
# 10+ χρόνια JAK αναστολείς: τι άλλαξε στη ζωή των ρευματοπαθών;

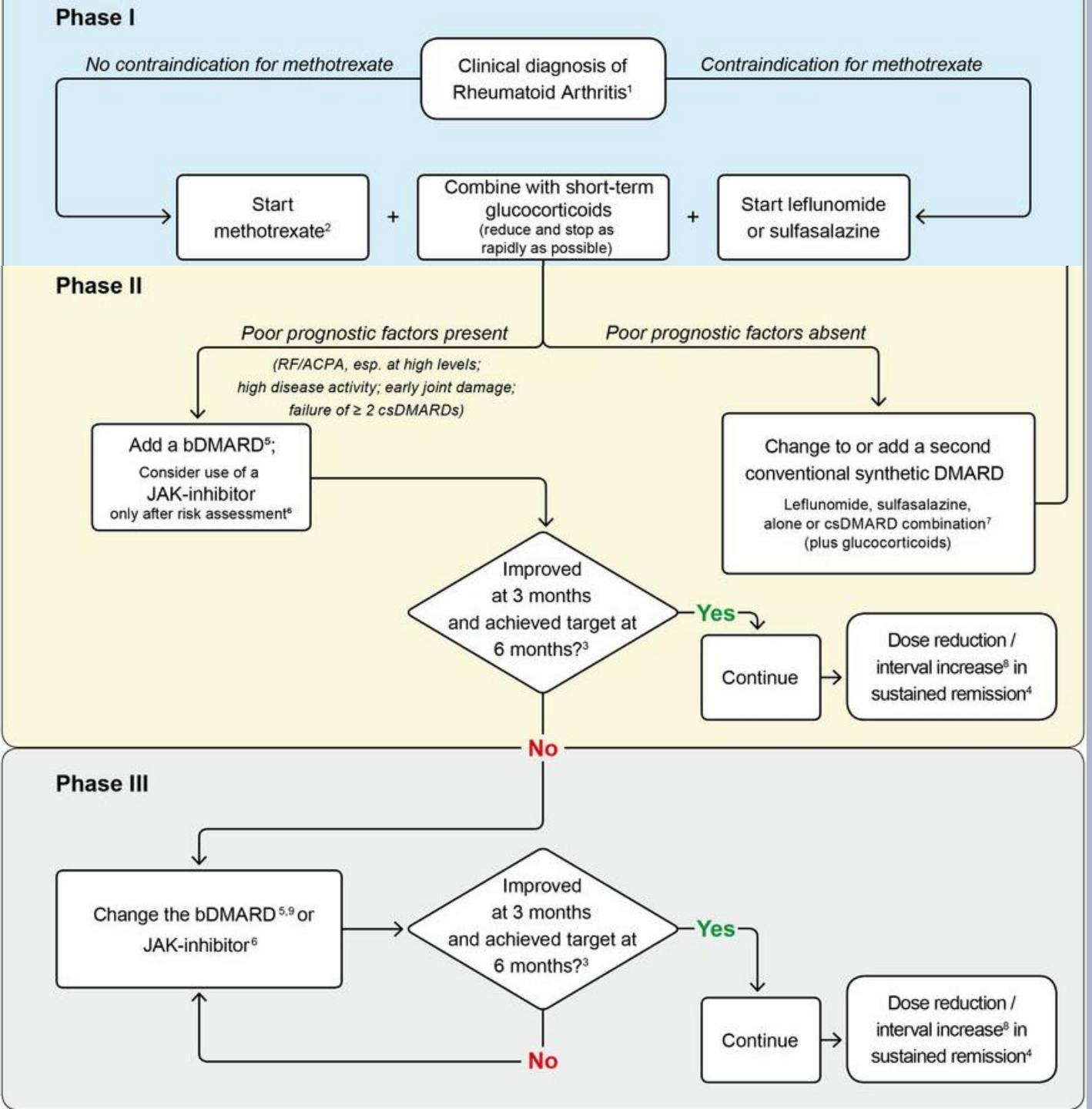
## Ασθενής με PA σε γρήγορη ύφεση με JAKi

**Ιωάννης Αντωνόπουλος**

**Ρευματολόγος**

# Σύγκρουση συμφερόντων

Καμία για την παρούσα ομιλία




Recommendation

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update FREE

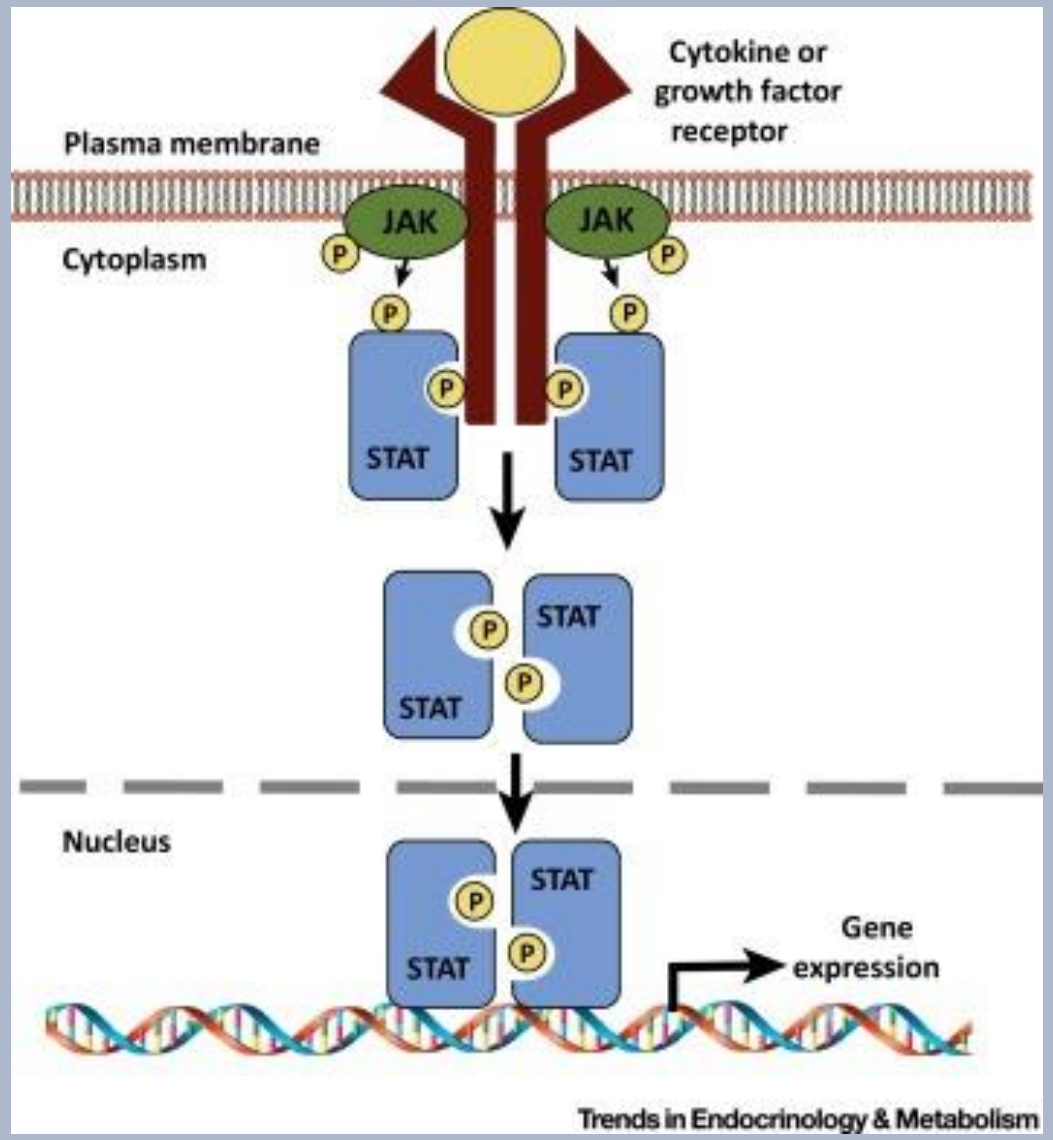
- ❑ αντι TNF
- ❑ αντι IL6
- ❑ αντι CD20
- ❑ ανταγωνιστής συνδιέγερσης
- ❑ αναστολείς JAK-STAT (JAKis)

