A szisztémás autoimmun kórképek terápiája

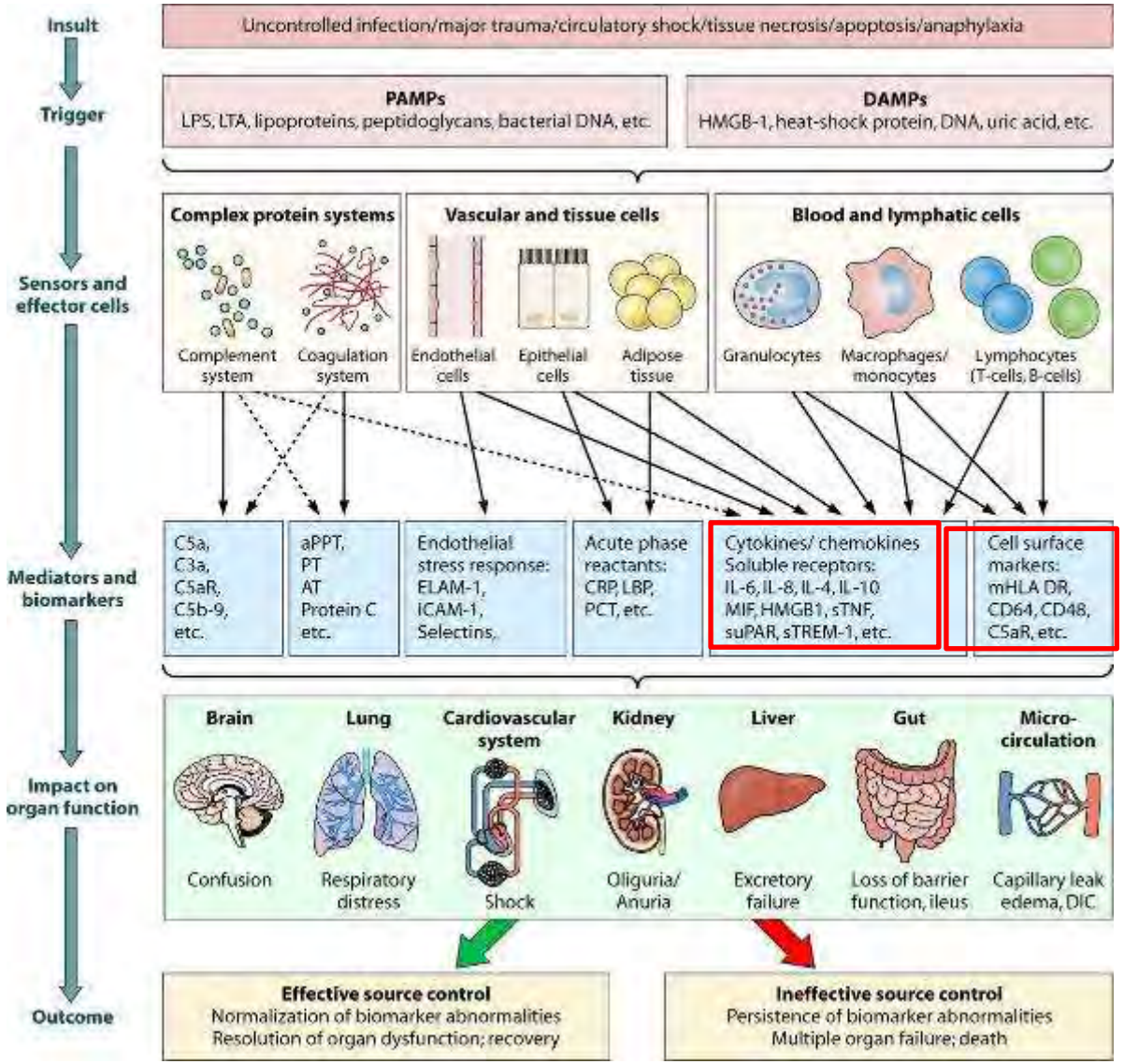
Prof. Dr. Nagy György

Reumatológiai és Immunológiai Klinika

2025 október 1.

SEMMELWEIS
EGYETEM 1769

A szisztémás gyulladás mediátorai



Fertőzés
Tumor

Autoimmun
Autoinflammációs
betegségek

Reinhart K et al. Clin. Microbiol. Rev. 2012;25:609-634

Immunválasz fertőzésekben

	Infectious agent	Disease	Humoral immunity				Cell-mediated immunity	
			IgM	IgG	IgE	IgA	CD4 T cells (macro-phages)	CD8 killer T cells
Viruses	Herpes zoster	Chickenpox						
	Epstein–Barr virus	Mononucleosis						
	Influenza virus	Influenza						
	Polio virus	Poliomyelitis						
Intra-cellular bacteria	*Rickettsia prowazekii*	Typhus						
	Mycobacteria	Tuberculosis, leprosy						
Extra-cellular bacteria	*Staphylococcus aureus*	Boils						
	Streptococcus pneumoniae	Pneumonia						
	Neisseria meningitidis	Meningitis						
	Corynebacterium diphtheriae	Diphtheria						
	Vibrio cholerae	Cholera						
Fungi	*Candida albicans*	Candidiasis						
Protozoa	*Plasmodium* spp.	Malaria						
	Trypanosoma spp.	Trypanosomiasis						
Worms	Schistosome	Schistosomiasis						

Figure 10-16 Immunobiology, 7ed. (© Garland Science 2008)

A kezelés célja gyulladásos reumatológiai betegségekben

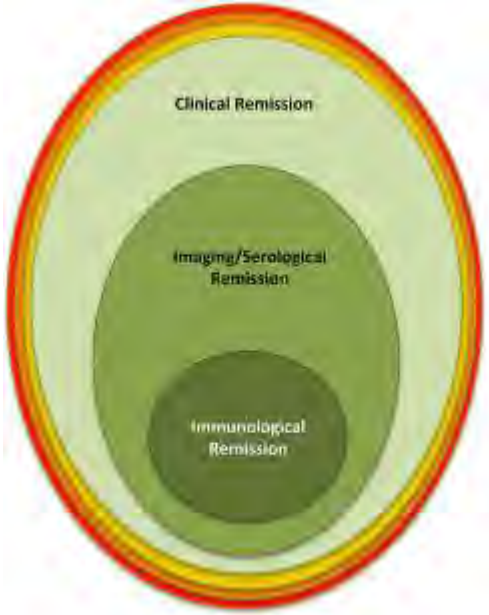
- fájdalomcsillapítás
- gyulladáscsökkentés

- mérsékelt/alacsony betegségaktivitás
- remisszió

- progresszió gátlás

- gyógyszermentes remisszió

- tolerancia indukció



Clinical remission
Absence or very low-level symptoms related to arthritis assessed by standardised scores and cut-offs (DAS28 <2.6, DAS44 <1.6, SDAI <3.3, CDAI <2.8, ACR/EULAR remission)

Imaging/Serological Remission
Clinical remission PLUS
- No signs of ultrasound synovitis
- No signs of MRI synovitis or osteitis
- No serologic signs of inflammation

Immunological Remission
Clinical and imaging/serological remission PLUS
- Rheumatoid factor and ACPA negative
- Rheumatoid factor and ACPA seroconversion is documented

Schett G et al Ann Rheum Dis. 2016 Aug;75(8):1428-37.

Szintetikus bázisterápiás szerek

- **methotrexate (MTX)**

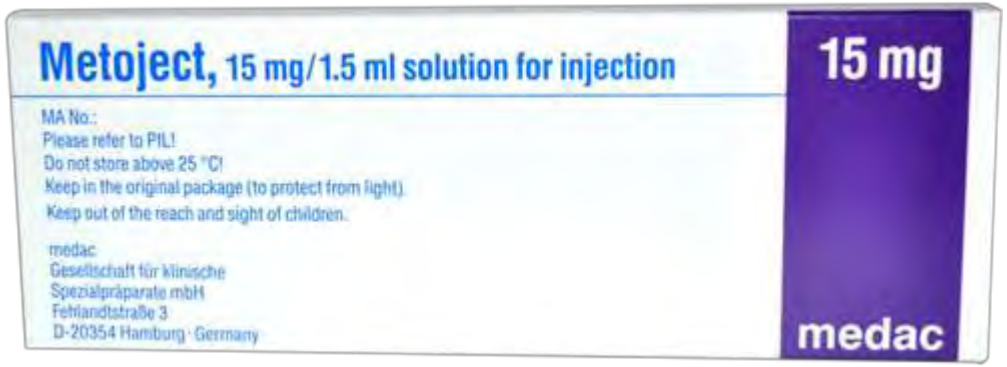
- chloroquin (CHL)
- sulfasalazin (SSZ)
- leflunomid (LEF)
- azathioprin (AZA)
- cyclosporin A (CSA)
- cyclophosphamid (CPH)

Az MTX RA-ban

évtizedek óta alkalmazott

minden ajánlás központi része

biztonságos és hatékony

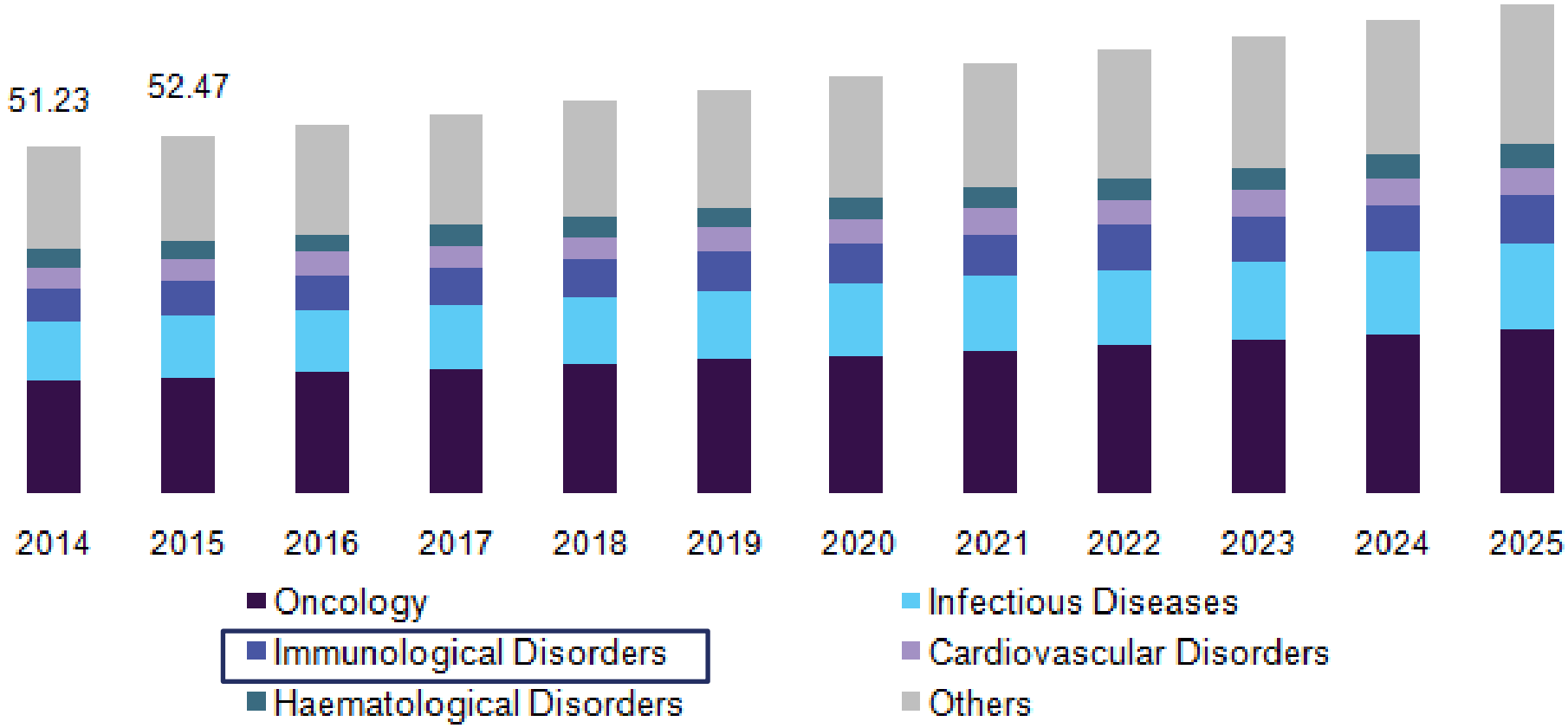


MTX mellékhatások

csontvelő-szuppresszió, hepatotoxicitás	***reverzibilis***
intersticialis pneumonitis	
nyálkahártya-károsodás, stomatitis ulcerosa	***dózis csökkentés, sz.e. elhagyás***
rossz közérzet, borzongás és láz, szédülés, a fertőzésekkel szembeni ellenállóképesség csökkenése	
émelygés, hányinger	***sc. adagolás***

Biológia terápiák 2014-2025

U.S. Biologics market share, by disease category, 2014 - 2025 (USD Billion)



https://www.grandviewresearch.com/industry-analysis/biologics-market

Célzott terápiák a reumatológiában

I: TNF-blokkolás
II: IL1-blokkolás
III: IL-6-blokkolás
IV: IL-17-blokkolás
V: IL12/23-blokkolás
VI: B-sejt-gátlás
VII: T-sejt-gátlás
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FERTŐZÉS ÉS TNF

Fertőzéseket követően egyes tumorok növekedése lassul

Streptococcus pyogenes baktérium közvetlenül a tumorba

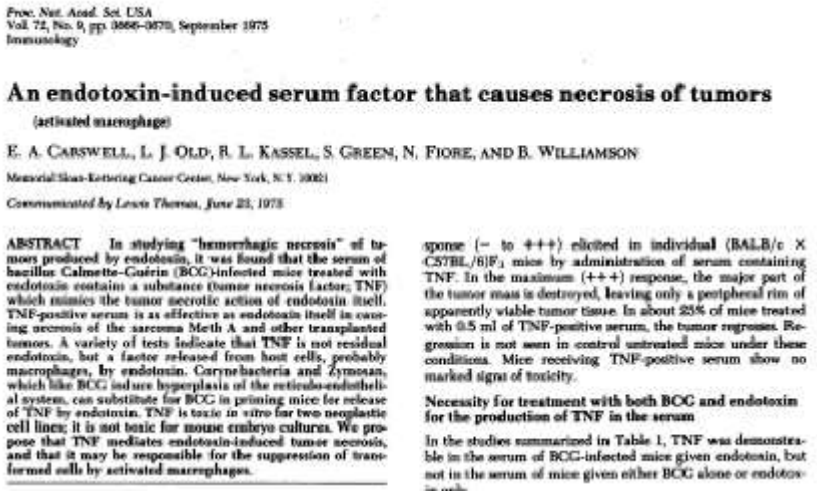
Első betege 16 éve fiú, nagy hasi tumorral, melyet négy naponta infiltrált.

A fiú esetét publikálta.

Coley WB. Annals of Surgery 1891;14:199-200
Roger, G.H. Séances et Mém Soc de Biol Paris 1890;2:573-580

1975: TNF

Carswell EA Proc Natl Acad Sci U S A. 1975 Sep;72(9):3666-70. An endotoxin-induced serum factor that causes necrosis of tumors.


Proc. Nat. Acad. Sci. USA
Vol. 72, No. 9, pp. 3666–3670, September 1975
Immunology

An endotoxin-induced serum factor that causes necrosis of tumors

(activated macrophage)

E. A. CARSWELL, L. J. OLD, R. L. KASSEL, S. GREEN, N. FIORE, AND B. WILLIAMSON

Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021

Communicated by Lewis Thomas, June 23, 1975

ABSTRACT In studying "hemorrhagic necrosis" of tumors produced by endotoxin, it was found that the serum of bacillus Calmette-Guérin (BCG)-infected mice treated with endotoxin contains a substance (tumor necrosis factor; TNF) which mimics the tumor necrotic action of endotoxin itself. TNF-positive serum is as effective as endotoxin itself in causing necrosis of the sarcoma Meth A and other transplanted tumors. A variety of tests indicate that TNF is not residual endotoxin, but a factor released from host cells, probably macrophages, by endotoxin. Corynebacteria and Zymosan, which like BCG induce hyperplasia of the reticulo-endothelial system, can substitute for BCG in priming mice for release of TNF by endotoxin. TNF is toxic *in vitro* for two neoplastic cell lines; it is not toxic for mouse embryo cultures. We propose that TNF mediates endotoxin-induced tumor necrosis, and that it may be responsible for the suppression of transformed cells by activated macrophages.

sponse (− to +++) elicited in individual (BALB/c × C57BL/6)F_1 mice by administration of serum containing TNF. In the maximum (+++) response, the major part of the tumor mass is destroyed, leaving only a peripheral rim of apparently viable tumor tissue. In about 25% of mice treated with 0.5 ml of TNF-positive serum, the tumor regresses. Regression is not seen in control untreated mice under these conditions. Mice receiving TNF-positive serum show no marked signs of toxicity.

Necessity for treatment with both BCG and endotoxin for the production of TNF in the serum

In the studies summarized in Table 1, TNF was demonstrable in the serum of BCG-infected mice given endotoxin, but not in the serum of mice given either BCG alone or endotox-

Cachectin azonosítása (RAV 264 sejt)

PURIFICATION OF CACHECTIN, A LIPOPROTEIN LIPASE–SUPPRESSING HORMONE SECRETED BY ENDOTOXIN-INDUCED RAW 264.7 CELLS

By B. BEUTLER, J. MAHONEY, N. LE TRANG, P. PEKALA,* AND A. CERAMI

*From the Laboratory of Medical Biochemistry, The Rockefeller University, New York 10021; and the *Department of Biochemistry, East Carolina University School of Medicine, Greenville, North Carolina 27834*

In the course of recent studies aimed at elucidating the biochemical mechanism of cachexia in rabbits infected with *Trypanosoma brucei*, it was noted (1) that animals with a minimal parasite burden became moribund and exhibited an extreme hypertriglyceridemia, with a marked elevation of plasma very low density lipoprotein (VLDL).[1] The hypertriglyceridemic state was remarkable in view of the severe wasting diathesis that accompanied this experimental infection. The elevation of plasma VLDL was shown to result from a clearing defect, caused by a loss of peripheral tissue lipoprotein lipase (LPL) activity.

A similar deficiency of LPL activity was noted (2) in C3H/HeN mice after

JEM 1985

lábjegyzet: igen hasonló a TNF-hez……

TNF = cachectin

Identity of tumour necrosis factor and the macrophage-secreted factor cachectin

B. Beutler*, D. Greenwald*, J. D. Hulmes†, M. Chang†, Y.-C. E. Pan†, J. Mathison‡, R. Ulevitch‡ & A. Cerami*

* Laboratory of Medical Biochemistry, The Rockefeller University, 1230 York Avenue, New York, New York 10021, USA
† Department of Biopolymer Research, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110, USA
‡ Department of Immunology, Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Road, La Jolla, California 92037, USA

In mammals, several well-defined metabolic changes occur during infection, many of which are attributable to products of the reticuloendothelial system[1–3]. Among these changes, a hypertriglyceridaemic state is frequently evident[4–7], resulting from defective triglyceride clearance, caused by systemic suppression of the enzyme lipoprotein lipase (LPL)[8]. We have found previously that macrophages secrete the hormone cachectin, which specifically suppresses LPL activity in cultured adipocytes (3T3-L1 cells)[10–12]. When originally purified from RAW 264.7 (mouse macrophage) cells, cachectin was shown to have a pI of 4.7, a subunit size of relative molecular mass (M_r) 17,000 and to form non-covalent multimers[12]. A receptor for cachectin was identified on non-tumorigenic cultured cells and on normal mouse liver membranes[12]. A new high-yield purification technique has enabled us to determine further details of the structure of mouse cachectin. We now report that a high degree of homology exists between the N-terminal

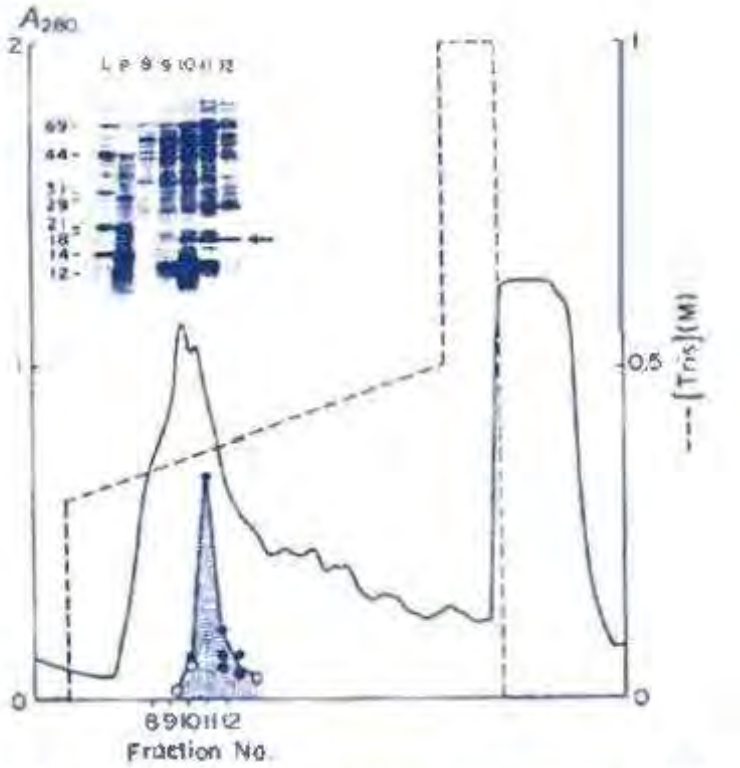


Fig. 1 Mono Q (FPLC anion exchange) chromatography. Crude concentrated RAW 267.4 medium, containing octyl glucoside as a dispersing agent, was applied to the column. Cachectin was eluted using a 0.3 M to 0.5 M Tris-Cl gradient, run at a flow rate 0.33 ml min^{-1}, over 34 min. Absorbance at 280 nm is indicated by

Nature 1985

TNF és fertőzés

Passive Immunization Against Cachectin/Tumor Necrosis Factor Protects Mice from Lethal Effect of Endotoxin

Abstract. *A highly specific polyclonal rabbit antiserum directed against murine cachectin/tumor necrosis factor (TNF) was prepared. When BALB/c mice were passively immunized with the antiserum or with purified immune globulin, they were protected against the lethal effect of the endotoxin lipopolysaccharide produced by* Escherichia coli. *The prophylactic effect was dose-dependent and was most effective when the antiserum was administered prior to the injection of the endotoxin. Antiserum to cachectin/TNF did not mitigate the febrile response of endotoxin-treated animals, and very high doses of endotoxin could overcome the protective effect. The median lethal dose of endotoxin in mice pretreated with 50 microliters of the specific antiserum was approximately 2.5 times greater the median lethal dose for controls given nonimmune serum. The data suggest that cachectin/TNF is one of the principal mediators of the lethal effect of endotoxin.*

B. BEUTLER*
I. W. MILSARK

obscure, it is believed that the toxic effects are mediated by factors produced

Science 1985

Nature medicine 1997

TNF inhibition and sepsis — sounding a cautionary note

Conflicting results from anti-TNF trials in sepsis patients suggest that timely administration of TNF inhibitor drugs is crucial.

