Συνδυαστική θεραπεία αντι-TNFs και κορτικοστεροειδών: επιπλέον κίνδυνος;

Γ.Π.Καμπάκης
Ρευματολόγος

Σύγκρουση συμφερόντων

Γ.Π. Καμπάκης

καμία σύγκρουση συμφερόντων

+

Λοιμώξεις
- Μυκοβακτηριδιακές
- Άτυπα μυκοβακτηρίδια
- Μυκητησιακές
- Ευκαιριακές
- Ιογενείς (VZV, HBV, HCV, HIV)
- Μικροβιακές

Αναπνευστικό
Δέρμα
Ουροποιητικό

Υποκείμενη νόσο (είδος/ βαρύτητα/ ενεργότητα)

Φαρμακευτική αγωγή
- DMARD
- αντιTNFa
- Κορτικοειδή
  - Δόση (παρούσα/ συνολική)
  - Διάρκεια

RCT
Μελέτες παρατήρησης
Μετα ανάλυση

DMARD λοιμώξεις

Table 4. Risk of infection associated with exposure to DMARDs with and without immunosuppressive activity, adjusted for covariates*

Medication	Coefficient estimate	Adjusted RR	95% CI	P
Mild infections				
Medication (vs. no DMARD and no CS)				
Immunosuppressant alone	−0.09	0.92	0.89–0.95	< 0.0001
Nonimmunosuppressant alone	−0.12	0.89	0.86–0.92	< 0.0001
Immunosuppressant and CS	0.11	1.12	1.08–1.17	< 0.0001
Nonimmunosuppressant and CS	0.10	1.10	1.05–1.16	0.0001
CS alone	0.14	1.15	1.11–1.19	< 0.0001
None	0.0	Ref.		
Serious infections				
Medication (vs. no DMARD and no CS)				
Immunosuppressant alone	−0.12	0.88	0.79–0.99	0.0320
Nonimmunosuppressant alone	−0.06	0.95	0.85–1.05	0.3088
Immunosuppressant and CS	0.48	1.62	1.46–1.79	< 0.0001
Nonimmunosuppressant and CS	0.48	1.61	1.43–1.82	< 0.0001
CS alone	0.64	1.90	1.75–0.06	< 0.0001
None	0.0	Ref.		

DMARD+ΚΣ λοιμώξεις

Use of Nonbiologic Disease-Modifying Antirheumatic Drugs and Risk of Infection in Patients With Rheumatoid Arthritis

DIANE LACAILLE,[1] DAPHNE P. GUH,[2] MICHAL ABRAHAMOWICZ,[3] ASLAM H. ANIS,[4] AND JOHN M. ESDAILE[5]

Arthritis & Rheumatism (Arthritis Care & Research)
Vol. 59, No. 8, August 15, 2008, pp 1074–1081
DOI 10.1002/art.23913

Table 3. Generalized estimating equation extension of multivariate Poisson regression analysis, modeling the risk of mild and serious infections*

Variable	Mild infections			Serious infections		
	Adjusted RR	95% CI	*P*	Adjusted RR	95% CI	*P*
Medication (vs. no DMARD and no CS)						
DMARD and CS	1.12	1.08–1.16	< 0.0001	1.63	1.5–1.77	< 0.0001
DMARD alone	0.9	0.88–0.93	< 0.0001	0.92	0.85–1.0	0.0502
CS alone	1.15	1.11–1.19	< 0.0001	1.9	1.75–2.05	< 0.0001
Prior event (yes vs. no)	1.23	1.21–1.26	< 0.0001	3.08	2.84–3.35	< 0.0001
Comorbidity index (per unit)	1.08	1.08–1.09	< 0.0001	1.11	1.1–1.12	< 0.0001
Age (per 10-year increase)	0.97	0.96–0.98	< 0.0001	1.19	1.16–1.22	< 0.0001
Sex (women vs. men)	1.28	1.24–1.31	< 0.0001	1.02	0.96–1.08	0.5583
RA duration (vs. incident cases)						
>5 years	1.11	1.07–1.15	< 0.0001	1.45	1.35–1.57	< 0.0001
0–5 years	1.04	1.01–1.07	0.0041	1.13	1.06–1.21	0.0003
SES (low vs. high)	1.39	1.34–1.45	< 0.0001	1.56	1.41–1.73	< 0.0001

