Τα πολλά πρόσωπα της φλεγμονής και τα αποτελέσματα του Tofacitinib: δεδομένα 10ετίας στη Ρευματοειδή Αρθρίτιδα

ΔΗΜΗΤΡΟΥΛΑΣ ΘΕΟΔΩΡΟΣ

Δ’ ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ ΑΠΘ

Disclosures and Acknowledgments

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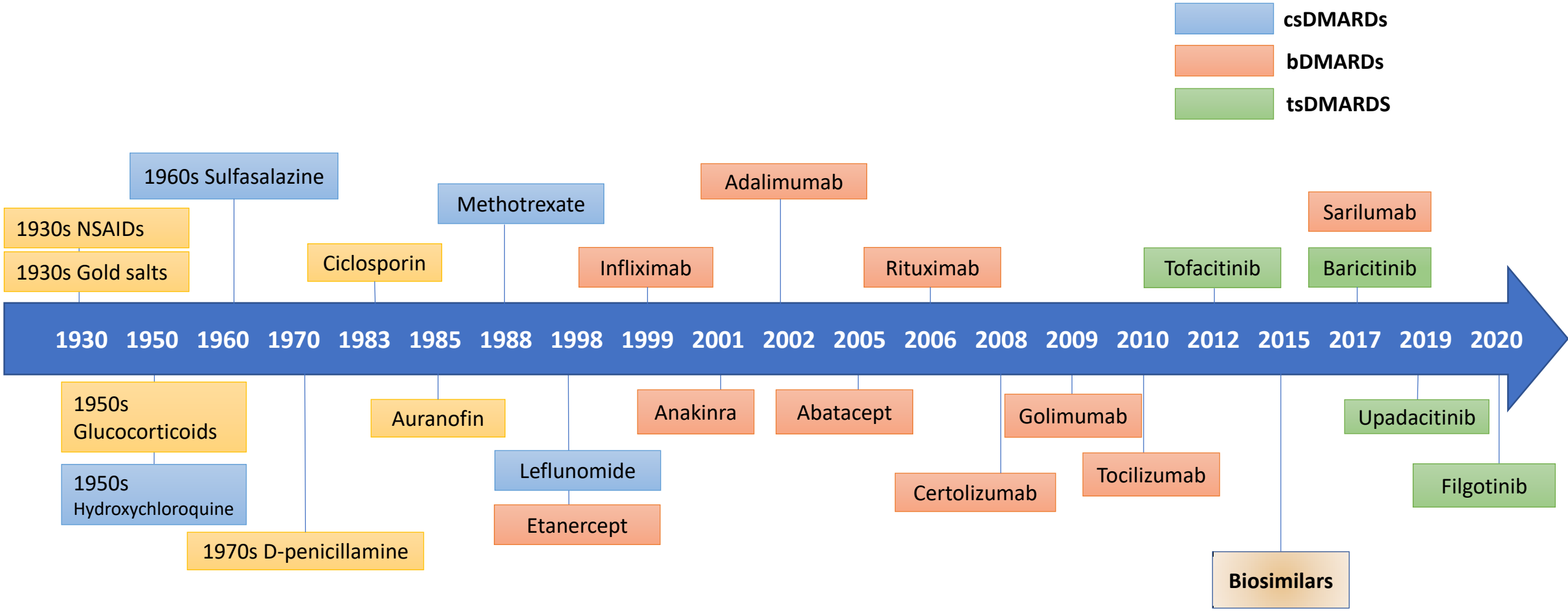
AbbVie, Amgen, Boehringer Ingelheim, DEMO, ELPEN, Genesis Pharma, Janssen, Gilead, Lilly, MSD, Novartis, Pfizer, SOBI, UCB, Vianex, Viatris

Δήλωση σύγκρουσης συμφερόντων:

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

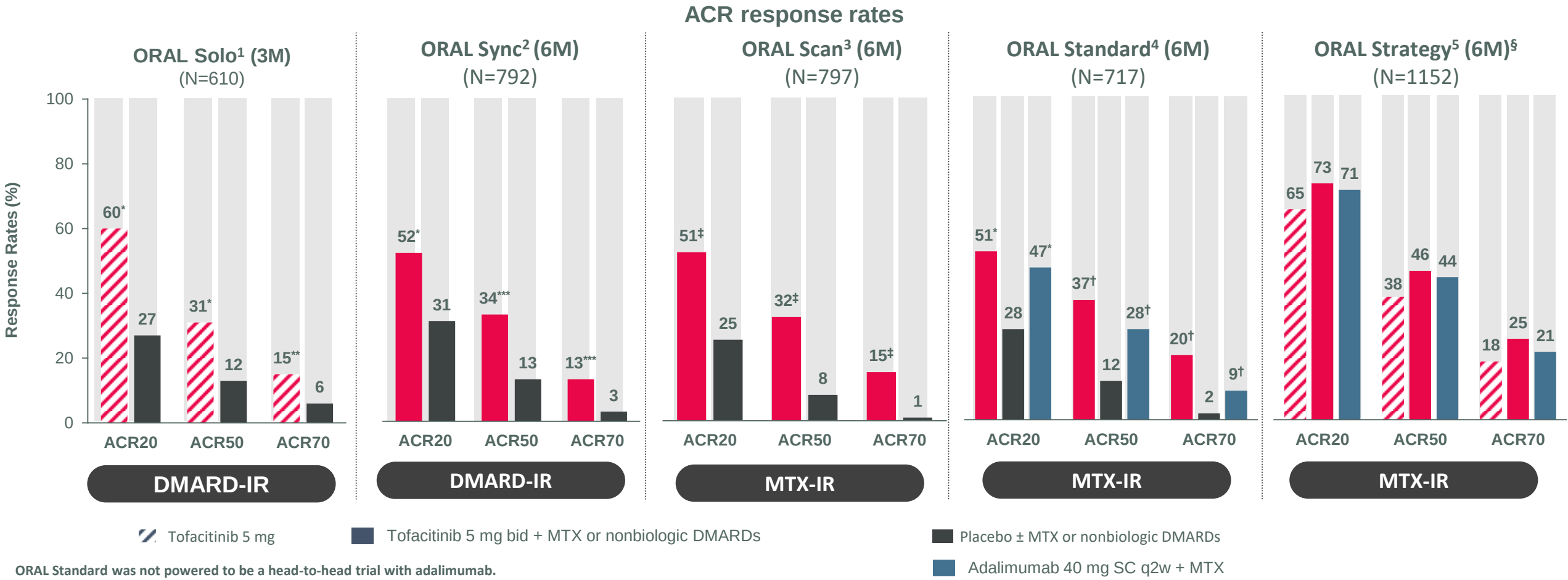
«*Για όλα τα φαρμακευτικά προϊόντα που αναφέρονται παρακαλείσθε να συμβουλεύεσθε/συμβουλευτείτε τις εγκεκριμένες Περιλήψεις Χαρακτηριστικών των Προϊόντων*»

Θεραπευτικές επιλογές για τη ρευματοειδή αρθρίτιδα μέσα στο χρόνο



Burmester et al. Nat Rev Rheumatol 13, 443-448 (2017) - adapted by speaker

Tofacitinib monotherapy and combination therapy demonstrated significant and consistent improvements in disease signs and symptoms



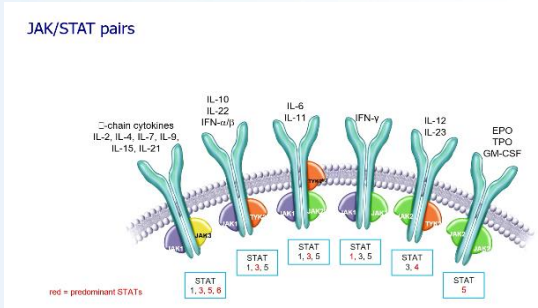
ORAL Standard was not powered to be a head-to-head trial with adalimumab.

1. Fleischmann et al. *N Engl J Med* 2012;367:495–507.
2. Kremer et al. *Ann Intern Med* 2013;159:253–61.
3. van der Heijde et al. *Arth Rheum* 2013;65:559–70.
4. van Vollenhoven et al. *N Engl J Med* 2012;367:508–19.
5. Fleischmann R et al. *Lancet* 2017; S0140-6736(17)31618-5.

*P<0.001 **P=0.003 ***P≤0.001 vs baseline †P≤0.05 ‡P<0.0001 §All patients receiving active treatment, no advancement penalty applied

ACR20 at month 6 was a primary endpoint in ORAL Sync, ORAL Standard, and ORAL Scan. ACR20 was a primary endpoint at month 3 and a secondary endpoint at month 6 in ORAL Step.

Story of JAK inhibitor approval



2012

FDA approval:
Tofacitinib (RA)[1]

2017

FDA approval:
Tofacitinib (PsA)[2]

EMA approval:
Tofacitinib (RA)[3]
Baricitinib (RA)[4]

2018

FDA approval:
Tofacitinib (UC)[3]
Baricitinib (RA)[1]

EMA approval:
Tofacitinib (PsA/UC)[5,6]

2019[a]

EMA and FDA approval:
Upadacitinib (RA)[1,2,7]

2020

FDA approval:
Tofacitinib (pcJIA)[8]

FDA Fast Track designation:
Delgocitinib (CHE)[9]

2021

FDA approval:
Tofacitinib (AS)[12]
Upadacitinib (PsA)[13]
Ruxolitinib (AD)[14]

EMA approval:
Baricitinib (AD)[10]
Filgotinib (RA)[11]

EMA approval:
Upadacitinib (PsA/AS/AD)[15,16]
Tofacitinib (pcJIA/AS)[17,18]
Filgotinib (UC)[19]
Abrocitinib (AD)[20]

2022

FDA approval:
Upadacitinib (AS/UC)[21,22]
Abrocitinib (AD)[23]
Ruxolitinib (V)[24]
Deucravacitinib (PsO)[25]

EMA approval:
Upadacitinib (UC)[26]

Το tofacitinib ως ο πρώτος JAK αναστολέας που έλαβε έγκριση για χρήση στην PA έχει τα περισσότερα δεδομένα καθημερινής κλινικής πρακτικής στην κατηγορία του

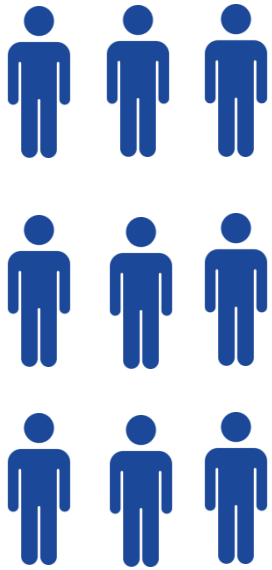
[a]In 2019, the JAK inhibitor peficitinib was approved for the treatment of RA in Japan.[27]
AD, atopic dermatitis; AS, ankylosing spondylitis; CHE, chronic hand eczema; EMA, European Medicines Agency; FDA, US Food and Drug Administration; JAK, Janus kinase; pcJIA, polyarticular course juvenile idiopathic arthritis; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; UC, ulcerative colitis; V, vitiligo.

1. Damsky W, et al. J Allergy Clin Immunol. 2021;147:814–826. 2. Coricello A, et al. Molecules. 2020;25:3321–3348. 3. Deallus. https://www.deallus.com/wp-content/uploads/2020/01/JAK-Inhibitors-White-Paper-WEB.pdf. 4. Lilly. https://investor.lilly.com/news-releases/news-release-details/european-commission-approves-once-
detail/xeljanz_to
severe-active-rh
13. Radi G, et al
12. Pfizer. https:
releases/news-r
15. AbbVie. http
detail/xeljanz-tofacitinib-citrate-receives-marketing. 16. Pfizer. https://www.pfizer.com/news/press-release/press-release-detail/pfizers-xeljanz-tofacitinib-receives-marketing. 17. Galapagos. https://www.glpg.com/press-release-2063-jyseleca-filgotinib-approved-in-the-european-union-for-the-treatment-of-ulcerative-colitis. 20. Pfizer. https://www.pfizer.com/news/press-release/press-release-detail/european-commission-approves-pfizers-cibinqor-abrocitinib. 21. AbbVie. https://news.abbvie.com/news/press-releases/rinvoq-upadacitinib-approved-by-us-fda-as-an-oral-treatment-for-adults-with-active-ankylosing-spondylitis.htm. 22. AbbVie. https://news.abbvie.com/news/press-releases/rinvoq-upadacitinib-receives-fda-approval-for-treatment-adults-with-moderately-to-severely-active-ulcerative-colitis.htm. 23. Pfizer. https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-pfizers-cibinqor-abrocitinib-adults. 24. Incyte. https://investor.incyte.com/news-releases/news-release-details/incyte-announces-us-fda-approval-opzelura(tm)-ruxolitinib-cream-0. 25. Bristol Myers Squibb. https://news.bms.com/news/details/2022/U.S.-Food-and-Drug-Administration-Approves-Sotyktu-deucravacitinib-Oral-Treatment-for-Adults-with-Moderate-to-Severe-Plaque-Psoriasis/default.aspx. 26. AbbVie. https://news.abbvie.com/news/press-releases/european-commission-approves-rinvoq-upadacitinib-for-treatment-adults-with-moderate-to-severe-ulcerative-colitis.htm. 27. Astellas. https://www.astellas.com/en/news/14651. All accessed 28 April 2023.

