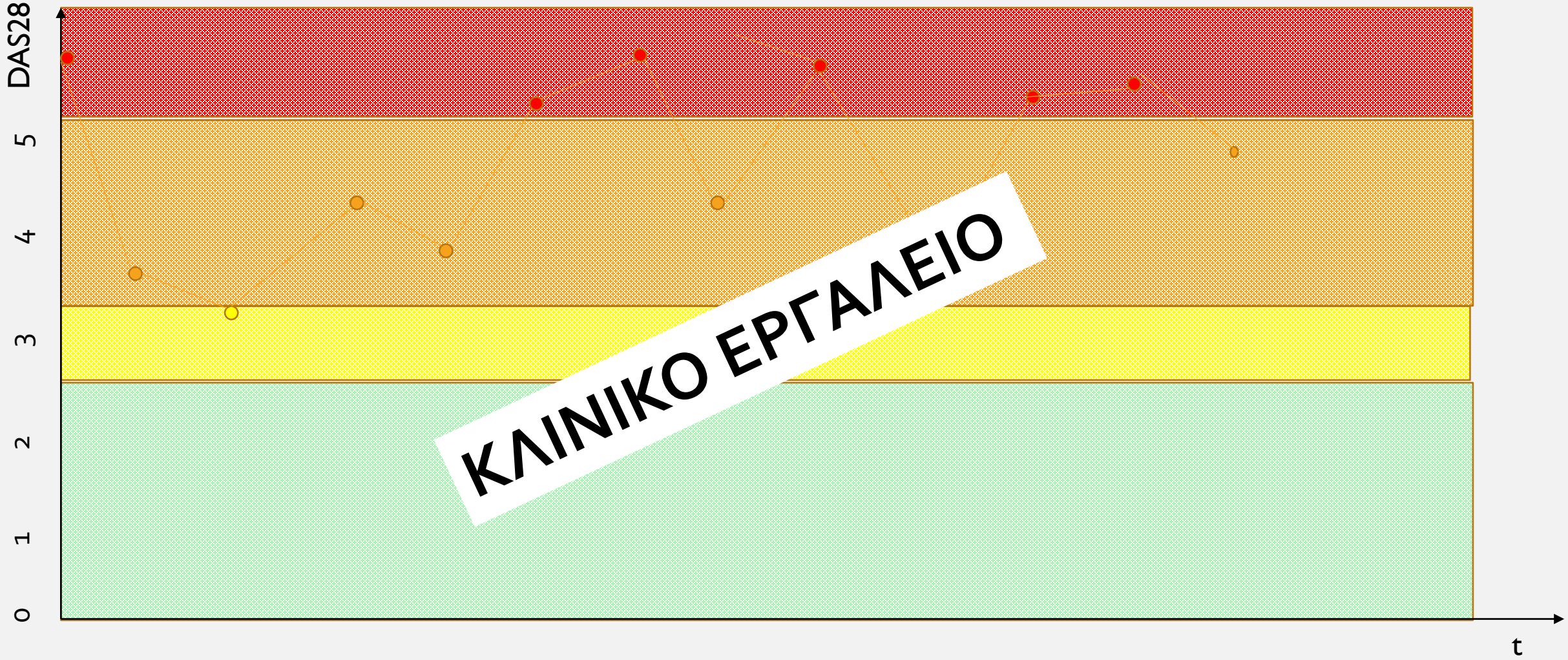
ΦΛΕΓΜΟΝΩΔΗΣ ΑΡΘΡΙΤΙΔΑ: Η ΜΕΤΑ ΤΟΥΣ ΒΙΟΛΟΓΙΚΟΥΣ ΕΠΟΧΗ ΚΑΙ Η ΘΕΣΗ ΤΩΝ ΜΙΚΡΩΝ ΜΟΡΙΩΝ

Κατερίνα Χατζηδιονυσίου
Α' Προπαιδευτικη Παθολογική Κλινική
Λαϊκό Γενικό Νοσοκομείο Αθηνών
Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

ΠΕΡΙΣΤΑΤΙΚΟ ΑΣΘΕΝΟΥΣ

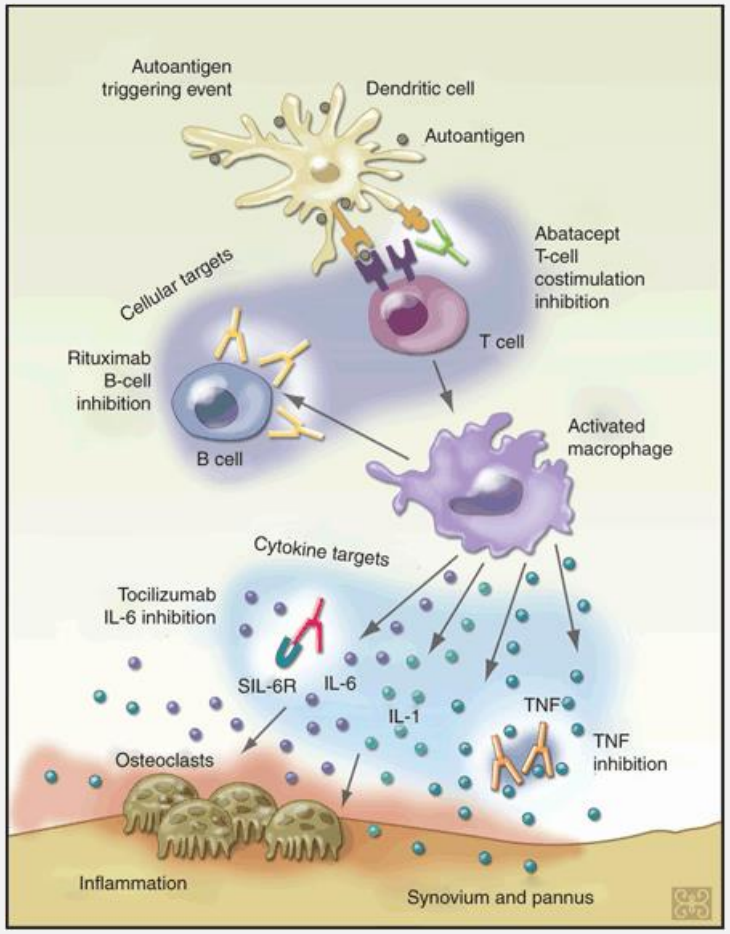
- Göran, 70 ετών
- Ν. Παρκινσον, υπέρταση, ΟΕΜ x 2
- PA, οροαρνητική, διαβρωτική
- csDMARDs (MTX, LEF, SAL), bDMARDs (5 anti-TNF, RTX, TCZ, ABA, ANK)
- Υψηλές δόσεις κορτικοστεροειδών
- Δευτεροπαθής αμυλοείδωση

Clinician Module

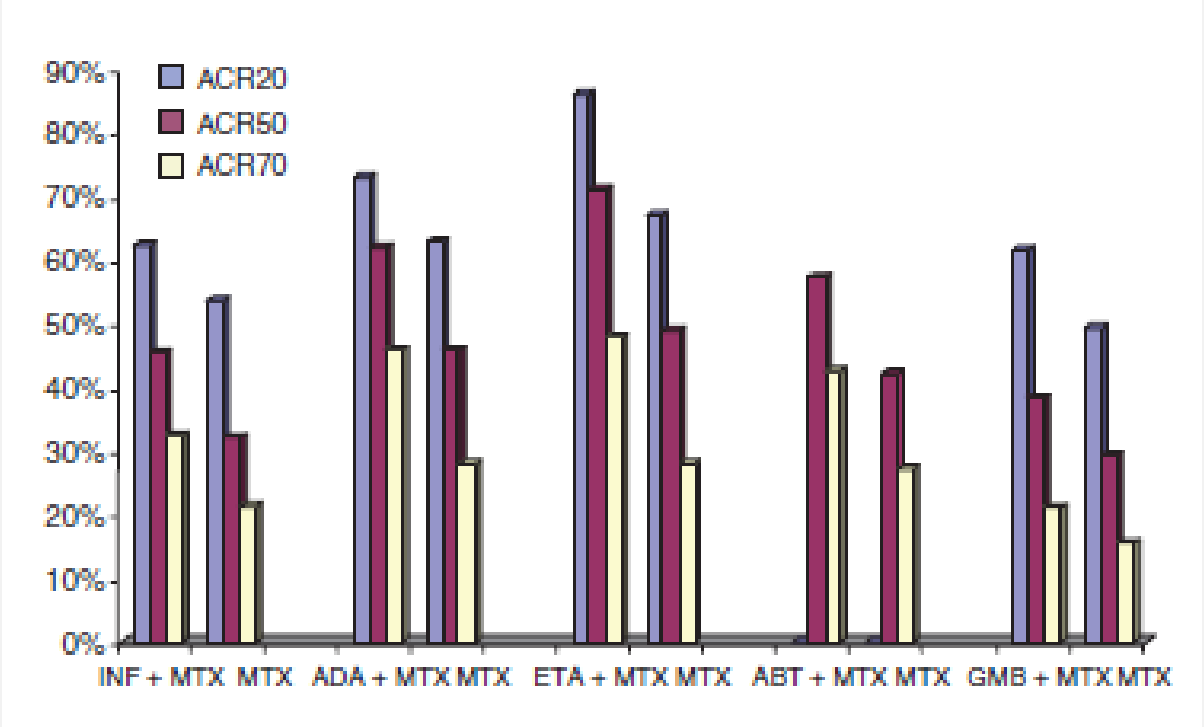


MTX sc	MTX sc SAL	MTXsc SAL INF	MTXcs SAL ETA	…. …. …..	LEF RTX	LEF ABA	LEF TCZ	????
GCs dose:	10mg/d	20mg/d	30mg/d	….	15mg/d	30mg/d	17,5mg/d	