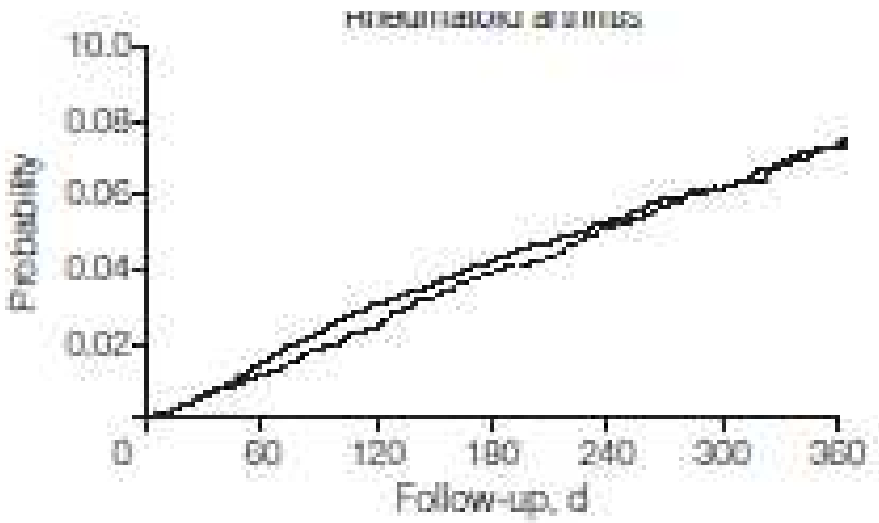
* RR = rate ratio; 95% CI = 95% confidence interval; DMARD = disease-modifying antirheumatic drug; CS = corticosteroids; RA = rheumatoid arthritis; SES = surrogate marker of socioeconomic status.

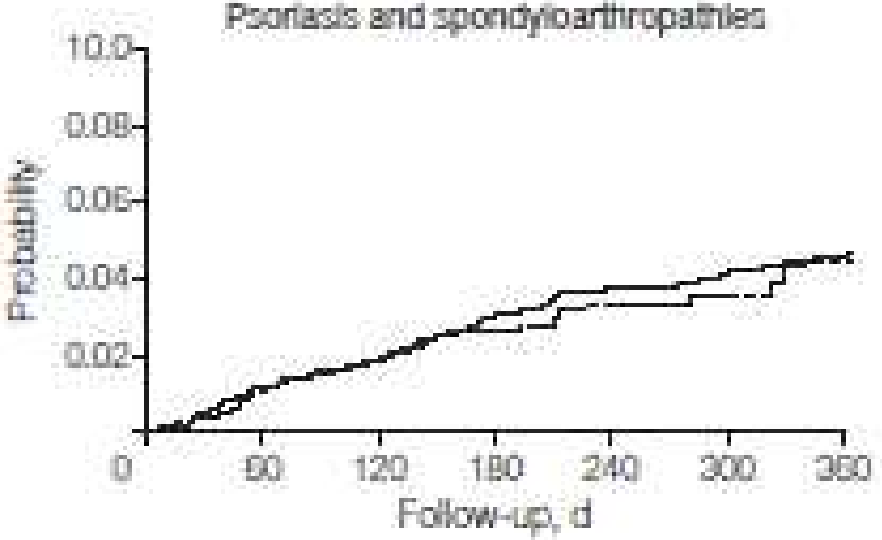
TNF λοιμώξεις

Initiation of Tumor Necrosis Factor-α Antagonists and the Risk of Hospitalization for Infection in Patients With Autoimmune Diseases

JAMA. 2011;306(21):2331-2339

TNF λοιμώξεις





JAMA. 2011;306(21):2331-2339

TNF+ΚΣ λοιμώξεις

	ΡΑ	ΦΝΕ	ΨΑ
5mg	**1.32**	1.09	**1.15**
5-10	**1.78**	0.93	**2.01**
>10mg	**2.95**	1.38	**2.77**

JAMA. 2011;306(21):2331-2339

Autoimmunity Reviews xxx (2012) xxx–xxx

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Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: Comparison of adalimumab, etanercept and infliximab in the GISEA registry

Fabiola Atzeni [a,*], Piercarlo Sarzi-Puttini [a,1], Costantino Botsios [b,1], Antonio Carletto [c,1], Paola Cipriani [d,1], Ennio Giulio Favalli [e,1], Elena Frati [f,1], Valentina Foschi [g,1], Stefania Gasparini [h,1], AnnaRita Giardina [i,1], Elisa Gremese [j,1], Florenzo Iannone [k,1], Marco Sebastiani [l,1], Tamara Ziglioli [m,1], Domenico Biasi [c,1], Clodoveo Ferri [l,1], Mauro Galeazzi [g,1], Roberto Gerli [n,1], Roberto Giacomelli [d,1], Roberto Gorla [m,1], Marcello Govoni [g,1], Giovanni Lapadula [k,1], Antonio Marchesoni [e,1], Fausto Salaffi [h,1], Leonardo Punzi [b,1], Giovanni Triolo [i,1], Gianfranco Ferraccioli [j,1]

Univariable and multivariable predictors of serious infections.

