ΕΠΙΣΤΗΜΟΝΙΚΗ ΕΤΑΙΡΕΙΑ ΓΙΑ ΤΗ ΜΥΟΣΚΕΛΕΤΙΚΗ ΥΓΕΙΑ - (ΕΠΕΜΥ)

5ο ΠΑΝΕΛΛΗΝΙΟ ΕΠΙΣΤΗΜΟΝΙΚΟ ΣΥΝΕΔΡΙΟ ΕΠΕΜΥ 2013
ΜΕ ΔΙΕΘΝΗ ΣΥΜΜΕΤΟΧΗ

«Η αντιμετώπιση των μυοσκελετικών παθήσεων με βάση τις πραγματικές ανάγκες και τις οικονομικές δυνατότητες»

Συνεδρία βιολογικών θεραπειών
«Μαθήματα από το παρελθόν και μελλοντικές προσδοκίες»

Αποτυχίες – εναλλαγές – κενά

Αμαλία Ραπτοπούλου
Ρευματολόγος, Βέροια

Σύγκρουση συμφερόντων
Conflict of interest

Καμία αμοιβή για αυτή την παρουσίαση

Εκπαιδευτικές-ερευνητικές-συμβουλευτικές επιχορηγήσεις την τελευταία διετία:

Abbvie

- **Υπάρχουν δεδομένα για το ποσοστό των ασθενών με PA που δεν μπορούμε να ελέγξουμε με τις διαθέσιμες βιολογικές θεραπείες;**

Health Technology Assessment 2011; Vol. 15: No. 14
ISSN 1366-5278

Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation

DAS28 κριτήρια ύφεσης και χαμηλής ενεργότητας νόσου

TABLE 107 The EULAR response criteria using DAS and DAS28

		Improvement in DAS or DAS28 from baseline		
DAS at end point	DAS28 at end point	≥ 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 2.4	≤ 3.2	Good		
> 2.4 and ≤ 3.7	> 3.2 and ≤ 5.1		Moderate	
> 3.7	> 5.1			None

Sequential use of biologic therapy in rheumatoid arthritis
Maya H. Buch
Current Opinion in Rheumatology 2010, 22:321–329

Ποσοστό ασθενών υπό βιολογική θεραπεία και υπολειπόμενη ενεργότητα

Tumour necrosis factor inhibitors

TNFi drugs heralded a new era in RA therapy; despite the highly impressive outcomes, it has become evident in both initial trial data and with the set-up of registries, **that a notable proportion (up to a third) fail to derive a significant benefit.** The basis for this remains unclear, although several studies have sought to explore the mechanisms.

Weinblatt ME, Arthritis Rheum 2003;48:3545.
Keystone EC, Arthritis heum 2004;50:140011.
Bathon JM, N Engl J Med 2000;343: 158693.
Weinblatt ME, N Engl J Med 1999;340: 2539.
Lipsky PE, N Engl J Med 2000;343:1594602.
St Clair EW, Arthritis Rheum 2004;50:343243.

The British Society for Rheumatology Biologics Register
Danish nationwide DANBIO database
Dutch Rheumatoid Arthritis Monitoring DREAM Registry
Finnish - ROB-FIN registry

•Hyrich KL, Rheumatology (Oxford) 2006; 45:1558–1565.
•Stergaard Mresults Scand J Rheumatol 2007; 36:151–154.
•Rheumatology (Oxford).2012 Sep;51(9):1610-7
•Vrikki L, et al. Clin Rheumatol 2011

Επιβίωση φαρμάκου - Danbio registry

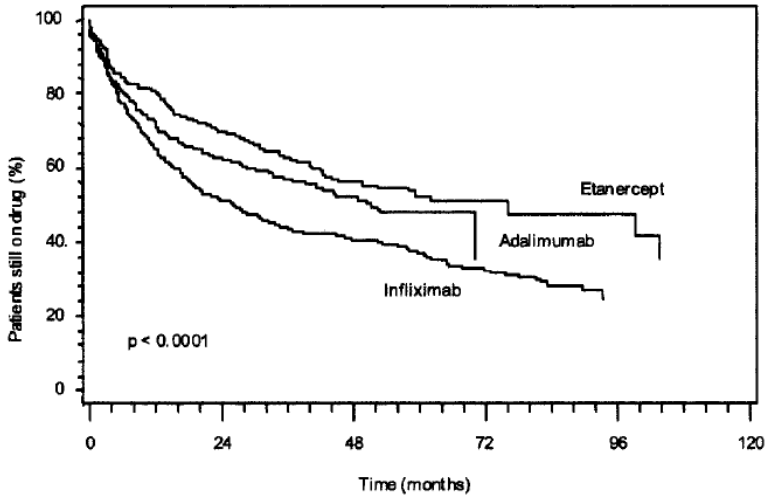
ARTHRITIS & RHEUMATISM
Vol. 62, No. 1, January 2010, pp 22–32
DOI 10.1002/art.27227

Direct Comparison of Treatment Responses, Remission Rates, and Drug Adherence in Patients With Rheumatoid Arthritis Treated With Adalimumab, Etanercept, or Infliximab

Results From Eight Years of Surveillance of Clinical Practice in the Nationwide Danish DANBIO Registry

2,326 patients, 2000-2009

The DANBIO register reported on long-term drug survival that ranged from 41 to 56% after 4 years of follow-up, depending on type of TNF-blocking agents



Withdrawn	Patients on drug					
185	517	230	108	17	8	Etanercept
282	675	307	98	1	–	Adalimumab
622	1134	424	205	78	6	Infliximab

Figure 3. Drug survival rate for each tumor necrosis factor α inhibitor. The number of withdrawals and the number of patients still receiving each drug at different time points are shown.

RHEUMATOLOGY

Rheumatology 2011;50:196–203
doi:10.1093/rheumatology/keq325
Advance Access publication 14 November 2010

Original article

Επιβίωση φαρμάκου - Dream registry

Long-term effectiveness and safety of TNF-blocking agents in daily clinical practice: results from the Dutch Rheumatoid Arthritis Monitoring register

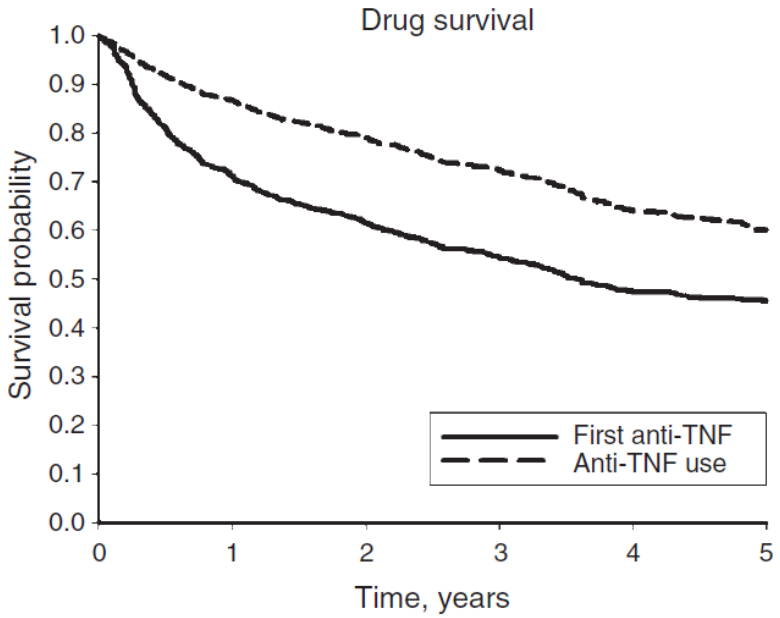
Wietske Kievit[1], Jaap Fransen[1], Eddy M. M. Adang[2], Alfons A. den Broeder[3], Hein J. Bernelot Moens[4], Henk Visser[5], Mart A. F. van de Laar[6] and Piet L. C. M. van Riel[1]

Drug survival

The 5-year drug survival (solid line, Fig. 1) of the first TNF-blocking agents was 45%, with the highest discon-

tinuation rate in the first year. The cumulative drug survival was 70% after 1 year, 62% after 2 years, 55% after 3 years, 47% after 4 years and 45% after 5 years. In total, 694 patients stopped their first anti-TNF in the course of 5 years. The reason for stopping the first TNF-blocking agent was inefficacy in 282 (41%) and adverse events in 243 (35%)

FIG. 1 Drug survival of the first TNF-blocking agents and TNF-blocking agents in general (including switching).



Differential drug retention between anti-TNF agents and alternative biological agents after inadequate response to an anti-TNF agent in rheumatoid arthritis patients

Επιβίωση φαρμάκου - Swiss registry

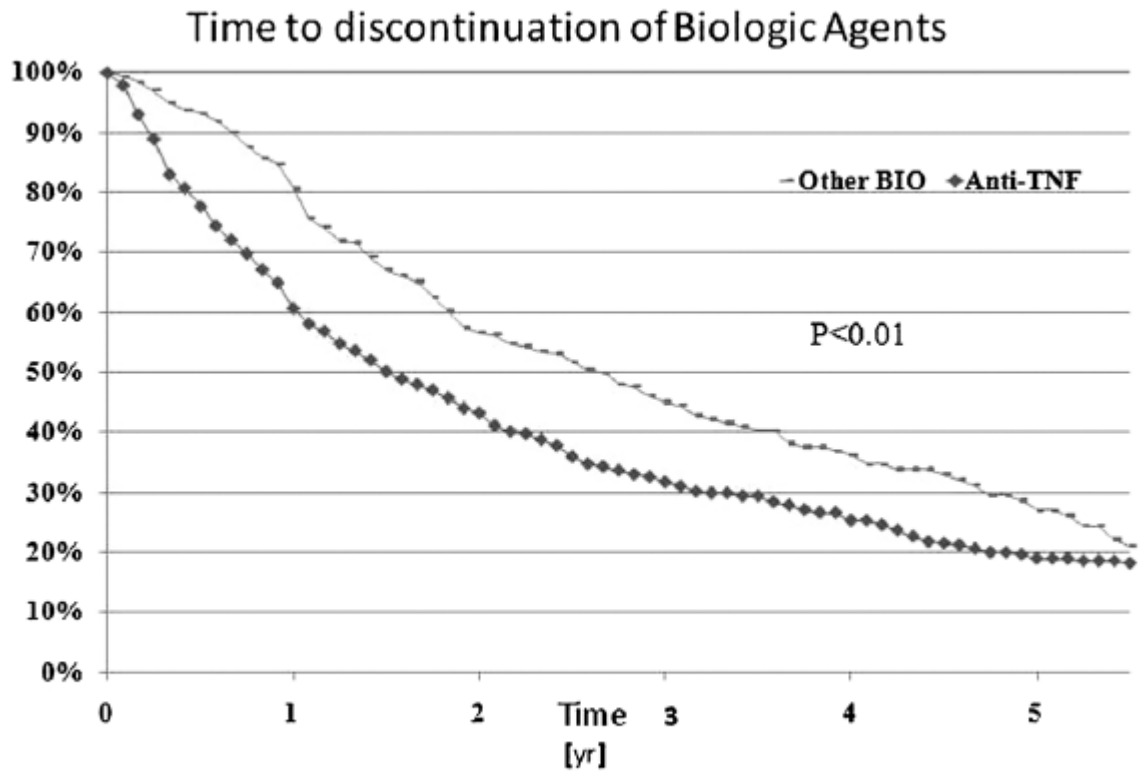


Figure 1 Time to discontinuation of biologic agents.

