Ρευματοειδής Αρθρίτιδα: Η σημασία του ανοσολογικού προφίλ στην καθημερινή κλινική πράξη

Δημήτρης Τσερώνης
Ρευματολόγος
Επιστημονικός Συνεργάτης
Δ ΠΠΚ ,ΠΓΝ «Αττικόν»

Σύγκρουση συμφερόντων

Παρούσα παρουσίαση :Τιμητική αμοιβή από UCB για την συγκεκριμένη ομιλία

Εκπαιδευτικές-ερευνητικές-συμβουλευτικές επιχορηγήσεις την τελευταία διετία:
UCB,Janssen, Lilly, AEnorasis, Genesis-Pharma, Pfizer, Abbvie,
Mylan, Novartis, GSK,

Κλινική περίπτωση ασθενούς με Ρευματοειδή Αρθρίτιδα

- **Νίκος 53 ετών** , υπάλληλος γραφείου , διαζευγμένος ,πατέρας 3 παιδιών

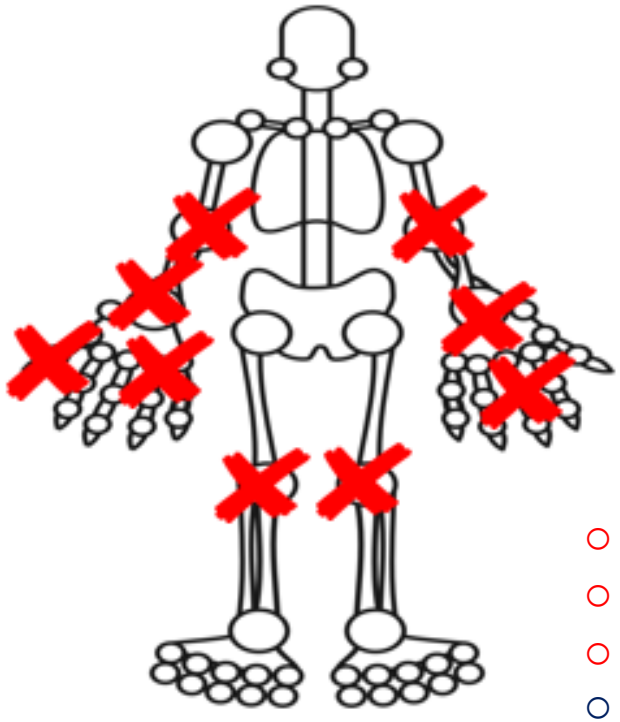
  - πρόσφατη διάγνωση **PA (+)** .. *Άνευ αγωγής*

- Καπνιστής : 20 pack years , Αλκοόλ : social drinker
  BMI :25 , δεν γυμνάζεται (καθιστική ζωή) , δυσλιπιδιαμία : άνευ αγωγής

- ✓ **αρθραλγίες** : κυρίως χεριών και γονάτων από **3 ετίας με ΠΔ**
- ✓ ε/ε : RF (++) , ACPA (+++) , ESR : 50 mm/Hg , CRP : Χ2 , λοιπά : κφ
- ✓ εκτίμηση και διάγνωση από Ρ/Μ στο εξωτερικό όπου εργαζόταν (Ρουμανία)
- ✓ δεν έλαβε αγωγή (επιθυμία του ίδιου λόγω σύντομου

Κλινική εκτίμηση και προσέγγιση

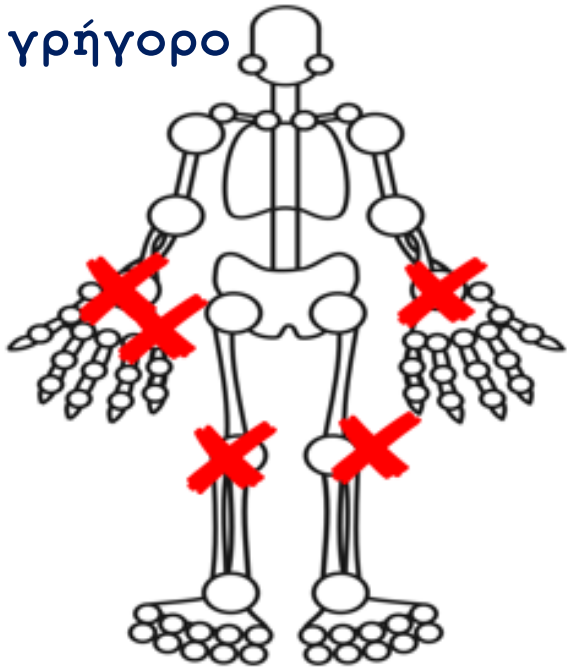
- ✓ Συμμετρική πολυαρθρίτδα
- ✓ Λοιπά : κφ



DAS28: **6,18**
HDA

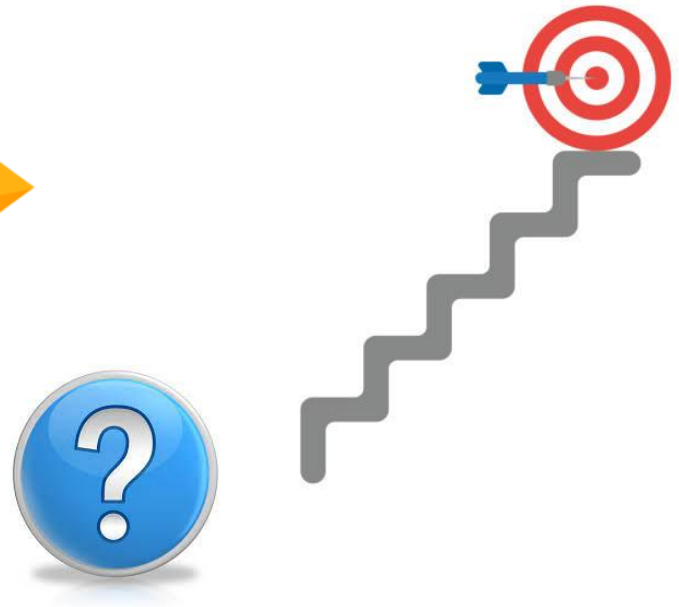
20 mg MTX + 15mg prednisone/day (γρήγορο taper)

- ○ ↑TKE , CRP x3
- ○ RF x10
- ○ anti-CCP x 12
- ○ β/χ : κφ



DAS28: **4,46**
MDA

εκτός θεραπευτικού στόχου

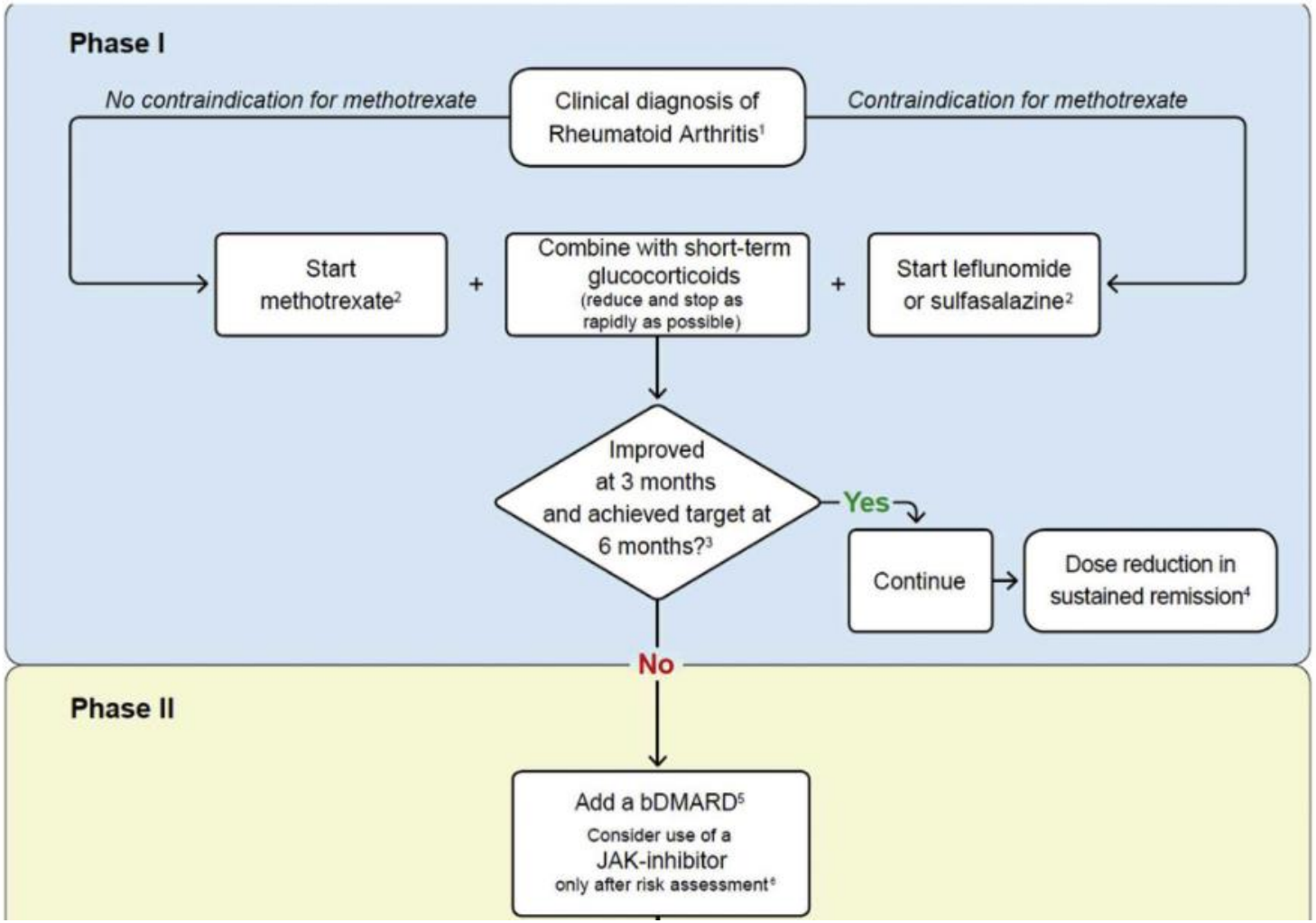


Treat to target

Το επόμενο βήμα

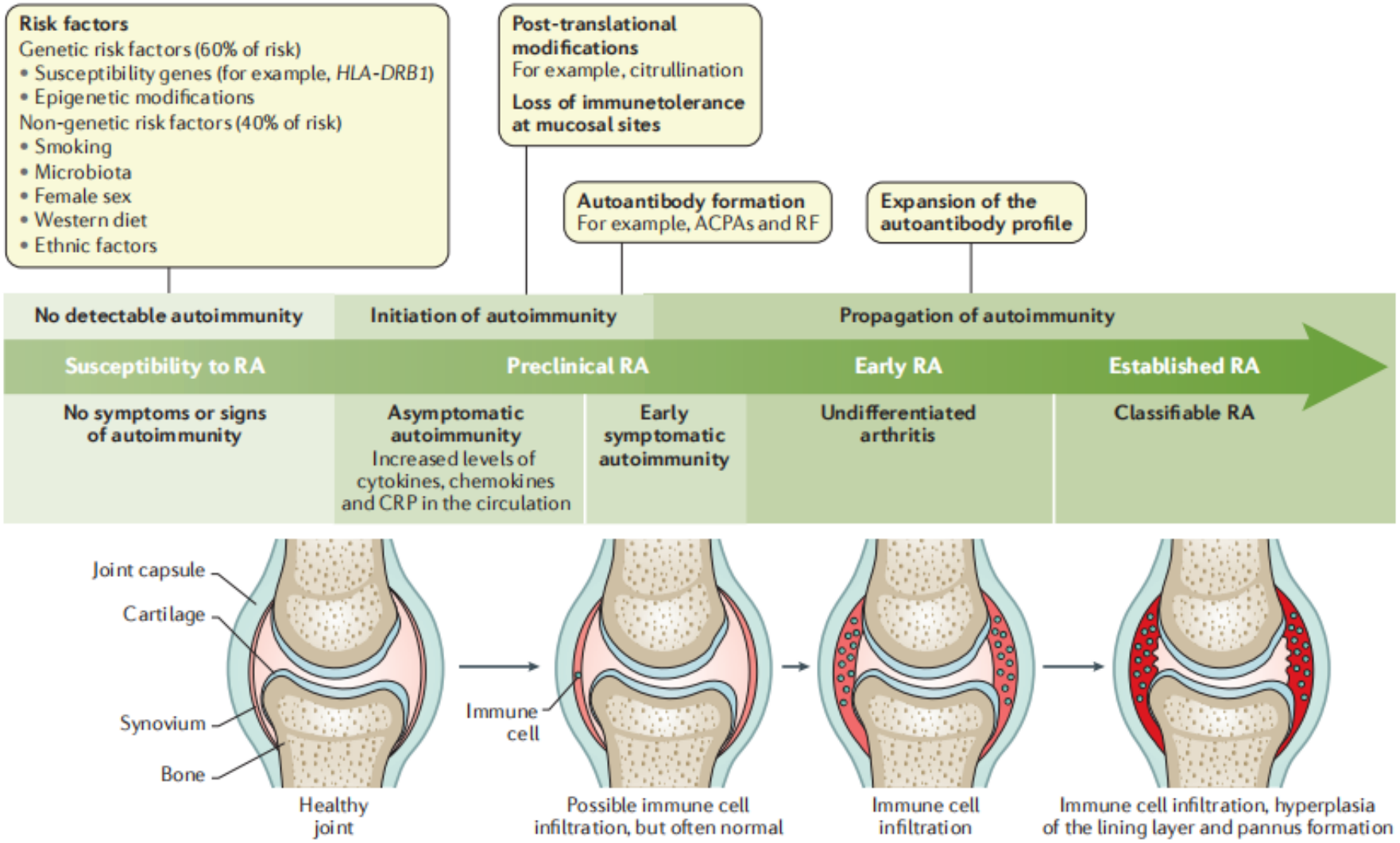
EULAR recommendations for the management of rheumatoid arthritis with synthetic and biologic disease-modifying antirheumatic drugs: 2025 update

eular
EUROPEAN ALLIANCE OF ASSOCIATIONS FOR RHEUMATOLOGY



Ann Rheum Dis. 2026 Mar 12:S0003-4967(26)00075-0. doi: 10.1016/j.ard.2026.01.023.

