ΑΚΑΛΥΠΤΕΣ ΘΕΡΑΠΕΥΤΙΚΕΣ ΑΝΑΓΚΕΣ ΣΤΗ ΡΕΥΜΑΤΟΕΙΔΗ ΑΡΘΡΙΤΙΔΑ- ΔΕΔΟΜΕΝΑ ΑΠΟ ΕΥΡΩΠΑΙΚΑ REGISTRIES

ΝΙΚΟΛΑΟΣ ΚΟΥΓΚΑΣ, ΡΕΥΜΑΤΟΛΟΓΟΣ
ΠΑΓΝΗ

ΠΕΡΙΓΡΑΜΜΑ

- Αποτελεσματικότητα
- Μονοθεραπεία και συγχορήγηση με DMARDS
- Επιβίωση των θεραπειών
- Αλλαγή(‘’switching’’) των θεραπειών
- Ποιότητα ζωής και λειτουργικότητα των ασθενών

REGISTRIES

- Αρχεία καταγραφής ασθενών με συστηματικά αυτοάνοσα νοσήματα και των θεραπειών τους
- Σημαντικά πλεονεκτήματα έναντι των RCT’s
  - Μακροπρόθεσμη καταγραφή αποτελεσματικότητας και τοξικότητας
  - Συμμετοχή όλων των ασθενών χωρίς αποκλεισμούς
  - Μεγάλο δείγμα ασθενών
  - Δυνατότητα σύγκρισης διάφορων θεραπευτικών σχημάτων

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ

- Πόσο εφικτή είναι στην πράξη η επίτευξη ύφεσης;

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ANTI-TNF

	Infliximab		Adalimumab		Etanercept		*p* Value[a]	*p* Value
	6 Months	12 Months	6 Months	12 Months	6 Months	12 Months	6 Months	12 Months
DAS28 remission								
No. of patients[b]	357	316	220	179	171	137		
Remission (*N*/%)	46/13	47/15	35/16	41/23	27/16	26/19	0.587	0.098
LUNDEX-corrected[c]								
No. of patients	560	560	435	435	302	302		
Remission (%)	12	12[d]	14	17[d]	14	15	0.619	0.049
CDAI remission								
No. of patients	334	296	187	161	143	121		
Remission (*N*/%)	19/5.7	23/7.8[d]	21/11	24/15[d,f]	14/9.8	8/6.6[f]	0.061	0.022
LUNDEX-corrected (%)	5.2[d]	6.1[d]	9.9[d]	11[d,f]	8.5	5.1[f]	0.015	0.001
ACR/EULAR remission								
Boolean-based definition								
No. of patients	334	305	183	144	144	118		
Remission (*N*/%)	23/6.9[d]	23/7.5[d,e]	29/16[d]	30/21[d]	17/12	20/17[e]	0.005	< 0.001
LUNDEX-corrected (%)	6.2[d]	6.0[d,e]	14[d]	16[d]	10	13[e]	< 0.001	< 0.001
SDAI-based definition								
No. of patients	306	276	154	121	125	108		
Remission (*N*/%)	17/5.6[d]	21/7.6[d]	18/12[d]	21/17[d]	14/11	9/8.3	0.024	0.009
LUNDEX-corrected (%)	5.1[d,e]	6.1[d]	11[d]	14[d,f]	9.8[e]	6.5[f]	0.003	< 0.001
DAS28 low disease activity								
Low disease activity (*N*/%)	75/21	85/27	64/29	61/34	41/24	42/31	0.073	0.309
LUNDEX-corrected (%)	19[d]	22	25[d]	26	21	24	0.034	0.336
EULAR response								
No. of patients	338	292	203	151	150	115		
Good (*N*/%)	68/20	76/26	49/24	45/30	29/19	28/24		
Moderate (*N*/%)	166/49	155/53	97/48	69/46	89/59	60/52		
No response (*N*/%)	105/31	61/21	57/28	36/24	33/22	28/24	0.137	0.674

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ

Baseline status	Patients in DAS28 remission, *n* (%)	
DAS28	BIOL (*n* = 775)	CON (*n* = 255)
>3.2 to 4.0	16 (45.7)	8 (33.3)
>4.0 to 5.1	33 (26.4)	16 (23.2)
>5.1 to 6.0	40 (22.1)	10 (13.5)
>6.0 to 7.0	28 (11.1)	4 (6.3)
> 7.0	9 (5.0)	1 (4.0)
Total	126 (16.3)	39 (15.3)

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ

Disease activity at 12 months for patients in DAS28 remission at 6 months.

Disease activity at 12 months	BIOL, *n* (%)	CON, *n* (%)
In remission (DAS28 <2.6)	56 (54.9%)	18 (58.1%)
Low disease activity (DAS28 <3.2)	17 (16.7%)	7 (22.6%)
Moderate or high disease activity (DAS28 >3.2)	29 (28.4%)	6 (19.4%)
Total	102	31

BIOL, patients treated with biologics; CON, patients receiving conventional DMARD treatment (control group); DAS28, disease activity score based on 28 joint counts.

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ABA-TCZ

Table 2 Disease activity (including DAS28 variables), EULAR response rates and HAQ score at time points (observed data)

	Abatacept						Tocilizumab					
	Week 0 (baseline)	Week 6	Week 12	Week 24	Week 36	Week 48	Week 0 (baseline)	Week 6	Week 12	Week 24	Week 36	Week 48
Patients receiving drug (n)	150	138	118	96	76	60	178	154	124	95	59	31
Patients with response data (n)	104	76	79	57	47	38	97	69	65	51	37	19
Disease activity level (%)												
Remission	0	8	9	19	21	26	2	17	20	39	35	58
Low	1	8	14	21	6	21	3	9	15	16	16	0
Moderate	42	45	57	44	62	42	36	59	54	39	41	32
High	57	39	20	16	11	11	59	14	11	6	8	11
EULAR response rates (%)												
Good	–	11	22	40	23	45	–	29	34	45	54	58
Moderate	–	28	41	30	51	32	–	39	49	43	30	26
None	–	62	38	30	26	24	–	32	17	12	16	16

ΜΟΝΟΘΕΡΑΠΕΙΑ

- Πόσο συχνή είναι η μονοθεραπεία με βιολογικό παράγοντα;

OPEN ACCESS

EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update

Table 1 2013 Update of the EULAR recommendations (the table of 2010 recommendations can be seen in the online supplement or the original publication)

	Overarching principles
A.	Treatment of RA patients should aim at the best care and must be based on a shared decision between the patient and the rheumatologist
B.	Rheumatologists are the specialists who should primarily care for RA patients
C.	RA incurs high individual, societal and medical costs, all of which should be considered in its management by the treating rheumatologist
	Recommendations
1.	Therapy with DMARDs should be started as soon as the diagnosis of RA is made
2.	Treatment should be aimed at reaching a target of remission or low disease activity in every patient
3.	Monitoring should be frequent in active disease (every 1–3 months); if there is no improvement by at most 3 months after the start of treatment or the target has not been reached by 6 months, therapy should be adjusted
4.	MTX should be part of the first treatment strategy in patients with active RA
5.	In cases of MTX contraindications (or early intolerance), sulfasalazine or leflunomide should be considered as part of the (first) treatment strategy
6.	In DMARD-naïve patients, irrespective of the addition of glucocorticoids, csDMARD monotherapy or combination therapy of csDMARDs should be used
7.	Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more csDMARDs) for up to 6 months, but should be tapered as rapidly as clinically feasible
8.	If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another csDMARD strategy should be considered; when poor prognostic factors are present, addition of a bDMARD should be considered
9.	In patients responding insufficiently to MTX and/or other csDMARD strategies, with or without glucocorticoids, bDMARDs (TNF inhibitors*, abatacept or tocilizumab, and, under certain circumstances, rituximab†) should be commenced with MTX
10.	If a first bDMARD has failed, patients should be treated with another bDMARD; if a first TNF inhibitor therapy has failed, patients may receive another TNF inhibitor* or a biological agent with another mode of action
11.	Tofacitinib may be considered after biological treatment has failed
12.	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
13.	In cases of sustained long-term remission, cautious reduction of the csDMARD dose could be considered, as a shared decision between patient and physician
14.	When therapy needs to be adjusted, factors apart from disease activity, such as progression of structural damage, comorbidities and safety issues, should be taken into account