Table 1 Study population

Baseline characteristics	Alternative aTNF (N=853)	Non-aTNF-Bio (N=632)	p Value†
Type of biological	IFX N=171(20%) ETA N=247(29%) ADA N=435(51%)	RTX=348 (55%) TCZ=139 (22%) ABA=145 (23%)	

RHEUMATOLOGY

Rheumatology 2011;50:166–175
doi:10.1093/rheumatology/keq322
Advance Access publication 7 October 2010

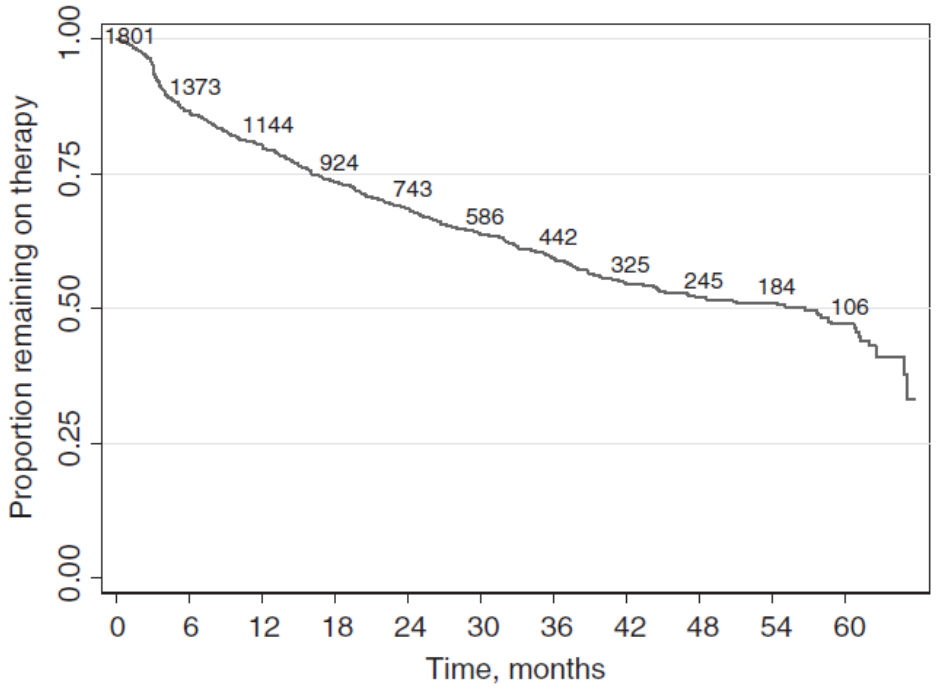
Original article

Επιβίωση φαρμάκου – Australian registry

Health-related quality of life and continuation rate on first-line anti-tumour necrosis factor therapy among rheumatoid arthritis patients from the Australian Rheumatology Association Database

Margaret P. Staples[1,2], Lyn March[3,4], Marissa Lassere[5,6], Chris Reid[1,7] and Rachelle Buchbinder[1,2]

FIG. 1 Proportion remaining on first-line anti-TNF therapy and number at risk at 6-month time points.



Rheumatology key messages

- After 5-year follow-up, 50% of patients remained on first-line anti-TNF therapy.

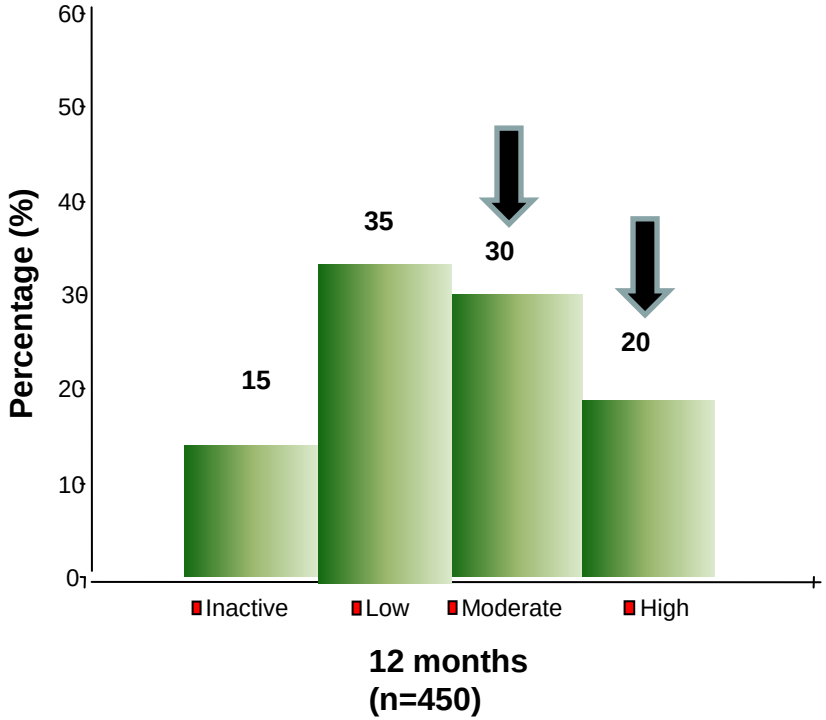
Anti-TNF στην κλινική πράξη

- Στο 1 έτος:
  - **15-20%** ύφεση
  - **30-35%** χαμηλή ενεργότητα νόσου

	Infliximab	Adalimumab	Etanercept	P value
	12 months	12 months	12 months	
DAS28 remission				
Remission (%)	**15**	**23**	**19**	0.098
DAS28 low disease activity				
Low disease activity (%)	**27**	**34**	**31**	0.309

Anti-TNF στην κλινική πράξη

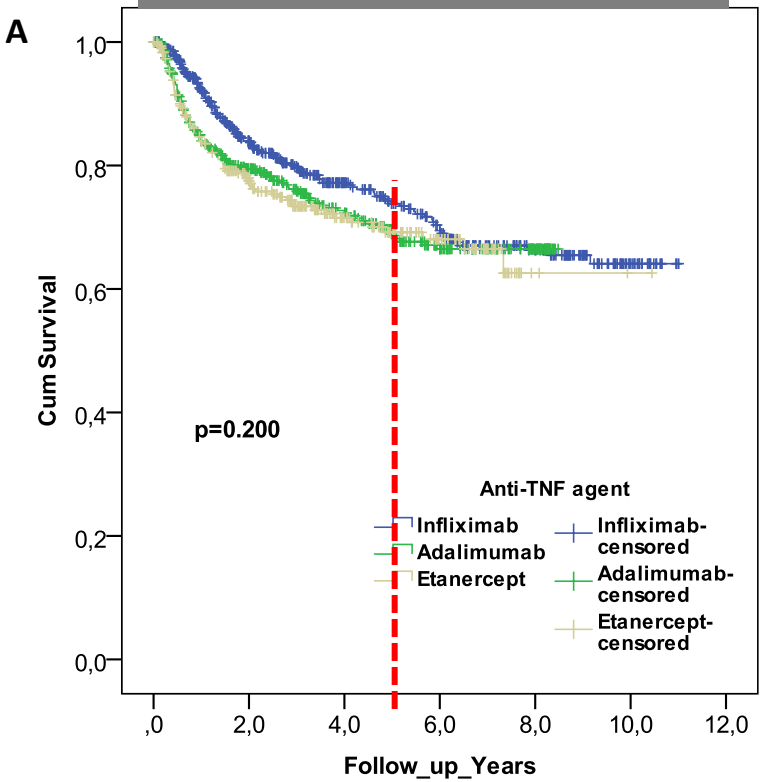
Σημαντικό ποσοστό ασθενών υπό βιολογικούς παράγοντες εξακολουθούν να έχουν υπολειπόμενη νόσο



