYANGIITIS.

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CLASSIFICATION CRITERIA FOR **EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS**

CONSIDERATIONS WHEN APPLYING THESE CRITERIA

- **These classification criteria should be applied to classify a patient as having eosinophilic granulomatosis with polyangiitis when a diagnosis of small- or medium-vessel vasculitis has been made**
- **Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria**

CLINICAL CRITERIA

Obstructive airway disease	+3
Nasal polyps	+3
Mononeuritis multiplex	+1

LABORATORY AND BIOPSY CRITERIA

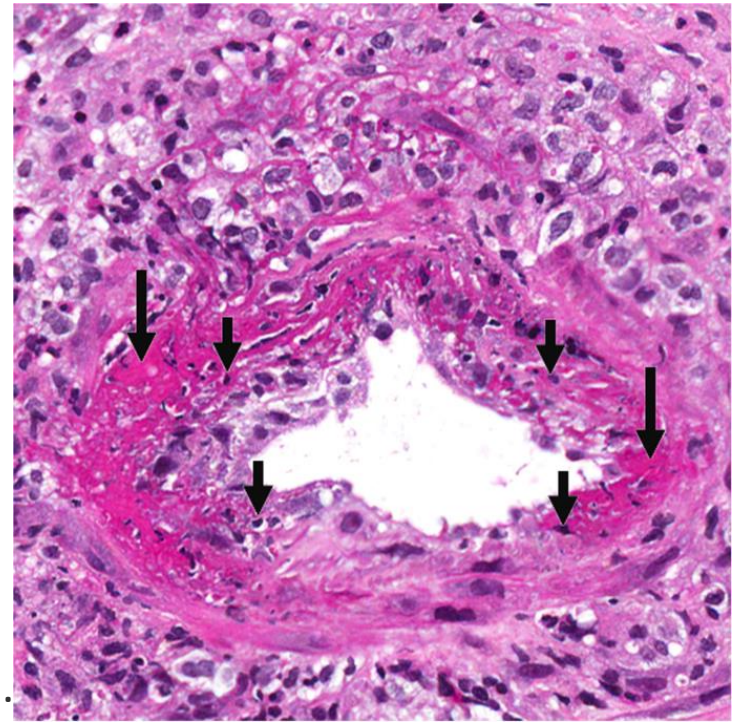
Blood eosinophil count ≥ 1 x10^9/liter	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA) or antiproteinase 3 (anti-PR3) antibodies	-3
Hematuria	-1

Sum the scores for 7 items, if present. A score of ≥ 6 is needed for classification of EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS.

Klasszifikáció

- Kisérvasculitis diagnózisa már megtörtént
- Alernatív diagnózisok kizárásra kerültek

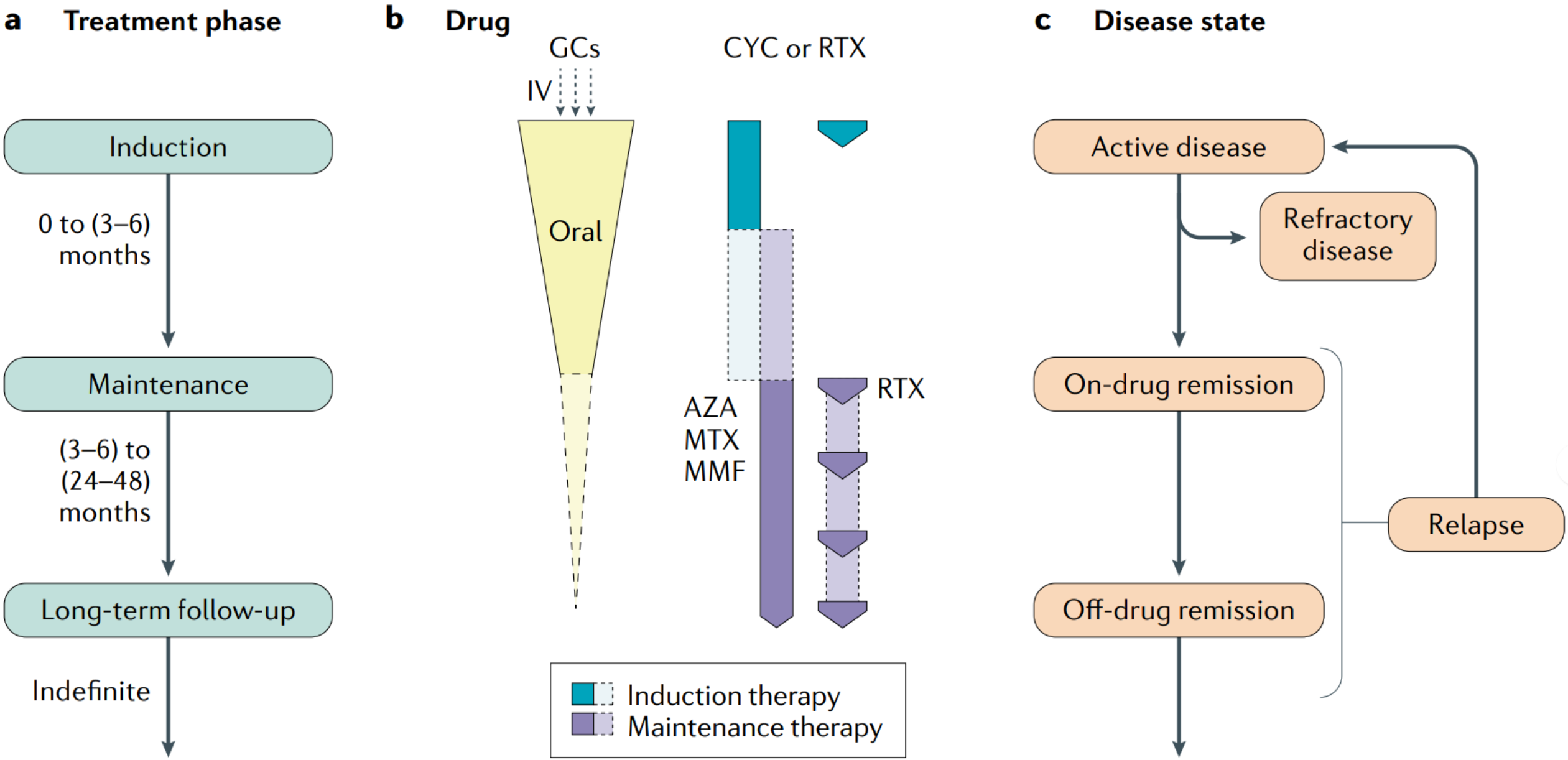
- Klinikai + képalkotó/laboratóriumi/hisztológiai kritériumok
  - Súlyozás jelentőség szerint
    - Pozitív (támogató) krétriumok
    - Negatív (ellene szóló) kritériumok