GEORGES E. GRAU
& DANIELA N. MARINELLI

Sepsis, a common cause of death in intensive care units, remains a major public health problem. Although potent antibiotics and drugs to treat cardiopulmonary failure are available, new therapeutic approaches that can be taken during the early stages of sepsis regardless of the causative organism are appealing. Inhibition of tumor necrosis factor-α (TNF), a major cytokine mediator

number of clinical trials have attempted to abrogate sepsis and septic shock in patients by inhibiting TNF using either anti-TNF antibodies or fusion proteins composed of the extracellular domain of the p55 (p55-IgG) or p75 TNF receptor combined with the Fc portion of IgG (ref. 2; Fig. 1). However, data are conflicting and clinical responses disappointing. In the most encouraging anti-

RA és TNF

Tumour necrosis factor α stimulates resorption and inhibits synthesis of proteoglycan in cartilage

J. Saklatvala

Strangeways Research Laboratory, Worts' Causeway, Cambridge CB1 4RN, UK

During inflammatory reactions, activated leukocytes are thought to produce a variety of small proteins (cytokines) that influence the behaviour of other cells (including other leukocytes). Of these substances, which include the interleukins, interferons and tumour necrosis factors (TNFs), interleukin-1 (IL-1) has been considered potentially a most important inflammatory mediator because of its wide range of effects (reviewed in refs 1, 2). *In vivo* it is pyrogenic and promotes the acute phase response; *in vitro* it activates lymphocytes[3] and stimulates resorption of cartilage[4] and bone[5,6]. Cartilage resorption is a major feature of inflammatory diseases such as rheumatoid arthritis, and IL-1 is the only cytokine hitherto known to promote it. TNFs are characterized by their effects on tumours and cytotoxicity to transformed cells[7–9], but share some actions with IL-1. I report here that recombinant human TNFα stimulates resorption and inhibits synthesis of proteoglycan in explants of cartilage. Its action is similar to and additive with IL-1, and it is a second macrophage-derived cytokine whose production in rheumatoid arthritis, or inflammation generally, could contribute to tissue destruction.

did TNFα (Fig. 1d): results for two concentrations of each cytokine demonstrate that responses were maximal. Supramaximal doses of the two agents in combination caused a rate of release that was considerably faster than that due to TNFα alone, but was not significantly greater than that seen with IL-1 alone. The failure of TNFα to augment the maximal response to IL-1 may be because the limit of the chondrocytes' ability to degrade their matrix *in vitro* was being approached.

The enzymatic mechanism by which the proteoglycan is degraded in cartilage is not understood. Normally, cartilage proteoglycans aggregate in a specific manner with hyaluronic acid, and it is thought that the large size of these aggregates causes them to be trapped in the matrix. Cartilage stimulated by IL-1 releases fragments of proteoglycan which, as judged by gel filtration, are smaller than normal proteoglycan monomers and are unable to aggregate with hyaluronic acid[10]. There is no evidence of degradation of their chondroitin sulphate chains. These changes suggest that degradation is by limited proteolysis of the protein core. The fragments of proteoglycan that were released by cartilage stimulated with TNF behaved similarly on gel filtration to those generated by stimulation with IL-1 (Fig. 2). The bulk of the fragments generated by stimulation with either agent emerged from a Sepharose 2B column at a region between the elution positions of intact proteoglycan and proteoglycan digested with papain (which consists largely of single-chain chondroitin sulphate peptides). Addition of hyaluronic acid to the proteoglycan fragments before chromatography caused little or no formation of aggregates. This suggested that the hyaluronate binding region was blocked or had been lost. When the proteoglycan fragments were chromatographed under dissocia-

TNF-nek szerepe lehet RA-ban
TNF porc lebontás
Nature 1986

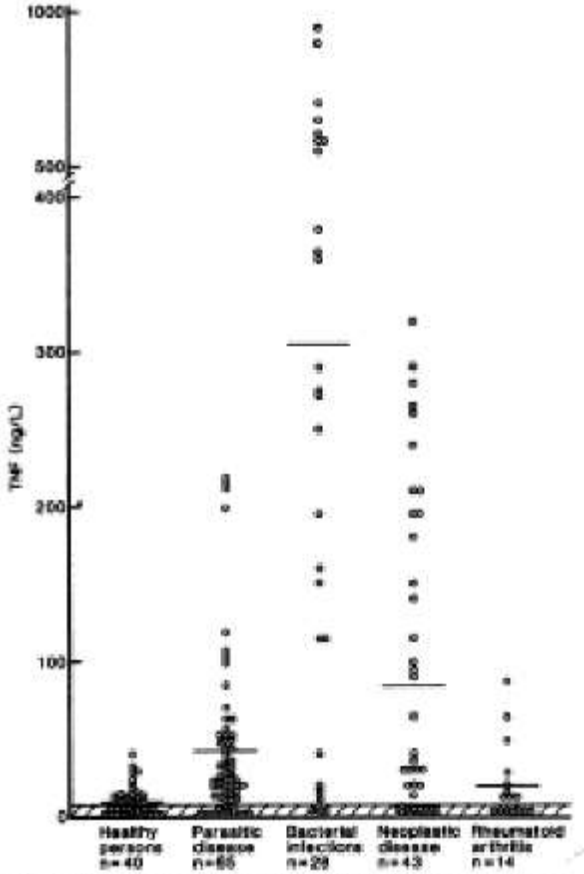


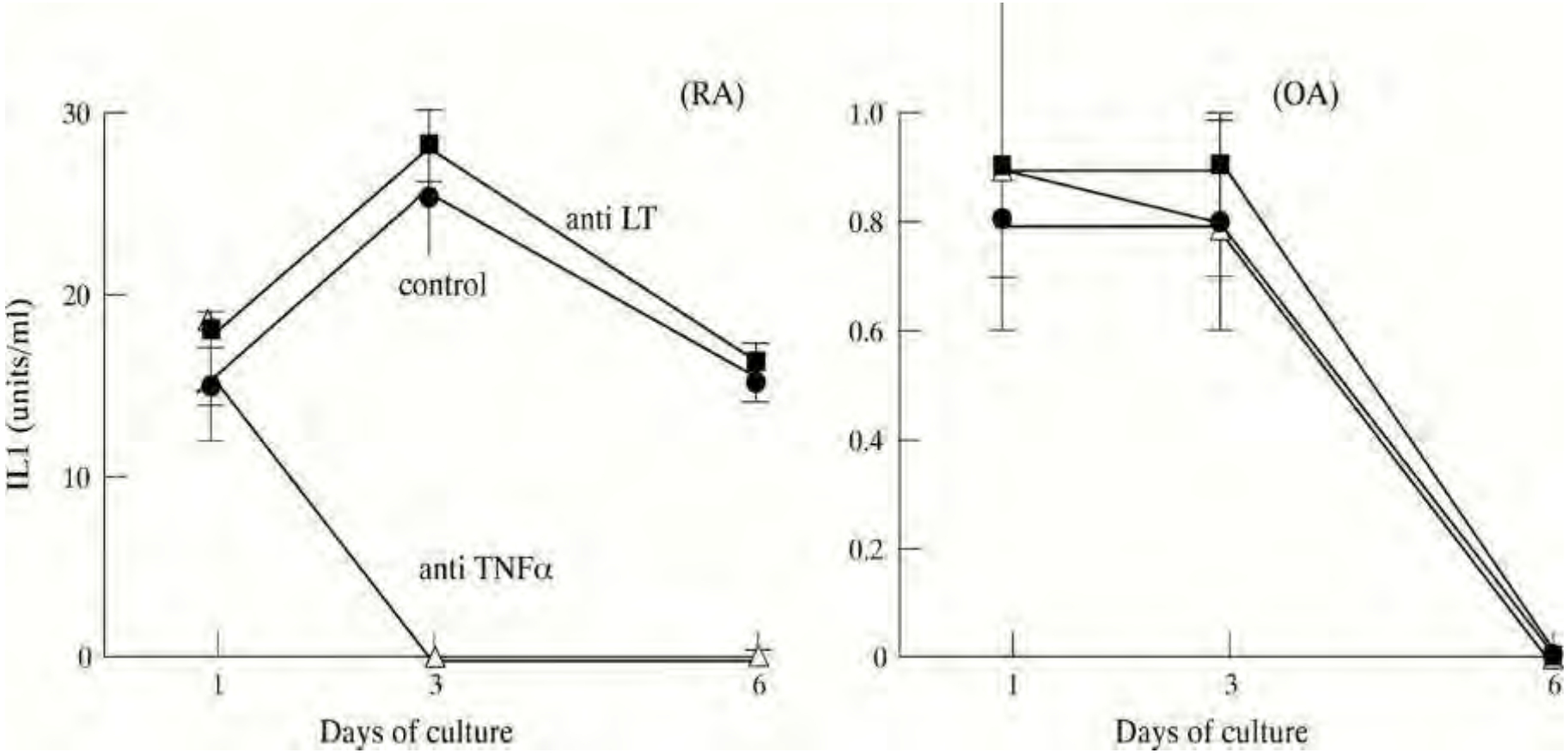
Fig. 4. Tumor necrosis factor concentrations in healthy and diseased persons

Dotted area represents values below the detection limit of the method. Horizontal lines represent mean values of TNF concentrations for each group

TNF szérum szint
Clin Chem 1987

Az első megfigyelés, mely TNF blokkolás terápiás szerepe mellett szól RA-ben

Synoviális sejtek IL1 termelése gátolható TNF blokkolással (*in vitro)*



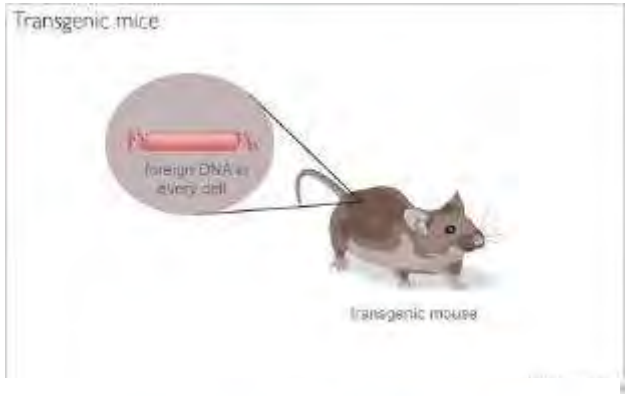
Brennan et al. Lancet 1989

Állatmodellek

TNF transzgenikus egér– súlyos destruktív arthritis

J: EMBO J. 1991

Kollias George



TNF-blokkoló kezelés- jól működik kollagén indukálta arthritisben *(in vivo)*

Proc Natl Acad Sci U S A. 1992

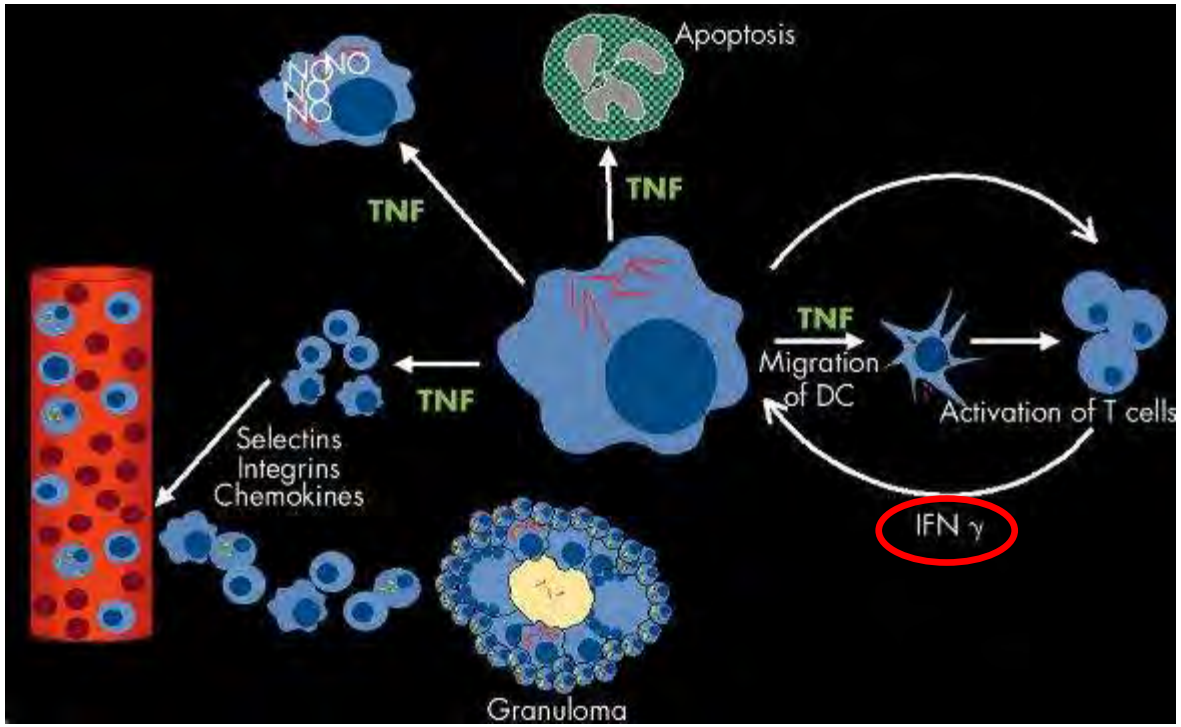
Maini N Ravinder

TNF deficiens egér- fokozott hajlam fertőzésekre, csökkent granuloma képződés, LPS rezisztencia

Proc Natl Acad Sci U S A. 1997

Lyoyd J Old

TNF szerepe a TBC baktérium elleni védekezésben



Stenger, S Ann Rheum Dis 2005;64:iv24-iv28

granuloma képződés

-a szervezet mycobactérum elleni védekezésének része

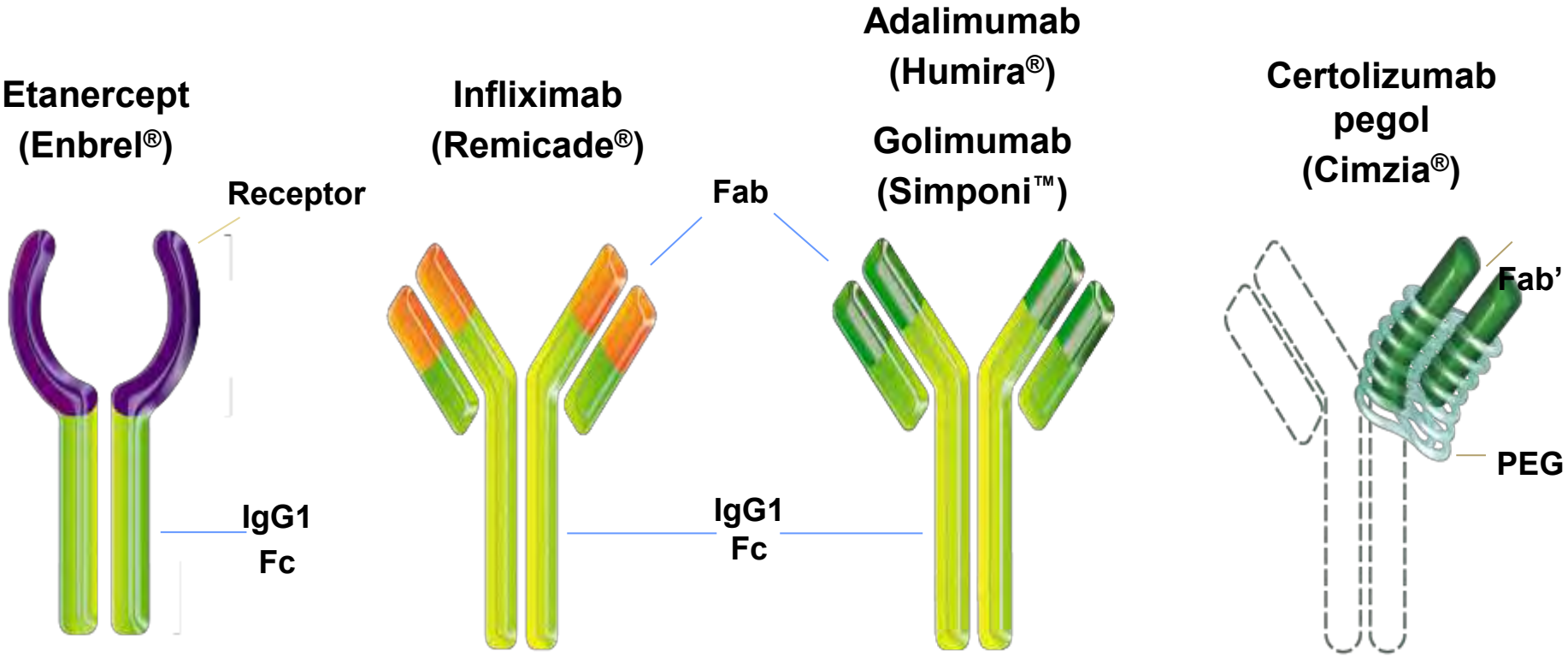
-TNF mediálja

-monocitát, limfocitát tartalmaz

TNF monocita apoptózis indít el

a granulomák élő baktériumokat tartalmazhatnak

I: TNF-gátlók



Recombinant receptor/Fc fusion protein

Monoclonal antibody

PEGylated Fab′ fragment 40 kDa PEG

Weir N, Athwal D, et al. Therapy. 2006;3:535-45

I: TNF-blokkolók

Indikációk (adalimumab): RA, SPA, arthritis psoriatica, psoriasis, gyermekkori psoriasis, Crohn, gyermekkori Crohn, colitis ulcerosa, uveitis, gyermekkori uveitis, JIA, hidradenitis suppurativa
Alkalmazás: sc vagy iv (infliximab)

Eltérő affinitás TNF-hez — alkalmazás gyakorisága
Eltérő immunogenitás — másodlagos hatástalanság

Immunszuppresszió, gátolja a granulomaképződést (IFNγ)
TBC

Hepatotoxicitás
Demyelinizációs betegség
Autoimmun folyamatok
Szívelégtelenség
Allergia, anaphylaxiás reakció

Célzott terápiák a reumatológiában

I: TNF-blokkolás
II: IL1-blokkolás
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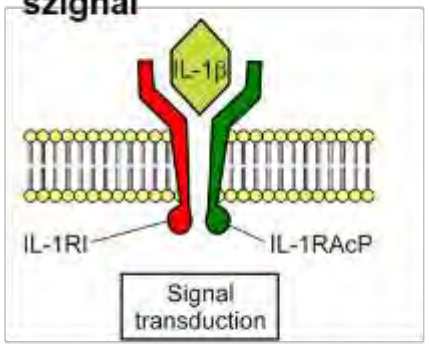
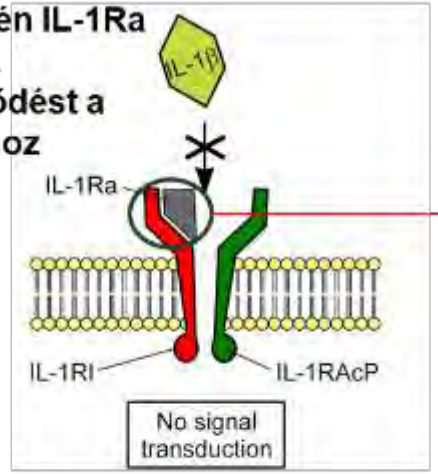
X: IFN gátlás
XI: CAR-T kezelés

II: IL-1 blokkolók

normál IL-1β szignál



az endogén IL-1Ra gátolja az IL-1β kötődést a receptorhoz



IL-1Ra – génje IL1rn
mutációjában nincs IL-Ra hatás
Betegség: DIRA

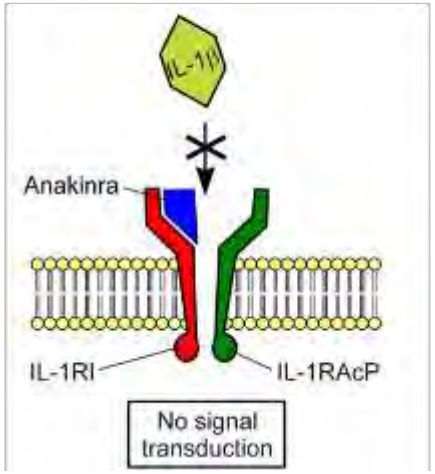
Canakinumab (ILARIS):

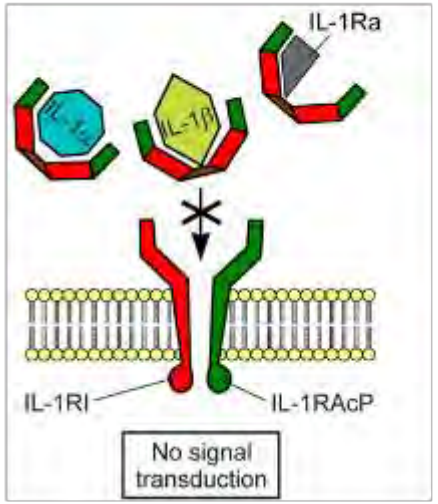
humán monoklonális IL-1β antitest

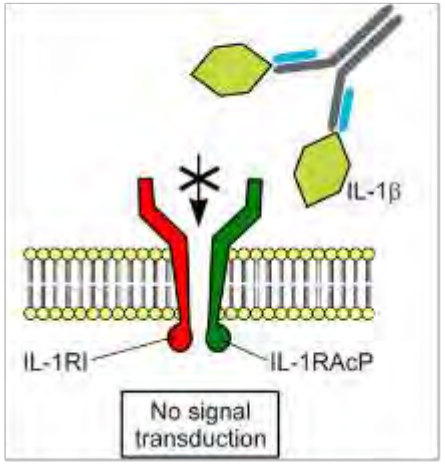
Rilonacept: fúziós protein, köti az IL-1α, IL-1β és IL-1Ra

(human interleukin-1 receptor, IL-1 receptor AP, IgG1 FP)

Anakinra: IL-1 receptor antagonista mimikáló







IL-1Ra, IL-1 receptor antagonista;
IL-1RAcP, IL-1 receptor accessory protein

Canakinumab/ilaris indikációk: Still kór, köszvény, CAPS, TRAPS, FMF, alkalmazás: sc.

