ΑΝΑΣΤΟΛΕΙΣ ΚΙΝΑΣΩΝ ΣΤΗΝ ΡΕΥΜΑΤΟΕΙΔΗ ΑΡΘΡΙΤΙΔΑ

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

OUTLINE

- A whole new DMARD category
- Do we need it?
- Is it efficacious?
- Is it safe?
- What is the target-population?
- Future?

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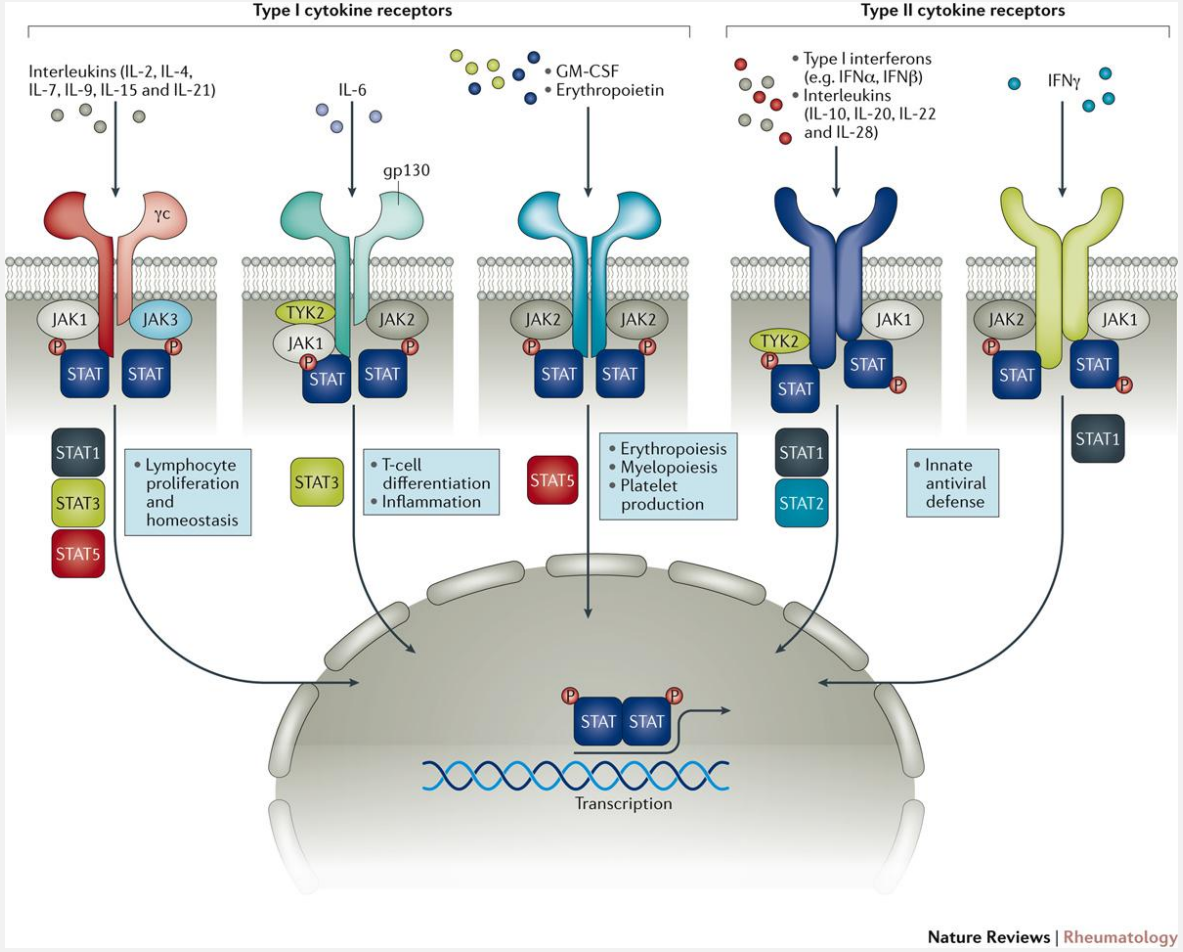
CYTOKINE RECEPTORS AND JAK SIGNALLING



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

THERAPEUTIC PRINCIPLE OF JAK INHIBITION

- JAKs are critical to immune function and homeostasis
- JAK isoform knock-out animals have severe clinical phenotypes
  - JAK1 deficient mice die perinatally
  - JAK2 knockout animals are embryonic lethal due to defective erythropoiesis
  - JAK3 deficient mice suffer from severe immunodeficiency sundrome
  - TYK2 deficient mice are viable but susceptible to viral infection due to reduced IFN response

Complete blockade of JAK isoforms is undesirable

- **Objective→ NOT to specifically block the JAK pathway completely, but to reversibly reduce the activity of one or more JAK isoforms**

JAK ISOFORM SELECTIVITY – DOES IT MATTER?

In vitro JAK isoform selectivity

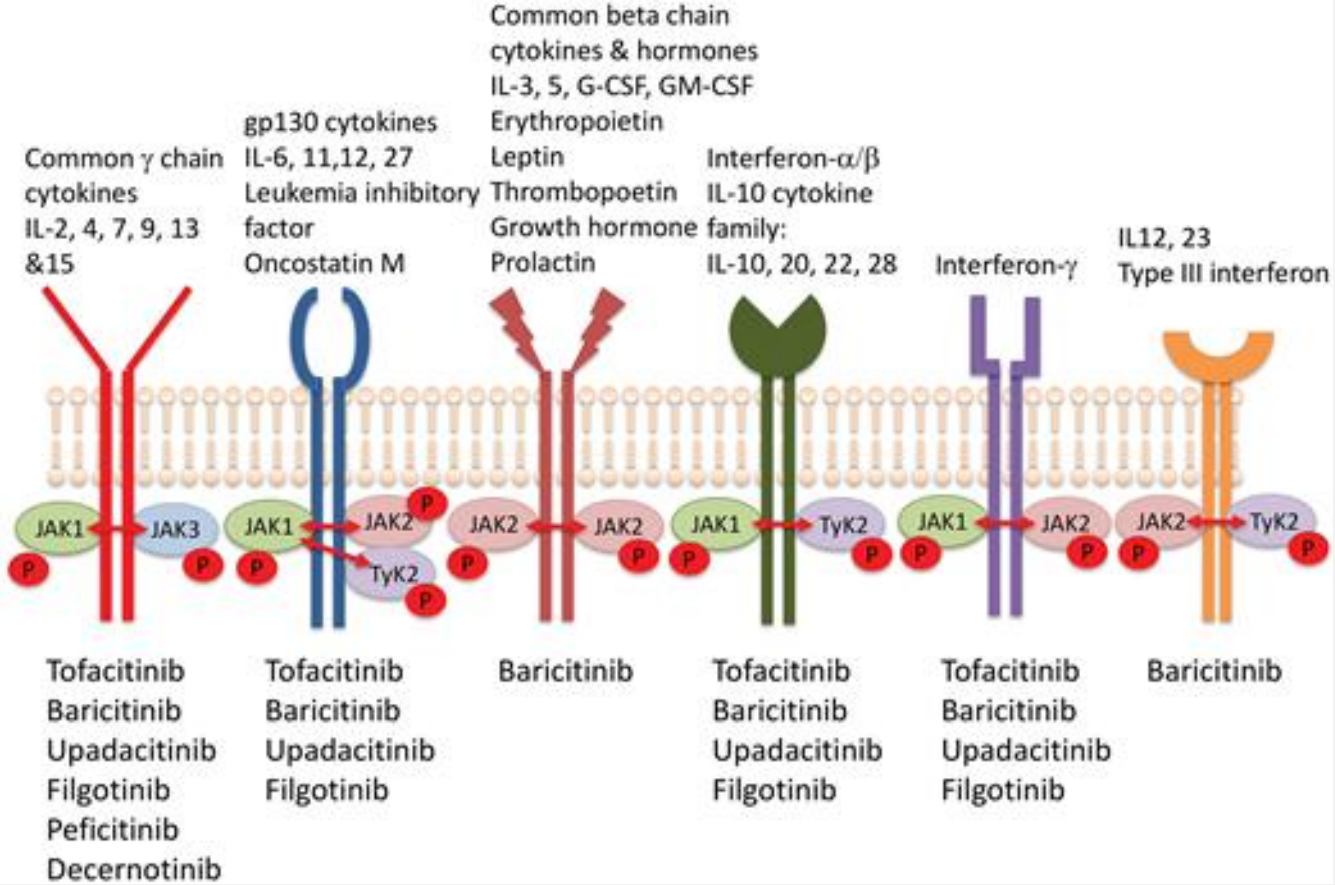
	Enzyme essay IC50 (nM)						
Compound	**JAK1**	**JAK2**	**JAK3**	**TYK2**	**JAK2:JAK1**	**JAK3:JAK1**	**TYK2:JAK1**
Tofacitinib	15.1	77.4	55.0	489	5.1	3.6	32.4
Baricitinib	4.0	6.6	787	61	1.5	196.8	15.3
Filgotinib	363	2400	>10 000	2600	6.6	>27.5	7.2
Upadacitinib	8	600	139	NA	75	17.4	NA
Peficitinib	3.9	5.0	0.7	4.8	1.3	0.2	1.2
Decernotinib	112	619	74.4	>10 000	5.5	0.67	>89

JAK: Janus kinase; IC50: half maximal inhibitory concentration; TYK2: Non-receptor Tyrosine-protein Kinase 2.

