‘’Τα πολλά πρόσωπα της φλεγμονής και τα αποτελέσματα του Tofacitinib: δεδομένα 10ετίας”

Σπονδυλοαρθίτιδες

Στυλιανός Πανόπουλος

Ρευματολόγος

΄Α Προπαιδευτική Παθολογική Κλινική, Γ.Ν.Α ΄΄ΛΑΙΚΟ΄΄

Δήλωση Σύγκρουσης Συμφερόντων

Για τη συγκεκριμένη ομιλία έχω λάβει τιμητική αμοιβή από την εταιρεία Pfizer

Έχω λάβει αμοιβή για ομιλίες και συμβουλευτικές δραστηριότητες από:

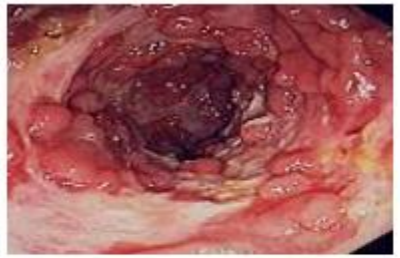
Pfizer, Abbvie, Amgen, Enorasis

Η Pfizer έχει ελέγξει το περιεχόμενο ώστε να ανταποκρίνεται στις ειδικές προδιαγραφές της αλλά δεν έχει επιβεβαιώσει ότι οι βιβλιογραφικές παραπομπές έχουν παρατεθεί ορθά.

Για όλα τα φαρμακευτικά προϊόντα που αναφέρονται παρακαλείσθε να συμβουλεύεστε / συμβουλευτείτε τις εγκεκριμένες Περιλήψεις Χαρακτηριστικών των Προϊόντων.

Τα πολλά πρόσωπα της φλεγμονής στις AxSpa/PsA

AxSpA

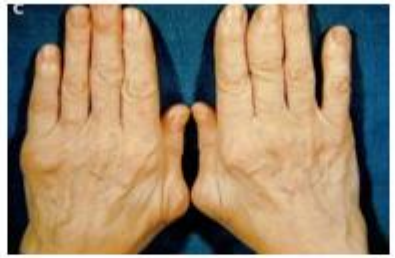


IBD

4–10%

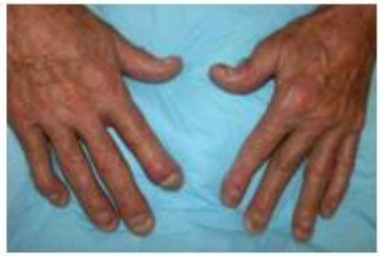
Uveitis

25–50%



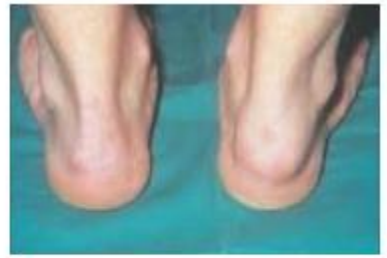
Peripheral arthritis

20-25 %



Dactylitis

5-7%

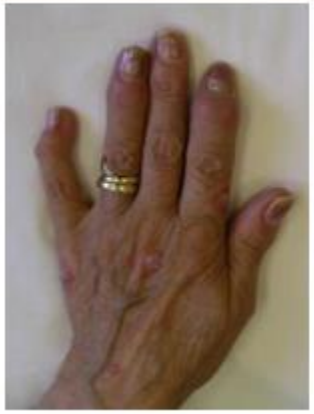
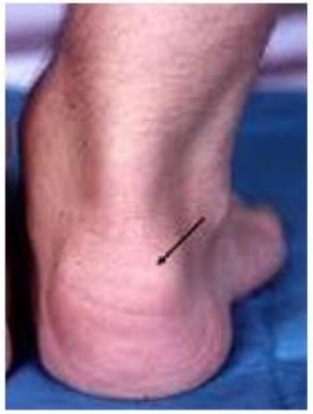
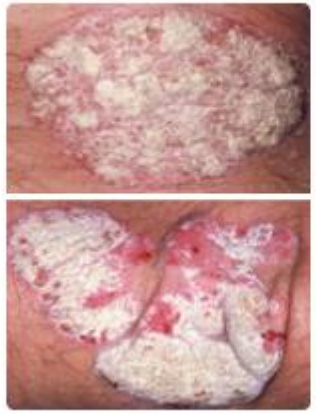
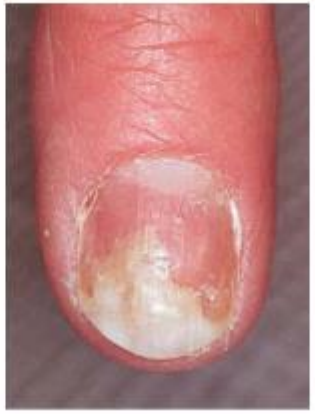
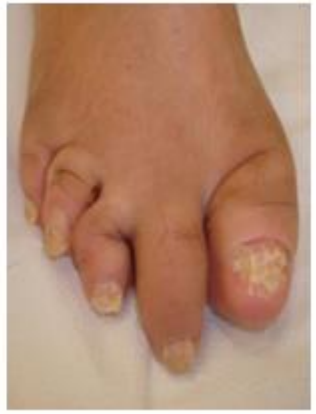
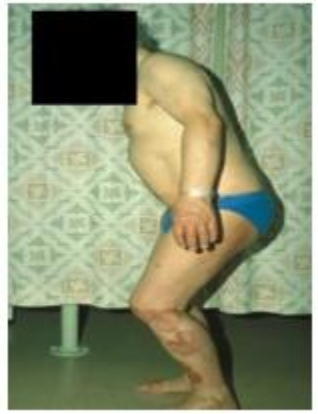


Enthesitis

25-30%

(40% HLA-B27)

PsA

Peripheral Arthritis	Enthesitis	Skin	Nails	Dactylitis	Axial Disease
					
>90%	>35-50%	>70-98%	44-80%	15-48%	16-50%

1. Ritchlin et al. N Engl J Med. 2017;376(21):2095-2096; 2. Ogdie et al. Ann Rheum Dis. 2019;78(suppl2): A922; 3. Mease et al. RMD Open. 2019;5(1):e000867; 4. Ritchlin et al. Ann Rheum Dis. 2009;68(9):1387-1394; 5.. Kaeley et al. Semin Arthritis Rheum. 2018;48(2):263-273; 6. Williamson et al. Rheumatology (Oxford). 2004;43(6):790-794. 7. Baraliakos X, et al. Clin Exp Rheumatol 2015;33(Suppl. 93):S31–5; 8. de Winter JJ, et al. Arthritis Res Ther 2018;18:196; 9. Kaeley GS, et al. Semin Arthritis Rheum 2018;48:263–73; 10. Sieper, J. and et al, 2017. Axial spondyloarthritis. The Lancet, 390(10089), pp.73-84

60% των ασθενών με SpA έχουν ενεργό φλεγμονώδη κολίτιδα ή υποκλινική φλεγμονή

Subclinical gut inflammation in axSpA is associated with[2–4]:

- Male sex
- High disease activity[a]
- Restricted spinal mobility[b]
- Younger age
- Early disease onset
- Radiographic sacroiliitis
- Bone marrow oedema of the SIJs[c]

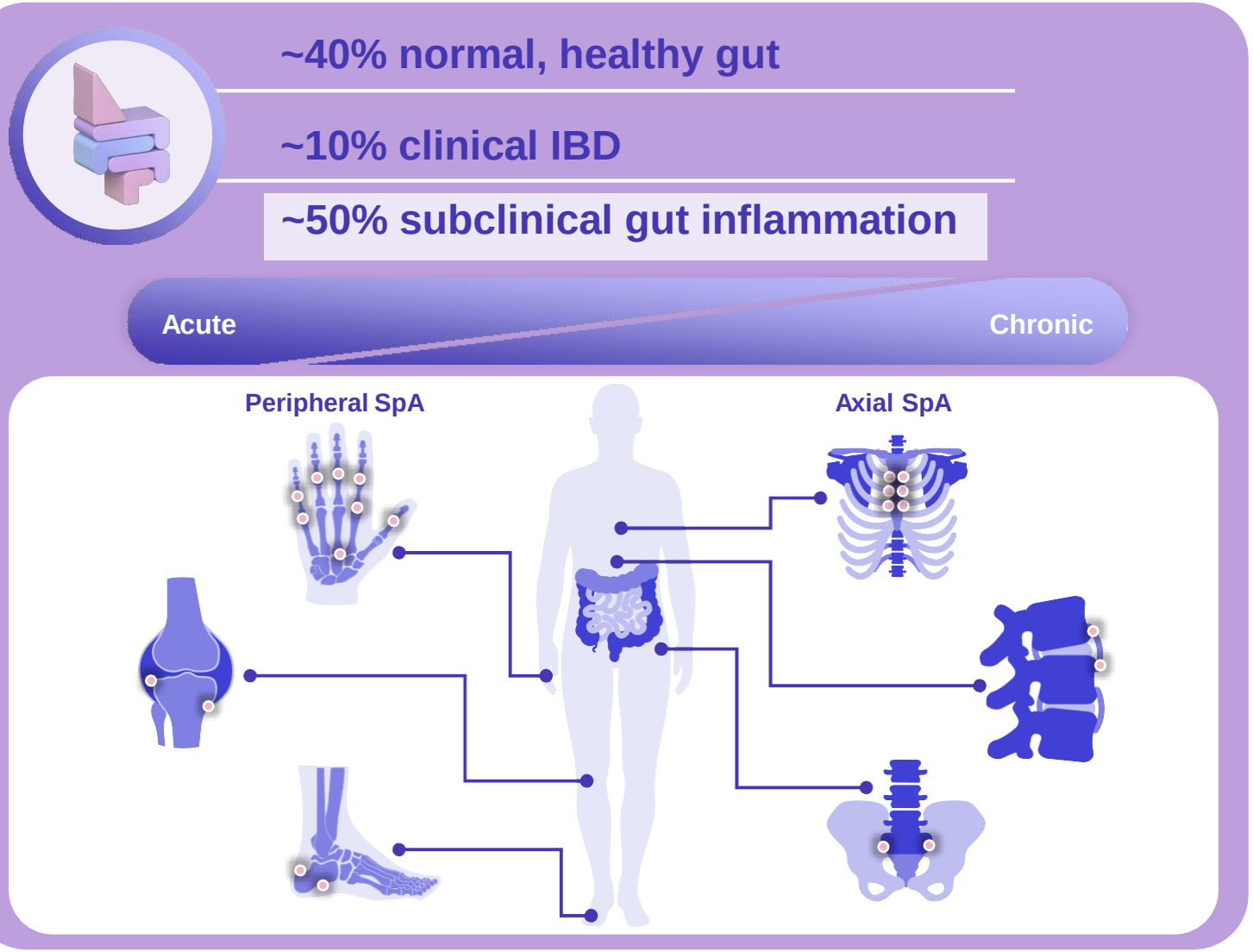


Figure adapted from Gracey E, et al. 2020.[1]

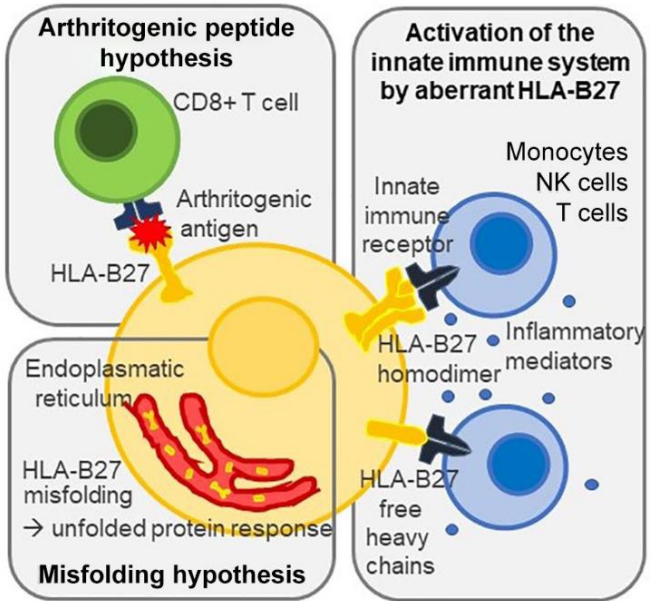
[a]Assessed by the Bath Ankylosing Spondylitis Disease Activity Index.[2] [b]Measured by the Bath Ankylosing Spondylitis Metrology Index.[2] [c]Measured by MRI; data show correlation between chronic gut inflammation and bone marrow oedema of SIJs.[4]

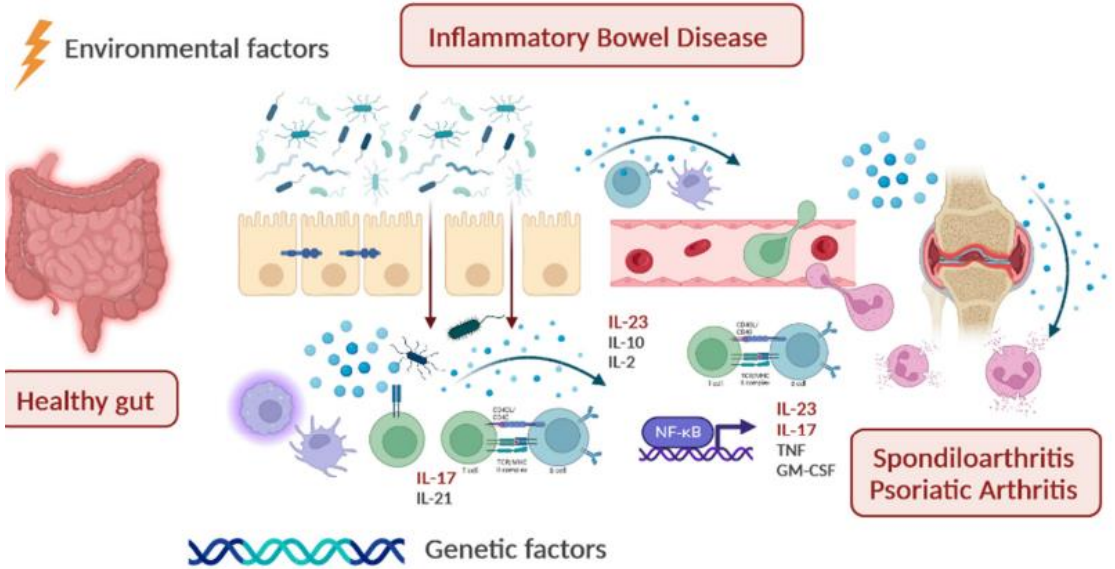
axSpA, axial spondyloarthritis; IBD, inflammatory bowel disease; MRI, magnetic resonance imaging; SIJ, sacroiliac joint; SpA, spondyloarthritis.

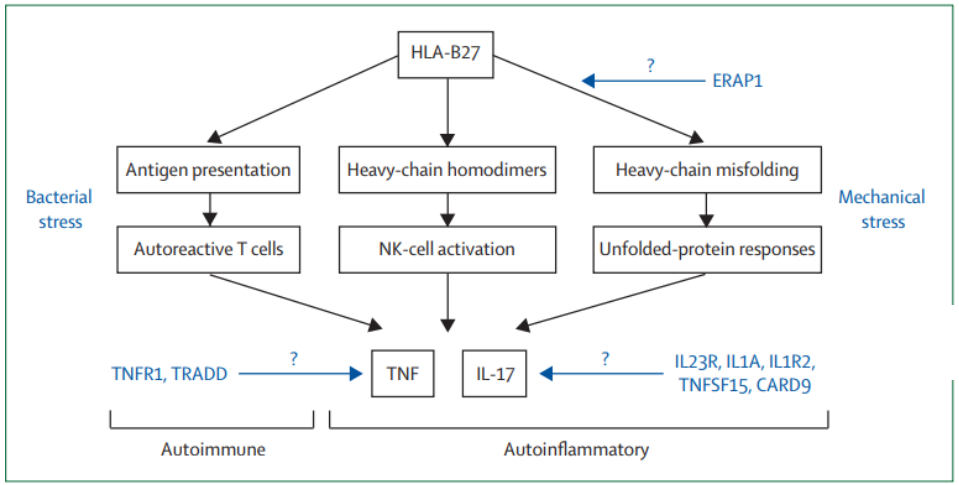
1. Gracey E, et al. *Nat Rev Rheumatol*. 2020;16:415–433. 2. Fragoulis G, et al. *World J Gastroenterol*. 2019;25:2162–2176. 3. Van Praet L, et al. *Ann Rheum Dis*. 2013;72:414–417. 4. Van Praet L, et al. *Ann Rheum Dis.* 2014;73:1186–1189.

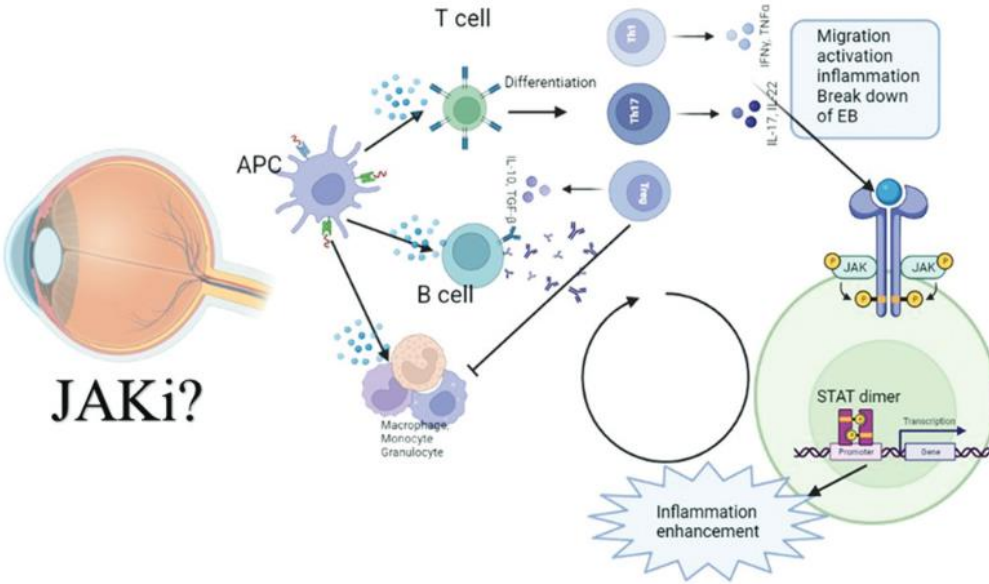
- Κοινοί παθογενετικοί μηχανισμοί στην αρθριτική, εντερική και οφθαλμική προσβολή→ ↑IL-17, IL-23, TNFa→ κοινοί θεραπευτικοί στόχοι

- αρθριτογόνα πεπτίδια-μοριακός μιμητισμος
- δυσλειτουργία HLA-B27
- μικροβιακή δυσβίωση-διάσπαση εντερικού φραγμού





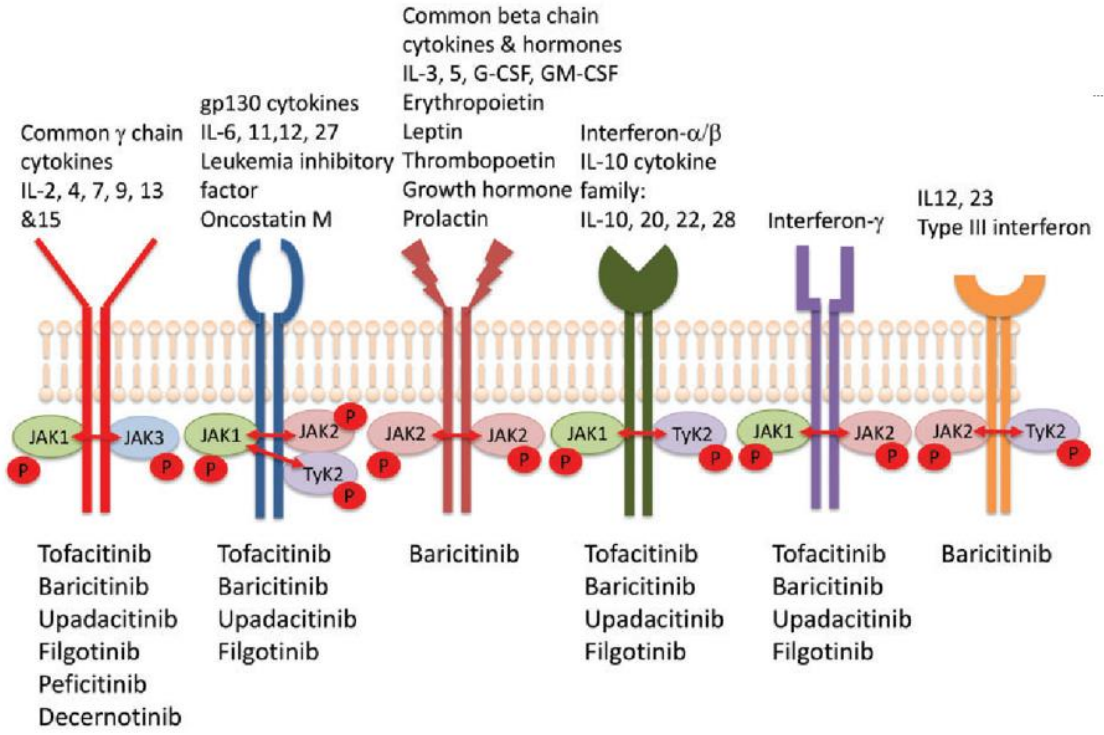




Dougados et al. Lancet 2011; 377: 2127–37;Felice et al. Int. J. Mol. Sci. 2023;24;Rademacher et al. Ther Adv Musculoskel Dis.2020;12: 1–20