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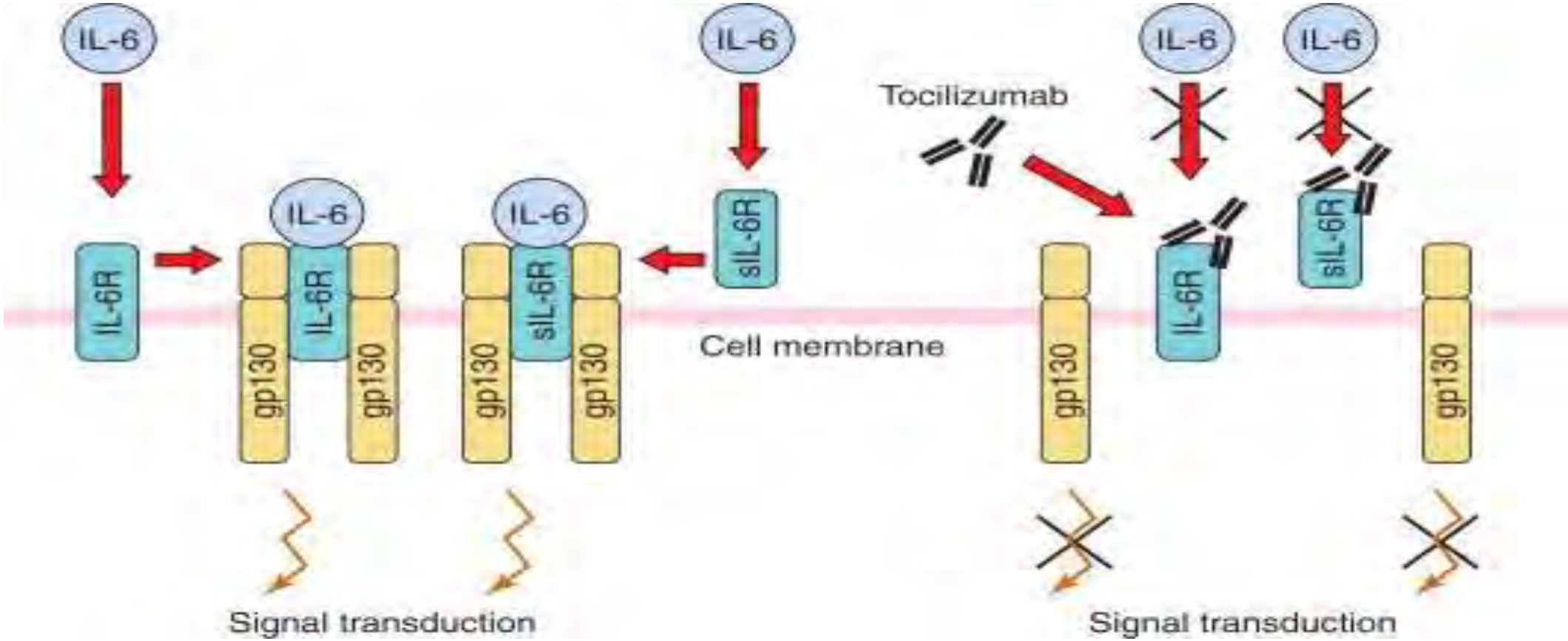
III: A tocilizumab humanizált, IL6-R elleni antitest



https://www.sciencedirect.com/topics/neuroscience/tocilizumab

III: Az IL-6-gátló tocilizumab/Roactemra

Indikációk:
RA, JIA, óriássejtes arteritis, GCA, kiméra antigén-receptor (CAR) T-sejt indukálta citokin felszabadulási szindróma
Alkalmazás: iv. és sc.

Közvetlenül az akut fázis válaszra hat
Fertőzések

Hepatotoxicitás
Neutropenia
Thrombocytopenia
Lipid paraméterek (CV rizikó?)
Diverticulitis
Allergia

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IV: Th17-sejtek

Gyulladásos sejtek

ROR-γt expresszió

IL-17, IL21, IL22 termelés

IL-17 proteinek, IL-17A–F

Két, diszulfid híddal összekötött monomer

RA-ban a szérum és a synovialis folyadék IL-17 szintje magasabb mint arthrosisban

IL-17 szerepe ismert

Osteoclast differenciálódásban

Synovialis szövet proliferációban

Synovialis érújdonképződés

Proinflammatorikus citokin termelődés

Th17-sejt szabályozó:

Bélflóra

Magas zsírtartalmú ételek

Magas sótartalmú ételek

IL-17 gátlók

ixekizumab

brodalumab

secukinumab

1. Kolls JK & Lindén A. Immunity. 2004; 21(4):467–476
2. Miossec P & Kolls JK. Nat Rev Drug Discov. 2012; 11(10):763–776
3. Kirkham BW et al. Immunology. 2014; 141(2):133–142
4. Martin DA et al. J Invest Dermatol. 2013; 133(1):17–26

1. Alunno A Med Inflamm 2015 ID751793
2. Burkett PR et al JCI 2015; 125; 2211-2219

IV: IL-17A-gátló secukinumab/Cosentyx

- Teljesen humán IL-17A-gátló antitest, amely erősen kötődik és neutralizálja a keringő citokint.
- Gyorsan csökkenti a keringő IL-17A szintjét és az ehhez kapcsolt jelátviteli aktivitásokat

Keringő IL-17A-blokkolók

- **Teljesen humán antitest**

  secukinumab – ***indikációk: PsO, PsA, axSpA, JIA, HS***

  Alkalmazás: sc.

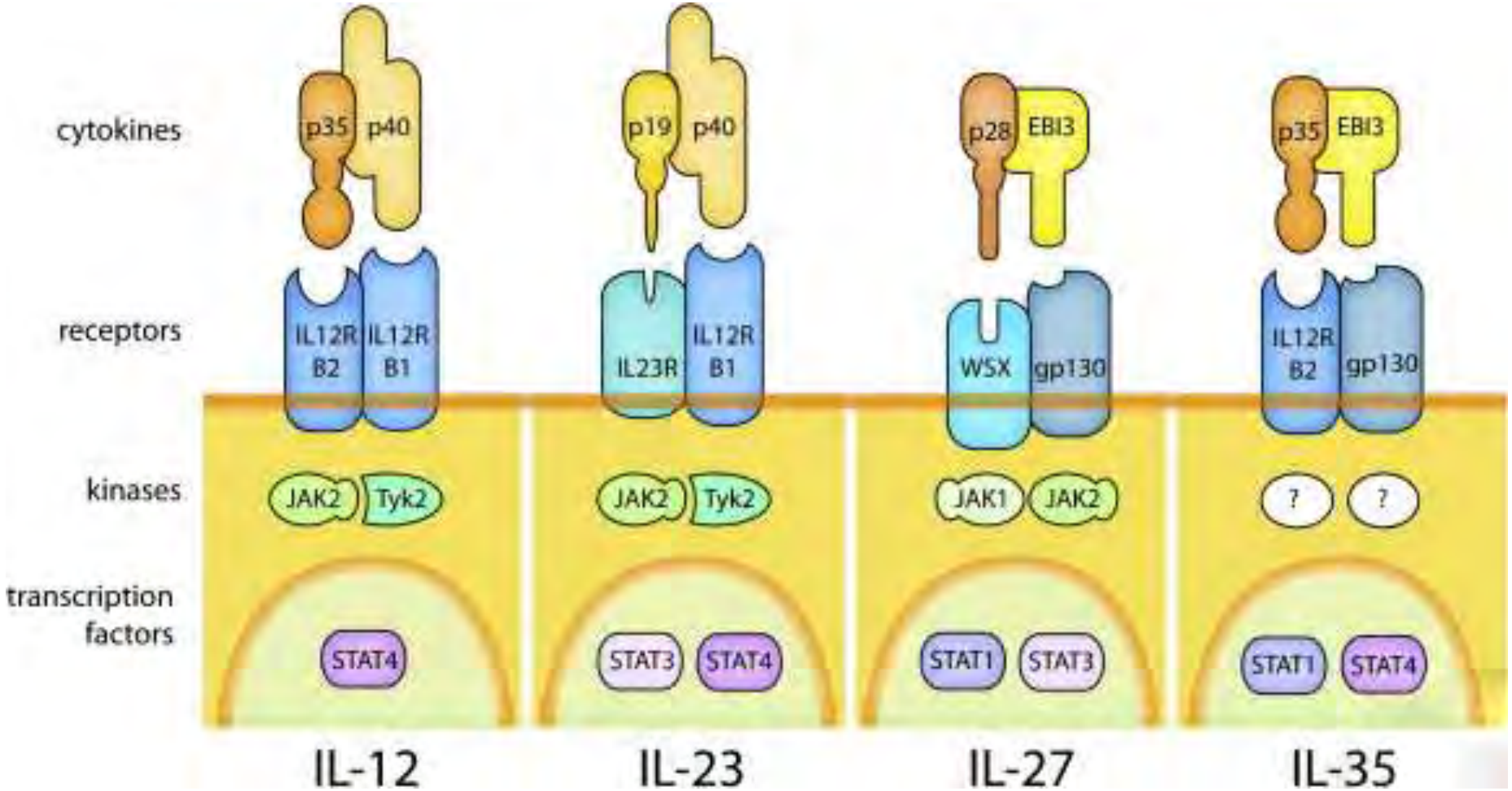
További IL-17 gátlók: brodalumab, ixekizumab, bimekizumab

Miossec P, et al. N Engl J Med. 2009;361:888–898.

Célzott terápiák a reumatológiában

I: TNF-blokkolás
II: IL1-blokkolás
III: IL-6-blokkolás
IV: IL-17-blokkolás
V: IL12/23-blokkolás
VI: B-sejt-gátlás
VII: T-sejt-gátlás
VIII: tsDMARD készítmények
IX: IVIG
X: IFN gátlás
XI: CAR-T kezelés

V: IL-12 citokin család

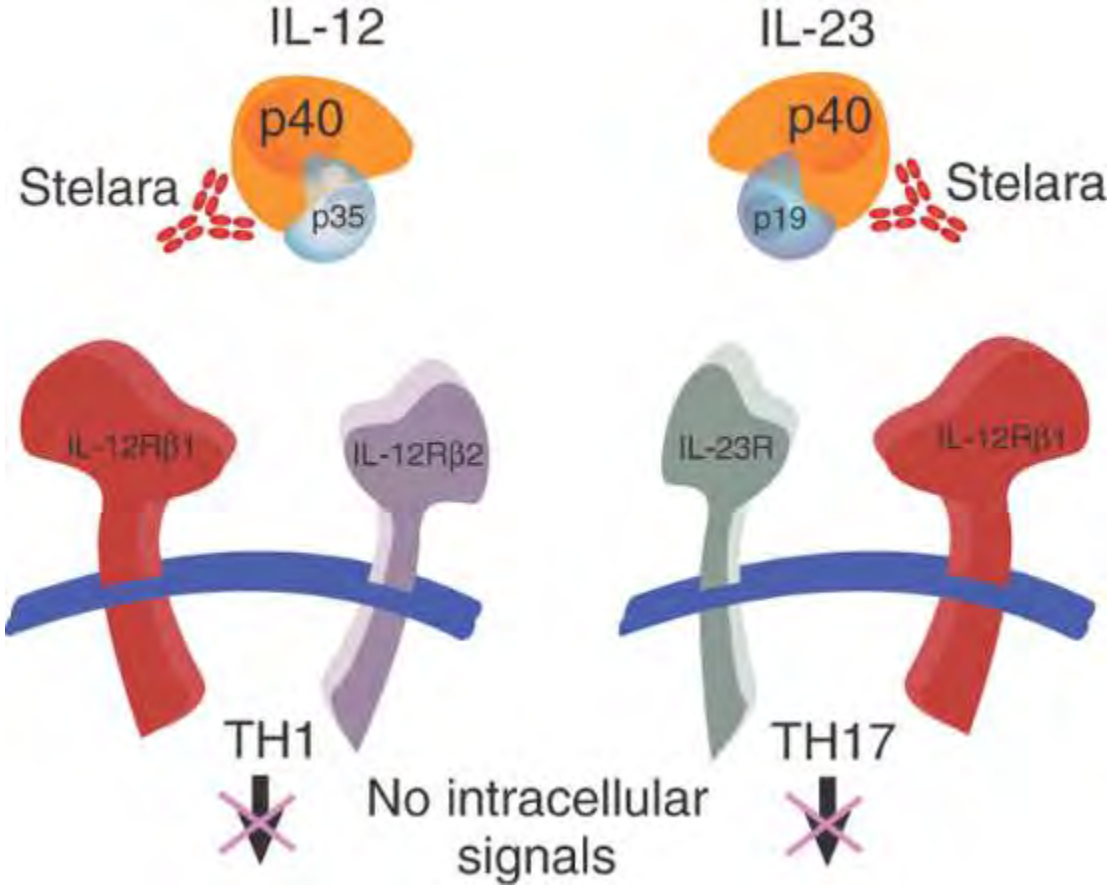


gyulladást fokozó

gyulladást gátló

van Wanrooij RL et al Genetic variations in interleukin-12 related genes in immune-mediated diseases. J Autoimmun. 2012 Jul 17.0

V: Az IL12/23-blokkoló ustekinumab/Stelara



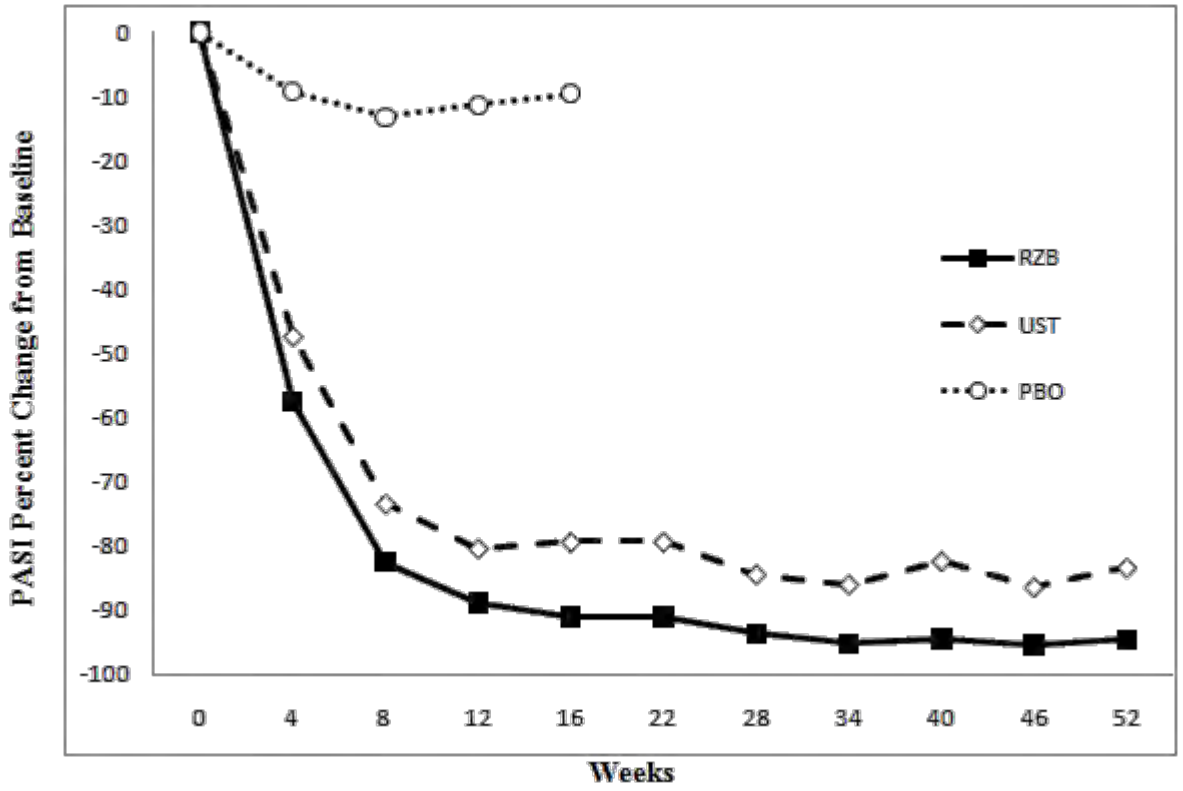
Indikációk: ***Crohn-betegség***
PsO, PsA, CB, CU
alkalmazás: sc és iv

Mellékhatások:
fertőzések
exfoliatív dermatitis

https://www.nature.com/articles/nbt1208-1317a

V: IL-23-blokkoló rizamkizumab/Skyrizi

Indikációk:
PsO, PsA, CU, CB
Alkalmazás: sc.



RZB = risankizumab
UST = ustekinumab
PBO = placebo

https://www.medicines.org.uk/emc/product/10199/smpc

Célzott terápiák a reumatológiában

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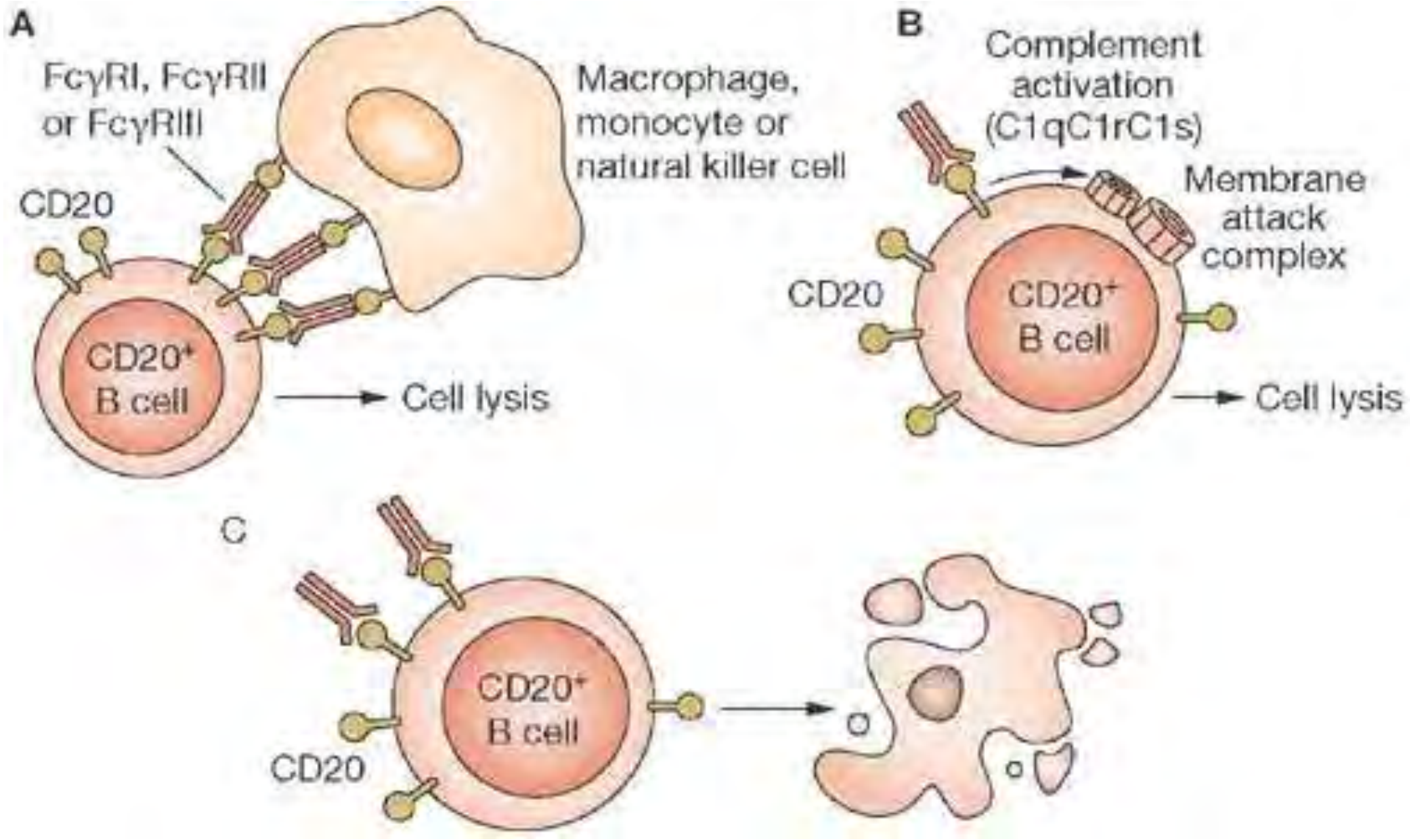
IX: IVIG
X: IFN gátlás
XI: CAR-T kezelés

VI: a rituximab hatásmechanizmusa



CD20 + sejtek depléciója

Dalakas MC (2008) B cells as therapeutic targets in autoimmune neurological disorders *Nat Clin Pract Neurol* 10.1038/ncpneuro0901

VI: rituximab indikációk, mellékhatások

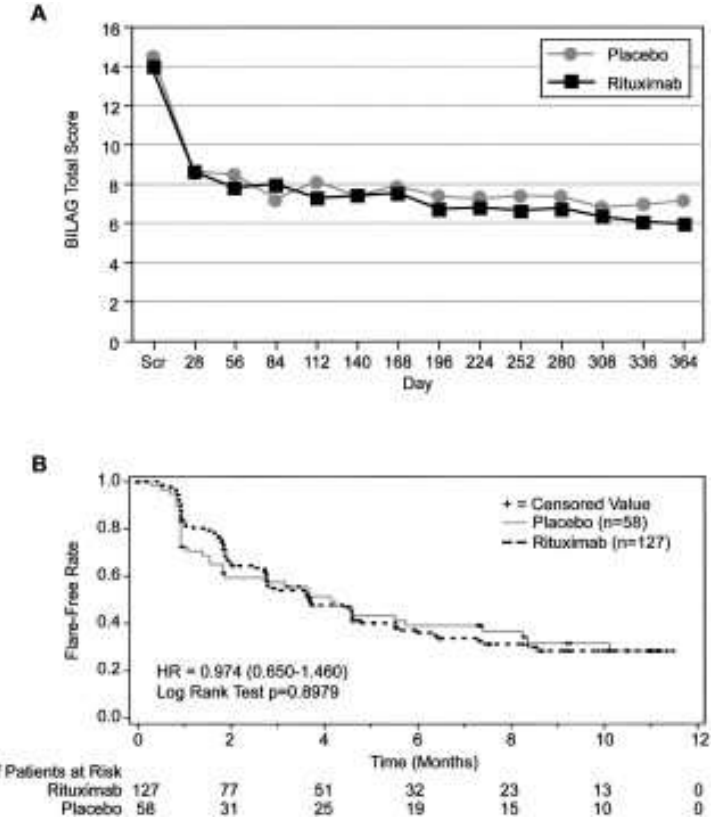
indikációk: RA, ANCA vasculitis
Non-Hodgkin's lymphoma (NHL),
chronic lymphocytic leukaemia (CLL) , pemphigus vulgaris
off label: SLE, myositis, szisztémás sclerosis
alkalmazás: iv.

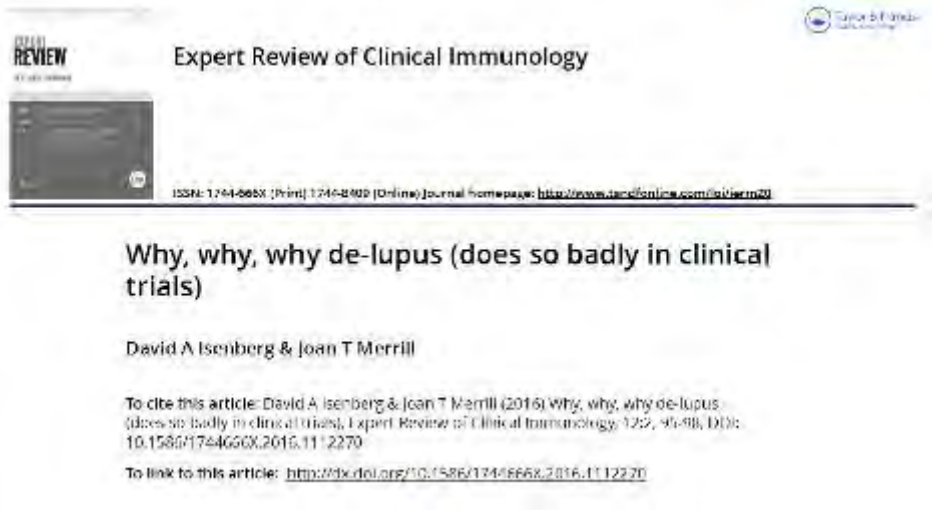
mellékhatások
Fertőzések (progresszív multifokális leukoencephalopathia,
hepatitis B reaktiválódás)

Neutropenia
Bőrreakciók, Stevens-Johnson szindróma
Allergia, infúziós reakció

VI: rituximab indikációk, mellékhatások

Rituximab hatékonysága SLE-ben, EXPLORER (fázis II/III) vizsgálat




Expert Review of Clinical Immunology

Why, why, why de-lupus (does so badly in clinical trials)

David A Isenberg & Joan T Merrill

Arthritis & Rheumatism 222-233, 28 DEC 2009 DOI: 10.1002/art.27233

VI: obinutuzumab LN

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 17, 2025 VOL. 392 NO. 15

Efficacy and Safety of Obinutuzumab in Active Lupus Nephritis

R.A. Furie,[1] B.H. Rovin,[2] J.P. Garg,[1] M.B. Santiago,[3,4] G. Aroca-Martinez,[3,5] A.E. Zuta Santillán,[3,6] D. Alvarez,[7] C. Navarro Sandoval,[7,8] A.M. Isla,[9] J.A. Tumlin,[10] A. Saxena,[11] T. Irazoque Palazuelos,[12] H. Raghu,[1] B. Yoo,[1] I. Hassan,[13] E. Martins,[13] H. Sehgal,[13] P. Kirchner,[13] J. Rose Terres,[1] T.A. Cleachi,[1] T. Schindler,[1] W.F. Pendergraft III,[1] and A. Malvar,[14] for the REGENCY Trial Investigators*

ABSTRACT

BACKGROUND

Obinutuzumab, a humanized type II anti-CD20 monoclonal antibody, provided significantly better renal responses than placebo in a phase 2 trial involving patients with lupus nephritis receiving standard therapy.