- JAK inhibitors are selective but not specific
- Ratio of IC50
- JAK selectivity dose window
- Highly potent compounds will have narrow windows

- The clinical impact of JAK isoform selectivity is dependent on dose, cell type, tissue penetration, genetics

JAK ISOFORM SELECTIVITY – DOES IT MATTER?



- All current JAKi approved and in development have a significant effect on JAK1
- JAK1 is involved in signalling transduction of IL-6, IFN and the common γ-chain cytokines including IL-2 and IL-15.
- Common side effects with IL-6 inhibition
- INF-γ suppression → important contributor to the clinical benefit?

→ potential explanation for herpes zoster reactivation

- JAK 2 targeting – GM-CSF → probably efficacious in RA

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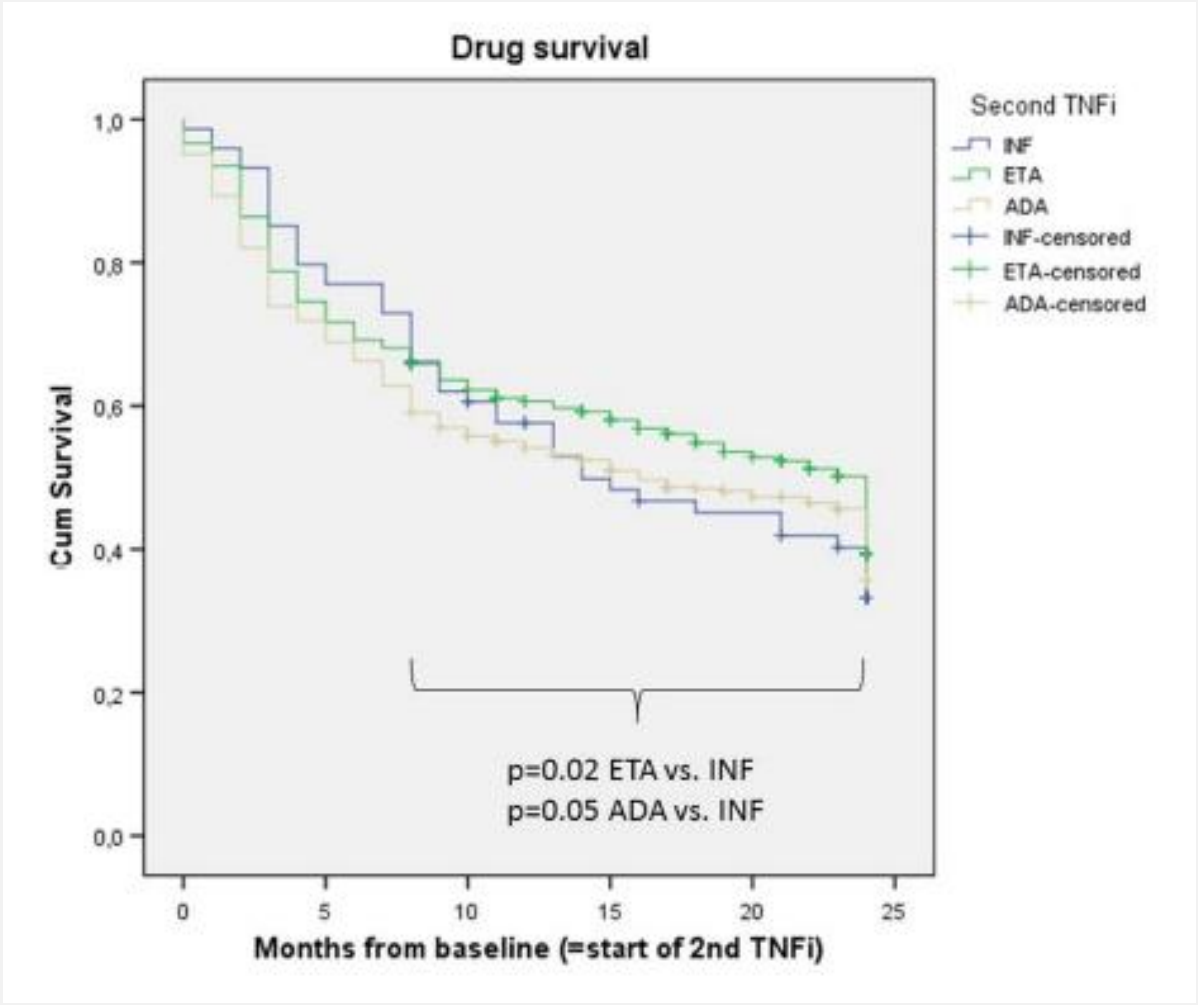
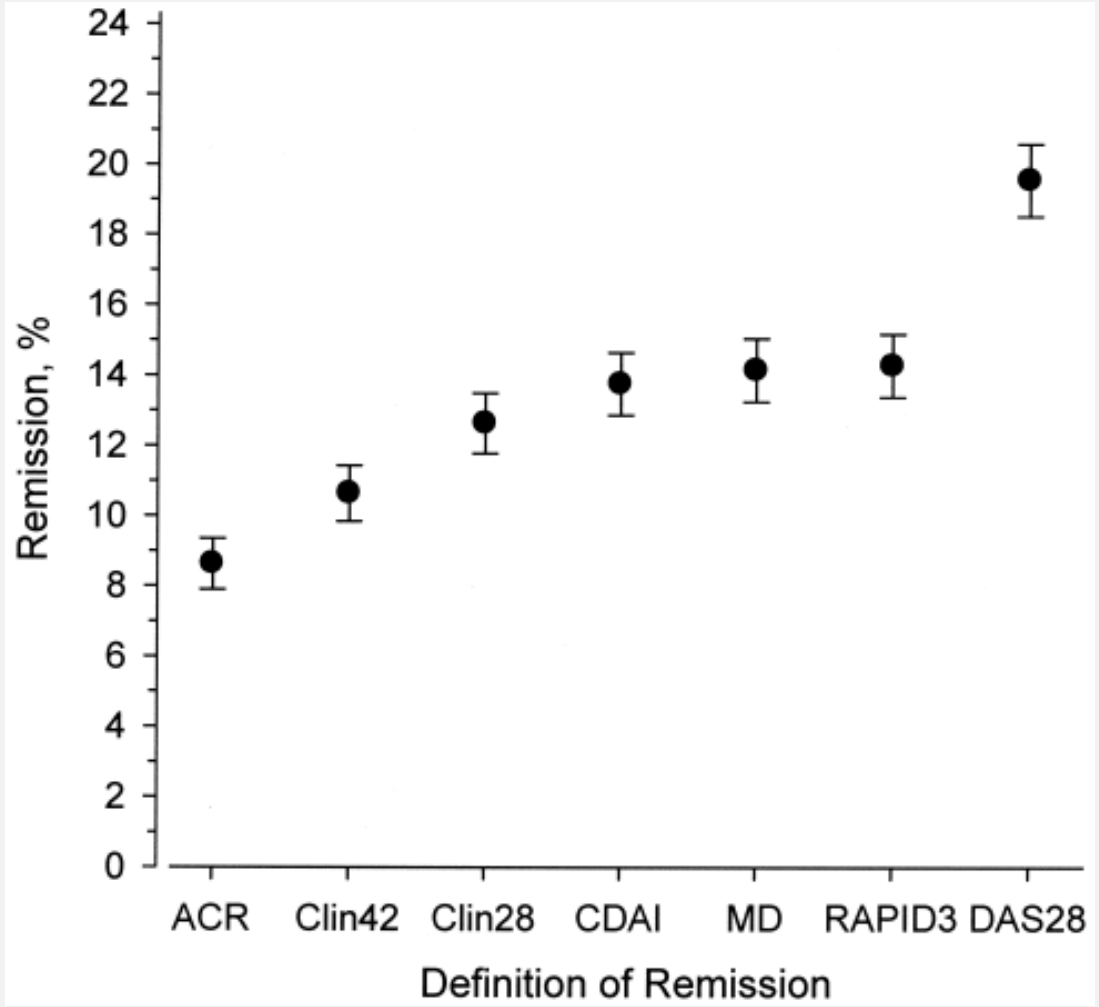
UNMET NEEDS