Αναστολείς JAK κινασών (JAKis)

❖ **οι JAKis παρουσιάζουν πλειοτρόπο δράση αναστέλλοντας συγχρόνως πολλαπλές κυτταροκίνες**



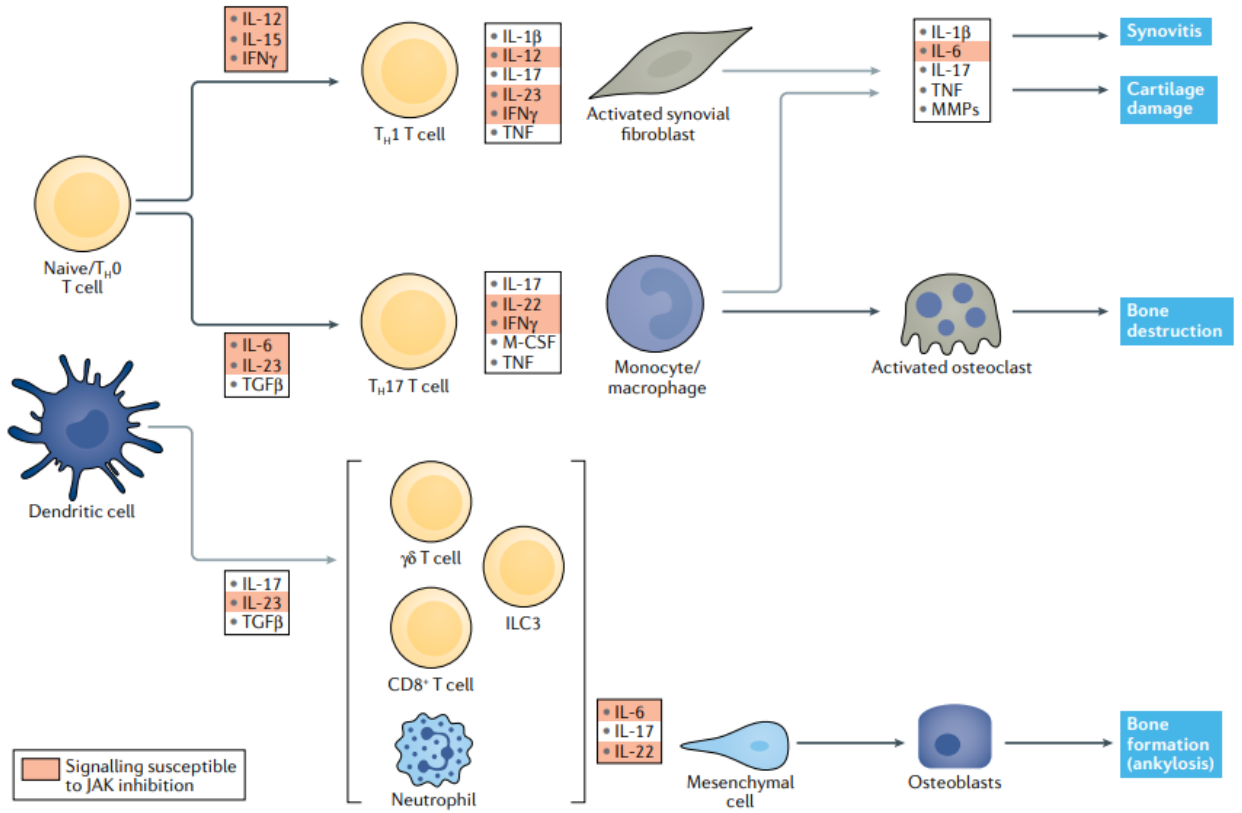
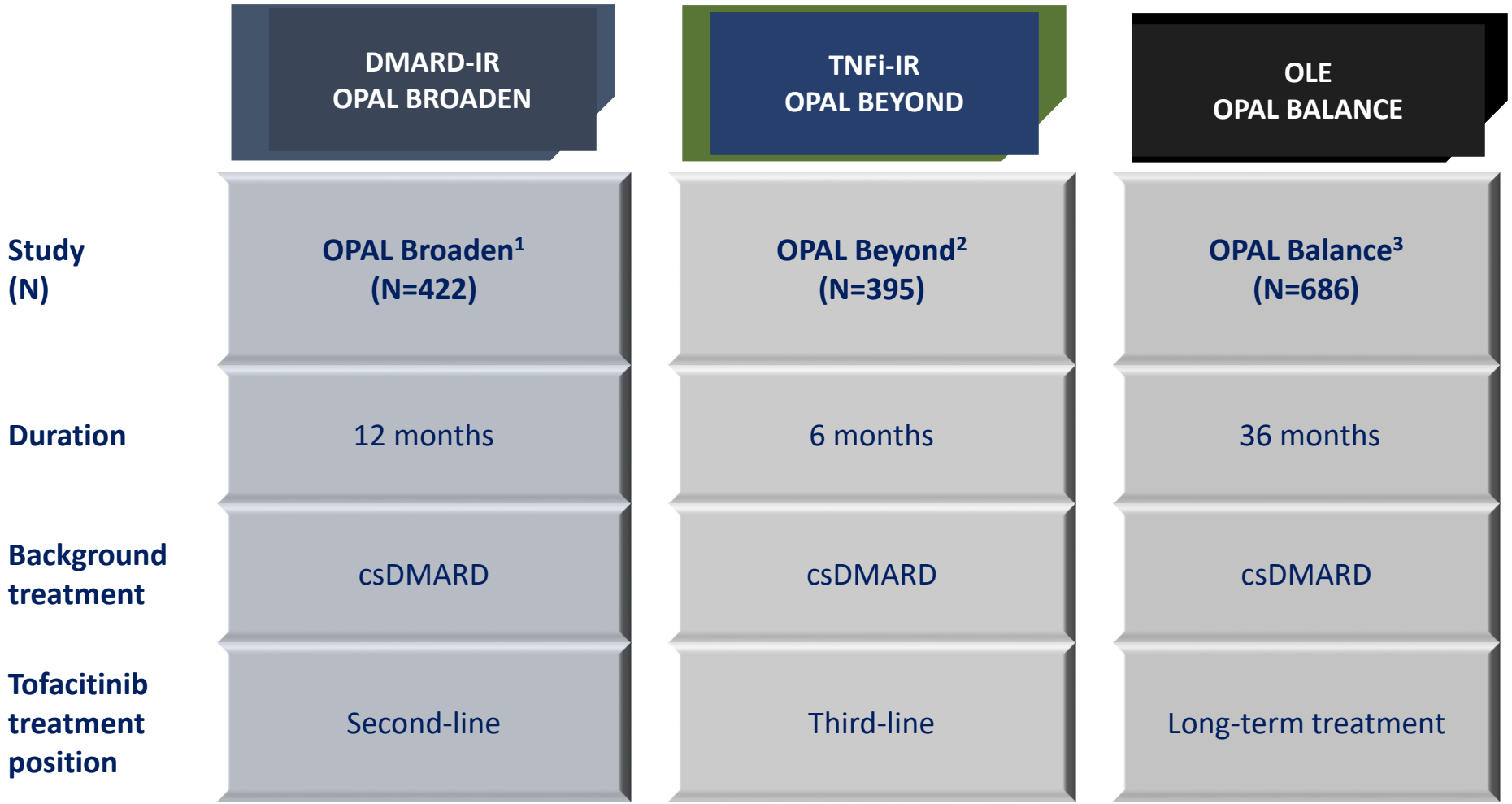


Fig. 3 | **Cytokine involvement in spondyloarthritis.** During pathological and non-immune cells. Various cytokines work in synergy to perpetuate

Choy et al.Rheumatology 2019;58:953-962

Το κλινικό πρόγραμμα του Tofacitinib στην ΨΑ



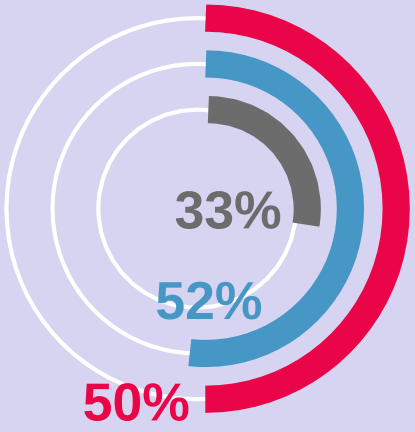
1. Mease et al. N Engl J Med 2017;377:1537–50.
2. Gladman et al. N Engl J Med 2017;377:1525–36;
3. Nash P, et al. Presented at ACR 2017; poster 620.

Βελτίωση στους δείκτες ενεργότητας της PsA και στις αναφορες ασθενών (PROs) την εβδομάδα 12

Co-primary endpoint

ACR20 response

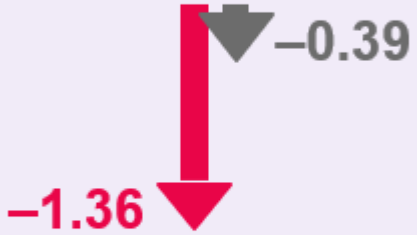
OPAL Broaden[1]



P≤0.05 tofacitinib vs placebo[a]

OPAL Beyond[2]
50% with tofacitinib 5 mg BID vs 24% on placebo, P<0.001[a]

LS mean $\Delta ASDAS_{CRP}$



P≤0.0001 vs placebo[a]

Co-primary endpoint

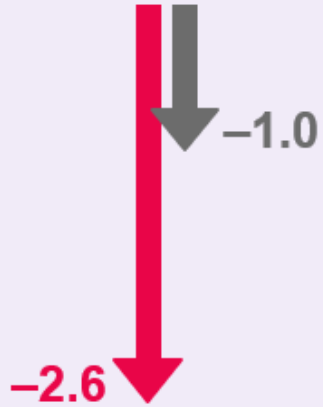
ΔHAQ-DI

OPAL Broaden[1]

P<0.01 tofacitinib vs placebo[a]

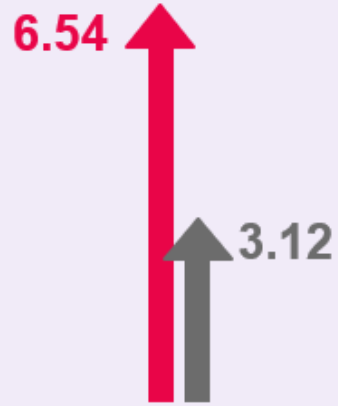
OPAL Beyond[2]
–0.39 with tofacitinib 5 mg BID vs –0.14 on placebo, P<0.001[a]

LS mean Δ back pain



P≤0.0001 vs placebo[a]

Improvement in FACIT-F total score (LS mean Δ)



P≤0.0008 vs placebo[a]

Trials should not be compared owing to differences in trial design, populations, and methodology.

Tofacitinib 5 mg BID Adalimumab 40 mg SC Q2W Placebo

Graphs adapted from Mease P, et al. 2017.[1]

OPAL Broaden population at baseline and Month 3: placebo (n=105), tofacitinib (n=107), adalimumab (n=106)[1]; OPAL Beyond population at baseline: placebo (n=131), tofacitinib (n=131).[2]

[a]Unadjusted P values. The result was significant at a P value of 0.05 or less according to the prespecified step-down testing procedure for global type I error control.[1,2] [b]Prespecified in the original study protocols; hierarchical testing failed at the LEI endpoint in OPAL Broaden and at the PASI75 endpoint in OPAL Beyond.[1,2] [c]Results were assessed among patients who had a baseline score >0.[1,2]

Δ, change from baseline; ACR20, ≥20% improvement in American College of Rheumatology score; BID, twice daily; HAQ-DI, Health Assessment Questionnaire Disability Index; LEI, Leeds Enthesitis Index; NS, not significant; OPAL, Oral Psoriatic Arthritis trial; PASI75, 75% improvement in Psoriasis Area and Severity Index; PsA, psoriatic arthritis; Q2W, every 2 weeks; SC, subcutaneous.

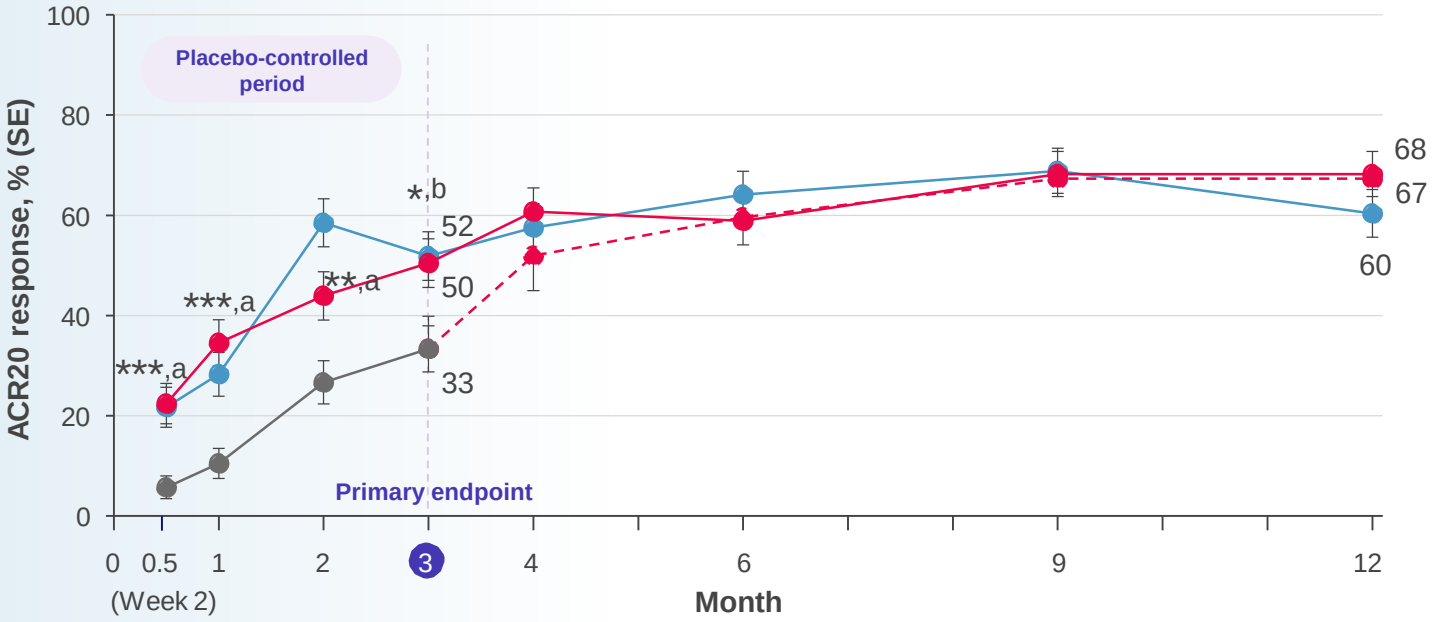
1. Mease P, et al. *N Engl J Med.* 2017;377:1537–1550 and supplementary appendix. 2. Gladman D, et al. *N Engl J Med.* 2017;377:1525–1536 and supplementary appendix.

Ταχεία βελτίωση σημείων και συμπτωμάτων την εβδομάδα 2, που διατηρήθηκε στον μήνα 12 για το Tofacitinib vs. Placebo

(ACR20 response, co-primary endpoint)

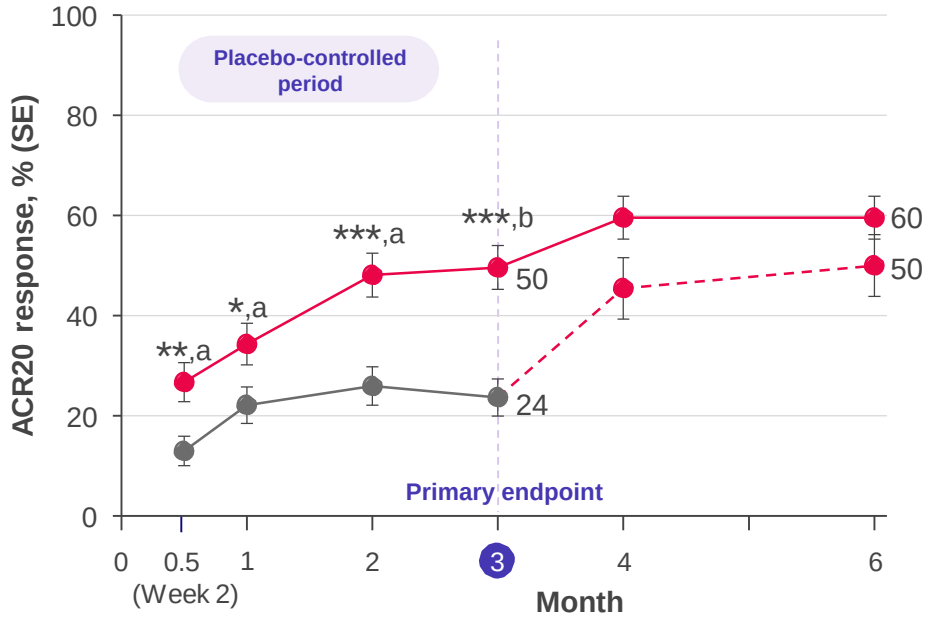
Placebo + csDMARD — Tofacitinib 5 mg BID + csDMARD — Placebo to Tofacitinib 5 mg BID + csDMARD — Adalimumab 40 mg Q2W + csDMARD

OPAL Broaden[1]



OPAL Broaden was not designed to demonstrate noninferiority or superiority of tofacitinib to adalimumab

OPAL Beyond[2]



Trials should not be compared owing to differences in trial design, populations, and methodology.

Figures adapted from Mease P, et al. 2017[1] (left) and Gladman D, et al. 2017[2] (right).

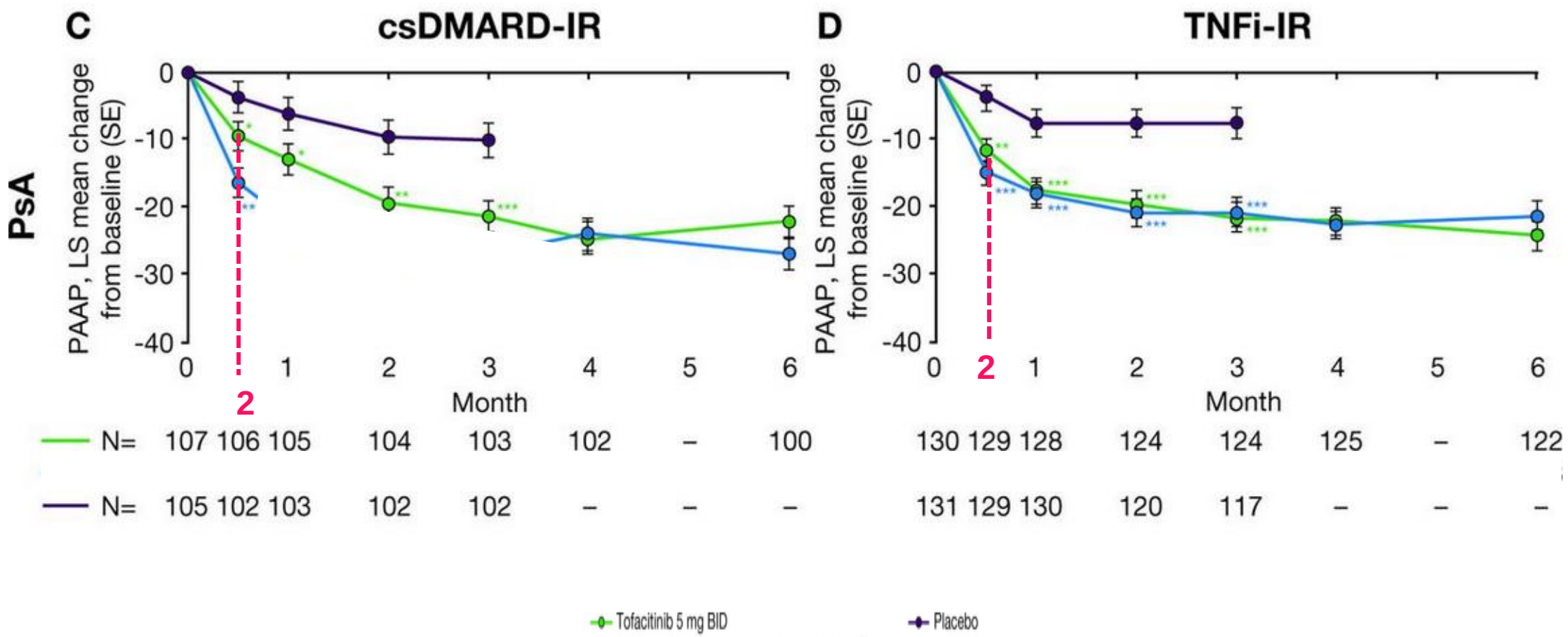
OPAL Broaden population at baseline and Month 3: placebo (n=105), tofacitinib (n=107), adalimumab (n=106).[1] OPAL Beyond population at baseline: placebo (n=131), tofacitinib (n=131).[2]

*P≤0.05 tofacitinib vs placebo, **P<0.01 tofacitinib vs placebo, ***P<0.001 tofacitinib vs placebo.

