NEFRITIS LÚPICA

¿CÓMO LA TRATAMOS?

UNIDAD DE INVESTIGACIÓN
DE ENFERMEDADES
AUTOINMUNES

biocruces
health research institute

eman ta zabal zazu

Guillermo Ruiz-Irastorza
Unidad de Enfermedades Autoinmunes
Servicio de Medicina Interna
BioCruces Health Research Institute
Hospital Universitario Cruces
Universidad del País Vasco / Euskal Herriko Unibertsitatea

Selena Gomez Goes Public with Lupus Diagnosis

NOVEMBER 17, 2015 BY CHARLES MOORE IN NEWS.

abuse addiction, but because: "I was diagnosed with lupus, and I've been through chemotherapy. That's what my break was really about. ... I wanted so badly to say, 'You guys have no idea. I'm in chemotherapy. You're assholes.' I locked myself away until I was confident and comfortable again."


PODEMOS HACERLO MEJOR ??

NEFRITIS LÚPICA

Hasta en el 40 % de los pacientes con LES

Predictor de mortalidad

Hasta un 25 % pueden llegar a IRT / diálisis / transplante

Table 3. International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis

Class I	**Minimal mesangial lupus nephritis** Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis** Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis**[a] Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis**[b] Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental(IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis** Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed Class V lupus nephritis show advanced sclerosis
Class VI	**Advanced sclerosis lupus nephritis** ≥90% of glomeruli globally sclerosed without residual activity

J Am Soc Nephrol 15: 241–250, 2004

Lupus nephritis management guidelines compared

Suzanne Wilhelmus[1], Ingeborg M. Bajema[1], George K. Bertsias[2,3], Dimitrios T. Boumpas[3,4], Caroline Gordon[5], Liz Lightstone[6], Vladimir Tesar[7] and David R. Jayne[8]

Nephrol Dial Transplant (2015) 0: 1–11

Adjunctive treatment	HCQ for all unless contraindicated; screening ophthalmologist for retinopathy at baseline and yearly after 5 years (recommended by most)

Lupus nephritis management guidelines compared

Suzanne Wilhelmus[1], Ingeborg M. Bajema[1], George K. Bertsias[2,3], Dimitrios T. Boumpas[3,4], Caroline Gordon[5], Liz Lightstone[6], Vladimir Tesar[7] and David R. Jayne[8]

Nephrol Dial Transplant (2015) 0: 1–11

Induction treatment Class III/IV without crescents (and/or other adverse parameters)	Oral glucocorticoids with or without three iv pulses methylprednisolone (MP) at start induction + ivCYC or MMF

MMF:

- Ranging from 2 to 3 g total daily dose
- Sometimes preferred over ivCYC in patients of African or Hispanic descent

ivCYC:

- Either high dose (NIH; 0.5–1 g/m^2 monthly for 6 months) or low dose (Eurolupus; 500 mg fortnightly for 3 months): low dose usually preserved for (European) Caucasians and sometimes only for relatively mild disease
- In case of low-dose ivCYC, combine pulses MP

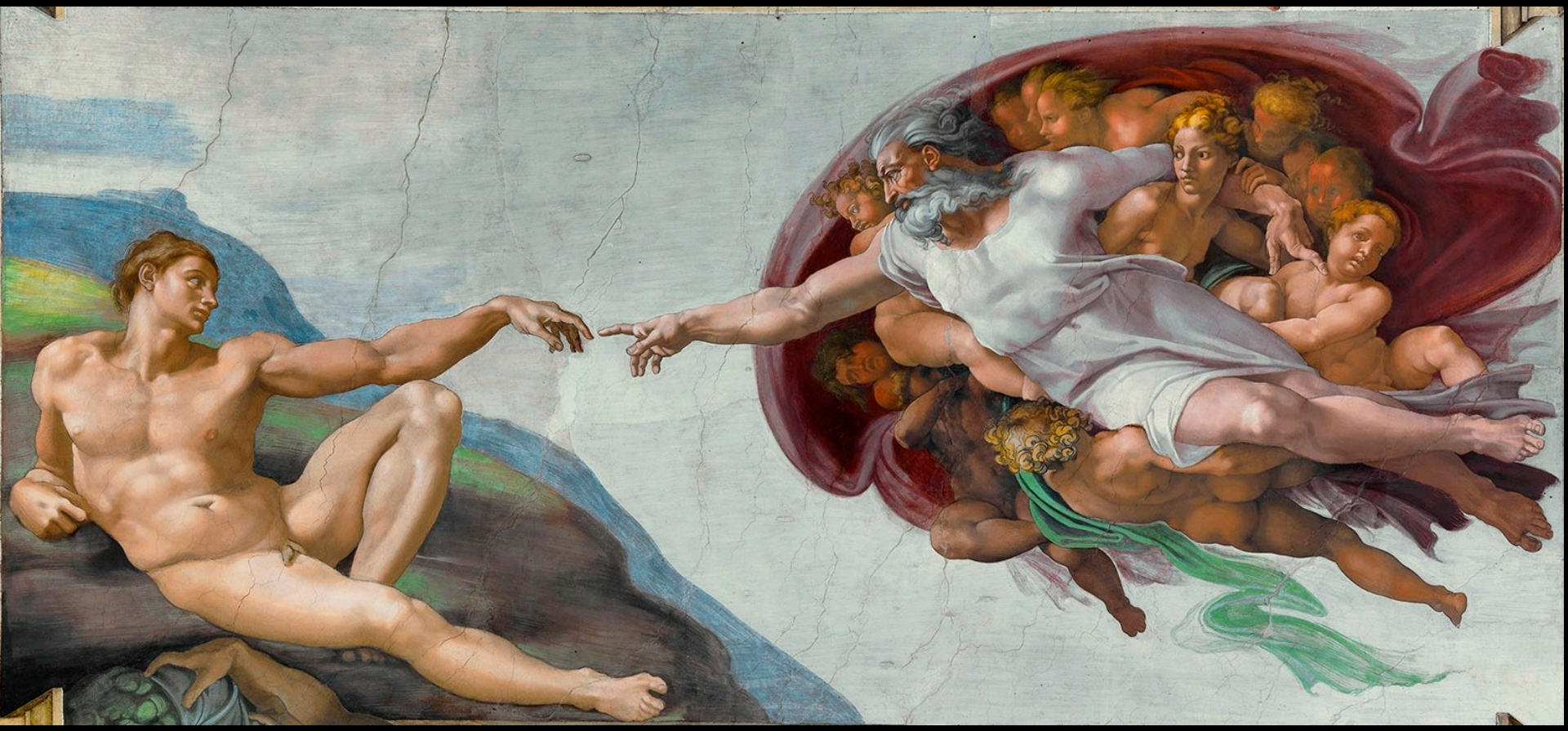
Lupus nephritis management guidelines compared

