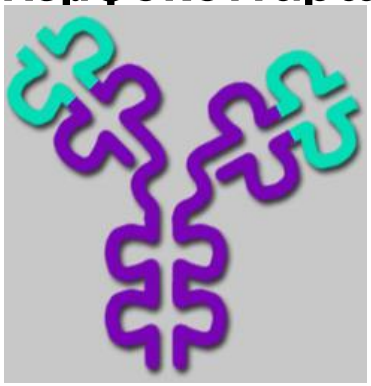
Rituximab (Mabthera) στην θεραπεία της Ρευματοειδούς Αρθρίτιδας

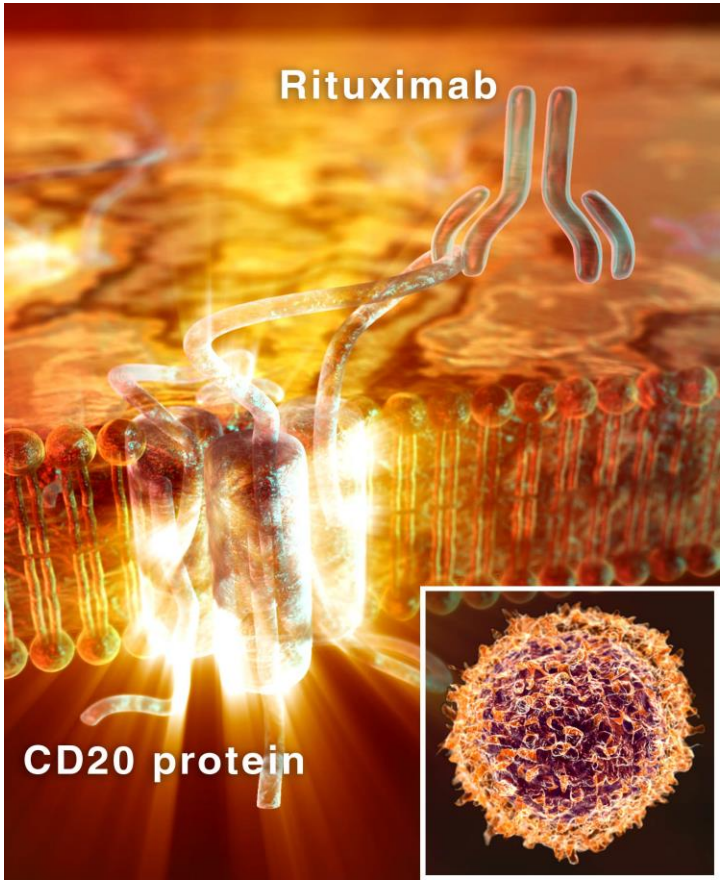
Βιδαλάκη Βαρβάρα
Ρευματολόγος
τ.αναπλ.Διευθύντρια
ΠΓΝΑ Γ.Γεννηματάς
Λαζαράκη 25 Γλυφάδα

Rituximab: ένα πρωτοποριακό μόριο

Rituximab

Ένα χιμαιρικό μονοκλωνικό αντίσωμα έναντι του CD20 υποδοχέα των Β-λεμφοκυττάρων

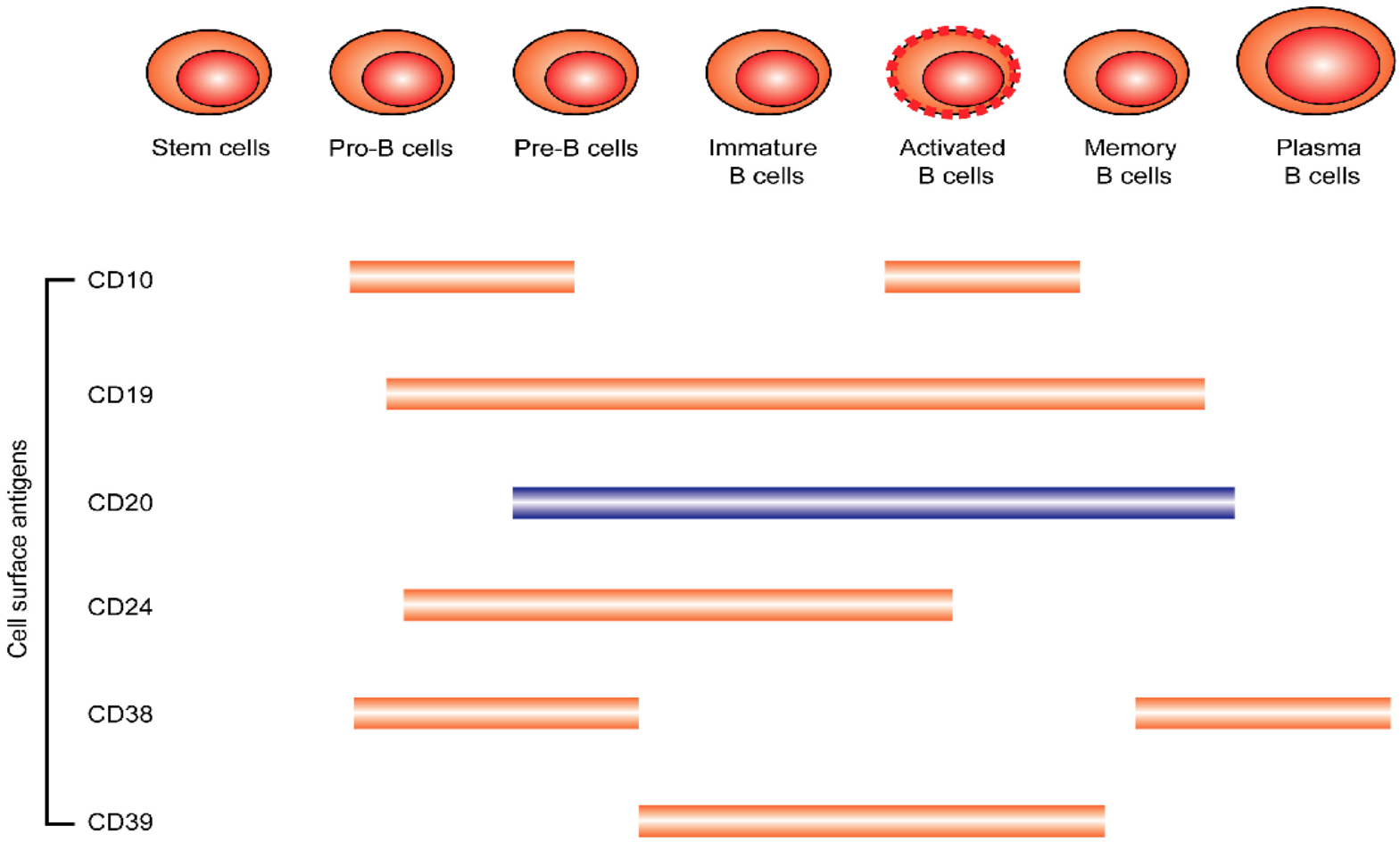




CD20 είναι μια φωσφορυλιωμένη πρωτεΐνη (33–37 kDa) στην επιφάνεια των Β-λεμφοκυττάρων
Εκφράζεται σε συγκεκριμένους πληθυσμούς

Shaw et al, 2003; Silverman & Weisman, 2003

Οντογένεση των β-λεμφοκυττάρων



Roitt et al, 2002; Sell & Max, 2001; Silverman & Weisman, 2003

Rituximab

Δεσμεύεται στο CD20 και καταστρέφει τα Β κύτταρα

με τρεις μηχανισμούς:

- **Εξαρτώμενη από το συμπλήρωμα κυτταροτοξικότητα** (CDC)
- **Αντισωματο- εξαρτώμενη κυτταροτοξικότητα** (ADCC) και
- **Επαγωγή της Απόπτωσης**

Panayi et al Rheumatology 2005; 44 (suppl 2) ; ii18-ii20

Eisenberg et al Clin.Immunol 2005 117 ; 207-213

Rituximab

Το 2006 το **Rituximab μαζί με μεθοτρεξάτη**

πήρε ένδειξη για την θεραπεία

της μέτριας έως σοβαρής ενεργού ΡΑ σε ενήλικες ασθενείς οι οποίοι είχαν ανεπαρκή απάντηση

σε ένα ή περισσότερους αντι-TNF παράγοντες.

Η δόση του είναι

δύο εγχύσεις των 1000 mg

χορηγούμενες την 1η και την 15η ημέρα.

A Randomised Evaluation oF Long-term Efficacy of rituXimab in RA (REFLEX)

ARTHRITIS & RHEUMATISM
Vol. 54, No. 9, September 2006, pp 2793–2806
DOI 10.1002/art.22025

Dr Stanley Cohen
University of Texas Southwestern Medical School, Dallas

Rituximab for Rheumatoid Arthritis Refractory to Anti–Tumor Necrosis Factor Therapy

Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Trial Evaluating Primary Efficacy and Safety at Twenty-Four Weeks

Stanley B. Cohen,[1] Paul Emery,[2] Maria W. Gr
Mark C. Genovese,[6] Edward C. Keystone,[7]
Matthew W. Cravets,[10] Eva W. Hessey,[1]
for the REFI

520 ασθενείς/ TNF-IR

Βαρειά PA- DAS28=6,9

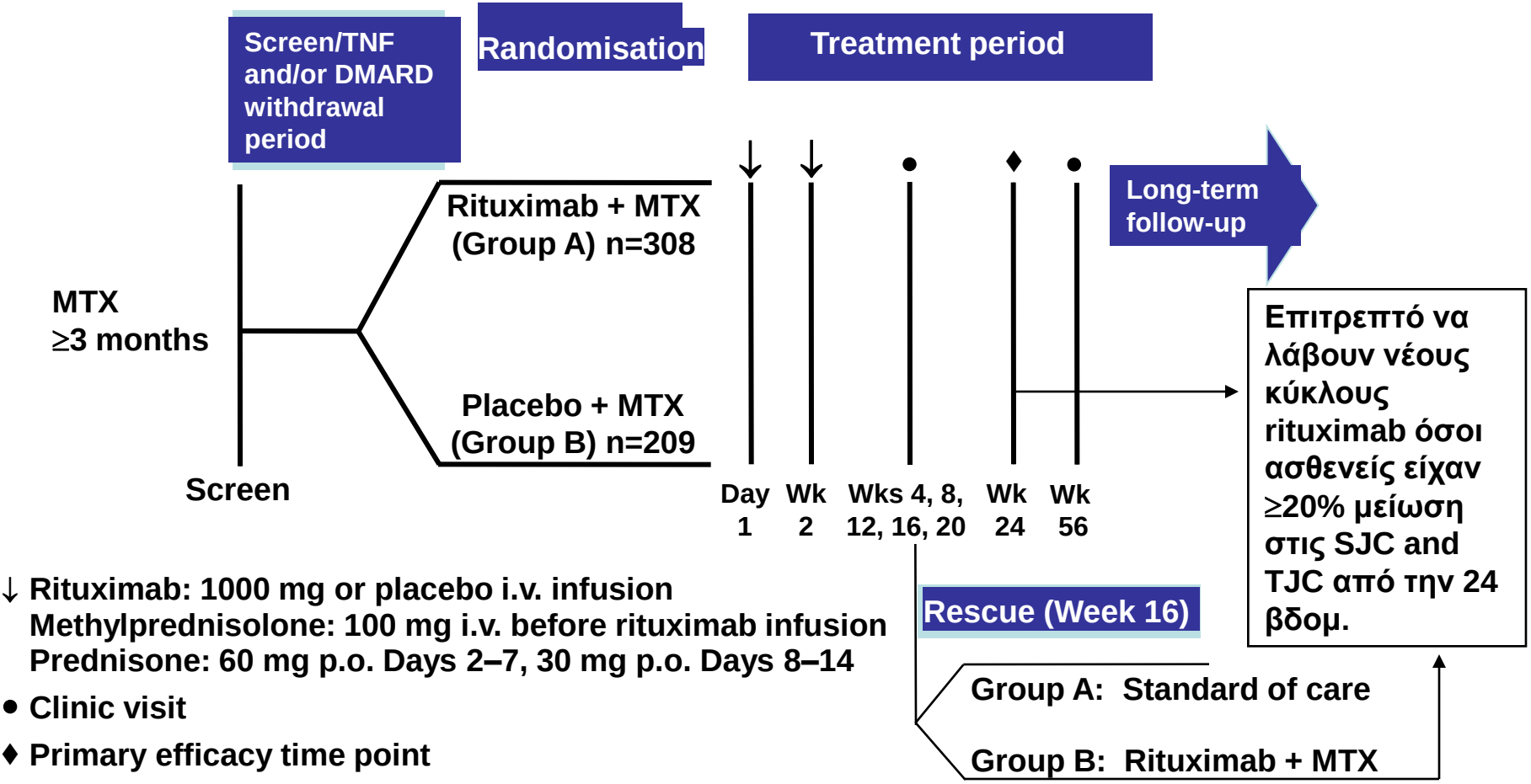
<u>Πρωτογενής στόχος: ACR20 την 24 βδομ.</u>

Δευτερογενής στόχος:

P.R.O=HAQ-DI, SF36, FACIT-F,

ACR50, ACR70,EULAR, DAS 28

REFLEX : Ασθενείς με PA και αντι-TNF IR

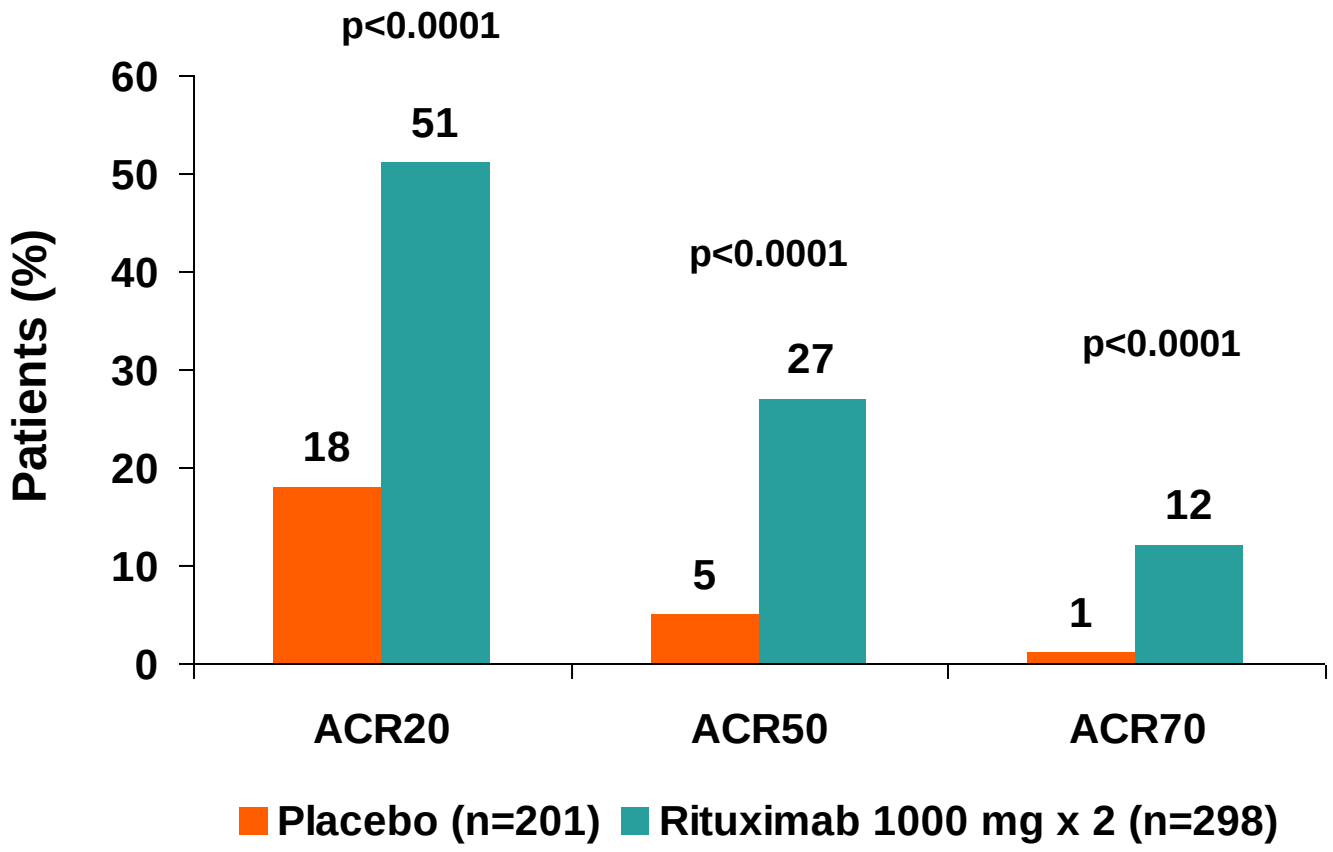


↓ Rituximab: 1000 mg or placebo i.v. infusion
Methylprednisolone: 100 mg i.v. before rituximab infusion
Prednisone: 60 mg p.o. Days 2–7, 30 mg p.o. Days 8–14