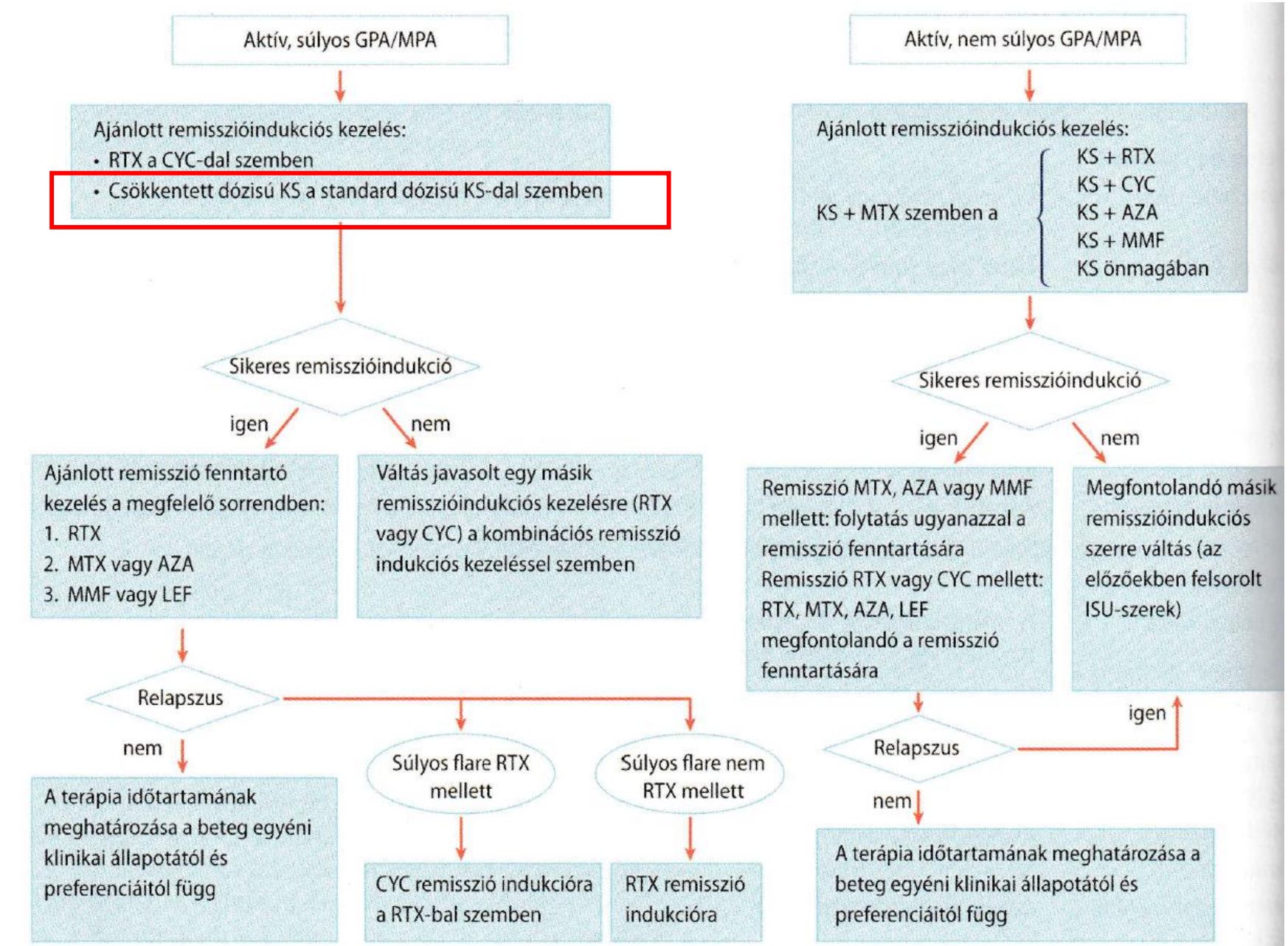
Arthritis & Rheumatology
Vol. 74, No. 3, March 2022, pp 386-406

Semin Immunopathol **44,** 325–345 (2022).

