Επιστημονική Εταιρεία
για τη Μυοσκελετική
ΥΓΕΙΑ - ΕΠΕΜΥ

Κλινικά διλήμματα στο Συστηματικό Ερυθηματώδη Λύκο

Δια βίου συνέχιση κορτιζονοθεραπείας στον ΣΕΛ;

Παπαλόπουλος Ιωάννης
Ρευματολόγος

Κέρκυρα, 19/04/2019

Επιστημονική Εταιρεία
για τη Μυοσκελετική
ΥΓΕΙΑ - ΕΠΕΜΥ

Καμία σύγκρουση συμφερόντων

ΣΕΛ και στεροειδή

- **“ Cornerstone” θεραπείας για 70 χρόνια παρά τη χρήση πολλών ανοσοκατασταλτικών φαρμάκων**

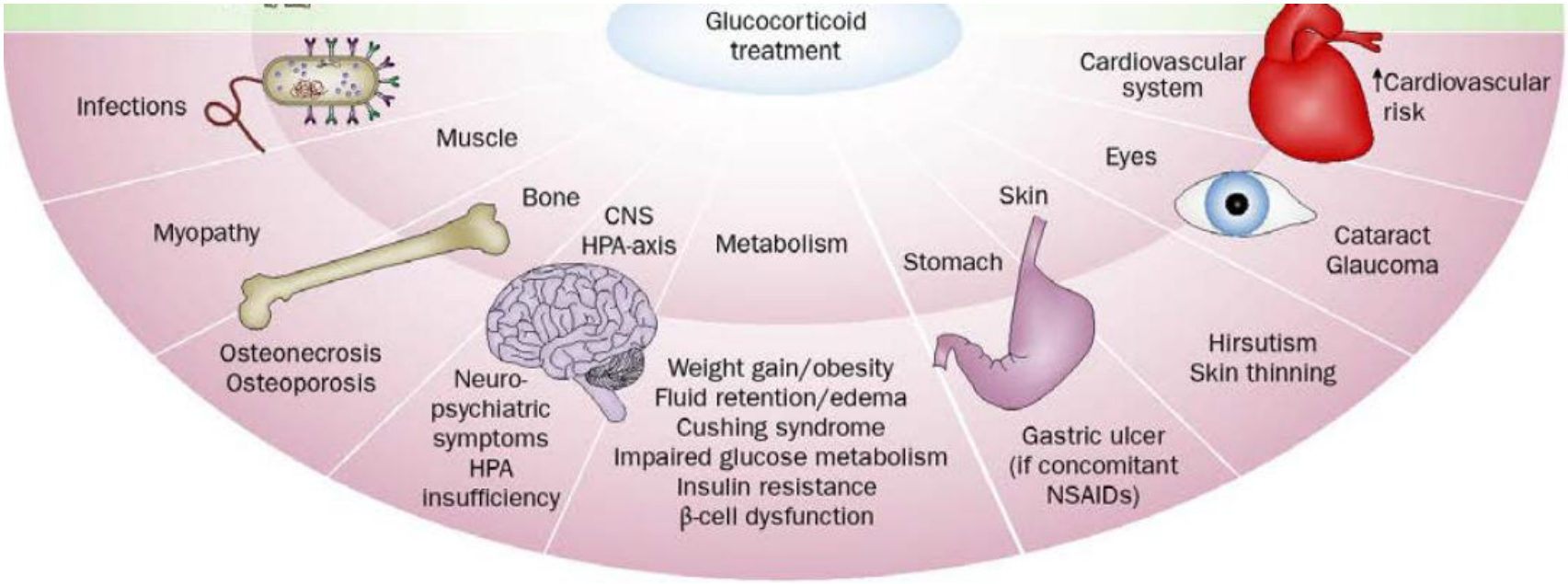
- **Η συντριπτική πλειοψηφία των ασθενών με ΣΕΛ έχουν λάβει GCs**

- **Σε διάφορες κοόρτες έως και 80% λαμβάνει για απροσδιόριστο χρόνο (“ indefinitely”) σε δόσεις < 7,5 mg prednisolone/day.**

EULAR on line course
Mosca et al. Clin Exp, 2011

GCs: "Doubled edged sword"

- **Σημαντικός λόγος βελτίωσης της επιβίωσης των ασθενών με ΣΕΛ από 50% στην 3ετία στα 1950s (Jessar, 1953)σε 90% στη 10ετία στα 2000s(Cervera, 2003).**