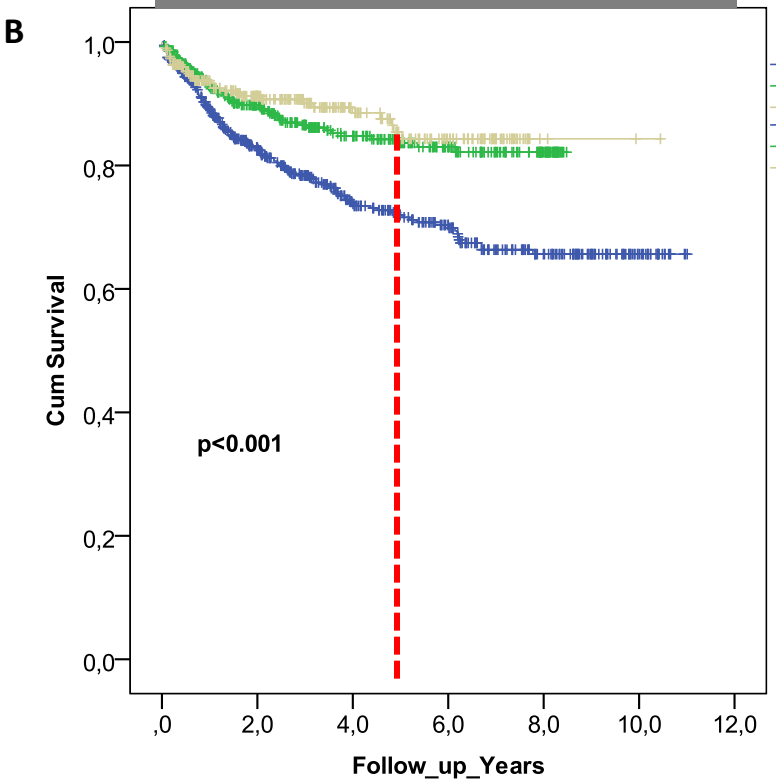
Μακροχρόνια (5 έτη) παραμονή στην αγωγή: 30-50%

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

Efficacy-related drug survival



Toxicity-related drug survival



Συμπεράσματα Ι

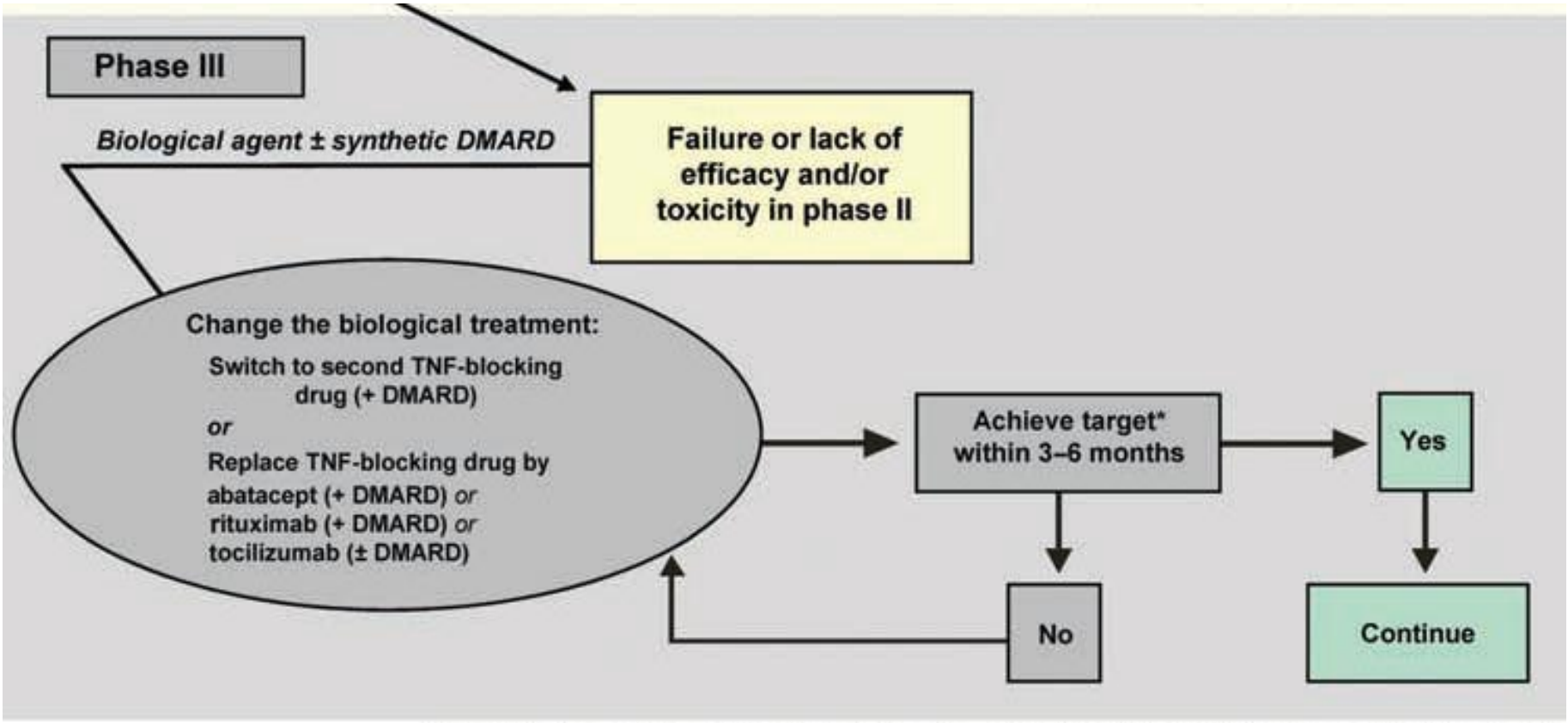
- Όπως προκύπτει από μελέτες και, κυρίως, τα αρχεία βιολογικών θεραπειών (registries), περίπου **το ένα τρίτο** των ασθενών υπό βιολογικές θεραπείες εμφανίζουν υπολειπόμενη ενεργότητα νόσου

- Στην πενταετία, **οι μισοί** περίπου ασθενείς εξακολουθούν να λαμβάνουν τον αρχικό βιολογικό παράγοντα

Υπάρχουν κριτήρια για την ακολουθούμενη στρατηγική επί αποτυχίας βιολογικού παράγοντα στη ΡΑ;

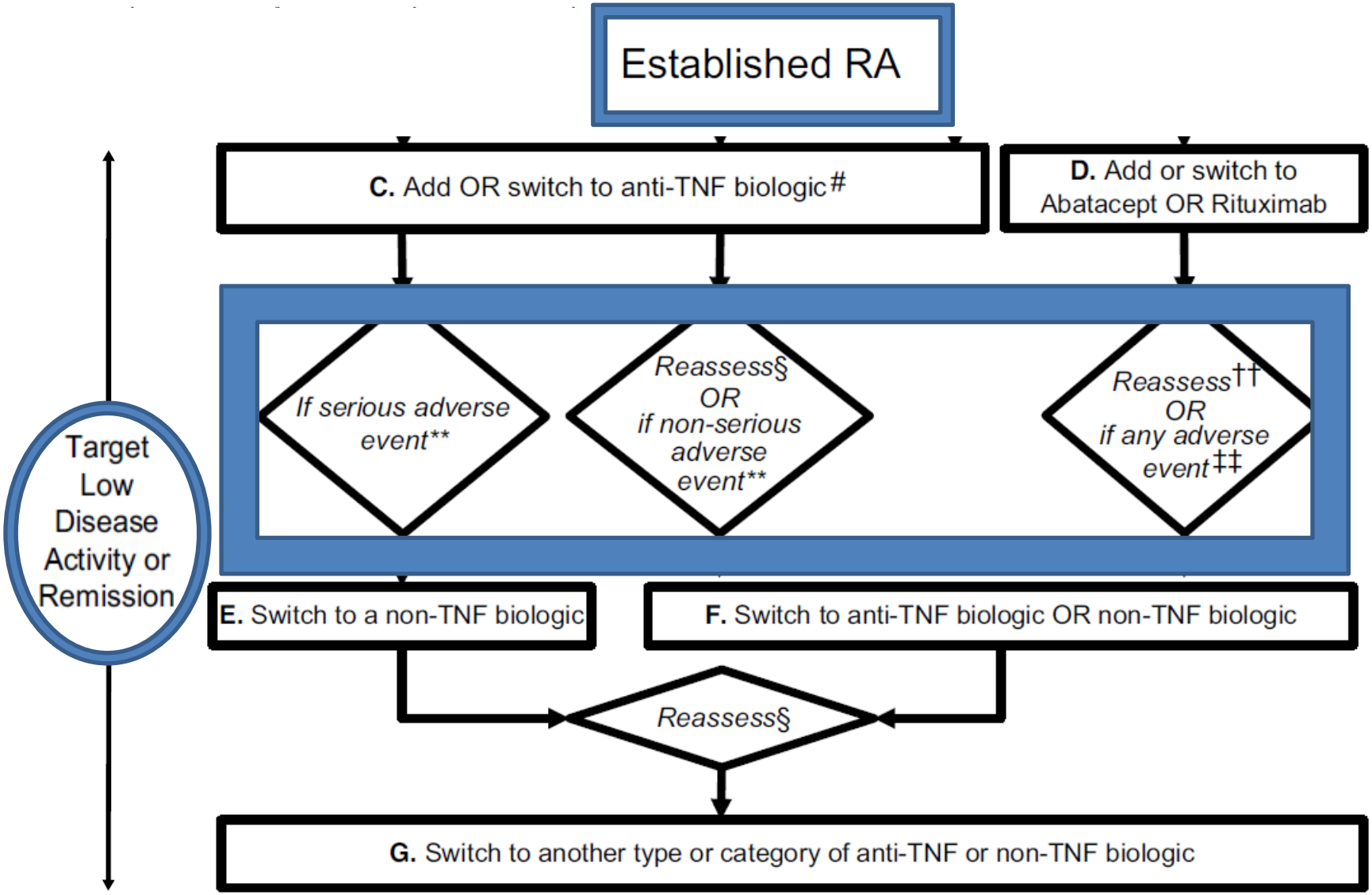
Ann Rheum Dis 2010

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



2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis

Arthritis Care & Research
Vol. 64, No. 5, May 2012, pp 625–639
DOI 10.1002/acr.21641



Παράγοντες που επηρεάζουν την επιλογή της θεραπείας

Thresholds in Disease Activity for Switching Biologics in RA Patients: Experience from a Large United States Cohort

Jie Zhang, PhD[1], Ying Shan, MD, MPH[2], George Reed, PhD[2], Joel Kremer, MD[3], Jeffrey D Greenberg, MD[4], Scott Baumgartner, MD[5], and Jeffrey R Curtis, MD, MS, MPH[1,6]

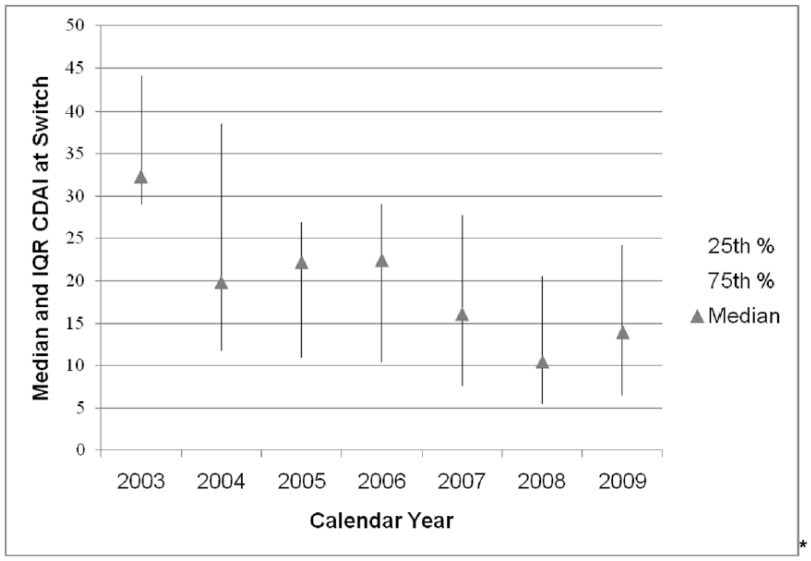
Arthritis Care Res (Hoboken). 2011 December ; 63(12): 1672–1679.