● Clinic visit

♦ Primary efficacy time point

Μελέτη REFLEX
Περισσότεροι ασθενείς στο Rituximab παρουσίασαν βελτίωση κατά ACR την εβδ 24



ARD Online First, published on May 3, 2010 as 10.1136/ard.2009.119222

Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate

Stanley B Cohen,[1] Edward Keystone,[2] Mark C Genovese,[3] Paul Emery,[4] Charles Peterfy,[5] Paul Peter Tak,[6] Matt Cravets,[7] Tim Shaw,[8] David Hagerty[7]

[1]Metroplex Clinical Research Center, Dallas, Texas, USA
[2]University of Toronto, Toronto, Canada
[3]Stanford University, Palo Alto, California, USA
[4]Leeds General Infirmary, Leeds, UK
[5]Synarc, San Francisco, California, USA
[6]AMC/University of Amsterdam, Amsterdam, The Netherlands
[7]Biogen Idec, Inc, San Diego, California, USA
[8]Roche Products Ltd, Welwyn Garden City, UK

Correspondence to
Dr S B Cohen, Metroplex Clinical Research Center, Dallas, Texas, USA;
scohen@arthdocs.com

Accepted 19 November 2009

ABSTRACT

Background Rituximab inhibited structural damage at 1 year in patients with rheumatoid arthritis (RA) who had had a previous inadequate response to tumour necrosis factor (TNF) inhibitors.

Objective To assess structural damage progression through 2 years.

Methods Intention-to-treat patients with one post-baseline radiograph (rituximab n=281; placebo n=187) received background methotrexate (MTX) and were randomised to rituximab (2×1000 mg infusions, 2 weeks apart) or placebo; patients were eligible for rituximab re-treatment every 6 months. By week 104, 82% of the placebo population had received ≥1 dose of rituximab. Radiographic end points included the change in total

87% who had no progression of joint damage at 1 year remained non-progressive at 2 years.

Conclusions Rituximab plus MTX demonstrated

REFLEX have been described previously.[9] Briefly, patients were included if they had active RA despite treatment with methotrexate (MTX) ≥10 mg/week and had experienced an inadequate response (lack of efficacy or intolerance) to at least one TNF inhibitor.

The study was performed in accordance with the Declaration of Helsinki. All participating sites received approval from their governing institutional review board (or equivalent) and all patients provided written informed consent.

Study protocol

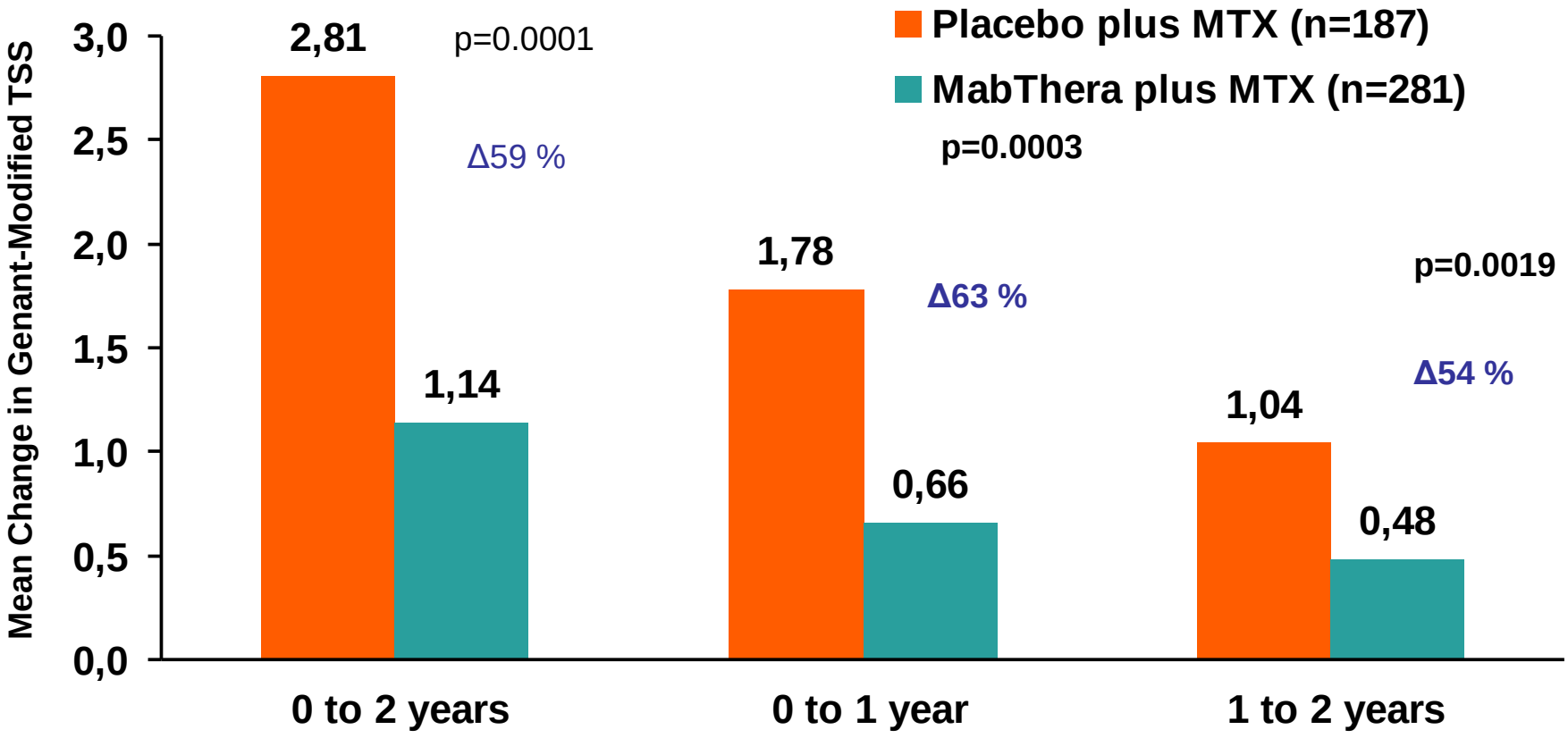
REFLEX was a randomised, double-blind, placebo-controlled, phase III study with an option for further treatment courses under a separate extension

corticosteroid treatment, consisting of intravenous methylprednisolone 100 mg before each infusion

Η πρώτη & μοναδική βιολογική θεραπεία με ακτινολογικά δεδομένα

σε ασθενείς με αποτυχία σε αντι-TNF

REFLEX:
Αναστολή εξέλιξης ακτινολογικών βλαβών



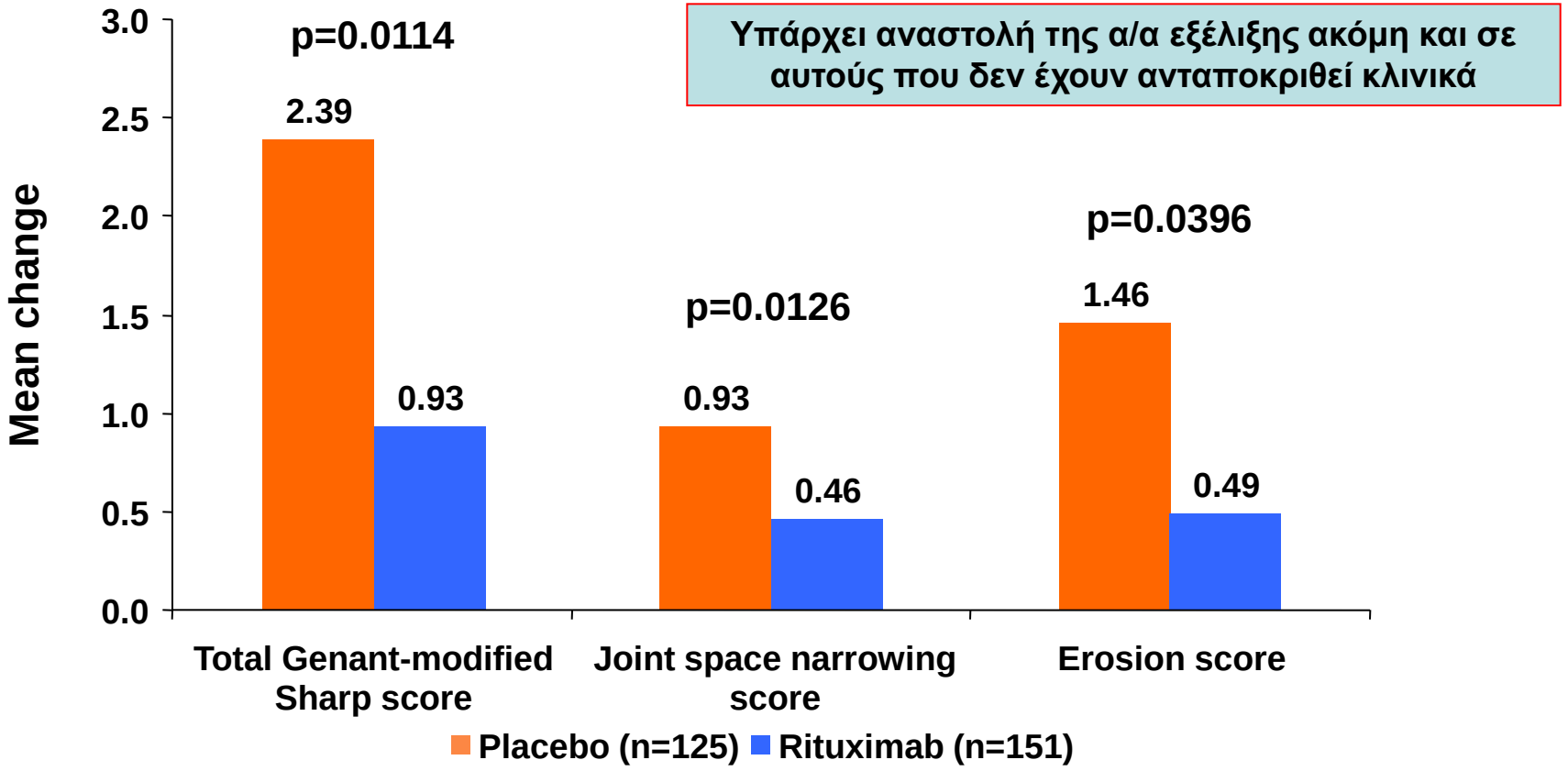
MTX=methotrexate; TSS=Total Sharp Score

Primary analysis: radiographs outside time window included, linear extrapolation from Week 24 or 56 for missing values

Poster #368

REFLEX study: σημαντική αναστολή ανεξάρτητα κλινικής ανταπόκρισης

Στους μη ανταποκριθέντες κατά ACR20 την εβδ. 24



Observed data were used to define ACR20 response

(Keystone et al, 2007)

Χορηγείται
σε επαναλαμβανόμενους κύκλους

ARTHRITIS & RHEUMATISM
Vol. 56, No. 12, December 2007, pp 3896–3908
DOI 10.1002/art.23059

Safety and Efficacy of Additional Courses of Rituximab in Patients With Active Rheumatoid Arthritis

An Open-Label Extension Analysis

Edward Keystone,[1] Roy Fleischmann,[2] Paul Emery,[3] Daniel E. Furst,[4] Ronald van Vollenhoven,[5] Joan Bathon,[6] Maxime Dougados,[7] Andrew Baldassare,[8] Gianfranco Ferraccioli,[9] Andrew Chubick,[10] James Udell,[11] Matthew W. Cravets,[12] Sunil Agarwal,[13] Simon Cooper,[14] and Fabio Magrini[14]

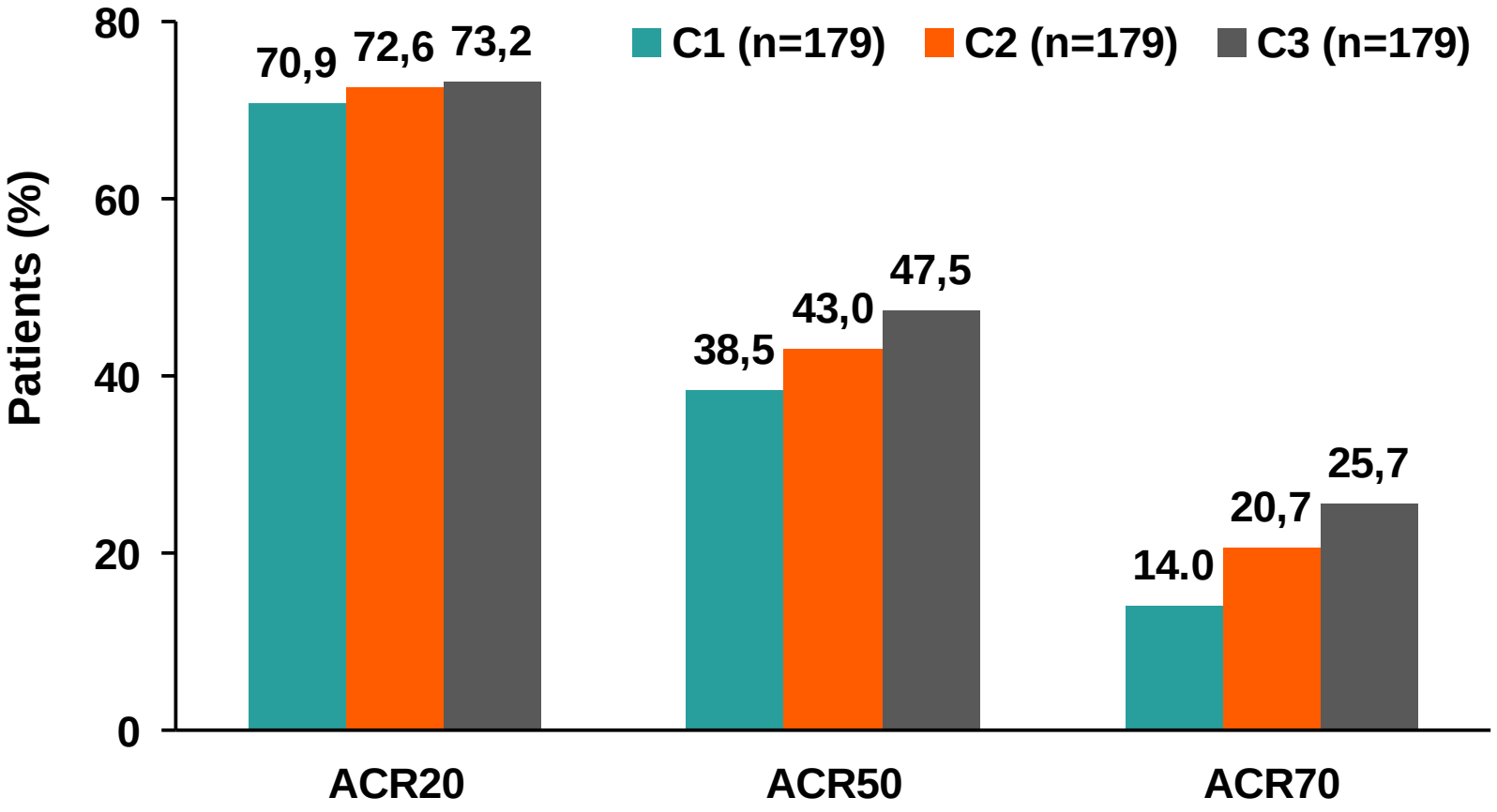
Objective. **To determine the safety and efficacy of additional courses of rituximab in patients with rheumatoid arthritis (RA).**

