ΒΙΟΛΟΓΙΚΕΣ ΘΕΡΑΠΕΙΕΣ ΣΕ "OFF-LABEL" ΕΝΔΕΙΞΕΙΣ

Σκληρόδερμα, μυοσίτιδες, αγγειίτιδες

Εαρινές Ημέρες, Βόλος, Ιούνιος 2018

ΣΤΑΜΑΤΗΣ-ΝΙΚΟΣ ΛΙΟΣΗΣ
Καθηγ. Παθολογίας-Ρευματολογίας
Ιατρικό Τμήμα Πανεπιστημίου Πατρών
Δ/ντής, Ρευματολογικό Τμήμα ΠΓΝΠ

ΣΥΓΚΡΟΥΣΗ ΣΥΜΦΕΡΟΝΤΩΝ

Honoraria

- Genesis Pharma
- GSK
- BMS
- MSD
- Novartis
- Janssen
- Pfizer
- Roche
- Actelion

Χρηματοδότηση Ερευν. προγραμμάτων (ΕΛΚΕ Πανεπ. Πατρών)

- Aenorasis
- ΕΡΕ-ΕΠΕΡΕ
- Specifar
- BMS
- Hospital Line
- MSD

Σκληρόδερμα

Off-label βιολογικές θεραπείες

Rituximab

Tocilizumab

Belimumab

RHEUMATOLOGY

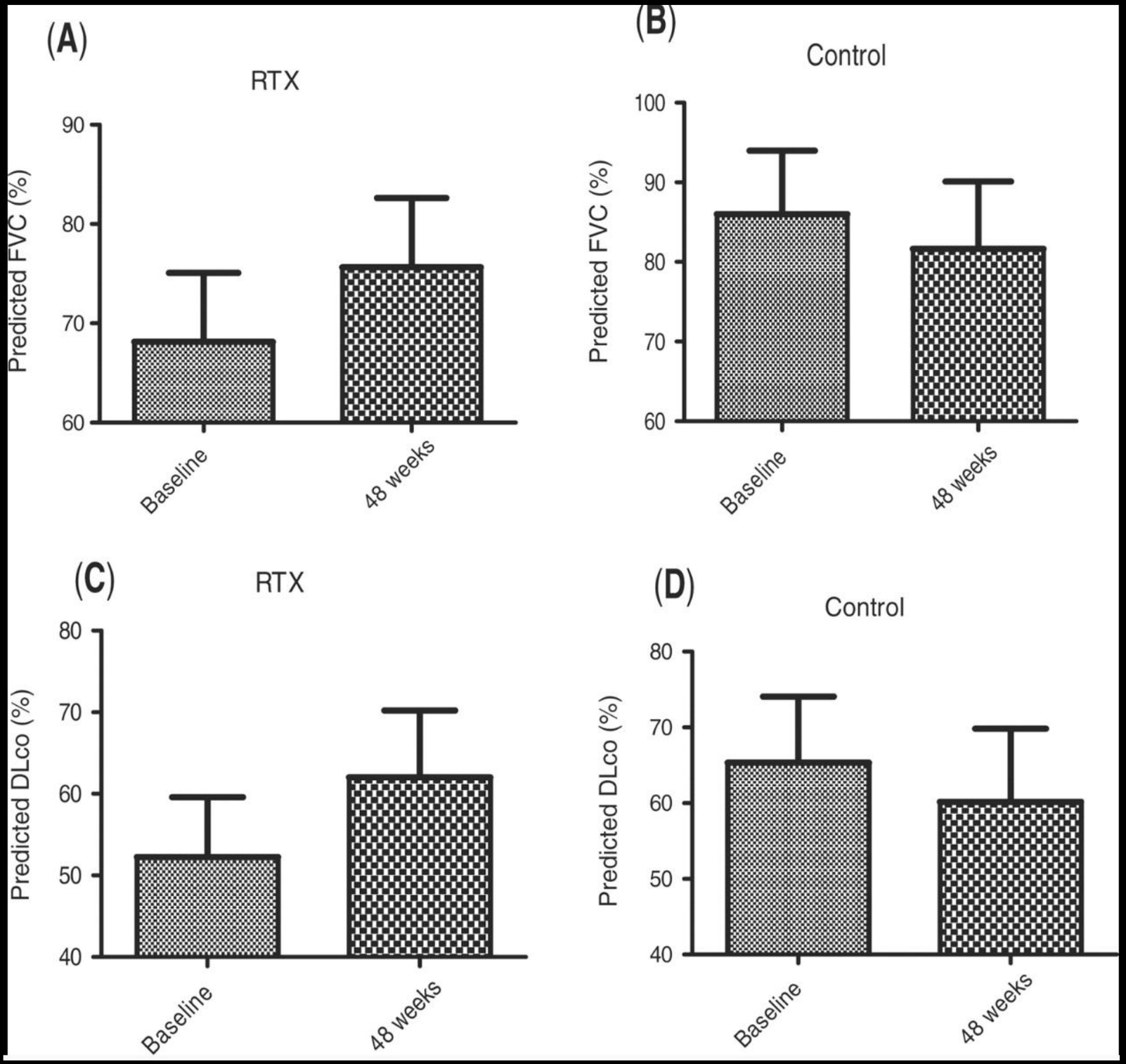
Rheumatology 2010;49:271–280
doi:10.1093/rheumatology/kep093
Advance Access publication 18 November 2009

Original article

Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study

Dimitrios Daoussis[1,*], Stamatis-Nick C. Liossis[1,*], Athanassios C. Tsamandas[2], Christina Kalogeropoulou[3], Alexandra Kazantzi[3], Chaido Sirinian[2], Maria Karampetsou[1], Georgios Yiannopoulos[1] and Andrew P. Andonopoulos[1]

Η μελέτη αυτή χρηματοδοτήθηκε από την EPE



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Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study

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A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease☆

Dimitrios Daoussis, MD[a,*,1], Konstantinos Melissaropoulos, MD[a,1], Georgios Sakellaropoulos[e], Ioannis Antonopoulos, MD[a], Theodora E. Markatseli, MD[b], Theodora Simopoulou, MD[c], Panagiotis Georgiou, MD[d], Andrew P. Andonopoulos, MD[a], Alexandros A. Drosos, MD[b], Lazaros Sakkas, MD, DM, PhD(UK), FRCP(UK)[c], Stamatis-Nick Liossis, MD[a]

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[b] *Department of Rheumatology, Ioannina University Hospital, University of Ioannina Medical School, Ioannina, Greece*
[c] *Department of Rheumatology, Larissa University Hospital, University of Thessaly Medical School, Larissa, Greece*
[d] *Department of Rheumatology, Agios Andreas District Hospital, Patras, Greece*
[e] *Department of Medical Physics, University of Patras, Patras, Greece*