	Univariate				Multivariate			
	HR[a]	95% CI[b]		p	AHR[c]	95% CI[b]		p
Age at start of anti-TNF treatment	1.03	1.02	1.04	<.0001	1.036	1.02	1.053	<.0001
Disease duration	1.009	0.99	1.03	0.3	1.004	0.98	1.025	0.709
DAS28	1.055	0.94	1.19	0.381	0.946	0.81	1.107	0.49
DI-HAQ	1.443	1.15	1.81	0.002	1.156	0.85	1.576	0.358
Etanercept	1				1			
Adalimumab	1.942	1.2	3.15	0.0007	2.224	1.12	4.421	0.023
Infliximab	4.291	2.84	6.47	<.0001	4.916	2.71	8.906	<.0001
DMARDs	2.178	1.59	2.98	<.0001	2.145	1.28	3.595	0.004
Corticosteroids	1.849	1.36	2.51	<.0001	1.633	1.01	2.644	0.046
Comorbidity	0.899	0.67	1.21	0.479	1.246	0.87	1.791	0.234

Univariable and multivariable predictors of serious infections.

	Univariate				Multivariate			
	HR[a]	95% CI[b]		p	AHR[c]	95% CI[b]		p
Age at start of anti-TNF treatment	1.03	1.02	1.04	<0.0001	1.036	1.02	1.053	<0.0001
Disease duration	1.009	0.99	1.03	0.3	1.004	0.98	1.025	0.709
DAS28	1.055	0.94	1.19	0.381	0.946	0.81	1.107	0.49
DI-HAQ	1.443	1.15	1.81	0.002	1.156	0.85	1.576	0.358
Etanercept	1				1			
Adalimumab	1.942	1.2	3.15	0.0007	2.224	1.12	4.421	0.023
Infliximab	4.291	2.84	6.47	<0.0001	4.916	2.71	8.906	<0.0001
DMARDs	2.128	1.59	2.98	<0.0001	2.145	1.28	3.595	0.004
Corticosteroids	1.849	1.36	2.51	<0.0001	1.633	1.01	2.644	0.046
Comorbidity	[illegible]	0.67	1.21	0.479	1.246	0.87	1.791	0.234

Arthritis Care & Research
Vol. 64, No. 8, August 2012, pp 1125–1134
DOI 10.1002/acr.21666

ORIGINAL ARTICLE

Time-Dependent Increased Risk for Serious Infection From Continuous Use of Tumor Necrosis Factor Antagonists Over Three Years in Patients With Rheumatoid Arthritis

RYOKO SAKAI,[1] YUKIKO KOMANO,[1] MICHI TANAKA,[1] TOSHIHIRO NANKI,[1] RYUJI KOIKE,[1] HAYATO NAGASAWA,[2] KOICHI AMANO,[2] ATSUO NAKAJIMA,[3] TATSUYA ATSUMI,[4] TAKAO KOIKE,[4]

Table 4. Multivariate analysis of independent risk factors for serious infections during continuous use of TNF antagonists in the Registry of Japanese Rheumatoid Arthritis Patients for Long-Term Safety database*

	RR (95% CI)†	*P*
TNF antagonist (infliximab or etanercept)	1.97 (1.25–3.19)	0.0045
Age by decade	1.45 (1.20–1.77)	< 0.001
Chronic pulmonary disease	1.77 (1.15–2.70)	0.009
Diabetes mellitus	1.20 (0.69–1.97)	0.49
Mean DAS28-CRP (per 1.0 increment)	1.33 (1.05–1.66)	0.015
Mean MTX dosage >8.0 mg/week‡	2.14 (1.15–3.87)	0.013
Mean prednisolone dosage ≥10 mg/day‡	2.49 (1.08–5.50)	0.027

Arthritis Care & Research
DOI 10.1002/acr.21713

Use of a Disease Risk Score to Compare Serious Infections Associated with Anti-TNF Therapy among High versus Lower Risk Rheumatoid Arthritis Patients

JR Curtis MD MS MPH[1,2], Fenglong Xie MS[1], Lang Chen PhD[1], Paul Muntner PhD[2], Carlos G. Grijalva MD MPH[3], Claire Spettell PhD[4], Joaquim Fernandes MS[4], Raechele M. Mcmahan MBA[5], John W. Baddley MD[6], Kenneth G. Saag MD MSc[1,2], Timothy Beukelman MD MSCE[1], , Elizabeth Delzell ScD[2]

