«Επιτυχής θεραπευτική προσέγγιση με τα εκτός ένδειξης φάρμακα;»

11ο Ετήσιο Πανελλήνιο Επιστημονικό Συνέδριο ΕΠΕΜΥ
«Κλινικά Διλήμματα στις Μυοσκελετικές Παθήσεις»

ΚΕΡΚΥΡΑ ΑΠΡΙΛΙΟΣ 2019

Μπούνια Κωνσταντίνα
Επικουρική Ρευματολόγος
Ρευματολογικό τμήμα
ΠΓΝΠατρών

Δεν υπάρχει σύγκρουση συμφερόντων

ΣΥΣΤΗΜΑΤΙΚΗ ΣΚΛΗΡΟΔΕΡΜΙΑ

- MMF
- RITUXIMAB
- TOCILIZUMAB

MMF

Ευεργετική δράση

- Δέρμα
- Διάμεση πνευμονοπάθεια
- Επιβίωση

ασφαλής επιλογή

Safety and Effectiveness of Mycophenolate in Systemic Sclerosis. A Systematic Review

Mohammed A. Omair[1,3], Abdulaziz Alahmadi[1], Sindhu R. Johnson[1,2]*

Table 2. Effect of mycophenolate mofetil on modified Rodnan skin score.

mrss

Author	Duration of Therapy (months)	Mean baseline MRSS	Median baseline MRSS	MRSS at end of study	Level of significance
Stratton et al.[19]	12	28	NA	17	$p < 0.001$
Vanthuyne et al.[25]	12	20	NA	13	$p < 0.0001$ for all patients $p = 0.002$ for skin group
Nihtyanova et al.[27]	60	NA	26	11	NA
Le et al.[31]	12	24.4	NA	17.5	$p < 0.001$
Mendoza et al.[20]	Mean 18.2	24.56	NA	14.5	$p = 0.0004$
Derk et al.[21]	12	22.5	21.5	8.4	$p < 0.0001$
Koutroumpas et al.[29]	12	17.2	NA	17.7	$p = 0.55$
Herrick et al.[23]					$p = 0.43$
Protocol 1	36	NA	24	NA	−1.81 (95%CI—4.08, 0.460)
Protocol 2	36	NA	32	NA	−4.46 (95%CI—6.69, −2.23)
Protocol 3	36	NA	23.5	NA	−3.10 (95%CI—4.27, −1.93)

Table 3. Effect of mycophenolate on pulmonary function.

FVC DLCO

	Duration of Therapy (months)	Baseline DLCO (% predicted)	DLCO at end of study (% predicted)	Level of significance	Baseline FVC (% predicted)	FVC at end of study (% predicted)	Level of significance
Stratton et al.[19]	12	66	63	Not significant	87	88	Not significant
Vanthuyne et al.[25]	12	63	76	p = 0.0009	NA	NA	NA
Le et al.[31]	12	77.4	79.2	p = 0.336	79.4	80.7	p = 0.264
Mendoza et al.[20]	18.2	69	70.5	p = 0.45	NA	NA	NA
Cuomo et al.[36]	5	60	NA	NA	104	NA	NA
Saketkoo et al.[37]	3	30	NA	NA	80	NA	NA
Zamora et al.[28]	24	50	NA	p = 0.84	72	NA	p = 0.57
Gerbino et al.[26]	24	51	NA	p = 0.38	NA	NA	NA
Derk et al.[21]	12	71.2	74.3	Not significant	99.2	105	Not significant
Koutroumpas et al.[29]	12	80.7	86.7	p = 0.66	79.5	87.1	p = 0.04
Simeon-Aznar et al.[22]	12	40	37	NA	64	64	NA
Liossis et al.[24]	4–6	64.2	75.4	p = 0.033	65.6		p = 0.057
Herrick et al.[23]							
Protocol 1	36	58.8	NA	NA	76	NA	NA
Protocol 2	36	76.1	NA	NA	93.3	NA	NA
Protocol 3	36	71.5	NA	NA	87.8	NA	NA

NA not available, DLCO diffusing capacity of carbon monoxide, FVC functional vital capacity, VC vial capacity, TLC total lung capacity

ΑΝΕΠΙΘΥΜΗΤΕΣ ΕΝΕΡΓΕΙΕΣ MMF

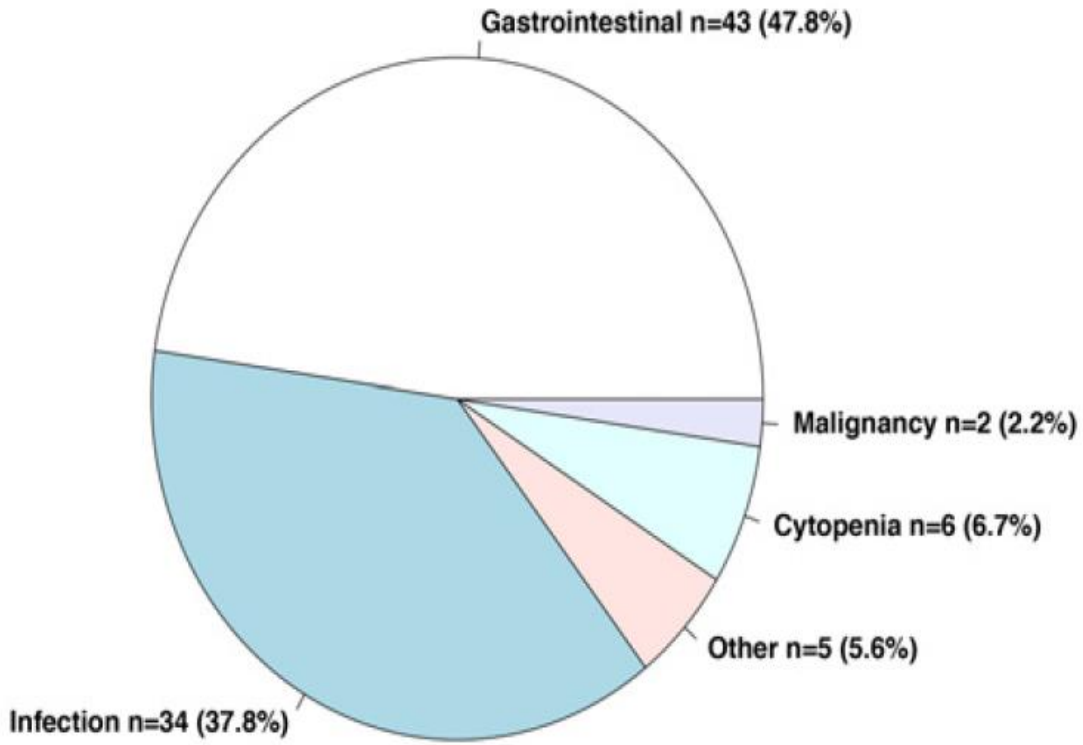


Fig 2. Circle chart of non-lethal adverse events in SSc patients treated with mycophenolate.

doi:10.1371/journal.pone.0124205.g002

Mycophenolate versus Placebo for Systemic Sclerosis-Related Interstitial Lung Disease: An Analysis of Scleroderma Lung Studies I and II

Elizabeth R. Volkmann, M.D., M.S.1, Donald P. Tashkin, M.D.1, Ning Li, Ph.D.2, Michael D. Roth, M.D.1, Dinesh Khanna, M.D., M.S.3, Anna-Maria Hoffmann-Vold, M.D., Ph.D.4, Grace Kim, Ph.D.5, Jonathan Goldin, M.D., Ph.D.5, Philip J. Clements, M.D., M.P.H.1, Daniel E. Furst, M.D.1, and Robert M. Elashoff, Ph.

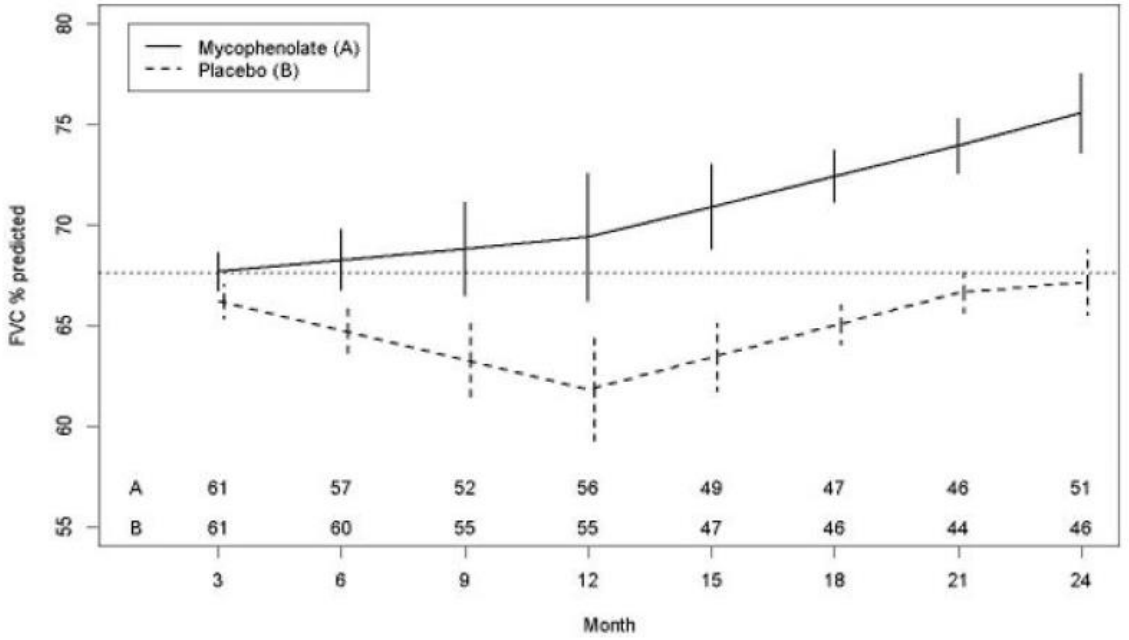


Figure 1. Course of the FVC% from 3 to 24 Months in SLS II Patients Assigned to MMF versus SLS I Patients Assigned to Placebo Using Joint Model Analysis

The test of the overall treatment group effect is significant at P<0.0001. Pre-specified covariates for this model included the baseline FVC%-predicted and baseline QILD-WL. The dotted line represents the mean baseline value for the entire cohort.

ΒΕΛΤΙΩΣΗ FVC

ΒΕΛΤΙΩΣΗ DLCO

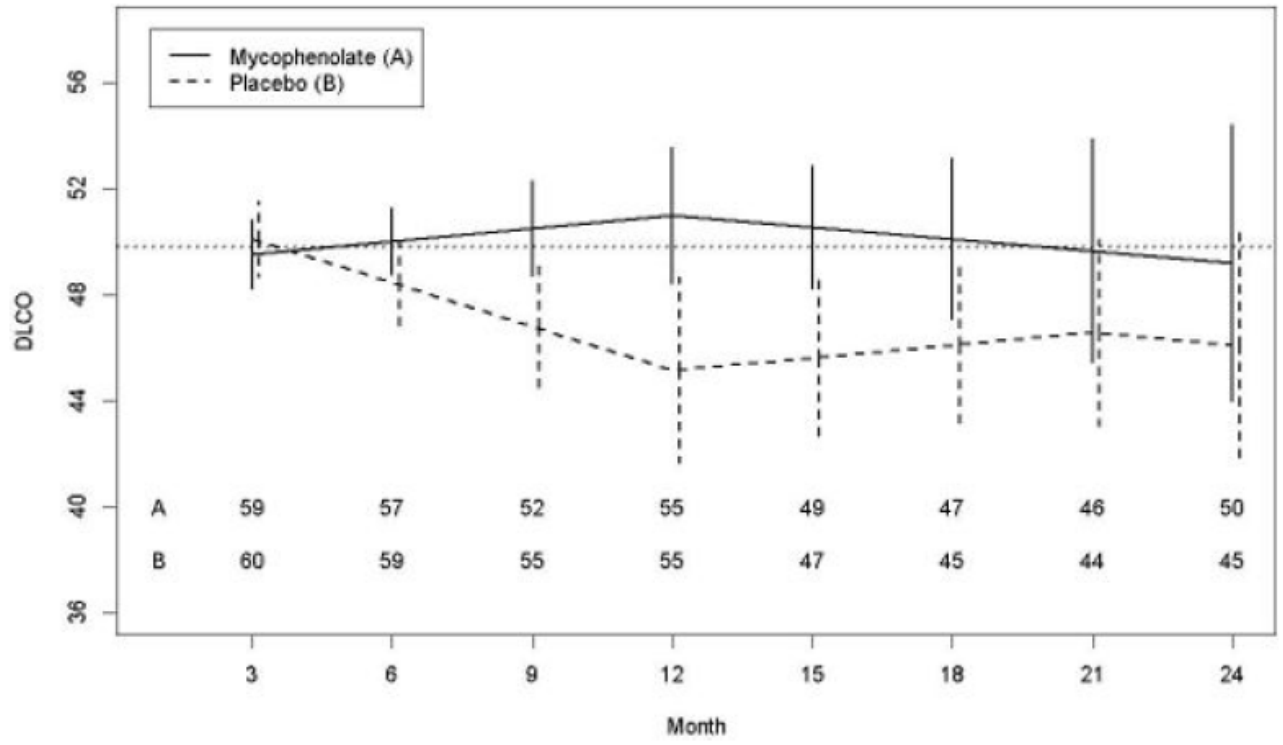


Figure 2. Course of the DLCO% from 3 to 24 Months in SLS II Patients Assigned to MMF versus SLS I Patients Assigned to Placebo Using Joint Model Analysis

The test of the overall treatment group effect is significant at P<0.0001. Pre-specified covariates for this model included the baseline DLCO%-predicted and baseline QILD-WL. The dotted line represents the mean baseline value for the entire cohort.

MRSS ΒΕΛΤΙΩΣΗ

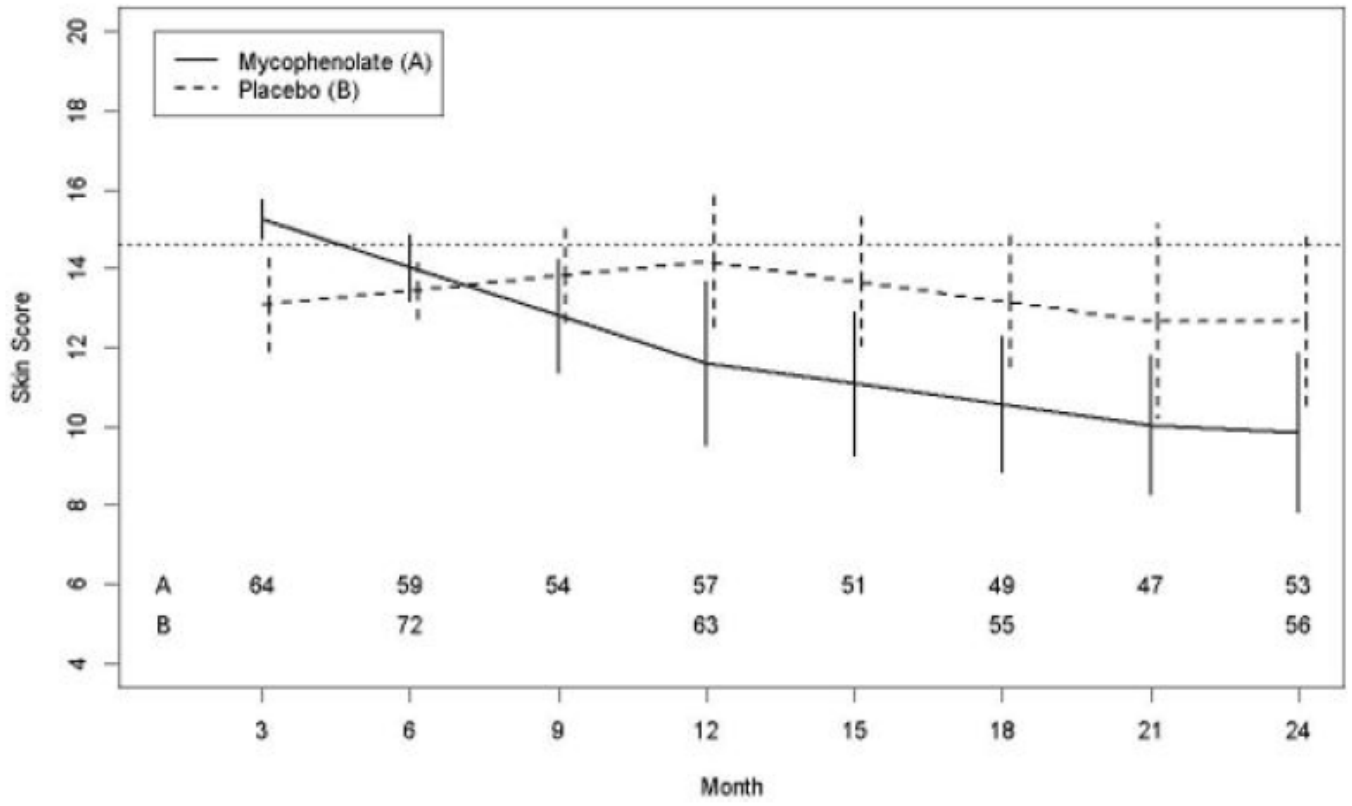
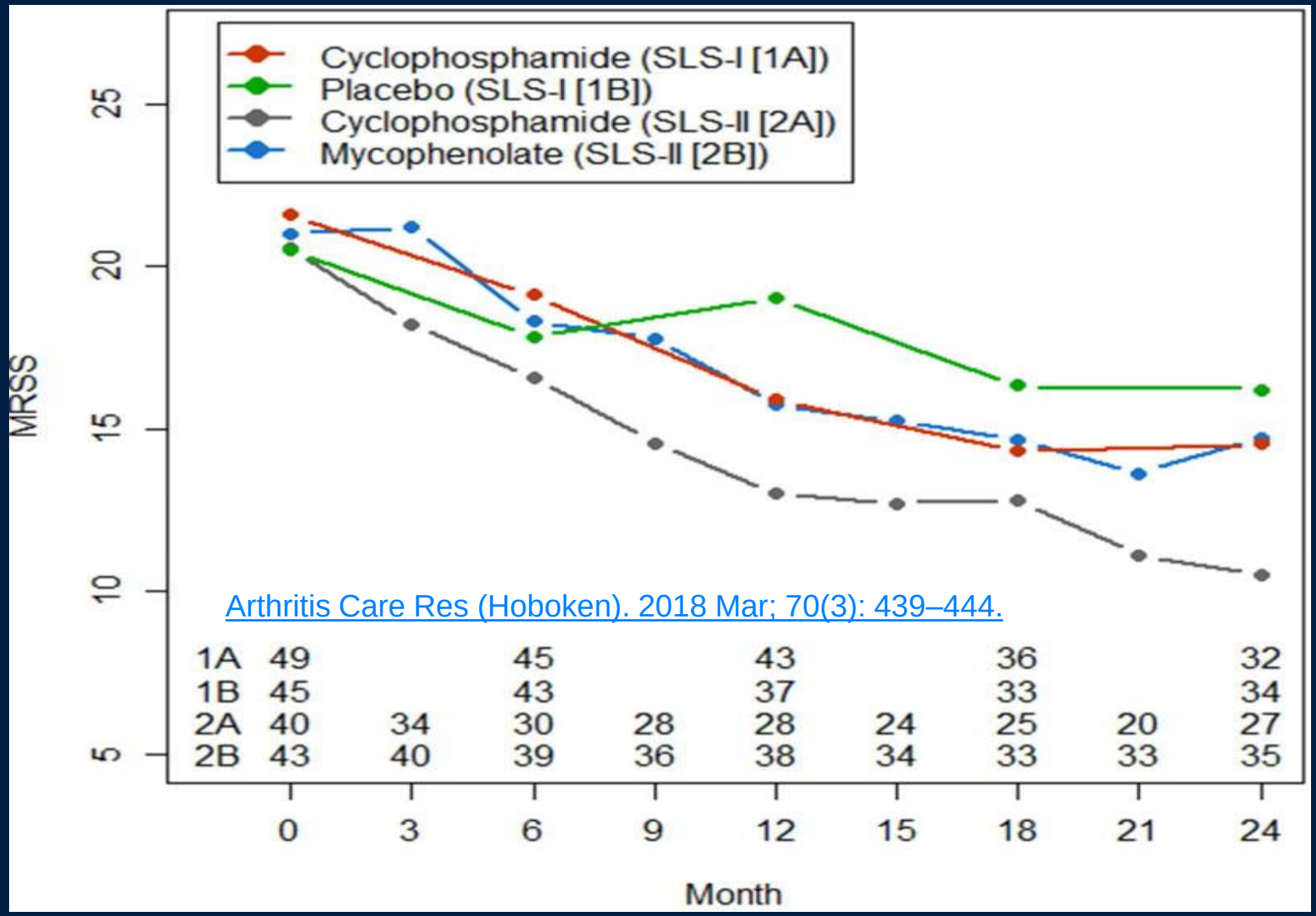


Figure 3. Course of the MRSS from 3 to 24 Months in SLS II Patients Assigned to MMF versus SLS I Patients Assigned to Placebo Using Joint Model Analysis

The test of the overall treatment group effect is significant at P<0.0001. The dotted line represents the mean baseline value for the entire cohort.

Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: post-hoc analyses from the Scleroderma Lung Study I and II

Rajaie Namas, MD,[1] Donald P. Tashkin, MD, MS,[2] Daniel E. Furst, MD,[3] Holly Wilhalme,[4] Chi-hong Tseng, PhD,[4] Michael D. Roth, MD,[2] Suzanne Kafaja, MD,[3] Elizabeth Volkmann, MD, MS,[3] Philip J. Clements, MD, MPH,[3] and Dinesh Khanna, MD, MS[1,†]



Arthritis Care Res (Hoboken). 2018 Mar; 70(3): 439–444.