; BID, twice daily; csDMARD, conventional synthetic disease-modifying antirheumatic drug; OPAL, Oral Psoriatic Arthritis trial; Q2W, every 2 weeks; SE, standard error.

1. Mease P, et al. *N Engl J Med.* 2017;377:1537–1550. 2. Gladman D, et al. *N Engl J Med.* 2017;377:1525–1536.

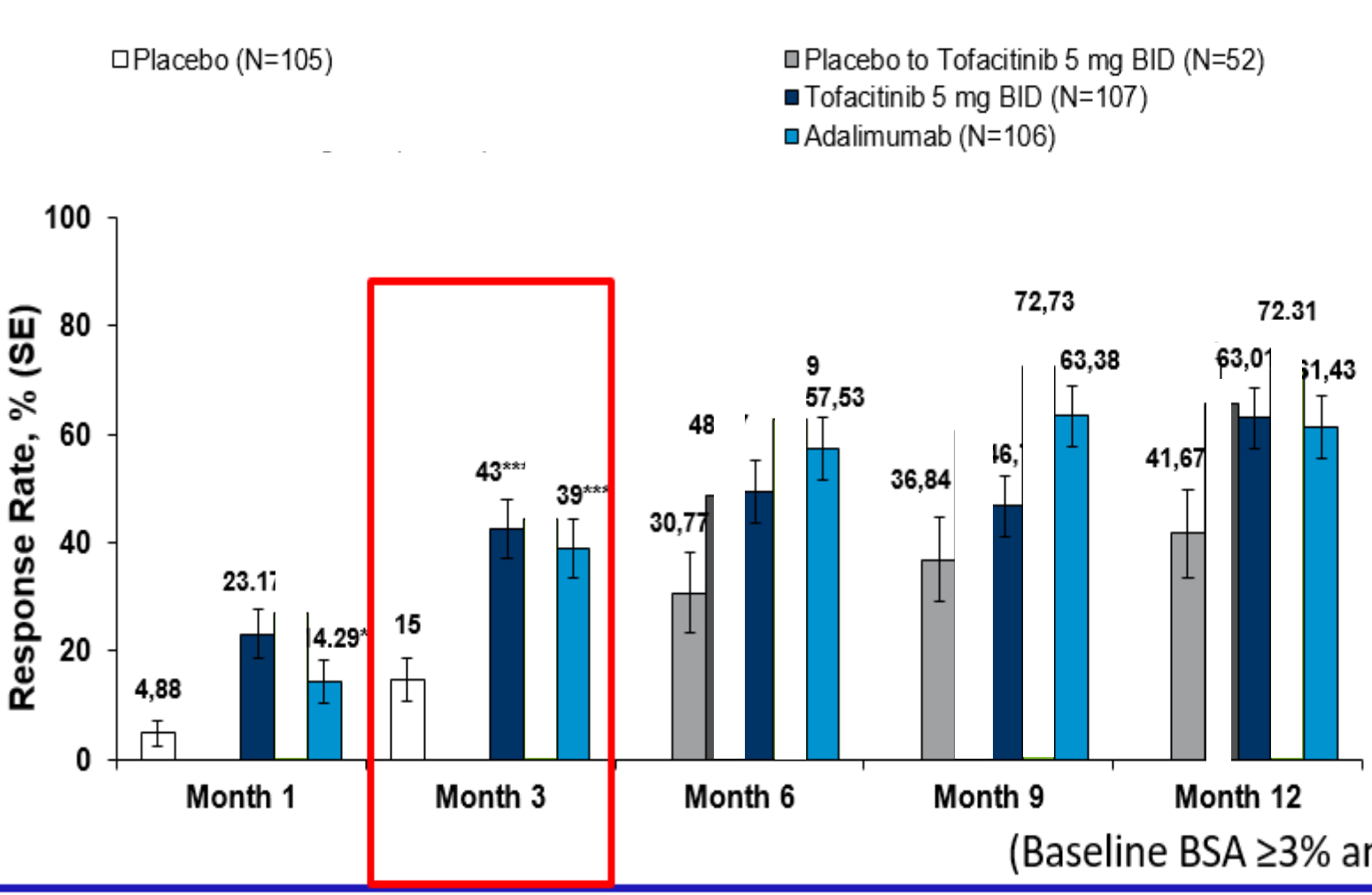
Μείωση του πόνου από την εβδομάδα 2



Ogdie et al. RMD Open 2020;6:e001042.

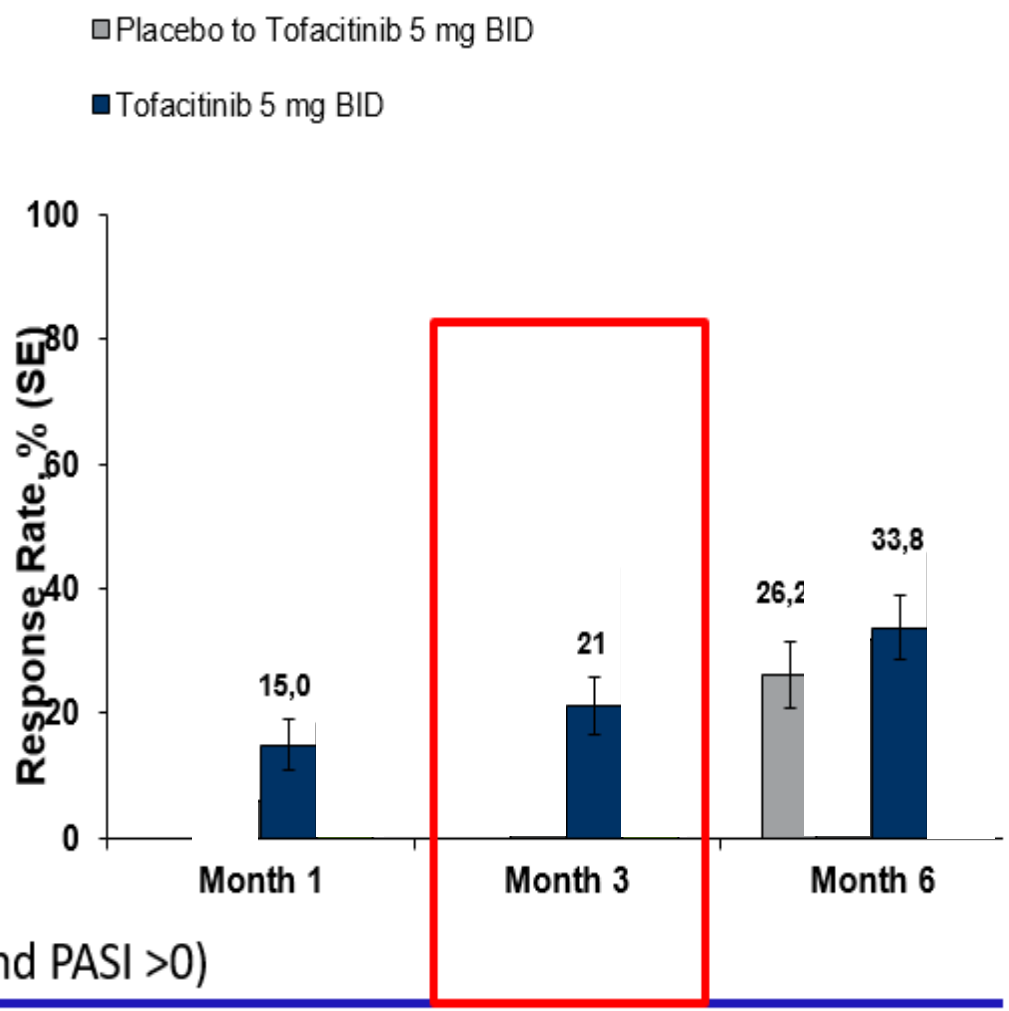
PASI75 RR Up to Month 12

OPAL Broaden bDMARDs naive[1]



PASI75 RR Up to Month 6

OPAL Beyond TNF-IR[2]

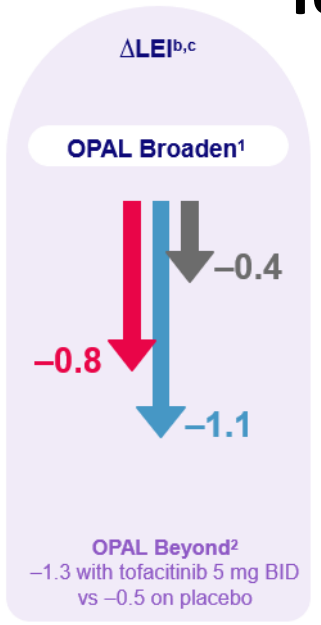


(Baseline BSA ≥3% and PASI >0)

1. Mease et al. N Engl J Med. 2017;377:1537–50; Supplementary appendix. 2. Gladman et al. N Engl J Med. 2017;377:1525–36; Supplementary appendix

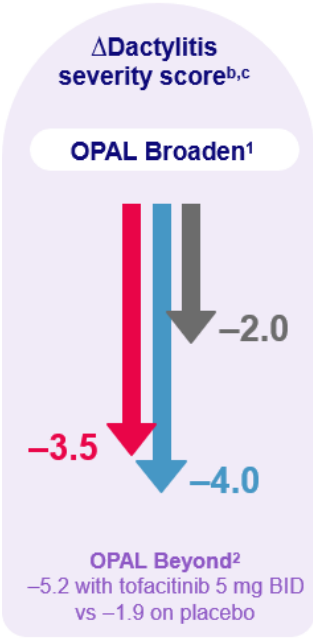
Tofacitinib-ενθεσίτιδα/δακτυλίτιδα

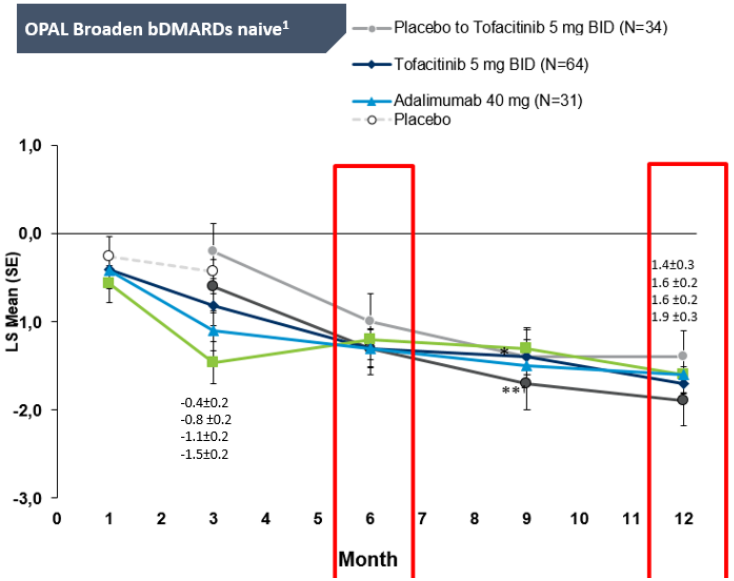
LEI: Leeds Enthesitis index

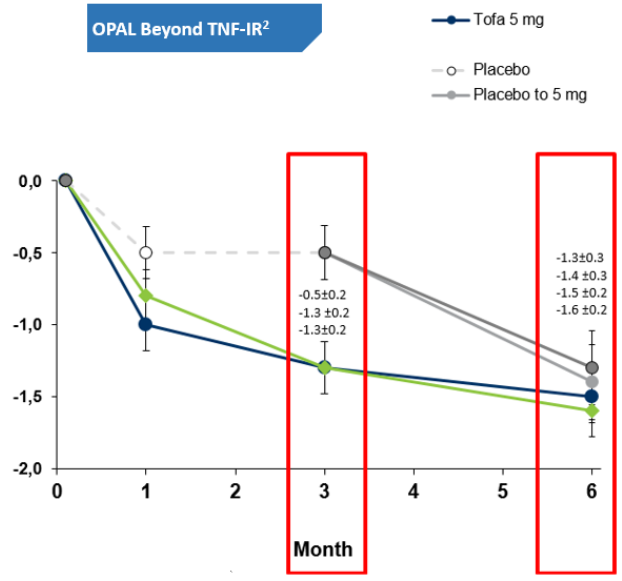


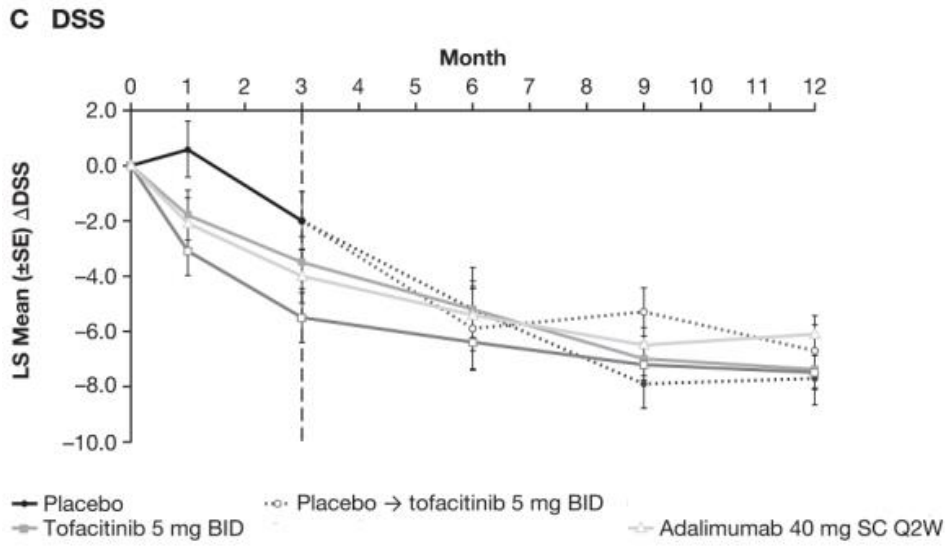
Tofacitinib 5 mg BID Adalimumab 40 mg SC Q2W Placebo

DSS: Daktylitis severity score





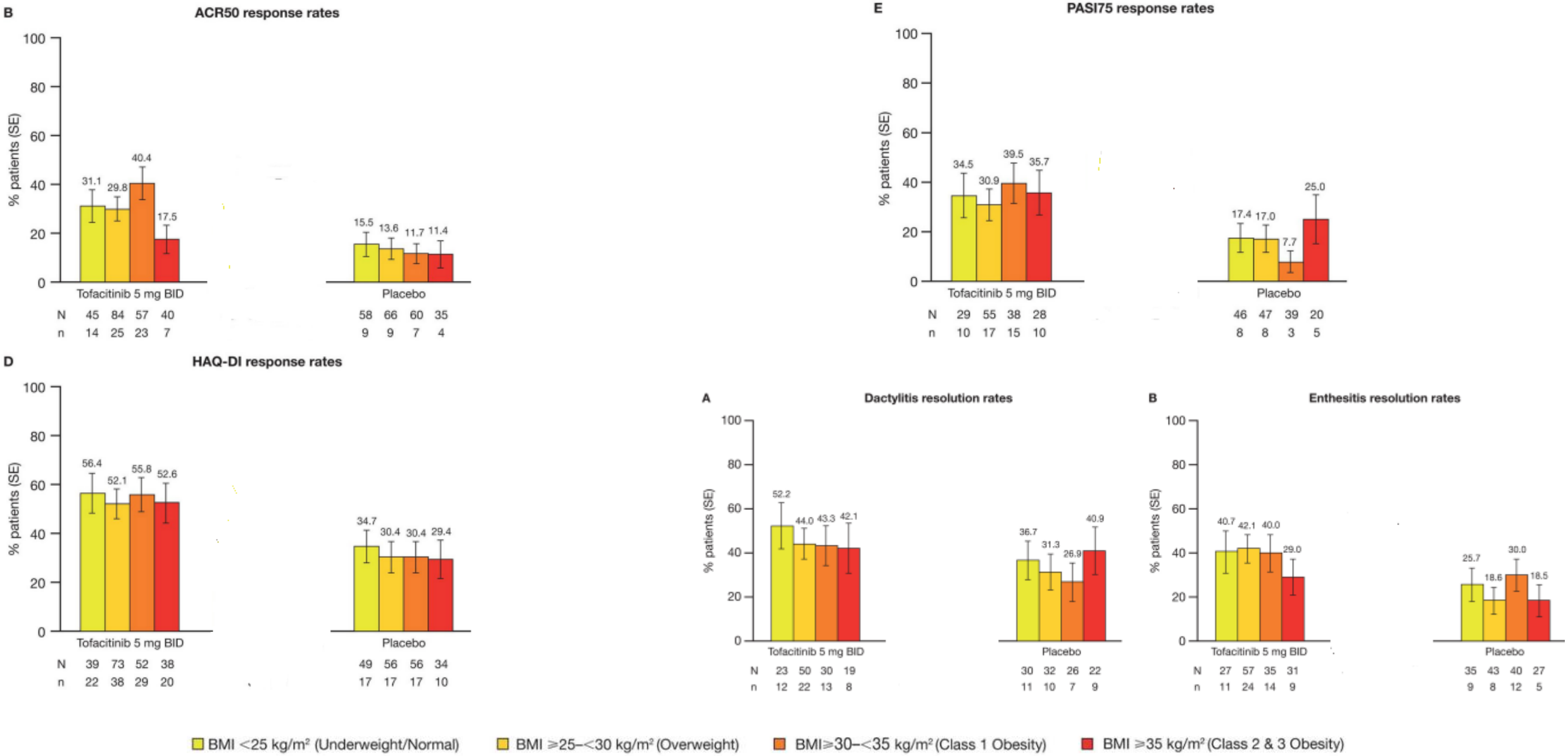




1. Mease et al. N Engl J Med. 2017;377:1537–50; Supplementary appendix. 2. Gladman et al. N Engl J Med. 2017;377:1525–36; Supplementary appendix

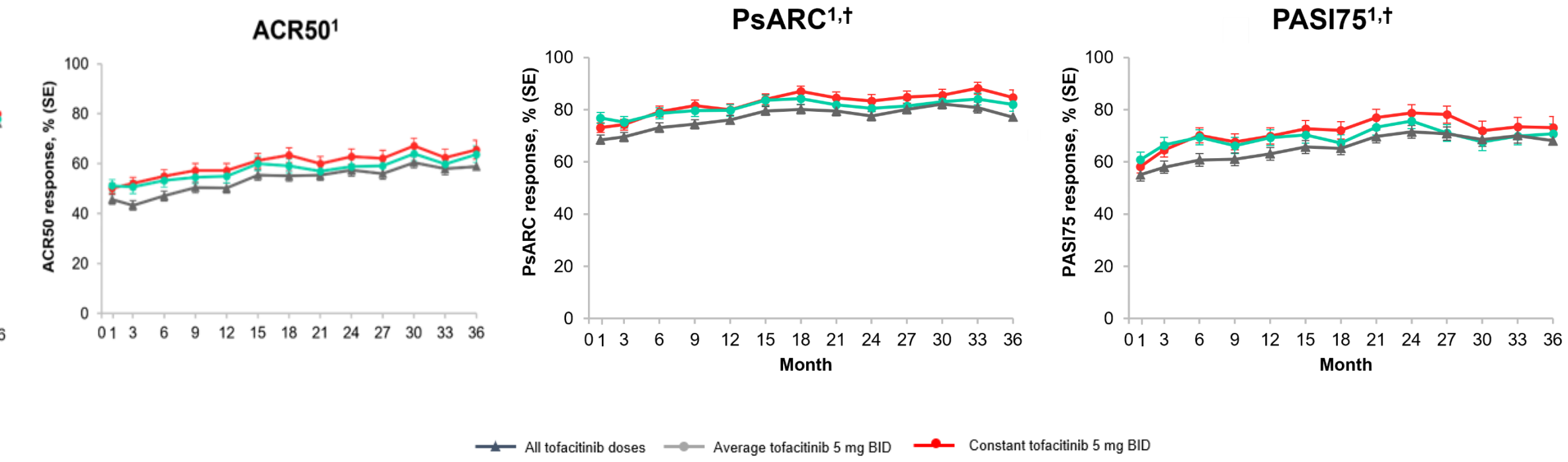
Η εγκεκριμένη δόση του tofacitinib στη PsA είναι 5 mg δις ημερησίως σε συνδυασμό με csDMARDs

Αποτελεσματικότητα σε ασθενείς με PsA και αυξημένο σωματικό βάρος



Giles et al.RMD Open. 2021 Jan;7(1):e001486.