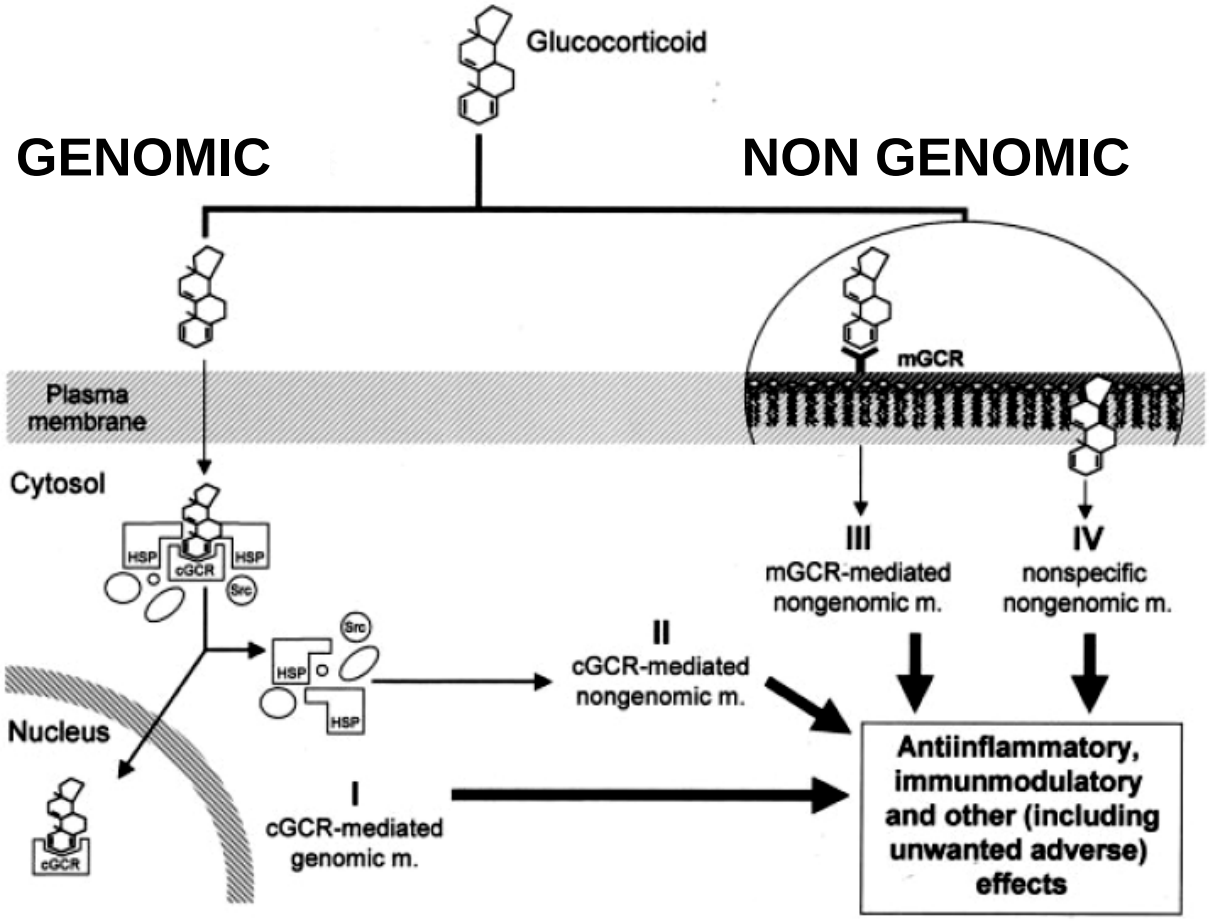
Suzanne Wilhelmus[1], Ingeborg M. Bajema[1], George K. Bertsias[2,3], Dimitrios T. Boumpas[3,4], Caroline Gordon[5], Liz Lightstone[6], Vladimir Tesar[7] and David R. Jayne[8]

Nephrol Dial Transplant (2015) 0: 1–11

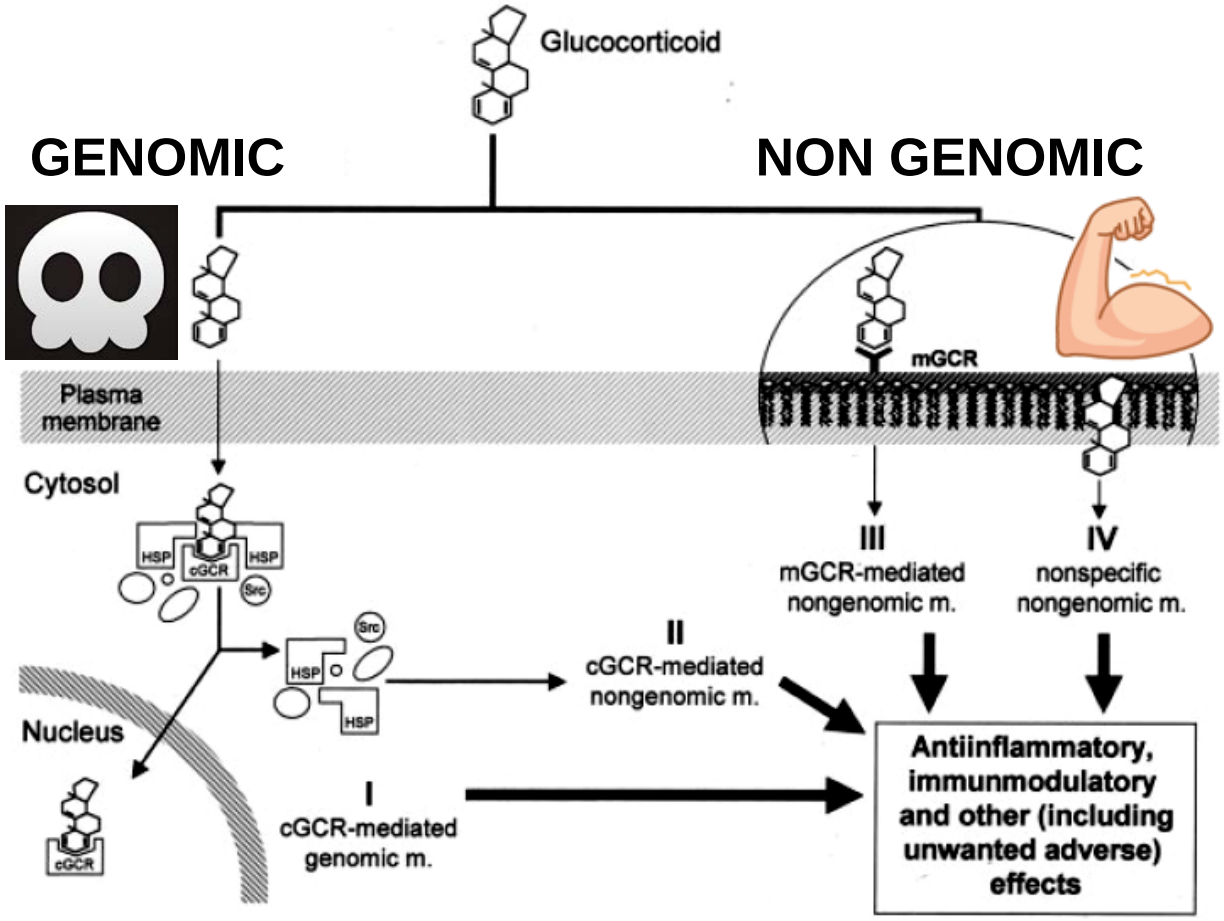
Glucocorticoids:

- MP dose ranging from 250 to 1000 mg/day (or weight dependent in children)
- MP not always recommended; dependent on combination with MMF or ivCYC, or on severity
- Oral dose ranging from 0.5 to 1 mg/kg/day, sometimes depending on combination with MP, MMF or ivCYC
- Tapering schedule: unclear