ΜΟΝΟΘΕΡΑΠΕΙΑ

- NOR-DMARD: 33%[1]
- BSRBR: 32%[2]
- RABBIT: 34%[3]
- ARTIS: 30%[4]
- ORA: 35%[5]
- AIR: 33%[5]
- LORHEN: 8%[6]
- Swiss Registry: 27%[7]
- DAMBIO: 19%[8]

- ETN,ADA, CTZ και TCZ έχουν πάρει εγκριση για μονοθεραπεία (ETN έχει εγκριθεί και για την αναστολή ακτινολογικών βλαβών)

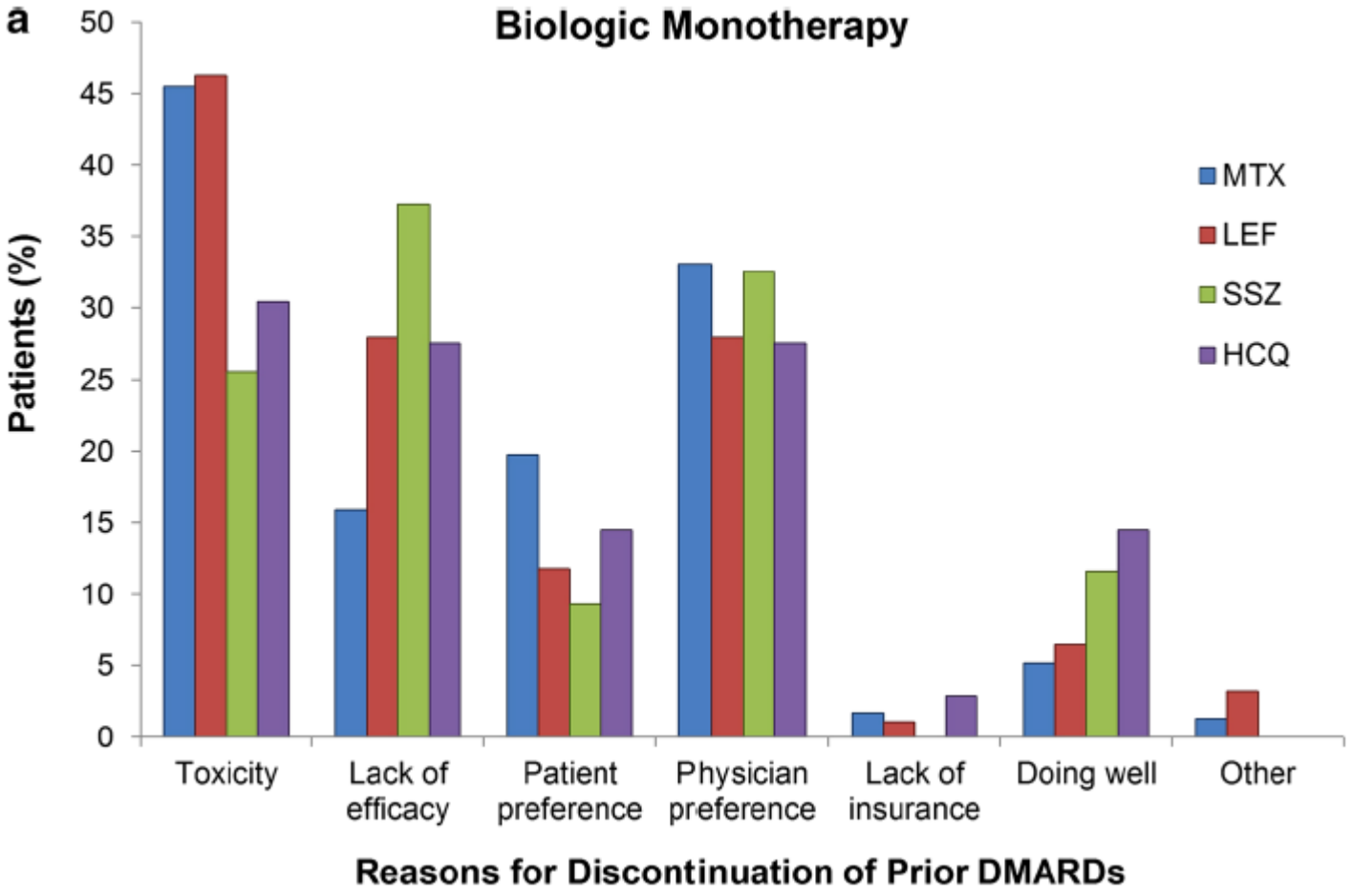
All registries/studies are anti-TNF focused, other than ORA (abatacept), AIR (rituximab) and RABBIT (anti-TNFs and anakinra).

1. Heiberg MS, et al. *Arth Care Res* 2008;59:234–240; 2. Soliman MM, et al. *Ann Rheum Dis* 2011;70(4):583–589; 3. Listing J, et al. *Arthritis Res Ther* 2006;8(3):R66; 4. Askling J et al. *Ann Rheum Dis* 2007;66;1339–1344; 5. Mariette X, et al. *Rheumatology (Oxford)* 2011;50(1):222–229; 6. Filipinni M et al.
BioMed Research International 2014, Article ID 416892, 8 pages; 7. Gabay C, et al. *Rheumatology* 2015;54:1664–1672; 8. Jørgensen TS, et al. *Rheumatology* 2015. pii:kev216. [Epub ahead of print].

ΜΟΝΟΘΕΡΑΠΕΙΑ

- Ποιοι είναι οι λόγοι που οδηγούν στη μονοθεραπεία;