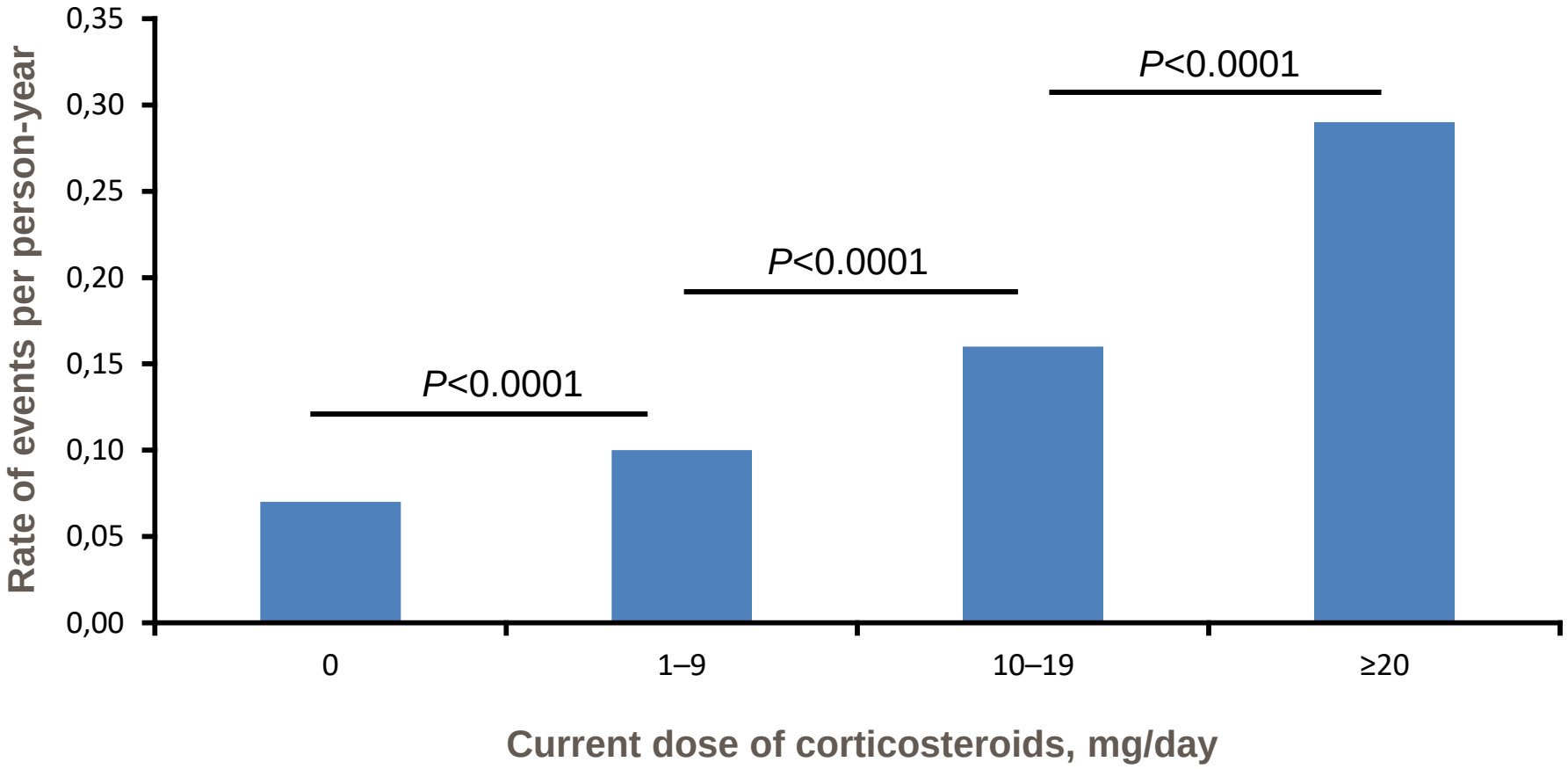
Hoes, J. N. *et al. Nat. Rev. Rheumatol.* 6, 693–702 (2010)

Αύξηση του damage με την αύξηση της δόσης στεροειδών

(Johns Hopkins Lupus Cohort)

Επιστημονική Εταιρεία για τη Μυοσκελετική ΥΓΕΙΑ - ΕΠΕΜΥ

The relationship between corticosteroid dose and the rate of damage accrual



Petri M, *et al. Arthritis Rheum* 2012; **64:**4021–4028.

Damage από τον ΣΕΛ ή από τα GCs?

Επιστημονική Εταιρεία για τη Μυοσκελετική ΥΓΕΙΑ - ΕΠΕΜΥ

Toronto Lupus Cohort (2003)
Mean follow up : 15 years
SLICC/ACR Damage Index (SDI)

❑Year 1

- **16% definitely secondary to GCs (ocular and musculoskeletal)**
- **42% possibly related to GCs (cardiovascular and neuropsychiatric)**
- **42% independent of GCs**

❑Year 15

- **49% definitely associated with CSs**
- **31% possibly related with CSs**
- **only 20% of new accrued damage was independent of GCs**

Time	SLE related	CS related*
1st year	42%	**58%**
>10 years	20%	**80%**

Gladman et al. J Rheum, 2003
Ruiz-Irastorza et al, Rheumatology (Oxford), 2012

Τι δείχνουν οι μελέτες για τη μακροχρόνια χρήση GCs?