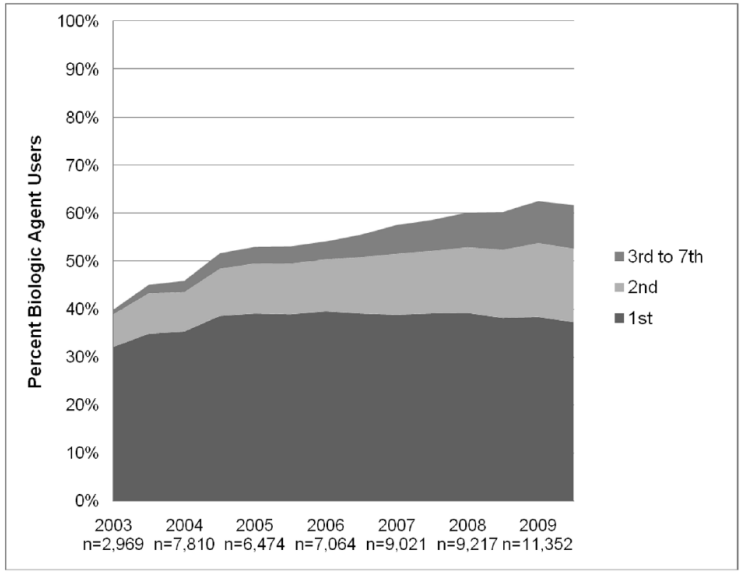
1

Υπάρχουσες θεραπείες

Πόσο εύκολα αλλάζουμε βιολογικό παράγοντα; στοιχεία από το Corona Registry

23.000 ασθενείς
2001-2009





Clin Rheumatol
DOI 10.1007/s10067-011-1779-1

ORIGINAL ARTICLE

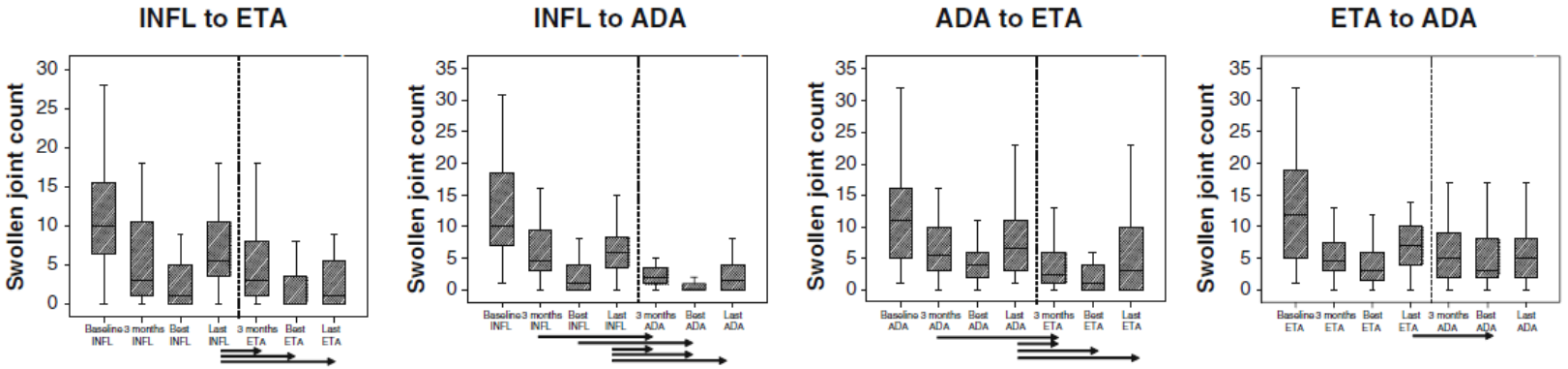
Outcomes of switching anti-TNF drugs in rheumatoid arthritis—a study based on observational data from the Finnish Register of Biological Treatment (ROB-FIN)

2

Αίτια διακοπής TNFi θεραπείας

479 patients, 1999-2009

Finnish - ROB-FIN registry



. The results suggest that a second TNF blocker can restore the response in cases of secondary LOE and maintain it after switching due to an AE.

Vrikki L, et al. Clin Rheumatol 2011

EXPERT REVIEWS

When is switching warranted among biologic therapies in rheumatoid arthritis?

Expert Rev. Pharmacoecon. Outcomes Res. 12(3), 319–333 (2012)

Αποτελεσματικότητα μετά από αλλαγή σε δεύτερο TNFi ανάλογα με τον λόγο της διακοπής της θεραπείας: μετα-ανάλυση

Response criteria	Studies (n)	Patients (n)	Responders, % (95% CI)
Findings of studies that analyzed switching owing to lack of efficacy			
EULAR	12	1183	71.5 (64.4–78.1)
ACR20	9	1003	54.3 (45.8–62.5)
ACR50	8	967	30.6 (24.5–37.0)
ACR70	7	954	11.9 (9.7–14.1)
Findings of studies that analyzed switching owing to adverse events			
EULAR	6	451	69.5 (50.4–85.7)
ACR20	4	335	62.5 (57.3–67.6)
ACR50	5	372	43.1 (29.9–56.8)
ACR70	5	372	20.0 (8.6–34.7)

Ann Rheum Dis. 2012 Jul;71(7):1134-42.

A comparative effectiveness study of adalimumab, etanercept and infliximab in biologically naive and switched rheumatoid arthritis patients: results from the US CORRONA registry.

Greenberg JD, Reed G, Decktor D, Harrold L, Furst D, Gibofsky A, Dehoratius R, Kishimoto M, Kremer JM; CORRONA Investigators

2

Αίτια διακοπής TNFi θεραπείας

US –Corrona registry

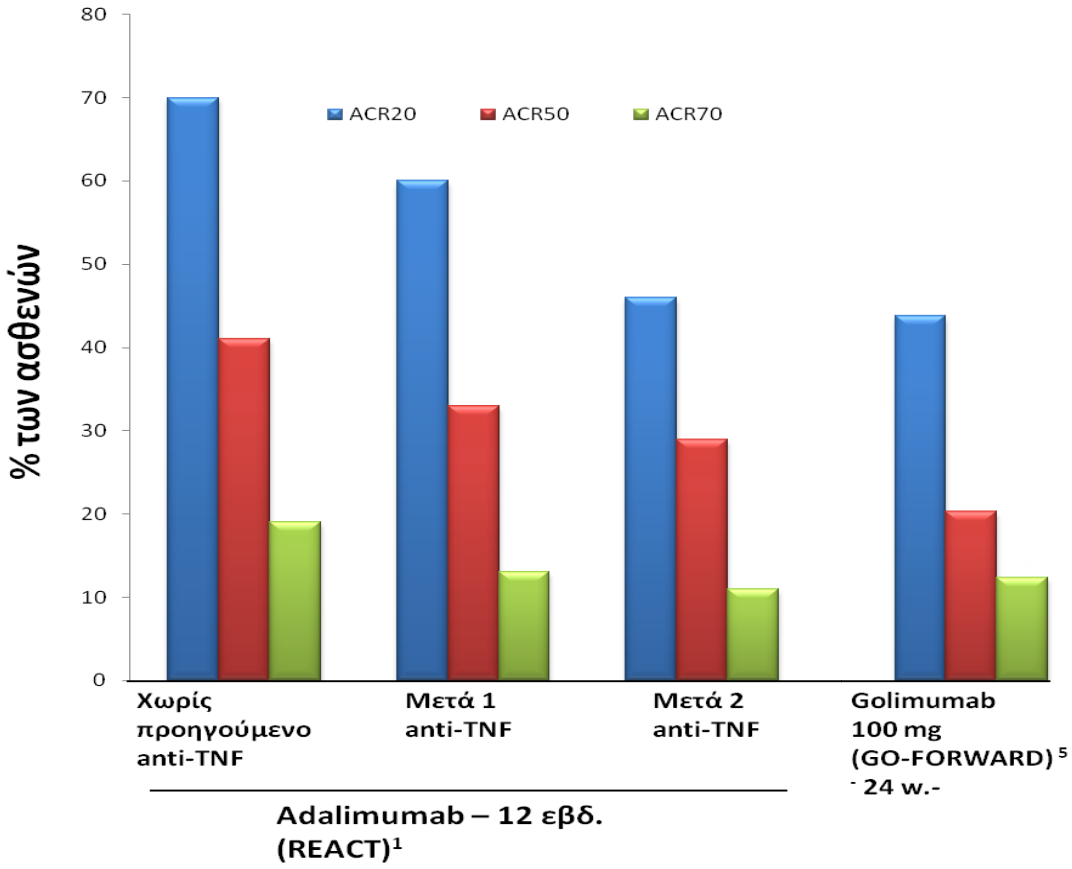
PURPOSE:

- To compare the effectiveness of anti-tumour necrosis factor (TNF) agents in biologically **naive** and **'switched'** rheumatoid arthritis (RA) patients.