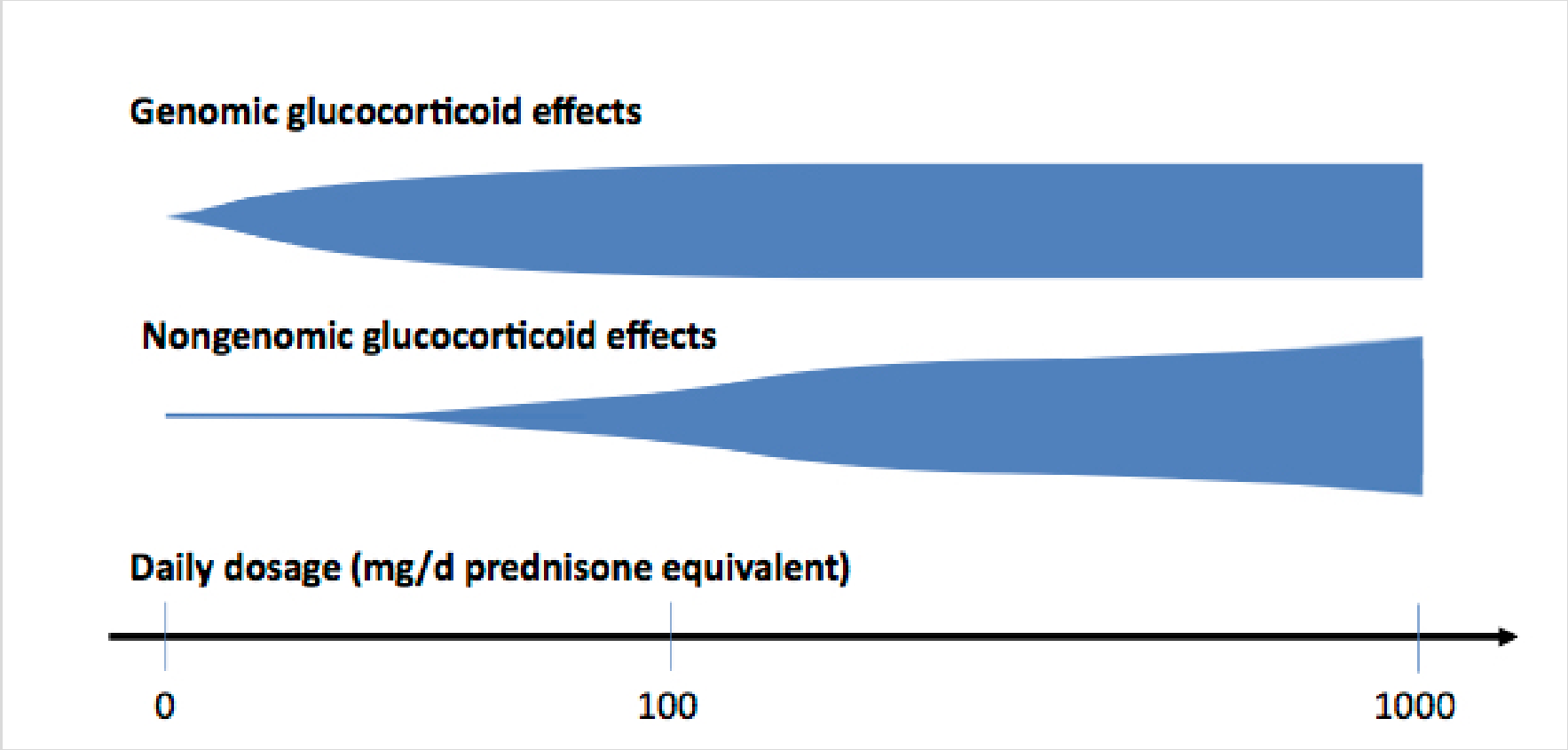


Buttgereit et al. Arthritis Rheum 2004; 50: 3408-17

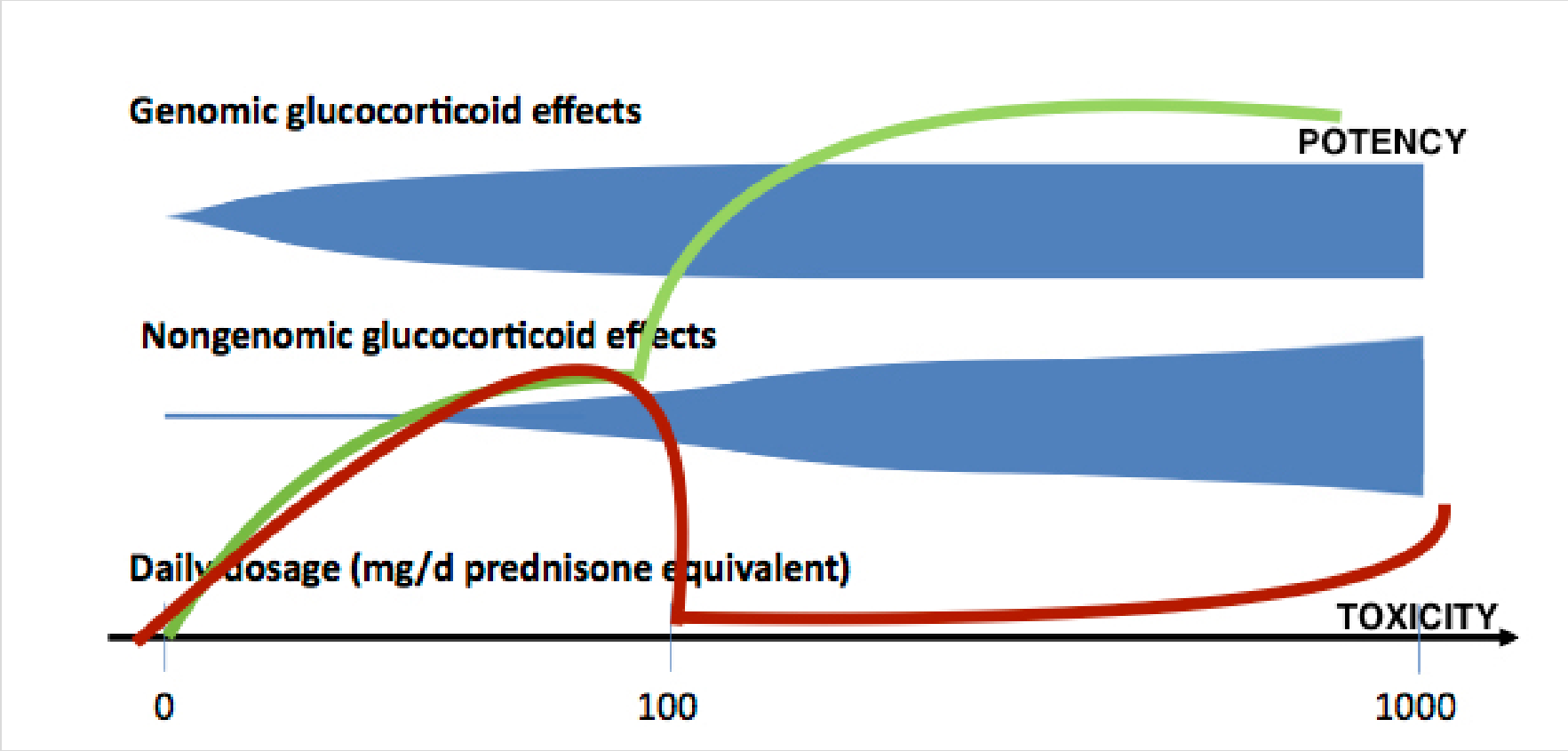


Buttgereit et al. Arthritis Rheum 2004; 50: 3408-17

LA VIA DEPENDE DE LA DOSIS



Matteson et al. *Rheum Dis Clin North Am* 2016;42:75–90



Matteson et al. *Rheum Dis Clin North Am* 2016;42:75–90

Dosis bajas: ≤ 7.5 mg/d	**BAJA POTENCIA, BAJA TOXICIDAD** 
Dosis medias: > 7.5 - 30 mg/d	**POTENCIA MEDIA, ALTA TOXICIDAD** 
Dosis altas: > 30 mg/d	**POTENCIA MEDIA-ALTA, MÁXIMA TOXICIDAD** 
Dosis muy altas: ≥ 100 mg/d	**ALTA POTENCIA, BAJA TOXICIDAD** 
Pulsos: ≥ 250 mg/d	**MÁXIMA POTENCIA, BAJA TOXICIDAD** 


ACTIVIDAD


ACTIVIDAD
DAÑO

Glucocorticoids cause damage in SLE patients

ARTHRITIS & RHEUMATISM
Vol. 43, No. 8, August 2000, pp 1801–1808

DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS AND ITS ASSOCIATION WITH CORTICOSTEROIDS

SUSAN G. BARR, LAURENCE S. MAGDER, and MI

with damage accrual in patients
hematosus: results from the
Collaborating Clinics

