11ο Κρητοκυπριακό Συμπόσιο Ρευματολογίας
Λευκωσία 20-22/09/2019

Tofacitinib στη Ρευματοειδή Αρθρίτιδα με στόχο το ενδοκυττάριο μονοπάτι JAK/STAT

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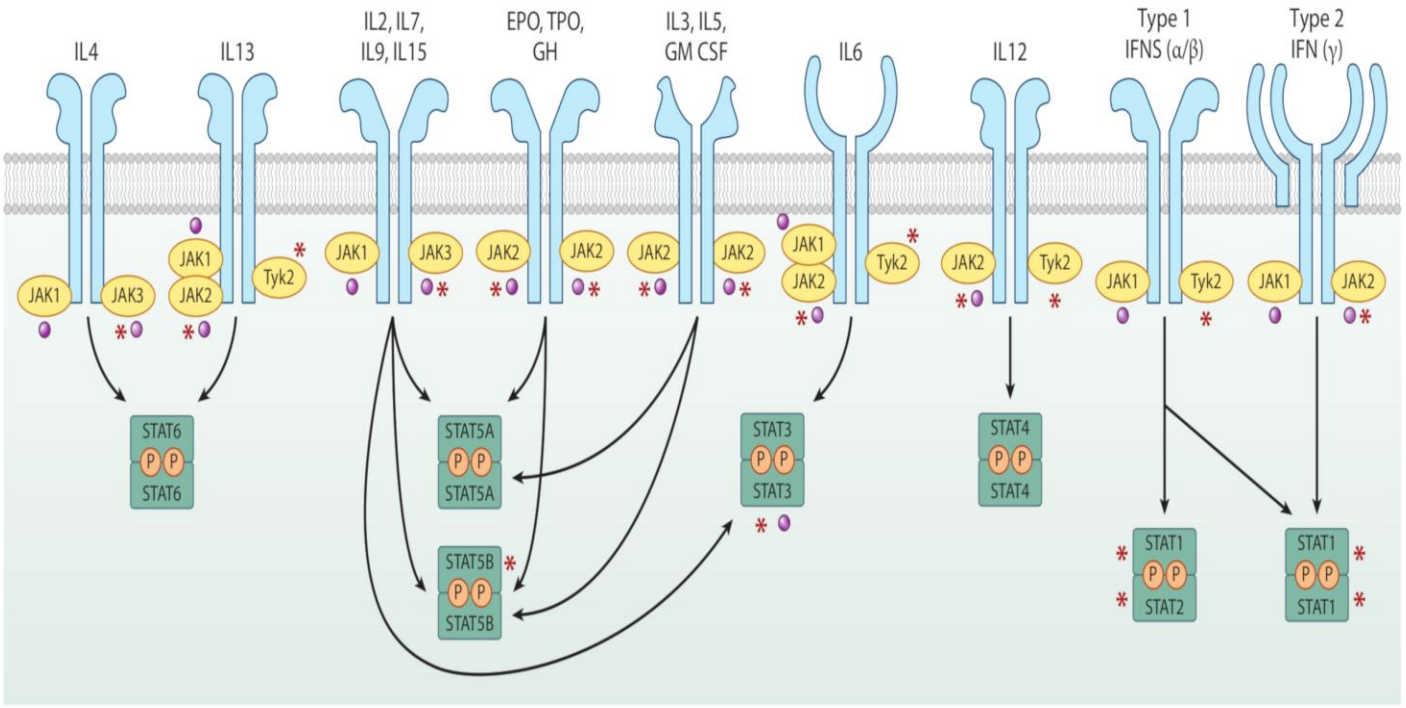
Μονάδα Ρευματολογίας και Κλινικής Ανοσολογίας, ΠΓΝ «Αττικόν»

Λευκωσία, 21/9/2019

ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΣΚΛΗΠΙΕΙΟ ΒΟΥΛΑΣ

ATTIKON

Τα μονοπάτια JAK/STAT



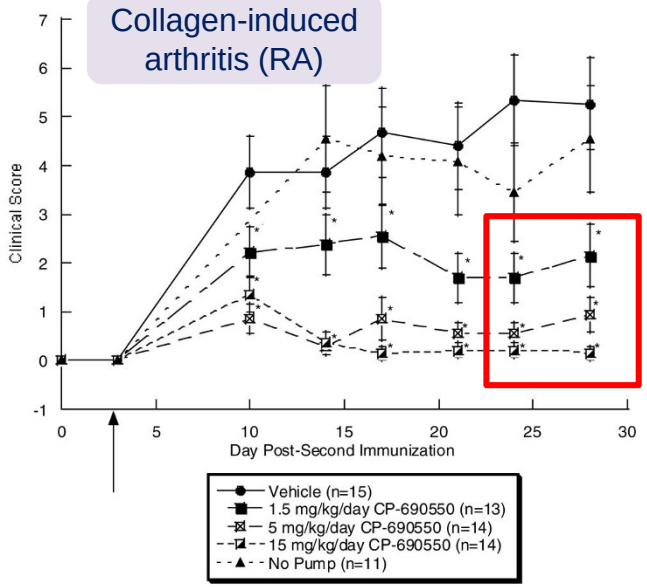
- Οι STATs ρυθμίζουν την <u>έκφραση *δεκάδων χιλιάδων* γονιδίων</u> (δράσεις σε ανοσοποιητικό, αιμοποιητικό, νευρο-αναπτυξιακές, μεταβολισμό)
- Το **βιολογικό αποτέλεσμα** των JAKs/STATs είναι **κυτταρο-/ιστο-ειδικό**
- Οι υποδοχείς κυτταροκινών όπως **TNF, IL-1, IL-17** <u>δεν σηματοδοτούν μέσω JAKs</u>

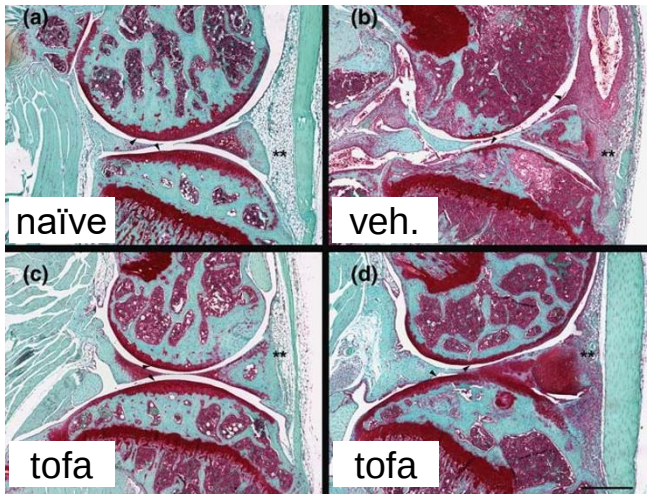
O'Shea JJ, et al. *Annu Rev Med*. 2015; 66:311-28; *Ann Rheum Dis*. 2013; 72 Suppl 2: ii111-5

Tofacitinib (JAK3/1 inhibitor) και PA

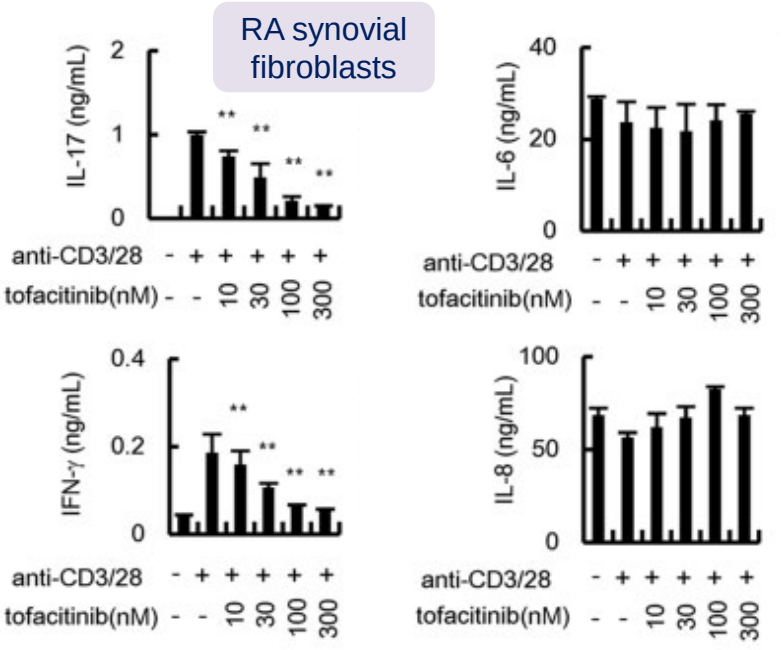
Προκλινικά και in vitro δεδομένα

Collagen-induced arthritis (RA)