RESULTS:

- **Response and remission outcomes** were **consistently inferior for switched** versus biologically naive patients.
- Among 2242 patients **no differences** in rates of drug response or remission were observed among the three anti-TNF
- **Persistence** was higher in **biologically naive** patients, for whom persistence was highest with infliximab.

Σταδιακά μειούμενη αποτελεσματικότητα TNFi μετά από συνεχόμενες αλλαγές παραγόντων



1.- *Bombardieri S, et al. Rheumatology (Oxford). 2007 ;46(7):1191-9.*

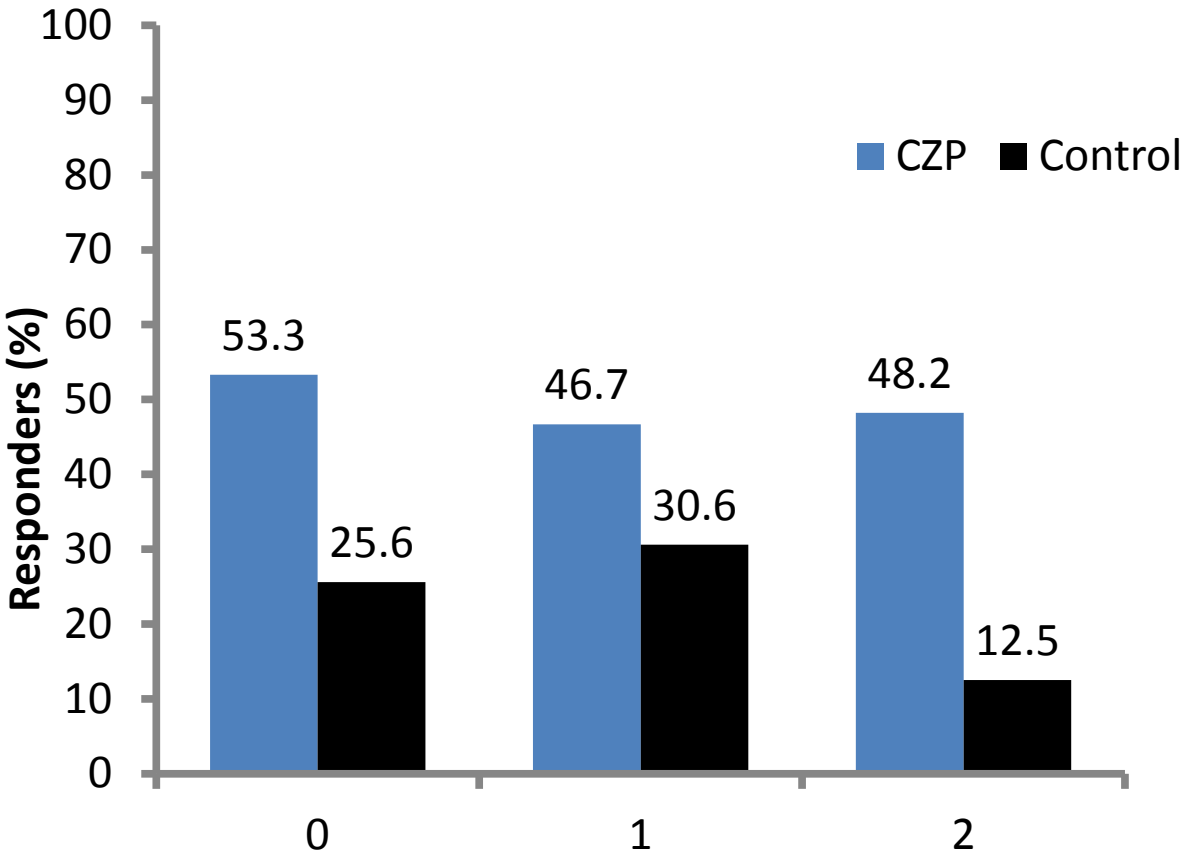
5.- *Smolen J, et al. Ann Rheum Dis 2008;67(Suppl II):50.*

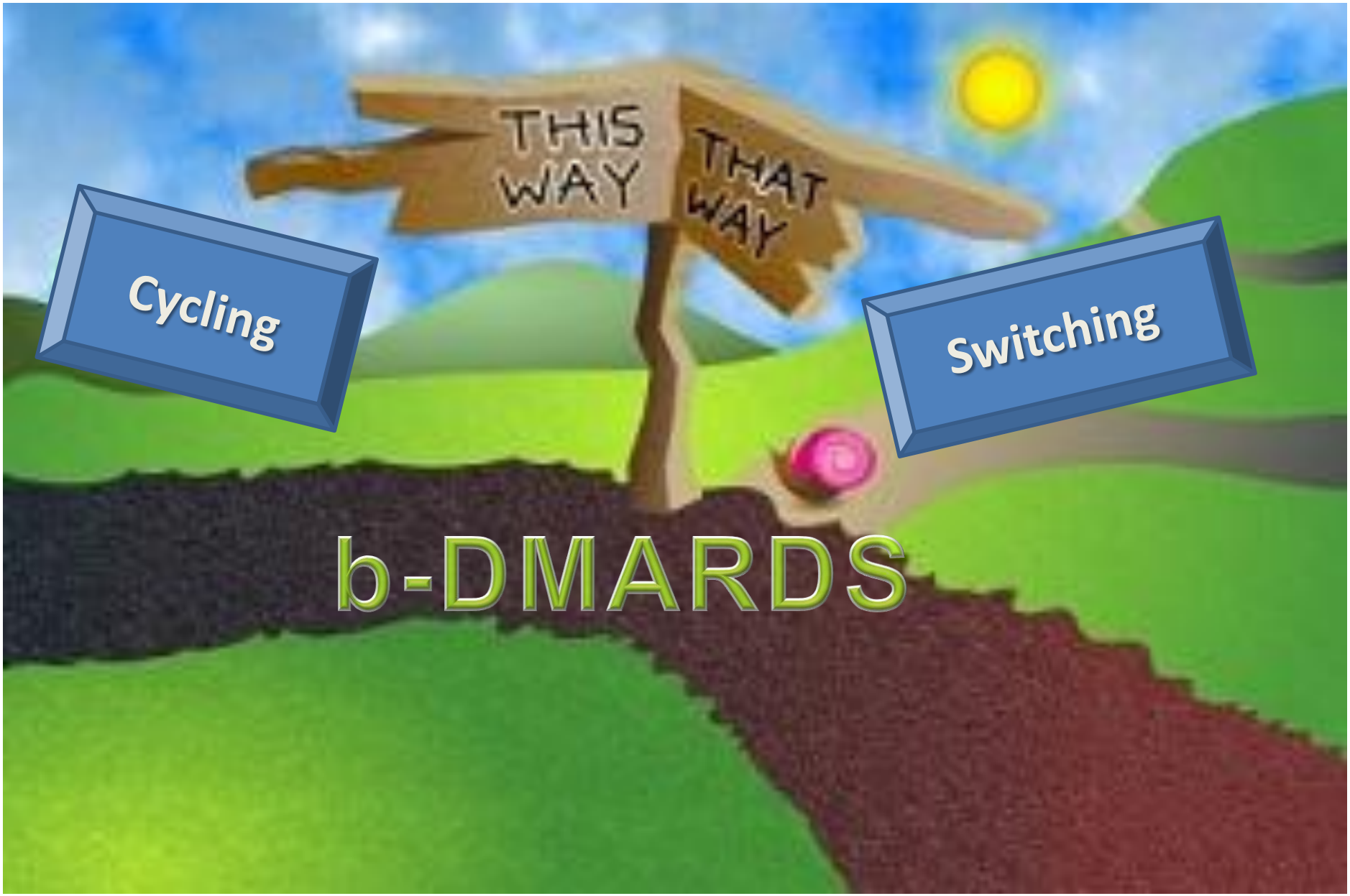
****-*** *Datos a 16 semanas: Kay J, et al. Arthritis Rheum. 2008 Apr;58(4):964-75.*

Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study

Michael E. Weinblatt[1], Roy Fleischmann[2], Tom W. J. Huizinga[3], Paul Emery[4], Janet Pope[5], Elena M. Massarotti[1], Ronald F. van Vollenhoven[6], Jürgen Wollenhaupt[7], Clifton O. Bingham III[8], Ben Duncan[9], Niti Goel[10], Owen R. Davies[11] and Maxime Dougados[12]