Terápia


a Treatment phase
Induction
0 to (3–6) months
Maintenance
(3–6) to (24–48) months
Long-term follow-up
Indefinite
b Drug
GCs
IV
Oral
CYC or RTX
AZA
MTX
MMF
RTX
Induction therapy
Maintenance therapy
c Disease state
Active disease
Refractory disease
On-drug remission
Relapse
Off-drug remission

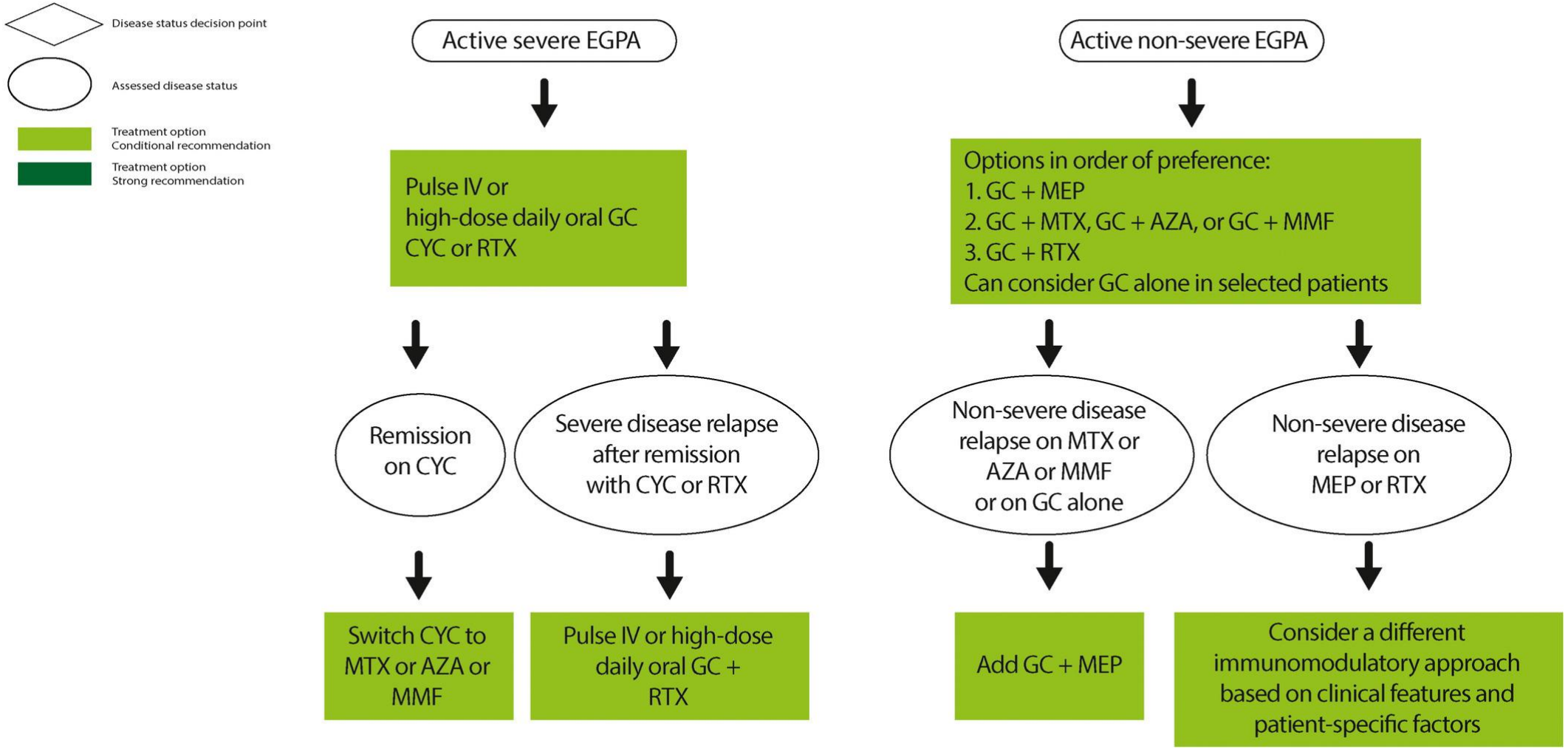
Kezelés



Immunológiai szemle 2022.04.: 43-56.

Kezelés - EGPA

Key recommendations for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA)



AZA = azathioprine, CYC = cyclophosphamide, GC = glucocorticoids, IV = intravenous, MEP = mepolizumab, MMF = mycophenolate mofetil, MTX = methotrexate, RTX = rituximab

Arthritis Care & ResearchVol. 73, No. 8, August 2021, pp 1088–1105

Long-term outcomes and prognostic factors for survival of patients with ANCA-associated vasculitis (AAV)

Background

Despite advances in diagnosis and treatment, patients with AAV have a poor prognosis, and the predicative factors are not well categorized. Evaluation of long-term outcomes in major European RCTs and identifying prognostic factors.