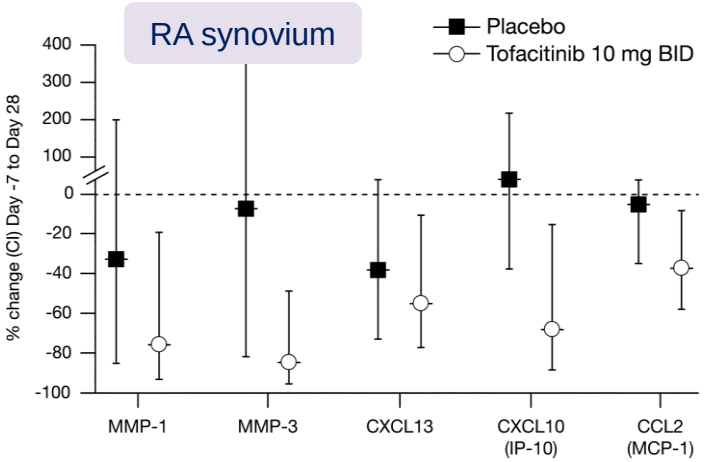




RA synovial fibroblasts

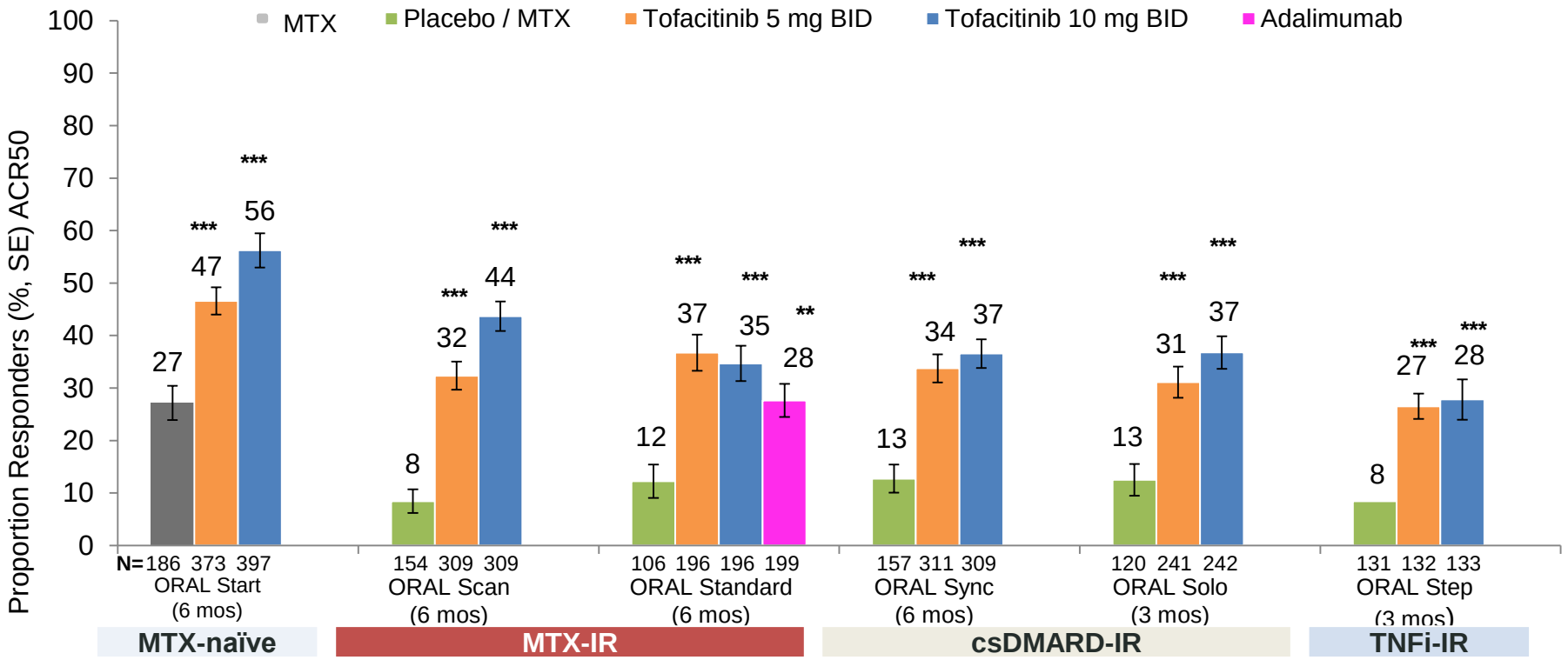


RA synovium



Maeshima K, et al. *Arthritis Rheum*. 2012; 64: 1790-8; Milici AJ, et al. *Arthritis Res Ther*. 2008; 10: R14; Boyle DL, et al. *Ann Rheum Dis*. 2015; 74: 1311-6

Tofacitinib: Proportion (%) of ACR50 Responders Across Studies (FAS, NRI)



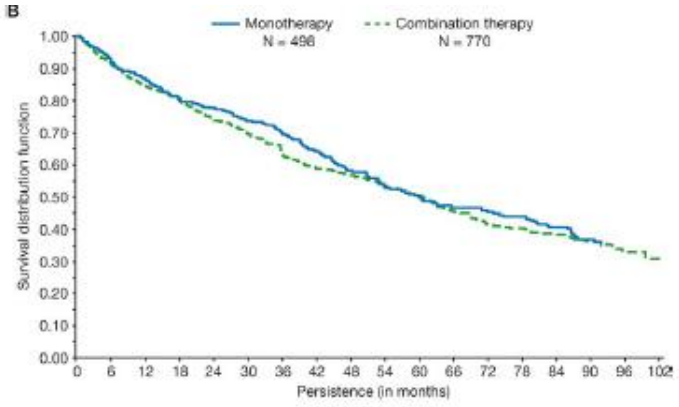
*$P \leq 0.05$; **$P < 0.001$; *** $P < 0.0001$ vs. placebo/MTX.
ACR=American College of Rheumatology; BID=twice daily; DMARD=disease-modifying antirheumatic drug; FAS=full analysis set; IR=inadequate response; MTX=methotrexate; NRI=non-responder imputation; SE=standard error; TNFi=tumor necrosis factor inhibitor.

1. Burmester G et al. *Lancet.* 2013;381:451-460. 2. Fleischmann R et al. *N Engl J Med*. 2012;367:495-507. 3. Kremer J et al. *Ann Intern Med*. 2013;159(4):253-261. 4. Van der Heijde D et al. *Arthritis Rheum.* 2013;65(3):559-570. 5. Van Vollenhoven RF et al. *N Engl J Med*. 2012;367:508-519. 6. Lee EB et al. *Arthritis Rheum.* 2012;64(suppl10):S1049, Abst 2486.

Real-life δεδομένα αποτελεσματικότητας του tofacitinib

Οι ανοικτές μελέτες επέκτασης του tofacitinib (ως 9.5 έτη)

- **4967 patients**
- Overall, 50.7% d/ced (AE >> inefficacy)
- Median drug survival 4.9 years
- 2-and 5-year drug survival rates: 75.5% and 49.4%, respectively
- Slightly higher for patients receiving tofacitinib monoTx vs. combination Tx



Baseline Variable (Index Baseline)	Comparison	Hazard Ratio (95% CI)	*P* value
Diabetes	Yes vs No	1.3 (1.1, 1.5)	0.0041
Hypertension	Yes vs No	1.2 (1.1, 1.3)	0.0002
Glucocorticoid use	Yes vs No	1.1 (1.0, 1.2)	0.0528
Anti-CCP status	CCP+ vs CCP−	0.8 (0.7, 0.9)	0.0001
Prior treatment[b]	MTX-IR vs TNFi-IR	0.8 (0.7, 0.9)	<0.0001
RF and anti-CCP status[b]	RF+/CCP+ vs RF−/CCP−	0.8 (0.7, 0.9)	0.0003

Pope JE, et al. ACR Open Rheumatol 2019;1(2):73-82

- **4481 patients**
- **~ 50% διακοπή θεραπείας**
- Διατήρηση αποτελεσματικότητας στο χρόνο (νι'αυτούς που έμειναν στη θεραπεία)

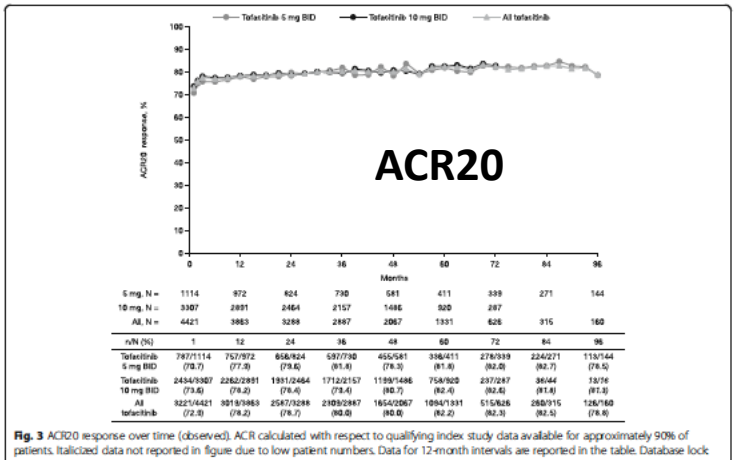


Fig. 3 ACR20 response over time (observed). ACR calculated with respect to qualifying index study data available for approximately 90% of patients. Italicized data not reported in figure due to low patient numbers. Data for 12-month intervals are reported in the table. Database lock