ACR20 with Prior TNF Inhibitor Use

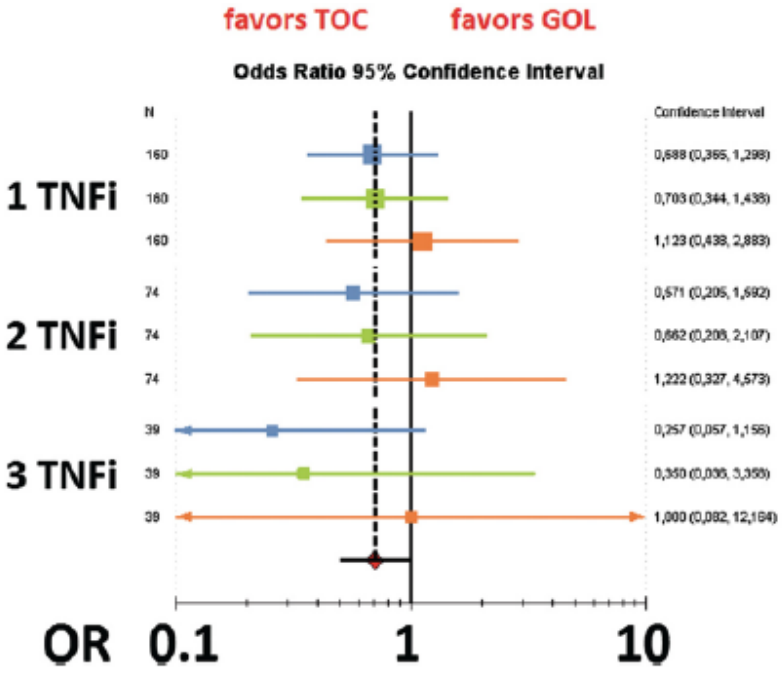


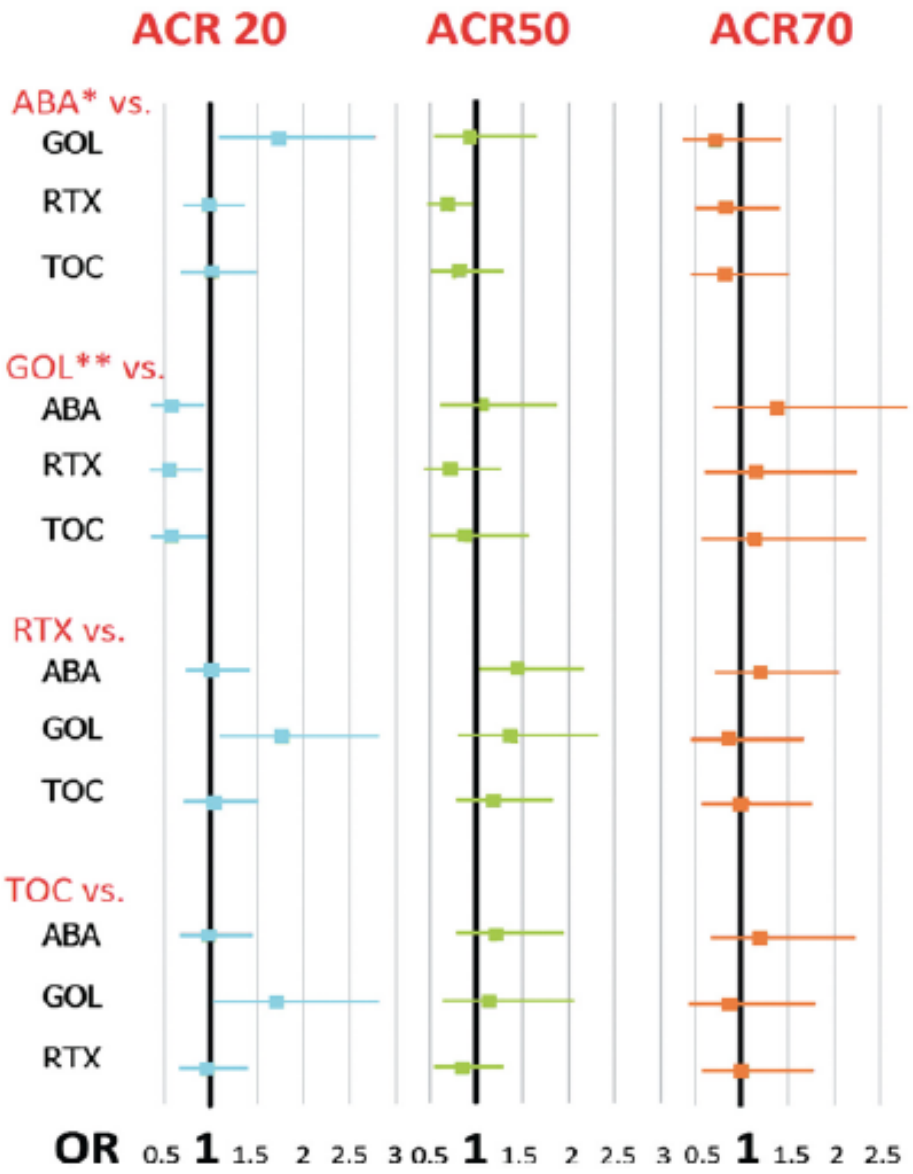

THIS WAY
THAT WAY
Cycling
Switching
b-DMARDS

Comparative effectiveness and safety of biological treatment options after tumour necrosis factor α inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis

Monika Schoels.[1,2] Daniel Aletaha.[3] Josef S Smolen,[1,3] John B Wong[2]

Ann Rheum Dis 2012;**71**:1303–1308.

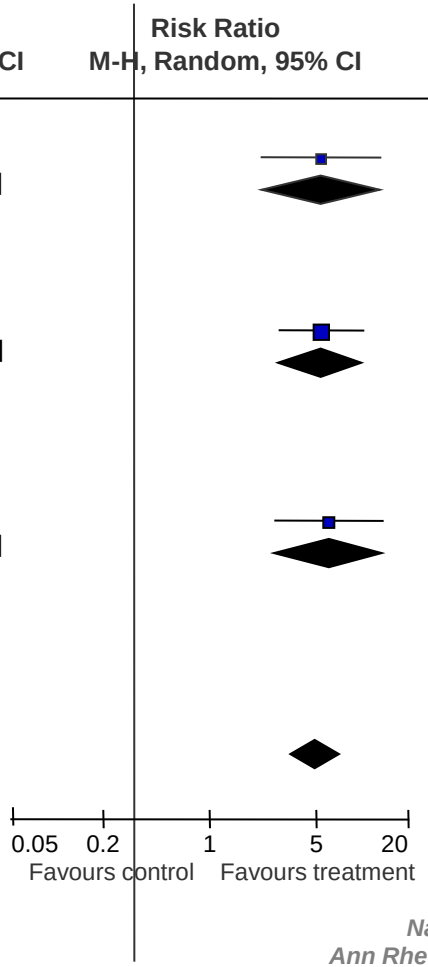




Συγκρίσιμη αποτελεσματικότητα βιολογικών μετά από αποτυχία TNFi

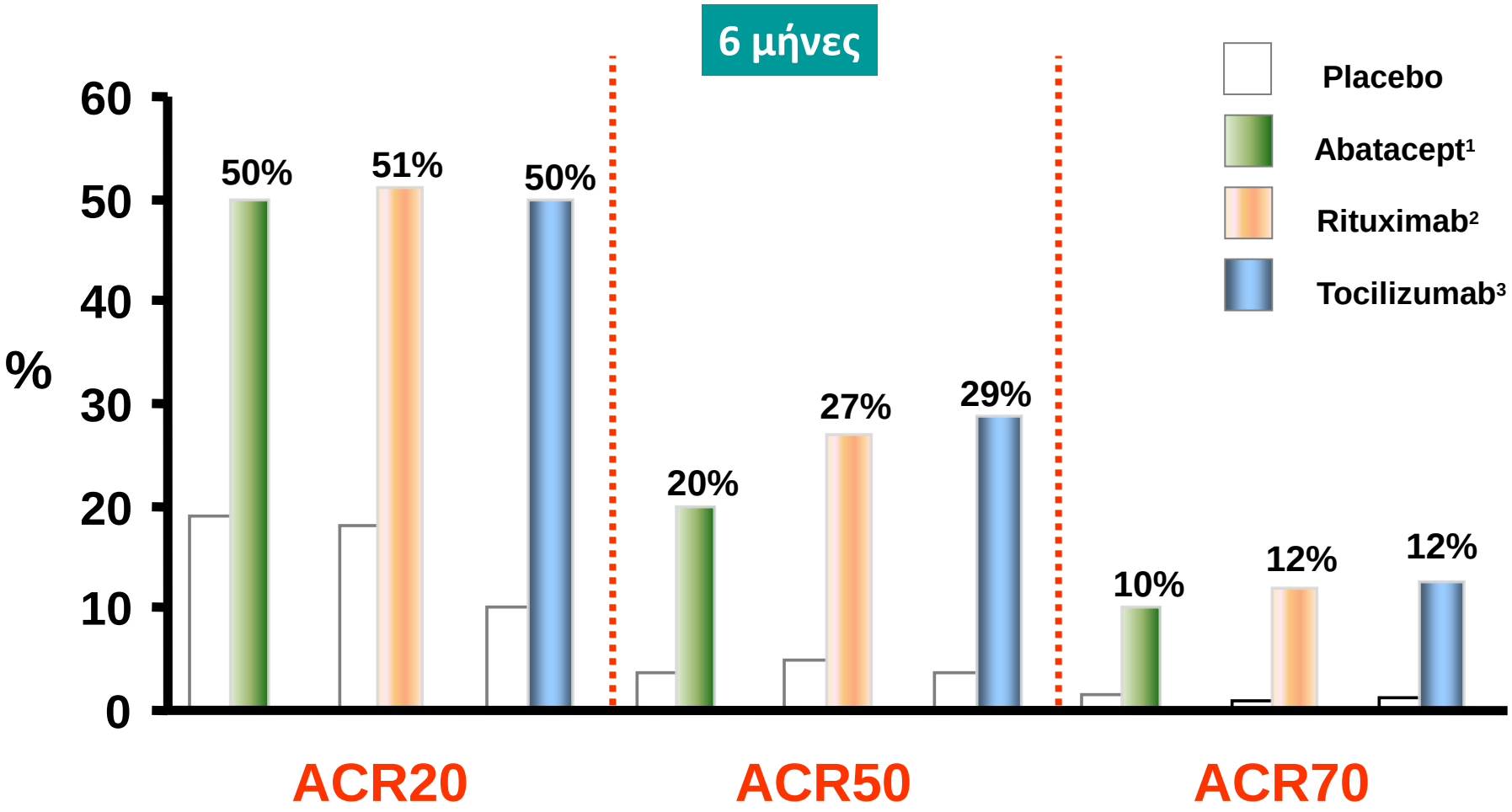
ACR 50
(6 μήνες)

Study or Subgroup	Favours control Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abatacept						
Genovese 2005 **ATTAIN**	52	258	5	133	17.3%	**5.36** [2.19, 13.10]
Rituximab						
Cohen 2006 **REFLEX**	80	298	10	201	34.5%	**5.40** **[2.87, 10.16]**
Tocilizumab						
Emery 2008 **RADIATE**	76	331	6	158	21.1%	**6.05** [2.69, 13.58]
Total (95% CI)		**1193**		**647**	**100.0%**	**5.00** **[3.45, 7.24]**
Total events	267		29			



Nam J L et al.
Ann Rheum Dis 2010

Αποτελεσματικότητα βιολογικών μετά αποτυχία TNFi: ACR απόκριση



[1] Genovese MC, NEJM 2005
[2] Cohen SB, A&R 2006
[3] Emery P, Ann Rheum Dis 2008

Highest clinical effectiveness of rituximab in autoantibody-positive patients with rheumatoid arthritis and in those for whom no more than one previous TNF antagonist has failed: pooled data from 10 European registries

Katerina Chatzidionysiou,[1] Elisabeth Lie,[2] Evgeny Nasonov,[3] Galina Lukina,[3] Merete Lund Hetland,[4] Ulrik Tarp,[5] Cem Gabay,[6] Piet L C M van Riel,[7] Dan C Nordström,[8] Juan Gomez-Reino,[9] Karel Pavelka,[10] Matija Tomsic,[11] Tore K Kvien,[2] Ronald F van Vollenhoven[1]

3 Χαρακτηριστικά νόσου

Αποτελεσματικότητα μετά από χορήγηση Rituximab σε οροθετικούς ασθενείς: συγκεντρωτικά δεδομένα από 10 ευρωπαϊκά registries

Conclusion In this large observational cohort of patients with RA treated with RTX, seropositive patients achieved significantly greater reductions in DAS28 at 6 months than seronegative patients. Effectiveness was best when RTX was used as the first biological agent or after failure of no more than one anti-tumour necrosis factor agent.