BIOLOGIC DMARDS

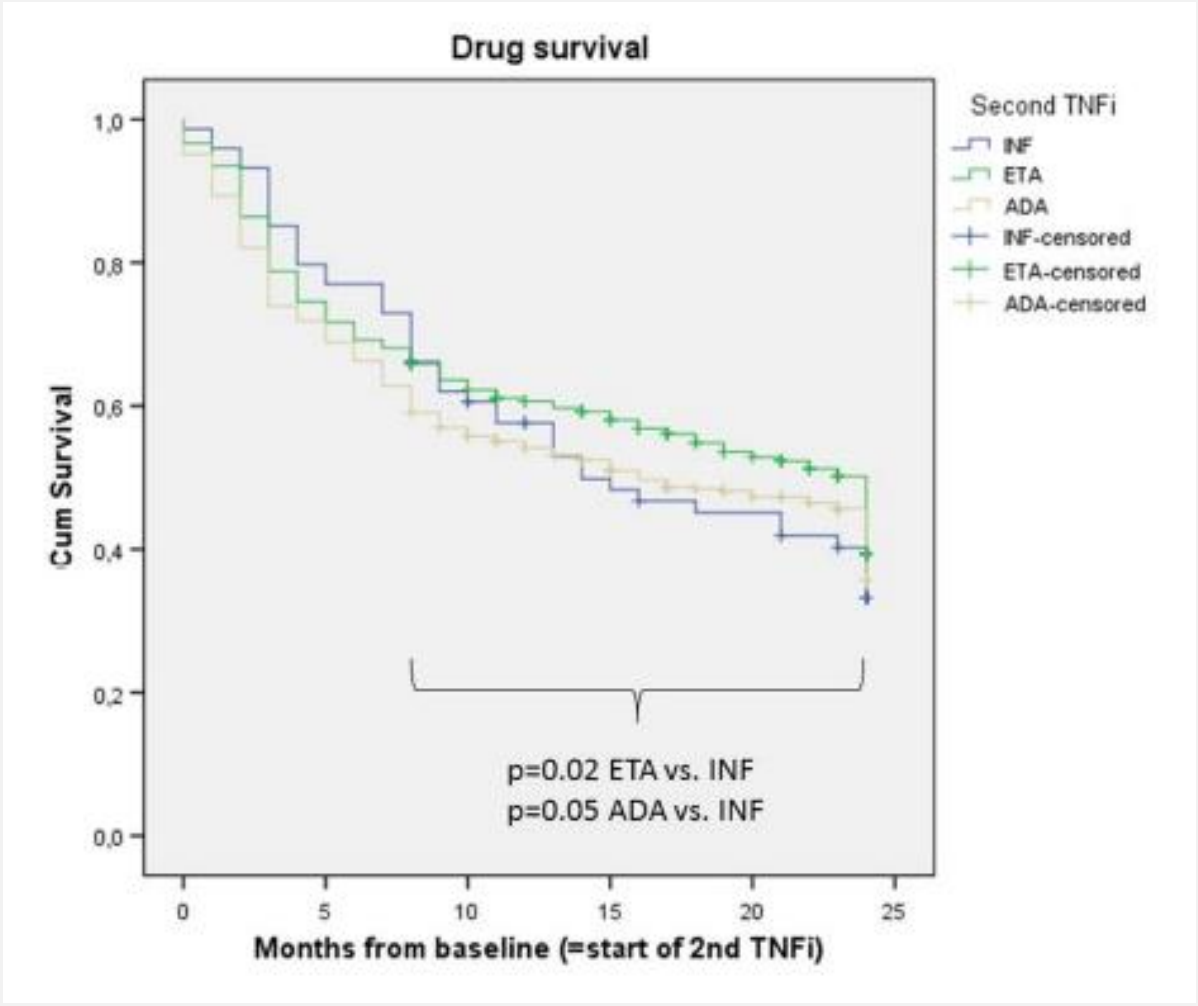


D. L. Scott. *Clinical Pharmacology & Therapeutics* 91, 30-43 (January 2012)

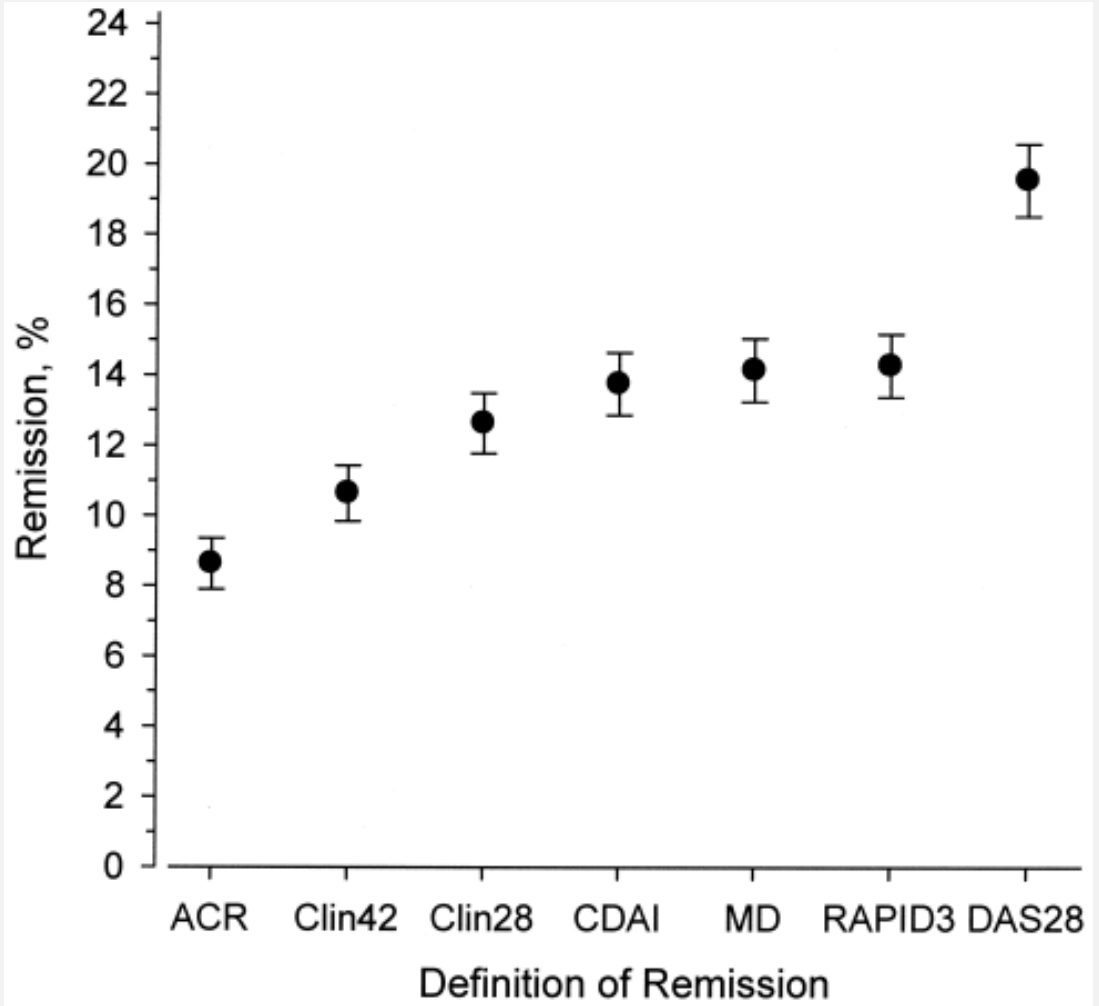


Chatzidionysiou K, van Vollenhoven. J Int Med, 2011

UNMET NEED

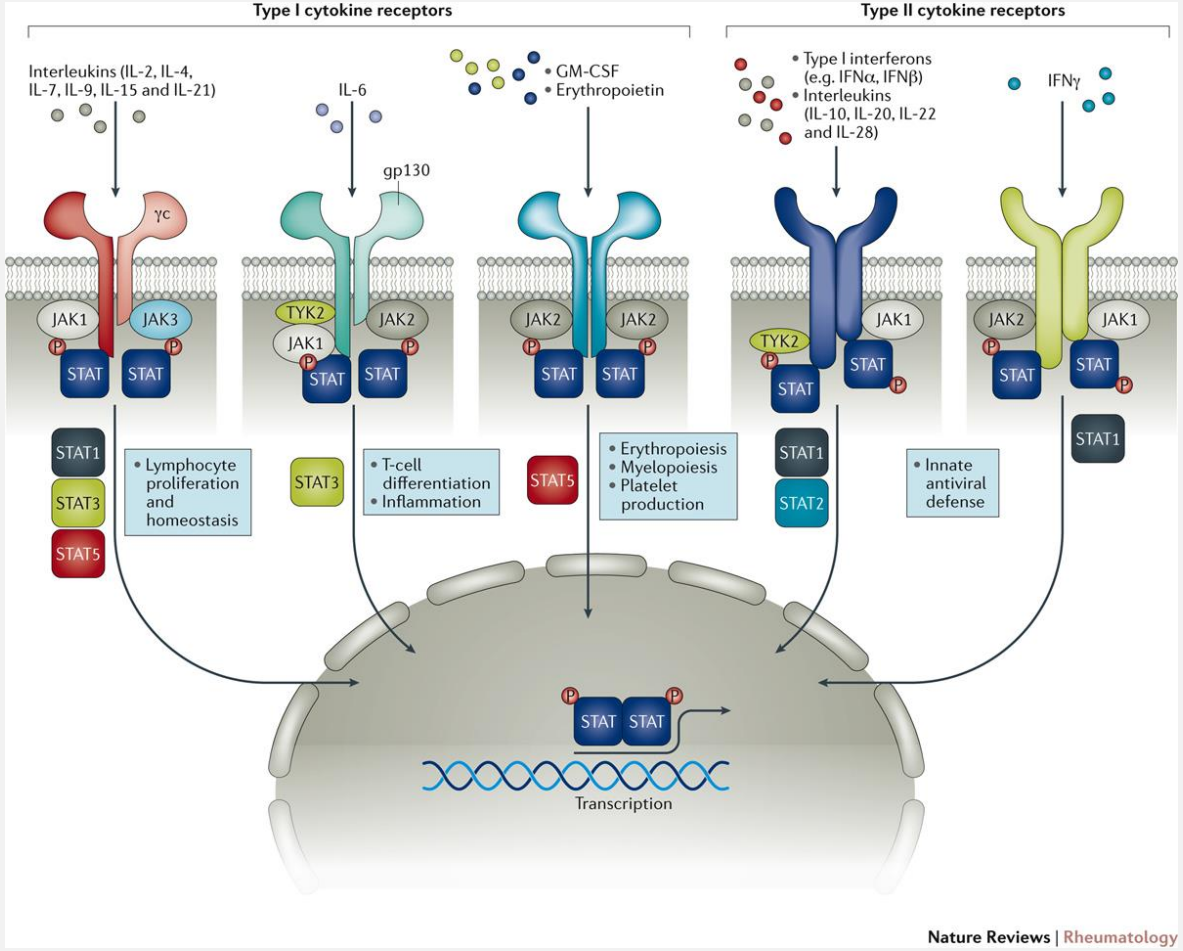


Chatzidionysiou K. et al., Ann Rheum Dis. Jan 2014



