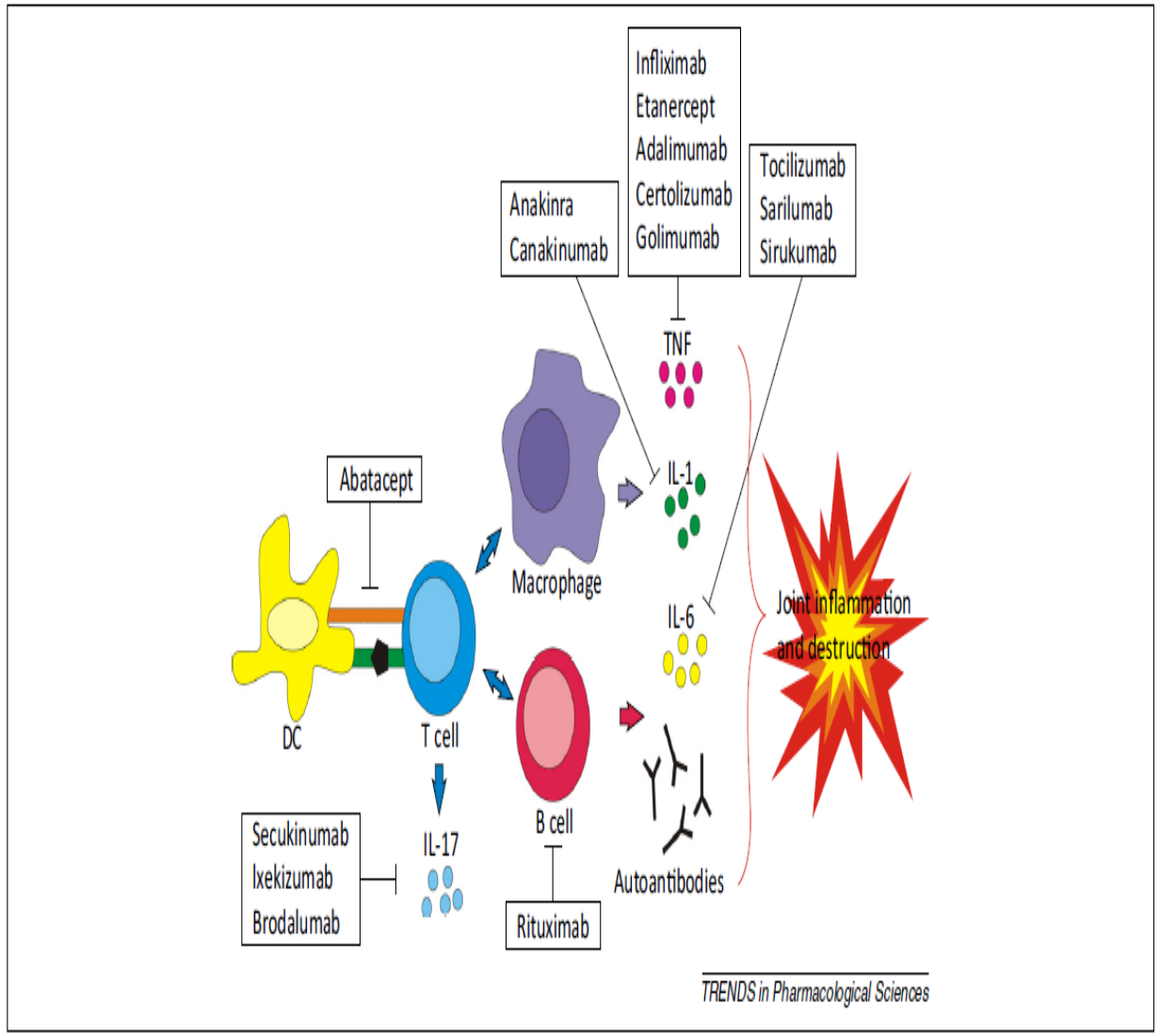
ΕΠΕΜΥ
Επιστημονική Εταιρεία
για τη Μυοσκελετική Υγεία
12° Πανελλήνιο Συνέδριο
Ολοκληρωμένη διαχείριση των Φλεγμονωδών
και των Μυοσκελετικών Παθήσεων

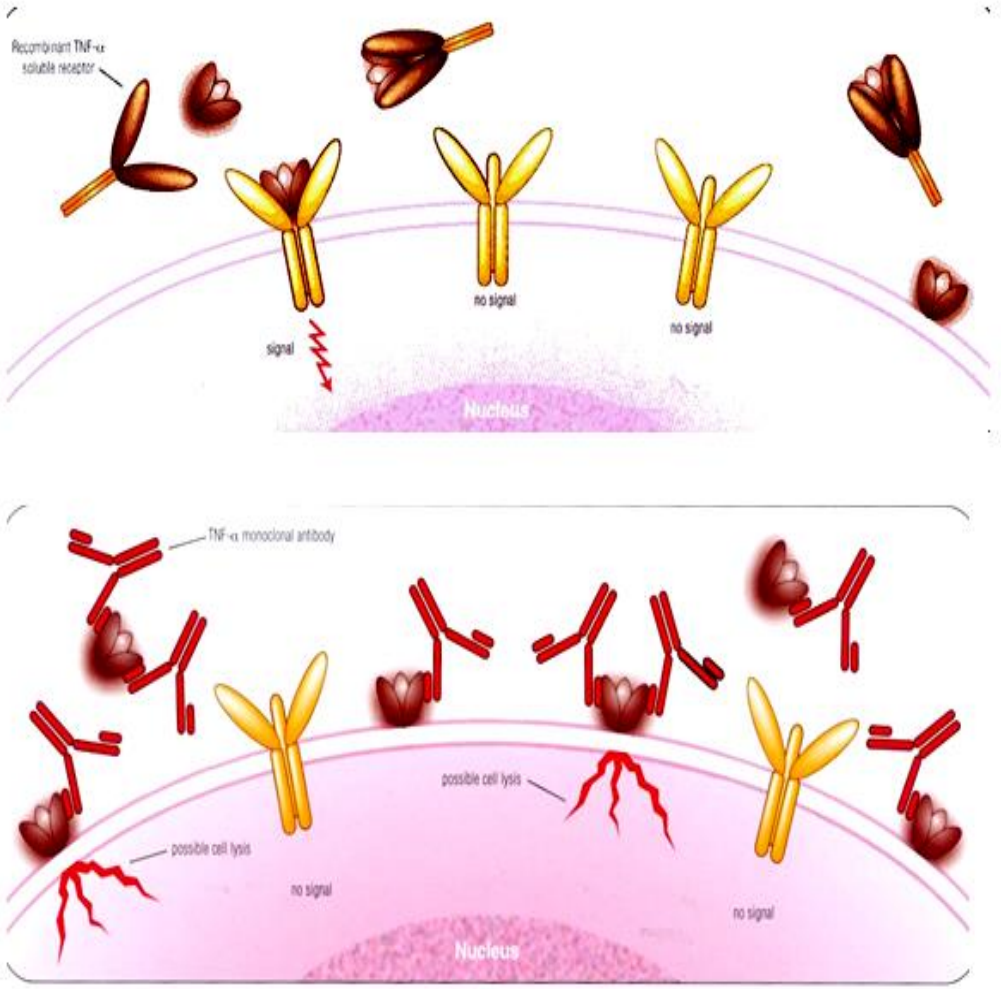
«Μεγαλομοριακοί βιολογικοί παράγοντες ή ενδοκυττάρια στόχευση με μικρομόρια;» Στη Ρευματοειδή Αρθρίτιδα και τις Αξονικές Σπονδυλαρθρίτιδες

ΔΗΜΗΤΡΟΥΛΑΣ ΘΕΟΔΩΡΟΣ
ΕΠΙΚΟΥΡΟΣ ΚΑΘΗΓΗΤΗΣ ΡΕΥΜΑΤΟΛΟΓΙΑΣ
Δ' ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ – ΙΠΠΟΚΡΑΤΕΙΟ ΝΟΣΟΣΚΟΜΕΙΟ
ΑΠΘ

- No conflict of Interest

ΒΙΟΛΟΓΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ



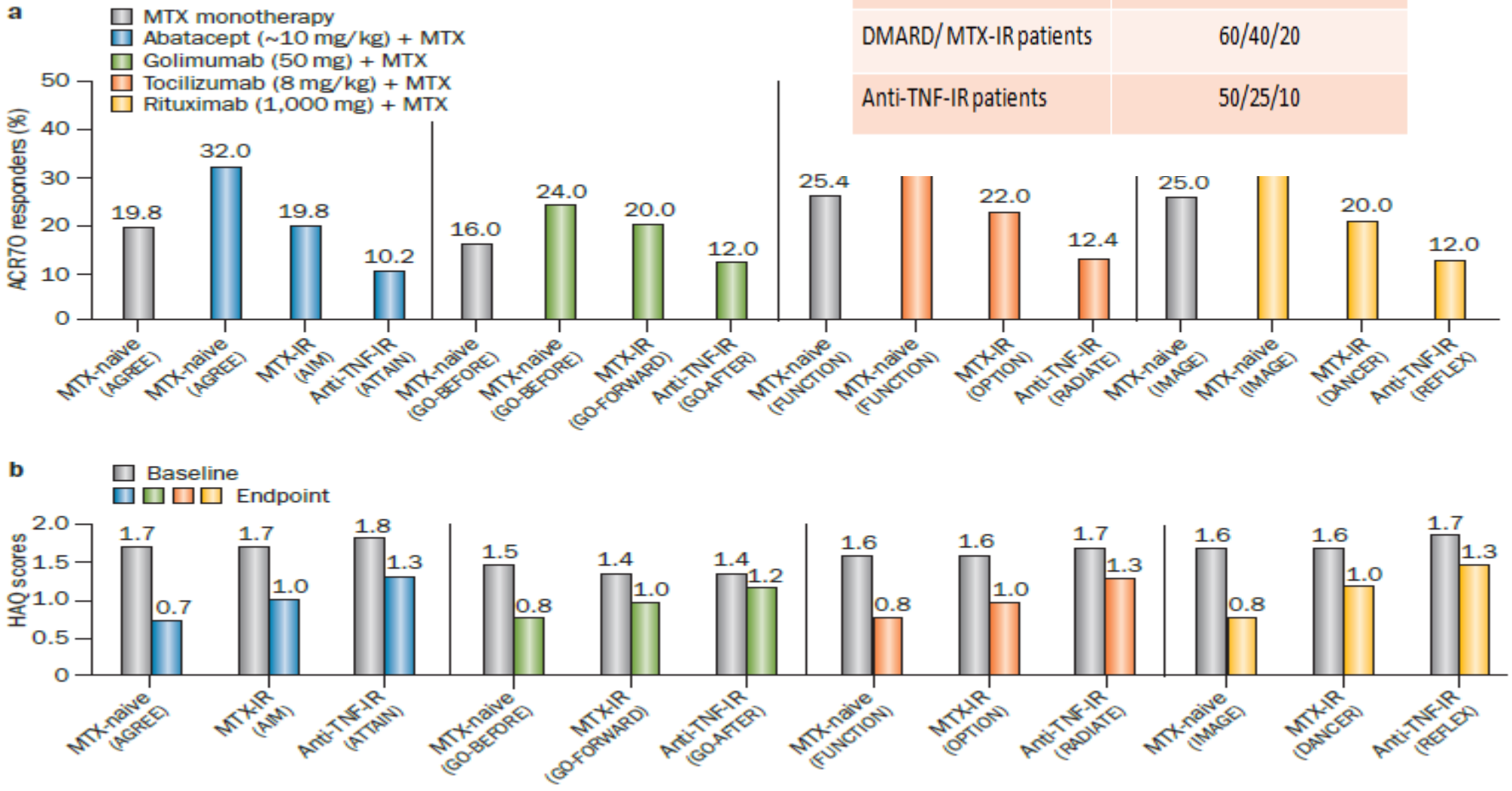


Koenders et al, Trends Pharm Sci 2015

Οι βιολογικοί παράγοντες στοχεύουν τα εξωκυτταρικά συστατικά του καταρράκτη της φλεγμονής

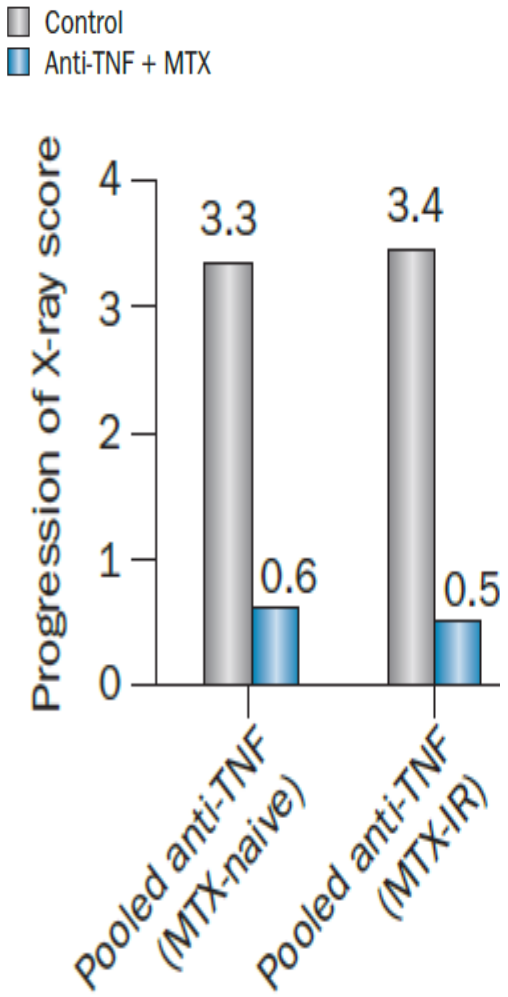
ΟΙ ΒΙΟΛΟΓΙΚΟΙ ΠΑΡΑΓΟΝΤΕΣ ΣΤΗ ΡΑ ΕΙΝΑΙ ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΙ

RA population	ACR 20/50/70
DMARD naïve patients	70/50/30
DMARD/ MTX-IR patients	60/40/20
Anti-TNF-IR patients	50/25/10

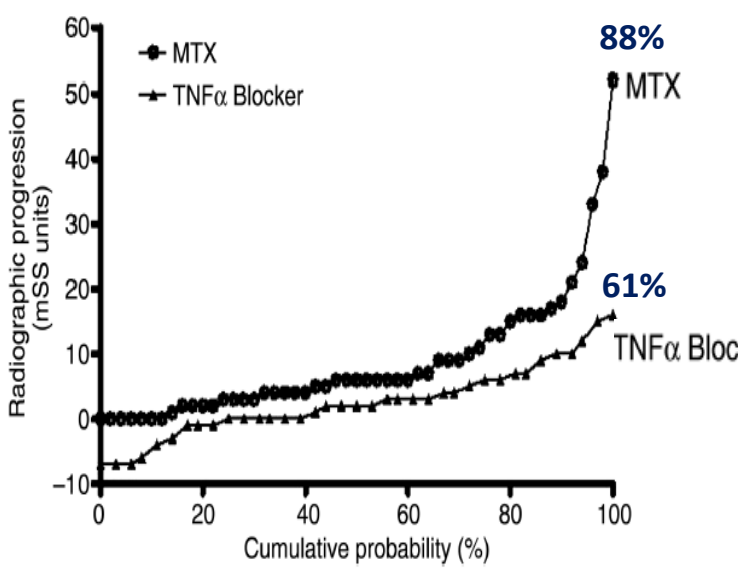


Smolen et al, Nat Rheum Rev 2015

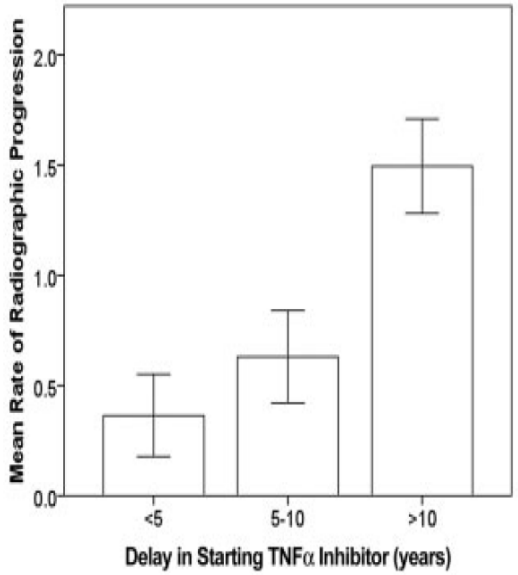
Anti-TNFs: Αναστολή προόδου ακτινολογικών βλαβών



Smolen J, et al. Nat Rev Rheumatol 2015



Eder L, et al. Ann Rheum Dis 2014



Haroon N et al. Arthritis & Rheumatol 2013

Anti-TNFs

↓ 50% ακτινολογικής επιδείνωσης

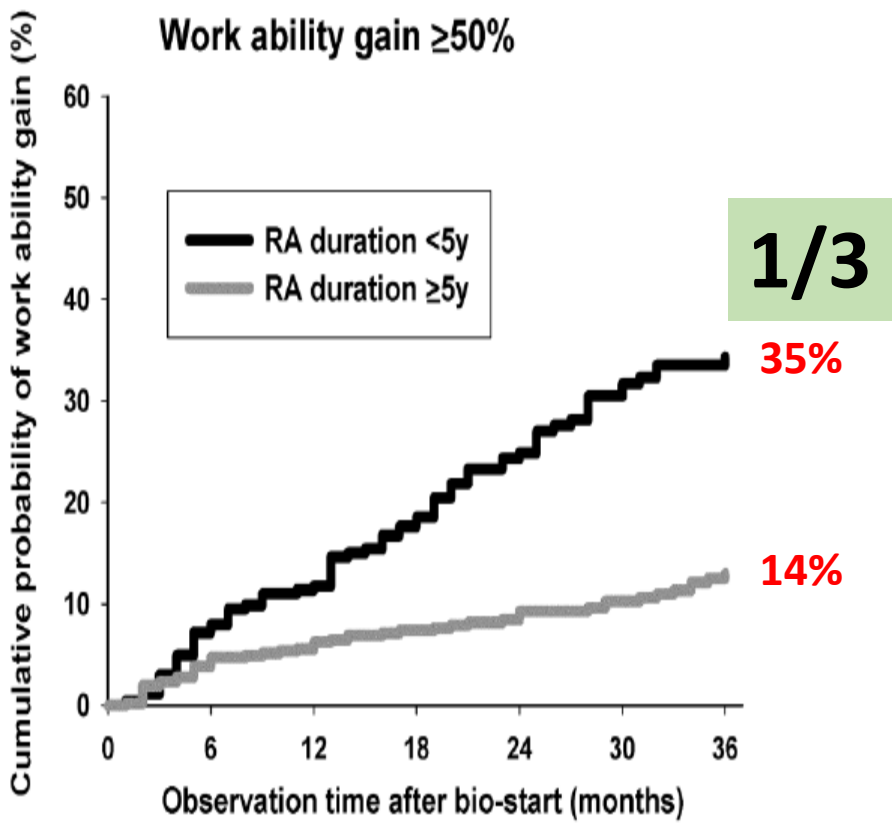
(mSASSS: ≥ 1 IU/year)

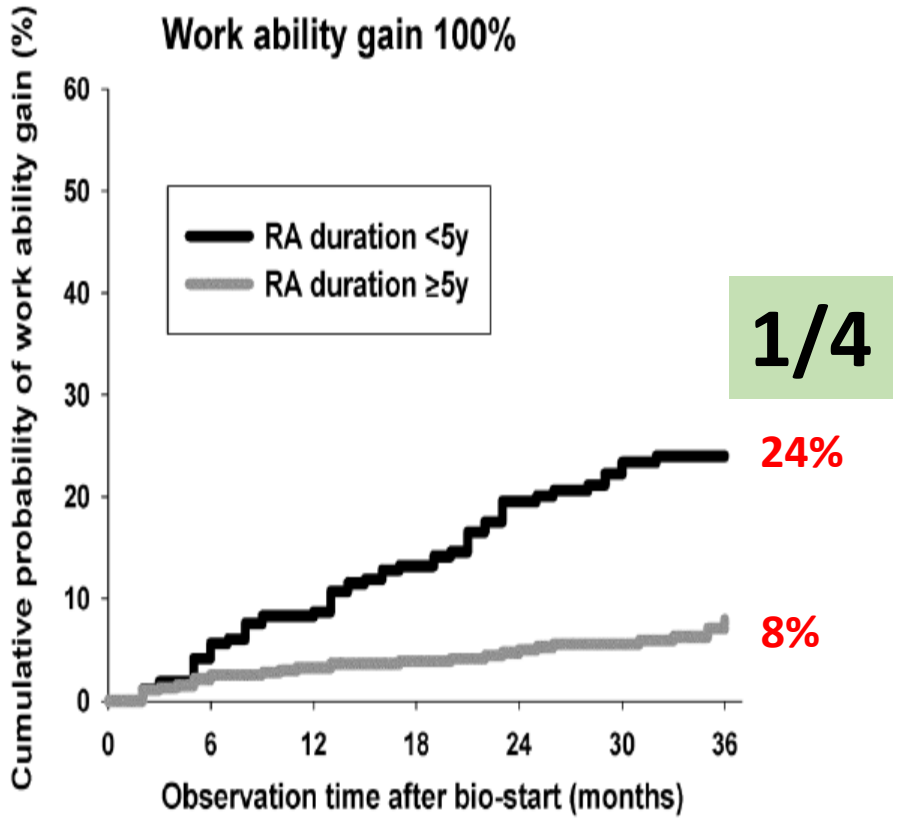
NSAIDs

Καμμιά επίδραση

Anti-TNFs - Αναπηρία

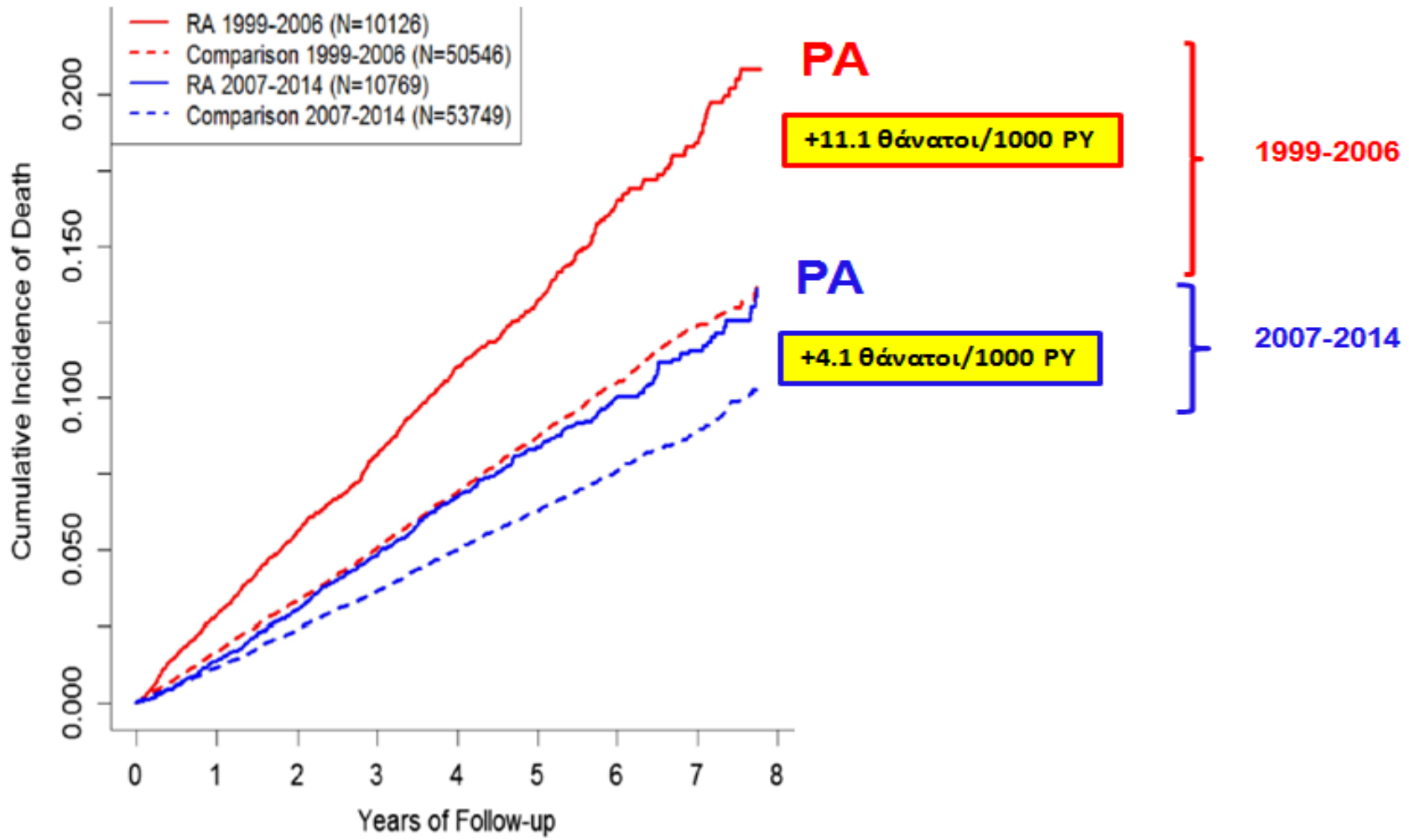
Ασθενείς με πλήρη αναπηρία που άρχισαν αγωγή με anti-TNFs





Olofsson T , et al. Ann Rheum Dis 2017

- **ΘΝΗΤΟΤΗΤΑ σχετιζόμενη με PA**



PA

+11.1 θάνατοι/1000 PY

1999-2006

PA

+4.1 θάνατοι/1000 PY

2007-2014

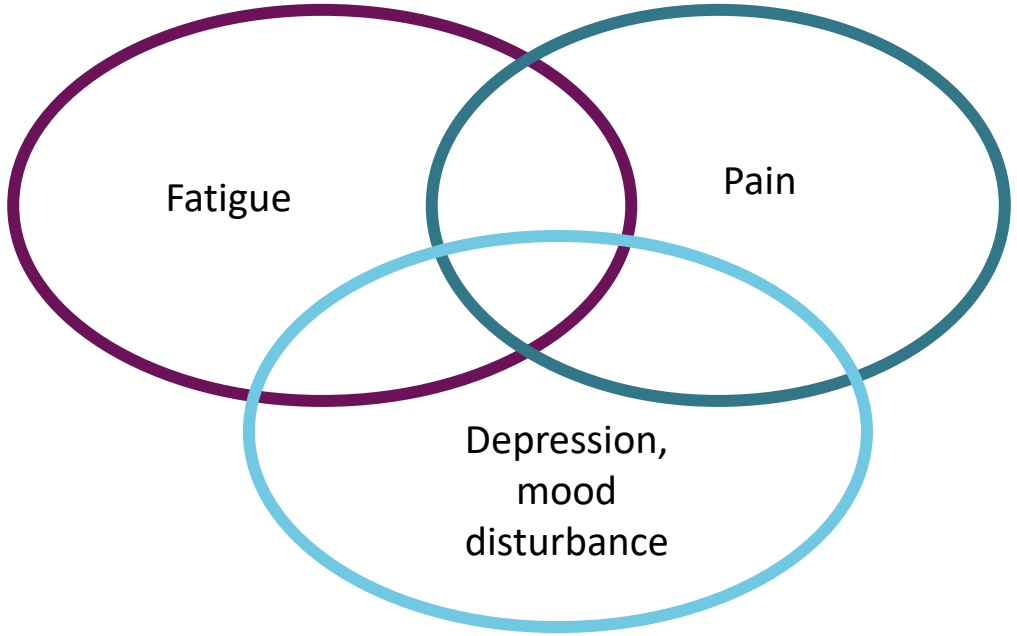
↓ ~ 50%

*Zhang Y et al, Ann Rheum Dis2017;*76:408–413.

Nature of unmet need is changing

- 38.8% of patients have severe fatigue[1]
- 61% of RA patients experience poor sleep[2]

Unmet needs are linked[3-5]



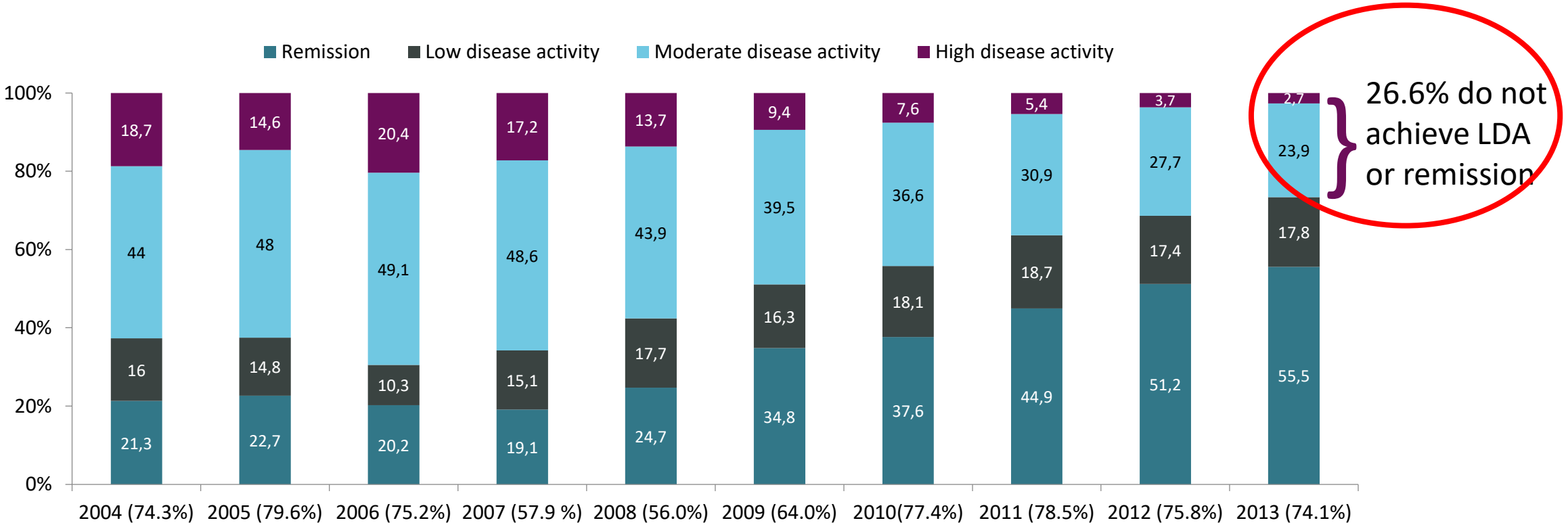
- Restrictions in social participation is associated with pain, fatigue, and psychological status[6]
- Fatigue impacts on work ability[7]

Clinical outcomes in RA have improved[8] but unmet needs remain, for example, pain, fatigue, and psychological issues

1. Druce KL, et al. *Rheumatology* 2015;54:964–971; 2. Løppenthin K, et al. *Clin Rheumatol* 2015;34(12):2029–2039; 3. Katz P, et al. *Arthritis Care Res* 2015, doi: 10.1002/acr.22577; 4. Matcham F, et al. *Clin Psychol Rev* 2015;39:16–29; 5. Louati K, et al. *Arth Res Ther* 2015;17:254; 6. Benka J, et al. *Disabil Rehabil* 2015;19:1–8; 7. Coi D, et al. *Int J Environ Res Public Health* 2015;12:13807–13822; 8. Kievet W, et al. *Rheumatology* 2013;52:1500–1508.