Δεδομένα κλινικών μελετών vs πραγματικής κλινικής πρακτικής

Randomised controlled trials (RCTs)

- Restriction in inclusion and exclusion criteria to achieve a homogeneous population
- Controlled design
- Protocol driven adherence and follow up
- Fewer comorbidities and con-meds



VS

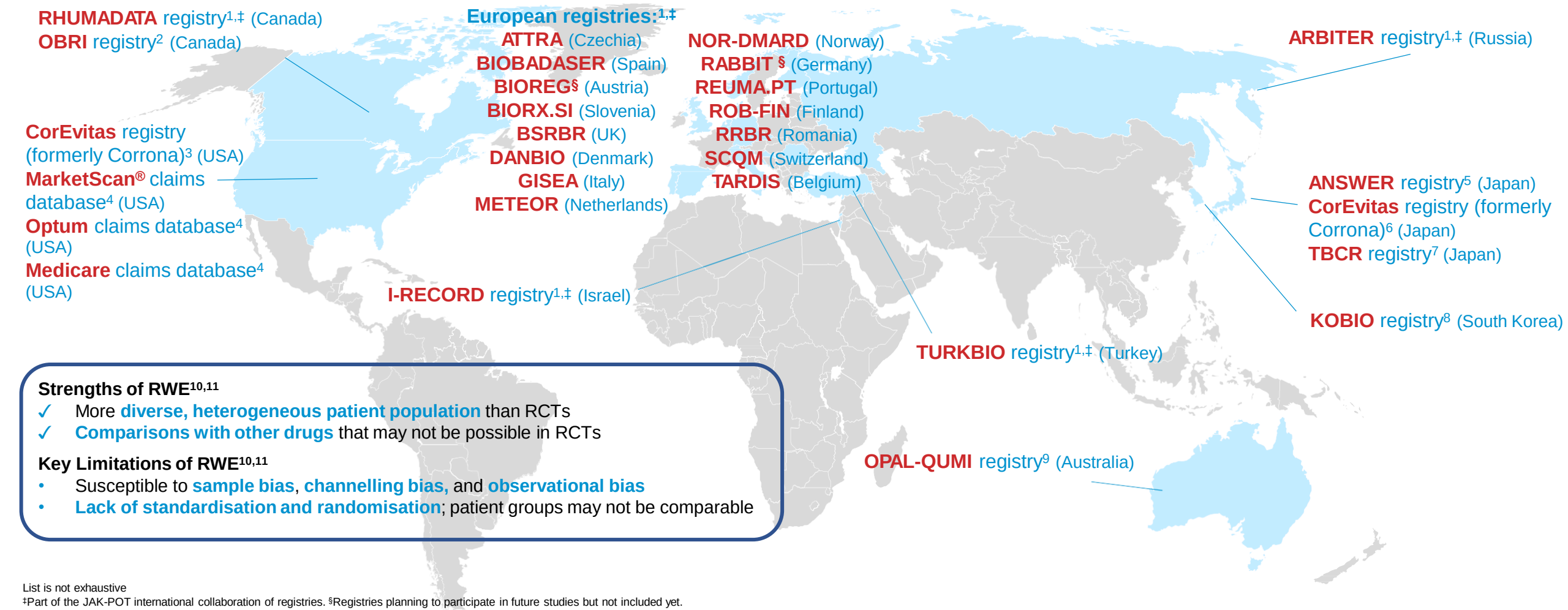
Real World Evidence (RWE)[a]

- Non-homogeneous population
- No control over design
- Patient driven adherence and clinician driven follow up
- Common comorbidities and
- Several con-meds

[a]RWE provides additional information on effectiveness in real-world clinical practice, to support and add to RCT data [4]

1. Katkade VB, et al. J Multidiscip Healthc. 2018;11:295–304. 2. Garrison LP Jr, et al. Value Health. 2007;10:326–335.
3. Berger ML, et al. Pharmacoepidemiol Drug Saf. 2017;26:1033–1039. 4. Sherman RE, et al. N Engl J Med. 2016;375:2293–2297.

Δεδομένα καθημερινής κλινικής πρακτικής για τους JAK αναστολείς



Strengths of RWE[10,11]

- ✓ More **diverse, heterogeneous patient population** than RCTs
- ✓ **Comparisons with other drugs** that may not be possible in RCTs

Key Limitations of RWE[10,11]

- Susceptible to **sample bias**, **channelling bias,** and **observational bias**
- **Lack of standardisation and randomisation**; patient groups may not be comparable

List is not exhaustive

‡Part of the JAK-POT international collaboration of registries. §Registries planning to participate in future studies but not included yet.

ATTRA=Appropriate Technology Transfer for Rural Areas; BIOREG=Biologica Register; BSRBR=British Society for Rheumatology Biologics Register for Rheumatoid Arthritis; Corrona=Consortium of Rheumatology Researchers of North America, Inc; DANBIO=Danish National Patient Registry; GISEA=Gruppo Italiano Studio Early Arthritis; JAK=Janus kinase; METEOR=Measurement of Efficacy of Treatment in the 'Era of Outcome' in Rheumatology; NOR-DMARD=The Norwegian Antirheumatic Drug Register; OBRI=Ontario Best Practices Research Initiative; OPAL=Oral Psoriatic Arthritis Trial; QUMI=Quality Use of Medicines Initiative; RA=rheumatoid arthritis; RABBIT=Rheumatoid Arthritis– Observation of Biologic Therapy; REUMA.PT=Rheumatic Diseases Portuguese Register; ROB-FIN=Finnish Register of Biological Treatment; RRBR=Romanian Registry of Rheumatic Diseases; RWE=real-world evidence; SCQM=Swiss Clinical Quality Management.

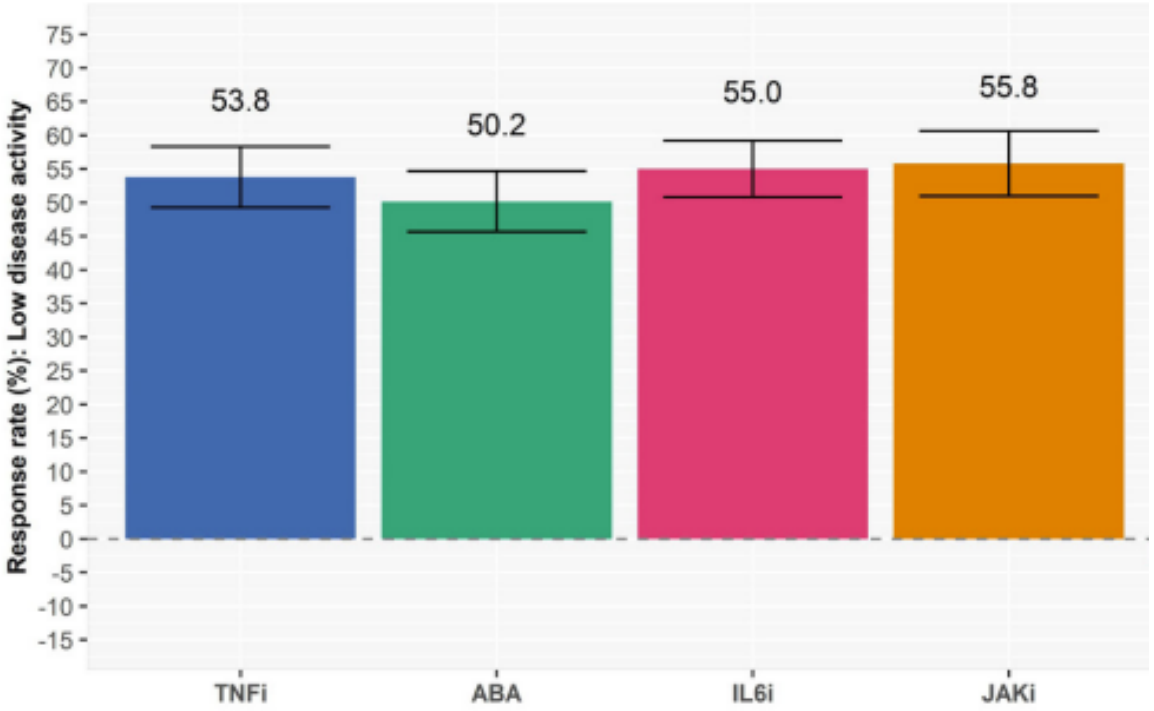
1. Lauper K, et al. [abstract]. Presented at: Annual Meeting of the European League Against Rheumatism. Virtual Congress, June, 2020. **2.** Movahedi M, et al. Presented at: Annual Meeting of the European League Against Rheumatism. Virtual Congress, June, 2020. **3.** Kremer JM, et al. *ACR Open Rheumatol*. 2021;3(3):173-184. **4.** Desai RJ, et al. *Rheumatology (Oxford)*. 2021; doi:10.1093/rheumatology/keab294. **5.** Ebina K, et al. *Clin Rheumatol*. 2021; doi:10.1007/s10067-021-05609-7. **6.** Tanaka Y, et al. [abstract] Presented at: Annual Meeting of the American College of Rheumatology. Virtual Congress, November, 2020. **7.** Takahashi N, et al. *Sci Rep* 2020;10:21907. **8.** Min HK, et al. *Clin Rheumatol*. 2021; doi: 10.21203/rs.3.rs-32790/v1. **9.** Bird P, et al. *Clin Rheumatol*. 2020;39(9):2545-2551. **10.** Katkade VB, et al. *J Multidiscip Healthc.* 2018;11:295-304. **11.** Camm AJ, et al. *Open Heart.* 2018;5(1):e000788. Ful

Αποτελεσματικότητα

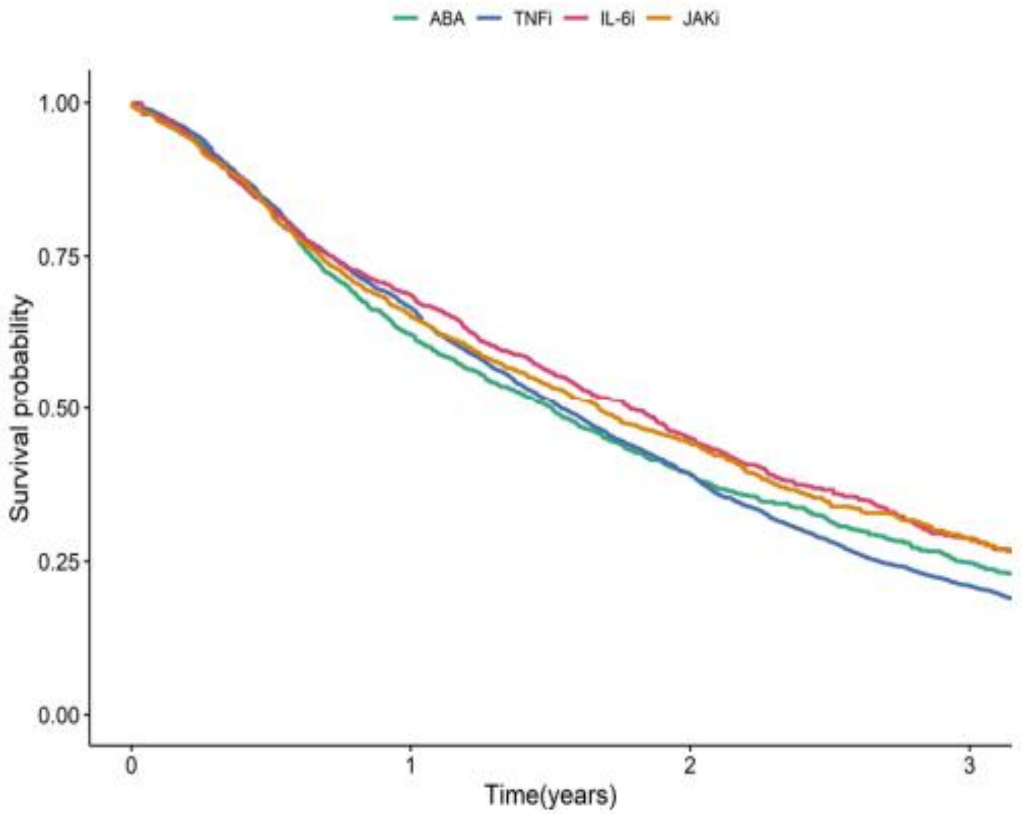
“JAK-POT” collaboration – comparative JAKi and bDMARD effectiveness

n=31,846 treatment courses
Real world data from registries of 16 countries

Adjusted CDAI low disease activity at 12 months



Drug survival



Lauper K et al. Ann Rheum Dis 2022;81:1358–1366

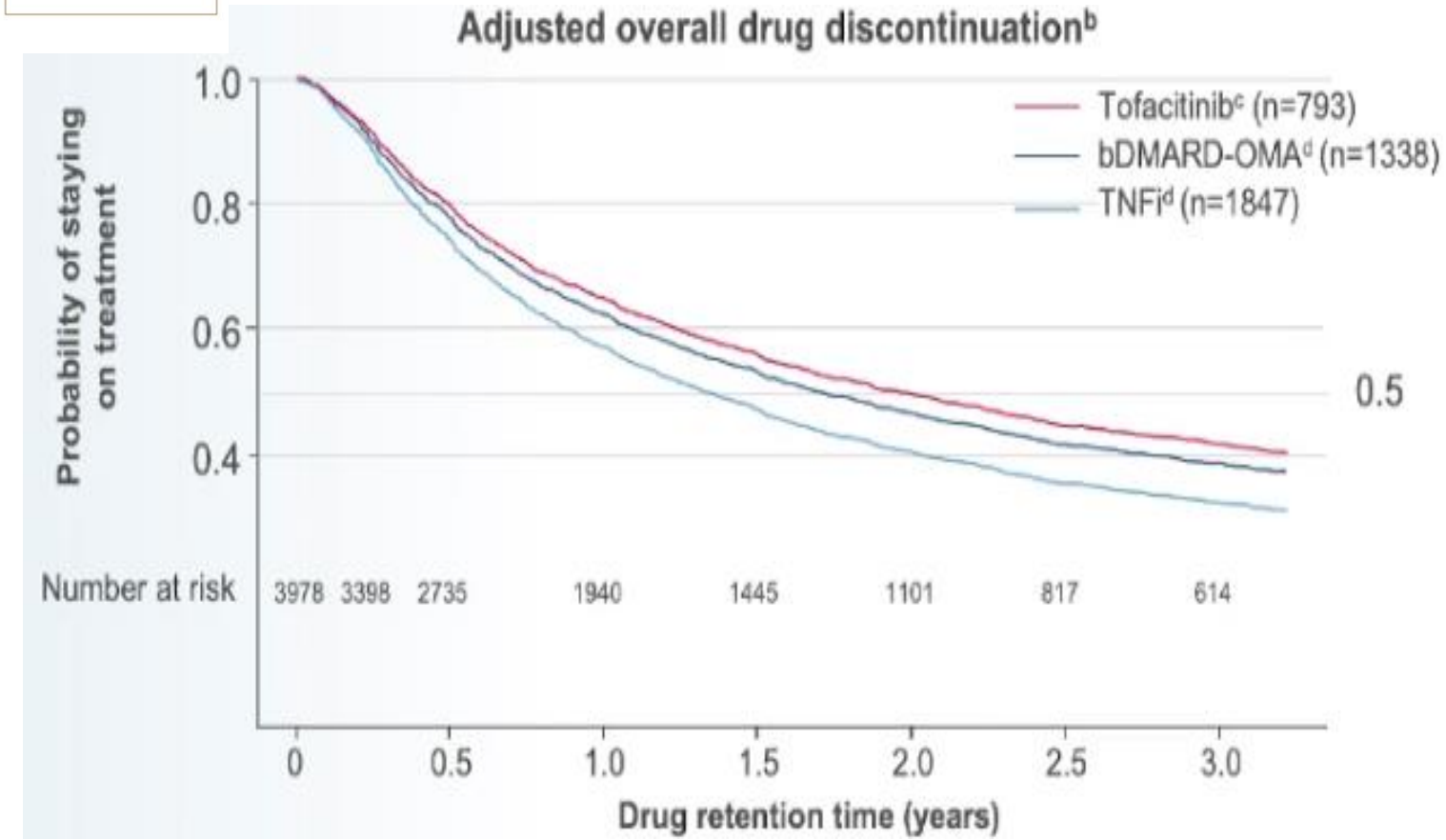
RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL ARTICLE

Comparative effectiveness of antitumour necrosis factor agents, biologics with an alternative mode of action and tofacitinib in an observational cohort of patients with rheumatoid arthritis in Switzerland

SCQM
Swiss observational registry
Swiss Clinical Quality Management in Rheumatic Diseases

4023 treatment courses of 2600 patients were included, 1862 on TNFi, 1355 on TOC/ABA and 806 on TOFA.