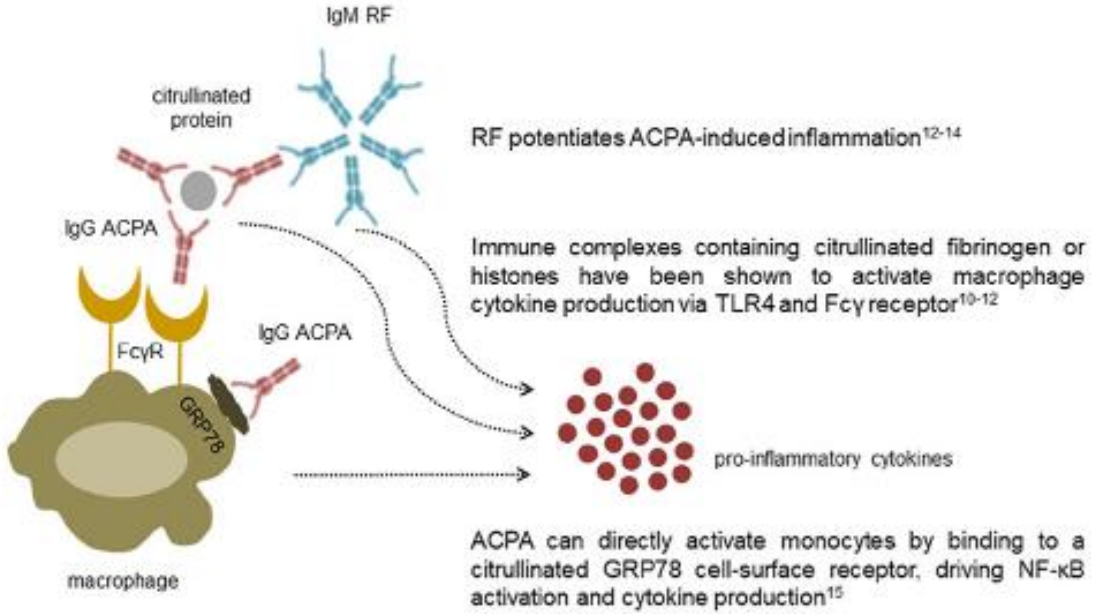
ο ρόλος των αυτό-αντισωμάτων στην παθογενεση

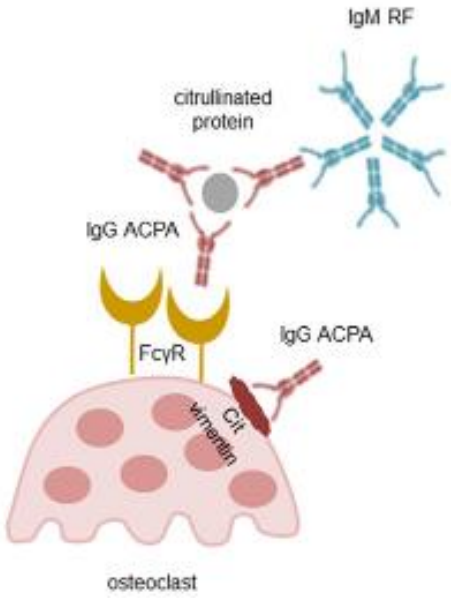


Nat Rev Dis Primers. 2018 Feb 8;4:18001. doi: 10.1038/nrdp.2018.1

ο ρόλος των αυτό-αντισωμάτων στην παθογενεση

- Η ενεργοποίηση των Μακροφάγων και Οστεοκλαστών





Patients with double positivity for ACPA and RF (at high titres) have increased joint and systemic bone damage[36,37]

OCs and OC precursors express citrullinated vimentin, and ACPA directed against mutated vimentin can induce OC activation in vitro and bone resorption in vivo after transfer to mice[34]

ACPA-induced OC differentiation depends on a combination of intracellular protein citrullination in the OC as well as autocrine production of IL-8[35]

OCs express FcγR in comparable amounts to macrophages and dendritic cells[31]

Cross-linking of FcγR on murine preosteoclasts leads to higher osteoclast numbers[32]

Desialylated IgG stimulate osteoclastogenesis[33]

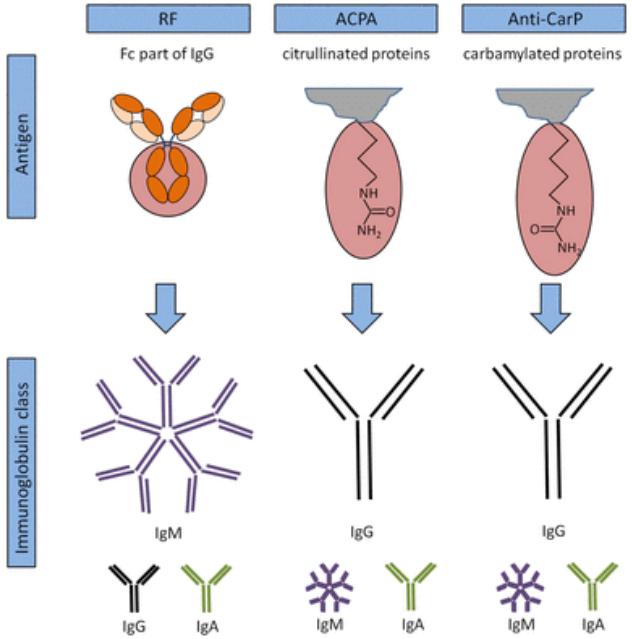
Front Med (Lausanne). 2018 Dec 3;5:339. doi: 10.3389/fmed.2018.00339

τα αυτο-αντισώματα στην διάγνωση της νόσου

Autoantibody	Sensitivity/specificity	References
RF	60–90%/85%	[145, 146, 52]
ACPA (CCP2)	41–74.8%/91–100%	[5, 13, 146, 45]
ACPA (CCP3)	77.5–78.8%/87.8–96.6%	[5, 13]
ACPA (CCP3.1)	74–83%/89.6–98.3%	[5, 13]
Anti-CarP (*carbamylated fetal calf serum)	35–46.8%/91.95–92.8%	[146, 147]
Anti-acetylated vimentin antibodies	36.6%/86.2%	[45]
Anti-PAD4-antibodies	21.72–40%/90.36–98.8%	[65, 148, 10]
Anti-PTX3	25.52%/91.37%*	[10]
Anti-DUSP11	27.93%/90.36%	[10]

1

2010 ACR/EULAR Classification criteria RA



Target population: Patients who (i) have at least 1 joint with clinical synovitis and (ii) with the synovitis not better explained by another disease.

	Score
A. Joint involvement (tender/swollen)	
1 large joint	0
2-10 large joints	1
1-3 small joints (± involvement of large joints)	2
4-10 small joints (± involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
B. Serology	
Negative RF & ACPA	0
Low-positive RF/low-positive ACPA	2
High-positive RF/high-positive ACPA	3

	Score
C. Acute-phase reactants	
Normal CRP & ESR	0
Abnormal CRP & ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

Add score of categories A-D:

≥ 6/10 = definite RA

1.Clin Rev Allergy Immunol. 2022 Oct;63(2):138-151. doi: 10.1007/s12016-021-08890-1.

τα αυτο-αντισώματα πριν από την διάγνωση της νόσου

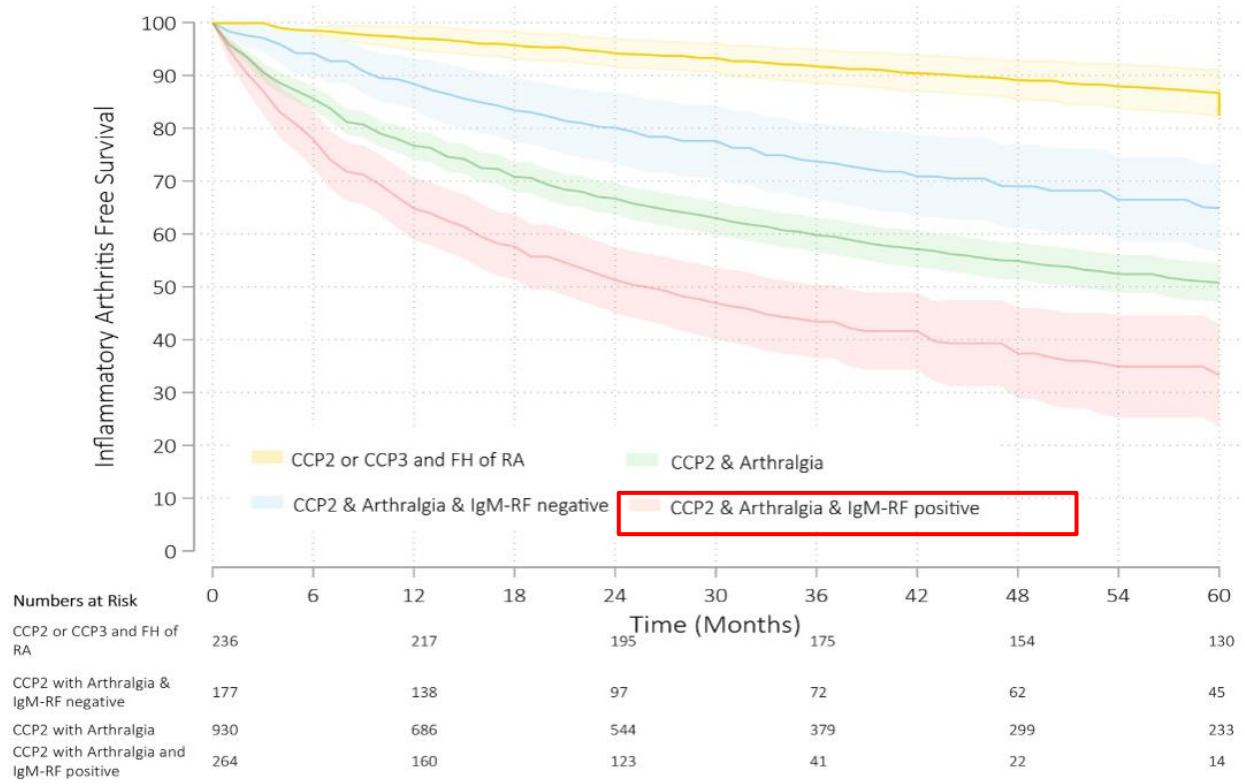
- 325 ασθενείς με πρώιμη αρθρίτιδα[1] : (1 έτος παρακολούθηση)

Table 1 Serology results of the Stop Arthritis Very Early early arthritis cohort[20 22 23]

	RA	Non-RA	LR	Non-RA diagnoses
n	132	193		
RF low, ACPA–	2.3%	4.1%	0.6	4 UDA, 1 SpA, 1 ReA, 1 remission
RF high, ACPA–	2.3%	2.1%	1.1	2 UDA, 1 Sjögren, 1 viral infection
ACPA low, RF–	1.5%	0.0	n.a.	–
ACPA high, RF–	4.5%	1.6%	3.3	3 UDA
ACPA+ and RF+	45.4%	2.1%	21.6	2 UDA, 1 remission
ACPA– and RF–	44.0%	90.2%	0.49	

LR, likelihood ratio; RA, rheumatoid arthritis; ReA, reactive arthritis; SpA, spondyloarthropathy; UDA, undifferentiated arthritis.