Not enough patients are achieving treatment goals

Percentage of patients with RA according to disease activity measured by DAS28 criteria[1]



On a daily basis clinicians see patients who are not achieving treatment goals despite advancement in current interventions[1]

DAS, disease activity score; LDA, low disease activity.

1. Haugeberg G, et al. *Arthritis Res Ther* 2015;17:219.

MEDITERRANEAN JOURNAL OF RHEUMATOLOGY | 29 1 2018

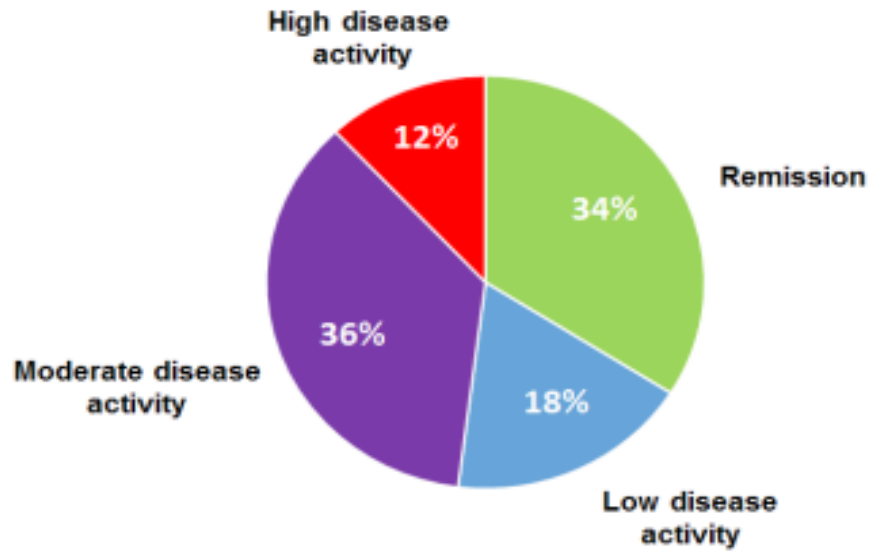
ORIGINAL PAPER

Multicenter Cross-sectional Study of Patients with Rheumatoid Arthritis in Greece: Results from a cohort of 2.491 patients

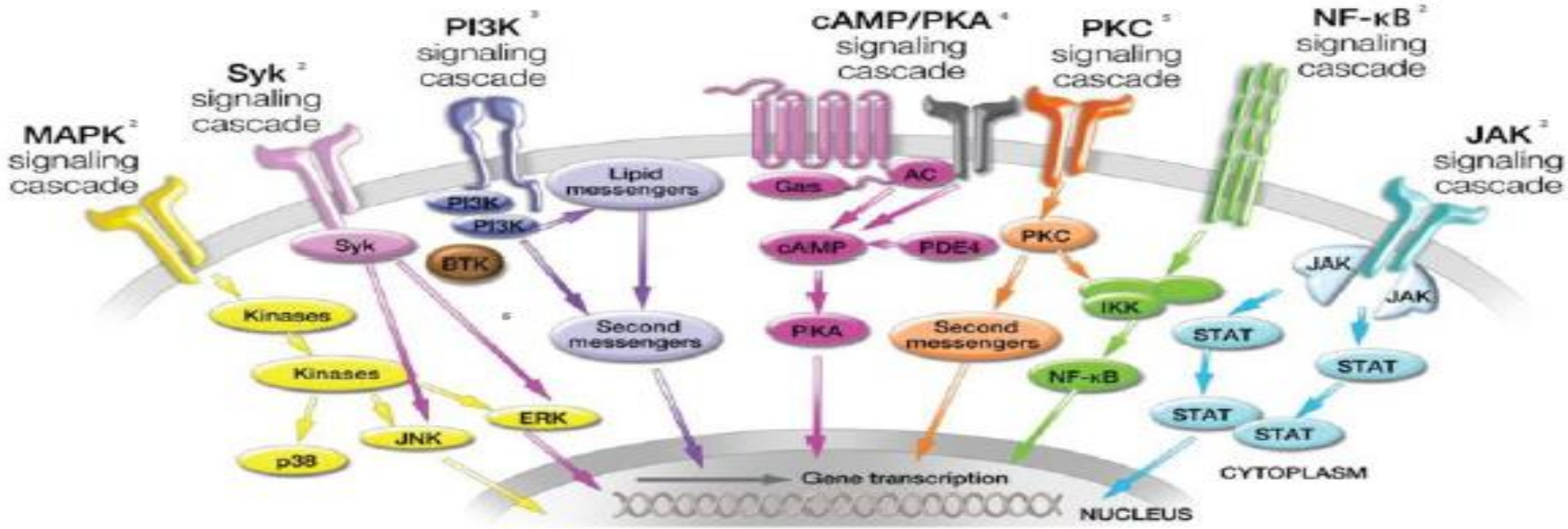
Konstantinos Thomas[1], Argiro Lazarini[1], Evripidis Kaltsonoudis[2], Alexandros Drosos[2], Ioannis Papalopoulos[3], Prodromos Sidiropoulos[3], Pelagia Katsimbri[1], Dimitrios Boumpas[1], Panagiota Tsatsani[4], Sousana Gazi[4], Kalliopi Fragkiadaki[1], Maria Tektonidou[1], Petros P. Sfikakis[1], Lina Pantazi[5], Kyriaki A. Boki[5], Eleftheria P. Grika[1], Panagiotis G. Vlachoyiannopoulos[1], Konstantina Karagianni[6], Lazaros I. Sakkas[6], Theodoros Dimitroulas[7], Alexandros Garyfallos[7], Dimitrios Kassimos[8], Gerasimos Evangelatos[9], Alexios Iliopoulos[9], Maria Areti[10], Constantinos Georganas[10], Konstantinos Melissaropoulos[11], Panagiotis Georgiou[11], Periklis Vounotrypidis[10], Konstantinos Ntelis[10], Clio P. Mavragani[1], Ilias Bournazos[10], Gikas Katsifis[12], Christos Mavrommatis[10], George D. Kitas[1,13], Dimitrios Vassilopoulos[1]

Table 2. Treatment characteristics.

Therapy	n	%
No therapy	94	**4%**
Corticosteroids only	74	**3%**
DMARD therapy	2323	**93%**
csDMARDs	2050	**82%**
bDMARDs	1036	**42%**
Corticosteroids	985	**40%**
Daily dose in mg, mean ± 1 S.D. (median)	**5.2 ± 3.5 (5)**	
NSAIDs	183	**7%**
Analgesics	536	**21%**

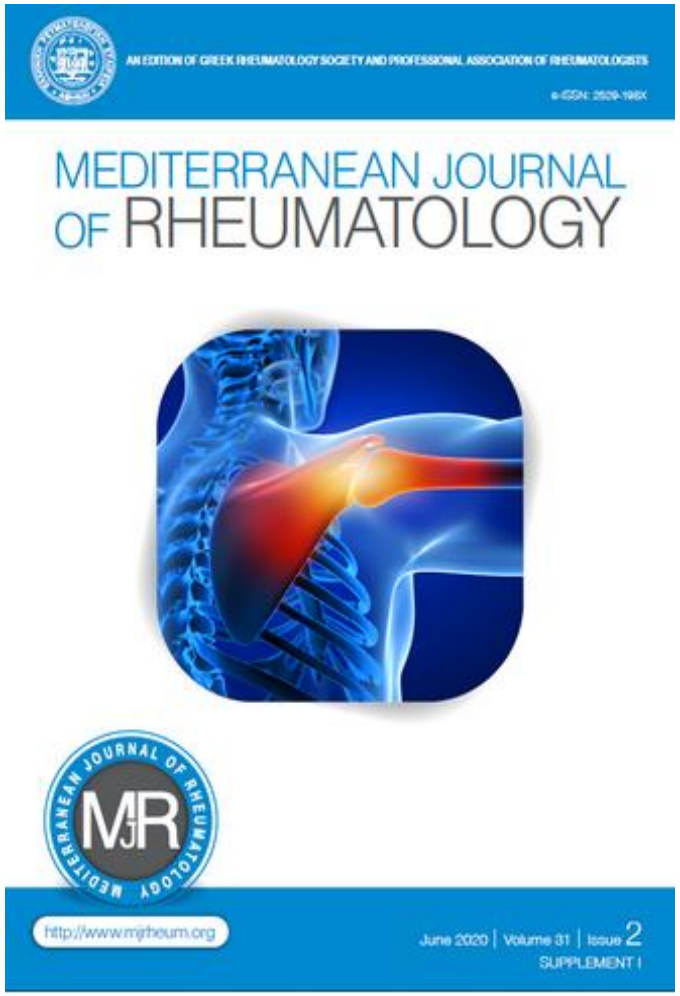


Cytokine signaling pathways



AC, adenylyl cyclase; BTK, Bruton's tyrosine kinase; cAMP, cydic adenosine monophosphate; ERK, extracellular signal-related kinases; IKK, inhibitor of kappa B kinase; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NFκB, nudear factor kappa B; PDE, phosphodiesterase; PI3K, phosphoinositide 3-kinase; PK, protein kinase; STAT, signal transducer and activator of transcription; Syk, spleen tyrosine kinase.

1. O'Sullivan L, et al. Molec Immunol. 2007;44:2497–2506;
2. Mavers M, et al. Curr Rheum Rep. 2009;11:378–85;
3. Rommel C, et al. Nat Rev Immunol. 2007;7:191–201; 4. Tasken K, et al. Physiol Rev. 2004;84:137–67;
5. Baier G, et al. Curr Opin Cell Biol. 2009;21:262–7; 6. Ruderman E, et al. Arthritis Res. Ther 2011;13:125.

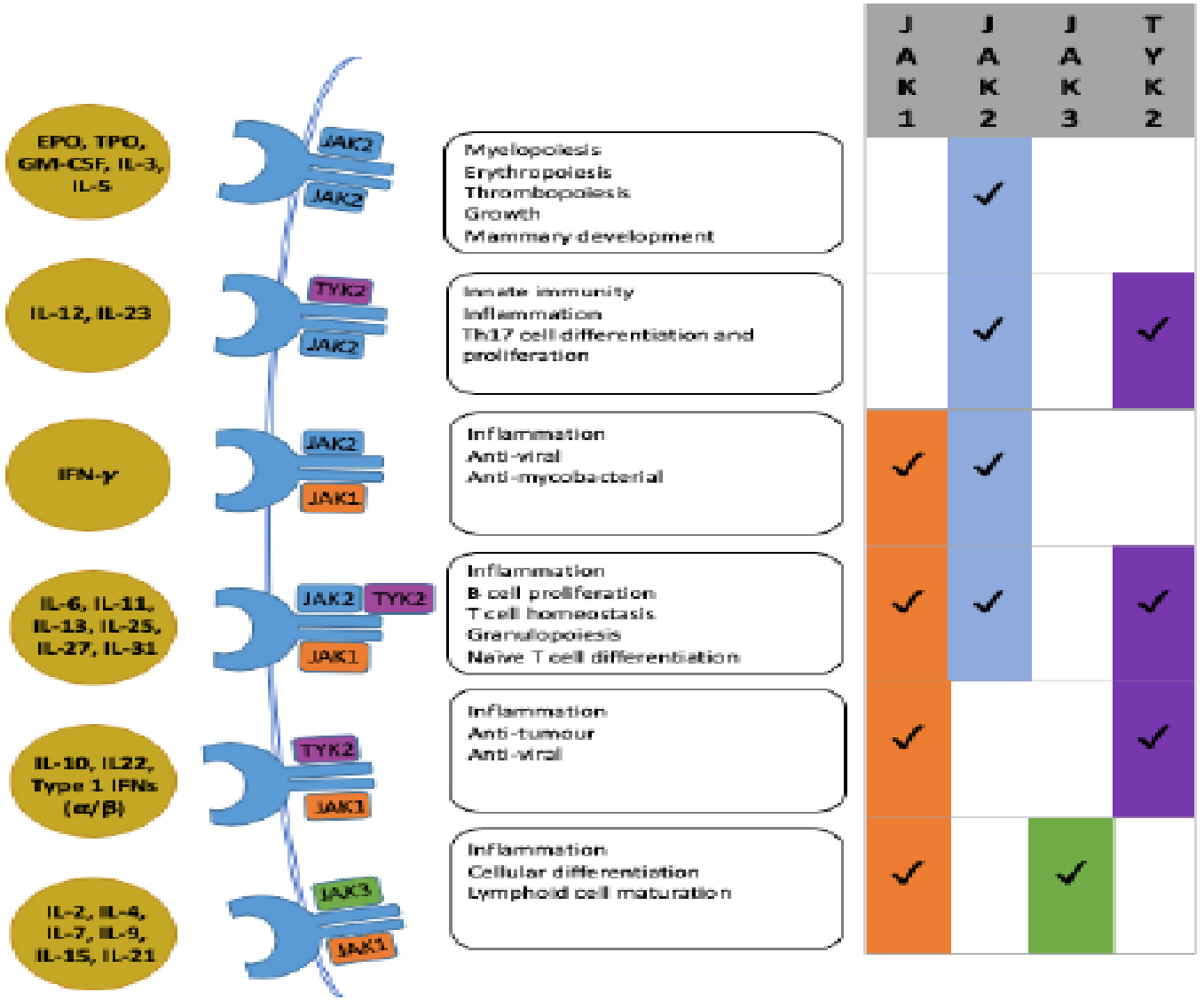


Basic Mechanisms of JAK Inhibition

Mediterr J Rheumatol 2020;31(Supp 1):100-4

Chung MA Lin, Faye AH Cooles, John D. Isaacs

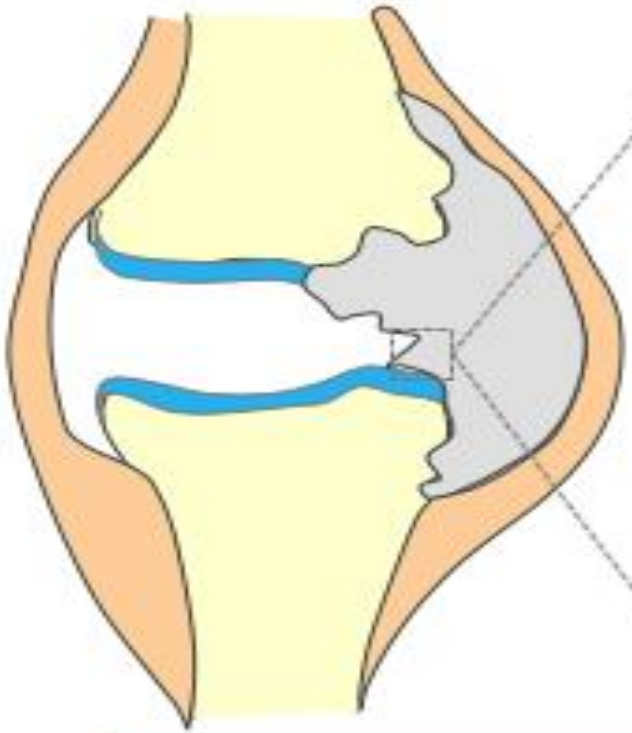
Translational and Clinical Research Institute, Newcastle University and Musculoskeletal Unit, Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, United Kingdom

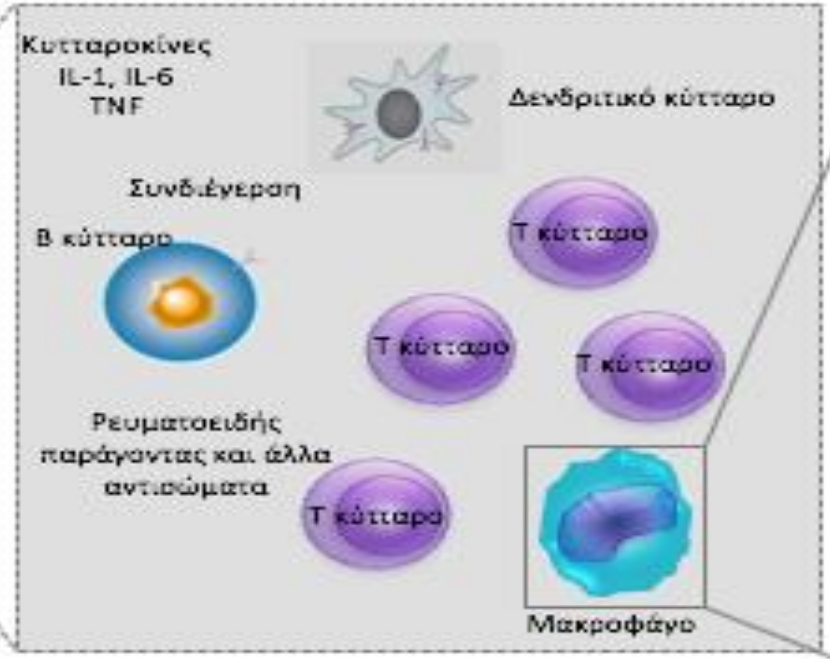


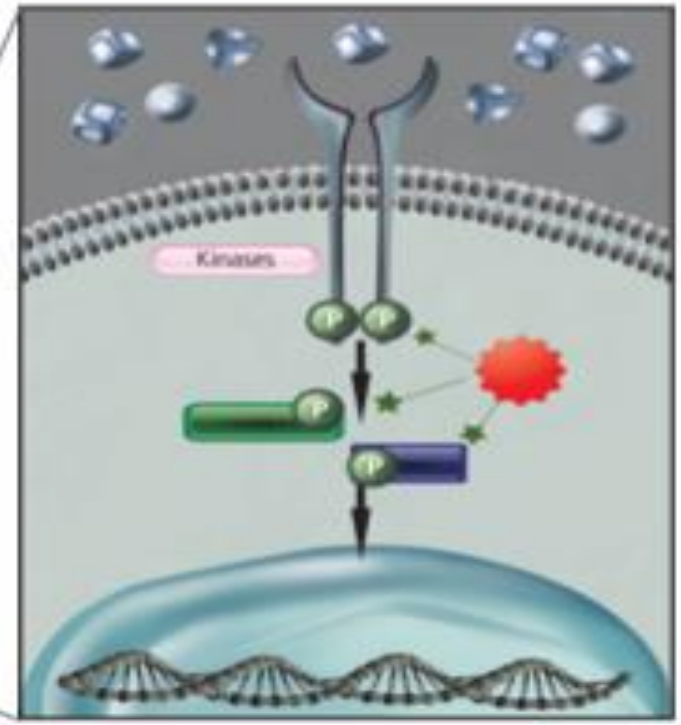
- ρύθμιση ανοσολογικής απάντησης
- αιμοποίηση
- σημαντικοί διαμεσολαβητές της φλεγμονής

Τα ενδοκυττάρια μονοπάτια μπορούν να στοχευθούν από μικρά μόρια

Ρευματοειδής αρθρίτιδα → Τ κύτταρο → Βιολογικοί παράγοντες που στοχεύουν κυτταροκίνες και την εξωκυττάρια σηματοδότηση[1] → Μικρά μόρια που στοχεύουν ενδοκυττάριες οδούς σηματοδότησης[2]

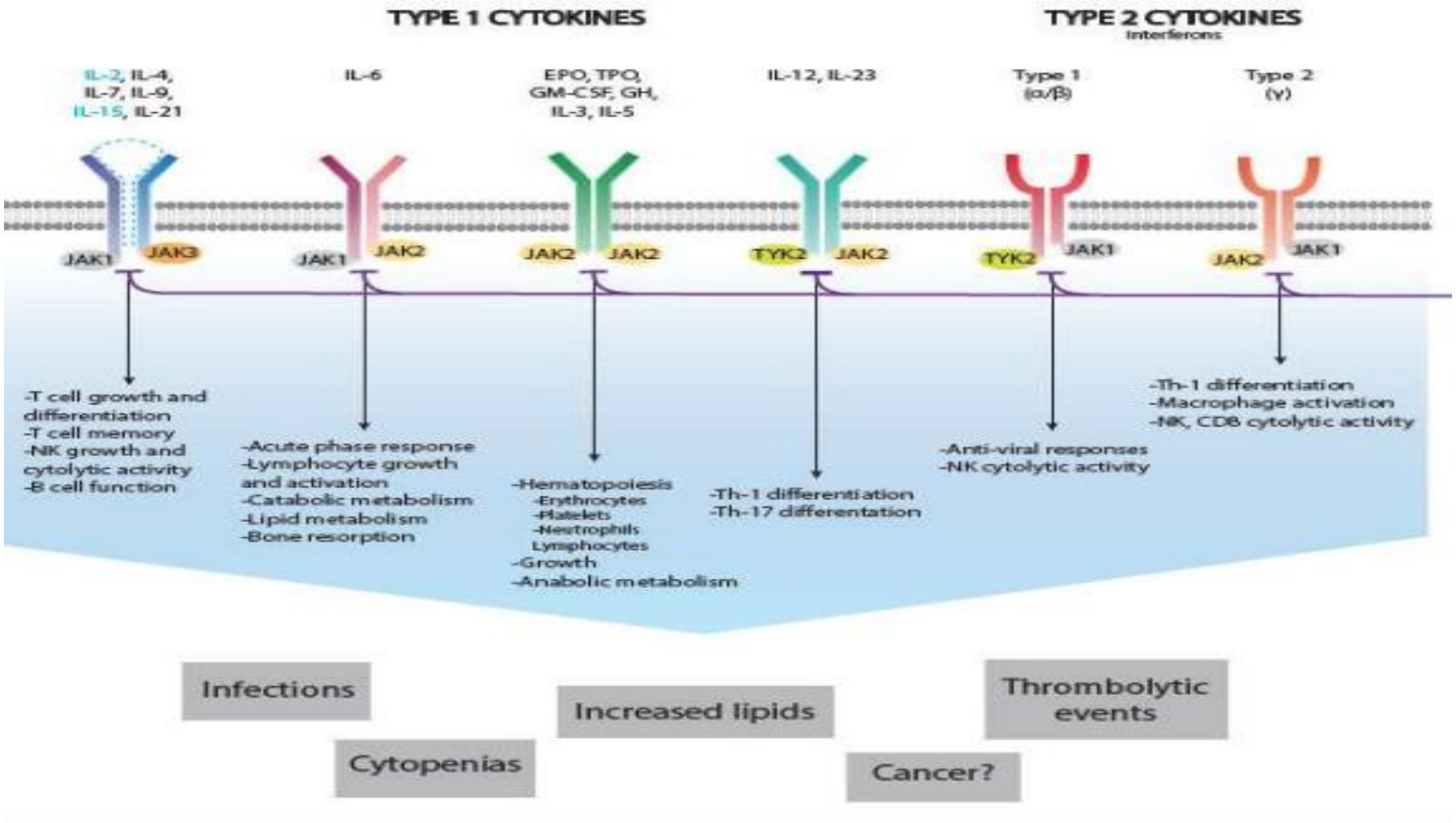






Ο καταρράκτης της φλεγμονής συνεχίζει μέσα στο κύτταρο

ΠΡΩΤΗΣ ΓΕΝΙΑΣ ΑΝΑΣΤΟΛΕΙΣ JAK INHIBITORS



Tofacitinib
JAK1/2/3

Baricitinib
JAK 1/2

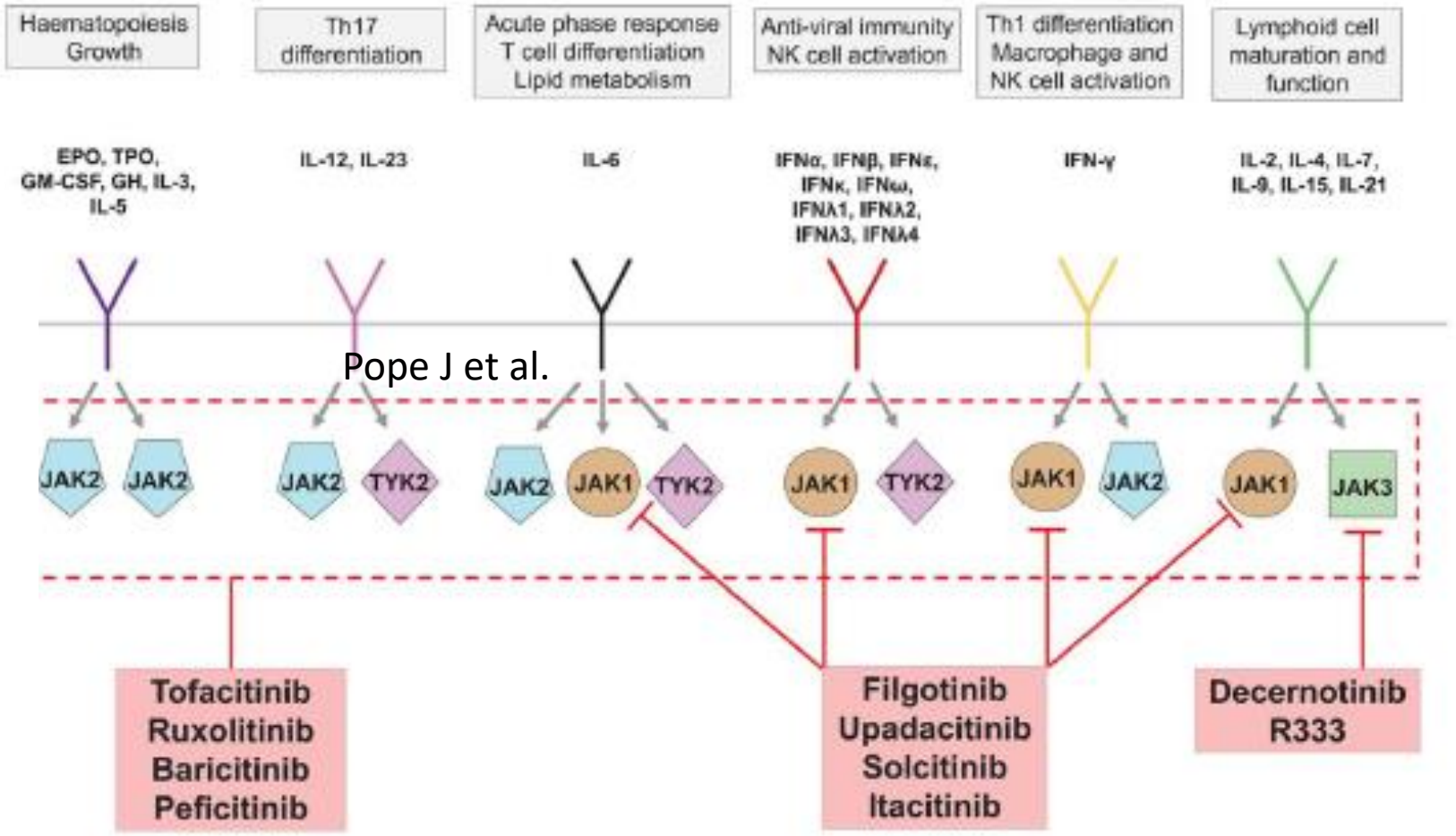
Gadina M et al Rheumatology 2019

Next generation jakinibs

- Εκλεκτική στόχευση

  Jak1

- Θεωρητικά η εκλεκτική στόχευση θα βελτίωνε την ασφάλεια και θα περιόριζε το εύρος ενδείξεων
- Στην πράξη όμως δεν φάνηκε σαφές όφελος όσον αφορά την ασφάλεια
- Μάλλον δεν περιορίζεται ιδιαίτερα το φάσμα ενδείξεων



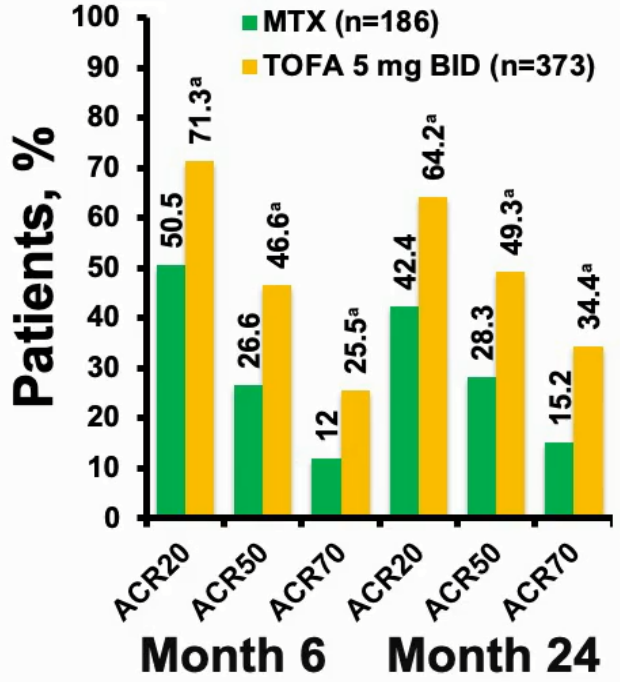
Pope J et al.