RITUXIMAB

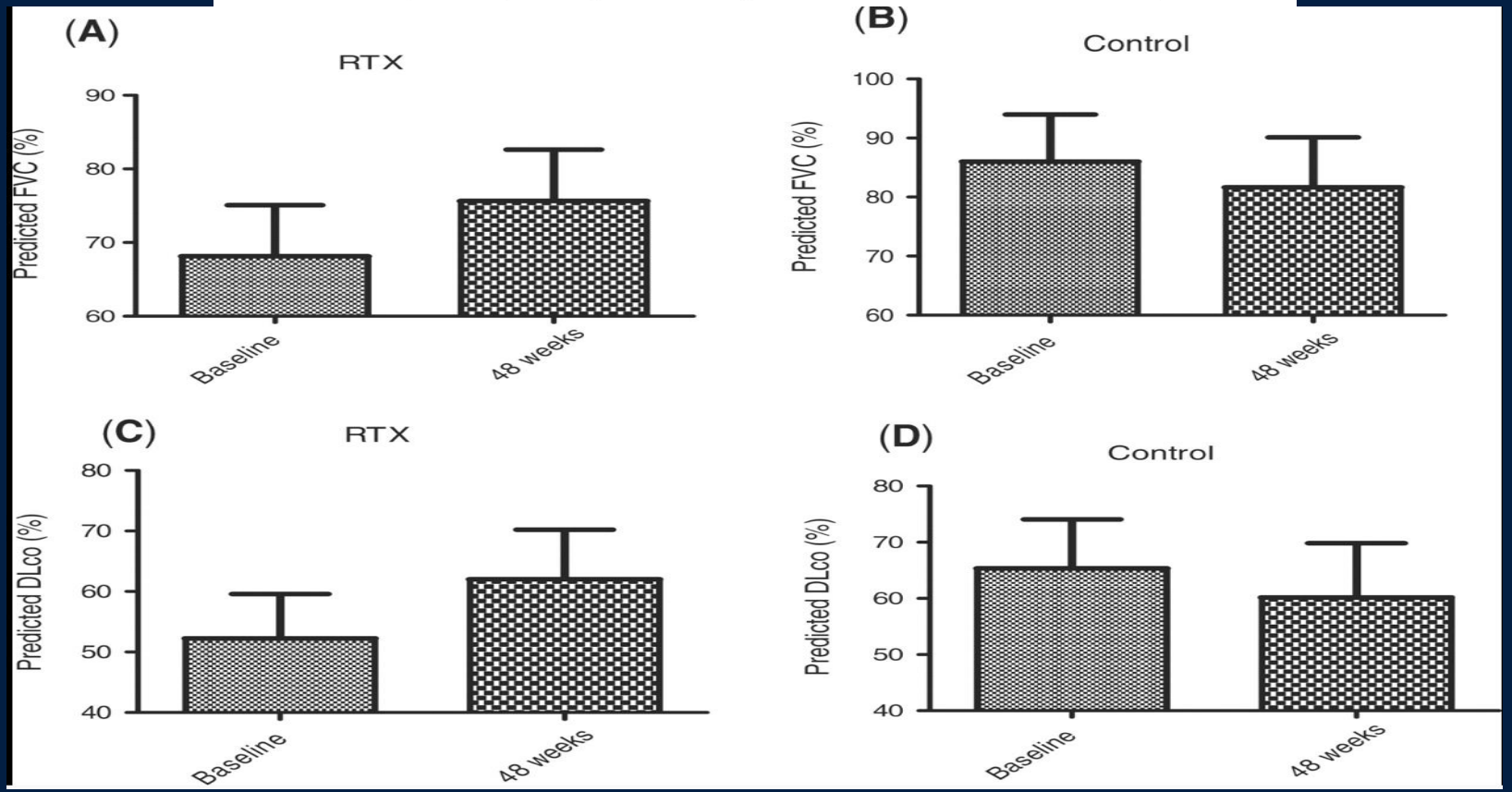
RHEUMATOLOGY

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]



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*
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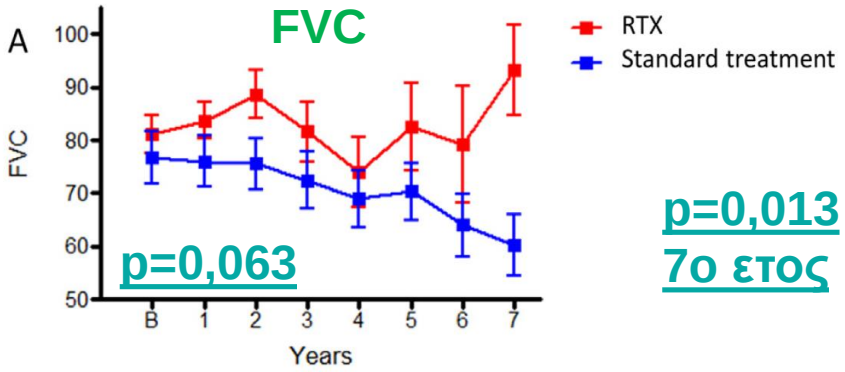
[d] *Department of Rheumatology, Agios Andreas District Hospital, Patras, Greece*
[e] *Department of Medical Physics, University of Patras, Patras, Greece*



p=0,013
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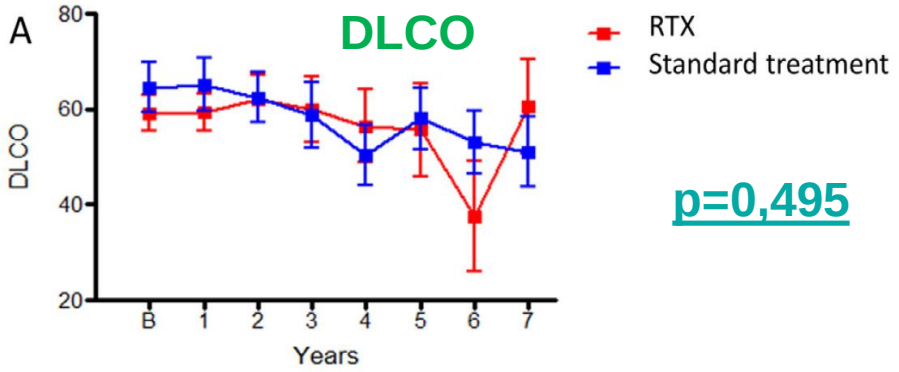
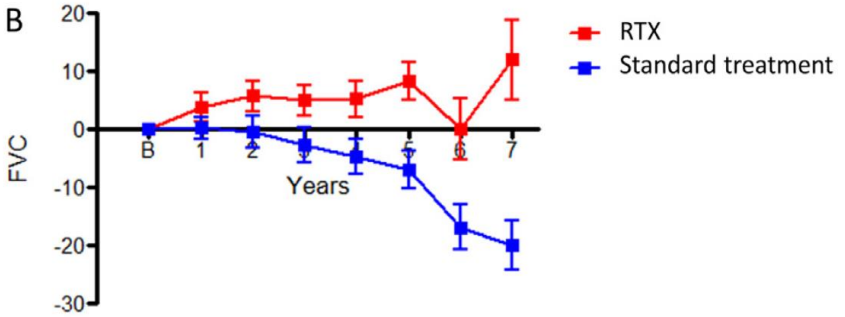
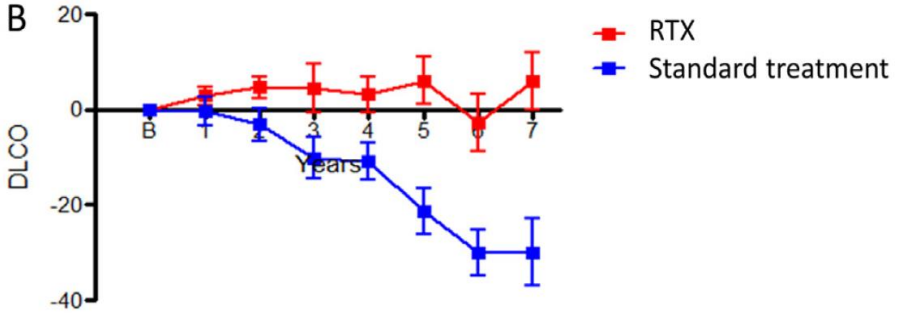
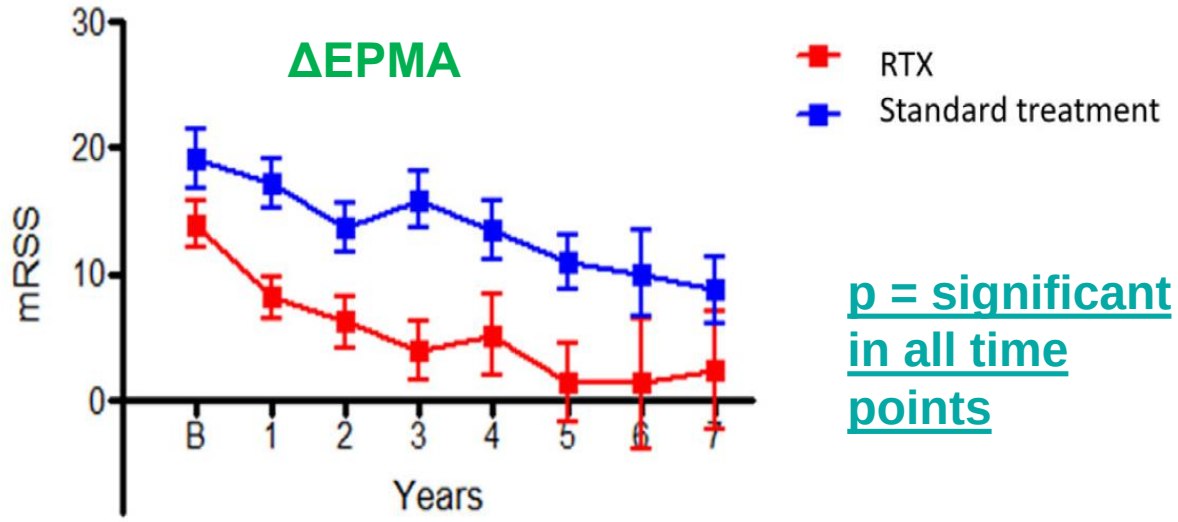


p=0,495

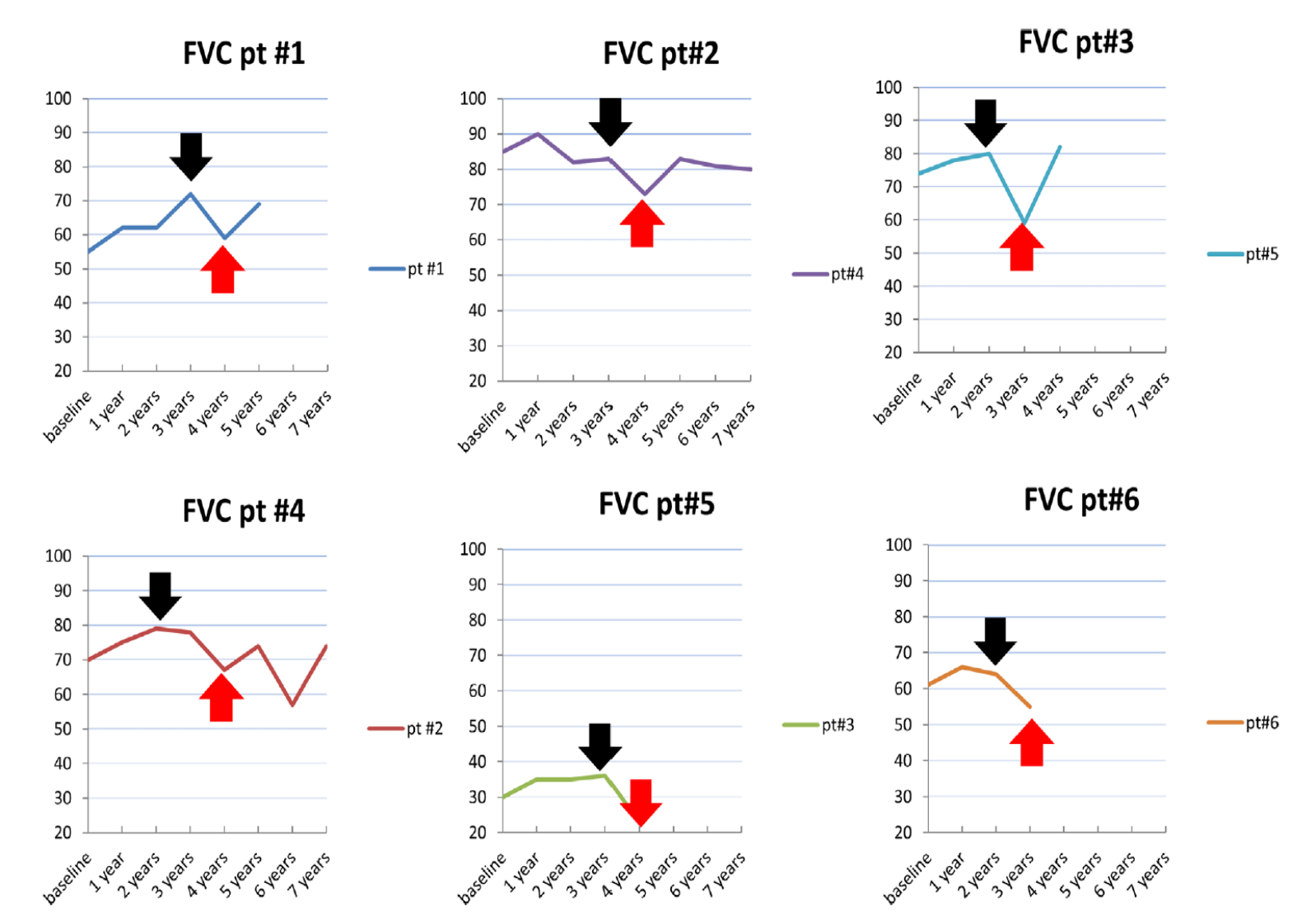






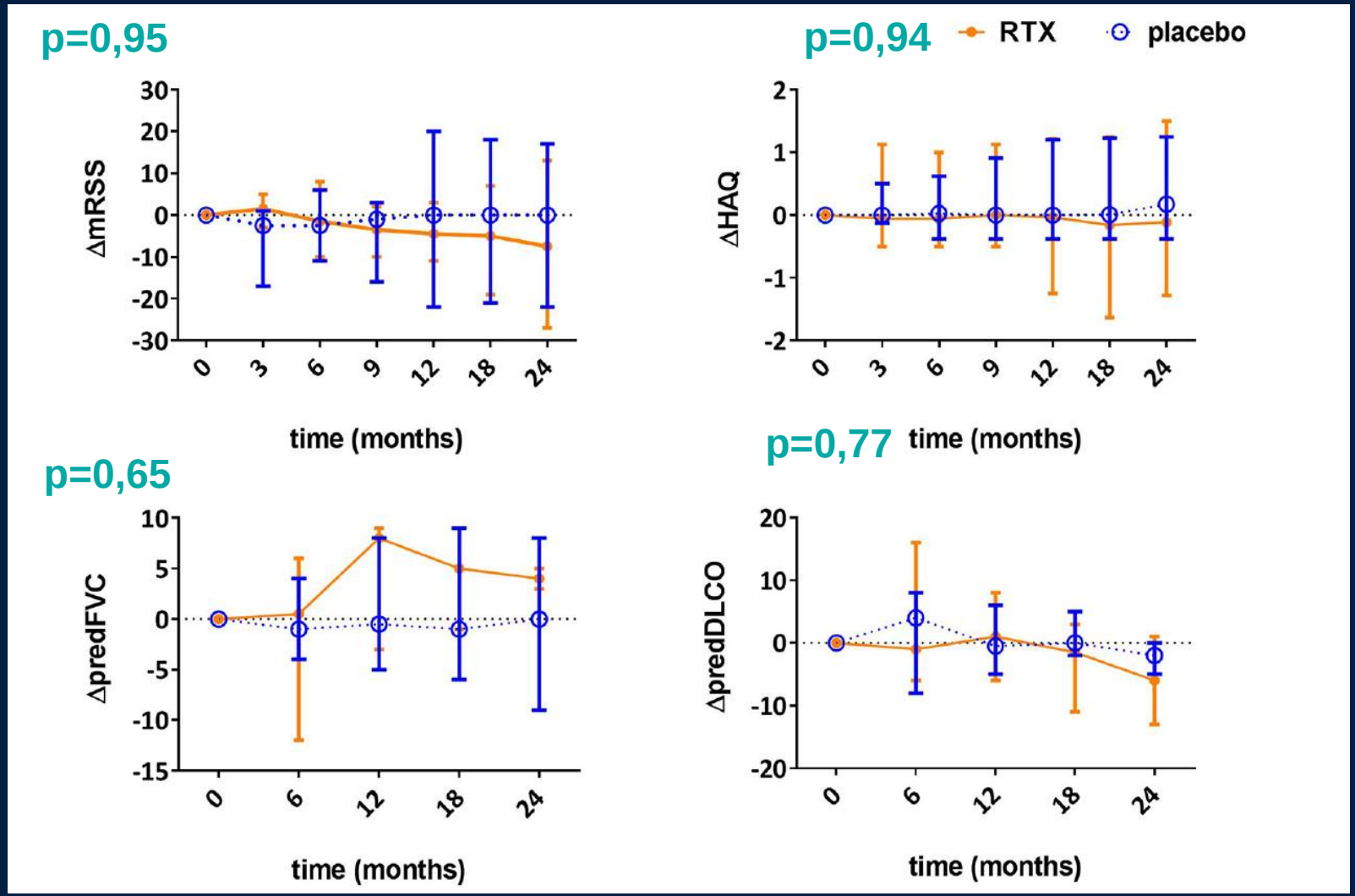
p = significant in all time points

ΔΙΑΚΟΠΗ ΚΙ ΕΠΑΝΕΝΑΡΞΗ RITUXIMAB



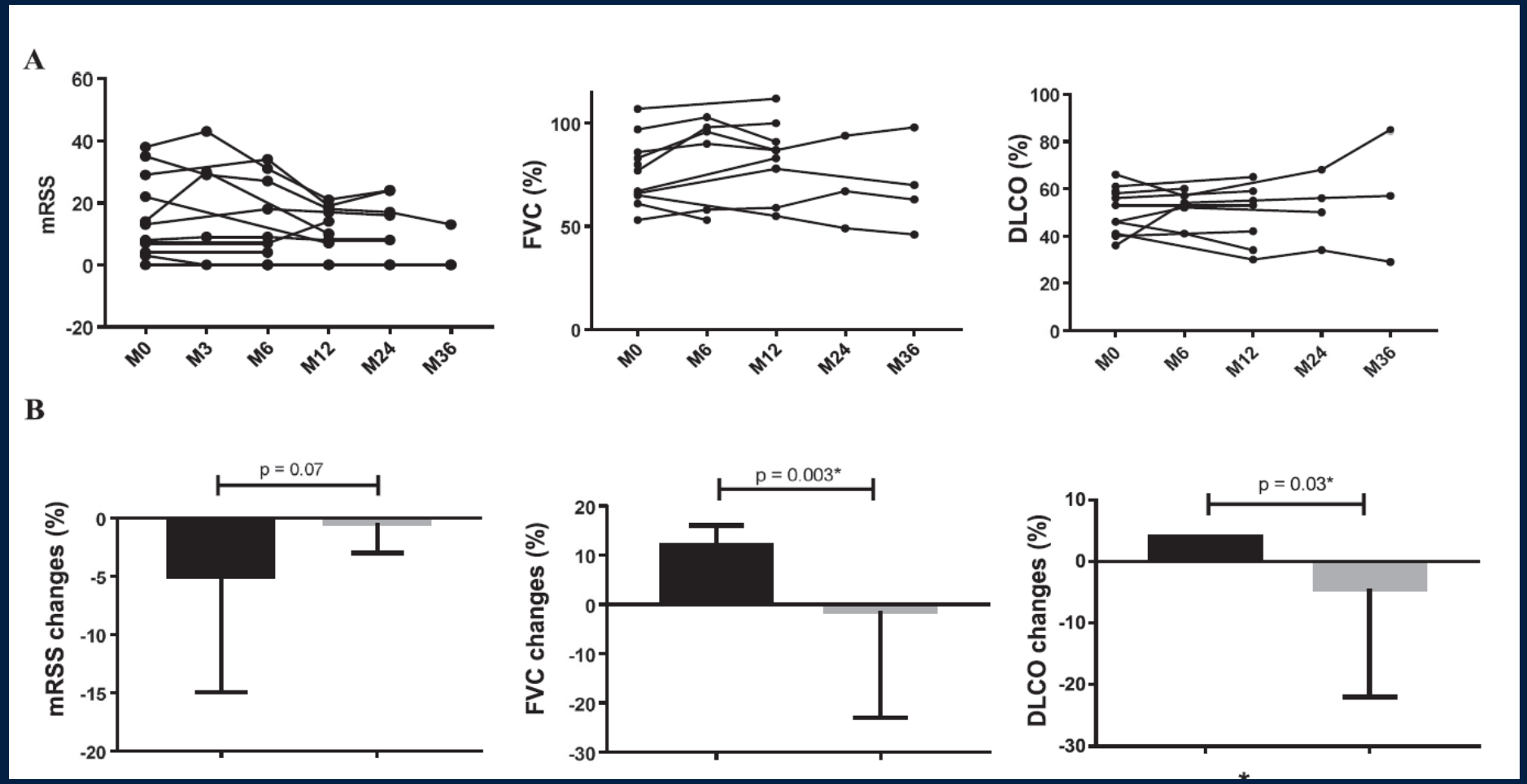
Rituximab in early systemic sclerosis

Maaike Boonstra,[1] Jessica Meijs,[1] Annemarie L Dorjée,[1] Nina Ajmone Marsan,[2] Anne Schouffoer,[1,3] Maarten K Ninaber,[4] Koen D Quint,[5] Femke Bonte-Mineur,[6] Tom W J Huizinga,[1] Hans U Scherer,[1] Jeska K de Vries-Bouwstra[1]