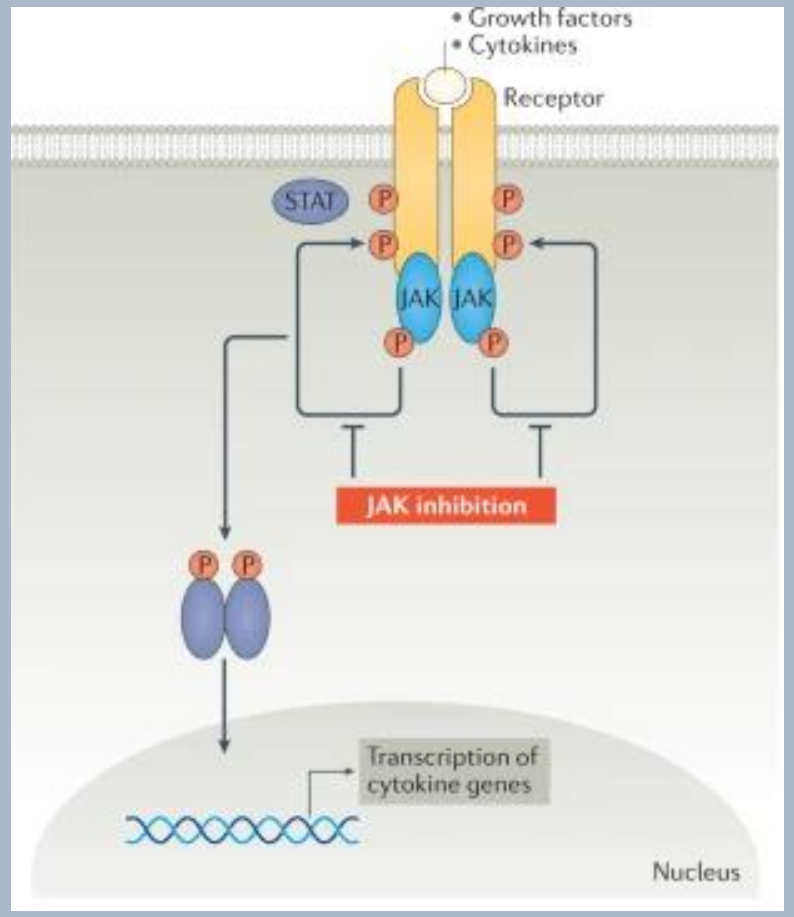
**Josef S Smolen et al. Ann Rheum Dis 2023;82:3-18**

**1989**
*Wilks discovers JAKs*

**1996**
*First JAK inhibition study*

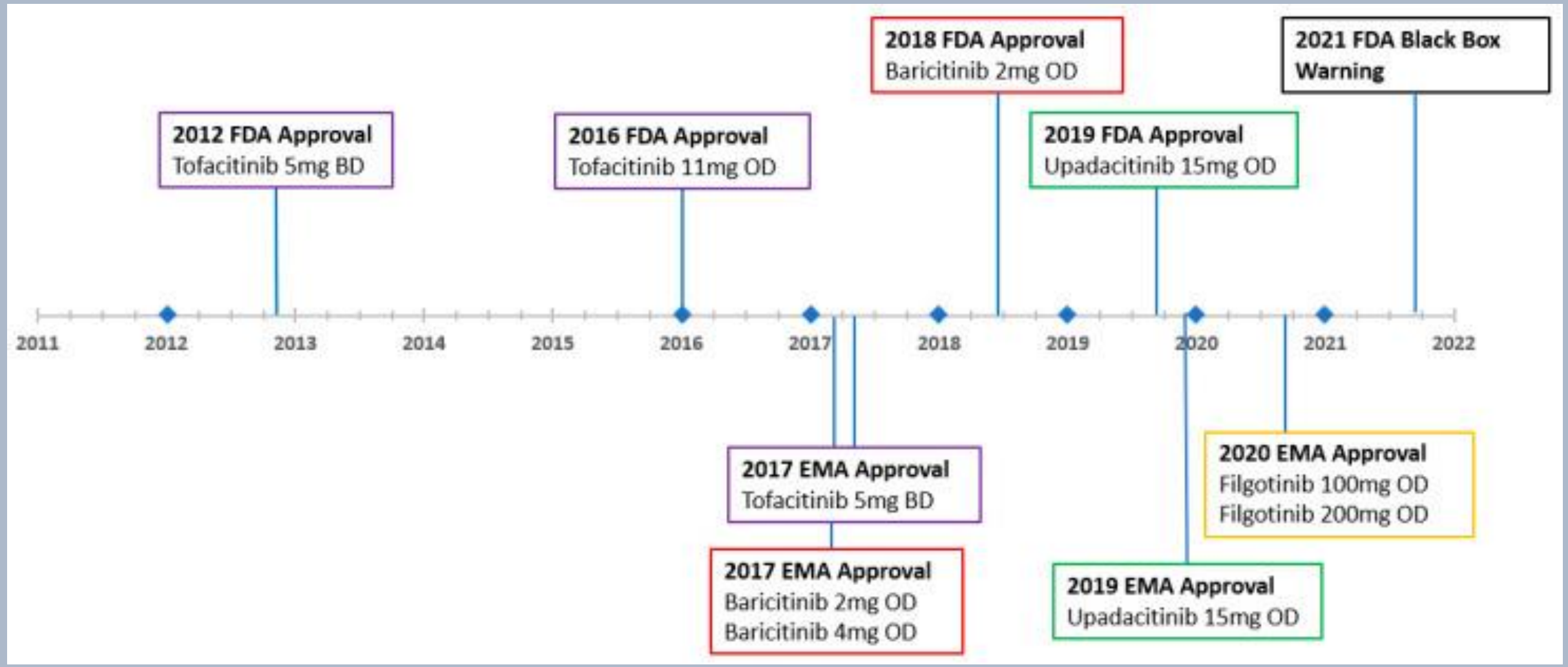
# JAKis μία νέα θεραπευτική κατηγορία




| JAKi | Manufacturer | JAK selectivity | Dose | Recommended by NICE for RA | FDA approval for RA | EMA approval for RA | Japan approval for RA |
|---|---|---|---|---|---|---|---|
| Tofacitinib | Pfizer (New York City, USA) | Pan-JAK | 5 mg BD<br>11 mg OD | Yes: severe RA | November 2021 | March 2017 | March 2013 |
| Baricitinib | Eli Lilly and Company (Indianapolis, Indiana, USA) | JAK1 and JAK2 | 2 mg OD<br>4 mg OD | Yes: severe RA | May 2018 | February 2017 | July 2017 |
| Upadacitinib | AbbVie (Chicago, Illinois) | JAK1 | 15 mg OD | Yes: severe RA | August 2019 | December 2019 | January 2020 |
| Filgotinib | Gilead Sciences, Inc. (Foster City, California, USA) and Galapagos Galapagos (Mechelen, Belgium) | JAK1 | 100 mg OD<br>200 mg OD | Yes: moderate RA | N/A | September 2020 | September 2020 |
| Peficitinib | Astellas Pharma Ltd. (Tokyo, Japan) | JAK3 | 25 mg OD<br>50 mg OD<br>100 mg OD<br>150 mg OD | N/A | N/A | N/A | March 2019 |