METHODS

In a phase 3, randomized, controlled trial, we assigned adults with biopsy-proven active lupus nephritis in a 1:1 ratio to receive obinutuzumab in one of two dose schedules (1000 mg on day 1 and at weeks 2, 24, 26, and 52, with or without a dose at week 50) or placebo. All patients received standard therapy with mycophenolate mofetil, along with oral prednisone at a target dose of 7.5 mg per day by week 12 and 5 mg per day by week 24. The primary end point was a complete renal response at week 76, defined by a urinary protein-to-creatinine ratio of less than 0.5 (with protein and creatinine both measured in milligrams), an estimated glomerular filtration rate of at least 85% of the baseline value, and no intercurrent event (i.e., rescue therapy, treatment failure, death, or early trial withdrawal). Key secondary end points at week 76 included a complete renal response with a prednisone dose of 7.5 mg per day or lower between weeks 64 and 76 and a urinary protein-to-creatinine ratio lower than 0.8 without an intercurrent event.

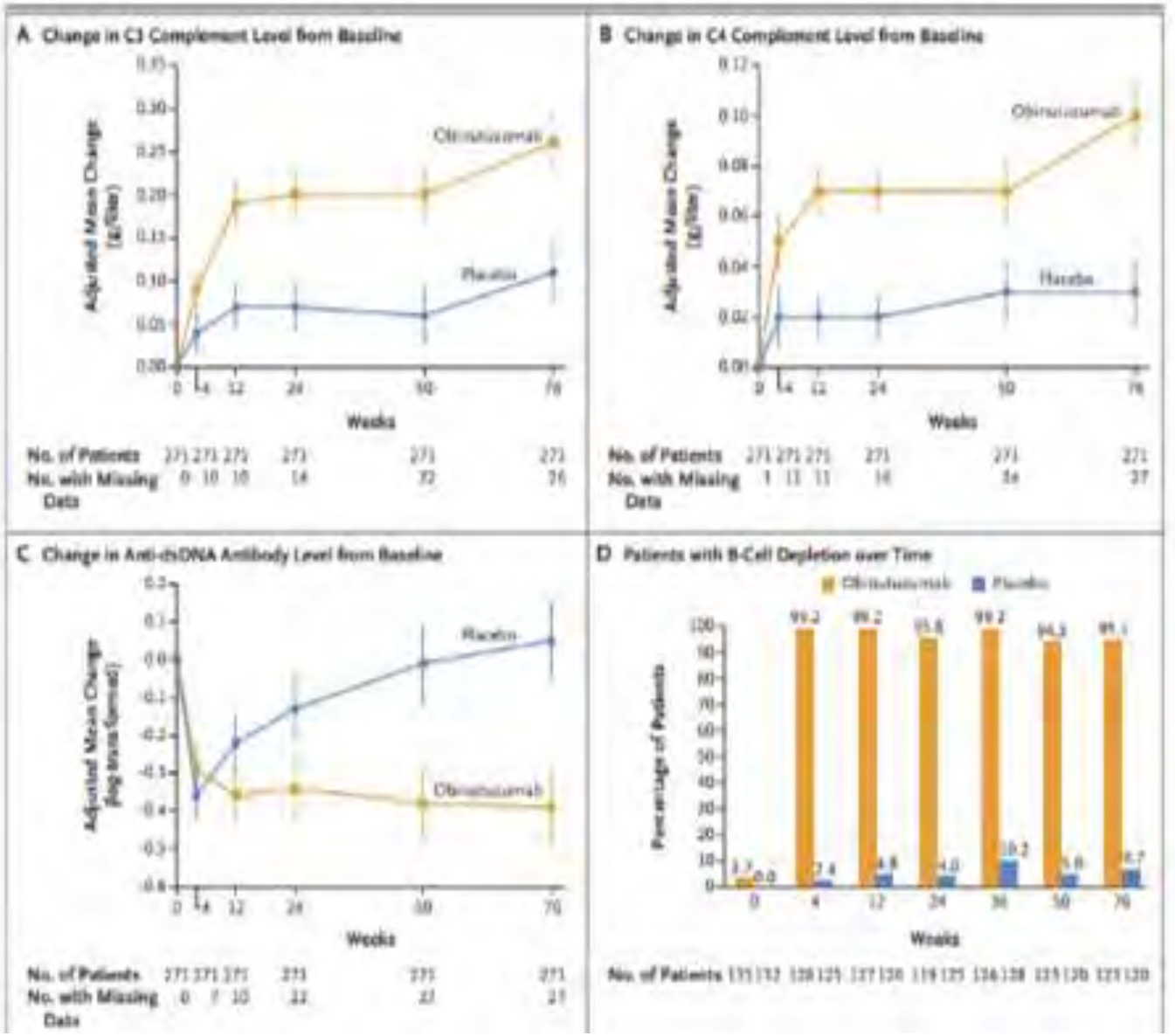
The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Furie can be contacted at rfurie@northwell.edu or at the Division of Rheumatology, Northwell Health, Donald and Barbara Zucker School of Medicine at Hofstra–Northwell, 865 Northern Blvd., Suite 302, Great Neck, NY 11021.

*A list of investigators in the REGENCY trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on February 7, 2025, at NEJM.org.

N Engl J Med 2025;392:1437-49.
DOI: 10.1056/NEJMoa2413391

CME



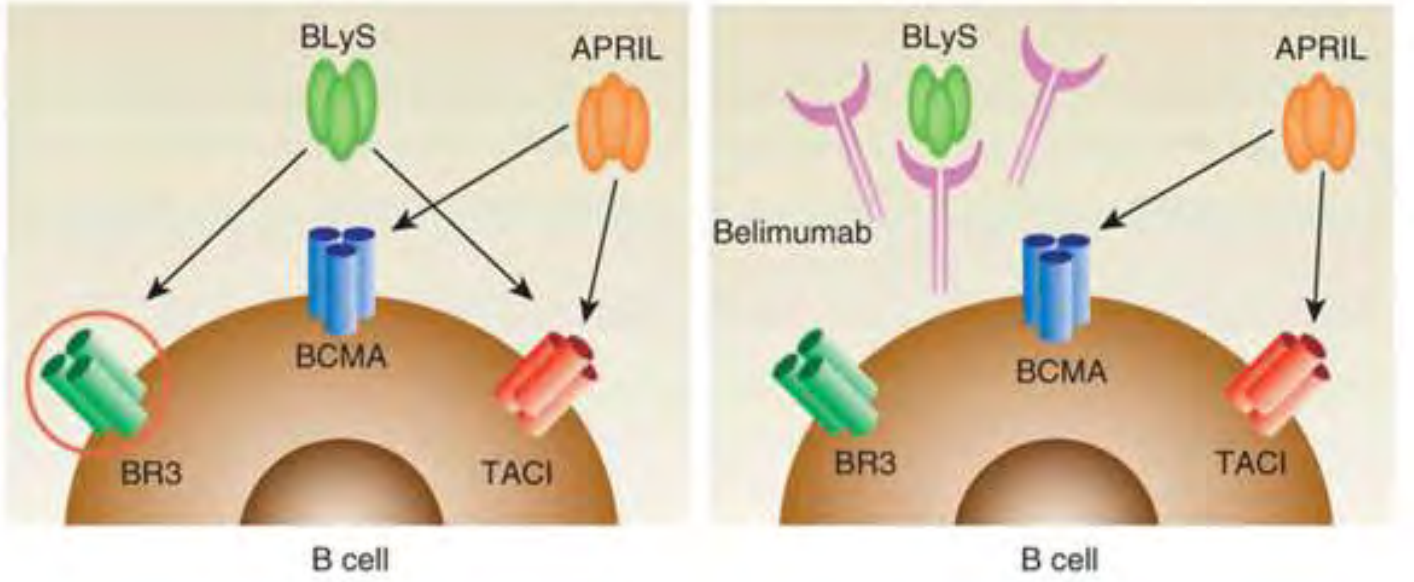
In LN OBI plus SOC was more efficacious than standard therapy alone in providing CRR

VI: Belimumab (BAFF/BLyS)

Indikáció: SLE, LN
Alkalmazás sc és iv

human monoclonal IgG1 antibody
BENLYSTA is indicated for the treatment of adult patients with active, autoantibody-positive SLE, receiving standard therapy

BUT its therapeutic effect is modest and may decrease over time……..



Nature Botechnology 30, 69-77 (2012) doi:10.1038/nbt.2076

Célzott terápiák a reumatológiában

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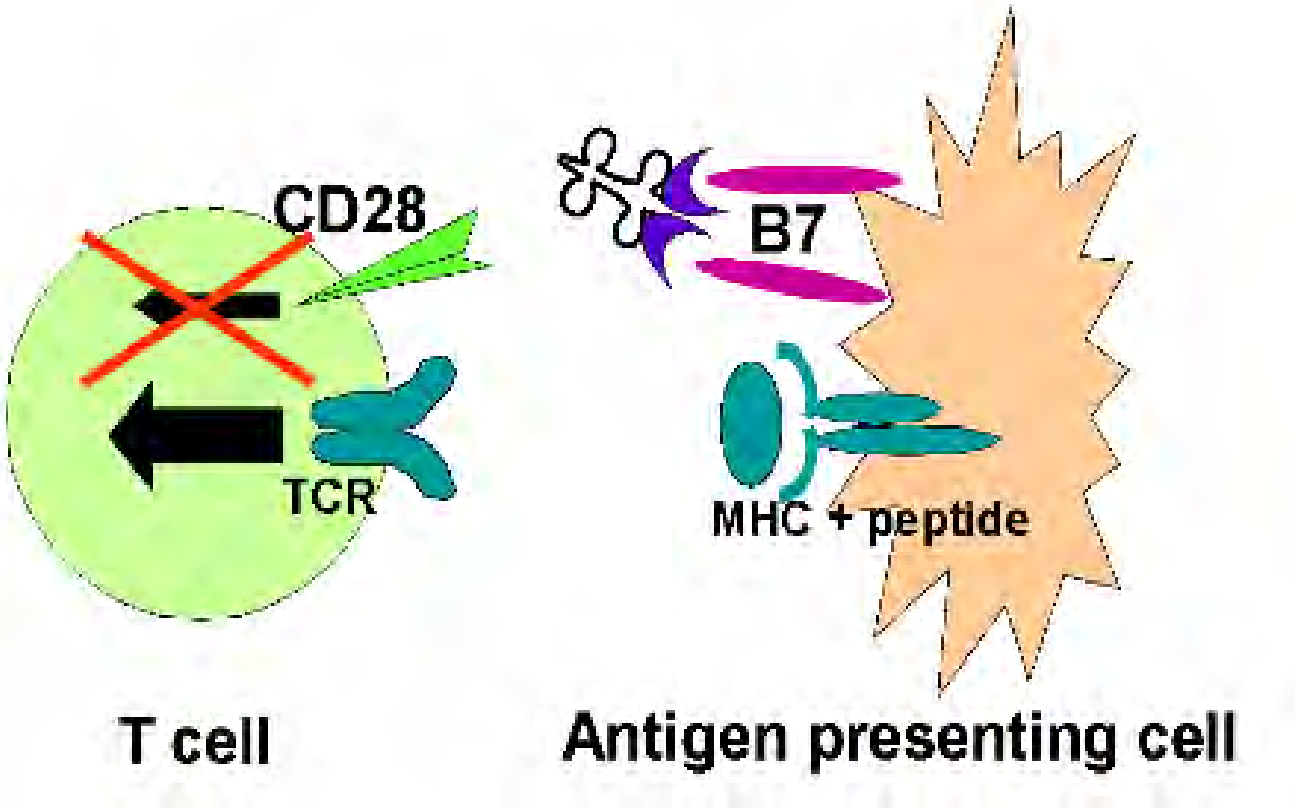
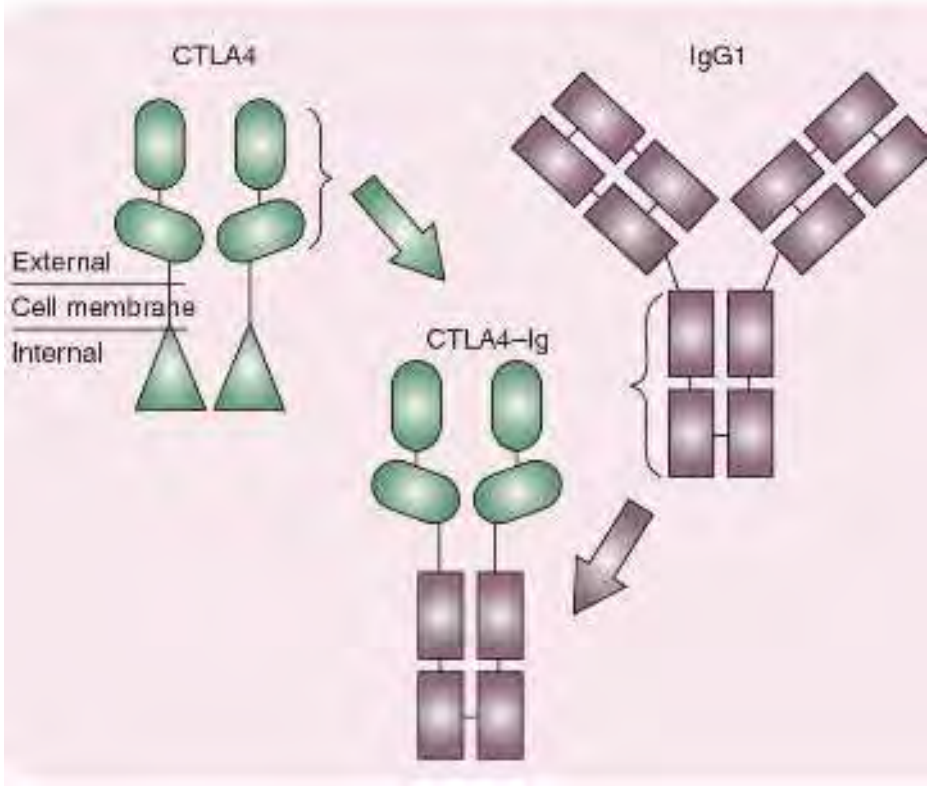
VII: T-sejt-gátlás
VIII: tsDMARD készítmények
IX: IVIG
X: IFN gátlás
XI: CAR-T kezelés

VII: Abatacept, a humán CTLA4 immunoglobulin fúziós protein





APC aktiváció gátlást is eredményez!

https://www.semanticscholar.org/paper/Abatacept%3A-the-first-in-class-costimulation-blocker-Westhovens/c480b4d30fb498927cd085bf58d06f86379a3e90

VII: Abatacept biztonságosság

Indikációk: RA, JIA, PsA

Alkalmazás sc és iv.

Sc. adalimumab és

sc. abatacept hasonló hatékonyság

A&R 2013 Weinblatt ME et al.

Fertőzések

Lokális reakció, allergia

Célzott terápiák a reumatológiában

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VIII: JAK3 gén mutációja

JAK3 gén mutációja a súlyos kombinált immunhiány (SCID) autoszomális recesszív formáját okozza

igen alacsony T-lymphocyta szám és funkcionálisan csökkent értékű B-sejtek
ú

a SCID-re súlyos fertőzések, hasmenés, atopiás dermatitis és a növekedés elmaradása jellemző

nature International weekly journal of science

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Letters to Nature

Nature 377, 65-68 (7 September 1995) | doi:10.1038/377065a0; Accepted 11 August 1995

Mutations of Jak-3 gene in patients with autosomal severe combined immune deficiency (SCID)

Paolo Macchi*, Anna Villa*||, Silvia Giliani†, Maria G. Sacco*, Annalisa Frattini*, Fulvio Porta*, Alberto G. Ugazio†, James A. Johnston‡, Fabio Candotti§, John J. O'Shea‡, Paolo Vezzoni* & Luigi D. Notarangelo†

1. *Istituto di Tecnologie Biomediche Avanzate, Consiglio Nazionale delle Ricerche, via Ampère 56, Milano, Italy
2. †Dipartimento Materno-Infantile, Università di Brescia, Brescia, Italy
3. ‡Lymphocyte Cell Biology Section, Arthritis and Rheumatism Branch, National Institute of Arthritis, Musculoskeletal and Skin diseases, and
4. §Clinical Gene Therapy Branch, National Center for Human Genome Research, National Institutes of Health, Bethesda, Maryland 20892, USA
5. ||To whom correspondence should be addressed.

SEVERE combined immune deficiency (SCID) represents a hetero-genous group of hereditary diseases. Mutations in the common γ-chain (γc), which is part of several cytokine receptors including those for interleukin (IL)-2, IL-4, IL-7, IL-9 and FL-15, are responsible for X-linked SCID[1,2], which is usually associated with a lack of circulating T cells and the presence of B lymphocytes (T⁻ B⁺ SCID). The gene(s) responsible for autosomal recessive T⁻ B⁺ SCID is still unknown. The Jak-3 protein kinase[3,4] has been found to associate with the γc-chain-containing cytokine receptors[4–9]. Therefore Jak-3 or other STAT proteins with which it interacts[10,11] are candidate genes for autosomal recessive T⁻ B⁺SCID7. Here we investigate two unrelated T⁻ B⁺SCID patients (both from consanguineous parents) who have homozygous mutations in the gene for Jak-3. One patient carries a mutation (Tyr100→Cys) in a conserved tyrosine residue in the JH7 domain

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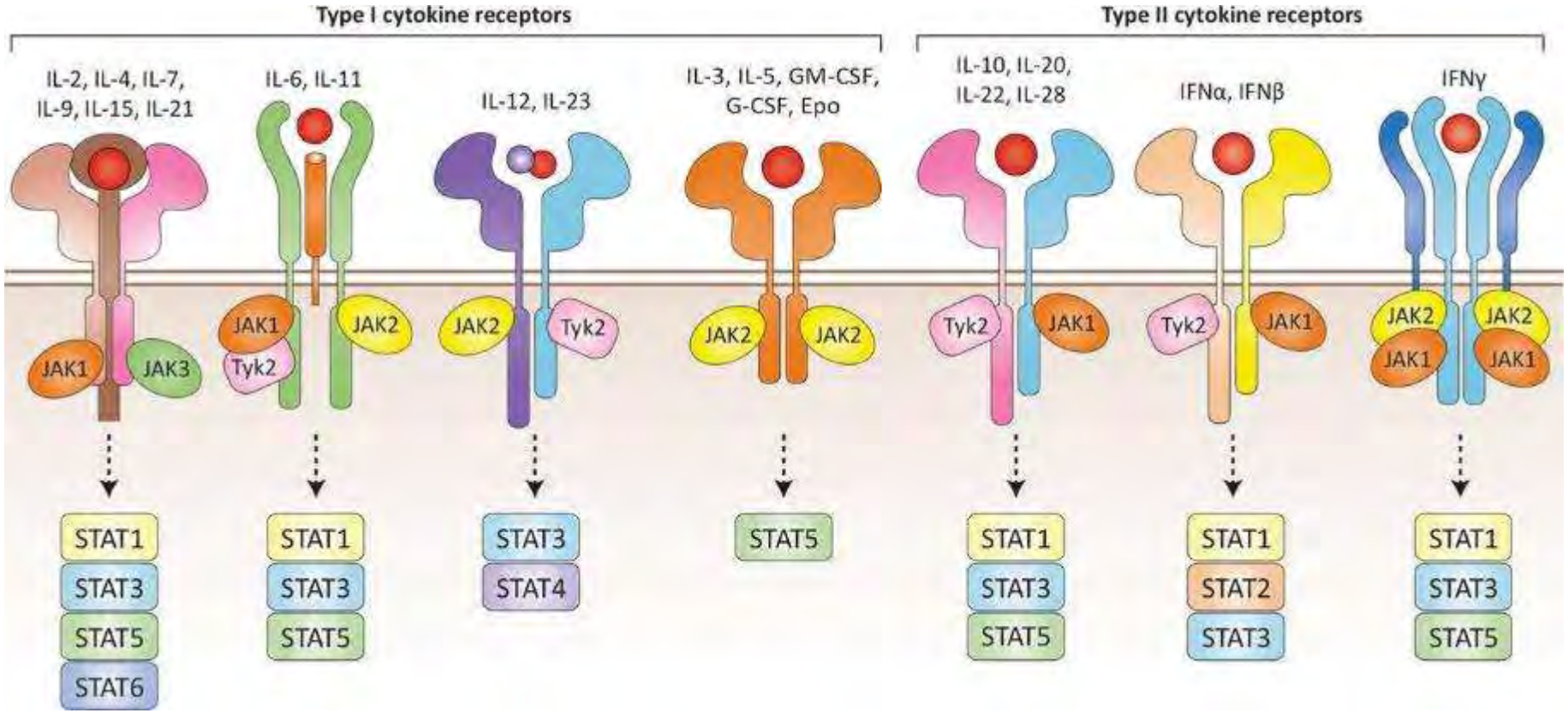
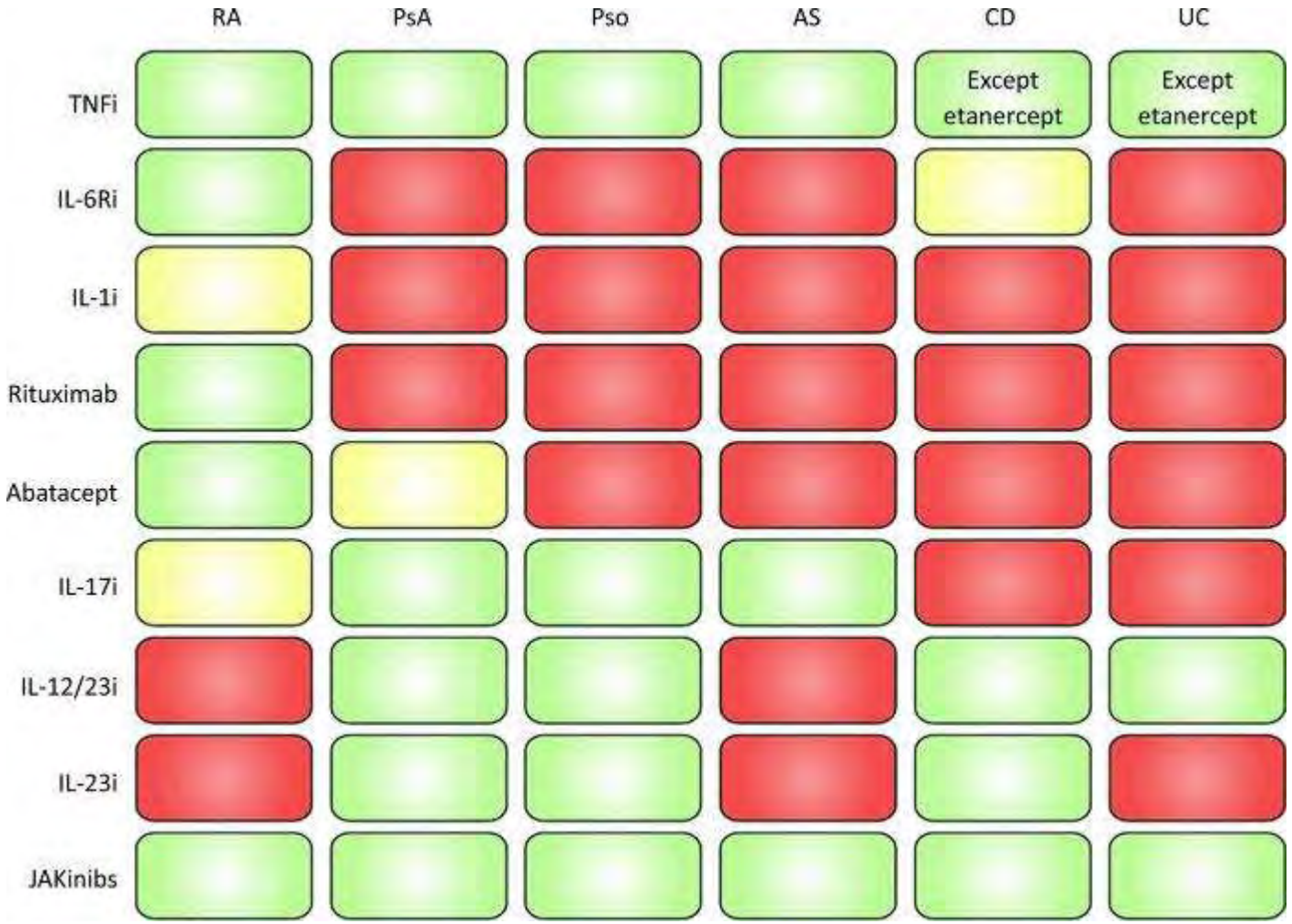
- Anna Villa
- Silvia Giliani
- Maria G. Sacco
- Annalisa Frattini
- Fulvio Porta
- more authors of this article