Gadina et al. J Leuk Biol 2018

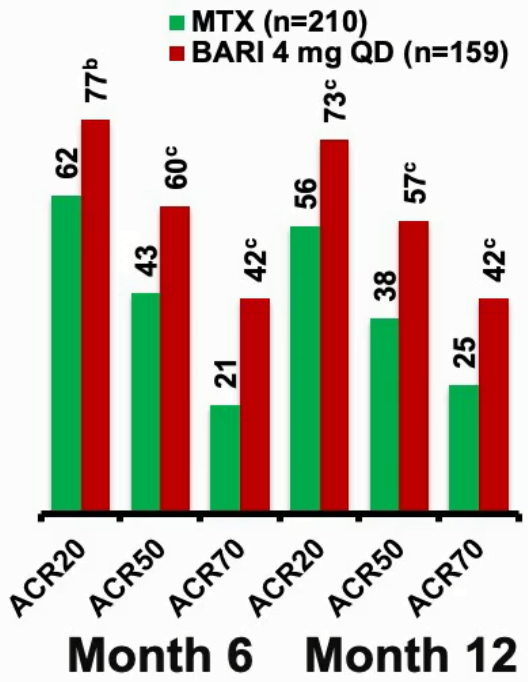
JAK Inhibit… ate Superior Clinica… t vs MTX S… eria

RA popula…	…R 20/50/70
DMARD naïve patients	70/50/30
DMARD/ MTX-IR pa…	60/40/20
Anti-TNF-IR patie…	…0/25/10

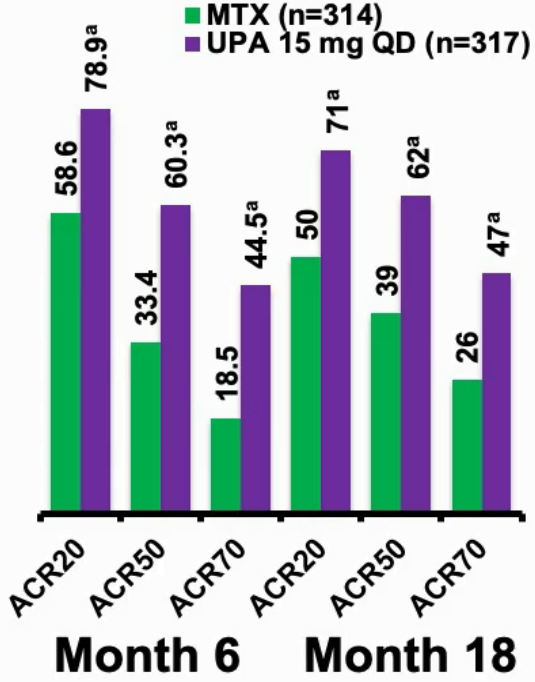
ORAL START[1]



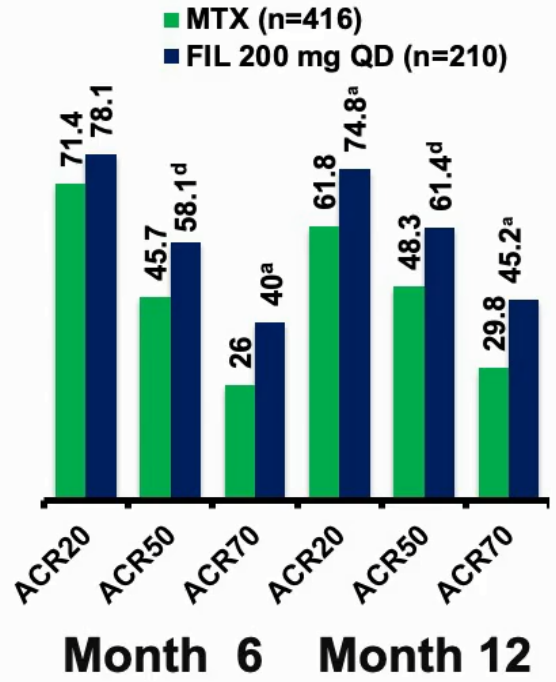
RA BEGIN



SELECT-EARLY[3,4]



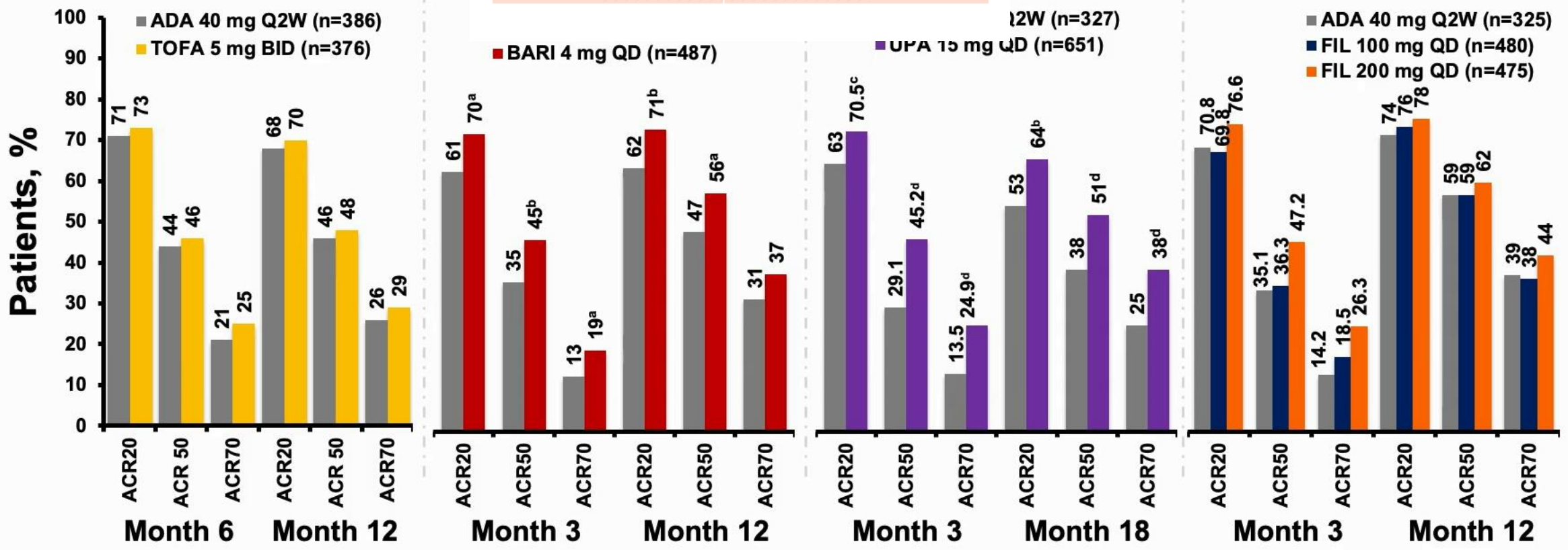
FINCH 3[5,6]



[a]*P*<0.001 vs MTX; [b]*P*≤0.01 vs MTX; [c]*P*≤0.05 vs MTX; [d]*P*<0.01 vs MTX; ACR20, American College Rheumatology 20% improvement criteria; ACR50, ACR 50% improvement criteria; ACR70, ACR 70% improvement criteria; BARI, baricitinib; FIL, filgotinib; MTX, methotrexate; TOFA, tofacitinib; UPA, upadacitinib. 1. Lee EB, et al. *N Engl J Med*. 2014;370(25):2377-2386; 2. Fleischmann R, et al. *Arthritis Rheumatol*. 2017;69(3):506-517; 3. van Vollenhoven R, et al. *Arthritis Rheumatol*. 2018;70(suppl 10). Abstract 891; 4. van Vollenhoven R, et al. *Ann Rheum Dis*. 2020;79(suppl 1). Abstract THU0217; 5. Westhovens R, et al. *Arthritis Rheumatol*. 2019;71(suppl 10). Abstract 927; 6. Westhovens R, et al. *Ann Rheum Dis*. 2020;79(suppl 1). Abstract SAT0158.

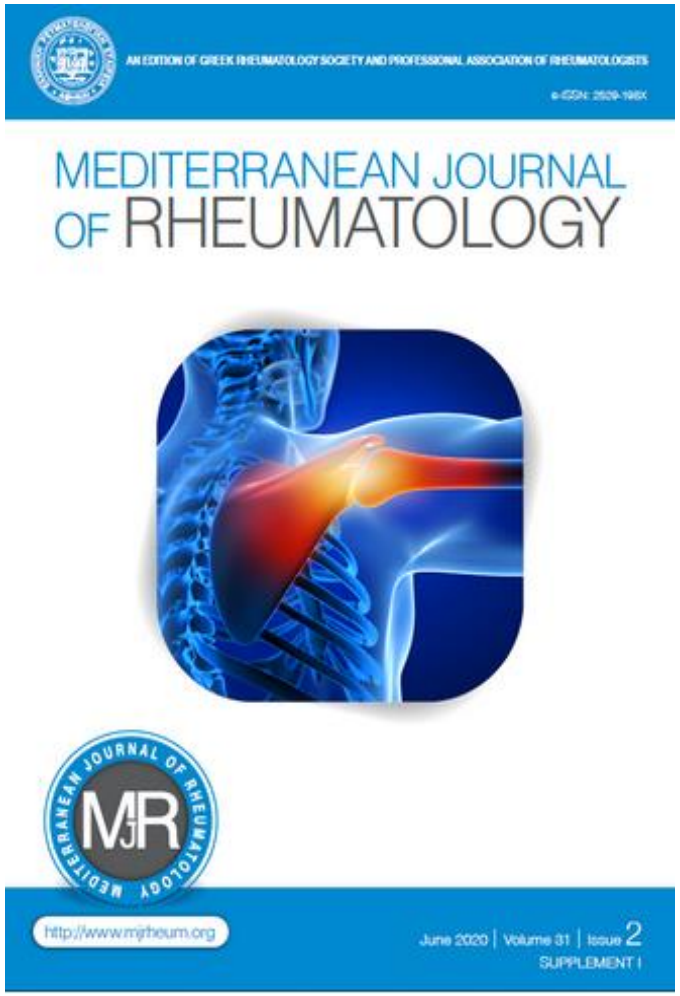
JAKi+MTX in MTX-IR RA

RA popula	R 20/50/70
DMARD naïve patients	70/50/30
DMARD/ MTX-IR pa	60/40/20
Anti-TNF-IR patien	30/25/10



[a]$P \leq 0.05$ vs ADA; [b]$P \leq 0.01$; [c]$P < 0.05$ vs ADA; [d]$P \leq 0.001$ vs ADA. ADA, adalimumab; JAKi, JAK inhibitor.

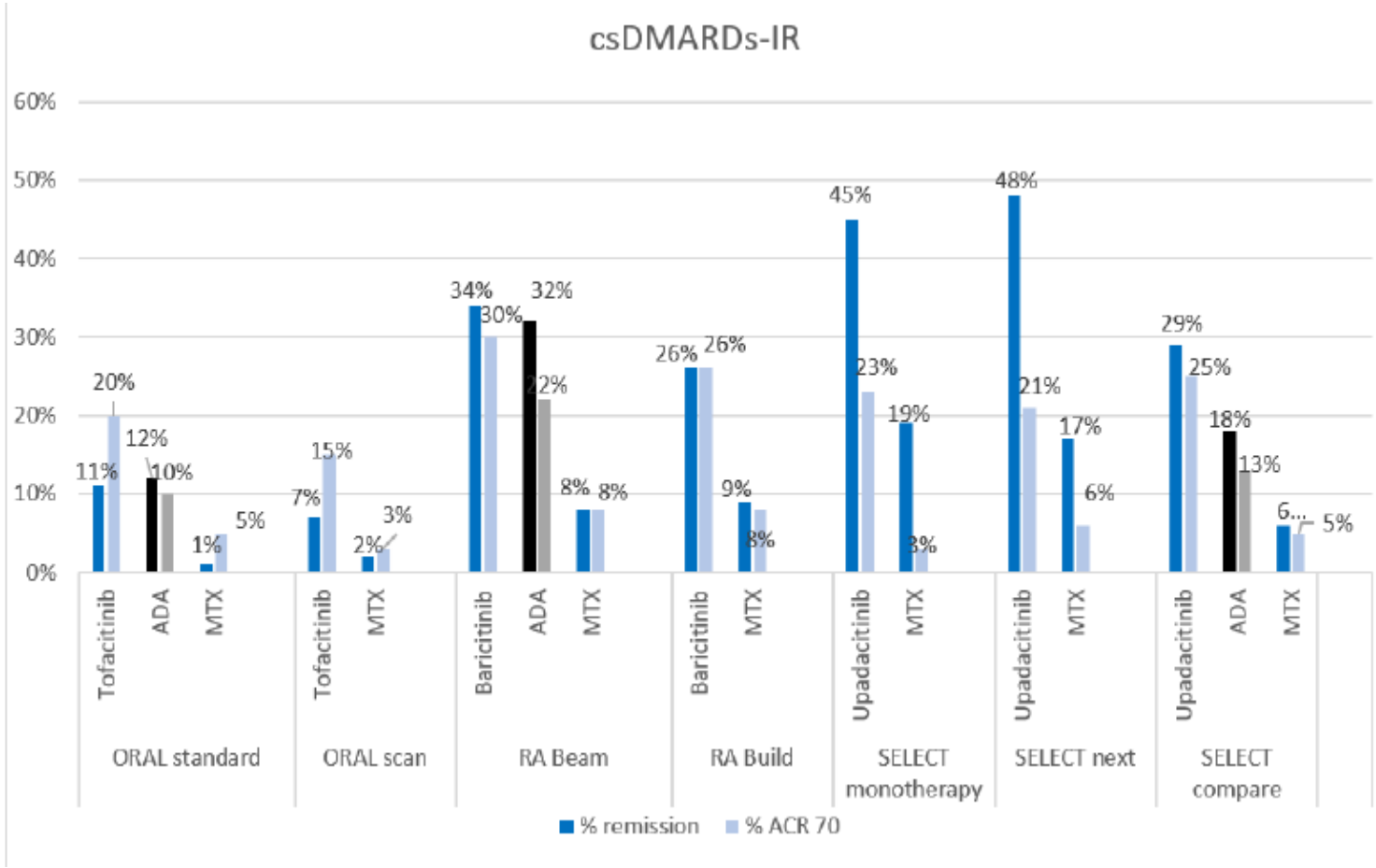
1. Fleischmann R, et al. *Lancet*. 2017;390(10093):457-468; 2. Taylor PC, et al. *N Engl J Med*. 2017;376(7):652-662; 3. Fleischmann R, et al. *Arthritis Rheumatol*. 2018;70(suppl 10). Abstract 890; 4. Fleischmann R, et al. *Ann Rheum Dis*. 2020;79(suppl 1). Abstract THU0201; 5. Combe B, et al. *Arthritis Rheumatol*. 2019;71(suppl 10). Abstract 506; 6. Combe B, et al. *Ann Rheum Dis*. 2020;79(suppl 1). Abstract THU0198.



Beyond Methotrexate and Biologics in RA – Efficacy of JAK Inhibitors and their Place in the Current Treatment Armamentarium

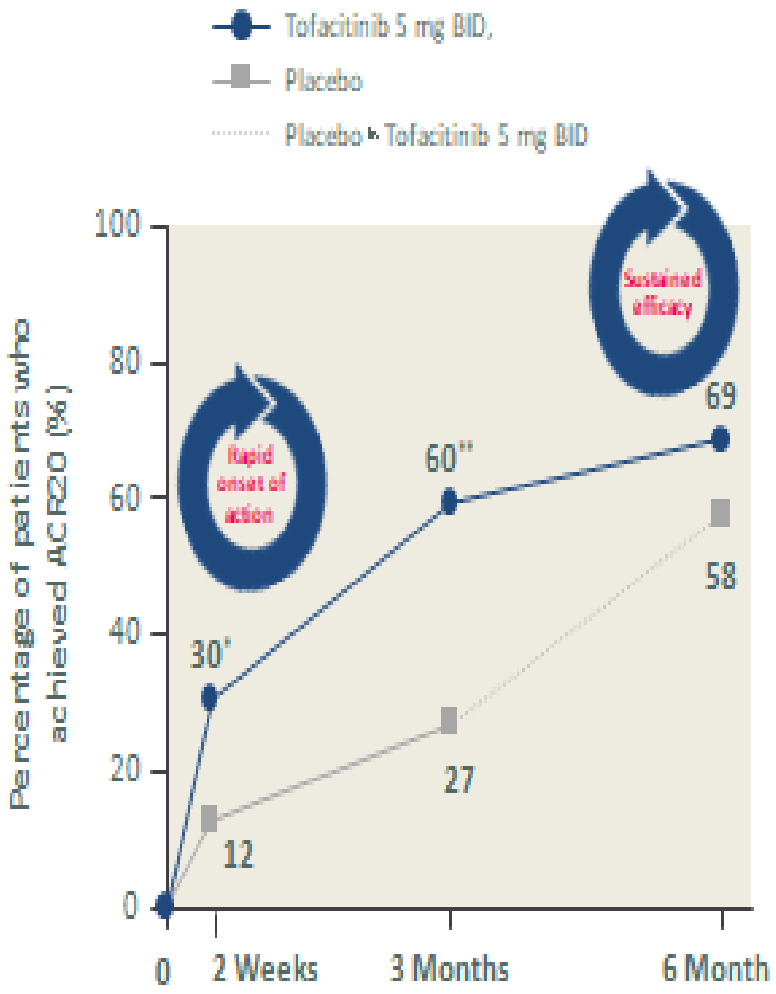
Katerina Chatzidionysiou

Department of Medicine, Solna, Karolinska Institutet, Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden

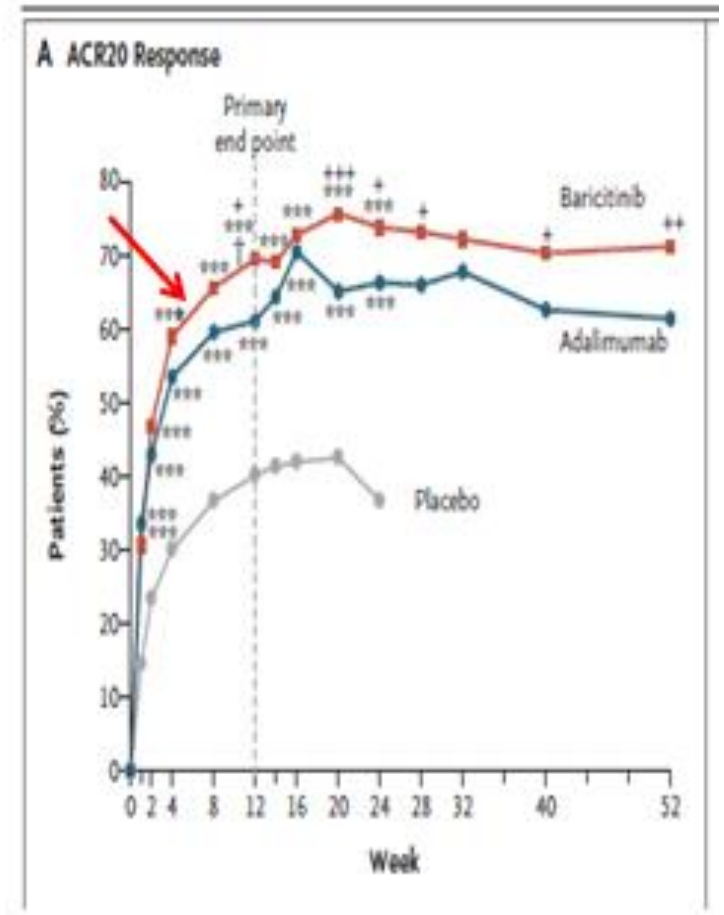


Mediterr J Rheumatol 2020;31(Supp 1):120-8

ORAL Solo in MTX-IR patients



RA BEAM in MTX-IR patients



AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

MEETING ABSTRACTS

Tofacitinib: Predictor of LDA Response
AC&R 2019; 71:71

Post hoc analysis of 2 Phase 3 studies of Tofa in biologic naïve pts.

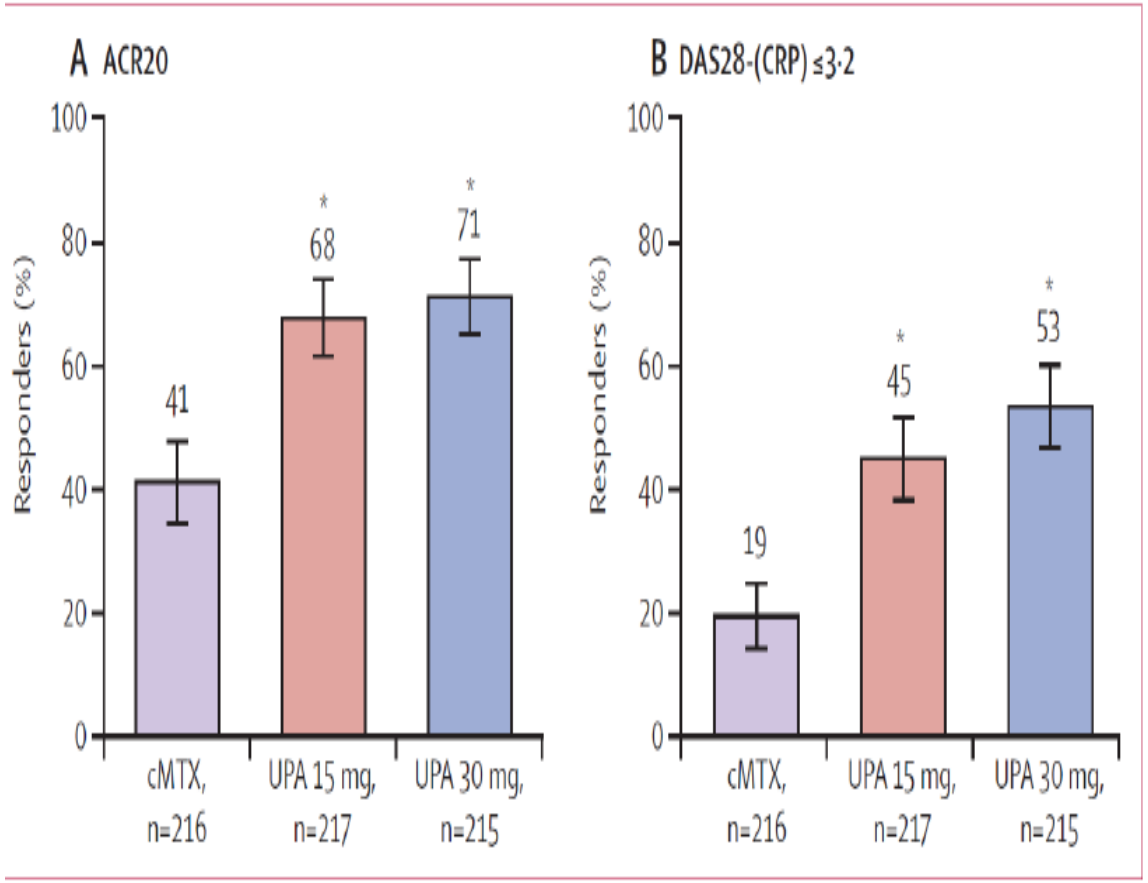
Relationship between early disease response and achievement of LDA and remission at wk 24 was studied

Lack of response by month 1 or 3 months predicted low probability of achieving LDA at month 6 in these biologic naïve pts groups

1. Fleischmann et al. *N Engl J Med*. 2012;367(6):495–507;
2. Taylor P et al *N Engl J Med*. 2017;372: 652-72

Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inadequate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study

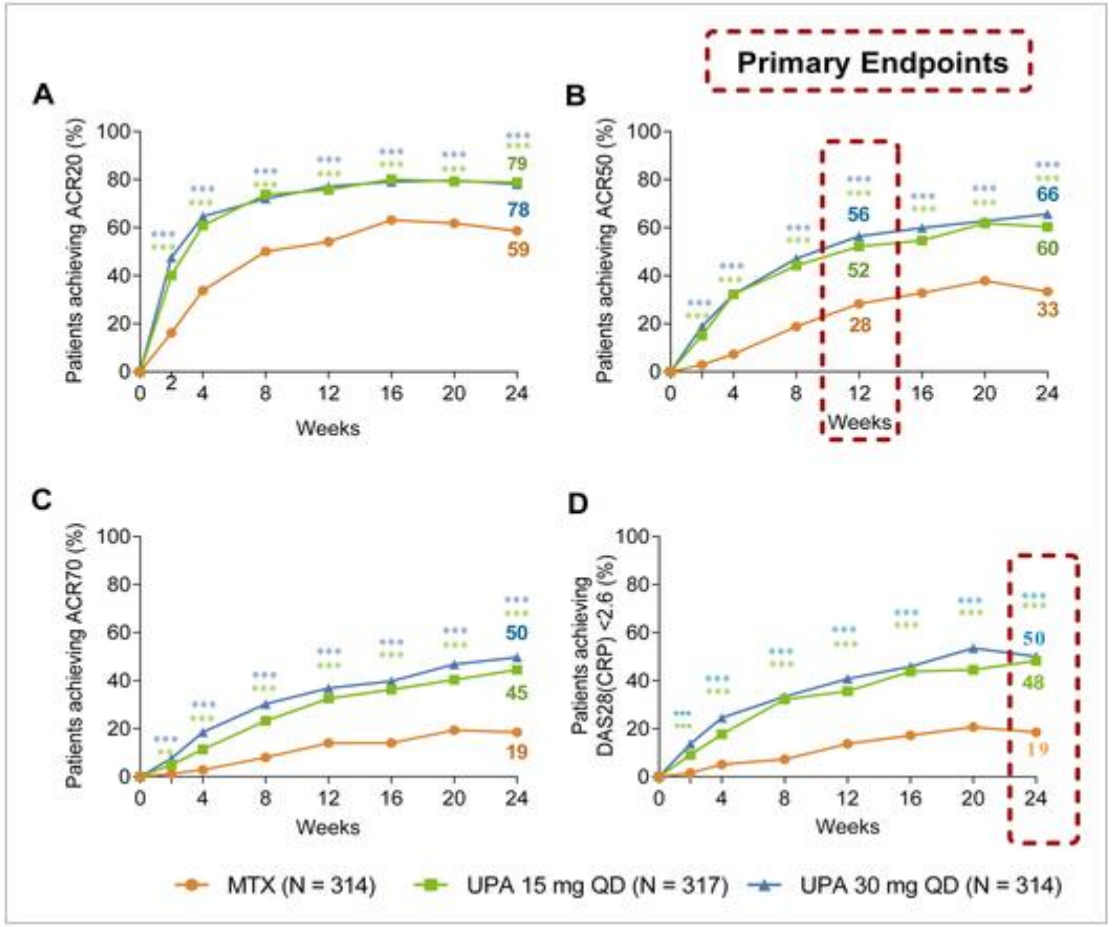
Josef S Smolen, Aileen L Pangan, Paul Emery, William Rigby, Yoshiya Tanaka, Juan Ignacio Vargas, Ying Zhang, Nemanja Damjanov, Alan Friedman, Ahmed A Othman, Heidi S Camp, Stanley Cohen



Lancet. 2019 Jun 8;393(10188):2303-2311

Efficacy and Safety of Upadacitinib Monotherapy in Methotrexate-Naive Patients With Moderately-to-Severely Active Rheumatoid Arthritis (SELECT-EARLY): A Multicenter, Multi-Country, Randomized, Double-Blind, Active Comparator–Controlled Trial

Ronald van Vollenhoven, Tsutomu Takeuchi, Aileen L. Pangan, Alan Friedman, Mohamed-Eslam F. Mohamed, Su Chen, Maureen Rischmueller, Ricardo Blanco, Ricardo M. Xavier, Vibeke Strand



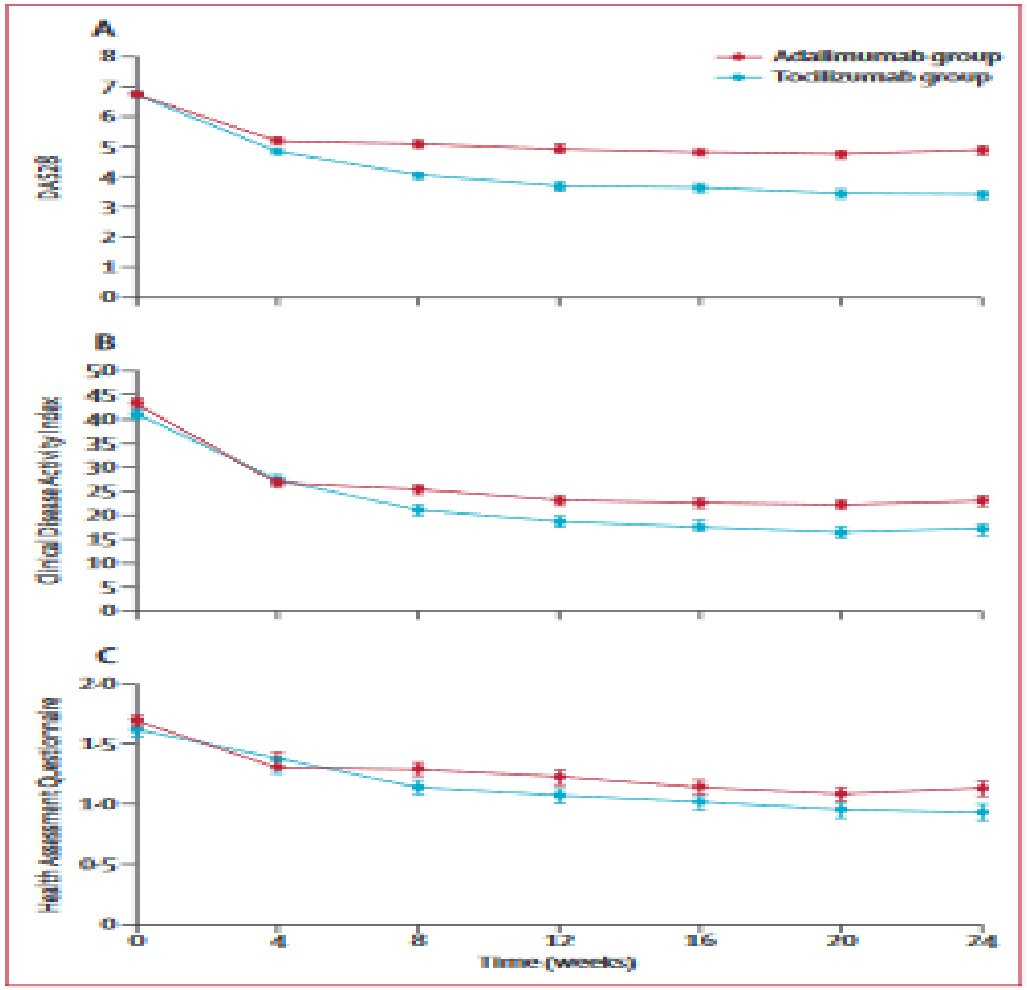
Arthritis Rheumatol 2020 Jul 8 (Ahead of print)