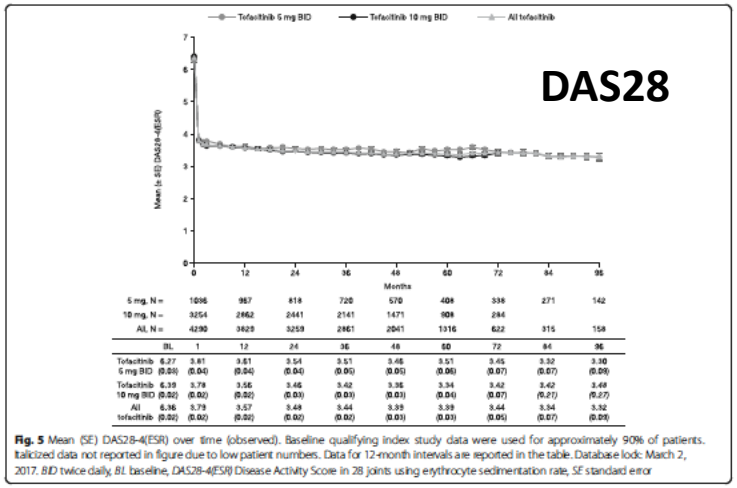


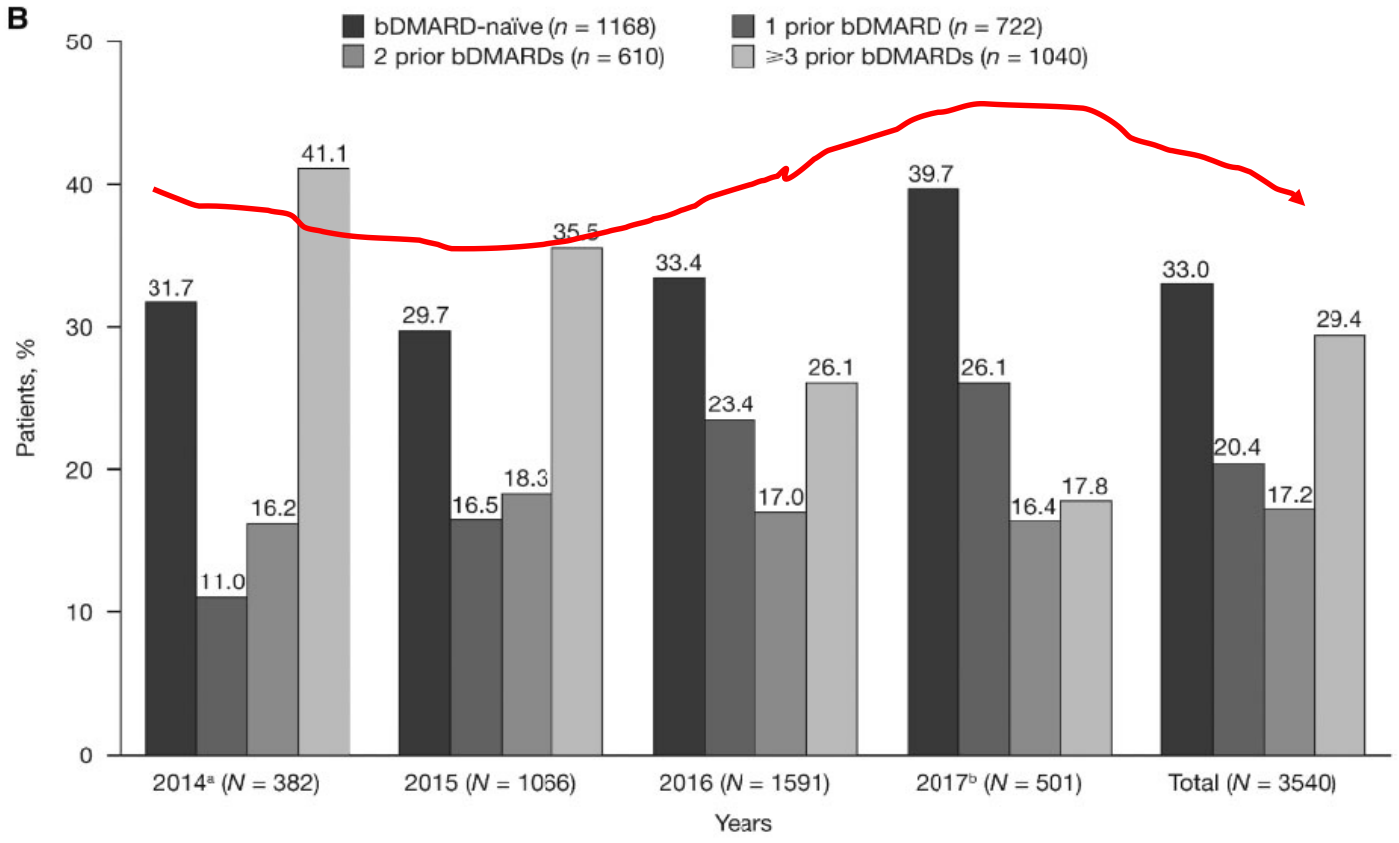
Fig. 5 Mean (SE) DAS28-4(ESR) over time (observed). Baseline qualifying index study data were used for approximately 90% of patients. Italicized data not reported in figure due to low patient numbers. Data for 12-month intervals are reported in the table. Database lock: March 2, 2017. *BID* twice daily, *BL* baseline, *DAS28-4(ESR)* Disease Activity Score in 28 joints using erythrocyte sedimentation rate, *SE* standard error

Wollenhaupt J, et al. Arthritis Res Ther. 2019;21(1):89

3 χρόνια tofacitinib στον Καναδά

Ιούνιος 2014 – Μάιος 2017
3678 ασθενείς

Προοδευτική αύξηση των ασθενών που έλαβαν tofacitinib ως bDMARD-naive

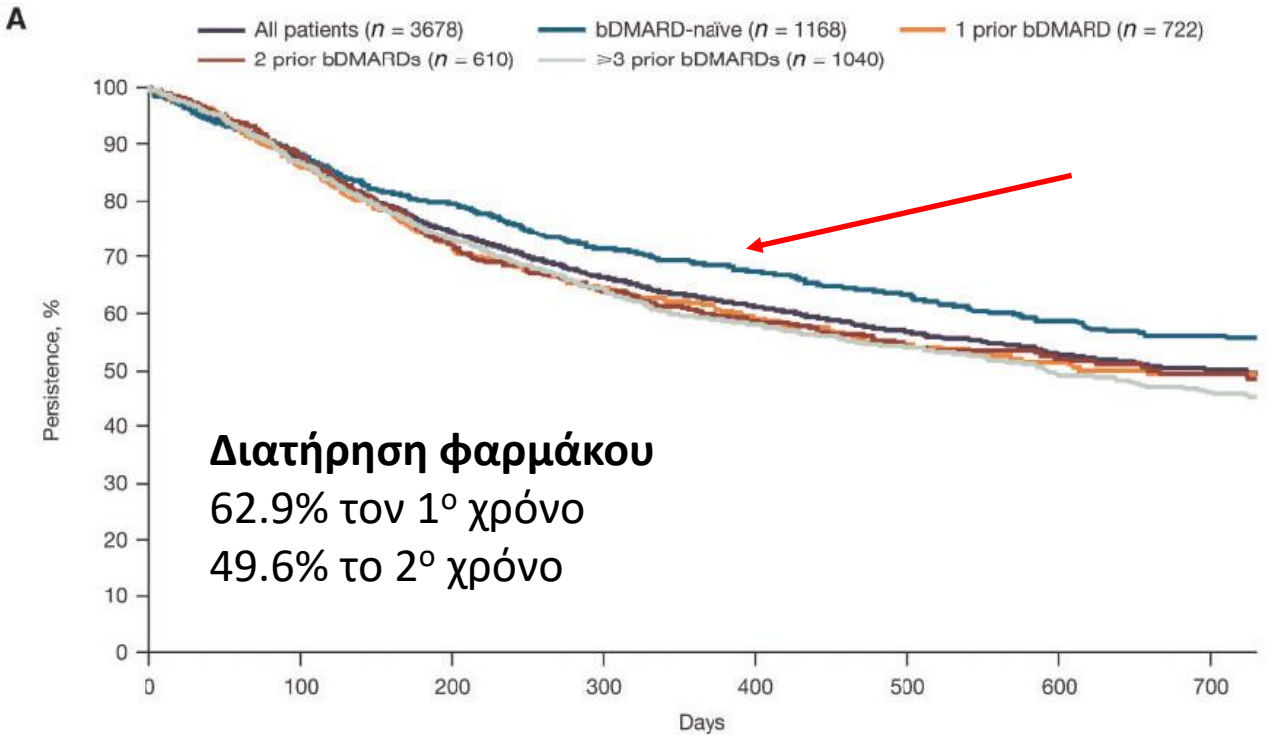


Pope JE, et al. Rheumatology (Oxford). 2019 Aug 13. pii: kez324

3 χρόνια tofacitinib στον Καναδά

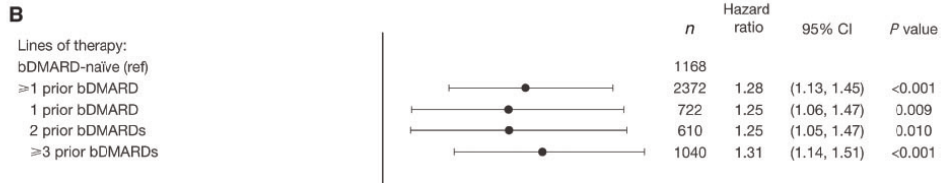
1226/3678 (**33.3%**) διέκοψαν

- 35.7% αναποτελεσματικότητα
- 26.9% AE



Διατήρηση φαρμάκου
62.9% τον 1ο χρόνο
49.6% το 2ο χρόνο

Προηγούμενη έκθεση σε bDMARD: Μεγαλύτερη πιθανότητα διακοπής tofacitinib (p < 0.001)