Significantly higher drug discontinuation with TNFis than with tofacitinib
HR 1.29 (95% CI 1.14–1.47)

No significant difference in drug discontinuation with bDMARD-OMA compared with tofacitinib
HR 1.09 (95% CI 0.96–1.24)

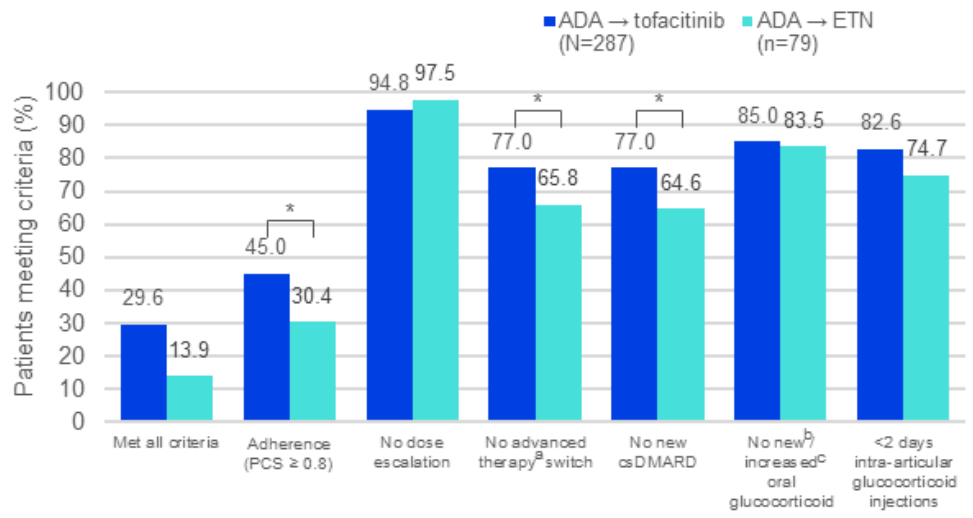
Finckh et al, 2020

Tofacitinib – RWE αποτελεσματικότητα (2η γραμμή)

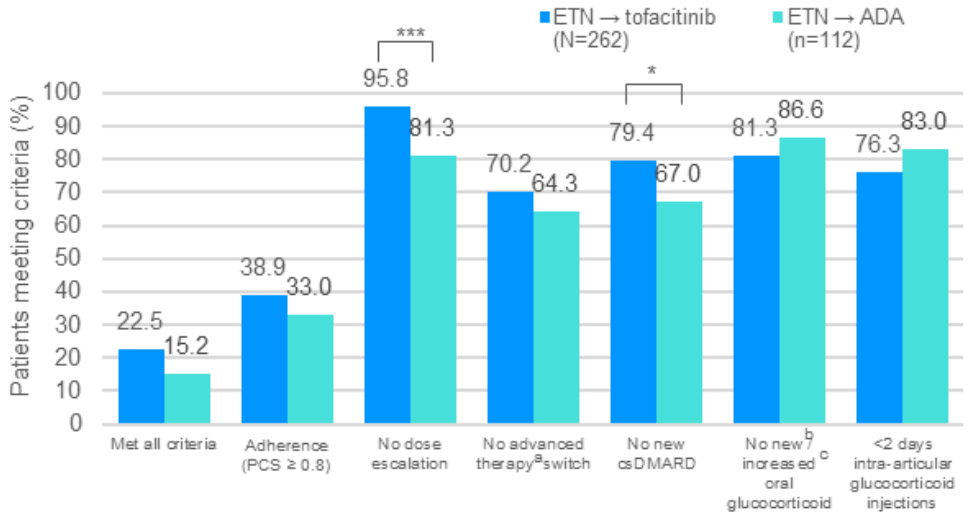
Tofa n=549

Effectiveness of Tofacitinib Post Switch From bDMARD

Switching from ADA → tofacitinib vs cycling from ADA→ ETN



Switching from ETN → tofacitinib vs cycling from ETN → ADA



Συμπέρασμα

- ✓ Υψηλότερη παραμονή στη θεραπεία
- ✓ Υψηλότερη αποτελεσματικότητα
- ✓ Υψηλότερη συμμόρφωση σε ασθενείς που άλλαξαν θεραπεία από ADA/ETN σε tofacitinib (**switching**) από ότι σε ασθενείς που έλαβαν δεύτερο TNFi (**cycling**)

A; study is from an abstract; ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; ETN, etanercept; JAK, janus kinase; USA, United States of America.

Harnett J, et al. Atlanta, USA.

RHEUMATOLOGY

Rheumatology 2023;62:89–97
https://doi.org/10.1093/rheumatology/keac285
Advance access publication 17 May 2022

Original article

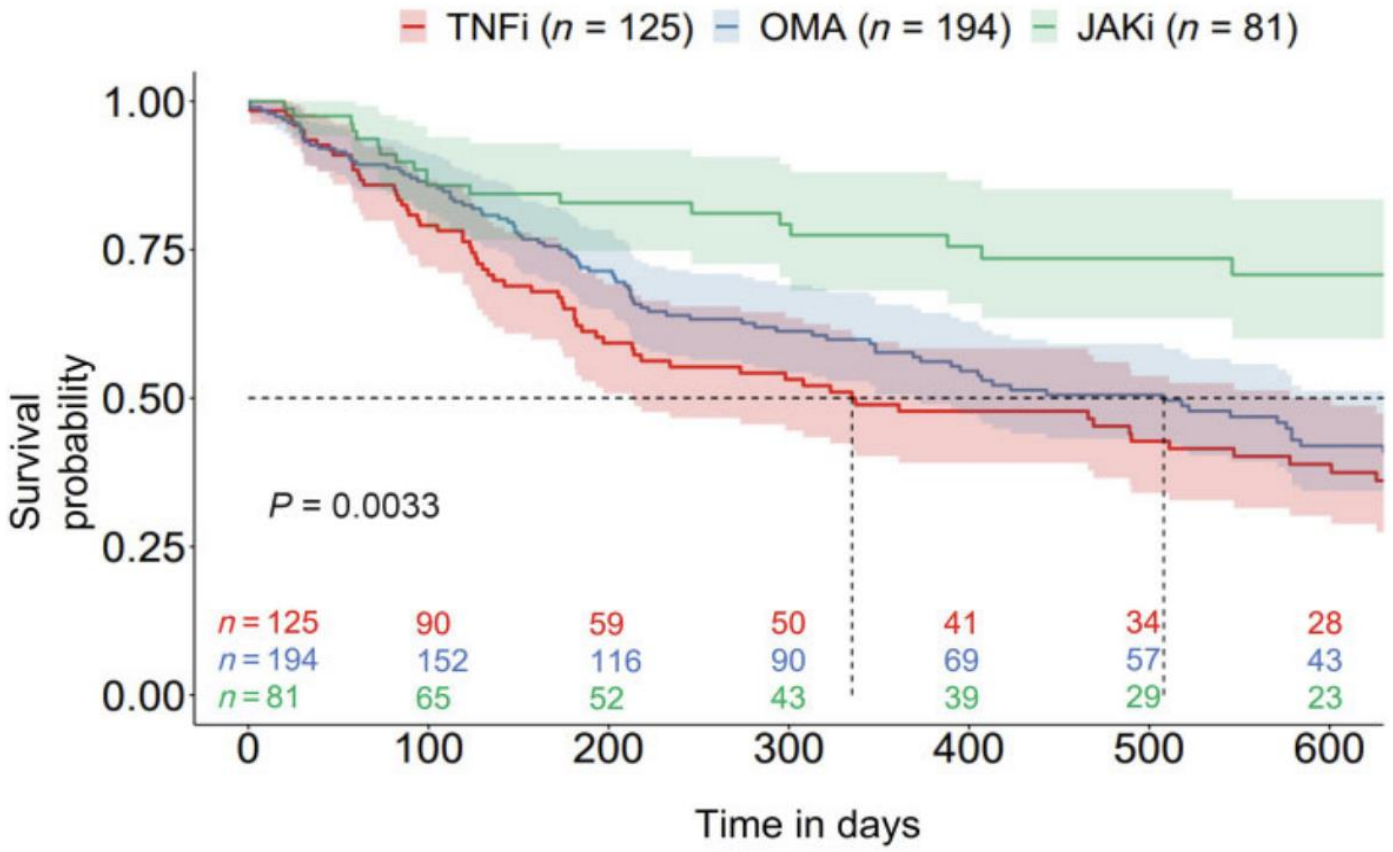
Comparison of drug retention of TNF inhibitors, other biologics and JAK inhibitors in RA patients who discontinued JAK inhibitor therapy

Andrea Amstad[1], Eleftherios Papagiannoulis[2], Almut Scherer[2], Andrea Rubbert-Roth [3], Axel Finckh[4], Ruediger Mueller[5], Jean Dudler[6], Burkhard Möller [7], Peter M. Villiger [8], Martin M. P. Schulz[9] and Diego Kyburz [1]

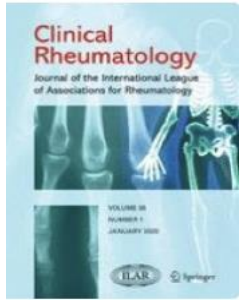
SCQM
Swiss observational registry

Swiss Clinical Quality Management in Rheumatic Diseases

Switched to	HR (mice)	HR (cc)
TNFi	reference	reference
OMA	0.82(0.6, 1.12)	0.76 (0.44, 1.34)
JAKi	0.48 (0.3, 0.76)	0.42 (0.19, 0.91)



Rheumatology (Oxford)2022 Dec 23;62(1):89-97



Real-world evaluation of effectiveness, persistence, and usage patterns of tofacitinib in treatment of rheumatoid arthritis in Australia

Tofa N=650

OPAL-QUMI

Australian observational registry

OPAL®
Optimising Patient outcomes in Australian rheumatoLogy
A Quality Use of Medicines Initiative (QUMI)

Main Study Objective

Assess disease activity outcomes using DAS28-4(ESR), CDAI, and SDAI scores

Eligibility Criteria for Study Cohort

Adults with RA who began treatment with tofacitinib or bDMARD (± csDMARD) and had ≥12 months of follow-up (March 2015–September 2018).

Baseline information (matched population)	Tofacitinib ± csDMARD (n=650)	bDMARD ± csDMARD (n=1300)
Female, n (%)	528 (81)	1056 (81)
Age, years, mean ± SD	61.0±12.7	60.8±13.1
Disease duration, months, median	120 (n=411)	107 (n=818)
CDAI score, n (% of column)	n=308	n=533
Remission	20 (7)	37 (7)
Low	53 (17)	82 (15)
Moderate	78 (25)	131 (25)
High	157 (51)	283 (53)
Concomitant medications, n (%)		
0 (monotherapy)	282 (43)	564 (43)
≥1 csDMARD	368 (57)	736 (57)

Study Methods & Analyses

Propensity score-matched populations

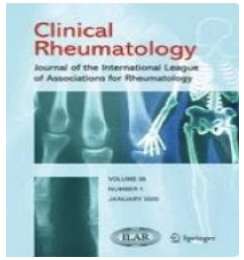
Study Limitations

- Specific geographical population may not be representative of the worldwide population (eg, patient characteristics, healthcare access)
- Data gaps were common when the primary data was captured at the time of the clinical consultation, particularly with respect to concomitant DMARD prescription data
- As a result of insufficient numbers, propensity score matching was not possible for the DAS28(ESR) score

Tofacitinib 5 mg twice daily is the approved dosage for the treatment of moderate to severely active rheumatoid arthritis in the EU, based on the EMA prescribing information. The prescribing information in other countries, including Switzerland, may be different. For details of licenced indications in your country of residence, please refer to the country-specific prescribing information.

bDMARD=biological disease-modifying antirheumatic drug; CDAI=Clinical Disease Activity Index; csDMARD=conventional synthetic disease-modifying antirheumatic drug; DAS28(ESR)=Disease Activity Score in 28 joints, erythrocyte sedimentation rate; OPAL-QUMI=Optimising Patient outcome in Australian rheumatoLogy-Quality Use of Medicines Initiative; RA=rheumatoid arthritis; SD=standard deviation; SDAI=Simplified Disease Activity Index.

Bird P, et al. Real-world evaluation of effectiveness, persistence, and usage patterns of tofacitinib in treatment of rheumatoid arthritis in Australia. *Clin Rheumatol*. 2020; 39(9):2545-2551.