Seminars in Arthritis and Rheumatism 46 (2017) 625–631

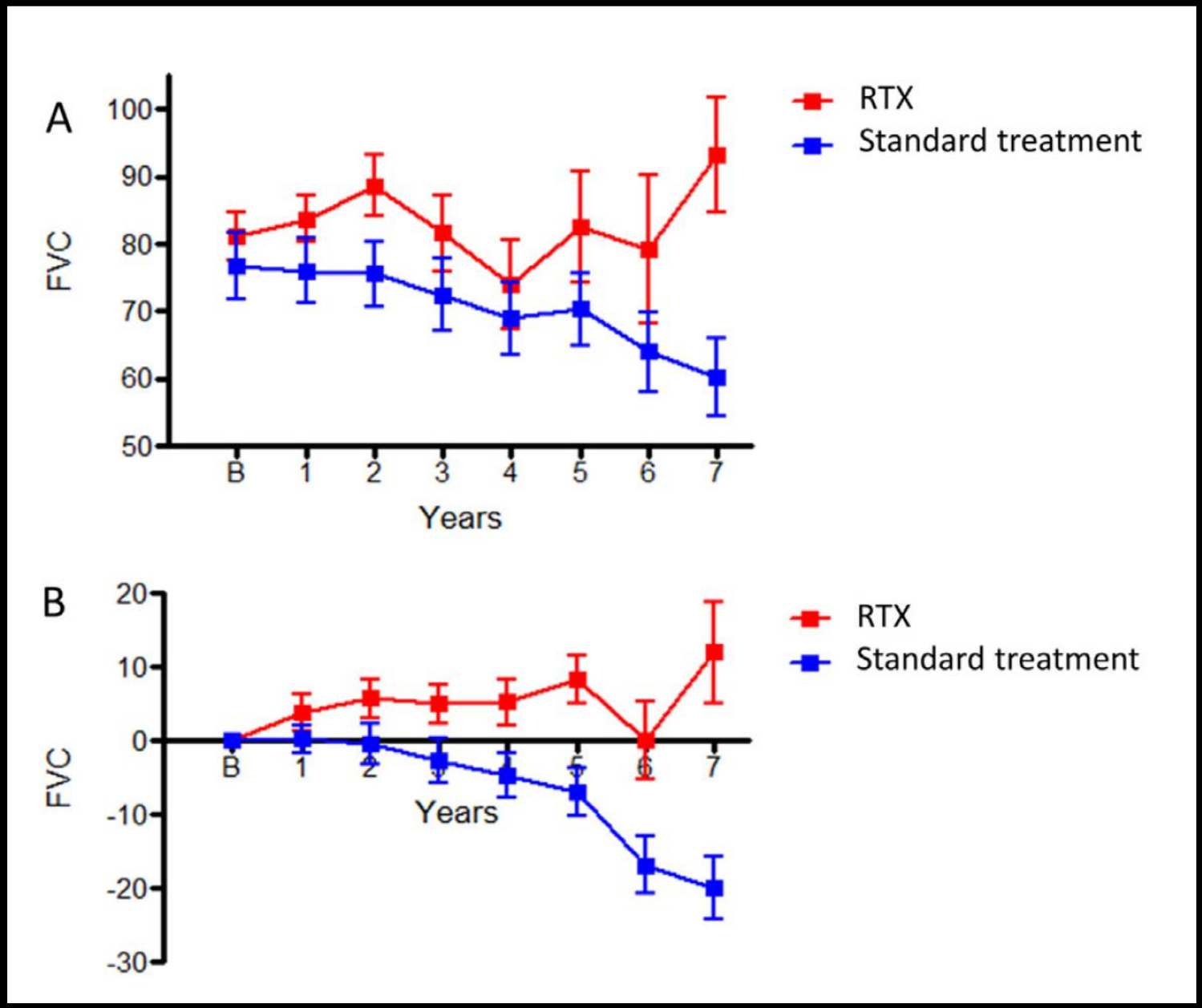
Table
Baseline demographic and clinical characteristics of the RTX cohort matched with the control cohort

	RTX cohort	Control cohort	*p* Value
Patients, *n*	33	18	
Age mean, years ± SD	54.3 ± 14.33	52.11 ± 16.10	*0.62*
Female sex (%)	25/33 (75.8)	16/18 (88.9)	*0.46*
Disease duration mean in years (range)	5.73 (1–28)	2.56 (1–10)	*0.012*
Autoantibodies positive			
Scl70 (%)	25/33 (75.8)	14/18 (77.8)	*1.00*
ACA (%)	3/33 (9.1)	3/18 (16.7)	*0.65*
Other (%)	5/33 (15.1)	1/18 (5.5)	*0.40*
Disease subtype			
Diffuse (%)	30/33 (90.9)	14/18 (77.8)	*0.22*
Limited (%)	3/33 (9.1)	4/18 (22.2)	*0.22*
Pulmonary hypertension (%)[a]	6/33 (18.2)	5/18 (27.8)	*0.48*
MRSS, mean ± SD	14.72 ± 10.52	17.78 ± 9.48	*0.31*
FVC, mean ± SD	80.60 ± 21.21	77.72 ± 18.29	*0.63*
DLCO, mean ± SD	59.22 ± 18.17	64.24 ± 25.56	*0.42*
Concurrent medication			
Prednisolone(or equivalent) (%)	18/33 (54.5)	17/18 (94.4)	
Methotrexate (%)	2/33 (6.1)	6/18 (33.3)	
Mycophenolate (%)	10/33 (30.3)	10/18 (55.5)	
Azathioprine (%)	0/33 (0.0)	2/18 (11.1)	
Hydroxychloroquine (%)	1/33 (3.0)	0/18 (0.0)	

p Value refers to the comparison of the variables presented between the two cohorts. Level of statistical significance is set to 0.05.

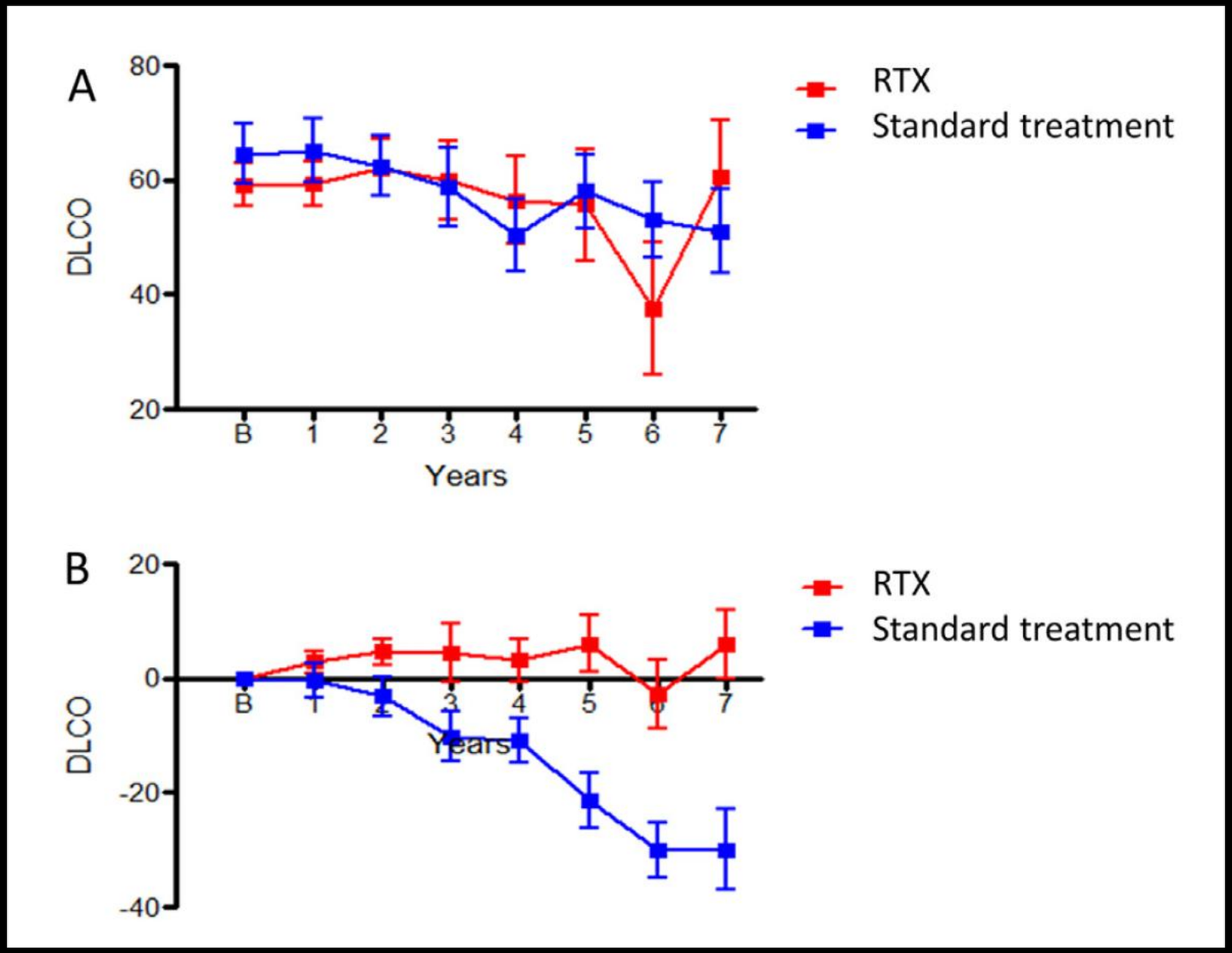
[a] Based on ultrasound PASP values.