The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide

F A Houssiau,[1] C Vasconcelos,[2] D D'Cruz,[3] G D Sebastiani,[4] E de Ramon Garrido,[5] M G Danieli,[6] D Abramovicz,[7] D Blockmans,[8] A Cauli,[9] H Direskeneli,[10] M Galeazzi,[11] A Gül,[12] Y Levy,[13] P Petera,[14] R Popovic,[15] R Petrovic,[16] R A Sinico,[17] R Cattaneo,[18] J Font,[19] G Depresseux,[1] J-P Cosyns,[20] R Cervera[19]

➢**73%** των ασθενών στη 10ετία συνέχιζε να λαμβάνει GCs

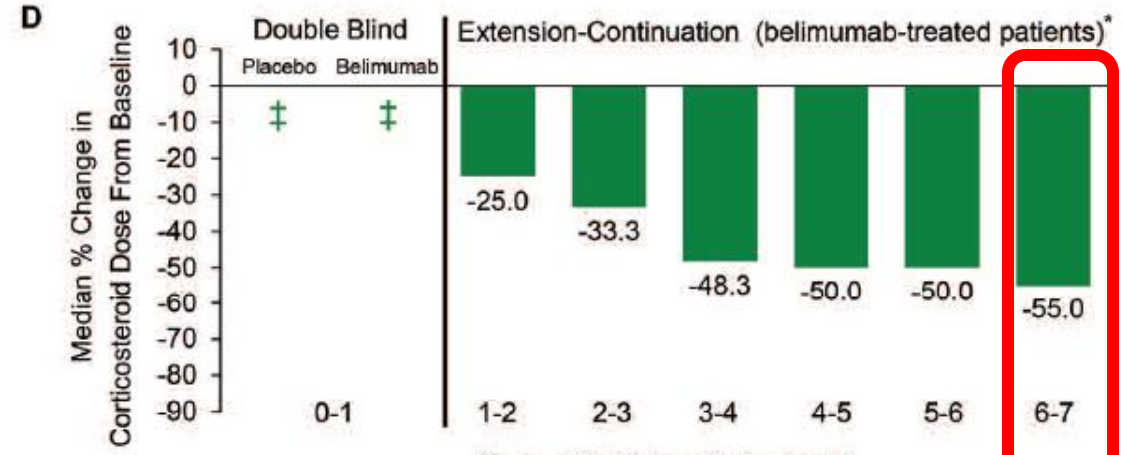
Table 2 Renal parameters, treatment and chronic damage in the Euro-Lupus Nephritis Trial Cohort at 10 years of follow-up

		IVCY	
	All	High dose	Low dose
Current serum creatinine (mg/dl)	1.0 (0.5)	1.0 (0.4)	1.0 (0.6)
Current 24 h proteinuria (g)	0.6 (1.2)	0.6 (1.3)	0.5 (1.0)
Ongoing GC therapy (% of patients)	73	71	75
Ongoing IS therapy (% of patients)	56	59	53
Ongoing BP lowering therapy (% of patients)	68	68	67
Additional IS drugs ever received† (n)	0.7 (0.9)	0.7 (0.9)	0.7 (0.9)
Ever received MMF (% of patients)	30	30	29
Cumulative IVCY dose (g)	7.6 (2.5)	9.5 (2.5)	5.5 (4.8)*
Current SLICC/ACR DI (score)	1.1 (1.1)	1.0 (1.2)	1.1 (1.1)
Cumulative cardiac/arterial events (n patients)	7	4	3
Cumulative cancers (n patients)	7	1	6

Τι δείχνουν οι μελέτες για τη μακροχρόνια χρήση GCs?

Disease Control and Safety of Belimumab Plus Standard Therapy Over 7 Years in Patients with Systemic Lupus Erythematosus

Ellen M. Ginzler, Daniel J. Wallace, Joan T. Merrill, Richard A. Furie, William Stohl, W. Winn Chatham, Arthur Weinstein, James D. McKay, W. Joseph McCune, Z. John Zhong, William W. Freimuth, and Michelle A. Petri; and the LBSL02/99 Study Group



	0-1		1-2	2-3	3-4	4-5	5-6	6-7
Median absolute change in corticosteroid dose from baseline, mg/d	0	0	-2.0	-2.5	-2.5	-3.0	-4.0	-4.0

Ginzler et al. J Rheumatol 2014;41;300-309

Τι δείχνουν οι μελέτες για τη μακροχρόνια χρήση GCs?

Επιστημονική Εταιρεία για τη Μυοσκελετική ΥΓΕΙΑ - ΕΠΕΜΥ

ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 6, June 2018, pp 868–877
DOI 10.1002/art.40439

Long-Term Safety and Efficacy of Belimumab in Patients With Systemic Lupus Erythematosus

A Continuation of a Seventy-Six–Week Phase III Parent Study in the United States

Richard A. Furie,[1] Daniel J. Wallace,[2] Cynthia Aranow,[3] James Fettiplace,[4] Barbara Wilson,[5] Prafull Mistry,[6] David A. Roth,[7] and David Gordon[7]

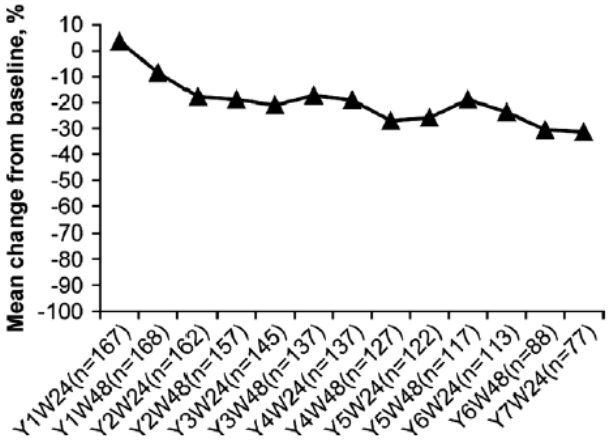


Figure 3. Mean percentage change from baseline in prednisone dose. Y1W24 = year 1, week 24.

