Διακοπή ή όχι των βιολογικών παραγόντων σε ασθενείς με φλεγμονώδεις αρθρίτιδες σε ύφεση?

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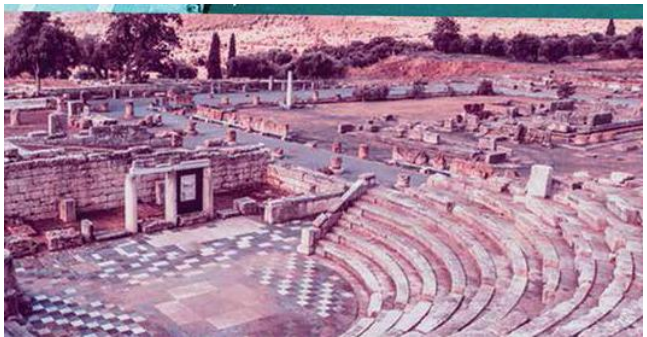
Εαρινές Ημέρες Ρευματολογίας
Καλαμάτα, 31/5-1/6/2019



ΠΑΝΕΠΙΣΤΗΜΙΑΚΟ
ΝΟΣΟΚΟΜΕΙΟ ΗΡΑΚΛΕΙΟΥ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΡΗΤΗΣ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

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

11. If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering bDMARDs, especially if this treatment is combined with a csDMARD

12. If a patient is in persistent remission, tapering the csDMARD could be considered

Smolen JS, et al. Ann Rheum Dis 2017;0:1

Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions

Table 1 DMARD tapering/withdrawal studies

Author	Acronym	Type	Arms*	N†	ERA/RA	DMARDs	MODE	IC	Type	SUS	REM‡	FO
Tanaka *et al*[24]	HONOR	UC	2	75	RA	ADA	STOP	REM	DAS28 <2.6	>6 m	48%	1
Saleem *et al*[25]	–	UC	1	47	ERA/RA	TNFi	STOP	REM	DAS28 <2.6	>6 m	15%–59%	2
Brocq *et al*[26]	–	UC	1	21	RA	TNFi	STOP	REM	DAS28 <2.6	>6 m	25%	1
Aguilar-Lonzano *et al*[28]	–	UC	1	45	RA	TOC	STOP	REM	DAS28 <2.6	–	44%	1
Naredo *et al*[60]	–	UC	1	77	RA	TNFi	TAP	REM	DAS28 <2.6	>6 m	55%	1
Iwamoto *et al*[61]	–	UC	1	40	RA	TNFi, TOC	STOP	REM	DAS28 <2.6	–	60%	0.5
Alivernini *et al*[52]	–	UC	1	42	RA	TNFi	TAP/STOP	REM	DAS44 <1.6	>6 m	61%	0.5
Tanaka *et al*[23]	RRR	UC	1	102	RA	IFX	STOP	LDA	DAS28 ≤3.2	>6 m	55%	1
van der Maas *et al*[27]	–	UC	1	51	RA	IFX	TAP	LDA	DAS28 ≤3.2	>6 m	16%–45%	1
Nishimoto *et al*[29]	DREAM	UC	1	187	RA	TOC	STOP	LDA	DAS28 ≤3.2	–	13%	1
van Herwaarden *et al*[30]	–	UC	1	22	RA	TOC	TAP	LDA	DAS28 ≤3.2	–	55%	0.5
Quinn *et al*[31]	20TNF	SA	2	20	ERA	IFX	STOP	REM	–§	–	70%	1
Klarenbeek *et al*[34]	BEST	SA	1	243	ERA	SD/IFX	TAP	REM	DAS44 <1.6	>6 m	23%	2
Nam *et al*[38]	IDEA	SA	1	14	ERA	ETA	STOP	REM	DAS44 <1.6	>6 m	42%	0.5
Nam *et al*[39]	EMPIRE	SA	1	9	EA/ERA	IFX	STOP	REM	TJC0/SJC0	–	25%	1
Huinzinga *et al*[41]	ACT-RAY	SA	1	238	RA	TOC	STOP	REM	DAS28 <2.6	–	14%	1
Detert *et al*[36]	HIT-HARD	SA	1	155	ERA	ADA	STOP	–¶	–¶	–	89%	1
Smolen *et al*[35]	OPTIMA	SA	2	207	ERA	ADA	STOP	LDA	DAS28 ≤3.2**	–	66%–81%	1
Soubrier *et al*[37]	GUÉPARD	SA	1	69	ERA	ADA	STOP	LDA	DAS28 ≤3.2	–	33%	<1
Emery *et al*[40]	AVERT	SA	1	222	ERA	ABA	STOP	LDA	DAS28 ≤3.2**	–	15%	1
ten Wolde *et al*[21]	–	RCT	2	285	RA	SD	STOP	REM	ACR	>6 m	62%	1
Ahern *et al*[22]	–	RCT	2	38	RA	SD	TAP	REM	TJC0/SJC0	>6 m	21%	0.5
Haschka *et al*[15]	RETRO	RCT	3	101	RA	All††	TAP/STOP	REM	DAS28 <2.6	>6 m	48%–61%	1
Emery *et al*[42]	PRIZE	RCT	3	193	ERA	MTX/ETA	STOP	REM	DAS28 <2.6	–	24%–63%	0.5
Fautrel *et al*[43]	STRASS	RCT	1	137	RA	TNFi	TAP	REM	DAS28 <2.6	>6 m	74%	1.5
Smolen *et al*[44]	PRESERVE	RCT	3	604	RA	ETA	TAP/STOP	LDA	DAS28 ≤3.2	>6 m	43%–79%	1
van Vollenhoven *et al*[45]	DOSERA	RCT	3	91	RA	ETA	TAP/STOP	LDA	DAS28 ≤3.2	>6 m	52%	1
van Herwaarden *et al*[46]	DRESS	RCT	2	180	RA	ADA, ETA	TAP	LDA	DAS28 ≤3.2	–	88%	1.5

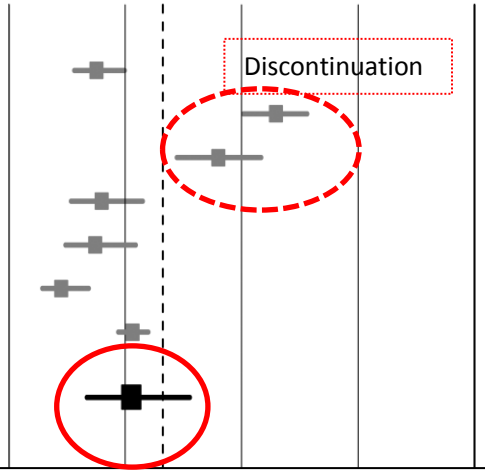
Schett G, et al. Ann Rheum Dis 2016;75:1428

Ερωτήματα ”taper” bDMARDs

- Σε ποιους ασθενείς - Πότε ?
- Ποιος ο κίνδυνος υποτροπής - Προγνωστικοί δείκτες flare ?
- Επανέλεγχος νόσου ?
- Αν υπό combo ποια από τις αγωγές taper ?