*Nat Rev Rheumatol **18**, 133–145 (2022)*




*J Clin Med. 2023 Oct; 12(20): 6690*

# Παρουσίαση περιστατικού

Medicine Matters® rheumatology

07-06-2019 | Rheumatoid arthritis | Case study | Article

## Tofacitinib in a patient with refractory severe rheumatoid arthritis

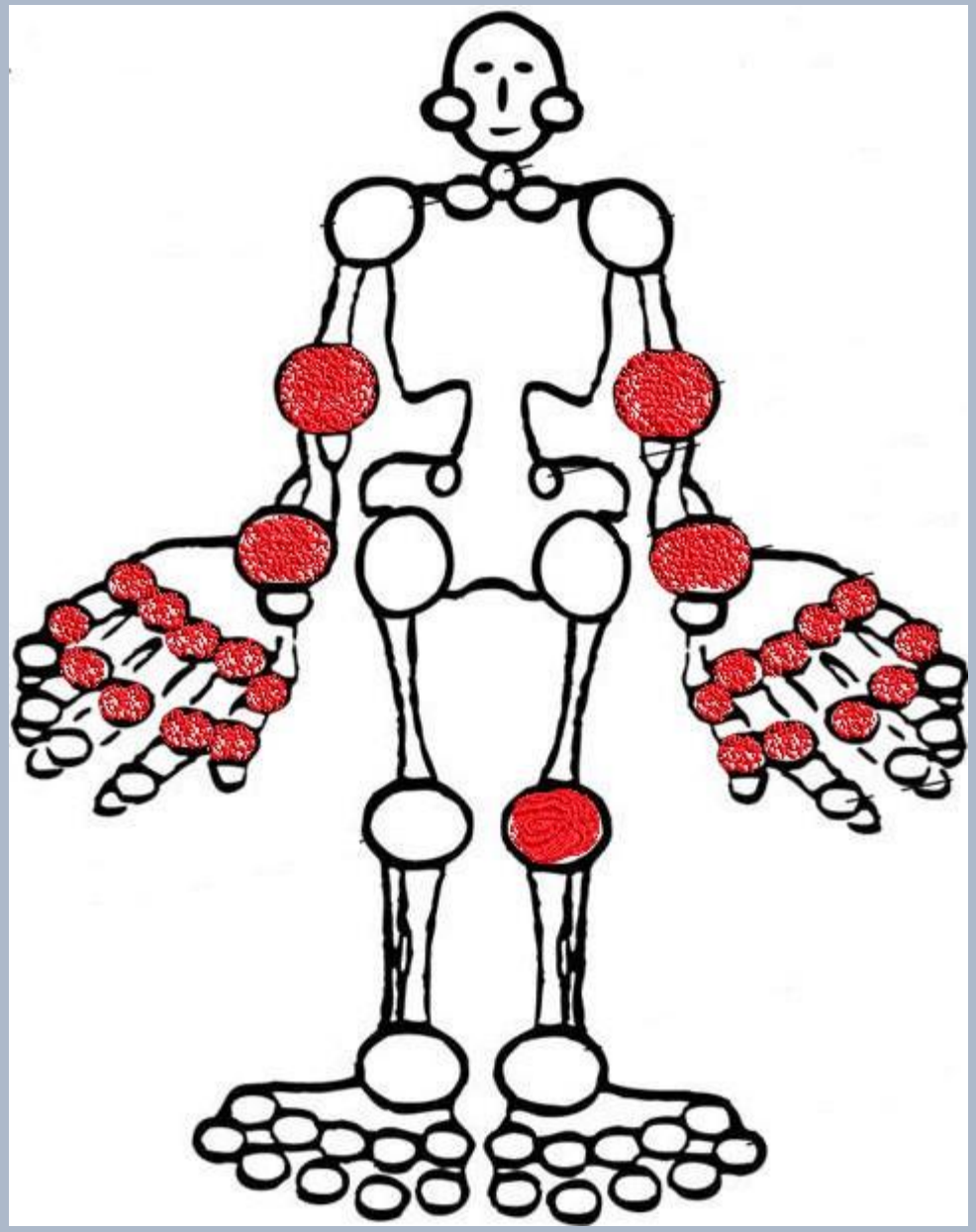
Authors: Paul Emery, John Fitton

# Ατομικό αναμνηστικό

- 75 ετων οροθετική ΡΑ 30 ετη
- υπερθυρεοειδισμός και θυρεοειδεκτομή 1967
- πεπτικό έλκος
- μονοκλωνική γαμμοπάθεια 2006

# Φαρμακευτικό ιστορικό

- στεροειδή και χρυσός (διακοπή λόγω εξαθήματος)
- MTX, AZA, κυκλοσπορίνη, σουλφασαλαζίνη (διακοπή λόγω ναυτίας, ανορεξίας, κακουχίας)
- συντήρηση με **πρεδνιζολόνη** 5-15mg OD
- 2001 λεφλουνομίδη καλη ανταπόκριση
- 2003 έξαρση DAS 5.4
- 2004 **etanercept** 25mg δύο φορές την εβδομάδα καλη ανταποκριση
- 2005 δευτερογενης αστοχία στο χρόνο
- 2006 **adalimumab** πρωτογενής αστοχία
- 2006 **rituximab** (clinical trial)  αστοχία μετά 3 κύκλους
- **tocilizumab** IV καλη ανταπόκριση, 2017 δευτερογενής αστοχία
- **abatacept** χωρις βελτίωση και κυτταρίτιδα στοματικά έλκη



- TJC 26, SJC 25
- VAS 100
- CRP 56mg/L
- DAS 28 8.07

- tofacitinib 5mg BD
- πρεδνιζολόνη 10mg OD
- ταχεία βελτίωση
- 4/52 ναυτία και υφεση
- 8/52 πνευμονία
  - 14/12 tofacitinib χωρίς στεροειδή
  - DAS 28 1.77 (TJC 0, SJC 0, CRP κφ)

# Αποτελεσματικότητα JAKis

- υπεροχή σε σχέση  με τη μεθοτρεξάτη
- σύγκριση με παραδοσιακούς βιολογικούς παράγοντες
- δυσανεξία στη μεθοτρεξάτη?