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

Clinical and epidemiological research

Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

Lianne Kearsley-Fleet[1], Rebecca Davies[1], Diederik De Cock[1], Kath D Watson[1], Mark Lunt[1], Maya H Buch[2, 3], John D Isaacs[4], Kimme L Hyrich[1, 5] the BSRBR-RA Contributors Group

Author affiliations +

Abstract

Objectives Biologic disease-modifying antirheumatic drugs (bDMARDs) have revolutionised treatment and outcomes for rheumatoid arthritis (RA). The expanding repertoire allows the option of switching bDMARD if current treatment is not effective. For some patients, even after switching, disease control remains elusive. This analysis aims to quantify the frequency of, and identify factors associated with, bDMARD refractory disease.

Methods Patients with RA starting first-line tumour necrosis factor inhibitor in the British Society for Rheumatology Biologics Register for RA from 2001 to 2014 were included. We defined patients as bDMARD refractory on the date they started their third class of bDMARD. Follow-up was censored at last follow-up date, 30 November 2016, or death, whichever came first. Switching patterns and stop reasons of bDMARDs were investigated. Cox regression identified baseline clinical factors associated with refractory disease. Multiple imputation of missing baseline data was used.

Results 867 of 13 502 (6%) patients were bDMARD refractory; median time to third bDMARD class of 8 years. In the multivariable analysis, baseline factors associated with bDMARD refractory disease included patients registered more recently, women, younger age, shorter disease duration, higher patient global assessment, higher Health Assessment Questionnaire score, current smokers, obesity and greater social deprivation.

Conclusions This first national study has identified the frequency of bDMARD refractory disease to be at least 6% of patients who have ever received bDMARDs. As the choice of bDMARDs increases, patients are cycling through bDMARDs quicker. The aetiopathogenesis of bDMARD refractory disease requires further investigation. Focusing resources, such as nursing support, on these patients may help them achieve more stable, controlled disease.

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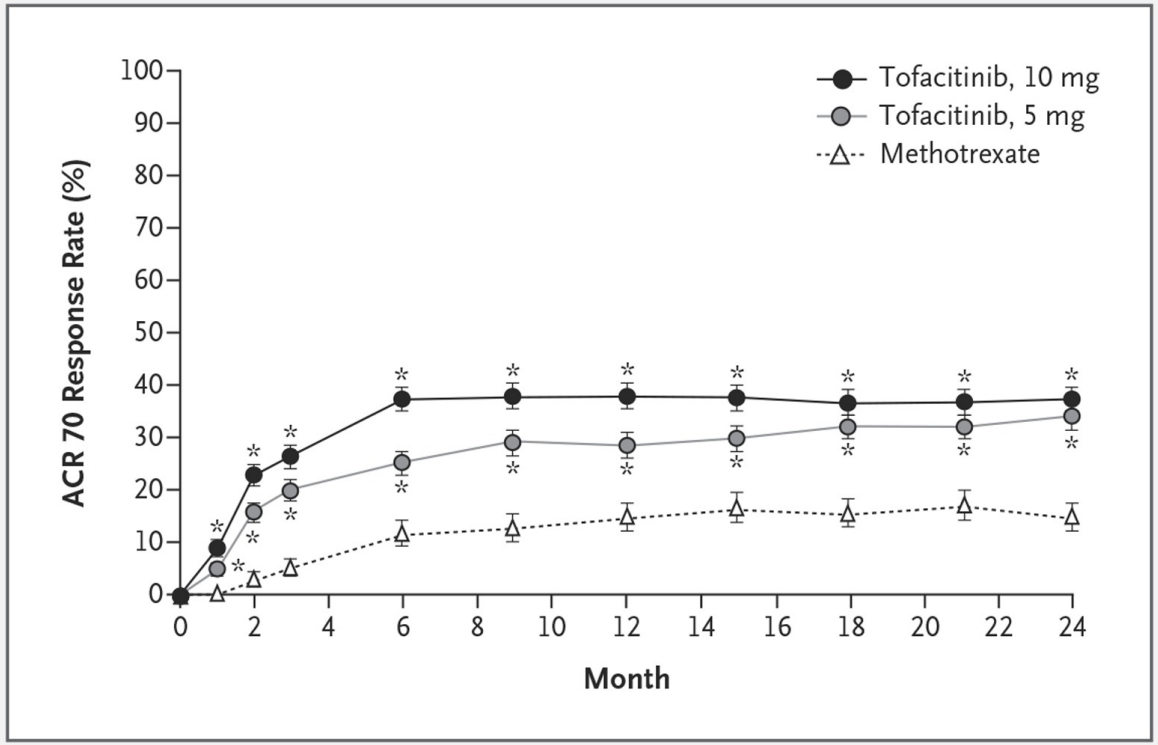
TOFACITINIB ΣΤΗΝ PA