RTX vs. Standard Tx: Επίδραση στην FVC



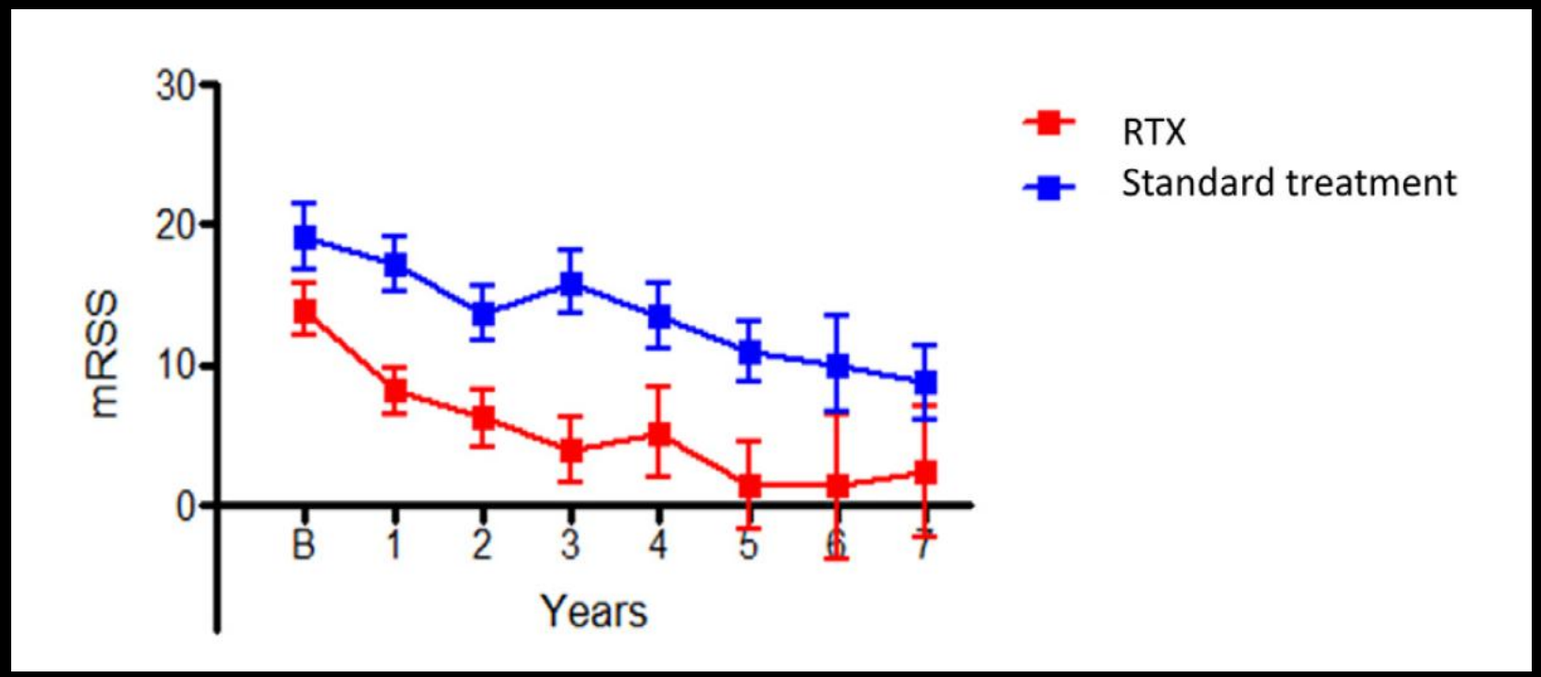
Seminars in Arthritis and Rheumatism 46 (2017) 625–631

RTX vs. Standard Tx: Επίδραση στη διαχυτική ικανότητα CO



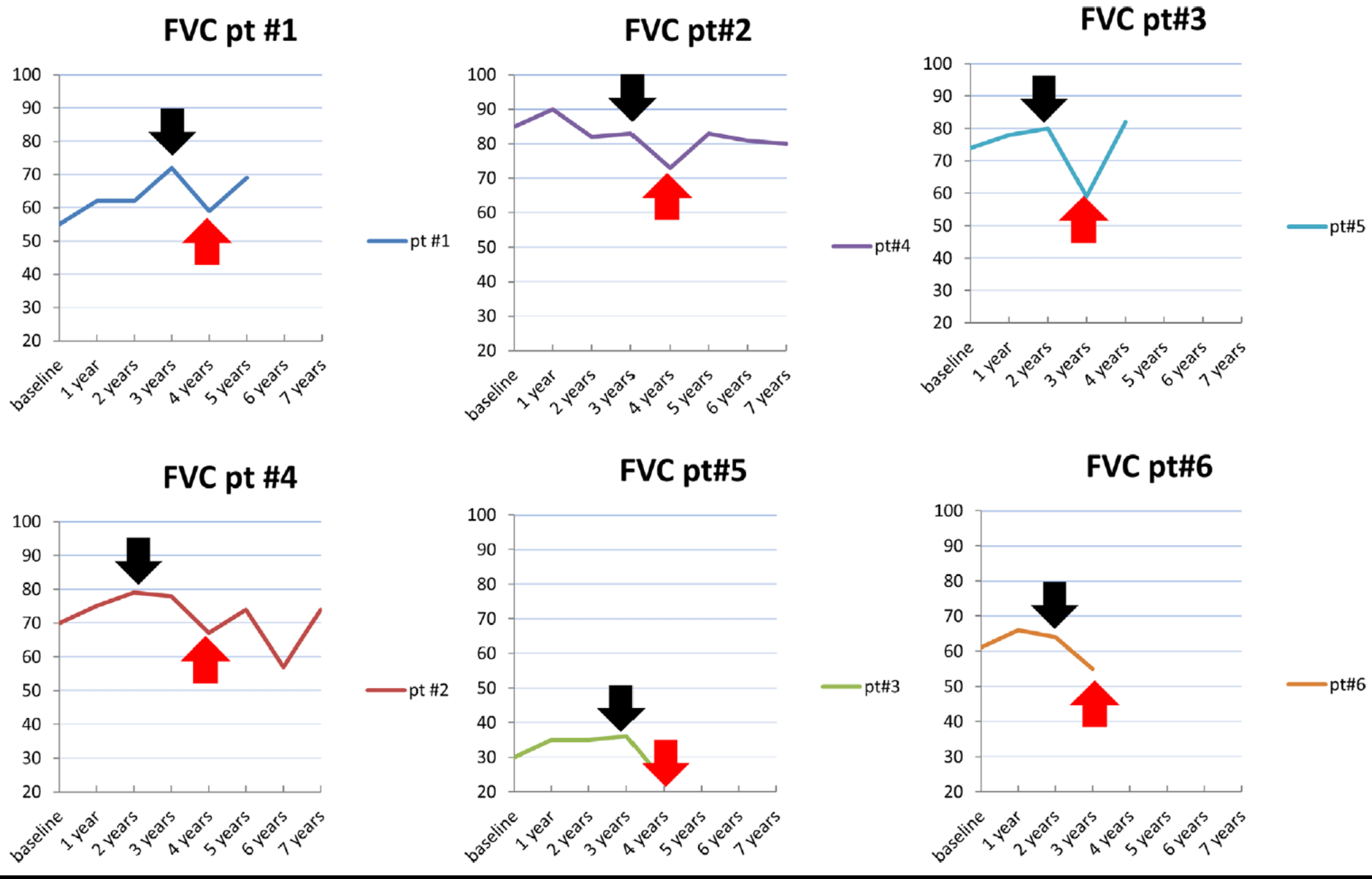
Seminars in Arthritis and Rheumatism 46 (2017) 625–631