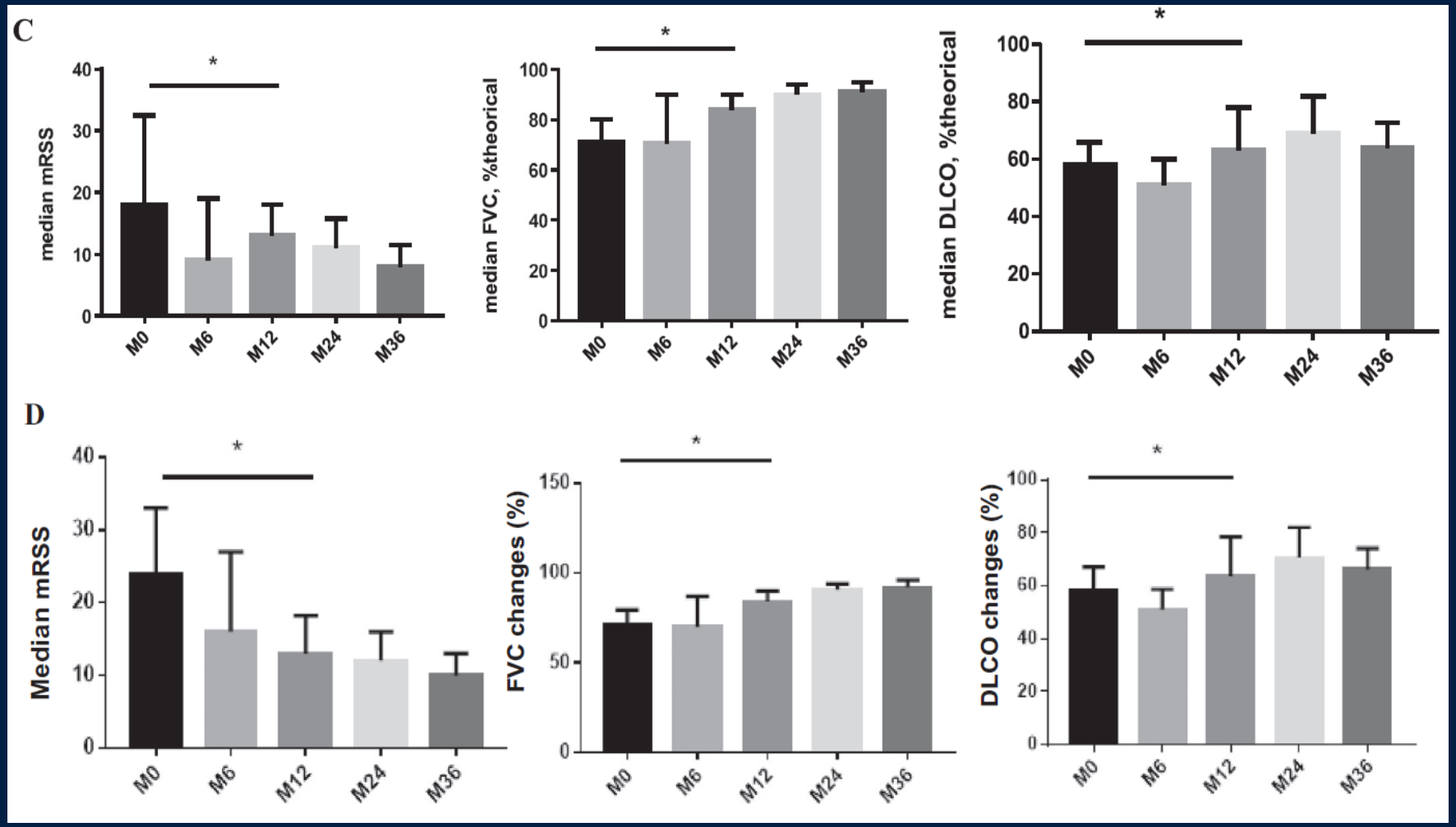


Efficacy and safety of rituximab in systemic sclerosis: French retrospective study and literature review

Mathilde Thiebaut a,b, David Launay c,d,e,f, Sébastien Rivière a, ThibaultMahévas a, Syrine Bellakhal g, Eric Hachulla c,d, Olivier Faina,b, Arsène Mekinian a,b,⁎Autoimmunity Reviews 17 (2018) 582–587



Skin and interstitial lung disease outcome under rituximab in our personal series and literature data. A: Changes ofmRSS, FVC and DLCO in 13 SSc patients after rituximab (personal series). B: Changes ofmRSS, FVC and DLCO in dSSc patients after rituximab (RTX+)vs dSSc not treated by rituximab (RTX-) (personal series).



C:mRSS, FVC and DLCO atM0,M6,M12,M24 and M36 in 53 SSc patients who received rituximab and D in 42 patients with diffuse SSc (personal series and literature date).

Intravenous cyclophosphamide *vs* rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial

Geetabali Sircar[1], Rudra Prosad Goswami[1], Dipankar Sircar[2], Alakendu Ghosh[1] and Parasar Ghosh[1]

Parameter	Rituximab ($n=30$)		
	Baseline, mean (S.D.)	6 months, mean (S.D.)	*P*-value
Forced vital capacity, %	61.30 (11.28)	67.52 (13.59)	0.002[a]
Forced vital capacity, l	1.51 (0.45)	1.65 (0.47)	<0.001
Modified Rodnan skin score at baseline	21.77 (9.86)	12.10 (10.14)	<0.001
Medsgers severity scale	8.33 (3.04)	4.67 (2.35)	<0.001
6-min walking test, m	359.63 (65.95)	409.60 (69.29)	<0.001
Pulmonary hypertension present (%)	4 (13)	5 (16)	

Parameter	CYC ($n=30$)			Difference at 6 months	*P*-value
	Baseline, mean (S.D.)	6 months, mean (S.D.)	*P*-value	Mean (95% CI)	
Forced vital capacity, %	59.25 (12.96)	58.06 (11.23)	0.496[a]	9.46 (3.01 to 15.90)*	0.003[b]
Forced vital capacity, l	1.42 (0.49)	1.42 (0.46)	0.356	0.23 (−0.013 to 0.47)**	0.091[b]
Modified Rodnan skin score at baseline	23.83 (9.28)	18.33 (7.69)	<0.001	−6.23 (−10.88, −1.58)***	0.001[b]
Medsgers severity scale	9.60 (2.44)	5.96 (2.81)	<0.001	−1.30 (−2.64, 0.04)#	0.036[b]
6-min walking test, m	335.90 (89.30)	349.14 (99.75)	0.428	60.46 (16.07, 104.84)****	0.001[b]
Pulmonary hypertension present (%)	5 (16)	5 (16)		##	

Rheumatology 2018;57:2106–2113

significantly fewer major adverse events than CYC

TABLE 3 Adverse events in rituximab and CYC groups

Adverse event	Rituximab group (30 patients)	CYC group (30 patients)
Upper respiratory tract infections	2 (6.67)	2 (6.67)
Pneumonia	1 (3.34)	4 (13.4)
Urinary tract infections	1 (3.3)	2 (6.67)
Herpes zoster	1 (3.3)	3 (10)
Cholecystitis (requiring cholecystectomy)	1 (3.3)	0
Premature ovarian failure	0	2 (6.67)
Gangrene	0	1 (3.34)
Malignancy	0	1 (3.34)
Leukopenia	0	2 (6.67)
Vomiting	0	4 (13.4)
Transfusion reactions	3 (10)	0

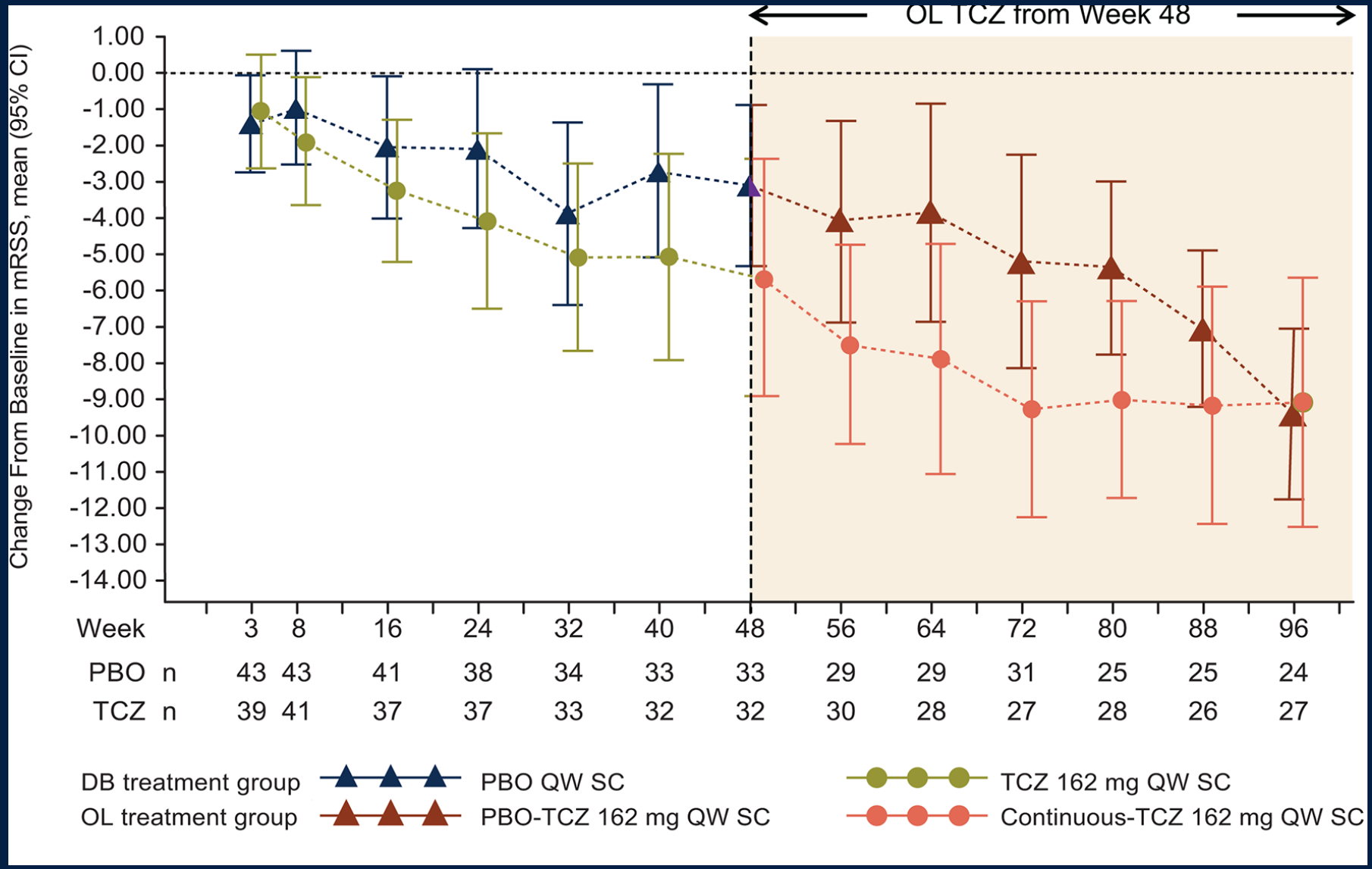
Values are *n* (%) of the total patient population.

TOCILIZUMAB

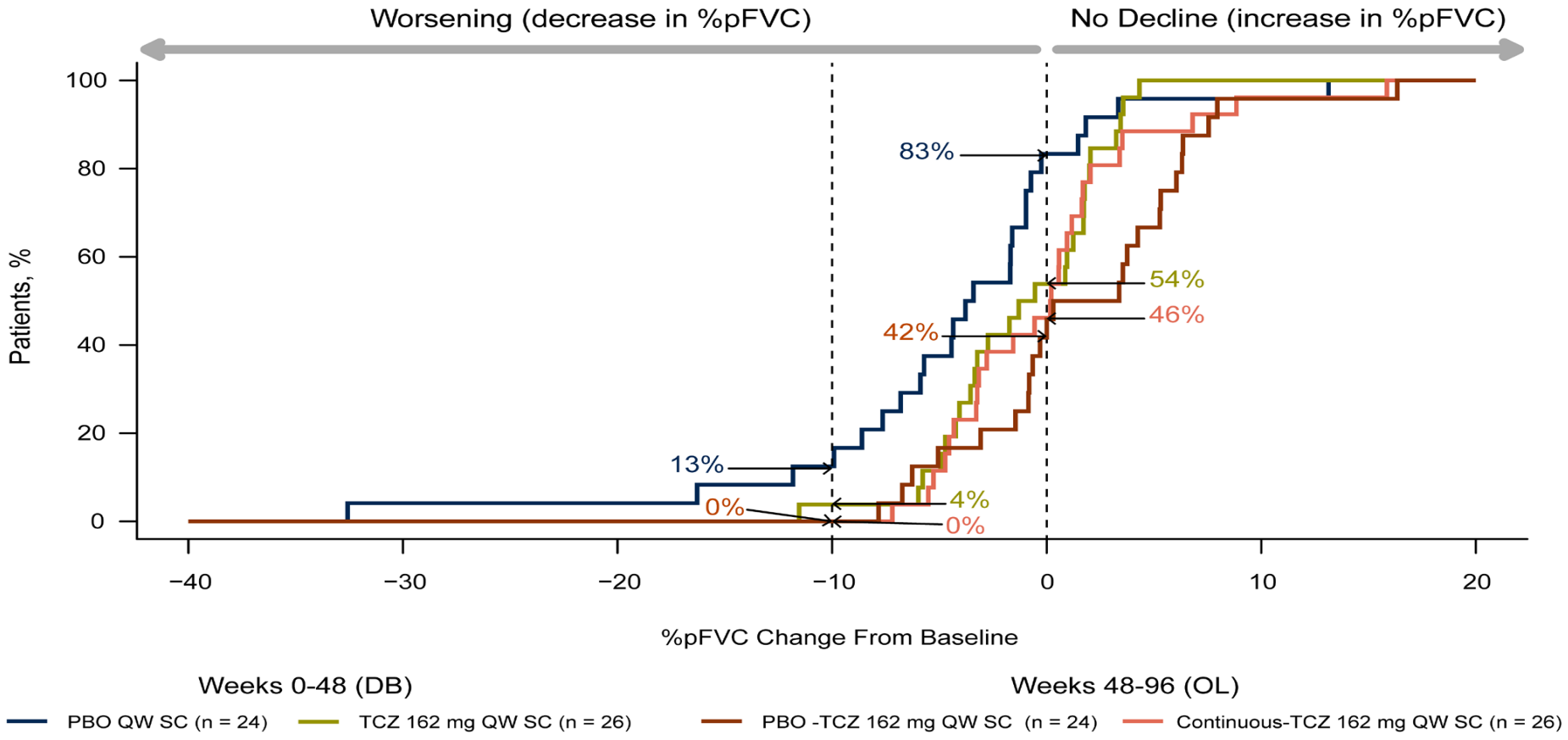
Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate)

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]

MRSS ΔEPMA



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



	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]

A.E.

Table 3 Adverse events (AEs, safety population)

	Double-blind period		Open-label period	
	Placebo QW SC n=44	Tocilizumab 162 mg QW SC n=43	Placebo-tocilizumab 162 mg QW SC n=31	Continuous-tocilizumab 162 mg QW SC n=30
Exposure, PY	36.8	34.5	30.6	30.3
AEs, n	244	283	126	153
Rate/100 PY (95% CI)	663.5 (582.9 to 752.2)	820.6 (727.8 to 922.0)	412.4 (343.5 to 491.0)	504.4 (427.6 to 590.9)
SAEs, n	28	23	11	5
Rate/100 PY (95% CI)	76.1 (50.6 to 110.0)	66.7 (42.3 to 100.1)	36.0 (18.0 to 64.4)	16.5 (5.4 to 38.5)
Patients with ≥1 SAE, n (%)	16 (36.4)	14 (32.6)	7 (22.6)	4 (13.3)
Patients with ≥1 serious infection, n (%)*	3 (6.8)	9 (20.9)	4 (12.9)	0
AEs leading to death, n	1	3	0	0
Rate/100 PY	2.72	8.70	0.00	0.00
Patients with AEs leading to withdrawal, n (%)	5 (11.4)	6 (14.0)	4 (12.9)†	0
Rate/100 PY	13.60	17.40	13.09	0.00
Patients with injection site reactions, n*	2 (4.5)	3 (7.0)	4 (12.9)	1 (3.3)

Συστηματικές αγγειίτιδες

MTX

AZA

MMF

Omalizumab

Mepolizumab

Tocilizumab

Biologics Will Pump Up the Vasculitis Market

Chris Fellner

Table 2 Leading Treatments for Vasculitis in the U.S. (2015)[4]

Drug Name *Brands*	Therapeutic Class	Indication(s)
Azathioprine *Imuran, Imurel, generics*	Immunosuppressive antimetabolite	Vasculitis
Cyclophosphamide *Endoxan, Cytoxan, generics*	Alkylating agent	Vasculitis
Immunoglobulin (IV) *Numerous brands, including Privigen, Kiovig, Gammagard*	IgG human antibody	KD, LVV
Methotrexate *Numerous generics*	Folic acid analog; anti-neoplastic/antimetabolite	Vasculitis
Mycophenolate mofetil *CellCept, Myfortic, generics*	IMPDH inhibitor	Vasculitis
Prednisone, prednisolone, methylprednisolone *Numerous generics*	Glucocorticoids	Vasculitis
Rituximab* *Rituxan (Biogen Idec/Genentech)*	CD-20 protein inhibitor	MPA, WG

*Only rituximab is approved by the Food and Drug Administration for the treatment of patients with vasculitis.

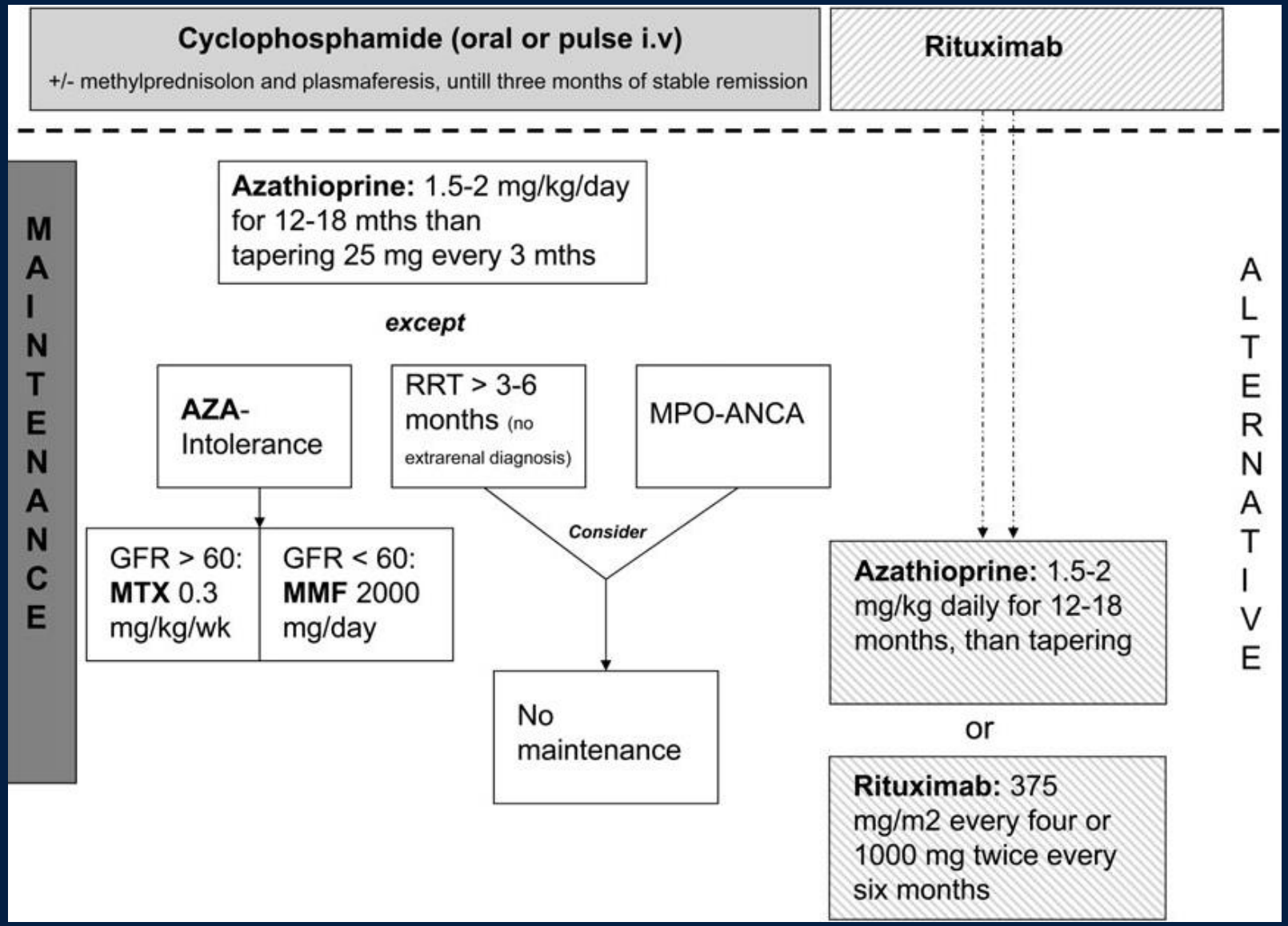
Table 3 Late-Stage Vasculitis Pipeline as of December 2015[4]

Product Name *Company*	Therapeutic Class	Targeted Indication(s)	Developmental Stage(s)
Abatacept (Orencia) *Bristol-Myers Squibb/Ono Pharmaceuticals*	Selective co-stimulating modulator (inhibits T cell activation)	BD, GPA, MPA†	Phase 2 (BD) Phase 3 (GPA)
Apremilast (Otezla) *Celgene*	PDE4 inhibitor	BD	Phase 3
Belimumab (Benlysta) *GlaxoSmithKline*	BLyS-specific inhibitor	GPA, MPA	Phase 3
Infliximab (Remicade) *Janssen Biotech*	TNF inhibitor	KD	Phase 3
Mepolizumab (Nucala) *GlaxoSmithKline*	IL-5 antagonist	eGPA	Phase 3
Tocilizumab (Actemra) *Genentech/Roche*	Anti–IL-6 monoclonal antibody	GCA, TA	Phase 3

Maintenance therapy in antineutrophil cytoplasmic antibody-associated vasculitis: who needs what and for how long?