Διατήρηση της θεραπευτικής απάντησης κατά ACR50, PsARC, PASI75



Η εγκεκριμένη δόση του tofacitinib στην Ψωριασική Αρθρίτιδα είναι 5mg BID σε συνδυασμό με MTX

Nash P, et al. *Lancet Rheumatol*. 2021;3(4):e270-e283.

Επίδραση του Tofacitinib στον υπολειπόμενο πόνο σε ασθενείς με RA/PsA

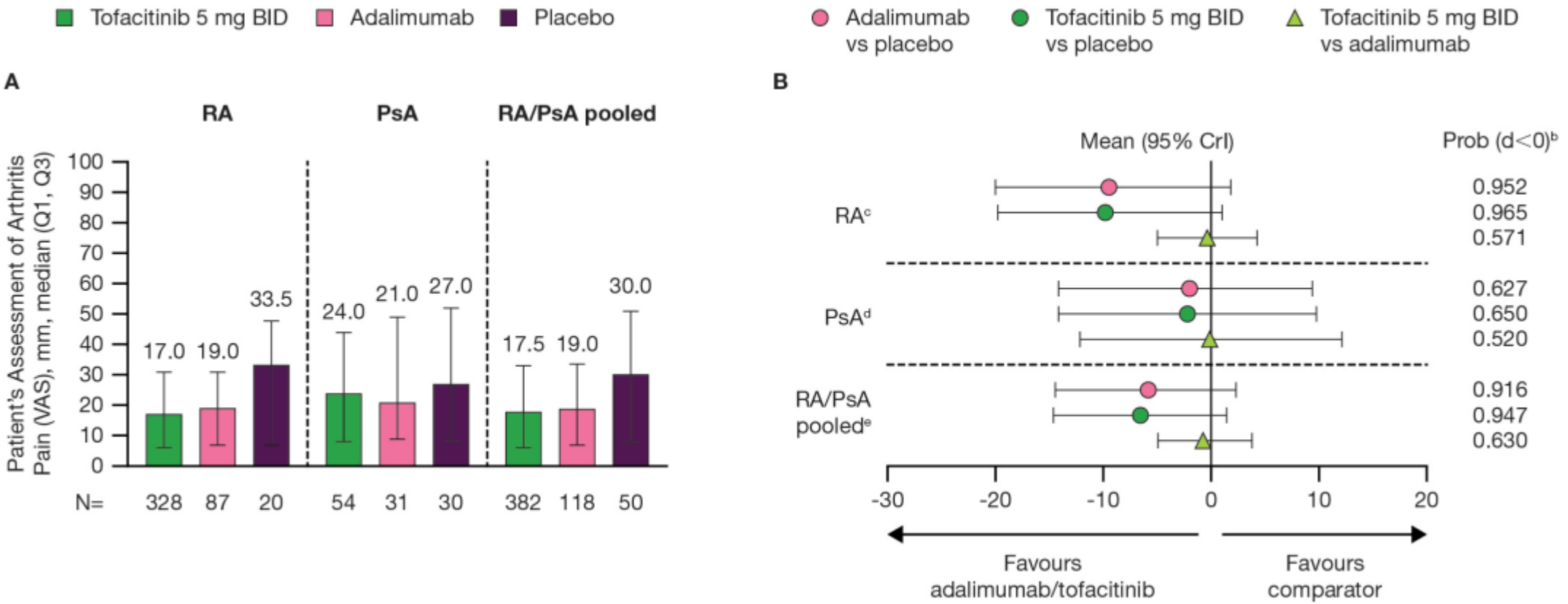
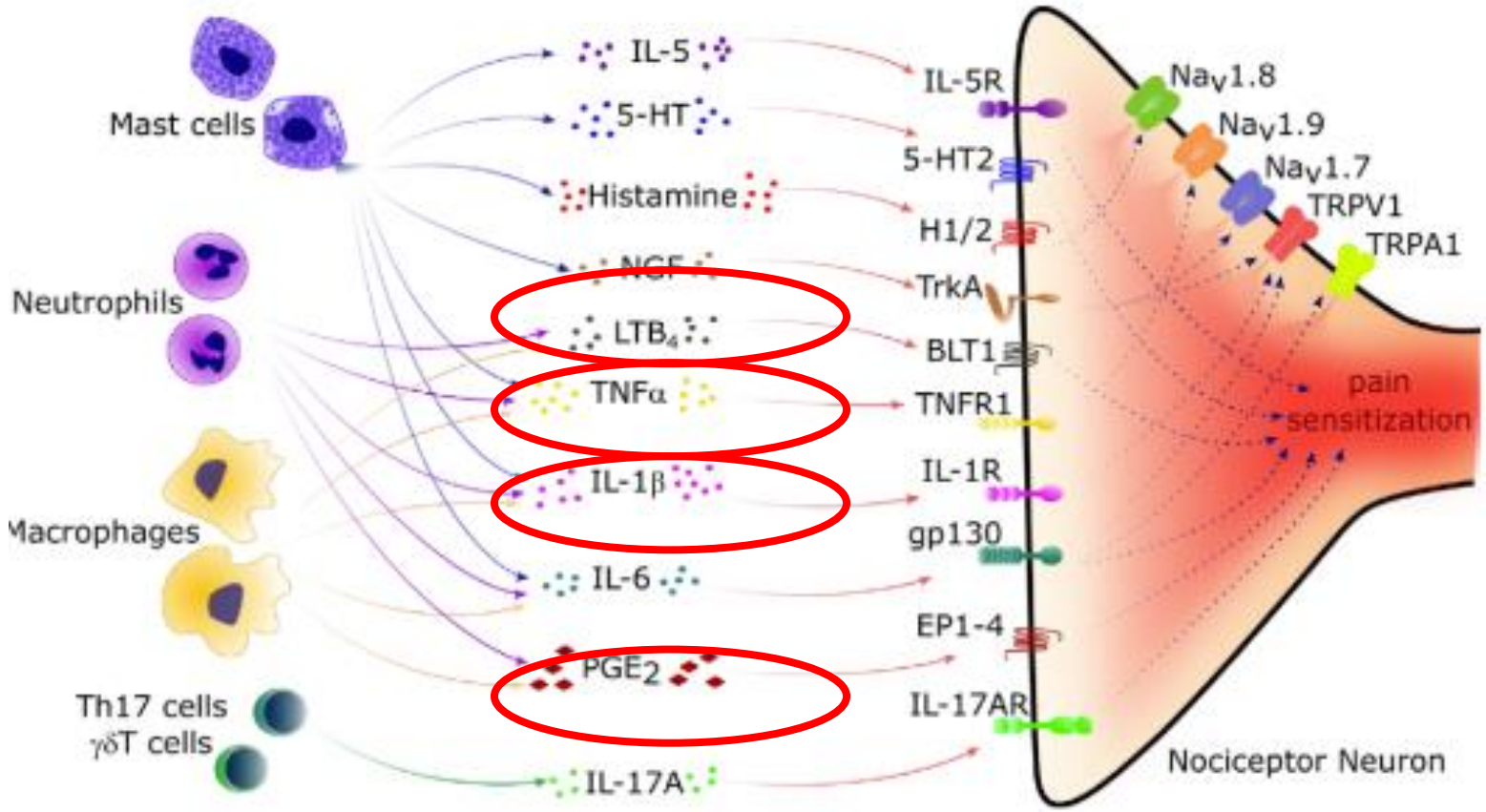


Figure 2 Patient's Assessment of Arthritis Pain in patients with an abrogation of inflammation[a] after 3 months of therapy:

Dougados et al. RMD Open 2022;8:e002478.

Οι JAKis μπορεί να έχουν άμεση επίδραση στον πόνο, ανεξάρτητα της φλεγμονής



Pinho-Ribeiro FA et al. Trends Immunol 2017

Adv Ther (2022) 39:2932–2945
https://doi.org/10.1007/s12325-022-02084-7

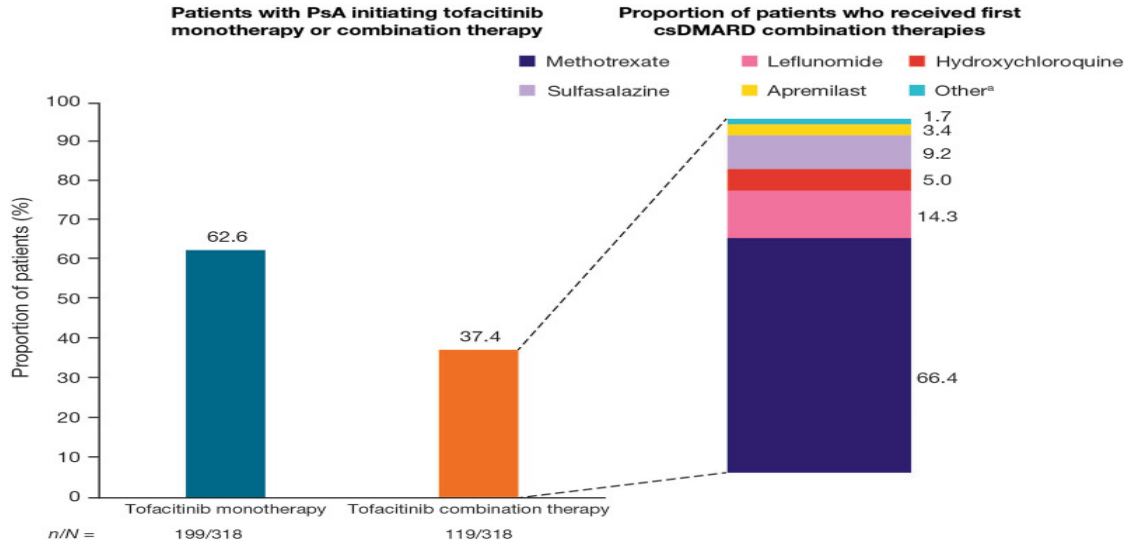
ORIGINAL RESEARCH

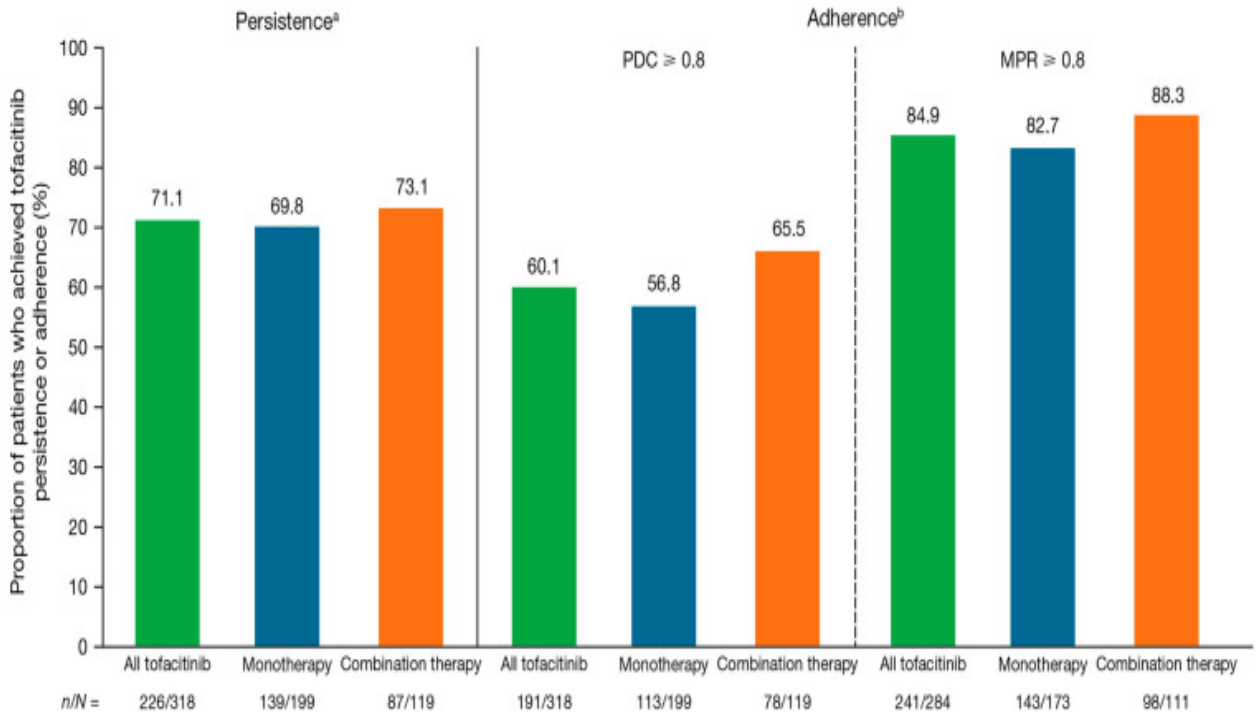
Early Real-World Experience of Tofacitinib for Psoriatic Arthritis: Data from a United States Healthcare Claims Database

Philip J. Mease · Pamela Young · David Gruben · Lara Fallon · Rebecca Germino · Arthur Kavanaugh

- max 2 έτη διάρκεια νόσου
- τουλάχιστον 1 προηγηθείσα θεραπεία (συνήθως secukinumab)
- 60 % μονοθεραπεία
- παραμονή 70% στους 6 μήνες, ανεξάρτητη της συγχορήγησης csDMARDS
- >80% συμμόρφωση

The approved use for tofacitinib in PsA is with combination with methotrexate (MTX)





The Journal of Rheumatology 2021;48:1552–8
doi:10.3899/jrheum.201204
First Release June 15 2021

The Journal of Rheumatology

Treatment With Tofacitinib in Refractory Psoriatic Arthritis: A National Multicenter Study of the First 87 Patients in Clinical Practice

Eva Galíndez-Agirregoikoa[1], Diana Prieto-Peña[2], José Luis Martín-Varillas[3], Beatriz Joven[4],

Table 1. Baseline characteristics of 87 patients with refractory PsA of clinical practice and the standard TOF therapy arm (5 mg/12 h) of the OPAL Beyond clinical trial.

	Clinical Practice, n = 87	RCT[20], n = 131	*P*
Baseline demographics			
Age, yrs, mean ± SD	52.8 ± 11.4	49.5 ± 12.3	0.047
Sex, M/F, n (%)	59/28 (67.8/32.2)	67/64 (51.1/48.9)	0.02
Disease characteristics			
PsA duration, yrs, mean ± SD	12.3 ± 9.3	9.6 ± 7.6	0.02
HAQ-DI[a], mean ± SD	1.4 ± 0.7 (n = 26)	1.3 ± 0.7	0.51
Swollen joint count, mean ± SD	5.7 ± 5.8	12.1 ± 10.6	< 0.001
Tender joint count, mean ± SD	8.0 ± 6.6	20.5 ± 13.0	< 0.001
Enthesitis, n (%)[b]	28 (32.2)	83 (63)	< 0.001
Dactylitis, n (%)[c]	16 (18.4)	66 (50)	< 0.001
PASI score, median [IQR][d]	5.0 [1–14]	7.6 [0.6–32.2]	–
Elevated CRP, n (%)[e]	55 (63.2)	85 (65)	0.002
Oral glucocorticoid use, n (%)	44 (50.6)	37 (28.0)	0.001
Concomitant csDMARD, n (%)	48 (55.2)	131 (100)	< 0.001
Methotrexate	30 (34.4)	98 (75)	–
Leflunomide	15 (17.2)	12 (9)	–
Sulfasalazine	6 (6.9)	21 (16)	–
Other	0 (0)	2 (2)	–
Previous use of anti-TNF-α, mean ± SD	2.4 ± 1.4	1.7 ± 1.0	< 0.001
Previous use of other non–anti-TNF-α biologics, n (%)	68 (78.2)	11 (8)	< 0.001
TOF monotherapy, n (%)	39 (44.8)	0 (0)	< 0.001

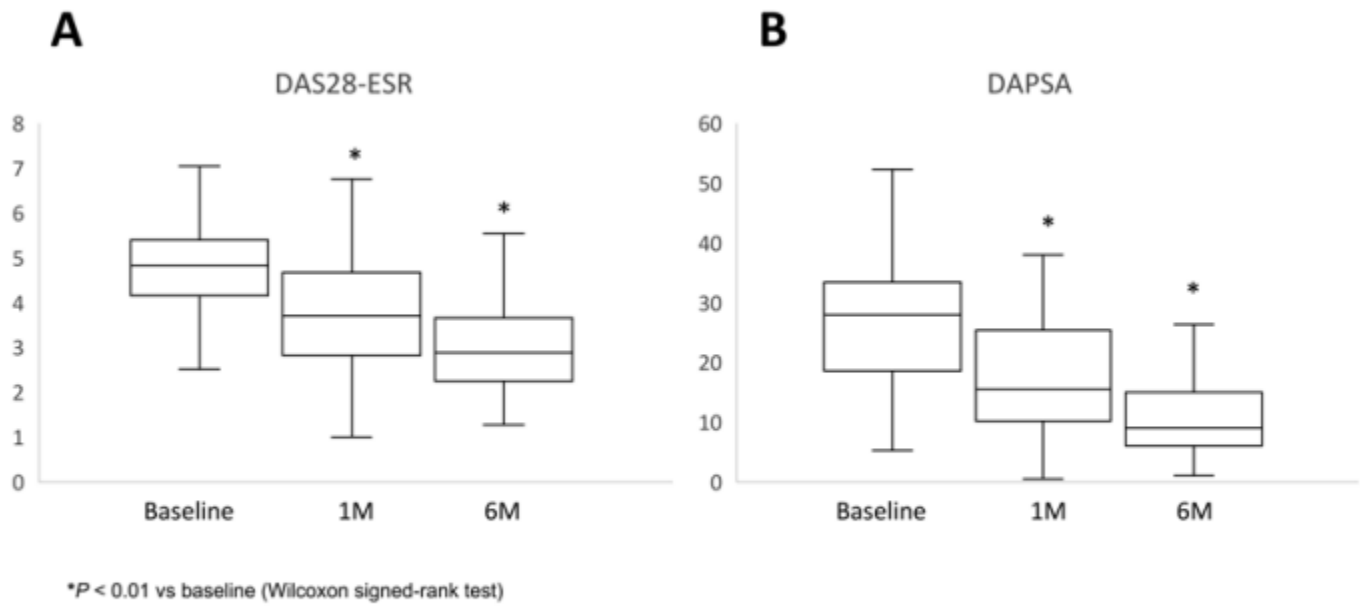


Figure 1. Improvement in disease activity indexes in 87 patients with refractory psoriatic arthritis following tofacitinib therapy. (A) Disease Activity Score in 28 joints based on erythrocyte sedimentation rate (DAS28-ESR). (B) Disease Activity in Psoriatic Arthritis Score (DAPSA). Bars represent median values with 95% CI.