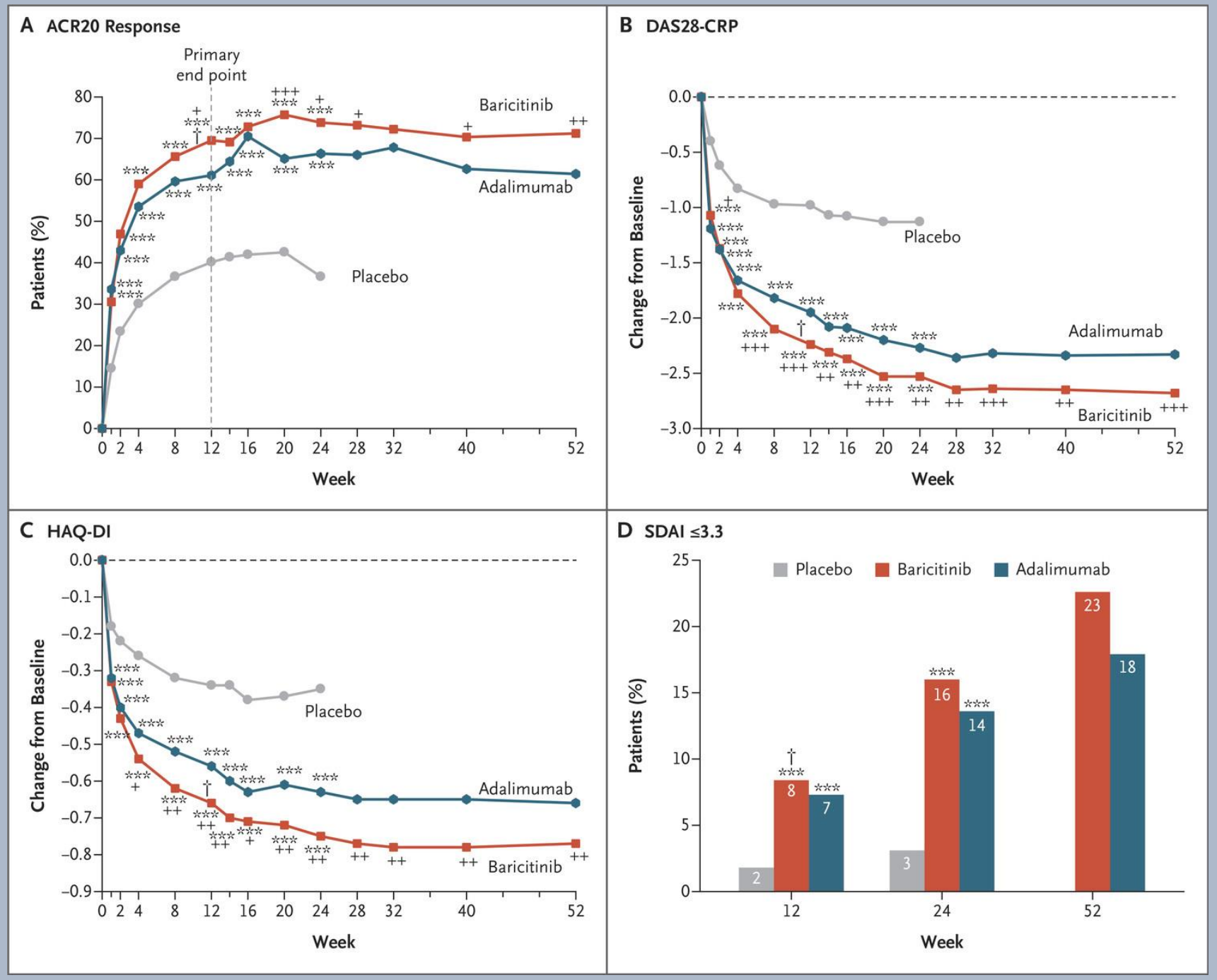
# RA BEAM

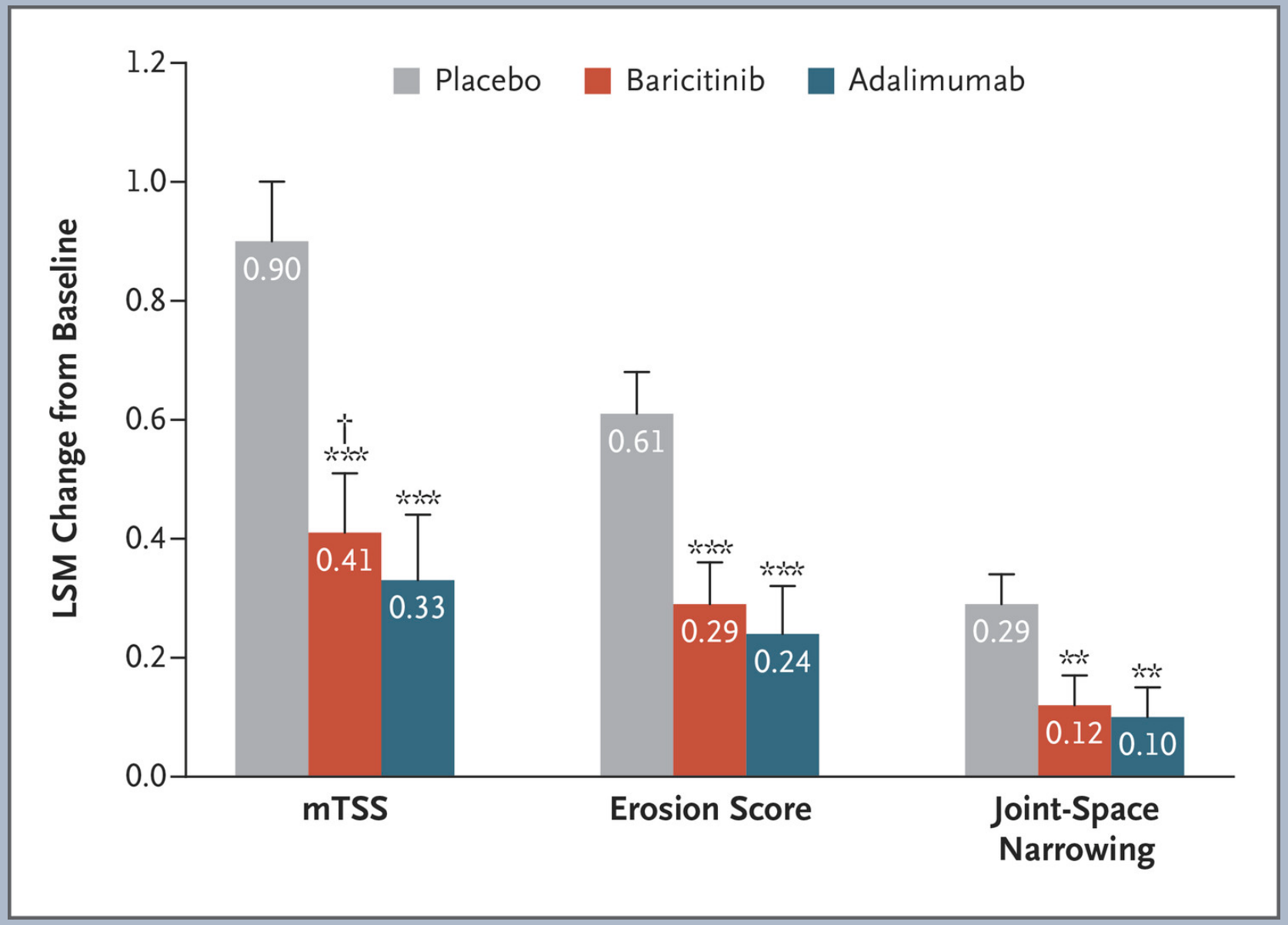
The NEW ENGLAND JOURNAL of MEDICINE

## Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis

**Authors**: Peter C. Taylor, M.D., Ph.D., Edward C. Keystone, M.D., Désirée van der Heijde, M.D., Ph.D., Michael E. Weinblatt, M.D., Liliana del Carmen Morales, M.D., Jaime Reyes Gonzaga, M.D., Sergey Yakushin, M.D., +9, and Yoshiya Tanaka, M.D., Ph.D. Author Info & Affiliations

**Published February 16, 2017** | **N Engl J Med 2017;376:652-662** | **DOI: 10.1056/NEJMoa1608345** | **VOL. 376 NO. 7**


A ACR20 Response
Primary end point
Baricitinib
Adalimumab
Placebo
Patients (%)
Week
B DAS28-CRP
Placebo
Adalimumab
Baricitinib
Change from Baseline
Week
C HAQ-DI
Placebo
Adalimumab
Baricitinib
Change from Baseline
Week
D SDAI ≤3.3
Placebo
Baricitinib
Adalimumab
Patients (%)
2
8
7
3
16
14
23
18
12
24
52
Week

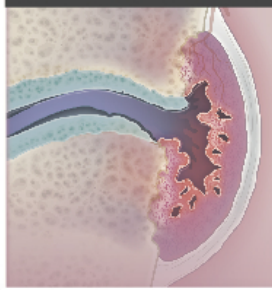

Placebo
Baricitinib
Adalimumab
LSM Change from Baseline
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.90
0.41
0.33
0.61
0.29
0.24
0.29
0.12
0.10
†
***
***
***
***
**
**
mTSS
Erosion Score
Joint-Space Narrowing