Σε ελάττωση δόσης bDMARD 30% ο κίνδυνος υποτροπών. Διπλάσιος σε περίπτωση διακοπής!!!

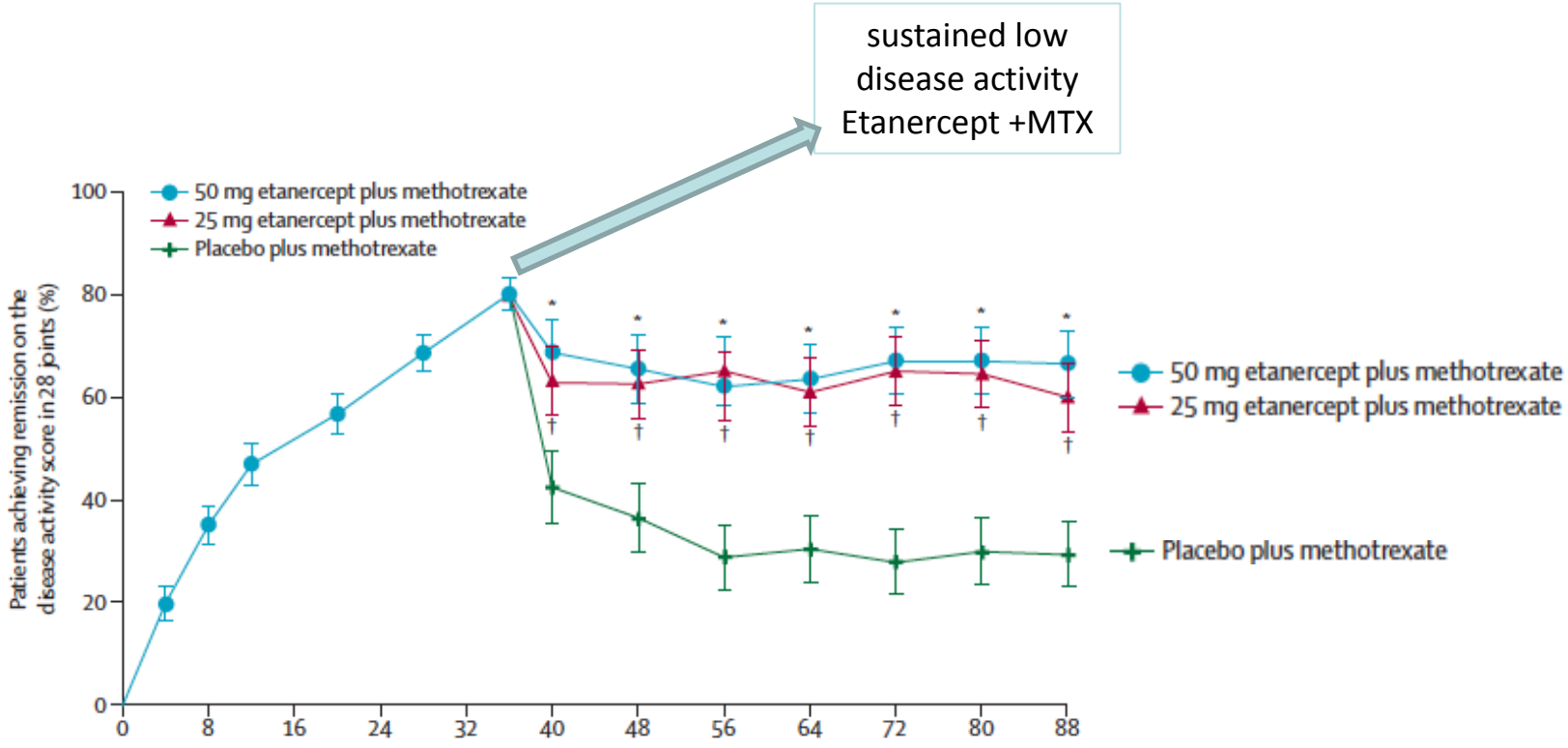
Study Arms	Medication	Characteristics	Followup	n	Flare Rate (95% CI)	Forest Plot
Good quality						
Smolen, *et al*[17], half dose	ETN	r[1], p	1 yr	202	0.19 (0.14–0.25)	
Smolen, *et al*[17], stop	ETN	s, p	1 yr	200	0.57 (0.51–0.64)	
Tanaka, *et al*[22]	IFX	s, a	1 yr	114	0.45 (0.36–0.54)	
van den Broek, *et al*[20]	IFX	s, a, e	1 yr	104	0.20 (0.13–0.29)	
Smolen, *et al*[16], stop	ADA	s, a, e	1 yr	102	0.19 (0.12–0.27)	
Raffeiner, *et al*[15]	ETN	r[2], p	1 yr	159	0.11 (0.07–0.17)	
Kavanaugh, *et al*[12]	TNFi	s, p	1 yr	717	0.27 (0.24–0.30)	
Pooled estimate				**1598**	**0.26 (0.17–0.39)**[h1]	



J Rheumatol. 2015 Nov;42(11):2012

PRESERVE

"…**withdrawal of etanercept worsened** symptoms despite methotrexate continuation.
Reduction to 25 mg etanercept every week maintained low disease activity in most patients…."



Lancet 2013, 381: 918

Flare rates for tapering TNF inhibitors between 51% and 77%.

Trial	Protocol	Flare rate	Relapse definition
POET	TNFi stop	51.2%	DAS28 >3.2 or ΔDAS28 >0.6
PRESERVE	TNFi stop TNFi dose 1/2	57.4% 20.9%	DAS28 >3.2 DAS28 >3.2
STRASS	TNFi extending interval	76.6%	DAS28 >2.6 or ΔDAS28 >0.6
DRESS	TNFi dose reduction	55%	ΔDAS28-CRP>0.6
Few RCTs investigated tapering of csDMARDs	combined tapering of csDMARDs and biologicals	35% and 56%.	

van Mulligen E, et al. Ann Rheum Dis 2019;**78**:746

TNFi taper or not?

Disease activity guided dose reduction and withdrawal of adalimumab or etanercept compared with usual care in rheumatoid arthritis: open label, randomised controlled, non-inferiority trial

Noortje van Herwaarden,[1] Aatke van der Maas,[1] Michiel J M Minten,[1] Frank H J van den Hoogen,[1, 2] Wietske Kievit,[3] Ronald F van Vollenhoven,[4] Johannes W J Bijlsma,[5] Bart J F van den Bemt,[6, 7] Alfons A den Broeder[1]

BMJ 2015;350:h1389

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Taper (/3months):

- ADA 40 mg / 21 days → 40 mg / 28 days → stop
- ETA: 50 mg / 10 days → 50 mg / 14 days → stop.