Methods

Multicenter
74 centers, 17 countries in Europe

848 patients
Enrolled 1995–2012 in 7 EUVAS (European Vasculitis Society) randomized clinical trials

- Newly diagnosed with AAV
- Compared to matched background population

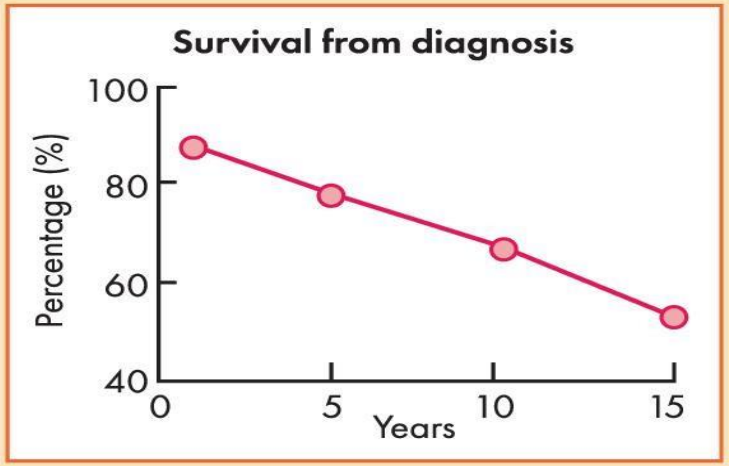
GPA 56% | MPA 44%

Median long-term follow-up
8 years (IQR: 2.9–13.6)

→ Survival
Causes of death
Prognostic factors

Results

Median survival from diagnosis: 17.8 years
*95% CI 15.7–20 years



Excess mortality compared to general population

- **14%** at 1 year
- **20%** at 10 years
- **29%** at 15 years

Main causes of death


26% Infection


14% Cardiovascular disease

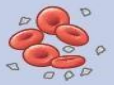

13% Malignancy

Negative prognostic factors:

Advanced age 

Male sex ♂

Low eGFR 

Low platelet count 

Conclusion

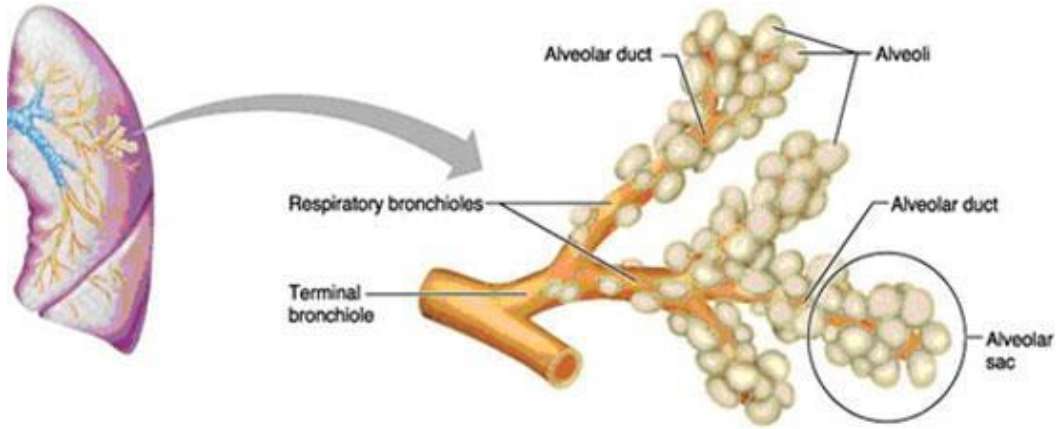
Patients with AAV have an increased risk of mortality compared to the general population. Treatment complications and organ damage are the main causes of limited survival. Infections are the leading cause of death.

ERA ndt NEPHROLOGY DIALYSIS TRANSPLANTATION

Sánchez Álamo B., Moi L. et al., on the behalf of the EUVAS. NDT (2022)
@NDTSocial

Interstitial lung disease (ILD)

- A tüdőszövet hegesedéséveljáró betegségek gyűjtőfogalma
- Heterogén betegségek csoportja (>150) hasonló klinikai megjelenéssel
- Betegségek a disztális légutakat/vaszkulaturát és parenchymát érintik