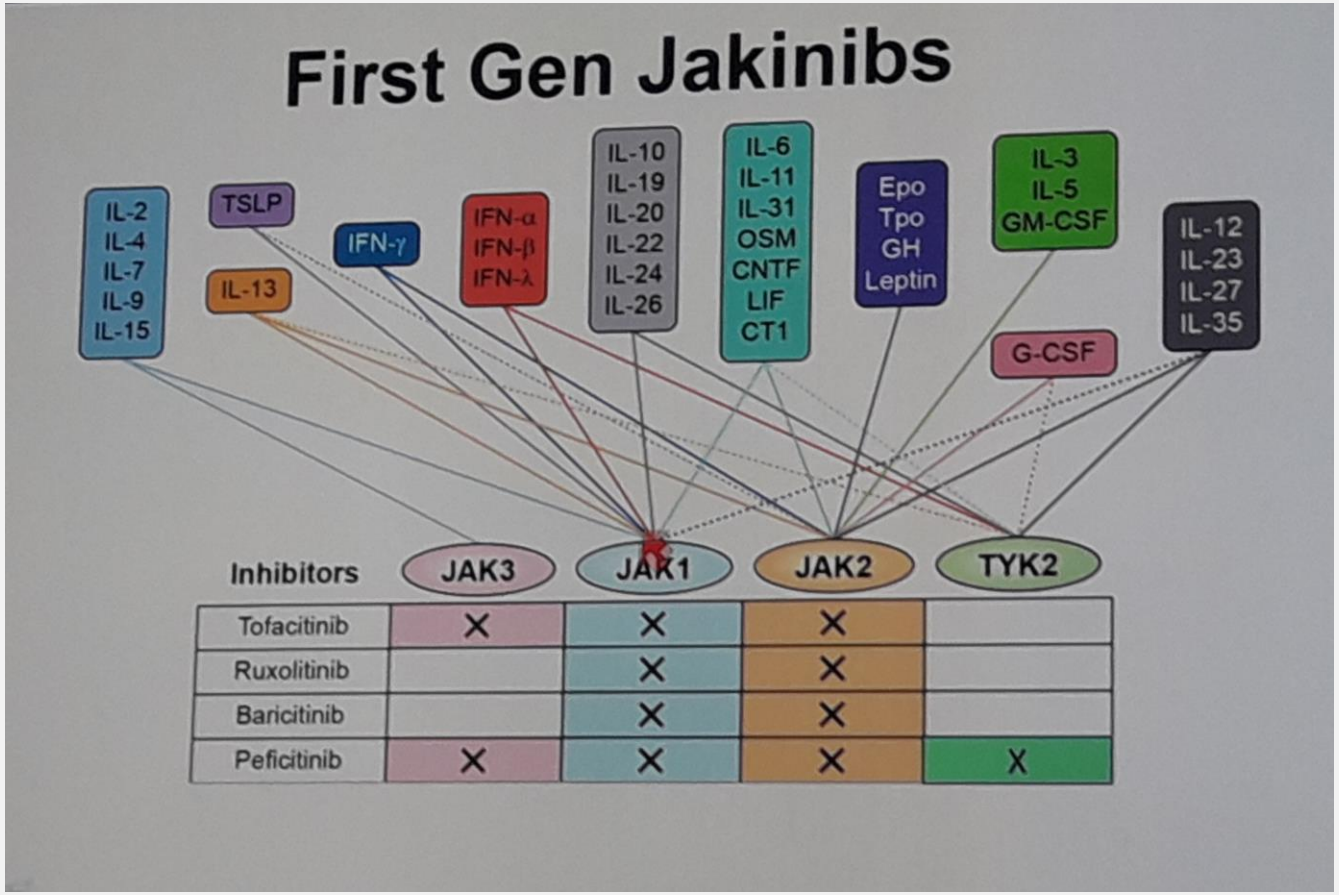
Sokka et al .
Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries. Arthritis Rheum. 2008

CYTOKINE RECEPTORS AND JAK SIGNALLING



Winthrop, K. L. (2017) The emerging safety profile of JAK inhibitors in rheumatic disease
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2017.23