- **50%** των ασθενών που λάμβαναν > 7,5 mg/day prednisone μείωσαν σε <7,5mg/day με την αγωγή με Belimumab στον 3ο χρόνο

- **13,3%** κατάφερε να διακόψει μόνιμα τα στεροειδή στη διάρκεια της 10ετούς παρακολούθησης

Τι δείχνουν οι μελέτες για τη μακροχρόνια χρήση GCs?
(Η ελληνική εμπειρία)

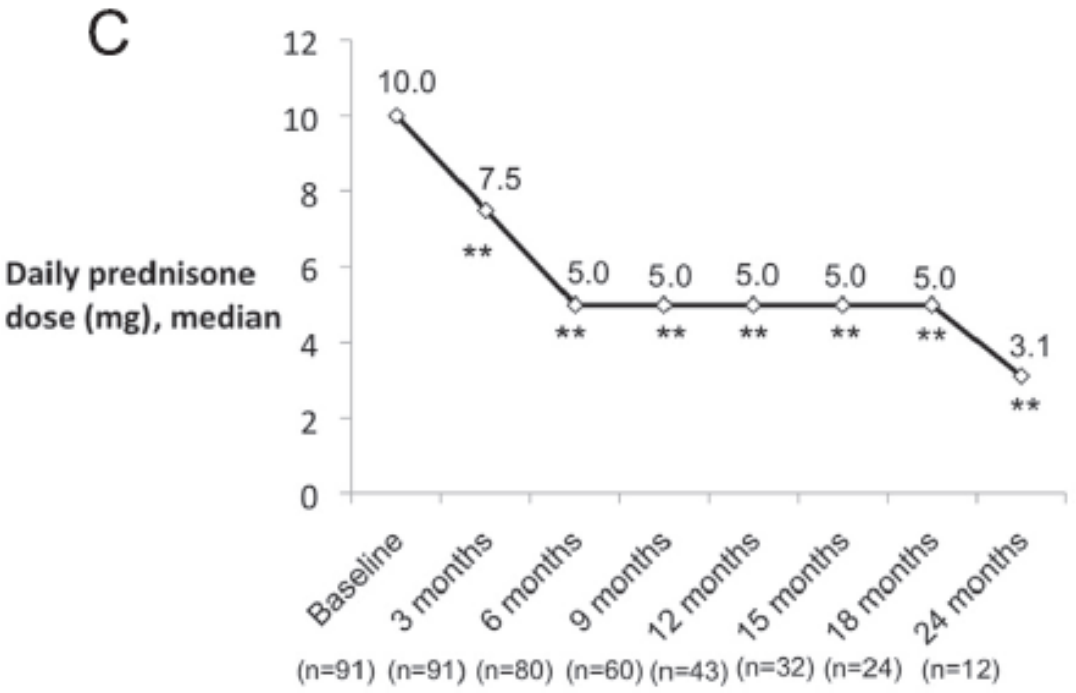
Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

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

Low disease activity—irrespective of serologic status at baseline—associated with reduction of corticosteroid dose and number of flares in patients with systemic lupus erythematosus treated with belimumab: A real-life observational study

Antonis Fanouriakis, MD[a,*], Christina Adamichou, MD[b], Sofia Koutsoviti, MD[c], Stylianos Panopoulos, MD[d], Chrysanthi Staveri, MD[e], Anastasia Klagou, MD[f], Christina Tsalapaki, MD[g], Lamprini Pantazi, MD[h], Styliani Konsta, MD[i], Clio P. Mavragani, MD, PhD[j], Despoina Dimopoulou, MD[k], Styliani Ntali, MD[l], Georgios Katsikas, MD[i], Kyriaki A. Boki, MD[h], Dimitrios Vassilopoulos, MD[g], Pinelopi Konstantopoulou, MD[f], Stamatis-Nick Liossis, MD, PhD[e], Antonia Elezoglou, MD[c], Maria Tektonidou, MD[d], Prodromos Sidiropoulos, MD, PhD[b], Abdulsamet Erden, MD[m], Petros P. Sfikakis, MD[d], George Bertsias, MD, PhD[b,1], Dimitrios T. Boumpas, MD, PhD[a,1]