- Σύμφωνα με το μοντέλο,
  σε νέο ασθενή που λαμβάνει πάνω από 7,5mg πρεδνιζολόνης ο συνολικός κίνδυνος εμφάνισης λοίμωξης ***μειώνεται*** μετά την έναρξη χορήγησης αντιTNF εφόσον αυτή επιτρέψει την διακοπή λήψης ΚΣ

ΚΣ λοιμώξεις

RESEARCH ARTICLE Open Access

The association between systemic glucocorticoid therapy and the risk of infection in patients with rheumatoid arthritis: systematic review and meta-analyses

William G Dixon[1,2*], Samy Suissa[2] and Marie Hudson[2]

Dixon et al. Arthritis Research & Therapy 2011, 13:R139
http://arthritis-research.com/content/13/4/R139

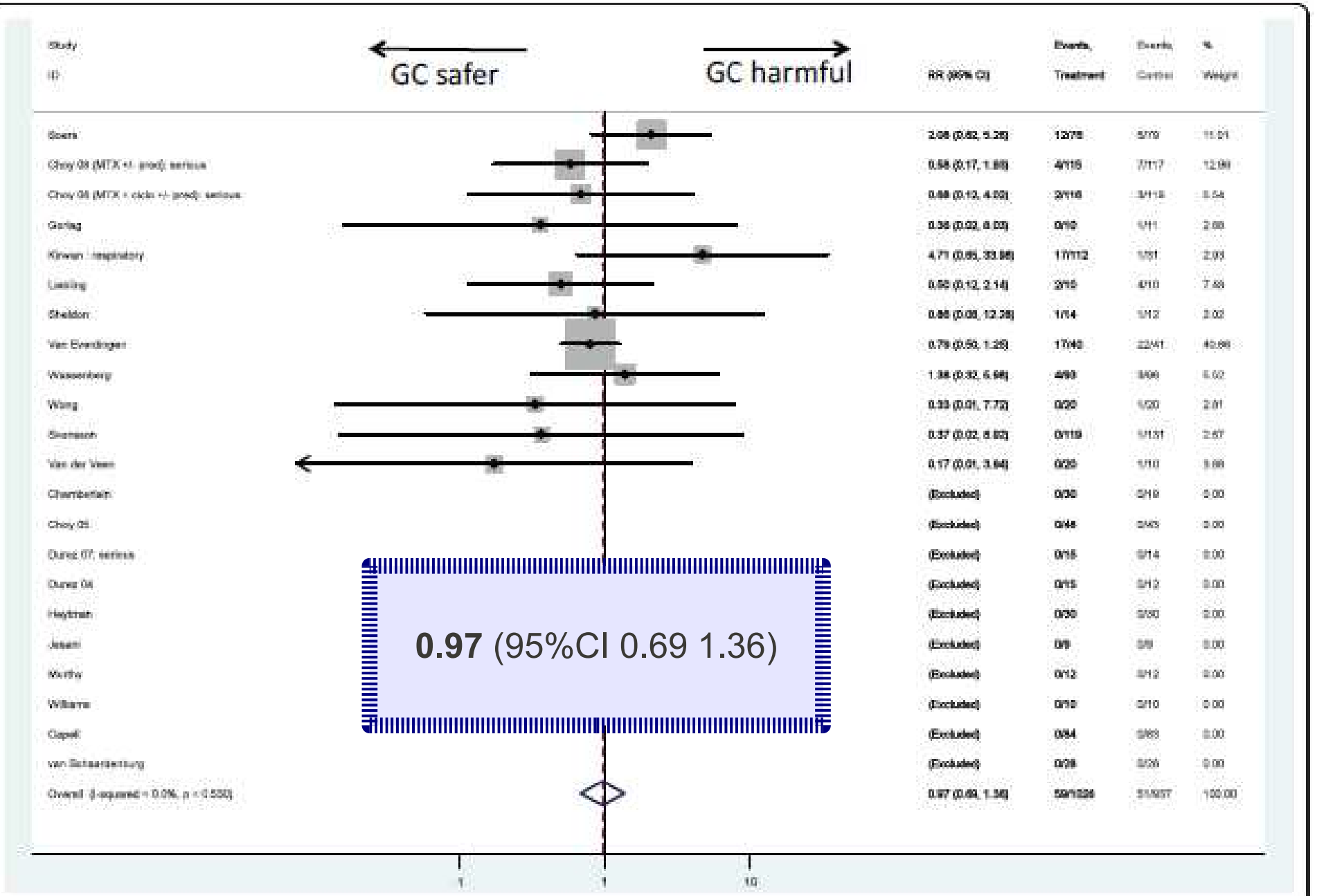
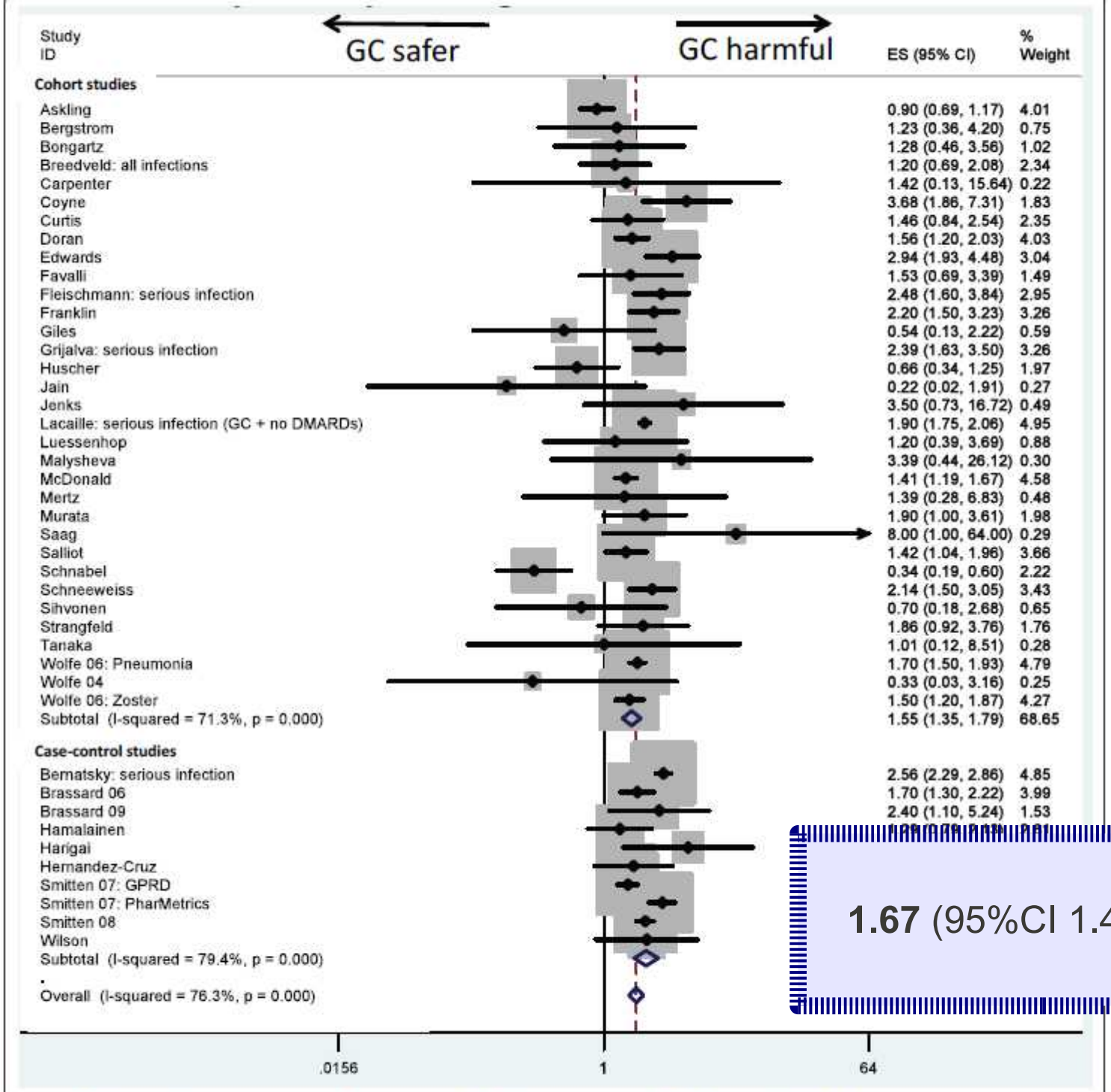


Figure 2 Meta-analysis of infection risk in randomized controlled trials of systemic glucocorticoid therapy.