- SRL + meta-analysis[2] : - 1609 (+) ACPA)



Αυξημένη επίπτωση RA σε ασθενείς με αρθραλγία ή πρώιμη αρθρίτιδα με «διπλή» (+) APCA/RF

1.RMD Open. 2024 Apr 19;10(2):e003851. doi: 10.1136/rmdopen-2023-003851
2.RMD Open. 2026 Feb 11;12(1):e006368. doi: 10.1136/rmdopen-2025-006368.

- Cohort study :
  - 106.492 RA
    -1:1 – RA (+)
  , RA(–)

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

ABSTRACT NUMBER: 0435

Comparative Outcomes in Seropositive and Seronegative Rheumatoid Arthritis: A Retrospective Cohort Study

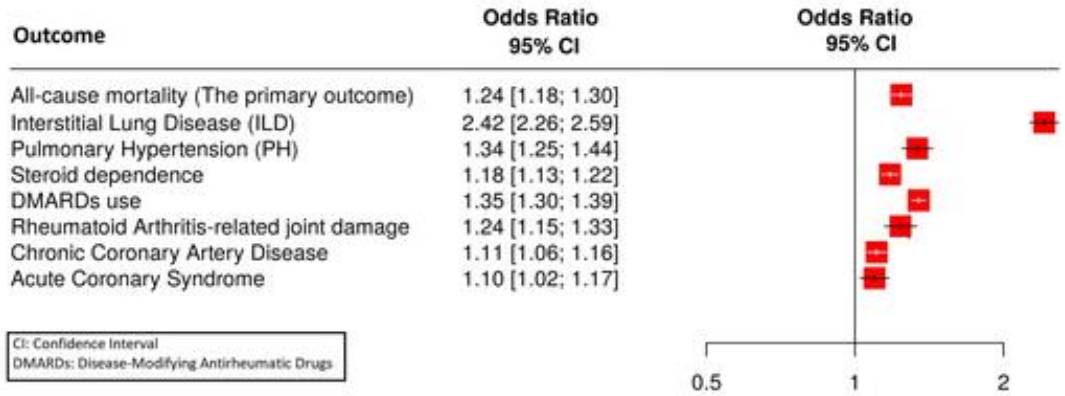
Ahmad Alomari[1], Reem Elmusa[2], Nikita Shah[3], Miguel Rodriguez[4] and Diala Alawneh[5], [1]UCF- North Florida hospital, Gainesville, FL, [2]UCF/ HCA - North florida hospital, Gainesville, FL, [3]UCF/HCA Florida North Florida Hospital, Gainesville, FL, [4]SIMED Rheumatology, Gainesville, FL, [5]University of Florida, Gainesville, FL

Meeting: ACR Convergence 2025

Keywords: Cardiovascular, CCP, interstitial lung disease, rheumatoid arthritis, Rheumatoid Factor

Outcome	Number of Patients with Event (%)		Odds Ratio (95% CI)	P Value
	Seropositive RA	Seronegative RA		
All-Cause Mortality	12,478 (23.4%)	10,048 (18.9%)	1.24 (1.16–1.27)	<0.001
DMARD Use	45,216 (84.9%)	39,872 (74.9%)	1.35 (1.30–1.40)	<0.001
Steroid Dependence	20,486 (38.5%)	17,184 (32.3%)	1.18 (1.13–1.23)	<0.001
RA-Related Joint Damage	15,927 (29.9%)	12,738 (24.0%)	1.24 (1.19–1.29)	<0.001
Interstitial Lung Disease (ILD)	7,329 (13.8%)	3,029 (5.7%)	2.42 (2.30–2.55)	<0.001
Chronic CAD	16,214 (30.5%)	14,516 (27.2%)	1.11 (1.06–1.16)	<0.001
Acute Coronary Syndrome (ACS)	5,479 (10.3%)	4,912 (9.2%)	1.10 (1.02–1.17)	0.008

Figure 3: Forest Plot showing Odds Ratio (OR) and Confidence Intervals (CI)



↑ θνησιμότητα , ↑δομικές αλλοιώσεις ↑ επίπτωση ILD, ↑ κορτικοεξάρτηση στους RA (+)

Η «οροθετικότητα» και η έκβαση της νόσου

- 1097 PA
  - 89,4 % γυναίκες , 56% ↑↑↑ RF (+)
  - μέση διάρκεια νόσου 12 έτη

Table 3 Bivariate comparisons between the high and non-high RF titer groups as to clinical outcomes in patients with rheumatoid arthritis

Outcomes	RF high titers $n = 616$ % (n) or mean (SD)	RF non-high titers $n = 481$ % (n) or mean (SD)	Effect sizes [95% CI][a]	p values[b]
Corticosteroid use	52.4% (323)	40.1% (193)	1.65 [1.29–2.09]†	< 0.001*
bDMARD use	39.3% (242)	31.0% (149)	1.44 [1.21–1.86]†	0.004*
Erosive disease	56.1% (340)	52.4% (249)	1.16 [0.91–1.48]†	0.227
Extra-articular disease	26.0% (159)	19.6% (94)	1.44 [1.08–1.92]†	0.013*
HAQ-DI	0.999 (0.796)	0.872 (0.728)	0.127 [0.036–0.218]‡	0.006*
DAS28-ESR	3.80 (1.52)	3.37 (3.37)	0.43 [0.23–0.62]‡	< 0.001*
DAS 28-CPR	3.41 (1.40)	3.12 (1.32)	0.09 [0.11–0.47]‡	0.001*
CDAI	14.09 (13.21)	11.63 (11.04)	2.46 [1.02–3.90]‡	0.001*
SF-12 physical	36.446 (6.526)	36.253 (7.102)	0.194 [− 0.639–1.027]‡	0.648
SF-12 mental	45.299 (12.464)	46.591 (12.096)	− 1.292 [− 2.786–0.203]‡	0.090

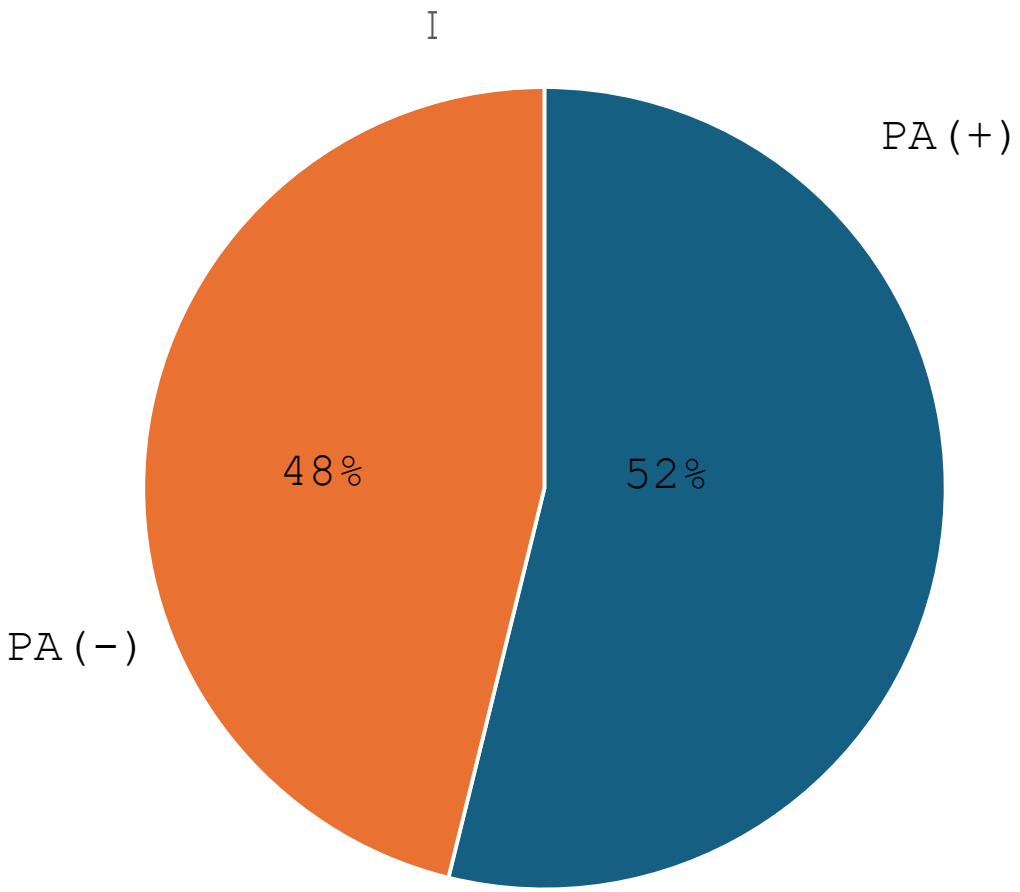
↑↑ RF συσχετίστηκαν με ↑ χρήση κορτιζόνης και bdmard, ↑ ενεργότητα ↓ HAQ και εξω-αρθρικές εκδηλώσεις

Rheumatol Ther. 2025 Feb;12(1):123-136. doi: 10.1007/s40744-024-00730-w. Epub 2024 Dec 19.

Η Ρευματοειδής Αρθρίτδα στην Ελλάδα

n: 2491

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)**	



Thomas K, Lazarini A, Kaltsonoudis E, Drosos AA, Papalopoulos I, Sidiropoulos P, et al. Multicenter Cross-sectional Study of Patients with Rheumatoid Arthritis in Greece: Results from a cohort of 2.491 patients. Mediterr J Rheumatol 2018; 29(1): 27-37.

Επιστροφή στον ασθενή μας

- Έναρξη ADALIMUMAB 40mg/ 14 ημέ

- Διατήρηση της MTX

- 15mg prednisone/day (με «γρήγορο» σβήσιμο)

Περίπου 6 μήνες μετά … περαιτέρω βελτίωση

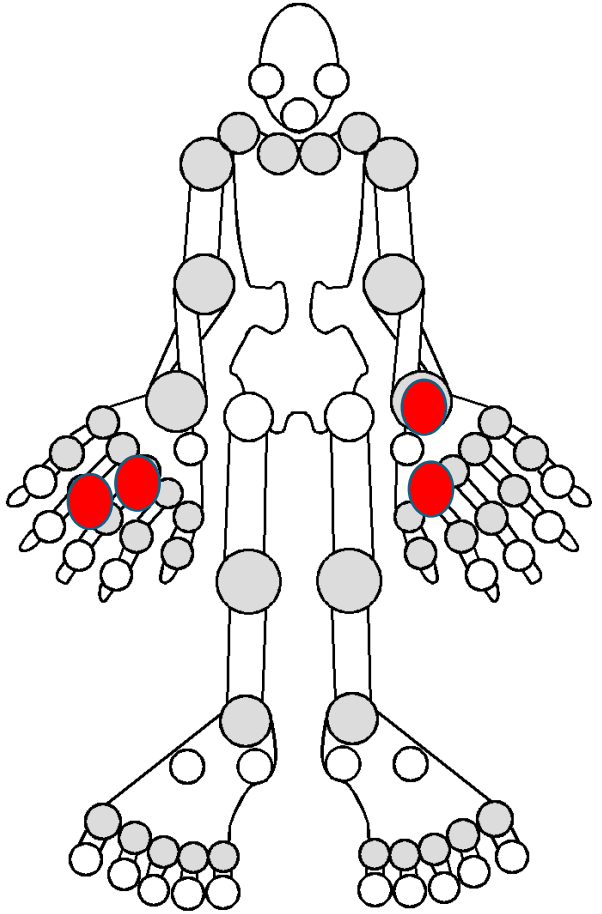
- **Κλινική εκτίμηση :**

- Tender Joints : 4
- Swollen Joints : 2
- VAS : 30/100
- Πρωινή Δυσκαμψία ~ 10 min

- **Εργαστηριακός έλεγχος** :

  ΤΚΕ : 20 , CRP (-)