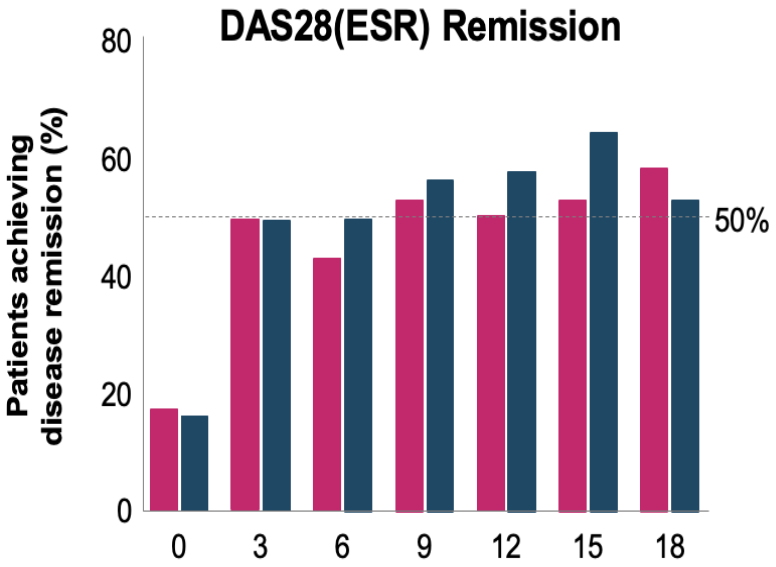


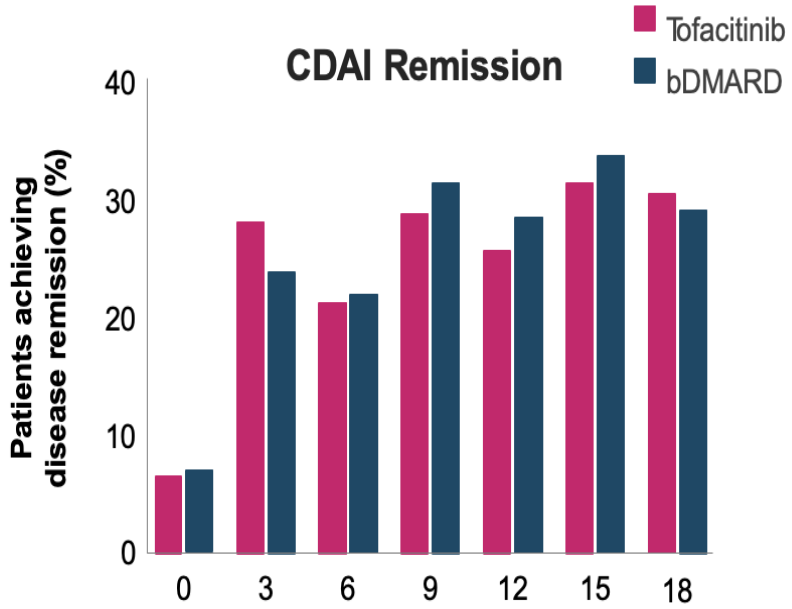
Real-world evaluation of effectiveness, persistence, and usage patterns of tofacitinib in treatment of rheumatoid arthritis in Australia

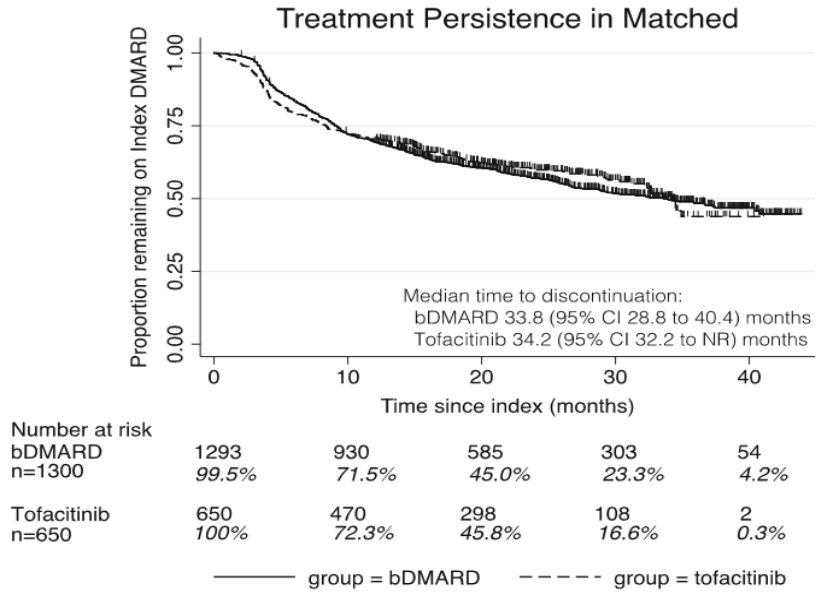
Tofa N=650

OPAL-QUMI
Australian observational registry

Similar remission rates with tofacitinib compared with bDMARDs over 18 months of follow-up





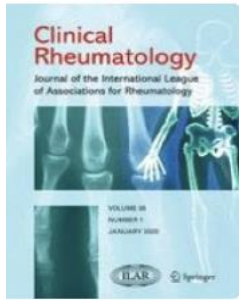


Tofacitinib 5 mg twice daily is the approved dosage for the treatment of moderate to severely active rheumatoid arthritis in the EU, based on the EMA prescribing information. The prescribing information in other countries, including Switzerland, may be different. For details of licenced indications in your country of residence, please refer to the country-specific prescribing information. Graphs created from Bird P, et al. 2020.

These groups are not limited to monotherapy and include patients on concomitant therapy.

bDMARD=biological disease-modifying antirheumatic drug; CDAI=Clinical Disease Activity Index; DAS28(ESR)=Disease Activity Score in 28 joints, erythrocyte sedimentation rate; OPAL=Oral Psoriatic Arthritis Trial; QUMI=Quality Use of Medicines Initiative; RA=rheumatoid arthritis.

Bird P, et al. Real-world evaluation of effectiveness, persistence, and usage patterns of tofacitinib in treatment of rheumatoid arthritis in Australia. *Clin Rheumatol.* 2020; 39(9):2545-



Clinical Rheumatology (2022) 41:53–62
https://doi.org/10.1007/s10067-021-05853-x

ORIGINAL ARTICLE

Real-world evaluation of effectiveness, persistence, and usage patterns of monotherapy and combination therapy tofacitinib in treatment of rheumatoid arthritis in Australia

[illegible]

Tofa mono N=282

BDMARD mono N=564

OPAL-QUMI
Australian observational registry
OPAL
Optimising Patient outcomes in Australian rheumatology
A Quality Use of Medicines Initiative (QUMI)

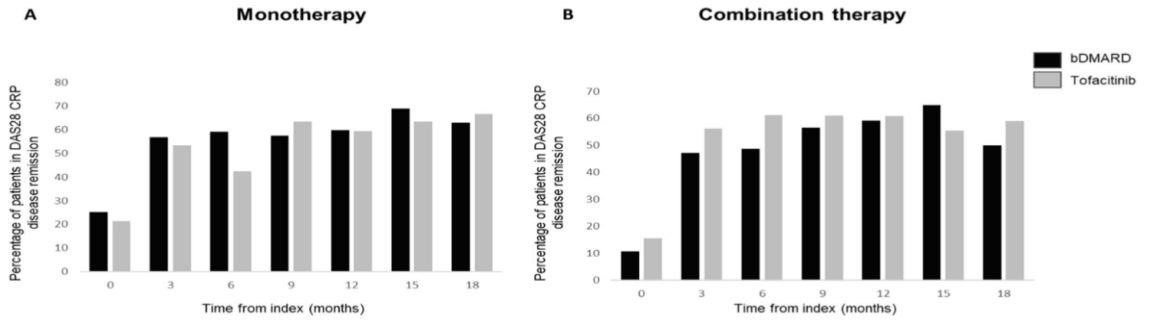
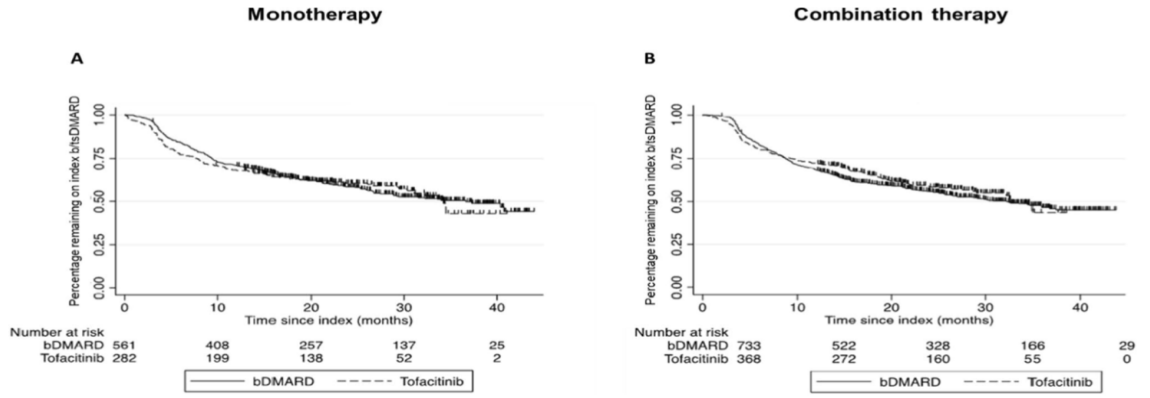


Fig. 2 Percentage of patients in DAS28-CRP disease remission in the **A** bDMARD and tofacitinib monotherapy population and **B** the bDMARD and tofacitinib combination therapy population



Συμπέρασμα

- Δεδομένα από το OPAL-QUMI δείχνουν μια τάση για αυξανόμενη χρήση του tofacitinib ως μονοθεραπεία
- Το tofacitinib κατέδειξε αποτελεσματικότητα και παραμονή στη θεραπεία παρόμοια με αυτήν των bDMARDs

Tofacitinib 5 mg twice daily is the approved dosage for the treatment of moderate to severely active rheumatoid arthritis in the EU, based on the EMA prescribing information.
The prescribing information in other countries, including Switzerland, may be different. For details of licenced indications in your country of residence, please refer to the country-specific prescribing information.
bDMARD=biological disease-modifying antirheumatic drug; CDAI=Clinical Disease Activity Index; csDMARD=conventional synthetic disease-modifying antirheumatic drug; DAS28(ESR)=Disease Activity Score in 28 joints, erythrocyte sedimentation rate; OPAL-QUMI=Optimising Patient outcome in Australian rheumatoLogy-Quality Use of Medicines Initiative; RA=rheumatoid arthritis; SD=standard deviation; SDAI=Simplified Disease Activity Index.
Bird P, et al. Real-world evaluation of effectiveness, persistence, and usage patterns of monotherapy and combination therapy tofacitinib in treatment of rheumatoid arthritis in Australia *Clin Rheumatol*. 2022; 41:53-62.

AB0421 Low rates of retention of biologic dmard monotherapy in patients with rheumatoid arthritisin real life settings FREE

A. Lazarini[1], K. Thomas[1], E. Kaltsonoudis[2], A. Drosos[2], P. Tsatsani[3], S. Gazi[3], L. Pantazi[4], K.A. Boki[4], P. Katsimbri[1], D. Boumpas[1], K. Fragkiadaki[1], M. Tektonidou[1], P.P. Sfikakis[1], K. Karagianni[5], L. Sakkas[5], E. Grika[1], P. Vlachoyiannopoulos[1], G. Evangelatos[6], A. Iliopoulos[6], T. Dimitroulas[7], A. Garyfallos[7], K. Melissaropoulos[8], P. Georgiou[8], M. Areti[9], C. Georganas[10], P. Vounotrypidis[11], G. Kitas[1], D. Vassilopoulos on behalf of Greek Rheumatology Society RA Study Group

✓155/611 (25%) RA patients on biologic DMARDS were on monotherapy

✓~ 50% interrupted treatment within a year

Low HAQ	(OR=0.48, 95% C.I.=0.23–0.99, p=0.047)
Corticosteroids at baseline	(OR=2.2, 95% C.I.=1.02–5.1, p=0.044)
Absence of serious adverse events	(OR=0.14, 95% C.I.=0.016–1.3,p=0.094)

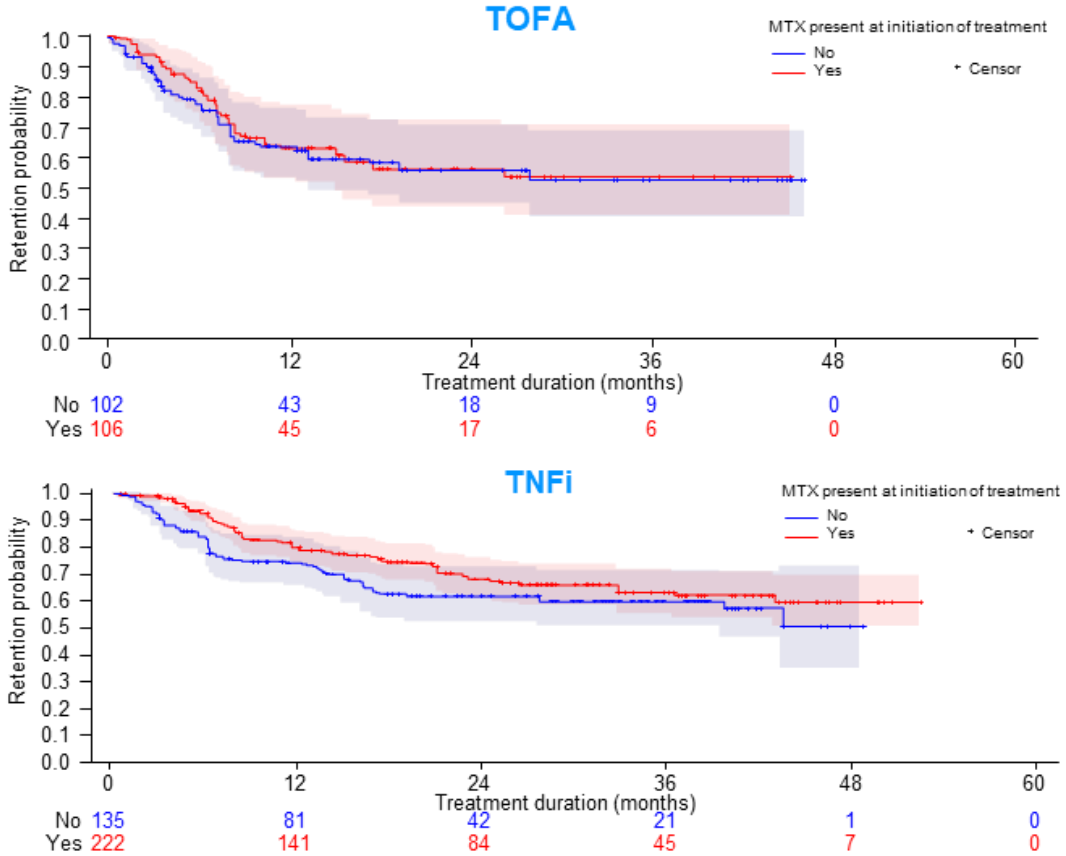
DOI:10.1136/annrheumdis-2018-eular.5780

Tofacitinib: μονοθεραπεία vs συνδυαστική θεραπεία

Tofacitinib Retention With and Without MTX
Data from the OBRI registry

Tofa n=208[1]

Propensity score weighted KM survival curves for time to discontinuation of tofacitinib or TNFi with MTX and without MTX[1]



Η παραμονή στη θεραπεία με tofacitinib είναι παρόμοια με τη χρήση csDMARDs ή χωρίς

CDAI, Clinical Disease Activity Index; JAKi, Janus Kinase inhibitor; KM, Kaplan-Meier; MTX, methotrexate; OBRI, Ontario Best Practices Research Initiative; csDMARDs; conventional synthetic disease modifying antirheumatic drugs, TNFi, tumour necrosis factor inhibitor.