VIII: JAK gátlók



Michael Bonelli et al. Ann Rheum Dis 2024;83:139-160

VIII: JAK gátlók



Michael Bonelli et al. Ann Rheum Dis 2024;83:139-160

VIII: JAK gátlók

Drug/JAK			Comparator (versus) / State of investigation	Rheumatoid arthritis	Psoriatic arthritis	Ankylosing spondylitis	Chronic plaque psoriasis	Ulcerative colitis	Crohn's disease	Atopic dermatitis	Systemic lupus erythm
Non-selective	Tofacitinib	JAK1-3	versus PLC							(topical)	
			versus TNF(R)i	ADA (NI)	ADA		ETN (NI)				
			State	Approved	Approved	Approved	Phase III[a]	Approved	Phase II	Phase II	Phase I[f]
	Peficitinib	JAK1-3	versus PLC								
			versus TNF(R)i								
			State	Appr. (JPN)			Phase II	Phase II			
	Baricitinib	JAK1,2	versus PLC				8/10 mg[e]				
			versus TNF(R)i	ADA (S)							
			State	Approved			Phase II			Approved	Phase III
Selective	Upadacitinib	JAK1,2	versus PLC								
			versus TNF(R)i	ADA (S)	ADA (NI/S)						
			State	Approved	Approved	Approved		Approved	Approved	Approved	Phase II[d]
	Filgotinib	JAK1	versus PLC								
			versus TNF(R)i	ADA (NI)							
			State	Appr. (EU)	Phase II	Phase II		Approved	Phase II		

Michael Bonelli et al. Ann Rheum Dis 2024;83:139-160

VIII: JAK gátlók

JAK			Infections		Hematologic		Liver and GIT	Throm-bosis	Lipids	Others	Malignancies
			Serious	URT	NEU	LYM	TA	VTE	HDL	CREA	Malignancies
			OI	HZ	Hb	PLT	GIP	PE	LDL	CPK	NMSC
Non-selective	Tofacitinib	JAK1-3	↑	↑	↓	↑	↑	↑*	↑	↑	↑*
			↑	↑↑	↔	↑	↔(?)	↑*	↑	↑	↔(?)
	Peficitinib	JAK1-3	↑	↑	↓	↓	↑	↔(?)	↑	↑	↔(?)
			↑	↑↑	↓	↔	↔(?)	↔(?)	↑	↑	↔(?)
	Baricitinib	JAK1,2	↑	↑	↓	↔	↑	↑	↑	↑	↔(?)
			↑	↑↑	↓	↑	↔(?)	↑(?)	↑	↑	↔(?)
Selective	Upadacitinib	JAK1,2	↑	↑	↓	↓	↑	↔(?)	↑	↑	↔(?)
			↑	↑↑	↓	↓	↔(?)	↔(?)	↑	↑	↔(?)
	Filgotinib	JAK1	↑	↑	↔	↔	↔	↔(?)	↑	↔	↔(?)
			↑	↔	↑	↓	↔(?)	↔(?)	↑	↑	↔(?)

Michael Bonelli et al. Ann Rheum Dis 2024;83:139-160

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X: IFN gátlás
XI: CAR-T kezelés

Immunglobulin kezelés alkalmazása

immunglobulin-pótló terápia

csökkent antitestképzõdéssel járó primer immunhiányos szindrómákban (primer immundeficienciák – PID).

Szekunder immunhiányos állapotokban (szekunder immundeficienciák – SID), olyan betegek esetében, akik súlyos vagy kiújuló fertõzésekben szenvednek és az antimikrobiális terápia hatástalan, valamint igazolt specifikus antitesthiány áll
fenn vagy **a szérum IgG-szintjük <4 g/l.**
Kanyaró elleni, expozíció

Immunglobulin kezelés alkalmazása

immunmoduláns kezelés

primer immun-thrombocytopenia (ITP)
Guillain–Barrészindróma
Kawasaki-betegség
krónikus gyulladásos demyelinisatiós polyradiculoneuropathia (CIDP)
multifocalis motoros neuropathia (MMN)

Továbbá olyan felnõtteknél, akik: immunszuppresszánsokkal, köztük kortikoszteroidokkal kezelt **aktív DM-ben szenvednek,** illetve akiknél ezekkel a gyógyszerekkel szemben intoleracia vagy ellenjavallat áll fenn

off label: SLE, myositis, szisztémás sclerosis, ANCA

Immunglobulin kezelés mellékhatások

anphalaxiás reakció (IgA hiány)

veseelégtelenség

aszeptikus meningitis

haemalytikus anaemia

tüdőoedema

thromboemboliás szövődmények

Célzott terápiák a reumatológiában

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Interferonok és dendritikus sejtek SLE-ben

Induction of Dendritic Cell Differentiation by IFN-α in Systemic Lupus Erythematosus

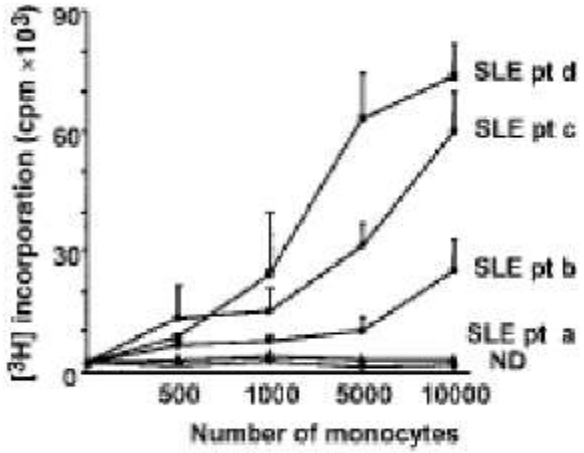
Patrick Blanco,[1*] A. Karolina Palucka,[1*] Michelle Gill,[1,2] Virginia Pascual,[1,2] Jacques Banchereau[1†]

Dendritic cells (DCs) are important in regulating both immunity and tolerance. Hence, we hypothesized that systemic lupus erythematosus (SLE), an autoimmune disease characterized by autoreactive B and T cells, may be caused by alterations in the functions of DCs. Consistent with this, monocytes from SLE patients' blood were found to function as antigen-presenting cells, in vitro. Furthermore, serum from SLE patients induced normal monocytes to differentiate into DCs. These DCs could capture antigens from dying cells and present them to CD4-positive T cells. The capacity of SLE patients' serum to induce DC differentiation correlated with disease activity and depended on the actions of interferon-α (IFN-α). Thus, unabated induction of DCs by IFN-α may drive the autoimmune response in SLE.

Lupus (SLE) is a systemic autoimmune disease characterized by a waxing and waning course and the involvement of multiple organs, including skin, kidneys, and central nervous system (*1*). Although SLE etiopathology is poorly understood, there is likely a role for environmental triggers, for instance viruses, acting in the context of susceptibility genes (*2*, *3*). Now, SLE therapy is based on nonspecific immunosuppression and symptom control; however, no cure for SLE has been found, and that is particularly needed for children, whose disease often progresses to chronic renal failure and/or death (*1*). Among the immunological features of SLE are high titers of autoantibodies predominantly specific for DNA and nucleosomes (*4*, *5*). Paradoxically, polyclonal hypergammaglobulinemia, high plasma cell numbers, and an increased frequency of pre–germinal center B cells (*6*, *7*) coincide with considerable B lymphopenia. Likewise, autoreactive T cells are found in the blood despite T lymphopenia (*8*, *9*). The systemic autoimmune response that characterizes SLE might be explained by alter-

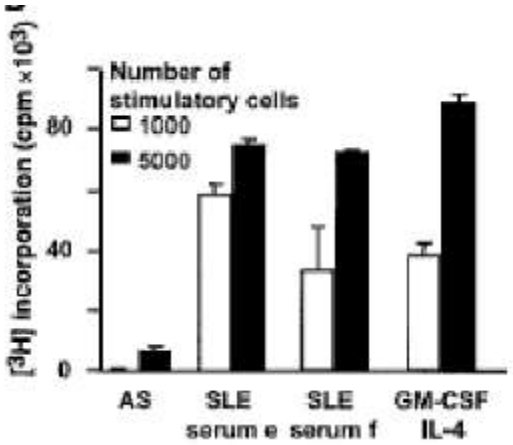
[1]Baylor Institute for Immunology Research, Dallas, TX 75204, USA. [2]The University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390, USA.
*These authors contributed equally to this work.
†To whom correspondence should be addressed. E-mail: jbanchereau@baylordallas.edu

MBER 2001 VOL 294 SCIENCE www.sciencemag.org

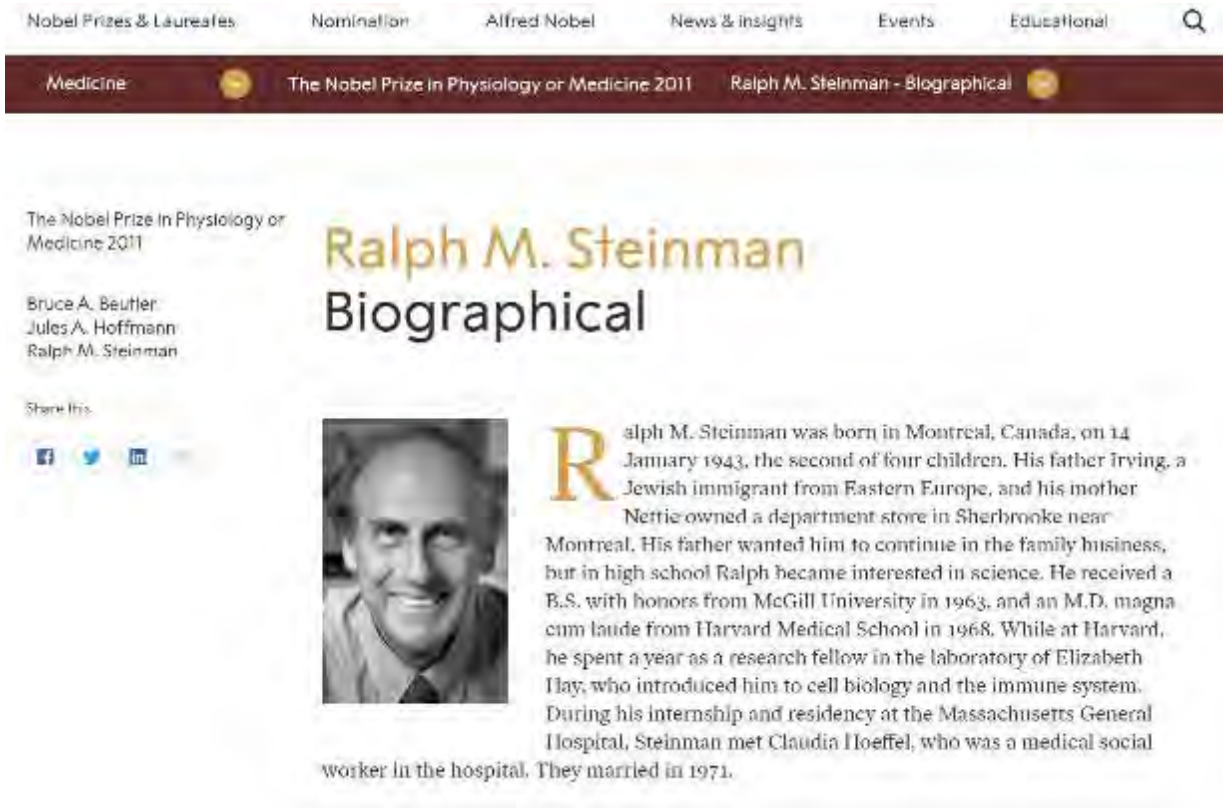


SLE moniciták CD4-sejt proliferációt okoznak

HD moniciták SLE szérummal történő inkubálást követően CD4-sejt proliferációt okoznak



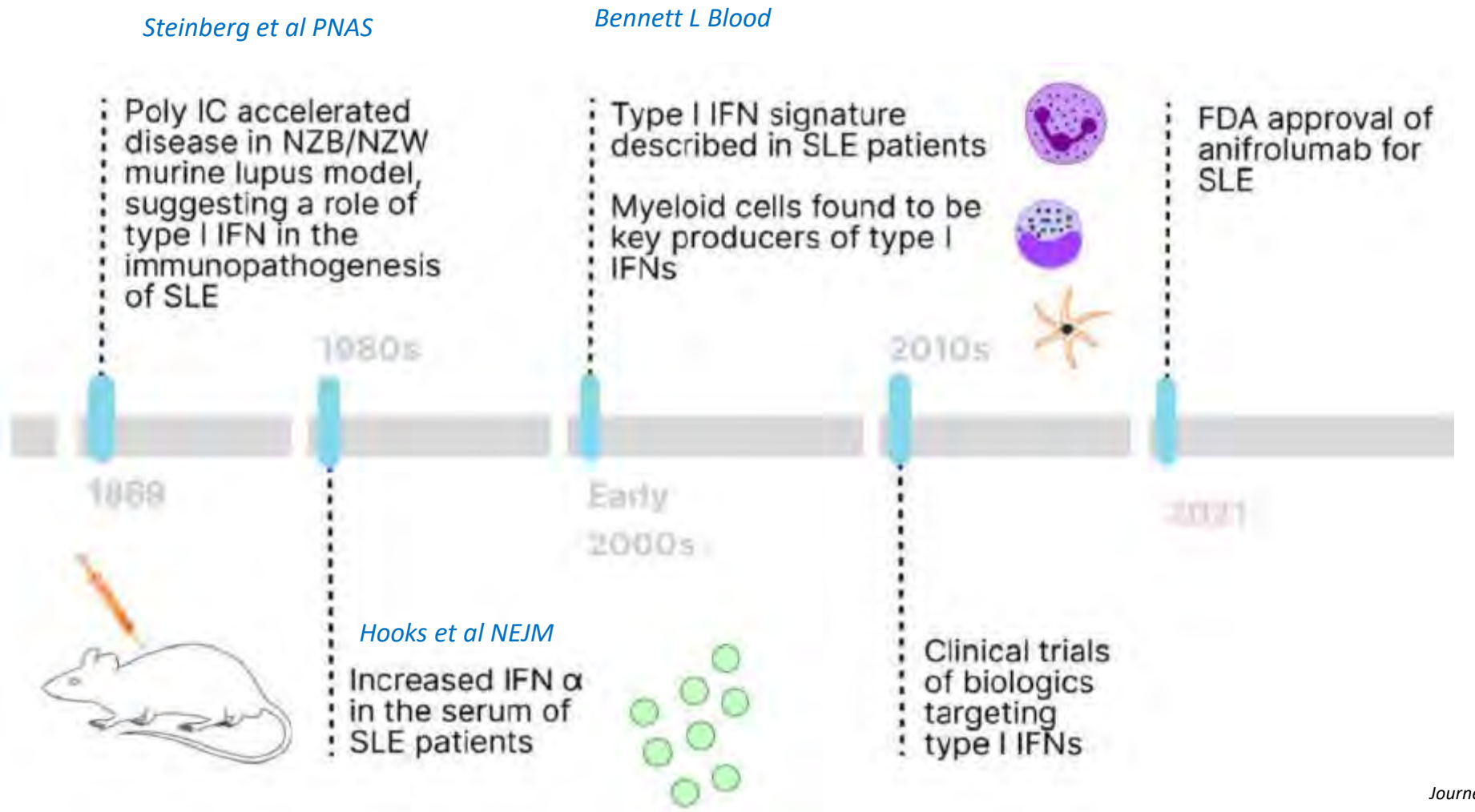
Dendritikus sejtek



In 1973, Steinman and Cohn discovered dendritic cells, a previously unknown class of immune cells that constantly formed and retracted their processes. This discovery changed the field of immunology.

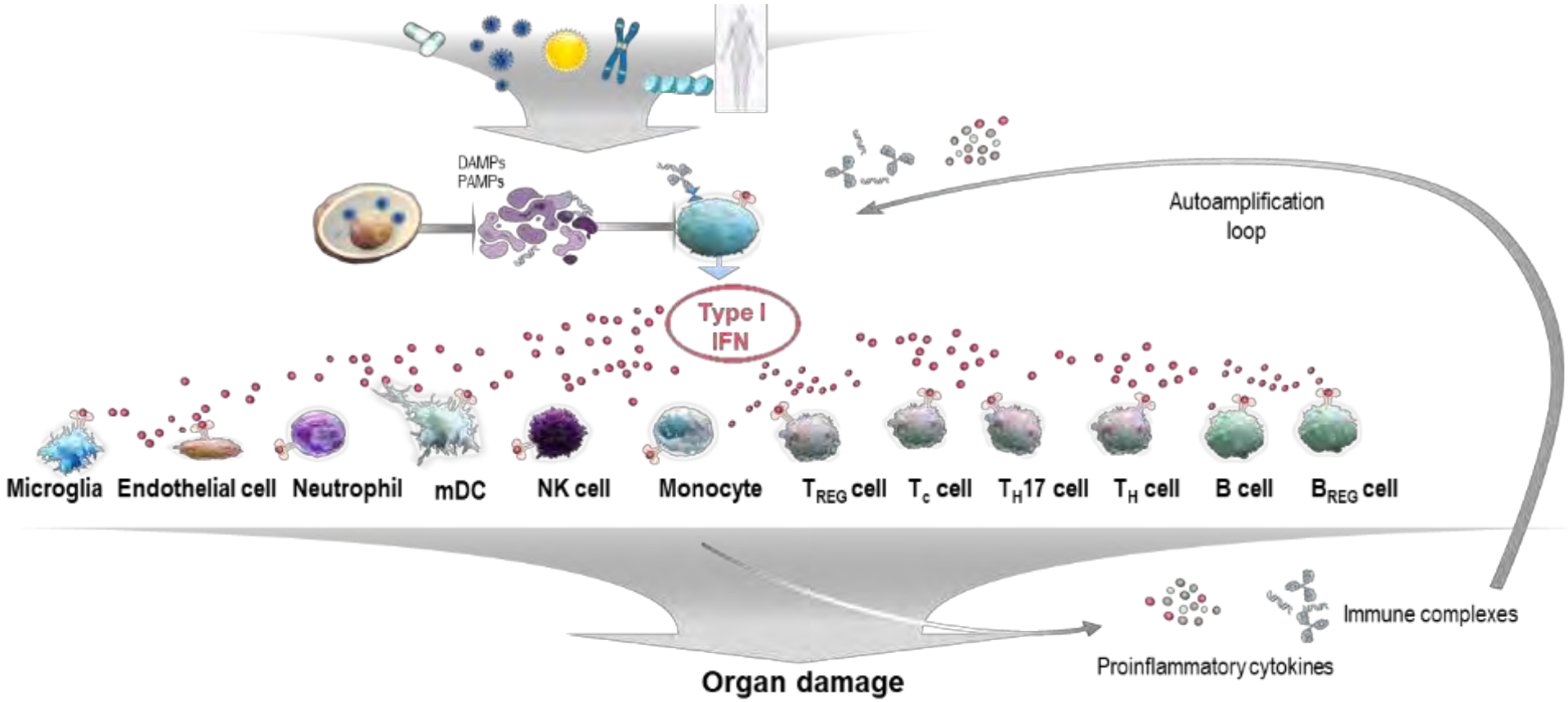
Steinman died on 30 September 2011, three days before his Nobel Prize was announced. Unaware of his death at the time of its announcement, the Nobel Committee made an unprecedented decision that his award would stand.

