Αντι-TNF 20 χρόνια μετά: pros and cons

Συνεδριο ΕΠΕΜΥ
Ρόδος, Σεπ 2022

Δαούσης Δημήτρης
Αναπλ Καθηγητής
Παθολογίας/Ρευματολογίας
Ιατρική Σχολή Πανεπιστημίου Πατρών

Σύγκρουση συμφερόντων

- Τιμητική αμοιβή για ομιλίες και συμμετοχή σε advisory boards από τις εταιρείες UCB, Pfizer, Novartis, BMS, MSD, Janssen, Abbvie, Aenorasis, Elpen, Demo

International Immunology, Vol. 27, No. 1, pp. 55–62
doi:10.1093/intimm/dxu102
Advance Access publication 19 November 2014

Anti-TNF therapy: past, present and future

Claudia Monaco, Jagdeep Nanchahal, Peter Taylor and **Marc Feldmann**

Kennedy Institute of Rheumatology, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Roosevelt Drive, Headington, Oxford OX3 7FY, UK

RHEUMATOLOGY

Rheumatology 2018;57:vii5–vii10
doi:10.1093/rheumatology/key059

Published in final edited form as:
Nat Rev Rheumatol. 2016 January ; 12(1): 49–62. doi:10.1038/nrrheum.2015.169.

TNF biology, pathogenic mechanisms and emerging therapeutic strategies

George D. Kalliolias and **Lionel B. Ivashkiv**
Arthritis & Tissue Degeneration Program and David Z. Rosensweig Center for Genomics Research, Hospital for Special Surgery, 535 E 70th Street, New York, New York 10021, USA.

20 years of experience with tumour necrosis factor inhibitors: what have we learned?

Roberto Caporali[1], Gloria Crepaldi[2], Veronica Codullo[1], Francesca Benaglio[1], Sara Monti[1], Monica Todoerti[1] and Carlomaurizio Montecucco[1]

Rheumatology International
https://doi.org/10.1007/s00296-022-05136-x

Rheumatology
INTERNATIONAL

REVIEW

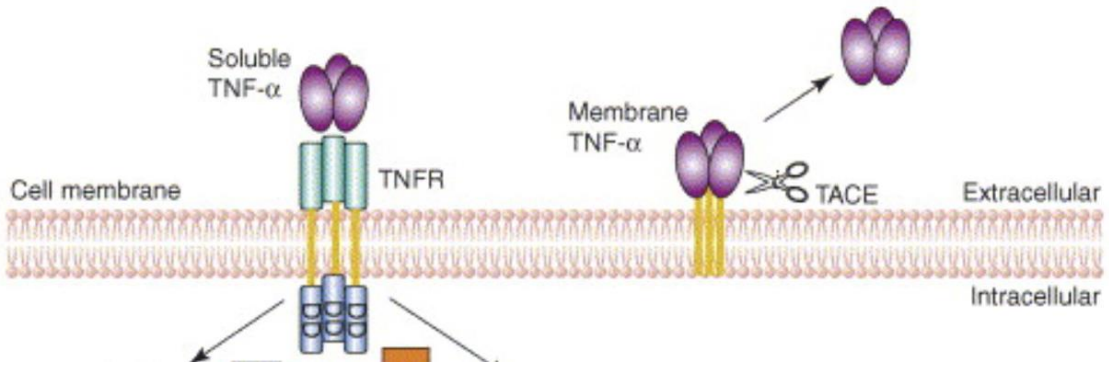
Check for updates

The second decade of anti-TNF-a therapy in clinical practice: new lessons and future directions in the COVID-19 era

Gerasimos Evangelatos[1,2] · Giorgos Bamias[3] · George D. Kitas[4,5] · George Kollias[1,6,7] · Petros P. Sfikakis[1,2]

TNFα

- Βασικός μεσολαβητής φλεγμονής
- Αλλά και σημαντικές ομοιοστατικές λειτουργίες



Box 1 | Functions of TNF

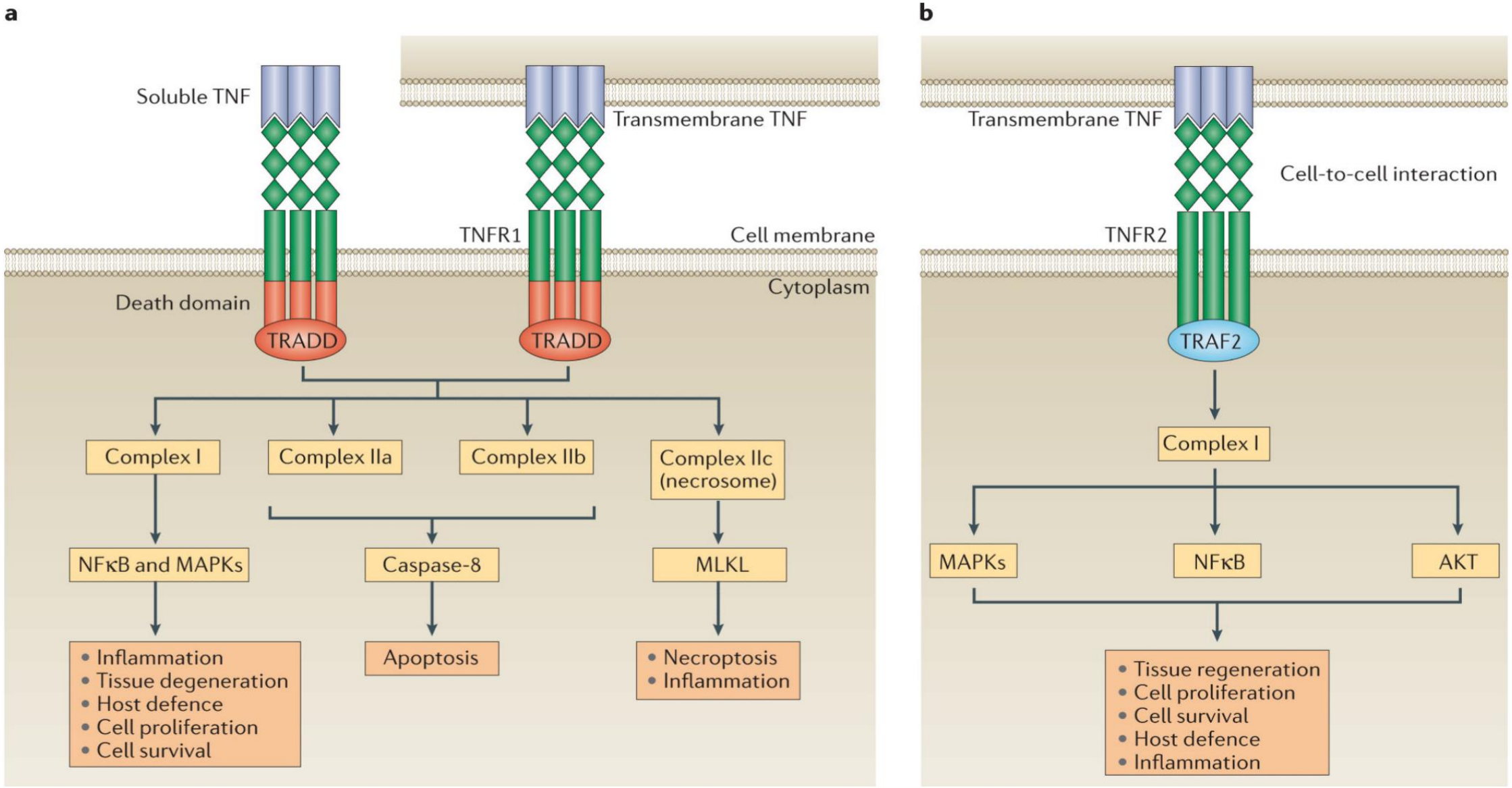
Homeostatic functions

- Defence against pathogens
- Organogenesis and development: lymphoid organ architecture
- Tissue regeneration: neuronal remyelination; cardiac remodelling; cartilage regeneration
- Immunoregulation: tolerization (desensitization) of macrophages, apoptosis of inflammatory cells
- Inhibition of tumorigenesis: necrosis, senescence (cytostatic effect)

Pathogenic functions

- Inflammation: induction of inflammatory mediators (cytokines, lipid mediators); recruitment of inflammatory cells (induction of chemokines and adhesion molecules, endothelial cell activation); survival of inflammatory cells; necroptosis
- Autoimmunity: inhibition of T_{REG} cells
- Tissue degeneration: induction of tissue-destructive enzymes; apoptosis; osteoclastogenesis
- Hypernociception: peripheral neuronal sensitization (effects on C and Aδ neurons); central neuronal sensitization (effects on spinal cord nociceptive neurons, microglial cells and astrocytes)
- Tumorigenesis: genotoxic effects (induction of *de novo* mutagenesis, impairment of DNA repair); induction of tumour-cell survival and proliferation; facilitation of tumour escape from immunosurveillance (effects on MDSCs and T_{REG} cells); facilitation of tumour metastasis (induction of EMT and MMPs)
- Atherogenesis: inflammation; endothelial cell activation; effect on lipid metabolism

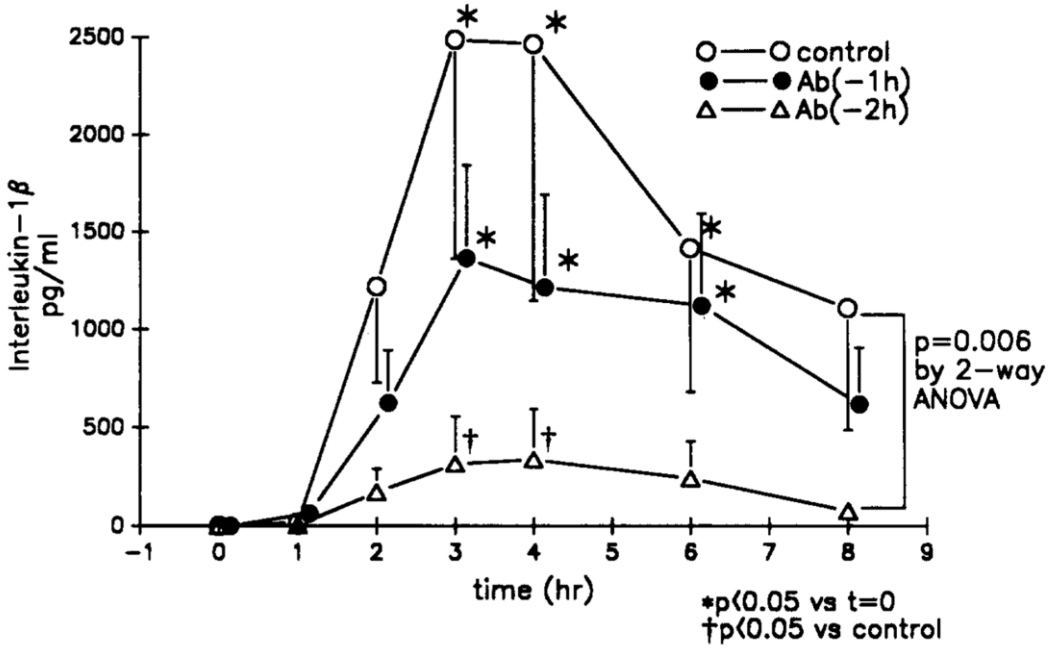
Πολύπλοκη σηματοδότηση….

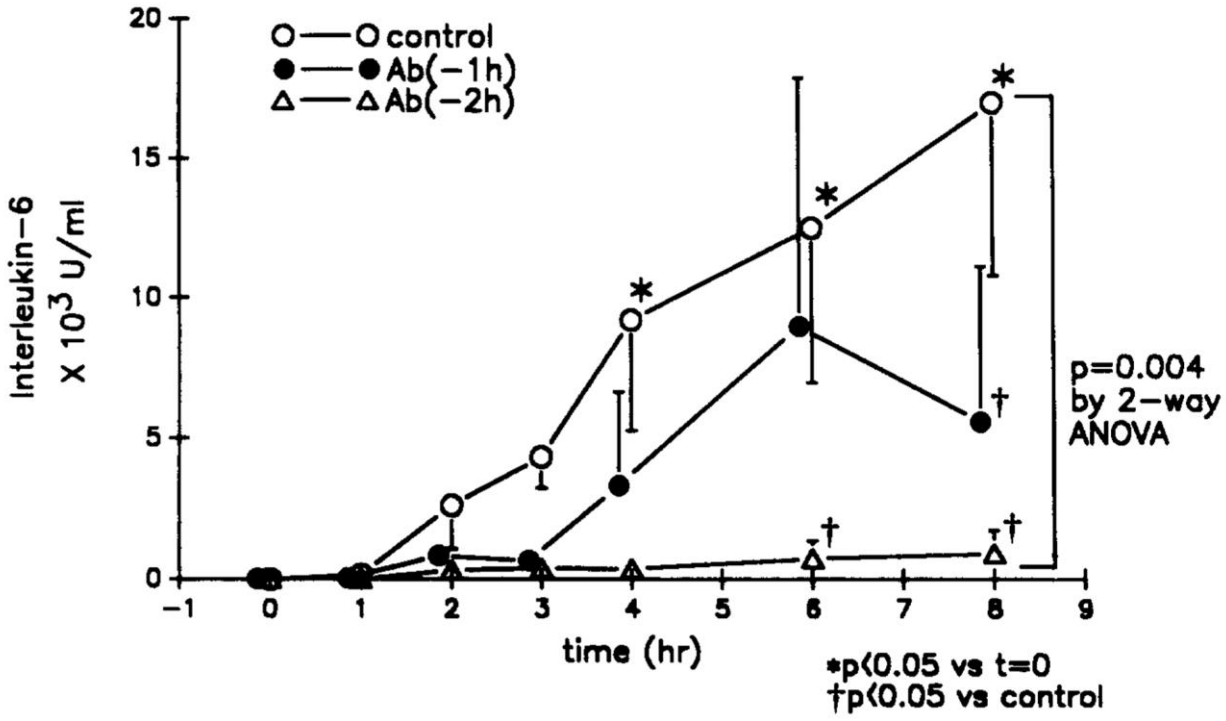


Ο TNF είναι κυταρροκίνη «πρώτης γραμμής»..

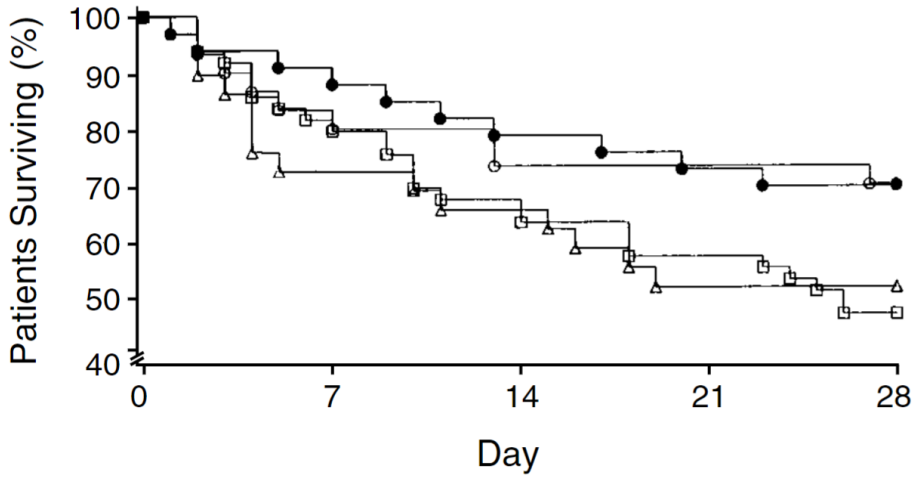
ANTIBODIES TO CACHECTIN/TUMOR NECROSIS FACTOR REDUCE INTERLEUKIN 1β AND INTERLEUKIN 6 APPEARANCE DURING LETHAL BACTEREMIA

By YUMAN FONG,* KEVIN J. TRACEY,*‡ LYLE L. MOLDAWER,* DAVID G. HESSE,* KIRK B. MANOGUE,‡ JOHN S. KENNEY,§ ANNETTE T. LEE,‡ GEORGE C. KUO,‖ ANTHONY C. ALLISON,§ STEPHEN F. LOWRY,* AND ANTHONY CERAMI‡





Η πρώτη προσπάθεια αναστολής TNF ήταν καταστροφική…..



Study Group	No. of Patients	No. of Deaths
Placebo (-●-)	33	10
0.15 mg/kg (-○-)	30	9
0.45 mg/kg (-△-)	29	14
1.5 mg/kg (-□-)	49	26

TREATMENT OF SEPTIC SHOCK WITH THE TUMOR NECROSIS FACTOR RECEPTOR:Fc FUSION PROTEIN

Charles J. Fisher, Jr., M.D., Jan M. Agosti, M.D., Steven M. Opal, M.D., Stephen F. Lowry, M.D., Robert A. Balk, M.D., Jerald C. Sadoff, M.D., Edward Abraham, M.D., Roland M.H. Schein, M.D., Ernest Benjamin, M.D., for the Soluble TNF Receptor Sepsis Study Group*

Η δεύτερη επίσης....

FULL ACCESS
RESEARCH ARTICLE

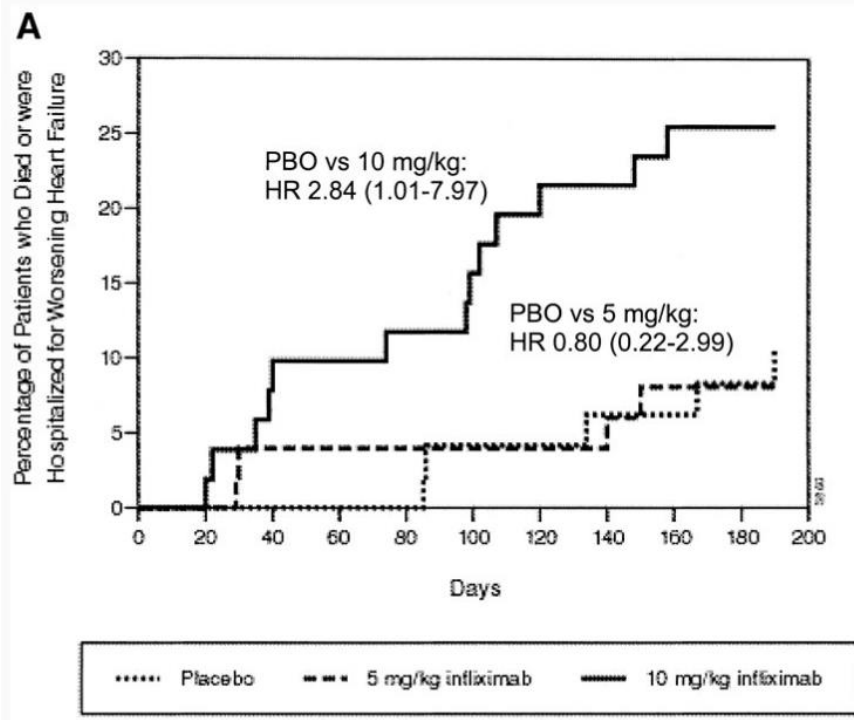
PDF/EPUB

Tools Share

Jump to

Randomized, Double-Blind, Placebo-Controlled, Pilot Trial of Infliximab, a Chimeric Monoclonal Antibody to Tumor Necrosis Factor-α, in Patients With Moderate-to-Severe Heart Failure