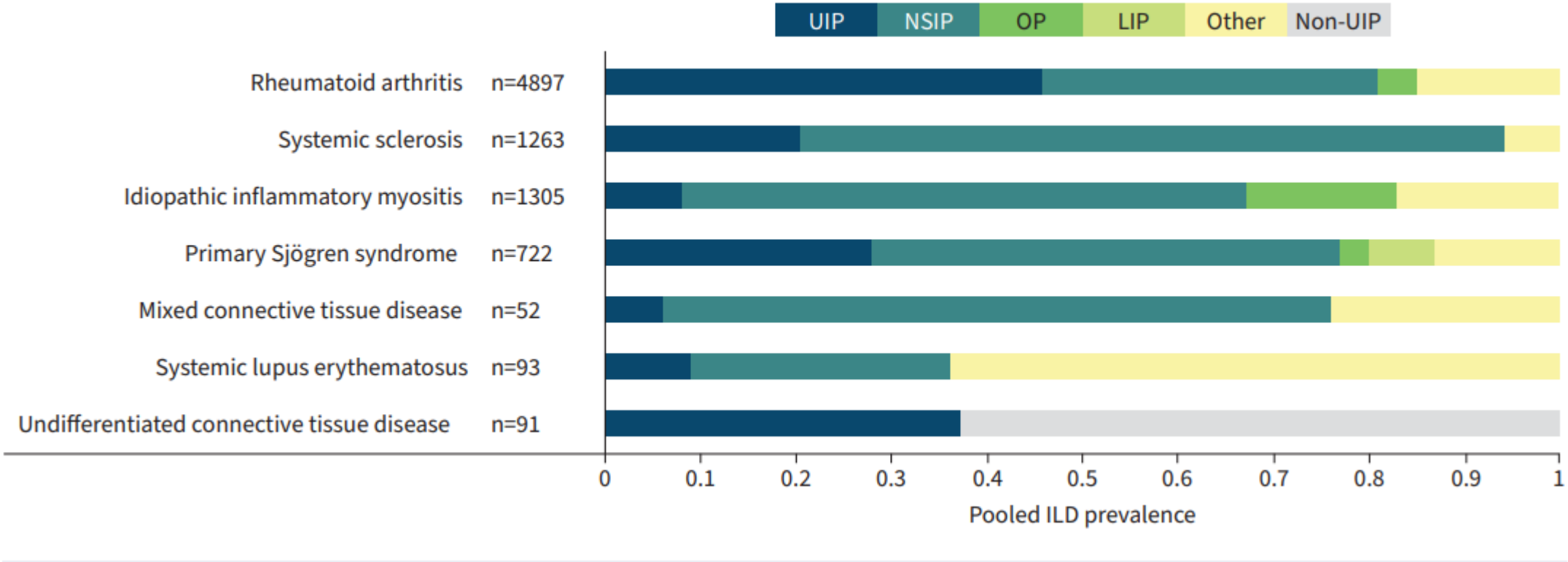


ILD – mikor gondoljunk rá?

- Ha a beteg panaszos
- Szűrés
  - Ha olyan az alapbetegsége, ahol gyakori
    - Ritka kórképek
      - IPF – Magyarországon kb 1000 beteg
      - SSc – 2000 beteg
      - Többi szisztémás autoimmun kórkép
      - Hiperszenzitiv pneumonitisz – 5000 beteg
    - Gyakori kórképek
      - RA – minden családorvosi praxisban 5-6 beteg!

- Elkésett
- Korai diagnózis = esély a kezelésre

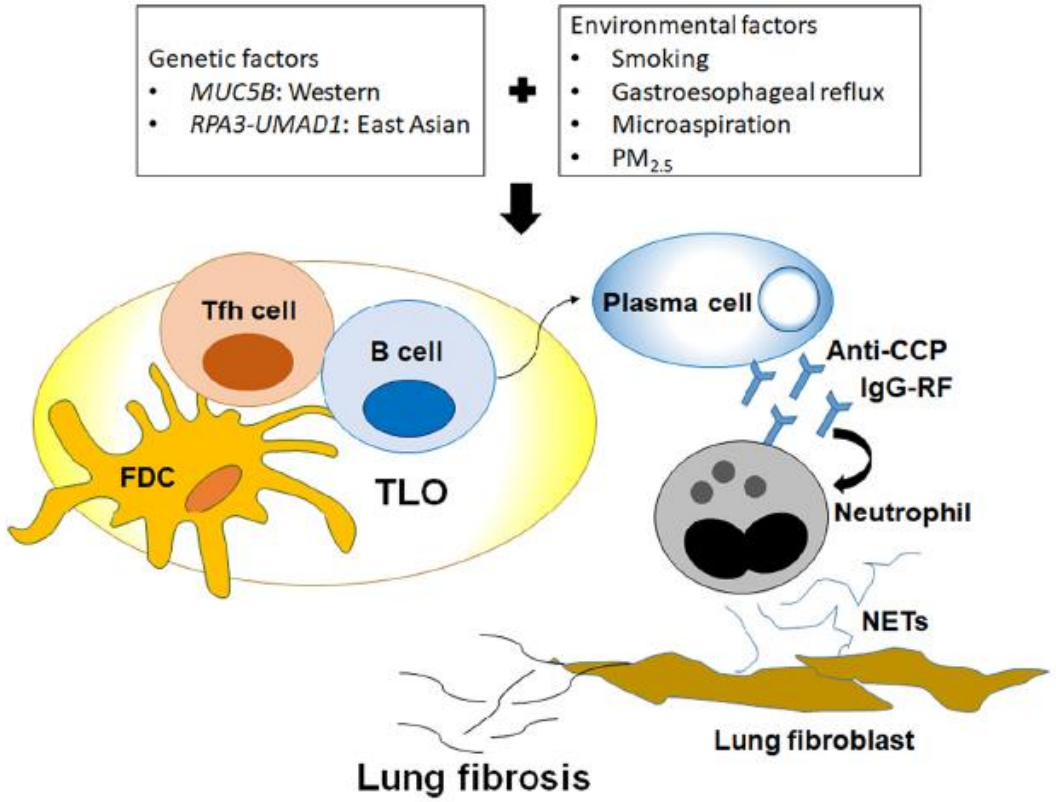
ILD típusainak prevalenciája kötőszöveti betegségeken



Eur Respir Rev 2023; 32: 220210

RA-ILD

- 10-50%-ban mutatható ki HRCT-vel
- ILD fellépése az RA diagnózisához képe
  - 10%-ban diagnózis előtt
  - 30%-ban 1-2 éven belül
- Klinikailag jelentős – 5-8%
- Kialakulásában prediktív:
  - Idősebb életkor,
  - Dohányzás,
  - Magas titerben reumatoid faktor és anti-CCP antitest
  - Férfi
  - Rosszul kontrollálható arthritis aktivitás



J. Clin. Med. 2022, 11, 410.

Autoimmunity Reviews 21 (2022) 103056

ILD-típusok RA-ban

Table 1—*Histopathologic Diagnosis of the SLBx Specimens From 18 Patients With RA-ILD*

Histopathologic Diagnosis	Subjects, No. (%)
UIP pattern	10 (55.6)
NSIP pattern	6 (33.3)
Mixed cellular and fibrotic	2 (11.1)
Fibrotic	4 (22.2)
IAD with OP pattern	2 (11.1)
FB	1
Chronic nonspecific bronchiolitis	1