Farewell,[4] John G Hanly,[5] Susan Manzi,[6]
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[17] Barri J Fessler,[17] Paul R Fortin,[18]
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uel Ramos-Casals,[27]
an,[29] Guillermo Ruiz-Irastorza,[30]
[33] Murat Inanc,[34]

doi:10.1093/rheumatology/keu148

Accrual of Organ Damage Over Time in Patients with Systemic Lupus Eryth

DAFNA D. GLADMAN, MURRAY B. UROW and LAI-SHAN TAM

Original article

Glucocorticoids and irreversible damage in pa with systemic lupus erythematosus

Ioana Ruiz-Arruza[1], Amaia Ugarte[1], Ivan
Jose-Alejandro Medina[1], Miguel-A

http://lup.sagepub.com

PAPER

The chronic damage in systemic lupus erythematosus by flares, glucocorticoids and antiphospholi results from a monocentri

F Conti, F Ceccarelli, C Perricone, I Leccese, L Ma
C Ales
Lupus Clinic, Reumatologia, Dipartimento di Medi

J Rheumatol 2009;36:560–4;

Prednisone, Lupus Activity, and Permanent Organ Damage

ZHANG, DENNIS COTTER, and MICHELLE PETRI

MAE
ren

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]

Lupus (2017) 0, 1–6
journals.sagepub.com/home/lup

PAPER

Effect of immunosuppressive therapies on survival of systemic lupus erythematosus: a propensity score analysis of a longitudinal cohort

CC Mok, SM Tse, KL Chan and LY Ho
Department of Medicine, Tuen Mun Hospital, Hong Kong, SAR China

Glucocorticoids cause damage in SLE patients

ARTHRITIS & RHEUMATISM
Vol. 43, No. 8, August 2000, pp 1801–1808

DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS AND ITS ASSOCIATION WITH CORTICOSTEROIDS

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Accrual of Organ Damage Over Time in Patients with Systemic Lupus Eryth

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Original article

Glucocorticoids and
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Ioana Ruiz-Arruza[1], Amaia U
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PAPER

The chronic damage in systemic lupus erythematosus
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C Alessa
Lupus Clinic, Reumatologia, Dipartimento di Medi

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ren

LUPUS SCIENCE & MEDICINE™

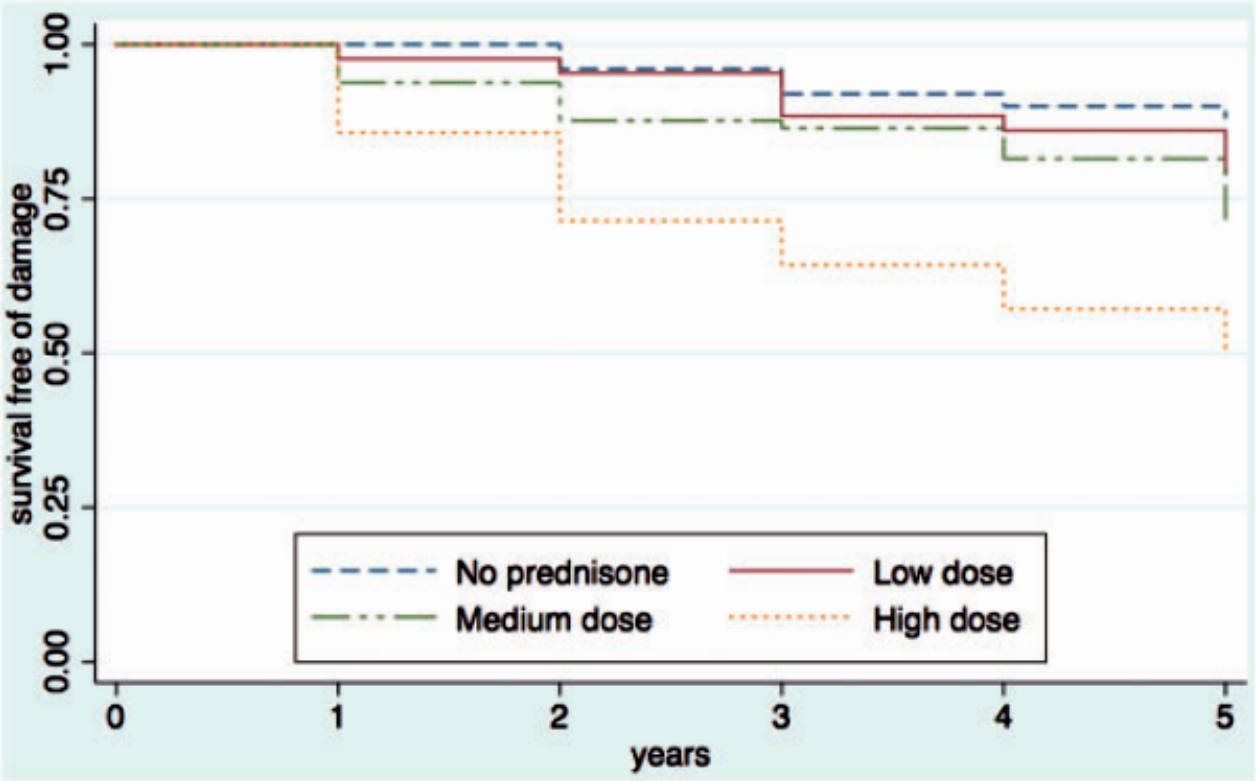
Independent association of glucocorticoids with damage accrual in SLE

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

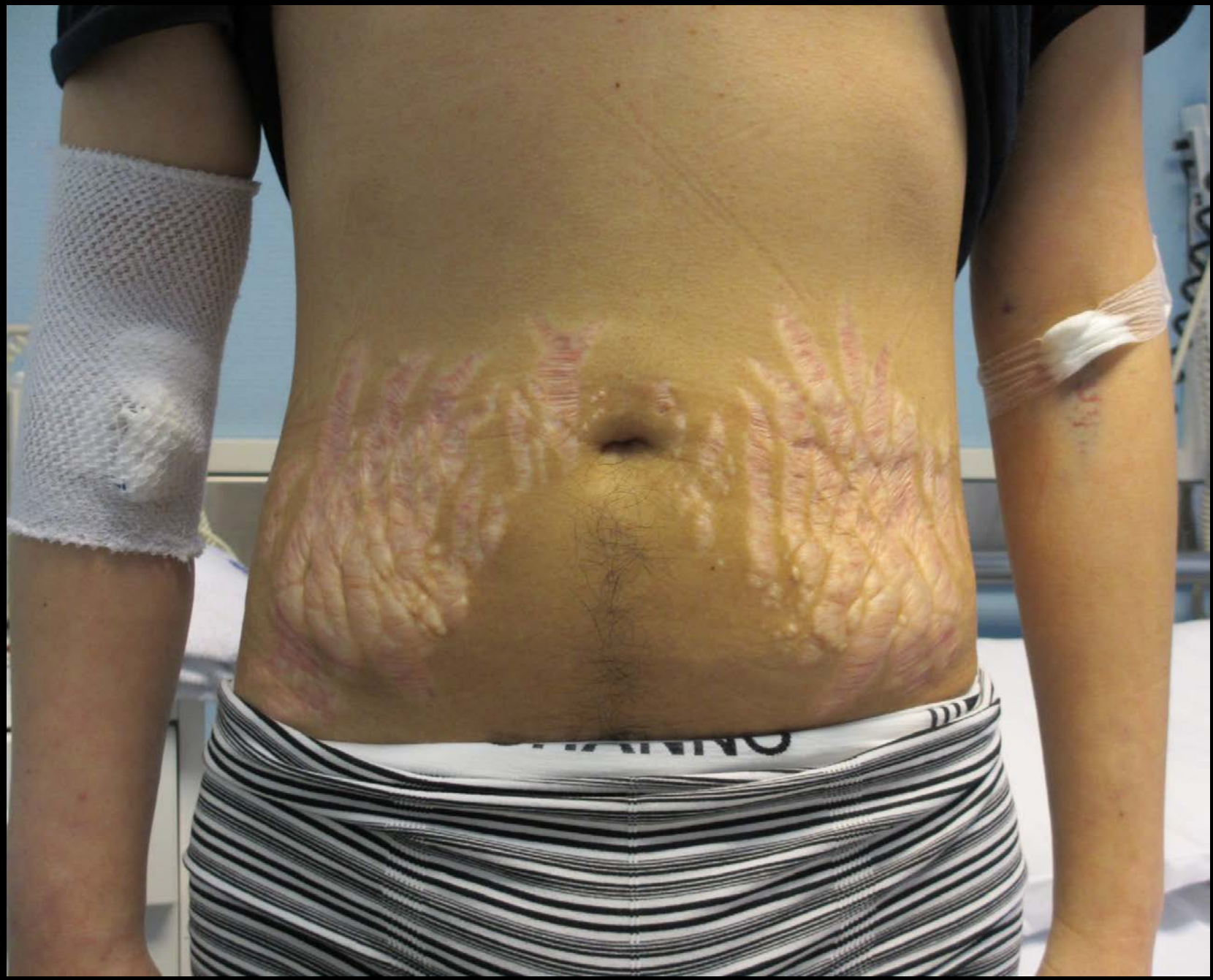
Table 3 Relationship between immunosuppressive drug treatment and all-cause mortality: Cox regression analyses