  λοιπά : κφ



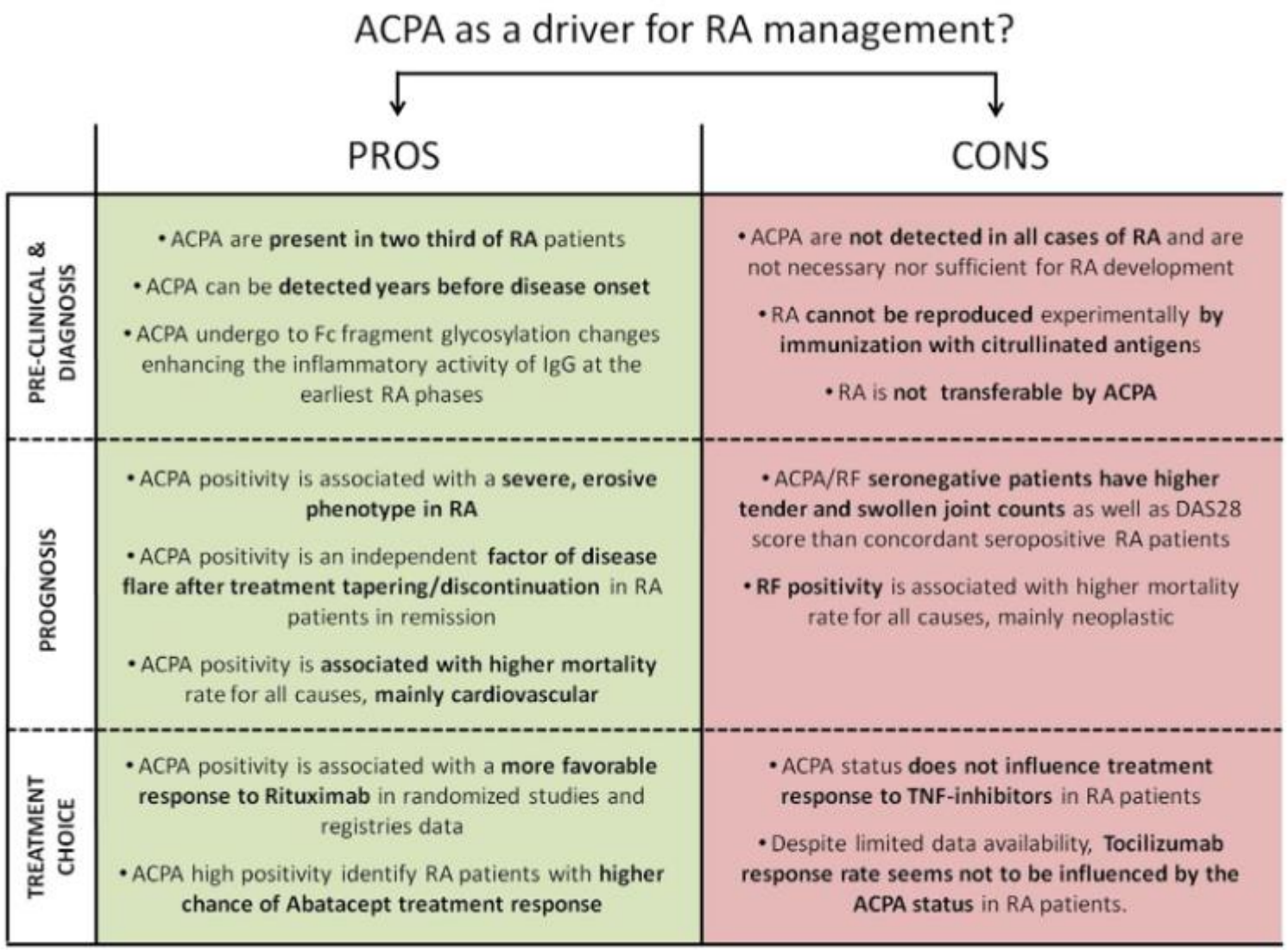
DAS28 : 3,88

Υπάρχουν διάφορες στην ανταπόκριση ανάλογα το RF/ACPA status ;

tsDMARDs	Αναστολείς JAK	Tofacitinib Baricitinib Upadacitinib Filgotinib

bDMARDs			
Anti-TNF	Anti-CD-20	Anti-IL-6	Αναστολέας συνδιέγερσης
(bs)Adalimumab Certolizumab pegol (bs)Etanercept Golimumab (bs)Infliximab	(bs)Rituximab	Tocilizumab	Abatacept*

ACPA (+) vs ACPA (-)



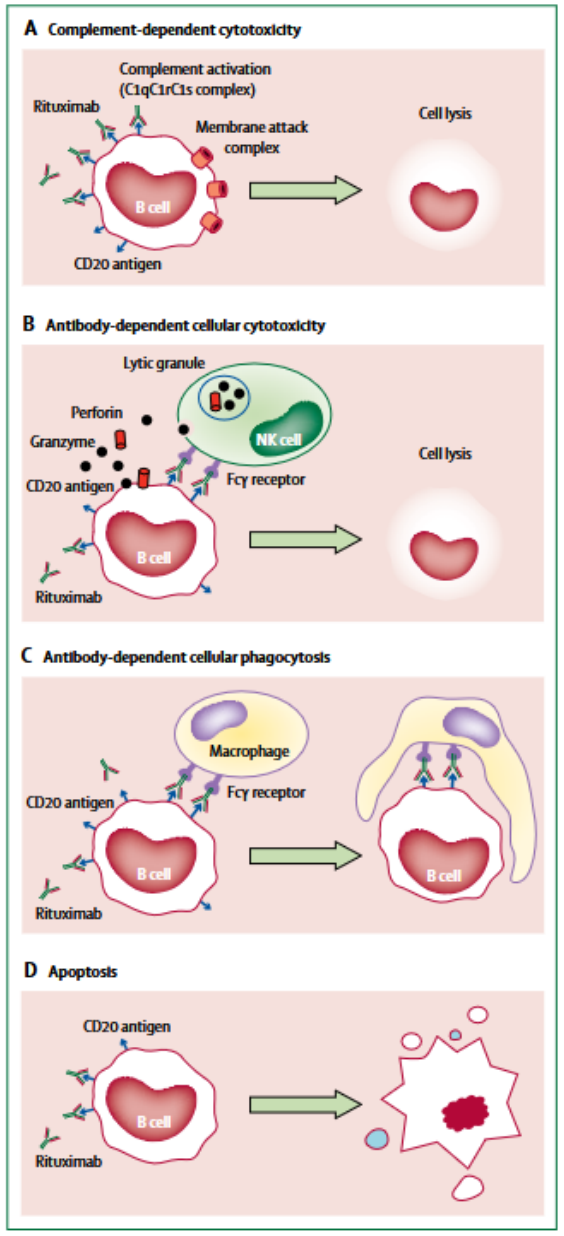
Autoimmun Rev. 2017 Nov;16(11):1096-1102. doi: 10.1016/j.autrev.2017.09.002.

Lessons for rituximab therapy in patients with rheumatoid arthritis

Leticia Garcia-Montoya, Catalina Villota-Eraso, Md Yuzaiful Md Yusof, Edward M Vital, Paul Emery

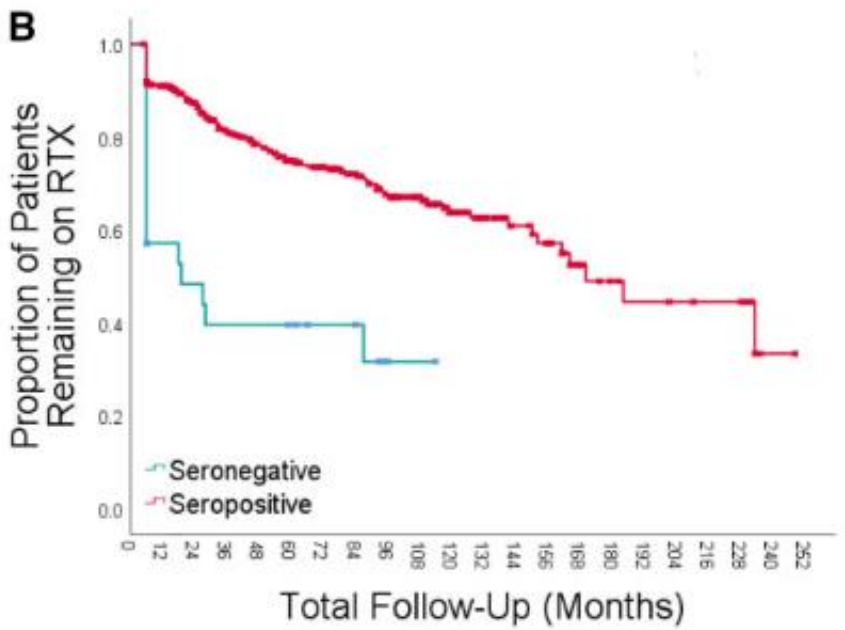
«Μεταξύ και άλλων παραγόντων φαίνεται ότι οι οροθετικοί ανταποκρίνονται καλύτερα»

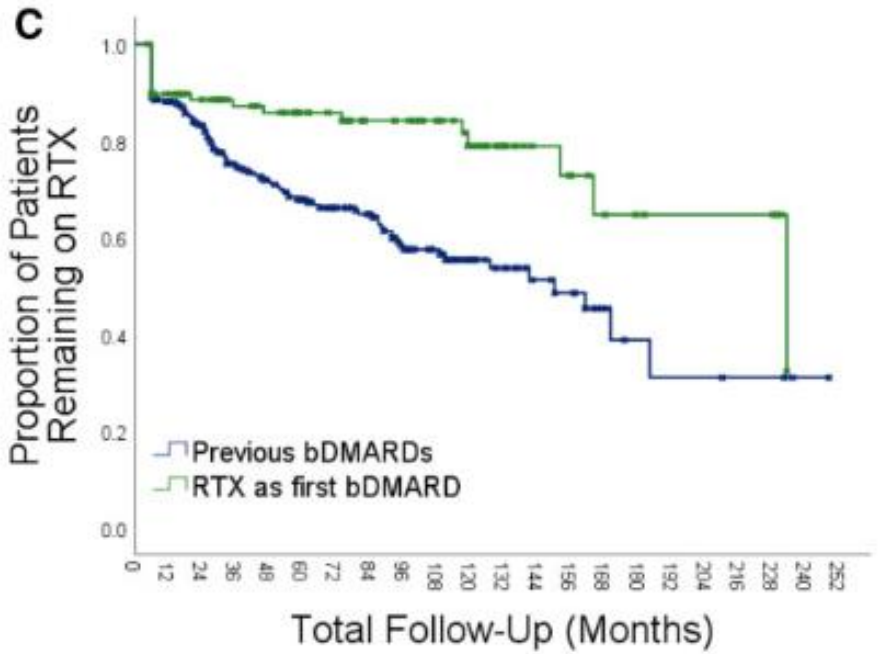
	Trial name	Number of patients randomly assigned	Patient characteristics	Treatment groups	Outcomes
Clinical trials					
Emery et al (2006)[7]	Dose-ranging assessment international clinical evaluation of rituximab in rheumatoid arthritis (DANCER)	465	Inadequate response to methotrexate or TNF inhibitors	(1) Methotrexate + rituximab placebo + steroids placebo; (2) methotrexate + rituximab placebo + intravenous steroids; (3) methotrexate + rituximab placebo + intravenous steroids + oral steroids; (4) methotrexate + 2 × rituximab 500 mg + steroids placebo; (5) methotrexate + 2 × rituximab 500 mg + intravenous steroids; (6) methotrexate + 2 × rituximab 500 mg + intravenous steroids + oral steroids; (7) methotrexate + 2 × rituximab 1000 mg + steroids placebo; (8) methotrexate + 2 × rituximab 1000 mg + intravenous steroids; and (9) methotrexate + 2 × rituximab 1000 mg + intravenous steroids + oral steroids	A higher proportion of patients who received 2 × rituximab 1000 mg had ACR70 and good EULAR-defined responses compared with the 2 × rituximab 500 mg groups, and the efficacy of rituximab was not influenced by steroids
		511	Inadequate response to methotrexate	(1) methotrexate + placebo; (2) methotrexate + 2 × rituximab 500 mg; and (3) methotrexate + 2 × rituximab 1000 mg	Both doses of rituximab doses had similar efficacy
		378	Inadequate response to methotrexate or TNF inhibitors	(1) methotrexate + two cycles of 2 × rituximab 500 mg; (2) methotrexate + 2 × rituximab 500 mg, with dose escalation to methotrexate + 2 × rituximab 1000 mg; and (3) methotrexate + two cycles of 2 × rituximab 1000 mg	Compared with patients receiving 2 × 500 mg rituximab, a higher proportion of patients who received 2 × rituximab 1000 mg dose had remission, achieved a good or moderate EULAR-defined response, and the ACR scores that were achieved at 24 weeks were maintained at 48 weeks
		755	methotrexate-naive	(1) methotrexate + placebo; (2) methotrexate + 2 × rituximab 500 mg; and (3) methotrexate + 2 × rituximab 1000 mg	Similar response rates observed in patients who received either dose of rituximab, and only patients who received 2 × rituximab 1000 mg had significantly reduced progression of joint damage
Mariette et al (2014)[22]	A comparative study to assess the effect of retreatment with two doses of mabthera on disease activity score in patients with active rheumatoid arthritis who have had an inadequate response or intolerence to anti-TNFα therapy (SMART)	100	Inadequate response to TNF inhibitors	24 weeks after methotrexate + 2 × rituximab 1000 mg: (1) rituximab 1000 mg; and (2) 2 × rituximab 1000 mg	Both doses of rituximab showed similar clinical efficacy after 2 years