ΑΙΤΙΕΣ ΔΙΑΚΟΠΗΣ ΤΩΝ DMARDS



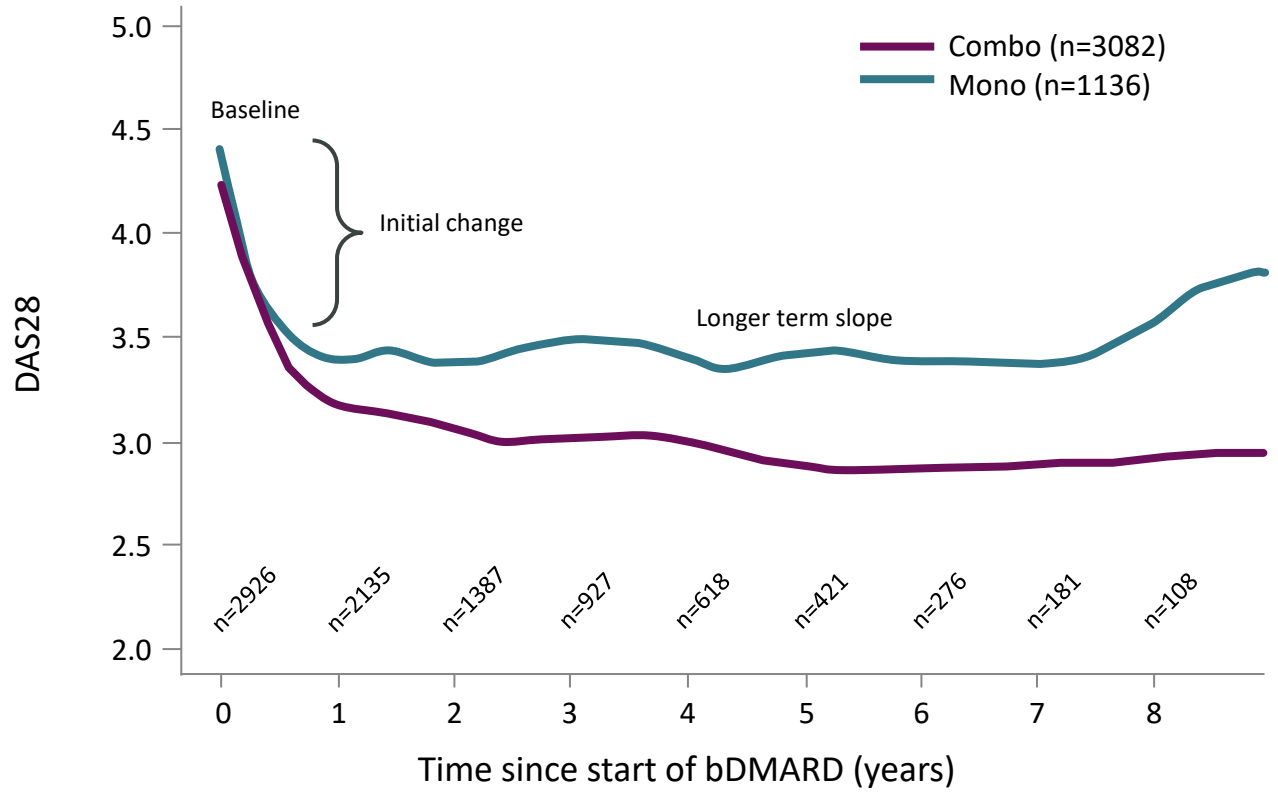
n=3923, 19% Monotherapy

Pappas D, Rheumatol Ther 2015

ΜΟΝΟΘΕΡΑΠΕΙΑ

- Υπερέχει όμως η μονοθεραπεία στην αποτελεσματικότητα;

Response rates with biologic monotherapy are lower than with combination therapy



bDMARD, biological disease modifying antirheumatic drug; csDMARD, conventional synthetic disease modifying antirheumatic drug; DAS, disease activity score; EULAR, European League Against Rheumatism; MTX, methotrexate; SCQM-RA, Swiss clinical quality management in rheumatoid arthritis; TNF, tumour necrosis factor.

1. Gabay C, et al. *Rheumatology* 2015;54:1664–1672; .

Efficacy among anti-TNFs in RA

EULAR responses at one year of treatment

	EULAR response (%)		
	Good	Moderate	None
DMARDs combined with anti-TNF agents	27.1	56.2	16.7
Anti-TNF agent (monotherapy)	18.9	46.7	34.4

Bazzani C, et al. *Autoimmun Rev* 2009;8:260-265.

ΕΠΙΒΙΩΣΗ ΤΩΝ ΒΙΟΛΟΓΙΚΩΝ

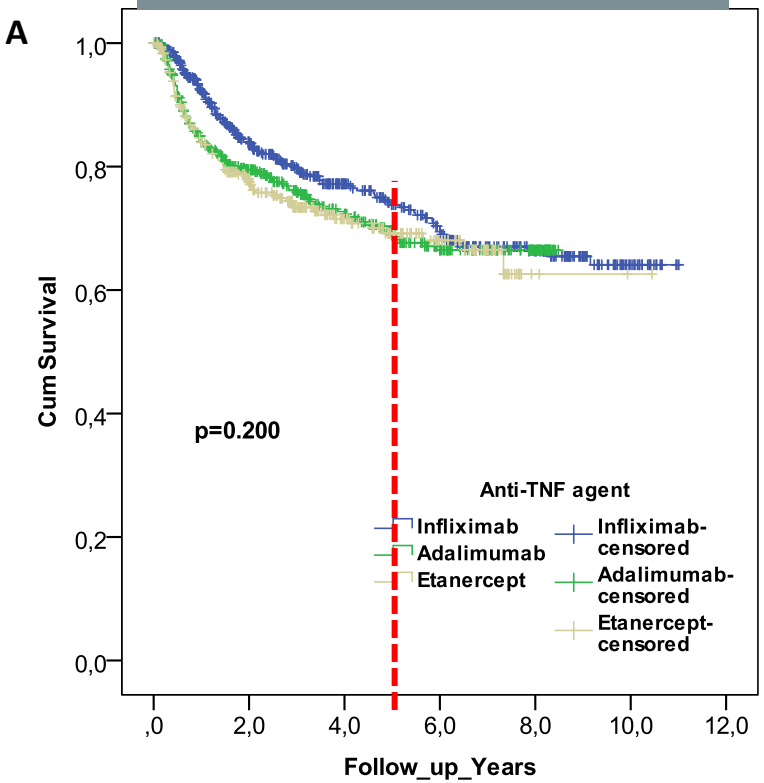
- Έχουν όλοι οι Anti-TNF την ίδια επιβίωση;

ΕΠΙΒΙΩΣΗ ΒΙΟΛΟΓΙΚΩΝ

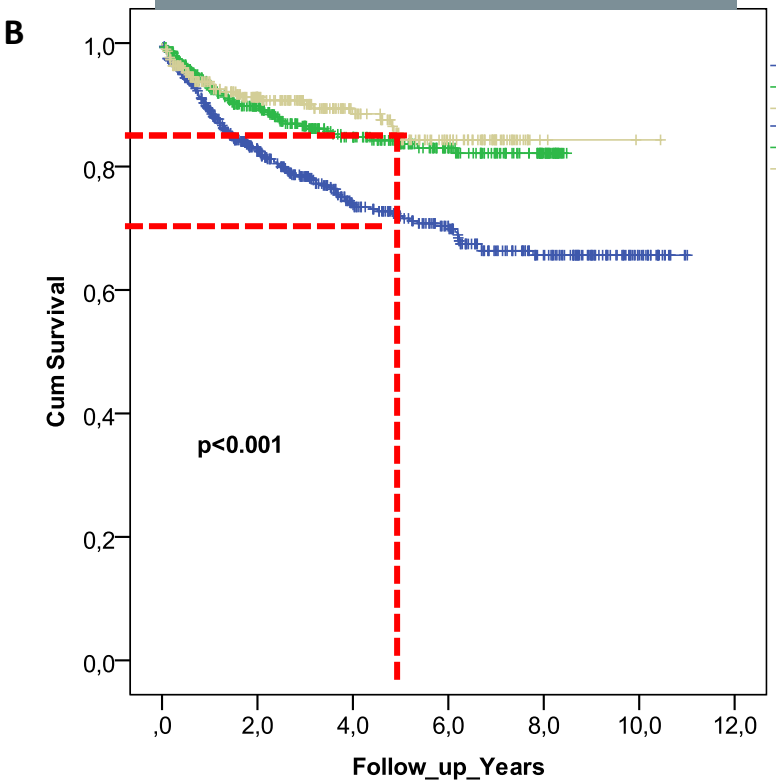
Comparable between agents efficacy-related drug survival but lower of infliximab due to toxicity

	1yr	5yrs
infliximab	64%	31%
adalimumab	67%	43%
etanercept	68%	49%

Efficacy-related drug survival

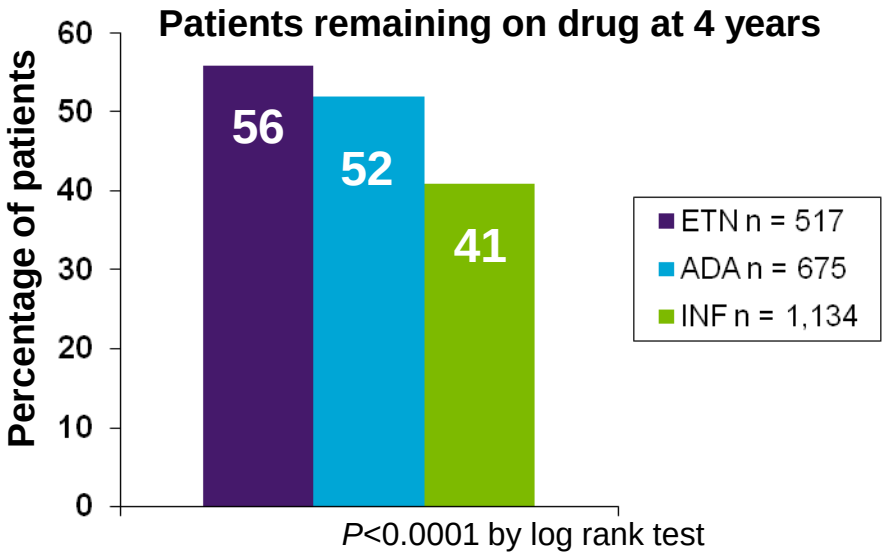


Toxicity-related drug survival



Discontinuation rates in RA

The drug adherence was highest for ETN and lowest for INF regardless of the reason for withdrawal