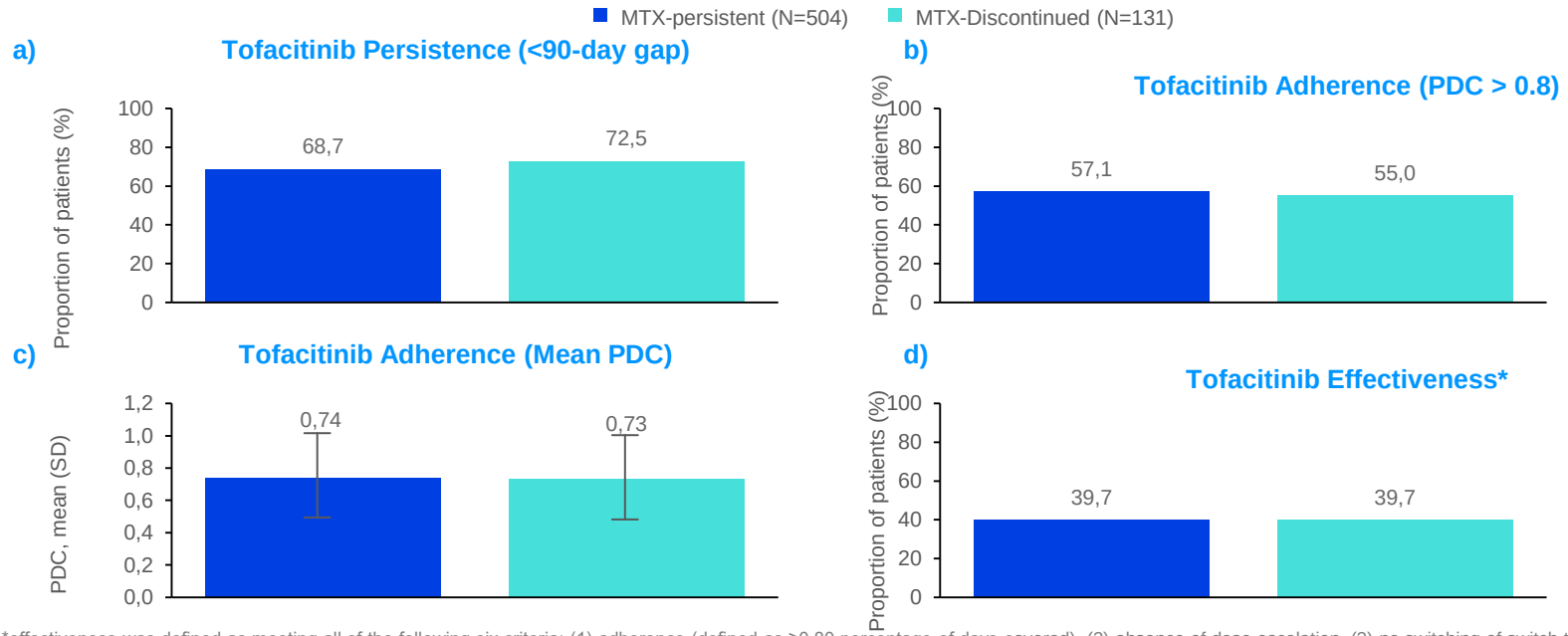
1. Movahedi M, et al. [Poster:0808]. Presented at ACR 2020. e-Congress.

Μπορώ να σταματήσω την MTX μετά την ύφεση με tofacitinib;

Persistence, Adherence and Effectiveness of Tofacitinib When Patients Continued or Discontinued MTX

Tofa N=671

- At 12 months, tofacitinib persistence (a), adherence (b) and mean PDC (c) were similar between MTX-persistence and MTX-discontinued cohorts
- Tofacitinib medication effectiveness was identical between patients in the MTX-persistence and MTX-discontinued cohorts (d)



*effectiveness was defined as meeting all of the following six criteria: (1) adherence (defined as ≥0.80 percentage of days covered), (2) absence of dose escalation, (3) no switching of switch to a biologic disease-modifying antirheumatic drug (bDMARD), (4) no addition of a nonbiologic DMARD, (5) no increase in oral glucocorticoids (GC) use, and (6) not more than one GC injection

Συμπέρασμα

Οι ασθενείς που διέκοψαν την MTX είχαν παρόμοια παραμονή στη θεραπεία, συμμόρφωση και αποτελεσματικότητα σε σχέση με αυτούς που παρέμειναν σε συνδυαστική θεραπεία.

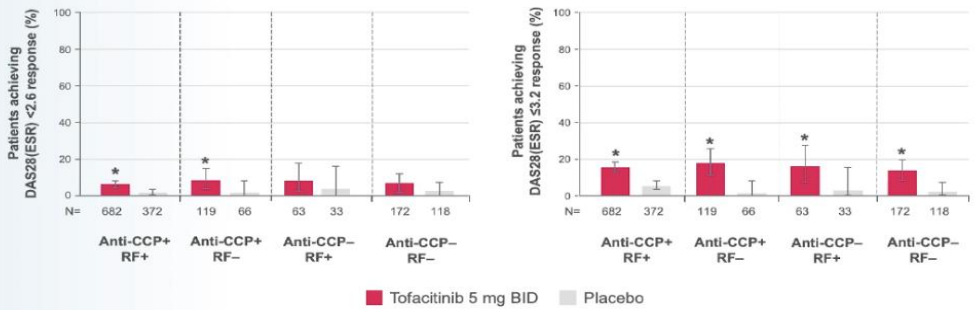
MS, study is from an abstract; MTX, methotrexate; PDC, proportion of days covered; SD, standard deviation; USA, United States of America.

Cohen S, et al. *Clinical Therapeutics* 2022; https://doi.org/10.1016/j.clinthera.2022.05.002 online ahead of print.

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ΤΟΥ TOFACITINIB ΜΕΤΑΞΥ ΣΥΓΚΕΚΡΙΜΕΝΩΝ ΠΛΗΘΥΣΜΩΝ

Tofacitinib was efficacious in seropositive and seronegative patients[1]

Post hoc analysis of pooled phase 3 studies: ORAL Step (TNFi-IR), ORAL Scan (MTX-IR), ORAL Solo (DMARD-IR), ORAL Sync (DMARD-IR), and ORAL Standard (MTX-IR)[1–6]

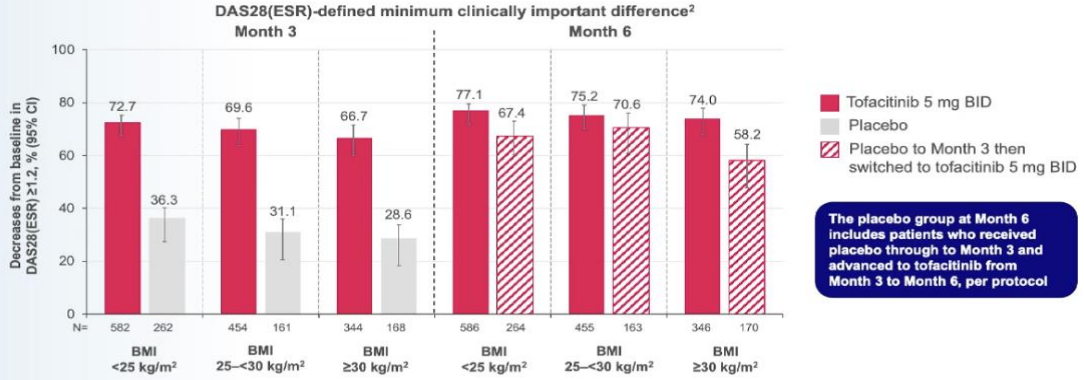


Adapted from Bird P, et al. 2019.[1]
*P≤0.005 vs placebo.[1]
BID, twice daily; CCP, cyclic citrullinated peptide; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; IR, inadequate responder; LDA, low disease activity; MTX, methotrexate; ORAL, Oral Rheumatoid Arthritis Trial; RF, rheumatoid factor; TNFi, tumour necrosis factor inhibitor.
1. Bird P, et al. *RMD Open*. 2019;5:e000742. 2. Burmester GR, et al. *Lancet*. 2013;381:451–460. 3. van der Heijde D, et al. *Arthritis Rheumatol*. 2019;71:878–891. 4. Fleischmann R, et al. *N Engl J Med*. 2012;367:495–507. 5. Strand V, et al. *Arthritis Care Res (Hoboken)*. 2017;69:592–598. 6. van Vollenhoven RF, et al. *N Engl J Med*. 2012;367:508–519.

22

Tofacitinib was efficacious across BMI categories[1,2]

Post hoc analysis of pooled phase 3 studies: ORAL Solo (DMARD-IR), ORAL Sync (DMARD-IR), ORAL Scan (MTX-IR), ORAL Standard (MTX-IR), and ORAL Step (TNFi-IR)[2]



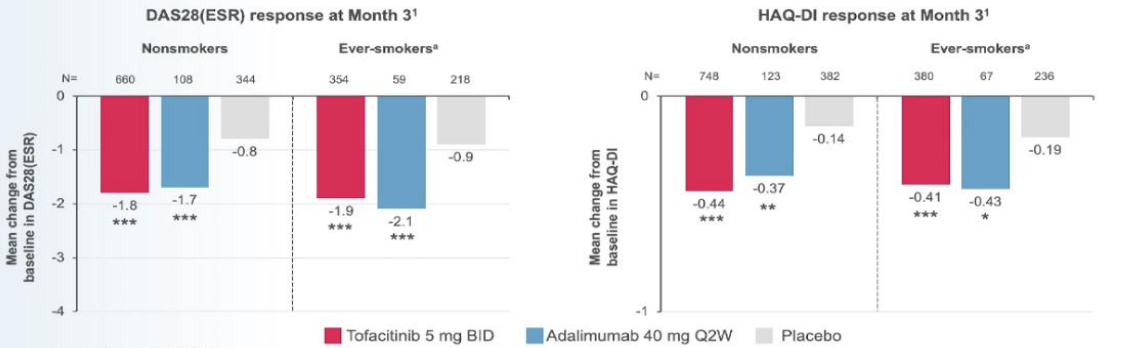
The placebo group at Month 6 includes patients who received placebo through to Month 3 and advanced to tofacitinib from Month 3 to Month 6, per protocol

Adapted from supplement to Dikranian AH, et al. 2022.[2]
BID, twice daily; BMI, body mass index; CI, confidence interval; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; IR, inadequate responder; MTX, methotrexate; ORAL, Oral Rheumatoid Arthritis Trial; TNFi, tumour necrosis factor inhibitor.
1. Dikranian AH, et al. *RMD Open*. 2022;8:e002103. 2. Supplement to: Dikranian AH, et al. *RMD Open*. 2022;8:e002103.

34

Tofacitinib was efficacious in nonsmokers and ever-smokers[1,a]

Post hoc analysis of pooled phase 3 studies: ORAL Step (TNFi-IR), ORAL Scan (MTX-IR), ORAL Solo (DMARD-IR), ORAL Sync (DMARD-IR), and ORAL Standard (MTX-IR)[1–6]



Adapted from Kremer JM, et al. 2013.[1]
Rates vs placebo using normal approximation to the binomial using the 5 phase 3 studies as strata; changes from baseline vs placebo using a longitudinal, mixed-effect linear model, including all visits to account for repeated measures of the patients; the 5 phase 3 studies, baseline values, and randomised treatment as terms in the model.[1]
*P<0.05 vs placebo, **P<0.001 vs placebo, ***P<0.0001 vs placebo.[1]
[a]Ever-smoker defined as current or ex-smoker.[1]
BID, twice daily; DAS28, Disease Activity Score in 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; IR, inadequate responder; MTX, methotrexate; ORAL, Oral Rheumatoid Arthritis Trial; Q2W, every 2 weeks; TNFi, tumour necrosis factor inhibitor.
1. Kremer JM, et al. Annual Meeting Abstract Supplement. *Arthritis & Rheumatism*. 2013;65:S599–S600. 2. Burmester GR, et al. *Lancet*. 2013;381:451–460. 3. van der Heijde D, et al. *Arthritis Rheumatol*. 2019;71:878–891. 4. Fleischmann R, et al. *N Engl J Med*. 2012;367:495–507. 5. Strand V, et al. *Arthritis Care Res (Hoboken)*. 2017;69:592–598. 6. van Vollenhoven RF, et al. *N Engl J Med*. 2012;367:508–519.