Lancet Rheumatol. 2020 Aug;2(8):e497-e509. doi: 10.1016/S2665-9913(20)30033-3. Epub 2020 May 12

- 404 PA (RTX)
  - 89,1 % γυνάικες , 93% RF/ACPA (+)
  - Μέση ηλικία έναρξης RTX , 57 έτη
  - μέση διάρκεια νόσου 10 έτη





Χαμηλότερη παραμονή RTX στους οροαρνητικούς και σε αυτούς με προηγούμενη χρήση bdmard

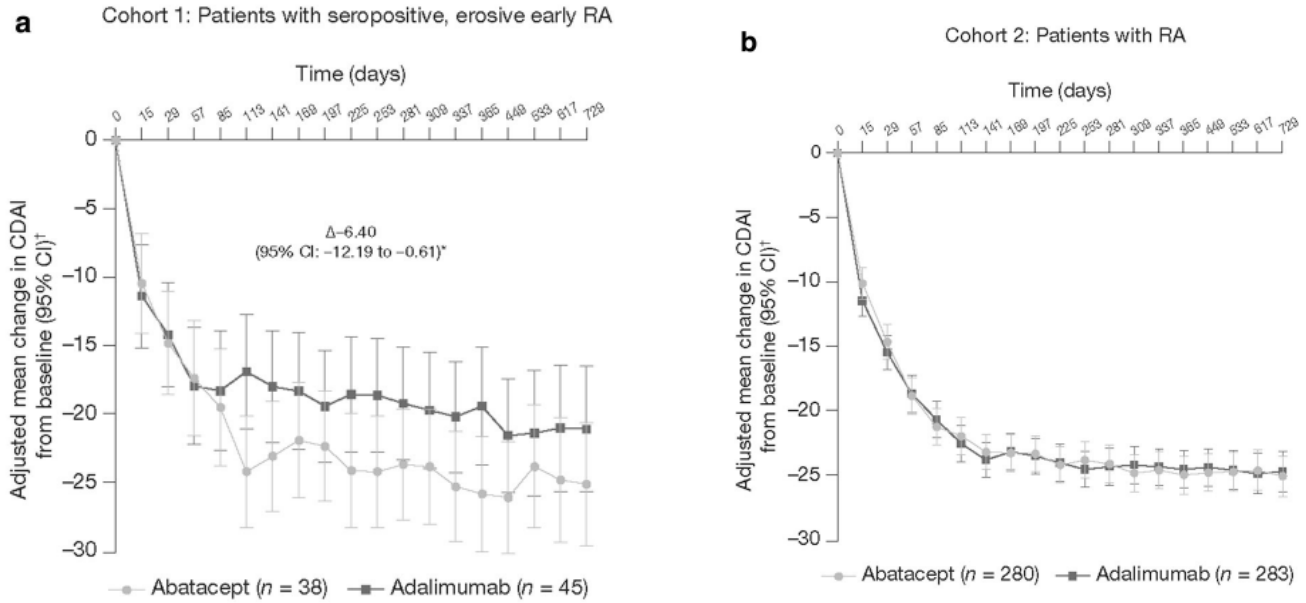
Rheumatology (Oxford). 2022 Feb 2;61(2):591-596. doi: 10.1093/rheumatology/keab248

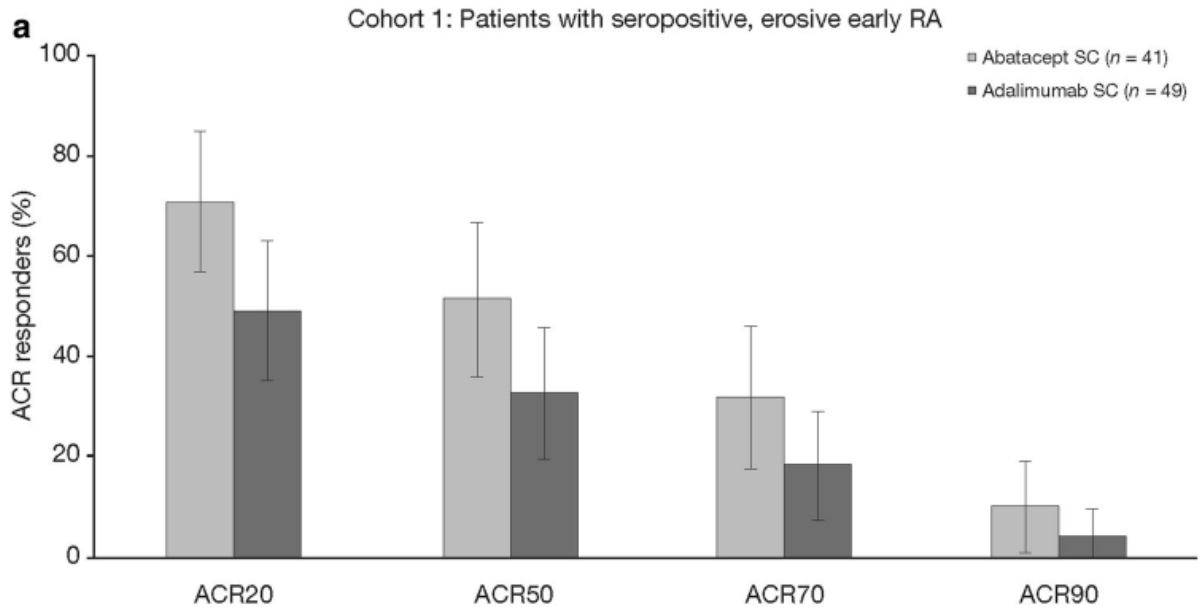
Rheumatol Ther (2019) 6:559–571
https://doi.org/10.1007/s40744-019-00174-7

ORIGINAL RESEARCH

Efficacy of Abatacept and Adalimumab in Patients with Early Rheumatoid Arthritis With Multiple Poor Prognostic Factors: Post Hoc Analysis of a Randomized Controlled Clinical Trial (AMPLE)

Roy Fleischmann · Michael Weinblatt · Harris Ahmad · Michael A. Maldonado · Evo Alemao · June Ye · Michael Schiff





- Στην συνολική κοορτή των ασθενών δεν φάνηκε διαφορά μεταξύ ABA και ADA

- Στην υποομάδα των οροθετικών ασθενών με την πρώιμη PA καταγράφη μια τάση υπερ του ABA

ABSTRACT NUMBER: 0813

Treatment Outcomes in Patients with Seropositive versus Seronegative Rheumatoid Arthritis in Czech Registry ATTRA Treated with JAK Inhibitors

Karel Pavelka[1] and Zlatuše Křístková[2], [1]Institute of Rheumatology and Department of Rheumatology, First Faculty of Medicine, Charles University, Prague, Czech Republic, [2]Institute of Biostatistics and Analyses, Ltd., Brno, Czech Republic

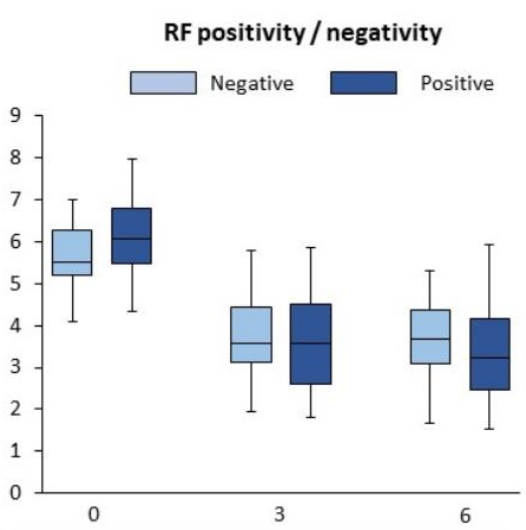
Meeting: ACR Convergence 2020

Keywords: Biologicals, CCP, rheumatoid arthritis, Rheumatoid Factor

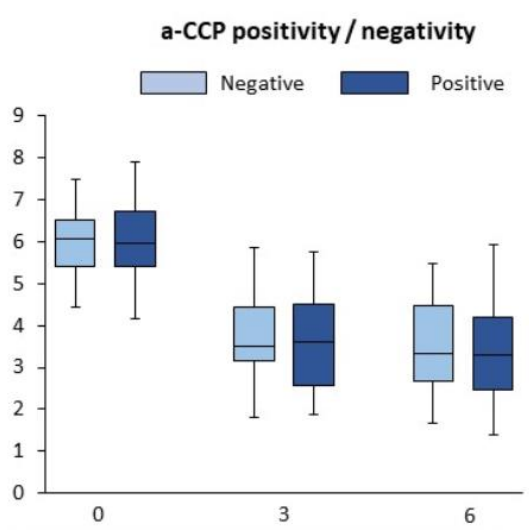
JAKi και «οροθετικότητα»

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

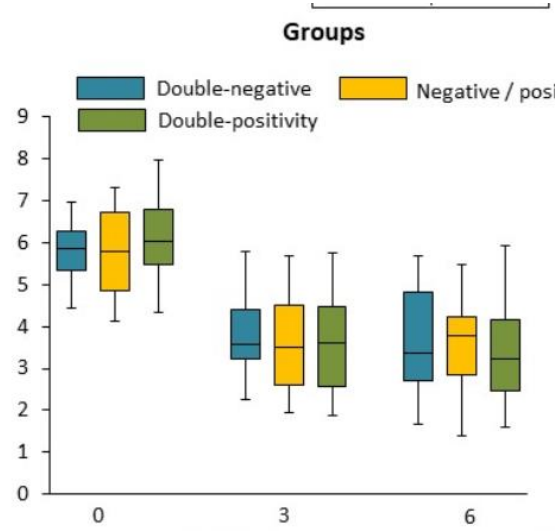
263 RA (JAKi)
(130 Tofa,
133 Bari)



	Initiation of treatment	3 months	6 months
RF-	5,5 (4,1; 7,0)	3,6 (2,0; 5,8)	3,7 (1,7; 5,3)
RF+	6,1 (4,3; 8,0)	3,6 (1,8; 5,8)	3,2 (1,5; 5,9)
P-value	**0,001**	0,661	0,250



	Initiation of treatment	3 monts	6 monts
a-CCP-	6,1 (4,4; 7,5)	3,5 (1,8; 5,8)	3,3 (1,7; 5,5)
a-CCP+	6,0 (4,2; 7,9)	3,6 (1,9; 5,8)	3,3 (1,4; 5,9)
P-value	0,710	0,621	0,522



	Initiation of treatment	3 months	6 monthsl
Double-negative	5,9 (4,4; 7,0)	3,6 (2,3; 5,8)	3,4 (1,7; 5,7)
Negative / positive	5,8 (4,1; 7,3)	3,5 (2,0; 5,7)	3,8 (1,4; 5,5)
Double-positive	6,0 (4,3; 8,0)	3,6 (1,9; 5,8)	3,2 (1,6; 5,9)
P-value	0,109	0,863	0,559

Δεν κατεγράφη διαφορά στην αποτελεσματικότητα μεταξύ RF/APCA(-) ΚΑΙ RF/ACPA(+)

JAKi και «οροθετικότητα»