- 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

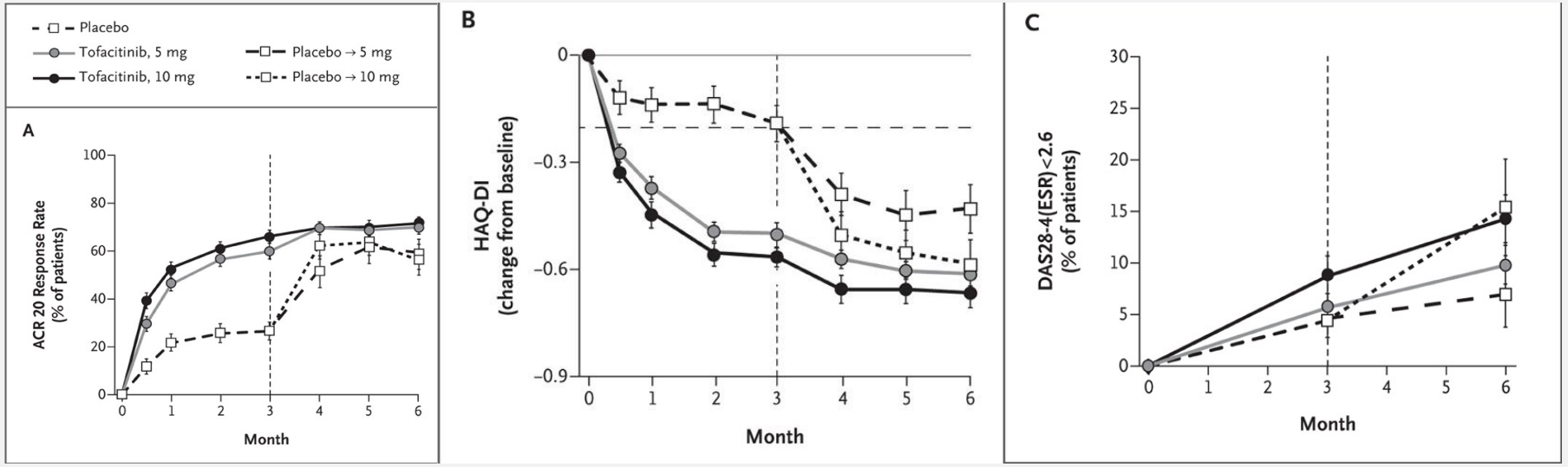


Tofacitinib > MTX

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

ORAL SOLO

TOFA MONO
csDMARDs or
bDMARDs IR



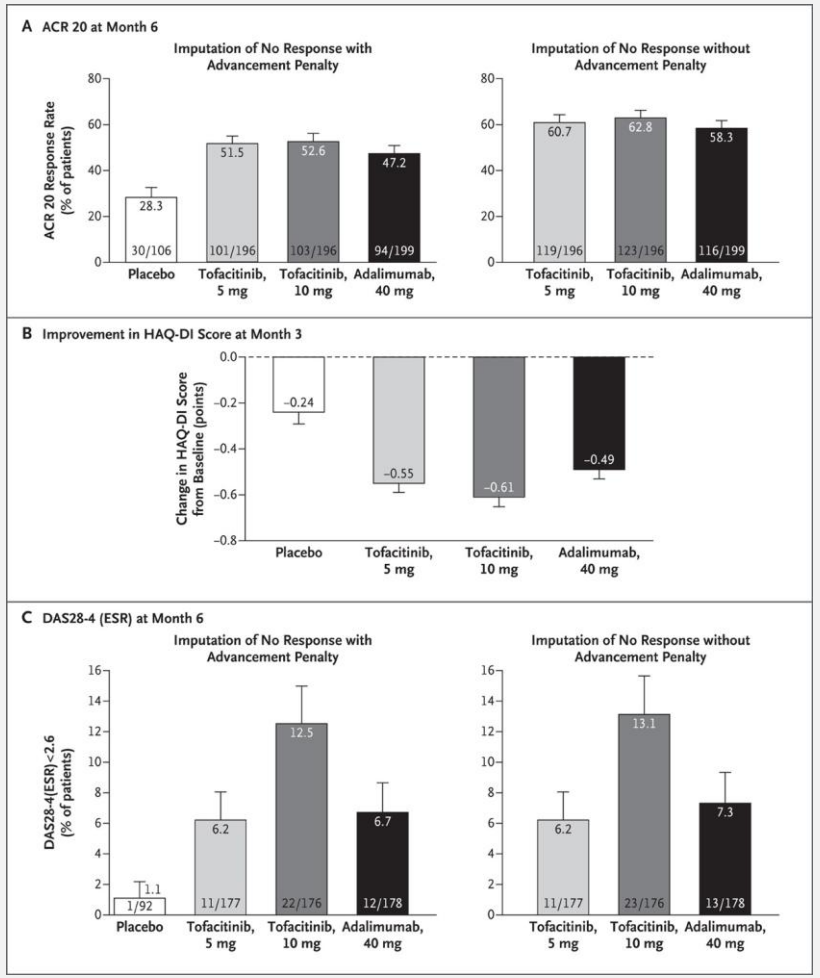
- Double-blind, placebo-controlled, monotherapy RCT
- 619 RA patients who had failed ≥1 csDMARD or bDMARD
- The primary end points of achieving an ACR20 and improvement of HAQ-DI from baseline at week 12 was met but there was no statistically significant difference in achieving a DAS28(ESR) < 2.6 between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

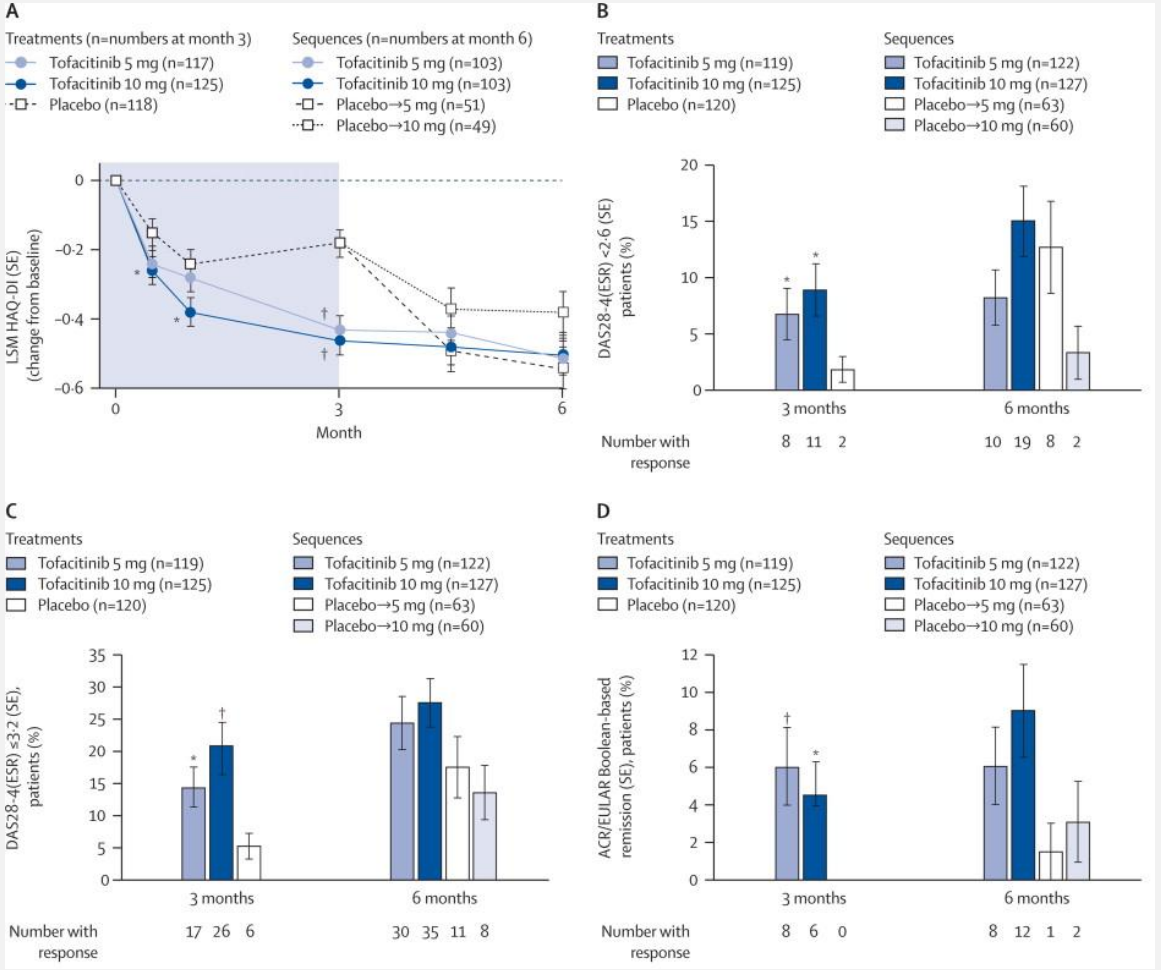


Van Vollenhoven R. et al, Tofacitinib or Adalimumab versus Placebo in Rheumatoid Arthritis. N Engl J Med 2012; 367:508-519

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.

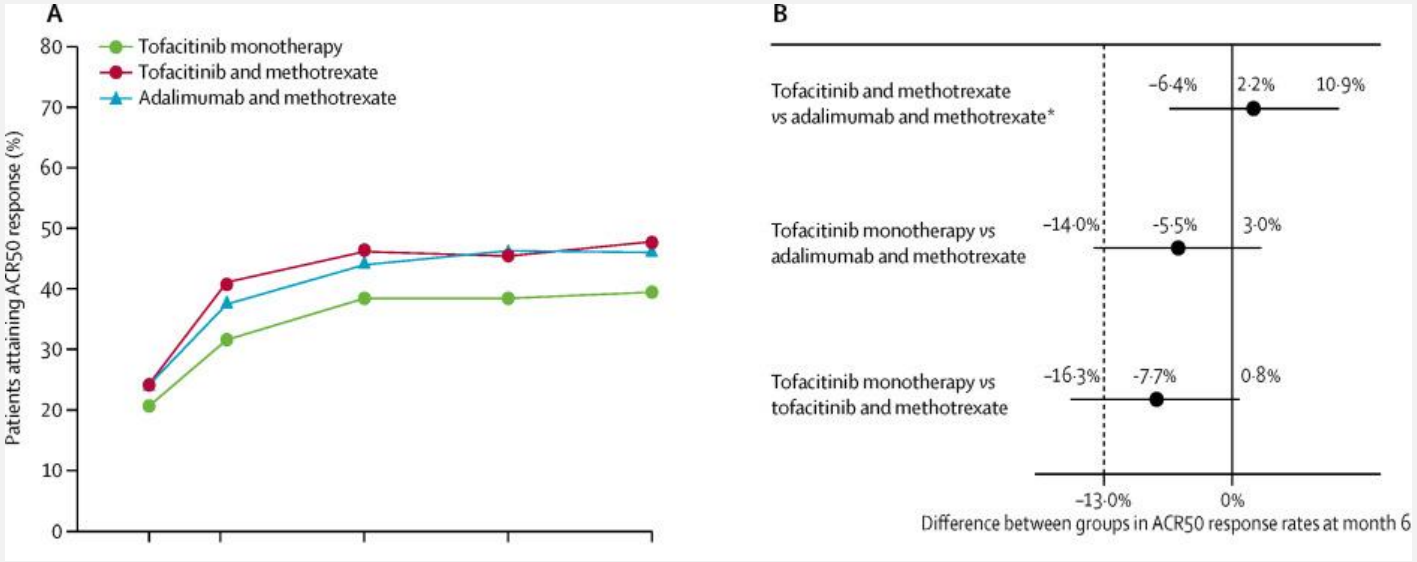


*Burmester G, Blanco R, Charles-Schoeman C et al.**Lancet** 381(9865), 451–460 (2013*