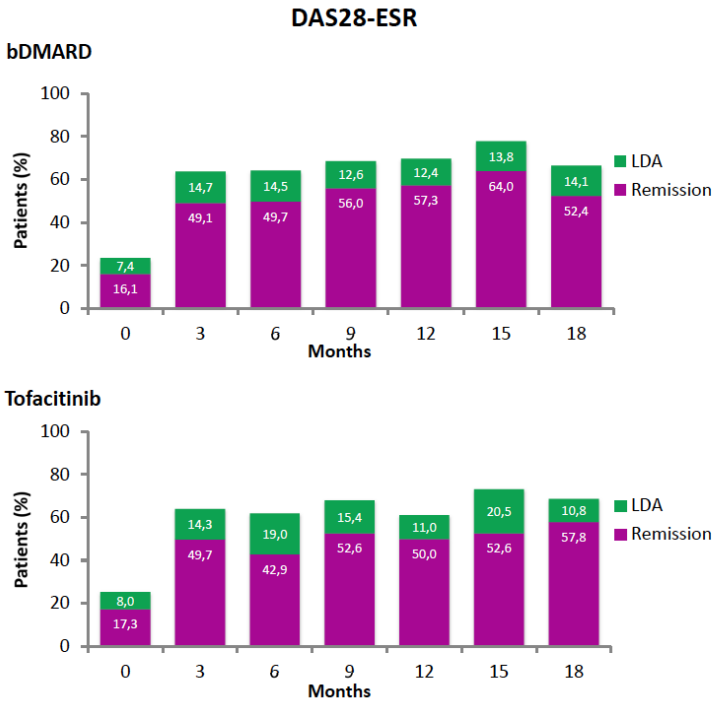


Pope JE, et al. Rheumatology (Oxford). 2019 Aug 13. pii: kez324

Σύγκριση αποτελεσματικότητας tofa και bDMARDs

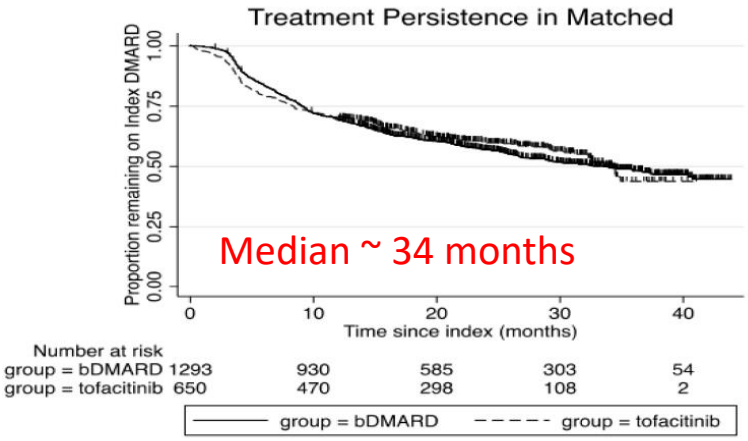
Μάρτιος 2015 – Σεπτέμβριος 2018

	bDMARD (n=1,300)	Tofacitinib (n=650)
Age (years) at index, mean (SD)	60.3 (13.1)	61.0 (12.7)
Female, n (%)	81.2%	81.2%
Disease duration at baseline (months), median (SD)	106.7 (124.5)	120 .1 (114.9)
Baseline concomitant DMARDs, n (%)		
MTX + cDMARD	294 (22.6%)	146 (22.5%)
MTX alone	300 (23.1%)	150 (23.1%)
cDMARD (excluding MTX)	142 (10.9%)	72 (11.1%)
Monotherapy*	564 (43.3%)	282 (43.4%)



Παρόμοια αποτελεσματικότητα

Παρόμοια διατήρηση φαρμάκου στο χρόνο



Περισσότεροι ασθενείς σε μονοθεραπεία με tofa (43.4% vs 33.4%)

Bird P, et al Ann Rheum Dis 2019;78:740-741 (abstract EULAR 2019)

Σύγκριση αποτελεσματικότητας tofa και bDMARDs

- MarketScan® databases (2011-2014)
- 21,832 patients with RA
  - 0.8% tofacitinib
  - 24.7% other DMARDs
  - 61.2% TNFi
  - 13.3% non-TNF biologics

Table 3 Proportion of patients who achieved therapy effectiveness and individual criteria at 1 year of follow-up (n = 16,305)

Effectiveness criteria	DMARDs		TNFi ± DMARDs		Non-TNF biologics ± DMARDs		Tofacitinib ± DMARDs	
	Percent	95% CI	Percent	95% CI	Percent	95% CI	Percent	95% CI
Effective therapy (satisfied all six criteria)	11.1	10.1–12.1	18.6	17.9–19.4	19.8	18.2–21.4	15.4	6.6–24.2
Criterion 1 High adherence	26.6	25.1–28.0	44.0	43.0–44.9	53.3	51.3–55.3	27.7	16.8–38.6
Criterion 2 No biologic or tofacitinib switch or addition	72.7	71.2–74.1	64.3	63.4–65.2	82.1	80.5–83.6	84.6	75.8–93.4
Criterion 3 No DMARD switch or addition	85.3	84.2–86.5	96.1	95.8–96.5	95.5	94.6–96.3	98.5	95.5–100
Criterion 4 No increase in dose or frequency of index drug	92.0	91.1–92.9	94.0	93.5–94.4	88.9	87.6–90.1	100.0[a]	–
Criterion 5 No more than one glucocorticoid joint injection	91.3	90.3–92.2	88.8	88.2–89.4	72.8	71.0–74.6	87.7	79.7–95.7
Criterion 6 No new/increased oral glucocorticoid dose	81.4	80.2–82.7	83.3	82.6–84.1	78.0	76.3–79.7	76.9	66.7–87.2

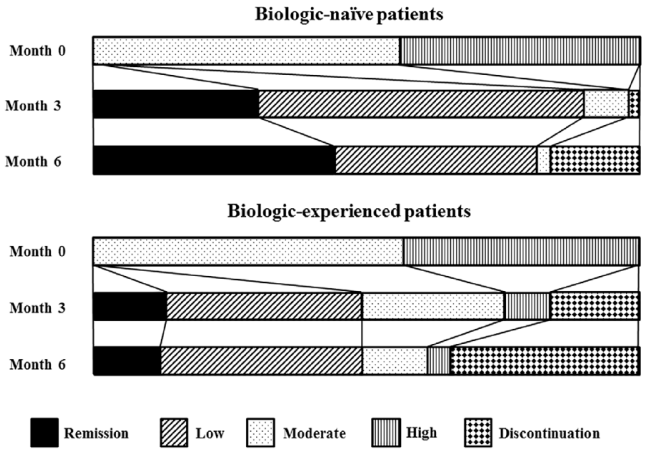
DMARD Disease-modifying antirheumatic drug, *TNFi* Tumor necrosis factor inhibitors
[a]Standard tofacitinib dose is usually not increased

Machado MAA, et al. Arthritis Res Ther. 2018;23;20(1):60

Σειρά χορήγησης και συγχορήγηση με MTX

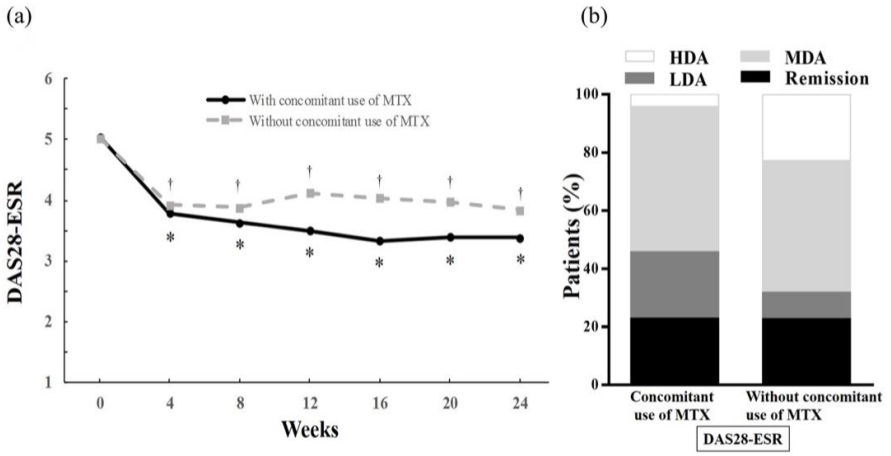
113 ασθενείς

	Total (n=113)
Baseline characteristics of RA	
Age, years, mean (95% CI)	63.7 (61.4-66.0)
Male/female	26/87
RA duration, years, mean (95% CI)	11.7 (9.8-12.9)
Anti-CCP (+), patient number (%)	99 (87.6)
Stage III/IV, patient number (%)	58 (51.3)
CDAI, mean (95% CI)	24.5 (22.5-26.6)
High CDAI (>22), patient number (%)	49 (43.4)
Concomitant MTX use, patient number (%)	82 (72.6)
Concomitant PSL use, patient number (%)	34 (30.1)



Καλύτερο αποτέλεσμα ως 1ος βιολογικός

Number of pts	**70**
Duration of RA (year)	**16.4 ± 10.0**
No prior use of biologic DMARDs, n (%)	22 (31.4)
Prior use of 3 or more biologic DMARDs, n	24 (34.3)
Concomitant MTX use, n (%)	48 (68.6)
DAS28-ESR	5.04 (1.33)