Anoek A. E. de Joode1, Jan Stephan F. Sanders1, Abraham Rutgers2 and Coen A. Stegeman1

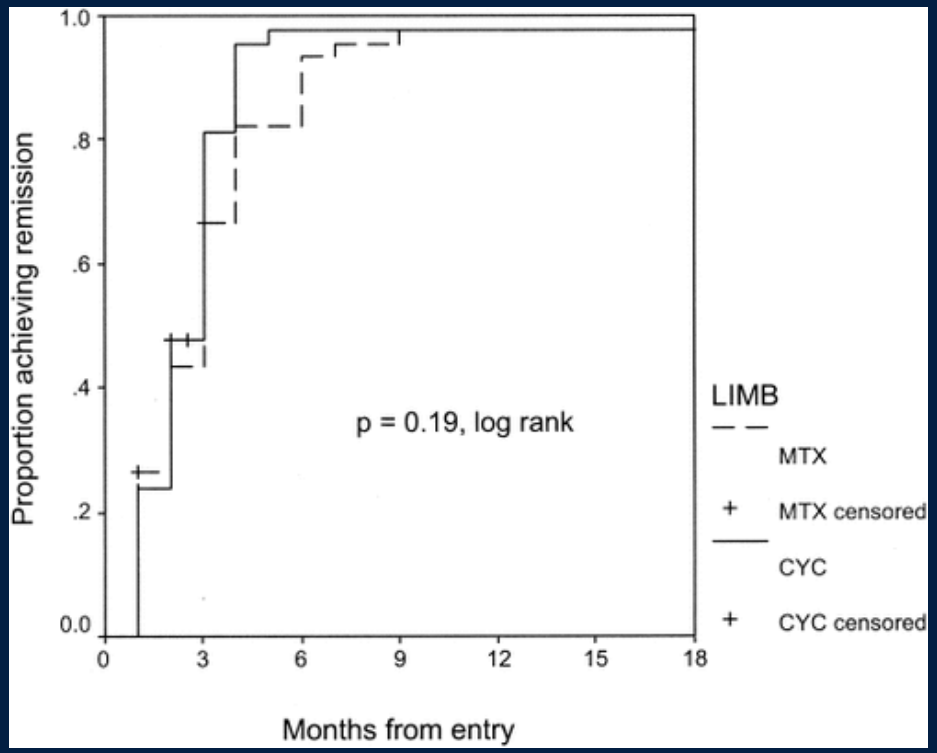
Nephrol Dial Transplant (2015) 30

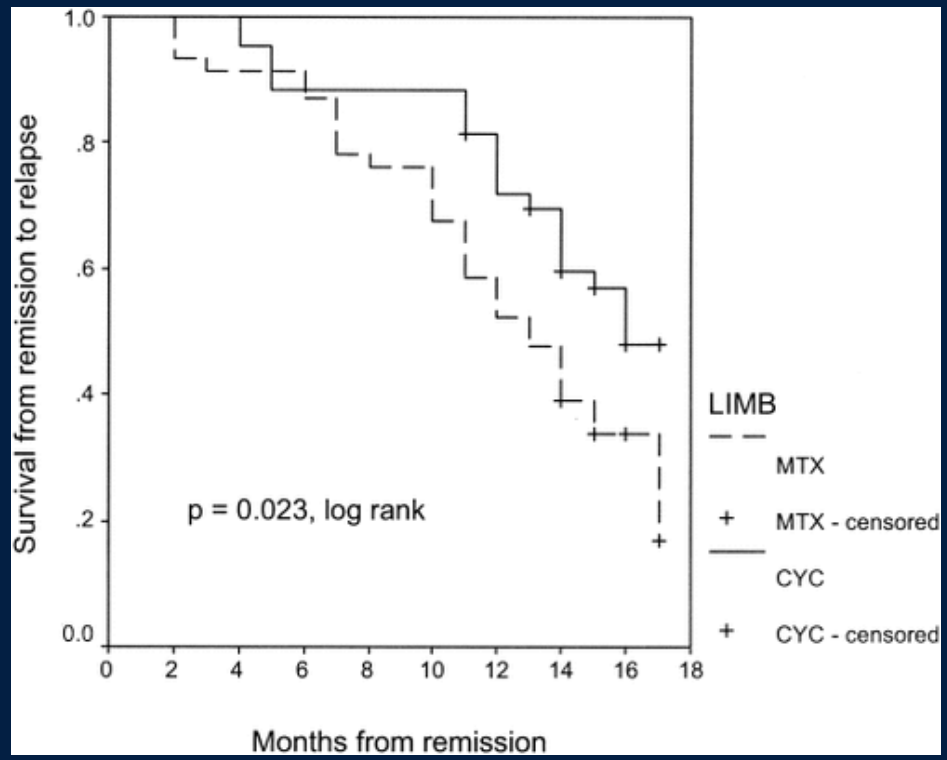


MTX

- Αποτελεσματική σε επαγωγή ύφεσης χωρίς σοβαρή προσβολή AAV
- Ασφαλής και αποτελεσματική για διατήρηση ύφεσης σε AAV

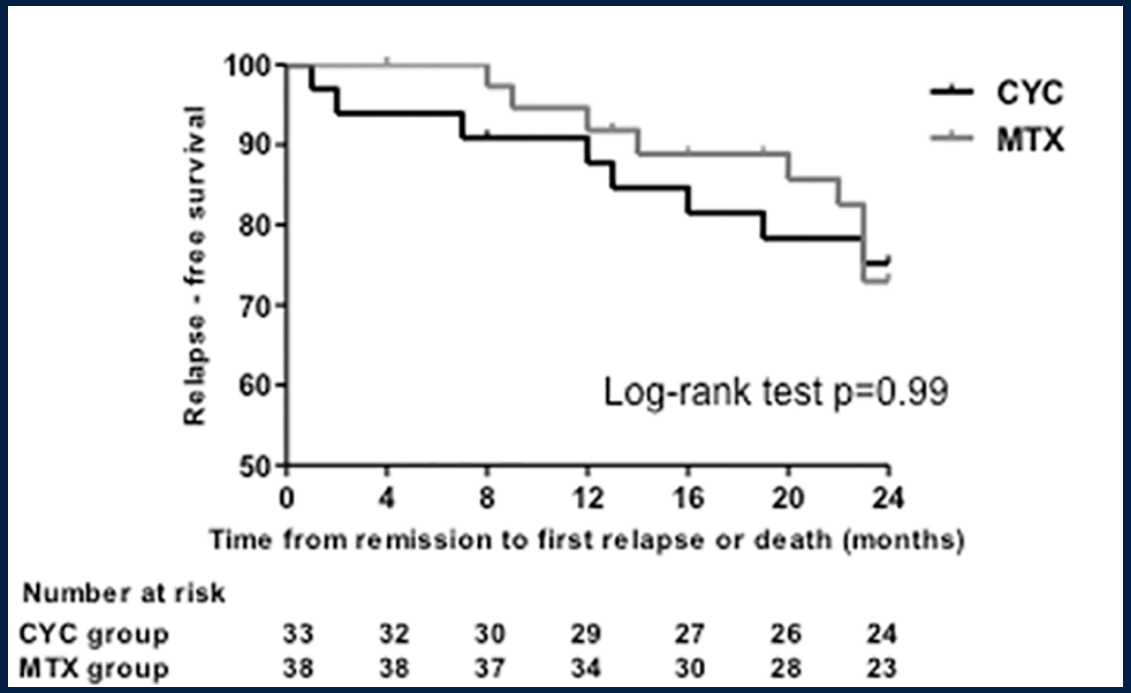
Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody–associated vasculitis

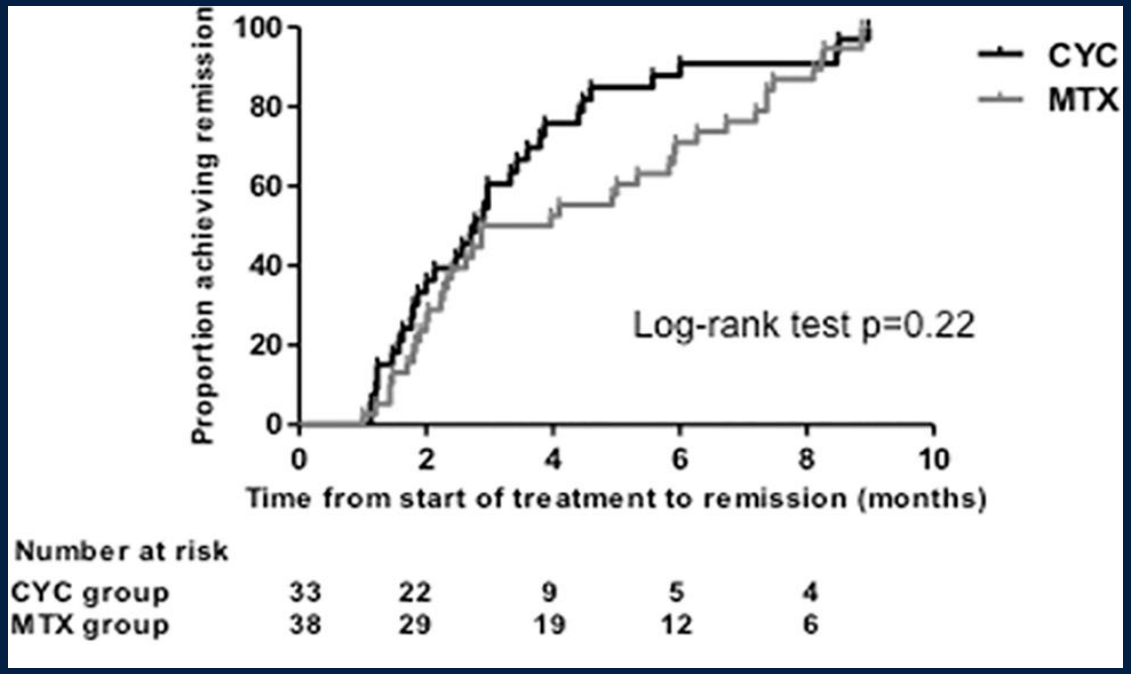




Επαγωγή ύφεσης

Arthritis & Rheumatism, Volume: 52, Issue: 8, Pages: 2461-2469, First published: 28 July 2005, DOI: (10.1002/art.21142)





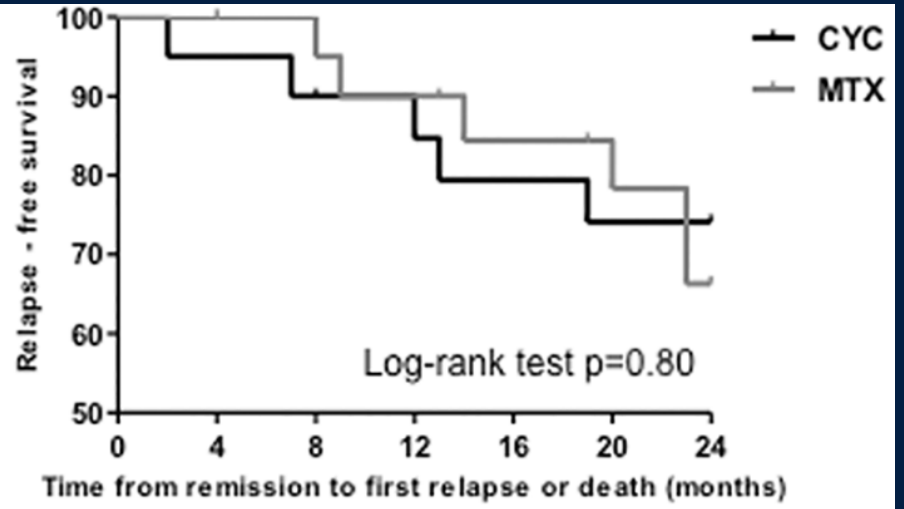
Methotrexate versus cyclophosphamide for remission maintenance in ANCA-associated vasculitis: A randomised trial
Federica Maritati et al

October 10, 2017

Επαγωγή ύφεσης

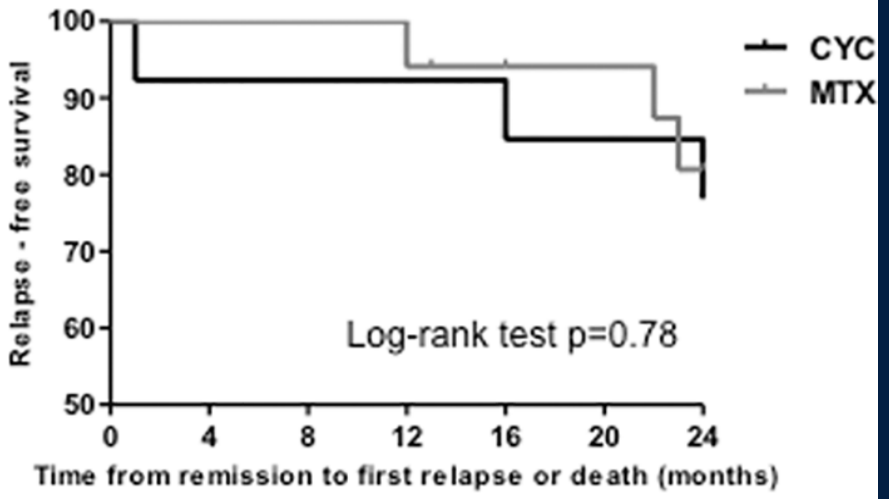
Συντήρηση ύφεσης

GPA+MPA



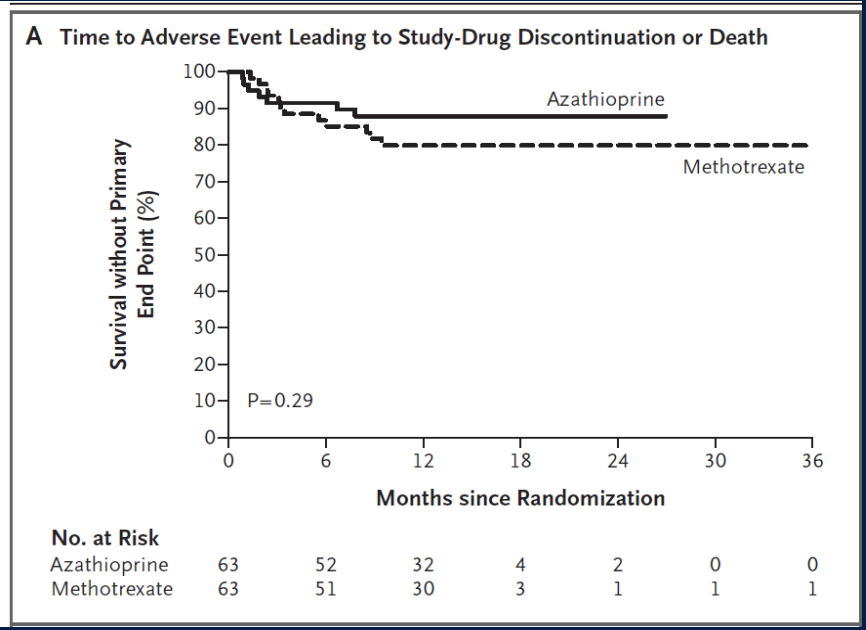
Number at risk							
CYC group	20	20	18	17	16	15	14
MTX group	21	21	20	19	16	14	11

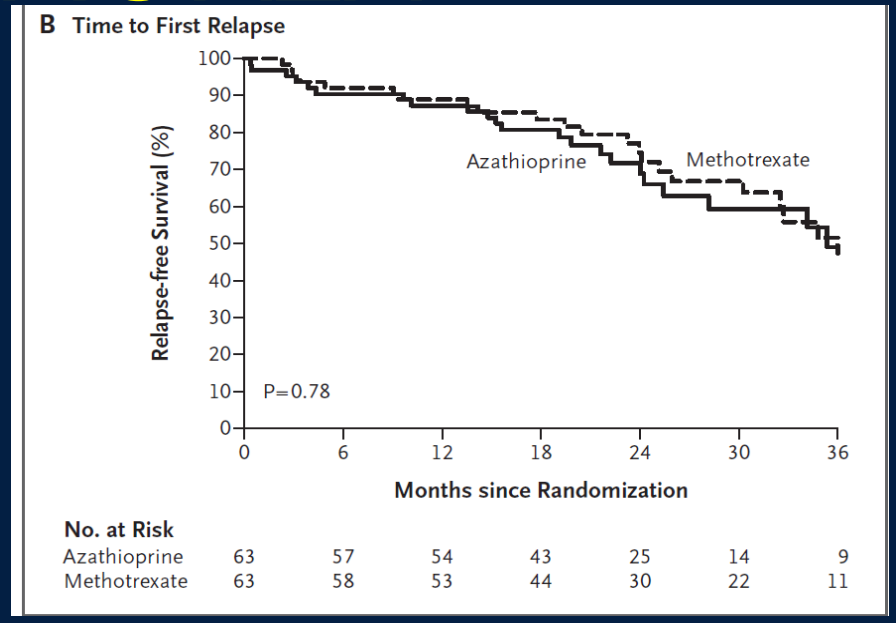
EGPA

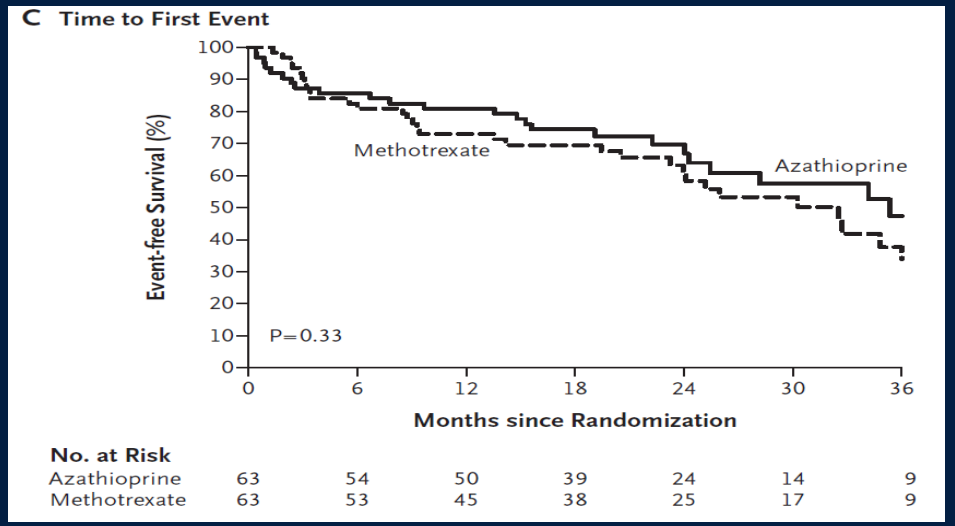


Number at risk							
CYC group	13	12	12	12	11	11	10
MTX group	17	17	17	17	15	14	12

MTX vs AZA





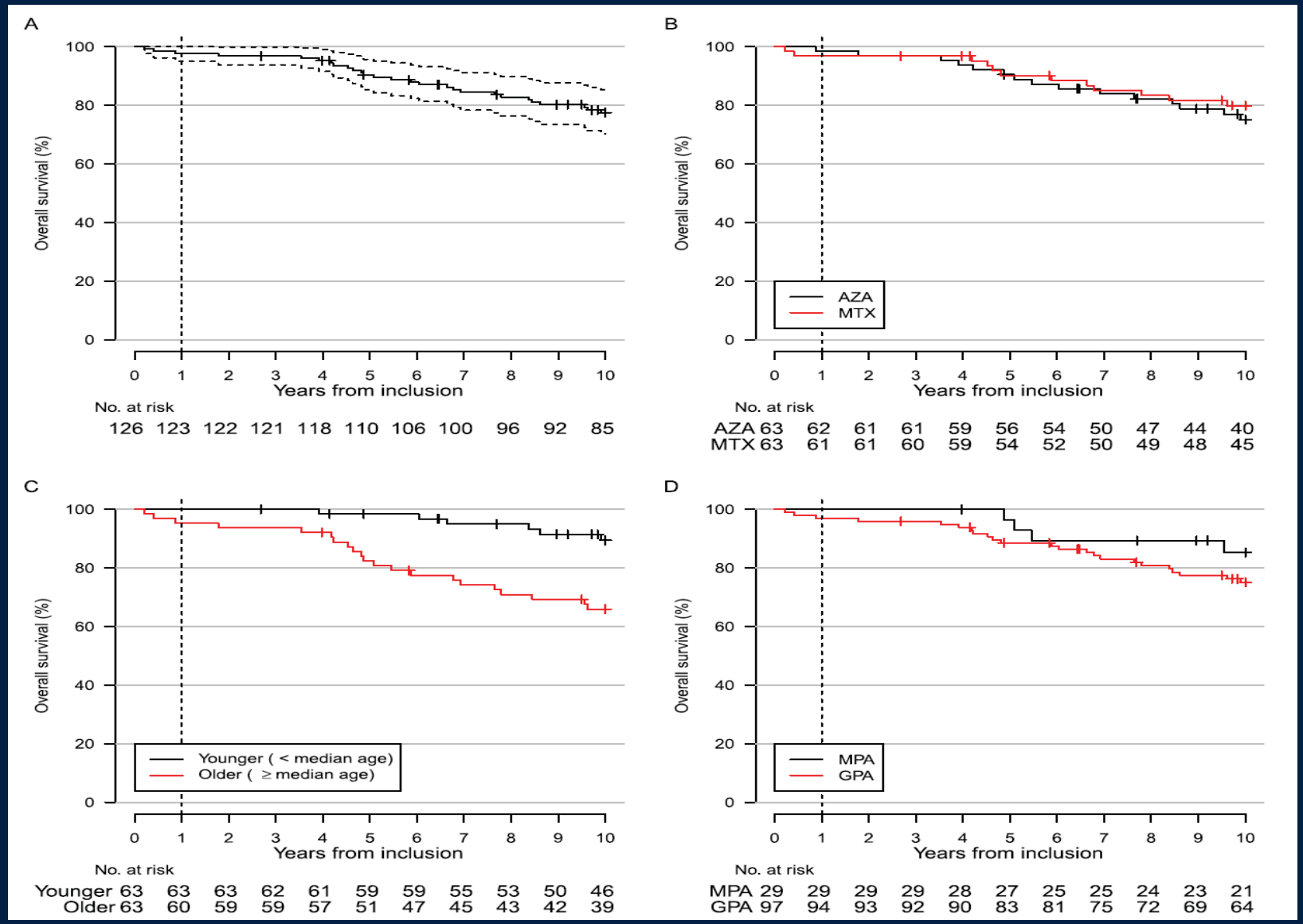


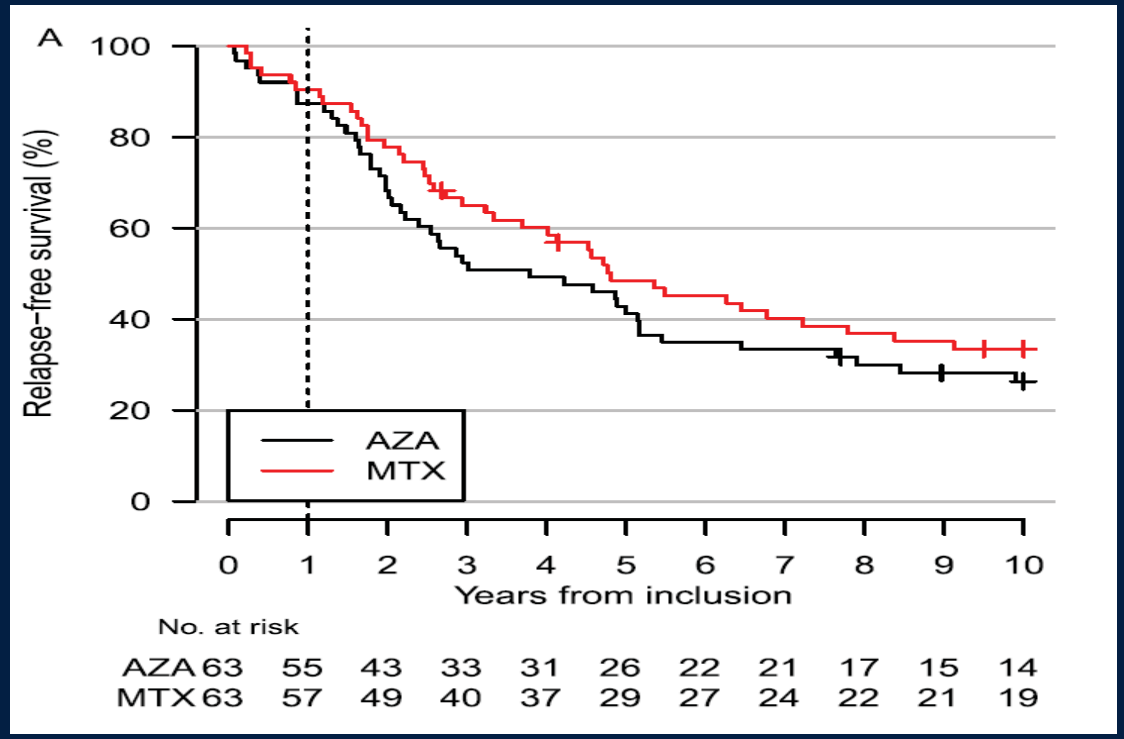
Pagnoux C, Mahr A, Hamidou MA, et al Azathioprine or methotrexate maintenance for ANCA-associated vasculitis. N Engl J Med. 2008 Dec 25;359