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')

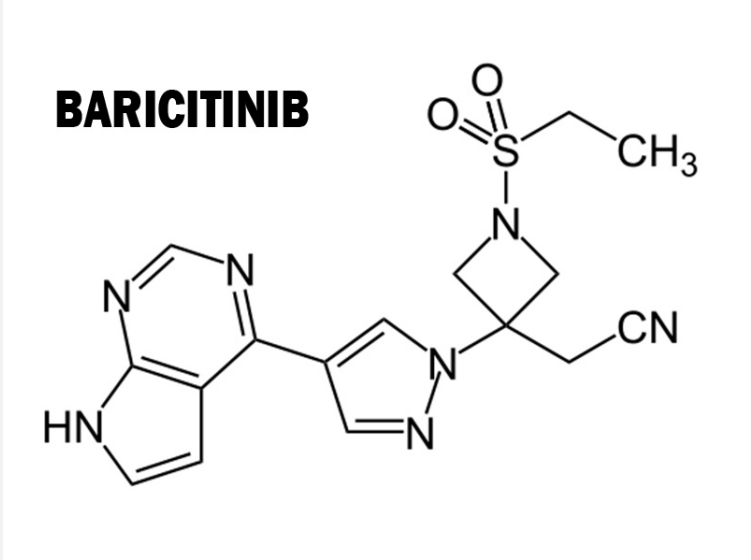


- **These results suggest that in a group of patients, more patients will achieve an ACR50 in 6 months if treated with the combination of MTX + either tofacitinib or ADA compared with treatment with tofacitinib monotherapy.**

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

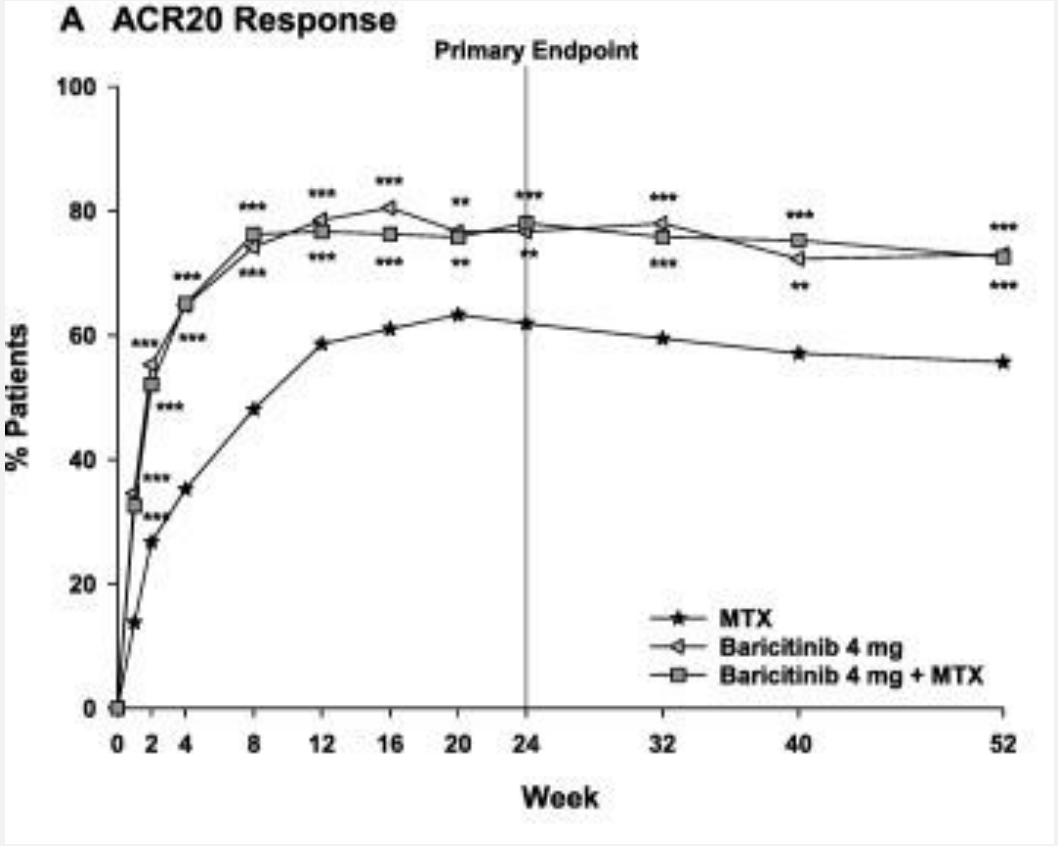
- reversible inhibition of JAK1 and JAK2



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



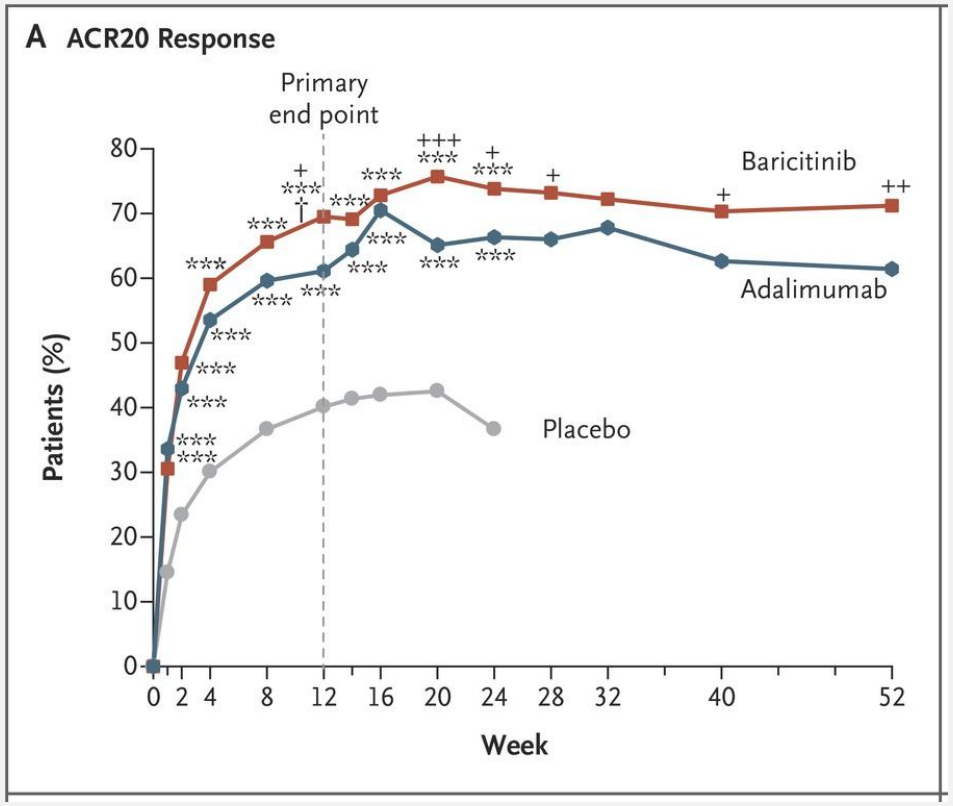
Fleischmann et al. Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. Arthritis Rheumatol. 2017 Mar; 69(3): 506–517.