Table 1 continued

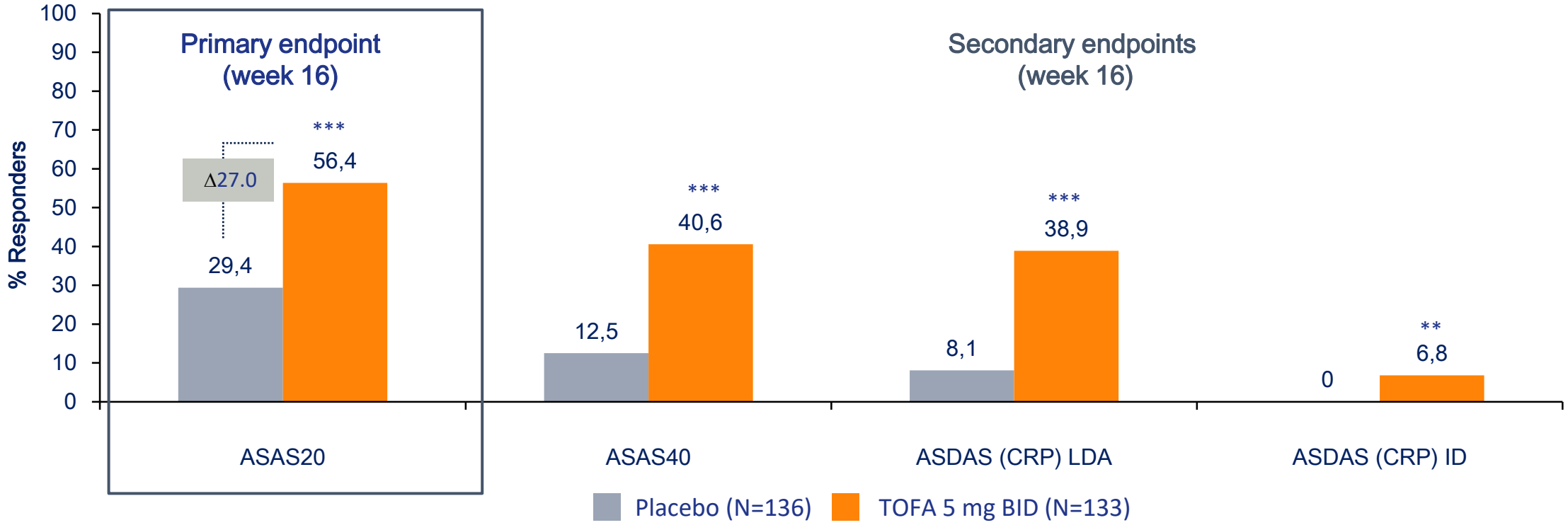
References	Publication	Type of study	Design[a]	Number of patients	Efficacy outcomes by tofacitinib
Maksymowych et al. [29]	Manuscript	Post hoc analysis	16-week phase II RCT in AS	164	About one-third of patients experienced significant reductions in axial MRI inflammation at week 12 Almost three times more achieving minimally important change (SPARCC) in MRI inflammation than with placebo
Galindez et al. [49]	Abstract	Primary study	Multicenter, clinical practice	87	Patients showed improvement in PASI, DAS28, DAPSA, and laboratory tests at months 1, 6, and 12
Korotaeva et al. [53]	Abstract	Primary study	Single-center, clinical practice	41	Significant improvements at 3 and 6 months in activity indexes and PROs, including BASDAI, DAPSA, PtGA
Chamurlieva et al. [54]	Abstract	Primary study	Single-center, clinical practice	41	The presence of enthesitis, PASI, and nail psoriasis at baseline has a negative impact on minimal disease activity at month 6
Gubar et al. [55]	Abstract	Primary study	Single-center, clinical practice	40	Greater efficacy in reducing active MRI sacroiliitis and decreasing activity of axial involvement (BASDAI, ASDAS)
Loginova et al. [56]	Abstract	Primary study	Single-center, clinical practice	41	Similar efficacy to adalimumab for achieving minimal disease activity/low activity/remission, according to DAPSA
Gubar et al. [57]	Abstract	Primary study	Single-center, clinical practice	40	High efficacy for reducing sacroiliitis inflammation and dactylitis at month 6, compared with baseline
Ungprasert et al. [25]	Manuscript	Systematic review and meta-analysis	18 RCTs in AS	2971	Tofacitinib was not different to older TNFi, secukinumab, certolizumab for achieving ASAS20
Gladman et al. [33]	Abstract	Systematic review and meta-analysis	25 RCTs	NI	Similar efficacy of tofacitinib 5 and 10 versus many bDMARDs and apremilast for the improvement of ACR20 and DHAQ-DI
Pham et al. [40]	Manuscript	Systematic review and meta-analysis	26 RCTs	5808	Faster time until onset of action compared to apremilast, methotrexate, and ustekinumab for ACR20
Song et al. [43]	Manuscript	Bayesian network meta-analysis	8 RCTs	3086	Tofacitinib 10 mg showed a highest efficacy (SUCRA ACR20 0.785)

Αγκυλοποιητική Σπονδυλίτιδα

Tofacitinib vs. Placebo στην ΑΣ (16 εβδ.)

Η χορήγηση Tofacitinib βελτίωσε σημαντικά τους δείκτες ενεργότητας στις 16 εβδομάδες

77% χωρις προηγούμενη λήψη bDMARD
23% μη ανταπόκριση σε bDMARD

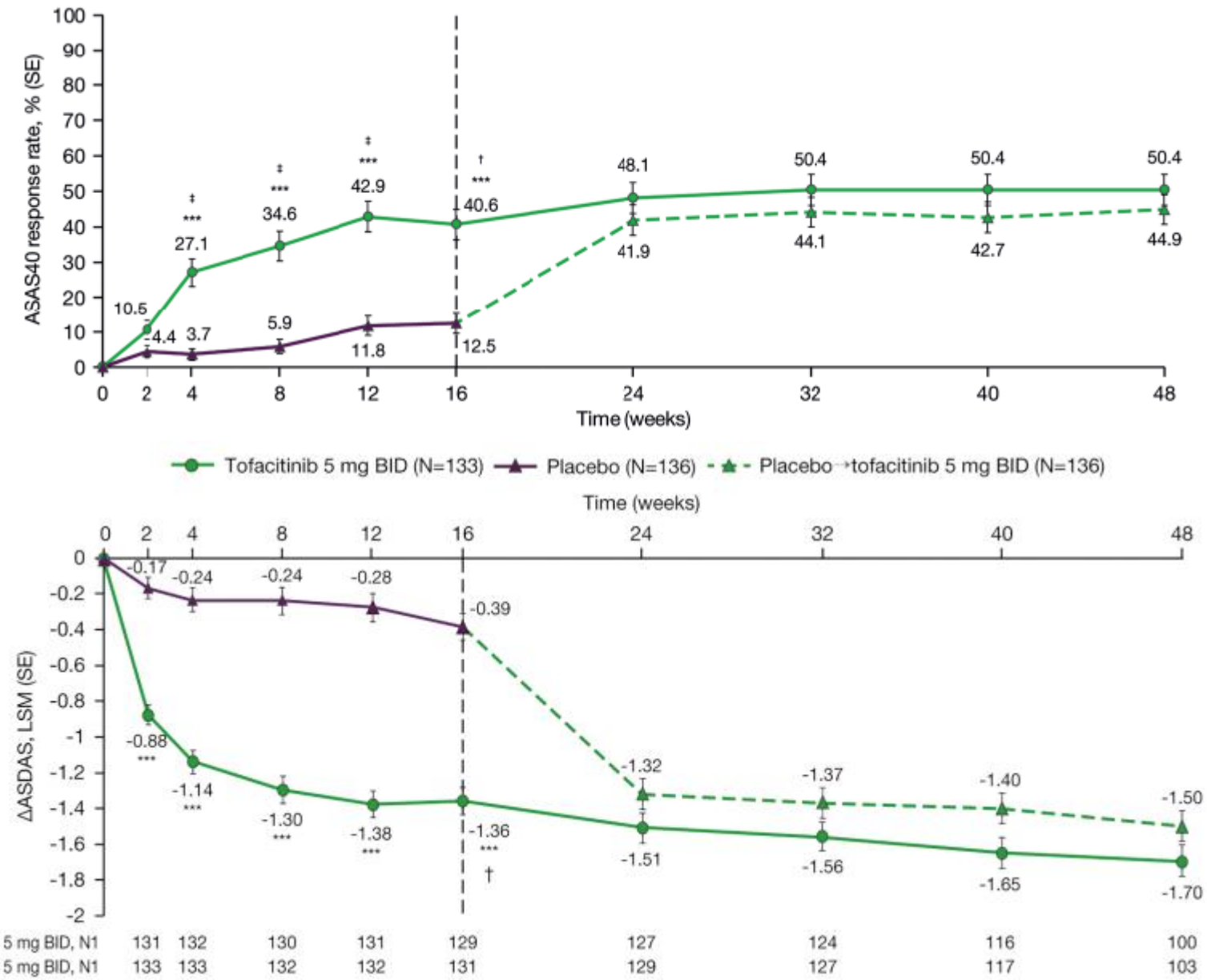


**p<0.01
ASAS20, 20% improvement in Assessment in Ankylosing Spondylitis response criteria; BID, twice a day; bMARD, biologic disease-modifying antirheumatic drug; CRP, c-reactive protein; ID, inactive disease (<1.3); IR, inadequate response; LDA, low disease activity (<2.1); TOFA, tofacitinib; TNFi, tumor necrosis factor inhibitor.

Adapted from:
1. Deodhar A, et al. Ann Rheum Dis. 2021; 80(8):1004-1013.

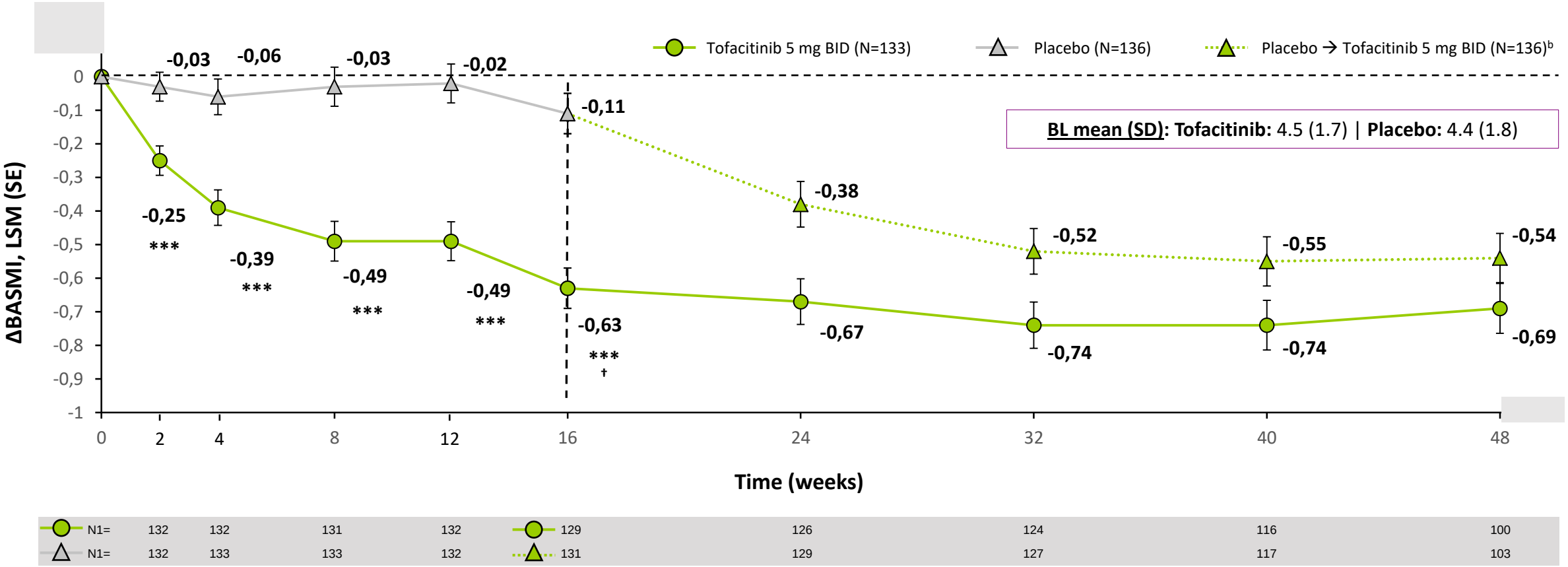
TOFA Study

- Ταχεία έναρξη δράσης
- 40% ASAS40 και ASDAS-LDA στην 16η εβδομάδα
- Παρόμοια αποτελεσματικότητα την 40η εβδομάδα στους ασθενείς που αρχικά έλαβαν PBO



Deodhar A, et al. Ann Rheum Dis. 2021; 80(8):1004-1013.

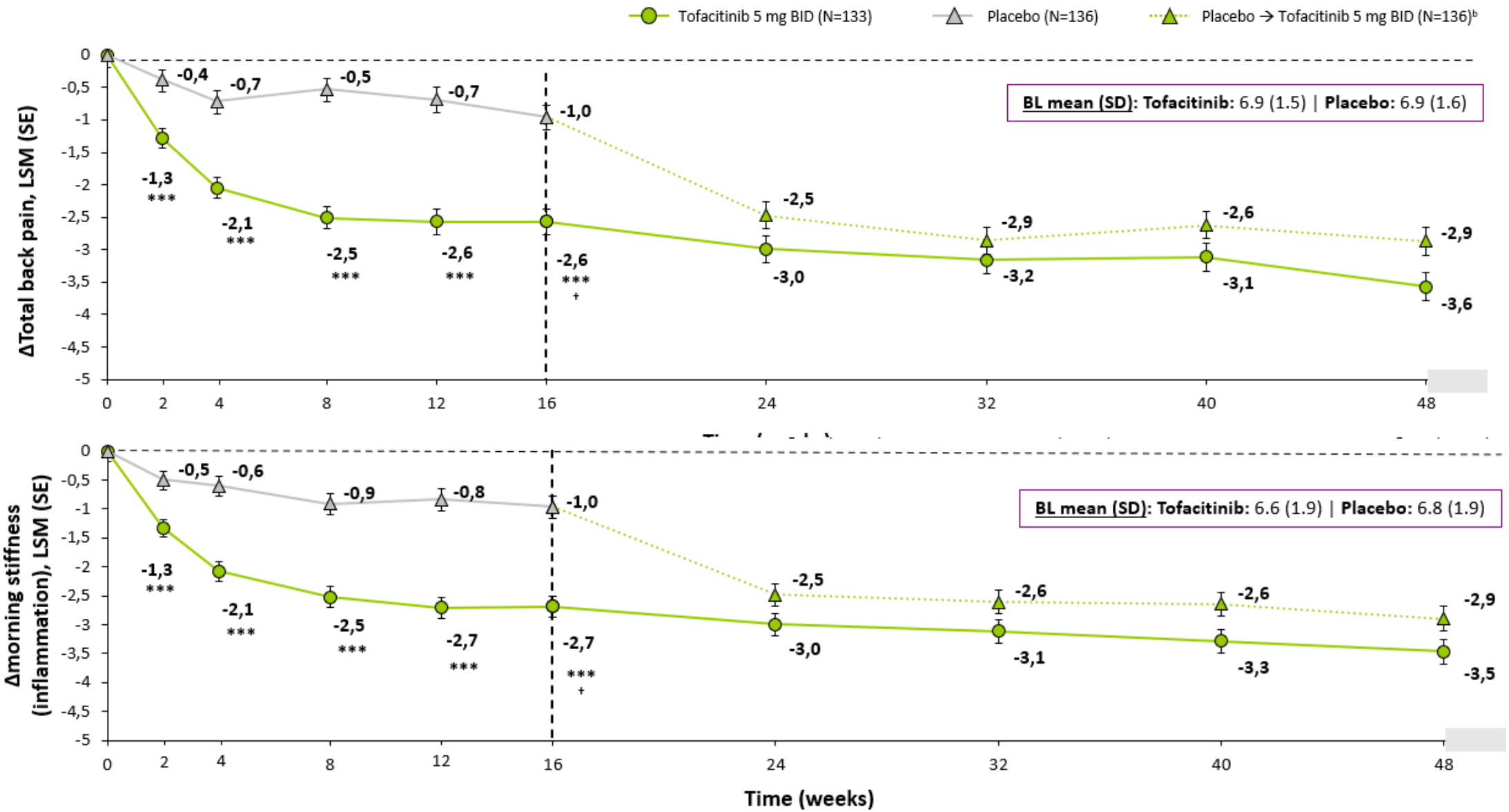
LS Mean ΔBASMI[a] at Week 16 and by Visit Up to Week 48



Data up to Week 16 are from the Week 16 analysis: data cutoff 19 December 2019; data snapshot 29 January 2020. Data for Weeks 24-48 are from the Week 48 final analysis. ***$P<0.001$ for comparing tofacitinib 5 mg BID vs placebo. †$P\leq0.05$ for comparing tofacitinib 5 mg BID vs placebo, according to the prespecified step-down testing procedure for global type I error control. [a]Mixed model for repeated measures included fixed effects of treatment group, visit, treatment-group-by-visit interaction, stratification factor (bDMARD treatment history: bDMARD naïve vs TNFi-IR or prior bDMARD use without IR) derived from the clinical database, stratification-factor-by-visit interaction, BL value, and BL-value-by-visit interaction. The model used a common unstructured variance-covariance matrix, without imputation for missing values. Two separate models were used. In the analyses of results through the first 16 weeks, the data cutoff of 19 December 2019 was used; the results through Week 16 are from this model. In the analyses of the results through Week 48 (including all post-BL data through Week 48), the Week 48 final data were used; the results from Week 24 through Week 48 are from this model. [b]Patients receiving placebo advanced to tofacitinib 5 mg BID at Week 16 (dashed line). Δ=change from BL; BASMI=Bath Ankylosing Spondylitis Metrology Index; bDMARD=biologic disease-modifying antirheumatic drug; BID=twice daily; BL=baseline; IR=inadequate response or intolerance; LS=least squares; LSM=least squares mean; N=number of patients in full analysis set; N1=number of patients with observation at visit; SE=standard error; TNFi=tumor necrosis factor inhibitor.

Deodhar A, et al. *Ann Rheum Dis.* 2021;0:1-10. doi:10.1136/annrheumdis-2020-219601.

LS Mean ΔTotal Back Pain[a] at Week 16 and by Visit Up to Week 48

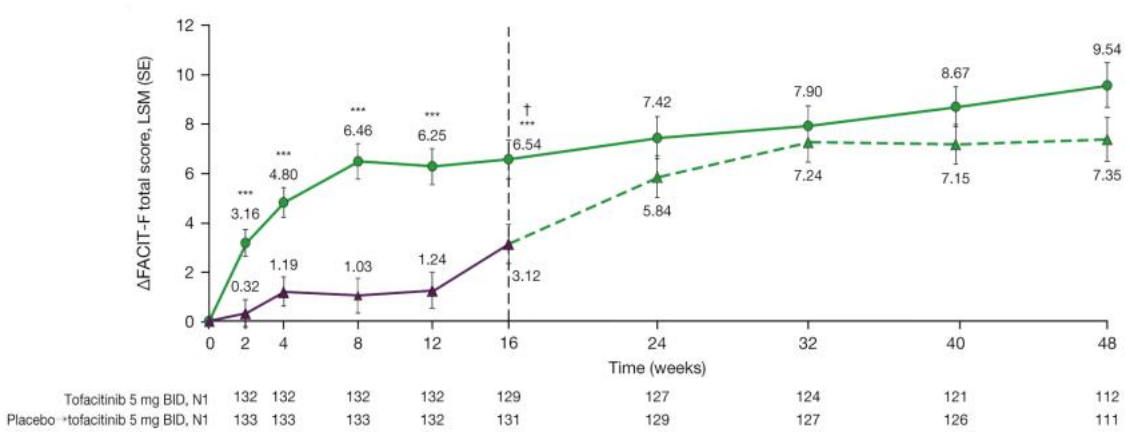


N1=	132	132	132	132	129	127	124	121	113
N1=	133	132	133	132	131	129	127	126	112

Deodhar A, et al. *Ann Rheum Dis.* 2021;0:1-10. doi:10.1136/annrheumdis-2020-219601

TOFA Study

Σημαντική βελτίωση στους δείκτες ποιότητας ζωής
και στην παραγωγικότητα



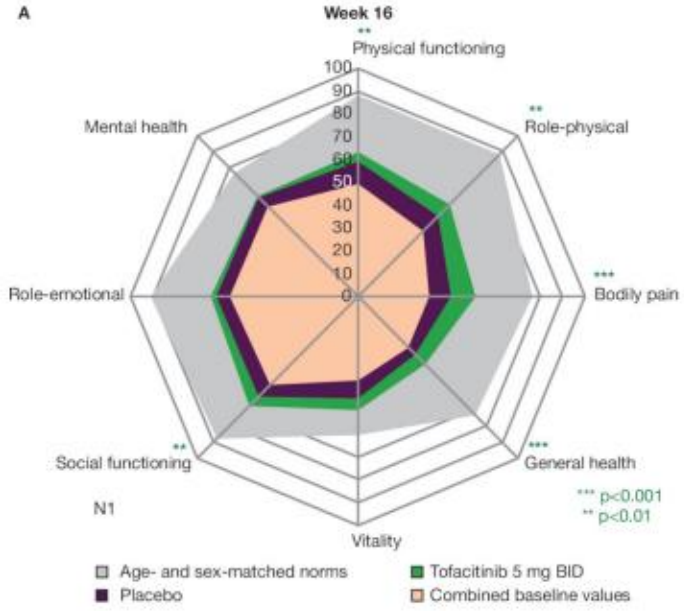
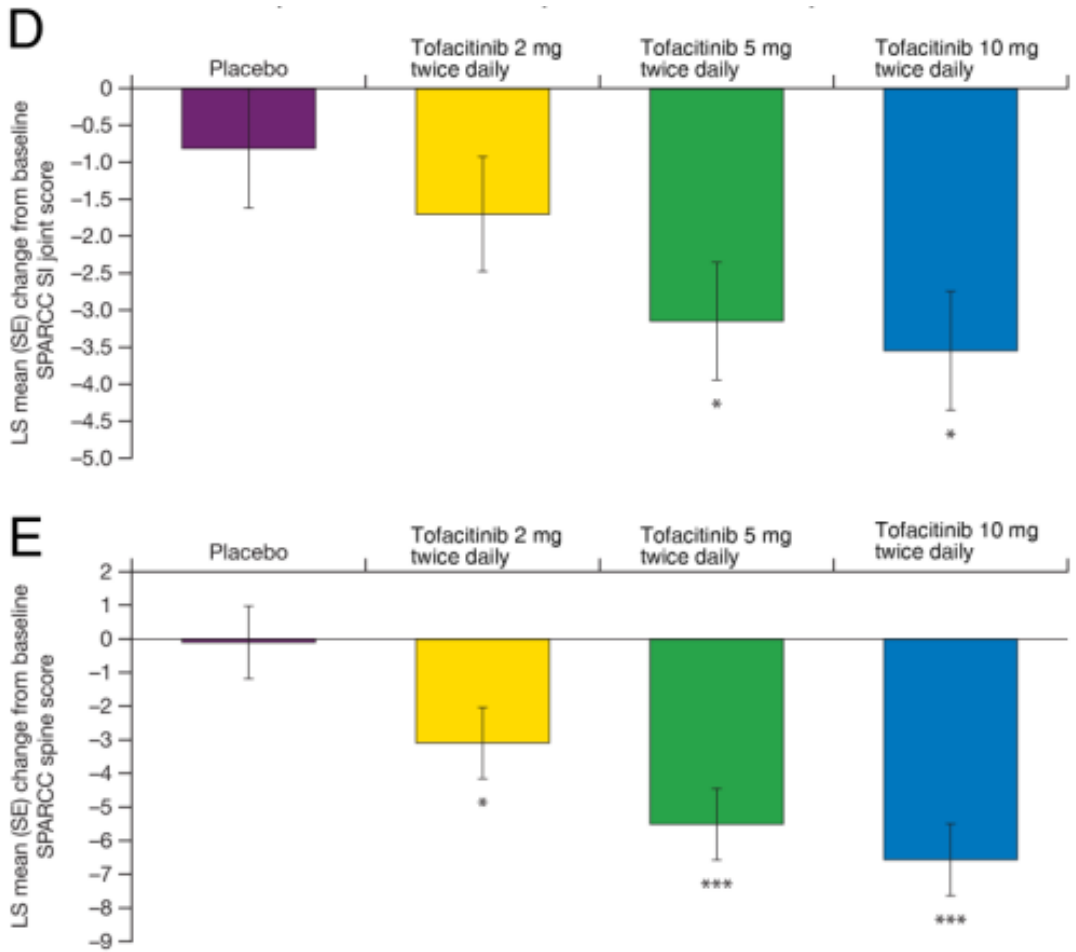