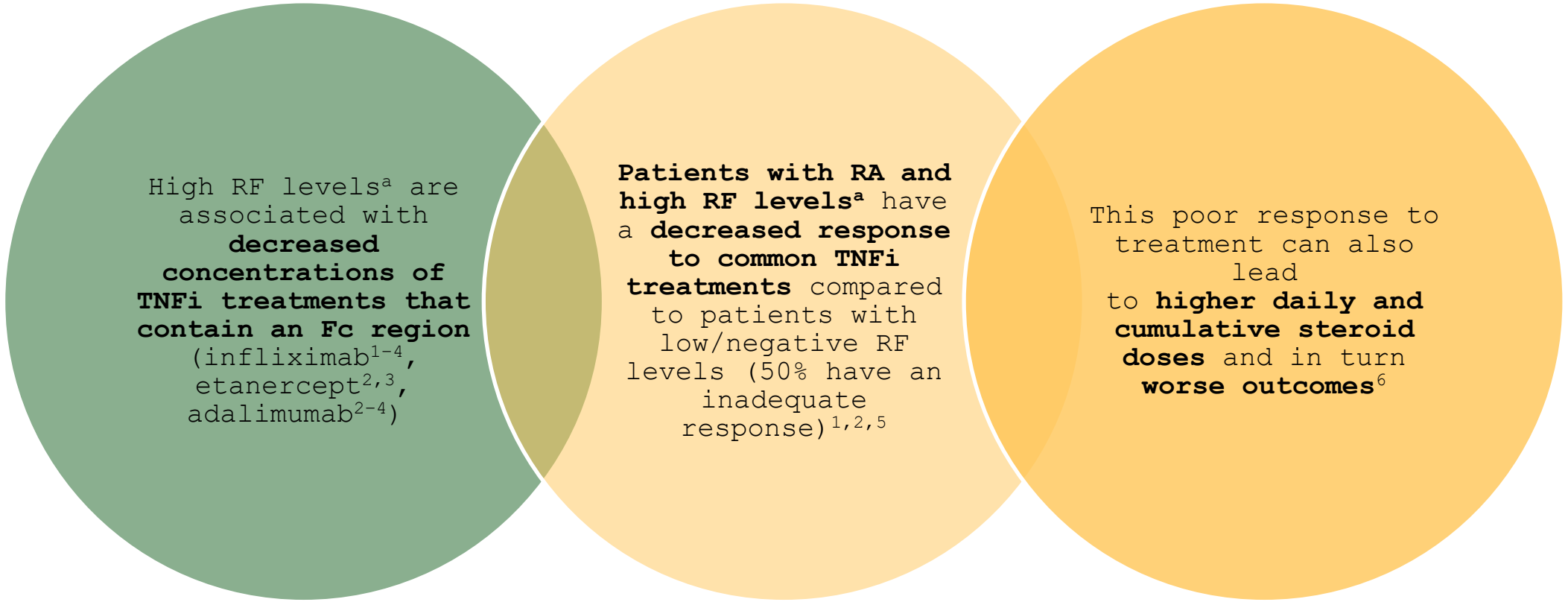
- 189 PA υπό θεραπεία με JAKI –
  -12 μήνες παρακολούθηση

Covariate	Bivariate analysis		Multivariate analysis	
	HR [95% CI]	*p* value	HR [95% CI]	*p* value
Previous bDMARDs (number)	1.18 [1.07–1.31]	0.001	1.11 [0.97–1.26]	0.125
CDAI	1.03 [1.00–1.05]	0.023	1.02 [0.99–1.05]	0.121
Previous JAK inhibitors (number)	1.48 [1.05–2.07]	0.025	1.20 [0.79–1.83]	0.381
Concomitant GC	1.68 [0.96–2.94]	0.072	1.43 [0.80–2.56]	0.223
Concomitant csDMARDs	0.64 [0.34–1.19]	0.158		
RA disease duration (years)	0.98 [0.96–1.01]	0.163		
RF (positivity)	0.71 [0.42–1.21]	0.210		
Age (years)	0.81 [0.48–1.38]	0.437		
Anti-CCP (positivity)	0.89 [0.48–1.66]	0.720		
Sex (female)	1.08 [0.53–2.21]	0.826		

Η πιθανότητα διακοπής δεν συσχετίστηκε με την οροθετικότητα των ασθενών

Sci Rep. 2024 Jan 2;14(1):172. doi: 10.1038/s41598-023-50379-8.

Τι γίνεται όμως με τους TNF(i)



a. High RF level cutoffs are defined as >160 IU/mL or >200 IU/mL in different studies. The >160 IU/mL cutoff is based on RF levels Quartile 4 (Q4) from the ANSWER observational study in Japanese adult patients with RA (177 patients in the Q4 RF>166 IU/mL)[8] and the >200 IU/mL cutoff is based on Q4 from a post-hoc analysis of the EXXELERATE phase 4 study (NCT01500278) in adult patients with RA (n=226) Q4 RF >203 IU/mL as well as the Q4 from a post-hoc analysis that included data from pooled RAPID trials Q4 RF ≥207.0 IU/mL (RAPID-1 [NCT00152386], RAPID-2 [NCT00160602], J-RAPID [NCT00791999], RAPID-C [NCT02151851]), and EXXELERATE (NCT01500278) Q4 >204 IU/mL. Overall, 1537 and 908 patients were included in pooled RAPID trials and EXXELERATE, respectively. Patients were classified into equal quartiles according to baseline RF. Patient demographics and baseline disease characteristics were similar between groups and across RF quartiles.[9,10]

Fc, Fragment crystallizable; IU, International units; Q, Quartile; RA, Rheumatoid arthritis; RF, Rheumatoid factor; TNFi, Tumor necrosis factor inhibitor.

1. Takeuchi T, et al. Arthritis Res Ther. 2017;19(1):194.
2. Bobbio-Pallavicini F, et al. Ann Rheum Dis. 2007;66(3):302–7.
3. Cuchacovich M, et al. Clin Rheumatol. 2014;33(12):1707–14.
4. Martinez Feito A, et al. Arthritis Rheumatol. 2023; 75 (suppl 9). Available at: https://acrabstracts.org/abstract/influence-of-rheumatoid-factor-on-serum-drug-levels-of-tnf-inhibitors-with-different-structures-in-rheumatoid-arthritis/. Accessed December 2023.
5. Santos-Moreno P, et al. Medicine (Baltimore). 2019;98(5):e14181.
6. Sobhy N, et al. Egypt Rheumatol. 2022;44(4):325–8.
7. van Zeben D, et al. Ann Rheum Dis. 1992;51(9):1029–35.
8. Nakayama Y, et al. Rheumatol Int. 2022;42(7):1227–34.
9. Tanaka Y, et al. Int J Rheum Dis. 2023;26(7):1248–59.
10. Smolen J, et al. Arthritis Rheumatol. 2023;75 (suppl 9). Available at: https://acrabstracts.org/abstract/do-high-rf-titers-impact-response-to-tnf-inhibitors-comparison-of-certolizumab-pegol-and-adalimumab-in-patients-with-ra-and-high-titers-of-rf-a-post-hoc-analysis-of-a-phase-4-trial/. Accessed December 2023.

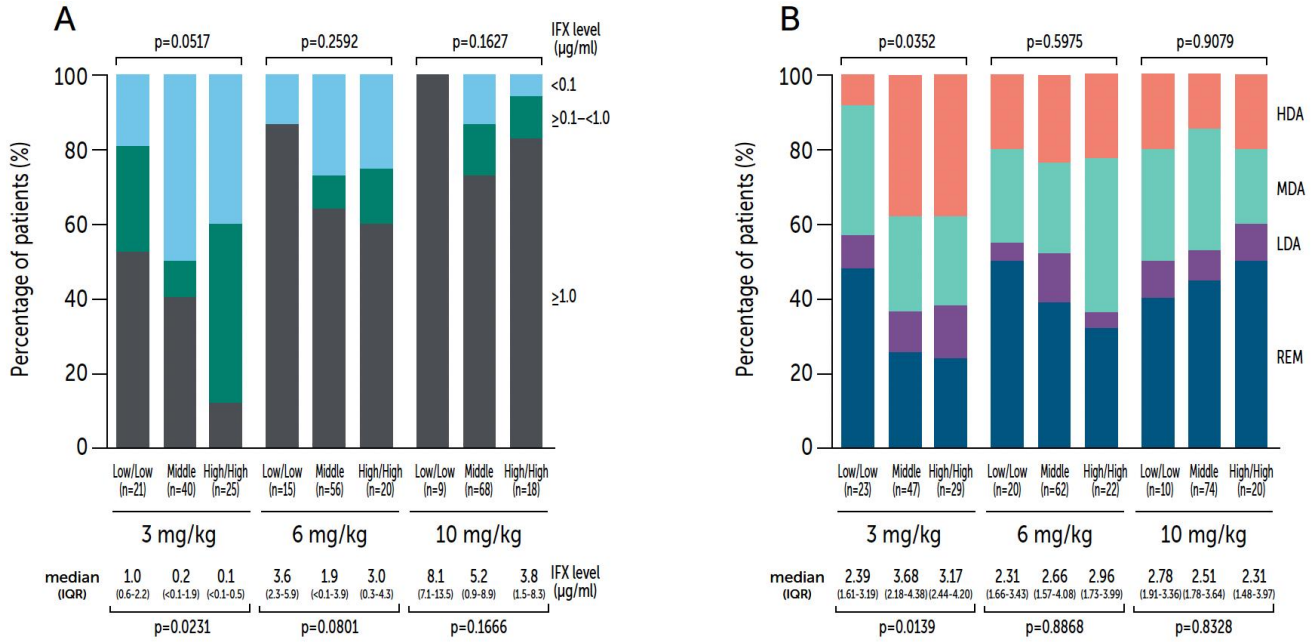
↑↑ τίτλοι RF/ACPA συσχετίστηκαν με ↓ επίπεδα φαρμάκου (inf)

Correlation of rheumatoid factor and anti-cyclic citrullinated peptide antibodies at baseline with serum infliximab levels

	Serum infliximab level							
	Week 2		Week 6		Week 10		Week 14	
	Rho	*p* Value	Rho	*p* Value	Rho	*p* Value	Rho	*p* Value
RF	−0.192	0.0007	−0.188	0.0009	−0.201	0.0004	−0.222	< 0.0001
Anti-CCP	−0.153	0.0071	−0.121	0.0344	−0.133	0.0195	−0.172	0.0025

- IFX serum levels correlate negatively with baseline RF and anti-CCP levels at all time points (W2 to W14) in 307 IFX-treated patients.[1]
- Patients with high RF/anti-CCP levels[a] have low serum IFX levels and poorer response to IFX 3 mg/kg therapy.[1]

Correlation of serum IFX levels (A) and disease activity (B) at Week 54 with the three stratified classes in each IFX dosing group



Adapted from Takeuchi T, et al. 2017

Study design: Patients with active RA (diagnosed according to 1987 American College of Rheumatology criteria) despite MTX treatment were treated with a standard dose (3 mg/kg) of an IFX originator (Remicade®; Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) at Weeks 0, 2, and 6 (W0, W2, and W6, respectively), after which they were randomized to three dosing groups and treated with 3, 6, or 10 mg/kg of IFX every 8 weeks from Week 14 to Week 46. Active RA was defined by the presence of at least six swollen joints, at least six tender joints, and an erythrocyte sedimentation rate ≥28 mm/h or a serum C-reactive protein (CRP) level ≥2.0 mg/dl.

a. "High/high-C" class corresponds to RF ≥160 IU/ml, anti-CCP ≥100 U/ml, "low/low-C" class corresponds to RF <55 IU/ml, anti-CCP <42 U/ml, and "middle-C" corresponds to neither low/low-C nor high/high-C.

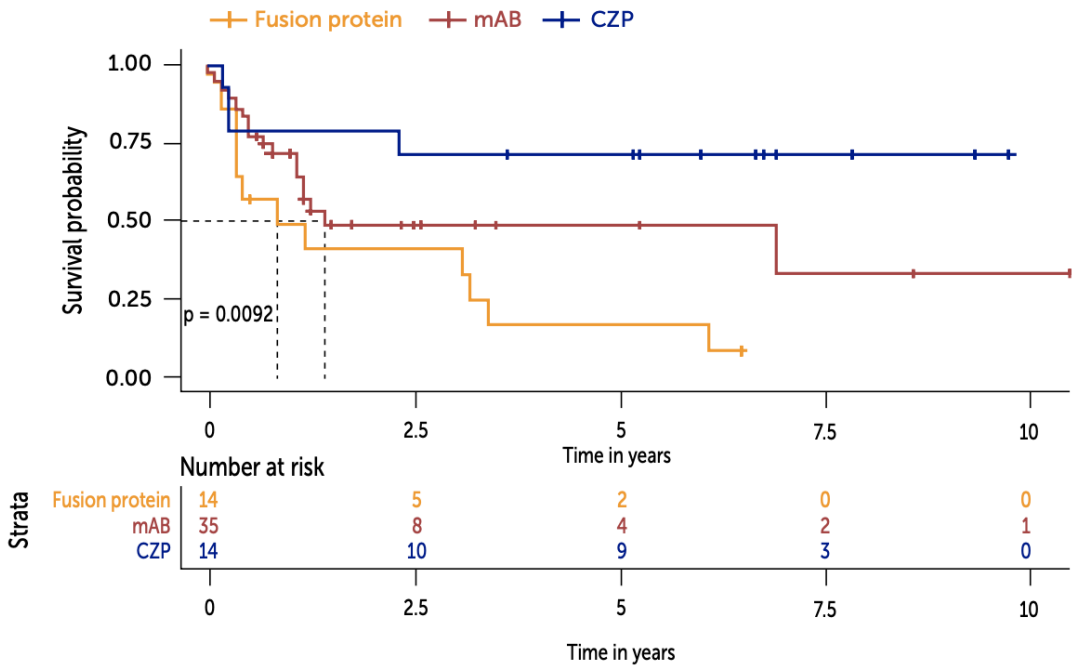
CCP, Anti-cyclic citrullinated peptide; CRP, C-reactive protein; HDA, High disease activity; IFX, Infliximab; LDA, Low disease activity; MDA, Moderate disease activity; REM, Remission; RF, Rheumatoid factor; TNFi, Tumor necrosis factor inhibitor.