Methods. **An open-label extension analysis of RA patients previously treated with rituximab was conducted. Patients who had participated in any of 3 double-blind trials were eligible for additional courses (2 infusions of 1,000 mg given 2 weeks apart) if they exhibited a swollen joint count and tender joint count of ≥8 with ≥16 weeks elapsing after the previous course. Safety was assessed in patients receiving all or a portion of a rituximab course. Efficacy was assessed 24 weeks after each course, using the American College of Rheumatology 20% criteria for improvement (ACR20), ACR50, ACR70, European League Against Rheumatism (EULAR) response criteria, Disease Activity Score in 28 joints, the disability index of the Health Assessment Questionnaire, and Short Form 36 scores, stratified according to prior tumor necrosis factor (TNF) inhibi**

ClinicalTrials.gov identifier: NCT00074438/NCT00468377.
Supported by Hoffman-LaRoche, Biogen Idec, Inc., and Genentech, Inc.
[1]Edward Keystone, MD, FRCP: Mount Sinai Hospital, and University of Toronto, Toronto, Ontario, Canada; [2]Roy Fleischmann, MD: University of Texas Southwestern Medical Center, Dallas; [3]Paul Emery, MD, FRCP: Leeds Teaching Hospital Trust, Leeds, UK; [4]Daniel E. Furst, MD: University of California, Los Angeles; [5]Ronald van Vollenhoven, MD, PhD: Karolinska Hospital and Institute, Stockholm, Sweden; [6]Joan Bathon, MD: Johns Hopkins School of Medicine, Baltimore, Maryland; [7]Maxime Dougados, MD: René Descartes University, Paris, France; [8]Andrew Baldassare, MD: Arthritis Consultants, and St. Louis University, St. Louis, Missouri; [9]Gianfranco Ferraccioli, MD: Catholic University, Rome, Italy; [10]Andrew Chubick, MD: Baylor University Medical Center, Dallas, Texas; [11]James Udell, MD: Arthri-

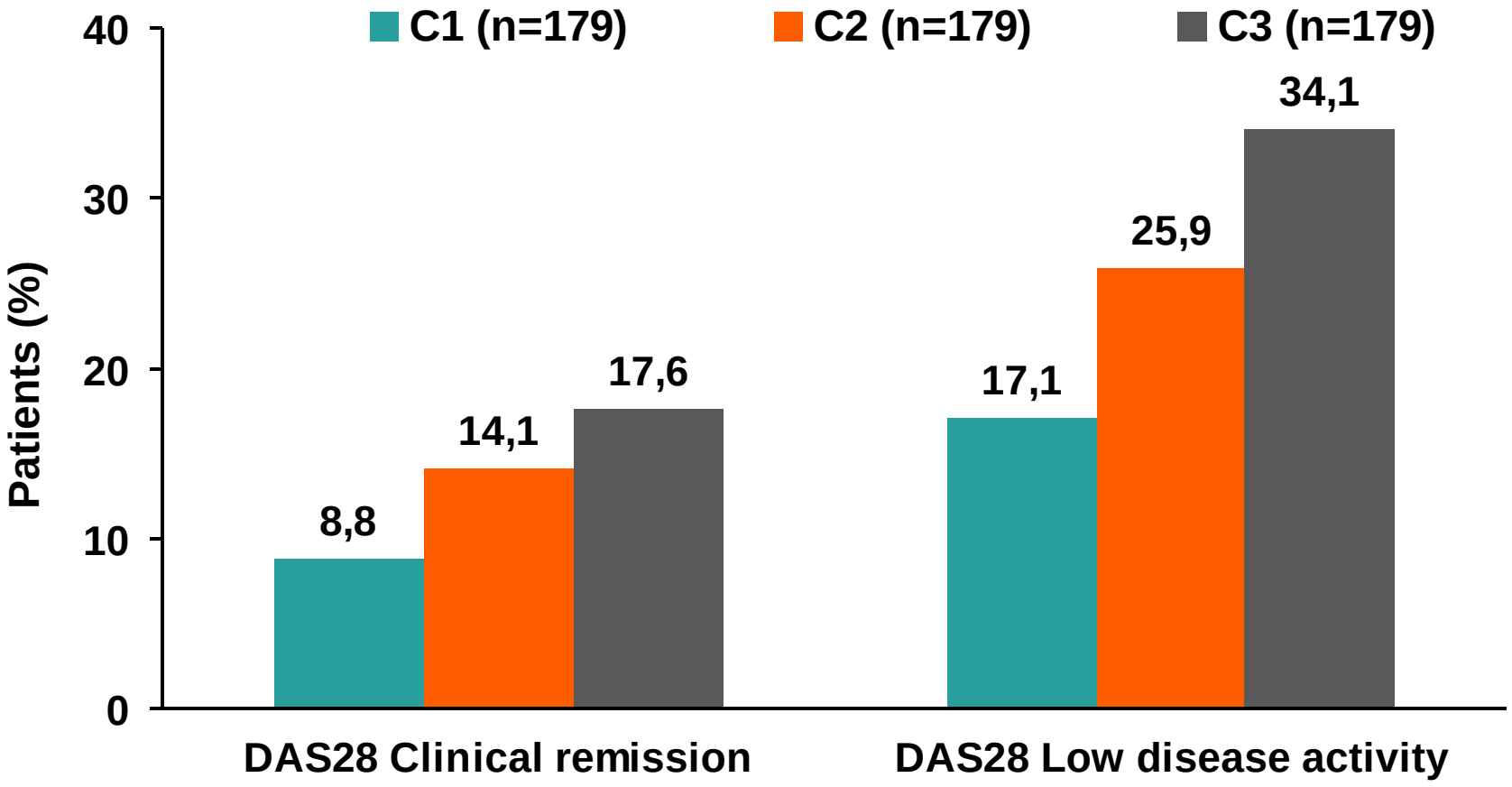
REFLEX TNF-IR: ACR κύκλοι 1-3

Ασθενείς που θεραπεύονται με επαναλαμβανόμενους κύκλους Rituximab παρουσιάζουν διατηρήσιμη και καλύτερη αποτελεσματικότητα



Poster #367

REFLEX TNF-IR: DAS28 χαμηλή δραστηριότητα & ύφεση κύκλοι 1-3
Ασθενείς που θεραπεύονται με επαναλαμβανόμενους κύκλους Rituximab παρουσιάζουν καλύτερη και διατηρήσιμη αποτελεσματικότητα



Clinical remission: DAS28 <2.6
Low disease activity: DAS28 ≤3.2

Poster #367

Efficacy and Safety of Retreatment in Patients with Rheumatoid Arthritis with Previous Inadequate Response to Tumor Necrosis Factor Inhibitors: Results from the SUNRISE Trial

PHILIP J. MEASE, STANLEY COHEN, NORMAN B. GAYLIS, ANDREW CHUBICK, ALAN T. KAELL, MARIA GREENWALD, SUNIL AGARWAL, MING YIN, and ARIELLA KELMAN

ABSTRACT. ***Objective.*** To assess the efficacy and safety of 1 versus 2 courses of rituximab over 48 weeks in patients with rheumatoid arthritis (RA).

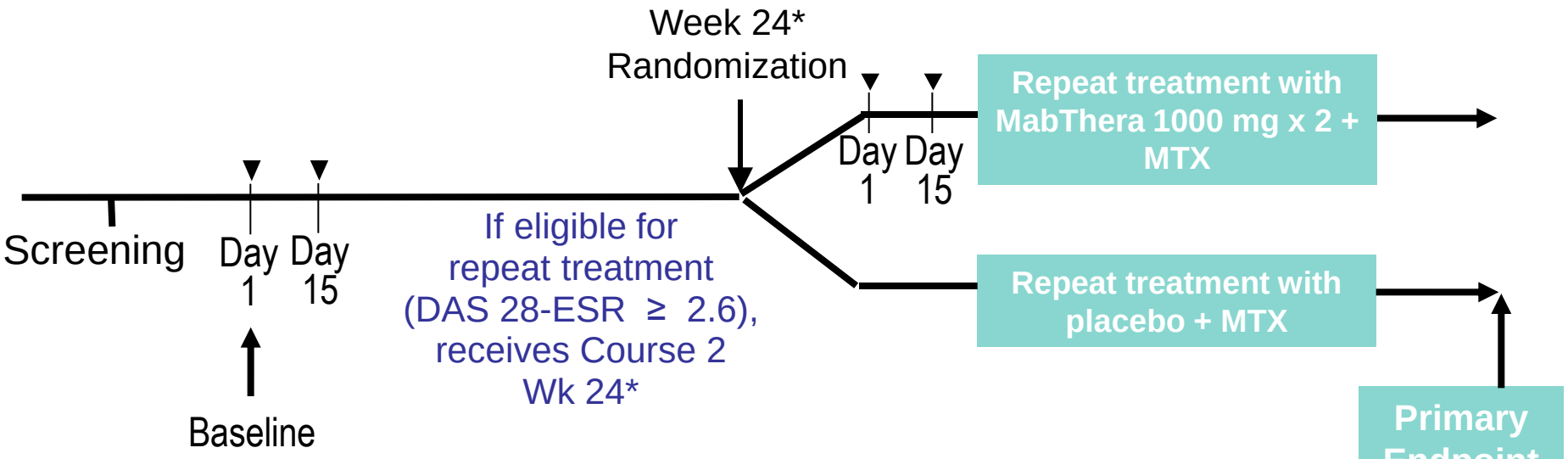
Methods. Adult patients taking methotrexate with a previous inadequate response to ≥ 1 tumor necrosis factor inhibitor received 1 course of open-label rituximab (2 × 1000 mg IV) at baseline. From Week 24, patients were randomized to receive an additional course of retreatment with rituximab or placebo. Efficacy responses at Week 48 relative to baseline were assessed.

Results. Of 559 patients who received the open-label first course of rituximab, 475 patients were randomized to a second course (rituximab retreatment: n = 318, placebo retreatment: n = 157). Relative to baseline, patients who took rituximab during retreatment had significantly improved efficacy at Week 48 compared to patients who took a placebo during retreatment [American College of Rheumatology (ACR20) criteria, 54% vs 45%, p = 0.02; change in Disease Activity Score-28 mean –1.9 vs –1.5, p = 0.006]. Differences in efficacy between groups were first observed following Weeks 28-32. Worsening of most components of the ACR core set occurred in the placebo-retreated patients with relative maintenance of these measures in rituximab-retreated patients. Randomized patients who had achieved week 24 ACR responses following the first course had greater odds of losing response if retreated with placebo (odds ratios for ACR20, ACR50, ACR70: 2.09, 2.03, and 4.09, respectively). Following retreatment, the proportion of patients experiencing any adverse events (AE), serious AE, infections, and serious infections were comparable between the rituximab and placebo retreatment groups.

Conclusion. Two courses of rituximab about 6 months apart resulted in improved and sustained efficacy at 1 year, compared with 1 course, with a similar safety profile. (First Release March 1 2010; J Rheumatol 2010;37:917–27; doi:10.3899/jrheum.090442)

Key Indexing Terms:
RITUXIMAB RHEUMATOID ARTHRITIS METHOTREXATE RETREATMENT

SUNRISE: σχεδιασμός



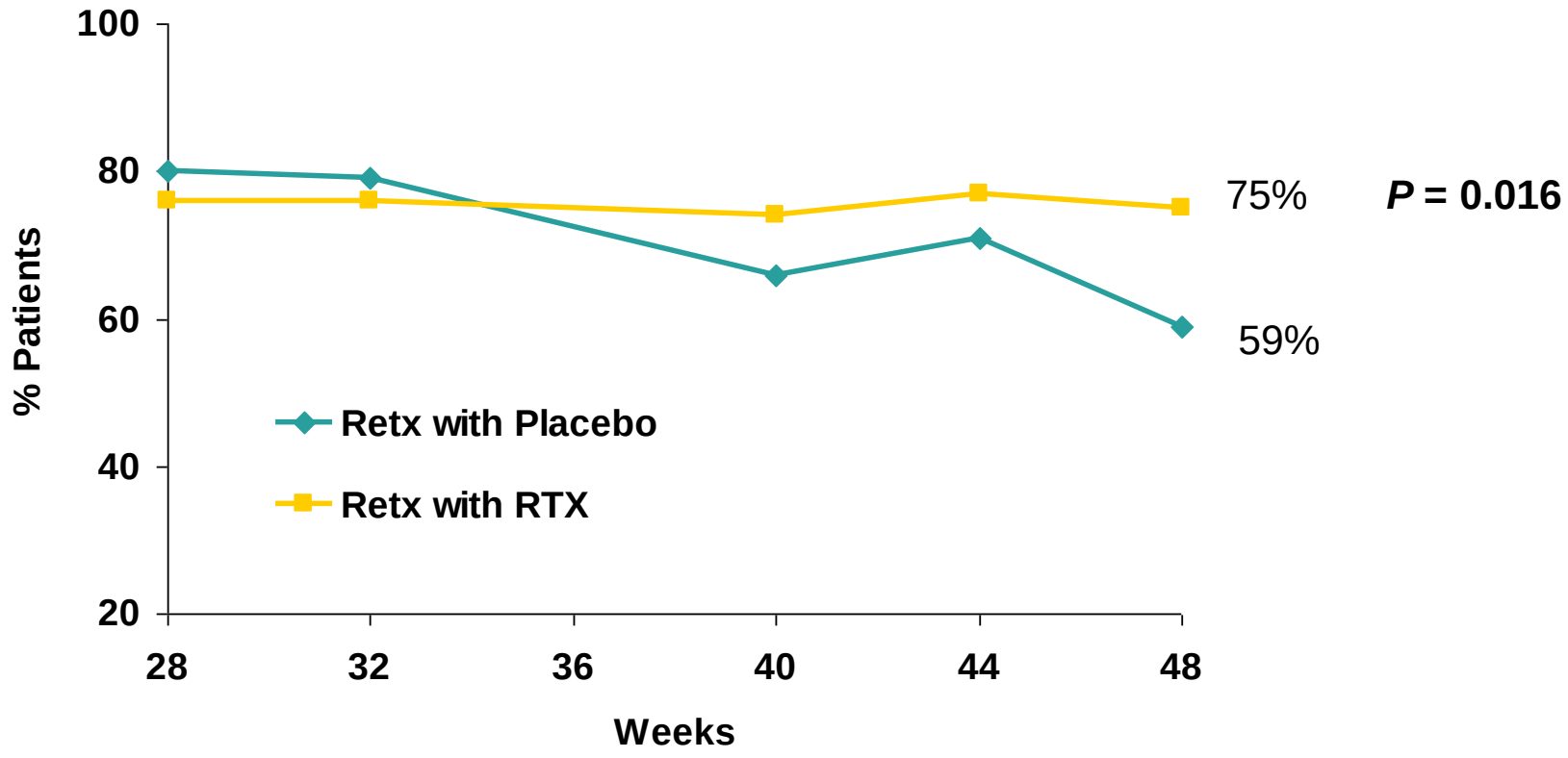
▼ MabThera 1000 mg

Methylprednisone 100 mg IV prior to each infusion; stable MTX all patients

***Randomization/repeat treatment allowed up to Week 40 with primary endpoint at Week 48**

SUNRISE:
Μεγαλύτερο ποσοστό ασθενών διατήρησε την ACR20 απάντηση κατά την διάρκεια του χρόνου στην ομάδα που πήρε δεύτερο κύκλο.