Hazard Ratio (95% CI) for drug withdrawal

	INF vs. ADA	INF vs. ETN	ADA vs. ETN
All patients (1089 events)	1.35 (1.15–1.58)	1.98 (1.63–2.40)	1.47 (1.20–1.80)
Lack of efficacy (727 events)	1.16 (0.95–1.41)	1.70 (1.35–2.15)	1.47 (1.15–1.87)
Adverse events (327 events)	1.77 (1.34–2.34)	2.65 (1.88–3.73)	1.50 (1.04–2.16)

The hazard ratio for withdrawal, adjusting for baseline DAS28, age, disease duration, seropositivity, concomitant MTX or prednisone, previous DMARDs, HAQ score and centre, was highest for INF and lowest for ETN.

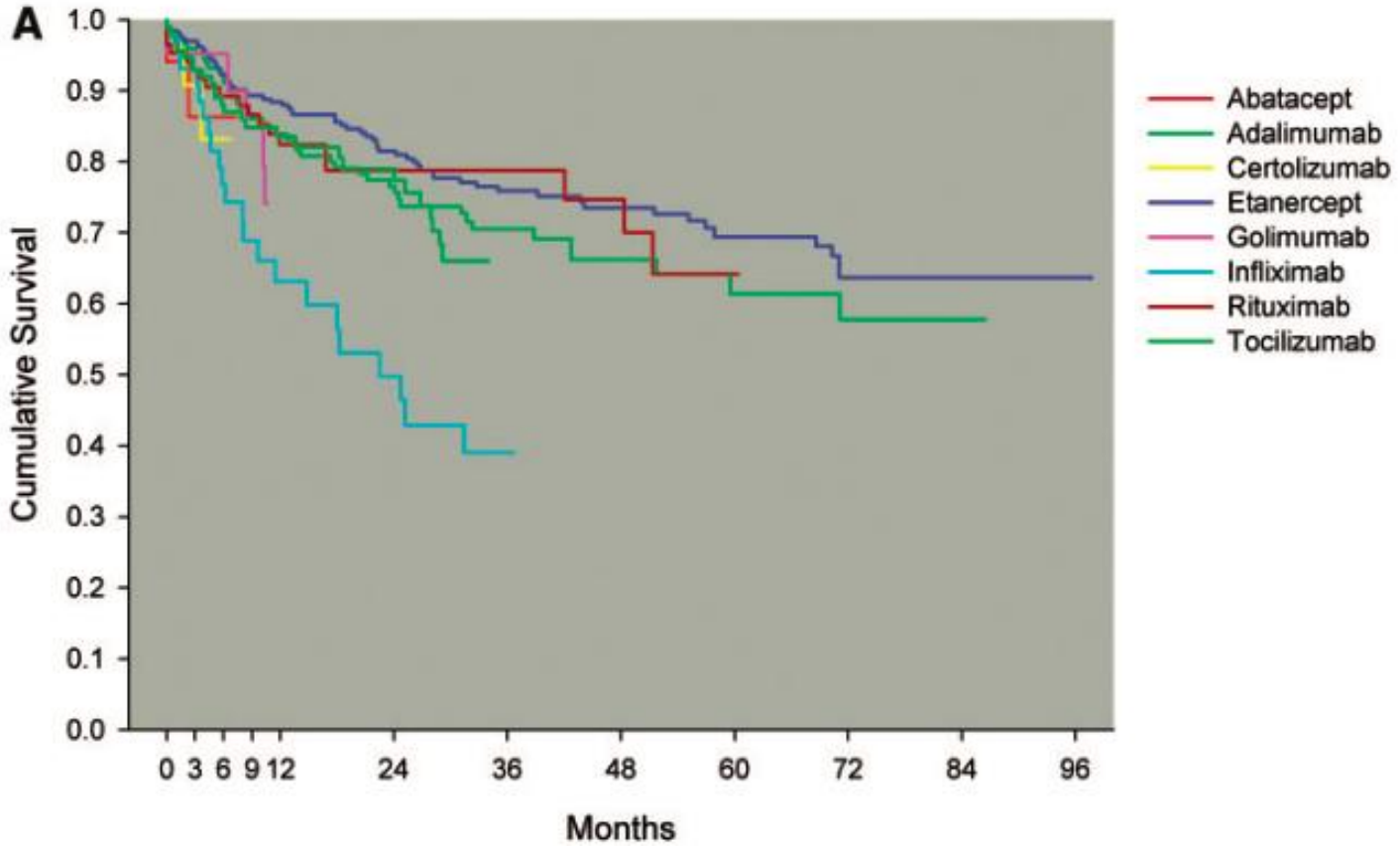
Hetland ML et al. *Arthritis Rheum* 2010;62:22-32.

ΕΠΙΒΙΩΣΗ ΤΩΝ ΒΙΟΛΟΓΙΚΩΝ

- Υπαρχουν διαφορές στην επιβίωση στη μονοθεραπεία;

ΕΠΙΒΙΩΣΗ ΤΩΝ ΒΙΟΛΟΓΙΚΩΝ

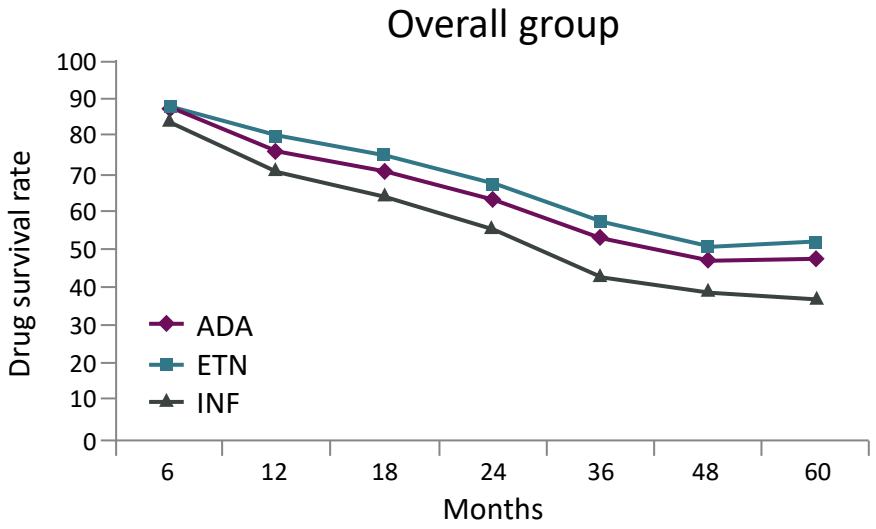
FIG. 2 Drug adherence, stratified by drug