Immunosuppressive agent	*HR[a] (95% CI) unadjusted for propensity score*	P *value*	*HR[a] (95% CI) adjusted for propensity score*	P *value*
Hydroxychloroquine	0.57 (0.38–0.87)	0.008	0.59 (0.37–0.93)	0.02
Mycophenolate mofetil	1.52 (0.94–2.44)	0.09	1.31 (0.79–2.17)	0.29
High-dose prednisolone	1.00 (0.60–1.69)	0.98	14.6 (0.94–226.24)	0.06
Azathioprine	0.70 (0.45–1.09)	0.12	0.46 (0.28–0.75)	0.002
Calcineurin inhibitors	1.01 (0.61–1.68)	0.96	0.91 (0.54–1.53)	0.73
Cyclophosphamide	1.27 (0.78–2.07)	0.34	1.11 (0.66–1.85)	0.70

FIG. 1 Kaplan–Meier survival free-of-damage curves according to prednisone dose received during the first year of follow-up



Low dose: ⩽7.5 mg/day; medium dose: ⩽30 mg/day; high dose: >30 mg/day.



Pulse methyl-prednisolone DOES NOT cause damage

ARTHRITIS & RHEUMATISM
Vol. 43, No. 8, August 2000, pp 1801–1808

DAMAGE IN SYSTEMIC LUPUS ERYTHEMATOSUS AN
ITS ASSOCIATION WITH CORTICOSTERO

ABRAHAM ZONANA-NACACH, SUSAN G. BARR, L

Ann Rheum Dis 2001;60:1145–1148

Osteonecrosis in patients with systemic lupus erythematosus develops very early after starting high dose corticosteroid treatment

K Oinuma, Y Harada, Y Nawata, K Takabayashi, I Abe, K Kamikawa, H Moriya

Autoimmunity Reviews 13 (2014) 206–214

Prednisone in lupus nephritis: How much is enough?

Guillermo Ruiz-Irastorza [a,b,*], Alvaro Danza [a,c,d], Isabel Perales [a,e], Irama Villar [a,b], Miriam Garcia [a], Sonia Delgado [f], Munther Khamashta [g]

doi:10.1093/rheumatology/keu148

Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus

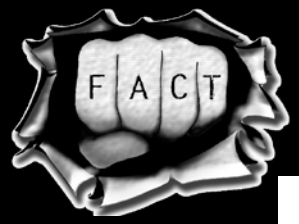
Ioana Ruiz-Arruza[1], Amaia Ugarte[1], Ivan Cabezas-Rodriguez[1], Jose-Alejandro Medina[1], Miguel-Angel Moran[1] and Guillermo Ruiz-Irastorza[1]

Rheumatol Int
DOI 10.1007/s00296-010-1597-9

ORIGINAL ARTICLE

Risk factors for avascular bone necrosis in patients with systemic lupus erythematosus

Mehmet Sayarlioglu · Nergis Yuzbasioglu · Murat Inanc · Sevil Kamali · Ayse Cefle · Ozcan Karaman · Ahmet Mesut Onat · Rustem Avan · Gozde Yildirm Cetin · Ahmet Gul · Lale Ocal · Orhan Aral



Glucocorticoids can increase proteinuria!!

Japanese Journal of Nephrology Vol. 29, No. 3, 1987

Mechanisms of steroid-enhanced proteinuria in nephrotic patients

HIROMICHI KUMAGAI, AKIRA HISHIDA, MITSUMASA NAGASE and NISHIO HONDA

Kidney International, Vol. 33 (1988), pp. 1169–1174

Prednisolone can increase glomerular permeability to proteins in nephrotic syndrome

JACK F.M. WETZELS, HENK E. SLUITER, ANDRIES J. HOITSMA, PIET J.J. VAN MUNSTER, and ROBERT A.P. KOENE

Nephron *44:* 344–350 (1986)

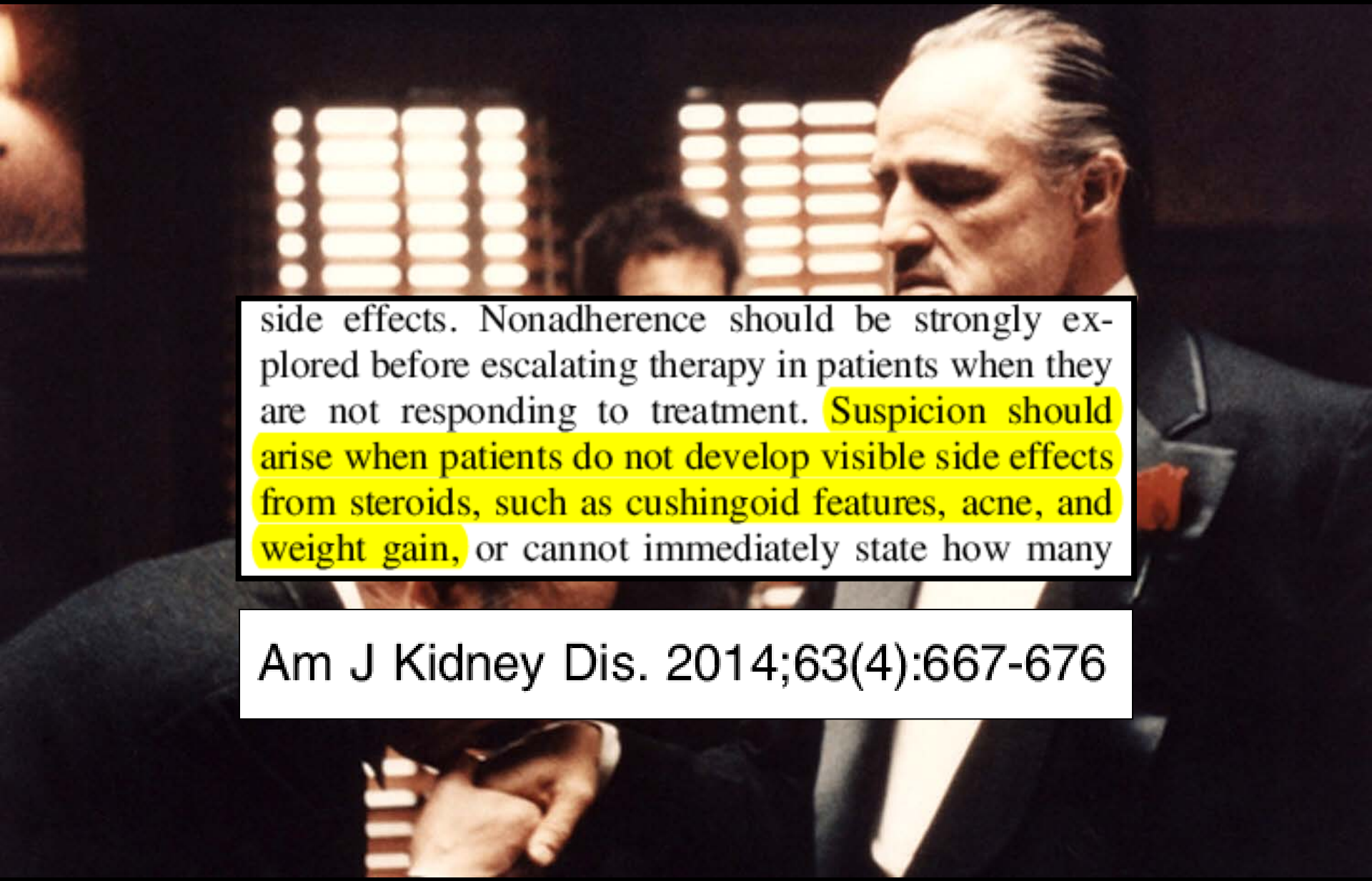
Prednisone-Induced Fluctuations of Proteinuria in Patients with a Nephrotic Syndrome