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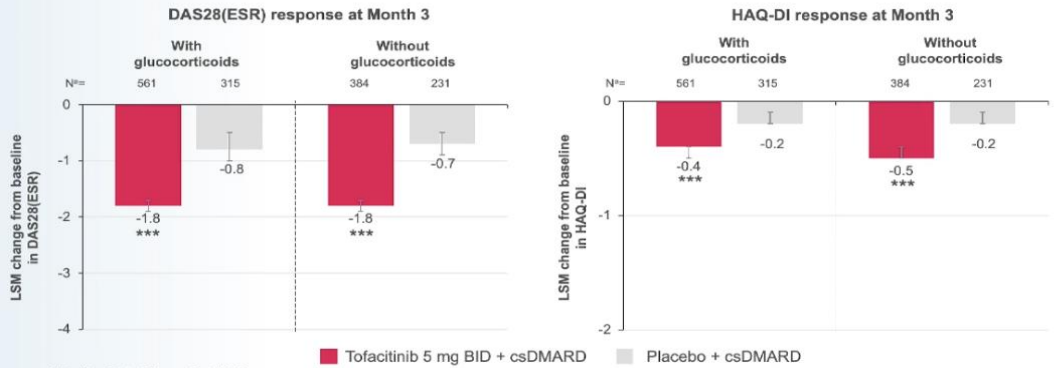
Tofacitinib was efficacious in patients with and without concomitant glucocorticoids

Post hoc analysis of pooled phase 3 studies: ORAL Step (TNFi-IR), ORAL Scan (MTX-IR), ORAL Sync (DMARD-IR), and ORAL Standard (MTX-IR)

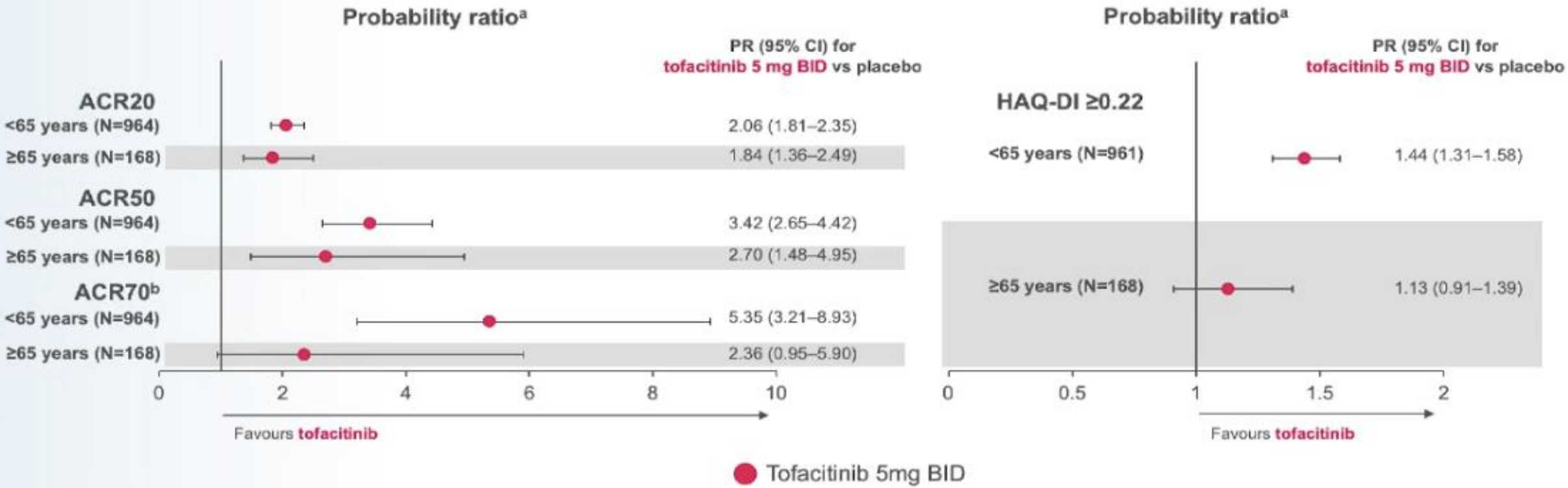


Adapted from Charles-Schoeman C, et al. 2018.
***P<0.0001 (without multiplicity adjustment for exploratory analysis) vs placebo within the respective subgroup.
[a]Patient numbers given are from the FAS for ACR responses; however, patient numbers varied among outcome measures.
ACR, American College of Rheumatology; BID, twice daily; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28, Disease Activity Score for 28 joints; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; IR, inadequate responder; LSM, least squares mean; MTX, methotrexate; ORAL, Oral Rheumatoid Arthritis Trial; TNFi, tumour necrosis factor inhibitor.
Charles-Schoeman C, et al. *J Rheumatol*. 2018;45:177–187.

31

Tofacitinib was efficacious in patients aged <65 and ≥65 years[1]

Post hoc analysis of pooled phase 3 studies at Month 3: ORAL Step (TNFi-IR), ORAL Scan (MTX-IR), ORAL Solo (DMARD-IR), ORAL Sync (DMARD-IR), ORAL Standard (MTX-IR)[1–6]



Adapted from Curtis JR, et al. 2017.[1]

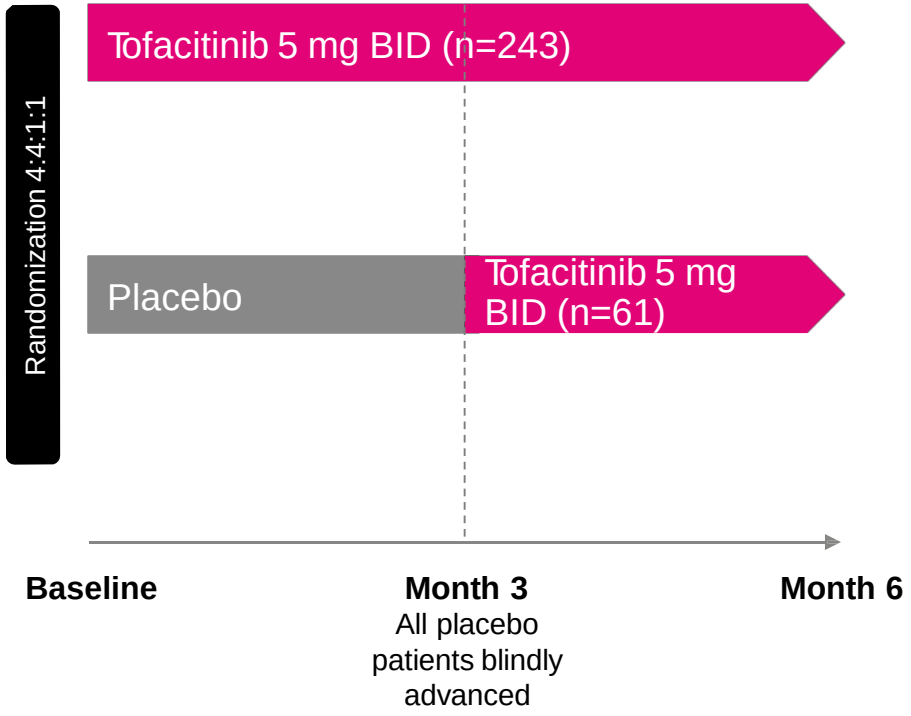
[a]Probability ratio is the proportion of responders in the tofacitinib group divided by the proportion of responders in the placebo group at Month 3. A PR >1 favours tofacitinib.[1] [b]Comparisons of ACR70 rates should be interpreted with caution because of the limited number of patients achieving this response.[1]

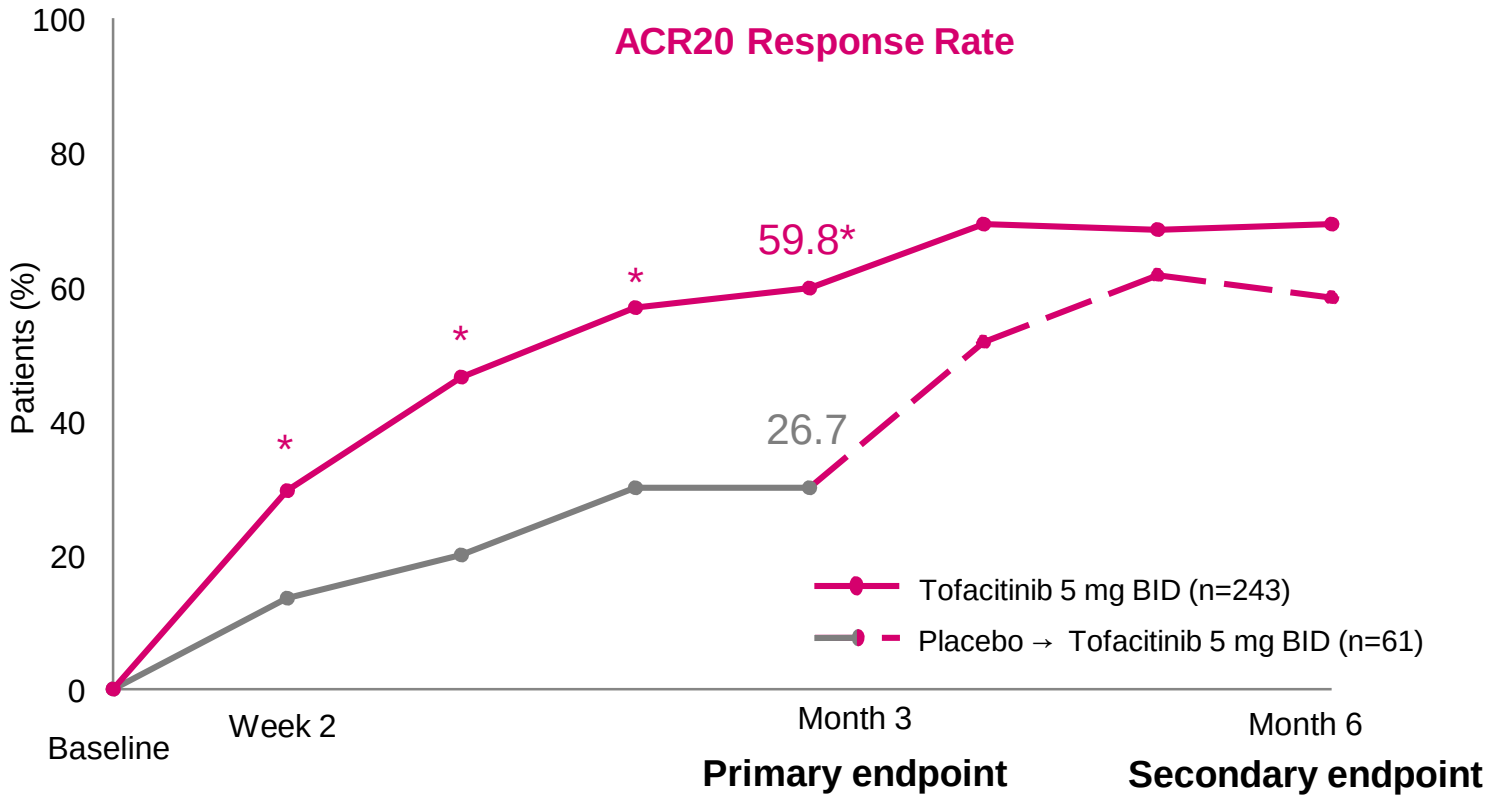
ACR20/50/70, ≥20%/50%/70% improvement in American College of Rheumatology score; BID, twice daily; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire Disability Index; IR, inadequate responder; MTX, methotrexate; ORAL, Oral Rheumatoid Arthritis Trial; PR, probability ratio; TNFi, tumour necrosis factor inhibitor.

1. Curtis JR, et al. *Clin Exp Rheumatol*. 2017;35:390–400. 2. Burmester GR, et al. *Lancet*. 2013;381:451–460. 3. van der Heijde D, et al. *Arthritis Rheumatol*. 2019;71:878–891. 4. Fleischmann R, et al. *N Engl J Med*. 2012;367:495–507. 5. Strand V, et al. *Arthritis Care Res (Hoboken)*. 2017;69:592–598. 6. van Vollenhoven RF, et al. *N Engl J Med*. 2012;367:508–519.

Ταχύτητα δράσης

Ταχύτητα δράσης





Tofacitinib 5 mg twice daily is the approved dosage for the treatment of moderate to severe active rheumatoid arthritis in the EU, based on the EMA prescribing information. The prescribing information in other countries, including Switzerland, may be different. For details of licenced indications in your country of residence, please refer to the country-specific prescribing information.

Adapted from Fleischmann R, et al. 2012.

*P<0.001 vs placebo

ACR20=≥20% improvement in American College of Rheumatology score; BID=twice daily; csDMARD-IR=conventional synthetic disease-modifying antirheumatic drug-inadequate responder; ORAL=Oral Rheumatoid Arthritis Trial; qd=once daily.

Fleischmann R, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med.* 2012;367(6):495-507. Reference available on request.

Ταχύτητα θεραπευτικής απόφασης

Post Hoc Analysis of Tofacitinib ORAL Standard Trial (CDAI-defined LDA, FAS, NRI, N=717)

Achievement of LDA Given Failure to Improve CDAI ≥6	Tofacitinib 5 mg BID		
	Probabilities of Achieving LDA at 6 Months (CDAI ≤10) (%)	NPV (%)	PPV (%)
Month 6			
Failure to improve at month 1	5/51 (9.8)	**90.2**	38.4
Failure to improve at month 3	0/36 (0)	**100**	37.4
Month 12			
Failure to improve at month 1	9/51 (17.6)	**82.4**	47.1
Failure to improve at month 3	1/36 (2.8)	**97.2**	47.7

Patients who do not improve CDAI ≥6 at 1 or 3 months are not likely to achieve LDA (CDAI ≤10) at 6 and 12 months

Tofacitinib 5 mg twice daily is the approved dosage for the treatment of moderate to severe active rheumatoid arthritis in the EU, based on the EMA prescribing information. The prescribing information in other countries, including Switzerland, may be different. For details of licenced indications in your country of residence, please refer to the country-specific prescribing information.

Table adapted from van Vollenhoven RF, et al. 2019.

Unless indicated otherwise, values are the number of patients who failed to meet the improvement threshold/the number who also achieved LDA (defined as CDAI ≤10) (%). BID=twice daily; CDAI=Clinical Disease Activity Index; DAS28-4(ESR)=Disease Activity Score in 28 joints with 4 variables, erythrocyte sedimentation rate; FAS=full analysis set; LDA=low disease activity; MTX-IR=methotrexate inadequate response; NPV=negative predictive value; NRI=nonresponder imputation; ORAL=Oral Rheumatoid Arthritis Trial; PPV=positive predictive value; RA=rheumatoid arthritis.

van Vollenhoven RF, et al. Tofacitinib in rheumatoid arthritis: lack of early change in disease activity and the probability of achieving low disease activity at month 6. *Arthritis Care Res (Hoboken).* 2019;71(1):71-79.

Ασφάλεια

Tofacitinib: τα περισσότερα δεδομένα σχετικά με την ασφάλεια

RMD Open
Rheumatic & Musculoskeletal Diseases

Original research

Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme

Stanley B Cohen,[1] Yoshiya Tanaka,[2] Xavier Mariette,[3] Jeffrey R Curtis,[4] Eun Bong Lee,[5] Peter Nash,[6] Kevin L Winthrop,[7] Christina Charles-

Table 2 IRs (95% CI) of AEs and SAEs (all-cause)

	All tofacitinib doses N=7061	Average tofacitinib 5 mg BID* N=3066
	22 874.5 PY	8171.3 PY
Median PY of exposure	3.1	1.4†
AEs	130.3 (127.0 to 133.6) (n=6117)	129.7 (124.7 to 134.9) (n=2484)
Discontinuations due to AEs	7.1 (6.8 to 7.5) (n=1634)	8.0 (7.4 to 8.7) (n=664)
SAEs	9.0 (8.6 to 9.4) (n=1857)	9.6 (8.9 to 10.3) (n=717)
Mortality‡	0.3 (0.2 to 0.3) (n=59)	0.3 (0.2 to 0.5) (n=29)

IRs are presented as the unit of patients with events per 100 PY.