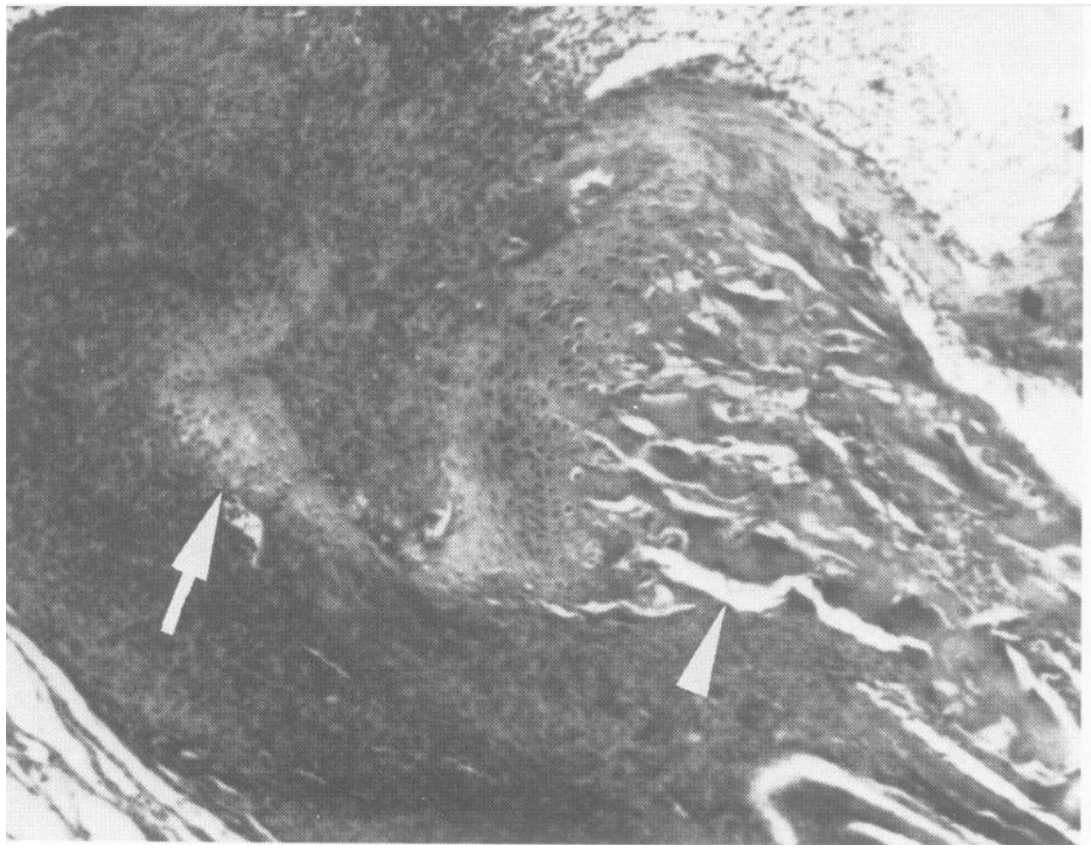
Results of the Anti-TNF Therapy Against Congestive Heart failure (ATTACH) Trial

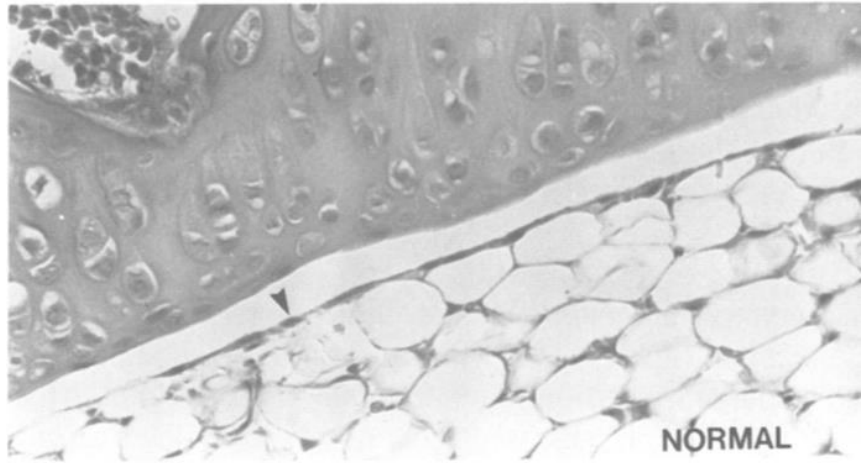


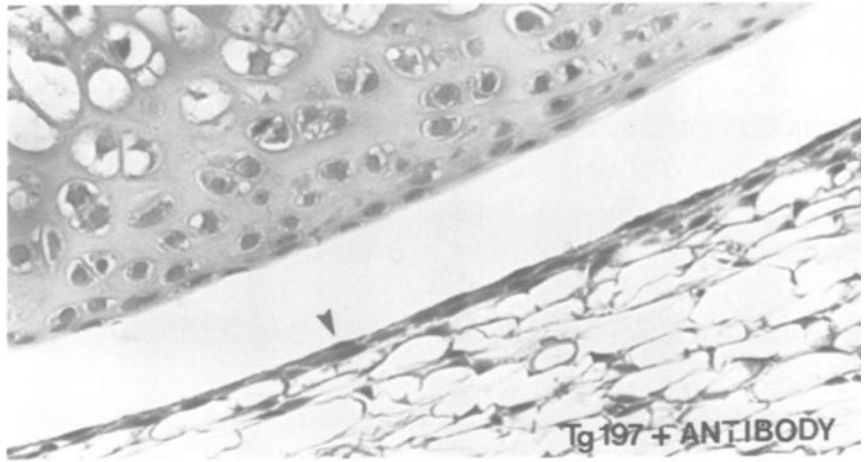
The EMBO Journal vol.10 no.13 pp.4025 – 4031, 1991

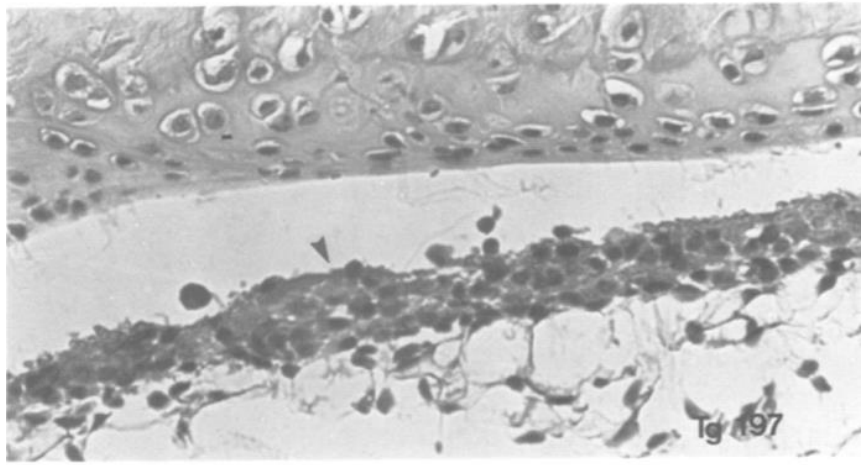
Transgenic mice expressing human tumour necrosis factor: a predictive genetic model of arthritis

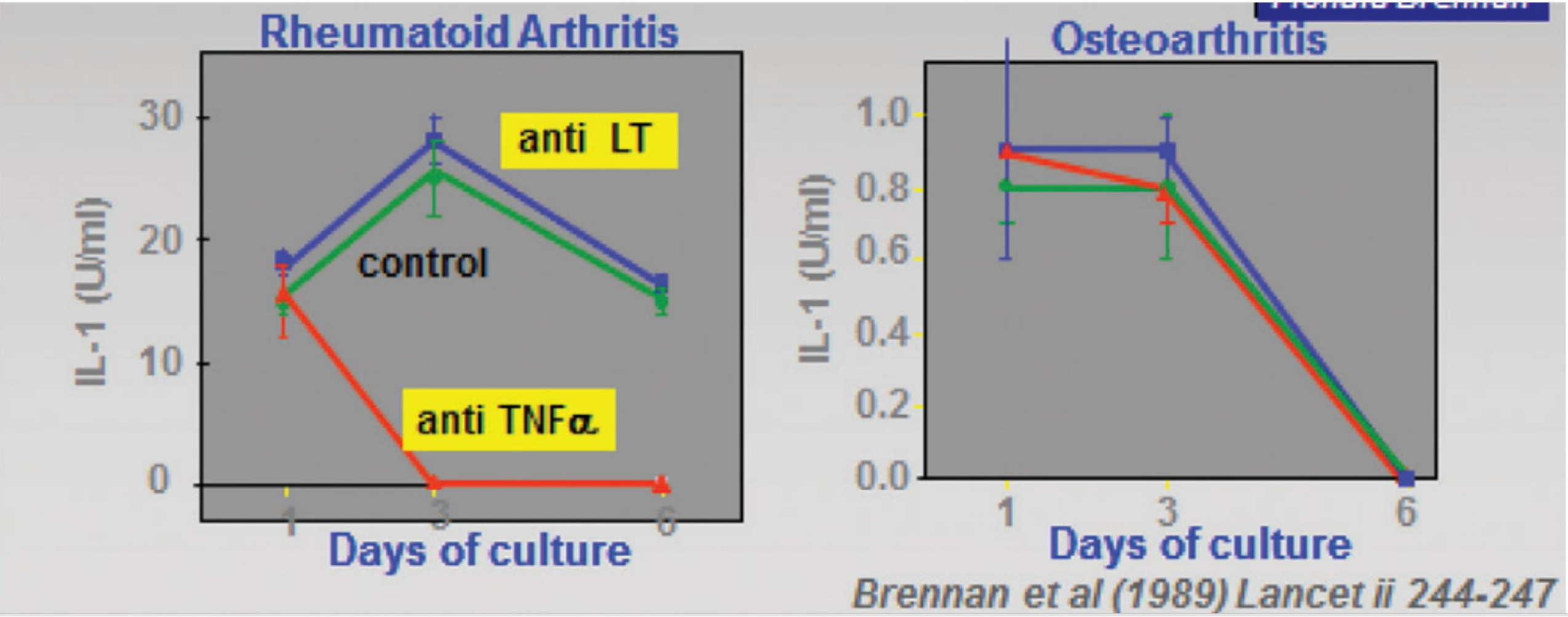
Jeanne Keffer, Lesley Probert, Haris Cazlaris, Spiros Georgopoulos, Evangelos Kaslaris[1], Dimitris Kioussis[2] and George Kollias





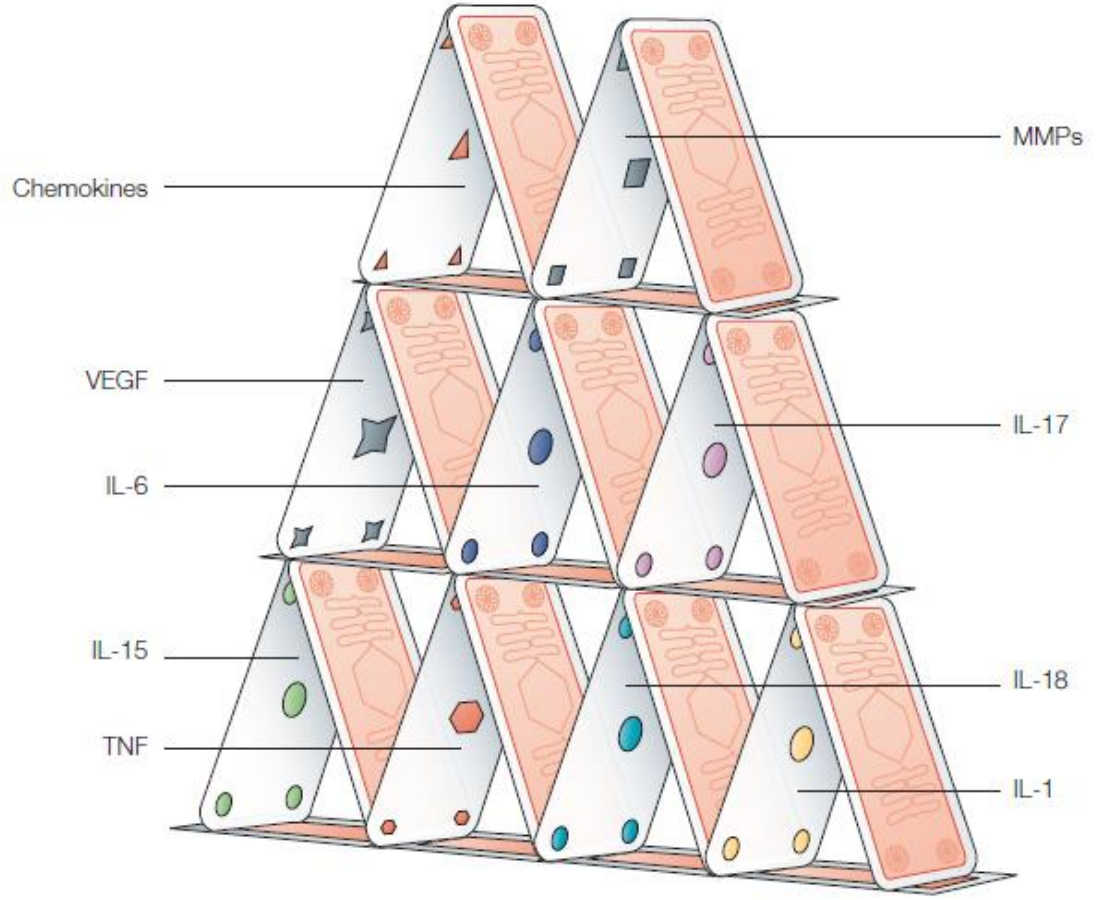






Συνεχής παραγωγή φλεγμονοδών κυτταροκινών σε ΡΑ υμένα
Η αναστολή TNF περιορίζει την παραγωγή άλλων κυτταροκινών

The inflammatory “house of cards”



Smolen J Nature Reviews 2001

Η πρώτη δοκιμή σε ΡΑ

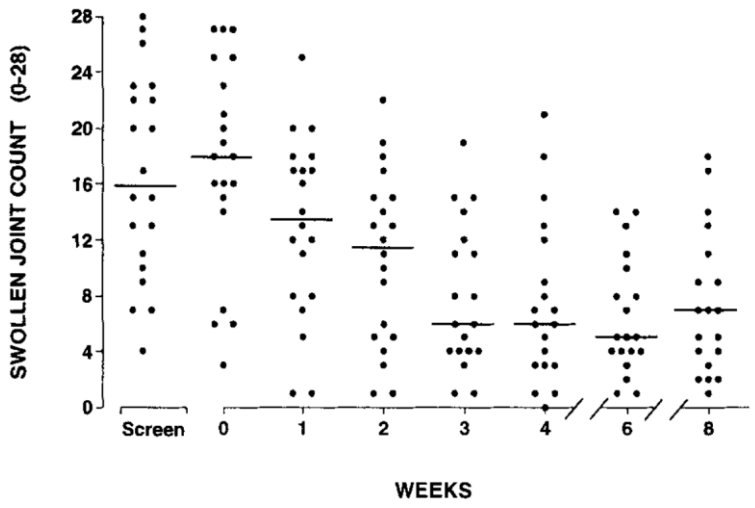
ARTHRITIS & RHEUMATISM Volume 36
Number 12, December 1993, pp. 1681–1690

TREATMENT OF RHEUMATOID ARTHRITIS WITH CHIMERIC MONOCLONAL ANTIBODIES TO TUMOR NECROSIS FACTOR α

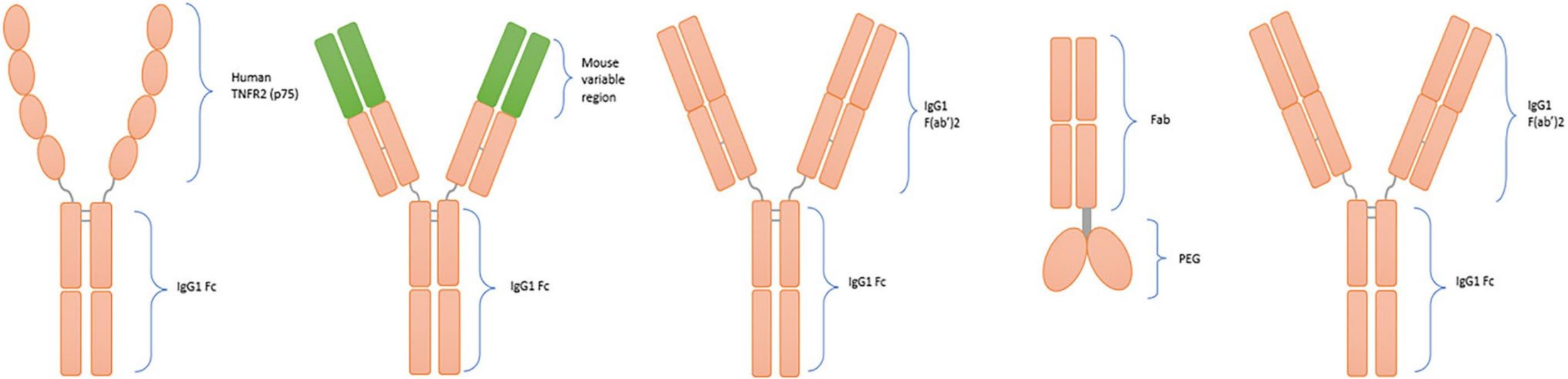
MICHAEL J. ELLIOTT, RAVINDER N. MAINI, MARC FELDMANN, ALICE LONG-FOX, PETER CHARLES, PETER KATSIKIS, FIONULA M. BRENNAN, JEAN WALKER, HANNY BIJL, JOHN GHRAYEB, and JAMES N. WOODY

Table 2. Changes in clinical assessments following treatment of rheumatoid arthritis patients with cA2*

Week of trial	Morning stiffness, minutes	Pain score, 0–10 cm	Ritchie index, 0–69	Swollen joint count, 0–28	Grip strength, 0–300 mm Hg		IDA, 1–4	Patient's assessment, no. grades improved, 0–3
					Left hand	Right hand		
Screen	135, 0–600	7.4, 4–9.7	23, 4–51	16, 4–28	84, 45–300	96, 57–300	3, 2.3–3.3	NA
0	180, 20–600	7.1, 2.7–9.7	28, 4–52	18, 3–27	77, 52–295	92, 50–293	3, 2–3.5	NA
1	20, 0–180 (<0.001†)	2.6, 0.6–7.8 (<0.001†)	13, 2–28 (<0.001; <0.002†)	13.5, 1–25 (>0.05)	122, 66–300 (>0.05)	133, 57–300 (>0.05)	2, 1.5–3.3 (<0.001†)	1, 1–3
2	15, 0–150 (<0.001†)	3.0, 0.3–6.4 (<0.001†)	13, 1–28 (<0.001†)	11.5, 1–22 (<0.003; <0.02†)	139, 75–300 (<0.03; >0.05†)	143, 59–300 (>0.05)	2, 1.5–3.2 (<0.001†)	1.5, 1–3
3	5, 0–150 (<0.001†)	2.2, 0.2–7.4 (<0.001†)	8, 0–22 (<0.001†)	6, 1–19 (<0.001; <0.002†)	113, 51–300 (>0.05)	142, 65–300 (>0.05)	2, 1.2–3.2 (<0.001†)	2, 1–2
4	15, 0–90 (<0.001†)	1.9, 0.1–5.6 (<0.001†)	10, 0–17 (<0.001†)	6, 0–21 (<0.001; <0.002†)	124, 79–300 (<0.02; >0.05†)	148, 64–300 (<0.03; >0.05†)	1.8, 1.3–2.7 (<0.001†)	2, 1–2
6	5, 0–90 (<0.001†)	1.9, 0.1–6.2 (<0.001†)	6, 0–18 (<0.001†)	5, 1–14 (<0.001†)	119, 68–300 (<0.04; >0.05†)	153, 62–300 (<0.05; >0.05†)	1.7, 1.3–2.8 (<0.001†)	2, 1–2
8	15, 0–60 (<0.001†)	2.1, 0.2–7.7 (<0.001†)	8, 1–28 (<0.001†)	7, 1–18 (<0.001†)	117, 69–300 (<0.03; >0.05†)	167, 53–300 (<0.03; >0.05†)	1.8, 1.5–2.8 (<0.001†)	2, 1–3



Η θεραπευτική επιτυχία οδήγησε σε νέα μόρια



Πως επιτυγχάνουν τα αντι-TNF το θεραπευτικό τους αποτέλεσμα?