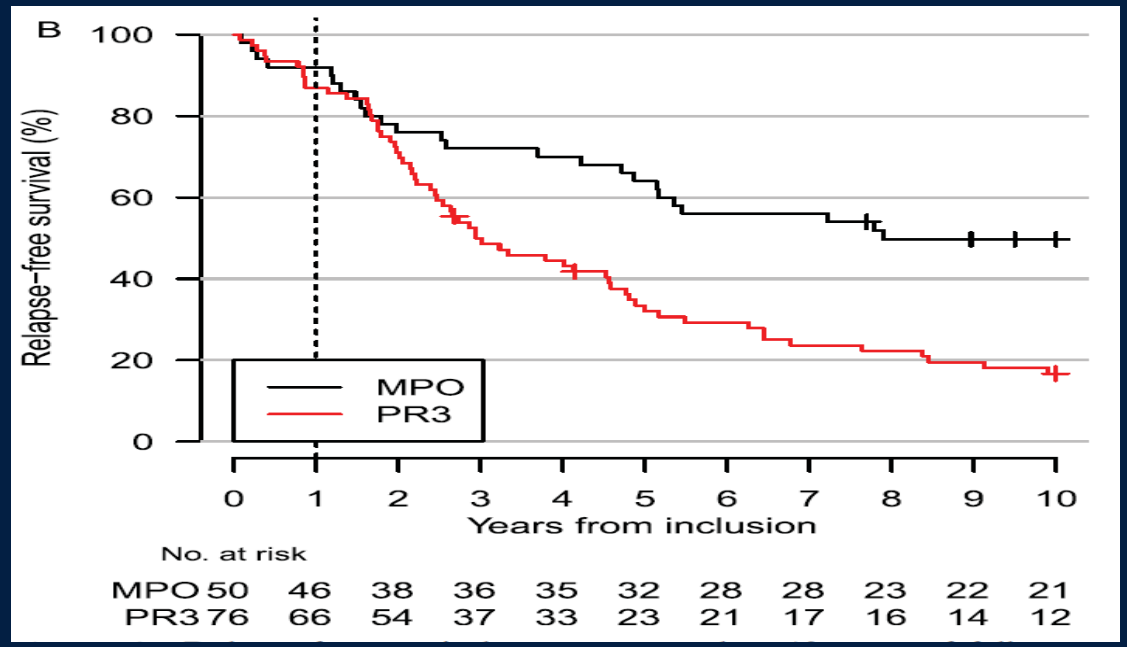
Outcomes Among Participants in the WEGENTTrial of Remission-Maintenance Therapy for GranulomatosisWith Polyangiitis (Wegener's) or Microscopic Polyangiitis

Xavier Puechal,1Christian Pagnoux, et al

ARTHRITIS & RHEUMATOLOGY Vol. 68, No. 3, March 2016, pp 690–701





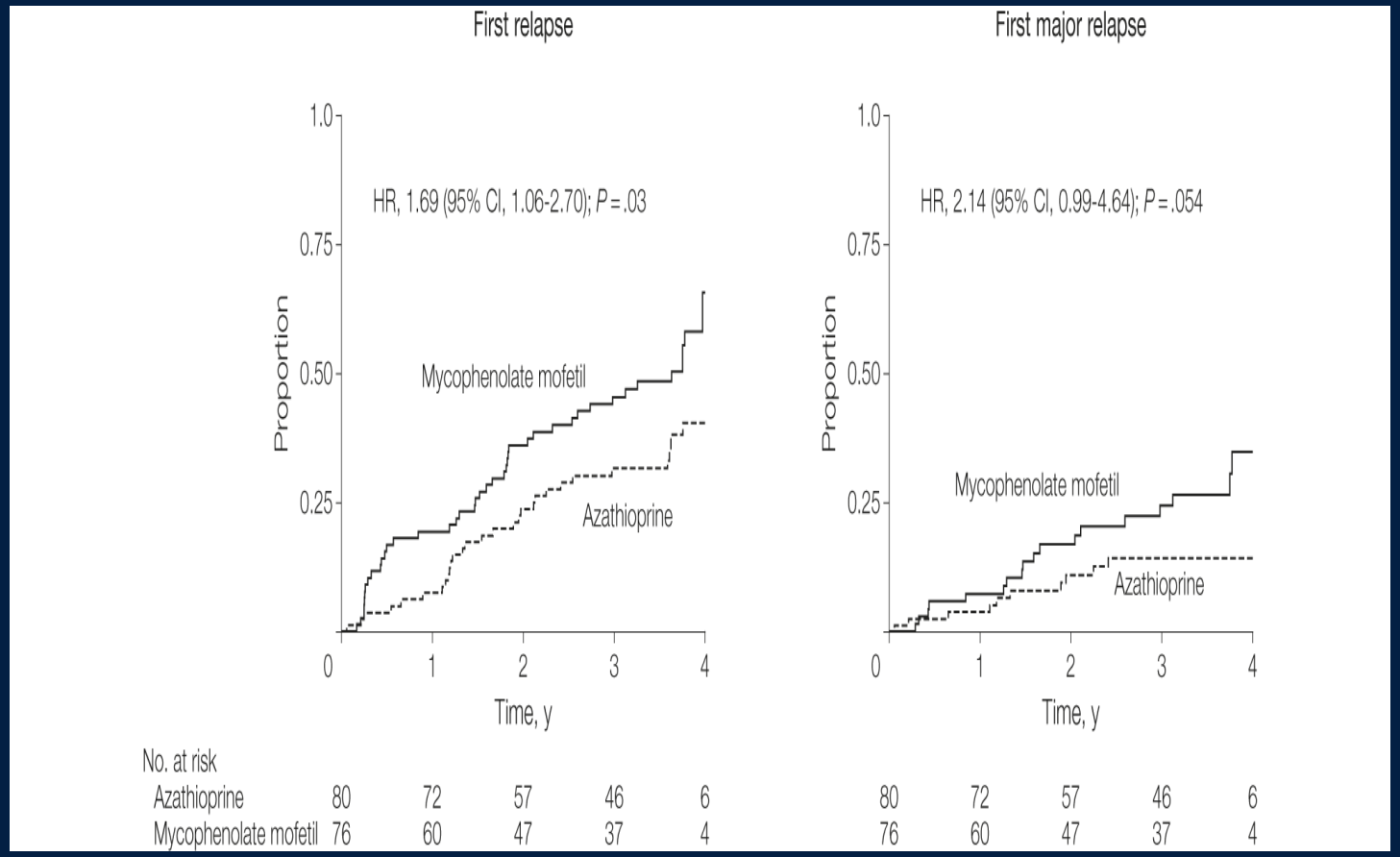


Αντι-PR3+: ισχυρός δείκτης πρόβλεψης της υποτροπης

MMF vs AZA

From: **Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis: A Randomized Controlled Trial**

JAMA. 2010;304(21):2381-2388. doi:10.1001/jama.2010.1658



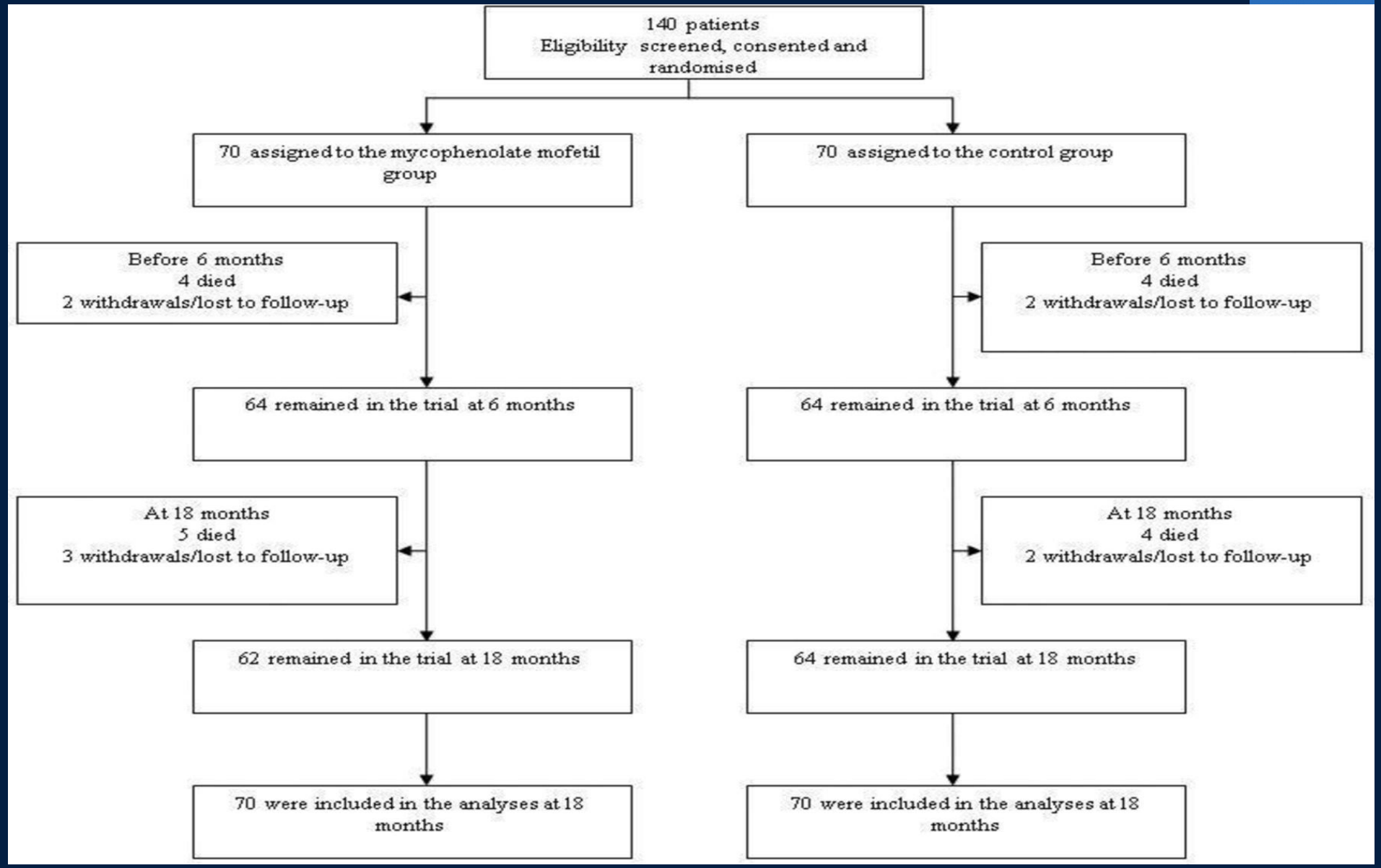
Patients were censored at first relapse or death. CI indicates confidence interval; HR, hazard ratio.

Vasculitis

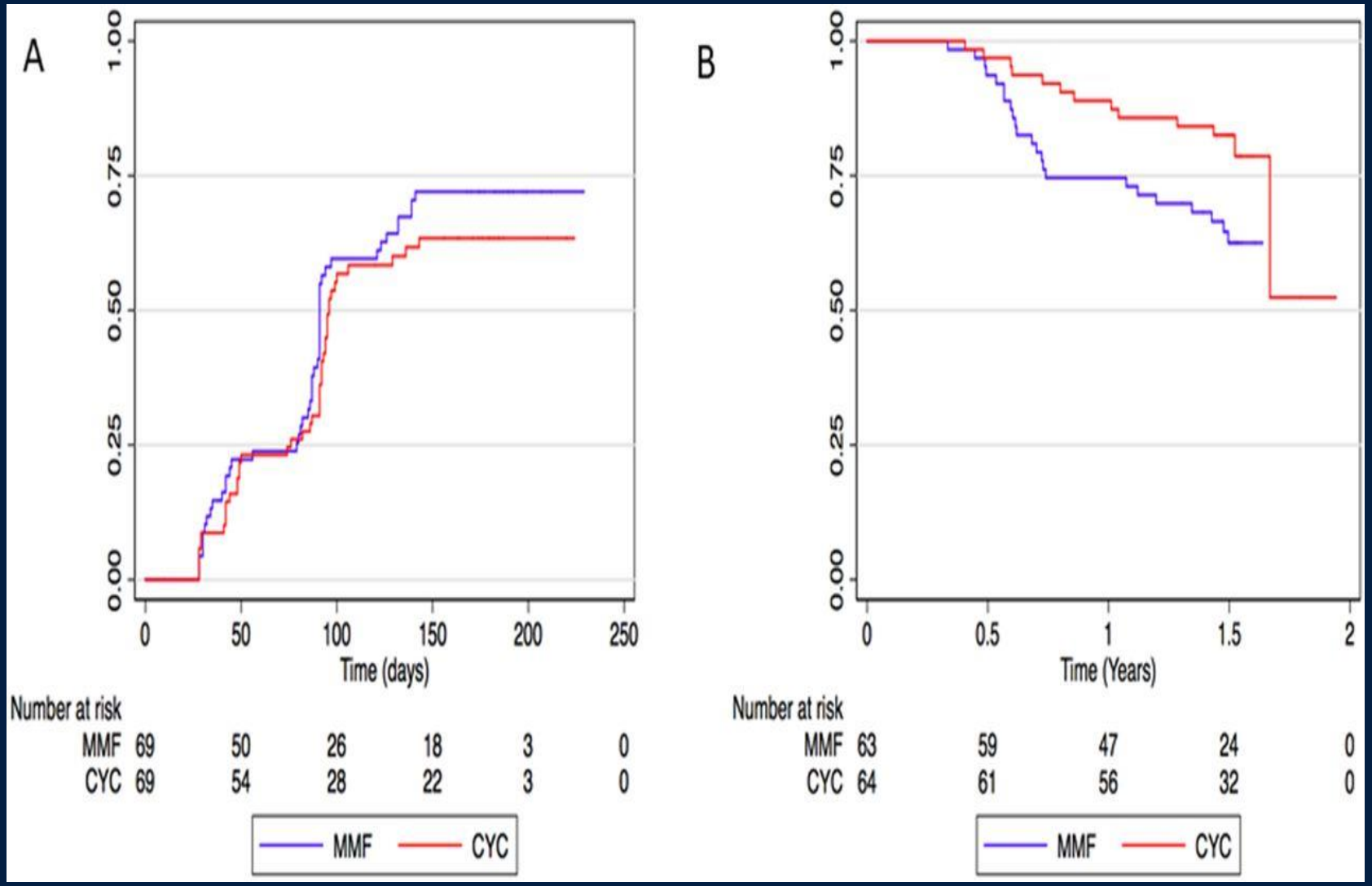
Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial

Rachel B Jones et al. Ann Rheum Dis 2019;78:399-405

ARD



Remission and relapse.

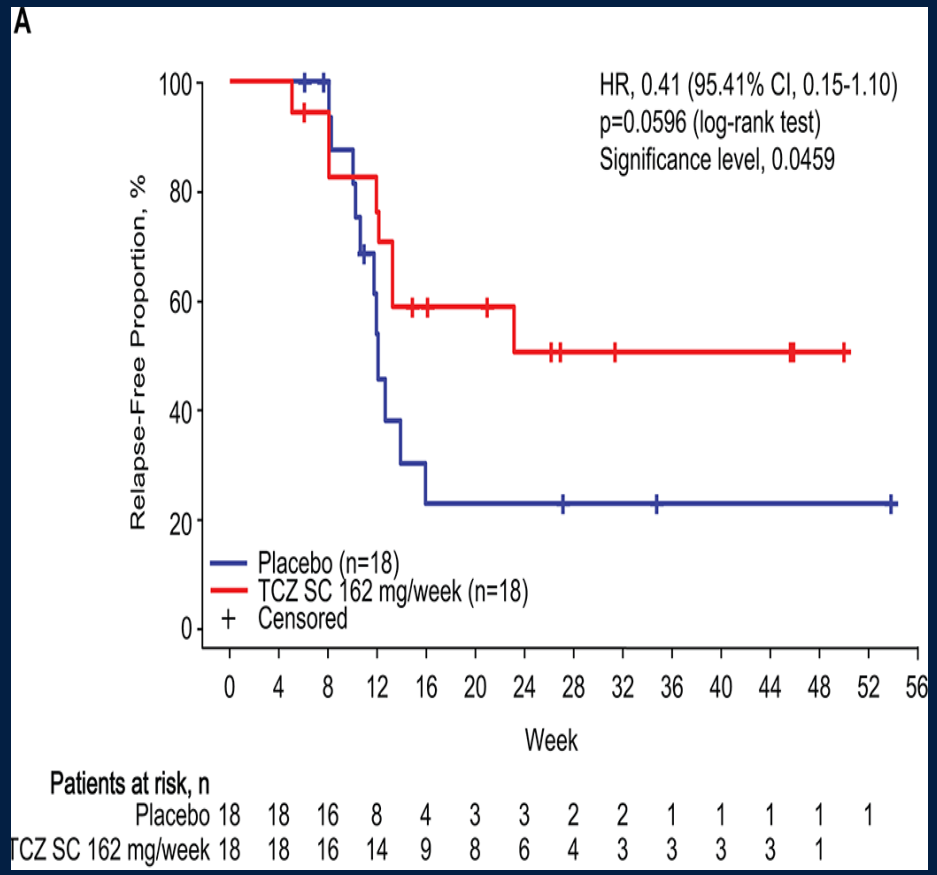


Rachel B Jones et al. Ann Rheum Dis 2019;78:399-405

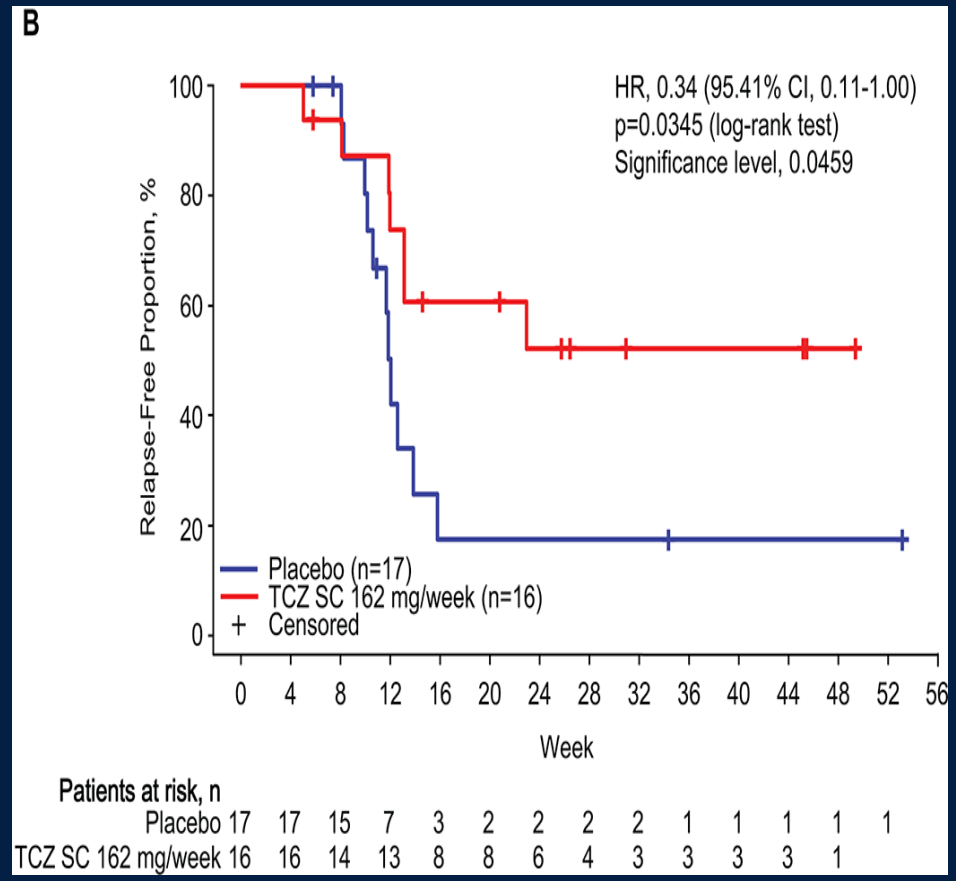
ARD

Efficacy and safety of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo-controlled, phase 3 trial in Japan (the TAKT study)

Yoshikazu Nakaoka,1 Mitsuaki Isobe,2 Syuji Takei,3 Yoshiya Tanaka,4 Tomonori Ishii,5
Shumpei Yokota,6 Akira Nomura,7 Seitaro Yoshida,7 Norihiro Nishimoto8



intent to treat population



Per protocol set sensitivity analysis

Efficacy of tocilizumab in Takayasu arteritis: Multicenter retrospective study of 46 patients

Arsene Mekinian [a, b, *], Mathieu Resche-Rigon [c], Cloé Comarmond [b, d, e, f], Alessandra Soriano [g], Joel Constans [h], Laurent Alric [i], Patrick Jego [j], Florian Busato [k], Matthieu Cabon [l], Robin Dhote [m], Lazaro Estibaliz [n], Isabelle Koné-Paut [o, p], Cédric Landron [q], Christian Lavigne [r], Bertrand Lioger [s], Martin Michaud [t], Marc Ruivard [u, v], Karim Sacre [w], Jacques Eric Gottenberg [l], Francis Gaches [u, v], Tiphaine Goulenok [w], Carlo Salvarani [g], Patrice Cacoub [b, d, e, f], Olivier Fain [a, b], David Saadoun [b, d, e, f, **], for the French Takayasu network

Table 1
Patients characteristics at the initiation and during tocilizumab treatment.