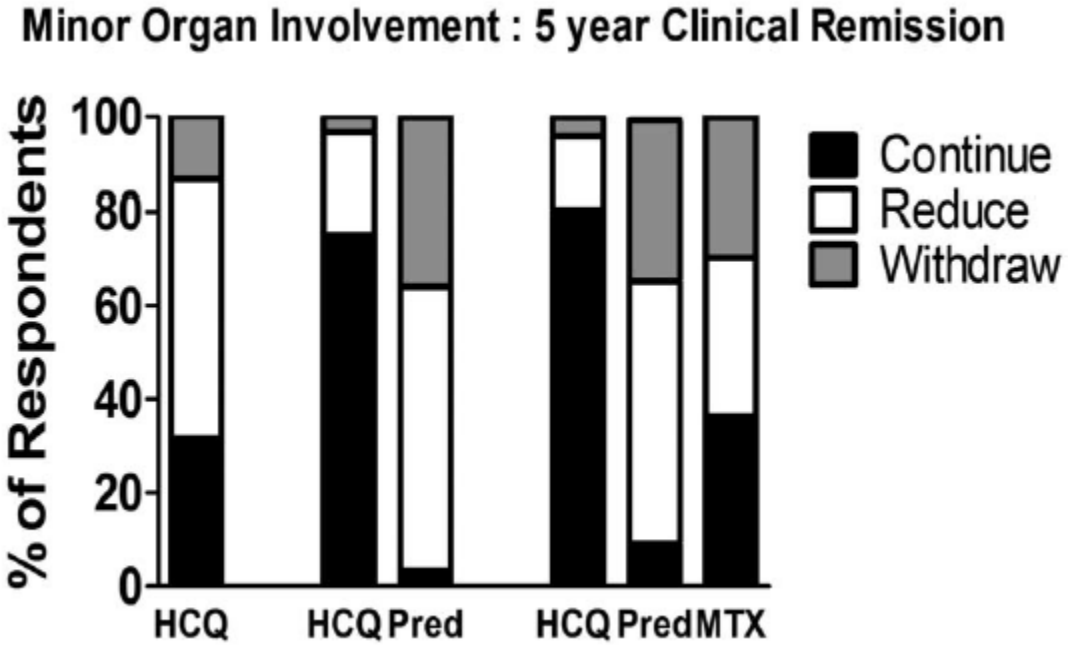


➢**23,3%** διέκοψε πλήρως τα GCs στους 12 μήνες

LUPUS SCIENCE & MEDICINE™

Clinicians approaches to management of background treatment in patients with SLE in clinical remission: results of an international observational survey

Pintip Ngamjanyaporn,[1,2] Eoghan M McCarthy,[1,3] Jamie C Sergeant,[1,3] John Reynolds,[1,3] Sarah Skeoch,[1,3] Benjamin Parker,[1,3] Ian N Bruce[1,3]



Lupus Science & Medicine 2017;4:e000173. doi:10.1136/lupus-2016-000173

LUPUS SCIENCE & MEDICINE™

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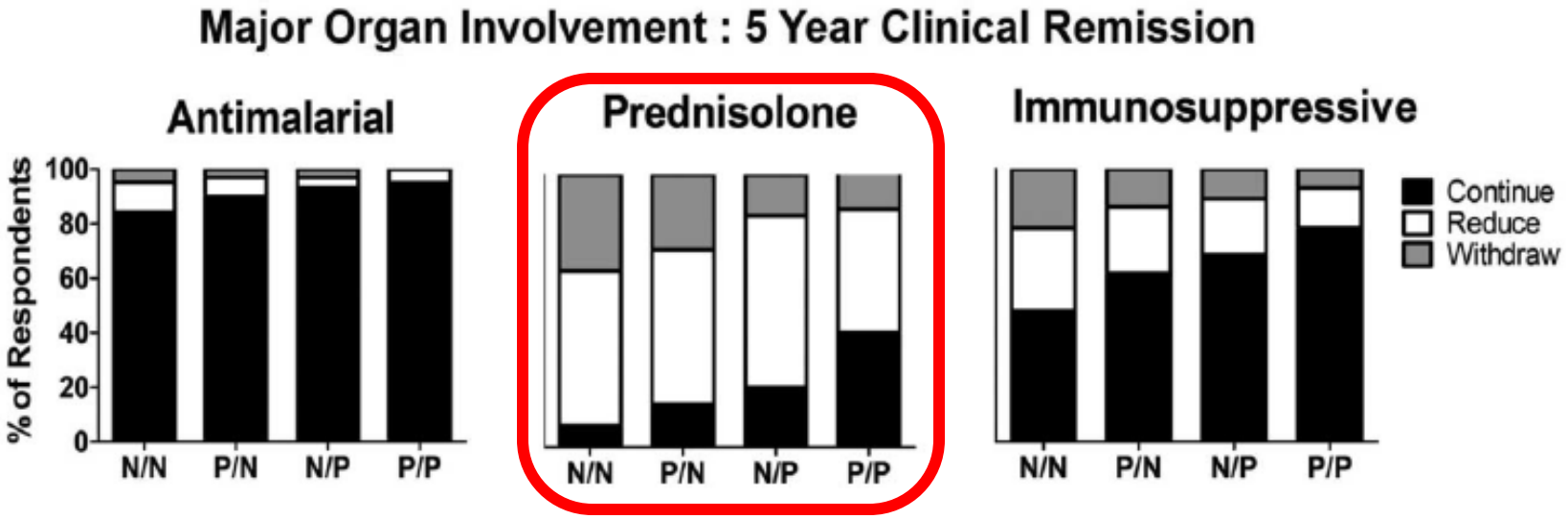

- Παρά την κλινική ύφεση, διατήρηση GCs, αν
  - Previous disease severity
  - Serological abnormalities (anti-dsDNA, C3, C4)

Lupus Science & Medicine 2017;4:e000173. doi:10.1136/lupus-2016-000173

Υπάρχει ασφαλής δόση στεροειδών?