Billmeier U *et al*. Anti-TNF antibodies in IBD

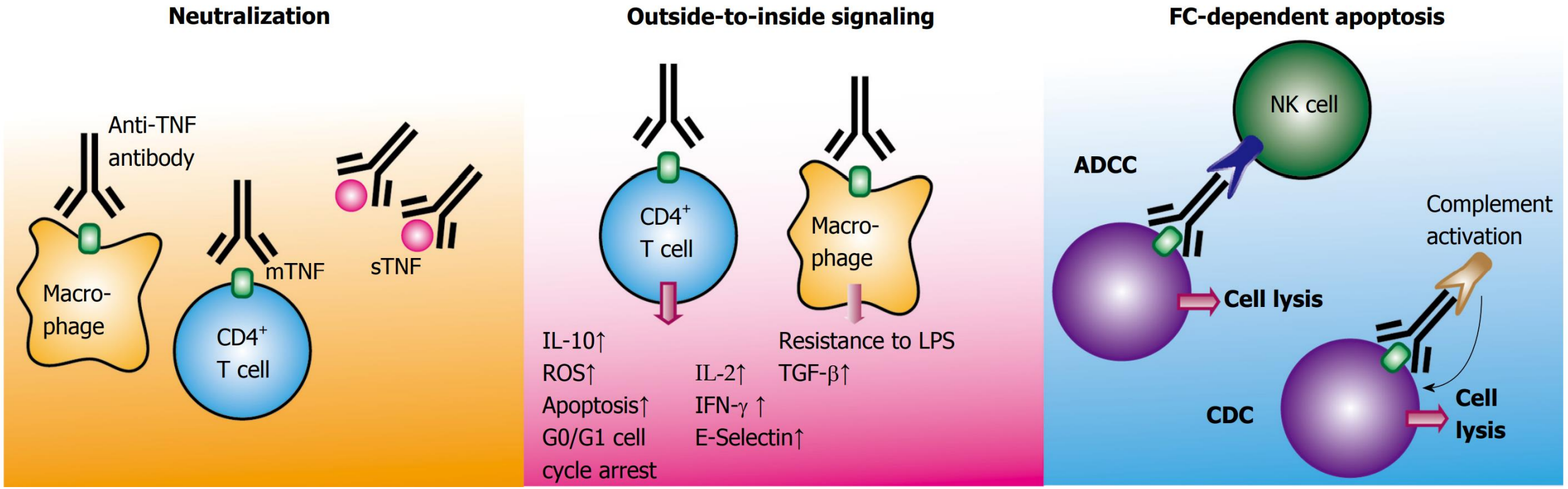
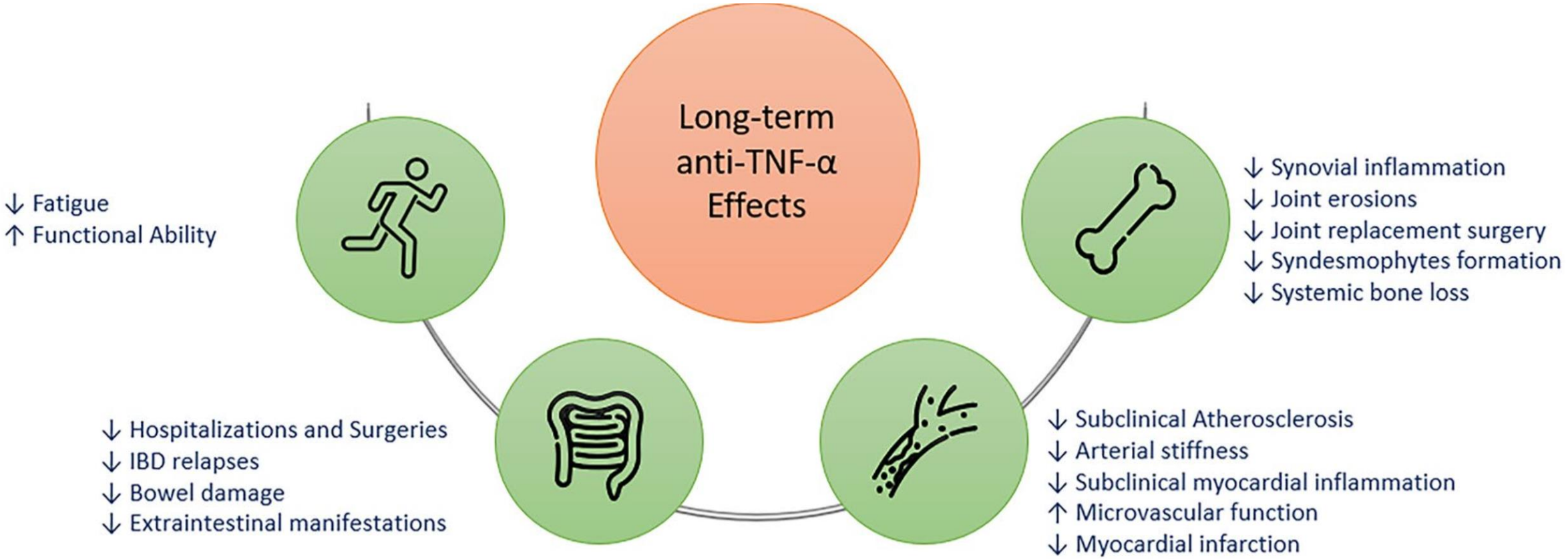


Table 1 anti-TNF-α indications by chronological order of first approval (either by Food and Drug Administration-FDA or European Medicines Agency-EMA)

Indication	Drug, year of first approval
Rheumatoid Arthritis	Etanercept, 1998 Infliximab, 1999 Adalimumab, 2002certolizumab pegol, 2009 Golimumab, 2009
Crohn's Disease	Infliximab, 1998Adalimumab, 2007Certolizumab pegol, 2008
Juvenile Idiopathic Arthritis	Etanercept, 1999 Adalimumab, 2008 Golimumab, 2016
Psoriatic Arthritis	Etanercept, 2002 Infliximab, 2004 Adalimumab, 2005 Golimumab, 2009 Certolizumab pegol, 2013
Axial Spondyloarthritis	Infliximab, 2003Eanercept, 2003Adalimumab, 2006Golimumab, 2009Certolizumab pegol, 2013
Plaque Psoriasis	Etanercept, 2004 Infliximab, 2005 Adalimumab, 2007 Certolizumab pegol, 2018
Ulcerative Colitis	Infliximab, 2005Adalimumab, 2012 Golimumab, 2013
Paediatric Crohn's Disease	Infliximab, 2006 Adalimumab, 2012
Paediatric Plaque Psoriasis	Etanercept, 2008Adalimumab, 2015
Paediatric Ulcerative Colitis	Infliximab, 2011Adalimumab, 2020
Non-radiographic Axial Spondyloarthritis	Adalimumab, 2012Certolizumab pegol, 2013Etanercept, 2014Glimumab, 2015
Paediatric Enthesitis-Related Arthritis	Adalimumab, 2014
Hidradenitis Suppurativa	Adalimumab, 2015
Adolescent Hidradenitis Suppurativa	Adalimumab, 2016
Non-infectious Uveitis	Adalimumab, 2016
Paediatric non-infectious Uveitis	Adalimumab, 2017

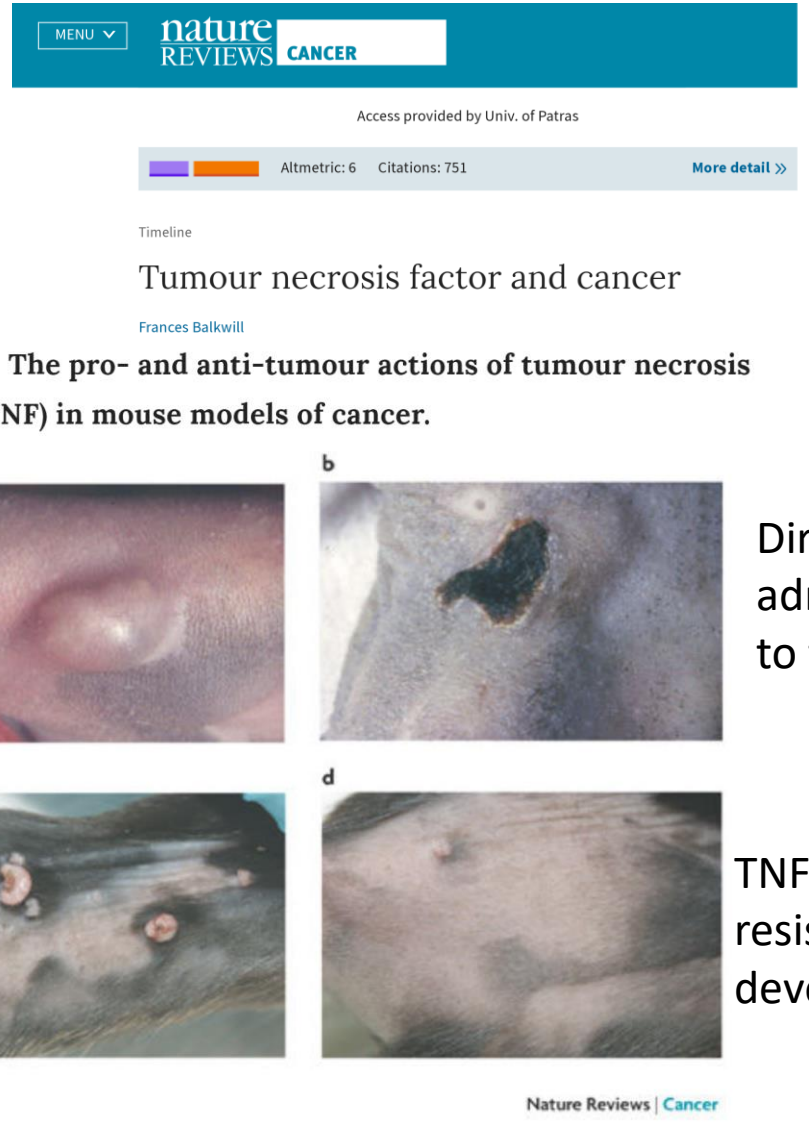
- Ενδείξεις για πολλά φλεγμονωδη νοσηματα που έχουν να κανουν με
  - Αρθρωσεις
  - Έντερο
  - Δερμα
  - Οφθαλμους

Τι έχουμε επιτύχει με τα αντι-TNF?



TNF και καρκίνος...

- In vitro ο TNF καταστρέφει καρκινικά κύτταρα
- In vivo όμως τα πράγματα είναι πιο περίπλοκα....



Direct TNF administration to tumor

TNF-/- mice resistant to tumor development

CONCISE REPORT

Incidences of overall and site specific cancers in TNFα inhibitor treated patients with rheumatoid arthritis and other arthritides – a follow-up study from the DANBIO Registry

Lene Dreyer,[1] Lene Mellemkjær,[2] Anne Rødgaard Andersen,[3] Philip Bennett,[4] Uta Engling Poulsen,[5] Torkell Juulsgaard Ellingsen,[6] Torben Høiland Hansen,[7] Dorte Vendelbo Jensen,[8] Louise Linde,[3] Hanne Merete Lindegaard,[9] Anne Gitte Rasmussen Loft,[10] Henrik Nordin,[11] Emina Omerovic,[12] Claus Rasmussen,[13] Annette Schlemmer,[14] Ulrik Tarp,[15] Merete Lund Hetland[3 16]

- **Επιβεβαιώθηκε η ασφάλεια των αντι-TNF**

Δεδομένα από αρχεία...

Variable	No of cancers among treated†	TNF-I treated versus non-treated HR‡ (95% CI)	p Value*
Ever TNF-I treatment			
Overall effect	152	1.02 (0.80 to 1.30)	
Plus adjustment for HAQ§		0.95 (0.74 to 1.22)	
Plus adjustment for CRP§		0.99 (0.77 to 1.26)	
Plus adjustment for DAS28§		0.96 (0.74 to 1.24)	
Men	48	0.83 (0.55 to 1.26)	p=0.24
Women	104	1.13 (0.83 to 1.53)	
Time since treatment initiation, years			
<1	41	1.04 (0.72 to 1.50)	
1–4	97	1.03 (0.79 to 1.35)	p=0.86
5+	14	0.88 (0.51 to 1.54)	
1+	111	1.01 (0.78 to 1.30)	
Cumulative duration of treatment, years			
<1	43	1.04 (0.73 to 1.48)	
1–2	39	1.19 (0.83 to 1.71)	p=0.69
2–3	29	1.09 (0.72 to 1.63)	
4+	41	0.86 (0.60 to 1.22)	
Age at treatment start, years			
<50	12	0.83 (0.38 to 1.82)	
50–64	69	0.97 (0.68 to 1.37)	p=0.76
≥65	71	1.10 (0.80 to 1.50)	

RHEUMATOLOGY

Rheumatology 2020;59:930–939
doi:10.1093/rheumatology/kez475
Advance Access publication 17 October 2019

Systematic Review and Meta-analysis

A meta-analysis of biologic therapies on risk of new or recurrent cancer in patients with rheumatoid arthritis and a prior malignancy

FIG. 2 Relative risk of cancer recurrence between biologic and csDMARDs

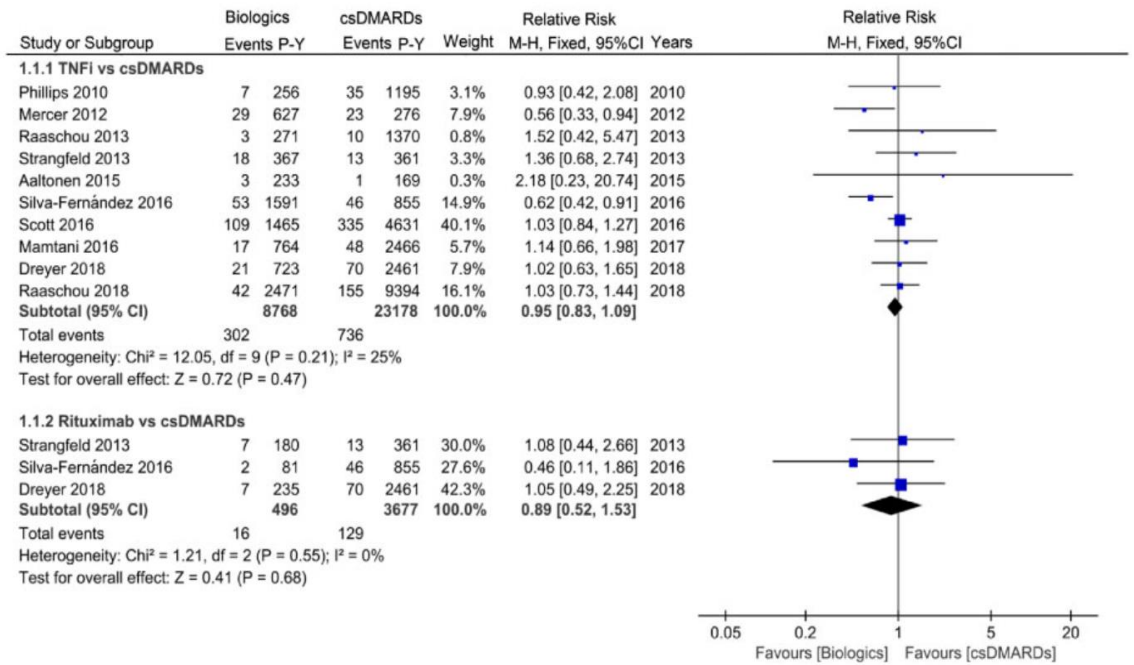
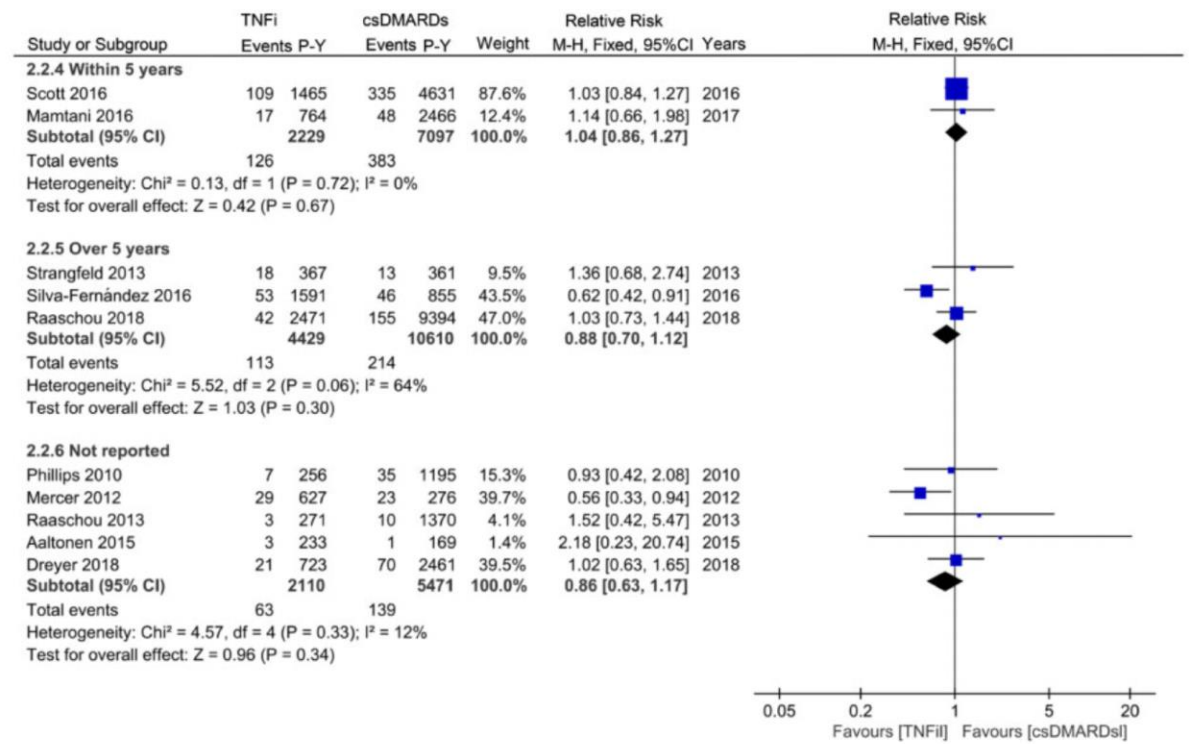


FIG. 4 Relative risk of cancer recurrence between TNFi and csDMARDs, stratified by intervals between prior cancer and TNFi (re-)initiation



Πιθανά μειώνουν τον καρδιαγγειακό κίνδυνο

EXTENDED REPORT

Relationship between exposure to tumour necrosis factor inhibitor therapy and incidence and severity of myocardial infarction in patients with rheumatoid arthritis

Audrey S L Low,[1] Deborah P M Symmons,[1,2] Mark Lunt,[1] Louise K Mercer,[1] Chris P Gale,[3,4] Kath D Watson,[1] William G Dixon,[1] Kimme L Hyrich,[1] on behalf of the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) and the BSRBR Control Centre Consortium

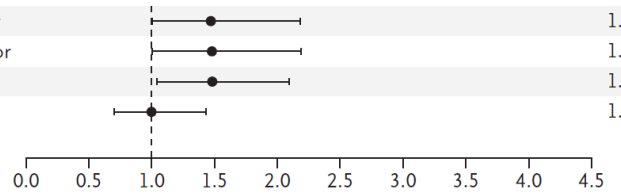
Table 2 Risk of MI compared between sDMARD and TNFi cohorts

	sDMARD; n=3058	TNFi; n=11 200
Median duration of follow-up per patient, years (IQR)	3.5 (1.8, 4.9)	5.3 (3.6, 6.4)
Total person-years of exposure, pyrs	10 337	55 636
Primary drug exposure model: on-TNFi+90 days		
Number of verified first MIs	58	194
Crude incidence rate of verified first MI per 10 000 pyrs (95% CI)	56 (43 to 73)	35 (30 to 40)
Unadjusted HR (95% CI)	Referent	0.78 (0.58 to 1.05)
HR adjusted for age and gender (95% CI)		1.19 (0.89 to 1.59)
HR after adjusting for PD* (95% CI)		0.61 (0.41 to 0.89)
Sensitivity analyses		
In subjects ever exposed to TNFi; PD-adjusted HR (95% CI)		0.67 (0.46 to 0.96)
Trimming the PD at 5%; PD-adjusted HR (95% CI)		0.56 (0.34 to 0.93)

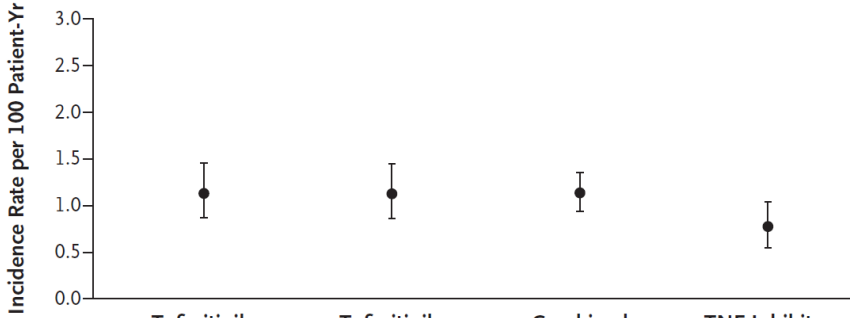
*Deciles of propensity score (PD). The PD included age, gender, DAS28, disease duration, health assessment questionnaire score, whether the patients used four or more sDMARDs prior to study registration (yes/no), whether the patients were recruited to the register before or after 30 June 2004, hypertension, diabetes, chronic lung disease, smoking (ever/never), antiplatelet therapy, NSAID/COX-2 inhibitor use, glucocorticoid use and statin use.