# SELECT CHOICE

The NEW ENGLAND JOURNAL of MEDICINE

## Upadacitinib or Abatacept for Rheumatoid Arthritis

PHASE 3, DOUBLE-BLIND, RANDOMIZED, ACTIVE-COMPARATOR TRIAL

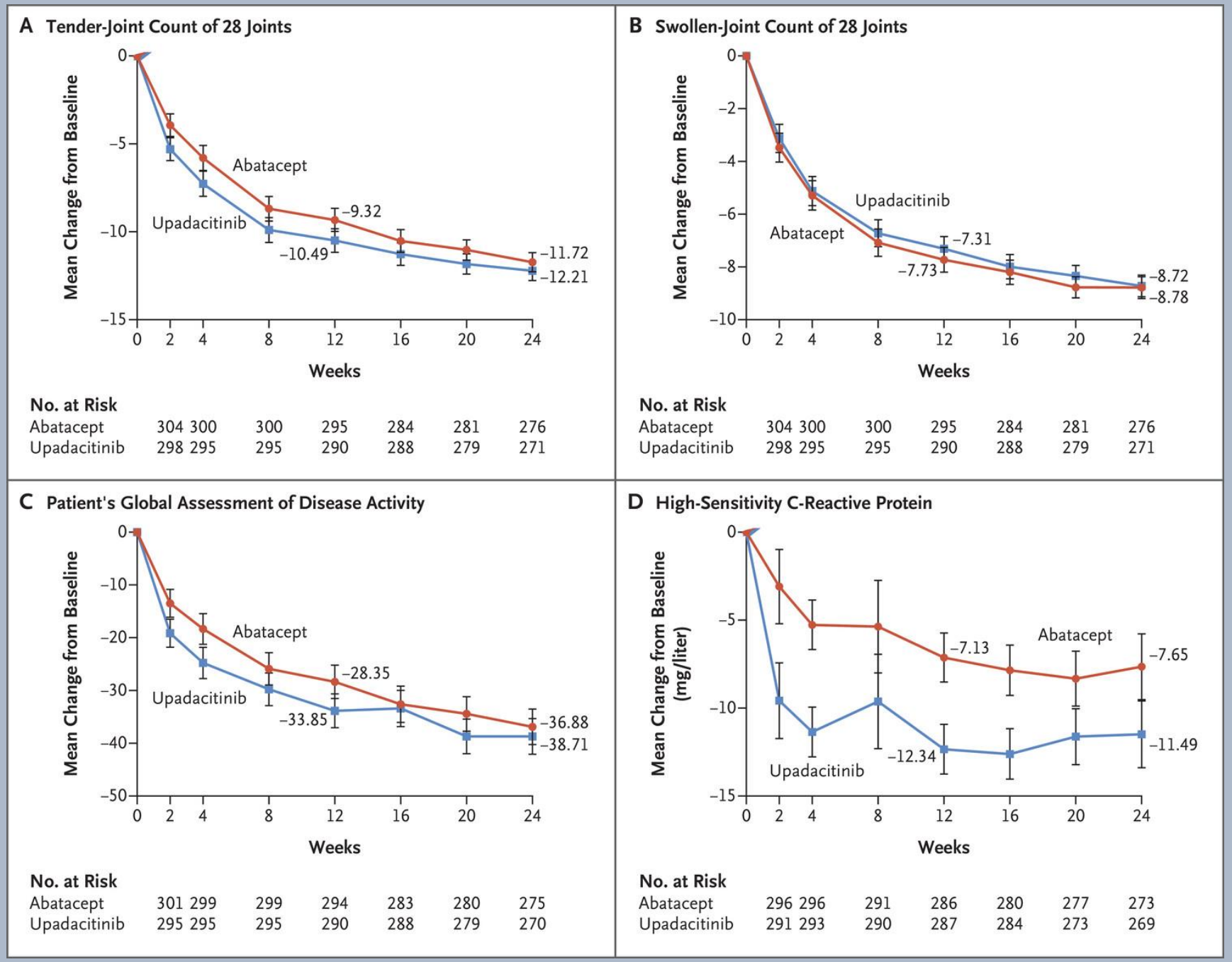


**612**
Patients with moderate-to-severe rheumatoid arthritis

| | Oral upadacitinib (15 mg once daily) | IV abatacept |
|---|---|---|
| |  (N=303) |  (N=309) |
| Change in DAS28-CRP at 12 wk (range, 0 to 9.4; higher score = greater disease activity) | −2.52 | −2.00 |
| | Difference, −0.52; 95% CI, −0.69 to −0.35; P<0.001 for noninferiority; P<0.001 for superiority | |
| Patients achieving clinical remission (DAS28-CRP <2.6) | 30.0% | 13.3% |
| | Difference, 16.8 percentage points; 95% CI, 10.4 to 23.2; P<0.001 for superiority | |

**Upadacitinib was superior to abatacept at 12 wk but was associated with more serious adverse events.**

A. Rubbert-Roth et al. 10.1056/NEJMoa2008250

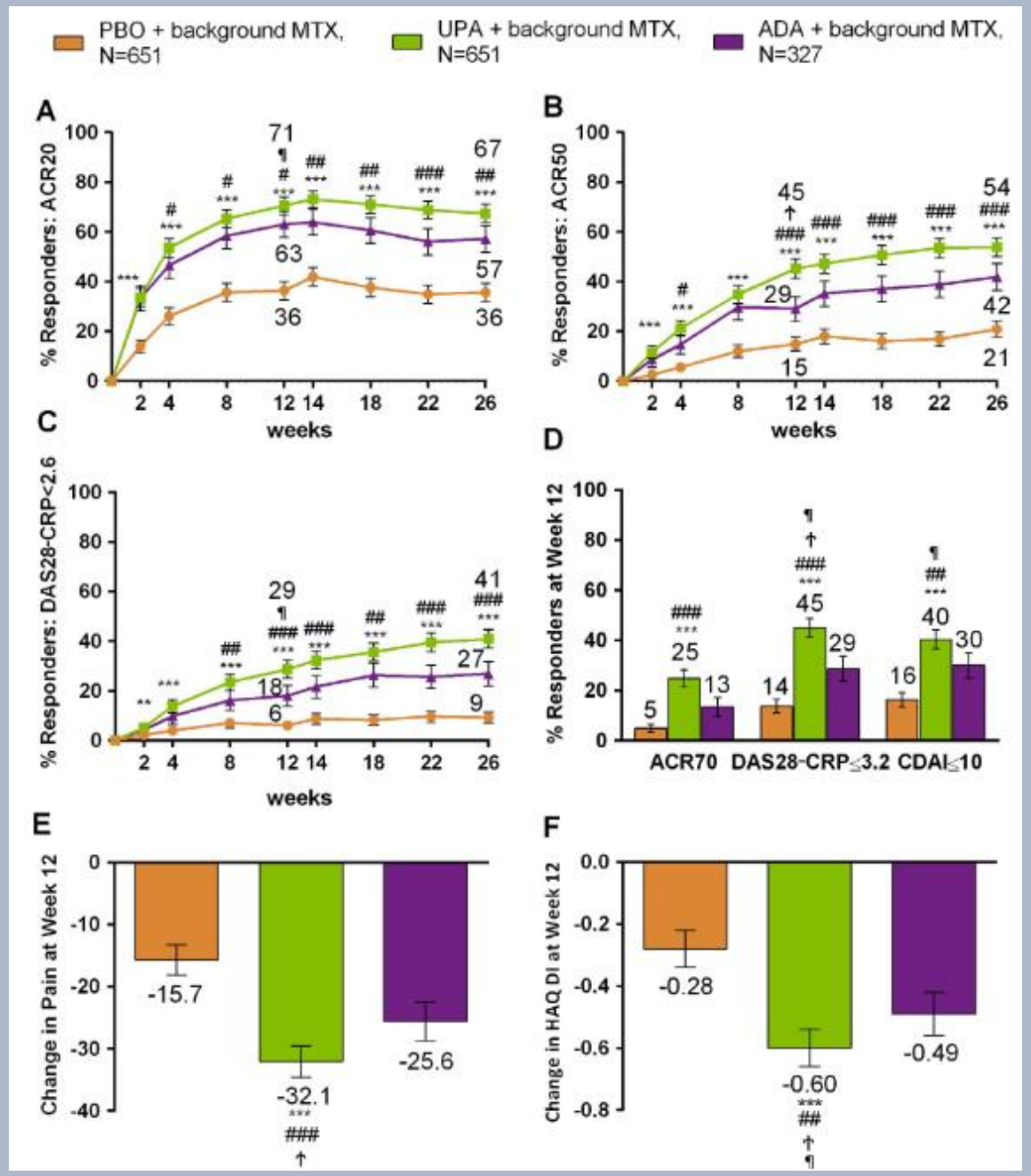

A Tender-Joint Count of 28 Joints
Mean Change from Baseline
0
−5
−10
−15
Abatacept
Upadacitinib
−9.32
−10.49
−11.72
−12.21
0 2 4 8 12 16 20 24
Weeks
No. at Risk
Abatacept 304 300 300 295 284 281 276
Upadacitinib 298 295 295 290 288 279 271
B Swollen-Joint Count of 28 Joints
Mean Change from Baseline
0
−2
−4
−6
−8
−10
Upadacitinib
Abatacept
−7.31
−7.73
−8.72
−8.78
0 2 4 8 12 16 20 24
Weeks
No. at Risk
Abatacept 304 300 300 295 284 281 276
Upadacitinib 298 295 295 290 288 279 271
C Patient's Global Assessment of Disease Activity
Mean Change from Baseline
0
−10
−20
−30
−40
−50
Abatacept
Upadacitinib
−28.35
−33.85
−36.88
−38.71
0 2 4 8 12 16 20 24
Weeks
No. at Risk
Abatacept 301 299 299 294 283 280 275
Upadacitinib 295 295 295 290 288 279 270
D High-Sensitivity C-Reactive Protein
Mean Change from Baseline (mg/liter)
0
−5
−10
−15
Abatacept
−7.13
−7.65
Upadacitinib
−12.34
−11.49
0 2 4 8 12 16 20 24
Weeks
No. at Risk
Abatacept 296 296 291 286 280 277 273
Upadacitinib 291 293 290 287 284 273 269