I ST GENERATION JAK INHIBITORS



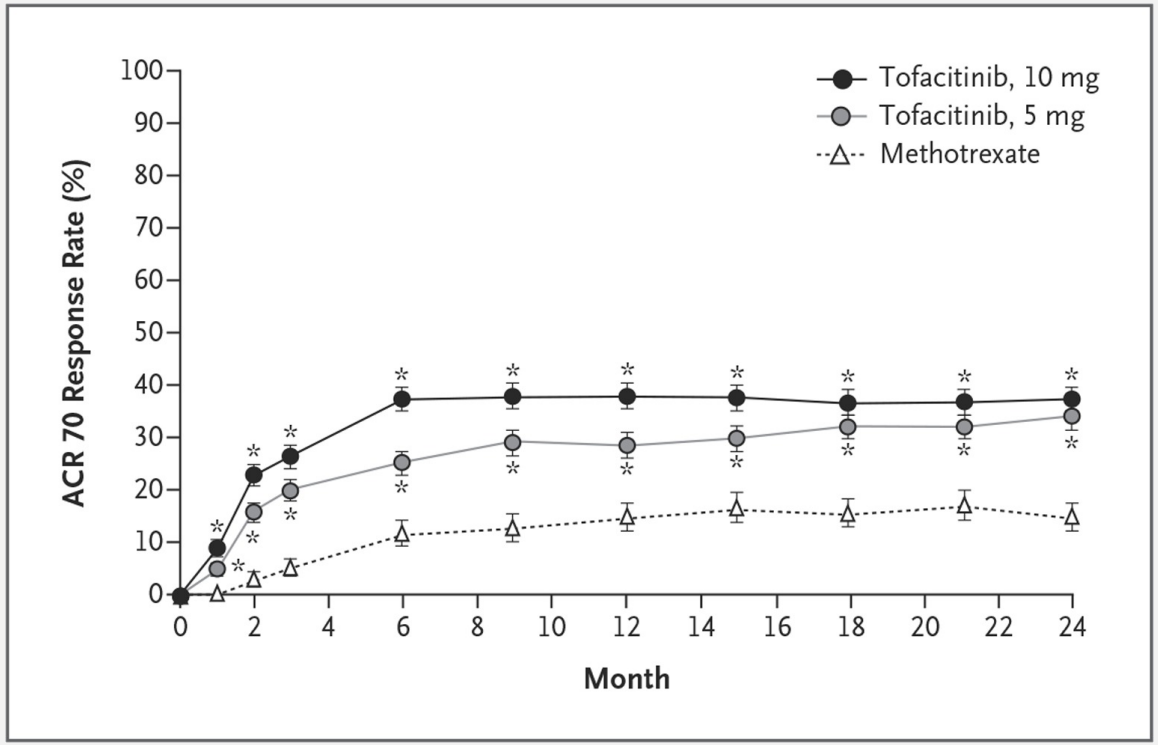
TOFACITINIB ΣΤΗΝ PA

- 7 phase III RCTs
  - 2 tofacitinib μονοθεραπεία
  - 3 μελέτες σε csDMARD IR se syndiasmo me csDMARD
  - 1 meleth se TNF IR
  - Tofa mono vs. Tofa+MTX vs. ADA+MTX

ORAL START

TOFA MONO
DMARD naive

- 956 patients RA
- DMARD naive
- Tofa monotherapy vs MTX
- The coprimary end points at month 6 were the mean change from baseline in the van der Heijde modified total Sharp score and the proportion of patients with an American College of Rheumatology (ACR) 70 response

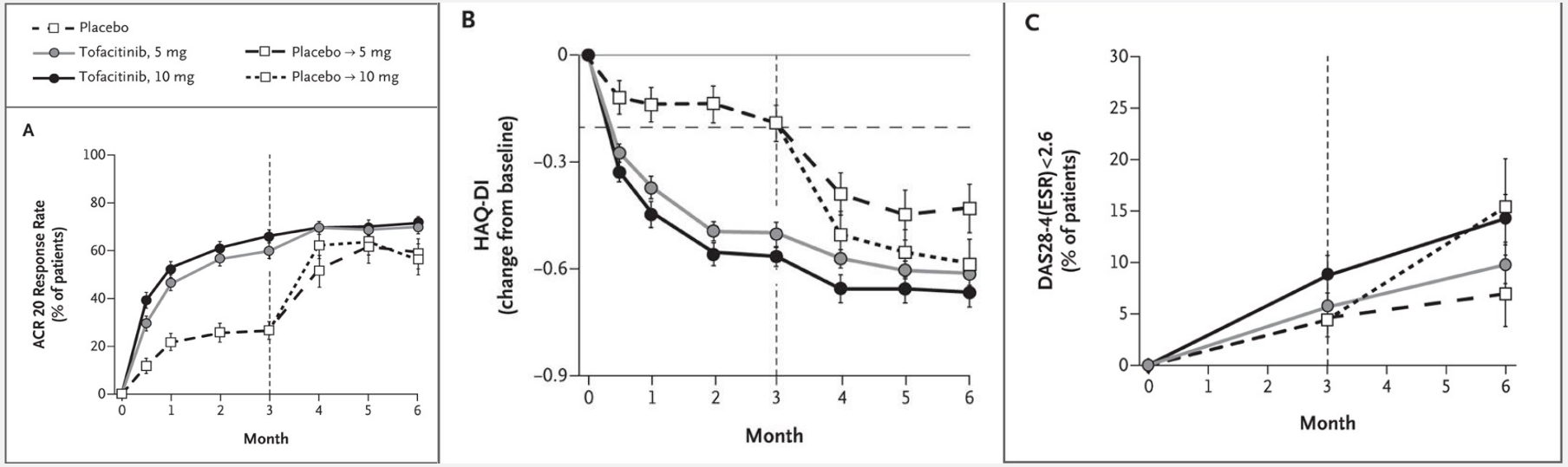


Tofacitinib > MTX

Lee et al, Tofacitinib versus Methotrexate in Rheumatoid Arthritis. N Engl J Med2014;370:2377-86.

ORAL SOLO

TOFA MONO
csDMARDs or
bDMARDs IR



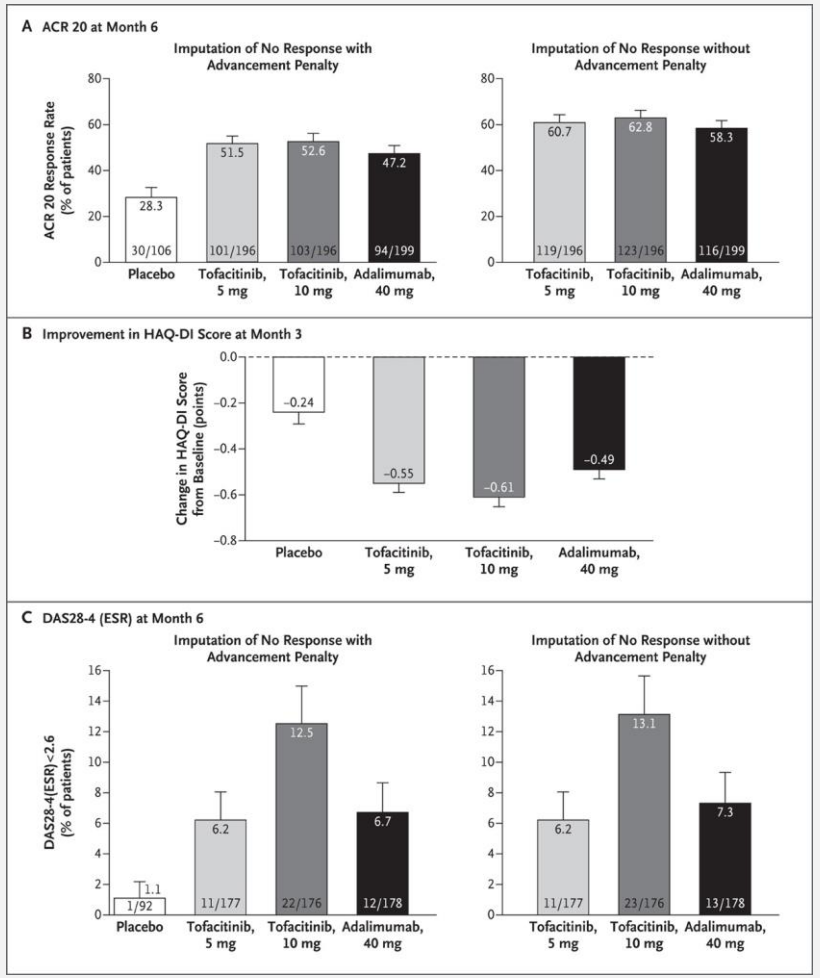
- Double-blind, placebo-controlled, monotherapy RCT
- 619 RA patients who had failed ≥1 csDMARD or bDMARD
- The primary end points of achieving an ACR20 and improvement of HAQ-DI from baseline at week 12 was met but there was no statistically significant difference in achieving a DAS28(ESR) < 2.6 between either tofacitinib group and placebo

Fleischman et al, Placebo-Controlled Trial of Tofacitinib Monotherapy in Rheumatoid Arthritis
N Engl J Med 2012; 367:495-507

ORAL STANDARD

TOFA+MTX
MTX IR

- tofacitinib 5 and 10 mg b.i.d. and an active comparator, ADA 40 mg every other week, compared with placebo
- Background MTX
- 717 patients, MTX – IR
- The primary end points were achieving an ACR20 at month 6, achieving DAS28 < 2.6 at month 6 and change from baseline in the HAQ-DI.
- Efficacy results for tofacitinib and ADA were comparable for all outcomes, although all tofacitinib responses were numerically higher