RA BEAM

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

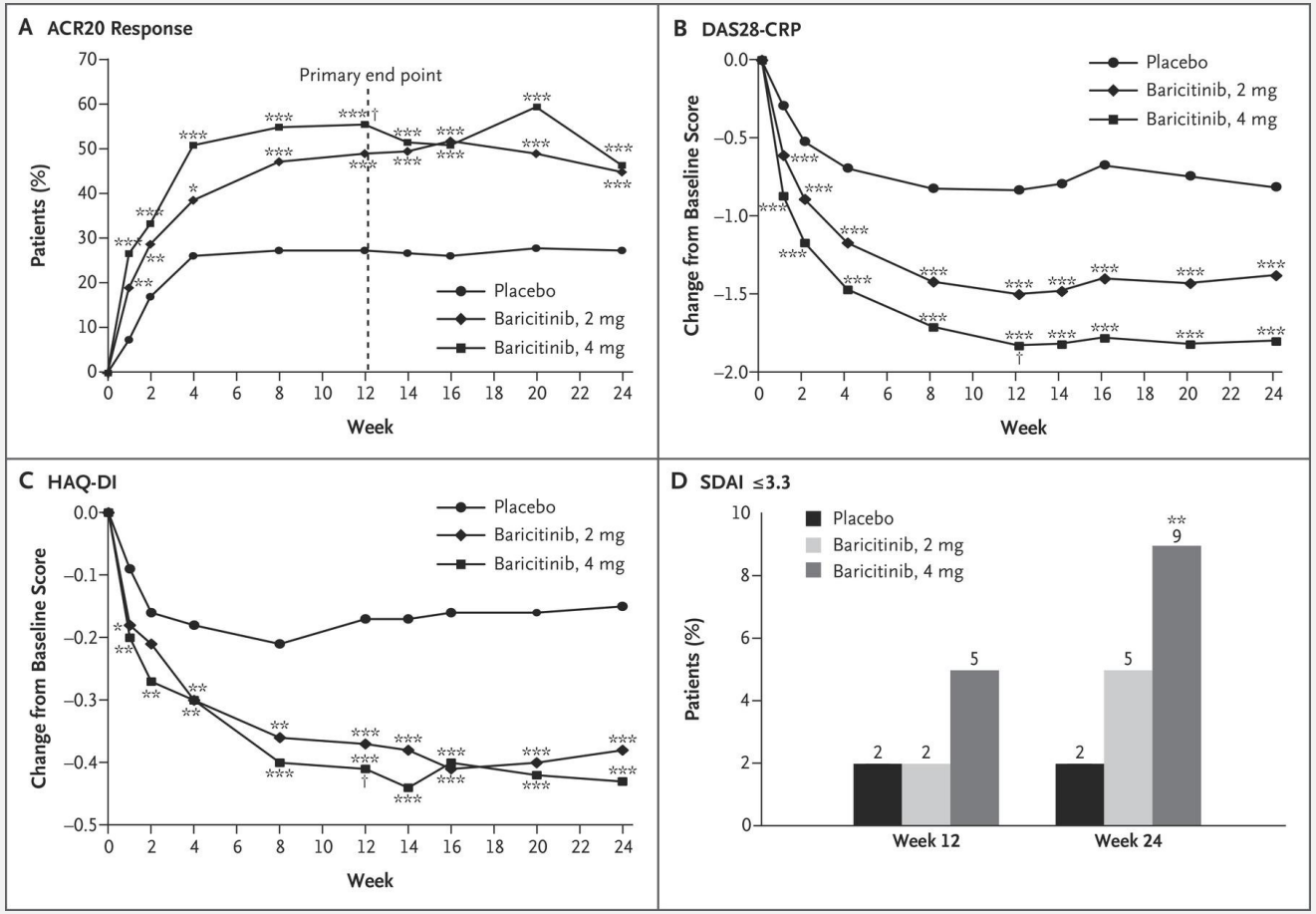
superiority — 70% vs 40% (p<0.001)

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

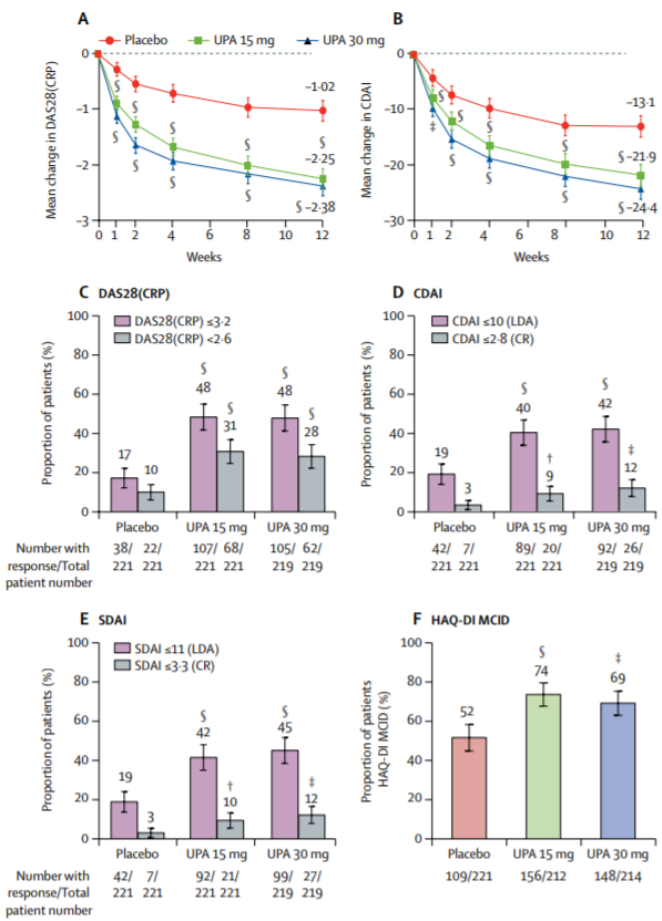


Genovese et al. Baricitinib in patients with refractory Rheumatoid Arthritis. N Engl J Med 2016

- 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)

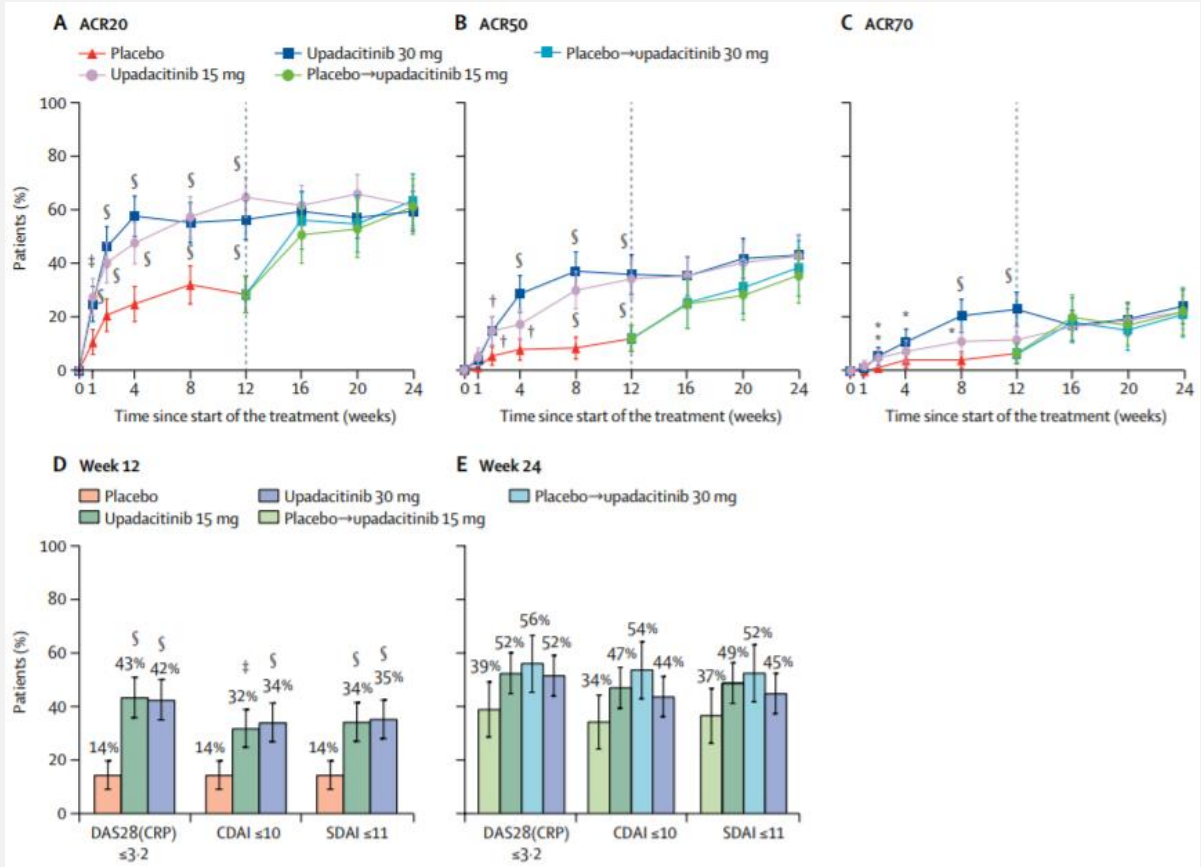
Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial

Gerd R Burmester, Joel M Kremer, Filip Van den Bosch, Alan Kivitz, Louis Bessette, Yihan Li, Yijie Zhou, Ahmed A Othman, Aileen L Pangan, Heidi S Camp



Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial

Mark C Genovese, Roy Fleischmann, Bernard Combe, Stephen Hall, Andrea Rubbert-Roth, Ying Zhang, Yijie Zhou, Mohamed-Eslam F Mohamed, Sebastian Meerwein, Aileen L Pangan



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INFECTIONS

- The IR of serious infections is 2.7/100 patient years (95% CI 2.5–3.9) and 2.9/100 patient years (95% CI 2.5–3.4) for tofacitinib and baricitinib, respectively.
- Both tofacitinib and baricitinib are associated with increased incidence of reactivation of herpes zoster (3–4/100 patient years).
- This is higher than placebo and exceeds those expected with biologic agents. Risk is highest in Japan and Korea.
- Concomitant glucocorticoid is an additional risk factor.
- Reactivation of herpes zoster appears to be a class effect and may be due to inhibition of IFN and IL-15, which are key anti-viral cytokines that signal through JAK1, JAK2 and JAK3.