ITT ACR20 Responder Subset at Week 24, n=218



P-value based on adjusted mean for baseline rheumatoid factor status and ≥20% Improvement in both SJC and TJC at Week 24

FRI0196 EFFICACY OF RITUXIMAB RETREATMENT IN CLINICAL PRACTICE: DATA FROM THE CERERRA COLLABORATION EULAR 2010

K. Chatzidionysiou [1,*], R. F. van Vollenhoven [1], E. Nasonov [2], G. Lukina [2], M. L. Hetland [3], U. Tarp [3], C. Gabay [4], P. L. C. M. van Riel [5], D. C. Nordström [6], J. Gomez-Reino [7], K. Pavelka [8], M. Tomsic [9], E. Lie [10], T. K. Kvien [10]

[1]Karolinska Institute, Stockholm, Sweden, [2]Inst of Rheumatology, Moscow, Russian Federation, [3]DANBIO, Hvidovre/Glostrup Univ Hosp, Copenhagen, Denmark, [4]Univ Hosp , Geneva, Switzerland, [5]Radboud Univ, Nijmegen, Netherlands, [6]ROB-FIN Univ Hosp, Helsinki, Finland, [7]Univ De Santiago, Coruna, Spain, [8]Charles Univ, Prague, Czech Republic, [9]Univ Med Center, Ljubljana, Slovenia, [10]Diakonhjemmet, Oslo, Norway

CERRERA Trial

10 Ευρωπαϊκά Registries-2048 ασθενείς με PA που άρχισαν Rituximab.

Στοιχεία των ασθενών στους 3,6,9,12 μήνες

Ασθενείς που έλαβαν και νέο κύκλο στην διάρκεια των 12 μηνών πέτυχαν σημαντικά καλύτερο DAS28

στους 12 μήνες από ότι στους 6μήνες.

	DAS28 improvement at 6 months(n=810)			DAS28 improvement at 12 months (retreated patients only) (n=124)		
	Positive	Negative	p	Positive	Negative	p
RF	2.0±1.5	1.7±1.5	0.02	2.3±1.4	1.8±1.2	NS
ACPA	2.1±1.4	1.5±1.5	0.006	2.6±1.3	2.1±1.3	NS
DOUBLE	2.1±1.4	1.4±1.5	0.009	2.8±1.2	1.3±0.7	0.004

SUNRISE μελέτη:Δεδομένα ασφάλειας

Table 3. Summary of safety events during randomized retreatment period. Data are number of patients (%).

Safety Events	Retreatment with Placebo (n = 155)	Retreatment with Rituximab (n = 320)
Adverse events	119 (77)	226 (71)
Serious adverse events	11 (7)	22 (7)
Infections	59 (38)	120 (38)
Serious infections	3 (2)	7 (2)
Adverse events leading to withdrawal	7 (4)	7 (2)
Deaths*	1 (0.6)	1 (0.3)

* One additional death in rituximab retreatment group after the Week 48 cutoff date.

Το προφίλ ασφάλειας δεν επηρεάζεται από την επανάληψη στο 6μηνο.

Πότε να χορηγήσουμε
τον επόμενο κύκλο;

Retreatment with rituximab based on a treatment to target approach provides better disease control

treatment to target

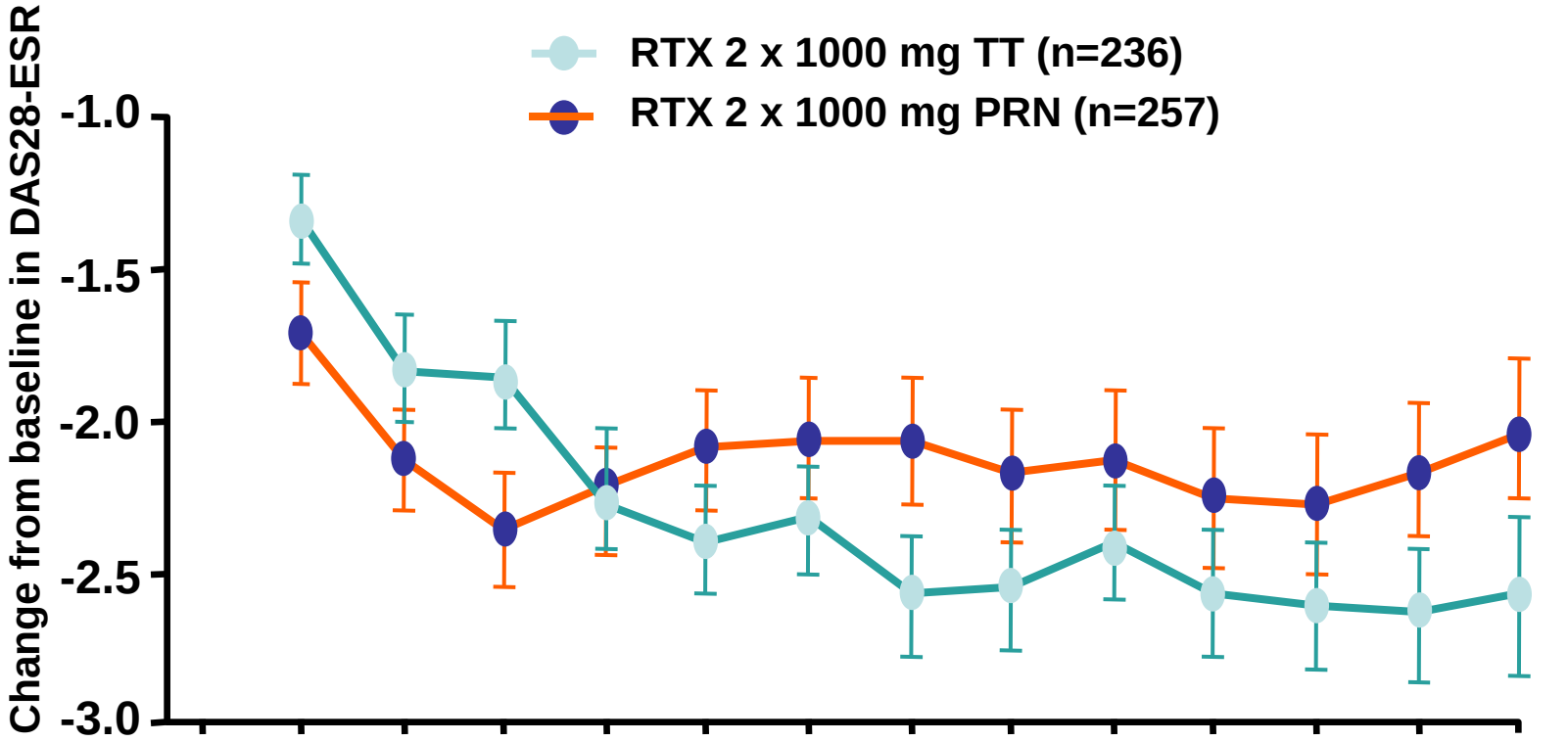
Ο ασθενής ελέγχεται την 24 βδομάδα μετά τον κύκλο θεραπείας και λαμβάνει νέο κύκλο εάν δεν είναι σε ύφεση (DAS28>/2,6)

P Emery, P Mease, A Rubbert-Roth, JR Curtis, G Muller-Ladner, N Gaylis, S Williams, H Tyrrell, M Reynard

treatment as needed

Ο ασθενής λαμβάνει κύκλο θεραπείας μετά την 16 βδομάδα κατά την κρίση του θεράποντος ιατρού και εφόσον έχει πάνω από 8 ευαίσθητες και 8 επώδυνες αρθρώσεις.

Στην θεραπεία με MabThera 2 x 1000 mg
η στρατηγική 'Treatment to target'
οδηγεί σε μεγαλύτερη βελτίωση του DAS28-TKE score στην πορεία του χρόνου
από την στρατηγική 'treatment as needed'



No. of pts:

	BL	8	16	24	32	40	48	56	64	72	80	88	96	104
RTX RTR	231	228	222	218	210	209	200	198	197	191	193	171	125
RTX PRN	226	245	234	223	217	220	209	201	202	195	190	187	185

FRI0202

Σε ασθενείς με PA
που απέτυχαν στον αντι-TNF
τι είναι καλύτερο να κάνουμε;

ARTHRITIS & RHEUMATISM
Vol. 56, No. 5, May 2007, pp 1417–1423
DOI 10.1002/art.22520

B Cell Depletion May Be More Effective Than Switching to an Alternative Anti–Tumor Necrosis Factor Agent in Rheumatoid Arthritis Patients With Inadequate Response to Anti–Tumor Necrosis Factor Agents

Axel Finckh,[1] Adrian Ciurea,[2] Laure Brulhart,[1] Diego Kyburz,[2] Burkhard Möller,[3] Silvia Dehler,[4] Sylvie Revaz,[5] Jean Dudler,[5] and Cem Gabay,[1] on behalf of the physicians of the Swiss Clinical Quality Management Program for Rheumatoid Arthritis

Objective. Patients with rheumatoid arthritis (RA) in whom the response to anti–tumor necrosis factor (anti-TNF) therapy is inadequate have several therape… anti-TN… with rit… tions ha… head comparisons are available. The aim of this study was to compare the effectiveness of RTX with that of an alternative anti-TNF agent in the management of pa- …se to … was …ement