Lee KH et al, CHEST / 127 / 6 / JUNE, 2005

Progresszív tüdőfibrózis

Ismert tüdőfibrózis esetén legalább 2-nek a 3 kritérium közül teljesülnie kell:

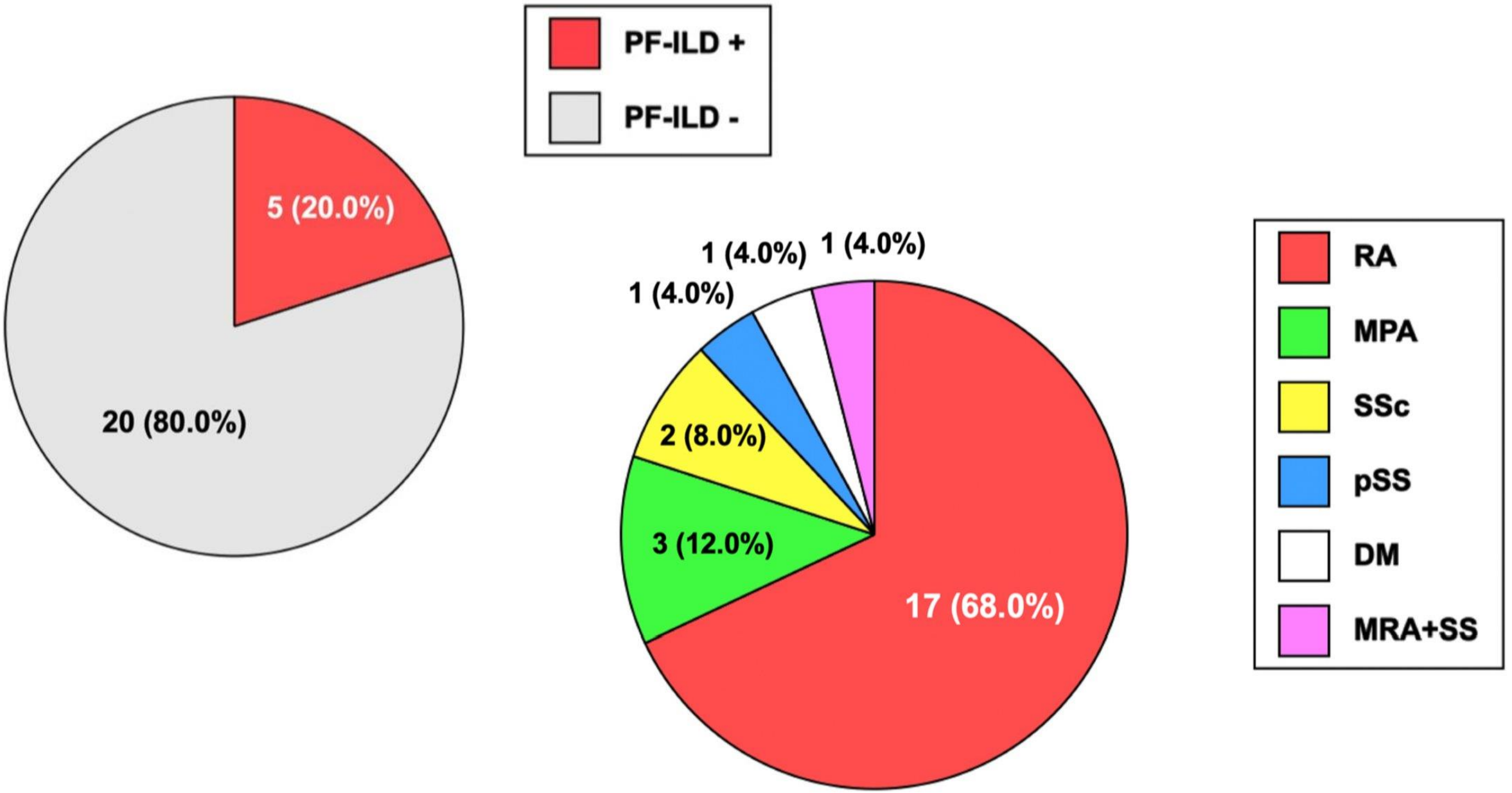
1. **Légzőszervi tünetek romlása**
2. **Fiziológiai eltérések**

- az FVC abszolút csökkenése meghaladja az 5%-ot az egy éves utánkövetés során
- a DLCO abszolút csökkenése meghaladja a 10%-ot az egy éves utánkövetés során

3. **A betegség progressziójának radiológiai bizonyítéka (az alábbiak közül egy vagy több):**

- A trakciós bronchiectasia és a bronchiolectasia kiterjedésének vagy súlyosságának növekedése
- Új tejüveg homály a hörgők trakciós bronchiectasiájával együtt
- Új finom retikuláció
- A retikuláris rendellenesség megnövekedett kiterjedése vagy fokozott durvasága
- Új vagy fokozott kiterjedésű lépesméz eltérés
- Fokozott lobáris térfogatvesztés

Raghu G, et al. Am J Respir Crit Care Med. 2022 May 1;205(9):e18-e47.