Μικρότερος καρδιαγγειακός κίνδυνος σε σχέση με Jakinibs σε ασθενείς υψηλού κινδύνου

A Hazard Ratio for Cancers, Excluding NMSC



B Incidence Rate for Cancers, Excluding NMSC



No. of Patients with First Event/Total No. (%)	62/1455 (4.3)	60/1456 (4.1)	122/2911 (4.2)	42/1451 (2.9)
No. of Patient-Yr	5491.48	5311.71	10,803.19	5482.30
Incidence Rate per 100 Patient-Yr (95% CI)	1.13 (0.87–1.45)	1.13 (0.86–1.45)	1.13 (0.94–1.35)	0.77 (0.55–1.04)
NNH (patient-yr) vs. TNF Inhibitor	276	275	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	55	55	—	—

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

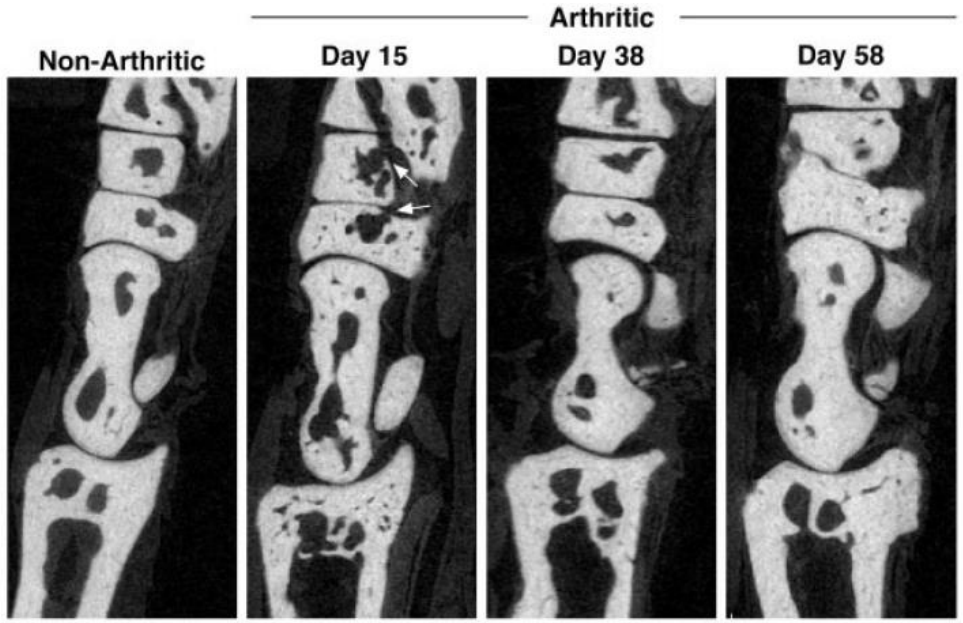
Δεδομένη η αναστολή ακτινολογικής εξέλιξης με αντι-TNF στην PA
Σε ΣΠΑ???

- Φλεγμονή
- Ύφεση φλεγμονής
- Παραγωγή νέου οστού

ARTHRITIS & RHEUMATISM
Vol. 64, No. 5, May 2012, pp 1540–1550
DOI 10.1002/art.33504

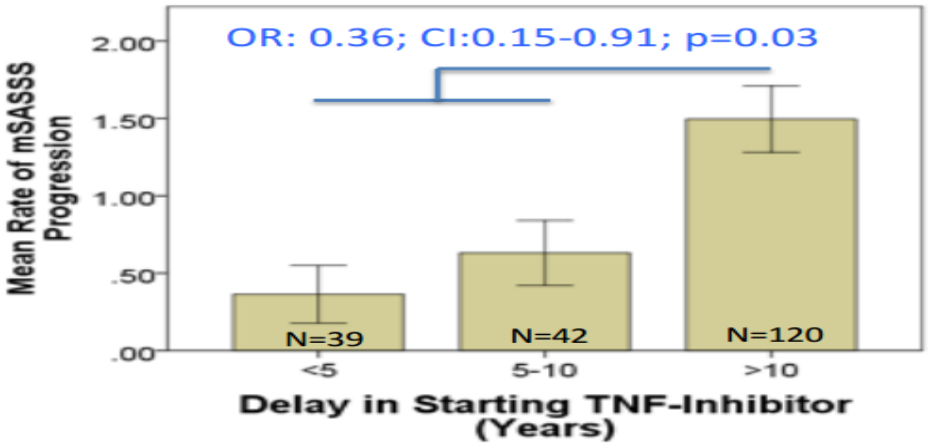
Resolution of Inflammation Induces Osteoblast Function and Regulates the Wnt Signaling Pathway

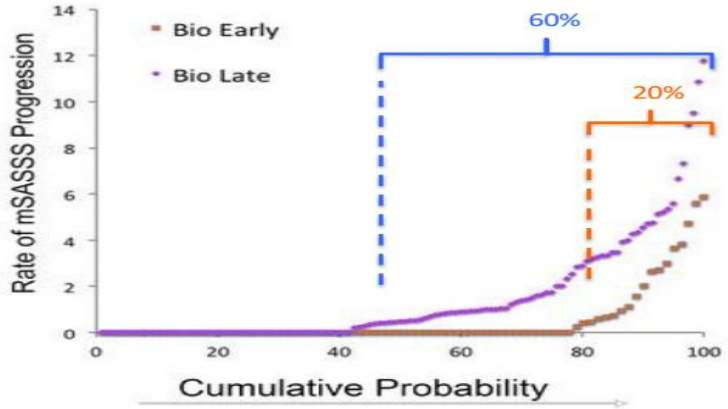
Melissa M. Matzelle,[1] Maxime A. Gallant,[2] Keith W. Condon,[2] Nicole C. Walsh,[3] Catherine A. Manning,[1] Gary S. Stein,[1] Jane B. Lian,[1] David B. Burr,[2] and Ellen M. Gravallese[1]



The Impact of TNF-inhibitors on radiographic progression in Ankylosing Spondylitis

Nigil Haroon, MD[1], Robert D. Inman, MD[1], Thomas J. Learch, MD[2], Michael H. Weisman, MD[2], MinJae Lee[3], Mohammad H. Rahbar[3], Michael M. Ward, MD[4], John D Reveille, MD[5], and Lianne S. Gensler, MD[6]

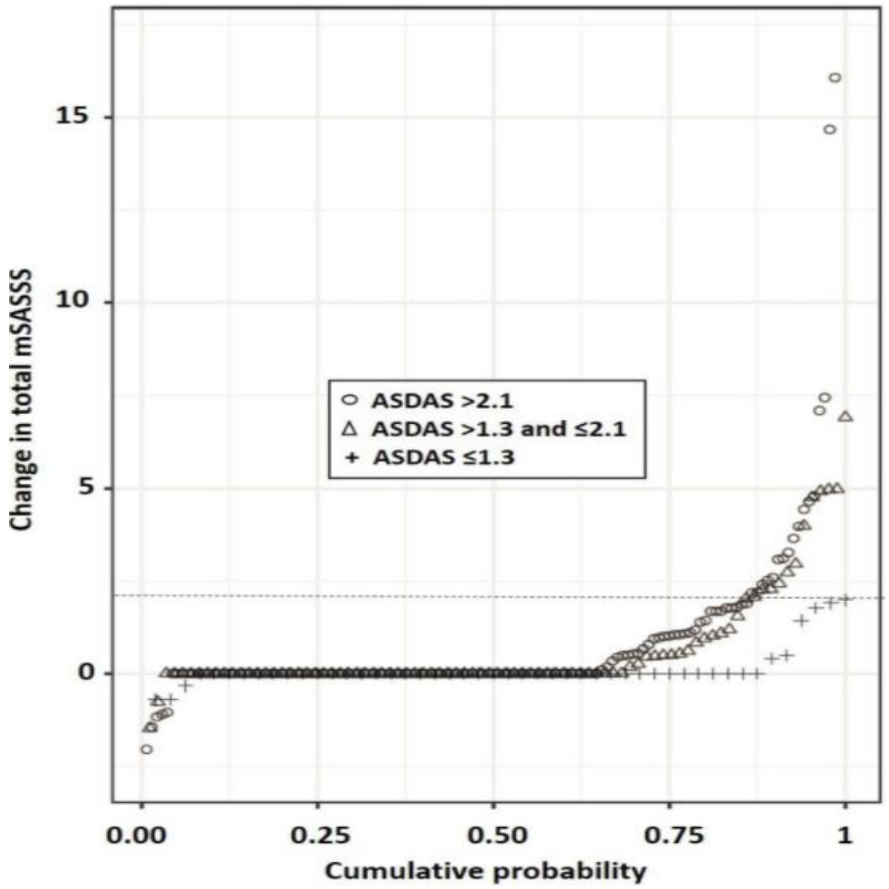




Arthritis Rheum 2013 Oct;65(10):2645-54. doi: 10.1002/art.38070.

TNF blockers inhibit spinal radiographic progression in ankylosing spondylitis by reducing disease activity: results from the Swiss Clinical Quality Management cohort

Christoph Molnar [1], Almut Scherer [1], Xenofon Baraliakos [2], Manouk de Hooge [3], Raphael Micheroli [4], Pascale Exer [5], Rudolf O Kissling [6], Giorgio Tamborrini [7], Lukas M Wildi [4], Michael J Nissen [8], Pascal Zufferey [9], Jürg Bernhard [10], Ulrich Weber [11] [12], Robert B M Landewé [13] [14], Désirée van der Heijde [3], Adrian Ciurea [4], Rheumatologists of the Swiss Clinical Quality Management Program



Ann Rheum Dis 2018;77:63-69

Πιθανά κεντρικότερος ο ρόλος στην θεραπευτική ΣΠΑ σε σχέση με ΡΑ

Anti-TNF

Psoriasis ✓
PsA-Peripheral SpA ✓
IBD ✓
AS, Axial SpA ✓
Uveitis ✓

Anti-IL-17

Psoriasis ✓
PsA-Peripheral SpA ✓
IBD ✗
AS, Axial SpA ✓
Uveitis ✗

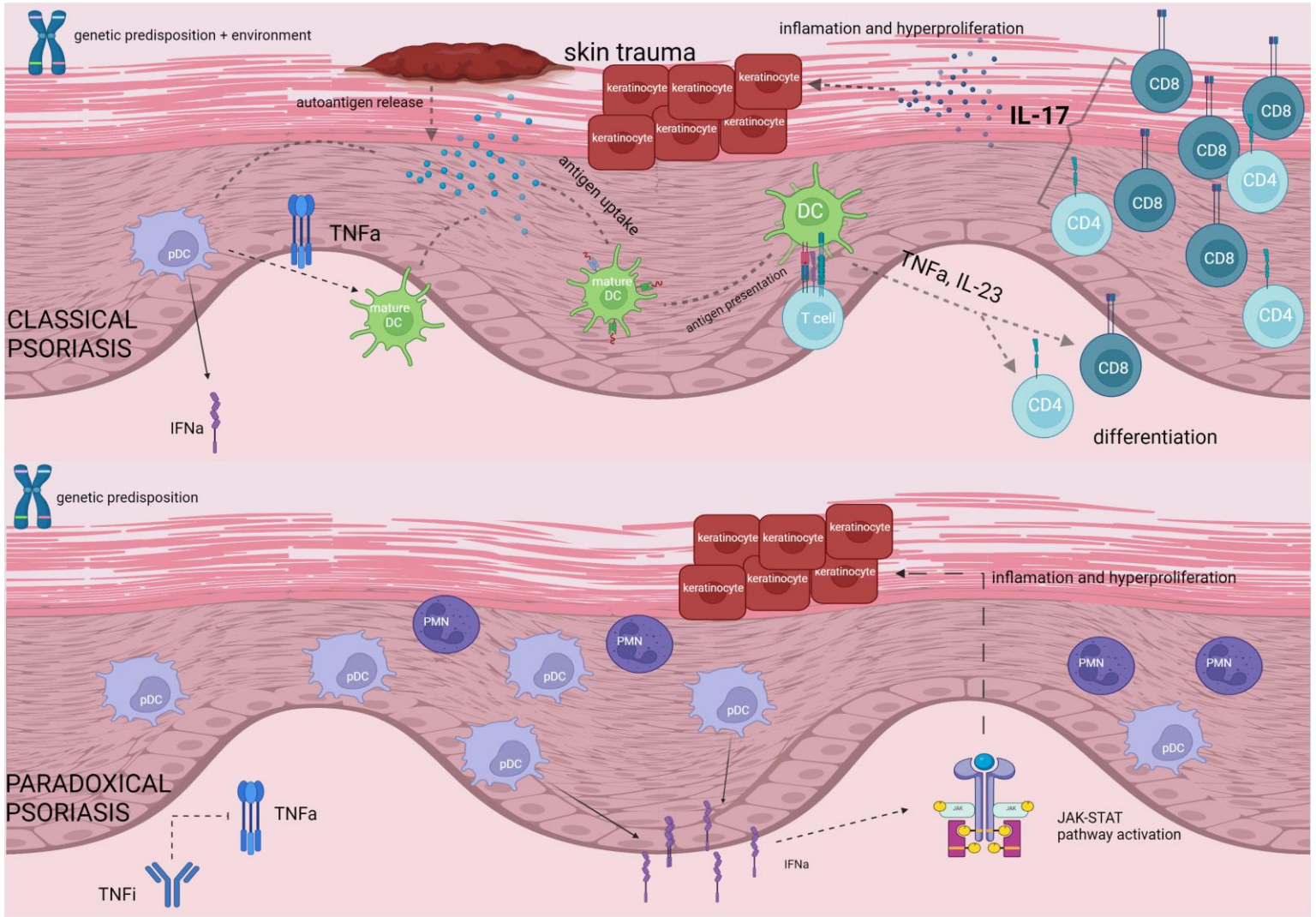
Anti-IL-12/23

Psoriasis ✓
PsA-Peripheral SpA ✓
IBD ✓
AS, Axial SpA ✗
Uveitis ✗

Ασφάλεια

- Λοιμώξεις (όπως σε όλα τα βιολογικά…). **Ευκαιριακές λοιμωξεις**
- Δεν έχει προκύψει κατι καινούργιο

Παράδοξη ψωρίαση..



Ασφαλή στην κύηση

Recommendation

The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation

	*Points to consider for use of antirheumatic drugs in pregnancy**	Grade of recommend
1	csDMARDs‡ proven compatible with pregnancy are hydroxychloroquine, chloroquine, sulfasalazine, azathioprine, ciclosporin, tacrolimus and colchicine. They should be continued in pregnancy for maintenance of remission or treatment of a disease flare.	B
2	csDMARDs‡ methotrexate, mycophenolate mofetil and cyclophosphamide are teratogenic and should be withdrawn before pregnancy.	B
3	Non-selective COX inhibitors (non-steroidal anti-inflammatory drugs, NSAIDs) and prednisone should be considered for use in pregnancy if needed to control active disease symptoms. NSAIDs should be restricted to the first and second trimesters.	B
4	In severe, refractory maternal disease during pregnancy methylprednisolone pulses, intravenous immunoglobulin or even second or third trimester use of cyclophosphamide should be considered.	D
5	csDMARDs‡, tsDMARDs§ and anti-inflammatory drugs with insufficient documentation concerning use in pregnancy should be avoided until further evidence is available. This applies to leflunomide, mepacrine, tofacitinib and selective COX II inhibitors.	B–D
6	Among bDMARDs¶ continuation of tumour necrosis factor (TNF) inhibitors during the first part of pregnancy should be considered. Etanercept and certolizumab may be considered for use throughout pregnancy due to low rate of transplacental passage.	B
7	bDMARDs¶ rituximab, anakinra, tocilizumab, abatacept, belimumab and ustekinumab have limited documentation on safe use in pregnancy and should be replaced before conception by other medication. They should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease.	D

Epidemiology

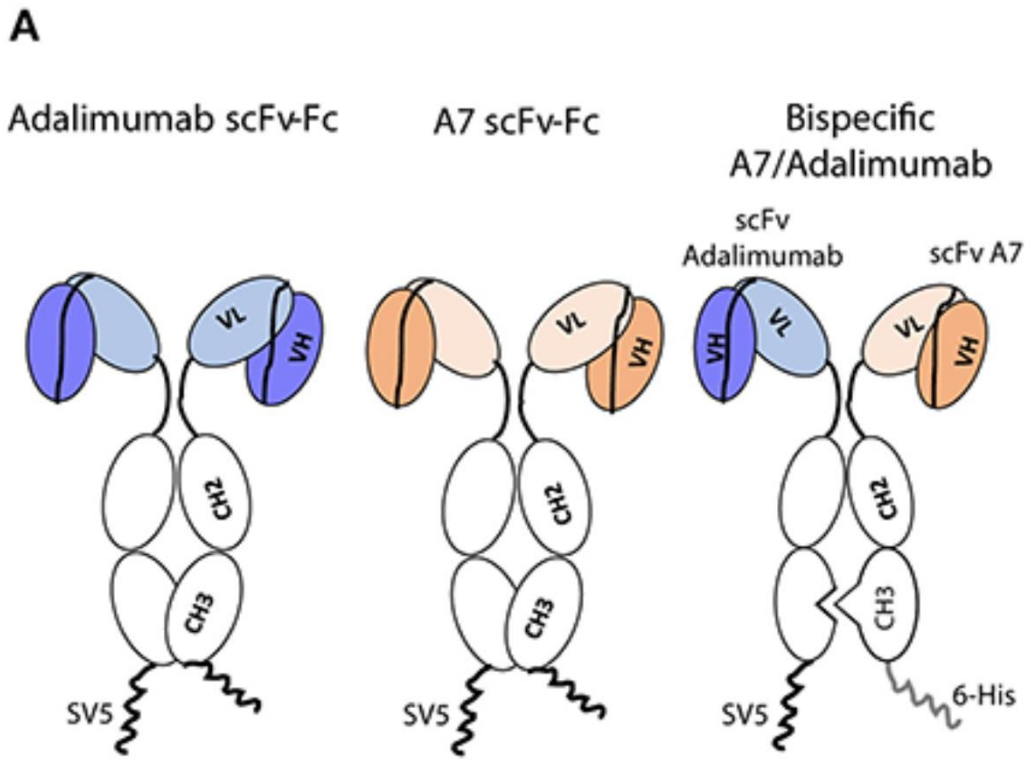
Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry FREE

- Δεν προέκυψε πρόβλημα στην πανδημία
- Δεν αυξάνουν τον κίνδυνο σοβαρής νόσου

1.06). Tumour necrosis factor inhibitor (anti-TNF) use was associated with a reduced odds of hospitalisation (OR 0.40, 95% CI 0.19 to 0.81), while no association

Novel Bispecific Antibody for Synovial-Specific Target Delivery of Anti-TNF Therapy in Rheumatoid Arthritis

Mathieu Ferrari[1], Shimobi C. Onuoha[1], Liliane Fossati-Jimack[1], Alessandra Nerviani[1], Pedro L. Alves[1], Sara Pagani[1], Cecilia Deantonio[2], Federico Colombo[1], Claudio Santoro[2], Daniele Sblattero[3] and Costantino Pitzalis[1*]



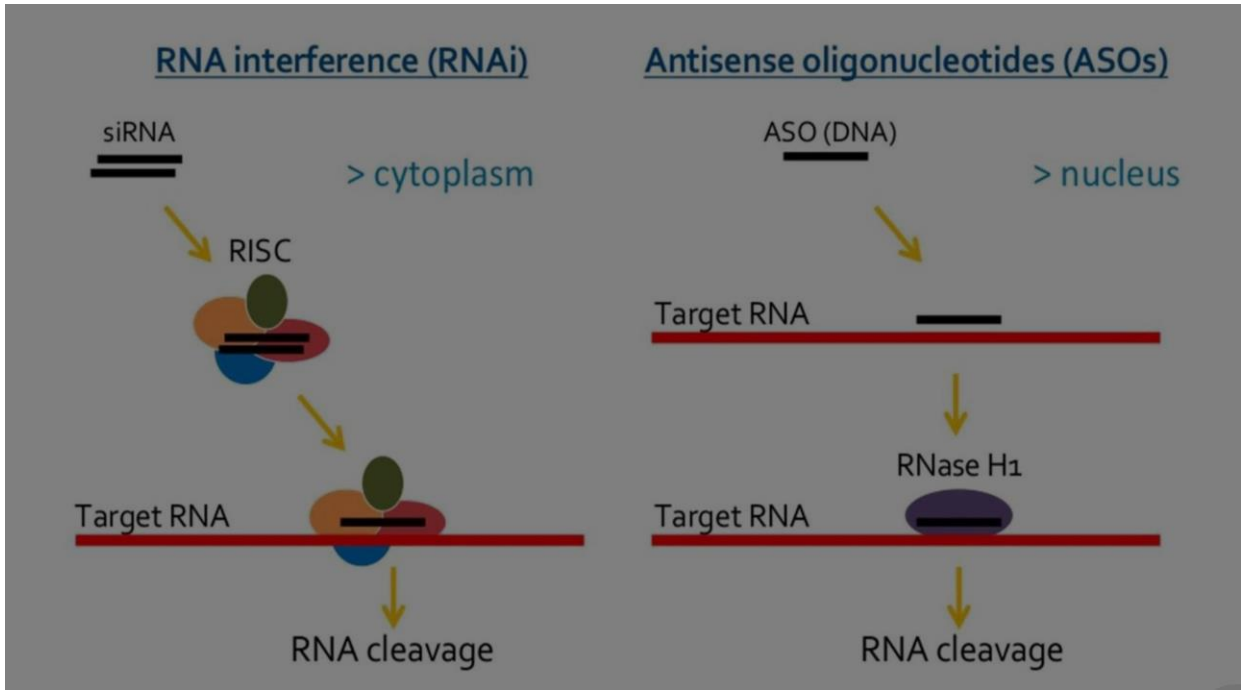
- Στοχευμένη χορήγηση σε ιστούς ενδιαφέροντος?