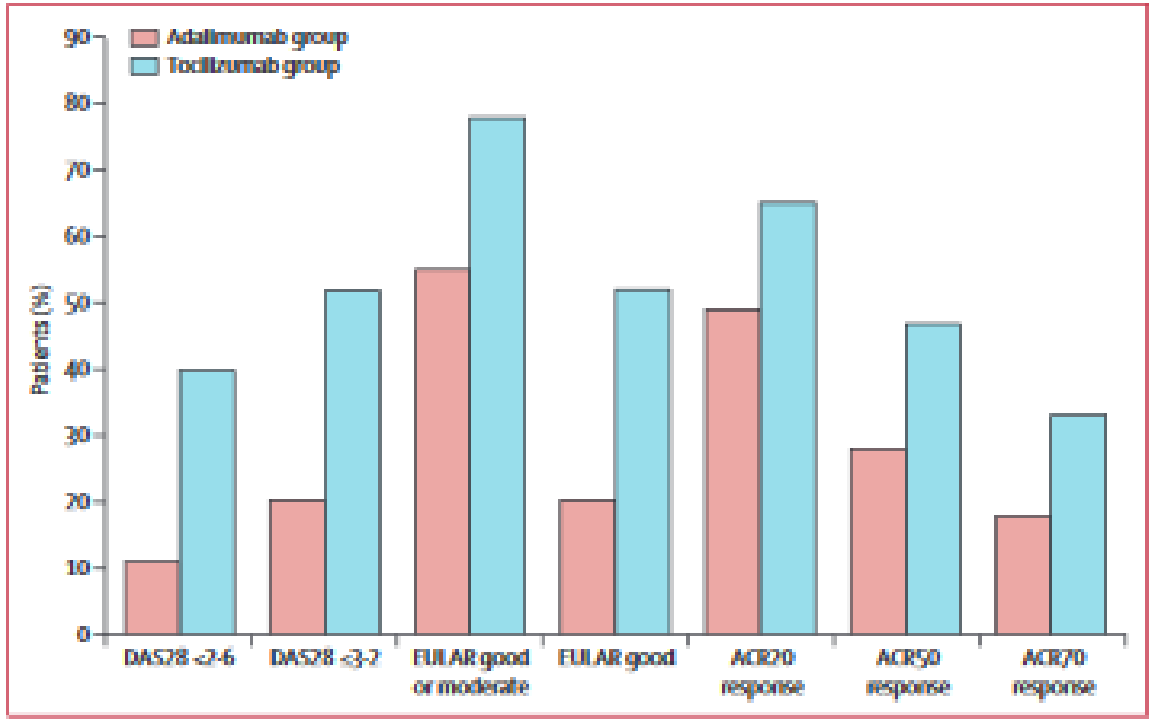
THE LANCET
FULL-TEXT ARTICLE

Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial

2013 May 4;381(9877):1541-50.

Cem Gabay, Paul Emery, Ronald van Vollenhoven, Ara Dikranian, Rieke Alten, Karel Pavelka, Micki Klearman, David Musselman, Sunil Agarwal, Jennifer Green, Arthur Kavanaugh*, on behalf of the ADACTA Study Investigators*





AN EDITION OF GREEK RHEUMATOLOGY SOCIETY AND PROFESSIONAL ASSOCIATION OF RHEUMATOLOGISTS
e-ISSN: 2529-198X

MEDITERRANEAN JOURNAL OF RHEUMATOLOGY

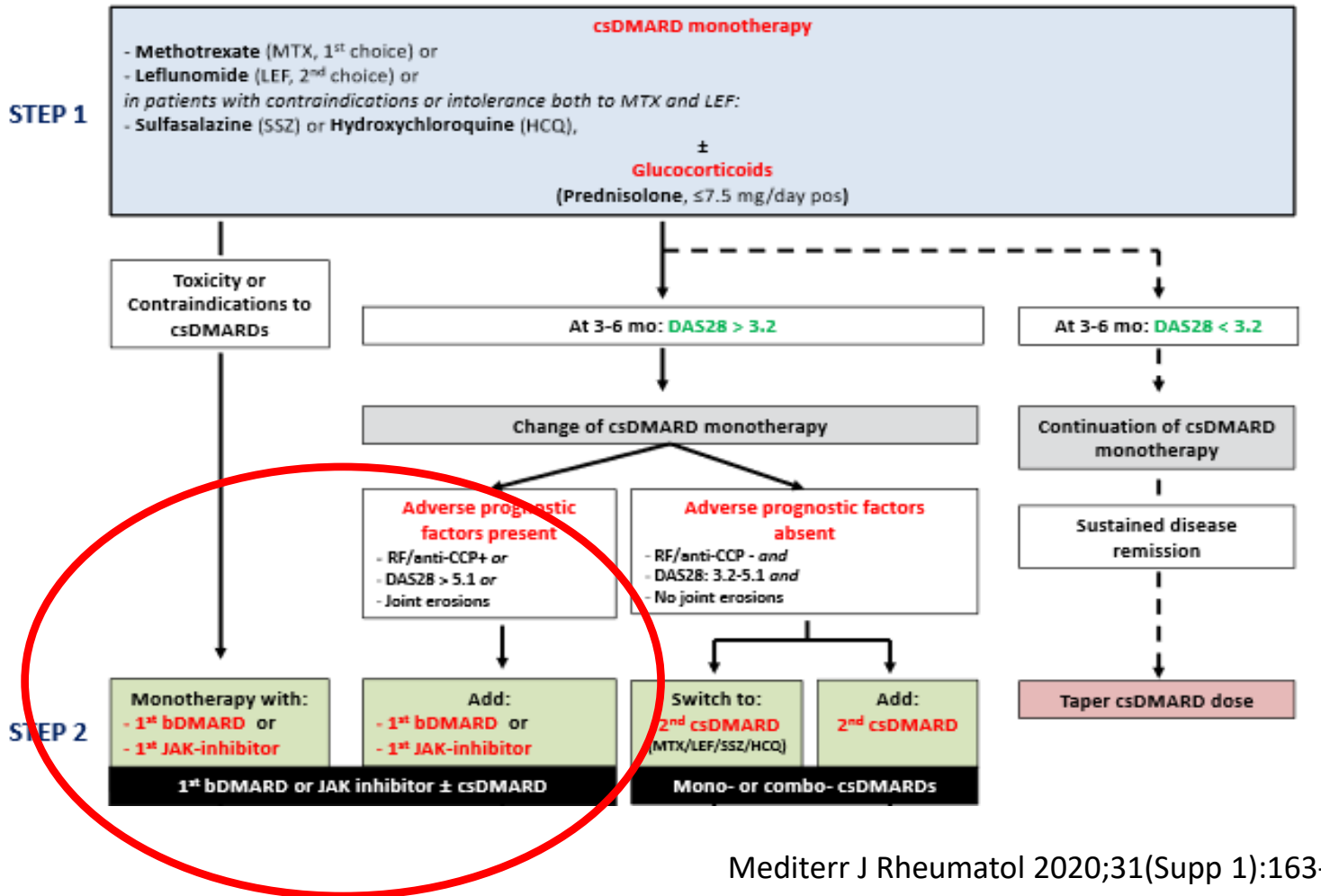
http://www.mjrheum.org

June 2020 | Volume 31 | Issue 2
SUPPLEMENT I

POSITION PAPER

Updated Greek Rheumatology Society Guidelines for the Management of Rheumatoid Arthritis

Dimitrios Vassilopoulos[1], Spiros Aslanidis[2], Dimitrios Boumpas[3], George Kitas[4], Spyridon N. Nikas[5], Dimos Patrikos[6], Petros P. Sfikakis[7], Prodromos Sidiropoulos[8]



Mediterr J Rheumatol 2020;31(Supp 1):163-71

Baricitinib in Patients with Ref
Rheumatoid Arthritis

Mark C. Genovese, M.D., Joel Kremer, M.D., Omid Zar
Charles Ludivico, M.D., Marek Krogulec, M.D., Li Xi
Scott D. Beattie, Ph.D., Alisa E. Koch, M.D., Tracy E. Ca
Terence P. Rooney, M.D., William L. Macias, M.D.,
Stephanie de Bono, M.D., Ph.D., Douglas E. Schlichti
and Josef S. Smolen, M.D.

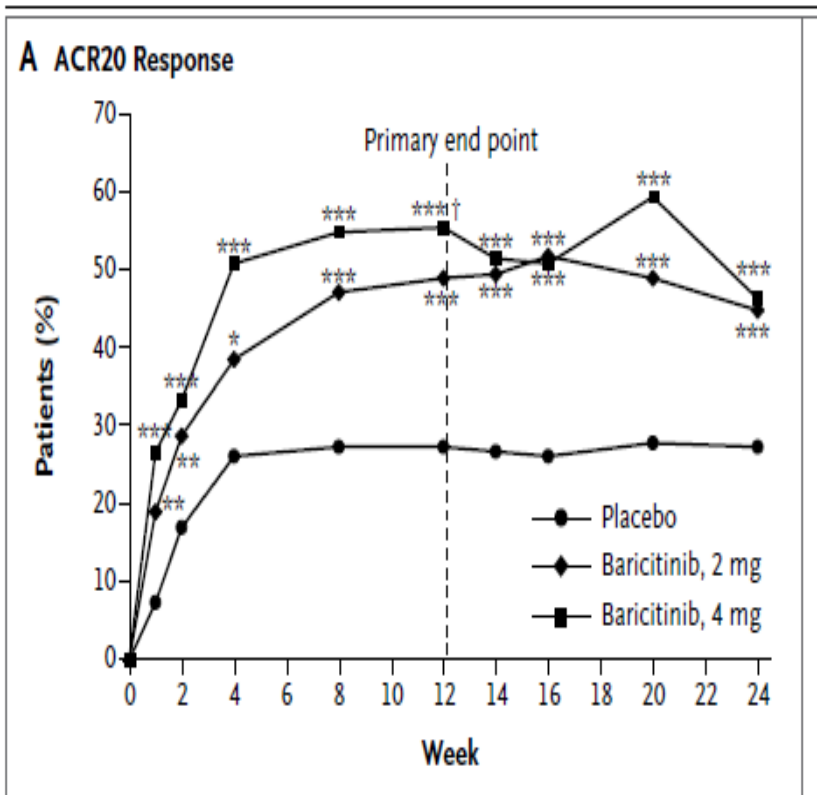
N Engl J Med 2016;374:1243-52.

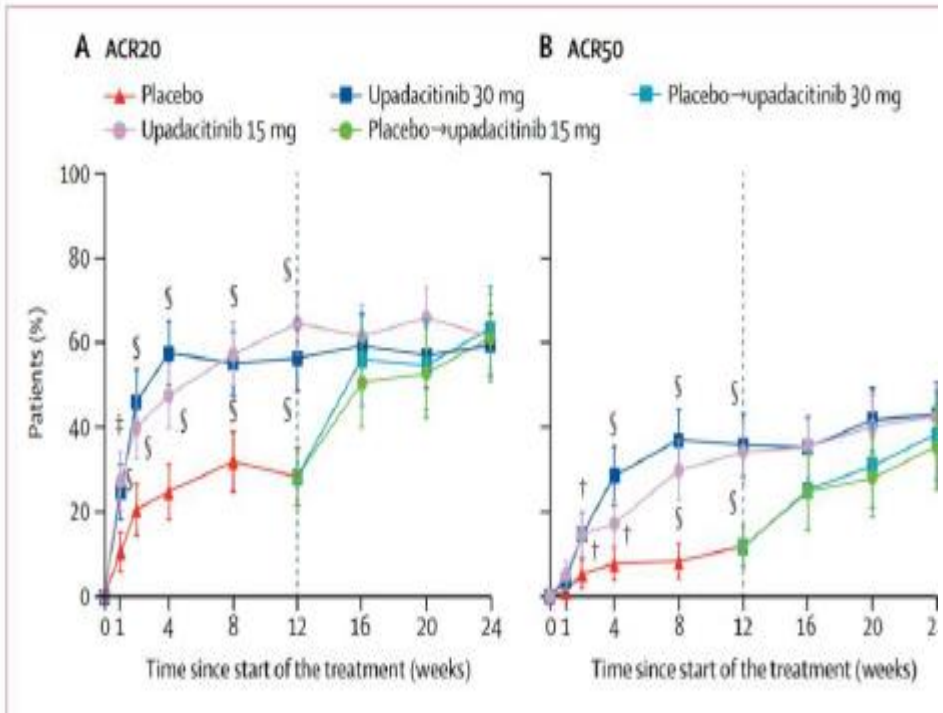
RA populatio	AC 20/50/70
DMARD naïve patient	0/50/30
DMARD/ MTX-IR patients	60/40/20
Anti-TNF-IR patient	/25/10

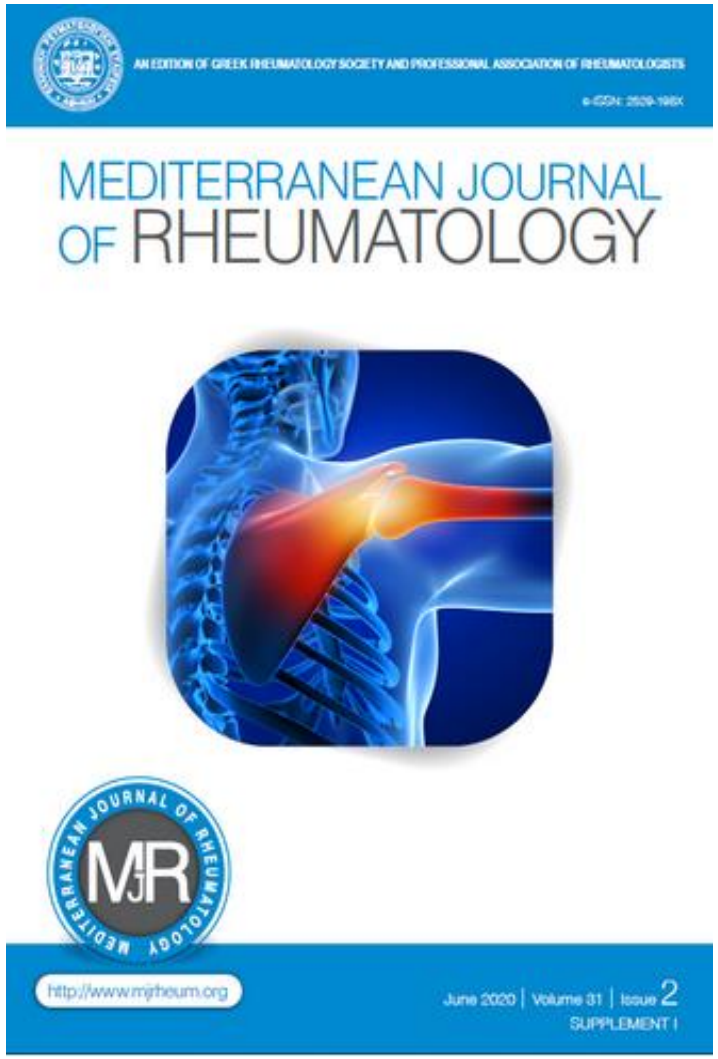
ib in patients with active rheumatoid arthritis refractory to biologic drugs (**SELECT-BEYOND**): a double-blind, randomised controlled

ombe B, Hall S, Rubbert-Roth A, Zhang Y, Zhou Y, Mohamed MF,

-2524. doi: 10.1016/S0140-6736(18)31116-4. Epub 2018 Jun 18.







Pain in Rheumatoid Arthritis: Could JAK Inhibition be the Answer?

Puja Mehta[1], Peter C. Taylor[2]

[1]Department of Rheumatology, University College London Hospital (UCLH), London, United Kingdom, [2]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom

- ✓Difficulties in measuring/assessing pain in RA
- ✓DAS 28 is an indicator of inflammation driven pain
- ✓Residual/remaining pain despite remission
- ✓Central sensitization
- ✓Management of pain remains an unmet need

Mediterr J Rheumatol 2020;31(Supp 1):112-9

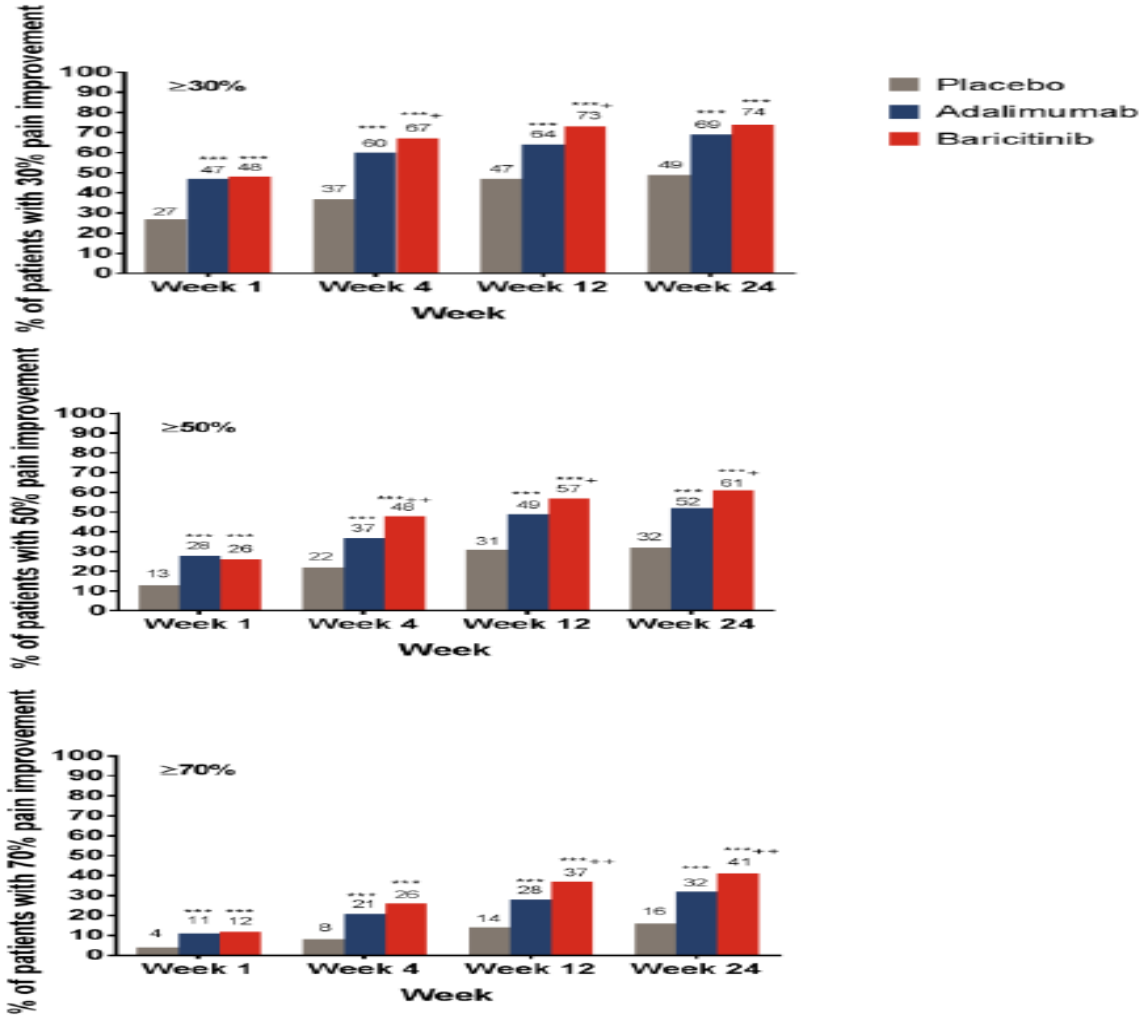
Article

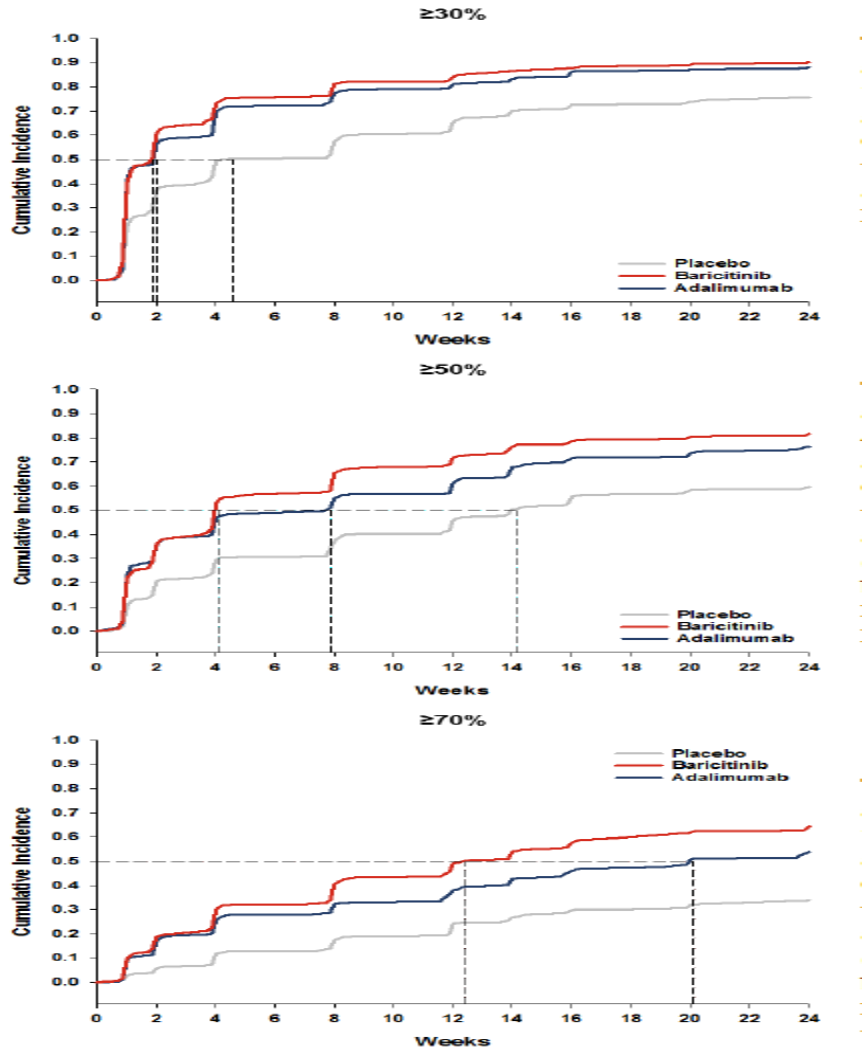
Achieving Pain Control in Rheumatoid Arthritis with Baricitinib or Adalimumab Plus Methotrexate: Results from the RA-BEAM Trial

Peter C. Taylor [1,*], Yvonne C. Lee [2], Roy Fleischmann [3], Tsutomu Takeuchi [4], Elizabeth L. Perkins [5], Bruno Fautrel [6], Baojin Zhu [7], Amanda K. Quebe [7], Carol L. Gaich [7], Xiang Zhang [7], Christina L. Dickson [7], Douglas E. Schlichting [7], Himanshu Patel [7], Frederick Durand [7] and Paul Emery [8]

Journal of Clinical Medicine

J. Clin. Med. 2019, *8*, 1394





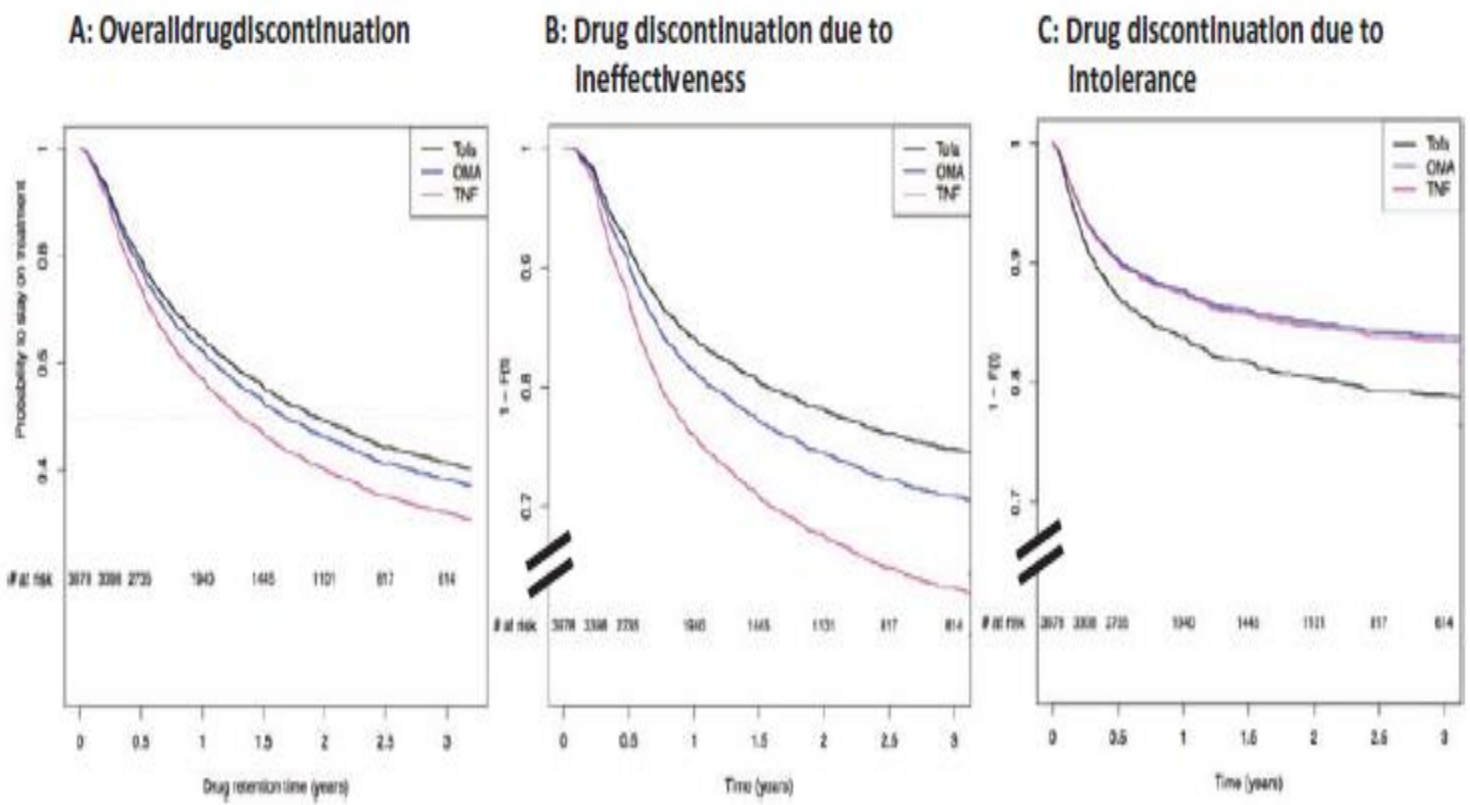
RMD Open
Rheumatic & Musculoskeletal Diseases

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

Finckh et al, 2020

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

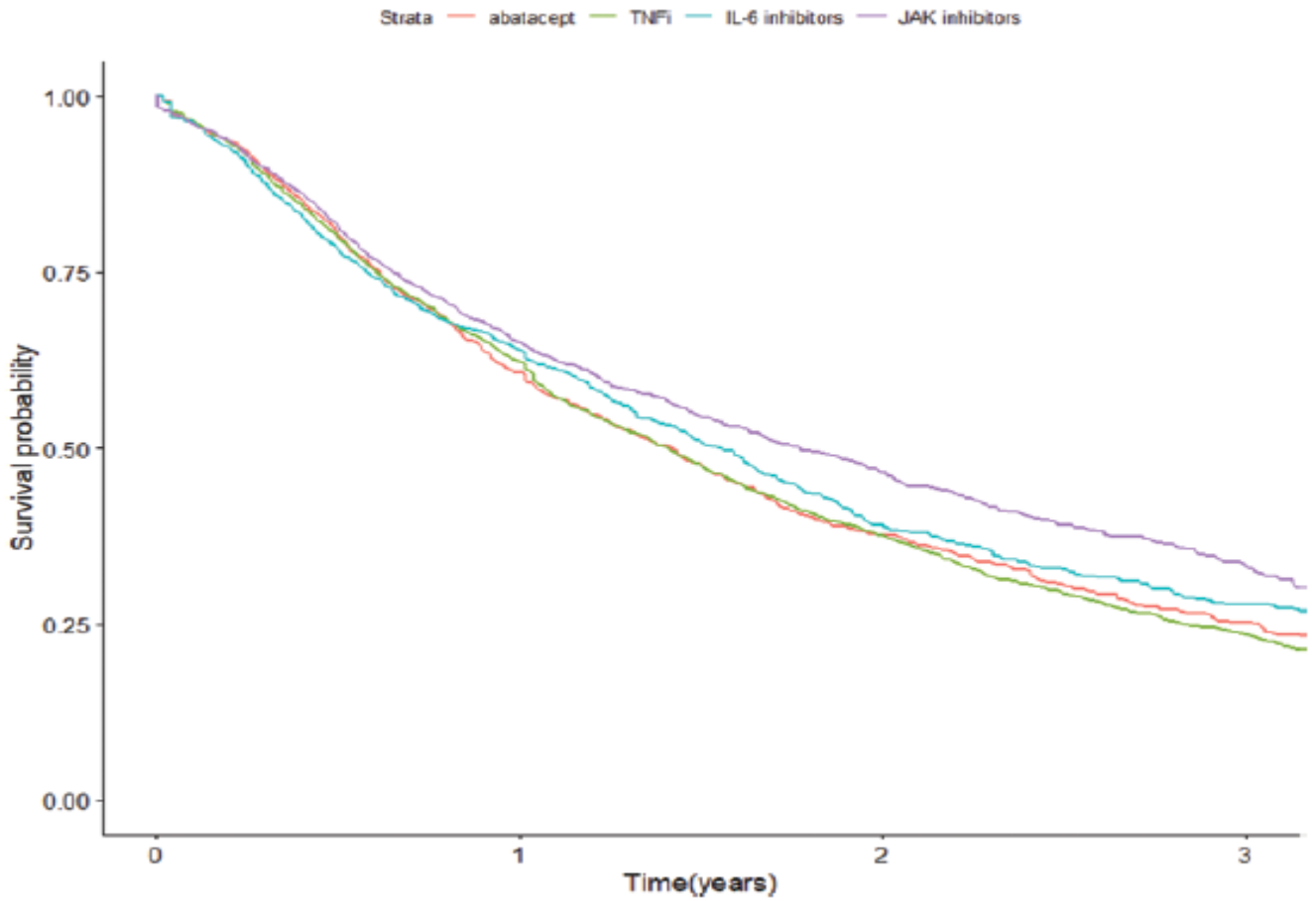


COMPARATIVE EFFECTIVENESS OF JAK-INHIBITORS, TNF-INHIBITORS, ABATACEPT AND IL-6 INHIBITORS IN AN INTERNATIONAL COLLABORATION OF REGISTERS OF RHEUMATOID ARTHRITIS PATIENTS (THE "JAK-POT" STUDY)

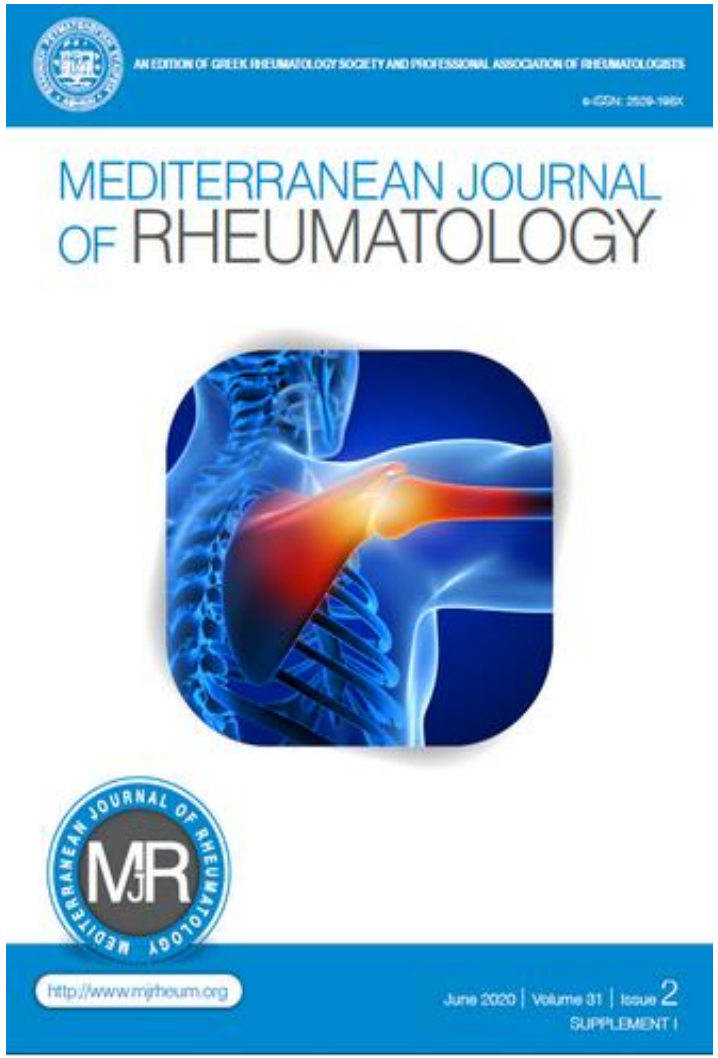
Table 1. Registers

Country, register	N	JAKi, n (%)
Austria, BIOREG*		
Belgium, TARDIS	6288	2113 (33.6)
Canada, RHUMADATA	528	114 (21.6)
Czech Republic, ATTRA	374	253 (67.6)
Denmark, DANBIO	4721	506 (10.7)
Finland, ROB-FIN	807	234 (29.0)
Germany, RABBIT*		
Italy, GISEA	757	250 (33.0)
Israel, I-RECORD	400	94 (23.5)
Netherlands, METEOR	1642	4 (0.2)
Norway, NOR-DMARD	507	99 (19.5)
Portugal, REUMA.PT	797	44 (5.5)
Romania, RRBR	593	328 (55.3)
Russia, ARBITER	526	483 (91.8)
Slovenia, BIORX.SI	583	146 (25.0)
Spain, BIOBADASER	781	139 (17.8)
Switzerland, SCQM	2956	796 (26.9)
Turkey, TURKBIO	2150	397 (18.5)
UK, BSRBR	1111	63 (5.7)

*Registers planning to participate in future studies but not included yet



Lauper K. et al, EULAR 2020. DOI: 10.1136/annrheumdis-2020-eular.346



Infections in Patients with Rheumatoid Arthritis in the Era of Targeted Synthetic Therapies

Konstantinos Thomas[1], Dimitrios Vassilopoulos[2]

Table 1. Risk factors associated with serious infections in patients with rheumatoid arthritis.