Παρόμοια αποτελέσματα με ή χωρίς MTX

Mori S, et al. Intern Med 2018;57:663-670

Iwamoto N, et al. PLoS One 2017;12:e0177057

Ζητήματα ασφάλειας του tofacitinib

ΑΕ ειδικού ενδιαφέροντος από το κλινικό πρόγραμμα της tofacitinib στη PA

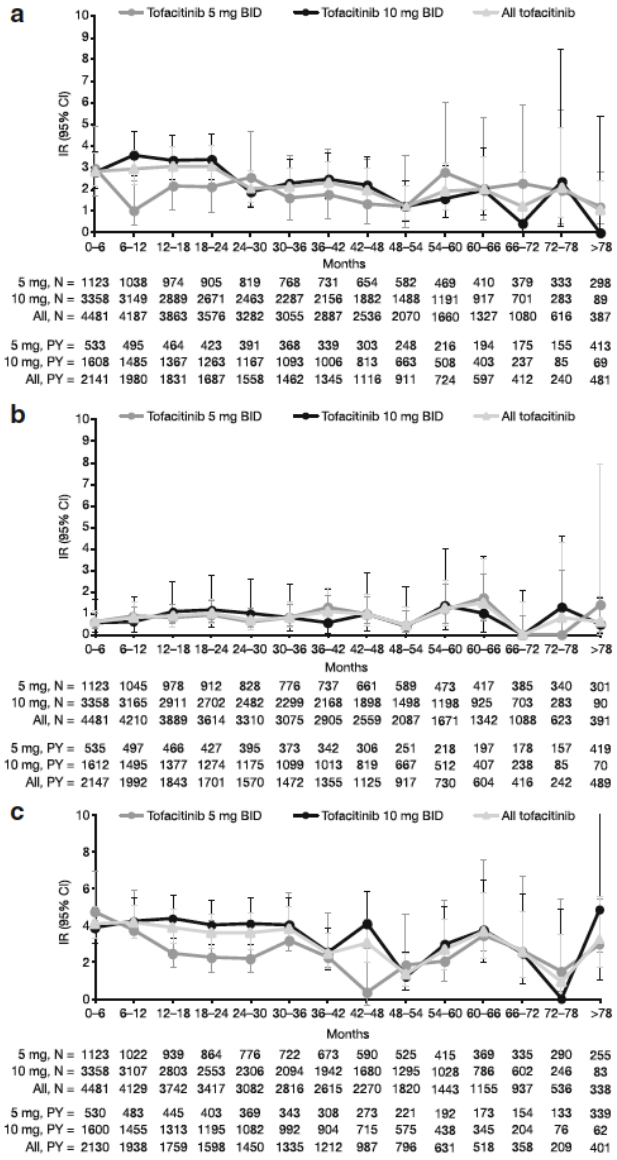
Incidence rate for selected safety events of interest, incidence rate/100 PY (95% CI)[†‡]	All tofacitinib (Phase I, II, III, LTE RA studies as of March 2017) N=7061; PY= 22,875[1§]
Serious infections	2.48 (2.28-2.69)
Opportunistic infections (excluding TB)[¶]	0.39 (0.31-0.47)
TB[¶]	0.16 (0.11-0.22)
Herpes zoster[¶]	3.63 (3.38-3.90)
Malignancies (excluding NMSC)[¶]	0.76 (0.65-0.88)
NMSC[¶]	0.56 (0.46-0.66)
MACE[¶]	0.38 (0.30-0.47)
Gastrointestinal perforation[¶]	0.12 (0.08-0.17)
Interstitial lung disease[¶]	0.18 (0.13-0.24)

Limitations to the LTE study include patient ineligibility to enrol (due to prior serious AE), patient discontinuation, dose changes at investigators' discretion, and changes in patient numbers and total exposure.
Information on AEs is limited to the time that patients are taking study drug and up to 28 days after discontinuation from the LTE.[1]
[†]Crude incidence rates (number of unique patients with events per 100 PY). [‡]PY is defined as the total follow-up time calculated up to the day of the first event.[1]
[§]Includes patients with RA taking tofacitinib as monotherapy and in combination with csDMARDs.[1] [¶]Adjudicated events.[1]

Data on file. Pfizer Inc, New York, NY

Οι ανοικτές μελέτες επέκτασης του tofacitinib (ως 9.5 έτη)

Ασφάλεια



Serious infections

Malignancies

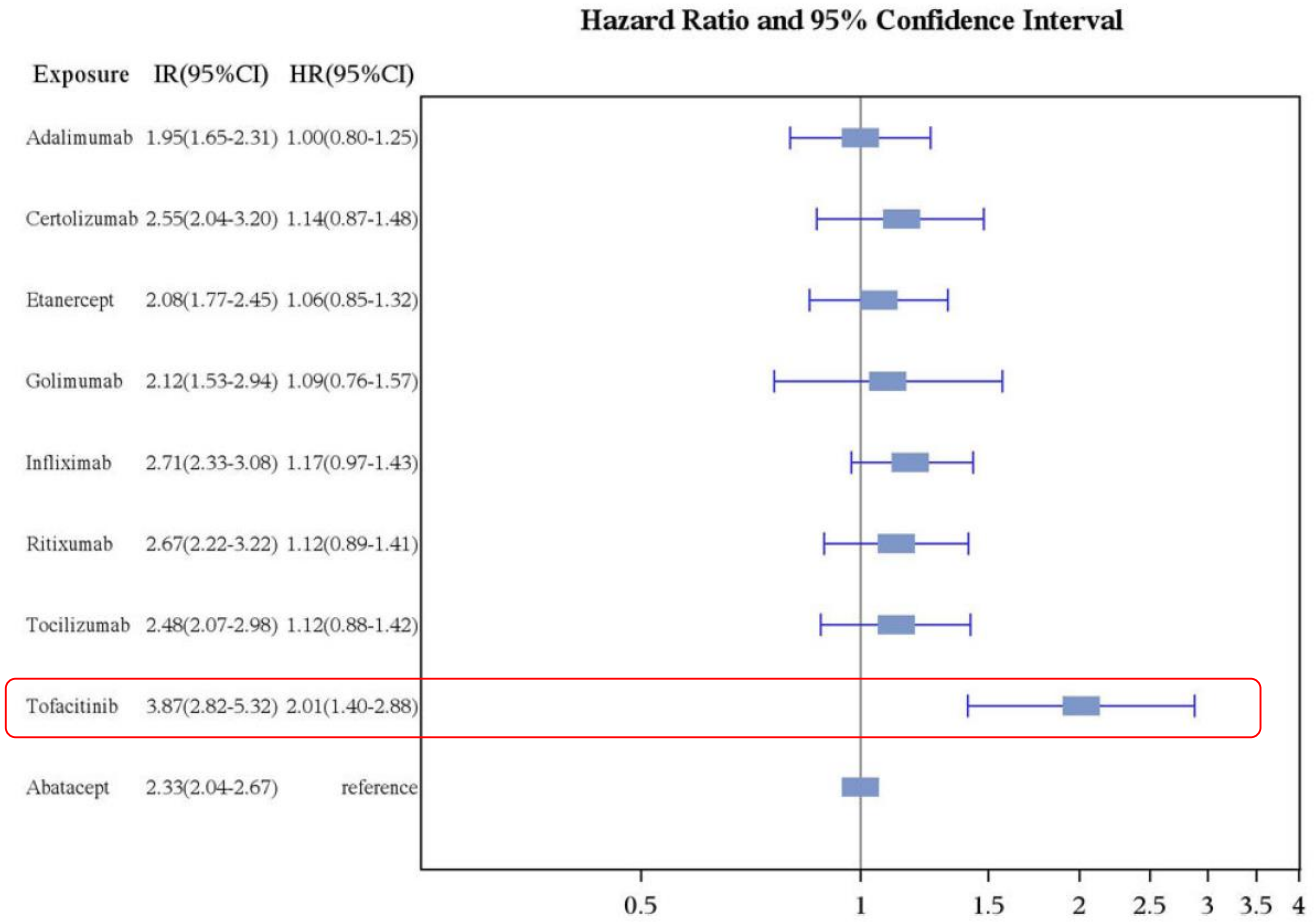
Herpes zoster

Wollenhaupt J, et al. Arthritis Res Ther. 2019;21(1):89

Tofacitinib και έρπης ζωστήρας

Medicare 2006-2013
Marketscan 2010-2014

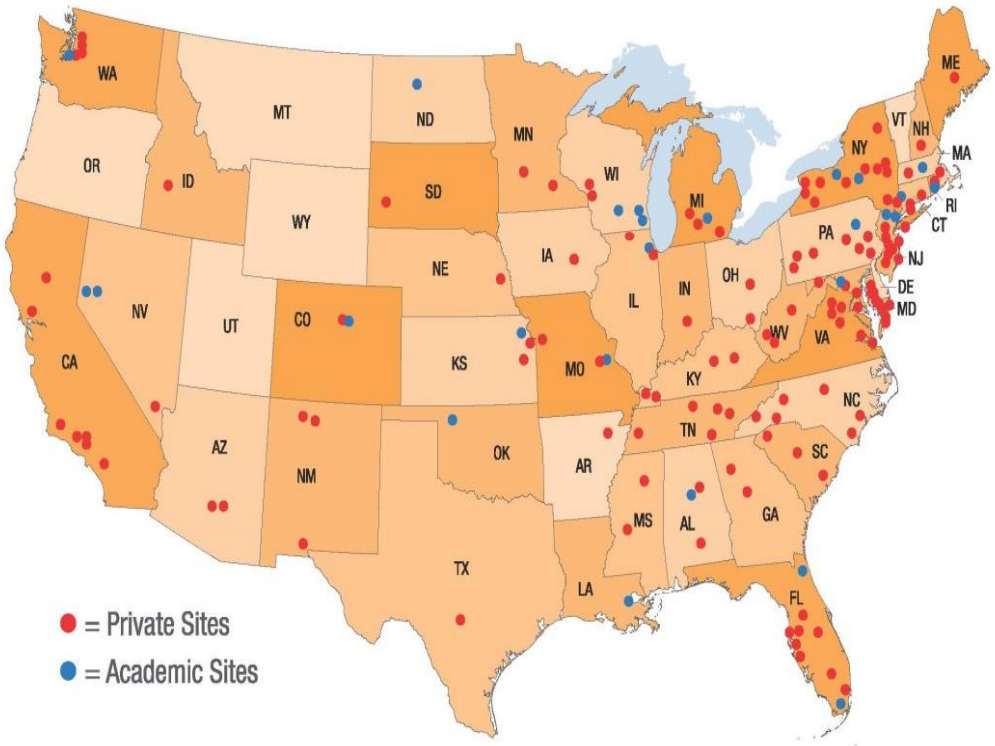
Tofacitinib	**2,526**
Anti-TNF	42,850
Abatacept	12,305
Rituximab	5,078
Tocilizumab	6,967