Open Access Review

Review: Local Tumor Necrosis Factor-α Inhibition in Inflammatory Bowel Disease

by Bahez Gareb [1,2,3,*], Antonius T. Otten [4], Henderik W. Frijlink [2], Gerard Dijkstra [4] and Jos G. W. Kosterink [1,5]

- Ο TNF μπορεί να στοχευθεί με πολλούς τρόπους πέρα από αντισώματα
- Στόχευση της παραγωγής του TNF?



Αντι-TNF μαζί με άλλο βιολογικό?

- Οι συνδυασμοί αντι-TNF με abatacept ή anakinra σε PA

- Αύξηση παρενεργειων χωρις αυξηση αποτελεσματικότητας

- Διπλή αναστολή TNF-IL17
- Ενδείξεις ενισχυμένης αποτελεσματικότητας

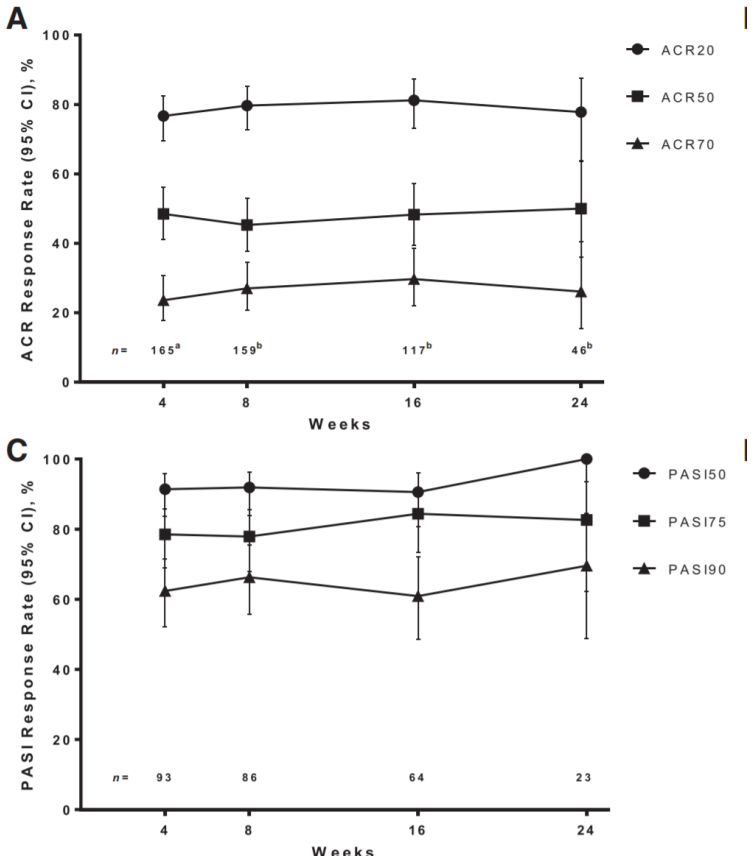
RHEUMATOLOGY
Rheumatology 2018;57:1972–1981
doi:10.1093/rheumatology/key173
Advance Access publication 18 July 2018

Original article

Dual inhibition of tumour necrosis factor and interleukin-17A with ABT-122: open-label long-term extension studies in rheumatoid arthritis or psoriatic arthritis

Mark C. Genovese[1], Michael E. Weinblatt[2], Philip J. Mease[3], Jacob A. Aelion[4,5], Paul M. Peloso[6], Kun Chen[7], Yihan Li[7], John Liu[8], Ahmed A. Othman[9], Amit Khatri[9], Heikki T. Mansikka[6] and Piotr Leszczyński[10]

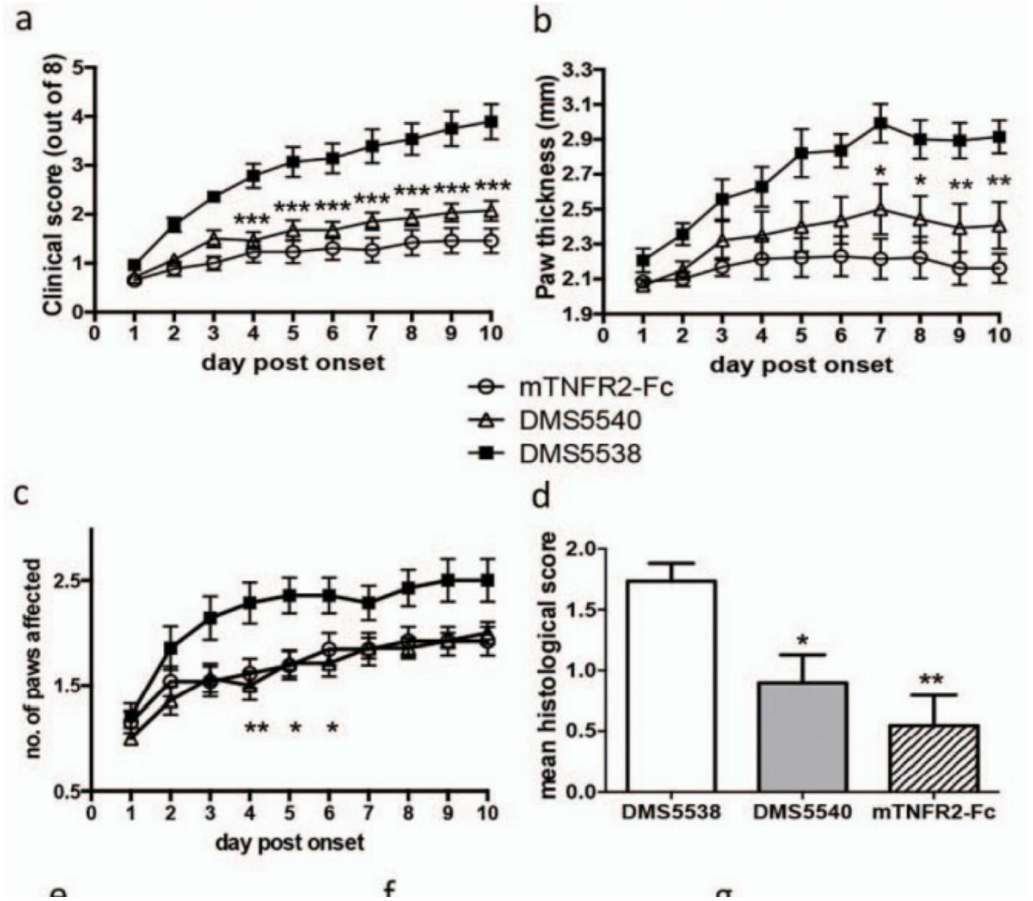
FIG. 3 Efficacy in the PsA OLE study

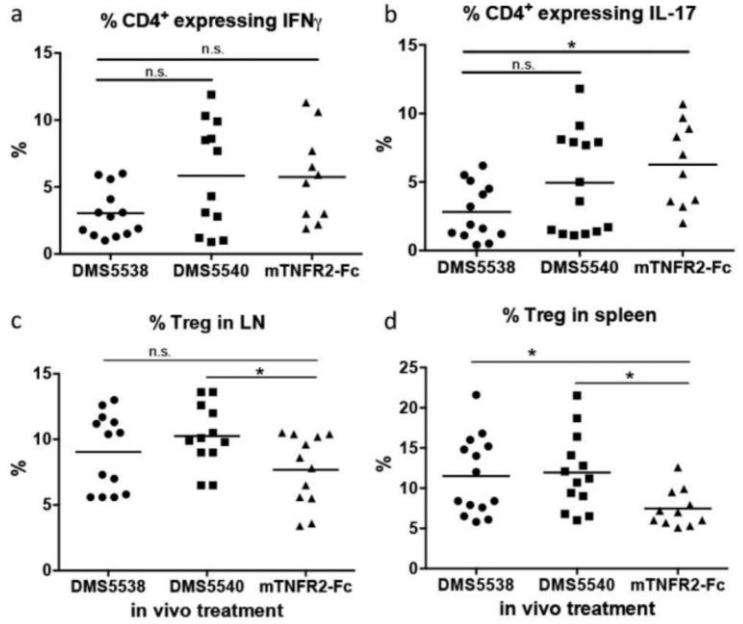


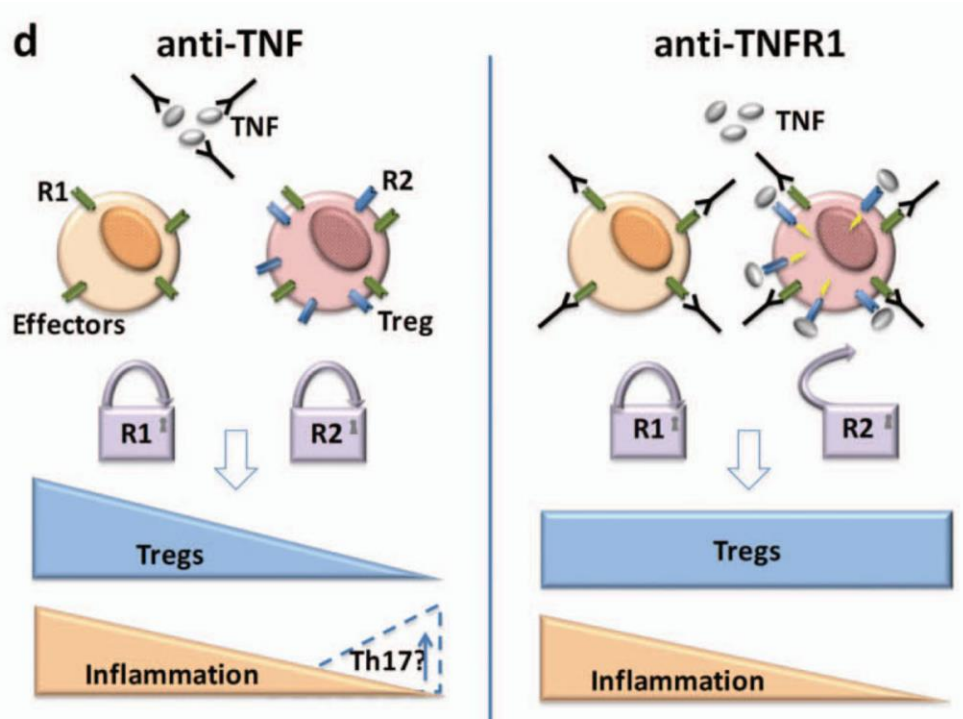
Email: jimdaoussis@hotmail.com

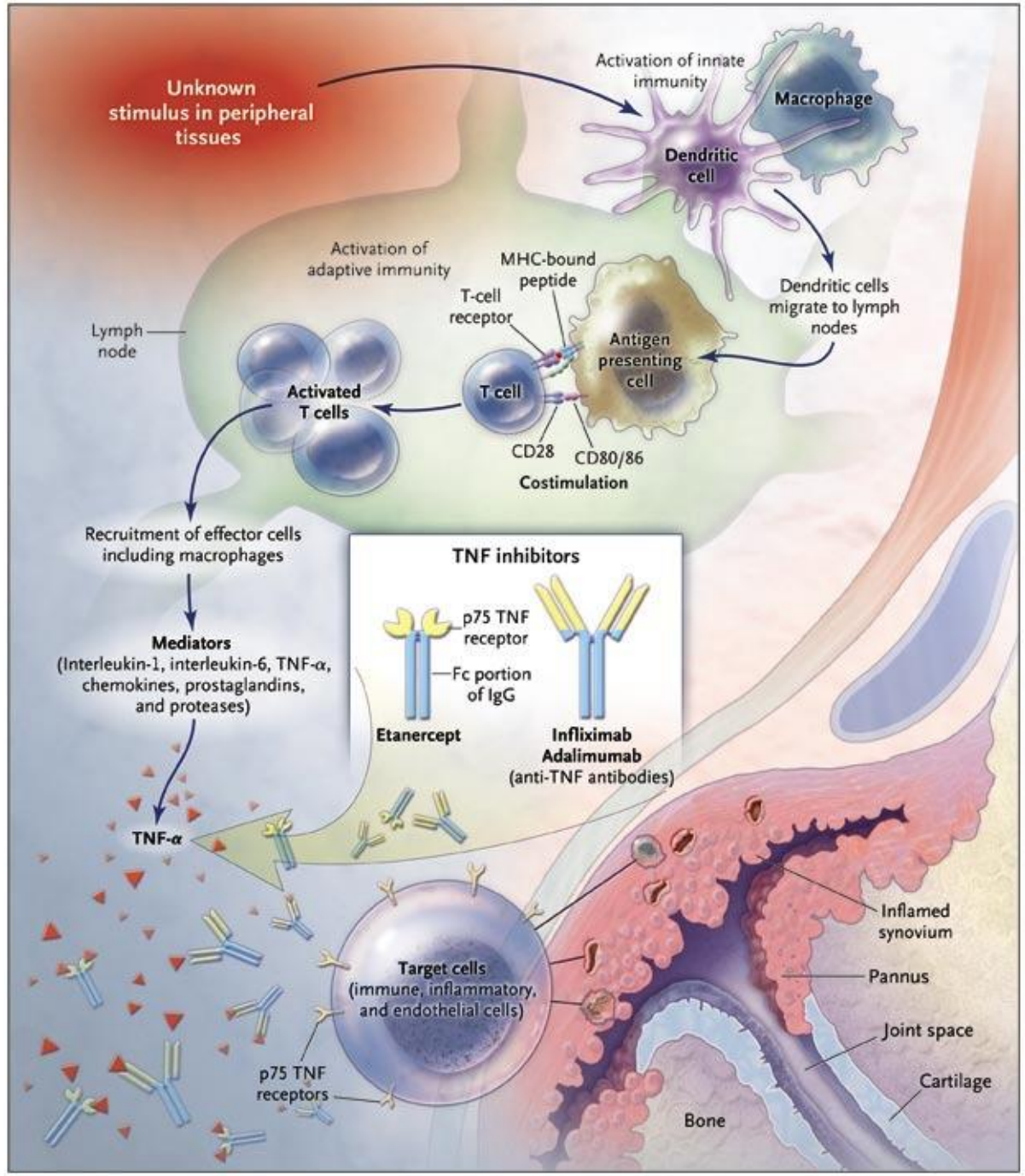
Selective Tumor Necrosis Factor Receptor I Blockade Is Antiinflammatory and Reveals Immunoregulatory Role of Tumor Necrosis Factor Receptor II in Collagen-Induced Arthritis

Fiona E. McCann,[1] Dany P. Perocheau,[1] Gerhard Ruspi,[1] Katrina Blazek,[1] Marie L. Davies,[2] Marc Feldmann,[1] Jonathan L. E. Dean,[1] A. Allart Stoop,[2] and Richard O. Williams[1]








Unknown stimulus in peripheral tissues
Activation of innate immunity
Macrophage
Dendritic cell
Dendritic cells migrate to lymph nodes
Activation of adaptive immunity
MHC-bound peptide
T-cell receptor
Antigen presenting cell
Lymph node
Activated T cells
T cell
CD28
CD80/86
Costimulation
Recruitment of effector cells including macrophages
Mediators
(Interleukin-1, interleukin-6, TNF-α, chemokines, prostaglandins, and proteases)
TNF-α
TNF inhibitors
p75 TNF receptor
Fc portion of IgG
Etanercept
Infliximab
Adalimumab
(anti-TNF antibodies)
Target cells
(immune, inflammatory, and endothelial cells)
p75 TNF receptors
Inflamed synovium
Pannus
Joint space
Cartilage
Bone

RHEUMATOLOGY

Rheumatology 2018;57:vii5–vii10
doi:10.1093/rheumatology/key059

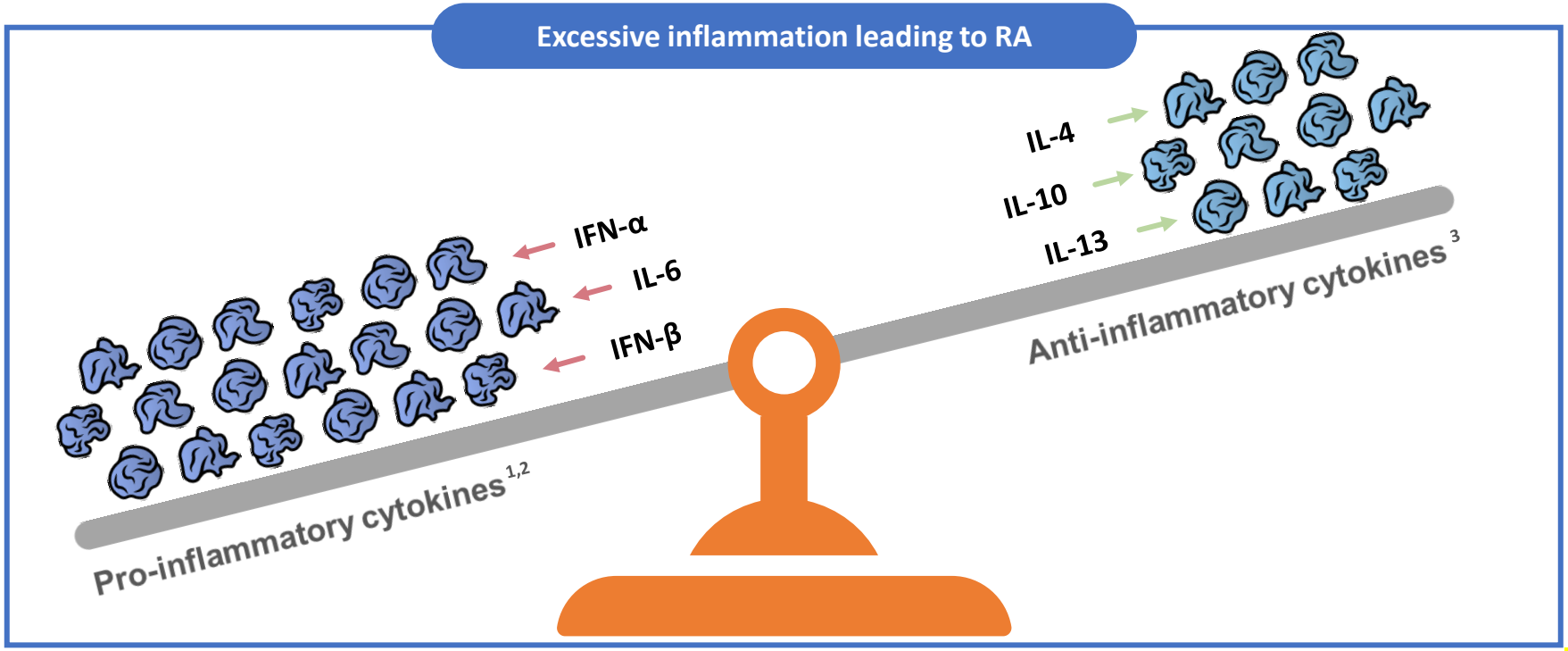
20 years of experience with tumour necrosis factor inhibitors: what have we learned?