➢ **UPON FLARE RETREATMENT:** back to last effective interval → back to the shortest registered interval → switched.

Groups: Dose reduction (DR) vs usual care (UC)

Outcomes

- Primary outcome: difference in cumulative incidence of **major flare** at 18 **(ΔDAS28>1.2 or ΔDAS20>0.6 + DAS28>3.2 X 3mo)**

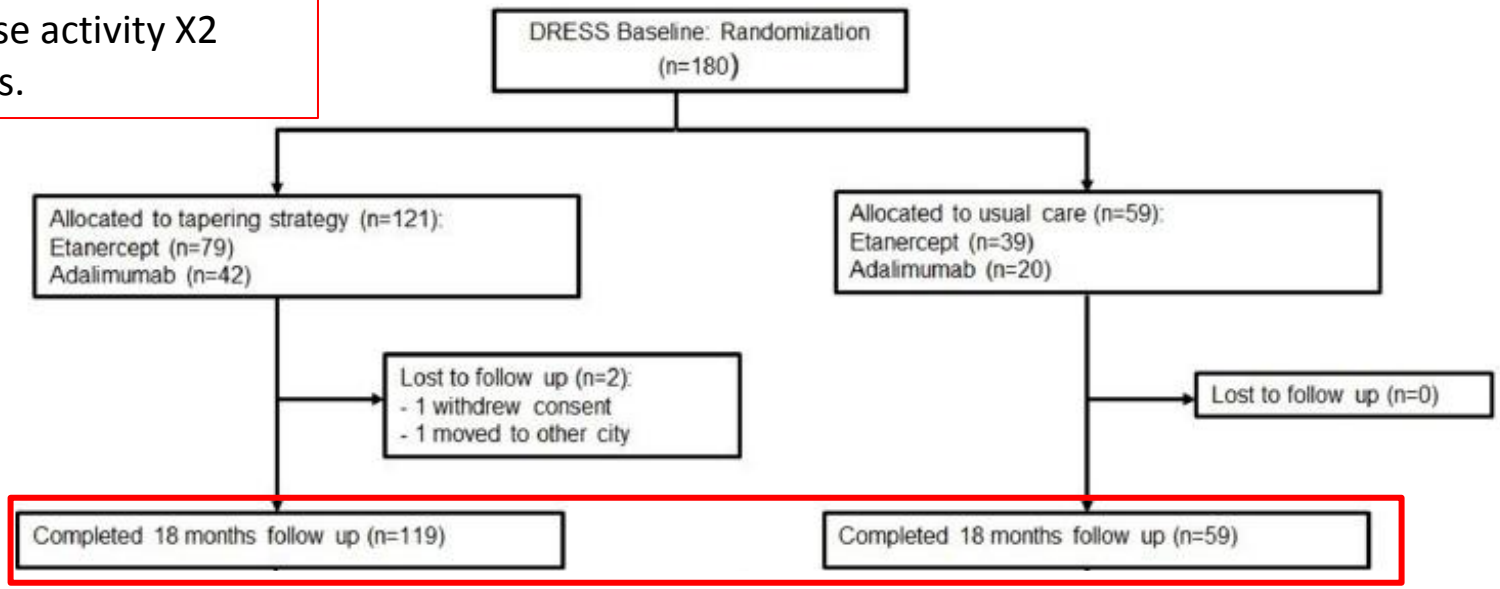
Design

- pragmatic, open label, randomised controlled, non-inferiority trial, stratified by the TNF inhibitor used.

BMJ 2015;350:h1389

ADA or ETN

- stable dose and interval for >6 months,
- stable low disease activity X2 subsequent visits.



BMJ 2015;350:h1389

Χαρακτηριστικά Ασθενών

Table 1 | Baseline patient characteristics

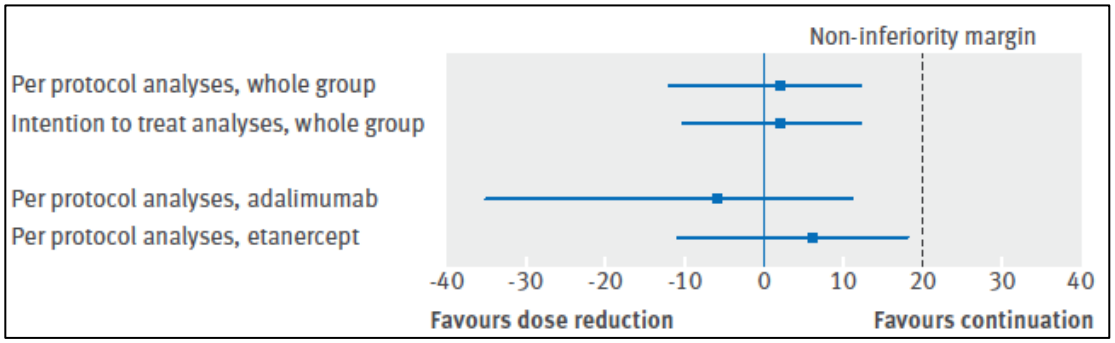
	Dose reduction (n=121)	Usual care (n=59)
General characteristics		
Age (years)*	59 (10.5)	58 (9.3)
Female sex	75 (62)	41 (69)
Current smoking	29 (24)	18 (31)
Body mass index*	27 (4.9)	26 (4.0)
Diagnosis according to 2010 or 1987 ACR criteria	114 (94)	58 (98)
Disease duration (years)†	10 (6–17)	10 (6–16)
Rheumatoid factor positive	94 (78)	49 (83)
Anti-citrullinated peptide antibodies positive	77 (64)	39 (68)
Erosive disease	99/116 (85)	54 (92)
SvdH score†	23 (6–50)	17.5 (8.5–46.5)
Treatment		
Etanercept/adalimumab	79/42 (65/35)	39/20 (66/34)
Duration of current TNF inhibitor treatment (years)*	3.5 (2.5)	3.6 (2.3)
Previous dose reduction attempt with current TNFi	21 (17)	11 (19)
Previous DMARD treatment†	2 (1–3)	2 (1–3)
Previous conventional synthetic DMARD combination treatment‡	30/100 (30)	22/49 (45)
Previous TNF inhibitor treatment†	0 (0–1)	0 (0–1)
Concomitant treatment		
DMARD	73 (60)	47 (80)
Methotrexate	58 (48)	41 (69)
Methotrexate dose (mg)*	15.8 (5.7)	16.1 (5.5)
Glucocorticoids	6 (5)	3 (5)
Non-steroidal anti inflammatory drugs	65 (54)	35 (59)