Curtis JR, et al. Ann Rheum Dis. 2016; 75(10): 1843–1847

Real-world data: CORRONA RA registry

Corrona sites from inception of RA Registry



US-based RA register

- 174 rheumatology practices across 41 states
- 656 participating rheumatologists
- Data collected from > 48,000 patients (as of June 2018)
- Interrogated to evaluate tofacitinib safety profile, with comparison to other therapies

RA=rheumatoid arthritis.

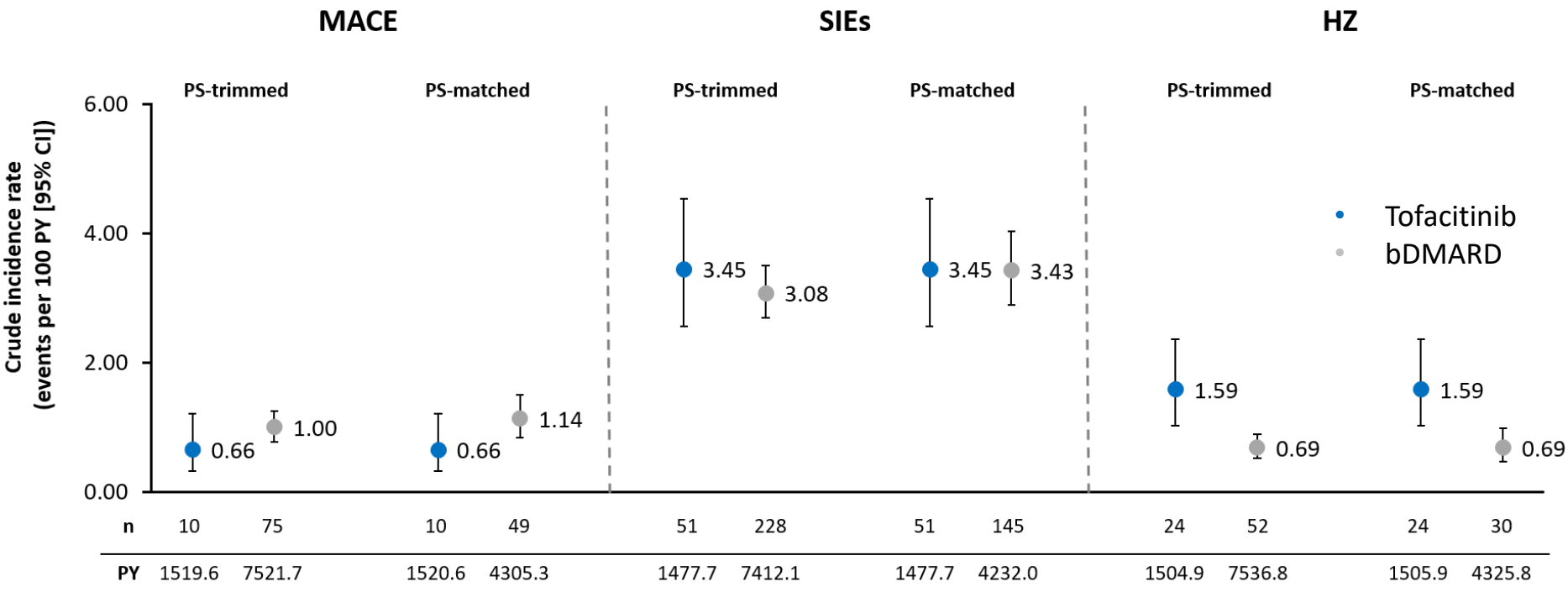
Kremer J, et al. Ann Rheum Dis 2019;78:82-83 (abstract EULAR 2019)

CORRONA RA registry: Demographics

Baseline characteristics	PS-trimmed population	
	Tofacitinib initiators (N=1117)	bDMARD initiators (N=5542)
Follow-up time, PY	1525.4	7584.3
Female, n (%)	908 (81.3)	4464 (80.6)
Age (years), mean (SD)	59.4 (12.1)	58.1 (12.9)
BMI (kg/m^2), mean (SD)	30.5 (7.7)	30.5 (7.5)
Duration of RA (years), mean (SD)	13.6 (10.3)	10.2 (9.9)
CDAI, mean (SD)	19.8 (13.4)	20.8 (14.0)
Current csDMARDs,[a] n (%)	617 (55.2)	4047 (73.0)
bDMARD-naïve, n (%)	127 (11.4)	1738 (31.4)
Number of prior bDMARDs, mean (SD)	2.6 (1.8)	1.4 (1.4)
Any prednisone use, n (%)	332 (29.7)	1645 (29.7)
Comorbid conditions, n (%)		
History of coronary heart disease	83 (7.4)	306 (5.5)
History of VTE	32 (2.9)	124 (2.2)
History of SIEs	146 (13.1)	521 (9.4)

Kremer J, et al. Ann Rheum Dis 2019;78:82-83 (abstract EULAR 2019)

Incidence rates by treatment (CORRONA RA registry)

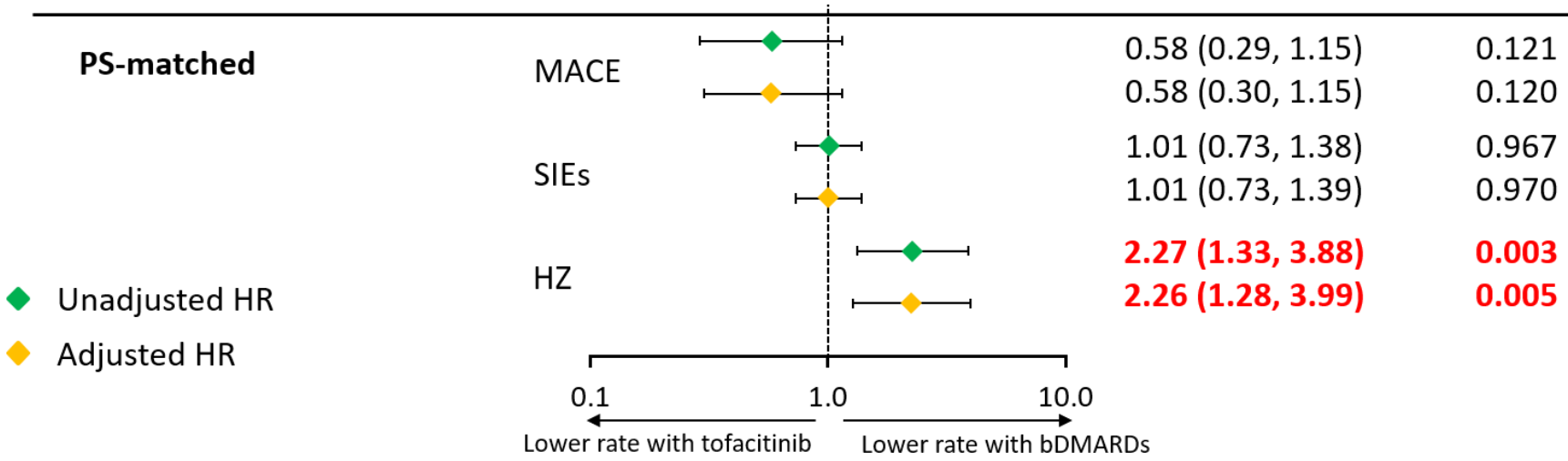


Ο ρυθμός επίπτωσης έρπητα ζωστήρα στην 5ετία του CORRONA ήταν σημαντικά χαμηλότερος από άλλες μελέτες και από τις RCT του φαρμάκου

[†]Incidence rate of safety events per 100 PY. [‡]No cases of serious Herpes zoster were reported during the study period among patients within the tofacitinib and csDMARD cohorts. One case of serious herpes zoster was reported within the bDMARD cohort.
bDMARD, biologic disease-modifying antirheumatic drug; CI=confidence interval; CORRONA=Consortium of Rheumatology Researchers of North America; csDMARD=conventional synthetic disease-modifying antirheumatic drug; PY=patient-years.

Kremer J, et al. Ann Rheum Dis 2019;78:82-83 (abstract EULAR 2019)

HR by treatment (CORRONA RA registry)



Kremer J, et al. Ann Rheum Dis 2019;78:82-83 (abstract EULAR 2019)

Tofacitinib και εμβολιασμός για έρπητα ζωστήρα

Recommendation						
2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases						
5. Herpes zoster vaccination may be considered in high-risk patients with AIIRD.	2b	2b	2b	4	B	9.1 7–10 93%

"This vaccine is preferably administered 4 weeks prior to initiation of bDMARDs or tsDMARDs, but not during the treatment with bDMARDs or tsDMARDs."