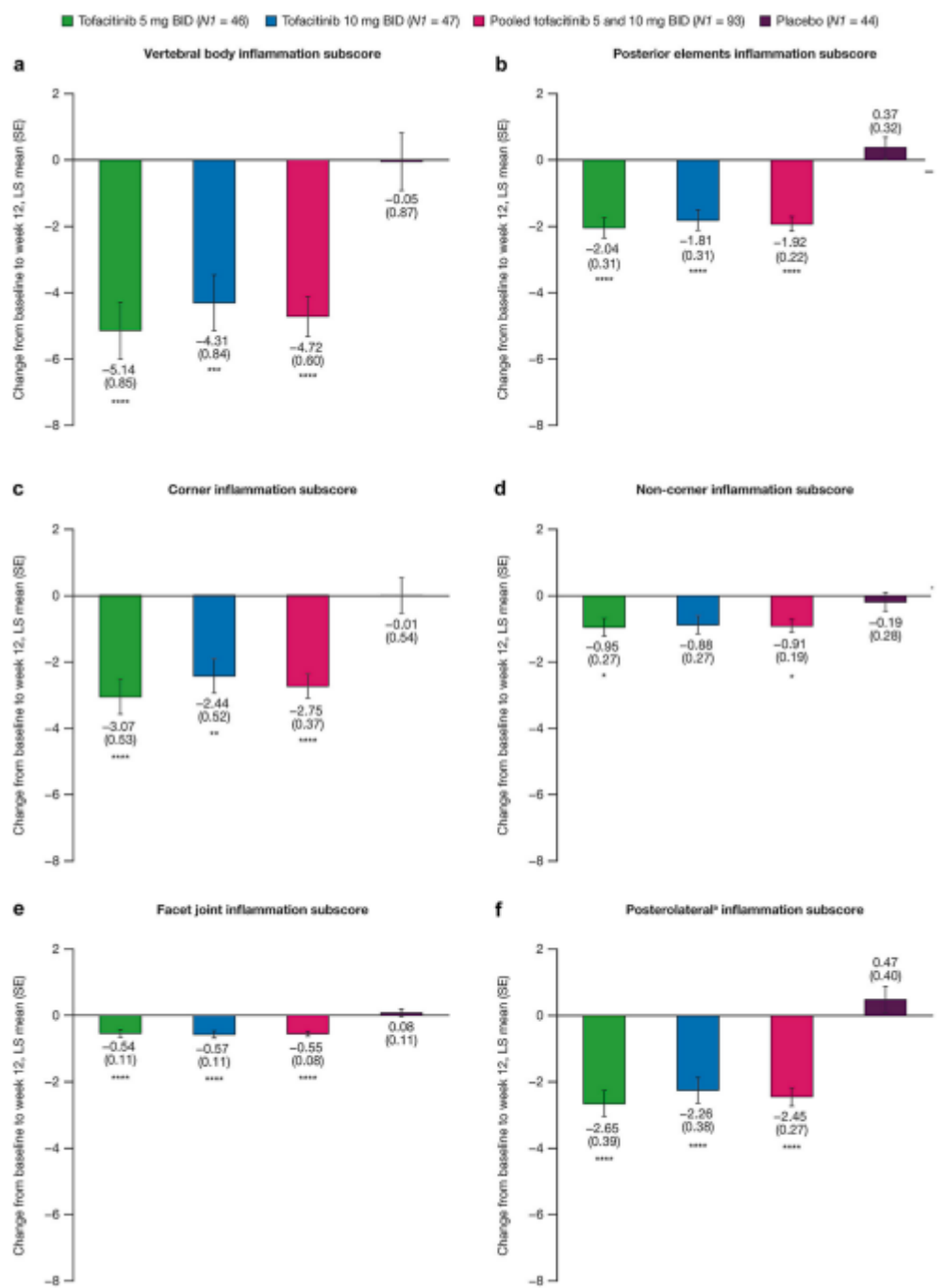
Table 1 Continued

PRO	Baseline, mean (SD) [N1] (range)		Week 16, LS mean Δ (SE) [N1]		Week 48, LS mean Δ (SE) [N1]	
	Tofacitinib 5mg twice daily (N=133)	Placebo (N=136)	Tofacitinib 5mg twice daily (N=133)	Placebo (N=136)	Tofacitinib 5mg twice daily (N=133)	Placebo→ tofacitinib 5mg twice daily (N=136)
EQ-VAS (0–100mm)††	46.9 (18.6) (10.0–95.0)	47.4 (21.9) [135] (5.0–95.0)	13.0 (1.84)*** [128]	2.89 (1.84) [130]	20.64 (1.88) [112]	18.00 (1.86) [111]
Work productivity						
WPAI††						
Activity impairment, %	56.5 (23.4) (0–90)	56.0 (21.4) (0–100)	–19.03 (1.97)*** [129]	–5.63 (1.97) [131]	–27.37 (2.34)** [112]	–19.77 (2.31) [112]
Absenteeism (work time missed), %	9.9 (22.4) [81] (0–100)	11.5 (24.6) [88] (0–100)	–3.65 (2.66) [74]	0.88 (2.62) [81]	–8.10 (2.14) [61]	–5.79 (2.05) [70]
Presenteeism (impairment while working), %	48.4 (26.3) [79] (0–100)	49.6 (22.2) [85] (0–90)	–19.83 (2.27)*** [71]	–6.94 (2.30) [77]	–25.35 (2.77) [58]	–23.00 (2.66) [70]
Overall work impairment, %	50.8 (27.4) [79] (0–100)	53.5 (23.1) [85] (0–100)	–21.49 (2.51)*** [71]	–7.64 (2.56) [76]	–27.63 (3.01) [58]	–23.22 (2.90) [69]

Deodhar A, et al. Ann Rheum Dis. 2021; 80(8):1004-

- Στατιστικά σημαντική υποχώρηση της οξείας φλεγμονής στην ΣΣ και στις ιερολαγόνιες αρθρώσεις μετά από 16 εβδομάδες αγωγής με Tofacitinib (vs. PBO)





Van der Heijde. Ann Rheum Dis. 2017;76:1340-1347
Ostergaard et al. Rheumatol Ther. 2023 Aug;10(4):1001-1020

Δεδομένα Tofacitinib στην ελκώδη κολίτιδα (RCTs)

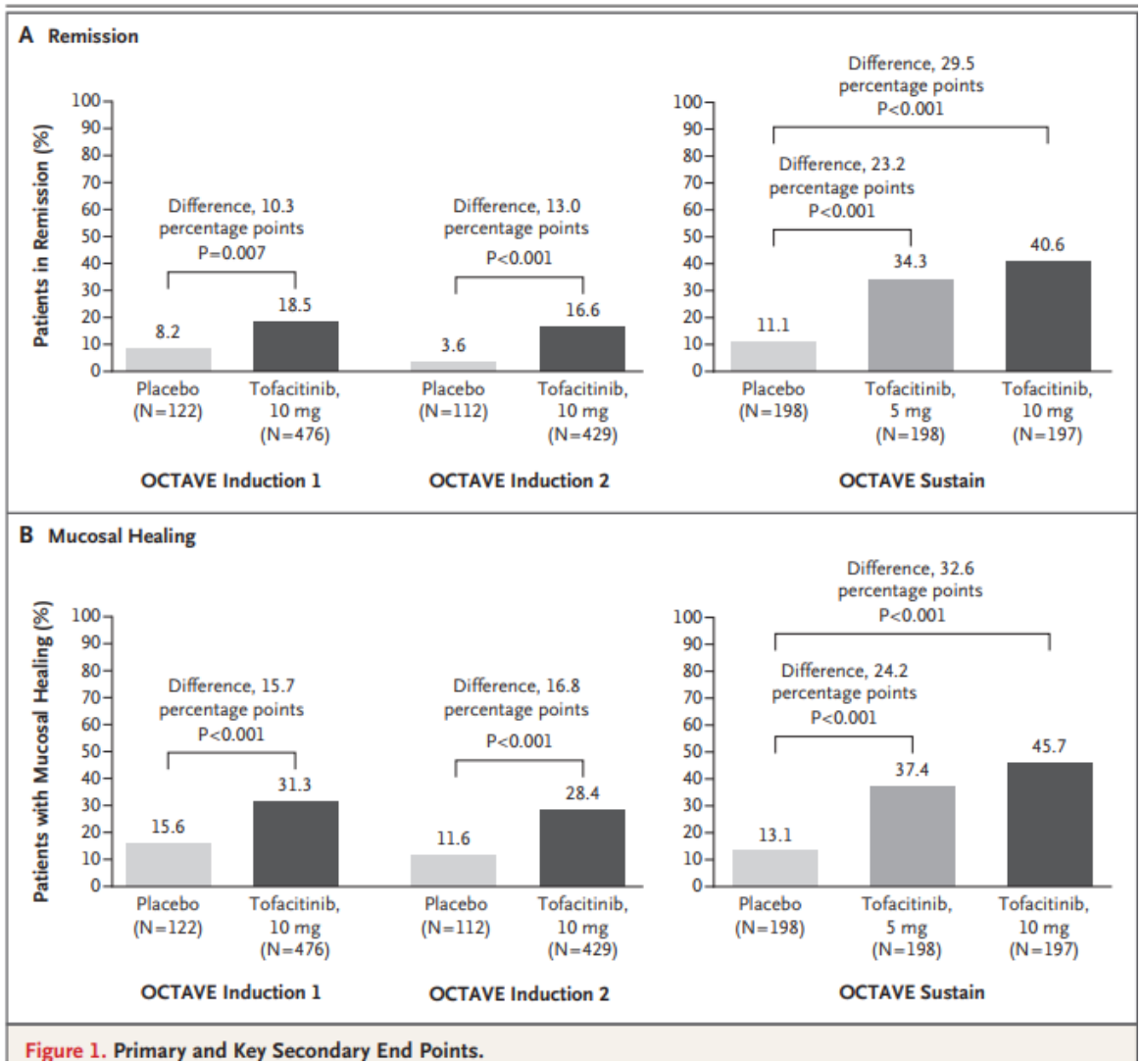
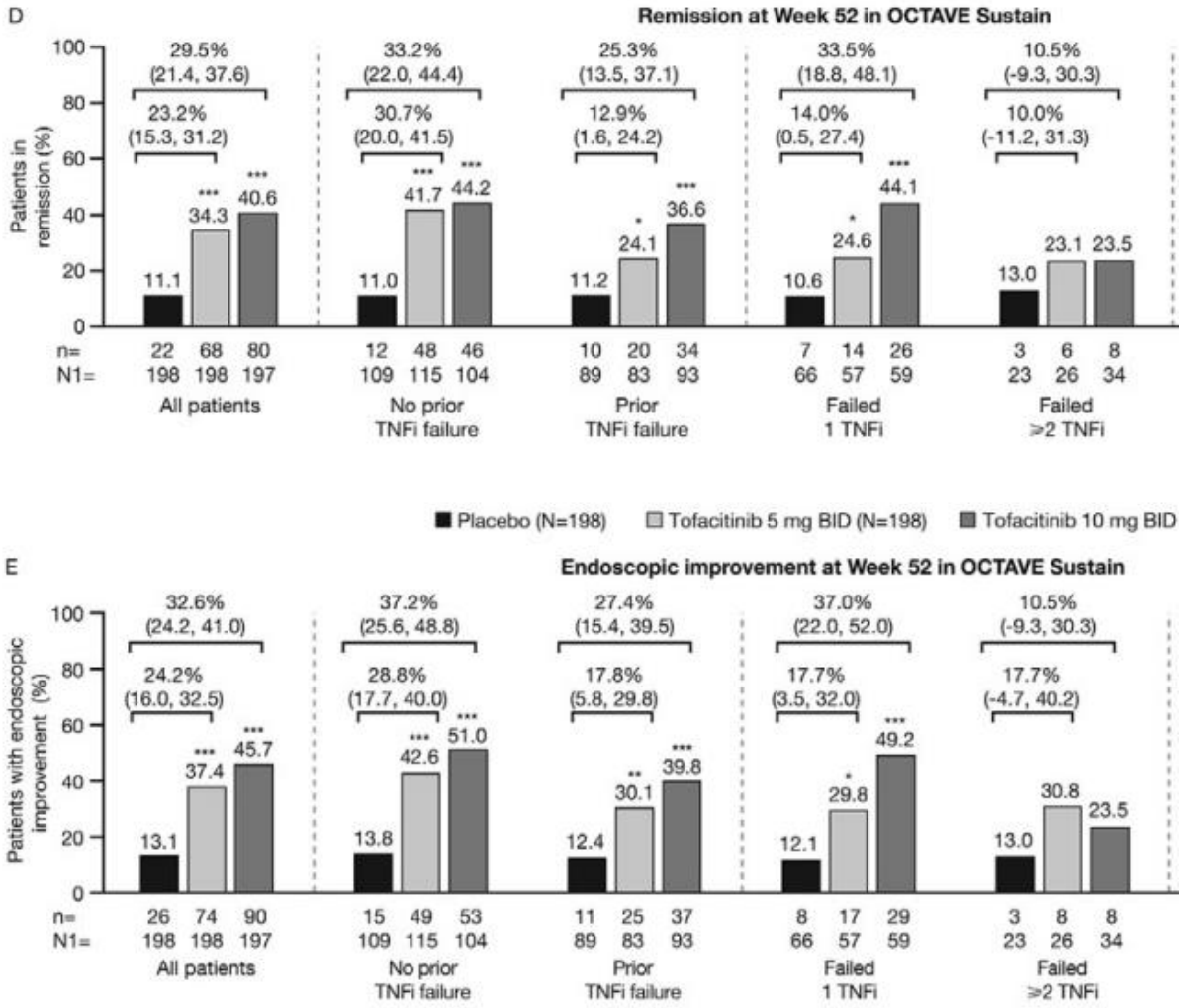


Figure 1. Primary and Key Secondary End Points.



Sandborn W et al.N Engl J Med 2017;376:1723-36

Real world δεδομένα Tofacitinib στην ελκώδη κολίτιδα

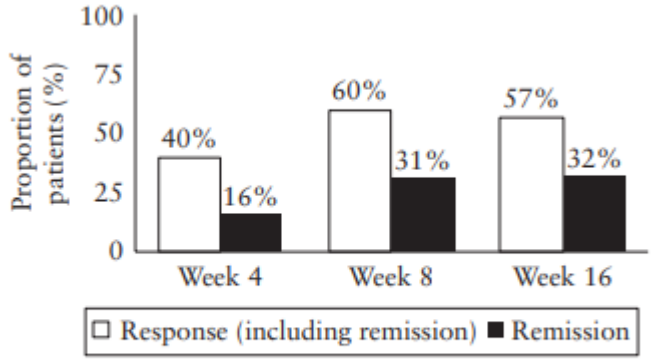
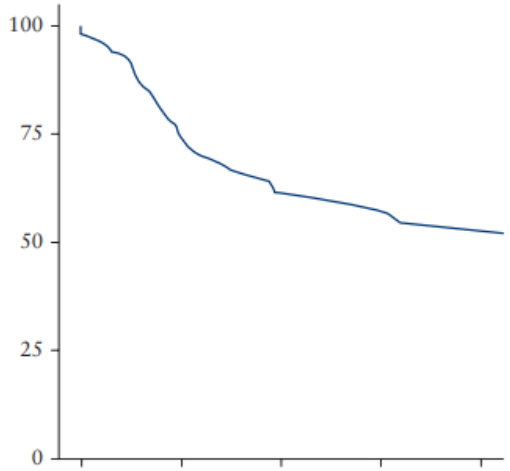
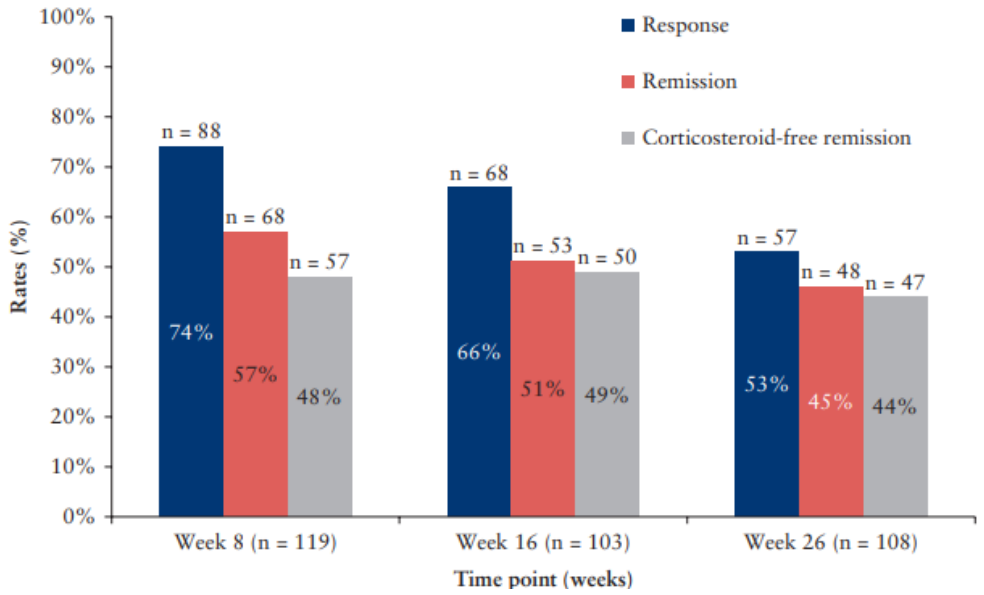


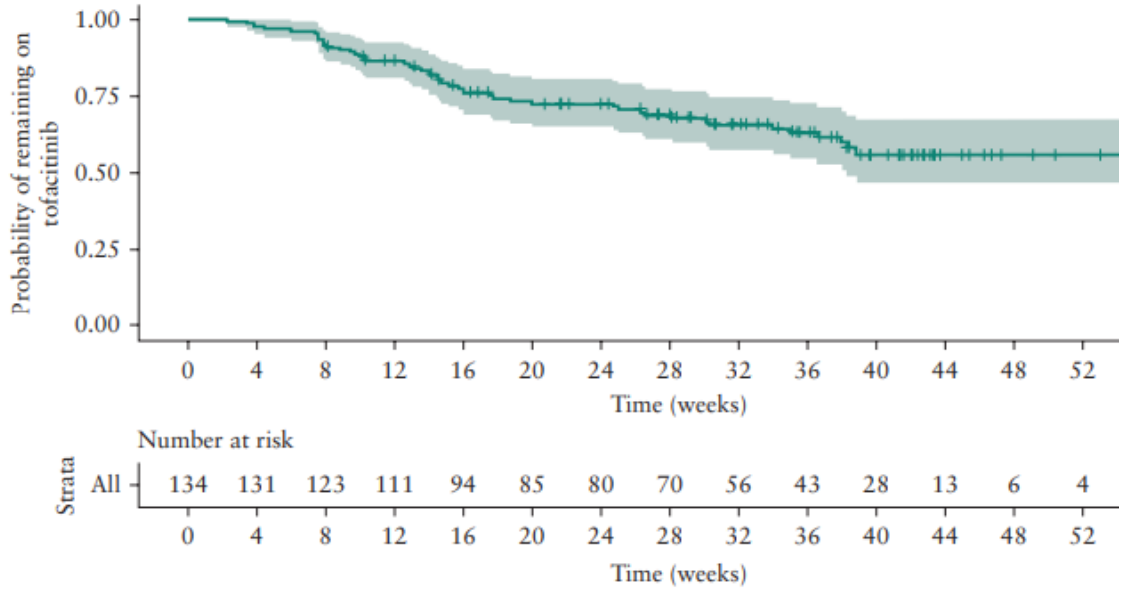
Figure 2. Short-term effectiveness of tofacitinib in ulcerative colitis [last-observation-carried-forward method].