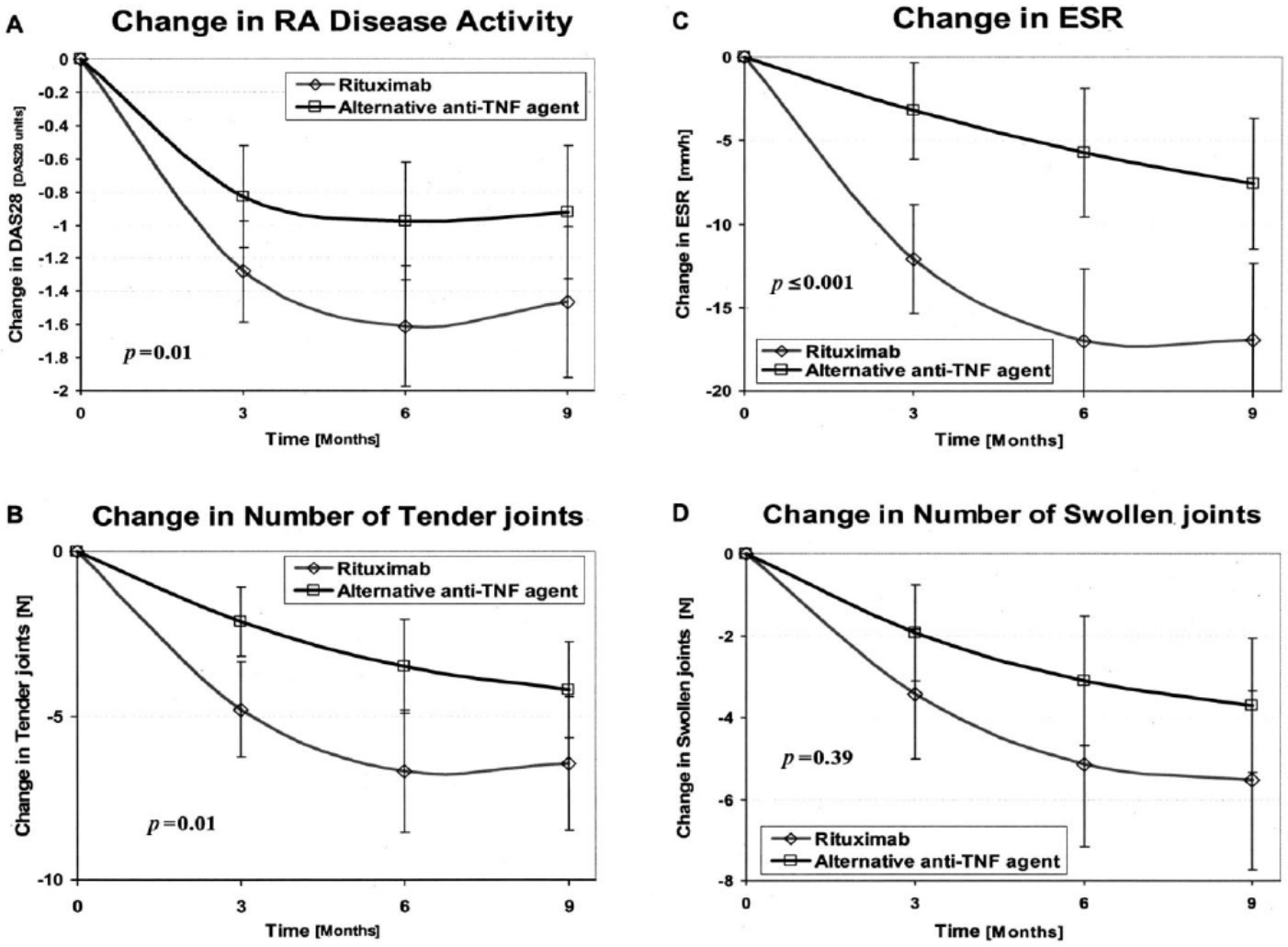
Είναι καλύτερα σε ασθενείς με PA

μετά την αποτυχία του πρώτου αντι-TNF

να χορηγήσουμε Rituximab

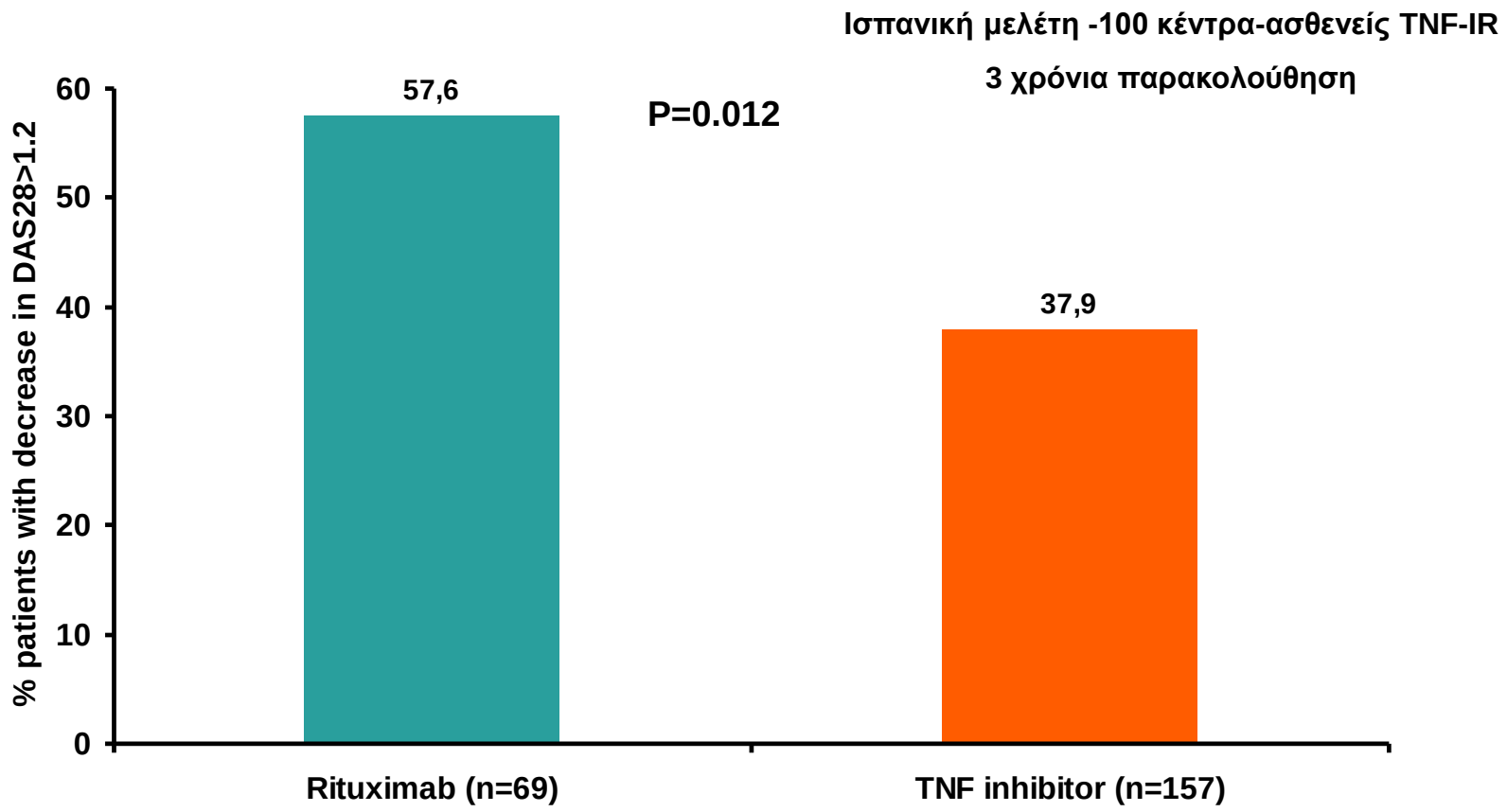
Σε ασθενείς με ανεπαρκή απάντηση σε αντι-TNF

η χορήγηση Rituximab είναι πιο αποτελεσματική από την εναλλαγή αντι-TNF



Finckh et al Arthritis Rheum.2007 V;56 No5 pp1417-1423

MIRAR: περισσότεροι ασθενείς υπό RTX είχαν μείωση DAS28>1.2 συγκριτικά με αυτούς υπό 2ο αTNF



Οι ασθενείς που λαμβάνουν Rituximab μετά την αποτυχία του αντι –TNF έχουν μεγαλύτερη πιθανότητα να εμφανίσουν μείωση του DAS28>1,2 από αυτούς που αντιμετωπίζονται με ένα άλλο αντι –TNF.

Gómez-Reino et al EULAR 2009 FRI0257

Μετά την αποτυχία στον αντι-TNF
ποια υποκατηγορία ασθενών με PA
θα ωφεληθεί από την αλλαγή σε Rituximab
αντί σε άλλο αντι-TNF;

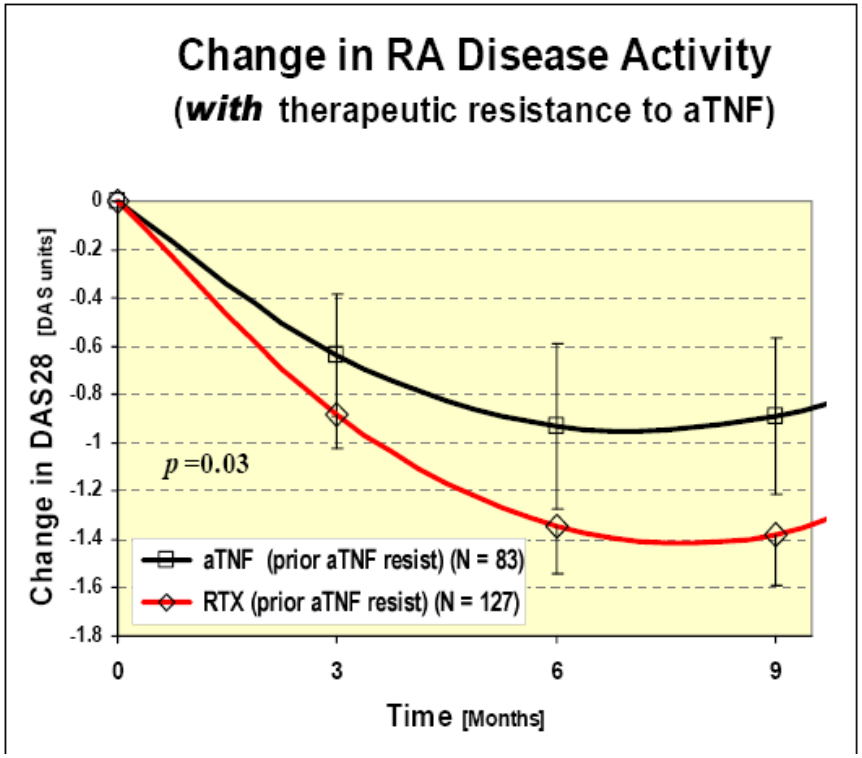
Which subgroup of rheumatoid arthritis patients benefits from switching to rituximab versus alternative anti-TNF agents after previous failure to anti-TNF agent?

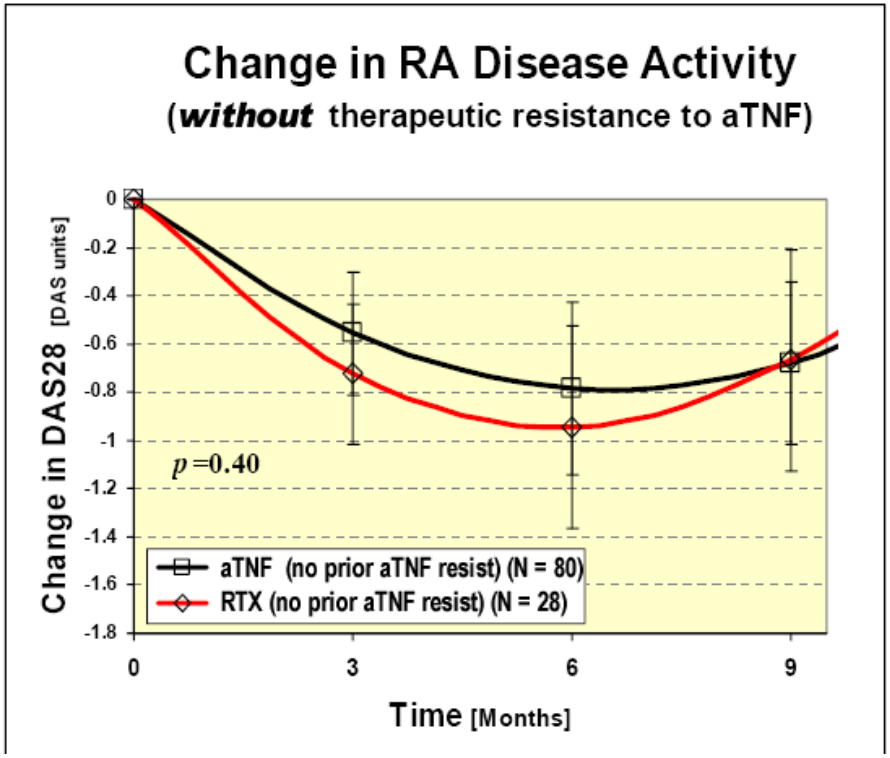
Axel Finckh, Adrian Ciurea, Laure Brulhart, Burkhard Möller, Ulrich A Walker, Delphine Courvoisier, Diego Kyburz, Jean Dudler and Cem Gabay

Ann
doi:1

Η βελτίωση του DAS28 είναι μεγαλύτερη

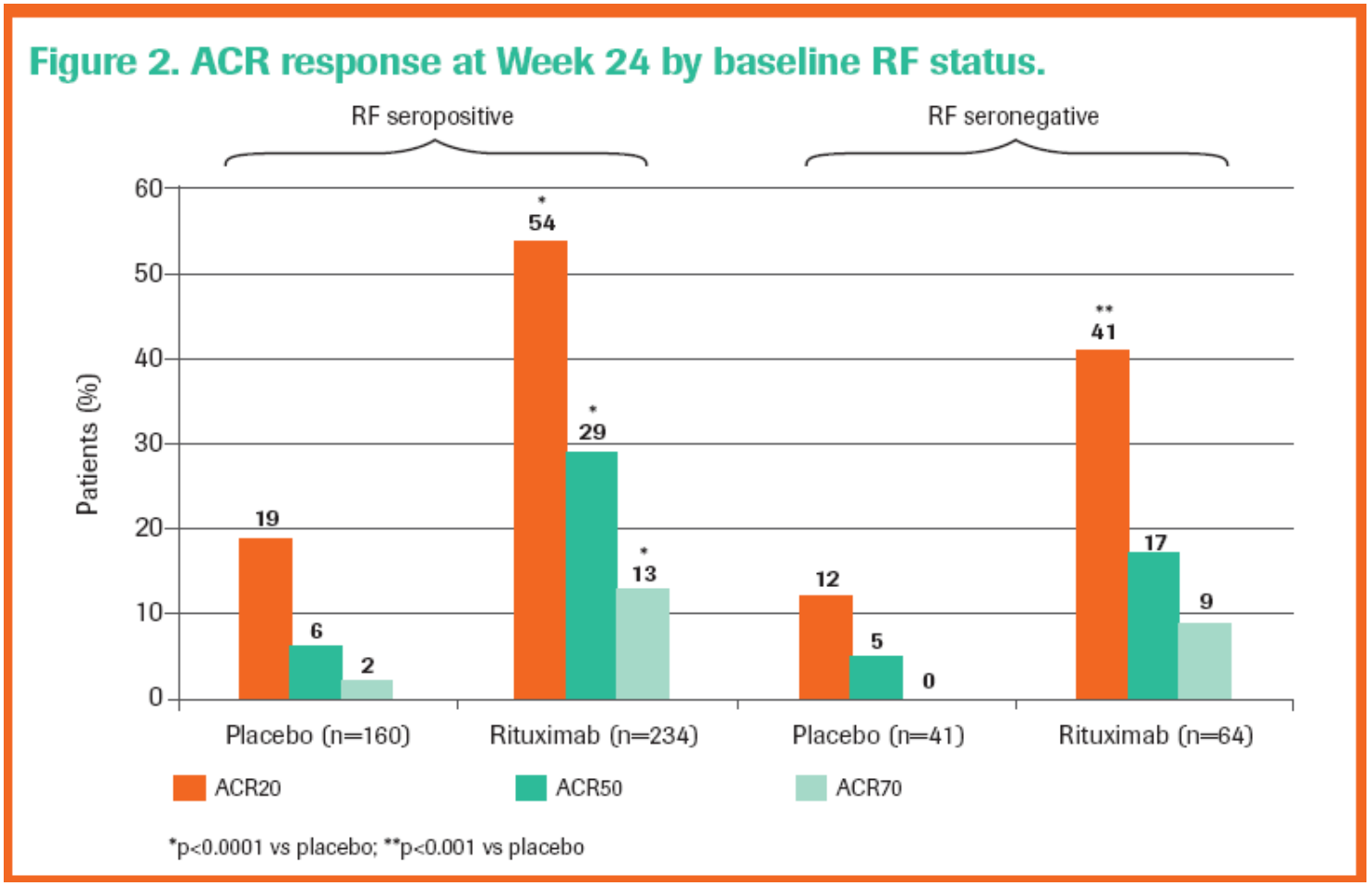
σε αυτούς που διέκοψαν τον αντι-TNF λόγω αναποτελεσματικότητας





Clinical Response Following the First Treatment Course with Rituximab: Effect of Baseline Autoantibody Status (RF, Anti-CCP)PP
Tak et al : FRI 0192, Eular 2009

Περισσότεροι οροθετικοί ασθενείς πετυχαίνουν ACR 20,50,70



FRI0196 EFFICACY OF RITUXIMAB RETREATMENT IN CLINICAL PRACTICE: DATA FROM THE CERERRA COLLABORATION EULAR 2010

K. Chatzidionysiou [1,*], R. F. van Vollenhoven [1], E. Nasonov [2], G. Lukina [2], M. L. Hetland [3], U. Tarp [3], C. Gabay [4], P. L. C. M. van Riel [5], D. C. Nordström [6], J. Gomez-Reino [7], K. Pavelka [8], M. Tomsic [9], E. Lie [10], T. K. Kvien [10]

[1]Karolinska Institute, Stockholm, Sweden, [2]Inst of Rheumatology, Moscow, Russian Federation, [3]DANBIO, Hvidovre/Glostrup Univ Hosp, Copenhagen, Denmark, [4]Univ Hosp , Geneva, Switzerland, [5]Radboud Univ, Nijmegen, Netherlands, [6]ROB-FIN Univ Hosp, Helsinki, Finland, [7]Univ De Santiago, Coruna, Spain, [8]Charles Univ, Prague, Czech Republic, [9]Univ M

CERRERA Trial

10 Ευρωπαϊκά Registries-2048 ασθενείς με PA που άρχισαν Rituximab.

Στοιχεία των ασθενών στους 3,6,9,12 μήνες

Οι οροθετικοί ασθενείς είχαν μεγαλύτερη βελτίωση του DAS28 στους 6 και στους 12 μήνες.

Είχαν καλύτερη EULAR απάντηση τον πρώτο χρόνο όσοι είχαν λάβει λιγότερο αριθμό βιολογικών θεραπειών πριν και είχαν χαμηλότερο HAG αρχικά.