Anifrolumab, mérföldkövek SLE-ben



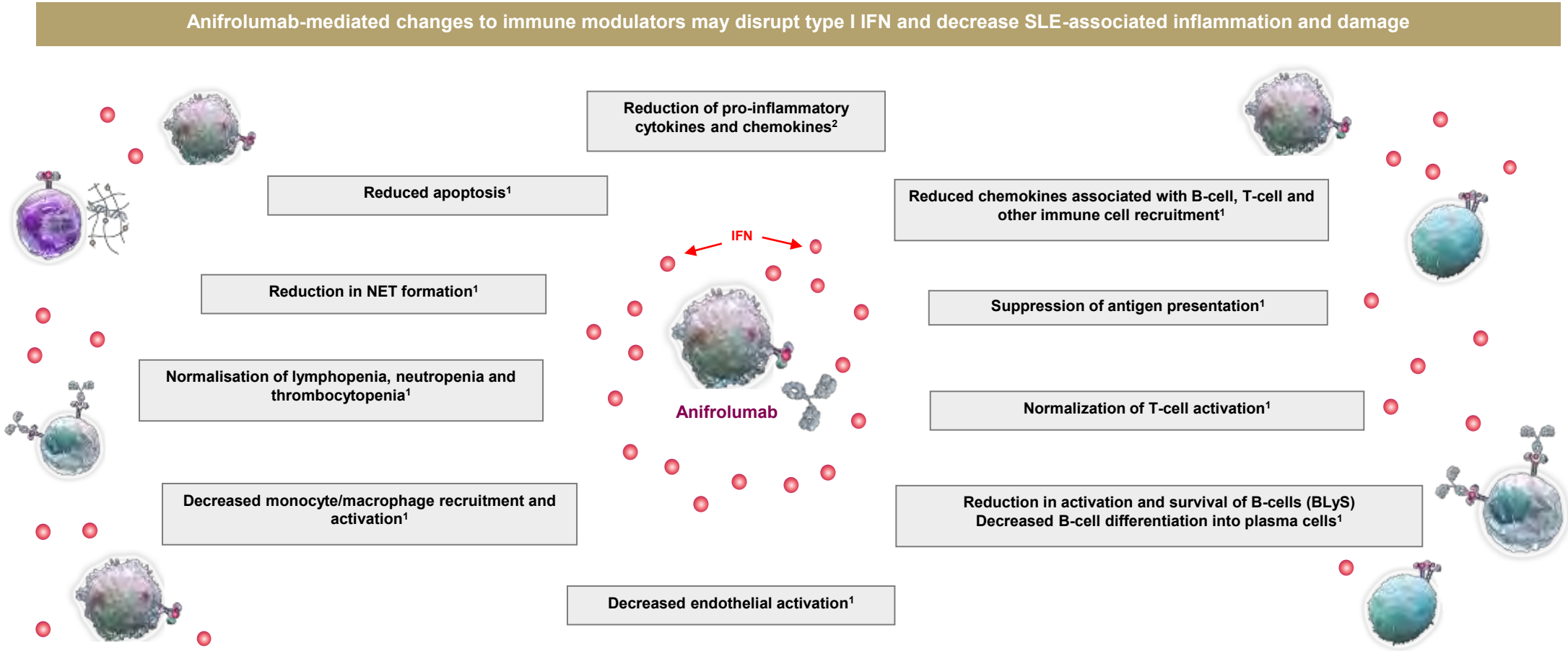
Sim, T.M et al A Journey from Bench to Bedside. Int. J. Mol. Sci. 2022, 23, 2505.

Interferonok SLE-ben



1. Rönnblom L, Leonard D. *Lupus Sci Med*. 2019;6(1):e000270. 2. West PK, et al. *Glia*. 2019;67(10):1821-1841. 3. Menon M, et al. *Immunity*. 2016;44(3):683-697. 4. Chan VS, et al. *Autoimmun Rev.* 2012;11(12):890-897. 5. Liu Z, Davison A. *Nat Med*. 2012;18(6):871-882.

Az anifrolumab hatásmechanizmusa SLE-ben



1. Casey KA, et al. *Lupus Sci Med*. 2018;5(1):e000286. 2. Casey KA, et al. *Arthritis Rheumatol*. 2021;73(3):459-471.

IFN-blokkolás SLE-ben (anifrolumab/Saphnelo)

Indikációk: autoantitest pozitív SLE

Alkalmazás iv.

ADISINSIGHT REPORT

Anifrolumab: First Approval

Emma D. Deeks[1]

Abstract

Anifrolumab (anifrolumab-fnia; Saphnelo™) is a monoclonal antibody antagonist of the type I interferon receptor (IFNAR). It is being developed by AstraZeneca (under license from Medimmune, now Bristol-Myers Squibb) for the treatment of autoimmune disorders, including systemic lupus erythematosus (SLE) and lupus nephritis, the underlying pathogenesis of which involves type I interferon. In July 2021, intravenous anifrolumab was approved in the USA for the treatment of adult patients with moderate to severe SLE who are receiving standard therapy. Anifrolumab (intravenous or subcutaneous) continues to be assessed in clinical studies in SLE in various countries, and the intravenous formulation is under regulatory review in the EU and Japan. This article summarizes the milestones in the development of anifrolumab leading to this first approval for the treatment of moderate to severe SLE.

Saphnelo approved in the EU for the treatment of moderate to severe systemic lupus erythematosus

Digital Features for this Adisinsight Report can be found at https://doi.org/10.6084/m9.figshare.16564056.

Anifrolumab (Saphnelo™): Key Points

IFNAR antagonist being developed by AstraZeneca for the treatment of autoimmune disorders, including SLE and lupus nephritis.

Received its first approval on 30 July 2021 in the USA.

Approved for the treatment of adult patients with moderate to severe SLE who are receiving standard therapy.

Key milestones in the development of anifrolumab for the treatment of systemic lupus erythematosus. *BLA* Biological License Application

IFN-blokkolás SLE-ben (anifrolumab/Saphnelo)

OPEN ACCESS

CLINICAL SCIENCE

Anifrolumab efficacy and safety by type I interferon gene signature and clinical subgroups in patients with SLE: post hoc analysis of pooled data from two phase III trials

Edward M Vital, Joan T Merrill, Eric F Morand, Richard A Furie, Ian N Bruce, Yoshiya Tanaka, Susan Manzi, Kenneth C Kalunian, Rubana N Kalyani, Katie Streicher, Gabriel Abreu, Raj Tummala

Handling editor Josef S Smolen

Corresponding to Dr Raj Tummala, BioPharmaceuticals R&D, AstraZeneca US, Gaithersburg, Maryland, USA; Raj.tummala@astrazeneca.com

Received 27 August 2021
Accepted 16 January 2022

ABSTRACT

Objectives To characterise the efficacy and safety of anifrolumab in patients with systemic lupus erythematosus (SLE) according to interferon gene signature (IFNGS), demographic and clinical subgroups.

Methods We performed post hoc analyses of pooled data from the 52-week phase III TULIP-1/TULIP-2 placebo-controlled trials of intravenous anifrolumab in moderate to severe SLE. Outcomes were assessed in predefined subgroups: IFNGS (high/low), age, sex, body mass index, race, geographic region, age of onset, glucocorticoid use, disease activity and serological markers.

Results In pooled data, patients received anifrolumab 300 mg (360/726) or placebo (366/726); 82.6% were IFNGS High. IFNGS high patients had greater baseline disease activity and were more likely to have abnormal serological markers versus IFNGS-low patients. In the total population, a greater proportion of patients

Key messages

What is already known about this subject?

- Systemic lupus erythematosus (SLE) is a heterogeneous disease, in which aspects of patient demographics and clinical characteristics are associated with disease severity and therapeutic response.
- Anifrolumab, a human monoclonal antibody that binds the type I interferon receptor subunit 1, has demonstrated efficacy with an acceptable safety profile in patients with moderate-to-severe SLE in phase III clinical trials.

What does this study add?

- This pooled analysis of two phase III trials adds to the knowledge of the efficacy and safety of

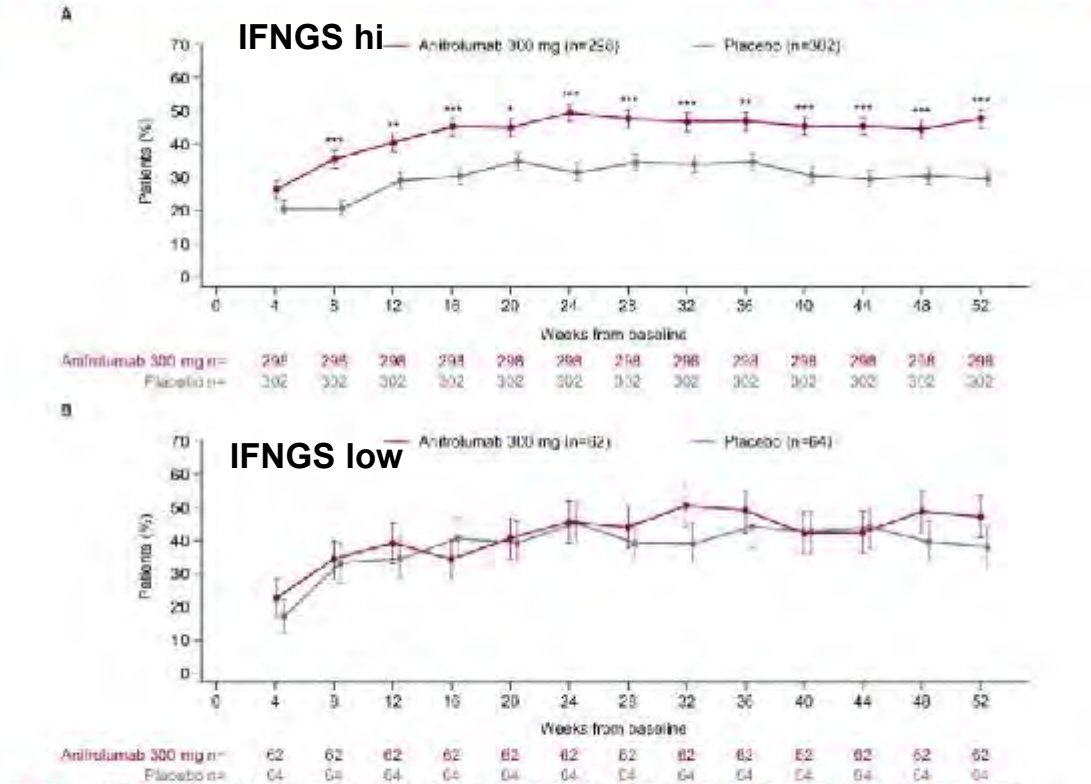
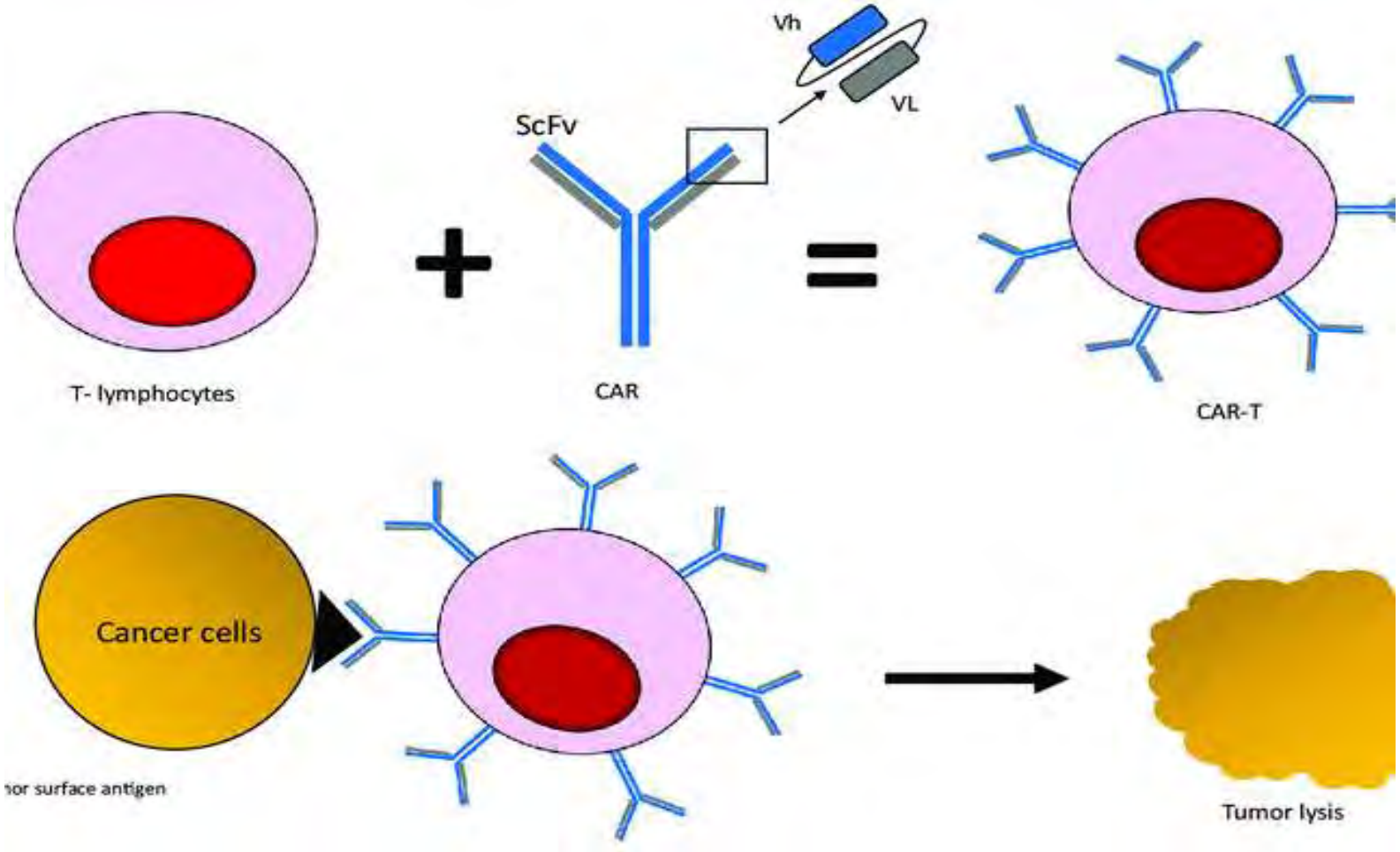


Figure 4 BICLA response estimates and SEs from weeks 4–52 in (A) type I IFNGS-high and (B) IFNGS-low patients in pooled TULIP data. The percentage of responders was calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors SLEDAI-2K score at screening, baseline GC dosage and study. Points represent response estimates plotted with SE. *Nominal p<0.05; **nominal p<0.01; ***nominal p<0.001. BICLA, British Isles Lupus Assessment Group based Composite Lupus Assessment; GC, oral glucocorticoid; IFNGS, interferon gene signature; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Célzott terápiák a reumatológiában

I: TNF-blokkolás
II: IL1-blokkolás
III: IL-6-blokkolás
IV: IL-17-blokkolás
V: IL12/23-blokkolás
VI: B-sejt-gátlás
VII: T-sejt-gátlás
VIII: tsDMARD készítmények
IX: IVIG
X: IFN gátlás
XI: CAR-T kezelés

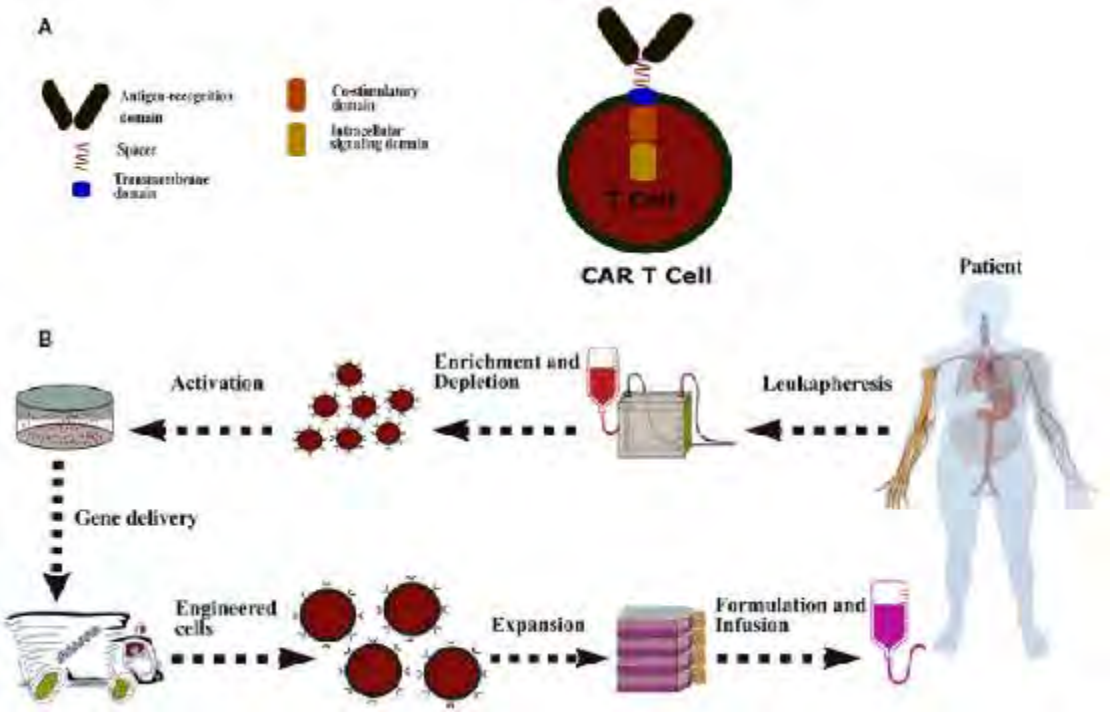
CAR-T koncepció, T-sejt, B-sejt



Egyesíti a B-sejt Ag-felismerő és a T-sejt effektor funkciókat

https://www.researchgate.net/figure/The-basic-principle-of-CAR-T-cell-therapy-a-T-lymphocytes-are-genetically-modified-to_fig2_351201877

CAR-T sejt kezelés alkalmazás



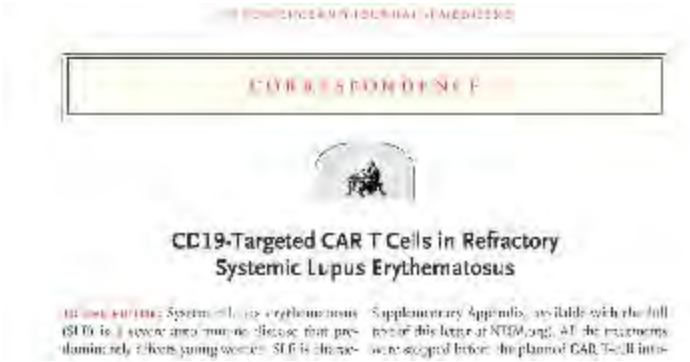
B-sejt lymphoma, ALL, MM hematológiai malignus betegségekben hatékony kezelés

MH: CRS 54-91%, terápia, szteroid, anti-IL6, anti-IL1, Solid tumorokban?

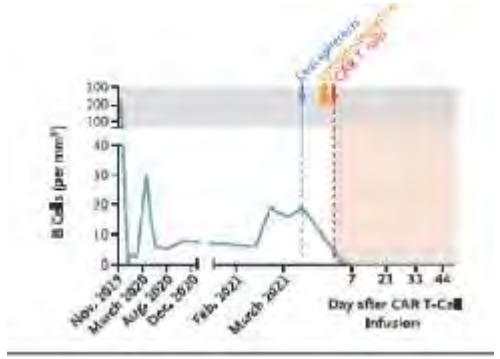
B-sejtek **jó terápiás célpont több gyulladásos** reum. **betegségben**, CD19 **targetálás jelentősebb** B-sejt depletiok okozhat mint CD20

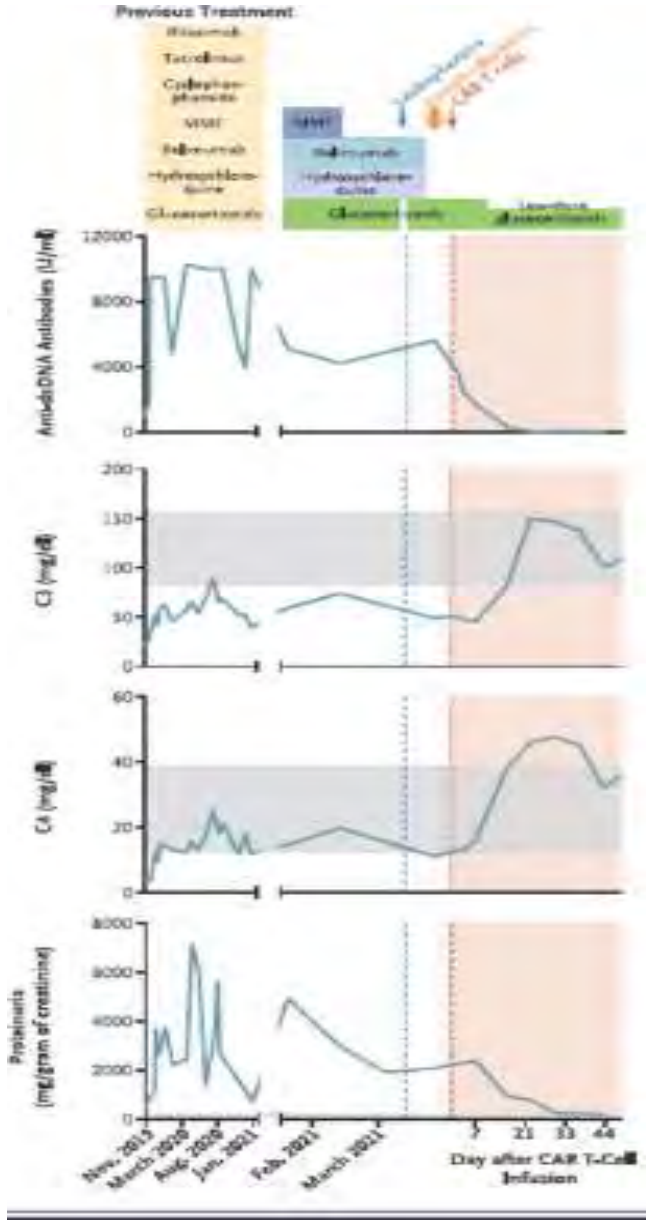
Sadeqi Nezhad M et al Front. Immunol. 11:603237.
doi: 10.3389/fimmu.2020.603237

CAR-T sejt kezelés SLE-ben



CD19-Targeted CAR T Cells in Refractory Systemic Lupus Erythematosus





20- éves SLE-s nő autolog CD-19 CAR-T sejt sikeres kezeléséről számolnak be, LN, pericarditis, arthritis, bőrérintettség és Libman-Sacks endocarditis

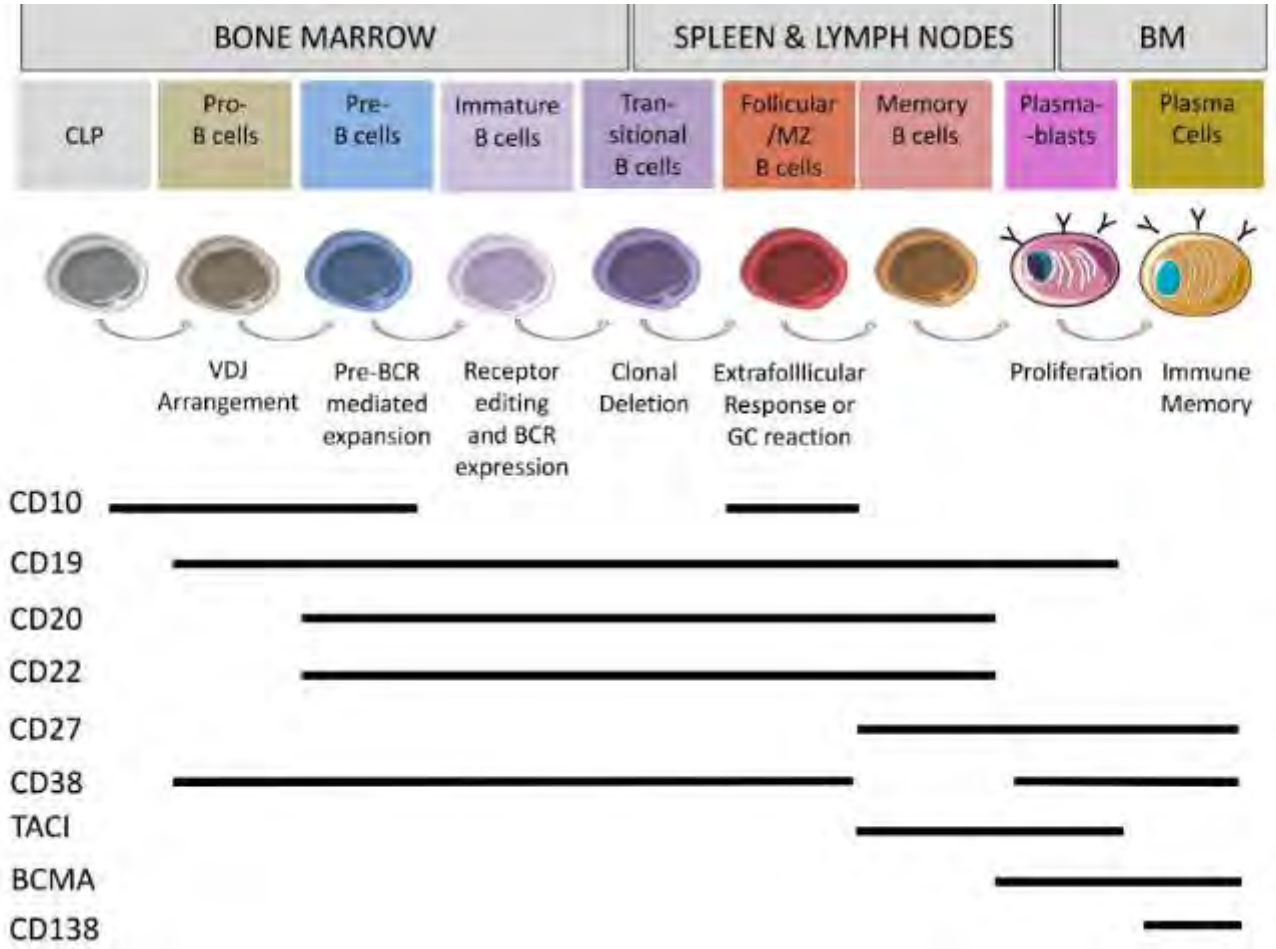
Korábbi sikertelen kezelések: hydrochloroquine, nagy dózis szteroid, cyclophosphamide, MMF, tacrolimus, belimumab, RTX