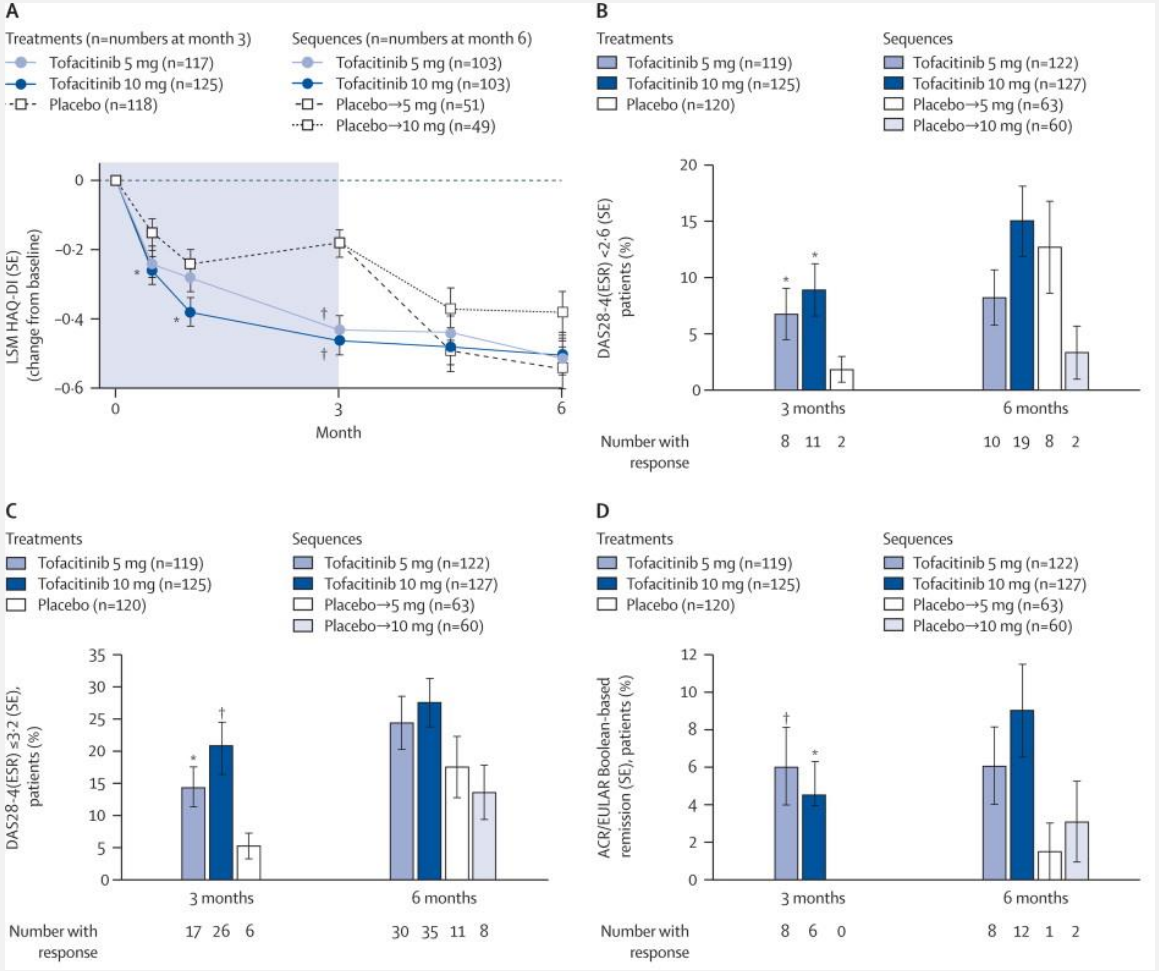


Van Vollenhoven R. et al, Tofacitinib or Adalimumab versus Placebo in Rheumatoid Arthritis. N Engl J Med 2012; 367:508-519

ORAL STEP

TOFA+MTX
TNFi IR

- 399 RA patients
- Failed at least one TNFi
- Background MTX
- The primary end points were the ACR20 responder rate, change from baseline in HAQ-DI and rate of patients achieving a DAS28(4) ESR < 2.6, all at month 3.

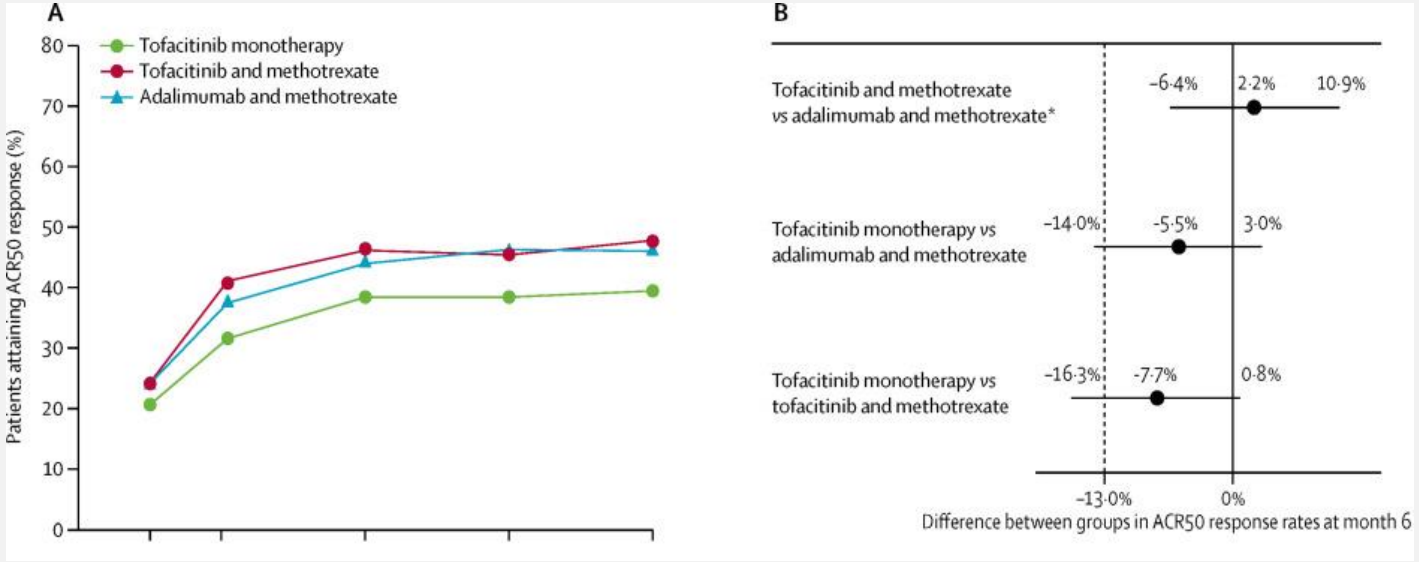


*Burmester G, Blanco R, Charles-Schoeman C et al.**Lancet** 381(9865), 451–460 (2013*

ORAL STRATEGY

MTX IR

- double-blind, phase 3b/4, head-to-head, non-inferiority, randomised controlled trial
- MTX – IR
- Tofa mono vs. tofa + MTX vs. ADA + MTX
- ACR50 at month 6
- The ACR50 response at month 6 was 38.3, 46 and 43.8% for the tofacitinib monotherapy, tofacitinib + MTX and ADA + MTX groups, respectively
- Tofacitinib 5 mg b.i.d. + MTX met the noninferiority criteria compared with ADA 40 mg + MTX as measured by the ACR50 response rate at month 6
- Tofacitinib 5 mg b.i.d. did not meet the noninferiority criteria compared with either tofacitinib 5 mg b.i.d. + MTX or ADA 40 mg + MTX ('inconclusive')

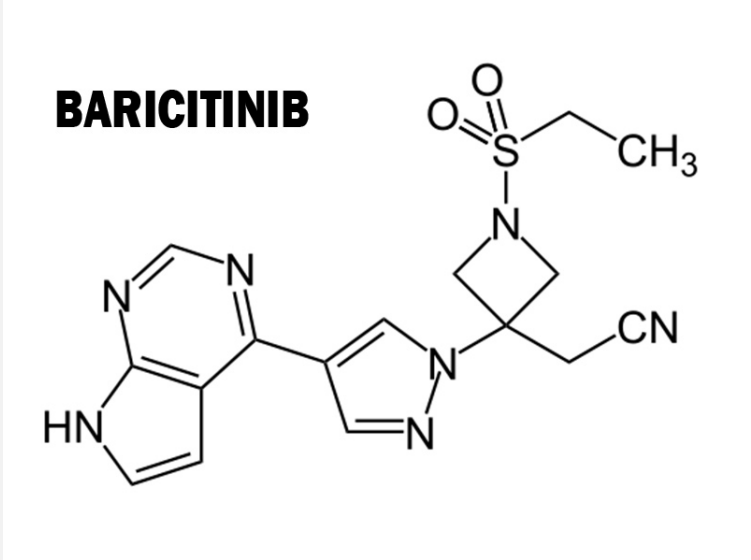


- **These results suggest that in a group of patients, more patients will achieve an ACR50 in 6 months if treated with the combination of MTX + either tofacitinib or ADA compared with treatment with tofacitinib monotherapy.**