Jack F.M. Wetzels[a], *Paul G.G. Gerlag*[b], *Henk E. Sluiter*[a], *Andries J. Hoitsma*[a], *Robert A.P. Koene*[a]

March, 1969
The Journal of PEDIATRICS

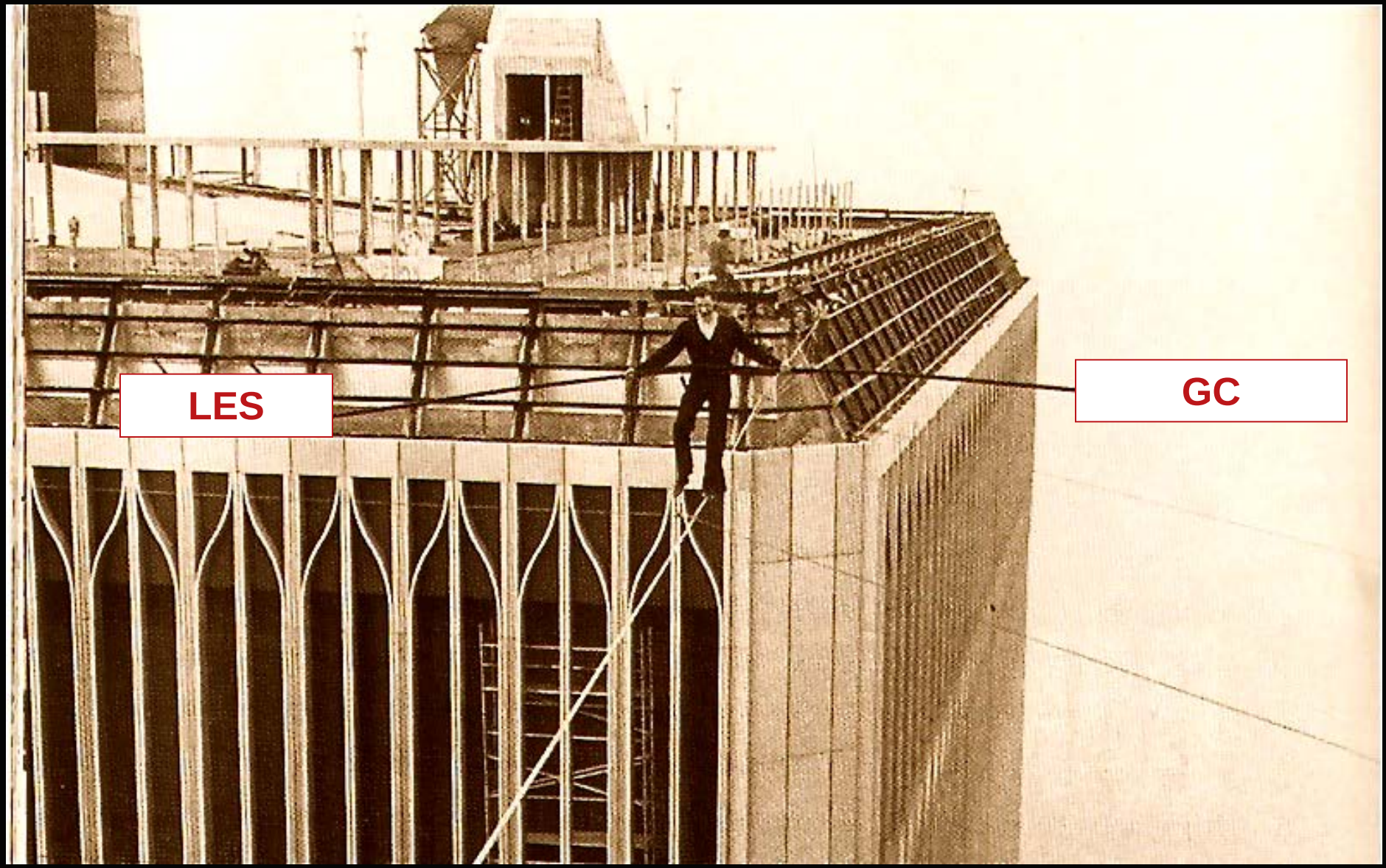
Increase in proteinuria due to steroid medication in chronic renal disease

Walter Heymann, M.D., and Warren E. Grupe, M.D.



side effects. Nonadherence should be strongly explored before escalating therapy in patients when they are not responding to treatment. Suspicion should arise when patients do not develop visible side effects from steroids, such as cushingoid features, acne, and weight gain, or cannot immediately state how many

Am J Kidney Dis. 2014;63(4):667-676


LES
GC

Lupus (2011) 20, 1484–1493
http://lup.sagepub.com

PAPER

Efficacy and safety of enteric-coated mycophenolate sodium in combination with two glucocorticoid regimens for the treatment of active lupus nephritis

M Zeher[1], A Doria[2], J Lan[3], G Aroca[4], D Jayne[5], I Boletis[6], F Hiepe[7], H Prestele[8], P Bernhardt[8] and Z Amoura[9]

Table 2 Complete and partial response rates at weeks 12 and 24 (ITT population)

		Comparison of treatment groups				
	All patients (n=81)	*Standard- dose steroids (n=42)*	*Reduced-dose steroids (n=39)*	*Lower limit of one-sided 97.5% CI for between-group difference*	p *value (non-inferiority)*	p *value (Chi square)*
Complete response						
Week 12	14 (17.3%)	9 (21.4%)	5 (12.8%)	−24.9%	0.43	0.31
Week 24	16 (19.8%)	8 (19.0%)	8 (20.5%)	−15.9%	0.098	0.87
Partial response				Not done		
Week 12	27 (33.3%)	16 (38.1%)	11 (28.2%)			0.34
Week 24	34 (42.0%)	20 (47.6%)	14 (35.9%)			0.29

The Journal of Rheumatology 2012; 39:11;

Renal Outcome in Patients with Lupus Nephritis Using a Steroid-free Regimen of Monthly Intravenous Cyclophosphamide: A Prospective Observational Study

REBECCA FISCHER-BETZ, GAMAL CHEHAB, OLIVER SANDER, STEFAN VORDENBÄUMEN, ADINA VOICULESCU, RALPH BRINKS, and MATTHIAS SCHNEIDER