CAR-T kezelés előtt lymphodepletio fludarabin + cyclophosphamide, kis dózis szteroid $1{,}1x10^6$ CD19 CAR-T/ttskg (CD4/CD8: 3/1)

Anti DNA 5000-4 csökkent, mh nem volt

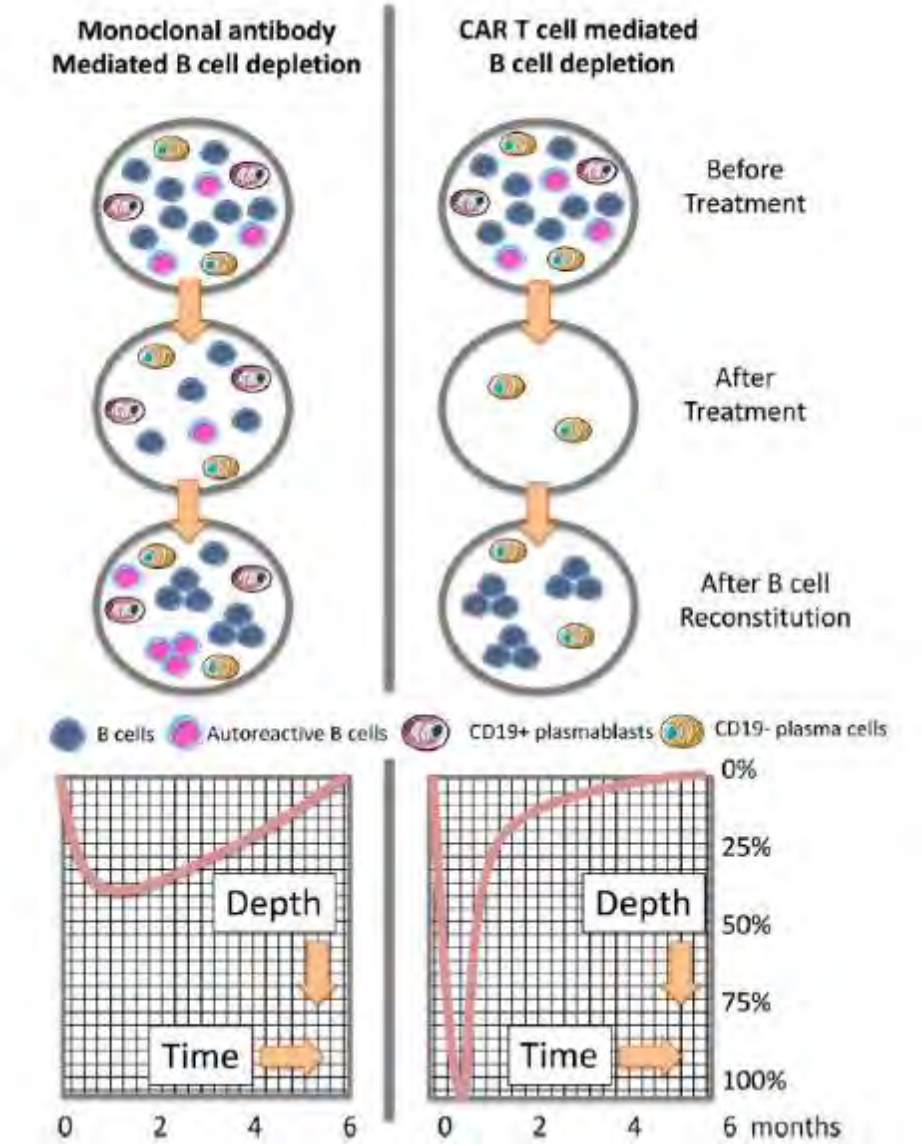
Mougiakakos D et al N Engl J Med. 2021 Aug 5;385(6):567-569. doi: 10.1056/NEJMc2107725. PMID: 34347960.

CD19/20 B sejtek



Schett G, Nagy G, Krönke G, *et al* B-cell depletion in autoimmune diseases *Annals of the Rheumatic Diseases* 2024;**83:**1409-1420.

Az antitest alapú (a-CD20) és sejt alapú (a-CD19 CAR-T) sejtdepléció AIB-ben



Schett G, Nagy G, Krönke G, *et al* B-cell depletion in autoimmune diseases *Annals of the Rheumatic Diseases* 2024;**83:**1409-1420.

CAR-T sejt kezelés systemás sclerosisban

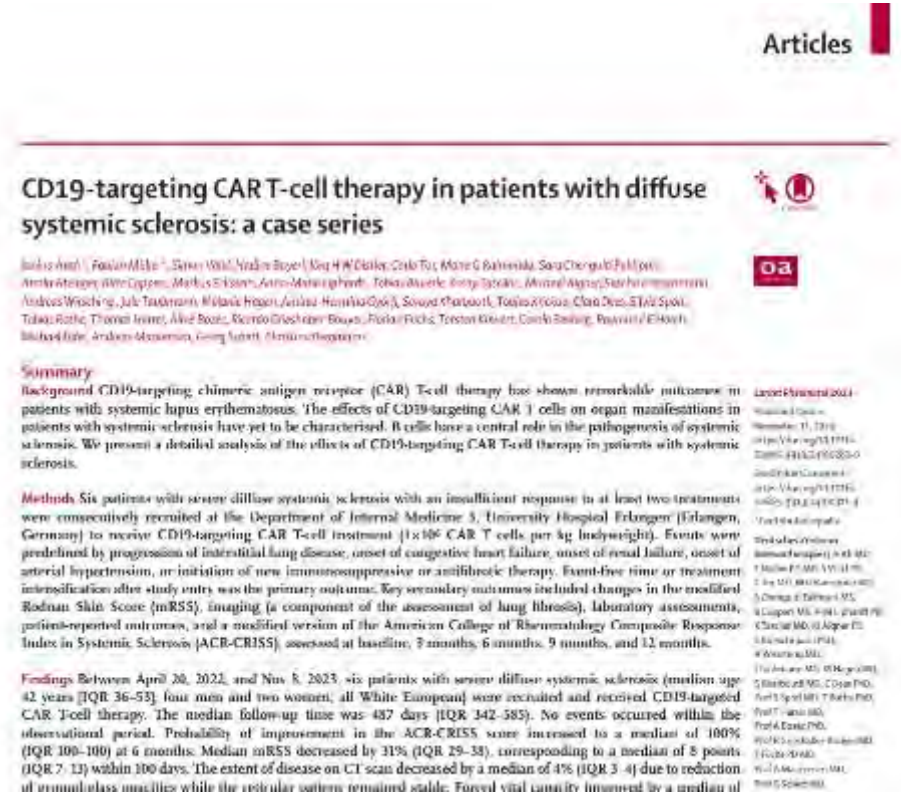
Hat súlyos diffúz szisztémás szklerózisban szenvedő beteget kezeltek

CD19-célzó CAR T-sejt kezelés

SSc események: intersticiális tüdőbetegség progressziója, pangásos szívelégtelenség kialakulása, veseelégtelenség kialakulása, artériás magas vérnyomás kialakulása vagy új immunszuppresszív vagy antifibrotikus terápia megkezdése.

Az eseménymentes idő vagy a kezelés intenzifikálása a vizsgálatba való belépés után volt az elsődleges eredmény.

A kulcsfontosságú másodlagos eredmények a módosított Rodnan bőrpontszám (mRSS), képalkotás (tüdőfibrózis), laboratóriumi értékelések változásai voltak.



Articles

CD19-targeting CAR T-cell therapy in patients with diffuse systemic sclerosis: a case series

oa

Summary

Background CD19-targeting chimeric antigen receptor (CAR) T-cell therapy has shown remarkable outcomes in patients with systemic lupus erythematosus. The effects of CD19-targeting CAR T cells on organ manifestations in patients with systemic sclerosis have yet to be characterised. B cells have a central role in the pathogenesis of systemic sclerosis. We present a detailed analysis of the effects of CD19-targeting CAR T-cell therapy in patients with systemic sclerosis.

Methods Six patients with severe diffuse systemic sclerosis with an insufficient response to at least two treatments were consecutively recruited at the Department of Internal Medicine 5, University Hospital Erlangen (Erlangen, Germany) to receive CD19-targeting CAR T-cell treatment (1×10⁶ CAR T cells per kg bodyweight). Events were predefined by progression of interstitial lung disease, onset of congestive heart failure, onset of renal failure, onset of arterial hypertension, or initiation of new immunosuppressive or antifibrotic therapy. Event-free time or treatment intensification after study entry was the primary outcome. Key secondary outcomes included changes in the modified Rodnan Skin Score (mRSS), imaging (a component of the assessment of lung fibrosis), laboratory assessments, patient-reported outcomes, and a modified version of the American College of Rheumatology Composite Response Index in Systemic Sclerosis (ACR-CRISS), assessed at baseline, 3 months, 6 months, 9 months, and 12 months.

Findings Between April 20, 2022, and Nov 8, 2023, six patients with severe diffuse systemic sclerosis (median age 42 years [IQR 36–53]; four men and two women; all White European) were recruited and received CD19-targeted CAR T-cell therapy. The median follow-up time was 487 days [IQR 342–585]. No events occurred within the observational period. Probability of improvement in the ACR-CRISS score increased to a median of 100% (IQR 100–100) at 6 months. Median mRSS decreased by 31% (IQR 29–38), corresponding to a median of 8 points (IQR 7–13) within 100 days. The extent of disease on CT scan decreased by a median of 4% (IQR 3–4) due to reduction of groundglass opacities while the reticular pattern remained stable. Forced vital capacity improved by a median of

CAR-T sejt kezelés systemás sclerosisban

2022. április 20. és 2023. november 8. között hat súlyos diffúz szisztémás sclerosisban szenvedő beteget vettek be a vizsgálatba, akik CD19-célzott CAR T-sejt terápiában részesültek.

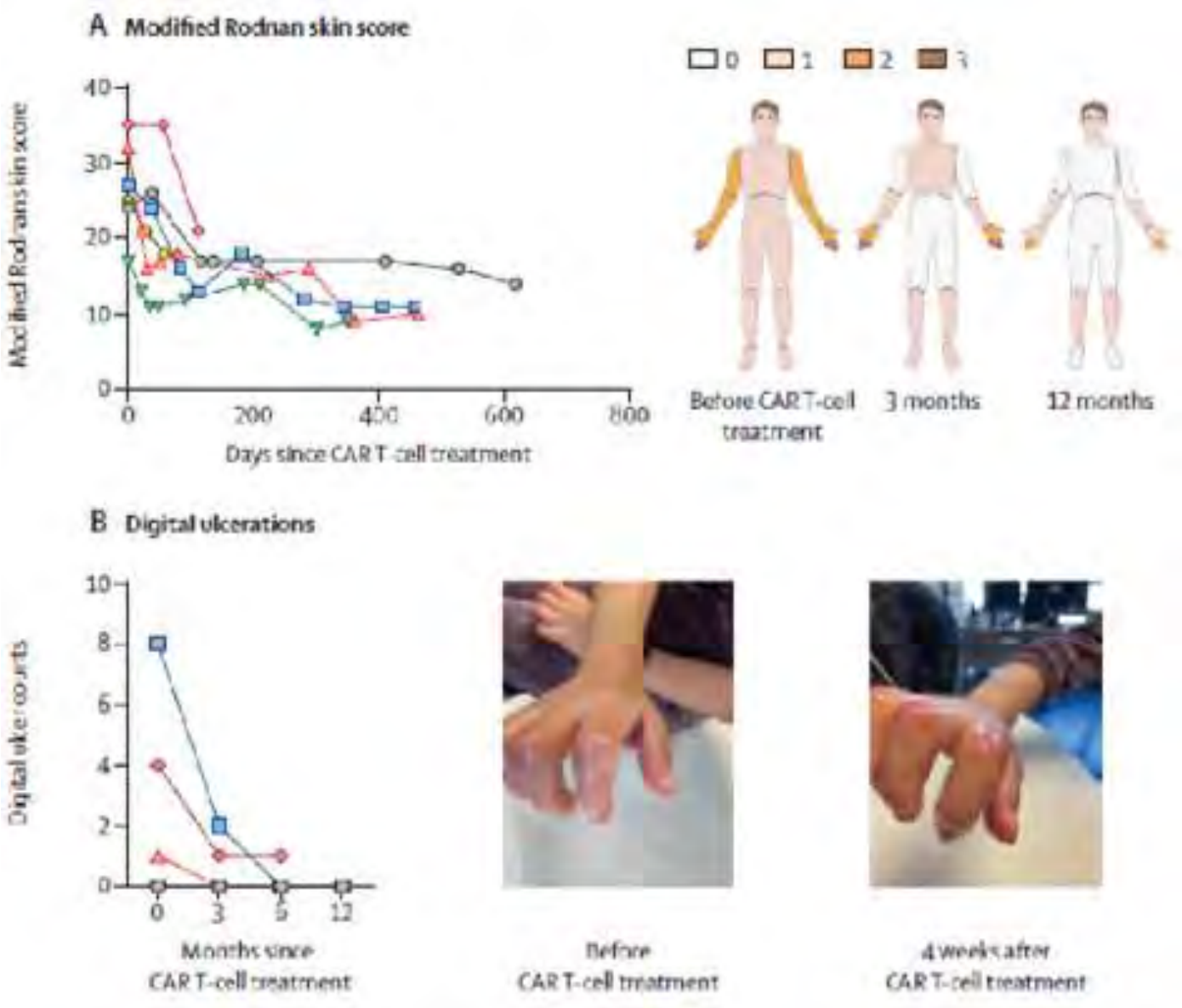
A megfigyelési időszakban semmilyen SSc esemény nem történt.

A medián mRSS 31%-kal csökkent, ami 8 pont mediánnak felel meg100 napon belül.

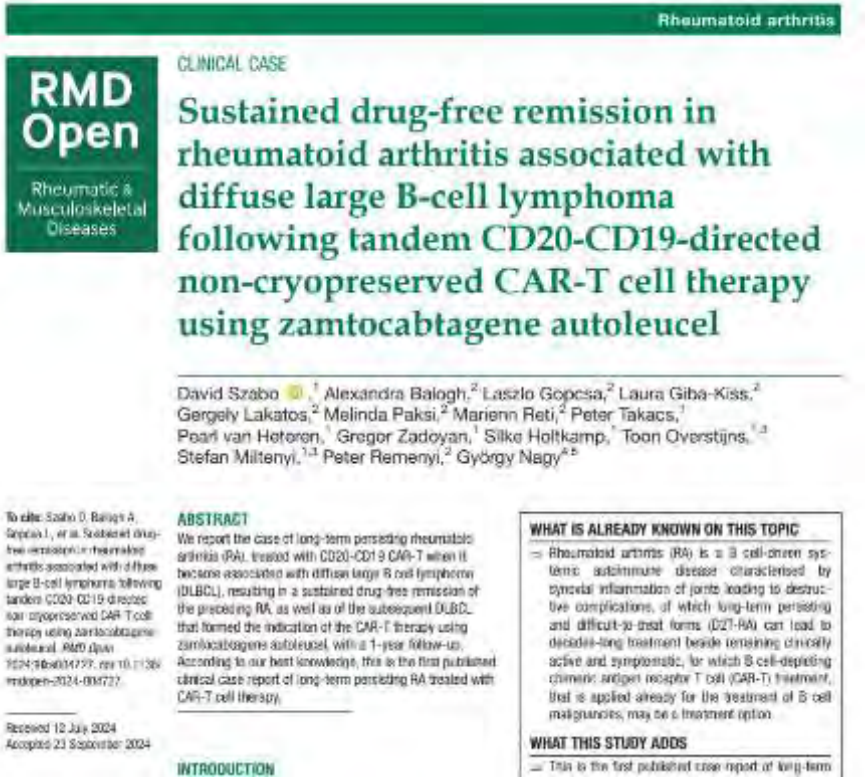
A CT-vizsgálat során a fibrosis mértéke átlagosan 4%-kal csökkent (GGO)

FVC 195 ml-rel javult

CAR-T sejt kezelés systemás sclerosisban



CAR-T sejtek RA-ban



Rheumatoid arthritis

RMD Open
Rheumatic & Musculoskeletal Diseases

CLINICAL CASE

Sustained drug-free remission in rheumatoid arthritis associated with diffuse large B-cell lymphoma following tandem CD20-CD19-directed non-cryopreserved CAR-T cell therapy using zamtocabtagene autoleucel

David Szabo, Alexandra Balogh, Laszlo Gopcsa, Laura Giba-Kiss, Gergely Lakatos, Melinda Paksi, Marienn Reti, Peter Takacs, Pearl van Heteren, Gregor Zadoyan, Silke Holtkamp, Toon Overstijns, Stefan Miltenyi, Peter Remenyi, György Nagy

To cite: Szabo D, Balogh A, Gopcsa L, et al. Sustained drug-free remission in rheumatoid arthritis associated with diffuse large B-cell lymphoma following tandem CD20-CD19-directed non-cryopreserved CAR-T cell therapy using zamtocabtagene autoleucel. RMD Open 2024;10:e004727. doi:10.1136/rmdopen-2024-004727

Received 12 July 2024
Accepted 23 September 2024

ABSTRACT

We report the case of long-term persisting rheumatoid arthritis (RA), treated with CD20-CD19 CAR-T when it became associated with diffuse large B cell lymphoma (DLBCL), resulting in a sustained drug-free remission of the preceding RA, as well as of the subsequent DLBCL, that formed the indication of the CAR-T therapy using zamtocabtagene autoleucel, with a 1-year follow-up. According to our best knowledge, this is the first published clinical case report of long-term persisting RA treated with CAR-T cell therapy.

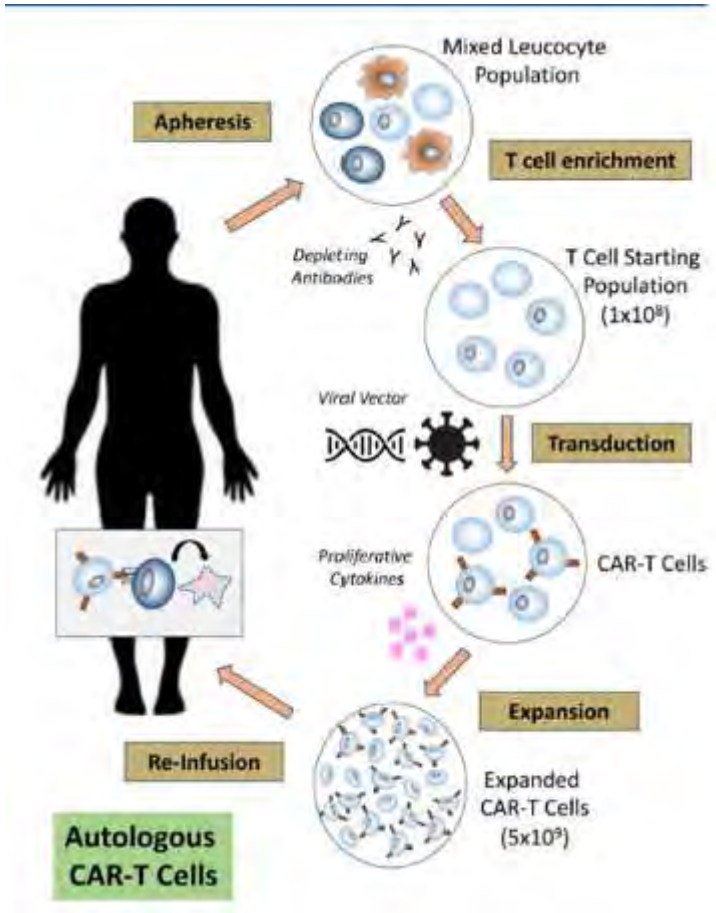
INTRODUCTION

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Rheumatoid arthritis (RA) is a B cell-driven systemic autoimmune disease characterised by synovial inflammation of joints leading to destructive complications, of which long-term persisting and difficult-to-treat forms (D2T-RA) can lead to decades-long treatment beside remaining clinically active and symptomatic, for which B cell-depleting chimeric antigen receptor T cell (CAR-T) treatment, that is applied already for the treatment of B cell malignancies, may be a treatment option.

WHAT THIS STUDY ADDS

- This is the first published case report of long-term



Schett G, Nagy G, Krönke G, *et al* B-cell depletion in autoimmune diseases *Annals of the Rheumatic Diseases* 2024;**83:**1409-1420.

Negyedik generációs CAR-T sejtek D2T RA-ban

Az RA egy autoimmun gyulladásos betegség, amelyet szimmetrikus ízületi gyulladás jellemez

Az RA kezelését forradalmasította a MOA-k (pl. TNFα, IL-6, CD20) kifejlesztése, ami jobb betegségkontrollt eredményez.

Az RA-s betegek akár 30%-a azonban még mindig nem éri el a célértéket (T2T), annak ellenére, hogy számos immunmoduláló gyógyszeres ciklust alkalmaznak

Az ilyen betegeket „nehezen kezelhető (D2T)" RA-nak nevezzük

Vizsgálták egy új, autológ, negyedik generációs CD19-célzott kiméra antigén receptor (CAR) T-sejtek, amelyek IL-6 és TNFα ellen AB-ket választanak ki (CD19/aIL-6/aTNFα) a D2T RA kezelésében

Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban

Három, több hagyományos és biológiai szerre nem reagáló RA-s beteget kezeltek ezekkel az új, negyedik generációs CAR T-sejtekkel.