	DAS28 improvement at 6 months(n=810)			DAS28 improvement at 12 months (retreated patients only) (n=124)		
	Positive	Negative	p	Positive	Negative	p
RF	2.0±1.5	1.7±1.5	0.02	2.3±1.4	1.8±1.2	NS
ACPA	2.1±1.4	1.5±1.5	0.006	2.6±1.3	2.1±1.3	NS
DOUBLE	2.1±1.4	1.4±1.5	0.009	2.8±1.2	1.3±0.7	0.004

1687

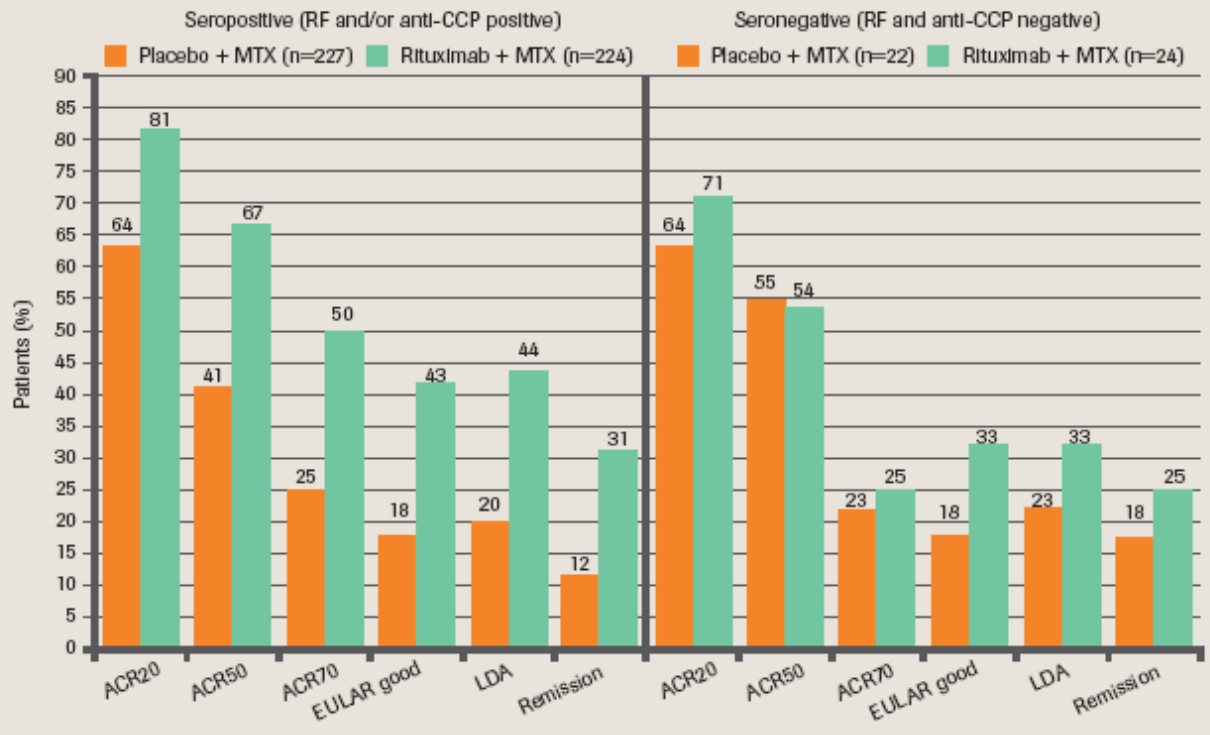
Effectiveness of rituximab + methotrexate in patients with early active rheumatoid arthritis and disease characteristics associated with poor outcomes (IMAGE subanalysis)

X Mariette[1], A Kivitz[2], J Isaacs[3], W Stohl[4], PP Tak[5], R Jones[6], A Jahreis[7], G Armstrong[8], T Shaw[9]

[1]Hôpital Bicêtre, Paris-Sud University, France; [2]Altoona Osteoporosis Center, Duncansville, PA, USA; [3]Newcastle University, Newcastle upon Tyne, UK; [4]USC, Los Angeles, CA, USA; [5]Academic Medical Centre/University of Amsterdam, Amsterdam, Netherlands; [6]Clinic for Rheumatic Diseases, Tuscaloosa, AL, USA; [7]Genentech Inc, South San Francisco, CA, USA; [8]Roche Products Ltd, Welwyn Garden City, UK

ACR 2009

Figure 5. EULAR and clinical responses at 52 weeks by autoantibody serotype subgroups



Τυχαιοποιημένη ελεγχόμενη με placebo
Ασθενείς με PA- naïve στην MTX

Η απάντηση στην θεραπεία με Rituximab

είναι εντονότερη στους οροθετικούς ασθενείς και σε αυτούς που είχαν υψηλότερο DAS28 και CRP στην αρχή

Είναι ασφαλές;

Longterm Safety of Patients Receiving Rituximab in Rheumatoid Arthritis Clinical Trials

RONALD F. van VOLLENHOVEN, PAUL EMERY, CLIFTON O. BINGHAM III, EDWARD C. KEYSTONE, ROY FLEISCHMANN, DANIEL E. FURST, KATHERINE MACEY, MARIANNE SWEETSER, ARIELLA KELMAN, and RAVI RAO

ABSTRACT. ***Objective.*** To evaluate the longterm safety of rituximab in clinical trials in patients with rheumatoid arthritis (RA).

Methods. Pooled analysis of safety data, including adverse events (AE) and infections, from patients treated with rituximab in combination with methotrexate in a global clinical trial program.

Results. A total of 2578 patients with RA received at least 1 course of rituximab. Safety analyses were based on 5013 patient-years of rituximab exposure. The most frequent AE was infusion-related reactions (25% of patients during the first infusion of Course 1). Less than 1% of infusion-related reactions were considered serious. Rates of AE and serious AE (SAE; 17.85 events/100 patient-yrs, 95% CI 16.72, 19.06) were stable following each course. The overall serious infection rate was 4.31/100 patient-years (95% CI 3.77, 4.92). Infections and serious infections over time remained stable across 5 courses at 4-6 events/100 patient-years. Compared with other patients with RA and with the general US population, there was no increased risk of malignancy.

Conclusion. In this longterm safety update in RA clinical trial patients, rituximab remained well tolerated over multiple courses. SAE and infections remained stable over time and by treatment course.

(J Rheumatol First Release Feb 1 2010; doi:10.3899/jrheum.090856)

Key Indexing Terms:
RITUXIMAB RHEUMATOID ARTHRITIS CLINICAL TRIALS

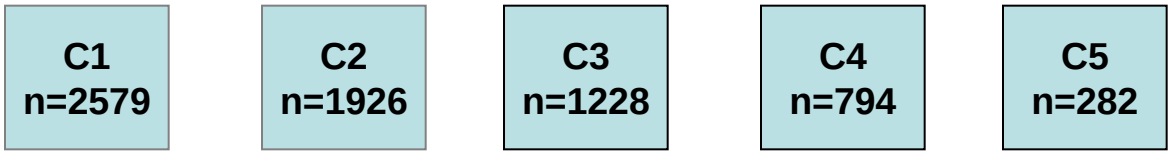
The goal of achieving effective treatment options for patients with rheumatoid arthritis (RA) has led to the development of biologic therapies that have improved our ability to control the signs and symptoms of RA, prevent structural joint damage, and attenuate functional losses[1-4]. Because RA is a chronic disease, therapies are administered over prolonged periods, a situation that requires continued vigilance of safety events.

Tumor necrosis factor (TNF) inhibitors have demonstrat-

malignancies[1-3,5]. Because of the immunomodulatory effects of RA therapies, it has become clear that specific safety adverse events (AE) should be monitored, especially more common infections, as well as less common events such as tuberculosis and lymphoma[6]. Moreover, RA itself has also been shown to increase the risk of serious infection, certain malignancies, and cardiovascular disease, either by the disease process or as a result of therapy[7-9].

Rituximab is approved for the treatment of non-

Μακροχρόνια ασφάλεια του MabThera : Μέχρι σήμερα έκθεση στο MabThera



Duration of observation	Patients (n=2579)
>1 year	2417
>2 years	1198
>3 years	743
>4 years	564
>5 years	109
Total exposure (patient-years)	5964

Το Rituximab είναι καλά ανεκτό και επιδεικνύει
ένα **σταθερά καλό profil ασφάλειας**
μακροπρόθεσμα με τους επαναλαμβανόμενους κύκλους
(πάνω από 6χρόνια)

Ποσοστό απόσυρσης λόγω ΑΕ: 5%

van Vollenhoven et al

Σ.Α.Ε κατά την επανάληψη του Rituximab

	1ος κύκλος (n=2579)	2ος κύκλος (n=1926)	3ος κύκλος (n=1228)	4ος κύκλος (n=794)	5ος κύκλος (n=282)
Έκθεση (pt-yrs)	2594	1877	900	409	119
AE/100 pt-yrs	379 (371-386)	313 (305-321)	319 (308-331)	330 (312-348)	330 (299-364)
ΣΑΕ/100 pt-yrs	18.3 (16.7-20.0)	17.4 (15.6-19.4)	16.6 (14.1-19.4)	12.0 (9.1-15.9)	13.4 (8.2-21.9)
Σ.Λ/100 pt-yrs	4.66 (3.90-5.57)	3.62 (2.86-4.60)	4.22 (3.07-5.80)	3.91 (2.40-6.38)	5.87 (2.80-12.30)
AEs που οδηγούν σε απόσυρση, n (%)	80 (3%)	41 (2%)	13 (1%)	4 (0.5%)	0

Ο συνολικός ρυθμός ΑΕ, ΣΑΕ,
παραμένει σταθερός κατά την διάρκεια του χρόνου και
δεν αυξάνεται με τους επαναλαμβανόμενους κύκλους.

Data cut April 2008.
Pt-yr=patient-year; SAE=serious adverse event; SIE=serious infection event

Συνολικά Σοβαρές Λοιμώξεις: 4,3 περ /100 ασθ-έτη

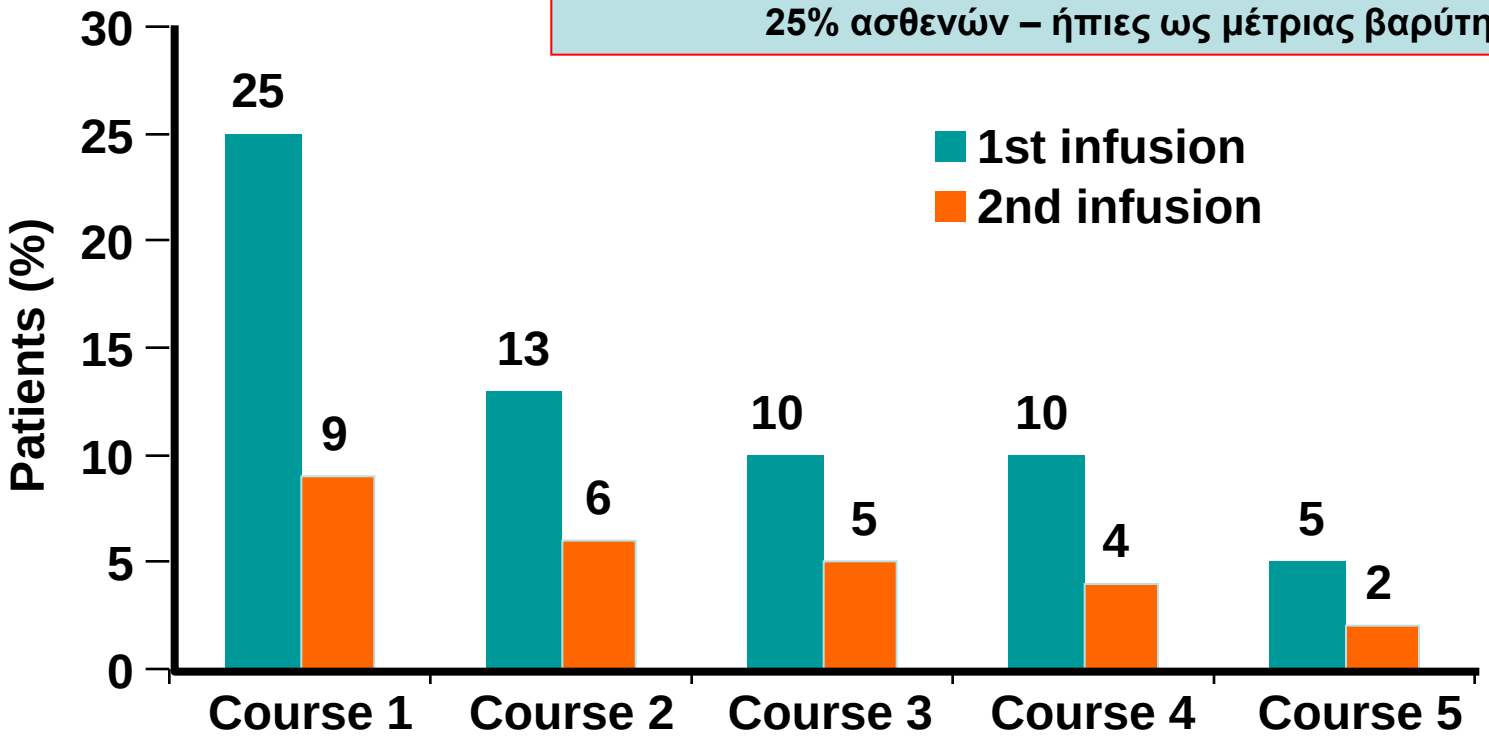
Η συχνότητα σοβαρών λοιμώξεων παραμένει σταθερά χαμηλή μεταξύ των κύκλων στην μακροχρόνια θεραπεία

Παρόμοια συχνότητα εμφάνισης με τους άλλους βιολογικούς.

- **ADA: 5,1/ 100 pt-y**
- **ETA: 4,2 / 100 pt-y**
- **ABA: 4,2-5,3 / 100 pt-y**

Αντιδράσεις κατά την έγχυση ανά κύκλο

Οι συνηθέστερες ΑΕ είναι <u>οι αντιδράσεις κατά την έγχυση</u>
25% ασθενών – ήπιες ως μέτριας βαρύτητας



Μακροπρόθεσμη ασφάλεια Rituximab
ΛΟΙΜΩΞΕΙΣ

- Δεν υπήρξε αναφορά ευκαιριακών λοιμώξεων, ούτε ΤΒ, ούτε αναζωπύρωση ιογενών λοιμώξεων.

- Έχουν αναφερθεί λίγα περιστατικά αναζωπύρωσης έρπητα ζωστήρα (0,98 περ/100 ασθ-έτη)

RITUXIMAB
ΣΥΜΠΕΡΑΣΜΑΤΑ

- **Διαφορετικό τρόπο δράσης (στοχεύει το CD19 Β κύτταρο).**
- **Εύκολο δοσολογικό σχήμα, μόνο με 2 κύκλους τον χρόνο (σταθερά κάθε 6 μήνες, σε ασθενείς που δεν έχει επιτευχθεί ύφεση DAS>2,6).**
- **Αποτελεσματικότητα που διατηρείται ή και βελτιώνεται με τους επαναλαμβανόμενους κύκλους.**
- **Τεκμηριωμένη αναστολή της ακτινολογικής εξέλιξης.**
- **Μακροχρόνια ασφάλεια, χωρίς αύξηση των ανεπιθύμητων ενεργειών, με τους επαναλαμβανόμενους κύκλους.**

Είναι ένα φάρμακο το οποίο
σε ασθενείς που απέτυχαν σε ένα αντι-TNF
και ιδιαίτερα σε οροθετικούς ασθενείς
εμφανίζει υψηλότερη αποτελεσματικότητα
και θεωρείται cost–effective εναλλακτική θεραπεία
έναντι της εναλλαγής TNF παραγόντων.