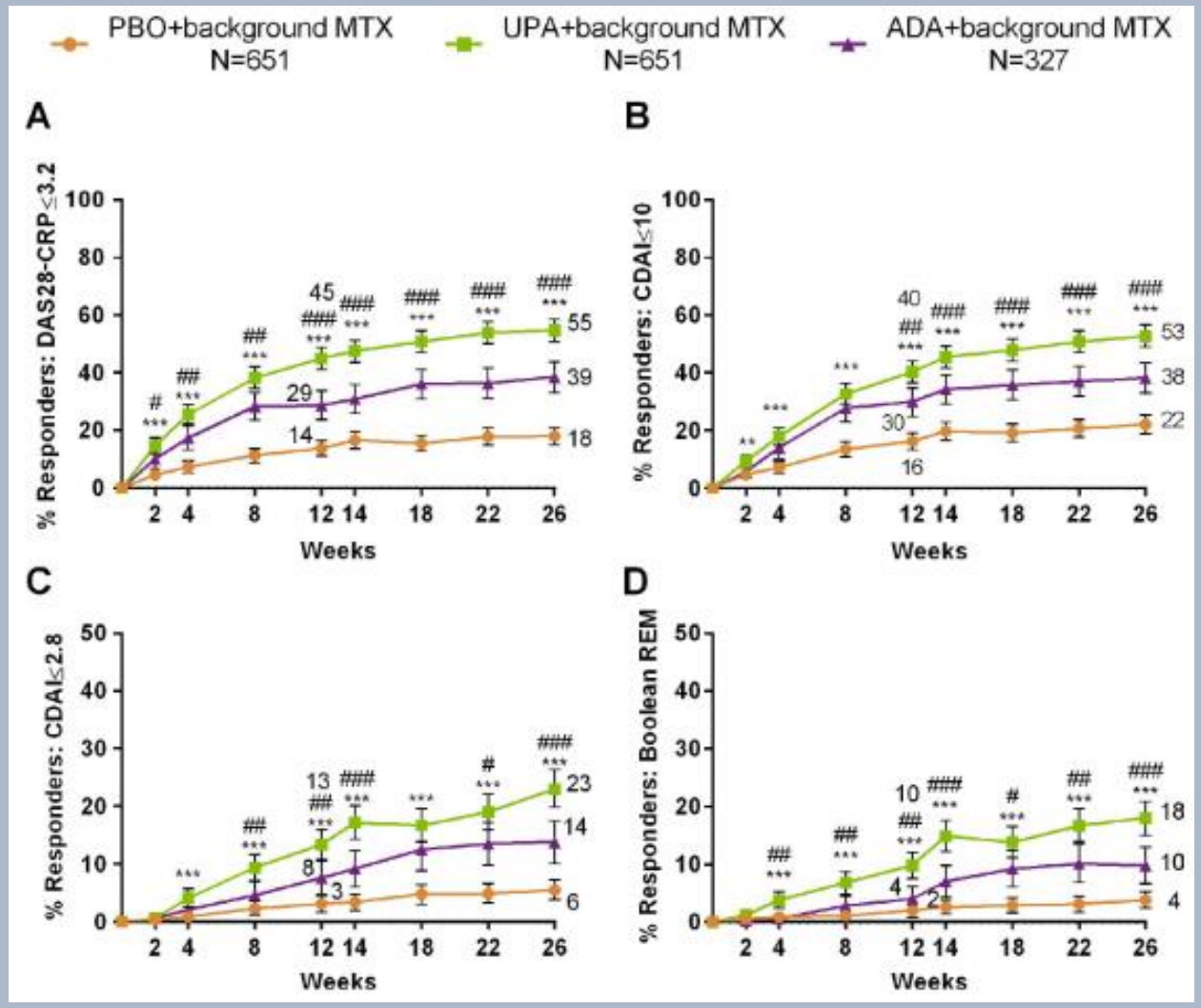
# SELECT COMPARE

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis & Rheumatology
Vol. 71, No. 11, November 2019, pp 1788–1800
DOI 10.1002/art.41032


## Upadacitinib Versus Placebo or Adalimumab in Patients With Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial


PBO + background MTX, N=651
UPA + background MTX, N=651
ADA + background MTX, N=327
A
% Responders: ACR20
weeks
B
% Responders: ACR50
weeks
C
% Responders: DAS28-CRP<2.6
weeks
D
% Responders at Week 12
ACR70
DAS28-CRP≤3.2
CDAI≤10
E
Change in Pain at Week 12
-15.7
-32.1
-25.6
F
Change in HAQ DI at Week 12
-0.28
-0.60
-0.49


PBO+background MTX N=651
UPA+background MTX N=651
ADA+background MTX N=327
A
% Responders: DAS28-CRP≤3.2
Weeks
B
% Responders: CDAI≤10
Weeks
C
% Responders: CDAI≤2.8
Weeks
D
% Responders: Boolean REM
Weeks

# Δυσανεξία στη μεθοτρεξάτη??

Υπεροχή

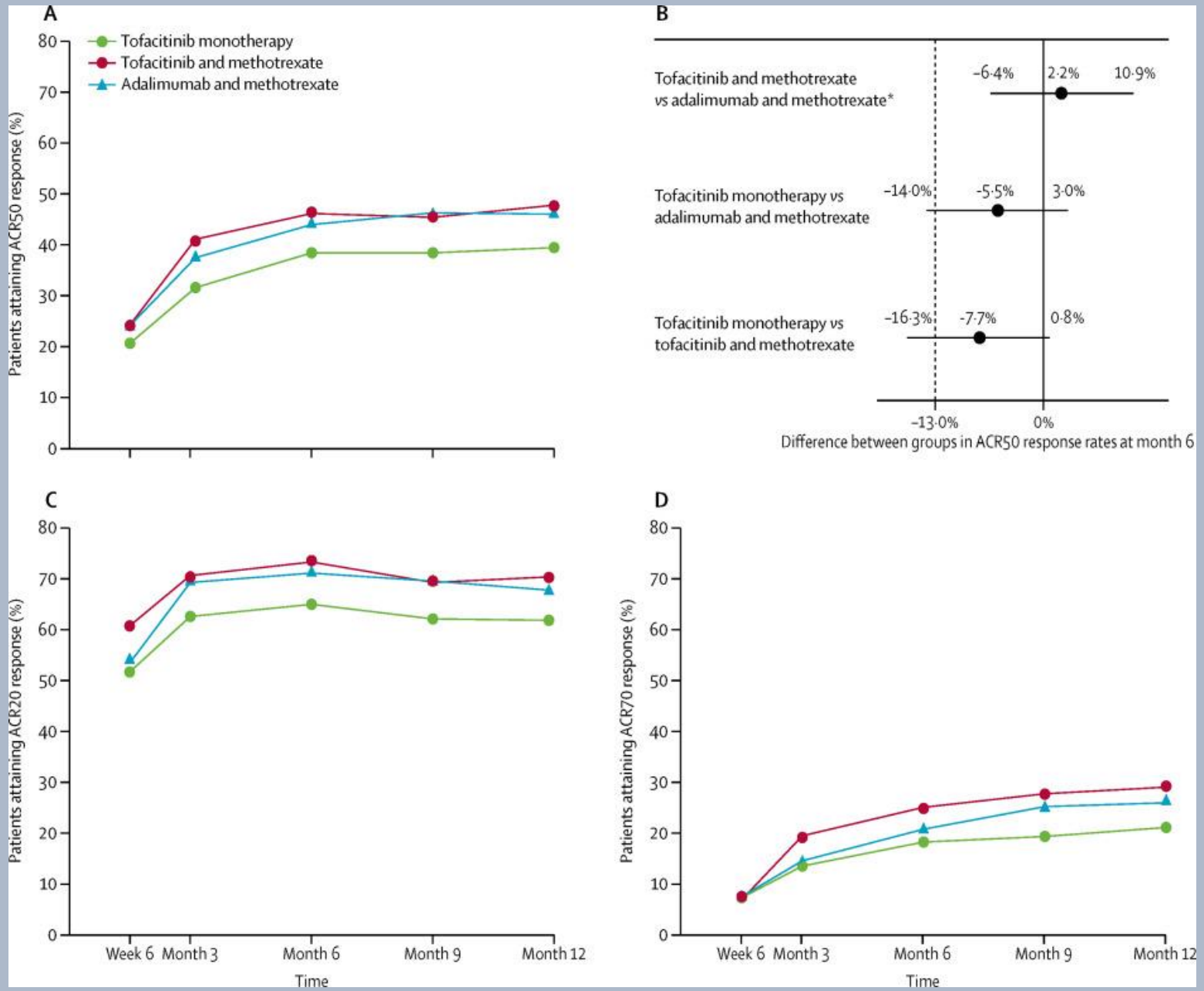
- Tocilizumab
- **JAKis**

THE LANCET

# Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial

Prof Roy Fleischmann, MD • Eduardo Mysler, MD • Stephen Hall, MD • Alan J Kivitz, MD • Prof Robert J Moots, MD • Zhen Luo, PhD • et al. Show all authors • Show footnotes