A vizsgálatot a Kínai Tudományos és Technológiai Egyetem Első Társult Kórházának etikai bizottsága hagyta jóvá (2023KY-379)

Valamennyi beteg írásos beleegyezését adta a Helsinki Nyilatkozat elveinek megfelelően.

A CD19/aIL-6/aTNFα CAR IL-6 és TNFα elleni antitestek IL-6 és TNF blokkoló képességét in vitro tesztelték.

Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban

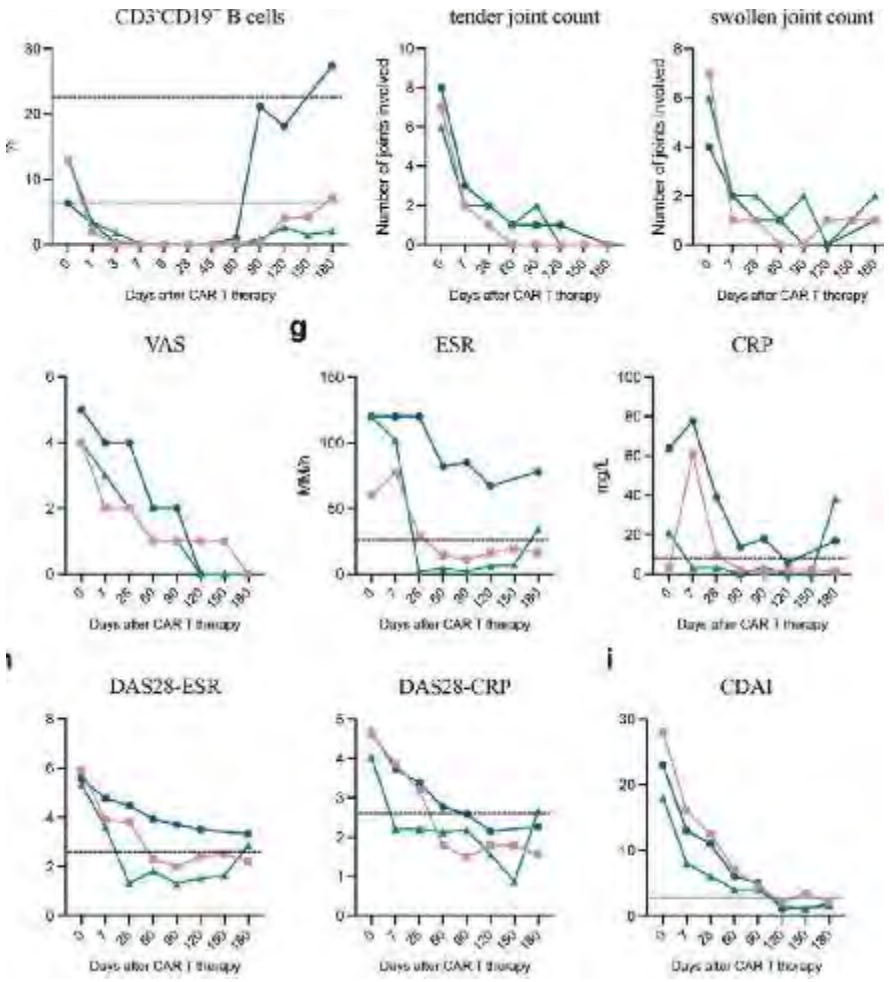
Valamennyi beteg korábban kapott glükokortikoidokat és többféle betegségmódosító DMARD-ot, beleértve a metotrexátot (3/3), a hidroxiklorokint (2/3), a leflunomidot (2/3), az iguratimodot (2/3), az etanerceptet (2/3), adalimumab (1/3), tofacitinib (1/3), baricitinib (2/3), abatacept (1/3), és etanerceptet

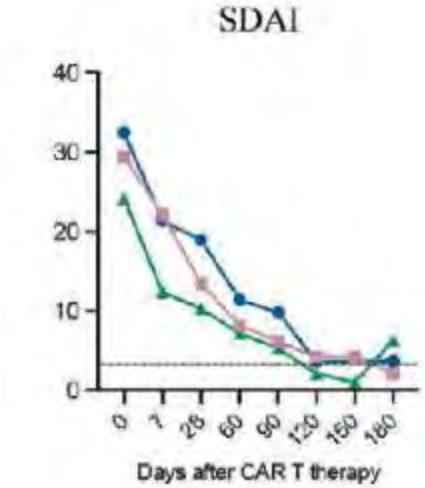
Az iguratimod megakadályozza az NF-κB aktiválódását, majd szelektíven gátolja a COX-2-t és számos gyulladásos citokint

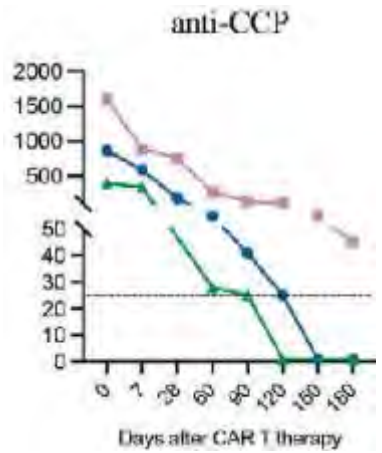
A CAR T-sejt-kezelést követően mindhárom beteg abbahagyta a biológiai DMARD-ok (bDMARD) kezelését.

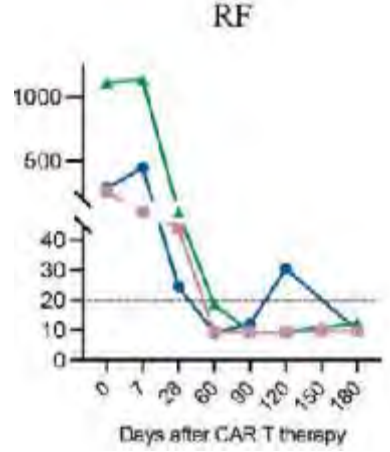
Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban



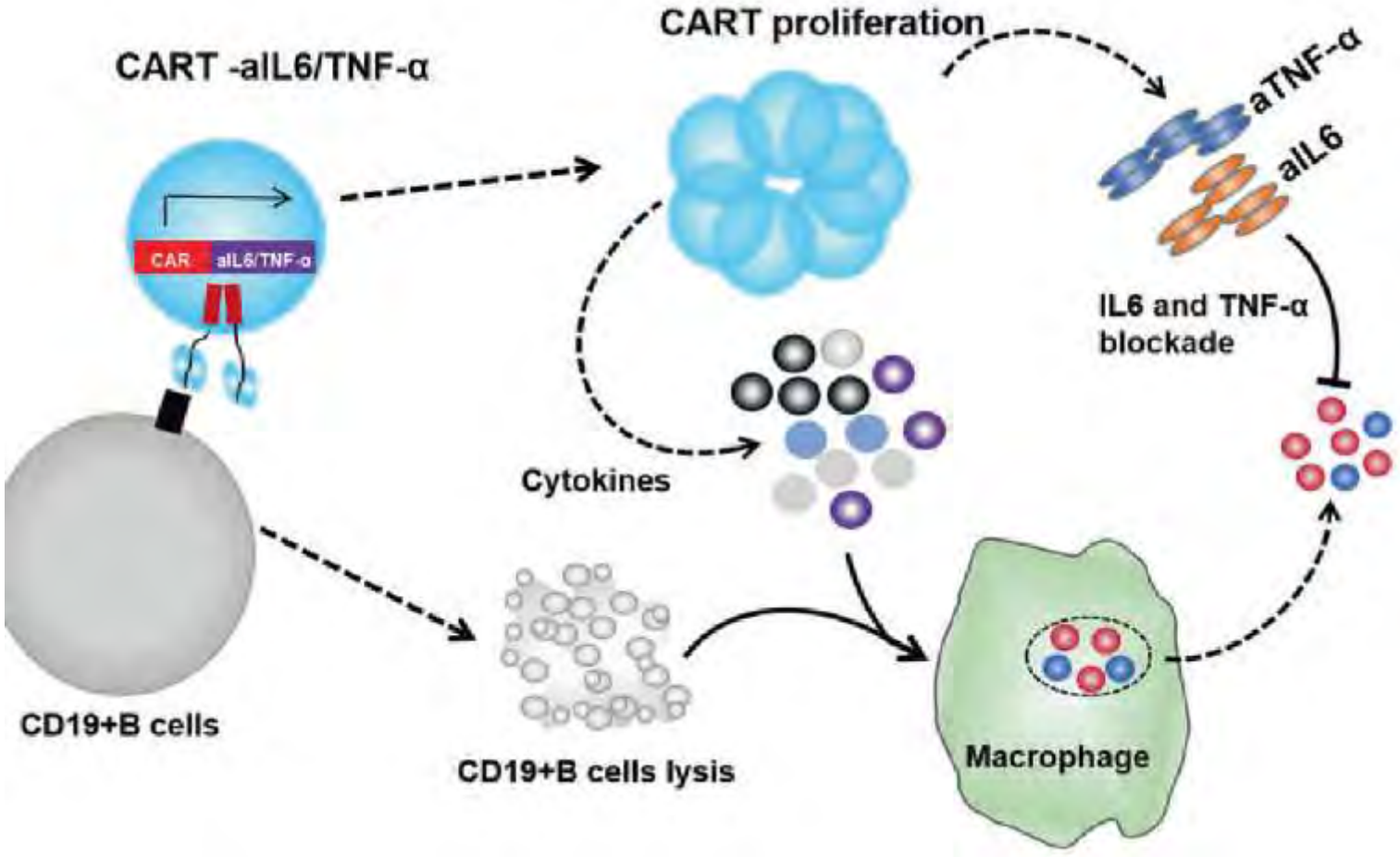






Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban



Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban

A CAR T-sejt infúziót mindhárom beteg jól tolerálta, és nem fordult elő súlyos mellékhatás

Nem fordult elő citokin felszabadulási szindróma (CRS) vagy immune effector cell-associated neurotoxicity syndrome (ICANS), nem volt láz, hipotenzió, fejfájás, légzési nehézség vagy neurológiai tünet (például zavartság, görcsrohamok, tudat- vagy viselkedésváltozások)

Az infúziót követően a CD19/aIL-6/aTNFα CAR T-sejtek gyorsan proliferáltak in vivo, a CAR kópiák csúcspontja a 9. napon az 1. betegnél, a 21. napon a 2. betegnél és a 14. napon a 3. betegnél.

Cell Res, January 09, 2025

Negyedik generációs CAR-T sejtek D2T RA-ban

**A vizsgálat a CAR T-sejtek erőteljes növekedését mutatja in vivo,
a CD19 B-sejtek teljes eliminációját, az RA-val kapcsolatos autoantitestek kiürülését
és magas szintű tartós klinikai válaszokat RA-s betegekben.**

Ez az első alkalom, hogy negyedik generációs CAR-t használnak az autoimmun betegségek kezelésére, és a citokin-gátlás és a B-sejt-kiürülés egy megközelítésben történő kombinálásának indoklása hatalmas lehetőségeket rejt magában az olyan betegségek, mint az RA, jobb kontrollálásában a jövőben.

Hosszú távú megfigyelés szükséges a kezelés tartós hatékonyságának és biztonságosságának megállapításához.

Az RA érzékeny a CD19-CAR T-sejt kezelésre, és ezzel a megközelítéssel az RA-specifikus autoimmunitás kezelhető

Cell Res, January 09, 2025

CAR-T fejlesztési irányok: in vivo CAR T sejtek

News & analysis

News

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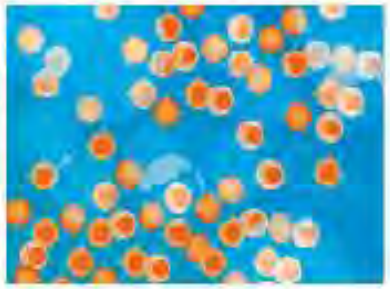
In vivo CAR T cells move into clinical trials

By Asher Mullard

Drug developers want to reprogramme immune cells directly in the body, opening up new gene therapy frontiers in cancer and autoimmunity.

Engineered immune cells called CAR Ts that can seek out and destroy B cells have transformed the treatment of some blood cancers, and are raising hopes for possible cures for autoimmune diseases. But these living cell therapies – made by harvesting cells from patients, ... the code for a CAR selectively to a subset of immune cells. Interius, Umoja and Kelonia have embraced engineered lentiviral vectors that make permanent changes in immune cells. Capstan, Myeloid Therapeutics, Orbital and Orna have instead prioritized lipid nanoparticles (LNPs) paired with RNA molecules, to induce transient surges of CAR expression in targeted cells. Larger pharmaceutical companies are on the case as well, with Sanofi disclosing last year that it had three in vivo CAR T programmes in preclinical development.

"The beauty of what we're



research group at the Paul-Ehrlich-Institut, early inspiration struck 20 years ago. Another ... them a fraction of the cost of a living cell therapy. And they could be better, for two key reasons too. Ex vivo CAR T recipients need to be treated with harsh chemotherapy regimens ahead of cell therapy transfusions to make room for the engineered immune cells, but lymphodepletion cannot be used during the generation of in vivo CAR Ts and so patients retain intact immune systems. And because the souped up in vivo immune cells are less exhausted than their ex vivo counterparts, they could be more active too. "There's a real, theoretical possibility that those cells will simply be better cancer fighters," says Johnson.

These expectations are founded on emerging data from up and coming gene therapy vectors, the delivery vehicles that will carry ... from cell therapies to gene therapies. "The distinctions between classes of therapies is blurring in front of our eyes," says Bot.

"The distinctions between classes of therapies is blurring in front of our eyes"

Lentiviral reprogramming

Years before ex vivo CAR T cell therapies first entered the clinic, researchers were already hard at work retooling lentiviral vectors to enable in vivo reprogramming of immune cells.

For Christian Buchholz, who heads the molecular biotechnology and gene therapy ... Buchholz. "You need to have a therapeutic strategy that will give those cells a selective advantage in vivo to finally get a readout". With B-cell depleting CAR Ts first entering the clinical in 2000, Buchholz saw an opportunity. A CD8-targeted CD19-CAR-loaded lentiviral vector transduced T cells in vivo in mice and wiped out B cells, he reported in 2018.

Several biotechs have embraced this strategy, with a few tweaks along the way. Each firm has chosen a preferred cell-targeting moiety, the antibody-based binder that defines which subset of cells are targeted. The glycoprotein matters too, acting as the entry key into engaged immune cells. And then there is the therapeutic payload, the CAR that enables the retrained T cells to seek out malignant foes. Layered on top of all that is manufacturing.

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CAR-T fejlesztési irányok: in vivo CAR T sejtek

In vitro CAR-T: a folyamat költséges és bonyolult, a betegek sejtjeinek kinyerésével, fáradságos növesztésével és laboratóriumi tervezésével egy kiméra antigénreceptor (CAR) expresszálására, majd a betegekbe való újbóli infúzióval valósul meg.

Az in vivo CAR T generálás készen kapható újraprogramozó vektorokkal történik, így hetekkel gyorsabb, mint az ex vivo CAR T-k jelenlegi folyamatai

Az ex vivo CAR T recipienseket kemoterápiás kezelésekkel kell kezelni a sejtterápiás transzfúzió előtt, ezzel szemben a limfodepléció elkerülhető az in vivo CAR T-k generálásakor, így a betegek immunrendszere ép marad.

Ráadásul az in vivo immunsejtek kevésbé kimerültek, mint ex vivo társaik, lehetnének aktívabbak is

In vivo CAR T eljárás gyorsabb, jobb és olcsóbb lehet

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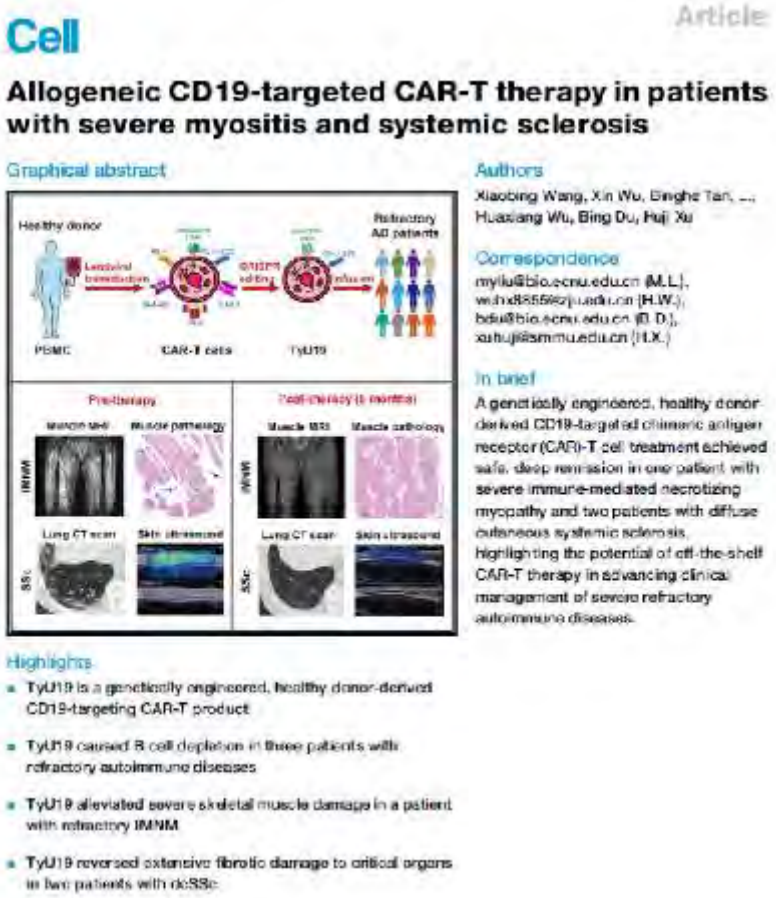
Allogén CAR-T sejt kezelés systemás sclerosisban és myositisben


Cell

Article

Allogeneic CD19-targeted CAR-T therapy in patients with severe myositis and systemic sclerosis

Graphical abstract

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In brief

A genetically engineered, healthy donor-derived CD19-targeted chimeric antigen receptor (CAR)-T cell treatment achieved safe, deep remission in one patient with severe immune-mediated necrotizing myopathy and two patients with diffuse cutaneous systemic sclerosis, highlighting the potential of off-the-shelf CAR-T therapy in advancing clinical management of severe refractory autoimmune diseases.

Highlights

- TyU19 is a genetically engineered, healthy donor-derived CD19-targeting CAR-T product
- TyU19 caused B cell depletion in three patients with refractory autoimmune diseases
- TyU19 alleviated severe skeletal muscle damage in a patient with refractory IMNM
- TyU19 reversed extensive fibrotic damage to critical organs in two patients with dcSSc

A legújabb tanulmányok feltárták az autológ CD19-célzott CAR-T terápiák használatát autoimmun betegségek kezelésére, és ígéretes hatékonyságról számoltak be.

Az autológ CAR-T terápiák drágák, és a személyre szabott termék gyártása során meghibásodhatnak.

Az egészséges donorból származó késztermék nagyban javítaná a CAR-T elérhetőségét.

Allogén CAR-T termékek refrakter autoimmun betegségek kezelésére?

Allogén CAR-T sejt kezelés systemás sclerosisban és myositisben

Az allogén kiméra antigén receptor (CAR)-T sejtek nagy ígéretet hordoznak a CAR-T terápia hozzáférhetőségének bővítésében

DE az allograft kilökődés kockázata akadályozta az alkalmazását

A CRISPR-Cas9 segítségével génmanipulált, egészséges donorból származó, CD19-re célzó CAR-T sejteket használtak az immunkilökődés problémájának megoldására.

Egy refrakter immunmediált necrotizáló myopathiában és két systemás sclerosisban szenvedő beteget kezeltek

Az infundált sejtek több mint 3 hónapig fennmaradtak, és a kezelést követő 2 héten belül teljes B-sejt-kiürülést értek el

Allogén CAR-T sejt kezelés systemás sclerosisban és myositisben

A 6 hónapos követés során mindhárom betegnél mély remissziót figyeltek meg citokin felszabadulási szindróma vagy egyéb súlyos nemkívánatos események nélkül.

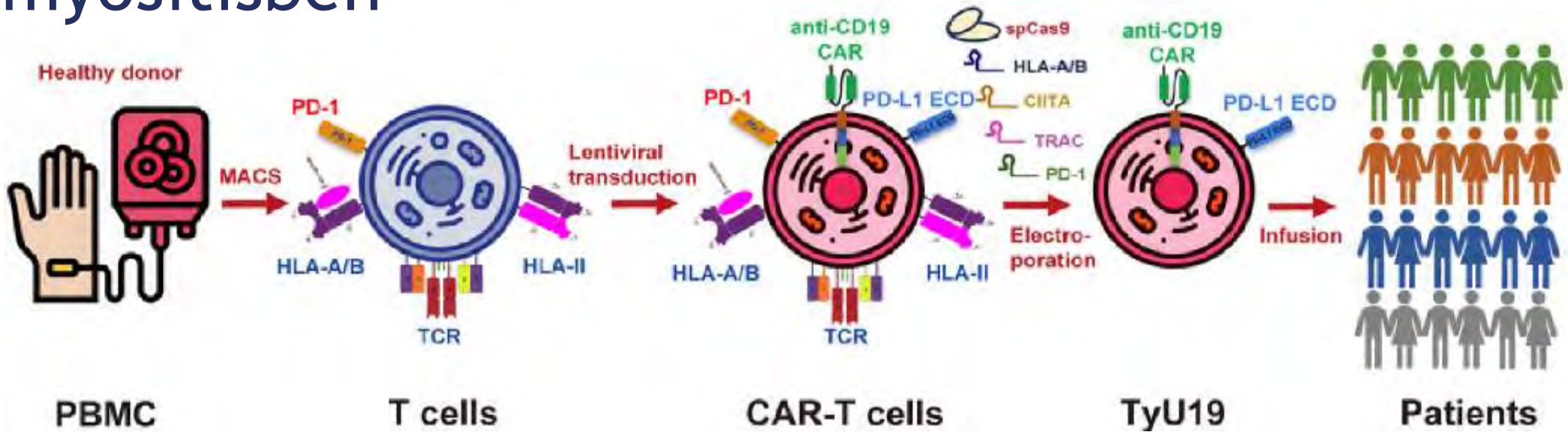
Kiváló klinikai választ figyeltek meg, a gyulladás és a fibrózis visszafordítása.

Ezek az adatok bizonyítják a készen kapható CAR-T sejtek nagy biztonságát és ígéretes immunmoduláló hatását a súlyos, refrakter autoimmun betegségek kezelésében.

Az immunközvetített necrotizáló myopathia (IMNM) súlyos szisztémás betegségautoimmun betegség

Az IMNM egyik legagresszívabb altípusa a jelfelismerő részecske (SRP)-IMNM, amelyet a vázizomzat anti-SRP autoantitest jellemez

Allogén CAR-T sejt kezelés systemás sclerosisban és myositisben



A PBMC-ből izolált T-sejteket először lentivírus kódolással transzdukáltukanti-CD19 CAR konstrukciót, **majd kiütötték a (HLA)-A, HLA-B, II. osztályú fő hisztokompatibilitás komplex transzaktivátor (CIITA),** T sejt receptor alfa állandó (TRAC) és a PD-1 elektroporáción alapuló CRISPR Cas9 génszerkesztéssel

Az allogén CD-19 CAR-T kiváló klinikai hatékonysága és biztonságosság igazolódott

Összegzés

Szintetikus készítmények

Célzott terápiák

IVIG

CAR T

mellékhatások (citokin vihar)

Köszönöm
a figyelmet!

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