Fleischmann R, Mysler E, Hall S et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a Phase IIIb/IV, double-blind, head-to-head, randomised controlled trial. ***Lancet****390(10093), 457–468 (2017)*

BARICITINIB

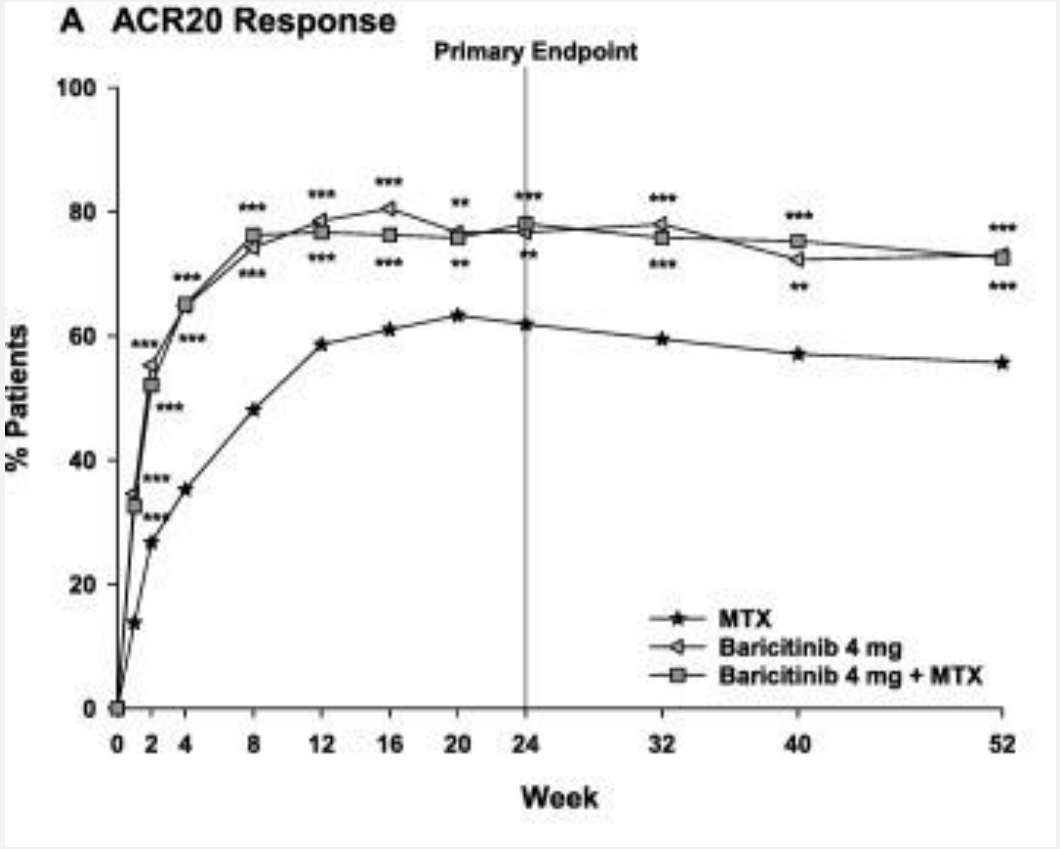
- reversible inhibition of JAK1 and JAK2



RA BEGIN

- Early, active RA
- DMARD naive >90%
- MTX mono vs. baricitinib mono vs. baricitinib + MTX
- noninferiority comparison of baricitinib mono to MTX mono

- The ACR20 response rate at week 24 for baricitinib monotherapy and MTX monotherapy was 77% and 62%, respectively ($P \leq 0.001$ for noninferiority).
- Baricitinib monotherapy was found to be superior to MTX monotherapy at week 24 ($P \leq 0.01$)
- Less progression in the SHS was observed in both baricitinib groups compared to MTX monotherapy; however, the treatment effect was statistically significant for baricitinib plus MTX but not for baricitinib monotherapy



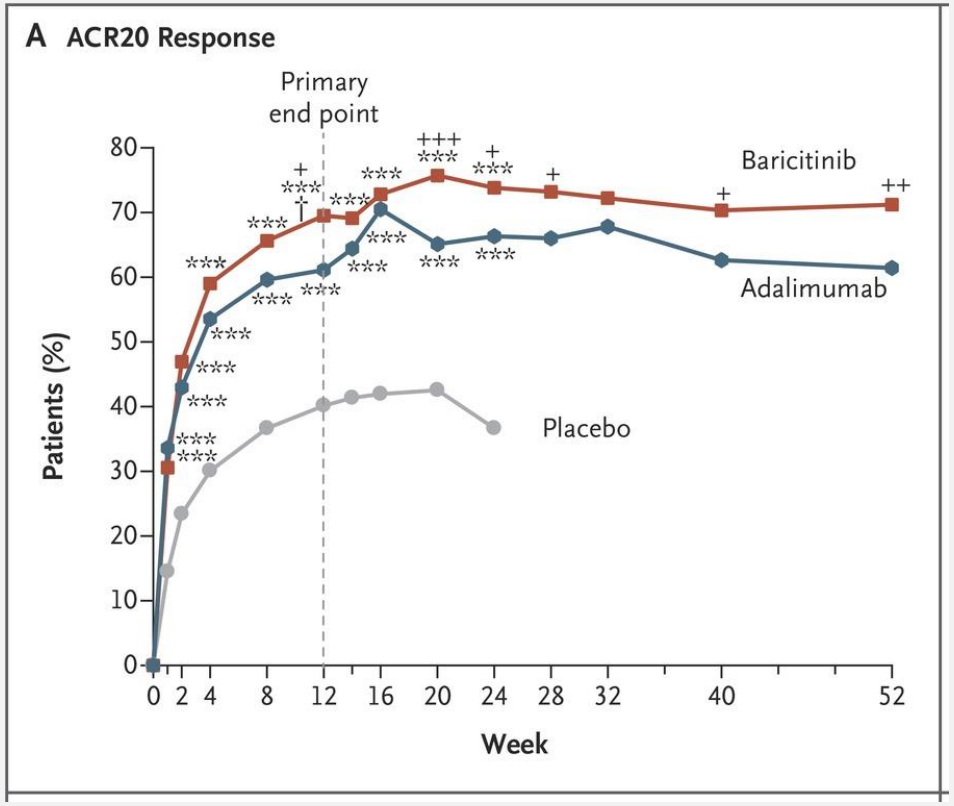
Fleischmann et al. Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. Arthritis Rheumatol. 2017 Mar; 69(3): 506–517.

RA BEAM

- 52-week, phase 3, double-blind, placebo- and active-controlled trial
- MTX IR
- 1307 p.
- Placebo vs. baricitinib vs. adalimumab