Published: June 16, 2017 • DOI: https://doi.org/10.1016/S0140-6736(17)31618-5 • 

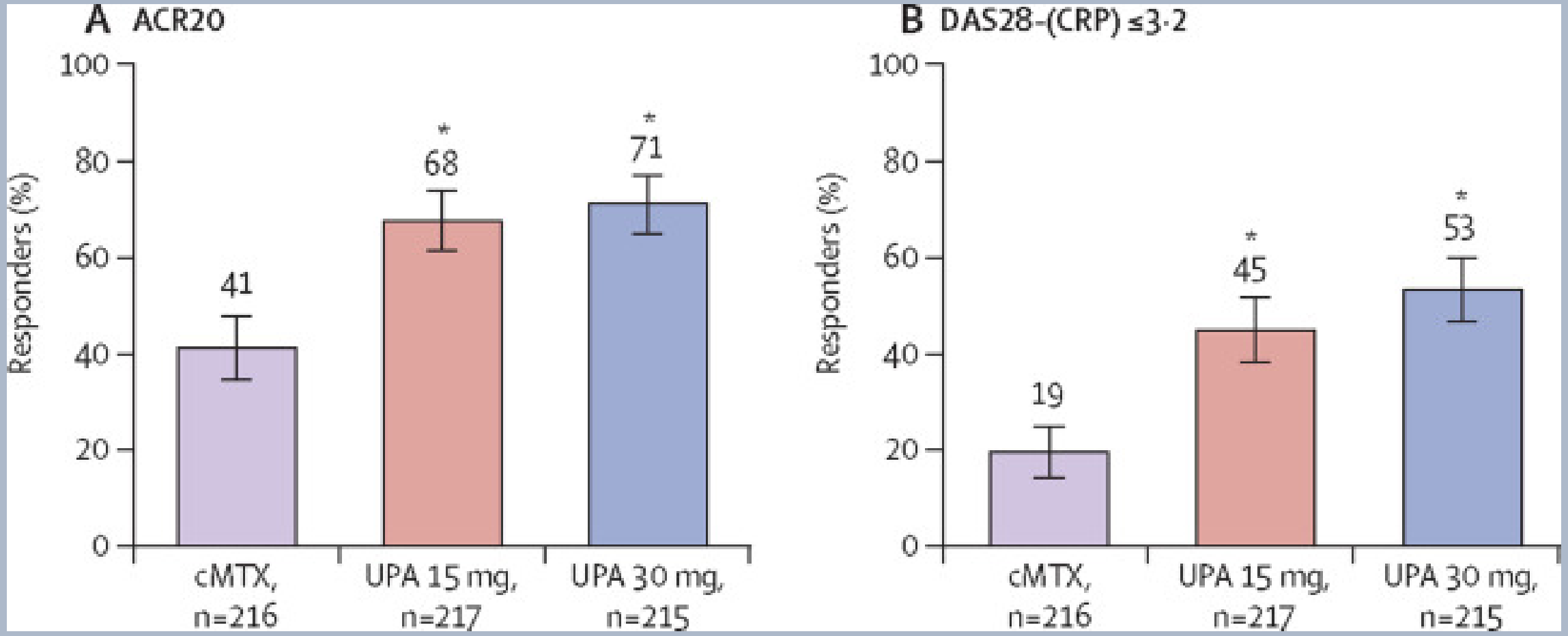

A
Tofacitinib monotherapy
Tofacitinib and methotrexate
Adalimumab and methotrexate
Patients attaining ACR50 response (%)
80
70
60
50
40
30
20
10
0
B
Tofacitinib and methotrexate vs adalimumab and methotrexate*
−6·4%
2·2%
10·9%
Tofacitinib monotherapy vs adalimumab and methotrexate
−14·0%
−5·5%
3·0%
Tofacitinib monotherapy vs tofacitinib and methotrexate
−16·3%
−7·7%
0·8%
−13·0%
0%
Difference between groups in ACR50 response rates at month 6
C
Patients attaining ACR20 response (%)
Week 6
Month 3
Month 6
Month 9
Month 12
Time
D
Patients attaining ACR70 response (%)
Week 6
Month 3
Month 6
Month 9
Month 12
Time

THE LANCET

# 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

Prof Josef S Smolen, FRCP • Aileen L Pangan, MD • Prof Paul Emery, FMedSci • Prof William Rigby, MD • Prof Yoshiya Tanaka, MD • Juan Ignacio Vargas, MD • et al. Show all authors

Published: May 23, 2019 • DOI: https://doi.org/10.1016/S0140-6736(19)30419-2


A ACR20
Responders (%)
100
80
60
40
20
0
41
*
68
*
71
cMTX, n=216
UPA 15 mg, n=217
UPA 30 mg, n=215
B DAS28-(CRP) ≤3·2
Responders (%)
100
80
60
40
20
0
19
*
45
*
53
cMTX, n=216
UPA 15 mg, n=217
UPA 30 mg, n=215

# Ασφάλεια JAKis

- Λοιμώξεις
- Έρπητας Ζωστήρας
- Καρκίνος
- MACEs
- Θρομβώσεις

The NEW ENGLAND JOURNAL of MEDICINE

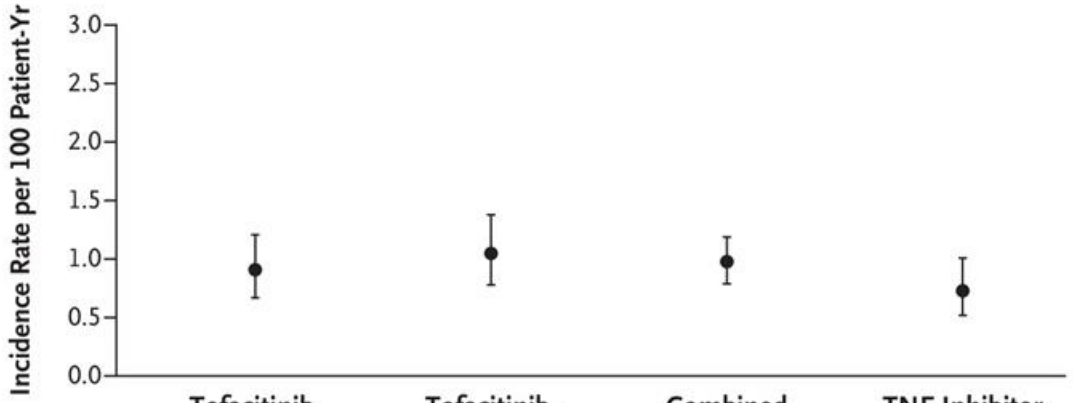
ORIGINAL ARTICLE

# Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis

**Authors**: Steven R. Ytterberg, M.D., Deepak L. Bhatt, M.D., M.P.H., Ted R. Mikuls, M.D., M.S.P.H., Gary G. Koch, Ph.D., Roy Fleischmann, M.D., Jose L. Rivas, M.D., Rebecca Germino, Ph.D., +6, for the ORAL Surveillance Investigators* Author Info & Affiliations

Published January 26, 2022 | N Engl J Med 2022;386:316-326 | DOI: 10.1056/NEJMoa2109927 | VOL. 386 NO. 4

**B** Incidence Rate for MACE




| | | | | |
|---|---|---|---|---|
| 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 | — | — |