Roberto Caporali[1], Gloria Crepaldi[2], Veronica Codullo[1], Francesca Benaglio[1], Sara Monti[1], Monica Todoerti[1] and Carlomaurizio Montecucco[1]

TABLE 1 Currently available TNFis for RA

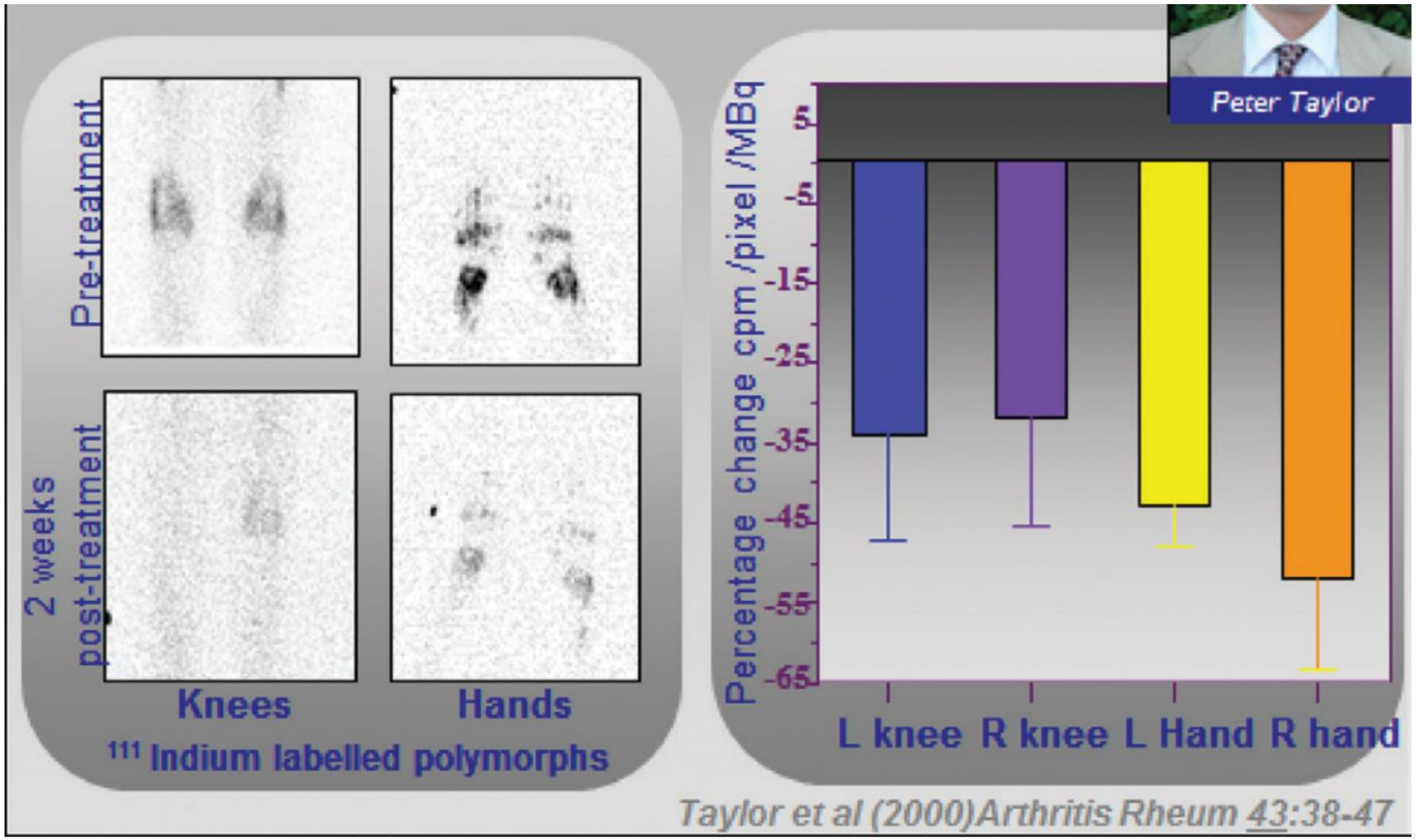
TNF inhibitor	Molecule type	Year of release	Half-life, days	Route of administration	Monotherapy approval
Adalimumab (ADA)	Human mAb IgG1	2003	14	Subcutaneous	Yes
Certolizumab pegol (CZP)	Humanized Fab fragment conjugated to a polyethylene glycol	2009	14	Subcutaneous	Yes
Etanercept (ETN)	Fusion protein of TNF receptor 2 and IgG1 Fc component	2000	4–6	Subcutaneous	Yes
Golimumab (GLM)	Human mAb IgG1	2009	14	Subcutaneous	No
Infliximab (IFX)	Chimeric mAb IgG1	1999	8–10	Intravenous	No

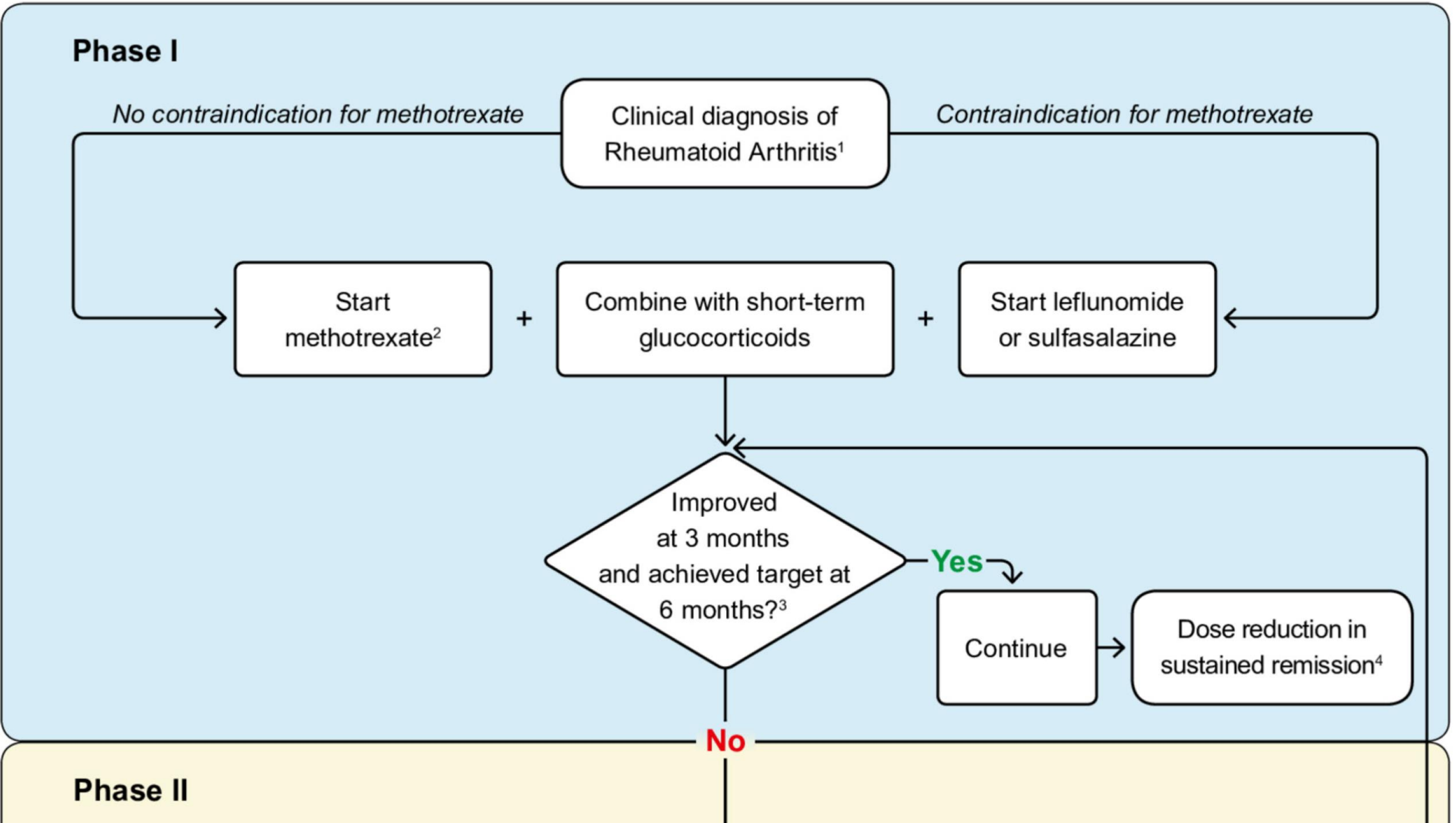
Elevated levels of pro-inflammatory cytokines mediate inflammatory conditions essential to RA[1,a]

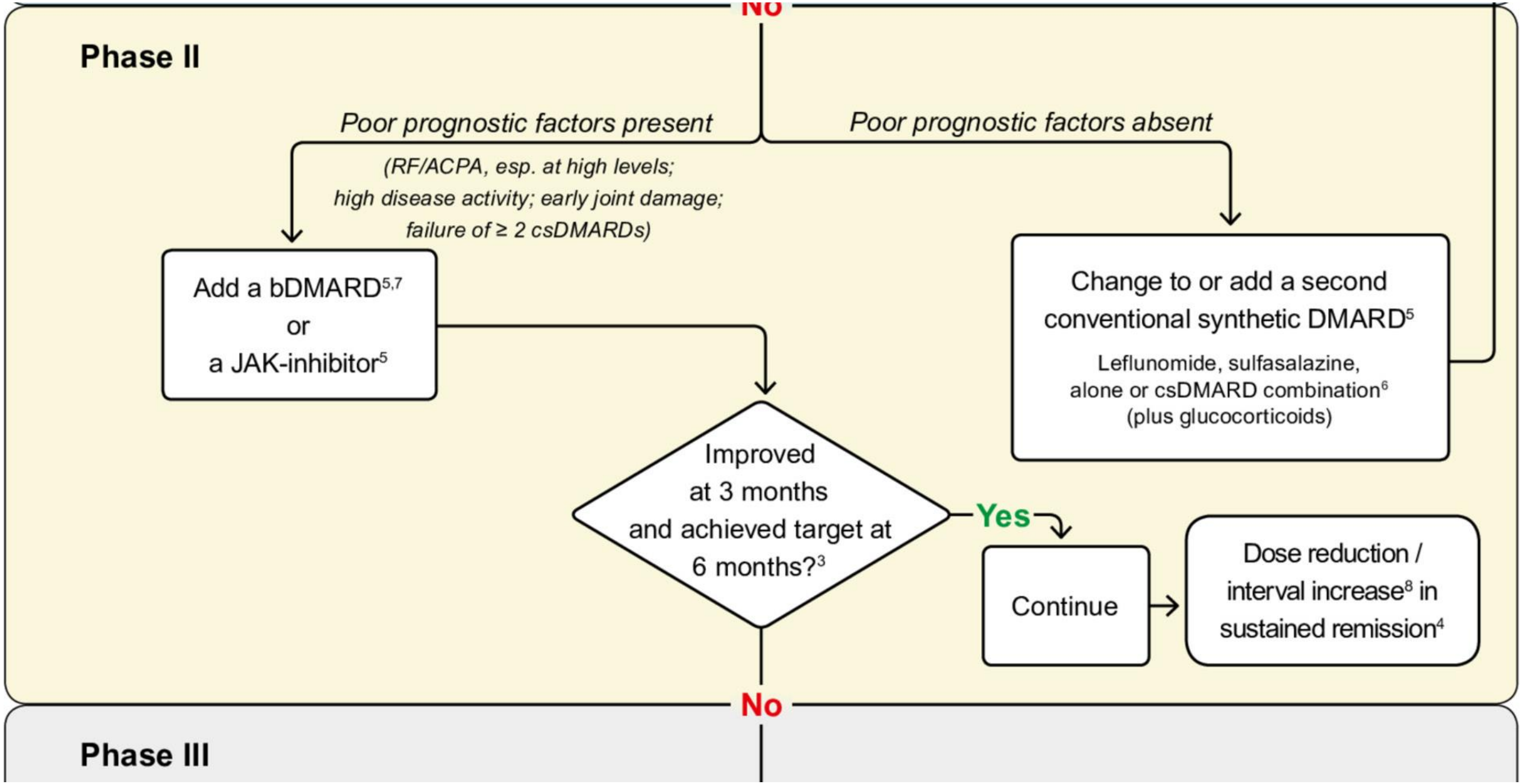


- [a] **Please note, cytokines listed here are examples and do not provide an exhaustive list**

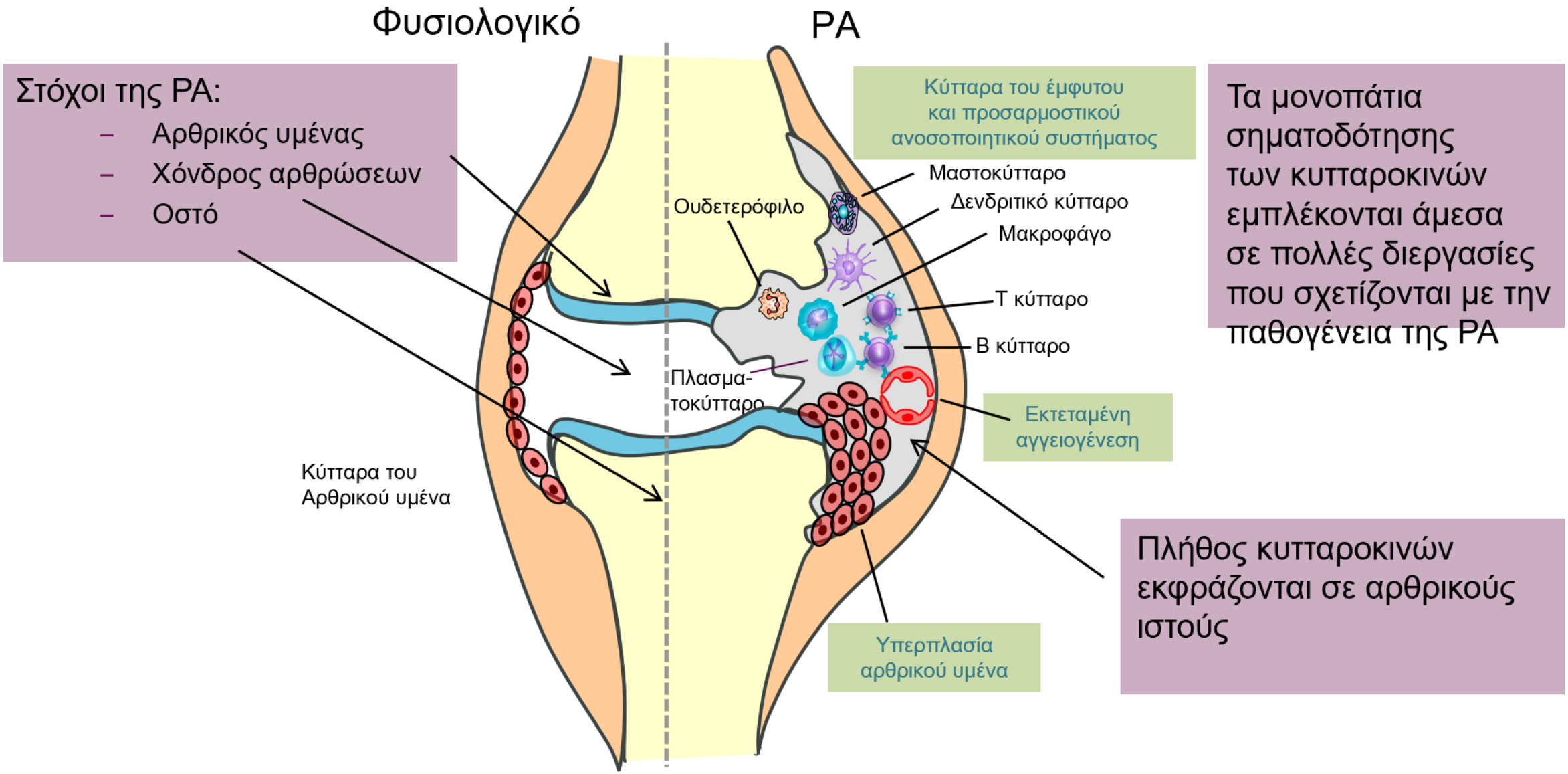
1. Malemud CJ. *Ther Adv Musculoskel Dis* 2018; 10:117–127. 2. Castañeda-Delgado JE, *et al. Front. Immunol* 2017; 8:285
- 3. Cytokines in Rheumatoid Arthritis (RA). Nalbant S, Birlik AM. Available at: www.intechopen.com/books/new-developments-in-the-pathogenesis-of-rheumatoid-arthritis/cytokines-in-rheumatoid-arthritis-ra- (accessed February 2020).


Pre-treatment
2 weeks post-treatment
Knees
Hands
111 Indium labelled polymorphs
Peter Taylor
Percentage change cpm /pixel /MBq
5
-5
-15
-25
-35
-45
-55
-65
L knee
R knee
L Hand
R hand
Taylor et al (2000)Arthritis Rheum 43:38-47


Phase I
No contraindication for methotrexate
Clinical diagnosis of Rheumatoid Arthritis[1]
Contraindication for methotrexate
Start methotrexate[2]
+
Combine with short-term glucocorticoids
+
Start leflunomide or sulfasalazine
Improved at 3 months and achieved target at 6 months?[3]
Yes
Continue
Dose reduction in sustained remission[4]
No
Phase II


No
Phase II
Poor prognostic factors present
(RF/ACPA, esp. at high levels;
high disease activity; early joint damage;
failure of ≥ 2 csDMARDs)
Poor prognostic factors absent
Add a bDMARD[5,7]
or
a JAK-inhibitor[5]
Change to or add a second
conventional synthetic DMARD[5]
Leflunomide, sulfasalazine,
alone or csDMARD combination[6]
(plus glucocorticoids)
Improved
at 3 months
and achieved target at
6 months?[3]
Yes
Continue
Dose reduction /
interval increase[8] in
sustained remission[4]
No
Phase III

- Η ΡΑ είναι μία συστηματική αυτοάνοση χρόνια φλεγμονώδης νόσος
  - Εκδηλώνεται κυρίως στις αρθρώσεις

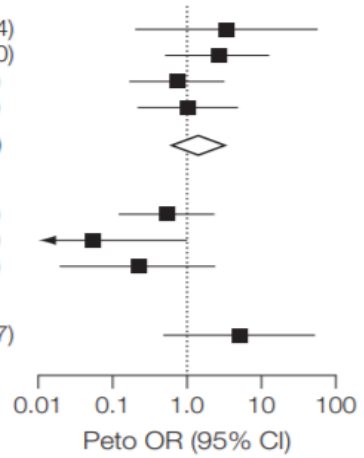


ΡΑ, ρευματοειδής αρθρίτιδα.

1. McInnes IB, et al. *Nat Rev Immunol* 2007;7:429–444. Figure adapted from Strand V, et al. *Nat Rev Drug Disc* 2007;6:75–92.