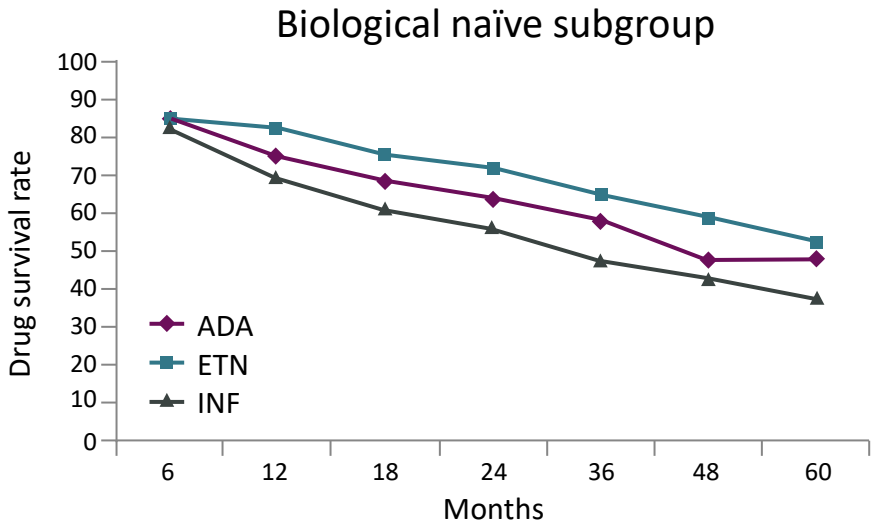
ΕΠΙΒΙΩΣΗ ΤΩΝ ΒΙΟΛΟΓΙΚΩΝ

- Πότε μειώνεται η επιβίωση;

Systematic review of EU registries*: Drug survival is higher in earlier lines of therapy



ADA	3194 (8)	3278 (7)	2538 (6)	3278 (7)	3278 (7)	1093 (3)	769 (2)
ETN	3333 (8)	3062 97)	2470 (6)	3062 (7)	3046 (6)	1636 (4)	517 (1)
INF	3356 (8)	3318 (7)	2881 (6)	3318 (7)	3198 (6)	1865 (4)	1134 (1)



ADA	1556 (5)	1339 (4)	1339 (4)	1339 (4)	1339 (4)	1093 (3)	769 (2)
ETN	1280 (5)	1064 (4)	1064 (4)	1064 (4)	1048 (3)	1117 (3)	517 (1)
INF	2027 (5)	1924 (4)	1924 (4)	1924 (4)	1804 (3)	1503 (3)	1134 (1)

N(n) = number of patients (number of studies)

After 1 year, drug survival on TNF inhibitors decreases, with a further decrease seen by year 5

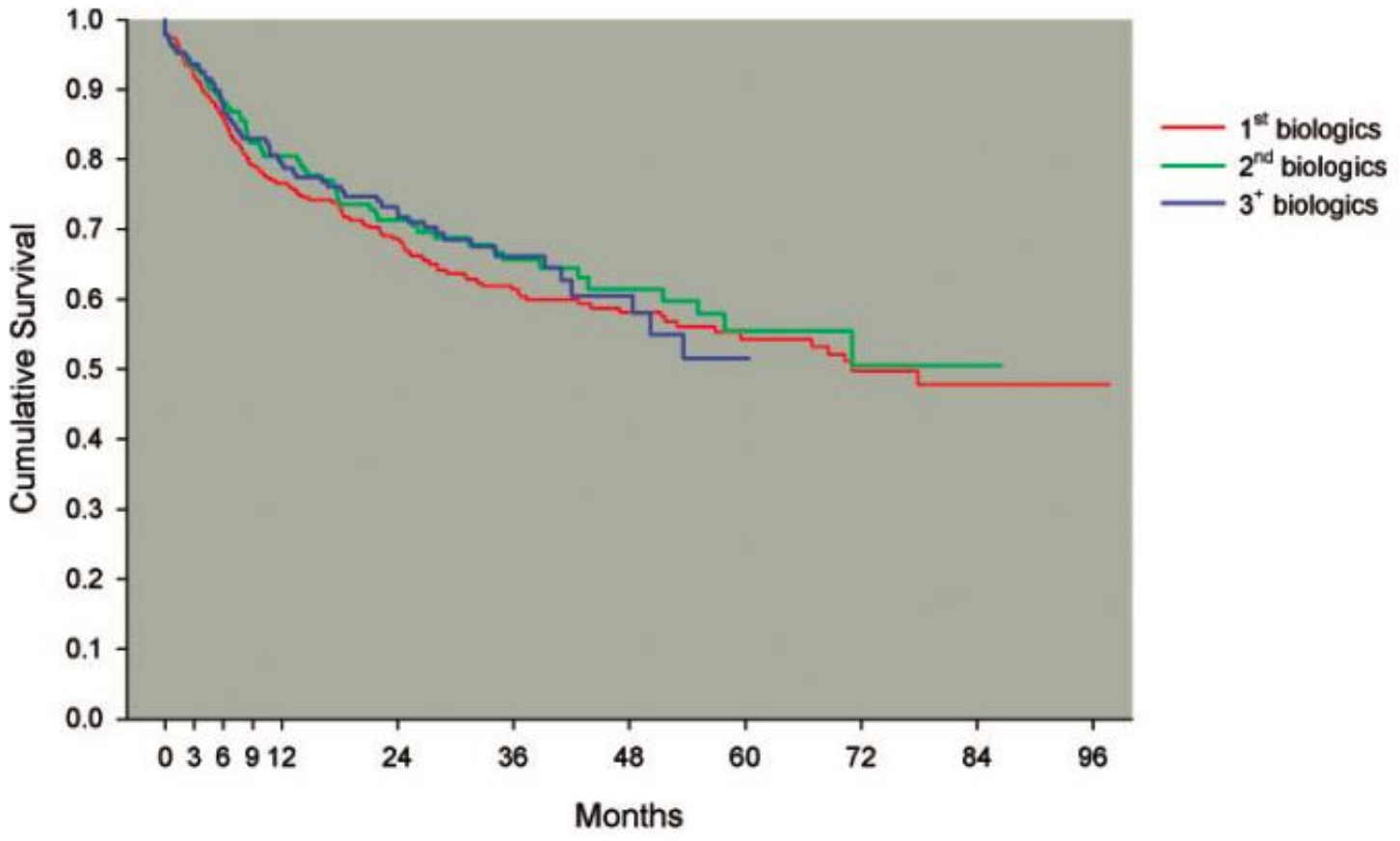
ADA, adalimumab; ETN, etanercept, INF, Infliximab.

1. Arora A, et al. *Int J Rheumatol* 2013; 2013: 764518.

*DREAM, SCQM, DANBIO, BSRBR, GISEA, LOHREN, RABBIT

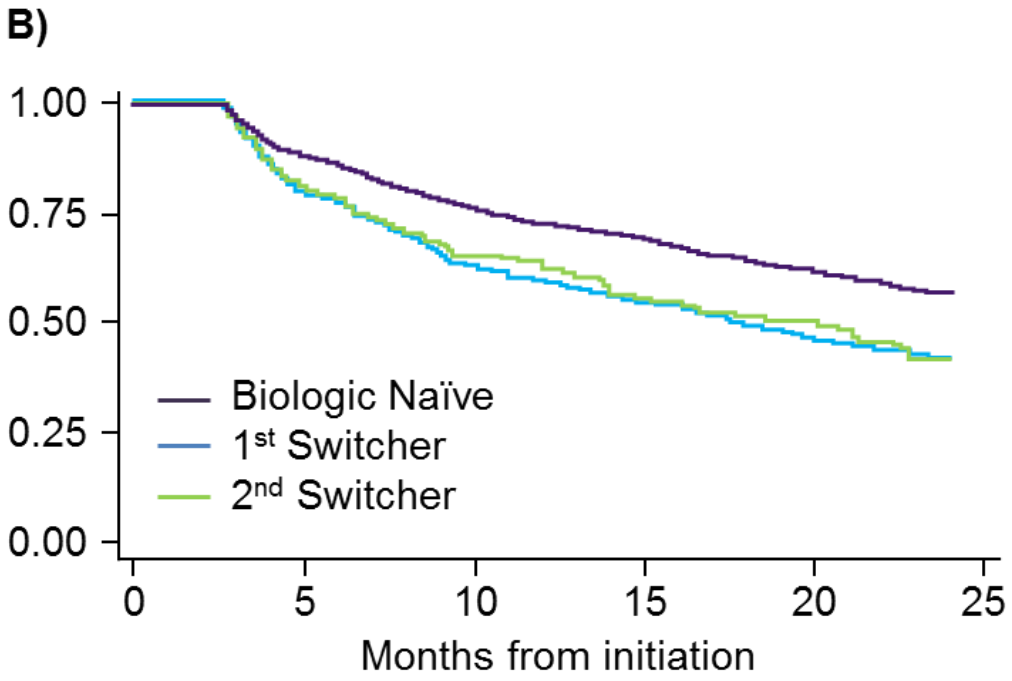
ΕΠΙΒΙΩΣΗ ΤΩΝ ΒΙΟΛΟΓΙΚΩΝ

FIG. 3 Drug adherence, stratified by first-, second- and third-line biologic monotherapy