1. Takeuchi T, et al. Arthritis Res Ther. 2017;19(1):194.

ασθενείς που έλαβαν CZP είχαν μεγαλύτερη παραμονή στην θεραπεία σε σχέση με άλλους TNF (i)

Retention rate of each molecular structure in patients with high RF levels (≥200 IU/mL)[a,1]

- 755 patients were treated with TNFis (132 with certolizumab pegol, 441 with mAB and 182 with fusion protein)
- High RF levels before TNFi initiation were associated with a longer retention rate in non-naïve patients treated with certolizumab pegol, in comparison with mAB and fusion protein treatments[1]



Adapted from López Medina C, et al. 2023

Study design: Longitudinal, retrospective, and multicenter study including patients with RA and treated with any TNFi (mAB, FP or PEG) between 2010–2022. RF levels before TNFi initiation and the dates of both initiation and treatment withdrawal were collected. Log-rank test was conducted and Kaplan-Meier curves were plotted to evaluate the retention rate to the three molecular structures according to the level of RF considering the quantiles of the baseline levels as cutoffs: <15, >60 and >200 IU/ml (negative, high, and very high levels, respectively). A sensitivity analysis was performed using a Propensity Score (PS) technique matching the PEG, mAB and FP populations according to the age, sex and previous TNFi use.[1]

a. High RF level cutoffs are defined as >160 IU/mL or >200 IU/mL in different studies. The >160 IU/mL cutoff is based on RF levels Quartile 4 (Q4) from the ANSWER observational study in Japanese adult patients with RA (177 patients in the Q4 RF>166 IU/mL)[2] and the >200 IU/mL cutoff is based on Q4 from a post-hoc analysis of the EXXELERATE phase 4 study (NCT01500278) in adult patients with RA (n=226) Q4 RF >203 IU/mL as well as the Q4 from a post-hoc analysis that included data from pooled RAPID trials Q4 RF ≥207.0 IU/mL (RAPID-1 [NCT00152386], RAPID-2 [NCT00160602], J-RAPID [NCT00791999], RAPID-C [NCT02151851]), and EXXELERATE (NCT01500278) Q4 >204 IU/mL. Overall, 1537 and 908 patients were included in pooled RAPID trials and EXXELERATE, respectively. Patients were classified into equal quartiles according to baseline RF. Patient demographics and baseline disease characteristics were similar between groups and across RF quartiles.[3,4]

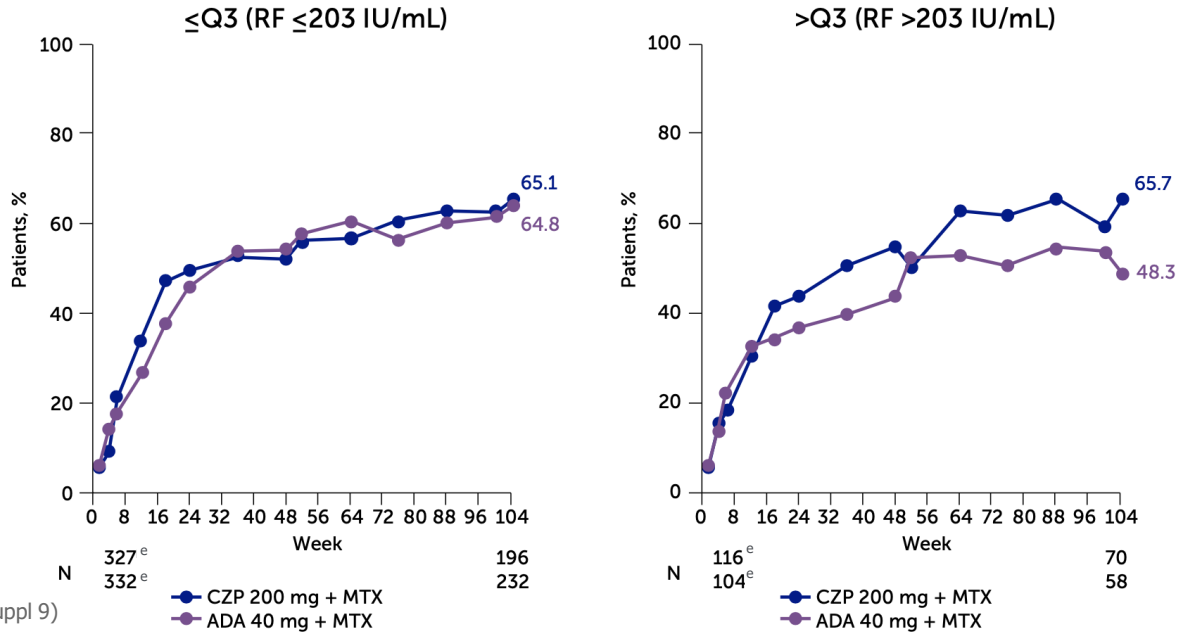
CZP, Certolizumab pegol; FP, Fusion protein; IU, International units; mAB, monoclonal antibody; PEG, Polyethylene glycol; Q, Quartile; RF, Rheumatoid factor; RA, Rheumatoid arthritis, TNFi, Tumor necrosis factor inhibitor.

1. López Medina C, et al. Arthritis Rheumatol. 2023;75 (suppl 9). https://acrabstracts.org/abstract/certolizumab-pegol-shows-longer-retention-rate-in-comparison-with-other-tnf-inhibitors-in-patients-with-rheumatoid-arthritis-and-high-rheumatoid-factor-titers-at-baseline-a-multicentre-and-retrospect/. Accessed December 2023.
2. Nakayama Y, et al. Rheumatol Int. 2022;42(7):1227–34.
3. Tanaka Y, et al. Int J Rheum Dis. 2023;26(7):1248–59.
4. Smolen J, et al. Arthritis Rheumatol. 2023;75 (suppl 9). Available at: https://acrabstracts.org/abstract/do-high-rf-titers-impact-response-to-tnf-inhibitors-comparison-of-certolizumab-pegol-and-adalimumab-in-patients-with-ra-and-high-titers-of-rf-a-post-hoc-analysis-of-a-phase-4-trial/. Accessed December 2023.

Certolizumab pegol-treated patients showed consistent probability of achieving LDA across baseline RF quartiles[a,b,c,1]

Proportion of patients achieving DAS28-CRP LDA[c,1]

- A **post-hoc analysis of the EXXELERATE trial** showed consistent achievement of DAS28-CRP LDA[c] in certolizumab pegol-treated patients with RA[1]



Adapted from Smolen J, et al. Arthritis Rheumatol. 2023;75(suppl 9)

CZP-treated patients with high RF levels had a **36%** better chance of achieving DAS28-CRP LDA[c] vs. ADA-treated patients[d,1]

Study design: EXXELERATE was a 104-week, randomized, single-blind (double-blind until Week 12 and investigator blind thereafter), parallel-group, head-to-head superiority study (EXXELERATE), eligible patients from 151 centers worldwide were aged 18 years or older with a diagnosis of rheumatoid arthritis at screening, as defined by the 2010 ACR/EULAR criteria, and had prognostic factors for severe disease progression, including a positive rheumatoid factor, or anti-cyclic citrullinated peptide antibody result, or both. Participants were randomly assigned (1:1) via an interactive voice and web response system with no stratification to receive certolizumab pegol plus methotrexate or adalimumab plus methotrexate. All study staff were kept masked throughout the study and participants were masked until Week 12. At Week 12, patients were classified as responders (by either achieving LDA according to DAS28-ESR ≤3.2 or DAS28-ESR reduction ≥1.2 from baseline) or as non-responders. Non-responders to the first TNF inhibitor to which they were randomized were switched to the other TNF inhibitor with no washout period. Primary endpoints were the percentage of patients achieving a 20% improvement according to the American College of Rheumatology criteria (ACR20) at Week 12 and LDA at Week 104 (Week 12 non-responders were considered LDA non-responders).[a,1]

a. The primary endpoints for superiority in the overall population on ACR20 at Week 12 and DAS28-ESR LDA at Week 104 were not met while secondary efficacy endpoint results were similar for both treatments.[2]
b. This is a post-hoc analysis of the head-to-head EXXELERATE study. In the initial trial, the primary end points of superiority were not met for the overall population, but the efficacy results demonstrated numerically comparable responses between both drugs. This post-hoc analysis was not designed to show statistical significance.[1]
c. Defined as DAS28 ≤2.7.[1]
d. Based on calculation of ratio of final data points (65.7/48.3=1.36).[1]
e. N at Week 2.[1]

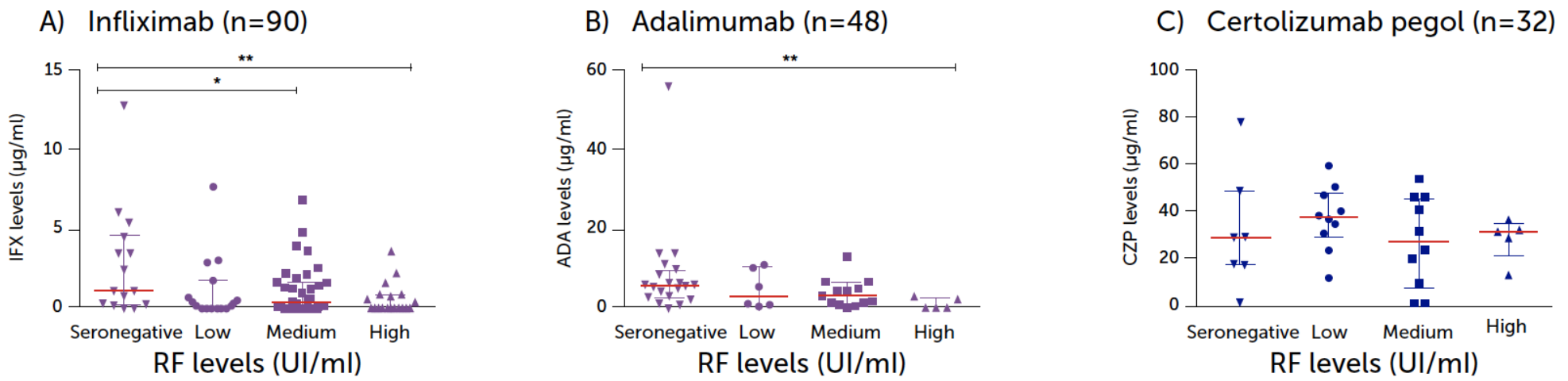
ACR, The American College of Rheumatology; ADA, Adalimumab; CZP, Certolizumab pegol; DAS28-CRP, Disease Activity Score 28 with C-reactive protein; DAS28-ESR, Disease Activity Score 28-erythrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; LDA, Low disease activity; Q, Quartile; RA, Rheumatoid arthritis; RF, Rheumatoid factor; TNF, Tumor necrosis factor.

1. Smolen J, et al. Arthritis Rheumatol. 2023;75 (suppl 9). Available at: https://acrabstracts.org/abstract/do-high-rf-titers-impact-response-to-tnf-inhibitors-comparison-of-certolizumab-pegol-and-adalimumab-in-patients-with-ra-and-high-titers-of-rf-a-post-hoc-analysis-of-a-phase-4-trial/. Accessed December 2023.
2. Smolen JS, et al. Lancet. 2016;388(10061):2763–74.