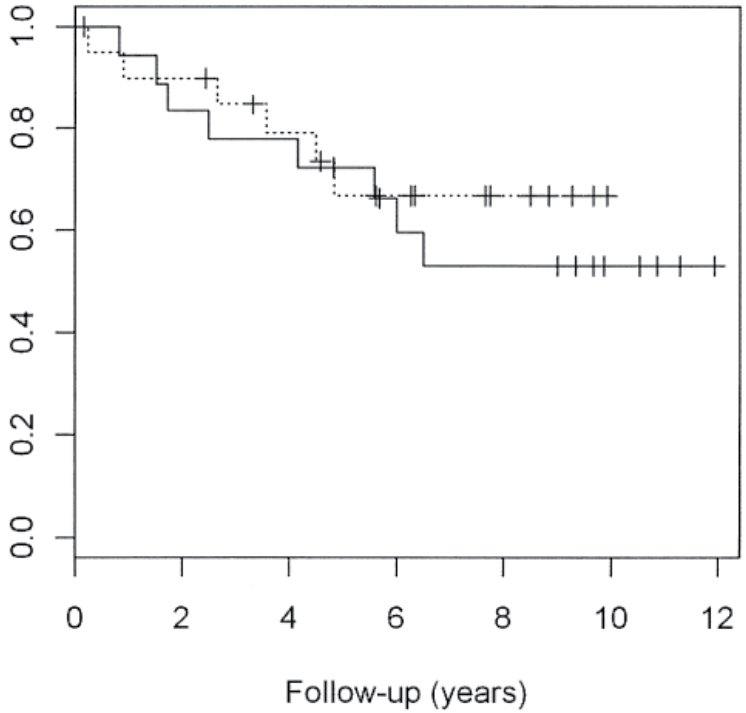


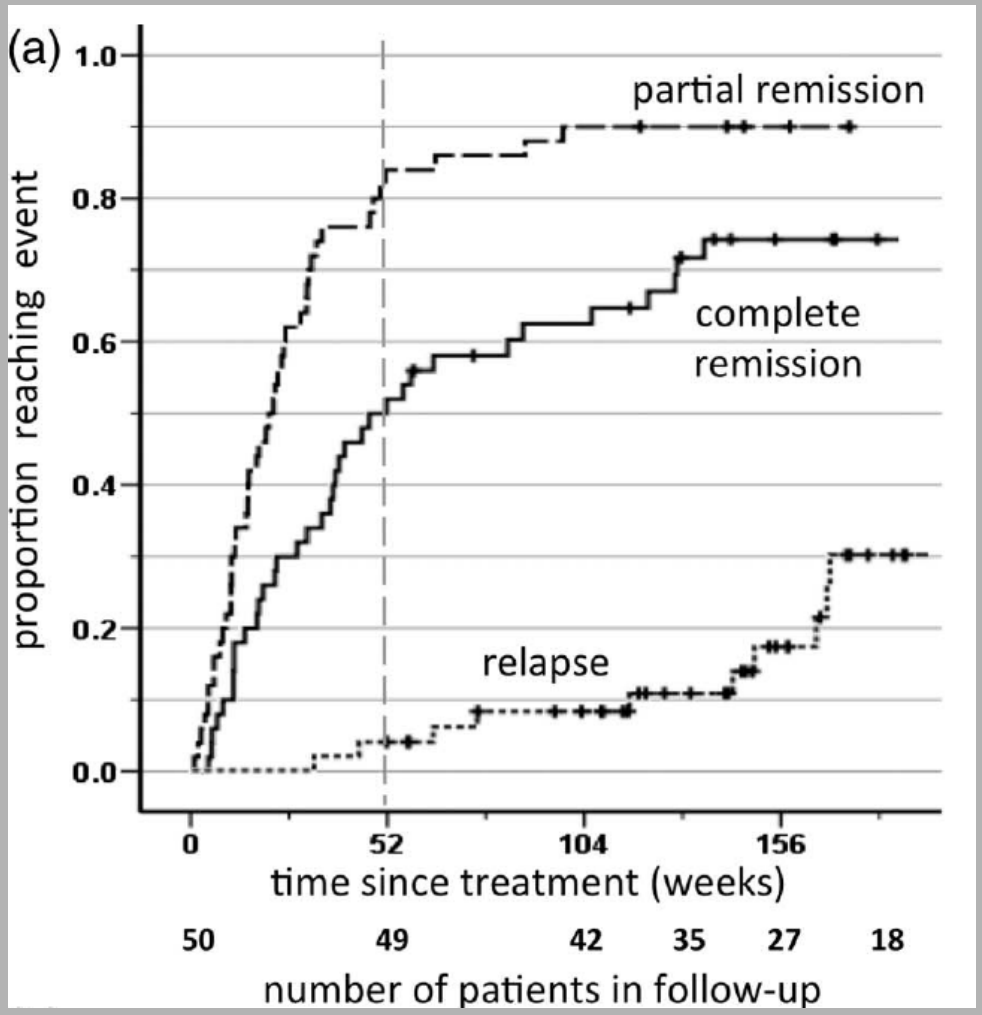
Figure 2. Kaplan-Meier analysis of the probability of an absence of flare during longterm followup in patients treated with ≥ 20 mg prednisone (solid line) versus patients treated with < 20 mg prednisone at baseline (dotted line). The HR for renal flare in the low-prednisone group compared with the high-prednisone group was 0.73 (95% CI 0.25–2.12, p = 0.57).

EXTENDED REPORT

Ann Rheum Dis 2013;**72**:1280–1286.

Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids

Marie B Condon,[1] Damien Ashby,[1] Ruth J Pepper,[1] H Terence Cook,[1,2] Jeremy B Levy,[1] Megan Griffith,[1] Tom D Cairns,[1] Liz Lightstone[1,2,3]



PRIMER PRINCIPIO DE ACCIÓN

En el lupus, usa HCQ como base

también en la nefritis!!

SEGUNDO PRINCIPIO DE ACCIÓN

No mantengas dosis de prednisona >5 mg/d

HAZ LO QUE SEA NECESARIO PARA EVITARLO

TERCER PRINCIPIO DE ACCIÓN

USA PULSOS

y

COMBINA TRATAMIENTOS

para

EMPEZAR MÁS ABAJO

y

REDUCIR DEPRISA

INDUCCIÓN

Autoinmunes

MP 250-500 iv

MP 250-500 iv

MP 250-500 iv

3 PULSOS DE 250-500 MG DE METIL-PREDNISOLONA DURANTE TRES DIAS

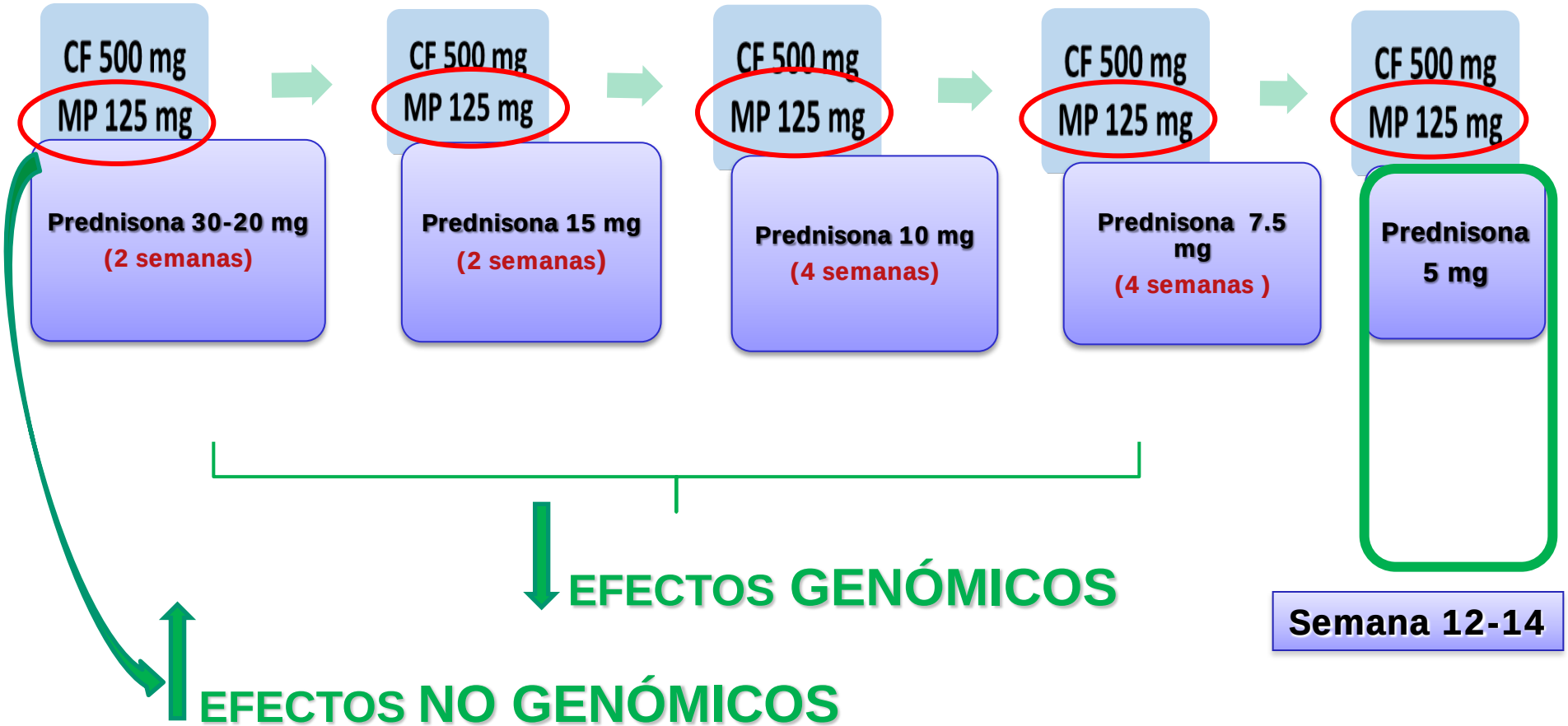
- Inicio durante el ingreso para la biopsia
  (salvo dudas diagnósticas o alta sospecha de cronicidad)
- En ocasiones, pulsos de MP previo a la biopsia
  - Alta sospecha clínica y demora en la biopsia
  - Afectación extrarrenal concomitante