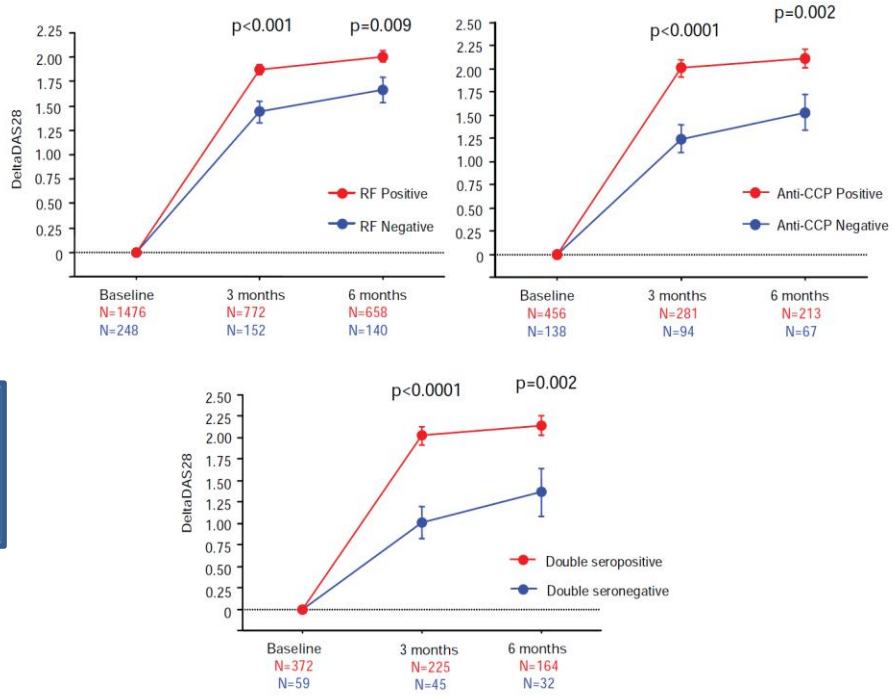


Figure 2 Mean ΔDAS28 (bars: SEM) during the first 6 months for seropositive and seronegative patients. At 3 and 6 months RF positive patients (A) as well as anti-CCP positive (B) and double positive patients (C) achieved significantly larger reductions of DAS28 compared to RF negative, anti-CCP negative and double negative patients, respectively.

Ann Rheum Dis 2011;**70**:1575–1580.

Επιβίωση φαρμάκου μετά από αλλαγή παράγοντα

CONCISE REPORT

Differential drug retention between anti-TNF agents and alternative biological agents after inadequate response to an anti-TNF agent in rheumatoid arthritis patients

Sophie Martin Du Pan,[1] Almut Scherer,[2] Cem Gabay,[1] Axel Finckh[1]

Ann Rheum Dis (2012).

Patients and methods

This is a nested cohort study within the Swiss RA registry (SCQM-RA), a population-based. observational cohort study of RA patients.

Alternative aTNF (N=853)
IFX N=171(20%)
ETA N=247(29%)
ADA N=435(51%)
Non-aTNF-Bio (N=632)
RTX=348 (55%)
TCZ=139 (22%)
ABA=145 (23%)

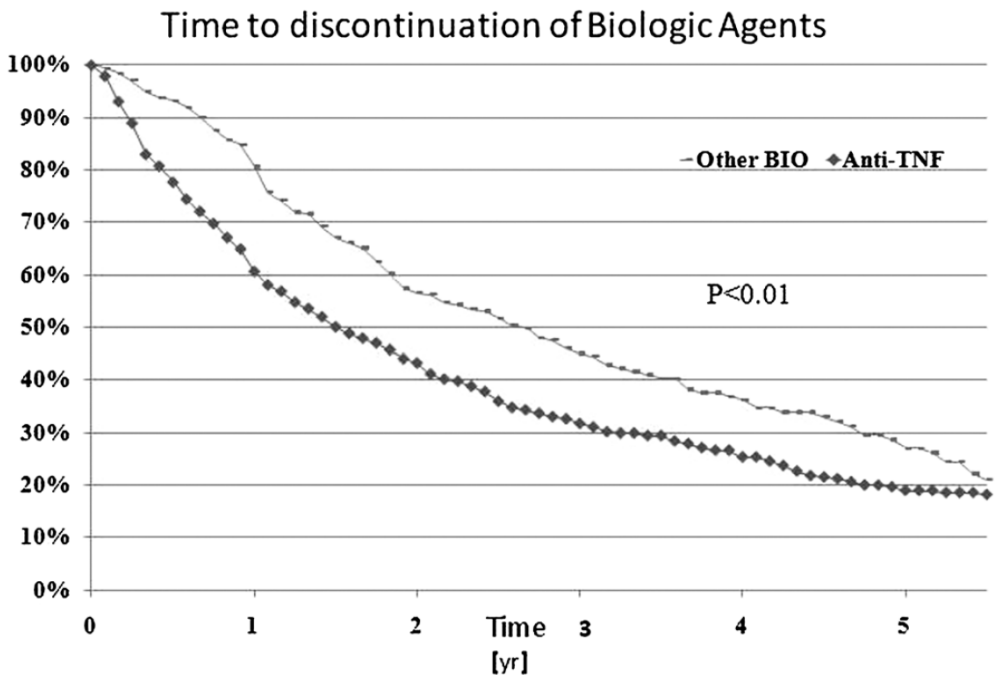


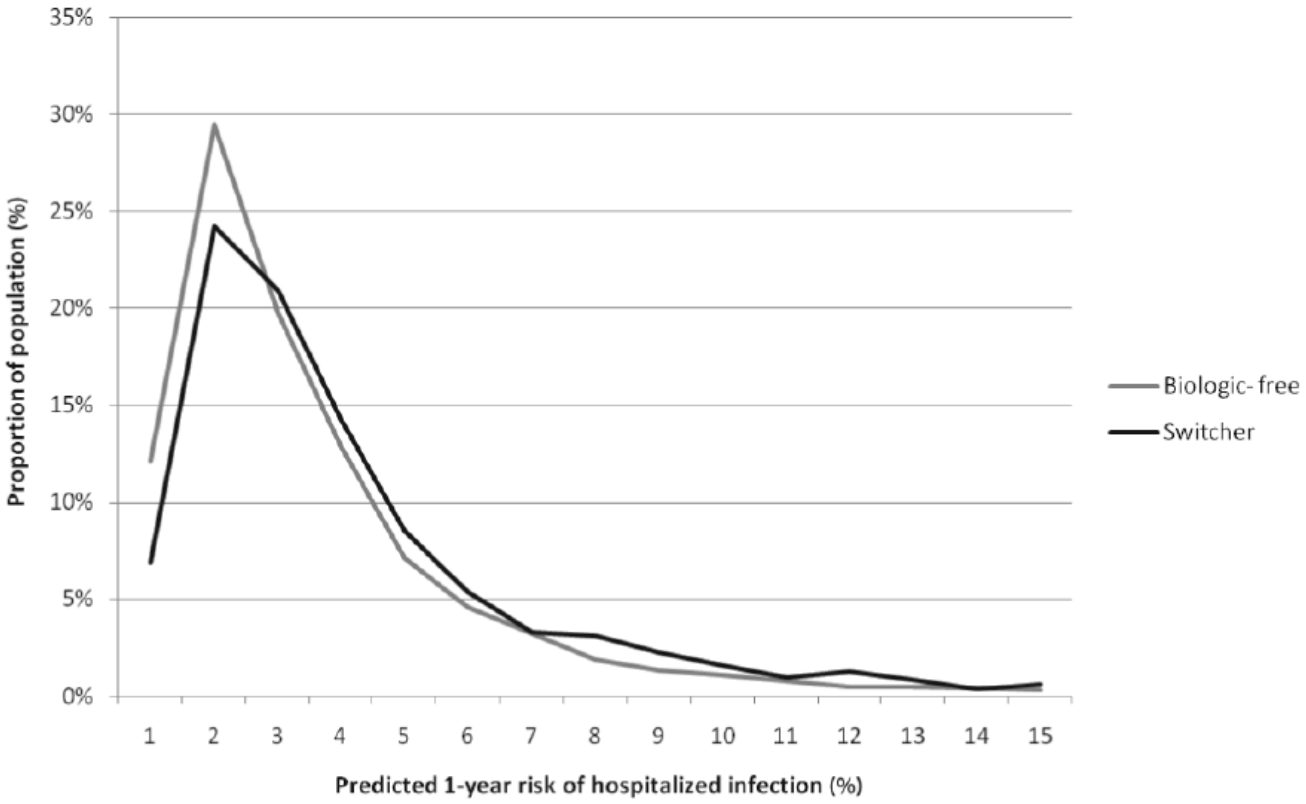
Figure 1 Time to discontinuation of biologic agents.