Ευχαριστώ πολύ

ΣΥΜΠΛΗΡΩΜΑ

Είναι ασφαλής η χορήγηση άλλων βιολογικών θεραπειών

μετά την διακοπή του Rituximab

σε ασθενείς με PA;

Safety of biological therapies following rituximab treatment in rheumatoid arthritis patients

M C Genovese,[1] F C Breedveld,[2] P Emery,[3] S Cohen,[4] E Keystone,[5] E L Matteson,[6] Y Baptiste,[7] A Chai,[8] L Burke,[7] W Reiss,[8] M Sweetser,[9] T M Shaw[7]

[1] Stanford University School of Medicine, Palo Alto, California, USA; [2] Leiden University Medical Center, Leiden University, Leiden, The Netherlands; [3] Leeds Teaching Hospitals Trust, the University of Leeds, Leeds, UK; [4] Metroplex Clinical Research Center, Dallas, Texas, USA; [5] University of Toronto, Toronto, Canada; [6] Mayo Clinic of Medicine, Rochester, Minnesota, USA; [7] Roche Products Ltd, Welwyn Garden City, UK; [8] Genentech, Inc, South San Francisco, California, USA; [9] Biogen Idec, Inc, Cambridge, Massachusetts, USA

Correspondence to: Dr M C Genovese, Division of Rheumatology, Stanford University Medical Center, 1000 Welch Road, Suite 203, Palo Alto, CA 94304, USA; genovese@stanford.edu

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ABSTRACT

Objective: To assess the safety of biological disease-modifying antirheumatic drugs (DMARD) in rheumatoid arthritis (RA) patients following rituximab.

Methods: RA patients who participated in an international rituximab clinical trial programme were included. Patients who had received one or more rituximab courses and en[illegible] addition[illegible] (SIE) w[illegible]

Result[illegible] receive[illegible] periphe[illegible] anothe[illegible] patient-years) occurred following rituximab but before another biological DMARD and 10 SIE (5.49 events/100 patient-years) occurred following another biological DMARD. SIE were of typical type and severity for RA patients. 153 had received one or more tumour necrosis factor inhibitor(s). No fatal or opportunistic infections occurred.

Conclusions: In this analysis, treatment with biological DMARD after rituximab was not associated with an increased serious infection rate. Sample size with limited follow-up restricts definitive conclusions.

METHODS

Patients and follow-up

Patients with active RA who received one or more courses of rituximab (either 2 × 500 mg or 2 × 1000 mg infusions given 2 weeks apart) during participation in one of nine trials in an international clinical trial programme were included in the [illegible]

SFU, patients were permitted to receive standard of care therapy, which may have included additional biological therapies at the discretion of the treating physician. Patients who received an additional biological agent comprised this study population. After the study treatment phase, patients were followed for at least one year for SFU. Patients remained in SFU if their CD19+ cell counts at the end of one year were below the lower limit of normal (LLN) or had returned to baseline values, whichever was less. SFU time was thus variable among patients.

185 ασθενείς από αυτούς που είχαν λάβει Rituximab χρειάστηκε να λάβουν άλλο βιολογικό παράγοντα.

88,6% την στιγμή της χορήγησης είχαν CD19<LLN

Η χρήση άλλων βιολογικών θεραπειών σε ασθενείς με ΡΑ που έλαβαν πριν θεραπεία με Rituximab δεν συσχετίστηκε με αυξημένο κίνδυνο σοβαρών λοιμώξεων

Table 2 Serious infection rate in patients who received treatment with another biological DMARD

	Overall (N = 2578)	Patients receiving any biological agent after rituximab treatment (n = 185)		Patients receiving TNF inhibitor after rituximab treatment (n = 153)	
		Before other biological agent	After other biological agent	Before other TNF inhibitor	After other TNF inhibitor
Total exposure, patient-years	5013	186.05	182.31	150.87	162.41
Serious infections, n	216	13	10	10	8
Serious infections/100 patient-years	4.31	6.99	5.49	6.63	4.93
95% CI	3.77 to 4.92	4.06 to 12.03	2.95 to 10.19	3.57 to 12.32	2.46 to 9.85

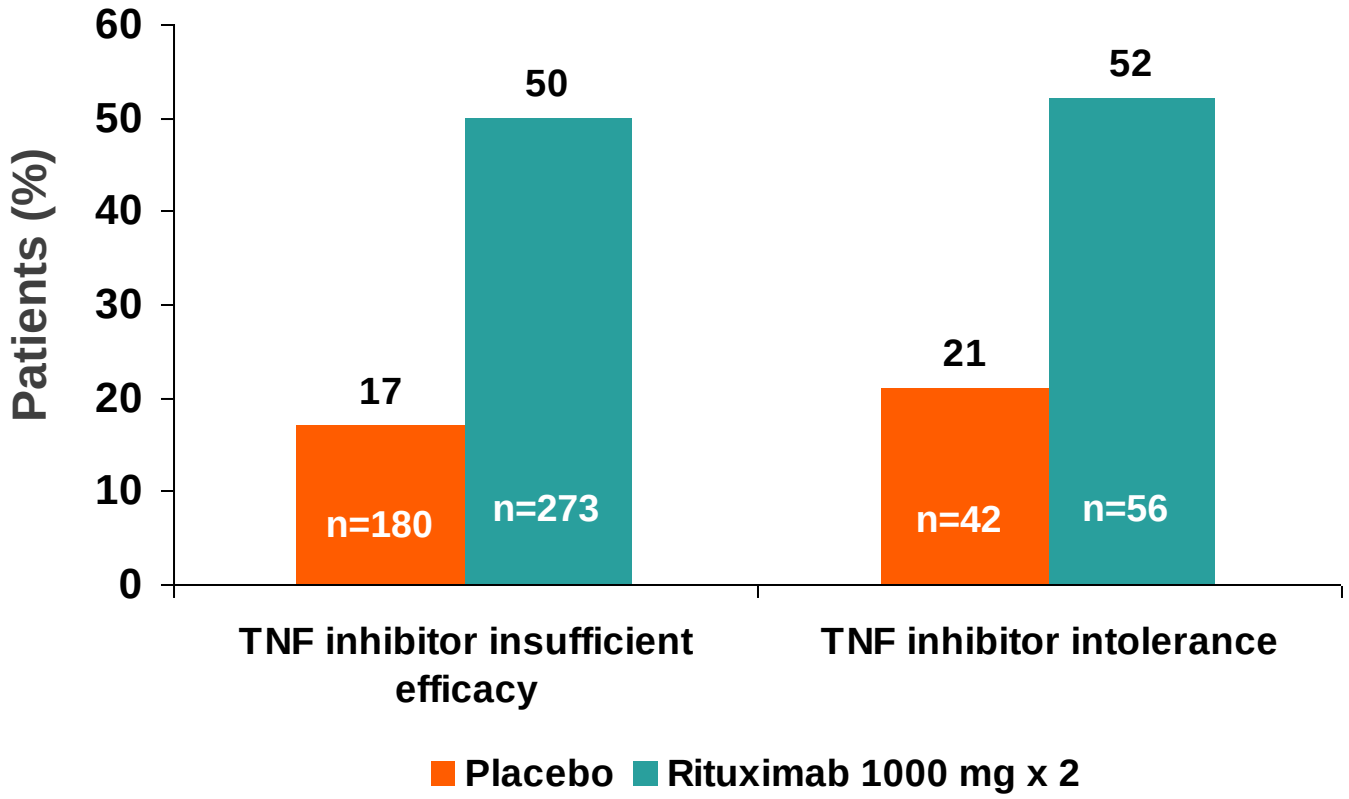
DMARD, disease-modifying antirheumatic drug; TNF, tumour necrosis factor.

Συνολικός ρυθμός σοβαρών λοιμώξεων: 4.31/100 pt-y (95%CIs 3.77–4.92)

Δεν υπήρξε αναφορά ευκαιριακών λοιμώξεων ούτε ΤΒ, ούτε αναζωπύρωση ιογενών λοιμώξεων.

REFLEX : ACR20
σε αποτυχία ή μη ανοχή του αντι-TNF

Οι ACR απαντήσεις στο Rituximab, ήταν ίδιες σε αυτούς που διέκοψαν το αντι-TNF λόγω αναποτελεσματικότητας ή λόγω μη ανοχής



Roche Data on file

ΜΑΚΡΟΠΡΟΘΕΣΜΗ ΑΣΦΑΛΕΙΑ MABTHERA
ΛΟΙΜΩΞΕΙΣ

MABTHERA® RITUXIMAB
B CELL THERAPY. LASTING SUCCESS.

- ***Β-κυτταρική ανεπάρκεια:σχετίζεται με λοιμώξεις από πυογόνα βακτήρια.***

- *πλειοψηφία των ασθενών*

  λοιμώξεις ήπιας-μέτριας βαρύτητας

  ΚΥΡΙΩΣ ΜΙΚΡΟΒΙΑΚΕΣ!!!

- ΣΥΝΗΘΩΣ ανώτερου & κατώτερου αναπνευστικού, ουροποιητικού και λοιμώξεις μαλακών μοριων

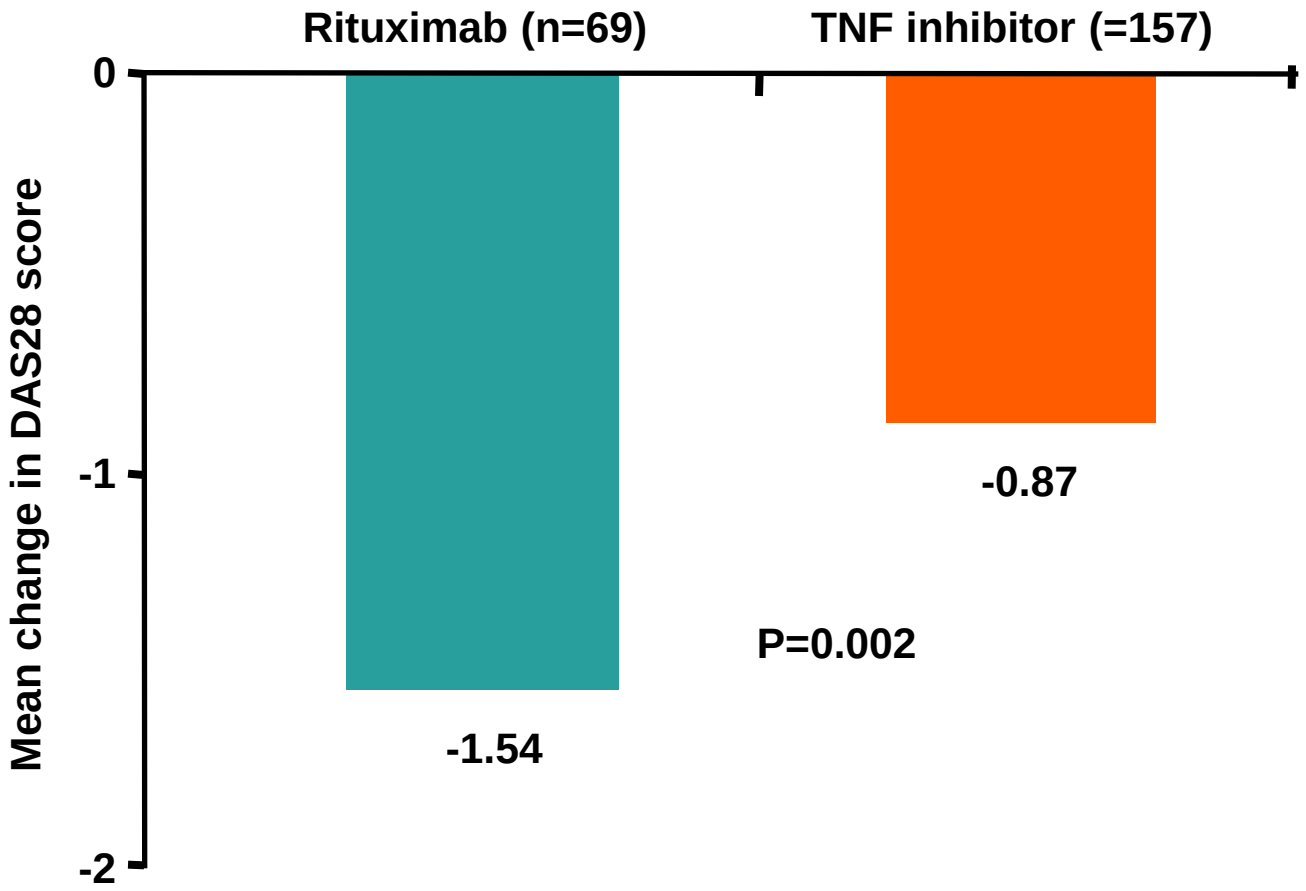
  -η συχνότητα εμφάνισης **σταθερή στους κύκλους**

  -οι πιο πολλές στους πρώτους 2-6Μ (συσχέτιση με κορτικοειδή)

Roche

Μεγαλύτερη μείωση του DAS28 στην ομάδα του MabThera®

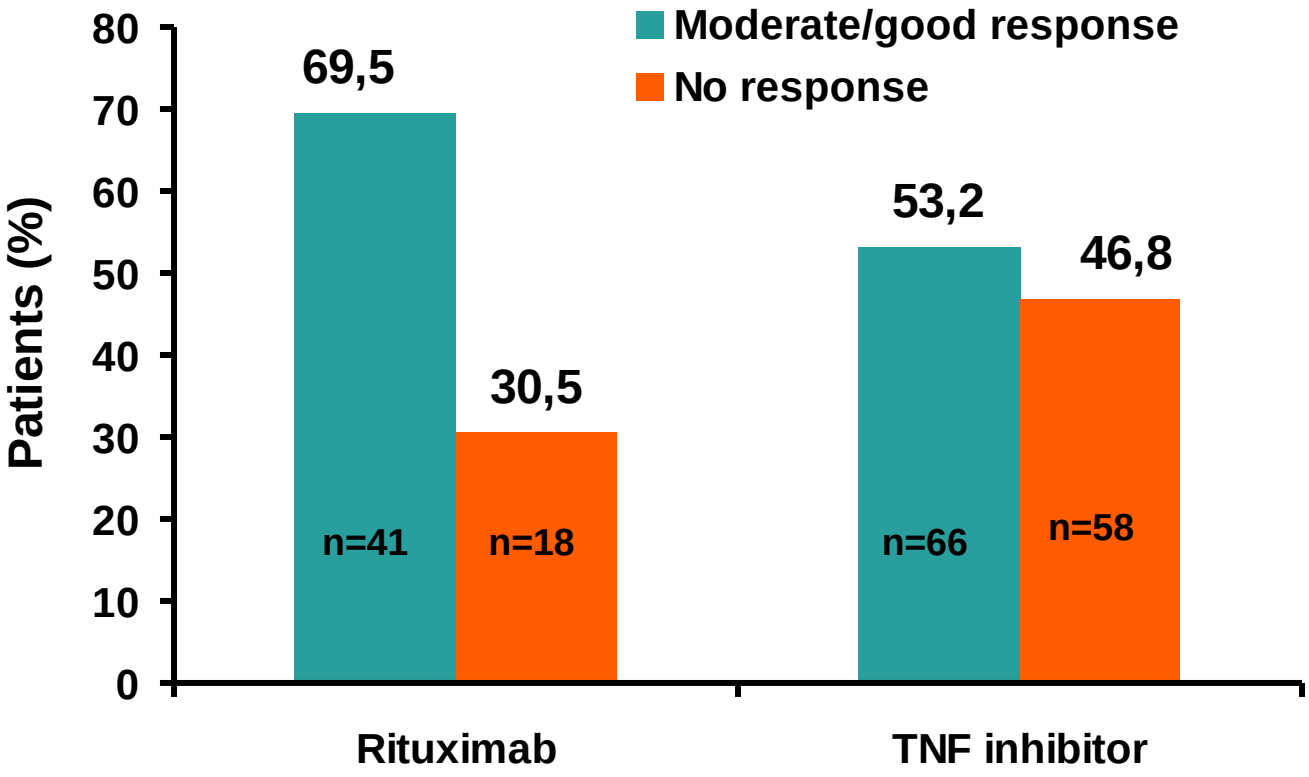
MABTHERA® RITUXIMAB
B CELL THERAPY. LASTING SUCCESS.