RHEUMATOLOGY

Rheumatology 2014;53:1470–1476
doi:10.1093/rheumatology/keu148
Advance Access publication 27 March 2014

Original article

Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus

Ioana Ruiz-Arruza[1], Amaia Ugarte[1], Ivan Cabezas-Rodriguez[1], Jose-Alejandro Medina[1], Miguel-Angel Moran[1] and Guillermo Ruiz-Irastorza[1]

Abstract

Objective. The aim of this study was to analyse the relationship between glucocorticoids and damage accrual in SLE.

Methods. We report an observational cohort study including 230 patients with SLE enrolled at diagnosis with 5 years of follow-up. Damage was calculated using the SLICC damage index. Glucocorticoid-related damage was defined as avascular osteonecrosis, osteoporotic fractures, diabetes mellitus or cataracts. Prednisone doses were calculated at the end of the fourth year of follow-up (prednisone-4). A categorical prednisone-4 variable was constructed: no prednisone, ⩽7.5 mg/day (low dose), >7.5 mg/day (medium–high dose). The relationship between methylprednisolone pulses and damage was also tested.

Results. By the fifth year, 188 patients (82%) had been treated with prednisone. Eighty-seven patients (37.8%) had accrued damage at 5 years. Patients with damage at year 5 had received a higher mean daily prednisone-4 dose (10.4 *vs* 6 mg/day, $P < 0.001$). The mean daily prednisone-4 dose was higher in patients accruing glucocorticoid-attributable damage (11 *vs* 7 mg/day, $P = 0.04$). Patients taking medium–high doses of prednisone-4 had a higher risk of accruing damage than those taking no prednisone [adjusted odds ratio (OR) 5.39, 95% CI 1.59, 18.27]. Patients taking medium–high doses of prednisone-4 were more likely to develop glucocorticoid-related damage than those on no prednisone (adjusted OR 9.9, 95% CI 1.1, 84). No differences were seen between patients on low doses and those on no prednisone. The cumulative dose of i.v. methylprednisolone-4 was not associated with global or glucocorticoid-related damage.

Conclusion. Prednisone causes damage in SLE. Doses <7.5 mg/day and methylprednisolone pulses are not associated with damage accrual.

Υπάρχει ασφαλής δόση στεροειδών?

Published in final edited form as:
J Rheumatol. 2009 March ; 36(3): 560–564. doi:10.3899/jrheum.080828.

➢**10ετής παρακολούθηση**

Relationship between Prednisone, Lupus Activity and Permanent Organ Damage

Mae Thamer, PhD[1], **Miguel A. Hernán, MD**[2], **Yi Zhang, MS**[1], **Dennis Cotter, MSE**[1], and **Michelle Petri, MD, MPH**[3]

Hazard ratio of organ damage (n = 141) by cumulative average dose of prednisone.

Cumulative average prednisone dose (mg/month)			Unadjusted model			Conventionally-adjusted model*			Weighted model*		
	% of patient months	no. of events	HR	95 % CI		HR	95 % CI		HR	95 % CI	
0	35.9	34	*Ref*			*Ref*			*Ref*		
>0–180	37.0	49	1.58	1.00	2.50	**2.01**	**1.11**	**3.63**	1.16	0.59	2.29
>180–360	14.9	29	**2.10**	**1.24**	**3.55**	**2.46**	**1.17**	**5.16**	1.50	0.67	3.39
>360–540	6.7	18	**3.04**	**1.67**	**5.53**	**3.54**	**1.55**	**8.12**	1.64	0.67	4.06
>540	5.5	21	**4.19**	**2.35**	**7.47**	**4.10**	**1.74**	**9.65**	**2.51**	**1.02**	**6.19**

*Adjusted for age, sex, race/ethnicity, baseline prednisone dose, baseline SLE activity, baseline organ damage, and time-varying covariates.

HR: hazard ratio; CI: confidence interval

✓**Δόσεις < 6mg/day prednisolone** δε σχετίζονται με damage

✓**Prespecified cut-off!!!**

Υπάρχει ασφαλής δόση στεροειδών?

Epidemiology and outcomes

LUPUS SCIENCE & MEDICINE™

Independent association of glucocorticoids with damage accrual in SLE

Diane Apostolopoulos,[1,2] Rangi Kandane-Rathnayake,[1] Sudha Raghunath,[2] Alberta Hoi,[1,2] Mandana Nikpour,[3] Eric F Morand[1,2]

- Even lower doses of glucocorticoid than previously suspected are associated with damage accrual in SLE. The threshold identified was a time-adjusted mean prednisolone of 4.4 mg/day.

➢**4ετής παρακολούθηση**

Apostolopoulos D, Kandane-Rathnayake R, Raghunath S, *et al. Lupus Science & Medicine* 2016;**3**:e000157. doi:10.1136/lupus-2016-000157

Επιστημονική Εταιρεία για τη Μυοσκελετική ΥΓΕΙΑ - ΕΠΕΜΥ

Treat-to-target in systemic lupus erythematosus: recommendations from an international task force