Conclusion After inadequate response to aTNF, and particularly after primary failure, patients on a non-aTNF-Bio agent have significantly higher drug retention rates.

The comparative risk of serious infections among rheumatoid arthritis patients starting or switching biological agents

Jeffrey R Curtis[1,2], Fenglong Xie[1], Lang Chen[1], John W Baddley[1], Timothy Beukelman[1], Kenneth G Saag[1,2], Claire Spettell[3], Raechele M McMahan[4], Joaquim Fernandes[3], Kevin Winthrop[5], and Elizabeth Delzell[2]

Ασφάλεια



Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation

K Malottki, P Barton, A Tsourapas, AO Uthman, Z Liu, K Routh, M Connock, P Jobanputra, D Moore, A Fry-Smith and Y-F Chen

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Οικονομικά δεδομένα

Conclusions: Evidence from RCTs suggests that RTX and ABT are more effective than supportive care. Data from observational studies suggest that the use of an alternative TNF inhibitor in patients who exhibit an inadequate response to a first TNF inhibitor may offer some benefit, but there remain uncertainties with regard to the magnitude of treatment effects and their cost-effectiveness. Future research should include head-to-head trials comparing the clinical effectiveness and cost-effectiveness of the technologies against each other and emerging biologics.

Παράγοντες που επηρεάζουν την επιλογή της θεραπείας

- Ανάγκη για μονοθεραπεία
- Συνοδά νοσήματα
- Ασθενείς σε αναπαραγωγική ηλικία
- Γνώμη του ασθενούς
- Ιδιαιτερότητες στον τρόπο ζωής του
- Συμμόρφωση

Συμπεράσματα II

Box 3 | Summary of when to switch or change class

Reason for discontinuation of the previous anti-TNF agent

- Secondary non-response: either switch to another TNF inhibitor or change to a drug of a different class
- Toxicity: either switch to another TNF inhibitor or change to a drug of a different class, but the risk of the same toxic effect needs to be considered

By number of previous anti-TNF agents

- If two anti-TNF have already been discontinued: change to a drug of a different class rather than switch to an alternative anti-TNF agent

- **Υπάρχει ανθεκτική στην αντι-TNF αγωγή αγκυλωτική σπονδυλαρθίτιδα και ποιές επιλογές υπάρχουν σε αυτές τις περιπτώσεις;**

REVIEW

CURRENT OPINION

Treatment of ankylosing spondylitis in patients refractory to TNF-inhibition: are there alternatives ?

Uta Kiltz, Frank Heldmann, Xenofon Baraliakos, and Juergen Braun

About half of the patients treated with TNF blockers show improvement of their disease activity of 50% and more by using Assessment of SpondyloArthritis International Society (ASAS) improvement criteria or the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). However, with the exception of very early disease states in young patients, less than one third of the patients reach the target remission.

- 46-week prospective longitudinal multicentre study of 60 AS patients

RESULTS:

- After 22 weeks, 58.3% of the patients were clinical responders
  - (50% or 20 mm reduction in the BASDAI).

Pedersen SJ, Ann Rheum Dis. 2010 Jun;69(6):1065-71

Current Opinion

Treatment of ankylosing spondylitis in patients refractory to TNF-inhibition: are there alternatives ?

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Table 1. Mode of action of the drugs

Drugs	Function
Abatacept	T-cell costimulation modulator
Anakinra	IL-1 receptor antagonists
Apremilast	PDE4-inhibitor
Bisphosphonates	Inhibition of macrophage migration, inhibition of proinflammatory cytokines
Rituximab	Anti-CD20 monoclonal antibody
Secukinumab	Antibody to IL-17A
Sulfasalazin	Reducing the synthesis of inflammatory mediators
Thalidomide	Inhibition of TNFα
Tocilizumab	Antihuman IL-6 receptor monoclonal antibody

Summary

Although some trends for efficacy were seen, there is at present insufficient evidence to support a recommendation for any of these compounds. So far, none of these new drugs have been shown to reach response rates compared to TNF-blockers.

Table 2. Comparison of studies

	Reference	Design	Number of patients	Disease	Treatment arms	Primary outcome	Results
Abatacept	Song *et al.* [22•]	Open-label prospective phase II	30	AS	TNF-inhibitor naive ($n=15$); TNF-inhibitor failure ($n=15$)	ASAS-40 at week 24	ASAS-40, % number of patients: TNF-inhibitor naive: 2.4–38.4%; TNF-inhibitor failure: 0–21.3%
	Lekpa *et al.* [23]	Case series	7	5 AS; 2 uSpA	Abatacept (single arm)	BASDAI50	None
Anakinra	Haibel *et al.* [24]	Open-label noncontrolled	20	AS	TNF-inhibitor naive	ASAS-20 (and 40) at week 24	Number of patients who reached ASAS-20 at week 24: 5 (4) of 20
	Tan *et al.* [25]	Open-label noncontrolled	9	AS	TNF-inhibitor naive	ASAS-20 at week 12	Number of patients who reached ASAS-20 at week 12; 6 of 9
Apremilast	Pathan *et al.* [26•]	Unpowered pilot study phase II	36	AS	Apremilast 30 mg BID orally after titration ($n=17$); placebo ($n=19$)	Change in BASDAI, BASFI, BASMI at week 12	Positive trends for apremilast
Bisphosphonate, pamidronate	Maksymowych *et al.* [27]	Randomized, double-blind, dose-response study	48	AS	60 mg pamidornate monthly for 6 months; 10 mg pamidornate monthly for 6 months	BASDAI	BASDAI decrease at 6 months (% of patients); 2.2 (34%) BASDAI decrease in 60-mg group; 0.9 (15%) BASDAI decrease in 10-mg group
	Santra *et al.* [28]	Open prospective trial	35	AS	60 mg pamidronate monthly (single arm)	ASAS-20; BASDAI-50	Number of patients who reached ASAS-20/BASDAI50 at 6 months; 22/26 ASAS-20 (85%); 20/26 BASDAI-50 (77%)
Rituximab	Song *et al.* [29••]	Open-label phase I	20	AS	TNF-inhibitor naive ($n=10$); TNF-inhibitor failure ($n=10$)	ASAS-40 at week 24	Percentage of patients who reached ASAS-40 at week 24; TNF-inhibitor naive: 50% (95% CI 22.3–77.8%);TNF-inhibitor failure: 30%
	Case reports [30–33]	Case report	11	6 AS, 2 uSpA; 3 PsA	Rituximab 500 and 1000 mg	Clinical endpoints	4 patients improved
Secukinumab	Baeten *et al.* [34••]	Double-blind, placebo-controlled proof of concept study	30	AS	2 × 10 mg/kg Seaukinumab; saline placebo infusion	ASAS-20 at week 6	Number of patients who reached ASAS-20 at week 6; 14/23 verum-treated patients; 1/6 placebo treated patients
Sulfasalazine	Braun *et al.* [35••]	Randomized, double-blind study for 16-weeks	566	AS	Etanercept 50 mg once weekly s.c. ($n=379$); sulfasalazine titrated to a maximum of 3 g/day ($n=187$)	ASAS-20 at week 16	Percentage of patients at week 16; ASAS-20: 75.9% in etanercept group; ASAS-20: 52.9% in sulfasalazine group
	Song *et al.* [36•,37]	Randomized, open label study for 48-weeks	76	Early axial SpA	Etanercept 25 mg twice weekly s.c. ($n=40$); sulfasalazine 2–3 g/day ($n=36$)	Change of active; inflammatory lesions in the SIJ and spine as detected; by MRI at 48 weeks	MRI scoring SIJ: etanercept group: reduction from 7.7 to 2.0 at week 48; sulfasalazine group: reduction from 5.4 to 3.5 at week 48; MRI scoring spine: etanercept group: reduction from 2.2 to 1.0 at week 48; sulfasalazine group: reduction from 1.4 to 1.3 at week 48
Thalidomide	Huang *et al.* [38]	12-month open study	30	AS	Thalidomide 200 mg/day	20% improvement in 4 of 7 indices (see text)	Number of patients who improved by 20%: 21/26
	Wei *et al.* [39]	6-month open study	13	3 juvenile As; 5 As; 4 As with peripheral arthritis; 1 PsA with axial involvement	Thalidomide 200 mg/day	ASAS-40 at week24; ASAS-20 at week 24	Number of patients at week 24; 4/8 patients (ASAS-40); 8/8 patients (ASAS-20)
Tocilizumab	Dudler *et al.* [40•]	Case series	18	9 AS; 6 uSpA; 3 PsA	Tocilizumab 8 mg/kg every 4 weeks	Clinical endpoints	No clinical benefit for axial and peripheral involvement
	Del Castillo Pinol *et al.* [41]	Case series	5	AS	Tocilizumab 8 mg/kg every 4 weeks	Clinical endpoints	1 patient had clinical benefit
	Case reports [41–43]	Case report	4	AS	Tocilizumab 8 mg over 2–4 weeks have been described	Clinical endpoints	Patients improved (BASDAI and/or ASDAS), no change in MRI inflammation

AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, ; BASMI, ; PsA, psoriatic arthritis; s.c., subcutaneously; SIJ, sacroiliac joints; SpA, Axial spondyloarthritis; uSpA, undifferentiated spondyloarthritis.

Συμπεράσματα III

CURRENT OPINION

Treatment of ankylosing spondylitis in patients refractory to TNF-inhibition: are there alternatives ?

Uta Kiltz, Frank Heldmann, Xenofon Baraliakos, and Juergen Braun

KEY POINTS

- For treatment of ankylosing spondylitis (AS) and axial spondyloarthritis, alternative strategies other than tumor necrosis factor (TNF) blockers are needed.
- Promising results have been shown for interleukin (IL)-17 blockade and apremilast. (PDE4-inhibitor)
- Anti-B-cell therapy might be beneficial in TNF-inhibitor naive patients with AS.
- Inhibition of IL-1 and IL-6 and inhibition of T-cell costimulation has been shown to be ineffective in AS.
- Outside biologicals, therapy with bisphosphonates, sulfasalazine and thalidomide might be benficial in selected cases.