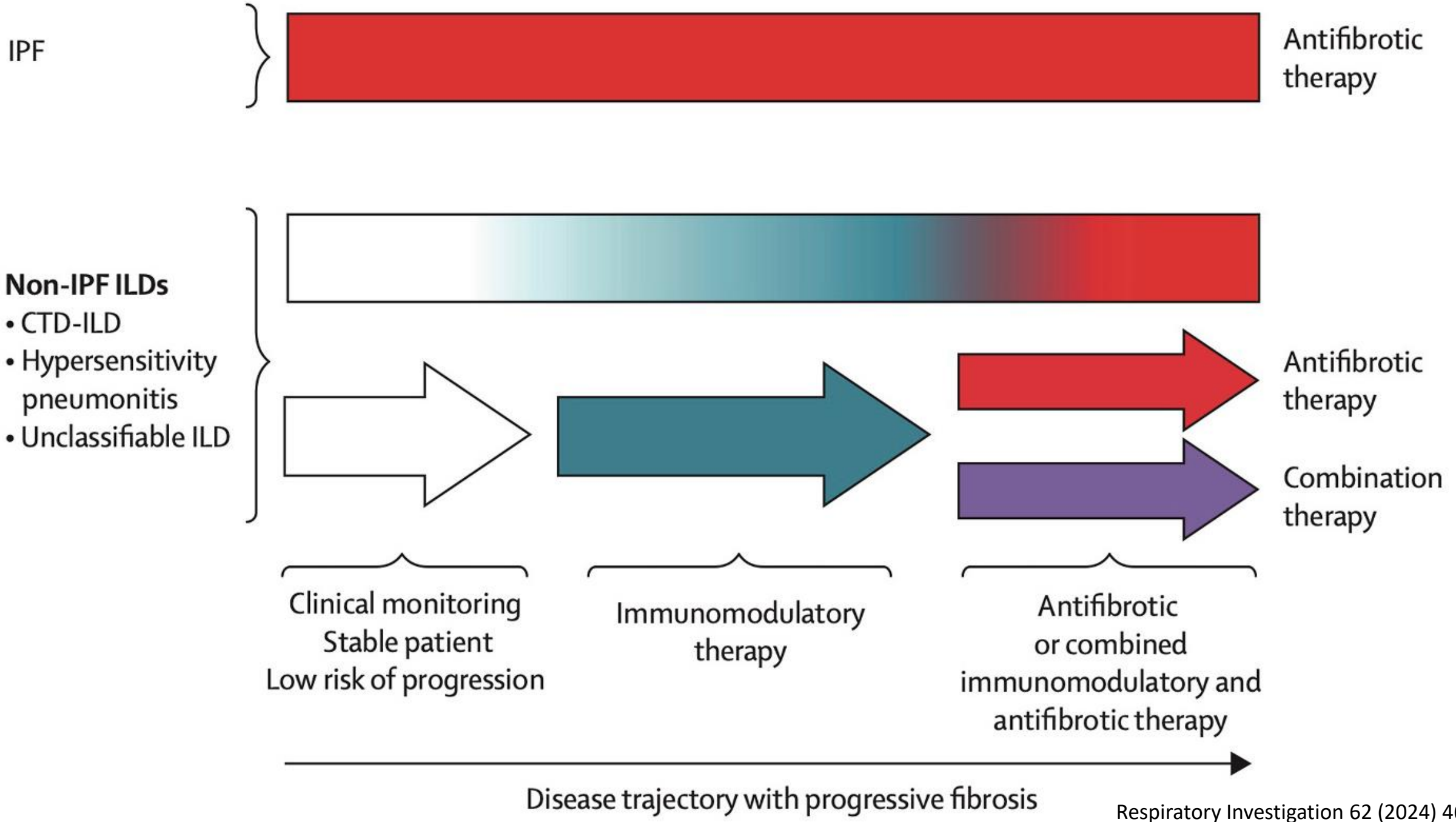


BMC Pulmonary Medicine (2022) 22:387

ILD kezelése – HA progrediál az ILD

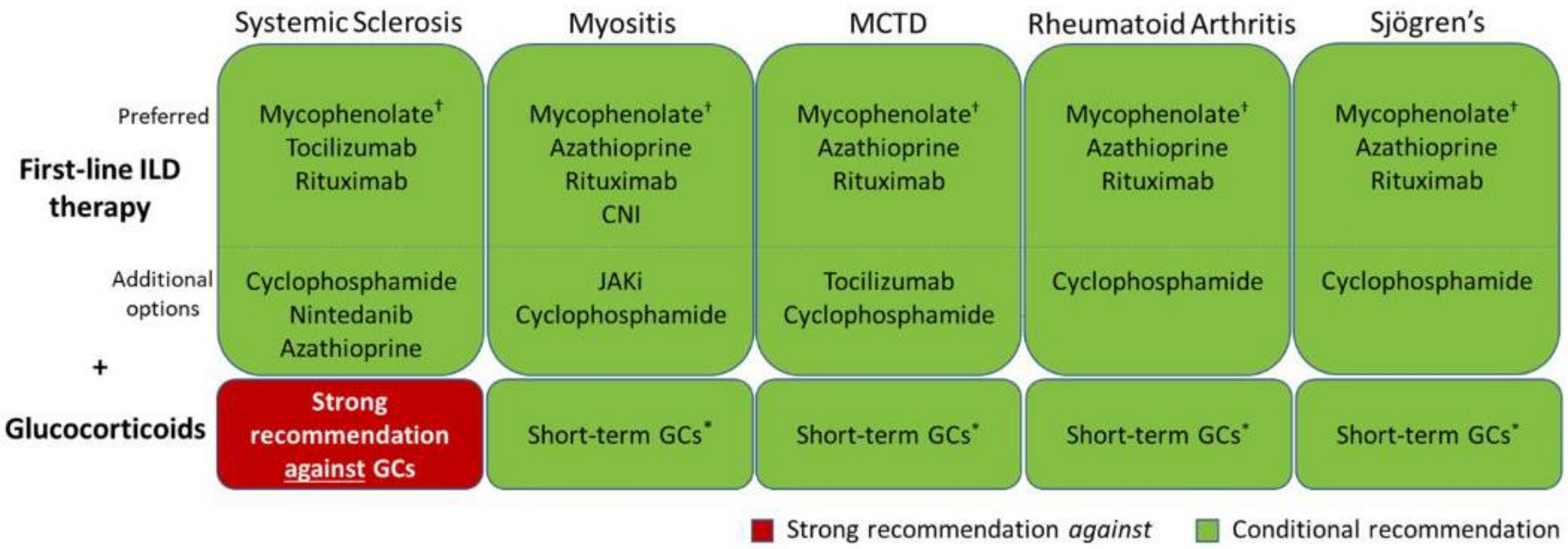
- **Mi a progresszív ILD?**
  - a **légzőszervi tünetek súlyosbodása**
  - **Légzésfunkción FVC, DLCO romlása**
  - **Mellkas HRCT-n progresszió**
- **Progresszióra hajlamosító tényezők**