RTX vs. Standard Tx: Επίδραση στο δέρμα



Seminars in Arthritis and Rheumatism 46 (2017) 625–631

Διακοπή & Επανέναρξη RTX



Seminars in Arthritis and Rheumatism 46 (2017) 625–631

Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial

Dinesh Khanna, Christopher P Denton, Angelika Jahreis, Jacob M van Laar, Tracy M Frech, Marina E Anderson, Murray Baron, Lorinda Chung, Gerhard Fierlbeck, Santhanam Lakshminarayanan, Yannick Allanore, Janet E Pope, Gabriela Riemekasten, Virginia Steen, Ulf Müller-Ladner, Robert Lafyatis, Giuseppina Stifano, Helen Spotswood, Haiyin Chen-Harris, Sebastian Dziadek, Alyssa Morimoto, Thierry Sornasse, Jeffrey Siegel, Daniel E Furst

Lancet 2016; 387: 2630–40

Κύριο καταληκτικό σημείο: Βελτίωση στο δέρμα…

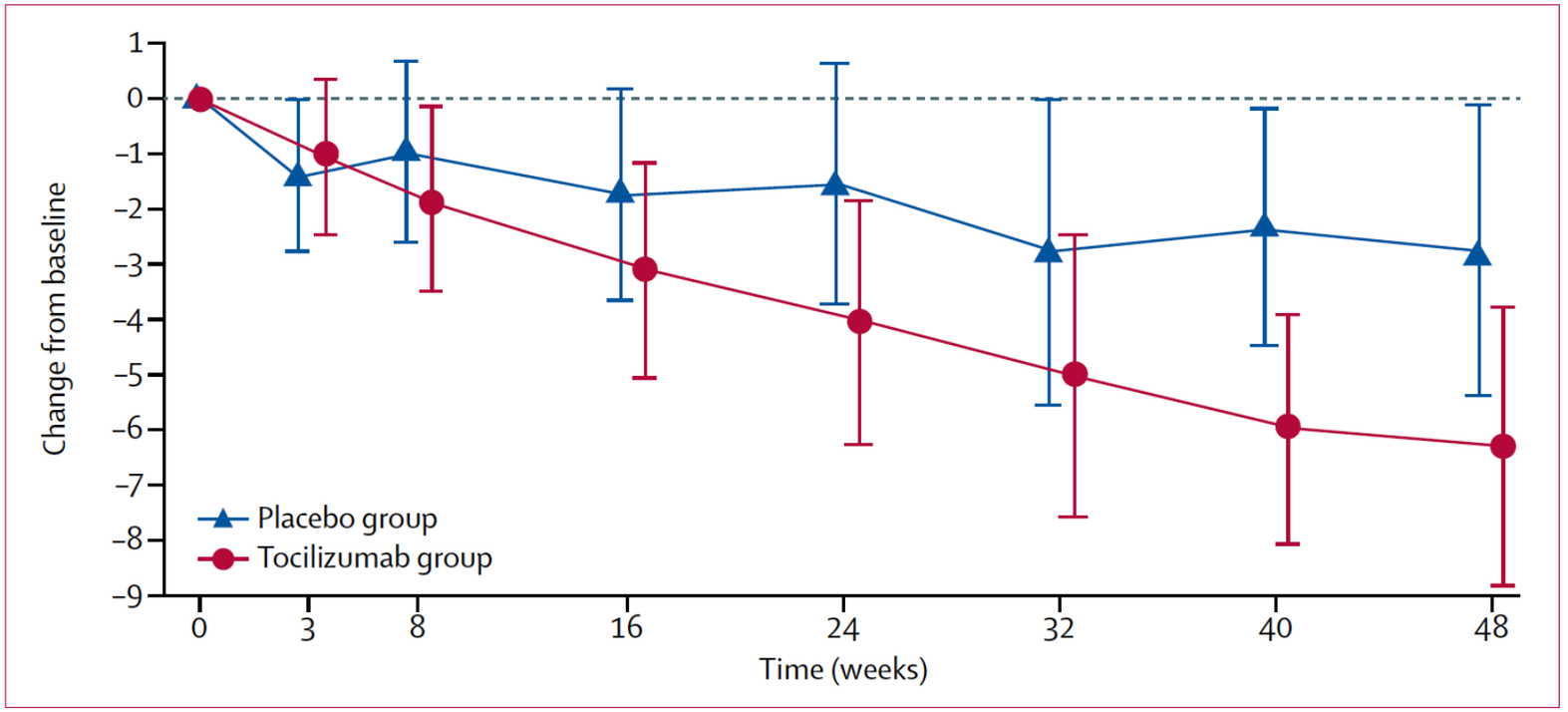


Figure 2: **Change (95% CI) from baseline in modified Rodnan skin score**

	24 weeks			48 weeks		
	Placebo group (n=44)	Tocilizumab group (n=43)	p value	Placebo group (n=44)	Tocilizumab group (n=43)	p value
Decrease ≥20%	12 (27%)	16 (37%)	0·36	12 (27%)	17 (40%)	0·26
Decrease ≥40%	6 (14%)	6 (14%)	1·00	3 (7%)	9 (21%)	0·069
Decrease ≥60%	2 (5%)	2 (5%)	1·00	0 (0%)	5 (12%)	0·026
Decrease ≥4·7 units	10 (23%)	16 (37%)	0·16	11 (25%)	16 (37%)	0·25

A change of 4·7 or more is deemed clinically important. Patients can be counted more than once. For example, a patient with a 43% improvement would be counted as having had decrease of both more than 20% and more than 40%.