Older age (> 65 years)
High disease activity (i.e. DAS28-score)
High disability score (i.e. HAQ score)
Comorbidities (i.e. chronic lung or kidney disease)
Glucocorticoid treatment (> 7.5 mg/day)
History of previous serious infections
Current immunosuppressive therapy (b- or ts-DMARDs)
History of previous DMARD failures

Mediterr J Rheumatol 2020;31(Supp 1):129-36

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA confirms Xeljanz to be used with caution in patients at high risk of blood clots

Share

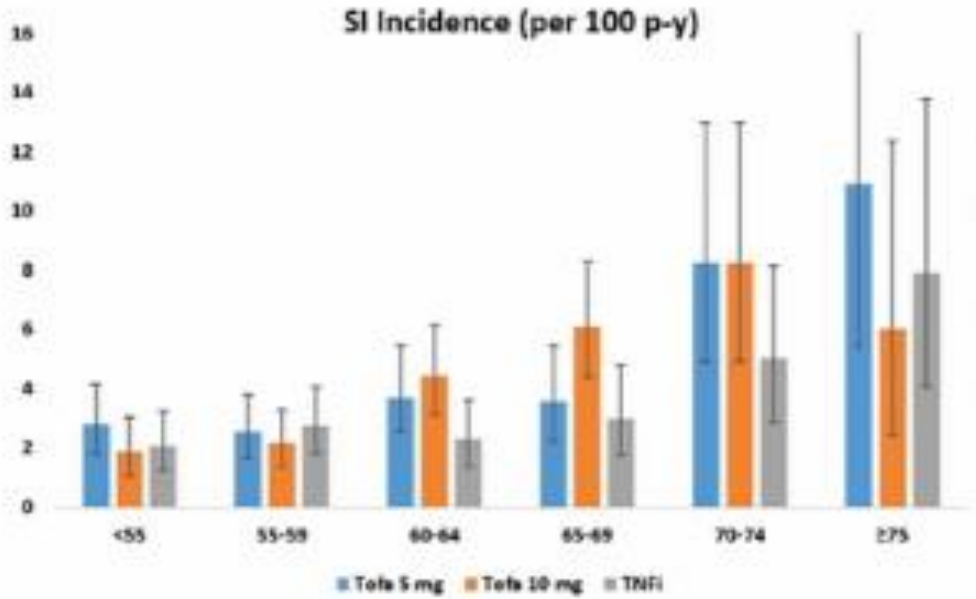
Press release 15/11/2019

EMA has concluded that Xeljanz (tofacitinib) could increase the risk of blood clots in the lungs and in deep veins in patients who are already at high risk.

As a result, the Agency is recommending that Xeljanz should be used with caution in all patients at high risk of blood clots. In addition, the maintenance doses of 10 mg twice daily should not be used in patients with ulcerative colitis who are at high risk of blood clots unless there is no suitable alternative treatment. Further, EMA is recommending that, due to an increased risk of infections, patients older than 65 years of age should be treated with Xeljanz only when there is no alternative treatment.

Tofacitinib – η μελέτη A3921133

- **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)



- **↑ SI με την ηλικία για όλες τις κατηγορίες (tofa 5 mg, tofa 10 mg, TNFi), αλλά**
- **Σημαντικότερη ↑ με την ηλικία στο tofa (10 mg > 5 mg)**
- **Μη στατιστικά σημαντική ↑ των θανατηφόρων SI στο tofa vs TNFi**

EMA Pharmacovigilance Risk Assessment Committee (PRAC), 31 Oct 2019

Permission by Kostas Thomas

RESEARCH ARTICLE Open Access

arthritis research&therapy

2015;17:362

Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials

Vibeke Strand[1], Sima Ahadieh[2], Jonathan French[3], Jamie Geier[4], Sriram Krishnaswami[2], Sujatha Menon[2], Tina Checchio[2], Thomas G. Tensfeldt[2], Elaine Hoffman[2], Richard Riese[2], Mary Boy[2] and Juan J. Gómez-Reino[5*]

66 randomized controlled trials and 22 long-term extension studies

Drug	No. trials	Serious infection incidence rate, patients with events per 100 pt-yrs (95% CI)	Patients (N)	Cumulative exposure (pt-yrs)
Abatacept	11	3.04	5953	6070
Rituximab	8	3.72	2926	2687
Tocilizumab	13	5.45	5547	4522
Infliximab	11	6.11	4592	3555
Etanercept	17	4.06	7141	13037
Certolizumab pegol	5	7.59	3212	1339
Golimumab	6	5.31	2820	1648
Adalimumab	18	5.04	6570	7095
TNFi	57	4.90	26492	29429
Tofacitinib, Phase 3, 5 mg BID	6	3.02	1587	1464
Tofacitinib, Phase 3, 10 mg BID	6	3.00	1609	1501
Tofacitinib, LTE, 5 mg BID	1	2.50	1452	4005
Tofacitinib, LTE, 10 mg BID	1	3.19	3375	5191
Tofacitinib, Phase 2, Phase 3, LTE (all doses)	14	2.93	5671	12664
Adalimumab (tofacitinib, Phase 3, ORAL Standard)	1	1.68	204	179

Fig. 2 Incidence rates for serious infections with biologic DMARDs and tofacitinib across RCTs* and LTE studies. The results displayed did not include the continuity factor to account for zero incidence rates due to the low percentage of zero incidence rates for serious infections within these trials (<10 %). Tofacitinib data as of April 2013. *Clinical trial data published between 1999 and 2013. *BID* twice daily, *CI* confidence interval, *DMARD* disease-modifying antirheumatic drug, *LTE* long-term extension, *pt-yrs* patient-years, *RCT* randomized controlled trial, *TNFi* tumor necrosis factor inhibitors

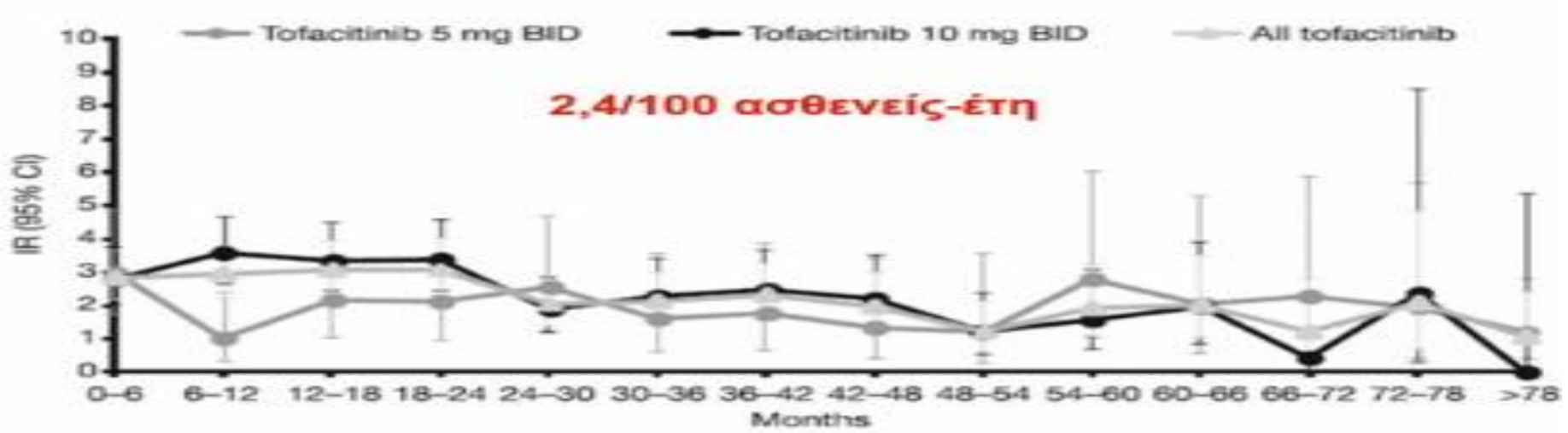
RESEARCH ARTICLE Open Access

arthritis research&therapy

Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study

Jürgen Wollenhaupt[1], Eun-Bong Lee[2], Jeffrey R. Curtis[3], Joel Silverfield[4], Ketti Terry[5], Koshika Soma[6], Chris Mojcik[6], Ryan DeMasi[7], Sander Strengholt[8], Kenneth Kwok[6], Irina Lazariciu[9], Lisy Wang[5*] and Stanley Cohen[10]

4481 patients, follow-up period 114 months (16291 patient-years)



- **Tofa 10 mg vs Tofa 5 mg: ↑ επίπτωση SIE (2.6 vs 1.9/100 p-y)**

A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis

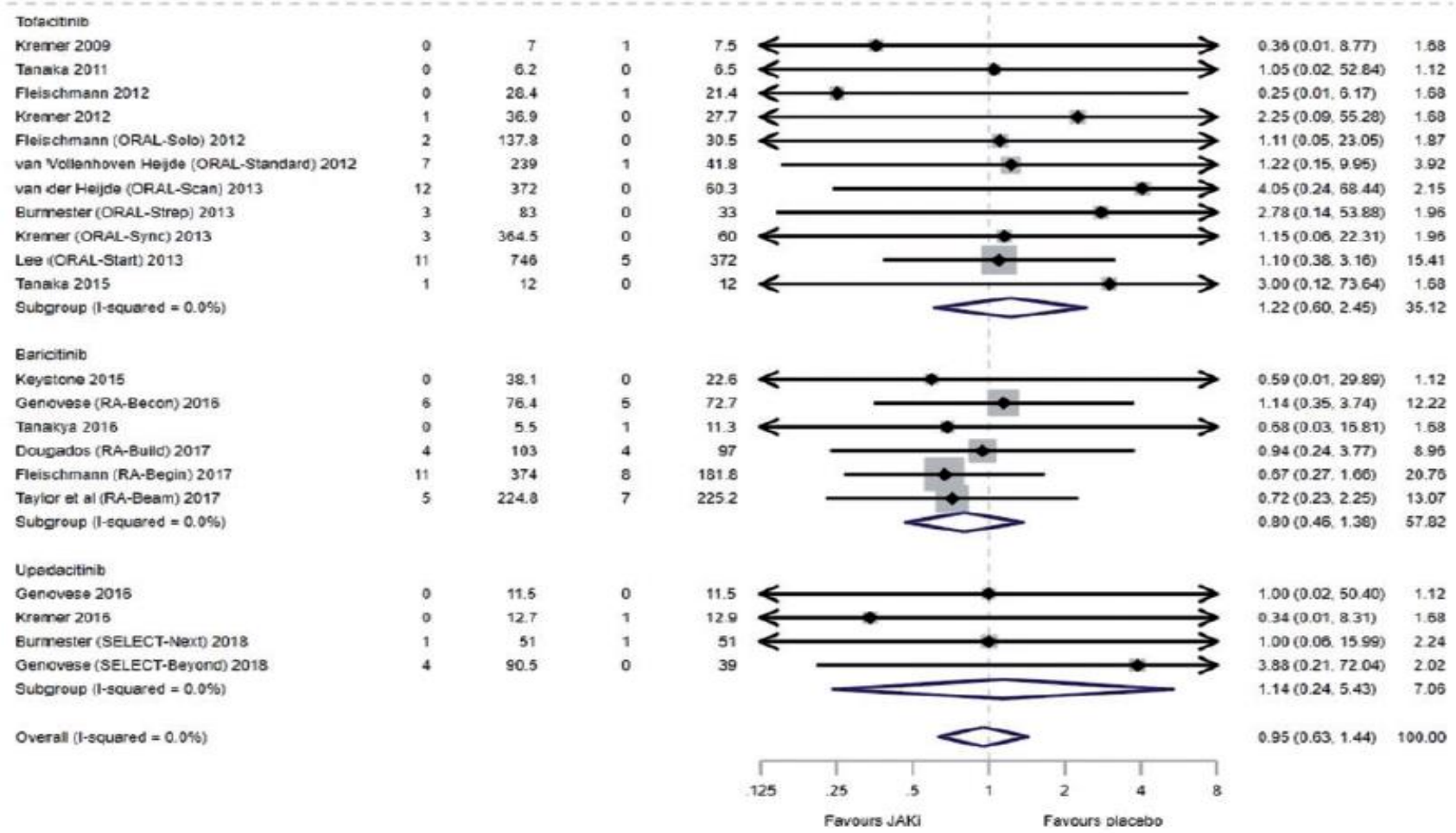
Katie Bechman [1], Sujith Subesinghe [1], Sam Norton [2], Fabiola Atzeni [3], Massimo Galli [4,5], Andrew P. Cope [1], Kevin L. Winthrop [5] and James B. Galloway [1]

Rheumatology (Oxford). 2019 Oct 1;58(10):1755-1766

11 studies (n=5888) participants in total – tofacitinib, upadacitinib, baricitinib

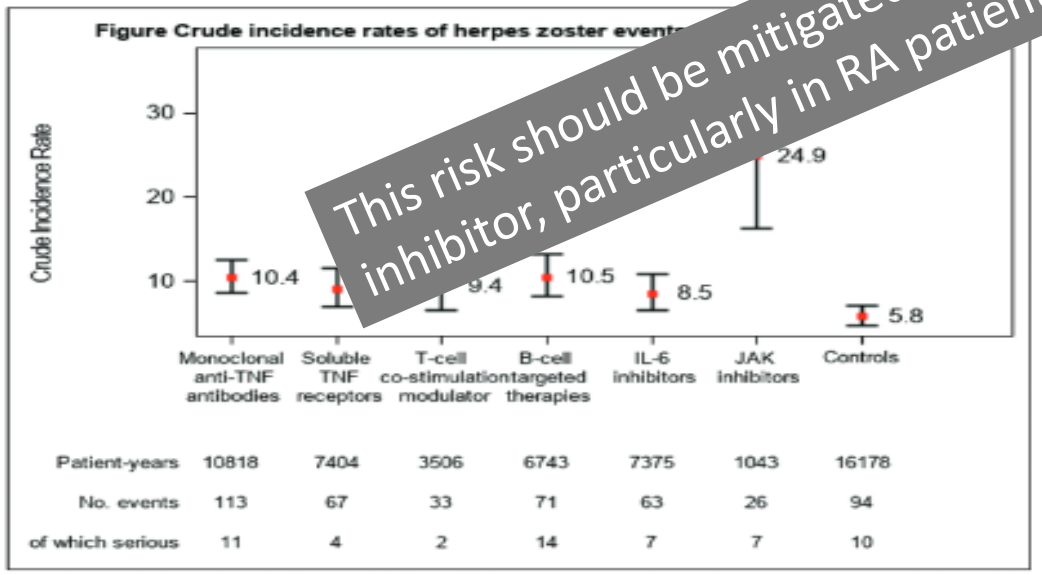
↑ risk for HZ
3.23 per 100 patient-years

Relatively small risk
Steroids X2



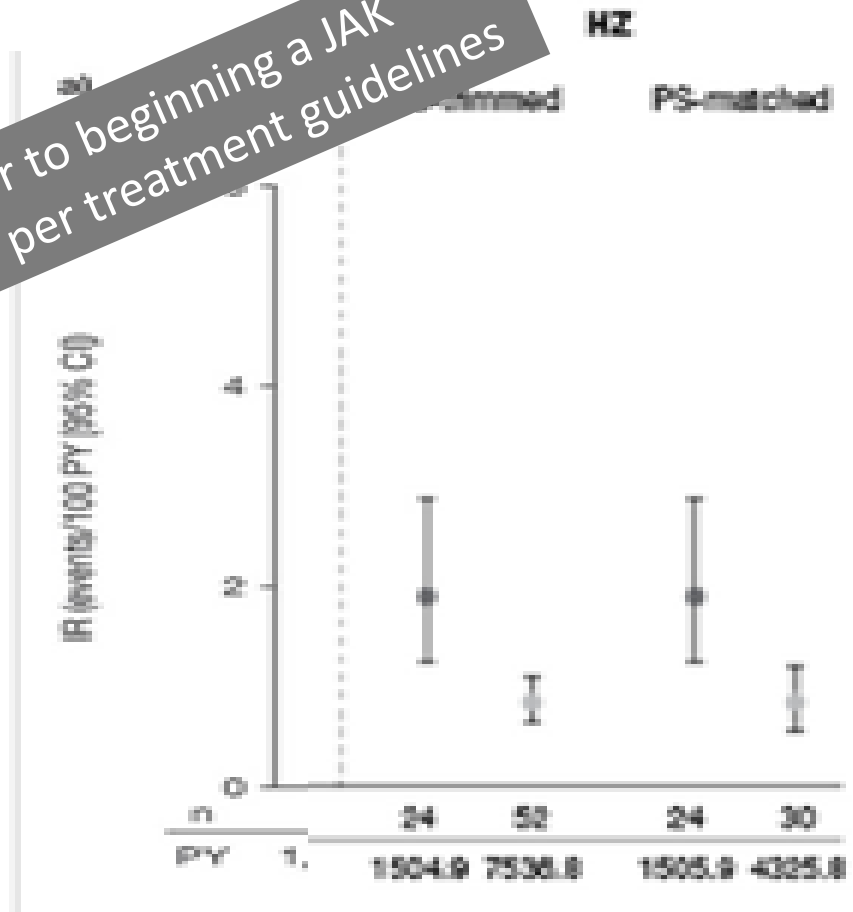
OP0238 RISK OF HERPES ZOSTER IN PATIENTS WITH RHEUMATOID ARTHRITIS UNDER BIOLOGICAL, TARGETED SYNTHETIC, AND CONVENTIONAL SYNTHETIC DMARD TREATMENT FREE

	Multivariate Analysis without IPW		Multivariate Analysis with IPW	
	Adjusted HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value
Female sex	1.42 (1.12-1.82)	**0.0042**	1.21 (0.96-1.53)	0.1095
Age per 10 years	1.23 (1.13-1.33)	**<.0001**	1.31 (1.2-1.43)	**<.0001**
Glucocorticoids, 5-10 vs 0 mg/d	1.16 (0.95-1.41)	0.1577	1.23 (1-1.52)	0.0501
Glucocorticoids, >10 vs 0 mg/d	1.58 (1.02-2.46)	**0.0417**	1.92 (1.27-2.92)	**0.0022**
csDMARD treatment	*Reference*		*Reference*	
Monoclonal TNFi antibodies	1.55 (1.20-2.00)	**0.0009**	1.63 (1.25-2.12)	**0.0003**
Soluble TNF receptors	1.32 (0.98-1.77)	0.0683	1.34 (0.98-1.83)	0.0631
T-cell co-stimulation modulator	1.41 (0.97-2.05)	0.0746	1.69 (1.17-2.45)	**0.0048**
B-cell targeted therapies	1.45 (1.07-1.97)	**0.0156**	1.66 (1.19-2.3)	**0.002**
IL-6 inhibitors	1.31 (0.97-1.77)	0.0737	1.55 (1.15-2.09)	
JAK inhibitors	3.55 (2.33-5.41)	**<.0001**	5.01 (3.45-7.2	



This risk should be mitigated by vaccination prior to beginning a JAK inhibitor, particularly in RA patients > 50 years, per treatment guidelines

Post-Approval Comparative Safety Study of Tofacitinib and Biologic DMARDs: Five-Year Results from a US-based Rheumatoid Arthritis Registry



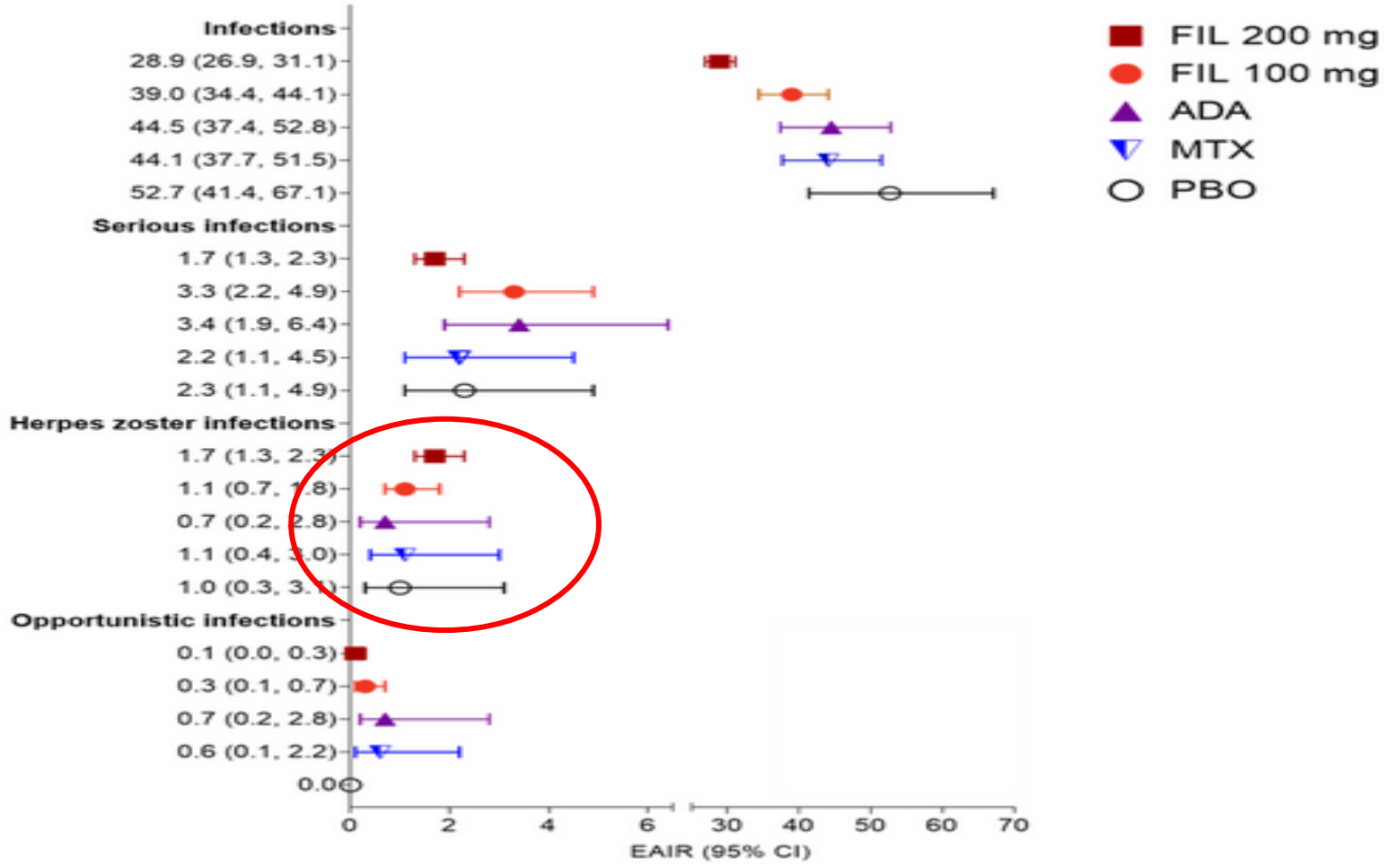
Strangfeld et al, dx.doi.org/10.1136/annrheumdis-2020-eular.3171

Kremer J et al, Arthritis Rheumatol. 2019; 71 (suppl 10).