BMJ 2015;350:h1389

Comparable rate of MAJOR flares taper vs stable during 18 months

The cumulative incidence of major DAS28-CRP flare: 12% & 10% in taper & usual care group

	Dose reduction (n=121)	Usual care (n=59)	Difference (95%CI)
Flares			
All flares	88 (73)	16 (27)	46% (30% to 58%)
Major flares	15 (12)	6 (10)	2% (–9% to 11%)

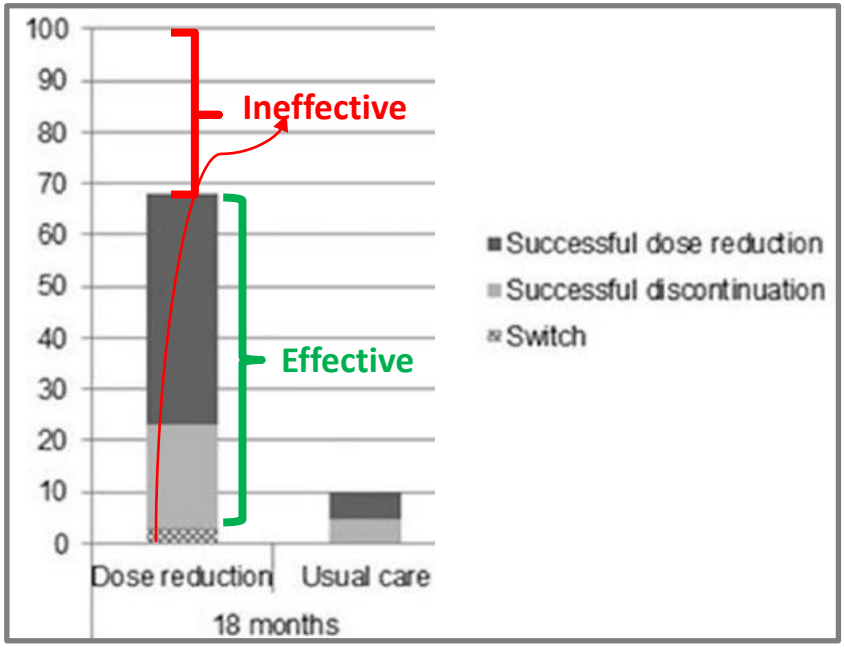


BMJ 2015;350:h1389

@ 18 months:
2/3 Taper or Discontinuation
1/3 Failure

In the dose reduction group (n=121), TNF inhibitor use at 18 months

- Discontinued in 24 patients (20%),
- Tapered in 52 (43%)
- No dose reduction was possible in 45 patients (37%)



BMJ 2015;350:h1389

Comparable disease activity of TAPER vs STABLE
(except for strict remission)

Table 2 | Disease activity levels at baseline and nine and 18 month follow-up

	Dose reduction (n=121)	Usual care (n=59)	P*
9 month follow-up			
DAS28-CRP score <3.2	89 (74)	54 (92)	0.005
DAS28-CRP score <2.6	73 (60)	48 (81)	0.005
2011 ACR/EULAR Boolean based remission	22 (18)	17 (29)	0.104
18 month follow-up			
DAS28-CRP score <3.2	103 (85)	53 (90)	0.464
DAS28-CRP score <2.6	86 (71)	47 (80)	0.218
2011 ACR/EULAR Boolean based remission	29 (24)	24 (41)	0.021

Data are number (%) of patients. ACR/EULAR=American College of Rheumatology/European League Against Rheumatism.
*χ^2, crude estimates without adjustments.

BMJ 2015;350:h1389

Predictors of relapse?

DRESS study

No clinical, laboratory, or cotreatment variables were significantly associated with successful dose reduction or discontinuation of TNF inhibitor treatment.

BMJ 2015;350:h1389

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BMJ 2015;350:h1389

BeST study:

- Multivariable predictors for restarting treatment were:
  - ✓ anti-CCP
  - ✓ High mean DAS until remission
  - ✓ Low baseline Health Assessment Questionnaire score
  - ✓ Last DMARD sulfasalazine

Ann Rheum Dis 2011;**70**:315

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No clinical, laboratory, or cotreatment variables were significantly associated with successful dose reduction or discontinuation of TNF inhibitor treatment.

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Ann Rheum Dis 2011;**70**:315

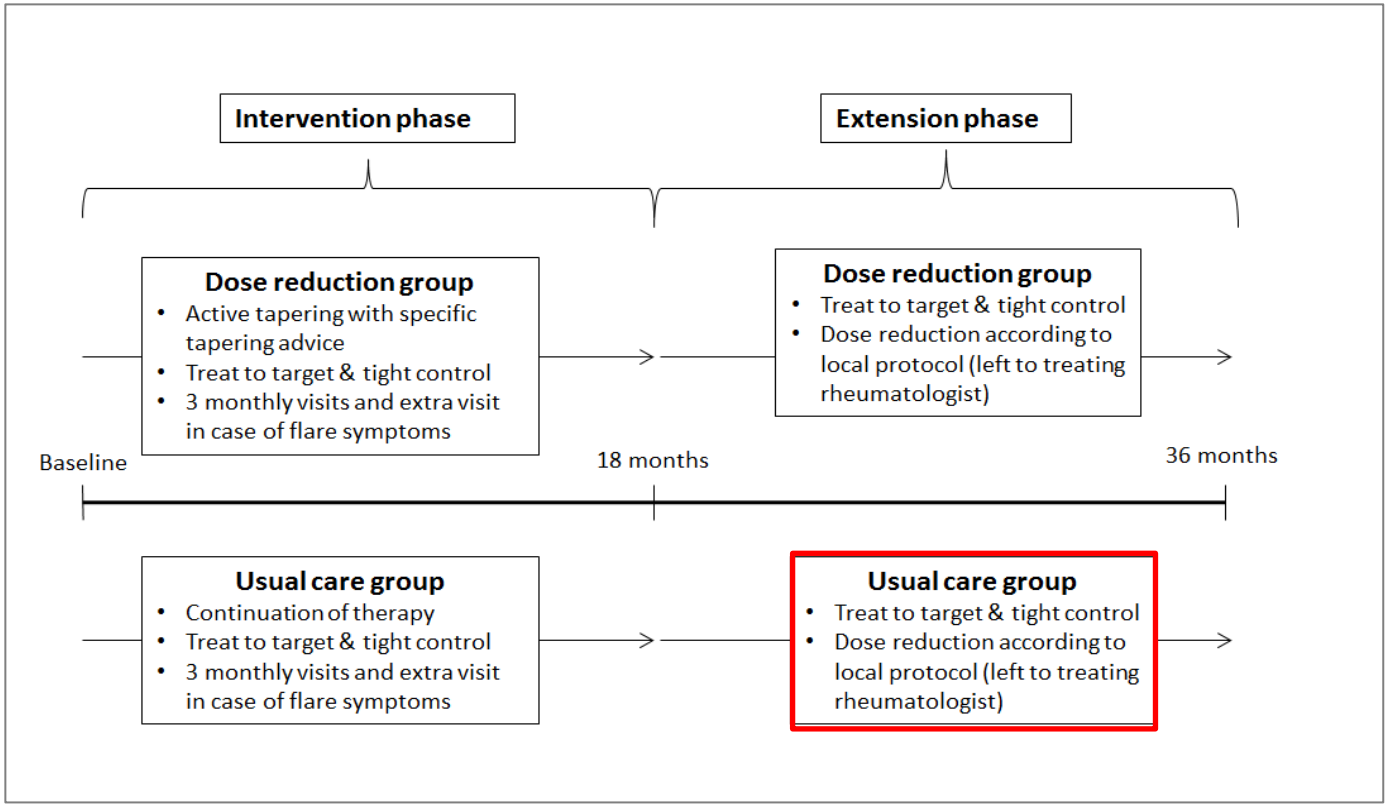
RRR study:

Not being in “Deep remission”?

Ann Rheum Dis 2010;**69**:1286

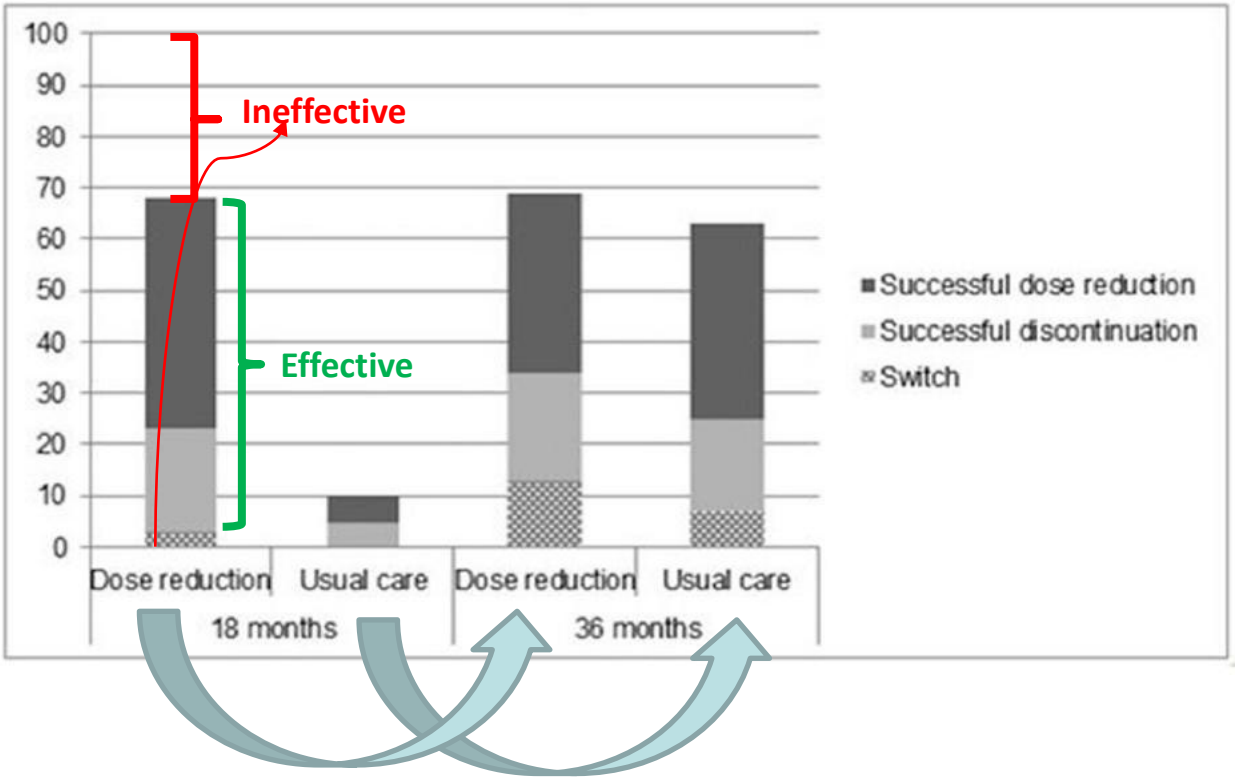
TNFi taper or not?

Long-term outcomes after disease activity-guided dose reduction of TNF inhibition in rheumatoid arthritis: 3-year data of the DRESS study - a randomised controlled pragmatic non-inferiority strategy trial



Bouman CAM, et al. Ann Rheum Dis 2017;**76**:1716

Gradual Taper of TNFi effective in 2/3 patients under close monitoring

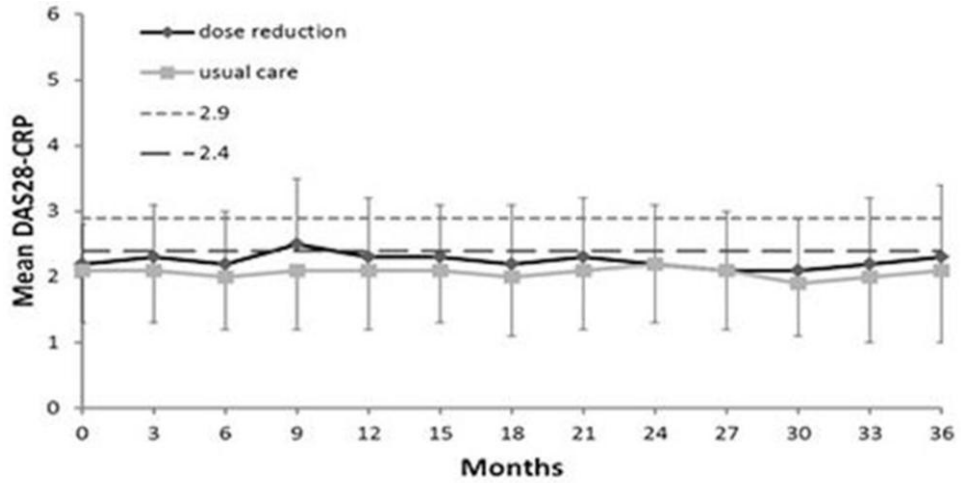


Bouman CAM, et al. Ann Rheum Dis 2017;**76**:1716

Comparable rate of MAJOR flares for the 3 years

The cumulative incidence from month 0–36

- 20/115 (17%) in the DR and
- 8/57 (14%) in the UC group



Bouman CAM, et al. Ann Rheum Dis 2017;**76**:1716

Conclusions

Disease activity guided TNFi taper in RA

- Is maintained up to 3 years
- Is efficacious (disease activity, functioning and quality of life)
- Large reduction in TNFi use,
- Would improve the cost-effective use of TNFi

Bouman CAM, et al. Ann Rheum Dis 2017;**76**:1716

Ερωτήματα ”taper” bDMARDs

- Σε ποιους ασθενείς - Πότε ?
- Ποιος ο κίνδυνος υποτροπής - Προγνωστικοί δείκτες flare ?
- Αν υπό “combo” ποια από τις αγωγές taper ?
- Επανέλεγχος νόσου ?