Genovese MC et al. Safety profile of baricitinib for the treatment of rheumatoid arthritis up to 5.5 years: an updated integrated safety analysis.

Winthrop KL et al. Herpes zoster and tofacitinib. Clinical outcomes and the risk of concomitant therapy. *Arthritis Rheumatol* 2017 ;69:1960–8.

Arthritis Rheumatol. 2017 Oct;69(10):1969-1977. doi: 10.1002/art.40187. Epub 2017 Sep 6.

The Safety and Immunogenicity of Live Zoster Vaccination in Patients With Rheumatoid Arthritis Before Starting Tofacitinib: A Randomized Phase II Trial.

Winthrop KL[1], Wouters AG[2], Choy EH[3], Soma K[2], Hodge JA[2], Nduaka CI[4], Biswas P[2], Needle E[5], Passador S[2], Mojcik CF[2], Rigby WF[6].

Author information

Abstract

OBJECTIVE: Patients with rheumatoid arthritis (RA) are at increased risk of herpes zoster, and vaccination is recommended for patients ages 50 years and older, prior to starting treatment with biologic agents or tofacitinib. Tofacitinib is an oral JAK inhibitor for the treatment of RA. We evaluated its effect on the immune response and safety of live zoster vaccine (LZV).

METHODS: In this phase II, 14-week, placebo-controlled trial, patients ages 50 years and older who had active RA and were receiving background methotrexate were given LZV and randomized to receive tofacitinib 5 mg twice daily or placebo 2-3 weeks postvaccination. We measured humoral responses (varicella zoster virus [VZV]-specific IgG level as determined by glycoprotein enzyme-linked immunosorbent assay) and cell-mediated responses (VZV-specific T cell enumeration, as determined by enzyme-linked immunospot assay) at baseline and 2 weeks, 6 weeks, and 14 weeks postvaccination. End points included the geometric mean fold rise (GMFR) in VZV-specific IgG levels (primary end point) and T cells (number of spot-forming cells/10^6 peripheral blood mononuclear cells) at 6 weeks postvaccination.

RESULTS: One hundred twelve patients were randomized to receive tofacitinib (n = 55) or placebo (n = 57). Six weeks postvaccination, the GMFR in VZV-specific IgG levels was 2.11 in the tofacitinib group and 1.74 in the placebo group, and the VZV-specific T cell GMFR was similar in the tofacitinib group and the placebo group (1.50 and 1.29, respectively). Serious adverse events occurred in 3 patients in the tofacitinib group (5.5%) and 0 patients (0.0%) in the placebo group. One patient, who lacked preexisting VZV immunity, developed cutaneous vaccine dissemination 2 days after starting tofacitinib (16 days postvaccination). This resolved after tofacitinib was discontinued and the patient received antiviral treatment.

CONCLUSION: Patients who began treatment with tofacitinib 2-3 weeks after receiving LZV had VZV-specific humoral and cell-mediated immune responses to LZV similar to those in placebo-treated patients. Vaccination appeared to be safe in all of the patients except 1 patient who lacked preexisting VZV immunity.

TRIAL REGISTRATION: ClinicalTrials.gov NCT02147587.

GASTROINTESTINAL PERFORATION

- Gastrointestinal perforation is associated with IL-6 inhibition.
- IL-6 signals via JAK1, JAK2 and TYK2. Therefore, inhibiting IL-6 signalling by JAKi may be associated with gastrointestinal perforation.
- IR of gastrointestinal perforation was 0.11/100 patient years (95% CI 0.07–0.17) for tofacitinib and 0.05/100 patient years (95% CI 0.01–0.13) for baricitinib.
- These were numerically lower than that was observed with tocilizumab reported in German biologic registry, which was 0.27/100 patient years

DEEP VEIN THROMBOSIS AND PULMONARY EMBOLUS

- Five cases of deep vein thrombosis and pulmonary embolus (DVT/PE) were observed in baricitinib- (IR 1.2/100 patient years) but none in the placebo-treated patients during RCTs
- The overall IR of DVT/PE was 0.5/100 patient years (95% CI 0.3–0.7)
- There was no association between platelet count and the occurrence of DVT/PE.

!!!
- FDA warning tofacitinib: 10mg x 2, patients >50 yo, with at least one cardiovascular risk factor → increased occurence of PE and death

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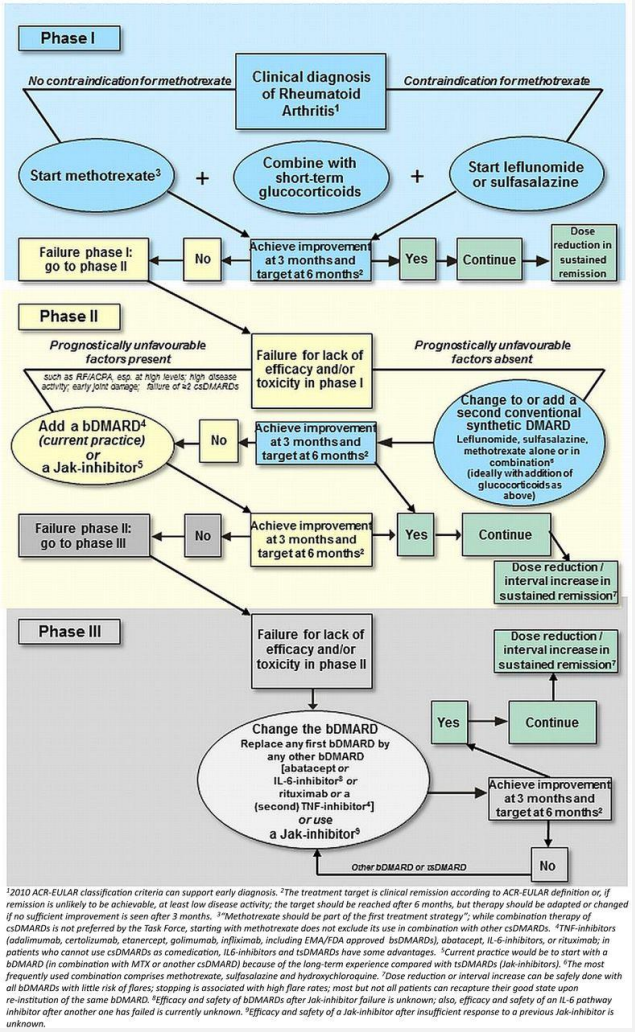
Η ΘΕΣΗ ΤΩΝ ΑΝΑΣΤΟΛΕΩΝ JAK ΣΤΗ ΘΕΡΑΠΕΥΤΙΚΗ ΑΛΥΣΙΔΑ



[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.

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§.*

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

ARD

OUTLINE

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ΠΑΡΟΝ/ΜΕΛΛΟΝ - ΑΝΑΠΑΝΤΗΤΑ ΕΡΩΤΗΜΑΤΑ

- Real-life effectiveness and safety (cardiovascular, 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!!!
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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? Efficacy and safety of particular bDMARDs before and after JAKi?
- 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
- Biomarkers, predictors of response → tailored treatment

EXTERNAL VALIDITY!!!

Observational studies

RCTs

REAL-LIFE EFFECTIVENESS AND SAFETY OF JAK INHIBITORS (TOFACITINIB, BARICITINIB) IN RHEUMATOID ARTHRITIS

Ημερομηνία

Αρχικά ασθενούς:

ΑΜΚΑ:

Ηλικία:

Φύλο:

Εκπαίδευση:

Κλινική:

Γενικά χαρακτηριστικά νόσου

'Ετος διάγνωσης: .....