Dixon *et al. Arthritis Research & Therapy* 2011, **13**:R139
http://arthritis-research.com/content/13/4/R139



1.67 (95%CI 1.49 1.87)

Figure 3 Meta-analysis of infection risk in observational studies, stratified by study design (1,

Dixon *et al. Arthritis Research & Therapy* 2011, **13**:R139
http://arthritis-research.com/content/13/4/R139

ΚΣ λοιμώξεις

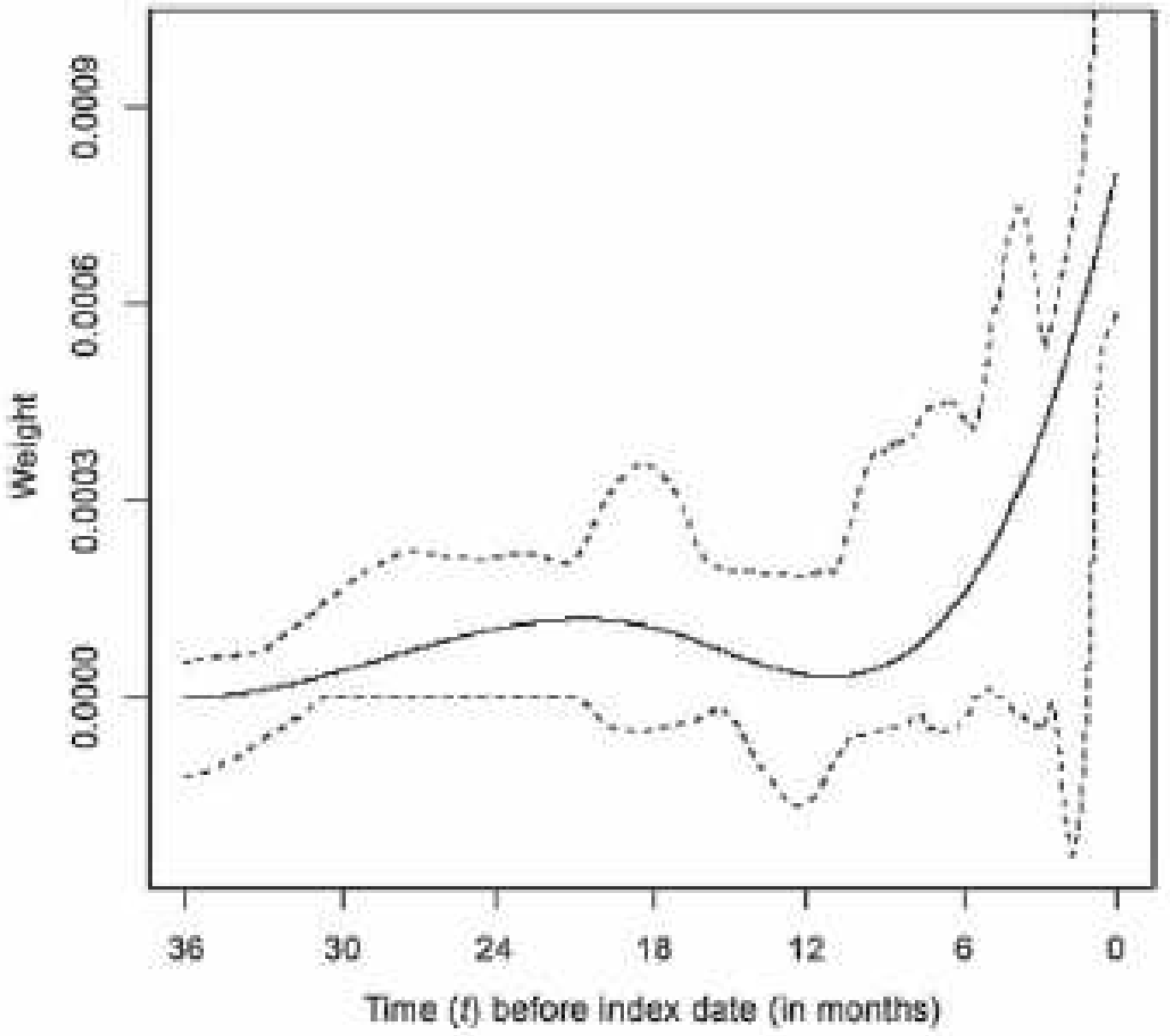
The influence of systemic glucocorticoid therapy upon the risk of non-serious infection in older patients with rheumatoid arthritis: a nested case–control study

W G Dixon,[1,2] A Kezouh,[2] S Bernatsky,[3] S Suissa[2]

Ann Rheum Dis 2012;**71**:1128–1133. doi:10.1136/annrheumdis-2011-200702

+ Η χρήση ΚΣ **αυξάνει** τον κίνδυνο λοιμώξεων
+ Ιδιαίτερα η **παρούσα** και η **πρόσφατη** δόση
+ λιγότερο η αθροιστική δόση πέραν της διετίας