INTEGRATED SAFETY ANALYSIS OF FILGOTINIB TREATMENT FOR RHEUMATOID ARTHRITIS FROM 7 CLINICAL TRIALS

M. C. Genovese[1], K. Winthrop[2], Y. Tanaka[3], T. Takeuchi[4], A. Kivitz[5], F. Matzkies[6], L. Ye[6], D. Jiang[6], Y. Guo[6], B. Bartok[6], R. Besuyen[7], G. R. Burmester[8], J. E. Gottenberg[9]

Figure 2. Rates of infections by treatment group per 100 patient-years



Ann Rheum Dis 2020:9(suppl1,);320

Annals of the Rheumatic Diseases

CLINICAL SCIENCE

Infections in baricitinib clinical trials for patients with active rheumatoid arthritis

2020 Oct;79(10):1290-1297

Kevin L Winthrop ,[1] Masayoshi Harigai ,[2] Mark C Genovese ,[3] Stephen Lindsey,[4] Tsutomu Takeuchi,[5] Roy Fleischmann ,[6] John D Bradley,[7] Nicole L Byers,[7] David L Hyslop,[7] Maher Issa,[7] Atsushi Nishikawa,[8] Terence P Rooney,[7] Sarah Witt,[7] Christina L Dickson,[7] Josef S Smolen,[9] Maxime Dougados[10]

There were 3492 patients who received baricitinib for 7860 patient-years (PY) of exposure (median 2.6 years, maximum 6.1 years)

8 RCT (ph. 1b-3) και 1 LTE με δεδομένα έως 6 έτη (Bari vs PBO)

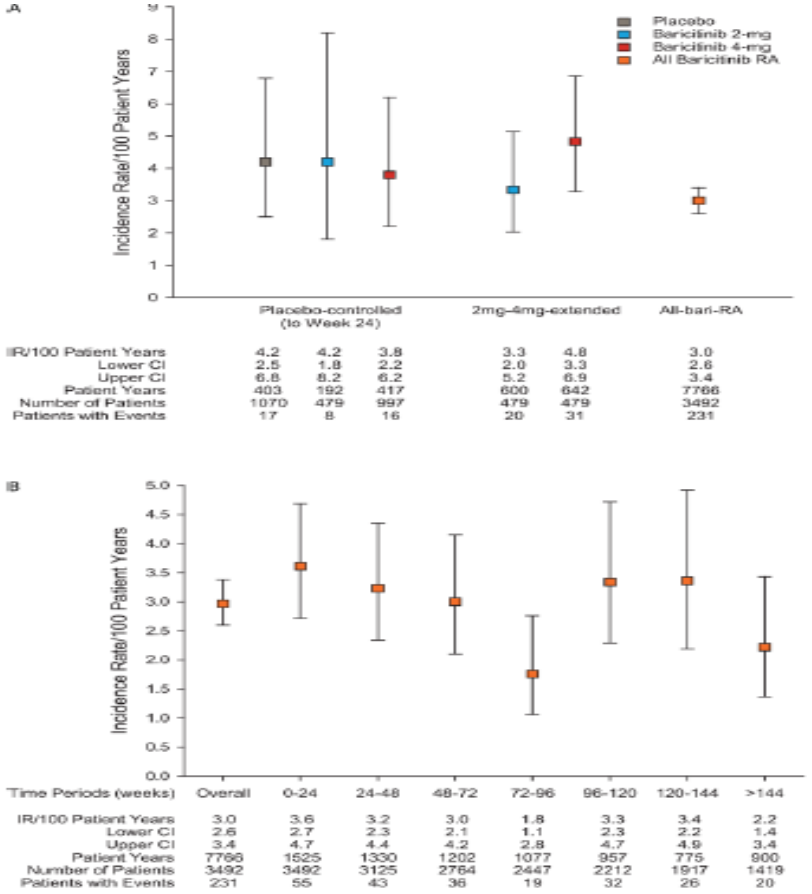
Συνολικές λοιμώξεις:

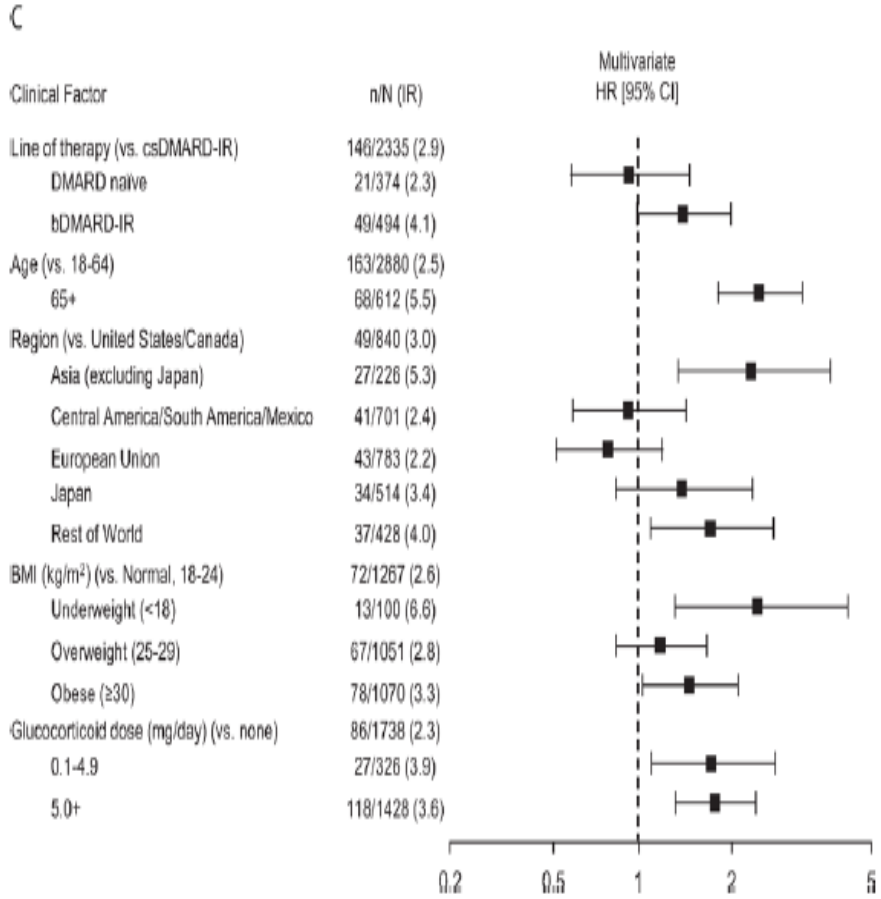
- ↑ επίπτωση σε bari 4 mg vs PBO (όχι σε bari 2 mg vs PBO)
- URTI, HZ και HSV

Σοβαρές λοιμώξεις:

- RCT IRs (PBO, 2 mg and 4 mg): 4.2, 4.2, και 3.8
- extended IRs (2 mg vs 4 mg): 3.3 vs 4.8
- παράγοντες κινδύνου: Ηλικία ≥65, υψηλό ή χαμηλό BMI, Ασία, GC ανεξαρτήτως δόσης
- Σταθερή επίπτωση κατά τη διάρκεια του follow-up

Επέκταση έως τα 8.4 έτη follow-up: IR: 2.7





THE LANCET Rheumatology

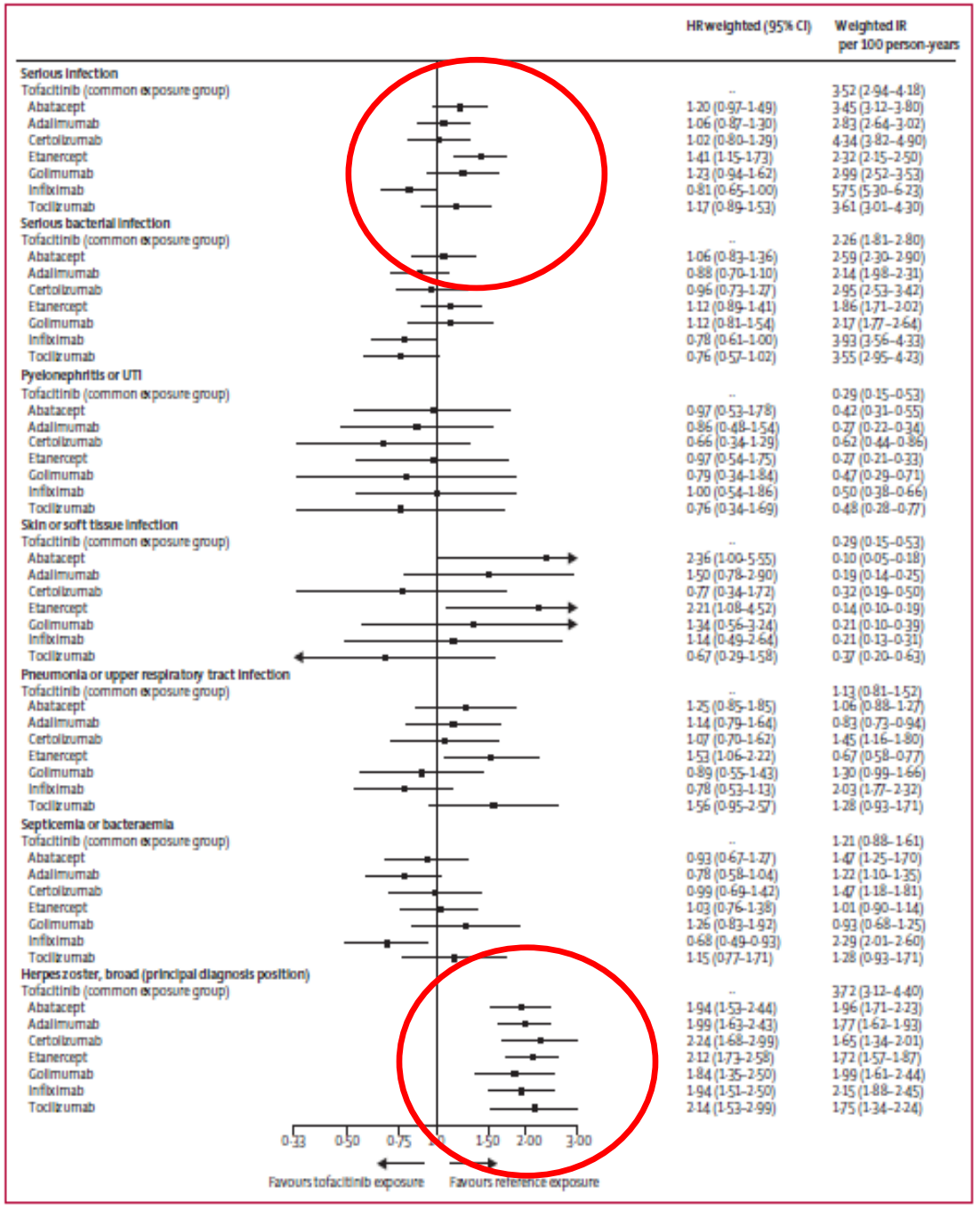
Volume 2, ISSUE 2, e84-e98, February 01, 2020

Risk of admission to hospital for serious infection after initiating tofacitinib versus biologic DMARDs in patients with rheumatoid arthritis: a multidatabase cohort study

Ajinkya Pawar, PhD • Rishi J Desai, PhD • Nileesa Gautam, BS • Seoyoung C Kim, MD

130.000 patients with RA initiating TOFA or bDMARDs (2012-1018)
6.278 (~ 5% ON TOFA)

		HR for serious infections
TOFA VS ETANERCEPT	↑*	1·41 (95% CI 1·15–1·73)
TOFA VS ABATACEPT	↑*	1·20 (95% CI 0·97–1·49)
TOFA VS GOLIMUMAB	↑	1·23 (95% CI 0·94–1·62)
TOFA VS TOCILIZUMAB	↑	1·17 (95% CI 0·89–1·53)
TOFA VS ADALIMUMAB	(-)	1·06(95% CI 0·87–1·30)
TOFA VS CERTOLIZUMB	(-)	1·02(95% CI 0·80–1·29)
TOFA VS INFLIXIMAB	↓	0·81(95% CI 0·65–1·00)



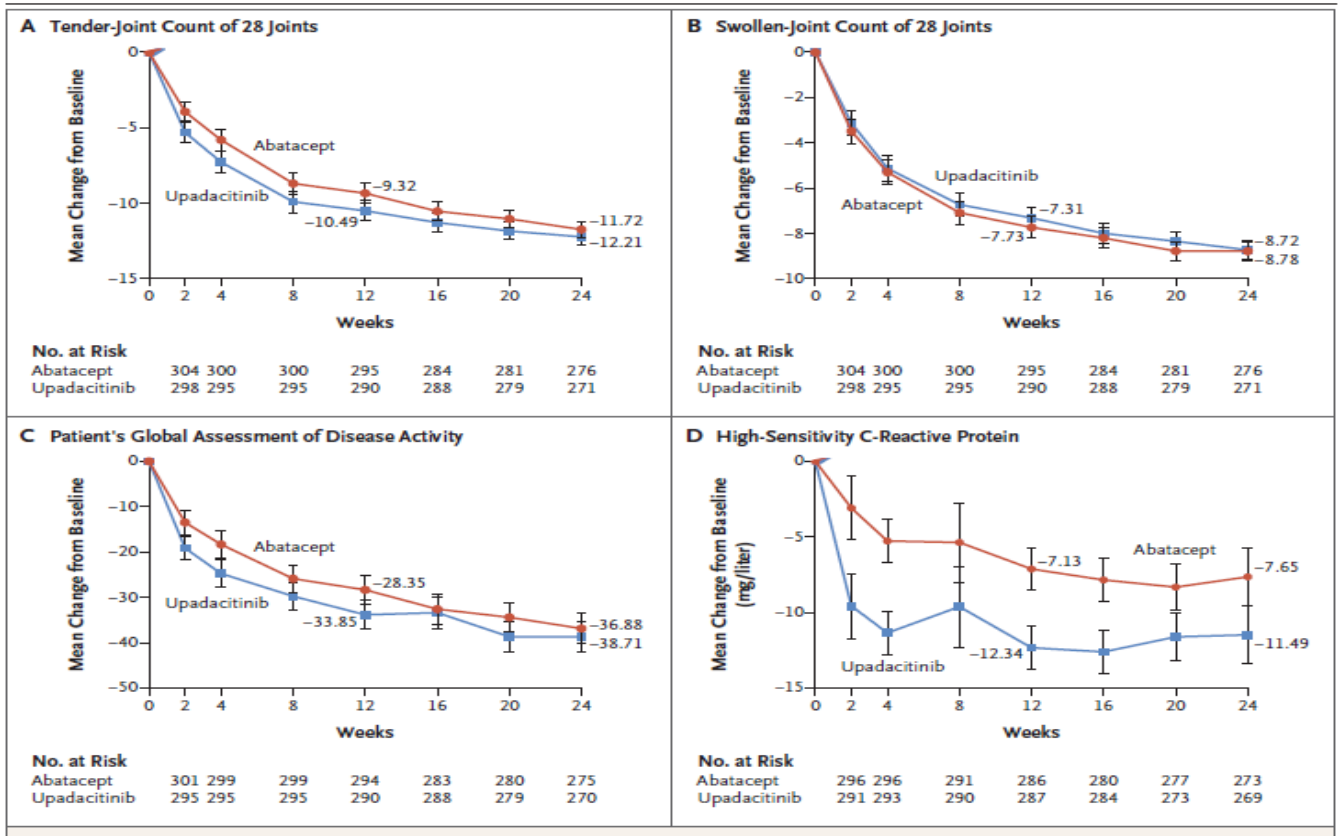
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 15, 2020 VOL. 383 NO. 16

Trial of Upadacitinib or Abatacept in Rheumatoid Arthritis

Andrea Rubbert-Roth, M.D., Jeffrey Enejosa, M.D., Aileen L. Pangan, M.D., Boulos Haraoui, M.D., Maureen Rischmueller, M.B., B.S., Nasser Khan, M.D., Ying Zhang, Ph.D., Naomi Martin, M.D., and Ricardo M. Xavier, M.D.

612 bDMARDs-IR patients upadacitinib (n=303) 15mg daily VS abatacept IV (n=309) in combination with cDMARDs



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 15, 2020 VOL. 383 NO. 16

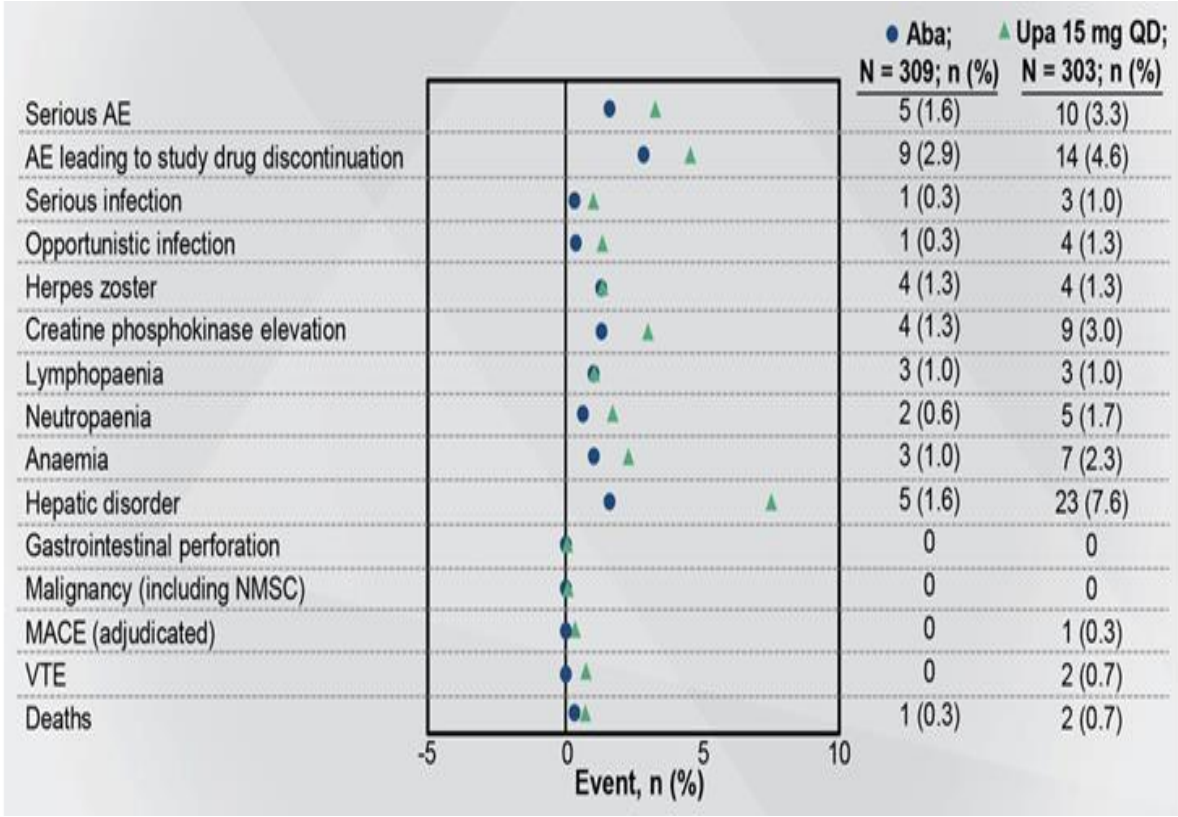
Trial of Upadacitinib or Abatacept in Rheumatoid Arthritis

Andrea Rubbert-Roth, M.D., Jeffrey Enejosa, M.D., Aileen L. Pangan, M.D., Boulos Haraoui, M.D., Maureen Rischmueller, M.B., B.S., Nasser Khan, M.D., Ying Zhang, Ph.D., Naomi Martin, M.D., and Ricardo M. Xavier, M.D.

612 bDMARDs-IR patients upadacitinib (n=303) 15mg daily VS abatacept IV (n=309) in combination with cDMARDs

Table 3. Adverse Events through Week 24.

Event	Upadacitinib (N=303)		Abatacept (N=309)	
	no. of patients	*% (95% CI)*	*no. of patients*	*% (95% CI)*
Any adverse event	209	69.0 (59.9–79.0)	189	61.2 (52.8–70.5)
Serious adverse event	10	3.3 (1.6–6.1)	5	1.6 (0.5–3.8)
Adverse event leading to discontinuation of trial drug	14	4.6 (2.5–7.8)	9	2.9 (1.3–5.5)
Death*	2	0.7 (0.1–2.4)	1	0.3 (0.0–1.8)
Treatment-emergent	1	0.3	0	
Non–treatment-emergent	1	0.3	1	0.3
Serious infection	3	1.0 (0.2–2.9)	1	0.3 (0.0–1.8)
Opportunistic infection	4	1.3 (0.4–3.4)	1	0.3 (0.0–1.8)
Herpes zoster infection	4	1.3 (0.4–3.4)	4	1.3 (0.4–3.3)
Hepatic disorder	23	7.6 (4.8–11.4)	5	1.6 (0.5–3.8)
Gastrointestinal perforation	0		0	
Cancer, including nonmelanoma skin cancer	0		0	
Major adverse cardiovascular event†	1	0.3 (0.0–1.8)	0	
Venous thromboembolic event†	2	0.7 (0.1–2.4)	0	

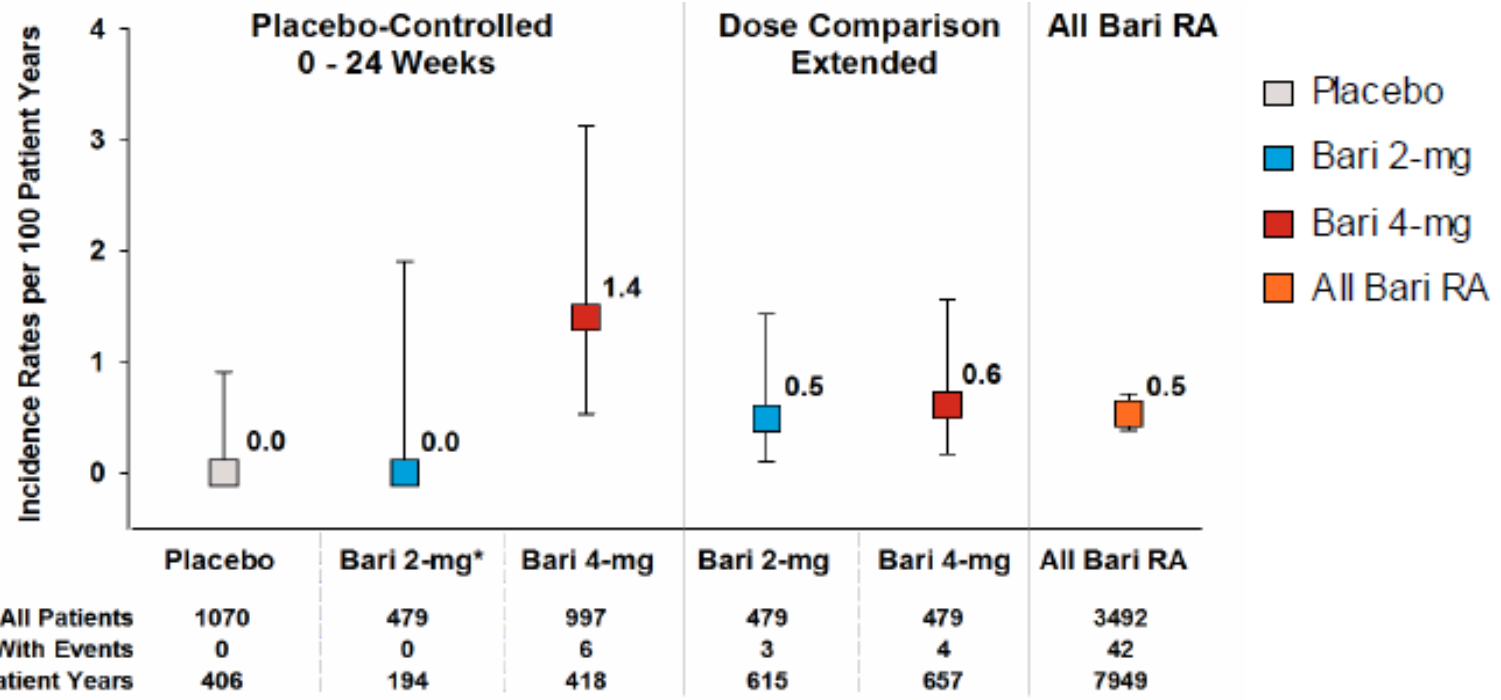


Arthritis & Rheumatology
Vol. 71, No. 7, July 2019, pp 1042–1055
DOI 10.1002/art.40841

American College of Rheumatology
Empowering Rheumatology Professionals

Cardiovascular Safety During Treatment With Baricitinib in Rheumatoid Arthritis

Peter C. Taylor,[1] Michael E. Weinblatt,[2] Gerd R. Burmester,[3] Terence P. Rooney,[4] Sarah Witt,[4] Chad D. Walls,[4] Maher Issa,[4] Claudia A. Salinas,[4] Chadi Saifan,[4] Xin Zhang,[4] Anabela Cardoso,[4] Miguel A. González-Gay,[5] and Tsutomu Takeuchi[6]



	Placebo	Bari 2-mg*	Bari 4-mg	Bari 2-mg	Bari 4-mg	All Bari RA
All Patients	1070	479	997	479	479	3492
With Events	0	0	6	3	4	42
Patient Years	406	194	418	615	657	7949

*Bari 2-mg data in the placebo-controlled analysis set is derived from 4 studies in which both baricitinib 2-mg and 4-mg were options during randomization. Events of DVT and PE were analyzed without adjudication.

Age
High BMI
COX-2 inhibitors
History of DVTE/PE

Annals of the Rheumatic Diseases

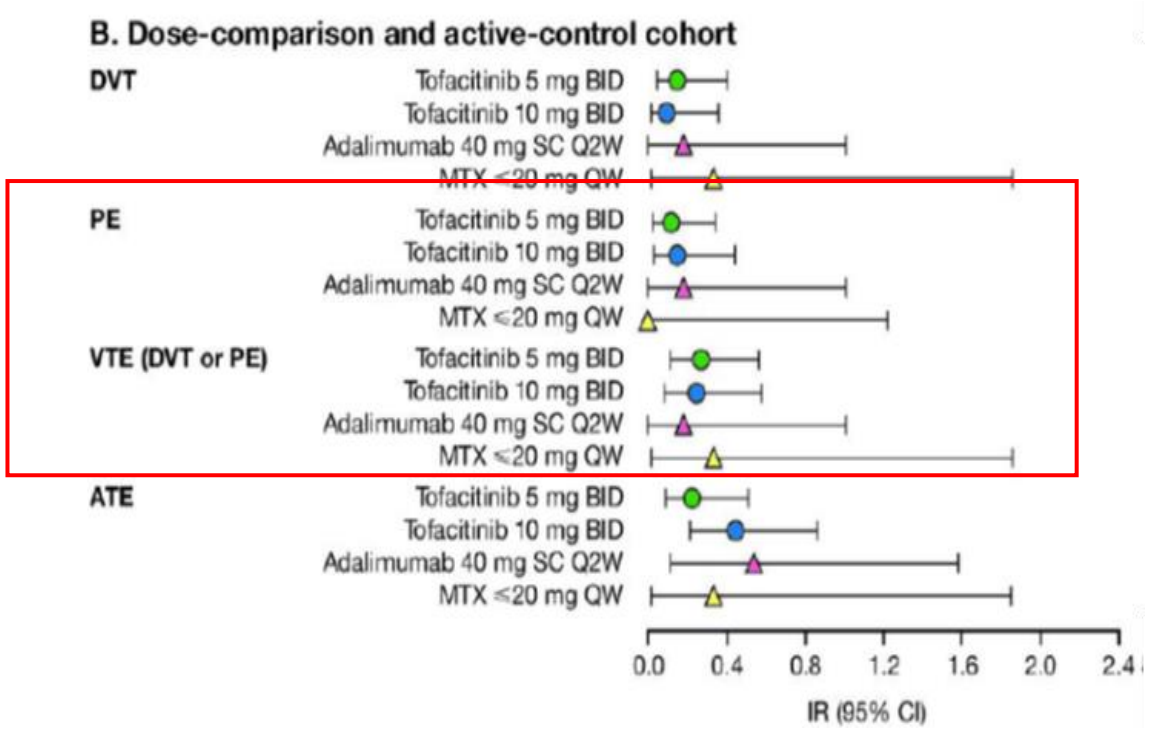
2020 Nov;79(11):1400-1413

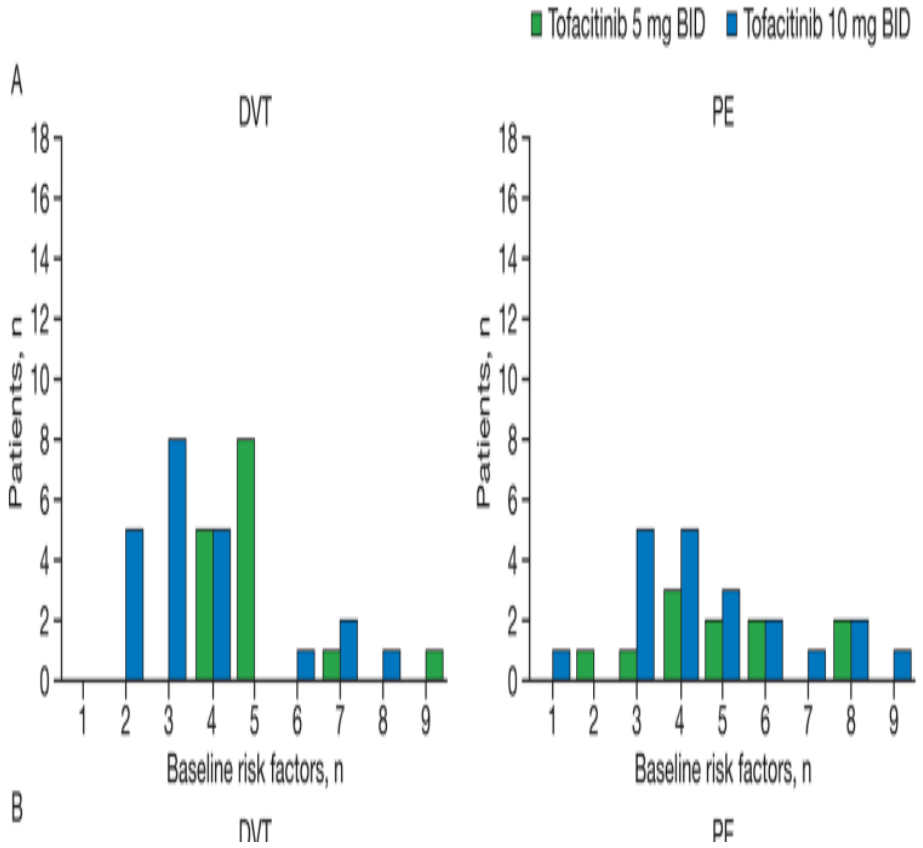
CLINICAL SCIENCE

Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data

Philip Mease ,[1] Christina Charles-Schoeman,[2] Stanley Cohen,[3] Lara Fallon,[4] John Woolcott,[5] Huifeng Yun,[6] Joel Kremer,[7] Jeffrey Greenberg,[8] Wendi Malley,[8] Alina Onofrei,[8] Keith S Kanik,[9] Daniela Graham,[9] Cunshan Wang,[10] Carol Connell,[11] Hernan Valdez,[12] Manfred Hauben,[13,14] Eric Hung,[13] Ann Madsen,[15] Thomas V Jones,[16] Jeffrey R Curtis [17]

12 410 tofacitinib-treated patients from the development programmes (RA: n=7964; PsO: n=3663; PsA: n=783)





- Οι ασθενείς με DVT στη δόση των 5 mg είχαν ≥4 παράγοντες κινδύνου
- Οι ασθενείς με PE στη δόση των 5 mg είχαν ≥2 παράγοντες κινδύνου

Annals of the Rheumatic Diseases

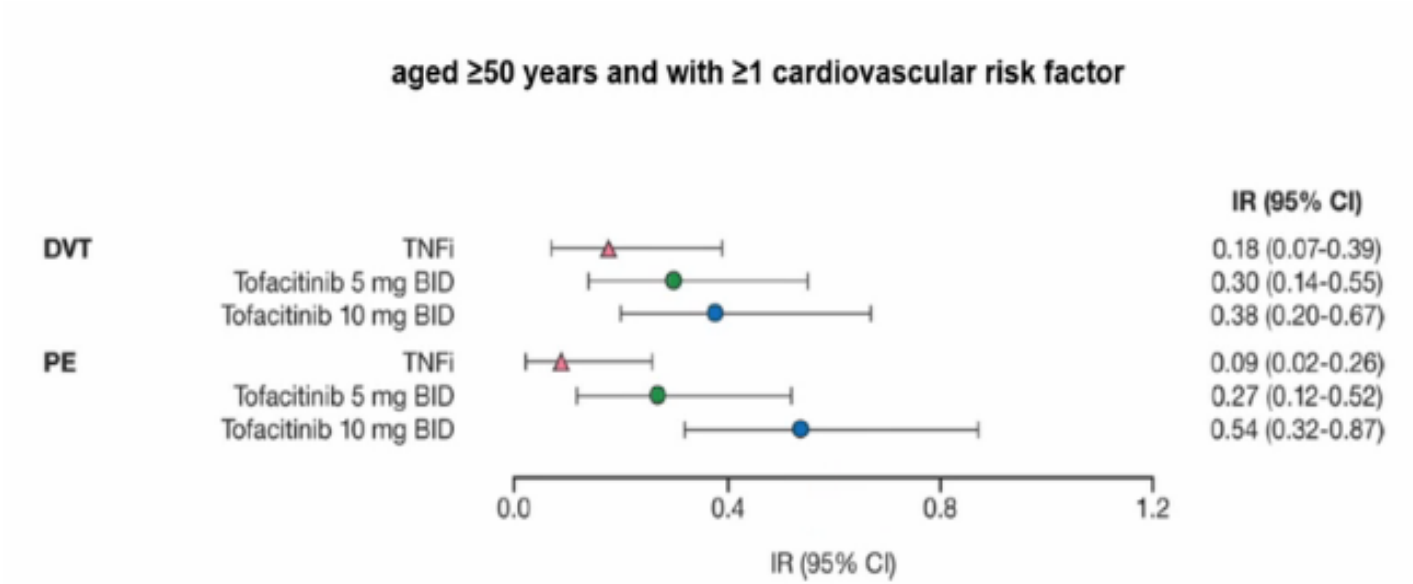
Ann Rheum Dis. 2020 Nov;79(11):1400-1413.