	Initiation of tocilizumab N = 46	At 3 months N = 29	At 6 months N = 36	At 12 months N = 19	At 18 months N = 12
Vascular symptoms	29/43 (67%)	5/29 (17%)	7/36 (19%)	2/19 (11%)	5/12 (42%)
Constitutional symptoms	16/43 (37%)	1/29 (3%)	0	0	1/12 (8%)
Radiological activity/progression	35/42 (83%)*	–	3/15 (20%)	2/12 (17%)	3/6 (50%)
NIH activity score	3 [2–3]*	0 [0–1]	0 [0]	0 [0]	0 [0]
C-reactive protein level (mg/l)	23 [16–40]*	1 [0–2]	1 [0–2]	0 [0–1]	0 [0–2]
Prednisone use (n; %)	39 (85%)	24 (83%)	26 (81%)	19 (100%)	12 (100%)
Prednisone dose (mg/day)	20 [10–45]*	15 [8–19]	7 [5–11]	5 [4.5–9]	5 [5–7]
DMARDs use (n; %)	18 (39%)	7/28 (25%)	11 (31%)	6 (30%)	3 (25%)
Tocilizumab continuation	–	28 (97%)	34 (94%)	16 (80%)	11 (92%)
NIH<2 + prednisone <7.5 mg/day	–	8 (28%)	24 (67%)	15 (79%)	9 (75%)

Values are medians [ranges] and numbers (frequencies).
*$p < 0.0001$ between baseline and all visits during the follow-up (Kruskall Wallis tests or Fisher test).

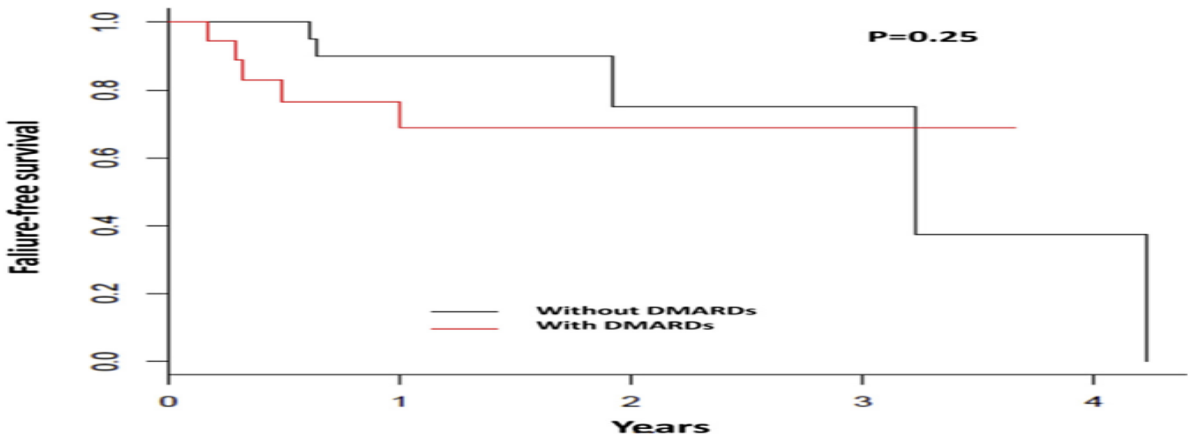


Fig. 4. Event-free survival in 46 TA patients according to tocilizumab used in monotherapy (n = 38) and combined with DMARDs (n = 18).

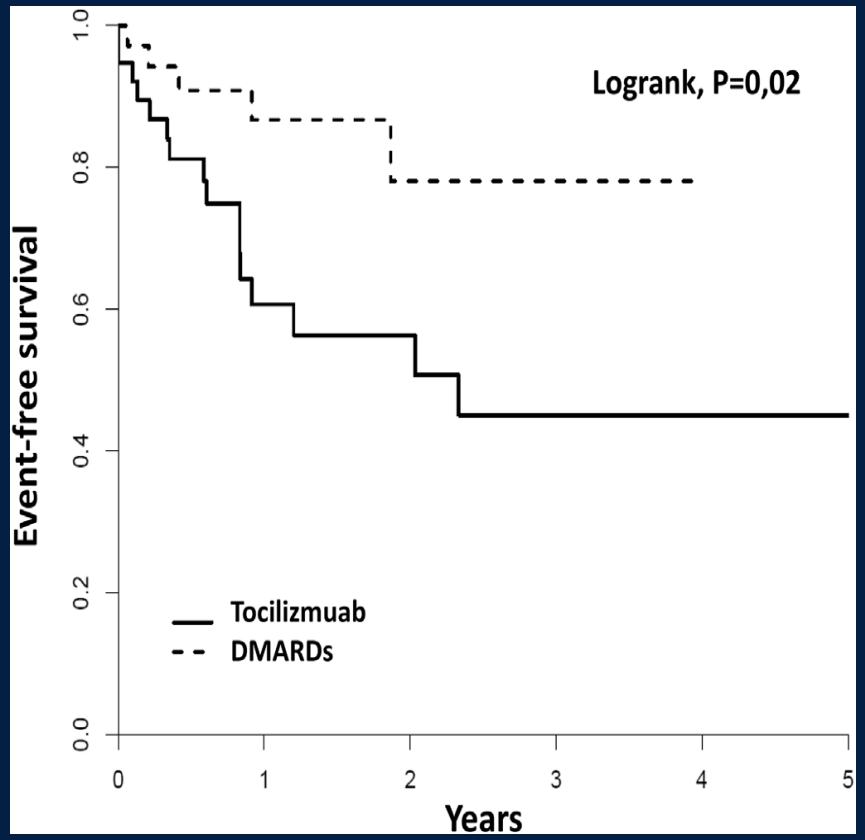


Fig. 5. Event-free survival under tocilizumab in comparison to DMARDs therapy.

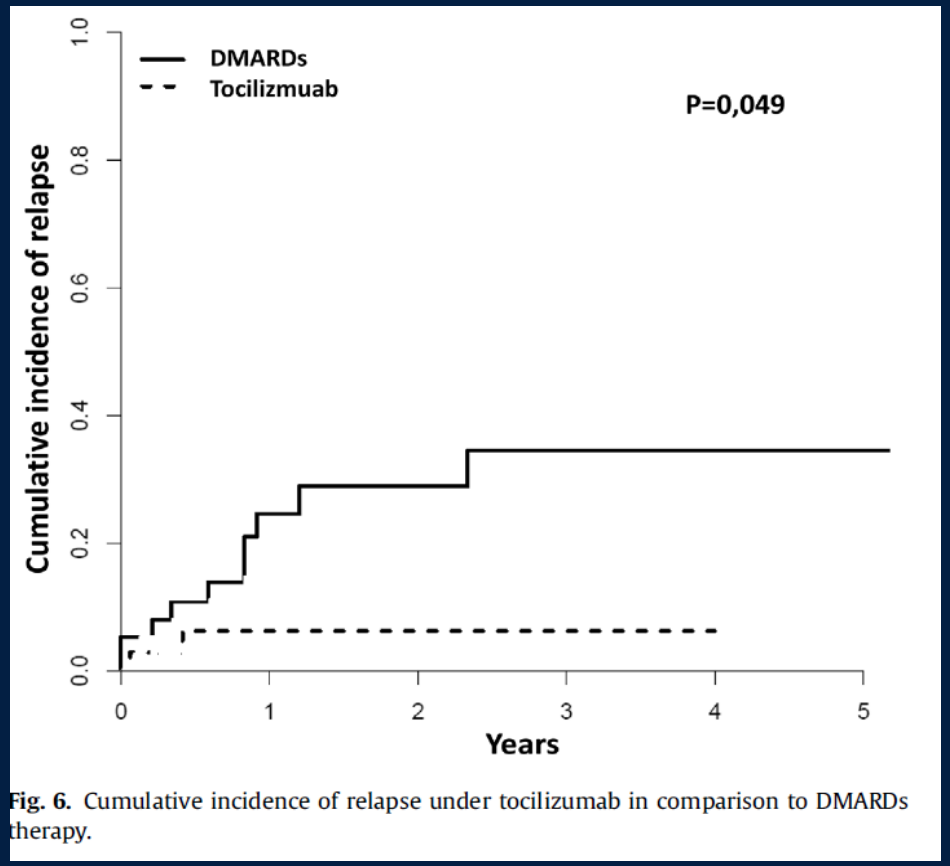


Fig. 6. Cumulative incidence of relapse under tocilizumab in comparison to DMARDs therapy.

Journal of Autoimmunity 91 (2018) 55–60

TOCILIZUMAB KAI ANCA -VASC

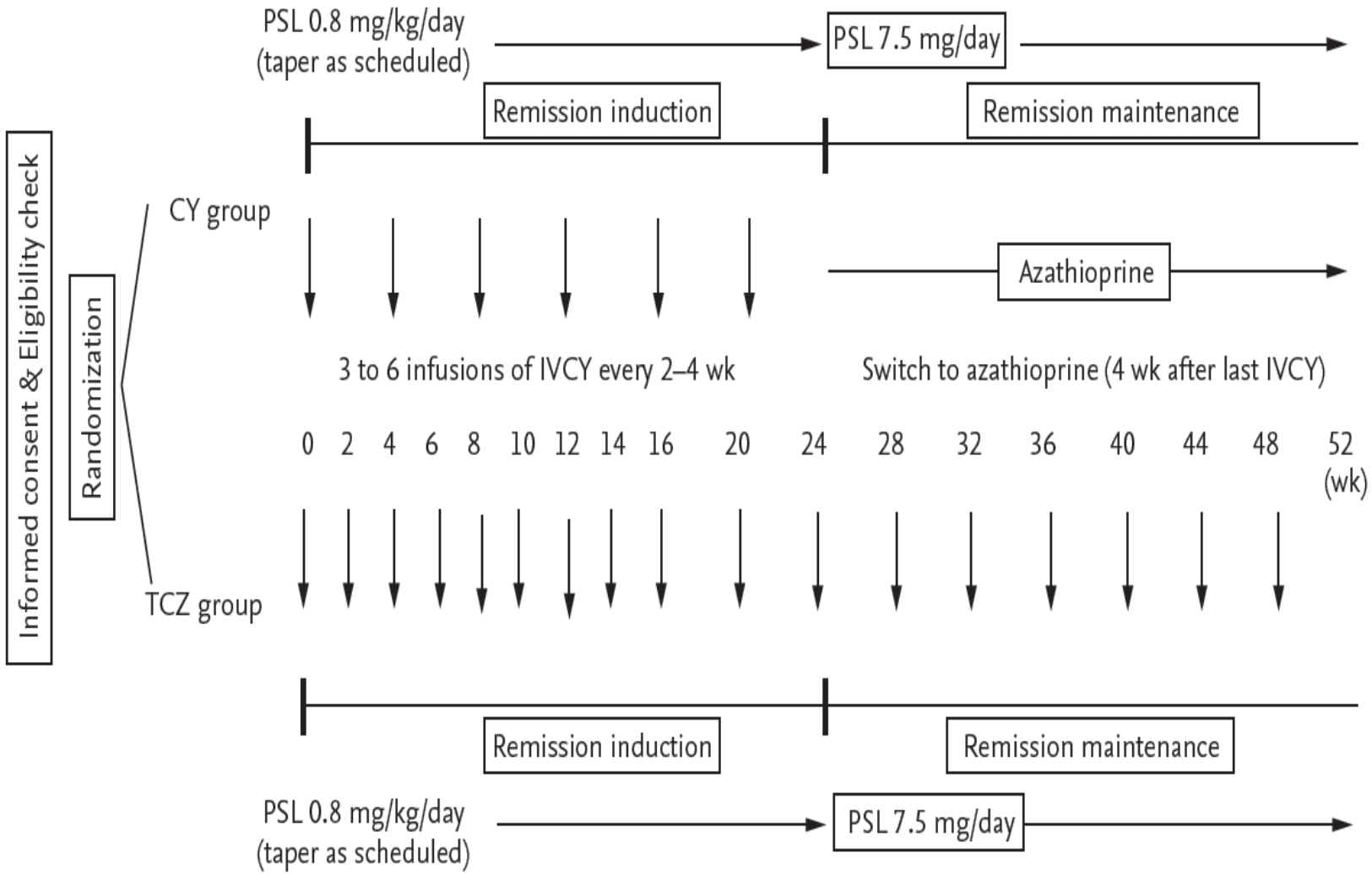
Table 1 Literature review of TCZ treatment in patients with primary AAV

Authors	Ref.	Year	Sex	Age (years)	Disease	Organ involvement	Disease duration (months)	Type of ANCA	Titer of ANCA (IU/mL)	CRP (mg/dL)	Histopathology
Takenaka et al.	[10]	2013	Female	47	Unclassifiable AAV	Aortitis, hypertrophic pachymeningitis, P	Not available	MPO-ANCA	392.0 U/mL	23.23	Not definite
Inoue et al.	[13]	2015	Female	70	GPA	O, optic disc edema	48.0	Not available	Not available	Not available	Not available
Berti et al.	[14]	2016	Male	32	MPA	A, D, O, P, R	24.0	MPO-ANCA	42 AU (<20)	10.1	Positive
Sakai et al.	[15]	2016	Male	63	MPA	D, N, P, R	5.3	MPO-ANCA	>300	0.3	Positive
		2016	Male	79	MPA	P, R	1.4	MPO-ANCA	71.4	9.1	Positive
		2016	Male	67	MPA	N, P, R	3.3	MPO-ANCA	165.0	7.2	Positive
		2016	Male	79	MPA	P, R	6.2	MPO-ANCA	>300	0.1	Positive
		2016	Male	77	MPA	N, P, R	2.0	MPO-ANCA	125.0	13.6	Positive
Case 1	–	2017	Female	73	MPA	P, R	3.0	MPO-ANCA	143.0	19.6	Positive
Case 2	–	2017	Male	76	MPA	P, R	1.0	MPO-ANCA/PR3-ANCA	103.0/9.2	8.0	Not performed
Sakai et al.	[15]	2016	Female	66	MPA (+SSc)	N, P, R	7.3	MPO-ANCA	104.0	12.0	Positive
		2016	Female	58	MPA	D, G, N, R	5.8	MPO-ANCA	51.2	4.9	Not performed

Authors	Proteinuria (g/day)	Max dosage of PSL before TCZ	Immunosuppressants or DMARDs before TCZ	Dosage of TCZ	Follow-up duration of using TCZ (months)	Daily dosage of PSL at starting TCZ	Outcome after TCZ	ADRs or AEs	Treatment after TCZ at final observation
Takenaka et al.	None	40 mg/day	IVCYC, POCYC	8 mg/kg/month	12.0	25 mg/day	Remission	None	PSL 4 mg/day
Inoue et al.	None	Not available	CYC	8 mg/kg/month and 162 mg s.c./2 weeks	24.0	Not available	Remission	None	PSL off
Berti et al.	1.2	mPSL 1.0 g pulse	IVCYC, RTX, MMF, MTX	8 mg/kg/month	36.0	50 mg/day	Remission	None	PSL 5 mg/qod + AZ 200 mg/day
Sakai et al.	0.62	None	None	8 mg/kg/2 weeks[a]	38.6	None	Remission	None	Drug free
	0.71	None	None	8 mg/kg/2 weeks[a]	6.6	None	Remission[b]	None	PSL 20 mg/day
	0.17	None	None	8 mg/kg/2 weeks[a]	33.5	None	Remission	None	Drug free
	0.81	None	None	8 mg/kg/2 weeks[a]	32.8	None	Low disease activity	Bacterial pneumonia, pneumothorax	Drug free
	<0.1	None	None	8 mg/kg/2 weeks[a]	28.9	None	Remission	Bronchitis and elevated total bilirubin	Drug free (exacerbation of only IP after TCZ at month 19)
Case 1	0.22	None	None	8 mg/kg/month	32.7	50 mg/day	Remission	Avascular necrosis	PSL 2 mg/day and RTX 375 mg/m^2 at month 28
Case 2	1.64	None	None	8 mg/kg/month	6.0	70 mg/day	Low disease	Cellulitis and skin ulcer	PSL 11 mg/day
Sakai et al.	0.16	None	None	8 mg/kg/2 weeks[a]	15.0	None	Flare	None	mPSL 1 g pulse and RTX, IVCYC
	1.34	None	None	8 mg/kg/2 weeks[a]	9.0	None	Ineffective	None	mPSL 500 mg pulse and IVCYC

Clin Rheumatol (2017) 36:2383–2392

Harigai M, et al. Targeted therapy in MPA and GPA



Corticosteroid-free treatment of tocilizumab monotherapy for microscopic polyangiitis: a single-arm, single-center, clinical trial

Ryota Sakai, Tsuneo Kondo, Jun Kikuchi, Akiko Shibata, Kentaro Chino, Ayumi Okuyama, Hirofumi Takei & Koichi Amano

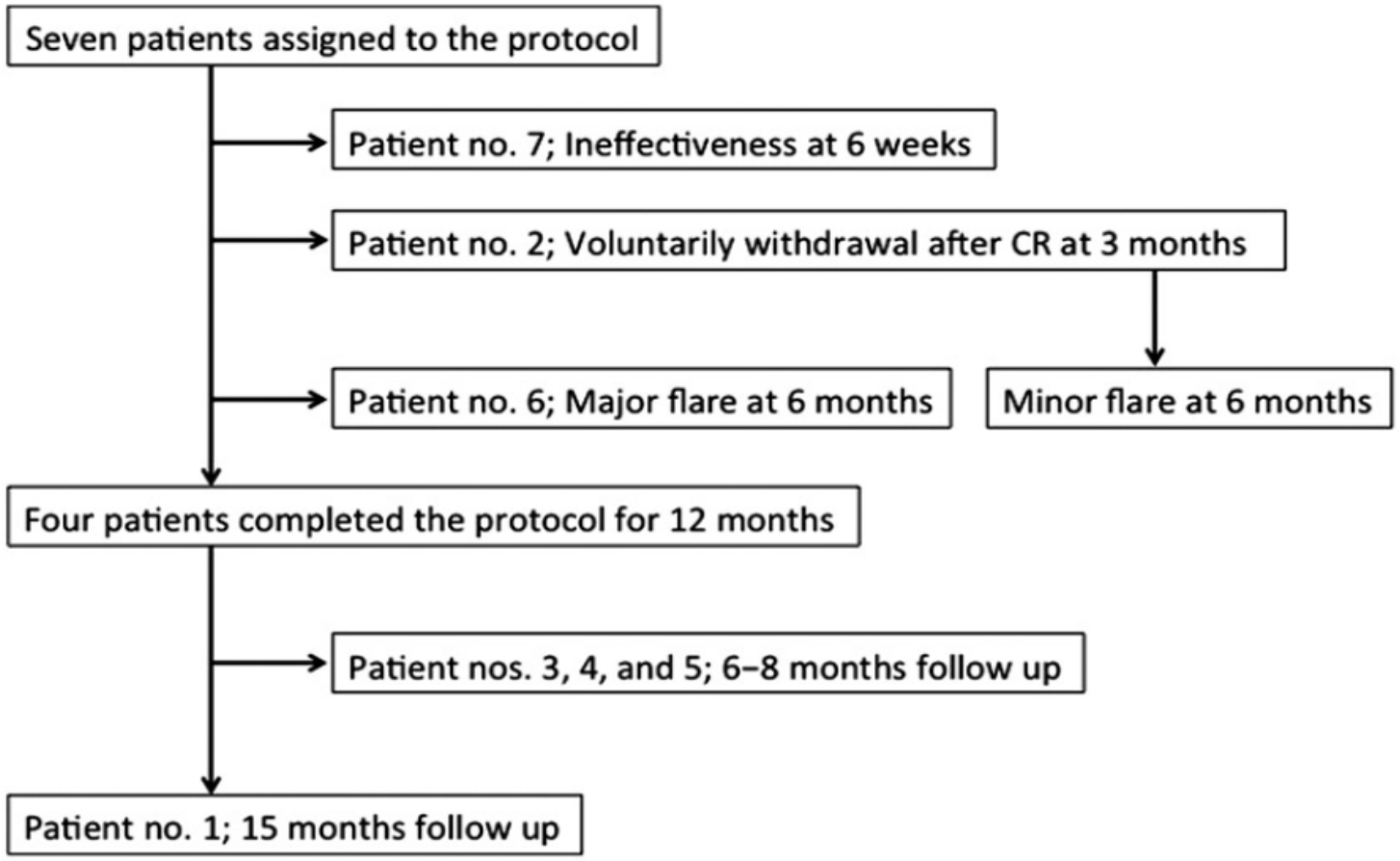


Figure 1. Patient's disposition during TCZ monotherapy. CR, complete remission.