TNFi or csDMRD taper?

Gradual tapering TNF inhibitors versus conventional synthetic DMARDs after achieving controlled disease in patients with rheumatoid arthritis: first-year results of the randomised controlled TARA study

Taper

- csDMARD taper: dose to ½ → ¼ → DC
- The TNFi taper: X2 interval → ½ dose → DC
- Taper duration: 6 months, with dose adjustments every 3 months as long as there was still a controlled disease.

Outcomes

- **Primary outcome: % disease flare within 1 year (DAS >2.4 and/or SJC>1)**

Design

- The TARA study was a superiority trial, powered to detect a 20% difference in flare rates between both tapering strategies

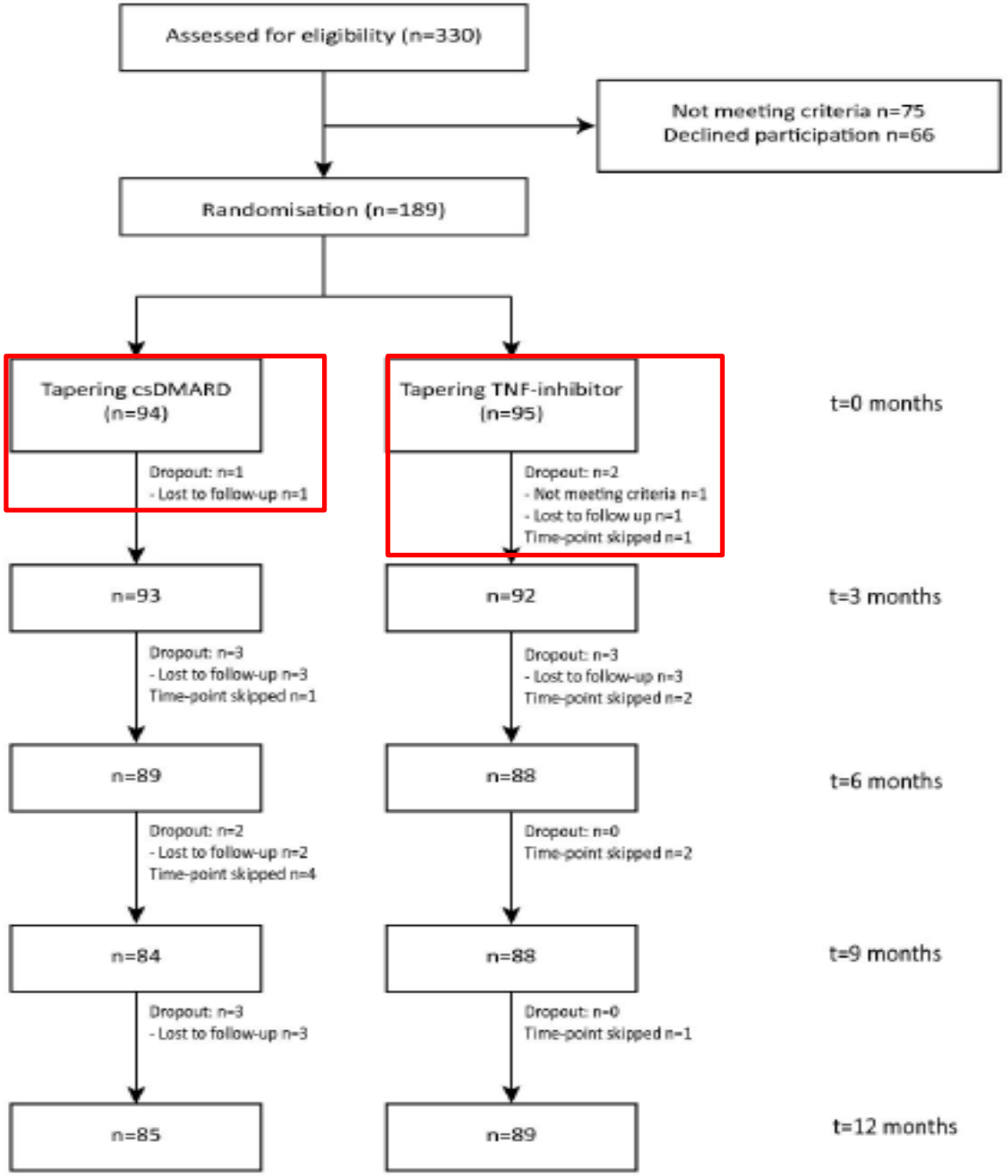
van Mulligen E, et al. Ann Rheum Dis 2019;**78**:746

Controlled RA:

- DAS ≤2.4

AND

- Swollen Joint Count (SJC) ≤1
- at 2 visits within 3mo



Χαρακτηριστικά Ασθενών

Table 1 Baseline characteristics of the csDMARD tapering group and the TNF inhibitor tapering group