Ronald F van Vollenhoven,[1] Marta Mosca,[2] George Bertsias,[3] David Isenberg,[4] Annegret Kuhn,[5] Kirsten Lerstrøm,[6] Martin Aringer,[7] Hendrika Bootsma,[8] Dimitrios Boumpas,[9] Ian N Bruce,[10] Ricard Cervera,[11] Ann Clarke,[12] Nathalie Costedoat-Chalumeau,[13] László Czirják,[14] Ronald Derksen,[15] Thomas Dörner,[16] Caroline Gordon,[17] Winfried Graninger,[18] Frédéric Houssiau,[19] Murat Inanc,[20] Søren Jacobsen,[21] David Jayne,[22] Anna Jedryka-Goral,[23] Adrian Levitsky,[1] Roger Levy,[24] Xavier Mariette,[25] Eric Morand,[26] Sandra Navarra,[27] Irmgard Neumann,[28] Anisur Rahman,[29] Jozef Rovenský,[30] Josef Smolen,[31] Carlos Vasconcelos,[32] Alexandre Voskuyl,[33] Anne Voss,[34] Helena Zakharova,[35] Asad Zoma,[36] Matthias Schneider[37]

Box 1 Treat-to-target in systemic lupus erythematosus: overarching principles and bullet points

- Overarching principle 1: The management of systemic lupus erythematosus (SLE) should be based on shared decisions between the informed patient and her/his physician(s).
- Overarching principle 2: Treatment of SLE should aim at ensuring long-term survival, preventing organ damage, and optimising health-related quality-of-life, by controlling disease activity and minimising comorbidities and drug toxicity.
- Overarching principle 3: The management of SLE requires an understanding of its many aspects and manifestations, which may have to be targeted in a multidisciplinary manner.
- Overarching principle 4: Patients with SLE need regular long-term monitoring and review and/or adjustment of therapy.

Recommendations:

1. The treatment target of SLE should be remission of systemic symptoms and organ manifestations or, where remission cannot be reached, the lowest possible disease activity, measured by a validated lupus activity index and/or by organ-specific markers.
2. Prevention of flares (especially severe flares) is a realistic target in SLE and should be a therapeutic goal.
3. It is not recommended that the treatment in clinically asymptomatic patients be escalated based solely on stable or persistent serological activity.
4. Since damage predicts subsequent damage and death, prevention of damage accrual should be a major therapeutic goal in SLE.
5. Factors negatively influencing health-related quality of life (HRQOL), such as fatigue, pain and depression should be addressed, in addition to control of disease activity and prevention of damage.
6. Early recognition and treatment of renal involvement in lupus patients is strongly recommended.
7. For lupus nephritis, following induction therapy, at least 3 years of immunosuppressive maintenance treatment is recommended to optimise outcomes.
8. Lupus maintenance treatment should aim for the lowest glucocorticoid dosage needed to control disease, and if possible, glucocorticoids should be withdrawn completely.
9. Prevention and treatment of antiphospholipid syndrome (APS)-related morbidity should be a therapeutic goal in SLE; therapeutic recommendations do not differ from those in primary APS.
10. Irrespective of the use of other treatments, serious consideration should be given to the use of antimalarials.
11. Relevant therapies adjunctive to any immunomodulation should be considered to control comorbidity in SLE patients.

van Vollenhoven RF, et al. Ann Rheum Dis 2014;73:958–967. doi:10.1136/annrheumdis-2013-205139

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8. Lupus maintenance treatment should aim for the lowest glucocorticoid dosage needed to control disease, and if possible, glucocorticoids should be withdrawn completely.

there are no studies specifically addressing this issue in SLE. Nonetheless, based on the available evidence and general pharmacological considerations, the task force supported the main recommendation to aim for the lowest glucocorticoid dosage during maintenance treatment, and the comment to withdraw glucocorticoids completely 'if possible'.

van Vollenhoven RF, et al. Ann Rheum Dis 2014;73:958–967. doi:10.1136/annrheumdis-2013-205139

2019 update of the EULAR recommendations for the management of systemic lupus erythematosus

Antonis Fanouriakis,[1] Myrto Kostopoulou,[2] Alessia Alunno,[3] Martin Aringer,[4] Ingeborg Bajema,[5] John N Boletis,[6] Ricard Cervera,[7] Andrea Doria,[8] Caroline Gordon,[9] Marcello Govoni,[10] Frédéric Houssiau,[11] David Jayne,[12] Marios Kouloumas,[13] Annegret Kuhn,[14] Janni L Larsen,[15] Kirsten Lerstrøm,[16] Gabriella Moroni,[17] Marta Mosca,[18] Matthias Schneider,[19] Josef S Smolen,[20] Elisabet Svenungsson,[21] Vladimir Tesar,[22] Angela Tincani,[23] Anne Troldborg,[24] Ronald van Vollenhoven,[25] Jörg Wenzel,[26] George Bertsias,[27] Dimitrios T Boumpas[1,28,29]

2.2 GC

2.2.1 GC can be used at doses and route of administration that depend on the type and severity of organ involvement (**2b/C**).	9.95 (0.22)
2.2.2 Pulses of intravenous methylprednisolone (usually 250–1000 mg per day, for 1–3 days) provide immediate therapeutic effect and enable the use of lower starting dose of oral GC (**3b/C**).	9.85 (0.36)
2.2.3 For chronic maintenance treatment, GC should be minimised to less than 7.5 mg/day (prednisone equivalent) (**1b/B**) and, when possible, withdrawn.	9.65 (0.65)
2.2.4 Prompt initiation of immunomodulatory agents can expedite the tapering/discontinuation of GC (**2b/B**).	9.90 (0.30)

Withdrawal of therapy in non-renal systemic lupus erythematosus: is this an achievable goal?