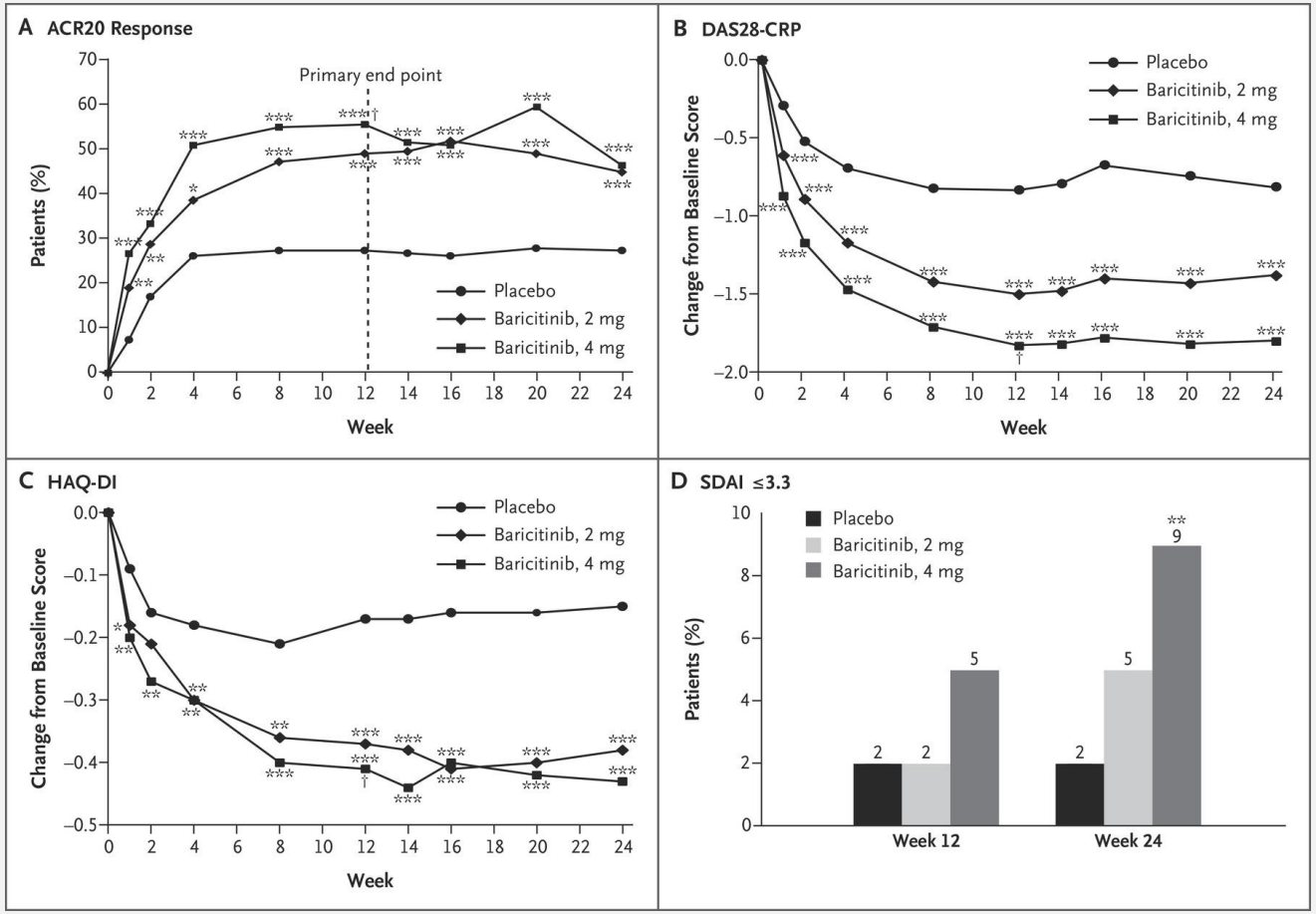
superiority — 70% vs 40% (p<0.001)

Non-inferiority — 70% vs 61% (p<0.01)



Taylor P. et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. N Engl J Med 2017; 376:652-662

RA-BEACON



Genovese et al. Baricitinib in patients with refractory Rheumatoid Arthritis. N Engl J Med 2016

- 527 patients
- At least 1 TNFi, other non-TNFi bDMARD or both
- End points: ACR20, HAQ-DI, DAS28-CRP and SDAI<3.3
- Significantly more patients receiving baricitinib at the 4-mg dose than those receiving placebo had an ACR20 response at week 12 (55% vs. 27%, P<0.001)

FUTURE JAK INHIBITORS

Lancet. 2018 Jun 23;391(10139):2503-2512. doi: 10.1016/S0140-6736(18)31115-2. Epub 2018 Jun 18.

Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial.

Burmester GR[1], Kremer JM[2], Van den Bosch F[3], Kivitz A[4], Bessette L[5], Li Y[6], Zhou Y[6], Othman AA[6], Pangan AL[6], Camp HS[6].

selective inhibitor of JAK1

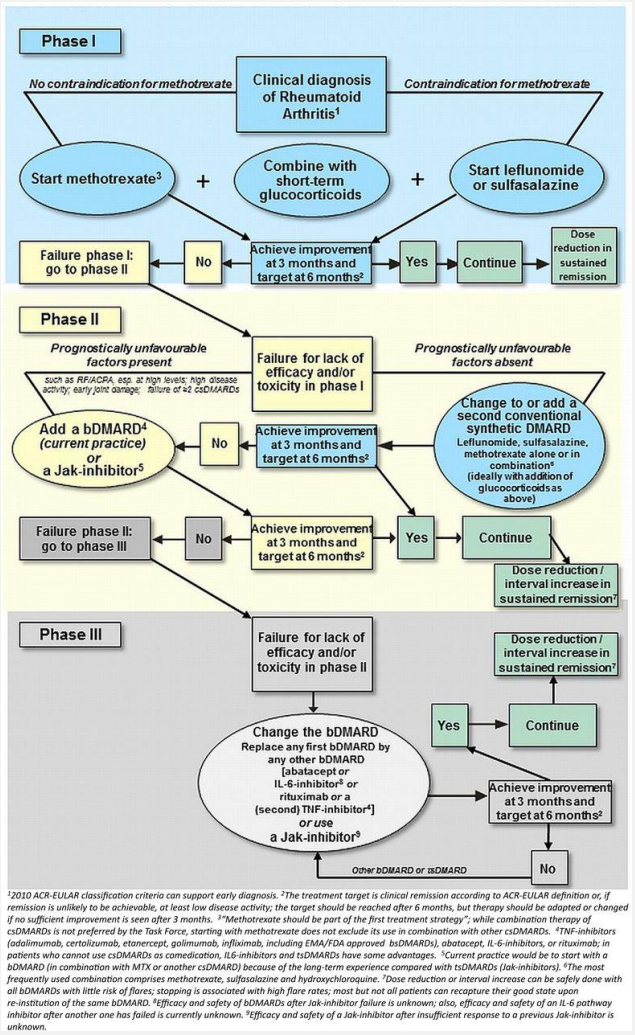
Lancet. 2018 Jun 23;391(10139):2503-2512. doi: 10.1016/S0140-6736(18)31115-2. Epub 2018 Jun 18.

Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial.

Burmester GR[1], Kremer JM[2], Van den Bosch F[3], Kivitz A[4], Bessette L[5], Li Y[6], Zhou Y[6], Othman AA[6], Pangan AL[6], Camp HS[6].

Peficitinib and decernotinib -> novel selective inhibitors of JAK3

Η ΘΕΣΗ ΤΩΝ ΑΝΑΣΤΟΛΕΩΝ JAK ΣΤΗ ΘΕΡΑΠΕΥΤΙΚΗ ΑΛΥΣΙΔΑ



[1]2010 ACR-EULAR classification criteria can support early diagnosis. [2]The treatment target is clinical remission according to ACR-EULAR definition or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if no sufficient improvement is seen after 3 months. [3]"Methotrexate should be part of the first treatment strategy"; while combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs. [4]TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved bsDMARDs), abatacept, IL-6-inhibitors, or rituximab; in patients who cannot use csDMARDs as comedication, IL6-inhibitors and tsDMARDs have some advantages. [5]Current practice would be to start with a bDMARD (in combination with MTX or another csDMARD) because of the long-term experience compared with tsDMARDs (Jak-inhibitors). [6]The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine. [7]Dose reduction or interval increase can be safely done with all bDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same bDMARD. [8]Efficacy and safety of bDMARDs after Jak-inhibitor failure is unknown; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. [9]Efficacy and safety of a Jak-inhibitor after insufficient response to a previous Jak-inhibitor is unknown.

Josef S Smolen et al. Ann Rheum Dis 2017;76:960-977

If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD or a tsDMARD* should be considered; current practice would be to start a bDMARD§*

SRF

ARD

ΠΑΡΟΝ/ΜΕΛΛΟΝ - ΑΝΑΠΑΝΤΗΤΑ ΕΡΩΤΗΜΑΤΑ

- Real-life effectiveness and safety (herpes zoster, malignancy) → REGISTRY DATA!!!
- JAK switching?
- Place in the treatment algorithm – sequential use
- Biomarkers, predictors of response → tailored treatment

EXTERNAL VALIDITY!!!

Observational studies

RCTs

ΠΑΡΟΝ/ΜΕΛΛΟΝ - ΑΝΑΠΑΝΤΗΤΑ ΕΡΩΤΗΜΑΤΑ

- Real-life effectiveness and safety (herpes zoster, malignancy) → REGISTRY DATA!!!
- JAK switching? Efficacy? Safety?
- Place in the treatment algorithm – sequential use
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EXTERNAL VALIDITY!!!