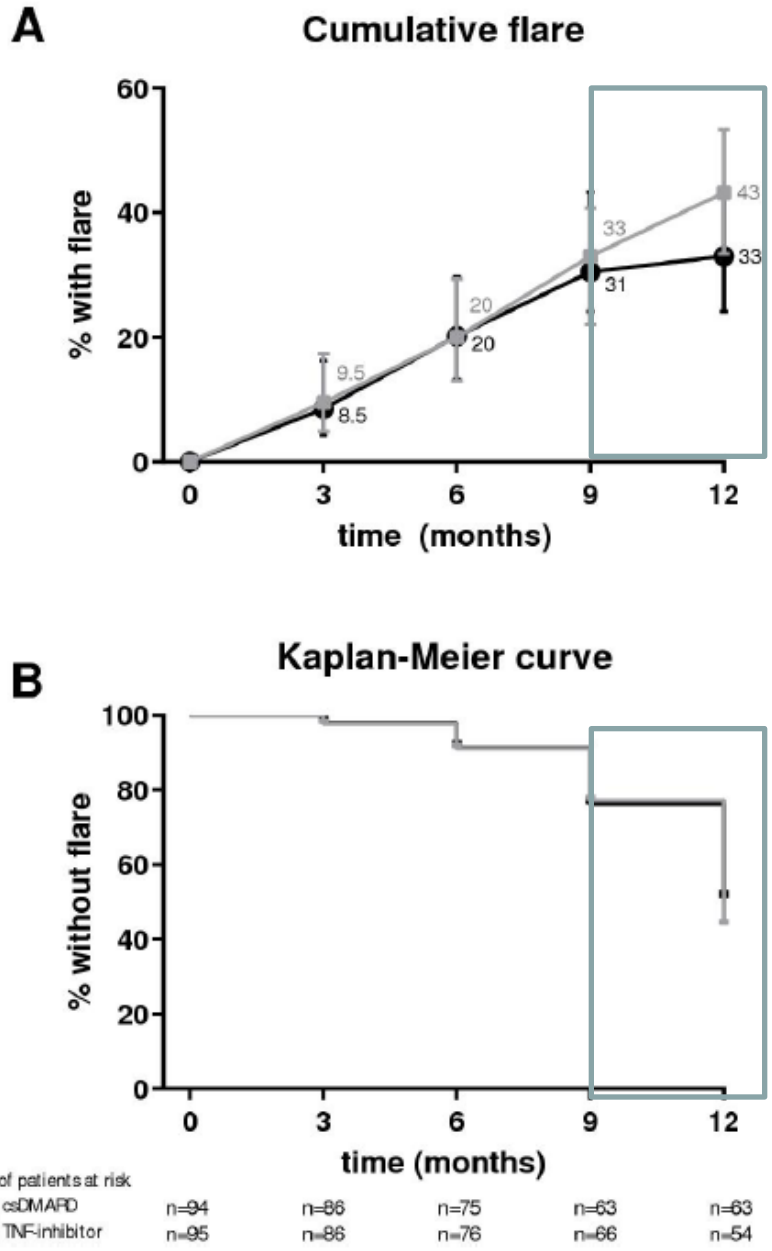
Characteristics	Tapering csDMARD (n=94)	Tapering TNF inhibitor (n=95)
Demographic		
Age (years), mean (95% CI)	55.9 (53.0 to 58.8)	57.2 (55.0 to 59.4)
Gender, female, n (%)	67 (71)	58 (61)
Disease characteristics		
Symptom duration (years), median (IQR)	6.0 (4.1–8.5)	6.4 (4.2–8.9)
RF positive, n (%)	50 (57)	59 (65)
ACPA positive, n (%)	62 (71)	67 (75)
Use of csDMARDs*		
MTX, n (%)	90 (96)	84 (88)
SASP, n (%)	10 (11)	12 (13)
HCQ, n (%)	24 (26)	37 (39)
Leflunomide, n (%)	2 (2)	4 (4)
Use of TNF inhibitor		
Etanercept, n (%)	51 (54)	52 (55)
Adalimumab, n (%)	37 (39)	40 (42)
Others, n (%)†	6 (6)	3 (3)
Radiographs (hand/foot)		
mTSS (0–488), median (IQR)	2 (0–6.5)	1 (0–3.5)
Erosion score (0–280), median (IQR)	0 (0–2.5)	0 (0–2)
JSN score (0–168), median (IQR)	0.5 (0–2.5)	0 (0–2.5)
Erosive disease, n(%)‡	37 (39)	26 (27)

At baseline REMISSION (DAS <1.6):

- 81% of csDMARD taper
- 88% of TNFi taper

van Mulligen E, et al. Ann Rheum Dis 2019;**78**:746

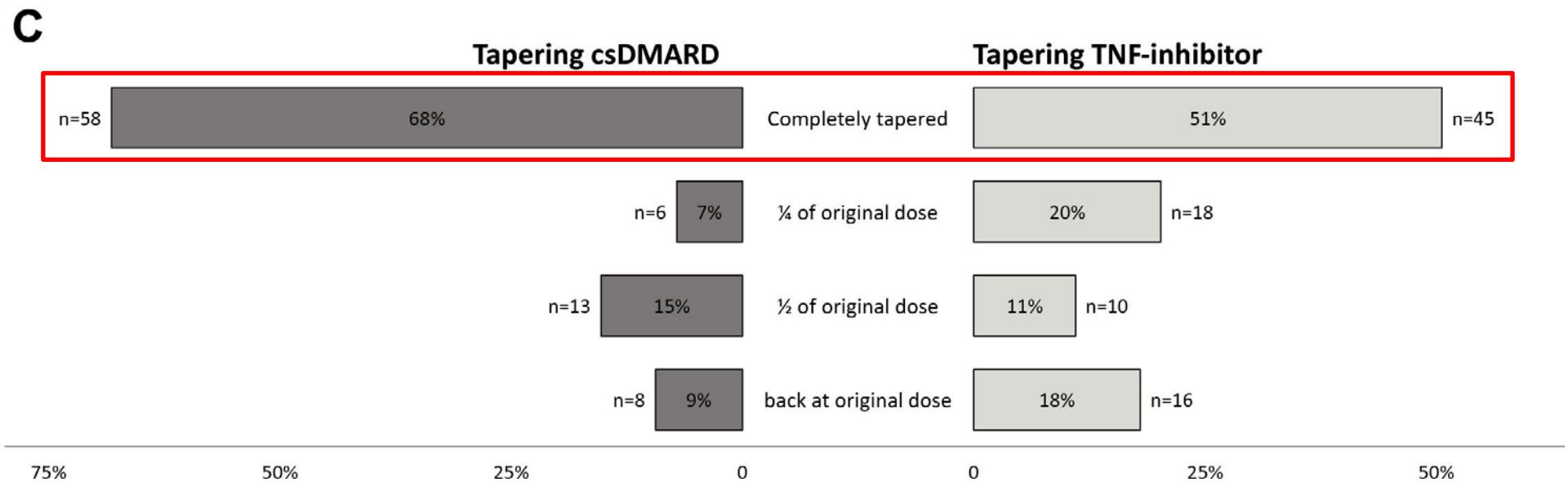
After 1 year, the cumulative flare rate was 33% csDMARD and 43% in the TNFi tapering group