	All tofacitinib doses N=7061	Average tofacitinib 5 mg BID* N=3066
	22 874.5 PY	8171.3 PY
Serious infection events†	2.5 (2.3 to 2.7) (n=576)	2.8 (2.5 to 3.2) (n=233)
HZ (non-serious and serious)	3.6 (3.4 to 3.9) (n=782)	3.5 (3.1 to 3.9) (n=269)
HZ (serious)	0.2 (0.2 to 0.3) (n=57)	0.3 (0.2 to 0.4) (n=23)
Opportunistic infection (excluding TB)	0.4 (0.3 to 0.5) (n=90)	0.3 (0.2 to 0.5) (n=28)
TB	0.2 (0.1 to 0.2) (n=38)	0.1 (0.1 to 0.2) (n=11)
Malignancy (excluding NMSC)	0.8 (0.7 to 0.9) (n=177)	0.8 (0.6 to 1.0) (n=64)
NMSC	0.6 (0.5 to 0.7) (n=129)	0.4 (0.3 to 0.6) (n=36)
Breast cancer (female patients)	0.2 (0.1 to 0.2) (n=30)	0.2 (0.1 to 0.3) (n=12)
Lung cancer	0.1 (0.1 to 0.2) (n=30)	0.1 (0.1 to 0.3) (n=12)
Lymphoma‡	0.05 (0.03 to 0.09) (n=12)	0.01 (0.00 to 0.07) (n=1)
GI perforations	0.1 (0.1 to 0.2) (n=28)	0.1 (0.0 to 0.2) (n=6)
DVT	0.2 (0.1 to 0.2) (n=36)	0.2 (0.1 to 0.3) (n=13)
PE	0.1 (0.1 to 0.2) (n=28)	0.1 (0.0 to 0.2) (n=8)
VTE§	0.3 (0.2 to 0.3) (n=59)	0.2 (0.1 to 0.4) (n=19)
ATE	0.4 (0.3 to 0.5) (n=84)	0.3 (0.2 to 0.5) (n=28)
MACE	0.4 (0.3 to 0.5) (n=85)	0.4 (0.3 to 0.6) (n=31)

Cohen et al. RMD Open 2020;6:e001395

Tofacitinib 5 mg twice daily is the approved dosage for the treatment of moderate to severe active rheumatoid arthritis in the EU, based on the EMA prescribing information. The prescribing information in other countries, including Switzerland, may be different. For details of licenced indications in your country of residence, please refer to the country-specific prescribing information.

Tofacitinib: τα περισσότερα δεδομένα σχετικά με την ασφάλεια

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Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme

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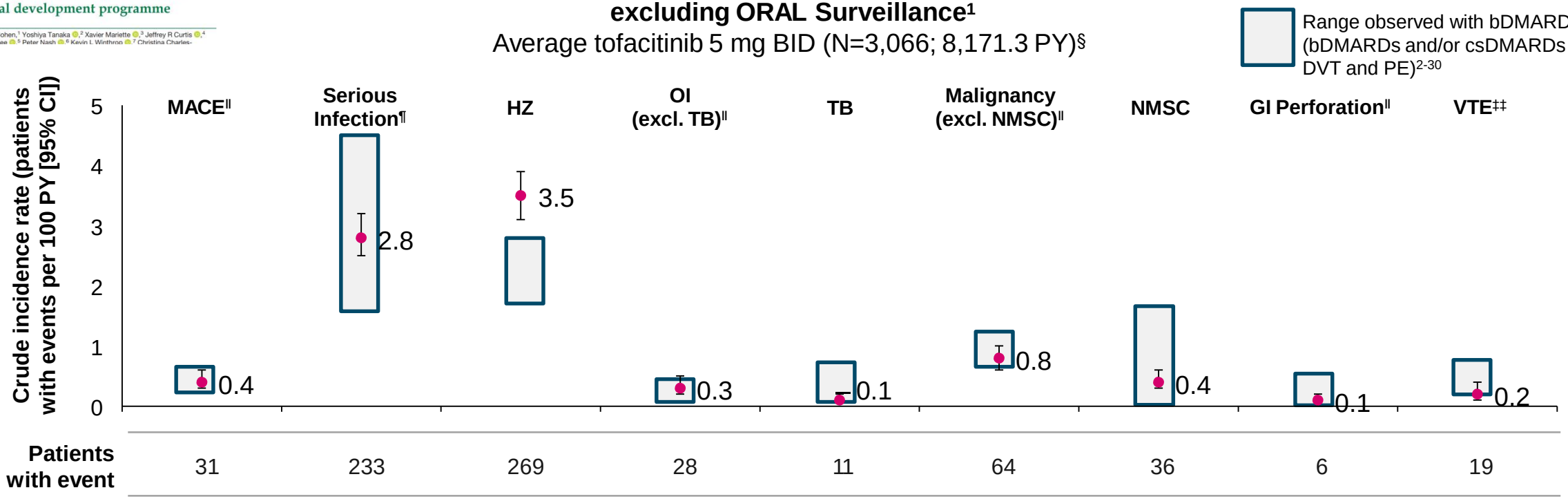
Integrated safety data in overall tofacitinib population—Phase I, II, III, IIIb/IV, LTE;‡ excluding ORAL Surveillance[1]

Average tofacitinib 5 mg BID (N=3,066; 8,171.3 PY)§



Conclusions cannot be drawn from comparisons across different studies as populations and other factors may vary considerably.

Tofacitinib 5 mg twice daily is the approved dosage for the treatment of moderate to severe active rheumatoid arthritis in the EU, based on the EMA prescribing information. The prescribing information in other countries, including Switzerland, may be different. For details of licenced indications in your country of residence, please refer to the country- specific prescribing information. Adapted from Cohen S, et al. 2020.

‡The database lock for the integrated safety data was March 2017. Incidence rates were based on the number of patients with events during the time between the first and last tofacitinib dose plus 28 days. §Average dosing was based on average daily dose: patients receiving <15 mg/day were assigned to the tofacitinib 5 mg BID group. **All tofacitinib doses: N=7,061, 22,874.5 PY.**
‖Adjudicated events. ¶Defined as requiring hospitalisation or parenteral antimicrobial therapy, or otherwise meeting SAE criteria. ‡‡Patients with a DVT event, a PE event, or both DVT and PE events. A total of five patients experienced a DVT and a PE event (may not have occurred at the same time).
AE=adverse event; BID=twice daily; CI=confidence interval; DVT=deep vein thrombosis; GI=gastrointestinal; HZ=herpes zoster; LTE=long-term extension; MACE=major adverse cardiac event; NMSC=nonmelanoma skin cancer; OI=opportunistic infection; ORAL=Oral Rheumatoid Arthritis Trial; PE=pulmonary embolism; PY=patient-year; RA=rheumatoid arthritis; SAE=serious adverse event; TB=tuberculosis; VTE=venous thromboembolism.

1. Cohen SB, et al. Long-term safety of tofacitinib up to 9.5 years: a comprehensive integrated analysis of the rheumatoid arthritis clinical development programme. *RMD Open.* 2020;6:e001395. Full references for this slide available at the end of the presentation. References available on request

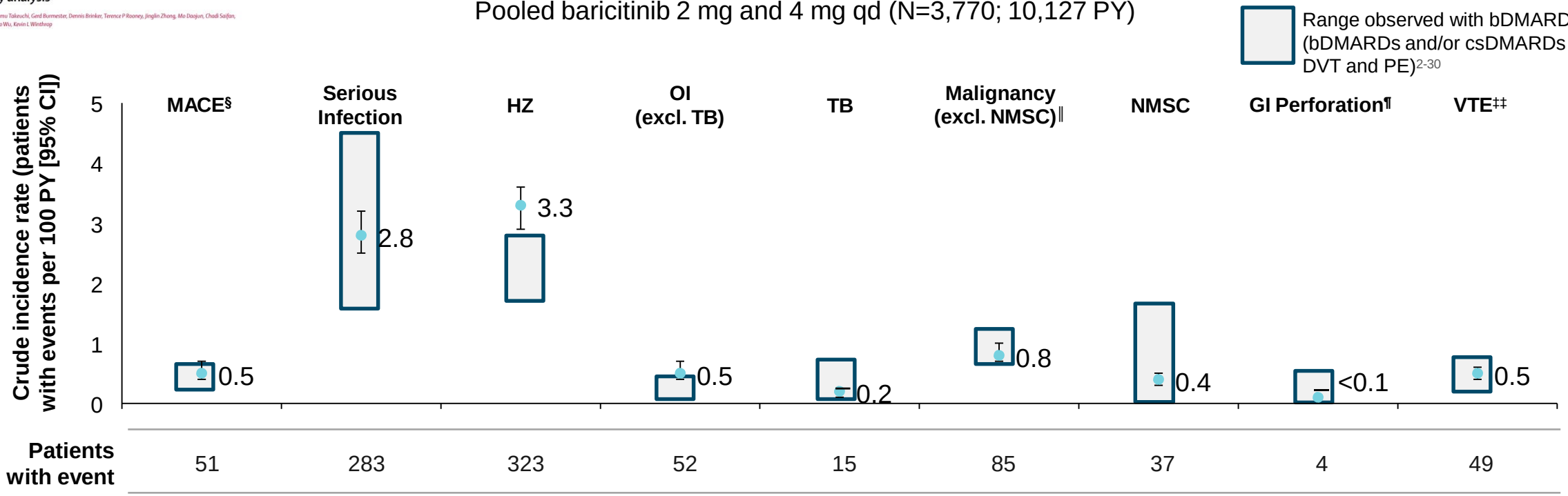
Παρόμοια δεδομένα ασφάλειας υπάρχουν και με άλλους JAKi

Safety profile of baricitinib for the treatment of rheumatoid arthritis over a median of 3 years of treatment: an updated integrated safety analysis

Mark C Genovese, Josef S Smolen, Tsutomu Takeuchi, Gerd Burmester, Dennis Brinker, Terence P Rooney, Jinglin Zhong, Mo Daojun, Chadi Saifan, Anabela Cardoso, Maher Issa, Wen-Shuo Wu, Kevin L Winthrop

Integrated safety data in overall baricitinib population—Phase Ib, II, III, LTE[1,‡]

Pooled baricitinib 2 mg and 4 mg qd (N=3,770; 10,127 PY)



Conclusions cannot be drawn from comparisons across different studies as populations and other factors may vary considerably.

Adapted from Genovese MC, et al. 2020.

‡The database lock for the integrated safety data was February 2018. Incidence rates were based on the number of patients with events including any post-drug follow-up time, with observation or exposure time censored at event onset date. The LTE trial, RA-BEYOND, was ongoing at the time of this analysis. §Adjudicated events. ‖As-treated analysis. ¶Exposure-adjusted incidence rate, calculated as the number of patients with an event per 100 patient-years of overall exposure time. Cases included a gastric perforation in the patient who was given placebo, a perforated appendix, a perforated diverticulum, an intestinal perforation, and a proximal intestinal perforation after knee surgery in the baricitinib-treated patients. ‡‡Patients with a DVT event, a PE event, or both DVT and PE events.

AE=adverse event; CI=confidence interval; DVT=deep vein thrombosis; GI=gastrointestinal; HZ=herpes zoster; LTE=long-term extension; MACE=major adverse cardiovascular event; NMSC=nonmelanoma skin cancer; OI=opportunistic infection; PE=pulmonary embolism; PY=patient-years; qd=once daily; RA=rheumatoid arthritis; TB=tuberculosis; VTE=venous thromboembolism.

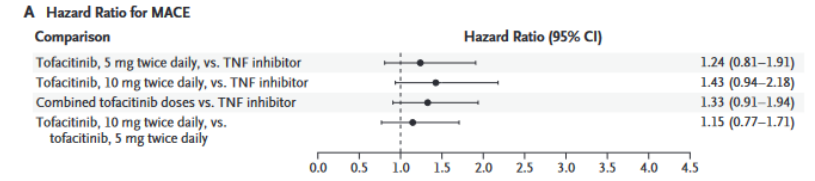
1. Genovese MC, et al. Safety profile of baricitinib for the treatment of rheumatoid arthritis over a median of 3 years of treatment: an updated integrated safety analysis. *Lancet Rheumatol.* 2020;2(6):347-357. Full references for this slide available at the end of the presentation. References available on request.

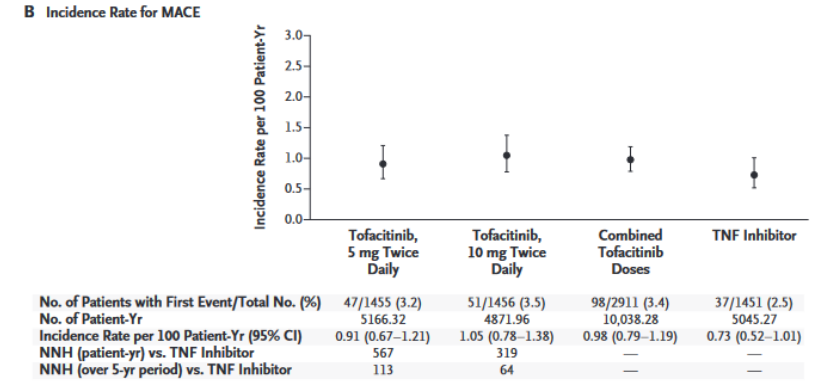
ORAL Surveillance Safety Trial: Tofacitinib vs. TNF Inhibitors

- Post-marketing τυχαιοποιημένη μελέτη ανοικτής ετικέτας (N=4370)
- tofa 5 vs tofa 10 vs TNFi (ADA ή ETN)
- Κριτήρια ένταξης: ≥50 ετών, μέτρια προς σοβαρή RA, MTX-IR, ≥1 καρδιαγγειακός παράγοντας κινδύνου (κάπνισμα, ΑΥ, ↑ Chol, ΣΔ, ιστορικό ΟΕΜ, οικογενειακό ιστορικό ΣΝ, εξωαρθρική RA)

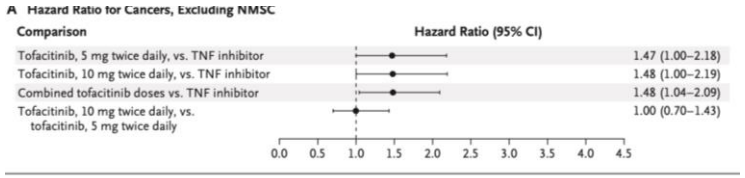
The approved dosage of tofacitinib in rheumatoid arthritis is 5 mg BID

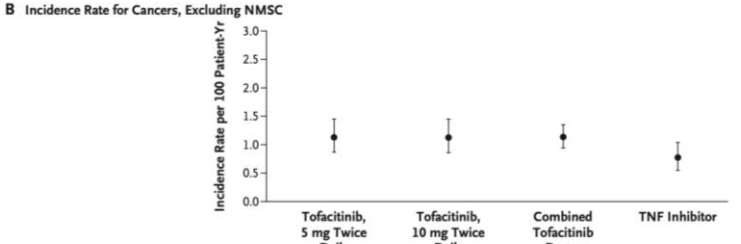
Ytterberg SR et al. N Engl J Med. 2022 Jan 27;386(4):316-326.