Table 3: **Changes from baseline in modified Rodnan skin score**

Lancet 2016; 387: 2630–40

Επίδραση στη λειτουργία της αναπνοής

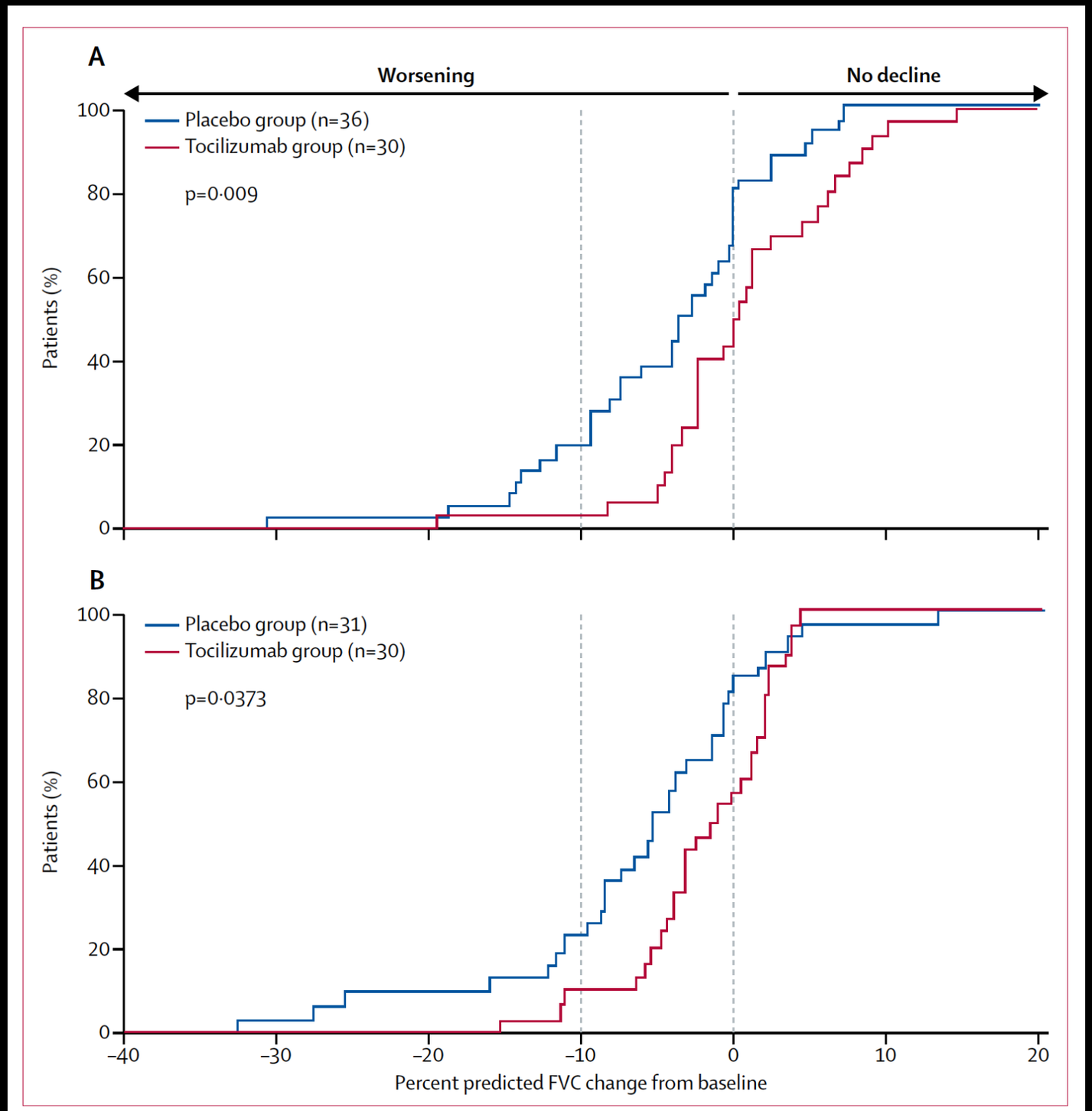


Figure 3: **Cumulative distribution of patients by change in percent predicted FVC**
Decline is shown as absolute change in percent predicted FVC. From baseline to 24 weeks (A), and from baseline to 48 weeks (B). FVC=forced vital capacity.

Lancet 2016; 387: 2630–40

TCZ: Περισσότερες Ανεπιθύμητες ενέργειες

	Baseline to 24 weeks		Baseline to 48 weeks	
	Placebo group (n=44)	Tocilizumab group (n=43)	Placebo group (n=44)	Tocilizumab group (n=43)
Patients with ≥1 adverse event	40 (91%)	38 (88%)	40 (91%)	42 (98%)
Patients with ≥1 infectious adverse event	18 (41%)	17 (40%)	22 (50%)	24 (56%)
Patients with injection site reactions	1 (2%)*	2 (5%)†	2 (5%)*	3 (7%)†
Patients with ≥1 serious adverse event	11 (25%)	9 (21%)	15 (34%)	14 (33%)
Patients with ≥1 infectious serious adverse event	1 (2%)	6 (14%)	2 (5%)	7 (16%)
Patients with ≥1 non-infectious serious adverse event	10 (23%)	5 (12%)	14 (32%)	10 (23%)
Withdrawals because of an adverse event	5 (11%)	4 (9%)	5 (11%)	6 (14%)
Deaths	1 (2%)	1 (2%)	1 (2%)	3 (7%)
Serious adverse events‡				
Infections and infestations	1 (2%)	6 (14%)	2 (5%)	7 (16%)

Lancet 2016; 387: 2630–40

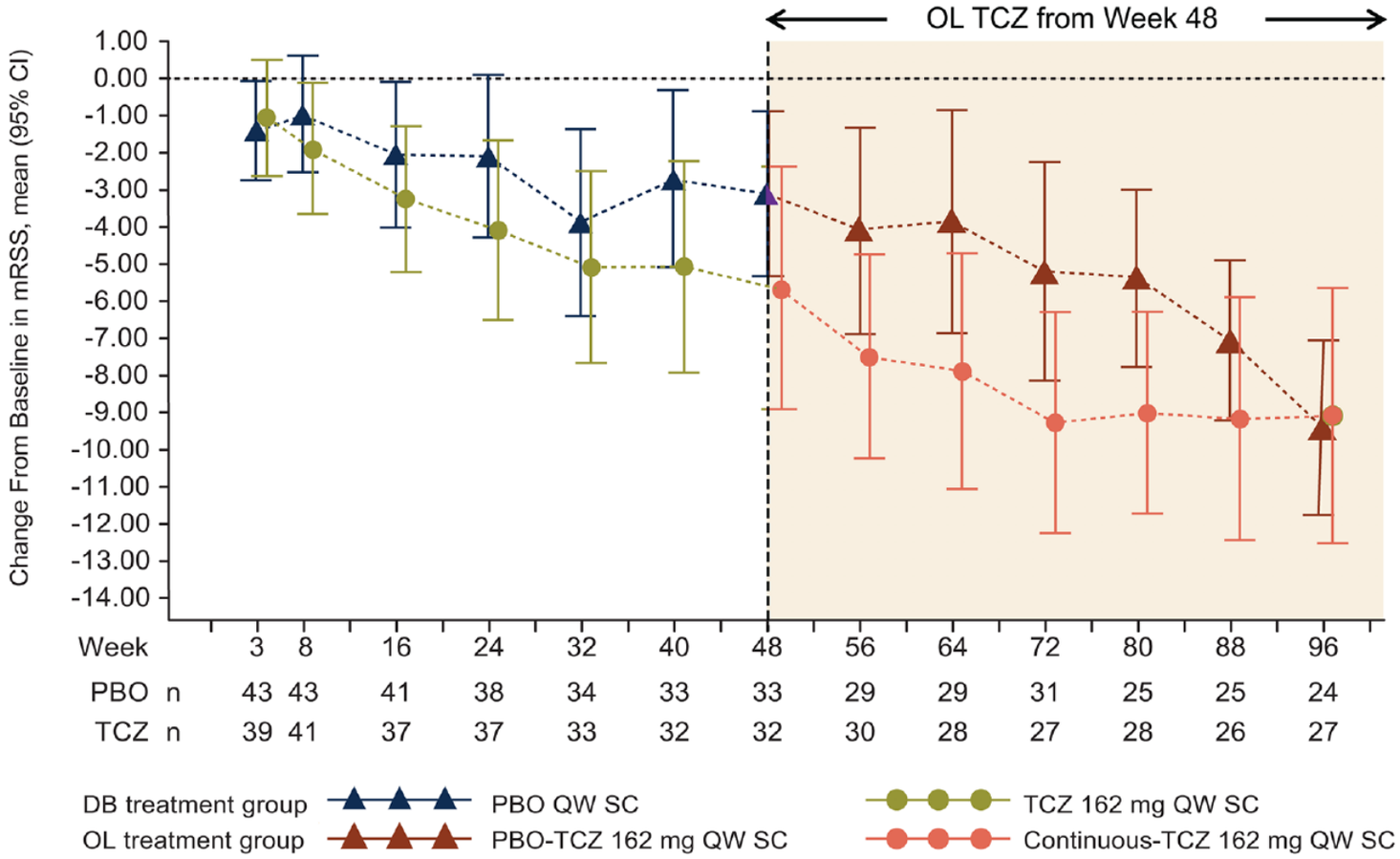
EXTENDED REPORT

Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate)

Dinesh Khanna,[1] Christopher P Denton,[2] Celia J F Lin,[3] Jacob M van Laar,[4] Tracy M Frech,[5] Marina E Anderson,[6] Murray Baron,[7] Lorinda Chung,[8] Gerhard Fierlbeck,[9] Santhanam Lakshminarayanan,[10] Yannick Allanore,[11] Janet E Pope,[12] Gabriela Riemekasten,[13] Virginia Steen,[14] Ulf Müller-Ladner,[15] Helen Spotswood,[16] Laura Burke,[16] Jeffrey Siegel,[3] Angelika Jahreis,[3] Daniel E Furst[17]

Khanna D, *et al*. *Ann Rheum Dis* 2018;**77**:212–220.