CORRONA: Effect of anti-TNFs in biologically naïve and switched patients

Drug persistency for biologically naïve patients versus those switched to anti-TNF agents



- Response, remission and persistence outcomes were diminished for patients who switched anti-TNF

TNF, tumour necrosis factor.

Greenberg JD, et al. *Ann Rheum Dis* 2012;71:1134–1142.

ΕΠΙΒΙΩΣΗ ΤΩΝ ΒΙΟΛΟΓΙΚΩΝ

- Ποια είναι η επιβίωση των non Anti-TNF;

Two -year drug survival and treatment effect of abatacept and tocilizumab

Treatment effect of abatacept and tocilizumab

	Baseline	Week 48	Week 96
Abatacept			
Median DAS28	5.2	3.2	2.9
Good-or-moderate EULAR		76%	79%
Remission rates		29%	38%
Tocilizumab			
Median DAS28	5.3	2.7	3.0
Good-or-moderate EULAR		87%	97%
Remission rates		49%	41%

- In RA patients (>99% TNFi failures) treated with abatacept and tocilizumab, 54-66% of patients respectively were still receiving the drug after 48 weeks and 39-58% after 96 weeks
- Due to the non-randomised study design, no direct comparison can be made

DAS, disease activity score; EULAR, European League Against Rheumatism; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

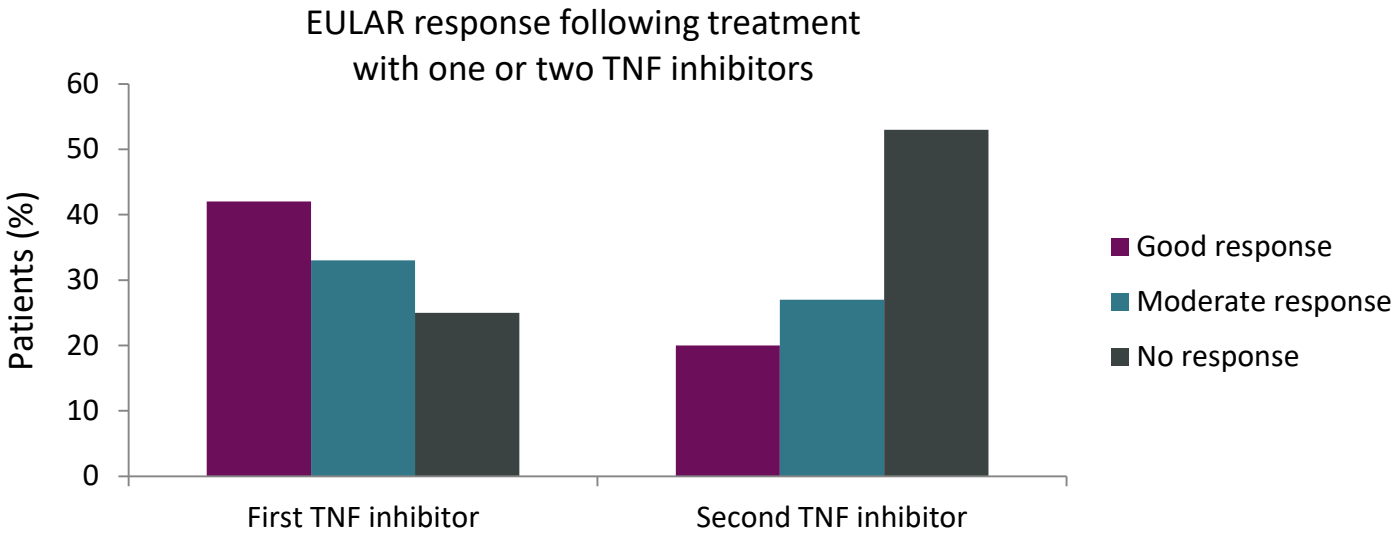
Leffers HC, *et al. Arthritis Rheum* 2012;64(10Suppl):1271.

ΑΛΛΑΓΗ ΒΙΟΛΟΓΙΚΩΝ-‘’SWITCHING’’

- Πόσο αποτελεσματικοί είναι οι Anti-TNF ως θεραπεία 3ης γραμμής;

Response to a second TNF inhibitor after failing a first TNF inhibitor

- 20–40% of patients treated with a TNF inhibitor fail to achieve an ACR20 response[1]
- An established treatment approach is to switch from one TNF inhibitor to another[1]
- Results from biologic registries show that efficacy may decline when switching from one TNF inhibitor to another[2]



Patients are less likely to respond to a second TNF inhibitor if they have failed a first

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; TNF, tumour necrosis factor.

1. Rubbert-Roth A, et al. *Arthritis Research & Therapy* 2009;11(Suppl 1):S1; 2. Karlsson JA, et al. *Rheumatology* 2008;47:507–513.

Anti-TNF Switching

Table 4 Unadjusted response and remission rates and adjusted likelihoods of achieving response/remission over time stratified by anti-TNF switch status

	6 Months			12 Months		
	Biologically naive	**First-time switcher**	**Second-time switcher**	**Biologically naive**	**First-time switcher**	**Second-time switcher**
mACR response						
No of patients	687	319	73	550	251	67
mACR 20						
Responders	30.5%	19.9%	17.3%	28.5%	14.7%	18.7%
Adjusted OR (95% CI)†	1	0.54 (0.38 to 0.76)*	0.42 (0.23 to 0.78)*	1	0.44 (0.30 to 0.66)*	0.50 (0.25 to 0.99)*
mACR50						
Responders	20.2%	9.4%	9.9%	18.9%	8.8%	9.3%
Adjusted OR (95% CI)†	1	0.42 (0.27 to 0.65)*	0.42 (0.20 to 0.86)*	1	0.49 (0.30 to 0.78)*	0.41 (0.17 to 0.99)*
mACR70						
Responders	10.3%	2.6%	4.9%	11.4%	3.7%	4.0%
Adjusted OR (95% CI)†	1	0.28 (0.14 to 0.55)*	0.50 (0.19 to 1.32)	1	0.39 (0.19 to 0.80)*	0.23 (0.05 to 1.05)
CDAI remission						
No of patients	745	334	75	590	263	67
Responders	15.4%	7.3%	1.2%	16.2%	8.8%	5.3%
Adjusted OR (95% CI)‡	1	0.57 (0.36 to 0.90)*	0.09 (0.01 to 0.71)*	1	0.63 (0.38 to 1.04)	0.32 (0.10 to 1.03)
DAS28–ESR remission						
No of patients	326	136	41	218	85	27
Responders	25.1%	7.6%	7.5%	29.3%	10.3%	9.4%
Unadjusted OR (95% CI)‡§	1	0.21 (0.08 to 0.56)*	0.29 (0.07 to 1.22)*	1	0.21 (0.07 to 0.65)*	0.31 (0.06 to 1.59)

Data presented are the percentage of patients or adjusted OR (95% CI).