FRI0257

Gómez-Reino et al EULAR 2009 FRI0257

MIRAR: περισσότεροι ασθενείς υπό RTX είχαν EULAR μέτρια/καλή ανταπόκριση συγκριτικά με αυτούς υπό 2ο αTNF



*p=0.037 versus TNF inhibitor group

Gómez-Reino et al EULAR 2009 FRI0257

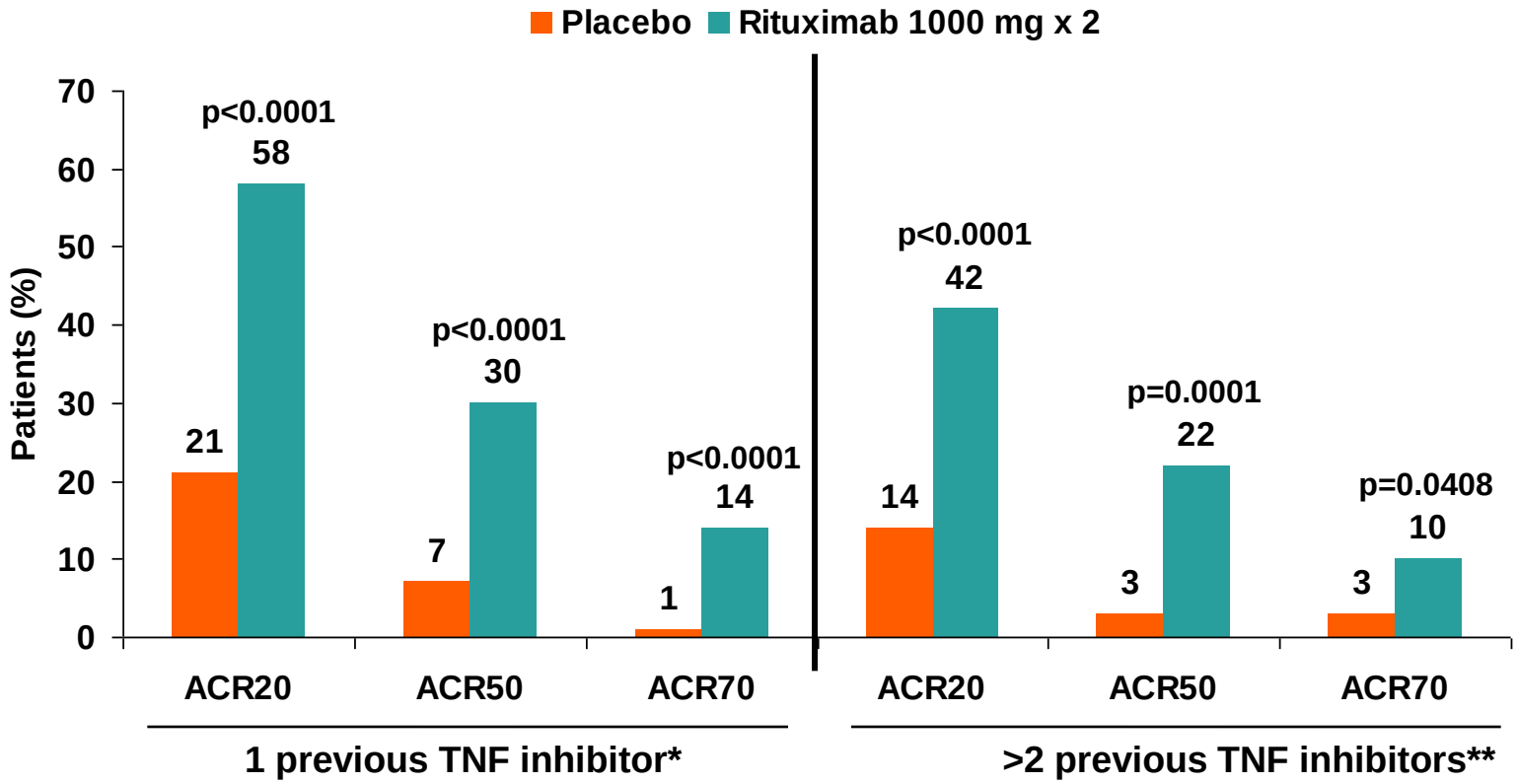
ACR 2009: Μακροχρόνια ασφάλεια του Rituximab (3095 ασθ) έναντι placebo (819 ασθ)

	All RTX exposure	Pooled placebo
Patients, n	3095	819
Total patient-years	7198	832
Infusion-related reactions, %	35	22
SAE rate/100 patient-years (95% CI)	16.5 (15.6–17.5)	15.7 (13.3–18.7)
Infection rate/100 patient-years (95% CI)	97.4 (95.1–99.7)	103.7 (97–110.9)
Serious infection rate/100 patient-years (95% CI)	4.25 (3.8–4.8)	4.33 (3.1–6.0)

- Most IRRs were CTC grade 1 or 2 and occurred after the first infusion of the first course
- <1% of IRRs were considered serious

Presentation 1952

REFLEX
Καλύτερο αποτέλεσμα στην ομάδα του Ritux.
σε σχέση με το placebo.
Καλύτερο αποτέλεσμα σε ασθενείς που είχαν αποτύχει σε ένα αντι- TNF από αυτούς σε >/δύο αντι- TNF

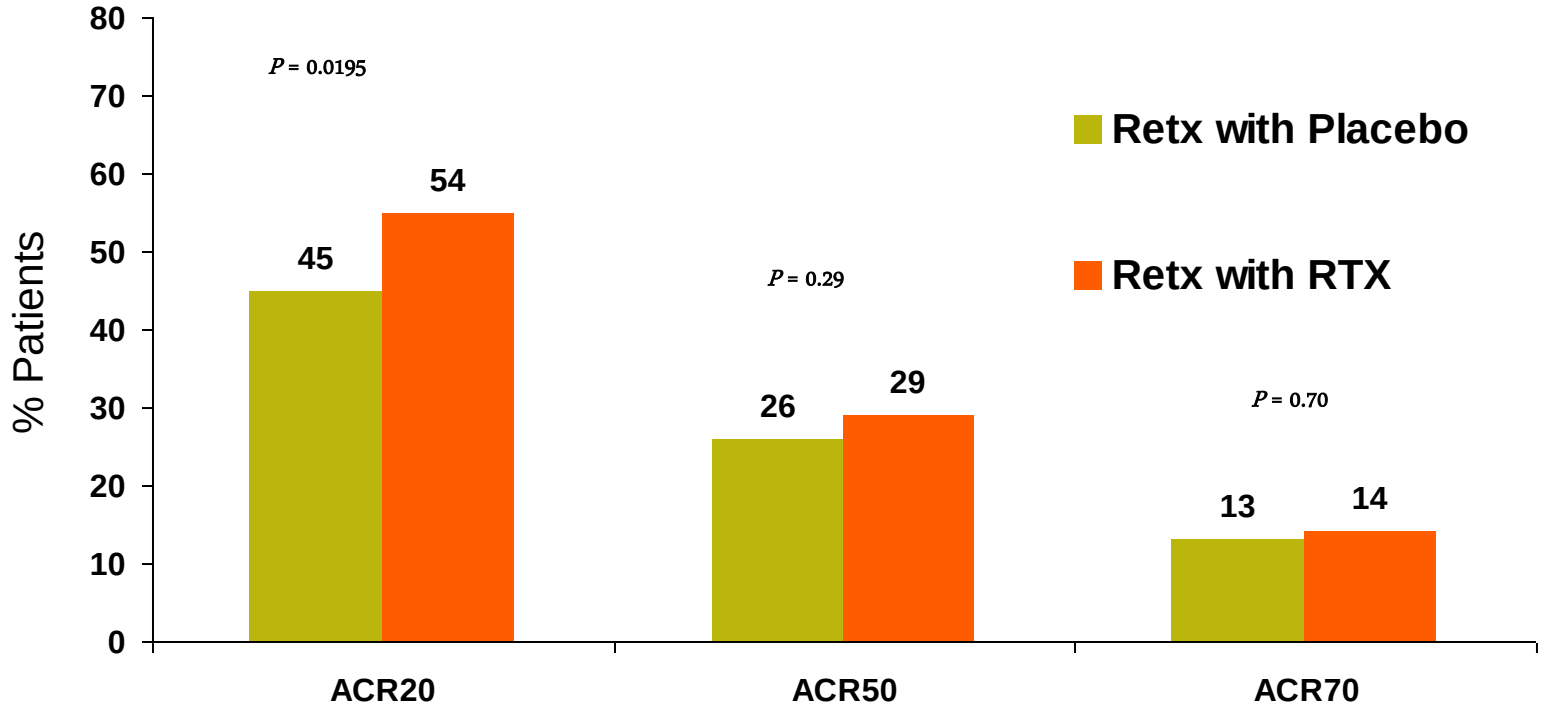


Evaluable patients; *placebo (n=121), rituximab (n=179); **placebo (n=80), rituximab (n=119)

Καλύτερο αποτέλεσμα όταν το Rituximab χορηγείται νωρίς

Kremer et al 2006

SUNRISE: ACR20/50/70 την 48 βδομ.(ITT)



P-values from CMH test, comparing the placebo retreated group with RTX retreated group

Μακροπρόθεσμη Ασφάλεια του Rituximab
ΚΑΡΔΙΑΓΓΕΙΑΚΟΣ ΚΙΝΔΥΝΟΣ

Έμφραγμα : 0,56 περ/100 pt-y

Παρόμοιο με αυτό του ΡΑ πληθυσμού (0,53)

Να μην χορηγείται σε Κ/Α σταδίου ΙΙΙ ή ασταθή στηθάγχη

ΝΑΙ σε ρυθμισμένο ασθενή με Κ/α νόσο.

Μακροπρόθεσμη Ασφάλεια του Rituximab
ΚΑΚΟΗΘΕΙΕΣ

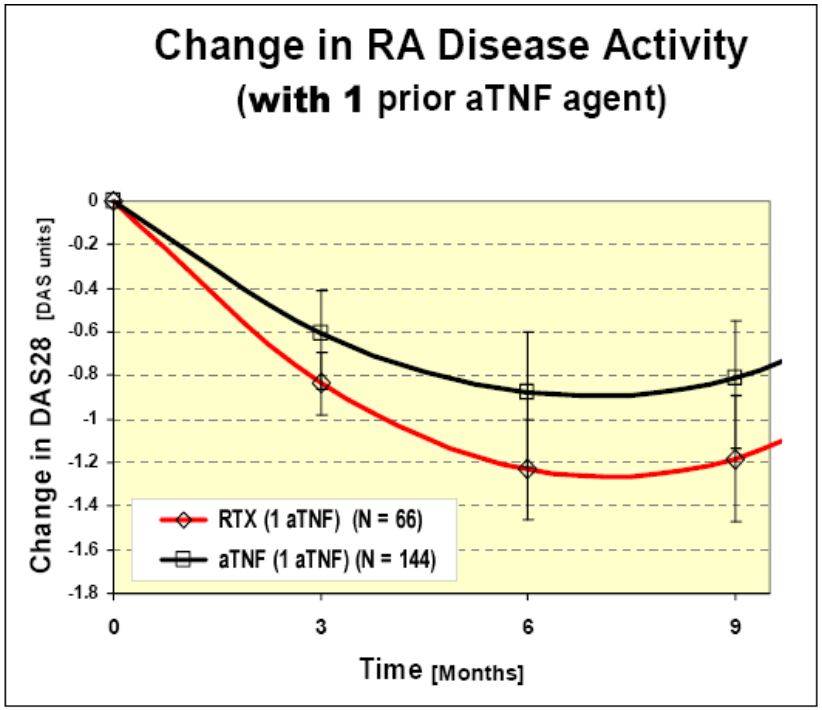
- Δεν διαπιστώθηκε αυξημένος κίνδυνος κακοήθειας συγκριτικά με τον P/A και γενικό πληθυσμό.
  SIR: 1,05 (95%CI 0,76-1,42)

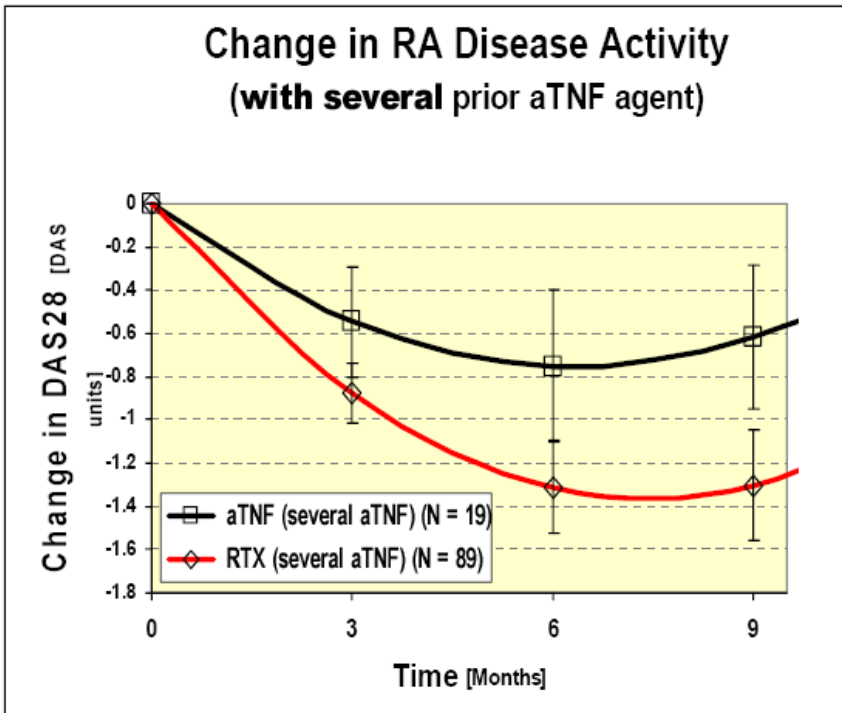
- Έχει αναφερθεί 1 περιστατικό λεμφώματος.

Which subgroup of rheumatoid arthritis patients benefits from switching to rituximab versus alternative anti-TNF agents after previous failure to anti-TNF agent?

Axel Finckh, Adrian Ciurea, Laure Brulhart, Burkhard Möller, Ulrich A Walker,
Delphine Courvoisier, Diego Kyburz, Jean Dudler and Cem Gabay

Βελτίωση του DAS28 εμφανίστηκε σε αυτούς που πήραν Rituximab ανεξάρτητα εάν είχαν προηγηθεί ένας ή περισσότεροι αντι-TNF





Μακροπρόθεσμη ασφάλεια : Σοβαρές λοιμώξεις ανά 100 ασθ.-έτη