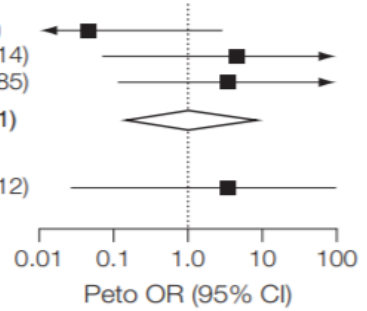
Skin cancer, nonmelanoma[a]

BRMs	No. of Studies	Peto OR (95% CI)	*P* Value
TNF inhibitors			
Certolizumab[53]	1	3.52 (0.21-58.74)	.38
Etanercept[56-61]	3	2.68 (0.55-13.00)	.22
Golimumab[62-66]	5	0.76 (0.18-3.22)	.70
Infliximab[25, 37, 38, 70-72]	3	1.07 (0.22-5.11)	.93
Overall	12	1.37 (0.59-3.19)	.46
Non-TNF inhibitors			
Abatacept[20, 25, 75]	3	0.54 (0.13-2.31)	.41
Anakinra[80]	1	0.06 (0.00-0.94)	.05
Tocilizumab[87, 88]	2	0.22 (0.02-2.44)	.22
Combination			
Abatacept + etanercept/BRM[20]	1	5.16 (0.50-53.67)	.17



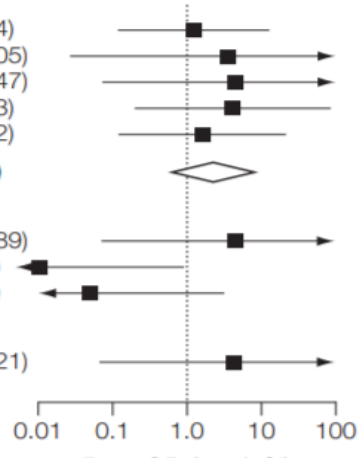
Skin cancer, melanoma[a]

BRMs	No. of Studies	Peto OR (95% CI)	*P* Value
TNF inhibitors			
Adalimumab[44]	1	0.04 (0.00-2.97)	.15
Etanercept[58, 60, 61]	1	4.50 (0.07-286.14)	.48
Infliximab[70-72]	1	3.51 (0.11-111.85)	.48
Overall	3	1.08 (0.11-10.21)	.95
Non-TNF inhibitors			
Anakinra[80]	1	3.50 (0.03-464.12)	.62



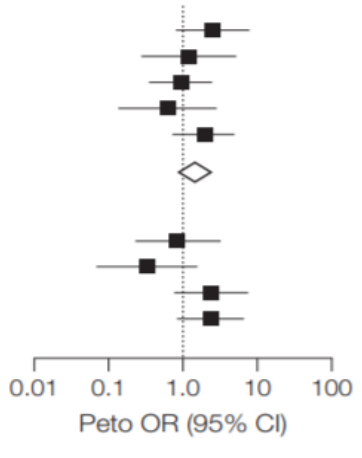
Lymphoma

BRMs	No. of Studies	Peto OR (95% CI)	*P* Value
TNF inhibitors			
Adalimumab[44, 45, 49]	3	1.23 (0.12-13.14)	.86
Certolizumab[53]	1	3.51 (0.03-458.05)	.61
Etanercept[55]	1	4.59 (0.07-284.47)	.47
Golimumab[62, 65]	2	4.18 (0.20-88.53)	.36
Infliximab[37, 38, 68, 70-72]	3	1.64 (0.12-21.92)	.71
Overall	10	2.14 (0.55-8.38)	.28
Non-TNF inhibitors			
Abatacept[76]	1	4.51 (0.07-285.89)	.48
Anakinra[80]	1	0.01 (0.00-0.94)	.05
Tocilizumab[88]	1	0.05 (0.00-3.19)	.16
Combination			
Anakinra + etanercept[21]	1	4.45 (0.07-287.21)	.48



Solid tumors[b]

BRMs	No. of Studies	Peto OR (95% CI)	*P* Value
TNF inhibitors			
Adalimumab[36, 43, 44, 47, 49]	5	2.35 (0.75-7.36)	.14
Certolizumab[51, 53]	2	1.14 (0.26-4.98)	.86
Etanercept[55, 58-61]	3	0.89 (0.33-2.39)	.81
Golimumab[62-66]	5	0.59 (0.13-2.76)	.50
Infliximab[25, 37, 38, 68-72]	5	1.82 (0.69-4.78)	.23
Overall	20	1.31 (0.78-2.20)	.31
Non-TNF inhibitors			
Abatacept[20, 25, 76, 77]	4	0.82 (0.22-3.01)	.76
Anakinra[78-81]	4	0.31 (0.07-1.49)	.14
Rituximab[26, 32, 82, 83]	4	2.28 (0.72-7.25)	.16
Tocilizumab[41, 86, 88, 89]	4	2.22 (0.79-6.20)	.13



- JAMA 2012

Μπορούμε να δώσουμε αντι-TNF σε ασθενείς με ιστορικό κακοήθειας?

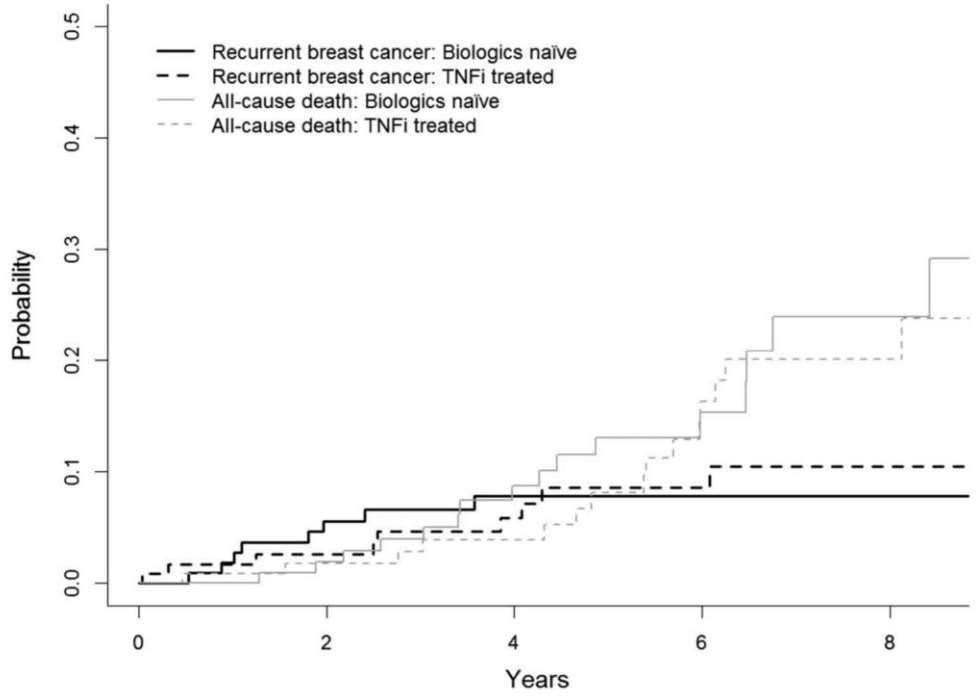
Clinical and epidemiological research

EXTENDED REPORT

TNF inhibitor therapy and risk of breast cancer recurrence in patients with rheumatoid arthritis: a nationwide cohort study

Pauline Raaschou,[1,2] Thomas Frisell,[1] Johan Askling,[1,3] for the ARTIS Study Group

- Η χρήση TNF αναστολέων σε ασθενείς με ιστορικό καρκίνου μαστού δεν φαίνεται να αύξησε τον κίνδυνο υποτροπής (χορήγηση μετά από 9.4 έτη από την διαγνωση)



Arthritis Research & Therapy

Arthritis Res Ther. 2009; 11(4): R127.
Published online 2009 Aug 24. doi: 10.1186/ar2794
PMCID: PMC274581
PMID: 1970330

Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years

Désirée van der Heijde,[1] David Salonen,[2] Barbara N Weissman,[3] Robert Landewé,[4] Walter P Maksymowych,[5] Hartmut Kupper,[6] Shaila Ballal,[7] Eric Gibson,[7] and Robert Wong[7], the Canadian (M03-606) study group and the ATLAS study group d.vanderheijde@kpnplanet.nl

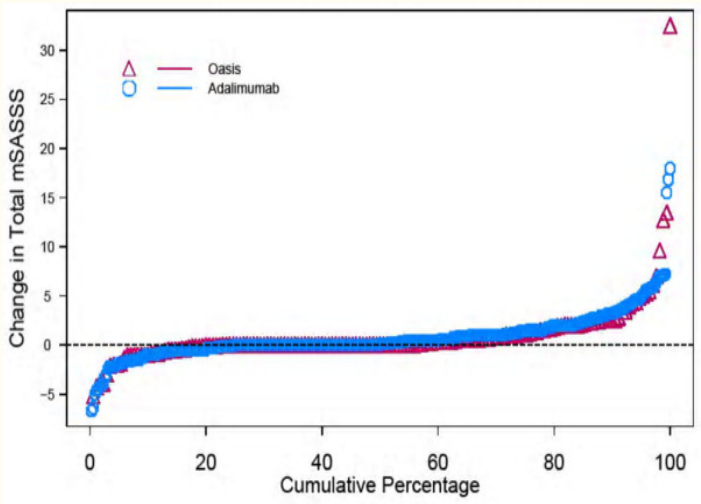


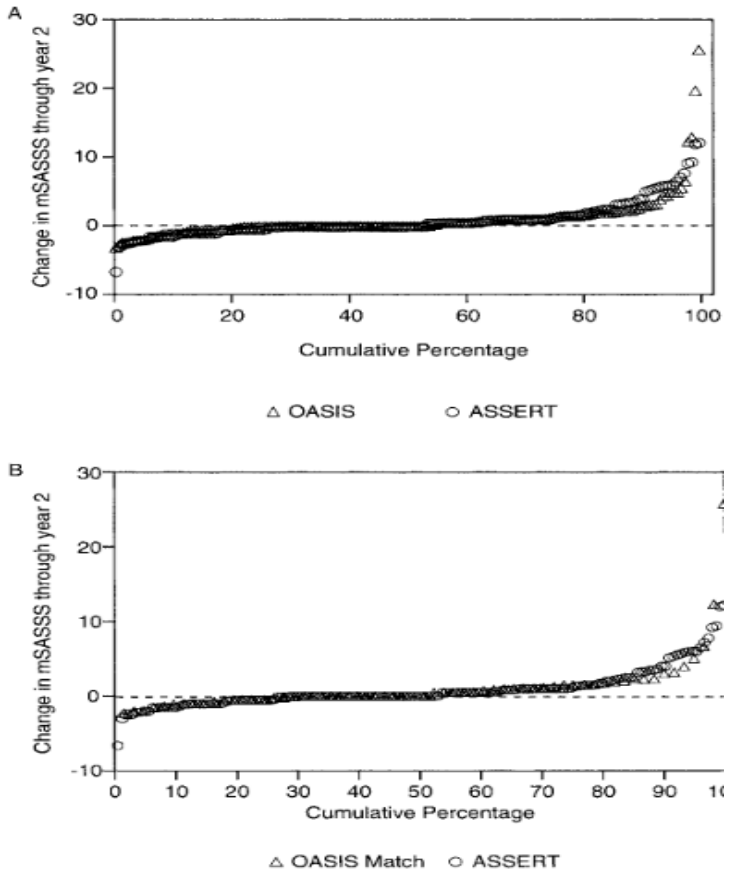
Figure 1

Probability plot of 2-year progression in the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). The cumulative probability plot illustrates the change in mSASSS values from baseline to 2 years in the adalimumab cohort (n = 307) and OASIS (n = 169) cohort (patients without total spinal ankylosis). In both cohorts, over 40% of the patients showed some change and about 10% of the patients showed a change of at least 5 in mSASSS from baseline to year 2. No significant differences between the adalimumab and OASIS cohorts were observed. OASIS, Outcome in Ankylosing Spondylitis International Study.

ARTHRITIS & RHEUMATISM
Vol. 58, No. 10, October 2008, pp 3063–3070
DOI 10.1002/art.23901

Radiographic Findings Following Two Years of Infliximab Therapy in Patients With Ankylosing Spondylitis

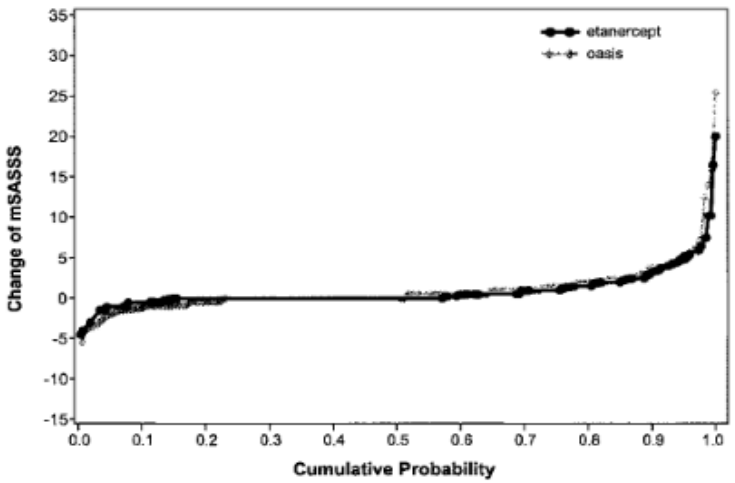
Désirée van der Heijde,[1] Robert Landewé,[2] Xenofon Baraliakos,[3] Harry Houben,[4] Astrid van Tubergen,[2] Paul Williamson,[5] Weichun Xu,[5] Daniel Baker,[5] Neil Goldstein,[6] Jürgen Braun,[3] and the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group



ARTHRITIS & RHEUMATISM
Vol. 58, No. 5, May 2008, pp 1324–1331
DOI 10.1002/art.23471

Radiographic Progression of Ankylosing Spondylitis After Up to Two Years of Treatment With Etanercept

D. van der Heijde,[1] R. Landewé,[2] S. Einstein,[3] P. Ory,[4] D. Vosse,[2] L. Ni,[5] S.-L. Lin,[5] W. Tsuji,[5] and J. C. Davis, Jr.[6]

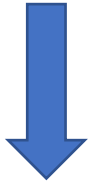


Θεραπευτική axSpA

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with secukinumab or ixekizumab over treatment with a different TNFi in patients with primary nonresponse to TNFi (new, PICO 10).

In adults with active AS despite treatment with the first TNFi used, we conditionally recommend treatment with a different TNFi over treatment with a non-TNFi biologic in patients with secondary nonresponse to TNFi (new, PICO 10).