Observational studies

RCTs

SWITCHING

	INF→ETA N=242	INF→ADA N=101	ETA→INF N=58	ETA→ADA N=329	ADA→INF N=16	ADA→ETA N=206
ΔDAS28 6 months	-1.6±1.5	-1.2±1.6	-1.2±1.6	-0.7±1.5	-0.6±0.9	-1.2±1.6

p=0.004

	Primary inefficacy	Secondary inefficacy	Intolerance
ΔDAS28 6 months	-1.2±1.6	-1.4±1.6	-1.1±1.5
LDA/remission	26%	40%	39%

p<0.0001

Chatzidionysiou K. et al., Ann Rheum Dis. Jan 2014

ΠΑΡΟΝ/ΜΕΛΛΟΝ - ΑΝΑΠΑΝΤΗΤΑ ΕΡΩΤΗΜΑΤΑ

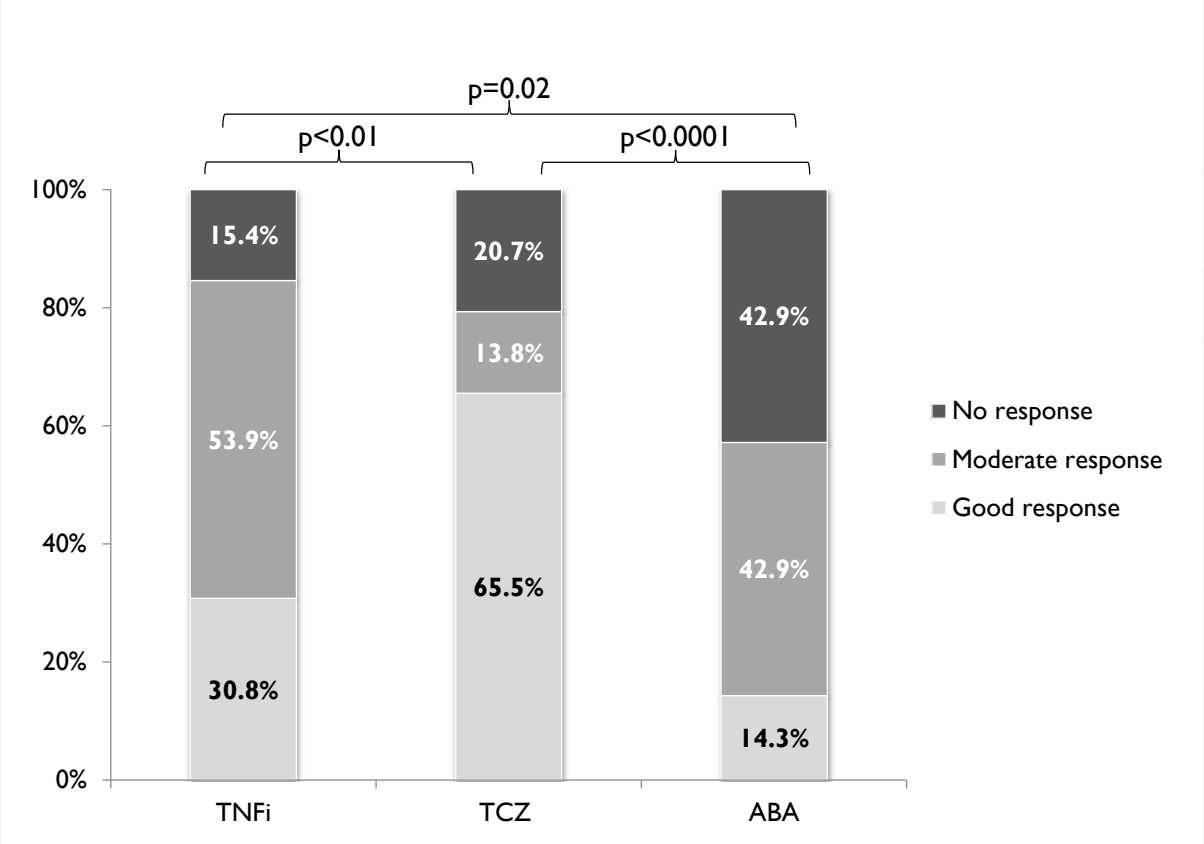
- Real-life effectiveness and safety (herpes zoster, malignancy) → REGISTRY DATA!!!
- JAK switching? Efficacy? Safety?
- Place in the treatment algorithm – sequential use? Efficacy and safety of particular bDMARDs before and after JAKi?
- Biomarkers, predictors of response → tailored treatment

EXTERNAL VALIDITY!!!

Observational studies

RCTs

SEQUENTIAL USE OF BIOLOGICS



EULAR responses at month 6 in the three treatment groups. P-values refer to pairwise comparisons of bDMARDs by means of Pearson's X^2-tests.

Walker et al. Rheumatology 2014

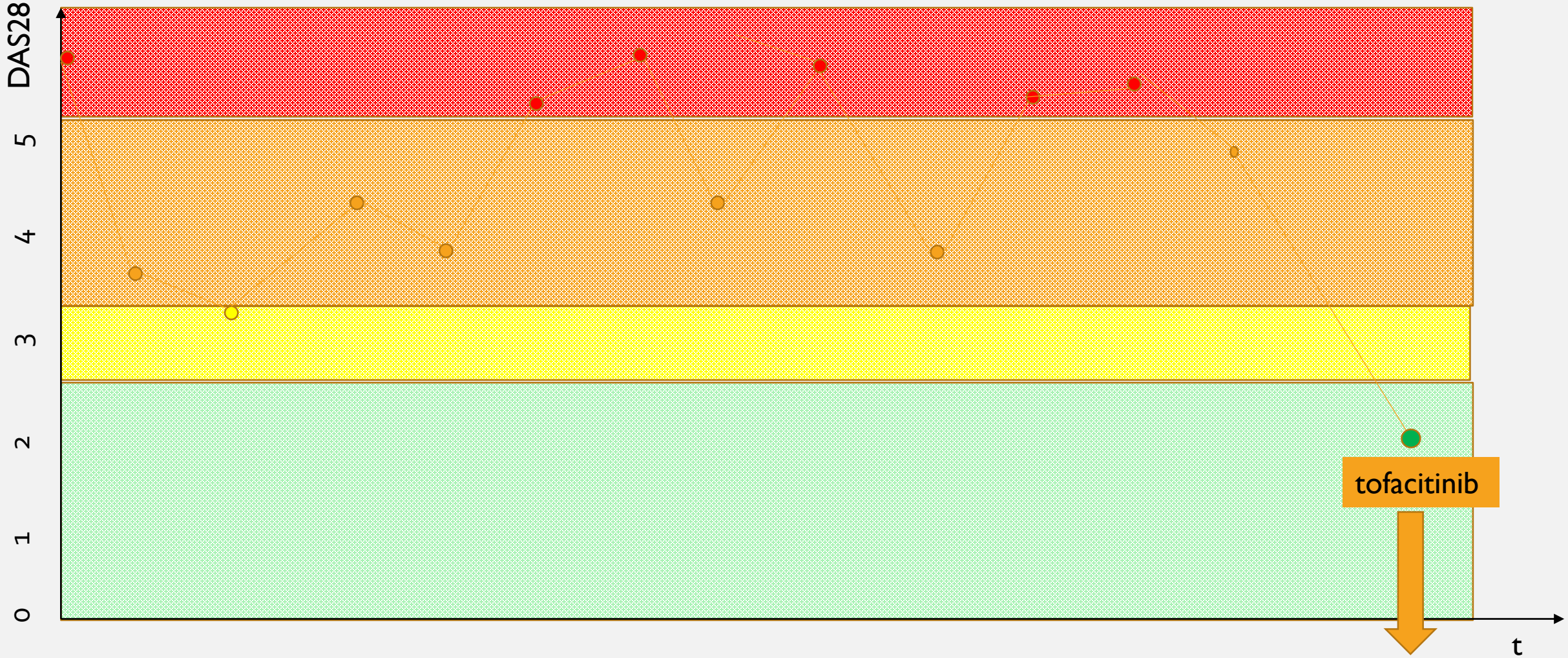
ΠΑΡΟΝ/ΜΕΛΛΟΝ - ΑΝΑΠΑΝΤΗΤΑ ΕΡΩΤΗΜΑΤΑ

- Real-life effectiveness and safety (herpes zoster, malignancy) → REGISTRY DATA!!!
- JAK switching? Efficacy? Safety?
- Place in the treatment algorithm – sequential use
- Biomarkers, predictors of response → tailored treatment

EXTERNAL VALIDITY!!!

Observational studies

RCTs



MTX sc	MTX sc SAL	MTXsc SAL INF	MTXcs SAL ETA	…. …. …..	LEF RTX	LEF ABA	LEF TCZ	????
GCs dose:	10mg/d	20mg/d	30mg/d	….	15mg/d	30mg/d	17,5mg/d	

Σας ευχαριστώ