ΚΣ λοιμώξεις

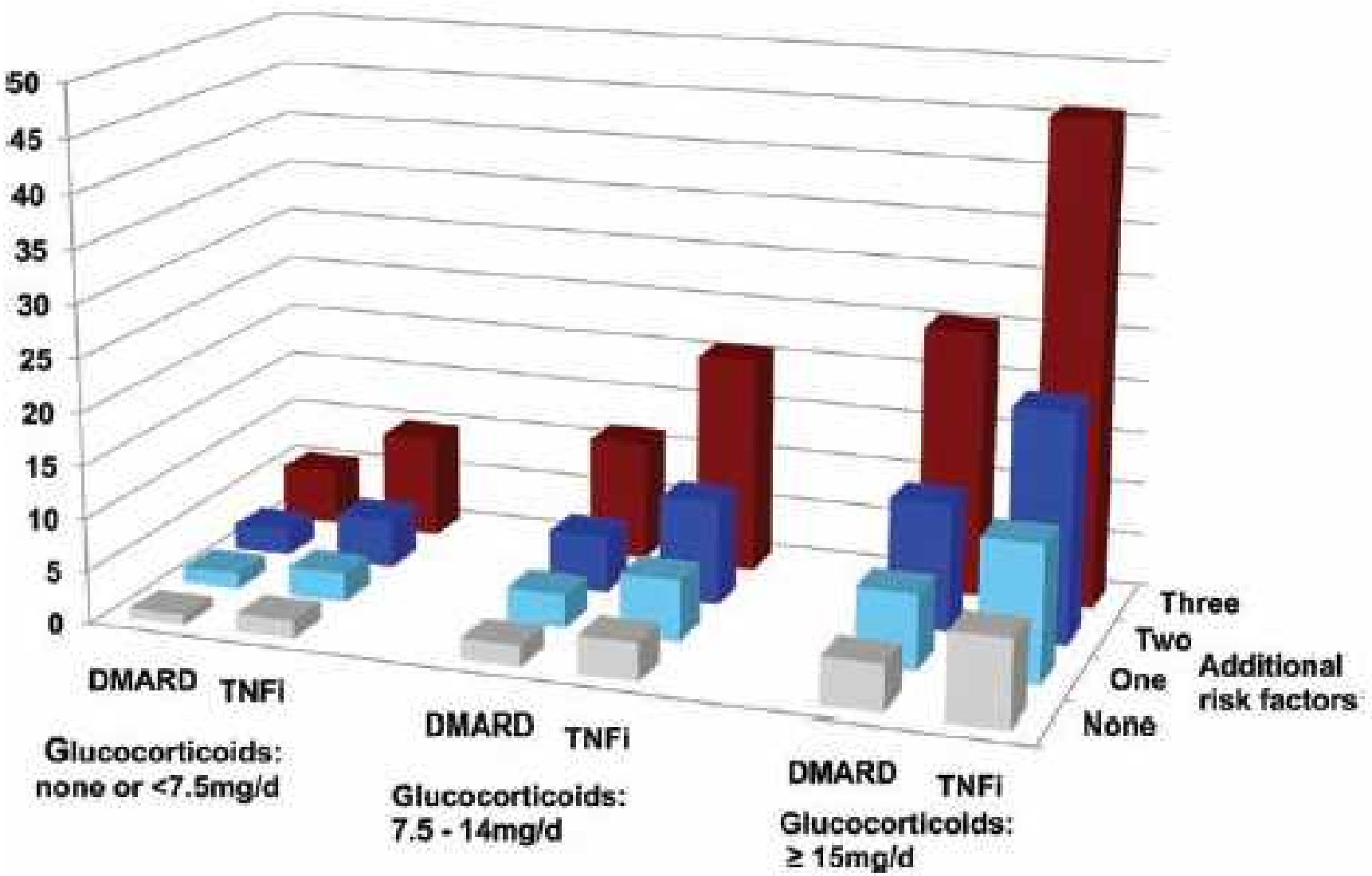


ΚΣ λοιμώξεις

Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case–control analysis

William G Dixon,[1] Michal Abrahamowicz,[2,3] Marie-Eve Beauchamp,[3] David W Ray,[4] Sasha Bernatsky,[5] Samy Suissa,[6] Marie-Pierre Sylvestre[7,8]

TNF + ΚΣ λοιμώξεις



Ann Rheum Dis 2011;**70**:1914–1920. doi:10.1136/ard.2011.151043

Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient?