The unique Fc-free structure of certolizumab pegol may lead to more stable levels compared to other TNFis[a,b,1]

- RF binds to Fc regions; therefore, it cannot bind to certolizumab pegol, due to its unique Fc-free structure[b]
- Certolizumab pegol is not impacted by high RF levels and its concentration remains stable over time, in contrast to infliximab and adalimumab, whose concentrations notably decrease after 6 months of treatment[1]

Median drug concentrations at 6 months according to baseline RF levels[1]



*p<0.05; **p<0.01
Adapted from Martinez-Feito A, et al. 2023

Study design: This is a retrospective cohort study of 168 patients with RA from the RA-Paz Registry, 1999-2019, where 90 patients received IFX, 48 ADA and 32 CZP. Patients were stratified into quartiles based on baseline RF levels: low (20-57 IU/ml), medium (57-380 IU/ml), high (>380 IU/ml) and seronegative (<20 IU/ml). Association between baseline RF levels and drug levels was assessed using non-parametric test (Mann-Whitney). *p<0.05; **p<0.01.[1]

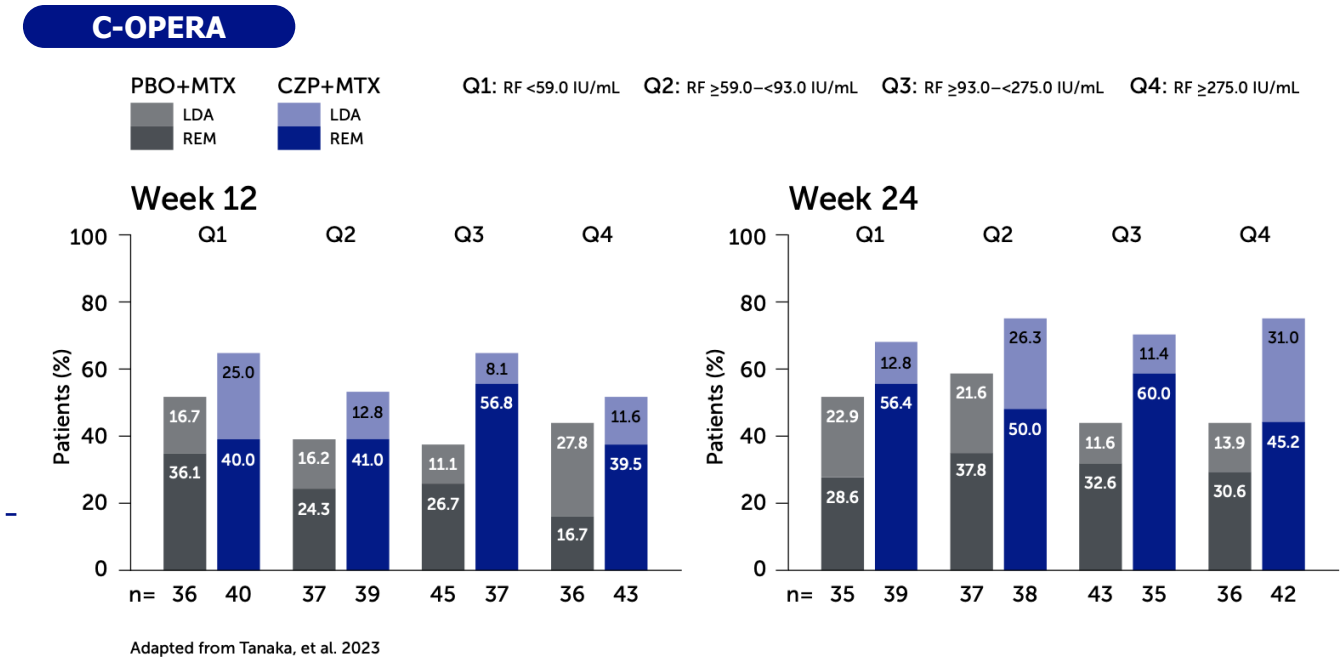
a. Please note that certolizumab pegol, adalimumab, and infliximab have different pharmacological profiles and therefore the median drug levels (ng/mL) cannot be the same.
b. Certolizumab pegol is a PEGylated Fab fragment that therefore lacks the Fc portion of immunoglobulin, while all other TNFis (e.g.: IFX and ADA) have an immunoglobulin Fc portion in their structures. Because RF can bind to the immunoglobulin Fc portion, it might bind to the Fc region of certain TNFis, leading to the formation of large immune complexes and influencing their clinical efficacy.[2,3]

ADA, Adalimumab; CZP, Certolizumab pegol; Fab, Fragment antigen-binding; Fc, Fragment crystallizable; IFX, Infliximab; RA, Rheumatoid arthritis; RF, Rheumatoid factor, TNFi, Tumor necrosis factor inhibitor.

1. Martinez Feito A, et al. Arthritis Rheumatol. 2023;75 (suppl 9). Available at: https://acrabstracts.org/abstract/influence-of-rheumatoid-factor-on-serum-drug-levels-of-tnf-inhibitors-with-different-structures-in-rheumatoid-arthritis/. Accessed December 2023.
2. Nakayama Y, et al. Rheumatol Int. 2022;42(7):1227–34.
3. Levy RA, et al. Immunotherapy. 2016;8(12):1427–36.

Certolizumab pegol showed consistent rates of patients reaching LDA or remission across baseline RF quartiles in patients with RA[a,1]

DAS28-ESR LDA and remission rates[1]



Adapted from Tanaka, et al. 2023

a. A post-hoc analysis including data from 6 trials: C-OPERA (NCT01451203) (316 patients) pooled RAPID trials (RAPID-1 [NCT00152386], RAPID-2 [NCT00160602], J-RAPID [NCT00791999], RAPID-C [NCT02151851]) (1537 patients), and EXXELERATE (NCT01500278) (908 patients). Patients who received CZP® or placebo/comparator with methotrexate (MTX) were categorized by baseline RF quartiles. Efficacy was assessed with Disease Activity Score-28 erythrocyte sedimentation rate (DAS28-ESR).[1]

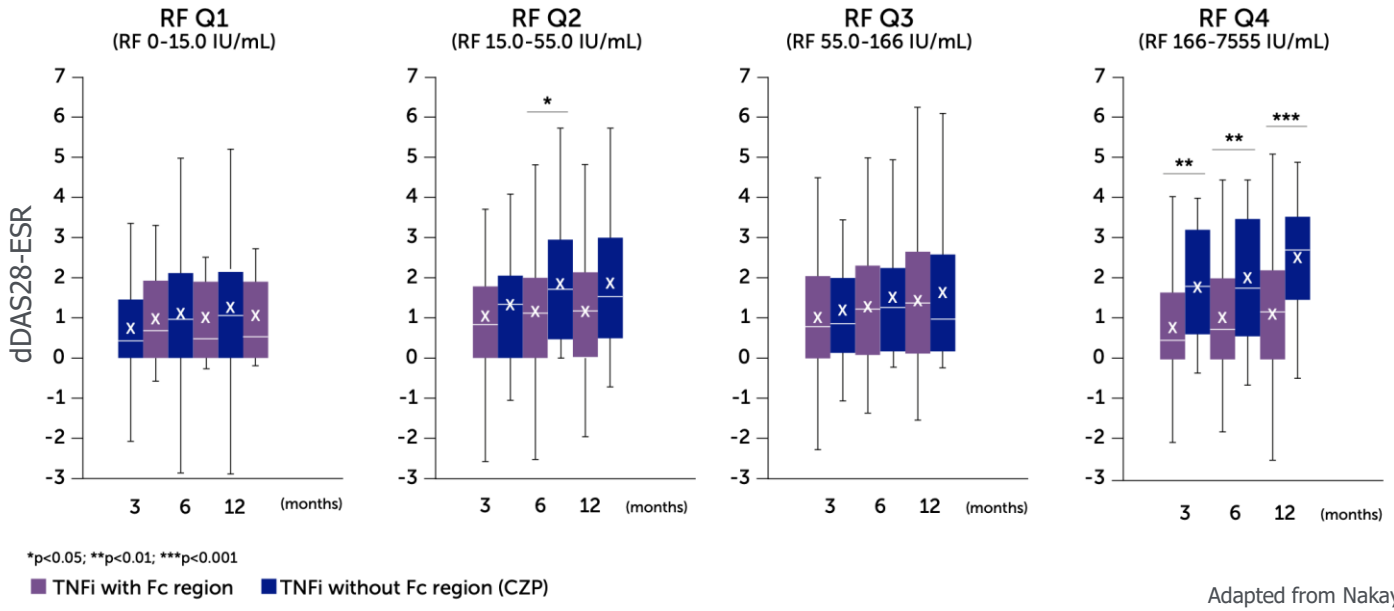
CZP, Certolizumab pegol; DAS28-ESR, Disease Activity Score 28-erythrocyte sedimentation rate; LDA, Low disease activity; MTX, Methotrexate; PBO, Placebo; Q, Quartile; RA, Rheumatoid arthritis; REM, Remission; RF, Rheumatoid factor.

1. Tanaka Y, et al. Int J Rheum Dis. 2023;26(7):1248–59.

Certolizumab pegol, the only Fc-free TNFi, may be more efficacious vs. other TNFis with an Fc region in RA patients with high RF levels[a,b,c,1]

DAS28-ESR change (dDAS28-ESR) between baseline and 3, 6 and 12 months[1]

- 705 RA patients treated with TNFis were classified into four RF quartiles.
- In patients with high RF levels, dDAS28-ESR of patients treated with certolizumab pegol was significantly higher than other TNFis with an Fc region at 3, 6, and 12 months after treatment.



Adapted from Nakayama, et al. 2022

Study design: An observational multicenter registry of 705 patients with RA in the Kansai district of Japan. Data from patients at seven institutes (Kyoto University, Osaka University, Osaka Medical College, Kansai Medical University, Kobe University, Nara Medical University, and Osaka Red Cross Hospital) were included. Patients with RA treated with one of five TNFis (ADA, CZP, ETN, GLM, and IFX, including both intravenous and subcutaneous agents but excluding bio-similar agents, all of which were introduced between 2011 and 2018) and whose data on baseline RF levels and baseline and 3-month post-treatment disease activity were available were included in our study. n=153 for TNFis with Fc and n=24 for TNFi without Fc (certolizumab pegol). *p<0.05, **p<0.01, ***p<0.001.[1]

a. CZP® is an Fc-free TNFi while all other TNFis (IFX, ADA, GLM, and ETN) have an Fc region. Because RF can bind to the Fc region of IgG, it might bind to the Fc region of certain TNFis, leading to the formation of large immune complexes and influencing their clinical efficacy.[1,2]
b. Based on an observational study of 705 patients with RA in Japan, not a head-to-head study. The objective of the study was to investigate whether the therapeutic efficacy is different between TNFis with and without the Fc region in RA patients depending on RF levels, particularly those with high RF levels. Patients were treated with one of five TNFis (ADA, CZP, ETN, GLM, and IFX). Dosing regimens were not disclosed.[1]
c. TNFis with Fc: adalimumab (ADA), etanercept (ETN), infliximab (IFX), golimumab (GLM); TNFi without Fc: certolizumab pegol (CZP).[1]

ADA, Adalimumab; CZP, Certolizumab pegol; DAS28-ESR, Disease Activity Score 28-erythrocyte sedimentation rate; ETN, Etanercept; Fc, Fragment crystallizable; GLM, Golimumab; IgG, Immunoglobulin G ; IFX, Infliximab; RA, Rheumatoid arthritis; RF, Rheumatoid factor; TNFi, Tumor necrosis factor inhibitor.

1. Nakayama Y, et al. Rheumatol Int. 2022;42(7):1227–34.
2. Levy RA, et al. Immunotherapy. 2016;8(12):1427–36.

Take home message

- Η οροθετική Ρευματοειδής Αρθρίτιδα συσχετίζεται με υψηλότερο φορτίο νόσου και χειρότερη έκβαση σε σχέση με την οροαρνητική Ρευματοειδή Αρθρίτιδα

- Οι ασθενείς με υψηλούς τίτλους αντισωμάτων RF/ACPA φαίνεται ότι ίσως ανταποκρίνονται καλύτερα σε κάποιες θεραπευτικές επιλογές

- Οι περισσότεροι TNF(i) παρουσιάζουν χαμηλότερα επίπεδα φαρμάκων σε ασθενείς με υψηλούς τίτλούς RF σε σχέση με τους «οροαρνητικούς» ασθενής PA ή σε «οροθετικούς» με χαμηλά επίπεδα RF

- Το Certolizumab Pegol λόγω της διαφορετικής του δομής (στερείται Fc- region) διατηρείται σε υψηλά θεραπευτικά επίπεδα ανεξάρτητα τον τίτλο του RF

- Η θεραπευτική επιλογή **δεν καθορίζεται από τον ανοσολογικό profil** των ασθενών , αλλά ορίζεται από τις κατευθυντήριες οδηγίες και εξατομικεύεται βάση του profil του κάθε ασθενή ξεχωριστά

Σας ευχαριστώ !