Shingrix (non-live vaccine): "*may replace the live-attenuated vaccine in patients with AIIRD*."

Furer V, et al. Ann Rheum Dis 2019;0:1–14; Winthrop KL, et al. Arthritis Rheumatol 2017;69:1969–77.

TB Incidence Rates (IRs) for tofacitinib patients by background country IRs* (phase II, III and LTE studies)

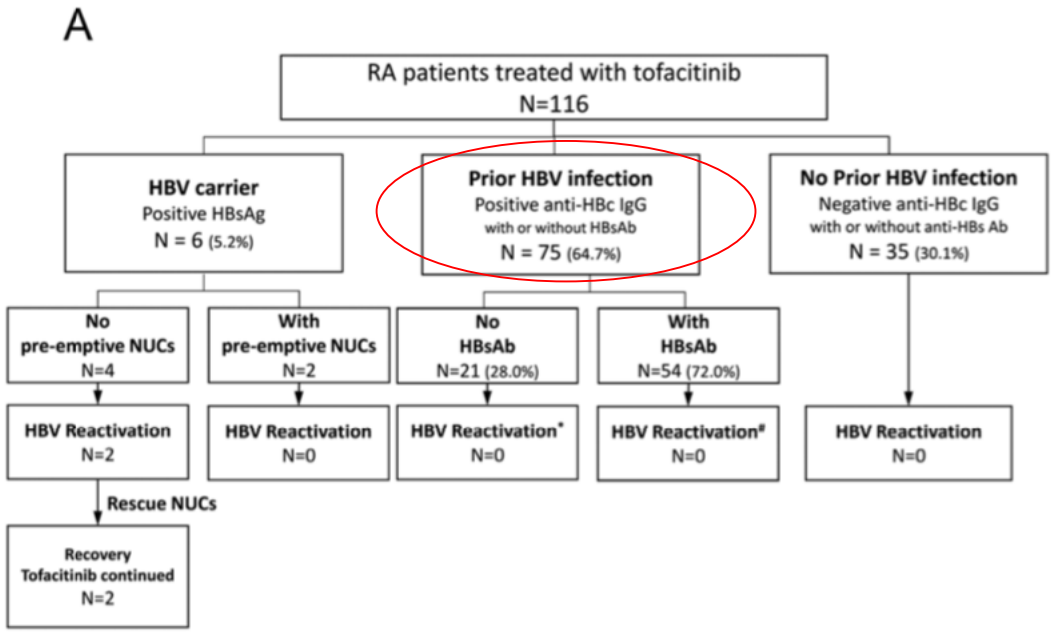
	TB cases with tofacitinib (n)	Tofacitinib exposure (patient-years)	Crude TB IR † (95% CI)
Low‡ (0.01)	1	4852.3	0.02 (0.003 to 0.15)
Medium§ (≥0.01 and ≤0.05)	4	5020.5	0.08 (0.03 to 0.21)
High¶ (>0.05)	21	2791.1	0.75 (0.49 to 1.15)

*TB background country IR categories from WHO, 2011 report for year 2010.[26]
†Crude incidence calculated TB cases per 100 patient-years.
‡Low TB incidence region (total study enrolment, n=2213); the USA (n=1098), Czech Republic (n=378), Germany (n=238), Slovakia (n=126), Australia (n=114), Canada (n=103), Austria (n=36), Italy (n=28), Sweden (n=17), Finland (n=16), Greece (n=15), Belgium (n=13), France (n=10), Denmark (n=9), New Zealand (n=9) Ireland (n=3).

Winthrop KL, et al. Ann Rheum Dis. 2016 ;75:1133-8.

Tofacitinib και λοίμωξη HBV

Ταϊβάν – 116 ασθενείς - Μονοκεντρική

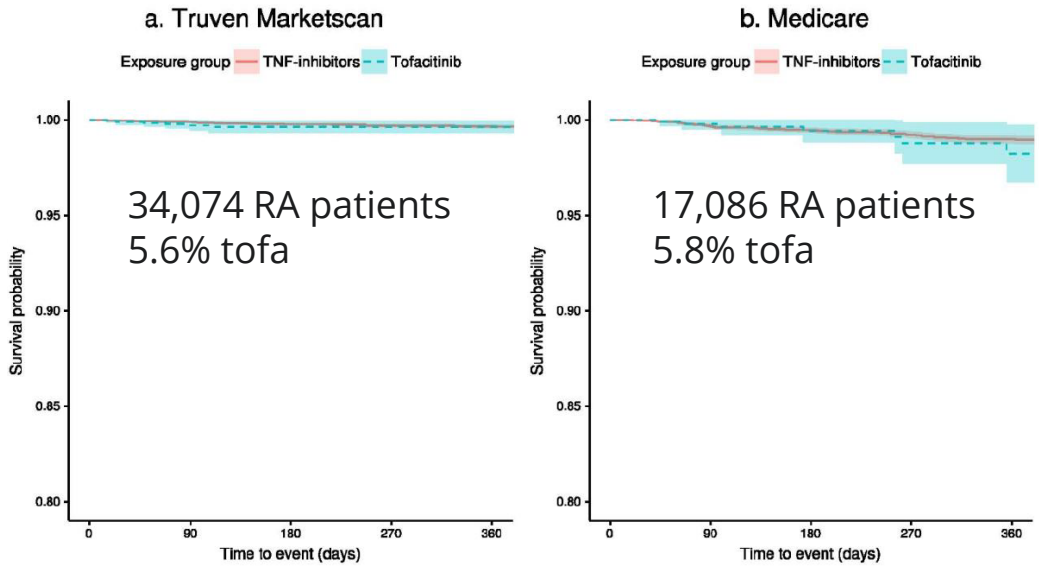


- Επανενεργοποίηση HBV λοίμωξης σε 2/4 HBsAg(+) ασθενείς που δεν έλαβαν προφυλακτική αντιική Tx.
- Καμία περίπτωση επανενεργοποίησης σε resolved HBV λοίμωξη [anti-HBc(+) χωρίς HBV-DNA)], χωρίς τη λήψη προφυλακτικής αγωγής

Chen YM, et al. Ann Rheum Dis. 2018;77:780-2

Tofacitinib και θρομβοεμβολικά επεισόδια

- Ο πιθανόν αυξημένος κίνδυνος για DVT/PE που αναδείχτηκε σε μία μελέτη δεν αφορά τη δόση της PA (5 mg bid)

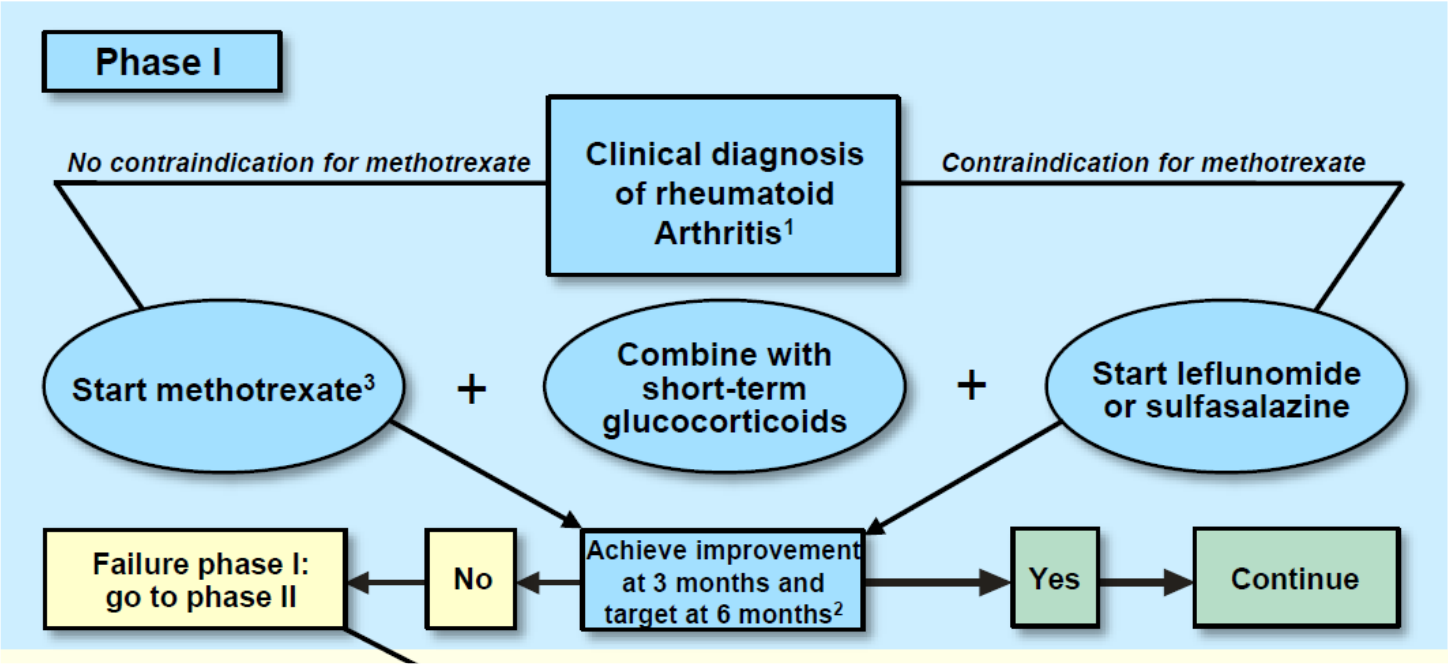


PS–adjusted HRs showed no significant differences in the risk of VTE between tofa-treated and TNFi–treated pts in either database: **1.33 (95% CI 0.78–2.24)**