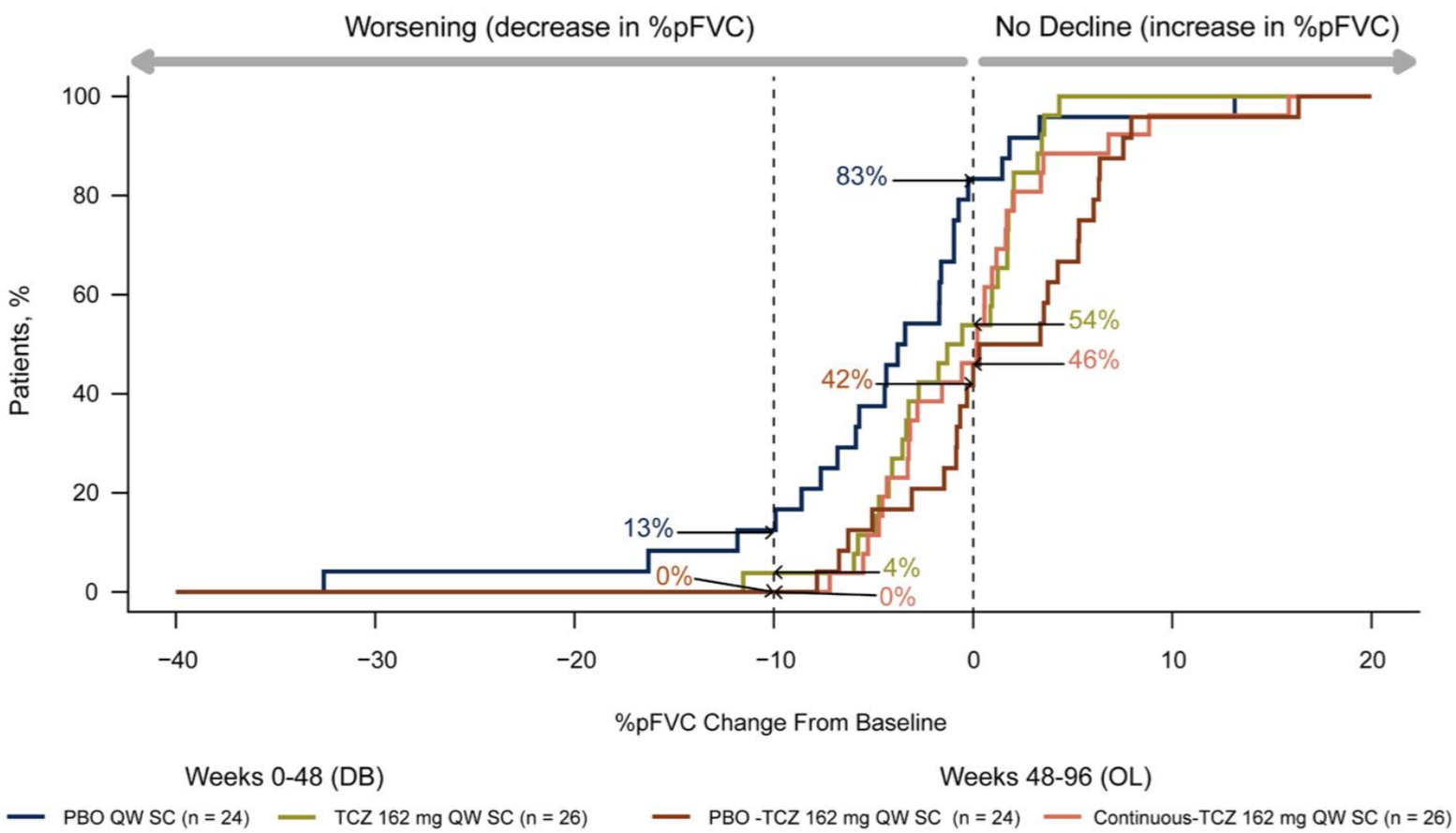
TCZ 96wk: Επίδραση στο Δέρμα



	PBO		TCZ	
Wk	Mean (SD) [95% CI] change from BL	Mean (SD) [95% CI] observed score	Mean (SD) [95% CI] change from BL	Mean (SD) [95% CI] observed score
24	-2.1 (6.7) [-4.3, 0.1]	23.2 (9.3) [20.2, 26.3]	-4.1 (7.3) [-6.5, -1.7]	21.8 (9.9) [18.5, 25.1]
48	-3.1 (6.3) [-5.4, -0.9]	22.3 (8.1) [19.4, 25.1]	-5.6 (9.1) [-8.9, -2.4]	19.6 (10.1) [15.9, 23.2]
72	-5.2 (7.9) [-8.1, -2.3]	19.8 (8.0) [16.9, 22.7]	-9.3 (7.5) [-12.2, -6.3]	16.0 (9.1) [12.4, 19.7]
96	-9.4 (5.6) [-11.8, -7.0]	15.3 (7.6) [12.1, 18.6]	-9.1 (8.7) [-12.5, -5.6]	16.2 (9.8) [12.3, 20.1]

Khanna D, *et al. Ann Rheum Dis* 2018;**77**:212–220.

TCZ 96wk: Επίδραση στη λειτουργία της αναπνοής



	Weeks 0-48 (DB)		Weeks 48-96 (OL)	
	PBO QW SC (n = 24)	TCZ 162 mg QW SC (n = 26)	PBO-TCZ 162 mg QW SC (n = 24)	Continuous-TCZ 162 mg QW SC (n = 26)
%pFVC change from baseline, n (%) [95% CI]				
Absolute decrease >0	20 (83) [63, 95]	14 (54) [33, 73]	10 (42) [22, 63]	12 (46) [27, 67]
Absolute decrease >10%	3 (13) [3, 32]	1 (4) [0, 20]	0 (0) [0, 14]	0 (0) [0, 13]

Khanna D, *et al*. *Ann Rheum Dis* 2018;**77**:212–220.

ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 2, February 2018, pp 308–316
DOI 10.1002/art.40358

Belimumab for the Treatment of Early Diffuse Systemic Sclerosis

Results of a Randomized, Double-Blind, Placebo-Controlled, Pilot Trial

Jessica K. Gordon,[1] Viktor Martyanov,[2] Jennifer M. Franks,[2] Elana J. Bernstein,[3] Jackie Szymonifka,[3] Cynthia Magro,[4] Horatio F. Wildman,[4] Tammara A. Wood,[2] Michael L. Whitfield,[2] and Robert F. Spiera[1]