CLINICAL SCIENCE

Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data

Philip Mease ,[1] Christina Charles-Schoeman,[2] Stanley Cohen,[3] Lara Fallon,[4] John Woolcott,[5] Huifeng Yun,[6] Joel Kremer,[7] Jeffrey Greenberg,[8] Wendi Malley,[8] Alina Onofrei,[8] Keith S Kanik,[9] Daniela Graham,[9] Cunshan Wang,[10] Carol Connell,[11] Hernan Valdez,[12] Manfred Hauben,[13,14] Eric Hung,[13] Ann Madsen,[15] Thomas V Jones,[16] Jeffrey R Curtis [17]

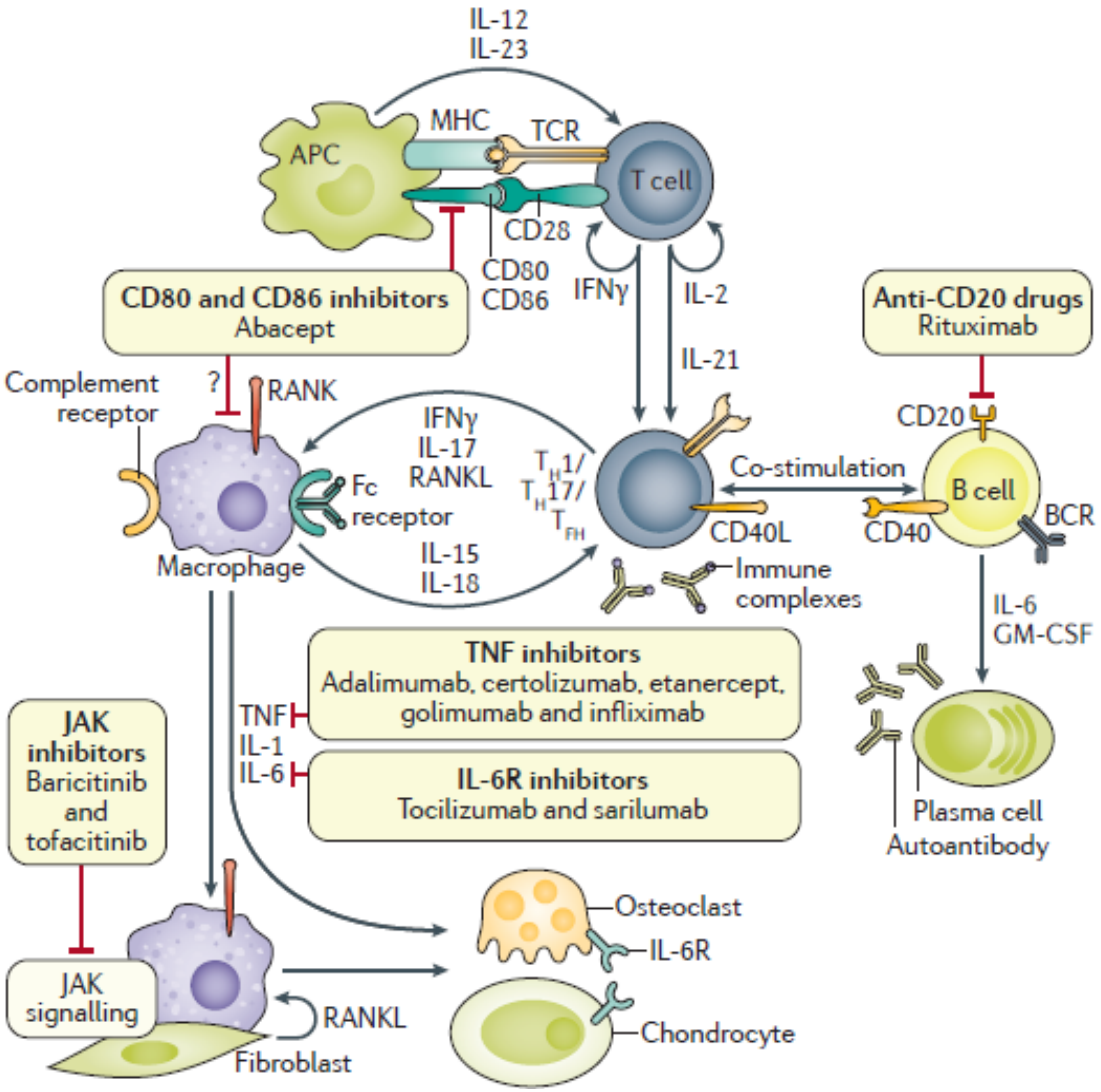
12 410 tofacitinib-treated patients from the development programmes (RA: n=7964; PsO: n=3663; PsA: n=783)



HRs για DVT/PE (tofacitinib 5 mg BID vs ADA): 1.66 (0.60–4.57) / 2.99 (0.81–11.06)

HRs για DVT/PE (tofacitinib 10 mg BID vs ADA): 2.13 (0.80–5.69)/5.96 (1.75–20.33)

JAK INHIBITORS: CHANGING PARADIGM IN RA MANAGEMENT AND TRIALS



Concepts

- Jak inhibitors continue to show promise in RA
  - Refractory to bDMARDS
  - Monotherapy
  - Rapid onset – 1-2 wks
  - Sustained – 24 wks

Caution: Herpes Zoster, thrombotic events

Smolen et al Nat Rev Dis **Primers**. 2018 Feb 8;4:18001.

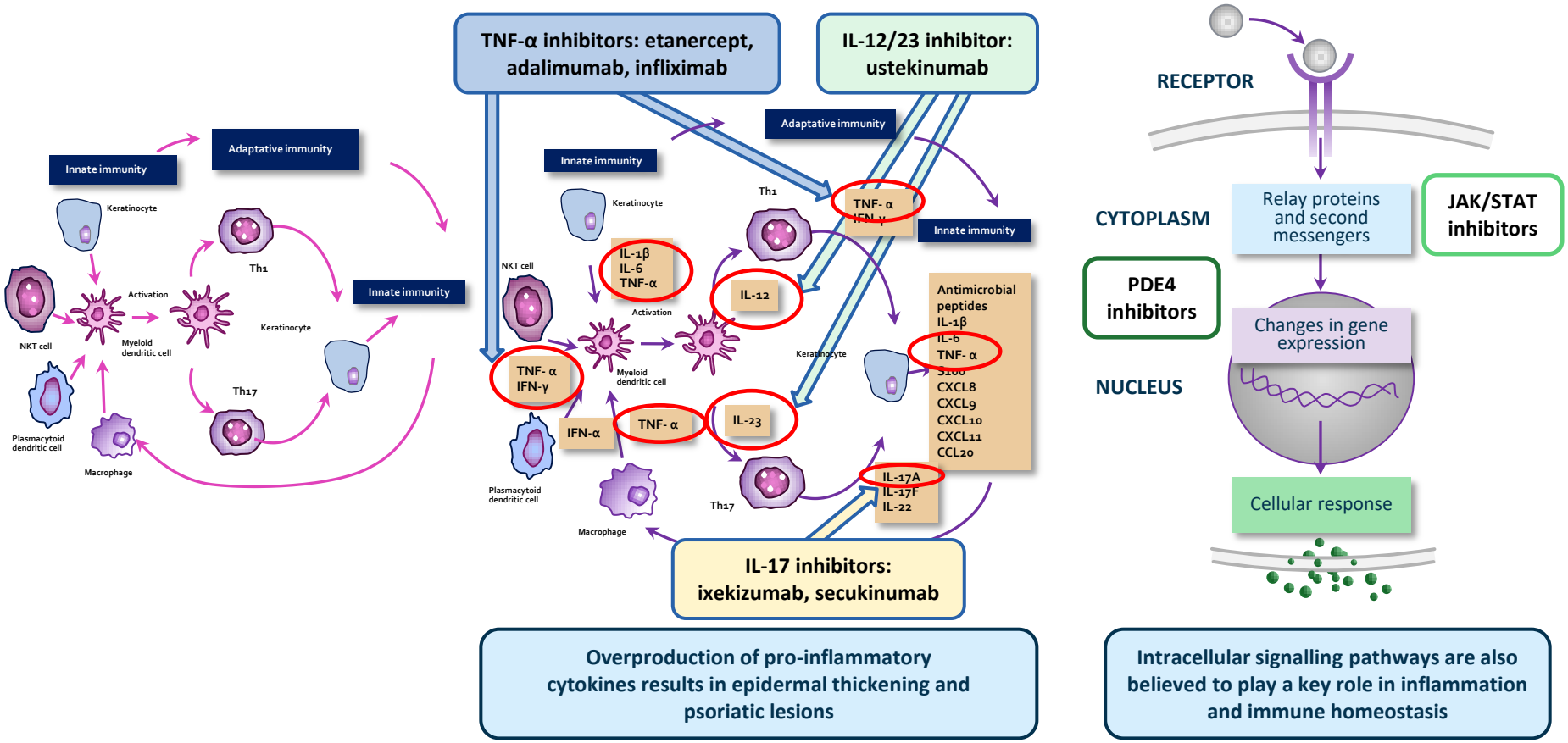
Therapeutic approaches in PsA

Targeted therapies are being developed to address all parts of the pathogenic pathway in psoriatic disease

Targeting **cells**

Biologics targeting **cytokines** and **extracellular** signalling

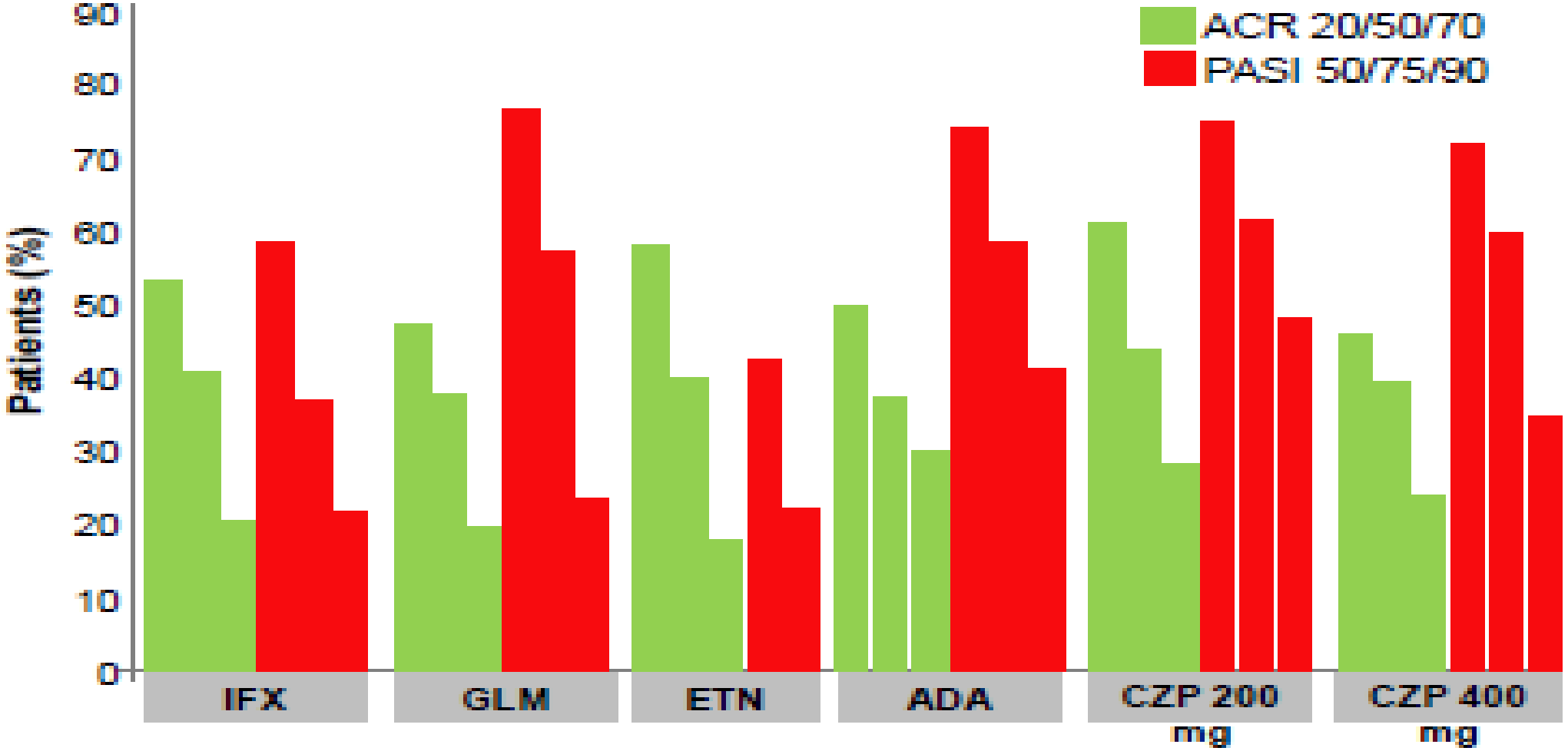
Small molecules targeting **intracellular** signalling pathways



IFN, interferon; IL, interleukin; NKT, natural killer T cell; TNF, tumour necrosis factor; JAK/STAT, janus kinase/signal transducer and activator of transcription; PDE4, phosphodiesterase 4.

Figure adapted from: 1. Nestle F, et al. N Engl J Med 2009;361:496–509; 2. Gooderham M. Skin therapy letter. http://www.skintherapyletter.com/2013/18.7/1.html. Accessed 6.11.19.

TNF INHIBITORS IN PSA

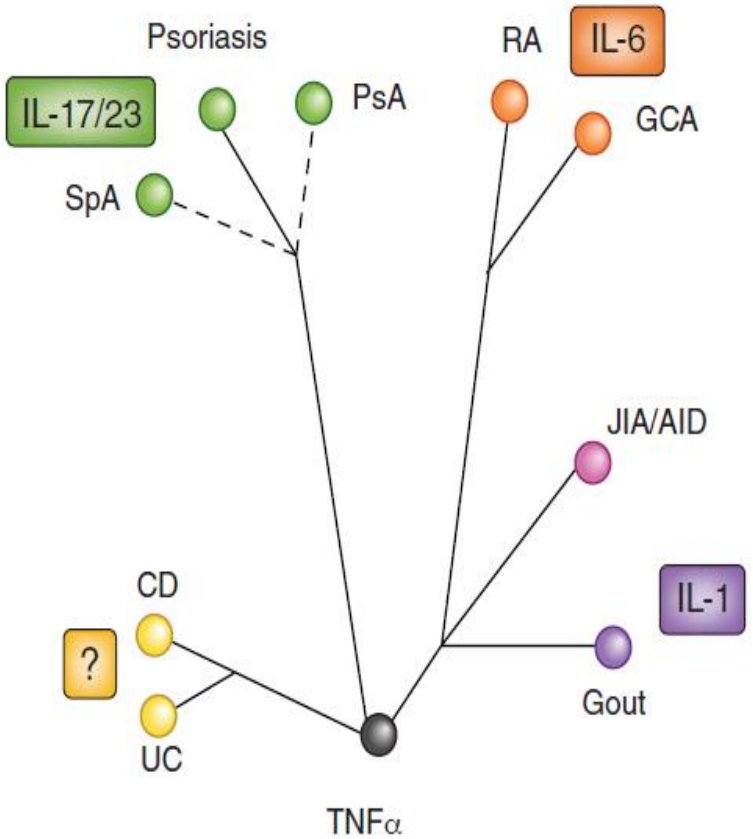


BEDSIDE TO BENCH

Toward a cytokine-based disease taxonomy

Georg Schett, Dirk Elewaut, Iain B McInnes, Jean-Michel Dayer & Markus F Neurath

a



b

CID	TNF	IL-6R	IL-1	IL-12/23	IL-17A
Rheumatoid arthritis					
Giant cell arthritis					
JIA/AID					
Gout					
Crohn's disease					
Ulcerative colitis					
Psoriasis					
Psoriatic arthritis					
Ankylosing spondylitis					
Multiple sclerosis					
Drugs	Adalimumab Certolizumab Etanercept Golimumab Infliximab	Tocilizumab Sarilumab*	Anakinra Canakinumab Rilonacept	Ustekinumab Briakinumab*	Brodalumab* Ixekizumab* Secucinumab*

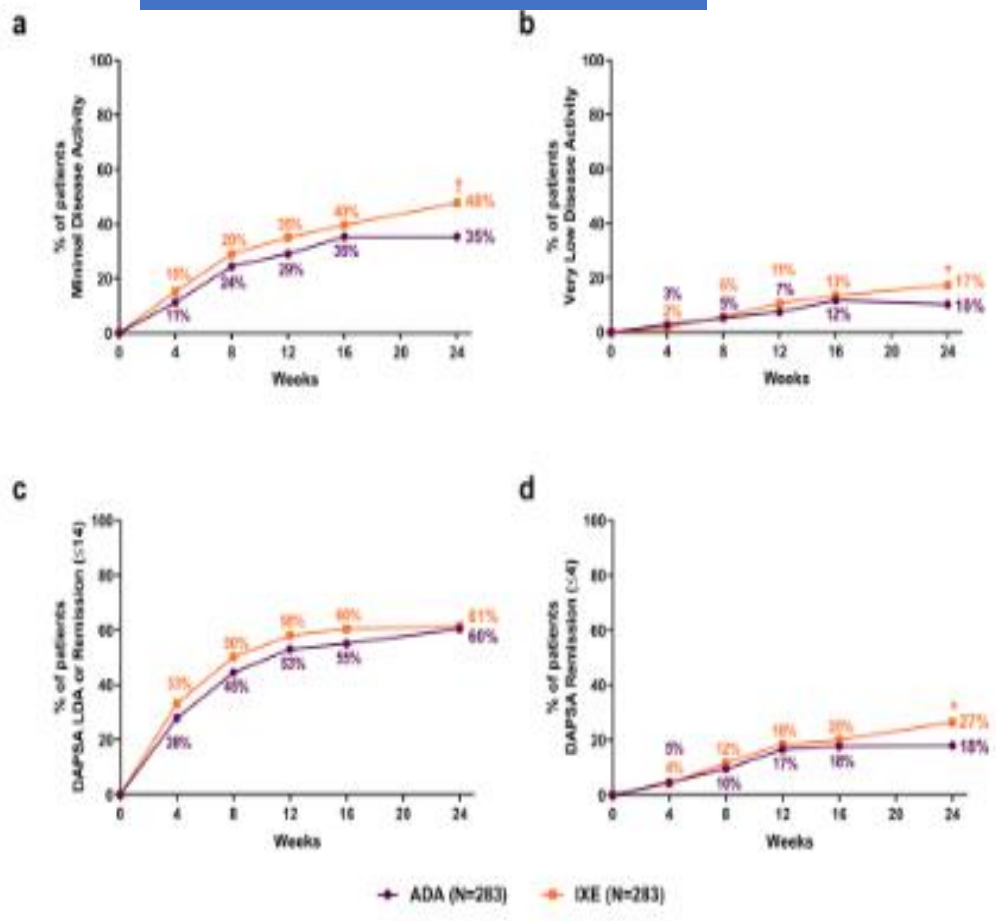
Nat. Med. 2014: 19;822–824

CLINICAL SCIENCE

A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial

Philip J Mease ,[1] Josef S Smolen,[2] Frank Behrens,[3] Peter Nash,[4] Soyi Liu Leage,[5] Lingnan Li,[5] Hasan Tahir,[6] Melinda Gooderham,[7] Eswar Krishnan,[5] Hong Liu-Seifert,[5] Paul Emery ,[8,9] Sreekumar G Pillai,[5] Philip S Helliwell,[10] The SPIRIT H2H study group

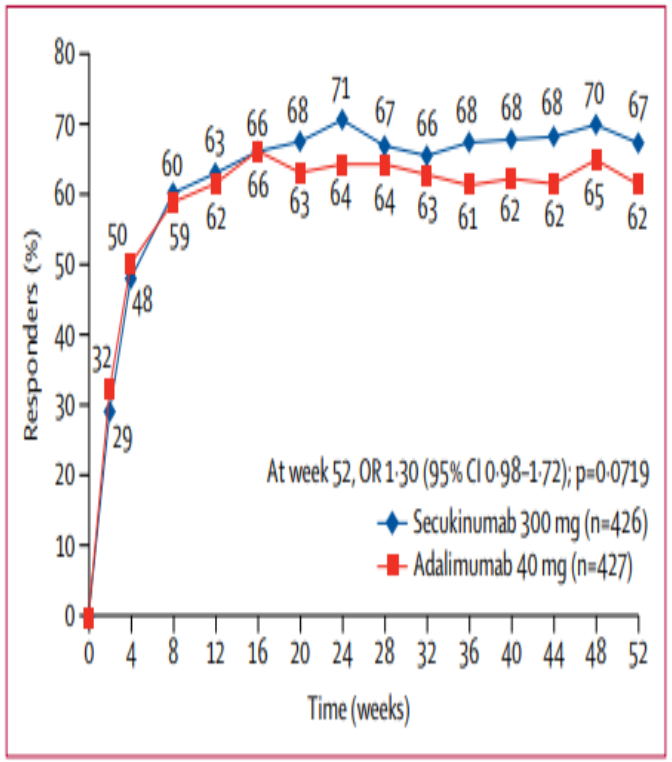
combined ACR50 and PASI 100 response

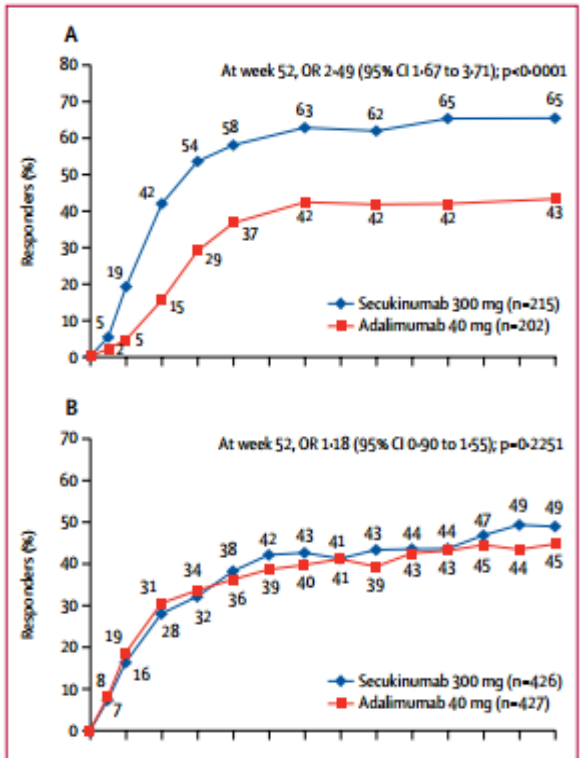


Mease PJ, et al. Ann Rheum Dis 2020;79:123–131

Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial

Iain B McInnes, Frank Behrens, Philip J Mease, Arthur Kavanaugh, Christopher Ritchlin, Peter Nash, Jordi Gratacós Masmitja, Philippe Goupille, Tatiana Korotaeva, Alice B Gottlieb, Ruvie Martin, Kevin Ding, Pascale Pellet, Shephard Mpofu, Luminita Pricop, on behalf of EXCEED Study Group

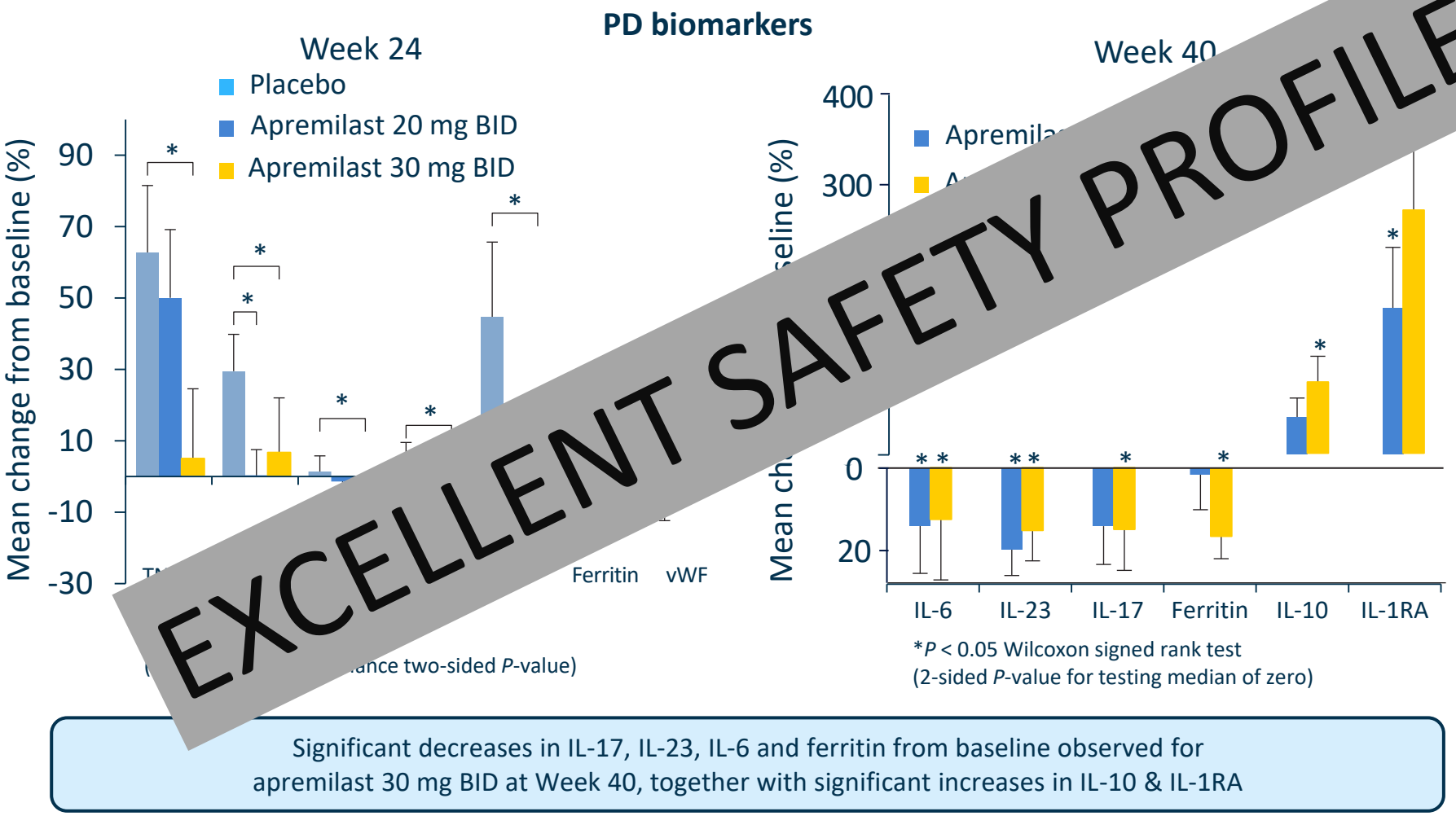




Mc Innes IB et al. Lancet. 2020 May 9;395(10235):1496-1505

Data from PALACE 1

Apremilast significantly reduces pro-inflammatory cytokines in peripheral blood (*in vivo*)



EXCELLENT SAFETY PROFILE

Significant decreases in IL-17, IL-23, IL-6 and ferritin from baseline observed for apremilast 30 mg BID at Week 40, together with significant increases in IL-10 & IL-1RA

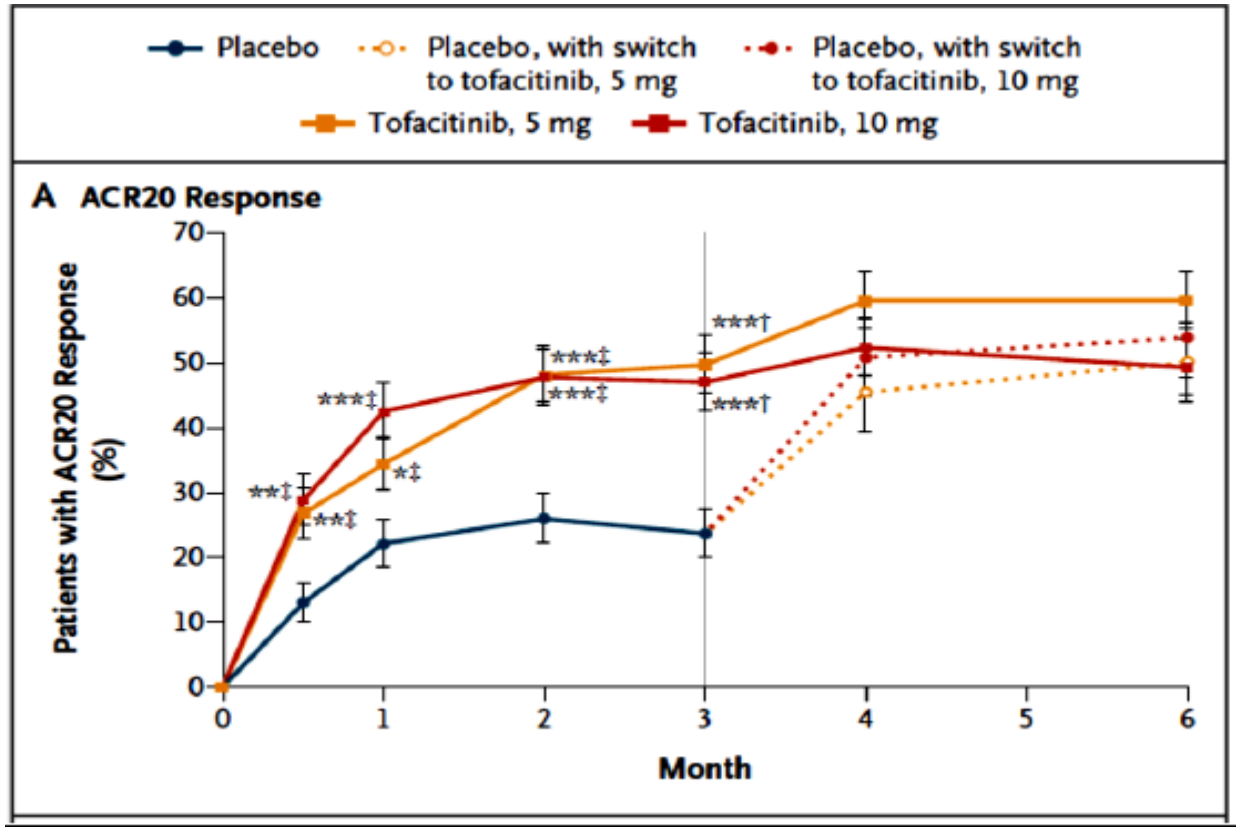
The use of Apremilast 20 mg DIP is not approved for use in the EU or US.
BID, twice daily; IL, interleukin; MCP, monocyte chemotactic protein; MIP, macrophage inhibitory protein; PD, pharmacodynamic; RA, receptor agonist; TNF, tumour necrosis factor; vWF, von Willebrand factor.

Schafer PH, et al. J Immunol Res 2015; 2015:906349.