Desai RJ, et al. Arthritis Rheumatol. 2019;71(6):892-90

Tofacitinib/JAKinibs και θεραπευτικός αλγόριθμος PA

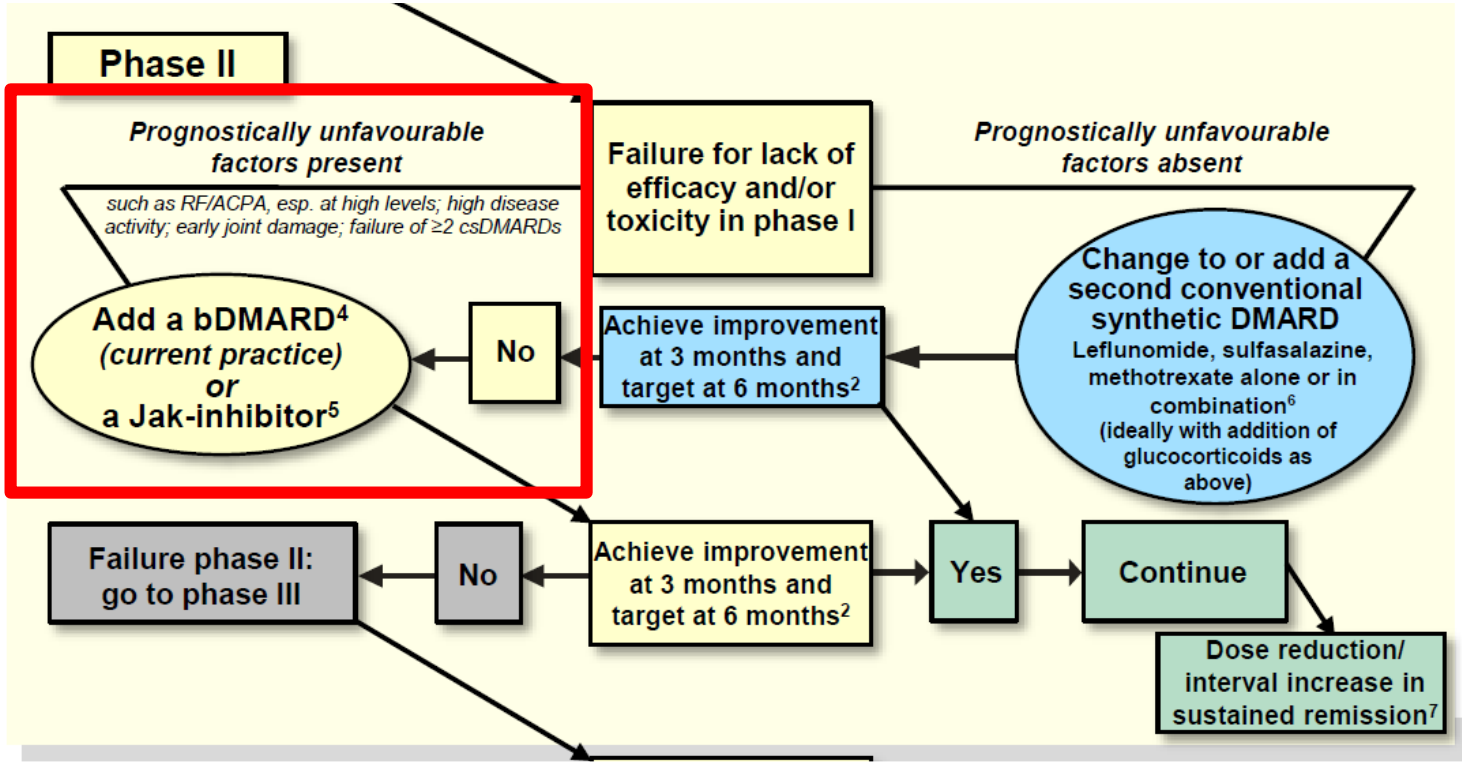
The current state-of-the-art in RA



EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update

Smolen JS et al. Annals of the Rheumatic Diseases 2017;76:960-977.

The current state-of-the-art in RA



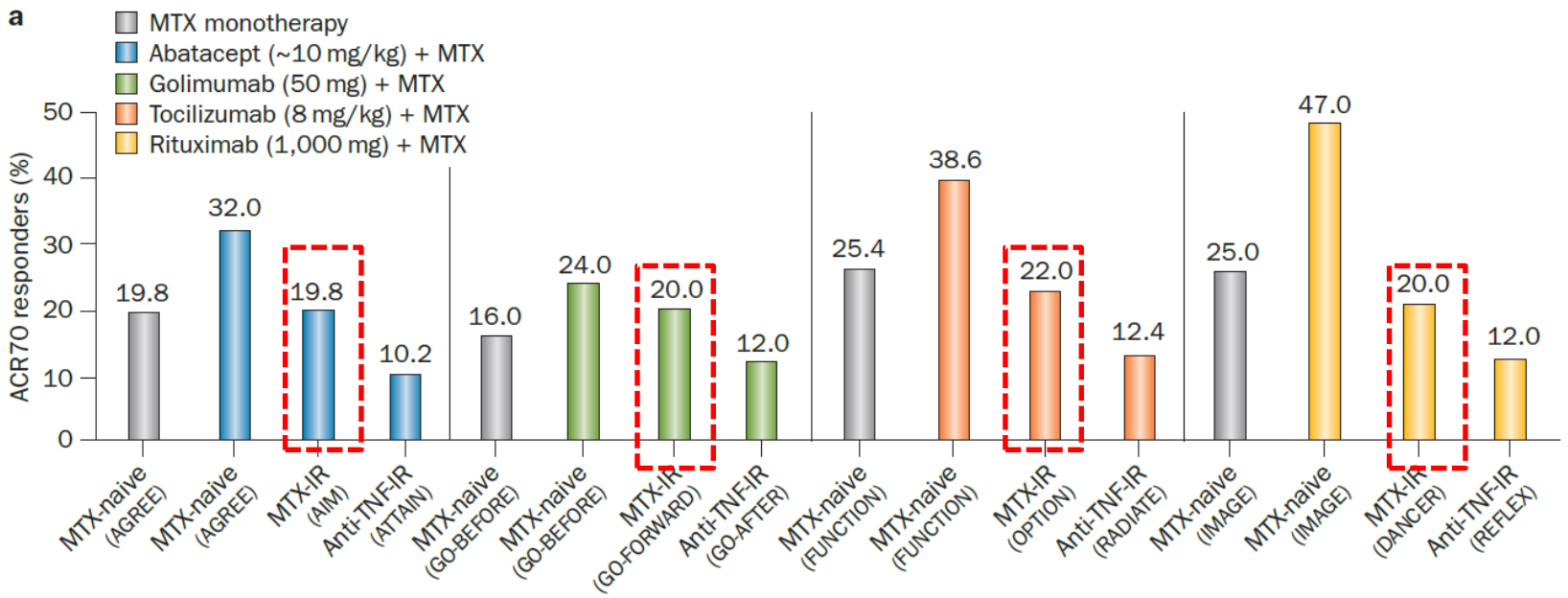
If the treatment target is not achieved with the first csDMARD strategy, when poor prognostic factors are present, addition of a bDMARD or a tsDMARD* should be considered;* ***current practice would be to start a bDMARD§.***

Επικαιροποίηση οδηγιών 2019: Ισάξια επιλογή τα bDMARDs και tsDMARDs;

Smolen JS et al. Annals of the Rheumatic Diseases 2017;76:960-977.

Υπάρχουν διαφορές μεταξύ των bDMARD όταν χρησιμοποιούνται ως 1η βιολογική θεραπεία ?

All bDMARDs achieve similar efficacy in patients with RA (ACR70 in MTX-Inadequate Responding patients)



bDMARD, biologic disease modifying antirheumatic drugs; MTX-IR, methotrexate inadequate responders

Smolen, Aletaha, Nat. Rev. Rheumatol. 11, 276–289, 2015

Συγκριτικά πλεονεκτήματα tofacitinib και JAKinibs

- Οδός χορήγησης
- Ταχύτητα δράσης
- Καλή αποτελεσματικότητα και ως μονοθεραπεία (συχνή η δυσανεξία σε cDMARDs)
- Ισάξιο προφίλ ασφάλειας (zoster?)

Συμπεράσματα – Πρακτικά μηνύματα για το tofacitinib στη ρευματοειδή αρθρίτιδα

- Αποτελεσματικό στην κλινική πράξη
  - Καλά δεδομένα και ως μονοθεραπεία
  - Καλύτερο όταν χορηγείται πριν την αποτυχία πολλαπλών βιολογικών παραγόντων
  - PO χορήγηση

- Ασφάλεια
  - Παρόμοιο προφίλ ασφάλειας με τους βιολογικούς παράγοντες, αναφορικά με λοιμώξεις, καρδιαγγειακό, νεοπλασίες
  - Πιθανόν αυξημένος κίνδυνος έρπητα ζωστήρα (* *CORRONA*)
  - Εμβολιασμοί (και για zoster)!!