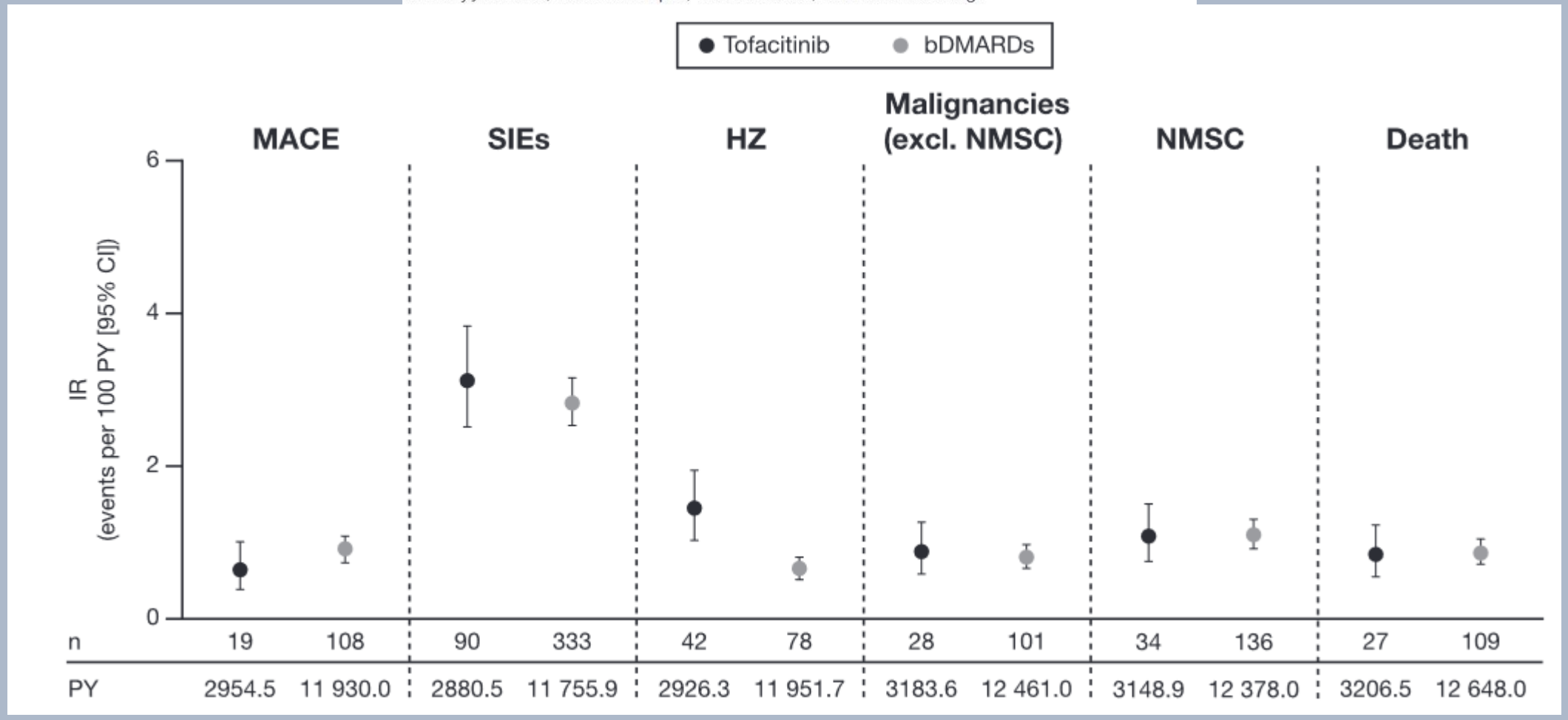
- tofacitinib **10mg**: περισσότερες θρομβώσεις σε σχέση με 5 mg ή adalimumab
- **καμία διαφορά** μεταξύ tofacitinib 5 mg και adalimumab

**ACR Open Rheumatology**
Vol. 3, No. 3, March 2021, pp 173–184
DOI 10.1002/acr2.11232


American College of Rheumatology
*Empowering Rheumatology Professionals*

# Postapproval Comparative Safety Study of Tofacitinib and Biological Disease-Modifying Antirheumatic Drugs: 5-Year Results from a United States–Based Rheumatoid Arthritis Registry

Joel M. Kremer,[1] Clifton O. BinghamIII,[2] Laura C. Cappelli,[2] Jeffrey D. Greenberg,[3] Ann M. Madsen,[4] Jamie Geier,[4] Jose L. Rivas,[5] Alina M. Onofrei,[6] Christine J. Barr,[6] Dimitrios A. Pappas,[7] Heather J. Litman,[6] Kimberly J. Dandreo,[6] Andrea B. Shapiro,[8] Carol A. Connell,[9] and Arthur Kavanaugh[10]



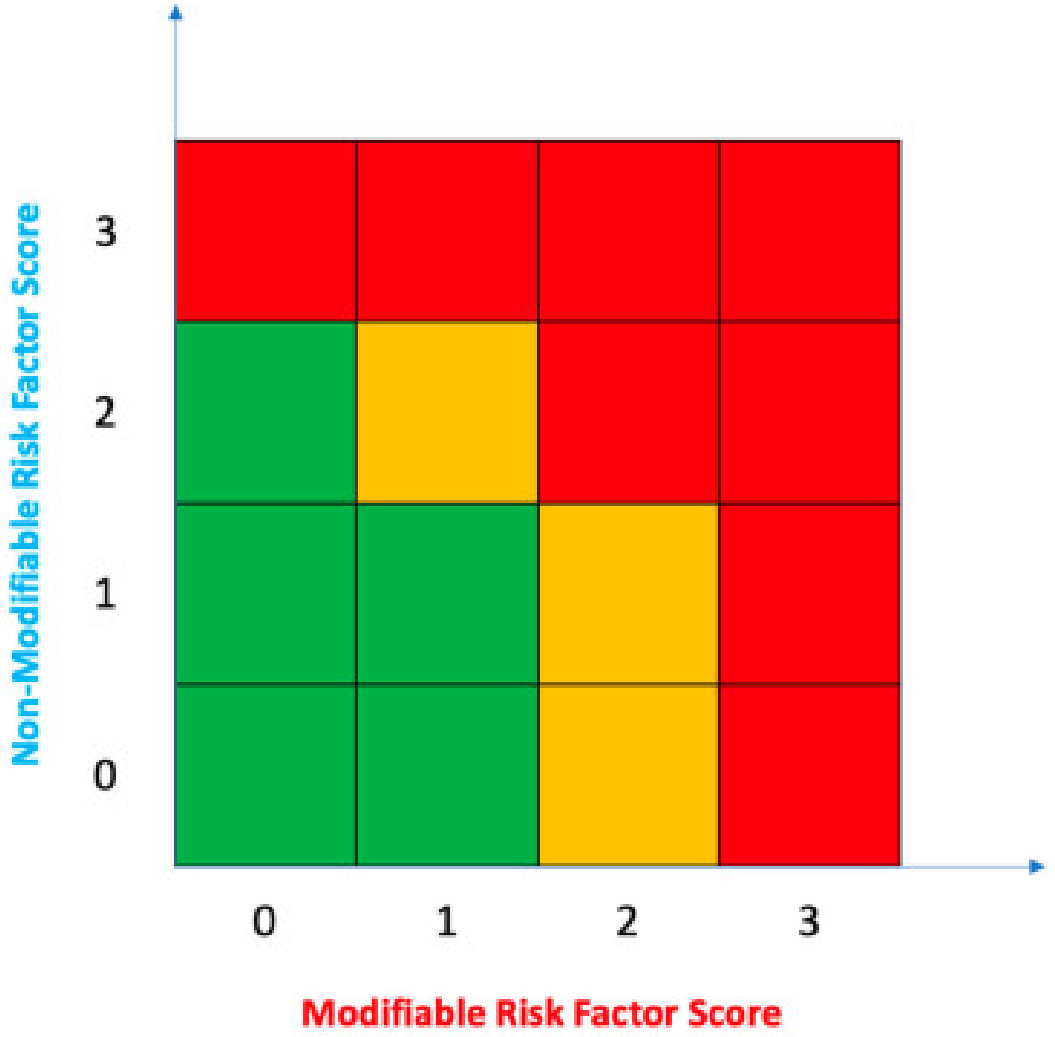
| **Non-Modifiable Risk Factors Scores:** | |
|---|---|
| Age > 65 | 1 |
| Male | 1 |
| Hx of MI, CVA, VTE | 3 |
| Hx of Malignancy | 3 |

Add risk factors for total NMRF Score

| **Modifiable Risk Factors Scores:** | |
|---|---|
| Poorly controlled HTN (BP > 140/90) | 1 |
| Poorly controlled DM (HbA1C > 75mmol/mol) | 1 |
| Poorly controlled Hyperlipdemia (LDL > 4nmol/L) | 1 |
| COCP | 1 |
| Smoking | 2 |

Add risk factors for total MRF Score

- JAKi likely safe
- Risk-benefit may be acceptable in certain cases after discussion with patient
- JAKi not advised




*J Clin Med. 2023 Oct; 12(20): 6690*

# Μηνύματα για το σπίτι

- μεγάλη ταχύτητα δράσης
- per os χορηγηση
- έλλειψη ανοσογονικότητας
- μικρός χρόνος ημίσειας ζωής
- αποτελεσματικότητα συγκρίσιμη ή και ανώτερη των βιολογικών παραγόντων
- καλή αποτελεσματικότητα και χωρίς ΜΤΧ
- καλό προφίλ ασφαλείας

# Ευχαριστώ για την προσοχή σας