Mod Rheumatol, 2016; 26(6): 900–907

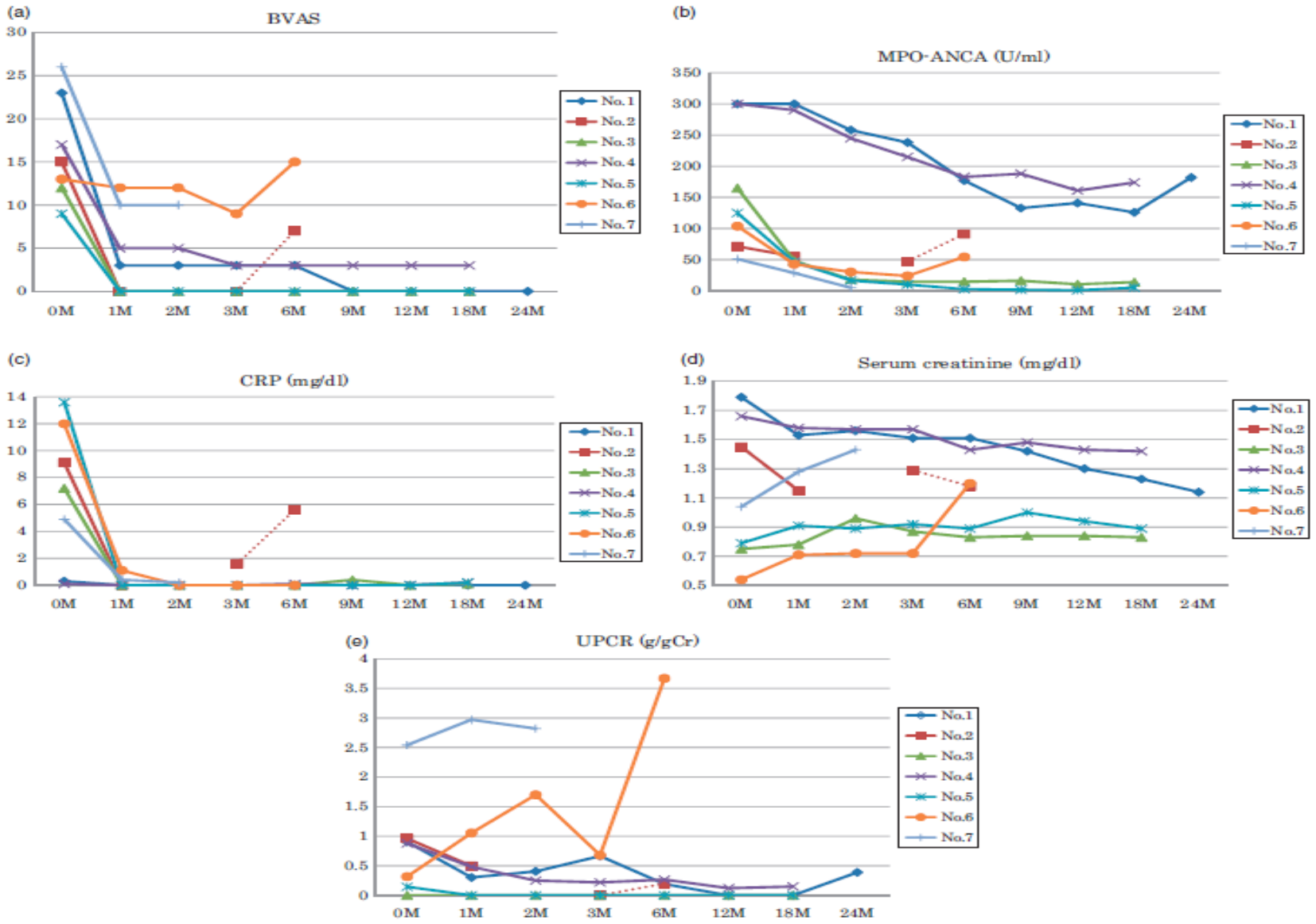


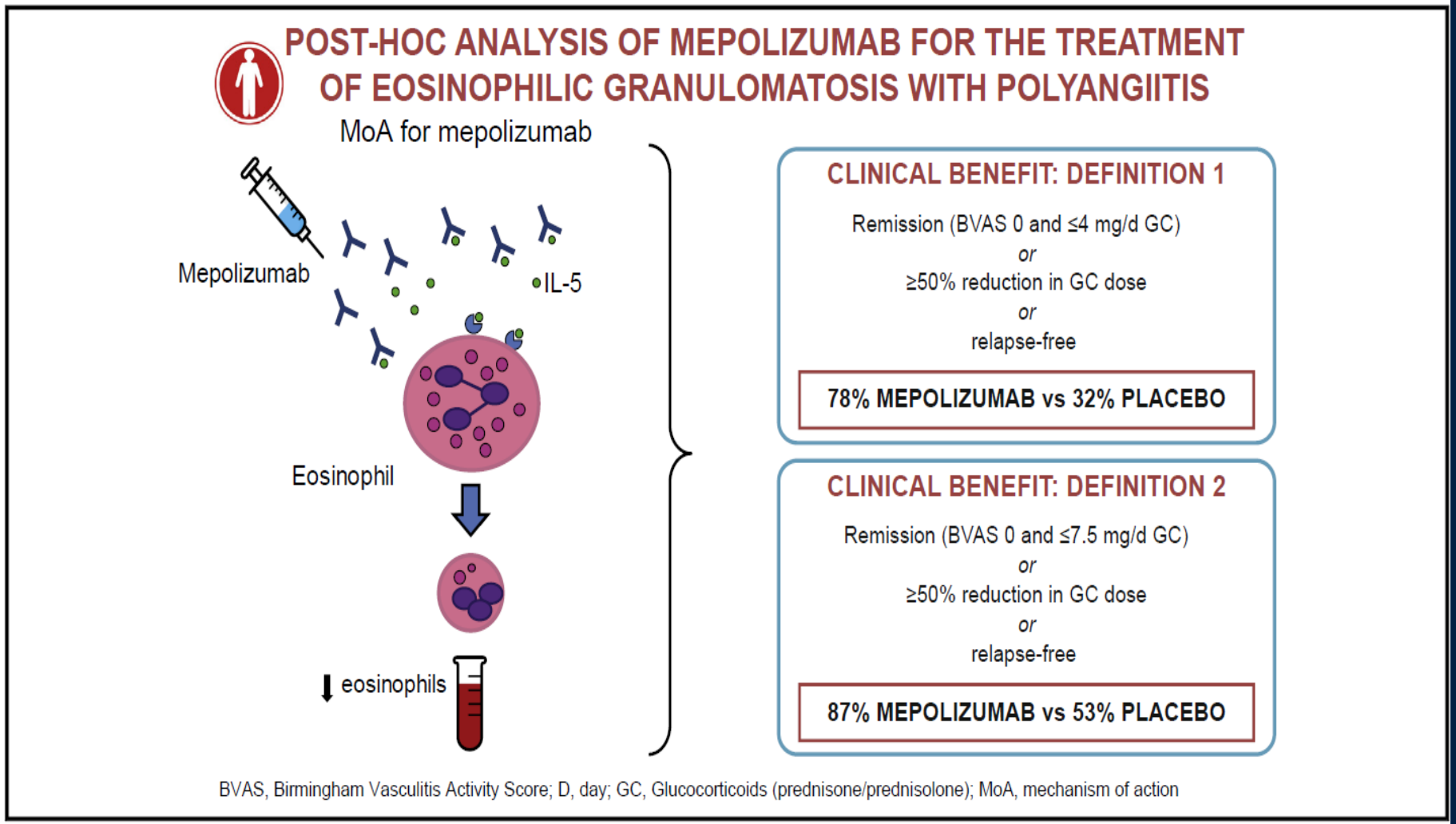
Figure 2. Changes in clinical parameters during TCZ monotherapy. Patient no. 2 lost his data at 2 months. (a) BVAS, (b) MPO-ANCA (U/ml), (c) CRP (mg/dl), (d) serum creatinine (mg/dl) and (e) UPCR (g/gCr). BVAS, Birmingham vasculitis activity score; Cr, serum creatinine; CRP, C-reactive protein; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; UPCR, urine protein/creatinine ratio.

MEPOLIZUMAB anti-IL-5 mAb

Evaluation of clinical benefit from treatment with mepolizumab for patients with eosinophilic granulomatosis with polyangiitis

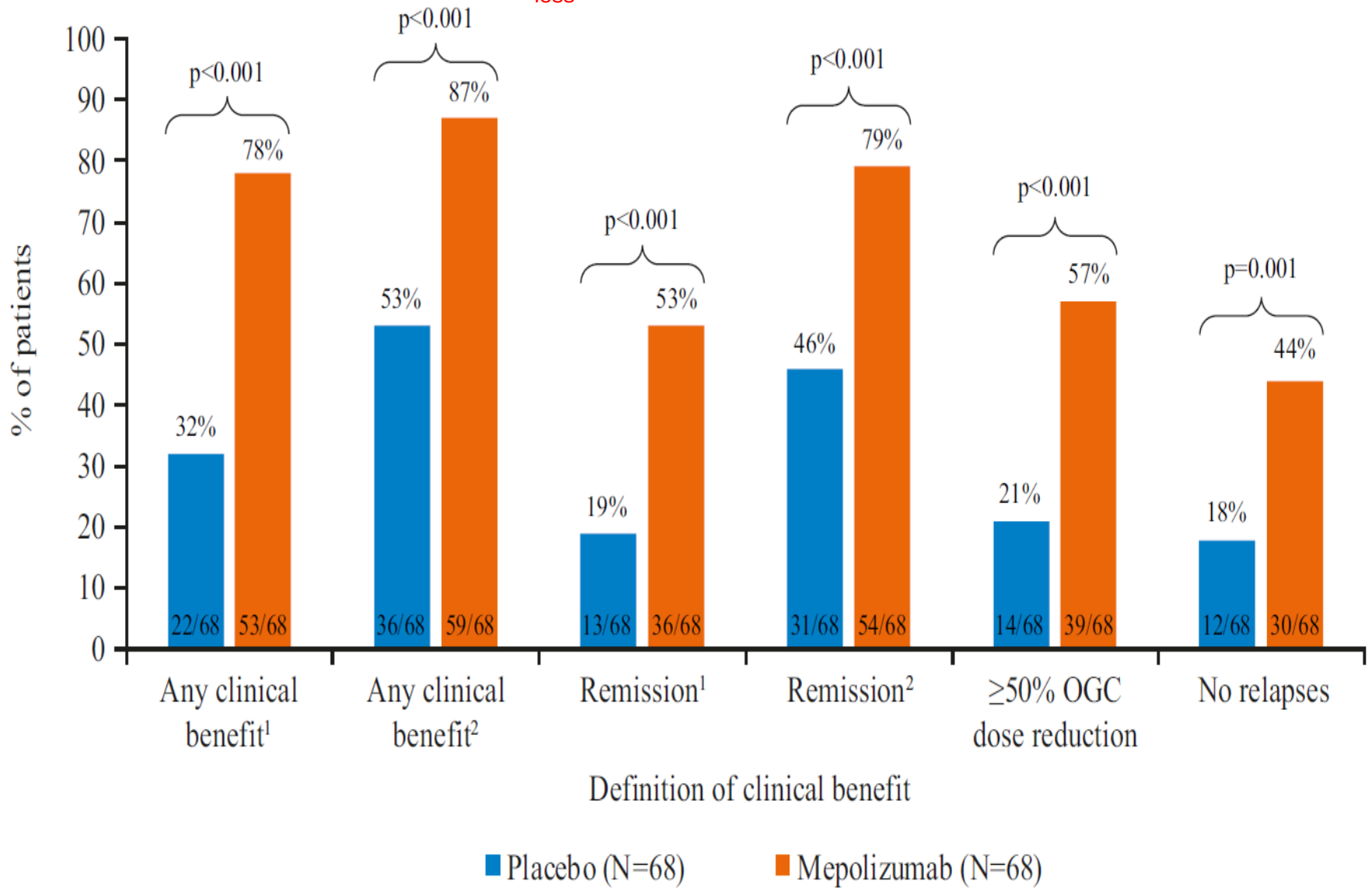
Jonathan Steinfeld, MD,et al

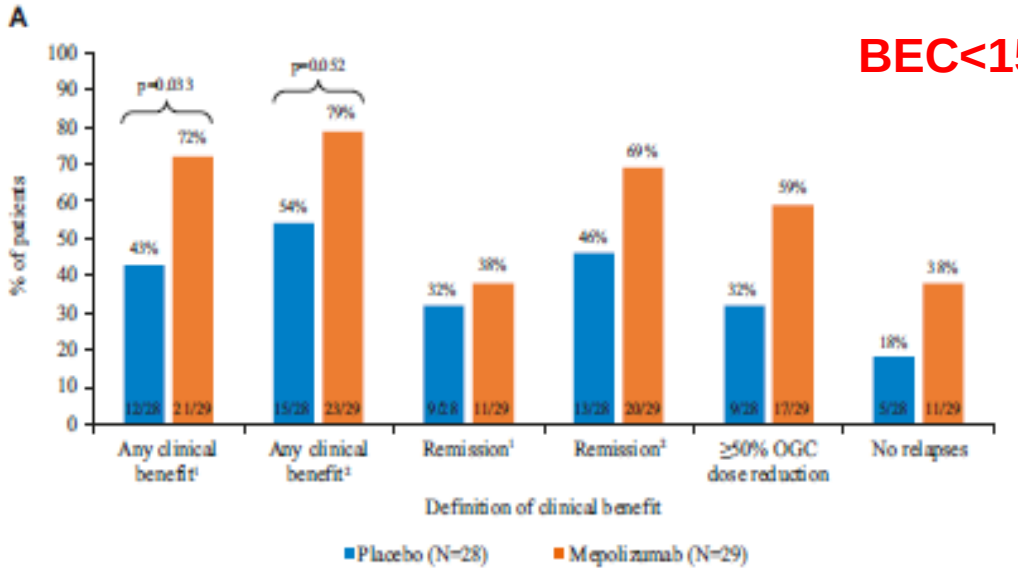
GRAPHICAL ABSTRACT

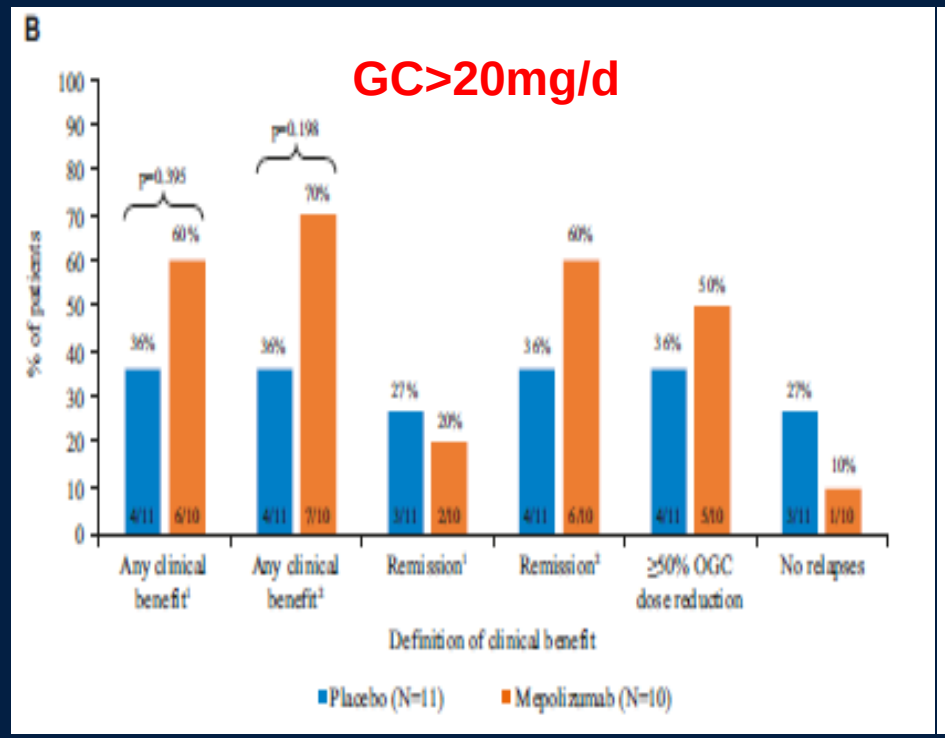


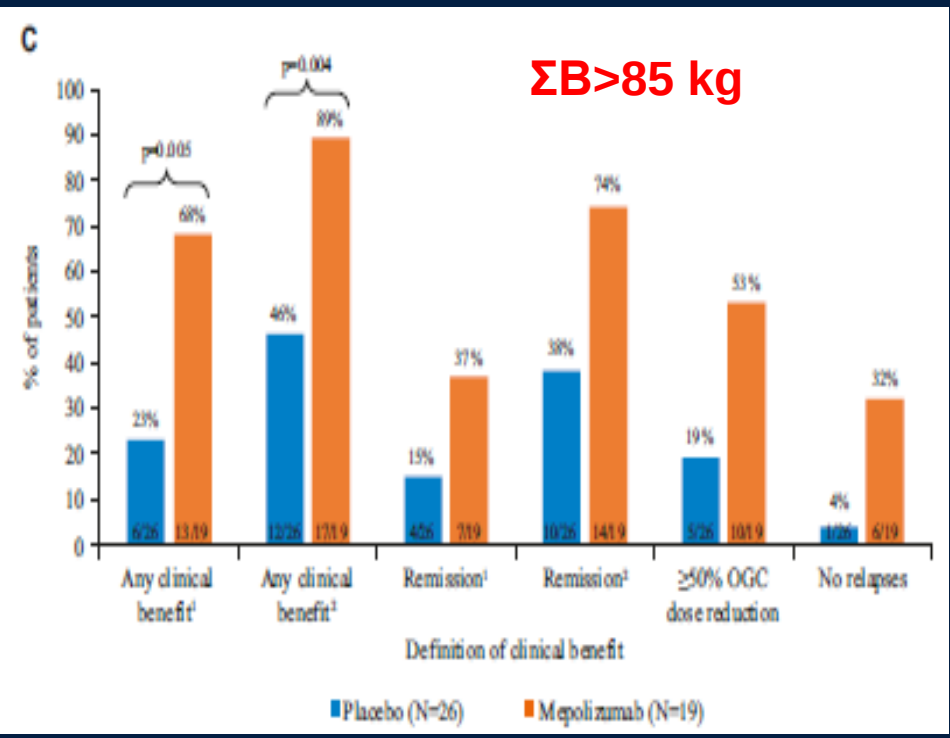
Clinical benefit 1
BVAS of 0 plus an OGC dose of 4 mg/d or less

Clinical benefit 2
EULAR remission criteria of a BVAS of 0 plus an OGCdose of 7.5 mg/d or less



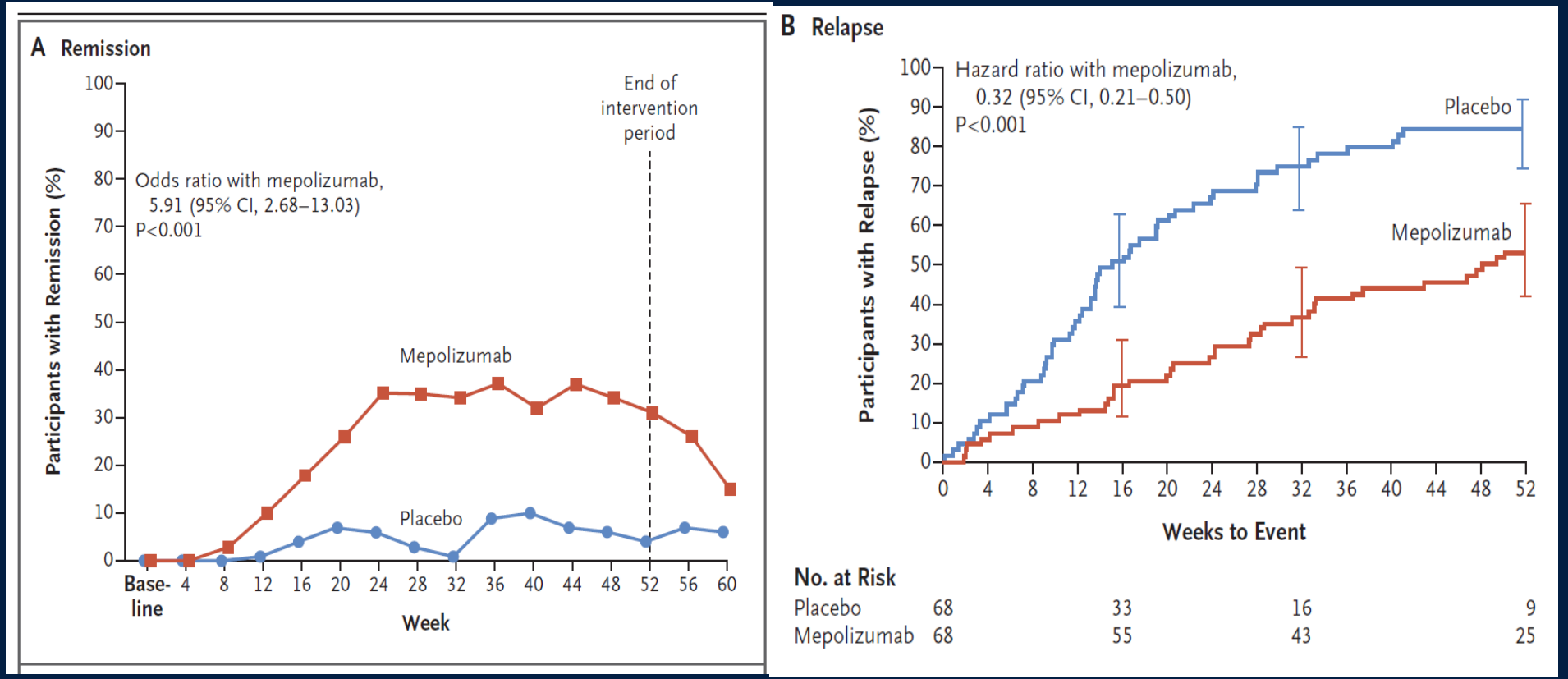

A
BEC<150
% of patients
p=0.033
p=0.052
43%
72%
54%
79%
32%
38%
46%
69%
32%
59%
18%
38%
12/28
21/29
15/28
23/29
9/28
11/29
13/28
20/29
9/28
17/29
5/28
11/29
Any clinical benefit¹
Any clinical benefit²
Remission¹
Remission²
≥50% OGC dose reduction
No relapses
Definition of clinical benefit
Placebo (N=28)
Mepolizumab (N=29)