ΑΛΛΑΓΗ ΒΙΟΛΟΓΙΚΩΝ-‘’SWITCHING’’

- Πόσο αποτελεσματική είναι η αλλαγή σε άλλη τάξη βιολογικής θεραπείας;

European Collaborative Registries for the Evaluation of Rituximab in RA (CERERRA) initiative

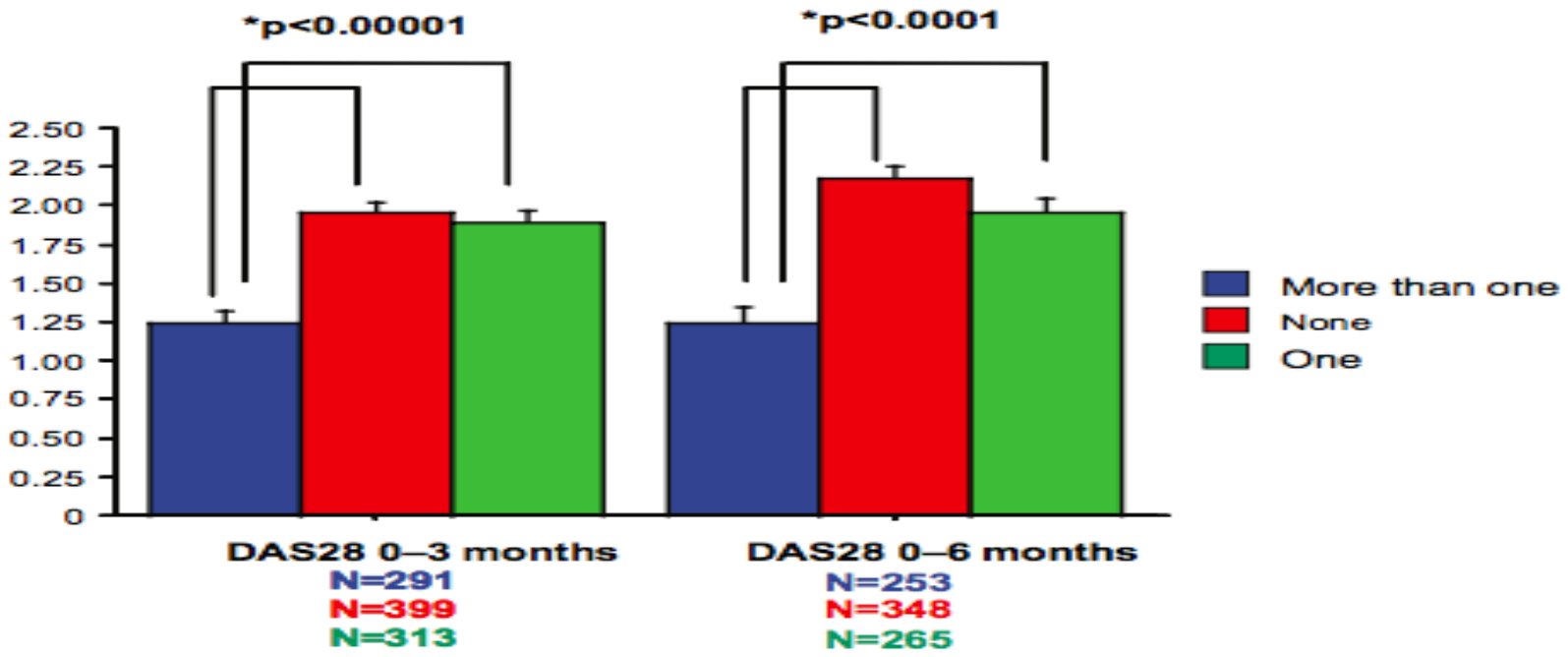


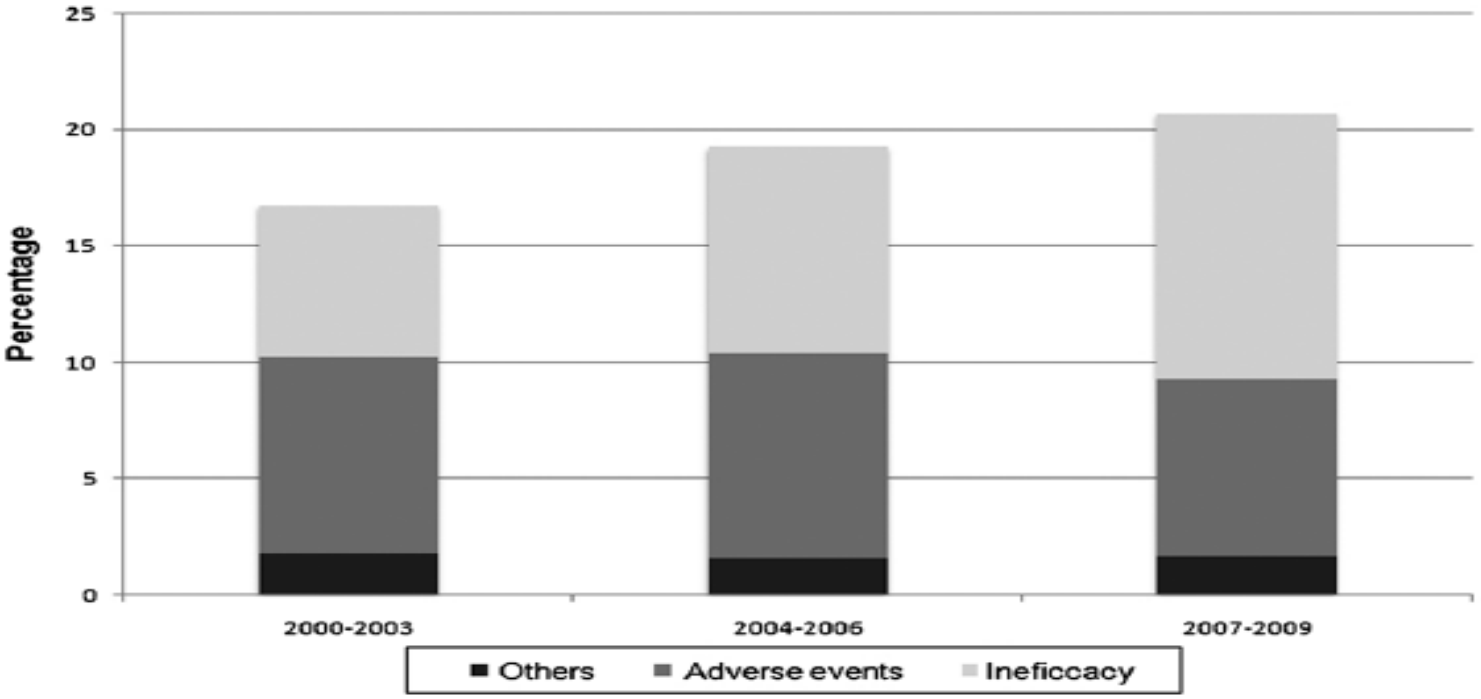
Figure 3 Mean DAS28 improvement (bars: SEM) for patients who failed none, one or more than one biologic DMARD. The mean reductions in DAS28 during the first 3 and 6 months were significantly greater for patients having failed at most one biologic compared to those who had two or more prior biologics ($p < 0.0001$).

ΑΛΛΑΓΗ ΒΙΟΛΟΓΙΚΩΝ-‘’SWITCHING’

- Ποιος είναι ο κύριος λόγος αλλαγής του βιολογικού παράγοντα;

Changes in discontinuation patterns of anti-TNFs in RA over 10 yrs.

Main reasons for discontinuation during first year of treatment.