	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily	Combined Tofacitinib Doses	TNF Inhibitor
No. of Patients with First Event/Total No. (%)	47/1455 (3.2)	51/1456 (3.5)	98/2911 (3.4)	37/1451 (2.5)
No. of Patient-Yr	5166.32	4871.96	10,038.28	5045.27
Incidence Rate per 100 Patient-Yr (95% CI)	0.91 (0.67–1.21)	1.05 (0.78–1.38)	0.98 (0.79–1.19)	0.73 (0.52–1.01)
NNH (patient-yr) vs. TNF Inhibitor	567	319	—	—
NNH (over 5-yr period) vs. TNF Inhibitor	113	64	—	—



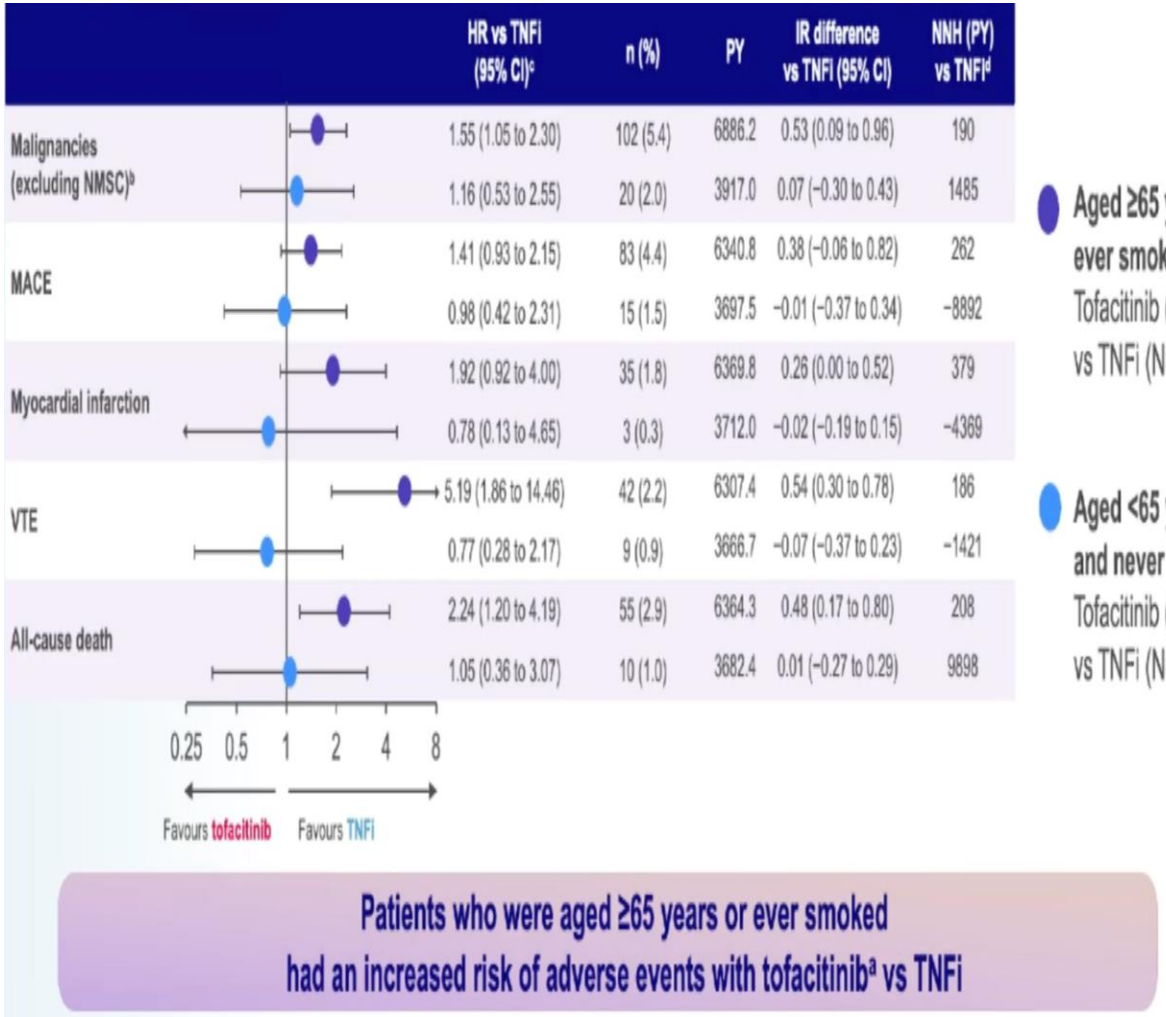


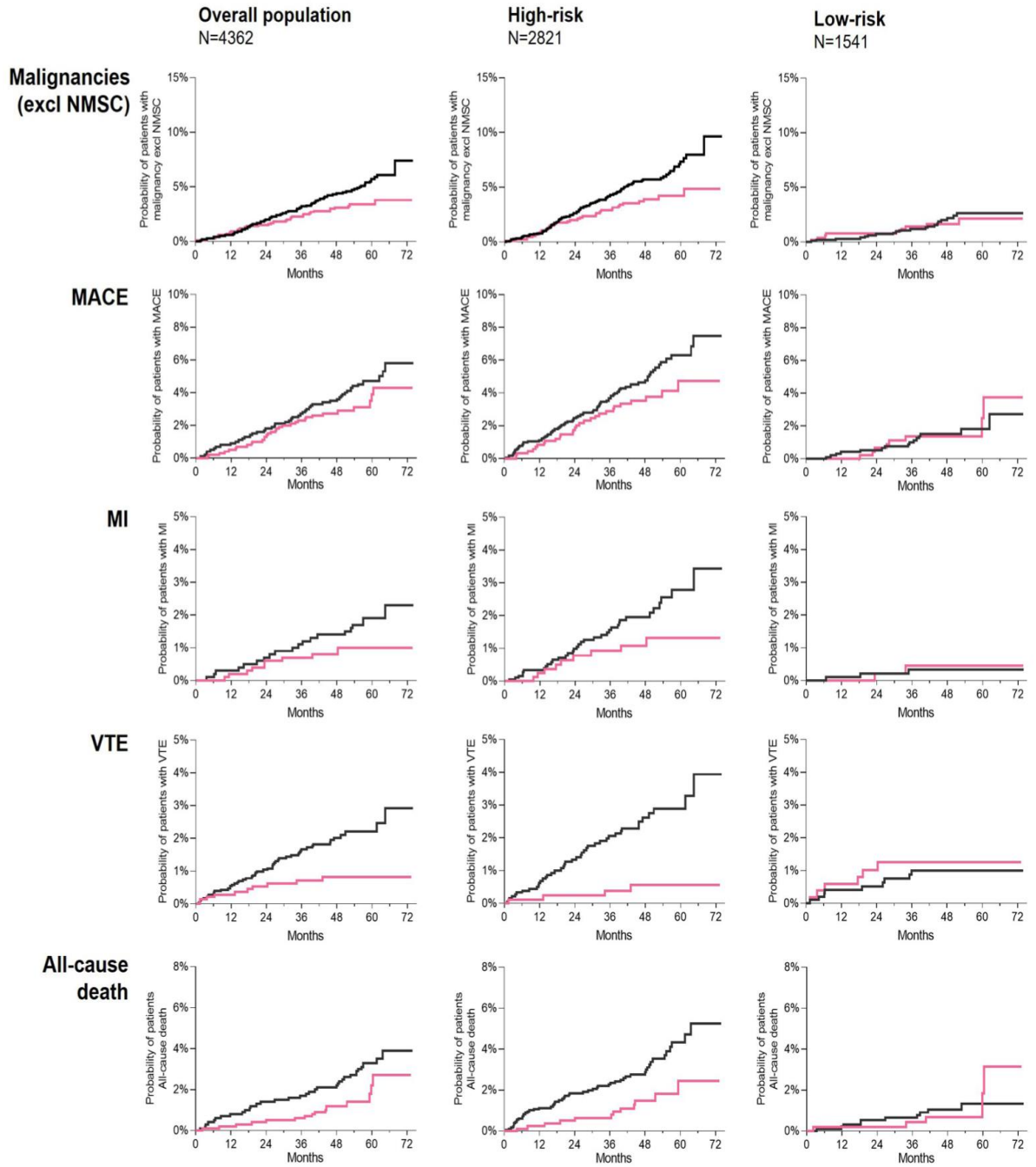
	Tofacitinib, 5 mg Twice Daily	Tofacitinib, 10 mg Twice Daily	Combined Tofacitinib Doses	TNF Inhibitor
No. of Patients with First Event/Total No. (%)	62/1455 (4.3)	60/1456 (4.1)	122/2911 (4.2)	42/1451 (2.9)
No. of Patient-Yr	5491.48	5311.71	10,803.19	5482.30
Incidence Rate per 100 Patient-Yr (95% CI)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

CLINICAL SCIENCE

Identification of two tofacitinib subpopulations with different relative risk versus TNF inhibitors: an analysis of the open label, randomised controlled study ORAL Surveillance

Lars Erik Kristensen,[1] Silvio Danese,[2] Arne Yndestad,[3] Cunshan Wang,[4] Edward Nagy,[5] Irene Modesto,[6] Jose Rivas,[6] Birgitta Benda[7]

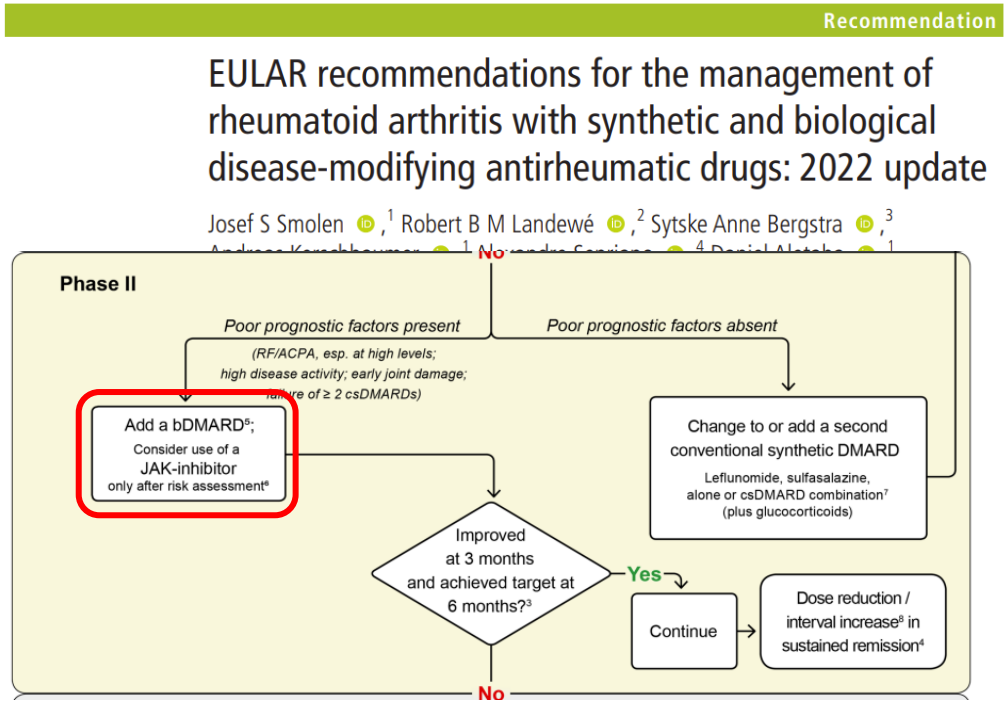




The approved dosage of tofacitinib in rheumatoid arthritis is 5 mg BID

Kristensen L, et al Ann Rheum Dis 2023

JAKi in the 2022 EULAR RA guidelines



Risk assessment

- Age > 65yrs
- History of current or past smoking
- Other CVD factors
  (DM, obesity, HTN)
- Other risk factors for malignancy
  (current or history)
- Risk for thromboembolic events
  (history of MI or heart failure, cancer, inherited blood clotting disorder, HRT, major surgery, immobility)

Smolen JS, et al. Ann Rheum Dis 2023;82:3–18

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Παγκόσμιες κλινικές μελέτες
(φάσης 1-3/4b, LTE)
34 στη ρευματολογία,
5 στη γαστρεντερολογία[1-4]

>13.000
ασθενείς σε RCT
σε 5 ενδείξεις[3-6]

>38.000
ανθρωποέτη
έκθεσης στο XELJANZ
σε RCT [3-6,α,β,γ]

Σε >505.000
ασθενείς έχει συνταγογραφηθεί
για όλες τις ενδείξεις παγκοσμίως[4,δ,ε,στ]

- 1. Burmester GR, et al. RMD Open 2021; 7:e001595. doi: 10.1136/rmdopen-2021-001595
- 2. Ytterberg SR, et al. N Engl J Med 2022; 386-316-326.
- 3. Deodhar 2022 et al. Abstract POS0296
- 4. DOF Global Patient Count 9-9-2022-Combo
- 4. 1025_BurmesterGR_RMD Open_2021_v7e001595
- 6. Ytterberg SR_NEJM_2022_Suppl.2022
- 7. XELJANZ Περίληψη Χαρακτηριστικών του Προϊόντος, 03/2023
- 8. Ruperto et al. 2021 Lancet

ΣΥΜΠΕΡΑΣΜΑΤΑ

- Το tofacitinib είναι ο μοναδικός JAKi με πάνω από 10 έτη κλινικής εμπειρίας
- Εμφανίζει παρόμοια αποτελεσματικότητα με τα bDMARDS
- Δεδομένα από τα μητρώα καταγραφής σε χώρες σε όλο τον κόσμο δείχνουν παραμονή στη θεραπεία παρόμοια με βιολογικούς παράγοντες και ίσως καλύτερη από τους anti-TNF
- Αποτελεσματικό σε μονοθεραπεία (απουσία ανοσογονικοτητας?)
- Το tofacitinib εμφανίζει την ίδια αποτελεσματικότητα ανεξάρτητα από την ηλικία, την οροθετικότητα, τη συγχορήγηση κορτικοειδών και τη παρουσία συννοσηροτήτων (π.χ παχυσαρκία)
- ➢Με προσοχή σε ασθενείς >65 ετών με ιστορικό καρδιαγγειακών συμβαμάτων, πρώην και νυν καπνιστές αλλά εξίσου αποτελεσματικό