M. Mosca[1], C. Tani[1], M. Aringer[2]

- **Απόσυρση στεροειδών σε:**
  - ✓ **Νεότερους ασθενείς με χαμηλή ενεργότητα**
  - ✓ **Απουσία ενεργών εκδηλώσεων από δέρμα-αρθρώσεις**
  - ✓ **Χωρίς ορολογικές αλλαγές (π.χ. αύξηση anti-dsDNA, μείωση C3, C4)**
- **Αναπάντητα ερωτήματα:**
  - ✓ **Πόσο διάστημα σε χαμηλή ενεργότητα νόσου πριν επιχειρηθεί απόσυρση?**
  - ✓ **Απαραίτητη κλινική και ορολογική ύφεση ή μόνο το πρώτο?**
  - ✓ **Πόσο γρήγορο το σχήμα απόσυρσης?**

Clin Exp Rheumatol 2013; 31 (Suppl. 78): S71-S74.

RHEUMATOLOGY

Rheumatology 2017;56:i114–i12
doi:10.1093/rheumatology/kew40
Advance Access publication 24 December 2016

The SLE review series: working for a better standard of care

It hasn't gone away: the problem of glucocorticoid use in lupus remains

Diane Apostolopoulos[1] and Eric F. Morand[1]

- **Research agenda to validate GC reduction strategies**
- **GC reduction should be recognized as a treatment endpoint itself in studies**

Rheumatology key messages

- No evidence-based guidelines on initiation, tapering and cessation of glucocorticoids exist for the management of SLE.
- Emerging evidence indicates glucocorticoid use compounds the effects of active disease on SLE damage accrual.
- Strategies to reduce the use of glucocorticoids in SLE are urgently needed.

EXPERT REVIEW OF CLINICAL IMMUNOLOGY
2018, VOL. 14, NO. 11, 877–879
https://doi.org/10.1080/1744666X.2018.1527219

EDITORIAL

Can we treat systemic lupus erythematosus and other autoimmune diseases without oral steroids?

Eugenia Enriquez Merayo[a], Savino Sciascia[b,c], Dario Roccatello[b,c] and Maria J. Cuadrado[a]

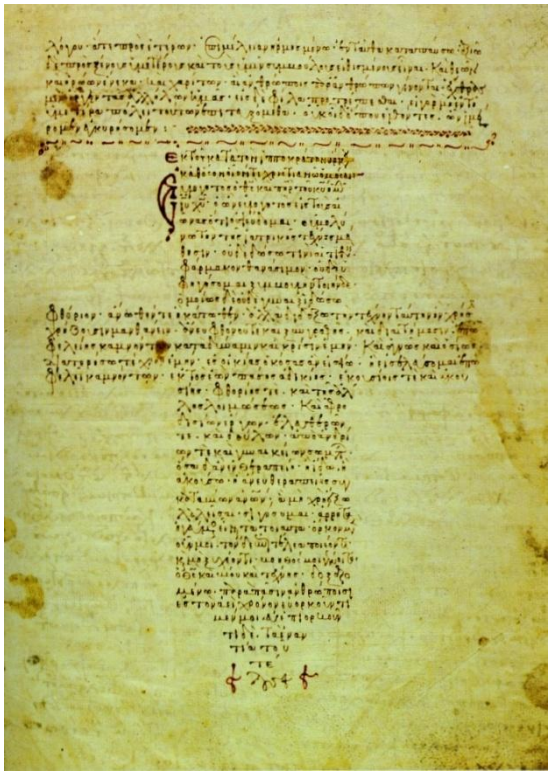
[a]Rheumatology Department, Clinica Universidad de Navarra, Madrid, Spain; [b]Center of Research of Immunopathology and Rare Diseases-Coordinating Center of the Network for Rare Diseases of Piedmont and Aosta Valley, Department of Clinical and Biological Sciences, University of Turin, Turin, Italy; [c]SCU Nephrology and Dialysis, S. Giovanni Bosco Hospital, Department of Clinical and Biological Sciences, University of Turin, Turin, Italy

ARTICLE HISTORY Received 15 July 2018; accepted 19 September 2018

KEYWORDS Glucocorticoid; systemic lupus erythematosus; immunosuppression; biologic; sparing agents; side effects; chronic damage; osteoporosis; infection

Συμπεράσματα

- **Τα στεροειδή είναι συνυπεύθυνα για το “damage” των ασθενών με ΣΕΛ**
- **Κατά τη θεραπεία συντήρησης, στόχοι:**
  - ✓ **Χαμηλότερη δυνατή δόση**
  - ✓ **Βραχύτερο δυνατό διάστημα**
  - ✓ **Έγκαιρο πλάνο απόσυρσης, αν είναι δυνατόν**
- **«Κορτικοεξαρτώμενοι» ασθενείς**
  - ✓ **Οπωσδήποτε <7,5 mg/d.**
  - ✓ **Βελτιστοποίηση ανοσοκατασταλτικής/ βιολογικής αγωγής**



«ἀσκεῖν περὶ τὰ νοσήματα δύο, ὠφελεῖν ἢ μὴ βλάπτειν»
(Ιπποκράτης, Επιδημιών το Πρώτο)