A Strangfeld,[1] M Eveslage,[1] M Schneider,[2] H J Bergerhausen,[3] T Klopsch,[4] A Zink,[1,5] J Listing[1]

Ann Rheum Dis 2011;**70**:1914–1920. doi:10.1136/ard.2011.151043

Table 2 Crude rates of serious infections per 100 patient-years (pyrs)

	Exposure time (pyrs)	Serious infections			Incidence rate ratio (IRR)
		n	Per 100 pyrs	95% CI	
Year 1					
DMARD treatment	1765	40	2.3	1.6 to 3.1	2.13
Anti-TNF agents	3041	147	4.8	4.1 to 5.7	
Year 2					
DMARD treatment	1696	40	2.4	1.7 to 3.2	1.36
Anti-TNF agents	2564	82	3.2	2.9 to 4.0	
Year 3					
DMARD treatment	1397	35	2.5	1.8 to 3.5	0.88
Anti-TNF agents	2186	48	2.2	1.6 to 2.9	

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

Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient?

A Strangfeld,[1] M Eveslage,[1] M Schneider,[2] H J Berqerhausen,[3] T Klopsch,[4] A Zink,[1,5] J Listing[1]

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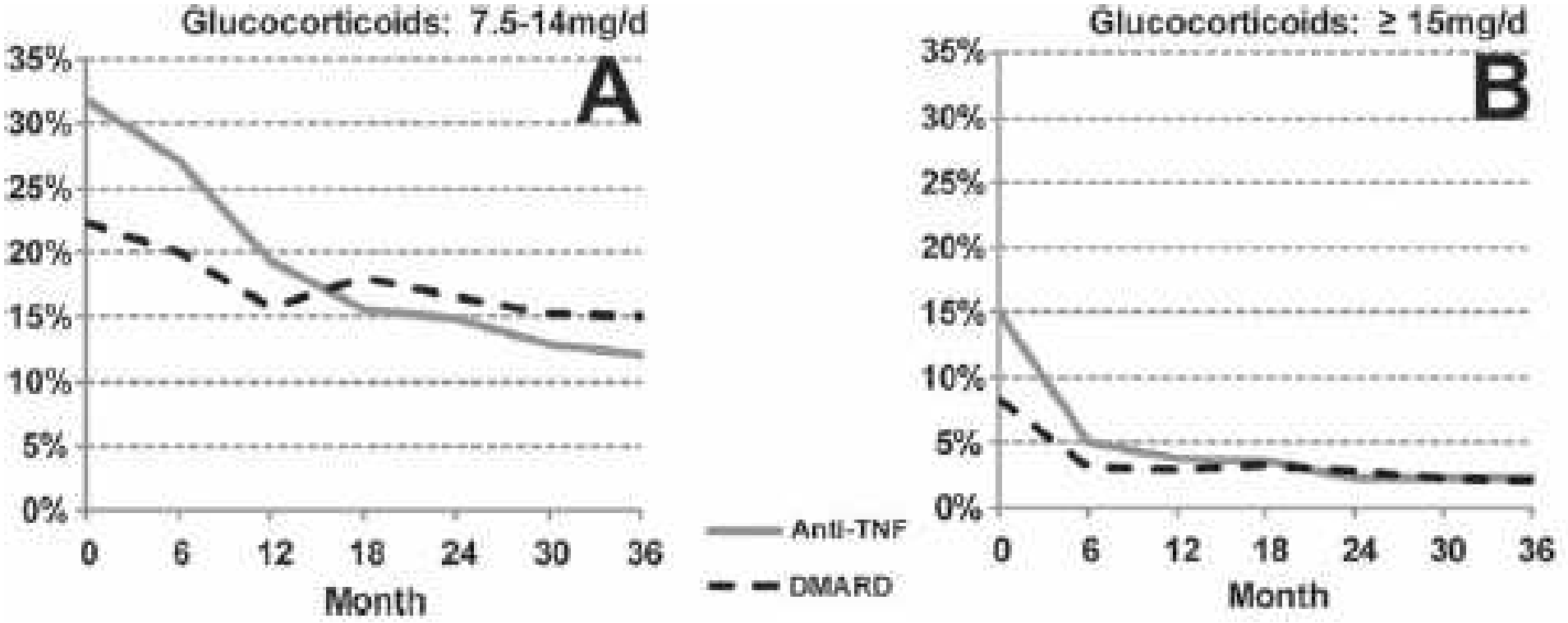

Συμπερασματικά...

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Υποκείμενη νόσο (είδος/ βαρύτητα/ ενεργότητα)

Φαρμακευτική αγωγή
- DMARD
- αντιTNFa
- Κορτικοειδή
  - Δόση (**παρούσα**/ συνολική)
  - Διάρκεια