SSc	Myositis	MCTD	RA	Sjögren
• Férfi nem • Alacsony FVC, DLCO • Romlás (>10%) FVC • Nagy kiterjedésű fibrózis • Lépesméz rajzolat • GERD • Magas KL6 szint	• Idős életkor • Szteroid refrakter kórkép • UIP mintázat • MDA-5, Ro 52	• ?	• UIP mintázat • Alacsony FVC, DLCO • Romlás (>10%) FVC, DLCO 6 hó alatt	• Magas lymphocyta szám BAL-ban



Respiratory Investigation 62 (2024) 465–480

Ajánlás – ACR 2023.



Ajánlás – ACR 2023.

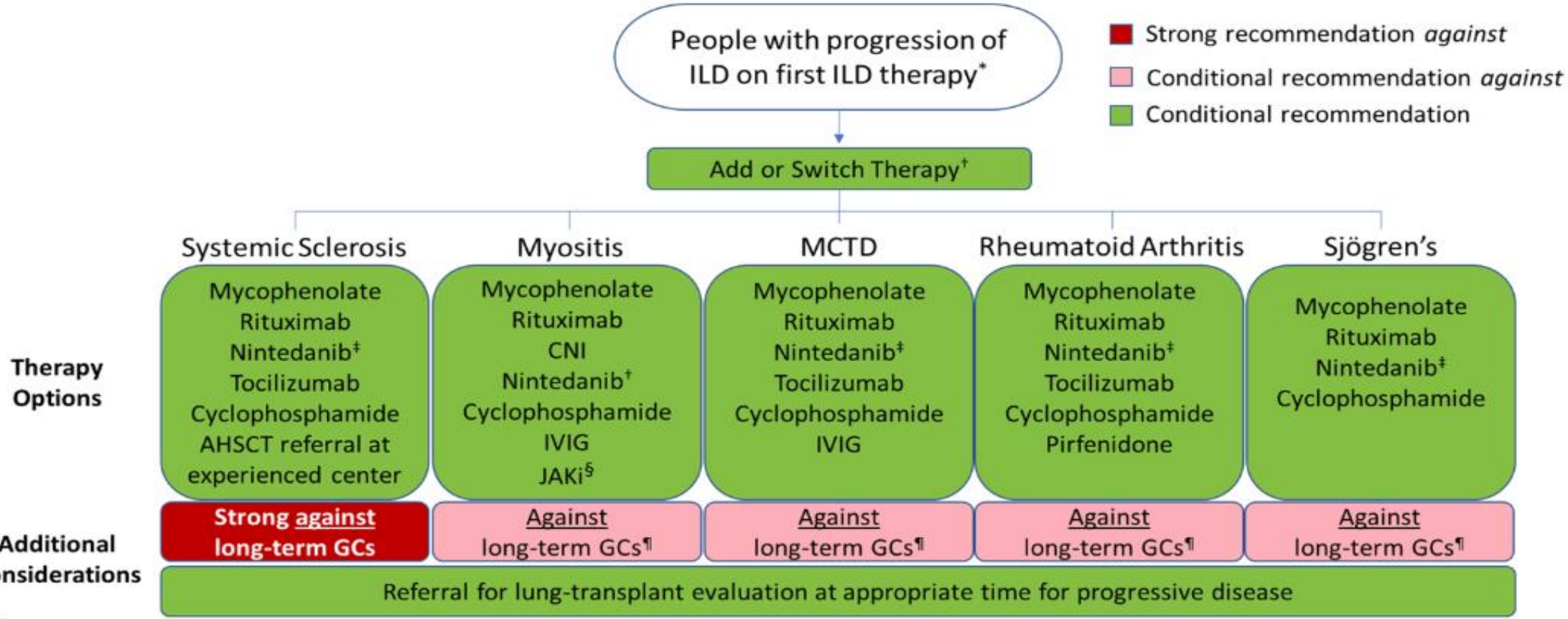
Korai kezelés CTD-ben:

Immunmoduláns szükséges! – UIP-nél is?

Upfront kezelés?

Immunmoduláns + fibrózisgátlás?

Legalább ott ahol van adat (SSc - SENSCIS)?



Köszönöm a figyelmet!