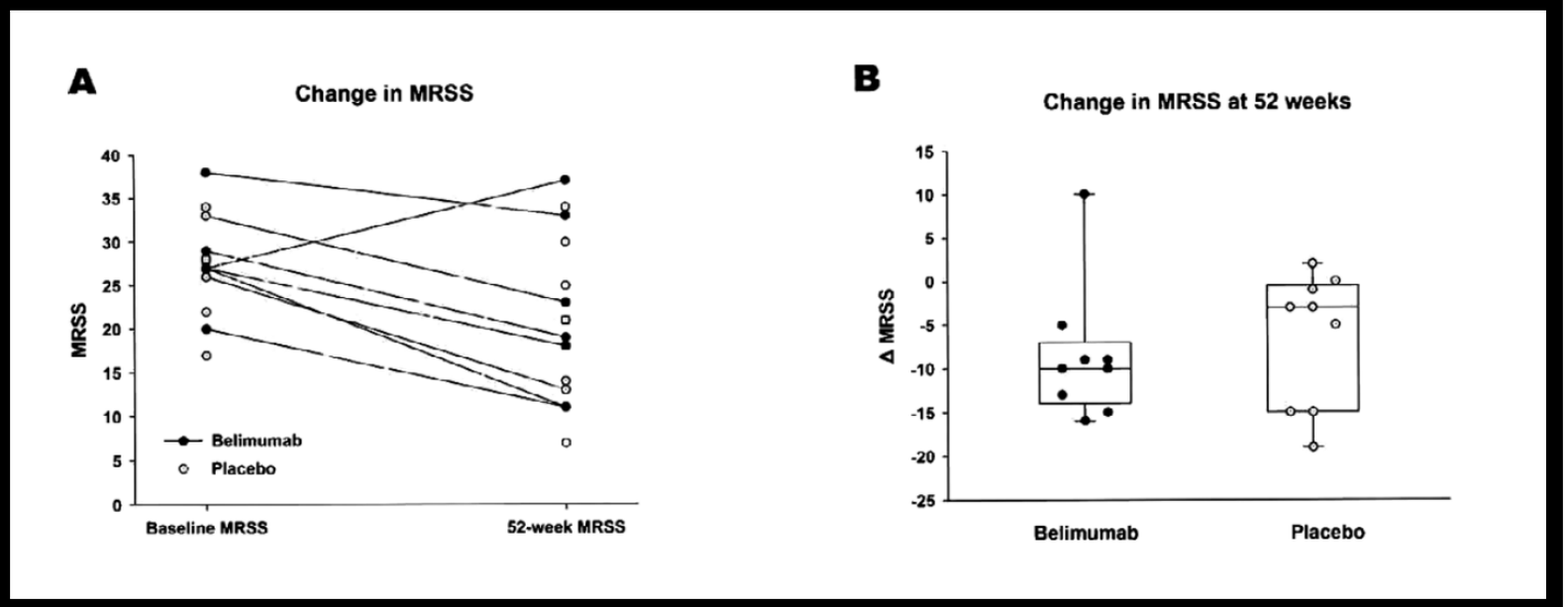


Table 2. Change in primary and secondary end points at 52 weeks*

	Belimumab + MMF (n = 9)	Placebo + MMF (n = 9)
MRSS, 0–51	–10 (–13, –9)	–3.0 (–15, –1)
SHAQ DI score, 0–3	–0.25 (–0.38, –0.25)†	0.00 (–0.13, 0.13)
VAS pain score, 0–150 mm	–10.5 (–40.5, 6.5)	–1.0 (–32.0, 0.0)
VAS RP score, 0–150 mm	–30.0 (–40.0, –14.0)‡	0.0 (–7.0, 22.0)
VAS ulcers score, 0–150 mm	–12.0 (–38.0, 1.0)	0.0 (–7.5, 4.0)
VAS breathing score, 0–150 mm	2.0 (0.0, 7.0)	0.0 (–7.0, 3.0)
VAS overall score, 0–150 mm	–14.0 (–29.0, –9.00)	–10.0 (–40.0, –6.0)
SF-36 MCS score, 0–100	7.50 (2.50, 18.50)	3.00 (0.00, 10.00)
SF-36 PCS score, 0–100	8.00 (–3.50, 19.00)	–3.00 (–3.00, 27.00)
PGA, 0–10	–4.43 (–8.05, –0.90)	–1.67 (–2.87, –0.90)
FVC, % predicted	5.00 (0.00, 8.00)	–2.00 (–6.00, 4.00)
DLco, % predicted§	2.00 (–7.00, 7.00)	0.00 (–6.00, 7.00)
CRISS score	0.61 (0.34, 0.88)	0.03 (<0.001, 0.80)

* Values are the median (interquartile range). MMF = mycophenolate mofetil; CRISS = composite response index in diffuse cutaneous systemic sclerosis (see Table 1 for other definitions).
† $P = 0.042$ versus placebo + MMF.
‡ $P = 0.029$ versus placebo + MMF.
§ Adjusted for hemoglobin level.

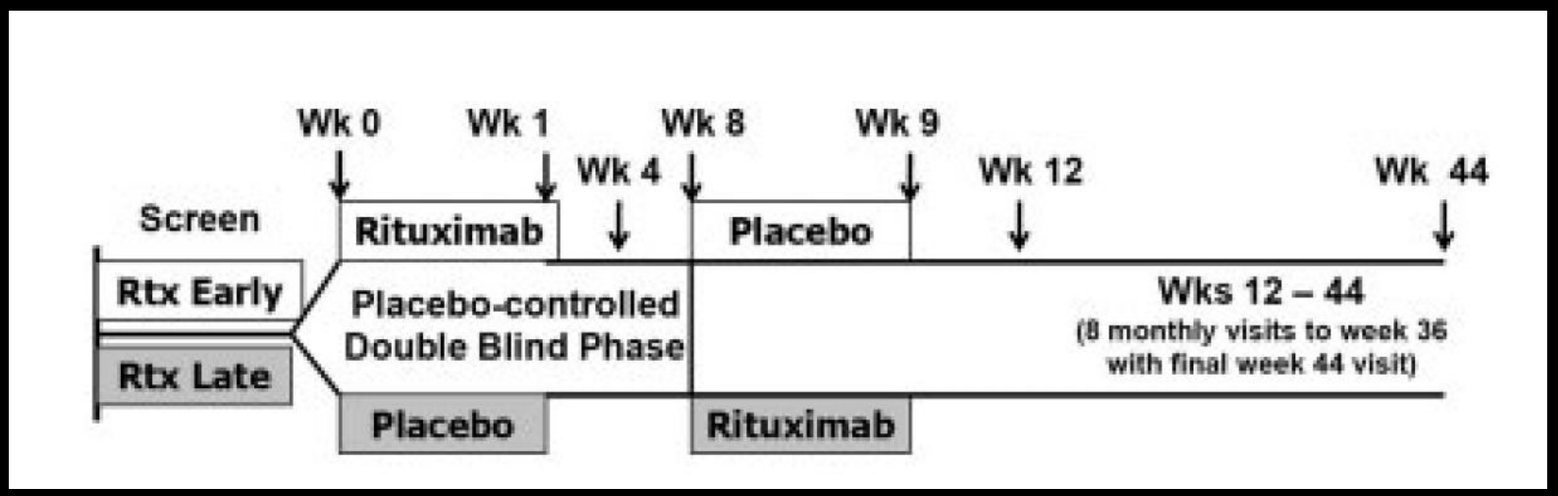
Φλεγμονώδεις μυοπάθειες

ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 314–324
DOI 10.1002/art.37754

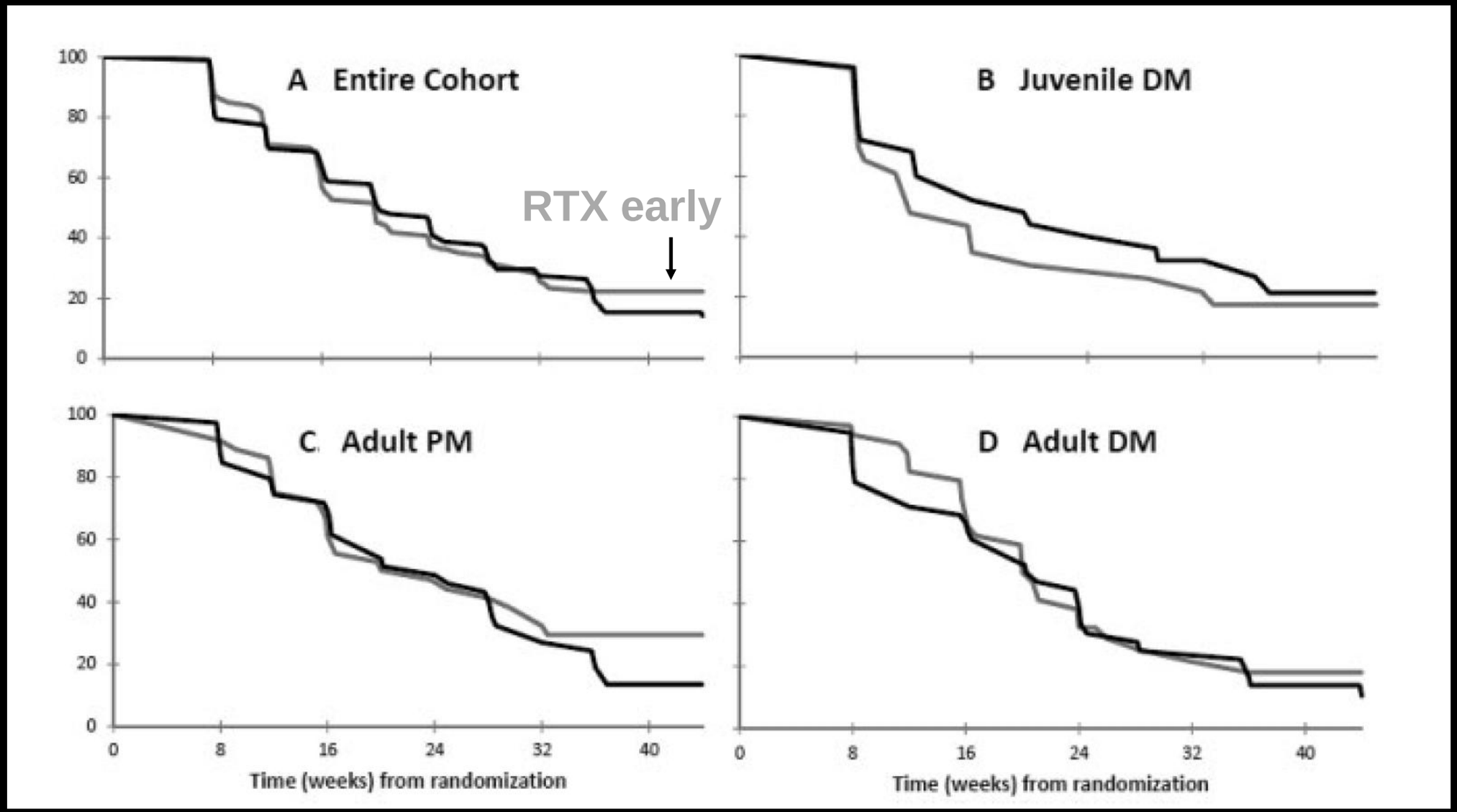
Rituximab in the Treatment of Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis

A Randomized, Placebo-Phase Trial

Chester V. Oddis,[1] Ann M. Reed,[2] Rohit Aggarwal,[1] Lisa G. Rider,[3] Dana P. Ascherman,[4] Marc C. Levesque,[1] Richard J. Barohn,[5] Brian M. Feldman,[6] Michael O. Harris-Love,[7] Diane C. Koontz,[1] Noreen Fertig,[1] Stephanie S. Kelley,[1] Sherrie L. Pryber,[8] Frederick W. Miller,[3] Howard E. Rockette,[1] and the RIM Study Group



Ποσοστά ασθενών που ΑΠΟΤΥΓΧΑΝΟΥΝ
(RTX σε ασθενείς με Φλ. Μυοπάθειες)



ARTHRITIS & RHEUMATISM
Vol. 65, No. 2, February 2013, pp 314–324

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis

M.E. Wechsler, P. Akuthota, D. Jayne, P. Khoury, A. Klion, C.A. Langford, P.A. Merkel, F. Moosig, U. Specks, M.C. Cid, R. Luqmani, J. Brown, S. Mallett, R. Philipson, S.W. Yancey, J. Steinfeld, P.F. Weller, and G.J. Gleich, for the EGPA Mepolizumab Study Team*

N Engl J Med 2017;376:1921-32.

Mepolizumab vs. Placebo in EGPA: Αποτελεσματικότητα

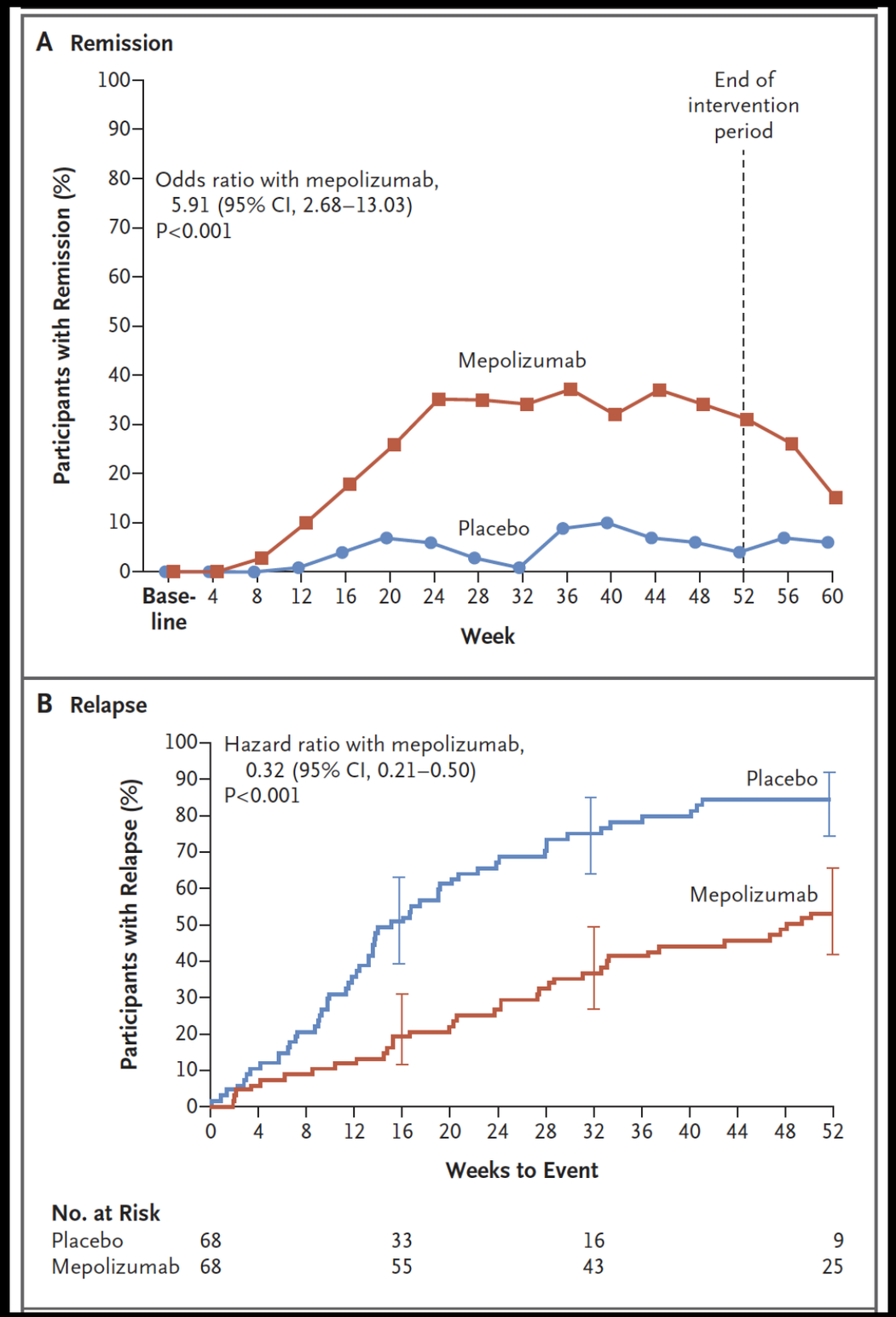
Table 2. Efficacy End Points in the Intention-to-Treat Population.*

End Point	Mepolizumab (N = 68)	Placebo (N = 68)	Odds Ratio or Hazard Ratio (95% CI)	P Value
	no. of participants (%)			
Primary end points				
Accrued weeks of remission over 52-wk period			5.91 (2.68–13.03)	<0.001
0 wk	32 (47)	55 (81)		
>0 to <12 wk	8 (12)	8 (12)		
12 to <24 wk	9 (13)	3 (4)		
24 to <36 wk	10 (15)	0		
≥36 wk	9 (13)	2 (3)		
Remission at wk 36 and wk 48	22 (32)	2 (3)	16.74 (3.61–77.56)	<0.001
Other end points				
Remission within the first 24 wk that was sustained until wk 52	13 (19)	1 (1)	19.65 (2.30–167.93)	0.007
First EGPA relapse	38 (56)	56 (82)	0.32 (0.21–0.50)	<0.001

N Engl J Med 2017;376:1921-32.

44% vs. 7% (mepo vs. Placebo) λάμβαναν Πρεδνιζόνη ≤ 4mg/d

Mepolizumab vs. Placebo in EGPA: Αποτελεσματικότητα



N Engl J Med 2017;376:1921-32.

ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 1, January 2018, pp 109–114
DOI 10.1002/art.40339

BRIEF REPORT

Rituximab for the Treatment of Adult-Onset IgA Vasculitis (Henoch-Schönlein)

Federica Maritati,[1] Roberta Fenoglio,[2] Evangeline Pillebout,[3] Giacomo Emmi,[4] Maria L. Urban,[1] Rossana Rocco,[1] Maria Nicastro,[1] Monia Incerti,[1] Matteo Goldoni,[5] Giorgio Trivioli,[1] Elena Silvestri,[4] Aladdin J. Mohammad,[6] David Jayne,[7] Per Eriksson,[8] Marten Segelmark,[8] Pavel Novikov,[9] Helen Harris,[10] Dario Roccatello,[2] and Augusto Vaglio[1]