Time of follow-up (weeks)	0	16	32	48	64
Patients at risk (number)	113	77	46	31	20
Patients mantaining tofacitinib (%)		77	62	58	55

*The reasons for tofacitinib discontinua on were: 26% primary non-response, 6% adverse events, 5% relapse, 2% partial response, 1% patient's choice

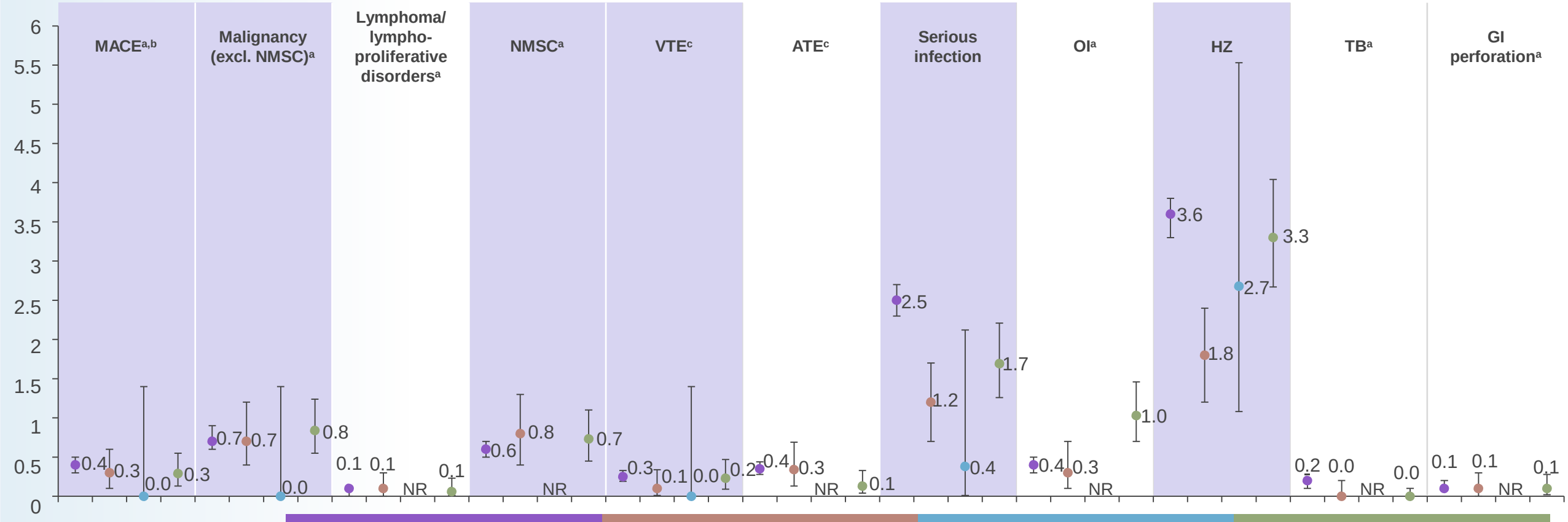




Chaparro et al.Journal of Crohn's and Colitis, 2021, 35–42
Honap et al. Journal of Crohn's and Colitis, 2020, 1385–1393

Ασφάλεια

AEs στα κλινικά προγράμματα του tofacitinib στην RA, PsA, AS, και UC



The approved dose of XELJANZ (tofacitinib citrate) for RA, AS, and PsA is 5 mg BID, and for UC is 10 mg BID for induction and 5 mg BID for maintenance.[5] Figure adapted from Burmester GR, et al. 2021,[1] Mease P, et al. 2020,[2] Deodhar A, et al. 2022,[3] and Sandborn WJ, et al. 2023.[4]
[a]Adjudicated events.[1,4] [b]MACE is defined as a composite of any myocardial infarction, stroke, or cardiovascular death.[1,3] [c]Drug exposures for RA and PsA were VTE: 24064.6 PY and 2098.4 PY, and ATE: 23957.1 PY and 2086.4 PY, respectively.[2] [d]Final data for the RA and PsA cohorts are from 18 April 2019 and 31 July 2019, respectively.[1,4] AESI, adverse event of special interest; AS, ankylosing spondylitis; ATE, arterial thromboembolism; BID, twice daily; CI, confidence interval; GI, gastrointestinal; HZ, herpes zoster; ISS, integrated safety summary; LTE, long-term extension; MACE, major adverse cardiovascular event;
MR, modified release; NMSC, nonmelanoma skin cancer; NR, not reported; OI, opportunistic infections; OLE, open-label extension; PsA, psoriatic arthritis; PY, patient-years; QD, once daily; RA, rheumatoid arthritis; TB, tuberculosis; UC, ulcerative colitis; VTE, venous thromboembolism.

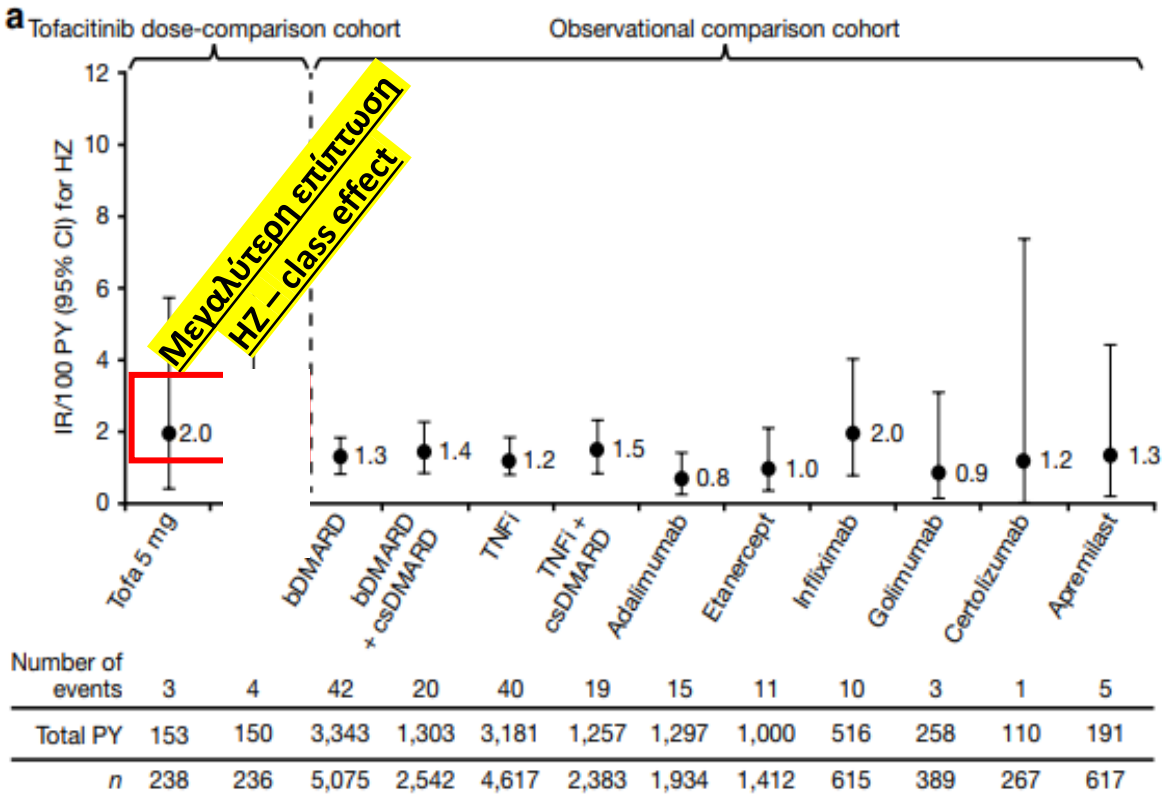
1. Burmester GR, et al. *RMD Open*. 2021;7:e001595. 2. Mease P, et al. *Ann Rheum Dis*. 2020;79:1400–1413. 3. Deodhar A, et al. *Ann Rheum Dis*. 2022;81(S1):394–395. 4. Sandborn WJ, et al. *J Crohns Colitis*. 2023;17:338–351 and supplementary appendix.

5. XELJANZ (tofacitinib citrate) Summary of Product Characteristics. Pfizer Inc. March 2023. https://ec.europa.eu/health/documents/community-register/html/h1178.htm#mod_download (accessed May 9, 2023).

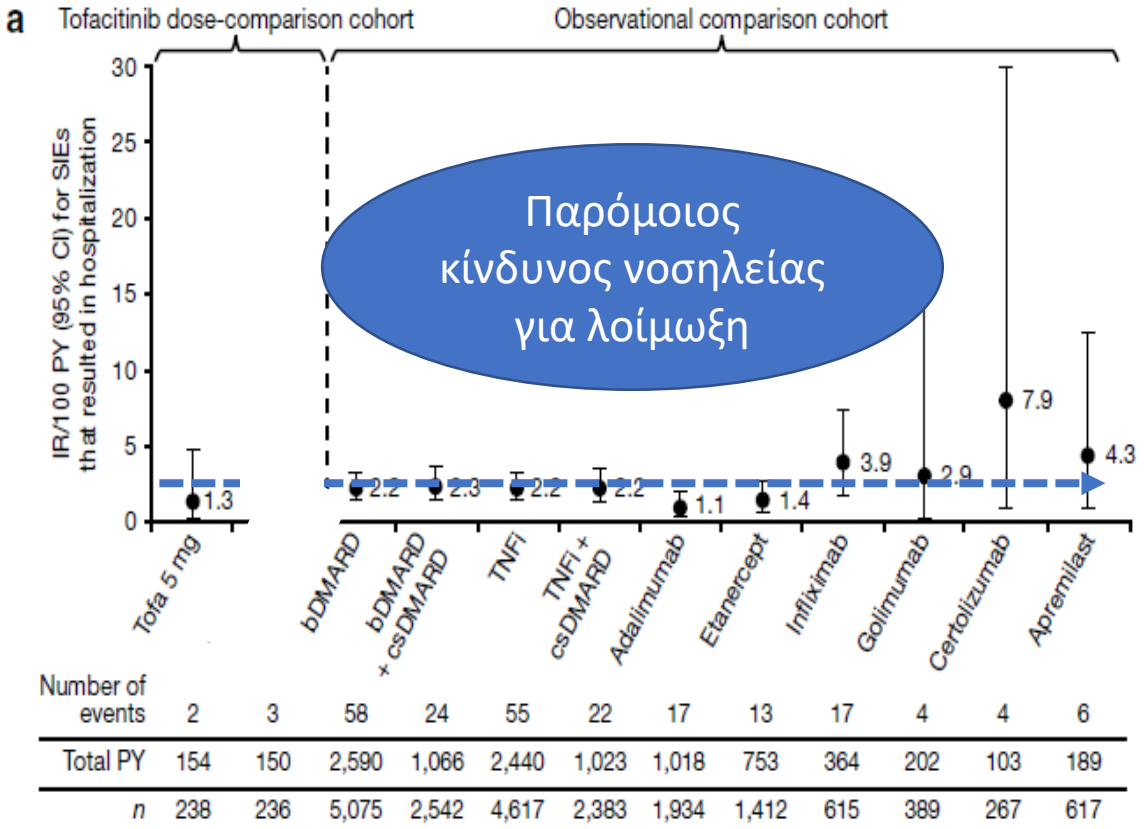
Tofacitinib στην Ψωριασική Αρθρίτιδα

- **Δεδομένα ασφάλειας**

HZ



Σοβαρές λοιμώξεις

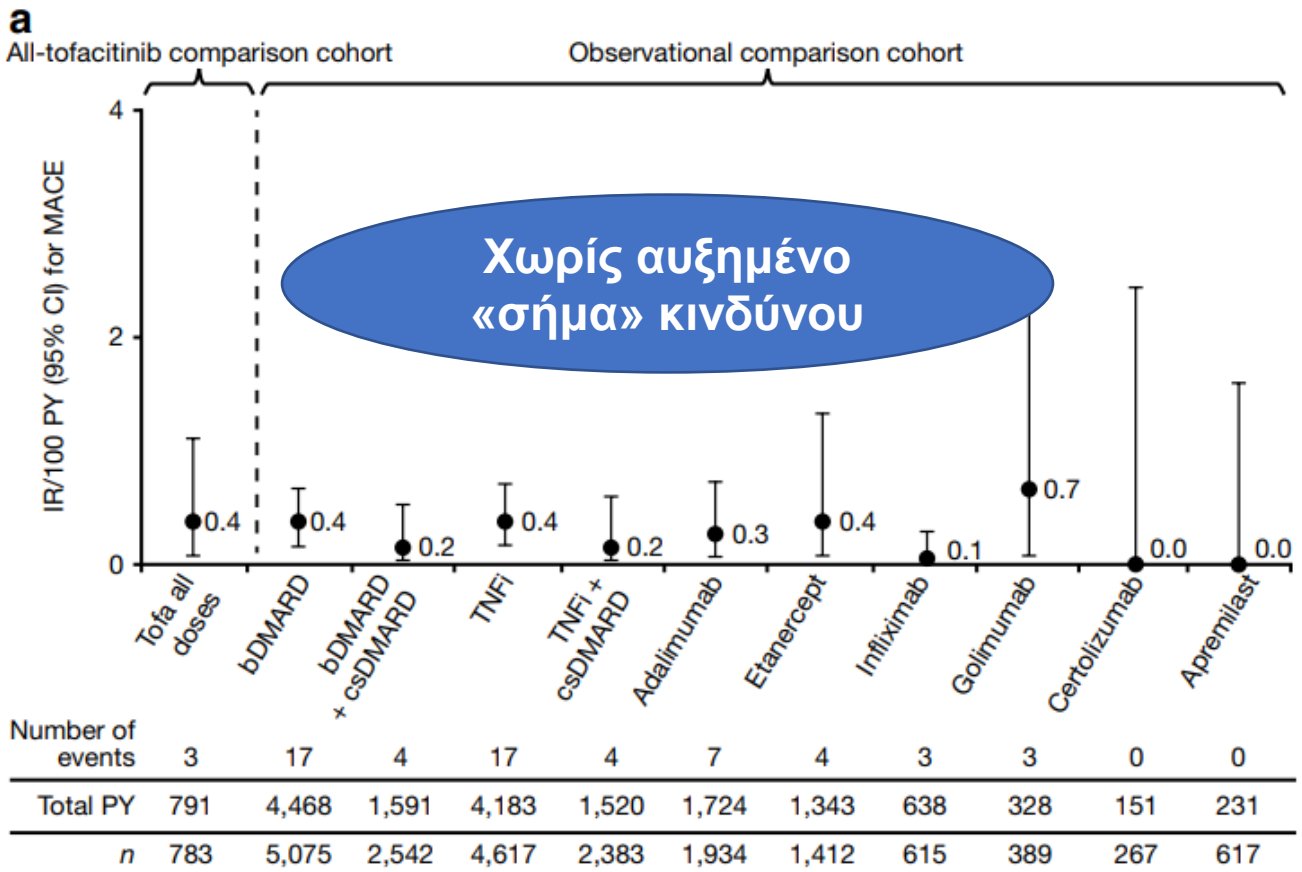


G. R. Burmester et al Springer 2020 doi.org/10.1007/s40264-020-00904-9

Tofacitinib στην Ψωριασική Αρθρίτιδα

- **Δεδομένα ασφάλειας**

Μείζονα Καρδιαγγειακά Συμβάντα



Key Points

In patients with active psoriatic arthritis (PsA), the safety profile of tofacitinib was generally consistent with that of other therapies in real-world settings.

Tofacitinib was associated with a higher risk for herpes zoster than were most other PsA therapies.

No new risks were identified compared with those already observed with tofacitinib treatment of rheumatoid arthritis.

Η εγκεκριμένη δόση του tofacitinib στη Ρευματοειδή αρθρίτιδα είναι 5mg BID σε συνδυασμό με MTX

G. R. Burmester et al Springer 2020 doi.org/10.1007/s40264-020-00904-9

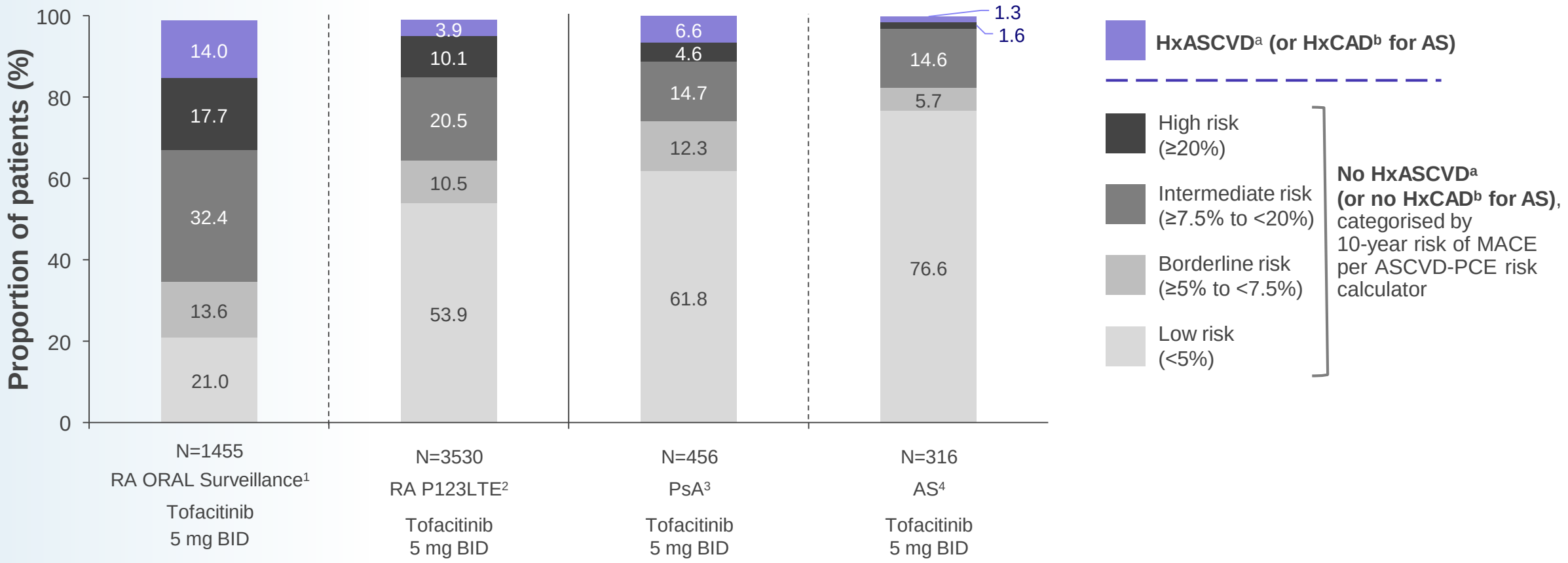
Δεδομένα ασφάλειας Tofacitinib στην ΑΣ (48 εβδ)

	Up to W16 (DB phase)		Up to W48 (DB and OL phases)	
Patients with events, n (%)	PBO (N=136)	Tofacitinib 5 mg BID (N133	PBO → Tofacitinib 5 mg BID (N=136)	Tofacitinib 5 mg BID (N=133)
AEs	70 (51.5)	73 (54.9)	93 (68.4)	103 (77.4)
SAEs	1 (0.7)	2 (1.5)	2 (1.5)	7 (5.3)
Severe AEs	0	2 (1.5)	0	6 (4.5)
Discontinued study drug due to AEs	1 (0.7)	3 (2.3)	3 (2.2)	8 (6.0)
Deaths	0	0	0	0
Most common AEs (>5% of any treatment group)				
Upper respiratory tract infection	10 (7.4)	14 (10.5)	18 (13.2)	21 (15.8)
Nasopharyngitis	10 (7.4)	9 (6.8)	17 (12.5)	11 (8.3)
Diarrhea	5 (3.7)	6 (4.5)	8 (12.5)	10 (7.5)
ALT increased	1 (0.7)	4 (3.0)	2 (1.5)	8 (6.0)
Arthralgia	8(5.9)	1 (0.8)	9 (6.6)	2 (1.5)
Headache	3 (2.2)	2 (1.5)	7 (5.1)	5 (3.8)
AEs of special interest				
HZ (serious and non-serious)	0	0	2 (1.5)**	3 (2.3)**
Opportunistic infection‡	0	0	0	0
Serious infections	0	1 (0.8)††	0	1 (0.8)††
ILD‡	0	0	0	0
Malignancies (including NMSC)‡	0	0	0	0
DVT, PE, or ATE‡	0	0	0	0
MACE‡	0	0	0	0
GI perforation‡	0	0	0	0
Hepatic events‡	0	1 (0.8)§	0	3 (2.3)¶

‡Adjudicated events; §Two sequential AST or ALT≥3xULN; ¶One patient had two sequential AST or ALT ≥3×ULN, which was unrelated DILI; one patient had AST or ALT ≥5×ULN, which was unlikely DILI; one patient had cholecystitis and recurrence of gallstones, which was unrelated DILI; **All cases were non-serious; ††Meningitis, did not meet opportunistic infection adjudication criteria.
AE, adverse event, ALT, alanine aminotransferase; BID, twice daily; DB, double-blind; DVT, deep vein thrombosis; GI, gastro-intestinal; HZ, herpes zoster; ILD, Interstitial lung disease; OL, open-label; ; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PBO, placebo; PsA, psoriatic arthritis; PE, pulmonary embolism; RA, rheumatoid arthritis; SAE, serious adverse event; TOFA, tofacitinib

Deodhar A, et al. Ann Rheum Dis. 2021;annrheumdis-2020-219601.