- Πρωτογενής αστοχία

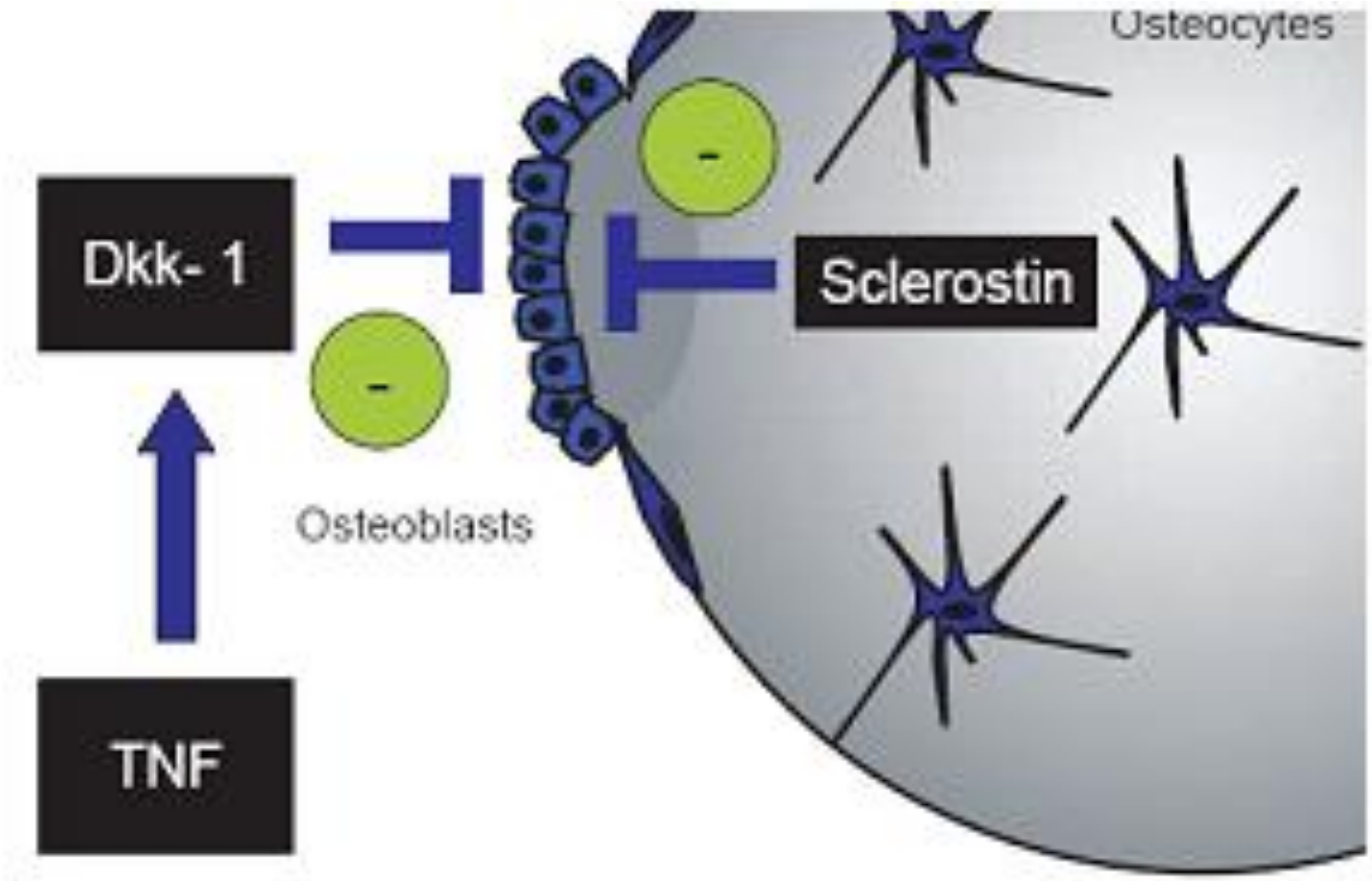


- Switching

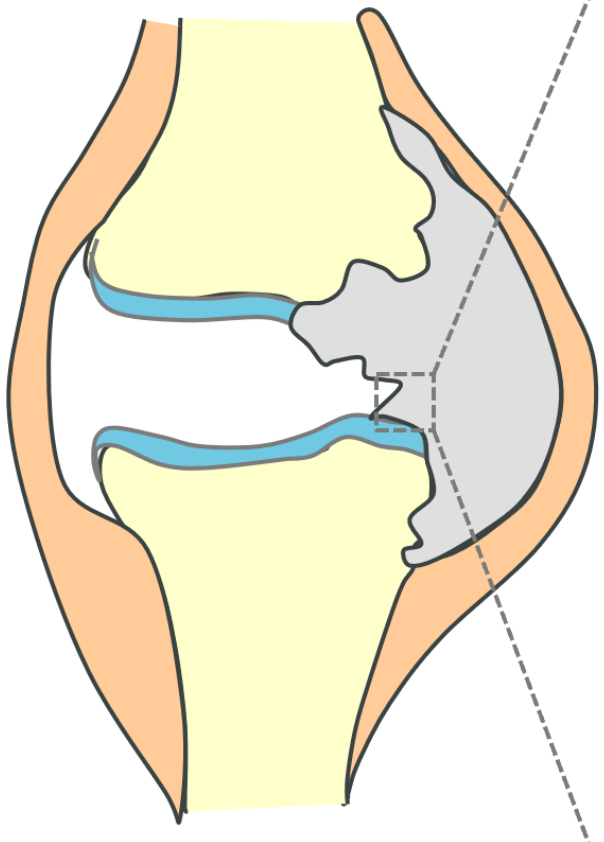
- Δευτερογενής αστοχία

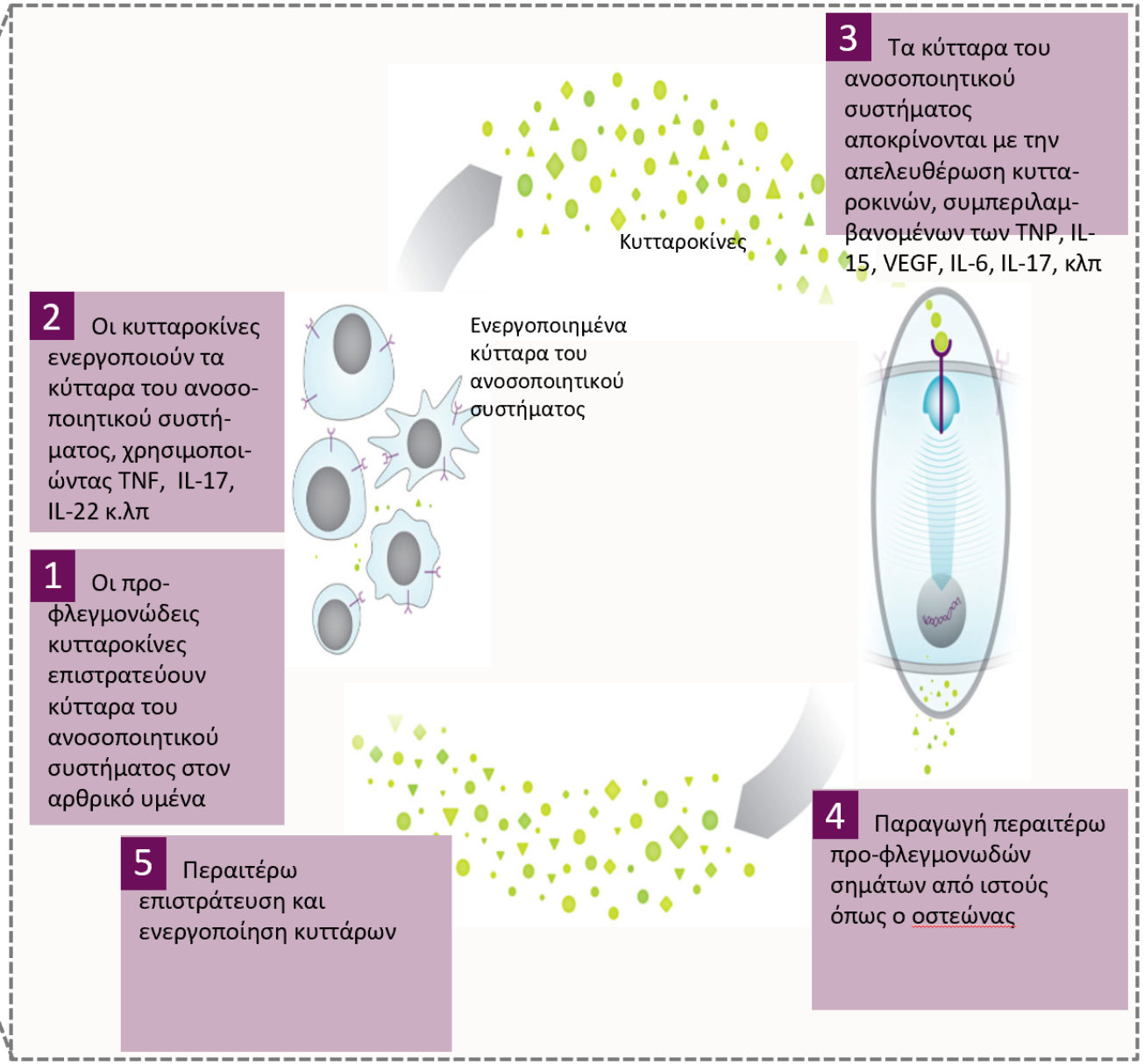
- cycling

Η φλεγμονή επάγει αναστολείς του Wnt μονοπατιού



Ο κύκλος της φλεγμονής





IL: ιντερλευκίνη, TNF: παράγοντας νέκρωσης όγκου? VEGF:αγγειακός ενδοθηλιακός αυξητικός παράγοντας.

1. McInnes IB, Liew FY. *Nat Clin Pract Rheumatol* 2005;1:31–39.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Reframing Immune-Mediated Inflammatory Diseases through Signature Cytokine Hubs

Georg Schett, M.D., Iain B. McInnes, M.D., Ph.D., and Markus F. Neurath, M.D.

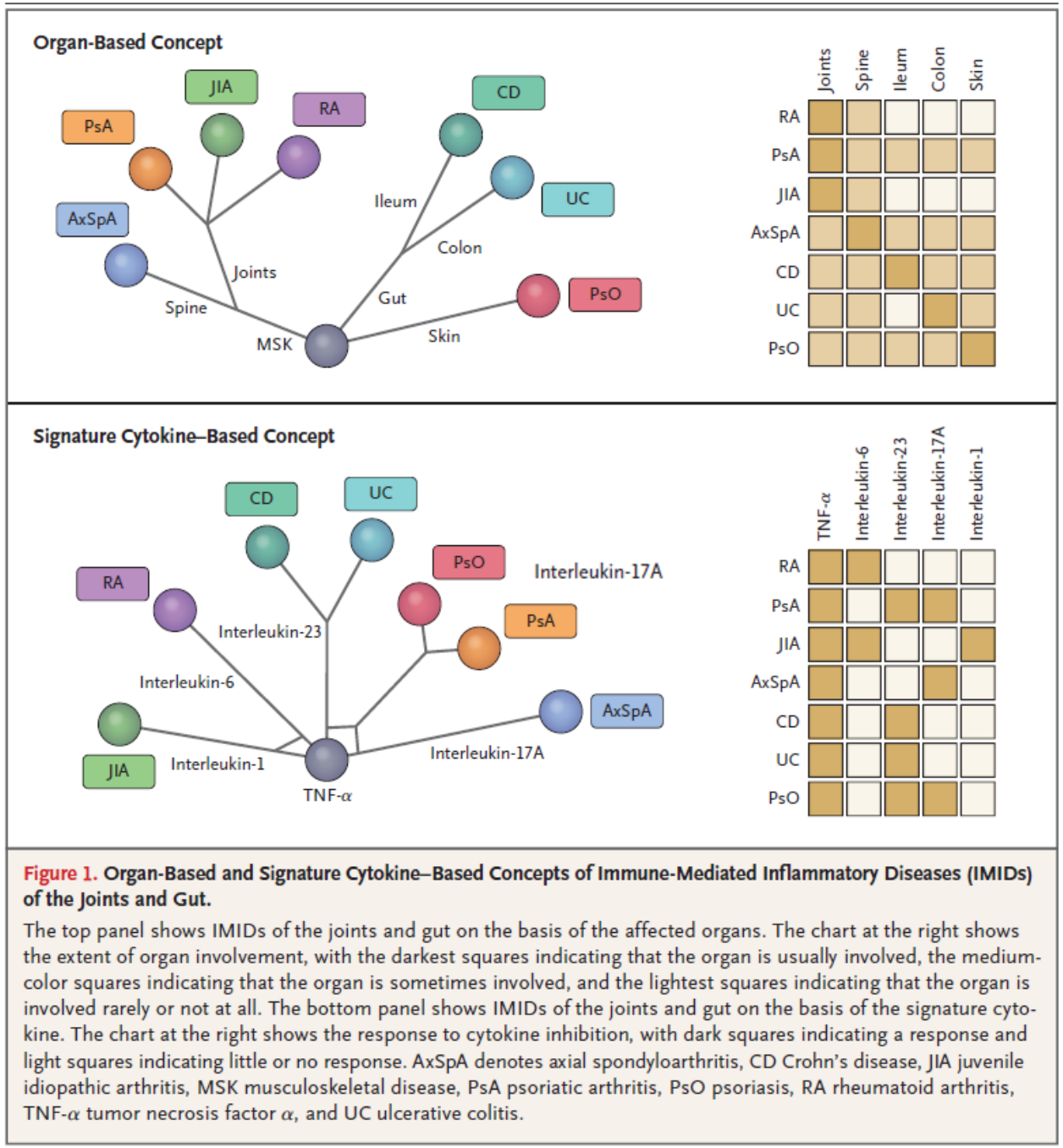
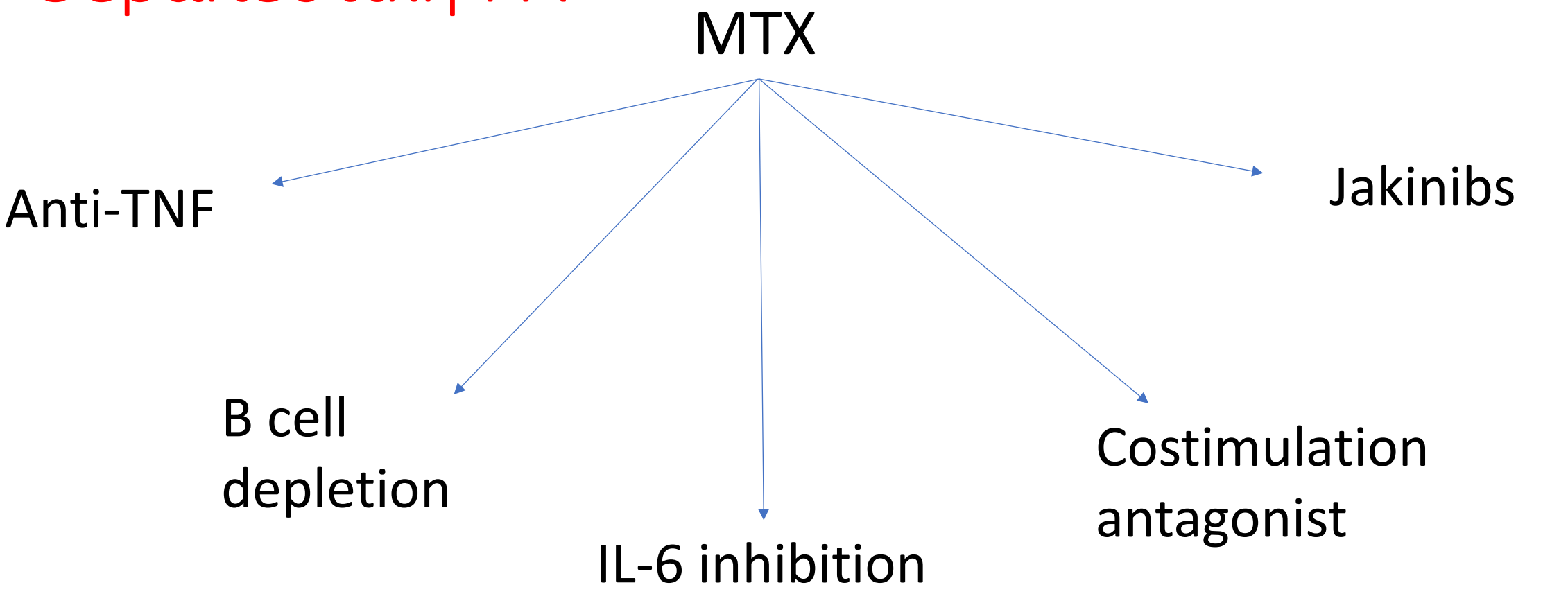


Figure 1. Organ-Based and Signature Cytokine–Based Concepts of Immune-Mediated Inflammatory Diseases (IMIDs) of the Joints and Gut.

The top panel shows IMIDs of the joints and gut on the basis of the affected organs. The chart at the right shows the extent of organ involvement, with the darkest squares indicating that the organ is usually involved, the medium-color squares indicating that the organ is sometimes involved, and the lightest squares indicating that the organ is involved rarely or not at all. The bottom panel shows IMIDs of the joints and gut on the basis of the signature cytokine. The chart at the right shows the response to cytokine inhibition, with dark squares indicating a response and light squares indicating little or no response. AxSpA denotes axial spondyloarthritis, CD Crohn's disease, JIA juvenile idiopathic arthritis, MSK musculoskeletal disease, PsA psoriatic arthritis, PsO psoriasis, RA rheumatoid arthritis, TNF-α tumor necrosis factor α, and UC ulcerative colitis.

Θεραπευτική PA



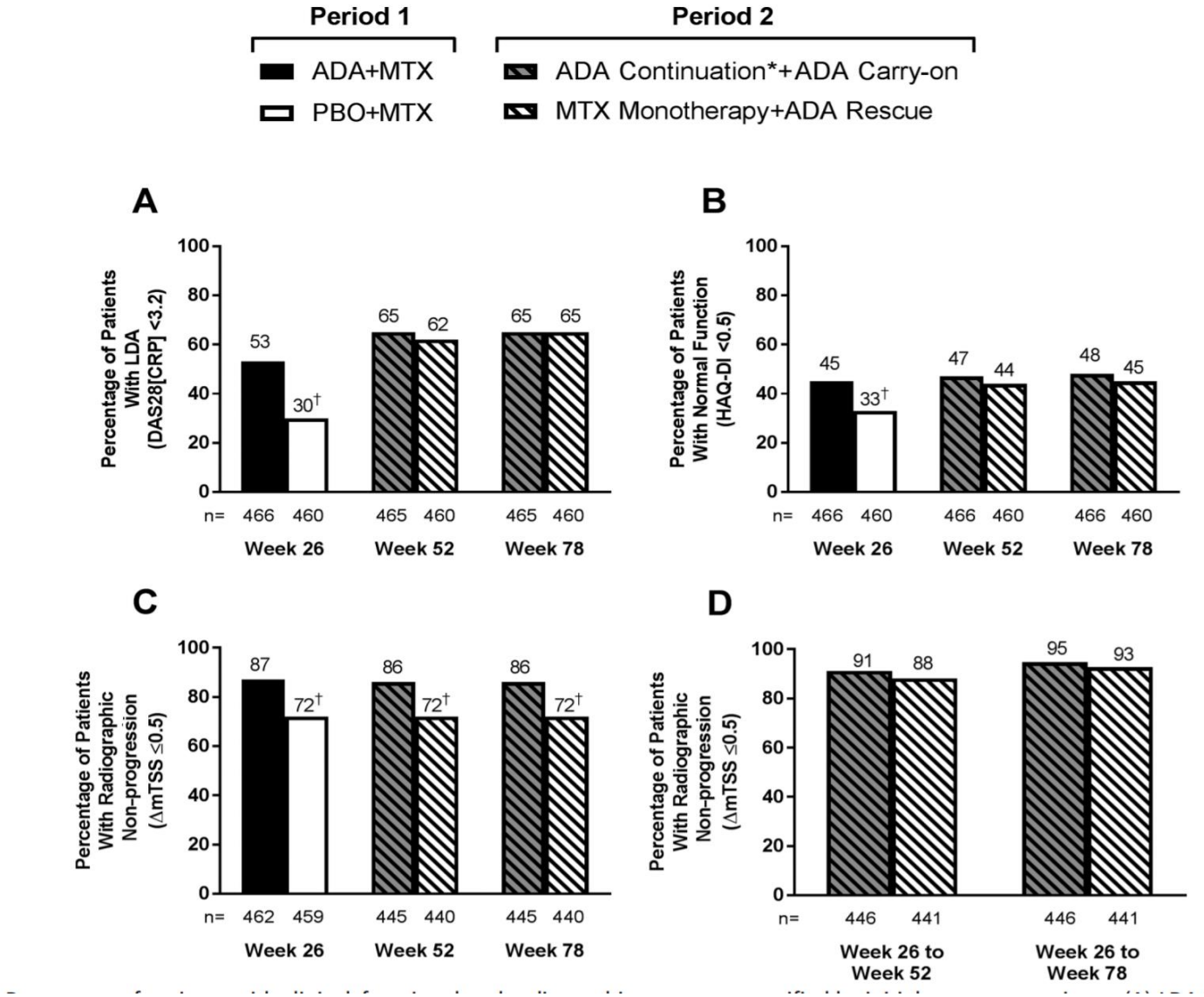
WHICH ONE IS BETTER?

OPEN ACCESS

CONCISE REPORT

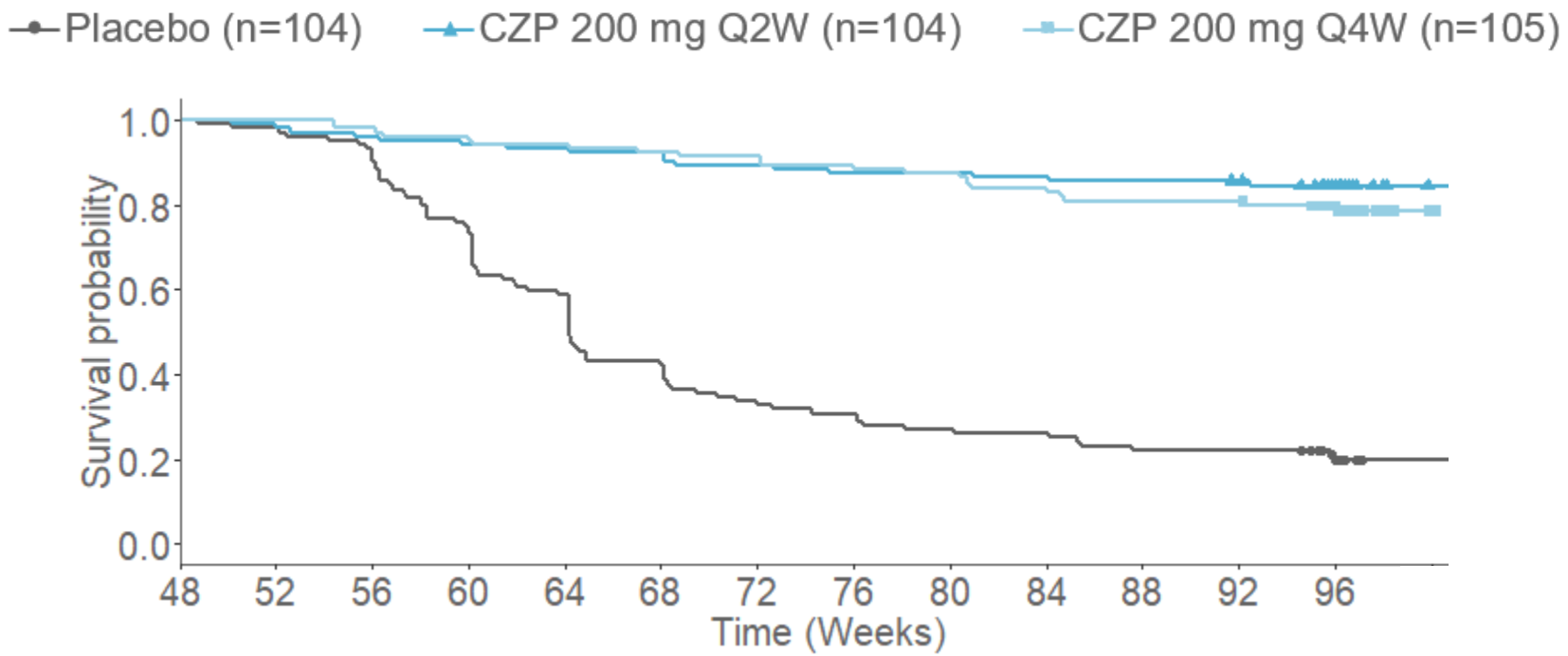
Testing treat-to-target outcomes with initial methotrexate monotherapy compared with initial tumour necrosis factor inhibitor (adalimumab) plus methotrexate in early rheumatoid arthritis

- Η πολύ επιθετική θεραπευτική αντιμετώπιση με χρήση βιολογικού άμεσα δεν φαίνεται να προσφέρει κάτι μακροπρόθεσμα



Tapering vs διακοπη βιολογικού

- Randomised Set, NRI



	Placebo (n=104)	CZP 200 mg Q2W (n=104)	CZP 200 mg Q4W (n=105)
Kaplan-Meier estimate of time to flare, weeks since randomization, median (95% CI)	16.1 (14.4, 20.1)	53 (NA, NA)	NA (NA, NA)
p-value vs PBO		<0.001	<0.001

- UCB Data on File (AS0005 Tables 26May2019. Table 4.2.1 and Figure 1). p-values are from stratified log-rank test (region and mNY classification are used as stratification factors).

NRI: Non-responder imputation; NA: not applicable. A patient is considered to have experienced a flare if the patient has: (i) an ASDAS ≥2.1 at 2 consecutive visits or an ASDAS >3.5 at any visit during Part B, or (ii) 2 ASDAS score missing at ≥2 consecutive visits or premature withdrawal from Part B for any reason.