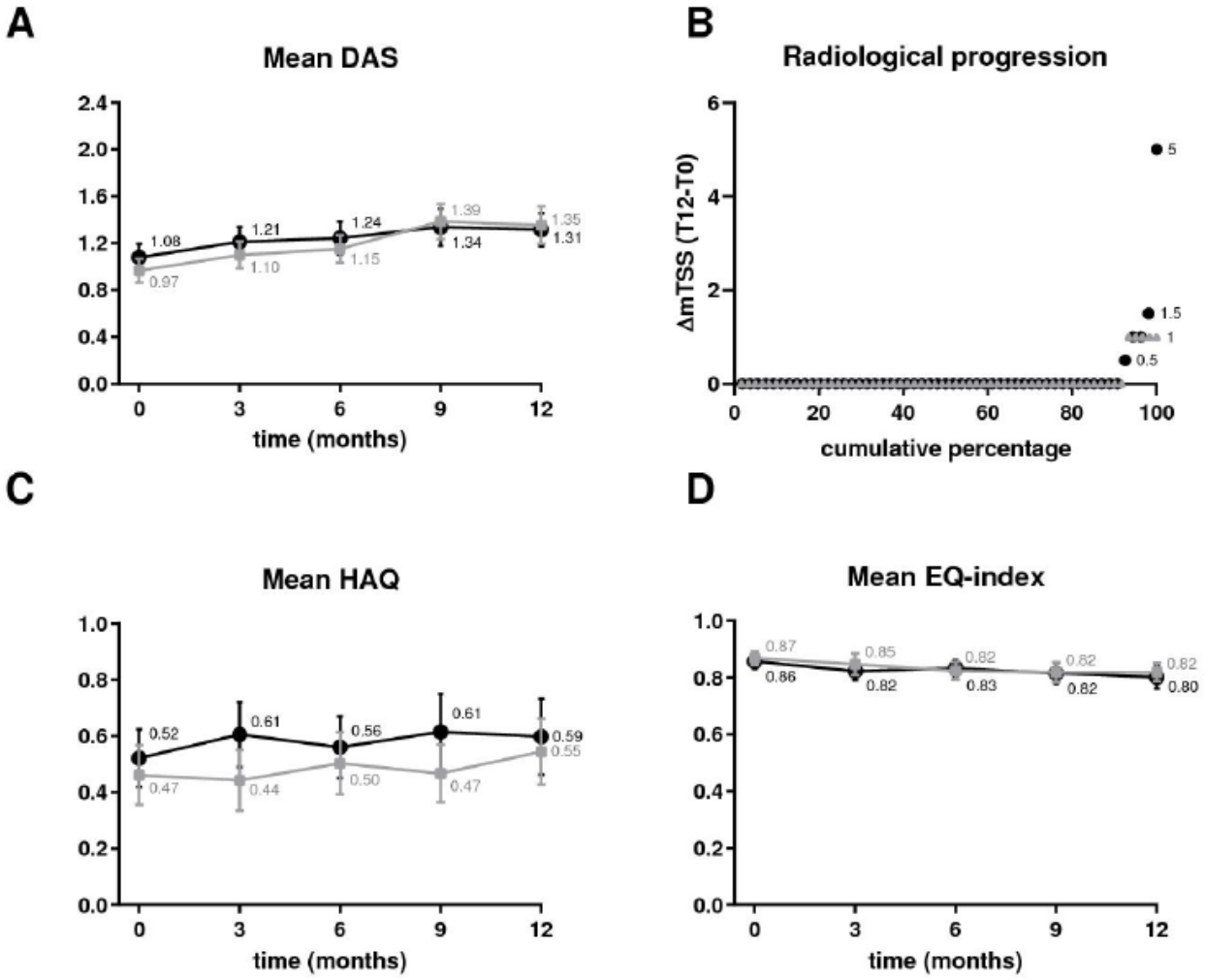
Επαναφορά μετά από υποτροπή:
DAS <2.4 with the last effective treatment strategy:
- ✓ 46% @3 months
- ✓ 67% @6 months

van Mulligen E, et al. Ann Rheum Dis 2019;**78**:746

There was an overall significant difference in tapering status after 12 months of follow-up between the two tapering strategies (p=0.02).



No significant differences were seen in DAS (p=0.72), HAQ-DI (p=0.63) and EQ-5D (p=0.58) after 1 year between both tapering strategies.



In conclusion:

- TARA study showed that up to 9 months, flare rates of tapering csDMARDs or TNF inhibitors were similar.
- After 1 year, a non-significant difference in flare rates was found of **10% in favour of csDMARD tapering.**
- Tapering TNF inhibitors was, therefore, not superior to tapering csDMARDs.
- From a societal perspective, it would be sensible to taper the TNF inhibitor first, because of possible cost reductions and less long-term side effects.

Re-escalation controls RA in the majority of relapsed

- Relapses were managed by TNF-blocker re-escalation
  - 41% (20/49) achieved remission again,
  - 39% (19/49) had low disease activity

Fautrel B, et al. Ann Rheum Dis 2016;75:5

- Adalimumab re-escalation: % DAS28 LDA
  - 6 months in 90%
  - 9 months in 100%

Tanaka Y, et al. Ann Rheum Dis 2015;74:389

Tocilizumab Taper - relapses

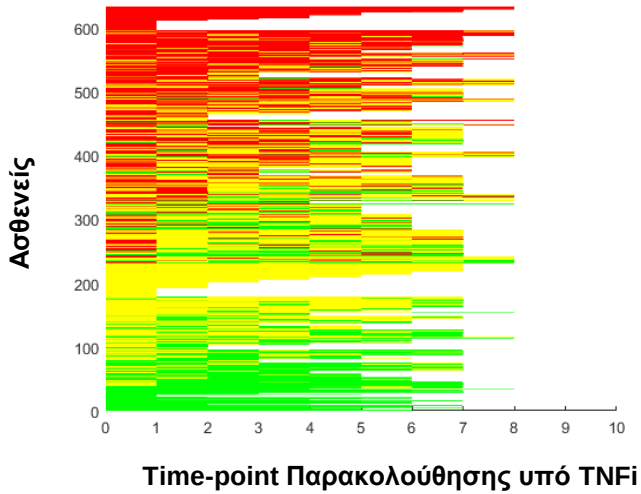
- 87% (1 year): LDA, TCZ stop, no DMARD
- 55% (1 year): Remission, TCZ stop, on MTX
- 41% (6 months): TCZ tapered 8 mg/kg → 4 mg/kg /4 wks lost LDA status

J Rheumatol. 2015 Nov;42(11):2012

Ελληνικό Αρχείο Βιολογικών Θεραπειών:

20-25% των υπό TNFi ασθενών με PA βρίσκεται <u>σε μόνιμα ύφεση-χαμηλή ενεργότητα</u>

Μακροχρόνιες πορείες των ασθενών βάσει DAS28 group



Genitsaridi I, et al. A&R (70) Supp: 9 Abstract: 2489. ACR 2018

Συμπεράσματα

Σε ασθενείς με:

- ✓ Σταθερά (2 φορές > 6 μήνες) ύφεση ή LDA (<1 αρθρώσεις)

- ✓ Αποδεκτή η σταδιακή ελάττωση του TNFi
  - Υποτροπές: 50-60% (1,5-3 έτη) σημαντικές 10-15%
  - Διακοπή: 10-20%
  - Ελάττωση: 50%

- ✓ Σταδιακή ελάττωση csDMARD “συγκρίσιμη” στο 1^{ο} έτος, πιθανά «υπερέχει»

- ✓ Σημαντική η κλινική παρακολούθηση και τροποποίηση αγωγής βάσει στόχου