B
GC>20mg/d
% of patients
p=0.395
p=0.198
36%
60%
36%
70%
27%
20%
36%
60%
36%
50%
27%
10%
4/11
6/10
4/11
7/10
3/11
2/10
4/11
6/10
4/11
5/10
3/11
1/10
Any clinical benefit¹
Any clinical benefit²
Remission¹
Remission²
≥50% OGC dose reduction
No relapses
Definition of clinical benefit
Placebo (N=11)
Mepolizumab (N=10)


C
ΣB>85 kg
% of patients
p=0.004
p=0.005
23%
68%
46%
89%
15%
37%
38%
74%
19%
53%
4%
32%
6/26
13/19
12/26
17/19
4/26
7/19
10/26
14/19
5/26
10/19
1/26
6/19
Any clinical benefit¹
Any clinical benefit²
Remission¹
Remission²
≥50% OGC dose reduction
No relapses
Definition of clinical benefit
Placebo (N=26)
Mepolizumab (N=19)

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*



The NEW ENGLAND JOURNAL of MEDICINE

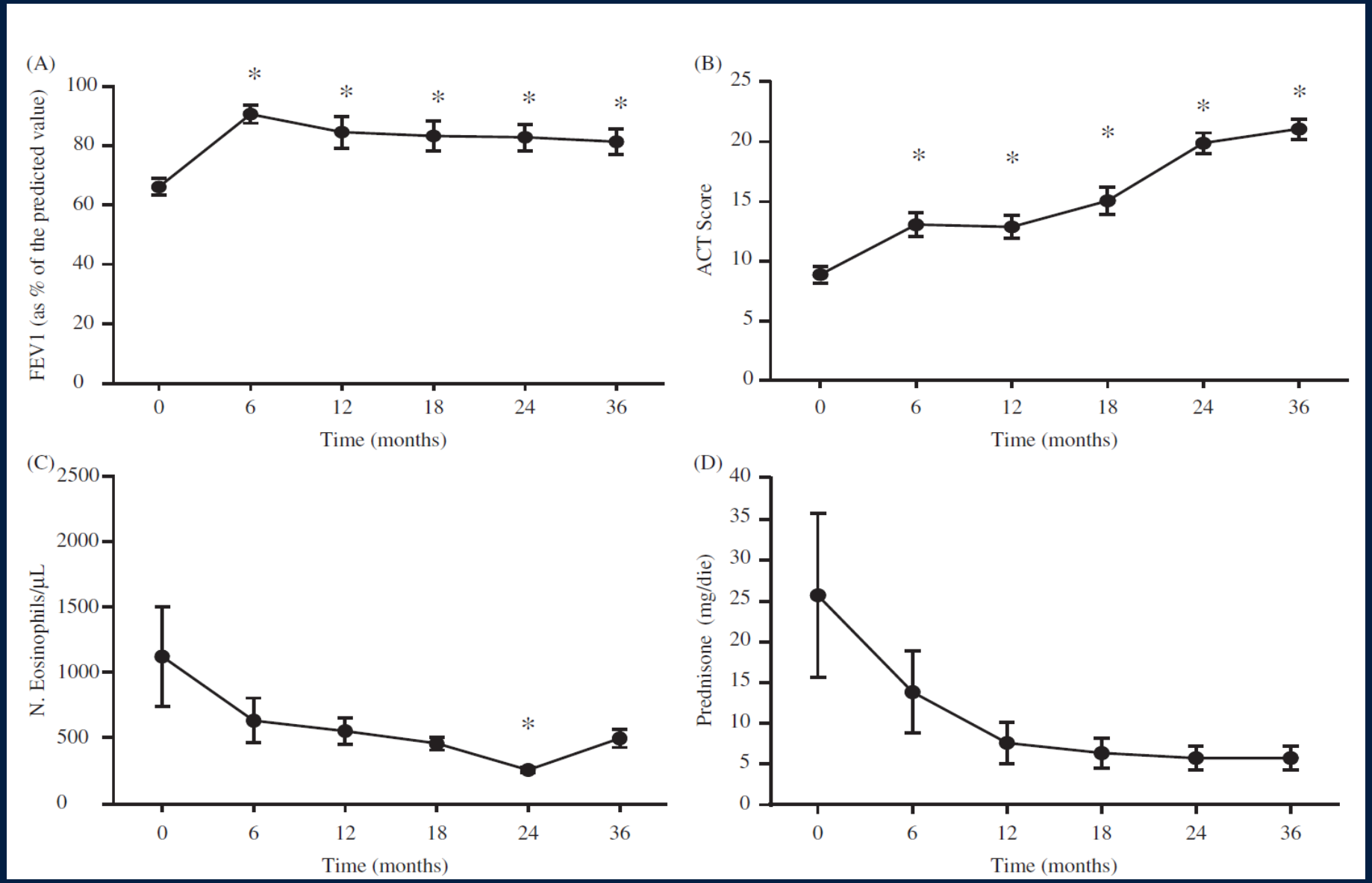
Table 3

Adverse Events and Serious Adverse Events*

Event	Mepolizumab (N = 68)	Placebo (N = 68)
	no. of participants (%)	
Adverse event		
Any event	66 (97)	64 (94)
Event considered by the investigator to be related to the trial agent	35 (51)	24 (35)
Event leading to trial-agent discontinuation or trial withdrawal	2 (3)	1 (1)
Death	1 (1)†	0
Serious adverse event‡		
Any event	12 (18)	18 (26)
Event considered by the investigator to be related to the trial agent	3 (4)	3 (4)
Systemic or local-site reaction§		
Systemic reaction	4 (6)	1 (1)
Local-site reaction	10 (15)	9 (13)
Anaphylaxis considered by the investigator to be related to the trial agent	0	0
Cardiovascular adverse event¶		
Arrhythmia	2 (3)	3 (4)
Stroke or TIA	1 (1)	0
Congestive heart failure	0	1 (1)
Myocardial infarction or unstable angina	1 (1)	1 (1)

OMALIZUMAB: anti human IgE mAb

Omalizumab in patients with eosinophilic granulomatosis with polyangiitis: a 36-month follow-up study Aikaterini Detoraki et al J Asthma, 2016; 53(2): 201–206



Celebi Sozener *et al. World Allergy Organization Journal* (2018) 11:39
https://doi.org/10.1186/s40413-018-0217-0

World Allergy Organization Journal

ORIGINAL RESEARCH Open Access

Omalizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA): single-center experience in 18 cases

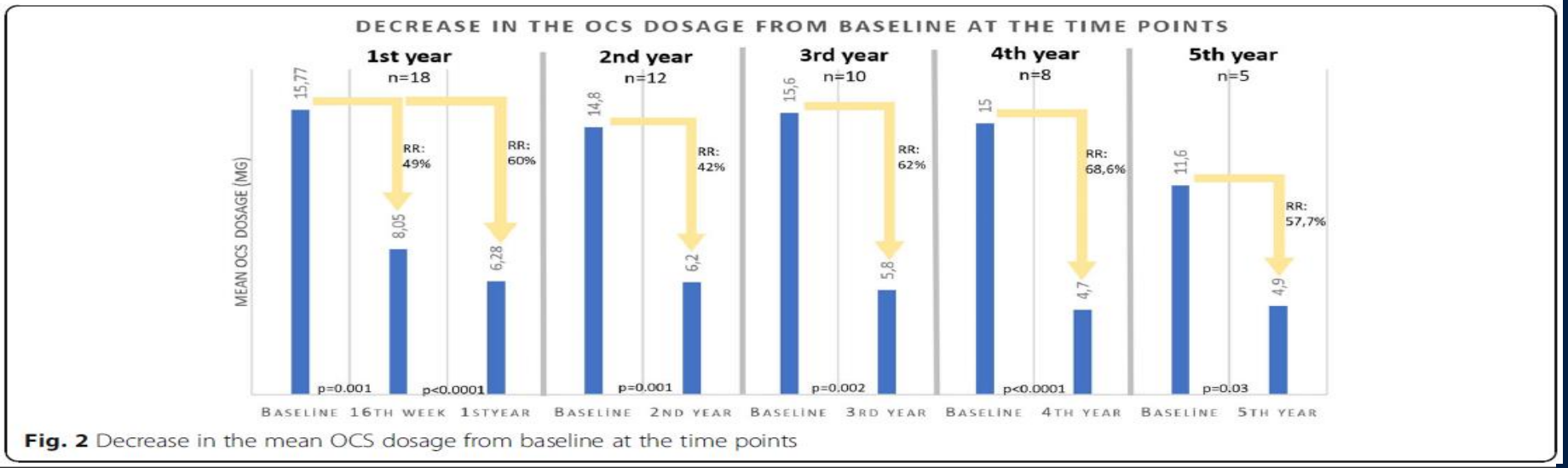


Fig. 2 Decrease in the mean OCS dosage from baseline at the time points

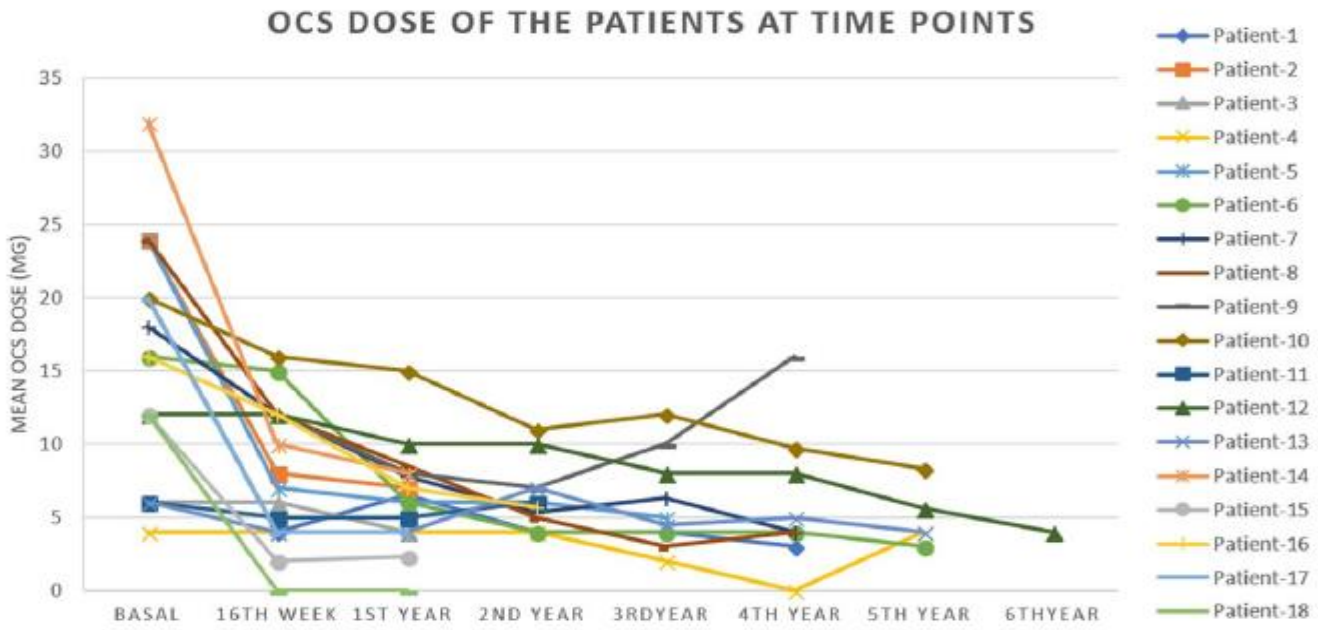


Fig. 3 Mean OCS dosage of the patients at the time points

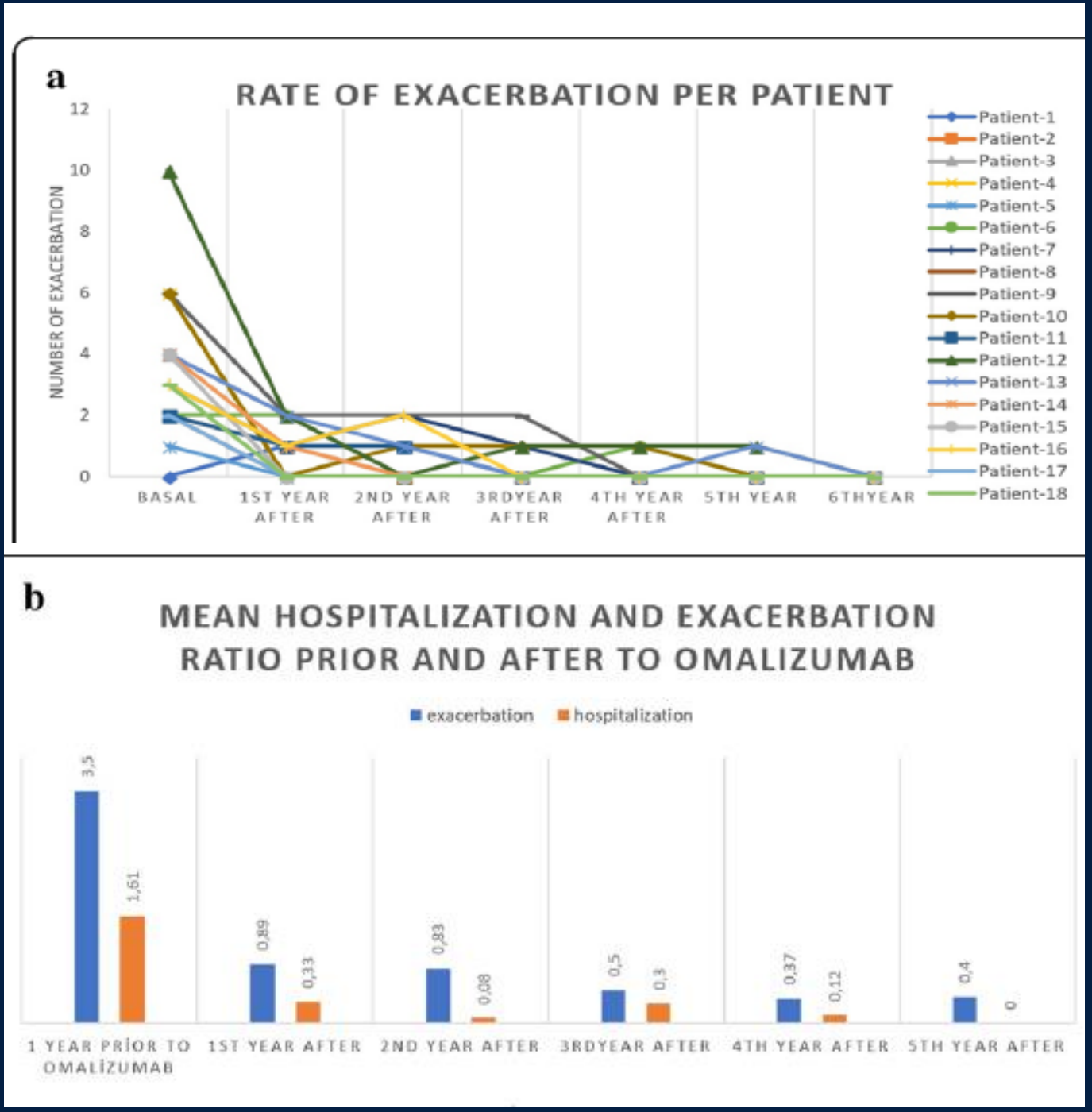
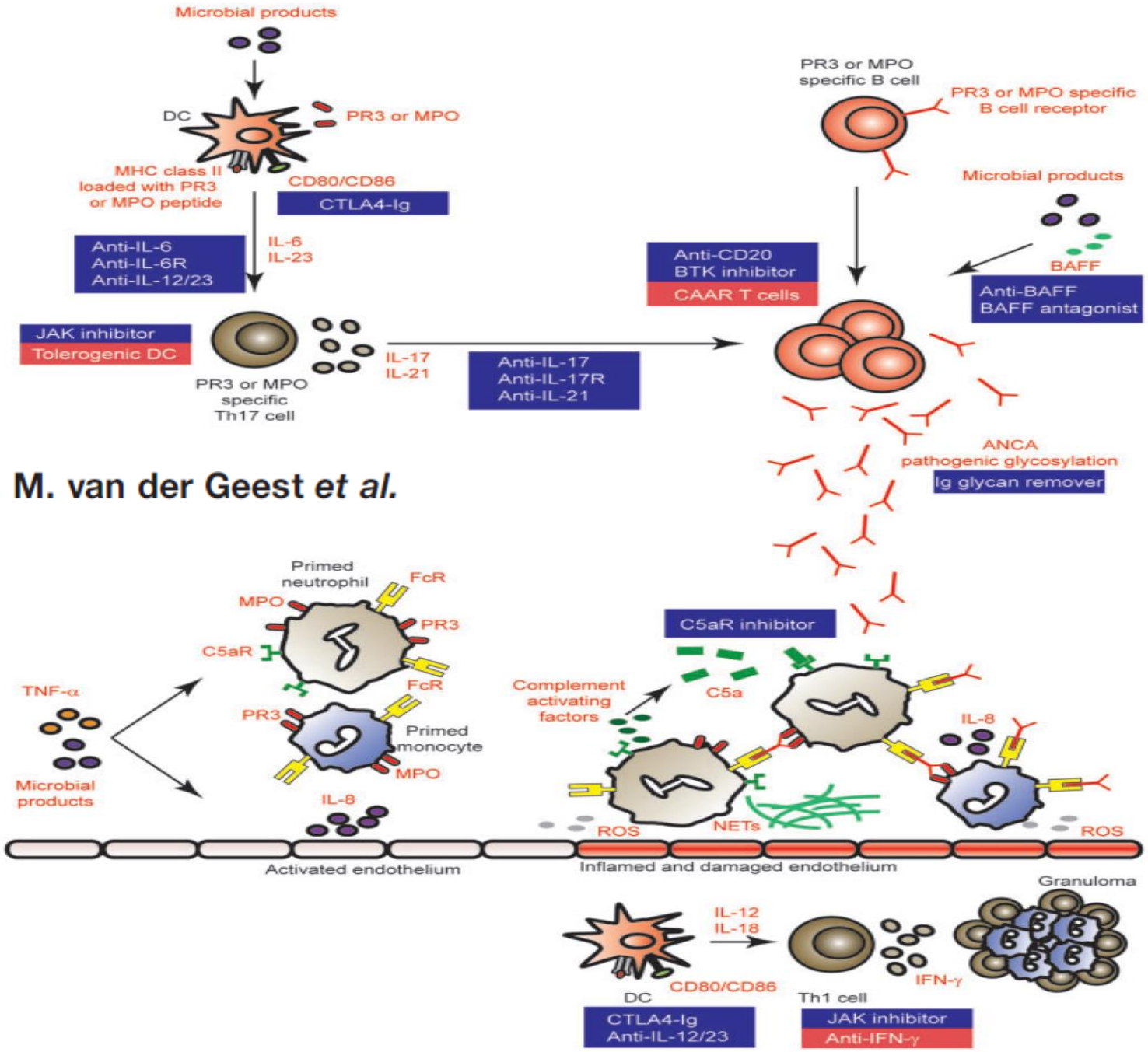

a
RATE OF EXACERBATION PER PATIENT
NUMBER OF EXACERBATION
12
10
8
6
4
2
0
BASAL
1ST YEAR AFTER
2ND YEAR AFTER
3RDYEAR AFTER
4TH YEAR AFTER
5TH YEAR
6THYEAR
Patient-1
Patient-2
Patient-3
Patient-4
Patient-5
Patient-6
Patient-7
Patient-8
Patient-9
Patient-10
Patient-11
Patient-12
Patient-13
Patient-14
Patient-15
Patient-16
Patient-17
Patient-18
b
MEAN HOSPITALIZATION AND EXACERBATION RATIO PRIOR AND AFTER TO OMALIZUMAB
exacerbation
hospitalization
3,5
1,61
0,89
0,33
0,93
0,08
0,5
0,3
0,37
0,12
0,4
0
1 YEAR PRİOR TO OMALİZUMAB
1ST YEAR AFTER
2ND YEAR AFTER
3RDYEAR AFTER
4TH YEAR AFTER
5TH YEAR AFTER

Table 1 Published cases of omalizumab use in urticarial vasculitis

References	Details	Age (years)	Complement levels	Systemic symptoms	Omalizumab		Effect of omalizumab
					Frequency (weeks)	Dose (mg)	
Del Pozo et al. [7]	Female with systemic lupus erythematosus (SLE)	51	Normal C3, low C4	Arthralgia (SLE)	Unknown, based on weight and IgE level		Partial resolution after 3 × doses
Varricchi et al. [8]	Female with Churg-Strauss syndrome (CSS)	44	Unknown	Asthma (CSS)	2	300	Complete, immediate resolution
Diez et al. [2]	Female	51	Normal	No	4	150	Complete resolution after 4–5 doses, relapse on cessation
	Female	54	Unknown	No	4	150	
	Female	28	Normal	No	4	300	Complete immediate resolution, relapse on cessation
Sussman et al. [3]	Unspecified adult		Unknown	Unknown	2	150	Complete resolution
Kai et al. [6]	Unspecified adult		Normal	No	4	150	Response, relapse on cessation
Ghazanfar et al. [4]	Male	68	Unknown	No	4	300	Complete resolution
Aurich et al. [9]	Female	36	Low C3 and C4	Nephrotic syndrome	4	300–600	No response over 19 months
Nucera et al. [10]	Female	47	Low C3 (0.17 g/L), normal C1q and anti C1q	No major organ dysfunction but arthralgia/abdominal pain	4	300	Complete resolution after 2nd injection. Complement levels returned to normal. Relapse on treatment cessation
Ivan Cherrez-Ojed (2018)	Female	57	Normal		4	150	Complete resolution

FIG. 1 Proven and potential immunological targets in AAV



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