Baseline CV risk profiles of patients in ORAL Surveillance and RA (P123LTE), PsA, and AS clinical programmes



The approved dose of XELJANZ (tofacitinib citrate) for RA, AS, and PsA is 5 mg BID, and for UC is 10 mg BID for induction and 5 mg BID for maintenance.[5]

Figure adapted from Charles-Schoeman C, et al. 2023,[1] Dougados M, et al. 2023,[2] Kristensen LE, et al. 2023,[3] and Deodhar A, et al. 2022.[4]

[a]History of ASCVD is defined as the composite history of CAD, cerebrovascular disease, or peripheral artery disease.[1] [b]CAD defined as having ≥1 of myocardial infarction, CHD, coronary artery procedure, or stable angina pectoris.[4]

AS, ankylosing spondylitis; ASCVD, atherosclerotic cardiovascular disease; BID, twice daily; CAD, coronary artery disease; CHD, coronary heart disease; CV, cardiovascular; Hx, history; MACE, major adverse cardiovascular event; ORAL, Oral Rheumatoid Arthritis Trial; P123LTE, phase 1, 2, and 3 and long-term extension; PCE, pooled cohort equation; PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis.

1. Charles-Schoeman C, et al. *Ann Rheum Dis.* 2023;82:119–129. 2. Dougados M, et al. *Ann Rheum Dis.* 2023;82:575–577. 3. Kristensen LE, et al. *Ther Adv Musculoskelet Dis.* 2023;15:1–17. doi: 10.1177/1759720X221149965.
4. Deodhar A, et al. *Ann Rheum Dis.* 2022;81(S1):394–395. 5. XELJANZ (tofacitinib citrate) Summary of Product Characteristics. Pfizer Inc. March 2023. https://ec.europa.eu/health/documents/community-register/html/h1178.htm#mod_download (accessed May 9, 2023).

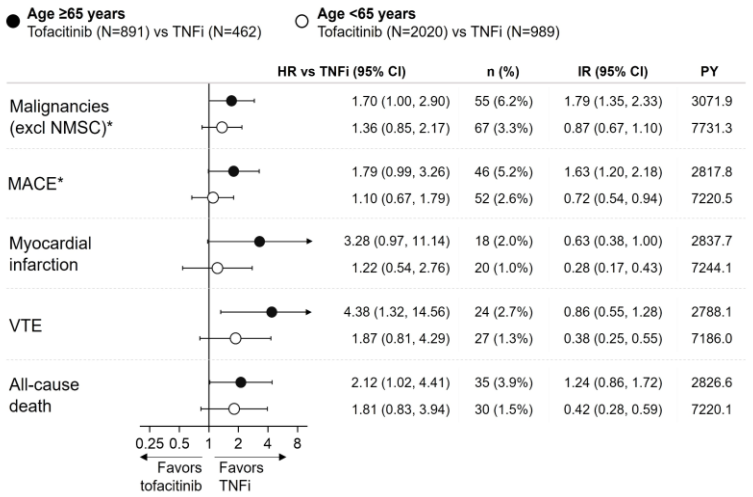
ORAL SURVEILLANCE

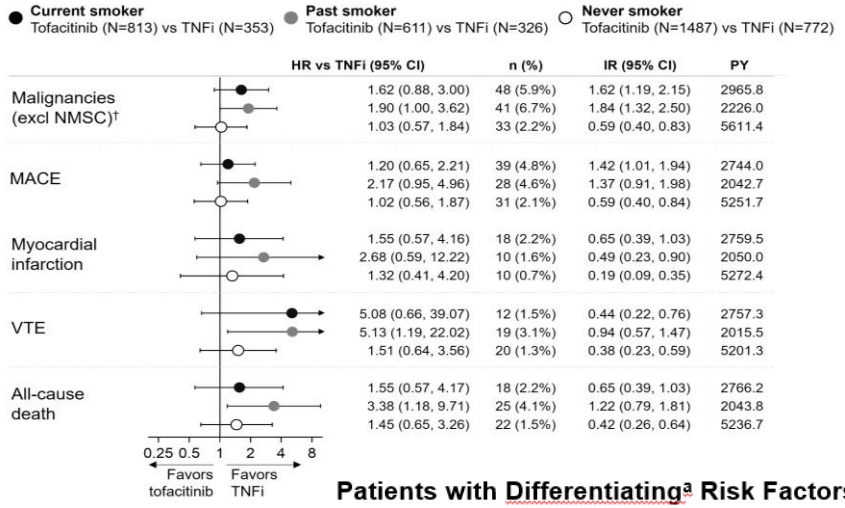
- Στην μελέτη ORAL, 60% ασθενών μέτριο έως σοβαρό καρδιαγγειακό κίνδυνο (vs. 30% στις TOFA RCTs)
- Ηλικία ≥65 έτη και κάπνισμα, ανεξάρτητοι παράγοντες κινδύνου → αυξημένη επίπτωση MACE και νεοπλασιών
- Αυξημένος κίνδυνος για MACE του TOFA vs. ADA/ETN, **μόνο σε ασθενείς με προηγούμενο ιστορικό MACE**
- Συγκρίσιμος κίνδυνος μεταξύ tofacitinib vs. ADA/ETN σε ομάδες χαμηλού κινδύνου

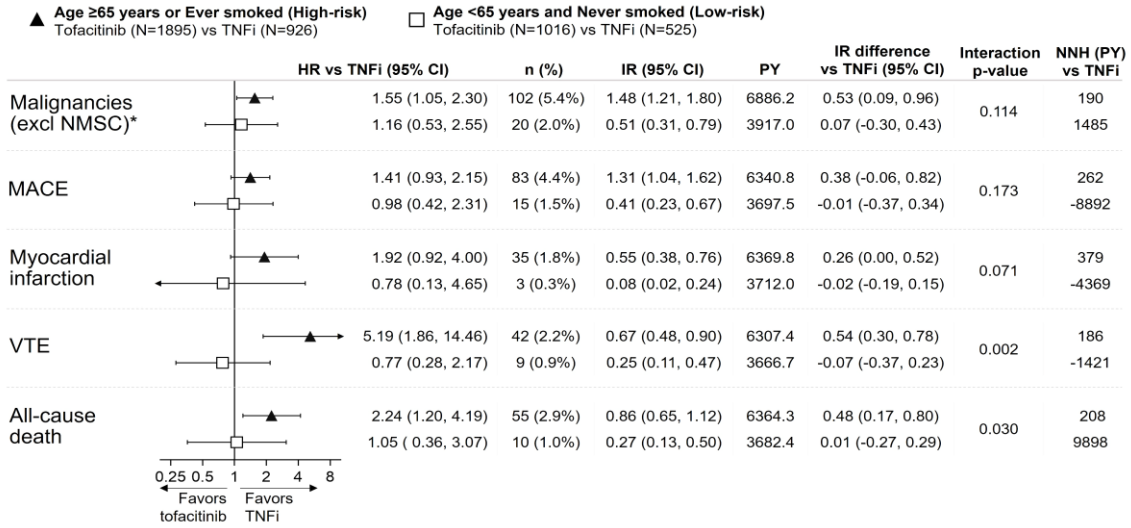
- Σύσταση EMA: should be used only if no suitable treatment alternatives are available: aged 65 years or above, increased risk of MACE (such as heart attack or stroke), smokers (current or past for a long time, increased risk of cancer.

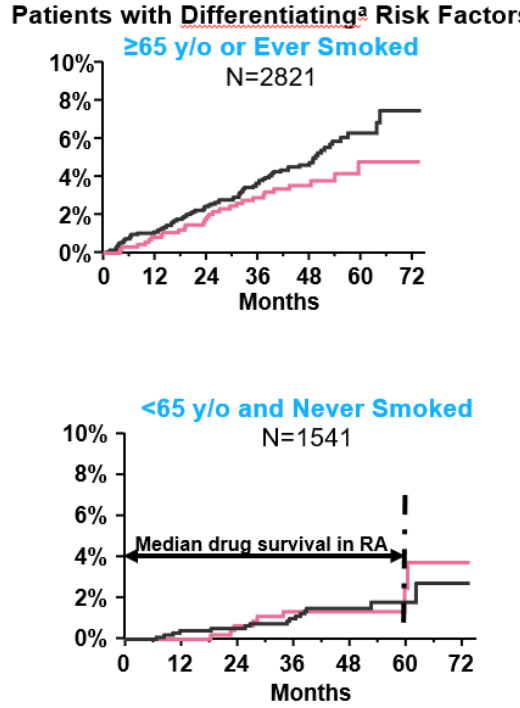
EULAR RA Recommendations 2022

8. If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, a bDMARD should be added; JAK-inhibitors may be considered, but pertinent risk factors* must be taken into account.









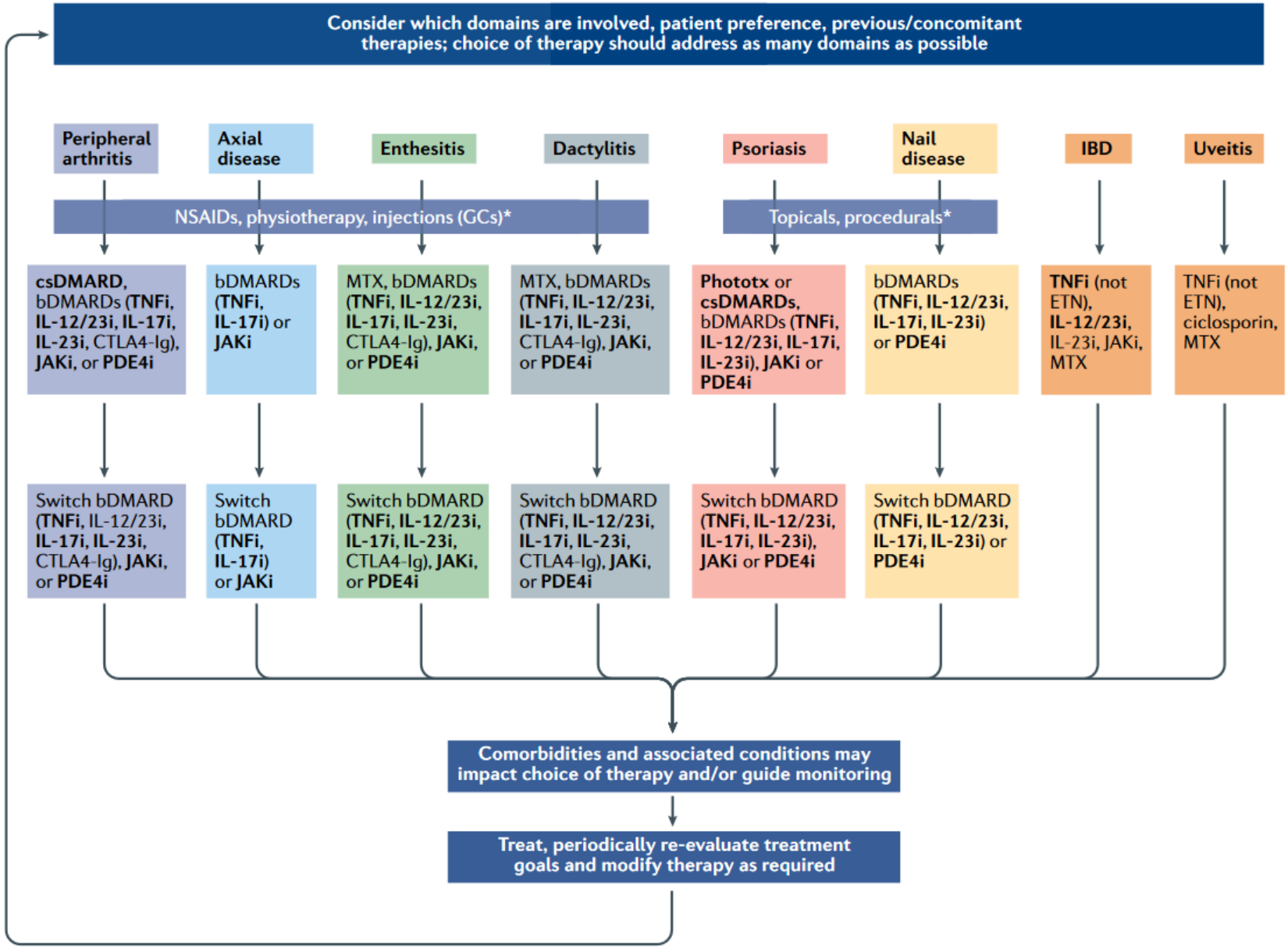
Kristensen et al. Ann Rheum Dis. 2023. Mar 17;ard-2022-223715.
Charles-Schoeman et al. Arthritis Rheumatol.2021;73 (supp 10)
https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-24-27-october-2022
Smolen et al. Ann Rheum Dis. 2023 Jan;82(1):3-18

2021 GRAPPA (Recs)

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021

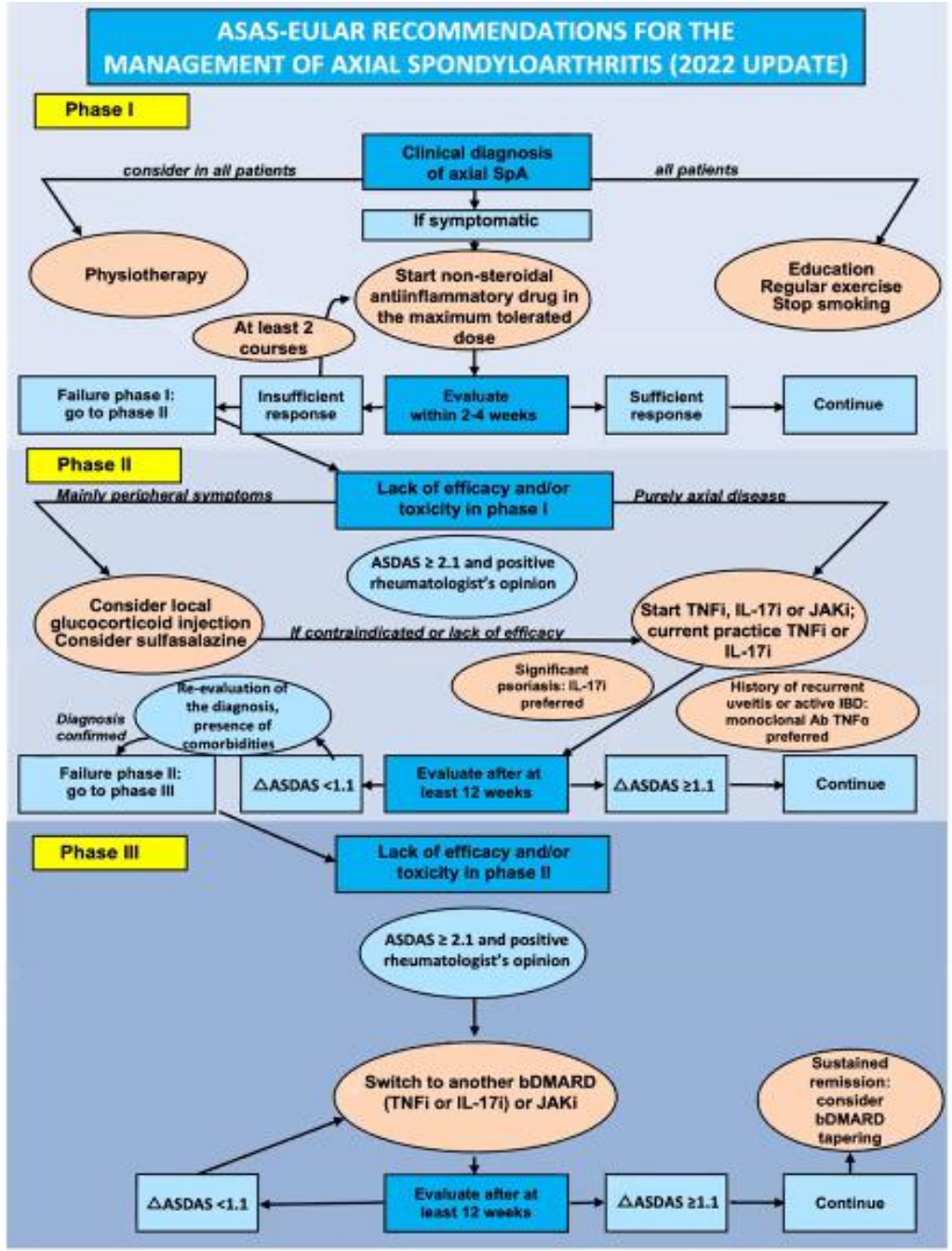
Laura C. Coates[1], Enrique R. Soriano[2], Nadia Corp[3], Heidi Bertheussen[4], Kristina Callis Duffin[5], Cristiano B. Campanholo[6], Jeffrey Chau[7], Lihi Eder[8], Daniel G. Fernández-Ávila[9], Oliver FitzGerald[10], Amit Garg[11], Dafna D. Gladman[12], Niti Goel[13], Philip S. Helliwell[14], M. Elaine Husni[15], Deepak R. Jadon[16], Arnon Katz[17], Dhruvkumar Laheru[18], John Latella[19], Ying-Ying Leung[20], Christine Lindsay[21], Ennio Lubrano[22], Luis Daniel Mazzuoccolo[23], Philip J. Mease[24], Denis O'Sullivan[25], Alexis Ogdie[26], Wendy Olsder[27], Penelope Esther Palominos[28], Lori Schick[29], Ingrid Steinkoenig[30], Maarten de Wit[31], D. A. van der Windt[5], Arthur Kavanaugh[32] and the GRAPPA Treatment Recommendations domain subcommittees,***

NATURE REVIEWS | RHEUMATOLOGY



Coates LC, et al. J Rheumatol. 2022 Jun;49(6 Suppl 1):52-54. doi: 10.3899/jrheum.211331. Epub 2022 Mar 15.

Tofacitinib is only recommended for RA, PsA, UC, AS, JIA



Ramiro S, et al. Ann Rheum Dis 2022;0:1–16. doi:10.1136/ard-2022-223296 1

Συμπεράσματα

- Οι αξονικές σπονδυλοαρθρίτιδες χαρακτηρίζονται από ένα ευρύ φάσμα αρθριτικών και εξωαρθρικών εκδηλώσεων που μοιράζονται κοινούς παθογενετικούς μηχανισμούς και μπορεί να αποτελούν κοινό θεραπευτικό στόχο.

- Το Tofacitinib έχει πλειοτρόπο ανοσοτροποποιητική δράση, αναστέλλοντας άμεσα ή έμμεσα πολλές κυτταροκίνες που κατέχουν κεντρικό ρόλο στην παθογένεια των σπονδυλοαρθριτίδων

- Με βάση δεδομένα 10-ετίας απο τυχαιοποιημένες κλινικές μελέτες και την καθημερινή κλινική πρακτική, το Tofacitinib επιδεικνύει υψηλό δείκτη αποτελεσματικότητας στην βελτίωση των δείκτων ενεργότητας αλλα και των συμπτωματων σε ασθενείς με PsA/AxSpA

- Το Tofacitinib έχει πολυ καλό προφίλ ασφάλειας, συγκρίσιμο με αυτό άλλων βιολογικών παραγόντων. Ειναι απαραίτητη η αξιολόγηση του καρδιαγγειακού κινδύνου, ιδιαίτερα σε ασθενείς άνω των 65 ετών με μακροχρόνιο ιστορικό καπνίσματος

- Συμφωνα με τις αναθεωρημένες συστάσεις της EULAR και της GRAPPA για την αντιμετώπιση της AxSpA και της PsA, οι JAKis μπορεί να είναι η 1^{η} επιλογή στο 2^{ο} θεραπευτικό βήμα, μετά από αποτυχιά σε ΜΣΑΦ (AS) ή συμβατικά DMARDs (PsA)

ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