The NEW ENGLAND JOURNAL of MEDICINE

Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors

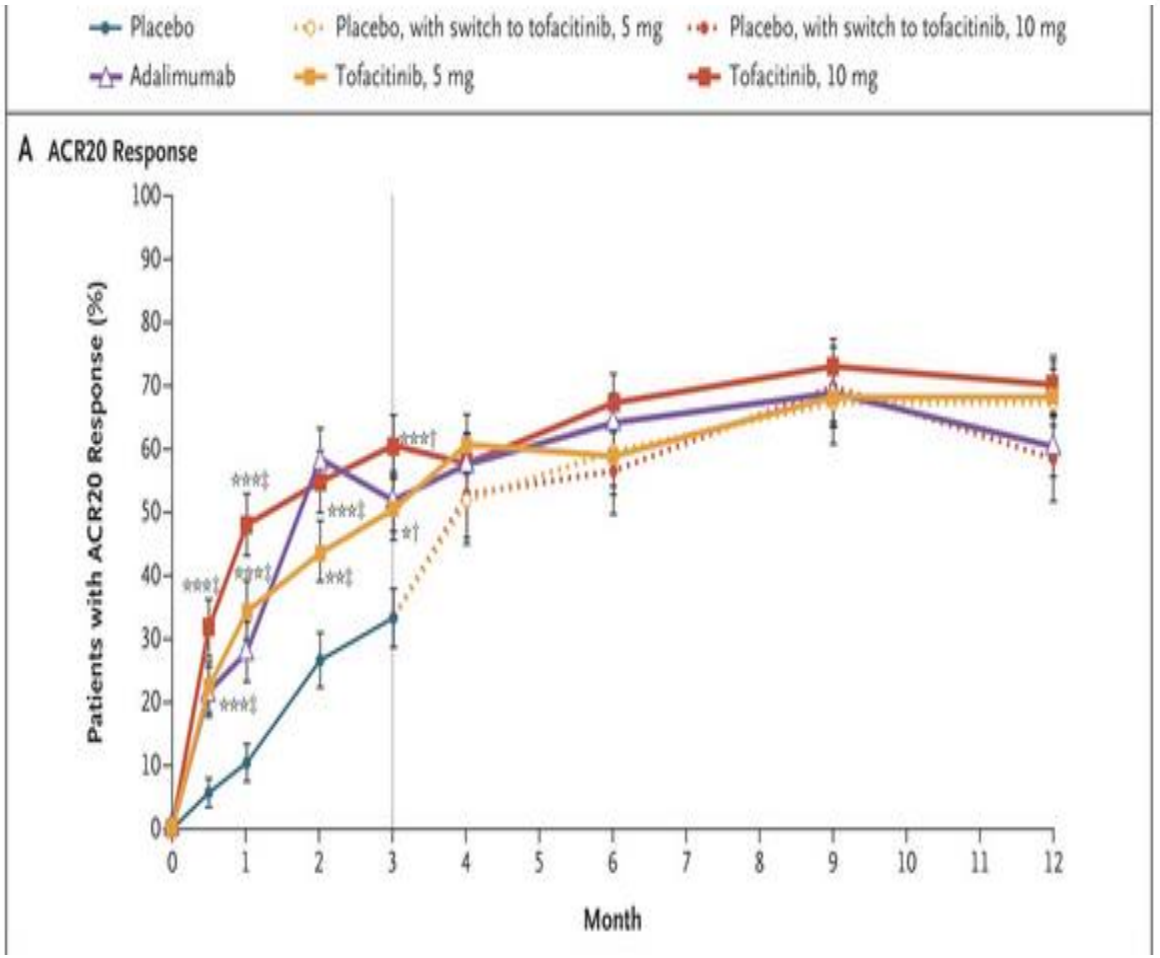
Dafna Gladman, M.D., William Rigby, M.D., Valderilio F. Azevedo, M.D., Ph.D., Frank Behrens, M.D., Ricardo Blanco, M.D., Andrzej Kaszuba, M.D., Ph.D., Elizabeth Kudlacz, Ph.D., Cunshan Wang, Ph.D., Sujatha Menon, Ph.D., Thijs Hendrikx, Ph.D., and Keith S. Kanik, M.D.



N Engl J Med 2017; 377:1525-1536

Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis

Philip Mease, M.D., Stephen Hall, M.D., Oliver FitzGerald, M.D., Désirée van der Heijde, Ph.D., Joseph F. Merola, M.D., Francisco Avila-Zapata, M.D., Dorota Cieślak, Ph.D., Daniela Graham, M.D., Cunshan Wang, Ph.D., Sujatha Menon, Ph.D., Thijs Hendrikx, Ph.D., and Keith S. Kanik, M.D.

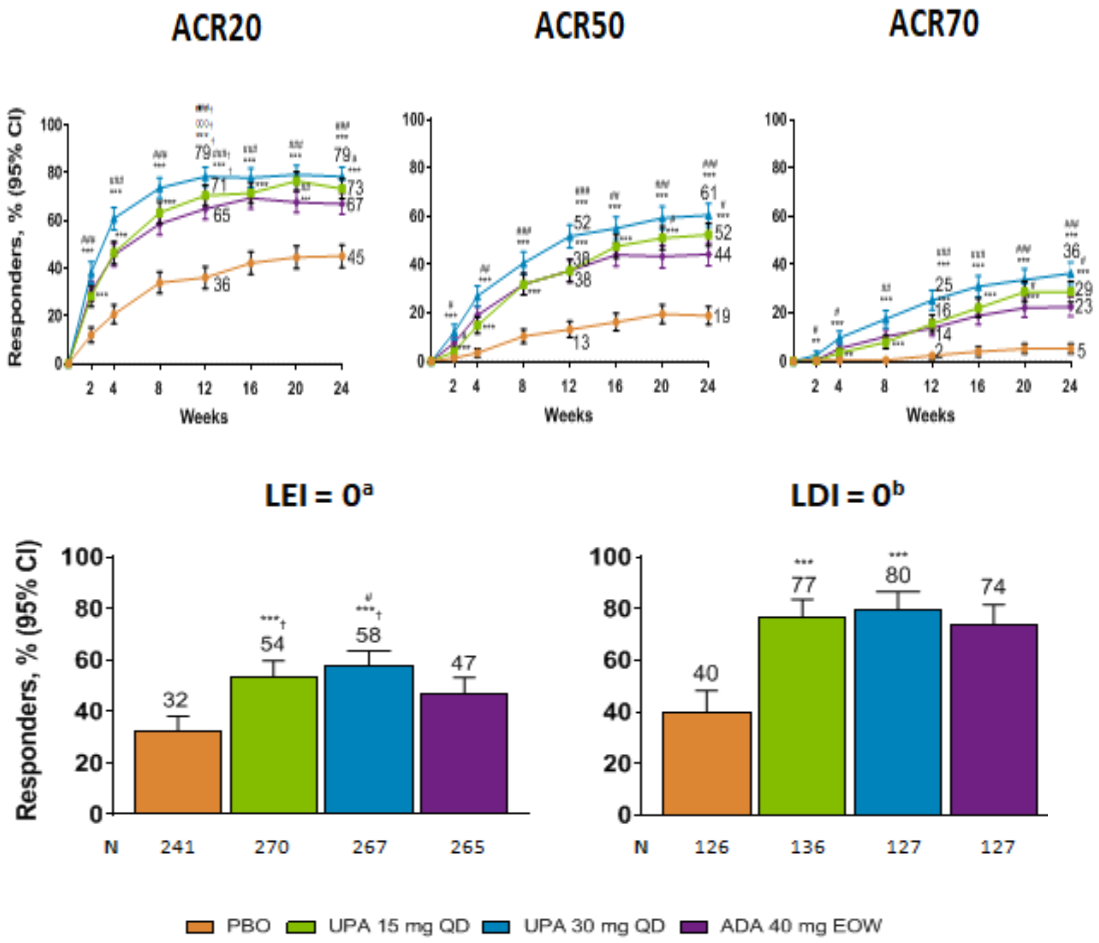


N Engl J Med 2017; 377:1537-1550

Scientific Abstracts
Late breaking abstracts Opening Plenary abstract session

LB0001 EFFICACY AND SAFETY OF UPADACITINIB VERSUS PLACEBO AND ADALIMUMAB IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS AND INADEQUATE RESPONSE TO NON-BIOLOGIC DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (SELECT-PsA-1): A DOUBLE-BLIND, RANDOMIZED CONTROLLED PHASE 3 TRIAL FREE

I. Mcinnes[1], J. Anderson[2], M. Magrey[3], J. F. Merola[4], Y. Liu[5], M. Kishimoto[6], S. Jeka[7], C. F. Pacheco Tena[8], X. Wang[2], L. Chen[2], P. Zueger[2], A. Pangan[2], F. Behrens[9]

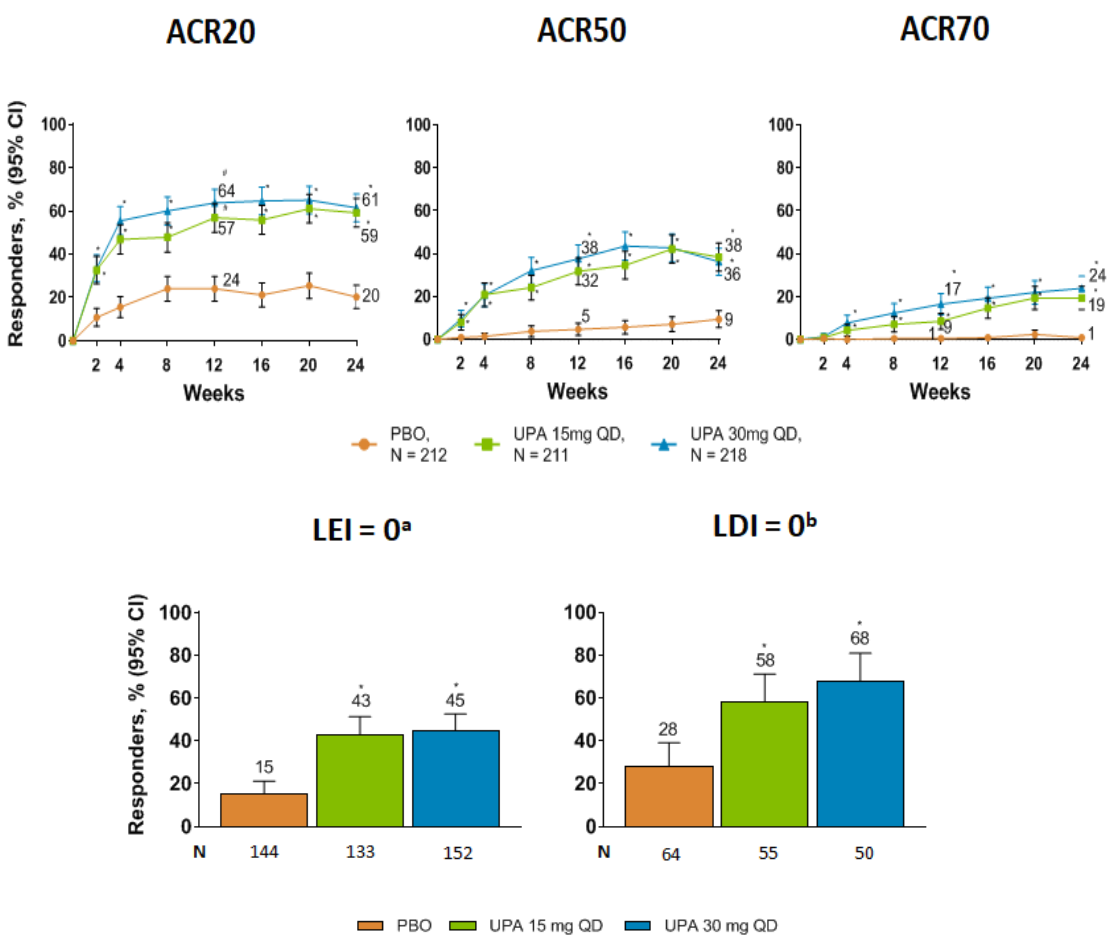


http://dx.doi.org/10.1136/annrheumdis-2020-eular.6727

Scientific Abstracts
Oral Presentations Update on new treatment options for psoriatic arthritis

OP0223 EFFICACY AND SAFETY OF UPADACITINIB IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS AND INADEQUATE RESPONSE TO BIOLOGIC DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (SELECT-PSA-2): A DOUBLE-BLIND, RANDOMIZED CONTROLLED PHASE 3 TRIAL FREE

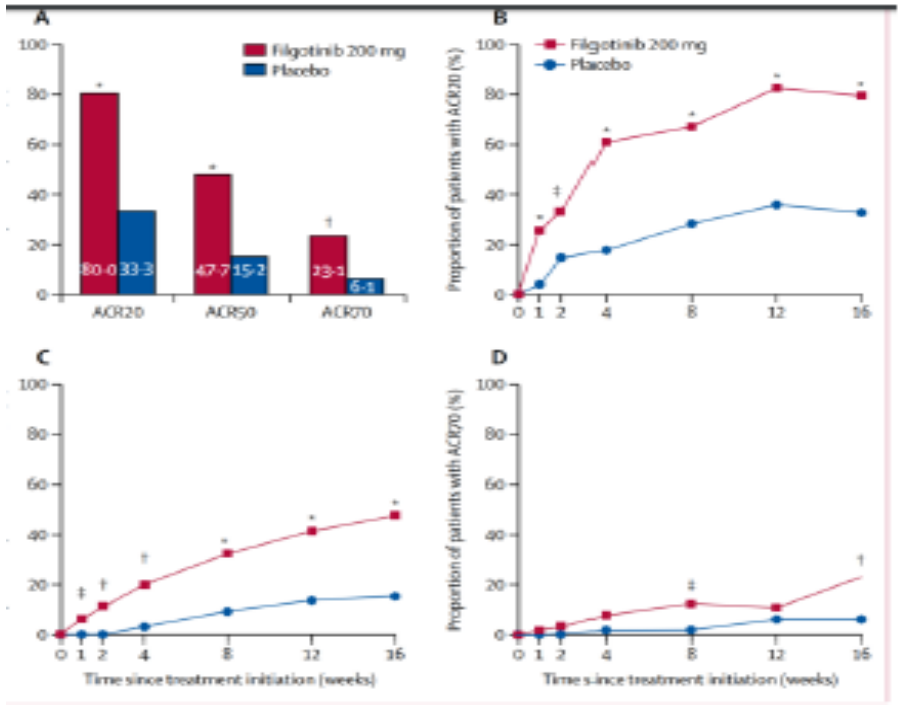
M. C. Genovese[1], A. Lertratanakul[2], J. Anderson[2], K. Papp[3], W. Tillett[4], F. Van den Bosch[5], S. Tsuji[6], E. Dokoupilova[7], M. Keiserman[8], X. Wang[2], S. Zhong[2], P. Zueger[2], A. Pangan[2], P. J. Mease[9]

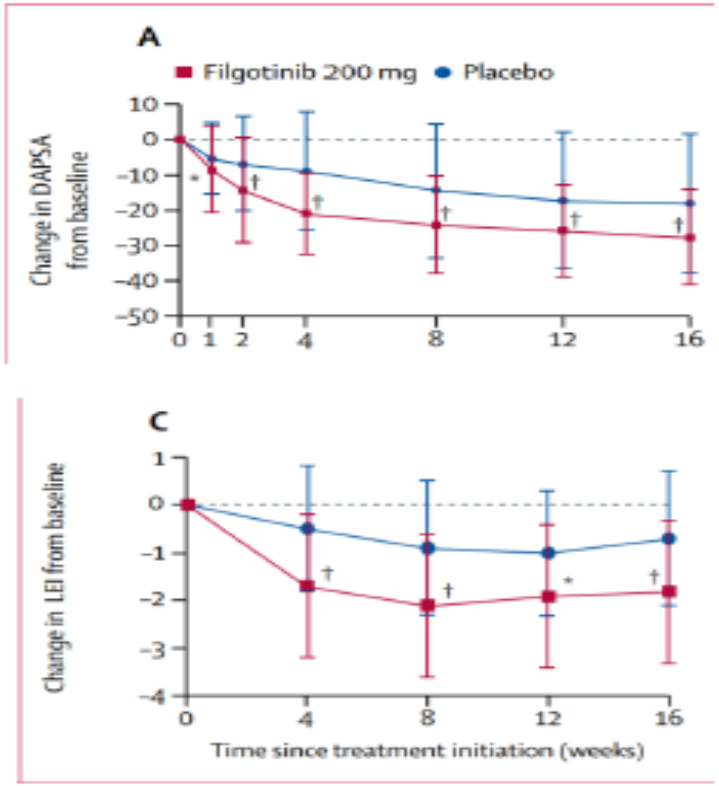


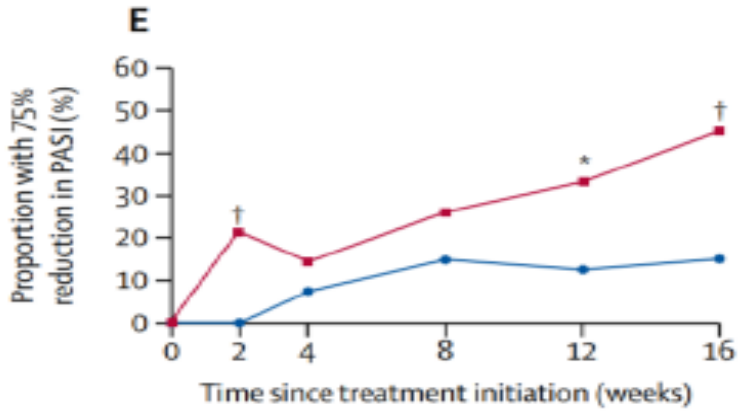
http://dx.doi.org/10.1136/annrheumdis-2020-eular.1229

Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial

THE LANCET
FULL-TEXT ARTICLE







Mease P ET al, Lancet. 2018 Dec 1;392(10162):2367-2377.

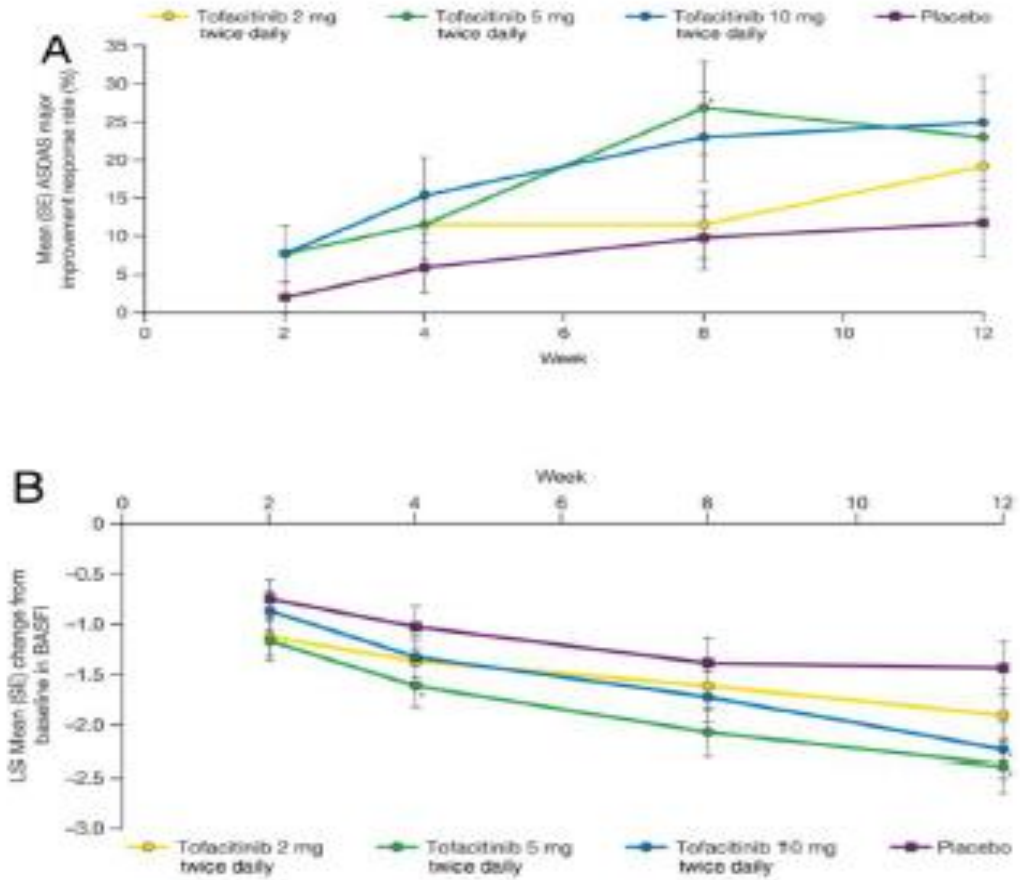
ARD Online First, published on January 27, 2017 as 10.1136/annrheumdis-2016-210322
Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

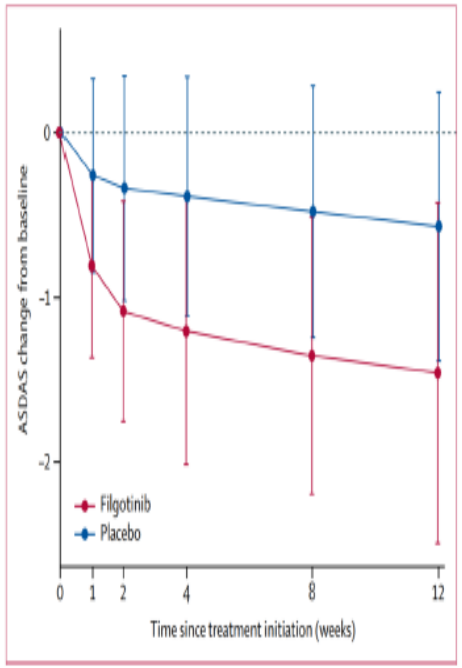
Tofacitinib in patients with ankylosing spondylitis: a phase II, 16-week, randomised, placebo-controlled, dose-ranging study

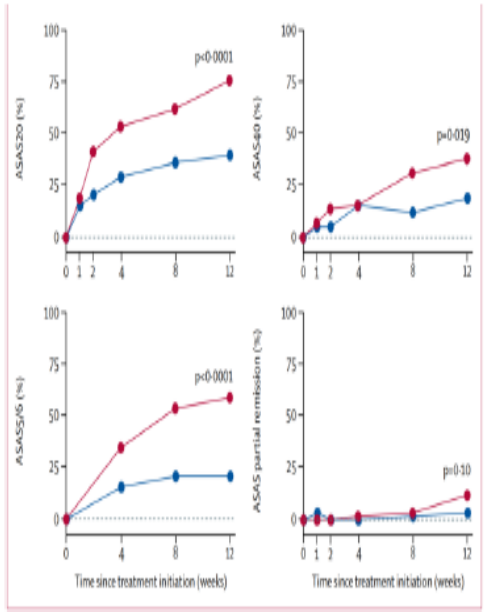
Désirée van der Heijde,[1] Atul Deodhar,[2] James C Wei,[3] Edit Drescher,[4] Dona Fleishaker,[5] Thijs Hendrikx,[6] David Li,[6] Sujatha Menon,[5] Keith S Kanik[5]



Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active ankylosing spondylitis (TORTUGA): results from a randomised, placebo-controlled, phase 2 trial

Désirée van der Heijde, Xenofon Baraliakos, Lianne S Gensler, Walter P Maksymowych, Vira Tseluyko, Oleg Nadashkevich, Walid Abi-Saab, Chantal Tasset, Luc Meuleners, Robin Besuyen, Thijs Hendrikx, Neelufar Mozaffarian, Ke Liu, Joy M Greer, Atul Deodhar, Robert Landewé



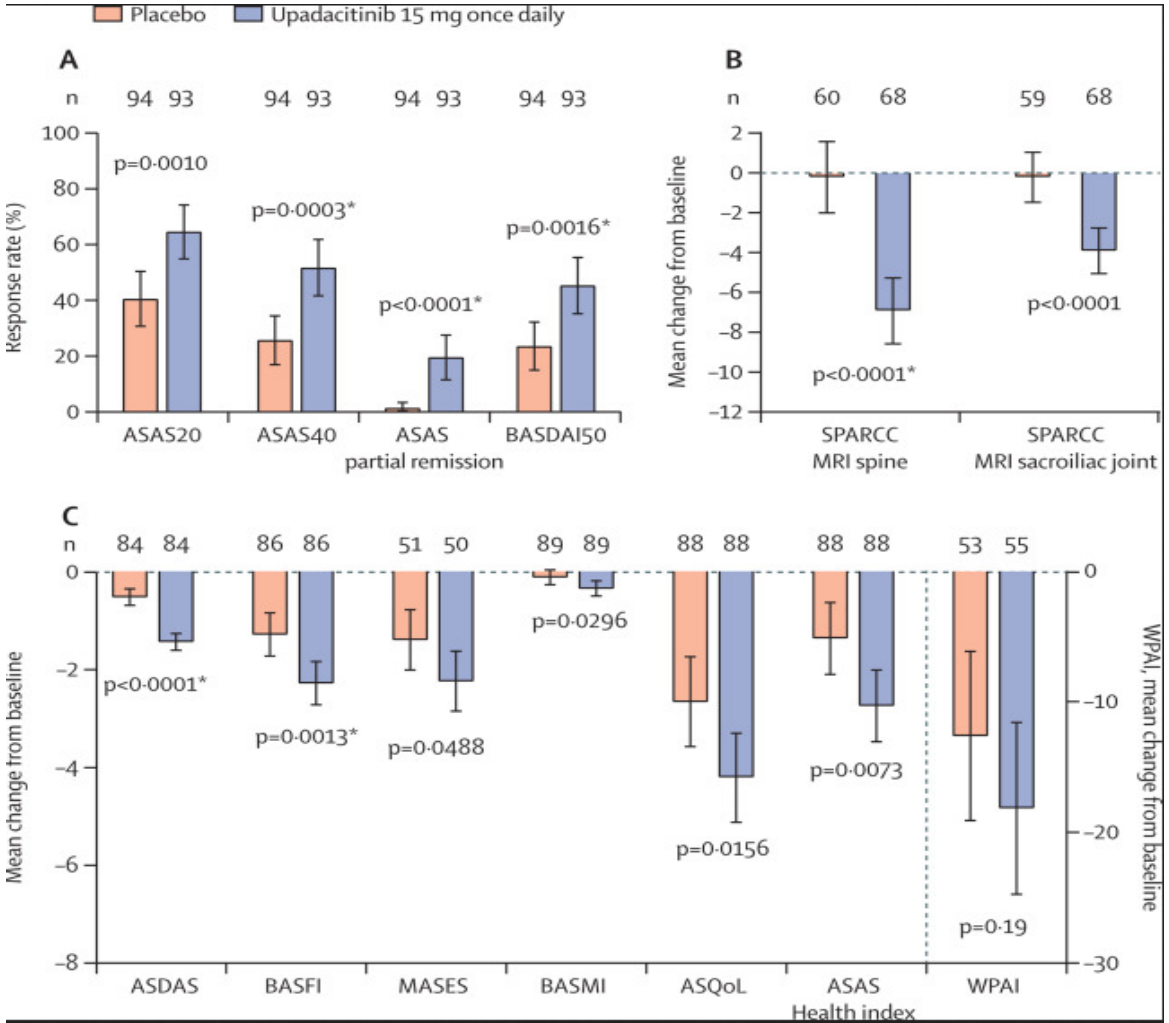


THE LANCET
Available online 12 November 2019
In Press, Corrected Proof

Articles

Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial

Prof Désirée van der Heijde MD [a], In-Ho Song MD [b], Aileen L Pangan MD [b], Prof Atul Deodhar MD, Prof Filip van den Bosch MD [d], Prof Walter P Maksymowych MD [e], Prof Tae-Hwan Kim MD [f], Mitsumasa Kishimoto MD [g], Andrea Everding MD [h], Yunxia Sui PhD [b], Xin Wang PhD [b], Alvina D Chu MD [b], Prof



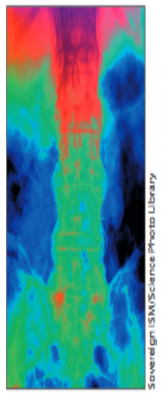
Comment

JAK inhibitors: promising for a wider spectrum of autoimmune diseases?

JAK and signal transducers and activators of the transcription signal transduction (known as STAT) pathway and upstream cytokine receptor signalling have a principal role in the pathogenesis of many inflammatory and autoimmune conditions, including inflammatory bowel disease, psoriasis, rheumatoid arthritis, spondyloarthritis, and systemic lupus erythematosus.[1] There are four JAKs in humans, JAK1, JAK2, and JAK3, and TYK2. Several JAK inhibitors have been developed over the past decade targeting a broad range of JAKs (ie, pan-JAK) or only specific JAKs (ie, selective JAK inhibitors), providing promising alternatives to parenteral biological disease-modifying antirheumatic drugs (DMARDs) in some autoimmune disorders.[2,3]

Three JAK inhibitors, tofacitinib (JAK1–3 inhibitor), baricitinib (JAK1 and JAK2 inhibitor), and upadacitinib (selective JAK1 inhibitor), have been approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis, with tofacitinib and baricitinib also approved by the European Medicines Agency, and

The results of the first randomised trial of upadacitinib versus placebo in patients with active ankylosing spondylitis and a previous inadequate response to at least two NSAIDs or intolerance or contraindication for NSAIDs are reported by Désirée van der Heijde and colleagues[8] in *The Lancet*. 187 eligible patients (71% male, mean age 45·4 years), enrolled from 62 sites in 20 countries, were randomly assigned 1:1 to upadacitinib 15 mg or placebo for a 14-week double-blind period. The study met its primary efficacy endpoint of Assessment of SpondyloArthritis International Society 40 (ASAS40) response (51·6% in upadacitinib group vs 25·5% in the placebo group), defined as at least a 40% improvement and an absolute improvement of two or more units (on a 0–10 scale) from baseline in at least three of four domains including patient global assessment of disease, spinal pain, function, and inflammation, with no worsening in the remaining domain. ASAS40 is a more challenging and a higher standard response criterion than ASAS20 that was



Published Online November 12, 2019 https://doi.org/10.1016/S0140-6736(19)32681-9
See Online/Articles https://doi.org/10.1016/S0140-6736(19)32534-6

Maria G Tektonidou
First Department of Propaedeutic Internal Medicine, School of Medicine, National and Kapodistrian University of Athens, Laikon Hospital, 11527, Athens, Attiki, Greece
mtektonidou@med.uoa.gr

- ✓ Biologic DMARDS effective drugs in inflammatory arthropathies
- ✓ Established treatment
- ✓ Long term data
- ✓ Relatively safe (cancer, lymphoma)
- ✓ Experience

- ✓Small molecules
- ✓Different mode of action
- ✓Additional therapeutic option
- ✓More effective than bDMARDS in RA (??)
- ✓No significant signals regarding safety (caution in VTE, infections, HZV)
- ✓Reproductive issues
- ✓Unexpected side effects?