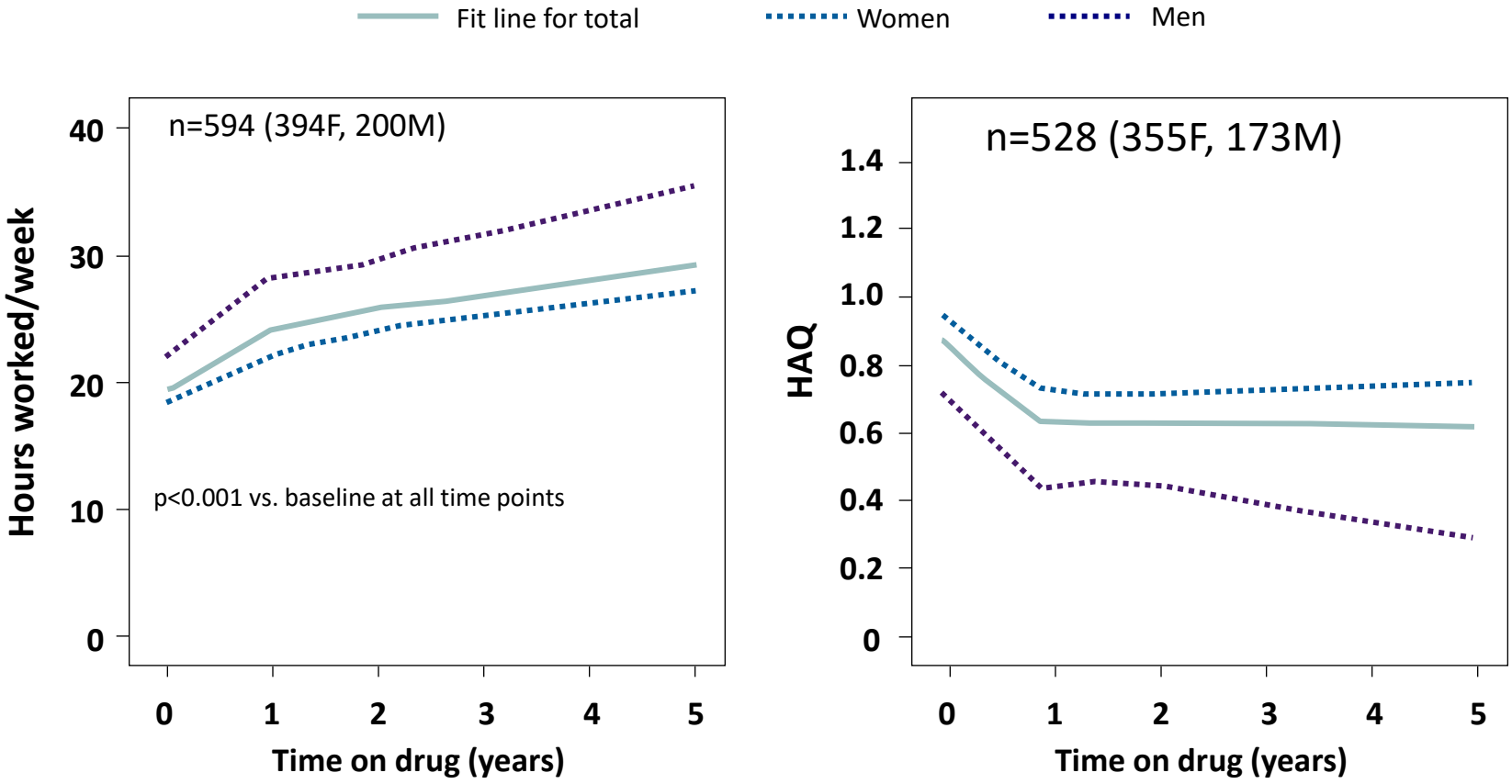
- Over time, the proportion of patients discontinuing tumor necrosis factor (TNF) inhibitors during the first year of treatment has increased
- Inefficacy, as a reason for discontinuation, is increasing
- The rate of discontinuation due to AEs has remained stable over the years.

Gomez-Reino JJ, et al. *ARD pub. Online Oct. 13* 2011

ΠΟΙΟΤΗΤΑ ΖΩΗΣ-ΛΕΙΤΟΥΡΓΙΚΟΤΗΤΑ

- Πόσο έχει βελτιωθεί η ποιότητα ζωής και η λειτουργικότητα με τις βιολογικές θεραπείες;

Biologic therapy, functional status and work ability in RA



HAQ, Health Assessment Questionnaire

Augustsson J, et al. *Ann Rheum Dis* 2010;69:126-131.

Functional status and biologics

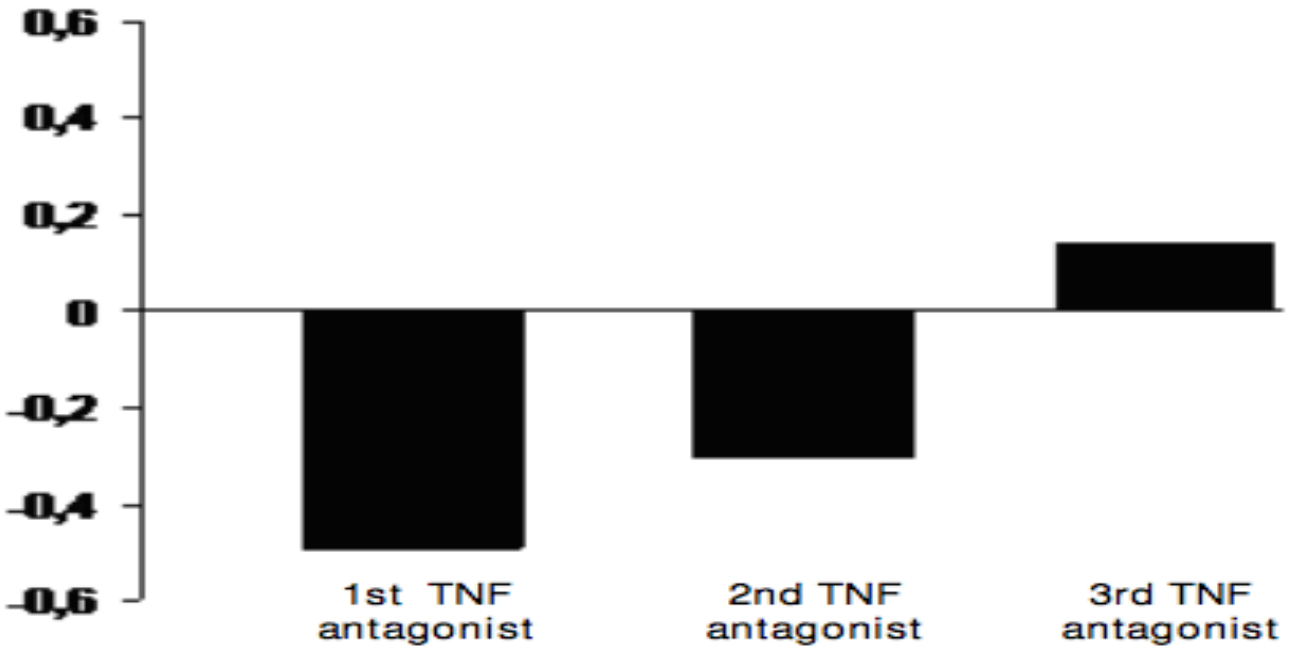


Figure 1
Mean cumulative change in HAQ from starting therapy in patients with rheumatoid arthritis following cycling between TNF antagonists.

ΣΥΜΠΕΡΑΣΜΑΤΑ

- Η εισαγωγή των βιολογικών παραγόντων άλλαξε ριζικά την πορεία της νόσου βελτιώνοντας την επιβίωση,την πρόγνωση και την ποιότητα ζωής των ασθενών
- Ωστόσο ακόμα υπάρχει σημαντικό ποσοστό ασθενών που δεν ανταποκρίνονται σε αυτές τις θεραπείες παρά την πληθώρα των επιλογών
- Ανάγκη για νέες πιο αποτελεσματικές και καινοτόμες θεραπείες


Cure