RF: θετικό αρνητικό

Anti-CCP: θετικό αρνητικό

Ακτινολογική εικόνα: διαβρώσεις: ΝΑΙ ΟΧΙ

Μείωση αρθρικού διαστήματος: ΝΑΙ ΟΧΙ

Εξωαρθρικές εκδηλώσεις:

.....

.....

Προηγούμενες θεραπείες	Λόγος διακοπής (primary inefficacy, secondary inefficacy, intolerance)
csDMARDs	
1.	1. .....
2.	2. .....
3.	3. .....
4.	4. .....
bioDMARDs χρονολογικά	
1.	1. .....
2.	2. .....
3.	3. .....
4.	4. .....
5.	5. .....

PA

ΣΥΝΝΟΣΗΡΟΤΗΤΕΣ

1. Καρδιαγγειακή νοσηρότητα και παράγοντες κινδύνου
   a. Κάπνισμα
      i. Ποτέ
      ii. Πρώην
      iii. Ενεργός – packet/year: .....
   b. Υπέρταση
      i. Ναι ρυθμισμένη
      ii. Ναι μη ρυθμισμένη
      iii. Οχι'
   c. Σακχαρώδης Διαβήτης: ΝΑΙ ΟΧΙ
   d. Υπερλιπιδαιμία ΝΑΙ ΟΧΙ
   d. Υψος Βάρος
   e. ΤΙΑ ή οξύ εγκεφαλικό επεισόδιο:
      ΝΑΙ ΟΧΙ
   f. Οξύ έμφραγμα μυοκαρδίου, ασταθή στηθάγχη: ΝΑΙ ΟΧΙ
2. Κακοήθη νεοπλάσματα ΝΑΙ ΟΧΙ
   Αν ναι διάγνωση και έτος διάγνωσης
   .....
3. Λοιμώξεις που χρειάστηκαν εισαγωγή σε νοσοκομείο τα τελευταία 5 έτη ΝΑΙ ΟΧΙ
4. Ψυχιατρική νόσος διεγνωσμένη από ψυχίατρο ΝΑΙ ΟΧΙ
   Αν ναι αγωγή: .....
6. Αρθροπλαστική ΝΑΙ ΟΧΙ Αν ναι έτος.....
7. Εμβόλια τον τελευταίο χρόνο:
   Γρίπης Πνευμονιόκοκκου
   Έρπητα Ζωστηρα Ηπατίτιτδας Β 'Αλλο
8. ΧΑΠ ή ενδιάμεση πνευμονοπάθεια ΝΑΙ ΟΧΙ
9. Χρόνια νεφρική ανεπάρκεια ΝΑΙ ΟΧΙ

***** Τα έγχρωμα κουτιά συμπληρώνονται ΜΟΝΟ στην πρώτη επίσκεψη**

Εκτίμηση ενεργότητας νόσου και PROs

SJC: ...../28 ...../66

TJC: ...../28 ...../68

ESR: .....

CRP:.....

VAS Pain: ...../10 (cm)

VAS Patient Global: ...../10 (cm)

VAS Physician Global: ...../10 (cm)

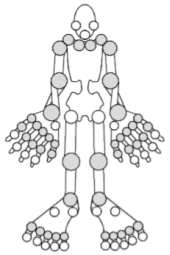
HAQ: ...../3

Κόπωση: ...../10 (cm)

EQ5D: .....

HAD score: .....

Παρούσα νόσος – συμπτώματα, κλινική εξέταση



Παρούσα φαρμακευτική αγωγή

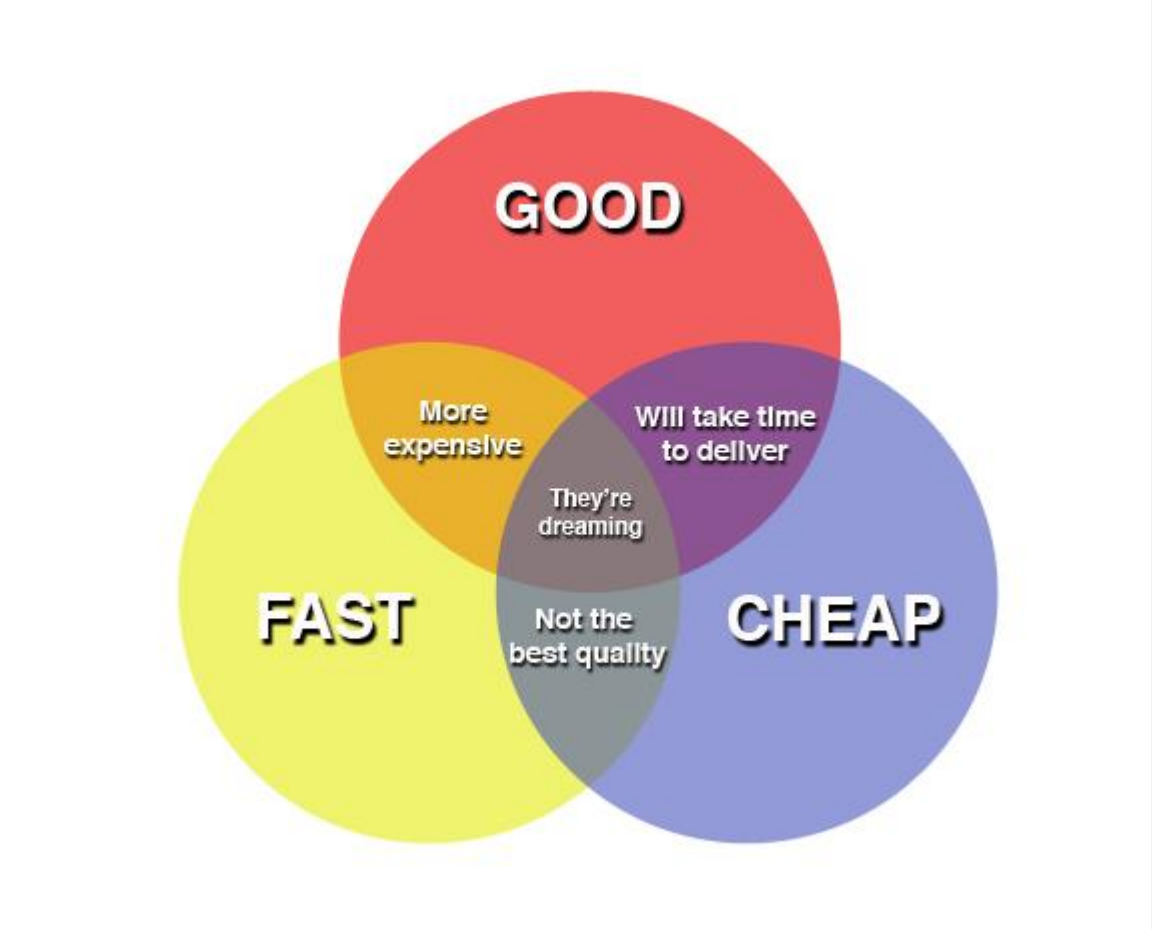
	Όνομα φαρμάκου	Δόση	Οδός χορήγησης	Ημερομηνία έναρξης	Ημερομηνία διακοπής	Λόγος διακοπής*
csDMARD						
bDMARD						
JAK inhibitor						
Κορτικοστεροειδή						

* primary inefficacy, secondary inefficacy, intolerance, other

Ανεπιθύμητες ενέργειες από την τελευταία επίσκεψη

ΝΑΙ ΟΧΙ αν ΝΑΙ περιγράψτε: .....

COST!!!


GOOD
More expensive
Will take time to deliver
They're dreaming
FAST
Not the best quality
CHEAP

TAKE HOME MESSAGES

- A whole new DMARD category
  - **Complete blockade of JAK isoforms is undesirable, objective is NOT to specifically block the JAK pathway completely, but to reversibly reduce the activity of one or more JAK isoforms**
  - **Selective but not specific, dose dependent**
  - **Selectivity might be significant for both efficacy and safety, but many side effects seen are a 'class effect'**
- Do we need it?
  - **Of course we do!!! Unmet needs, refractory patients**
- Is it efficacious?
  - **In all different patient populations (MTX naive, MTX IR, anti-TNF IR, non-TNFi- bDMARDs IR**
  - **FAST!!!**
- Is it safe?
  - **Infections, serious infections, Herpes zoster, malignancies, thromboembolic events!!**
- What is the target-population?
  - **All the above, patient preference**
- Future?
  - **REGISTRIES!!!! COST!!!! Prognostic factors?**

Σας ευχαριστώ