PULSOS QUINCENALES DE CICLOFOSFAMIDA 500 MG IV

PREDNISONA + HCQ

INDUCCIÓN

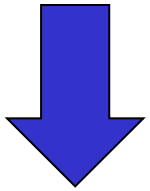
Autoinmunes



FIN DE INDUCCIÓN / MANTENIMIENTO

6, 9 ó 12 pulsos de CFM, según respuesta

Si remisión al menos parcial, Pr/Cr < 1 gr



AZA o MMF

FIN DE INDUCCIÓN / MANTENIMIENTO

MMF + Tacro

Rituximab + MMF

Belimumab + MMF + Tacro

FIN DE INDUCCIÓN / MANTENIMIENTO

MMF + Tacro

Rituximab + MMF

Belimumab + MMF + Tacro

MANTENIENDO PREDNISONA 5 mg/d

Diagnóstico y tratamiento de la nefritis lúpica

Documento de consenso del Grupo de Enfermedades Autoinmunes Sistémicas (GEAS) de la Sociedad Española de Medicina Interna (SEMI) y de la Sociedad Española de Nefrología (S.E.N.)

Guillermo Ruiz-Irastorza[1], Gerard Espinosa[2], Miguel A. Frutos[3], Juan Jiménez-Alonso[4], Manuel Praga[5], Lucio Pallarés[6], Francisco Rivera[7], Ángel Robles-Marhuenda[8], Alfons Segarra[9], Carlos Quereda[10]

- **Sugerimos que la duración del tratamiento con micofenolato sea de, al menos, dos años una vez alcanzada la remisión (2C). La dosis de micofenolato debe ser progresivamente disminuida antes de su suspensión definitiva (2C).**

- **Recomendamos que la dosis inicial de mantenimiento de azatioprina oscile entre 1,5 y 2 mg/kg/día (1B). La duración del tratamiento, así como la reducción paulatina de la dosis, seguiría la misma pauta que en el caso del micofenolato (2C).**

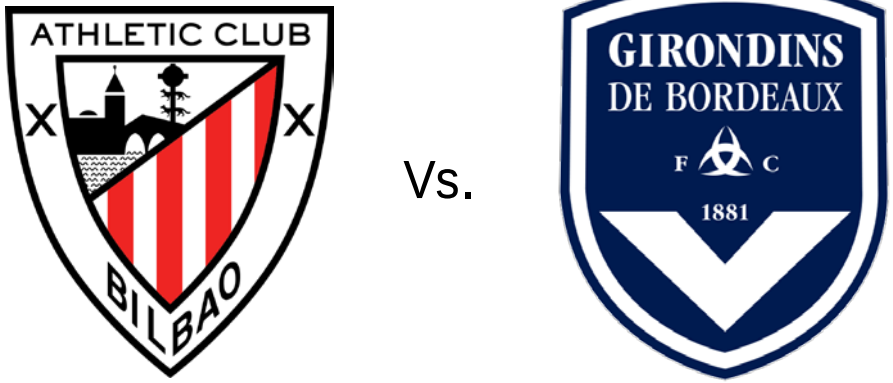
- **Sugerimos que el tratamiento con esteroides, a la menor dosis posible, se continúe mientras se mantenga el tratamiento con micofenolato o azatioprina (2C).**

Nefrología 2012; 32 (Suppl 1): 1-35

Review

Repeated pulses of methyl-prednisolone with reduced doses of prednisone improve the outcome of class III, IV and V lupus nephritis: An observational comparative study of the Lupus-Cruces and lupus-Bordeaux cohorts

Guillermo Ruiz-Irastorza [a,*], Amaia Ugarte [a], Cecile Saint-Pastou Terrier [b], Estibaliz Lazaro [b,c], Amalur Iza [a], Lionel Couzi [c,d], Ramon Saenz [a], Christophe Richez [c,e], Sabrina Porta [a,f], Patrick Blanco [c,g]



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	CRUCES (n=29)	BORDEAUX (n=44)	p
Age	43	35	0.001
Female	76%	81%	0.5
Caucasian	86%	77%	0.5
Class III	17%	45%	0.04
Class IV	69%	48%	
Class V	14%	7%	

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	CRUCES (n=29)	BORDEAUX (n=44)	p
Pred maximum dose	21 mg/d	42 mg/d	<0.001
Weeks to 5 mg/d	12	22	<0.001
Mean Pred 6 months	8.3 mg/d	21 mg/d	<0.001
Number of M-pred pulses	9.3	2.3	<0.001
HCQ	100%	63%	<0.001

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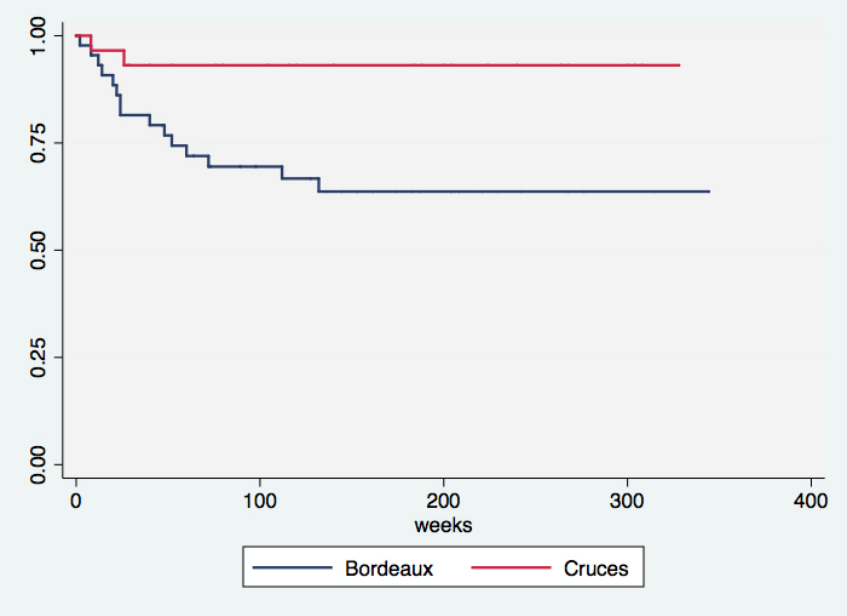
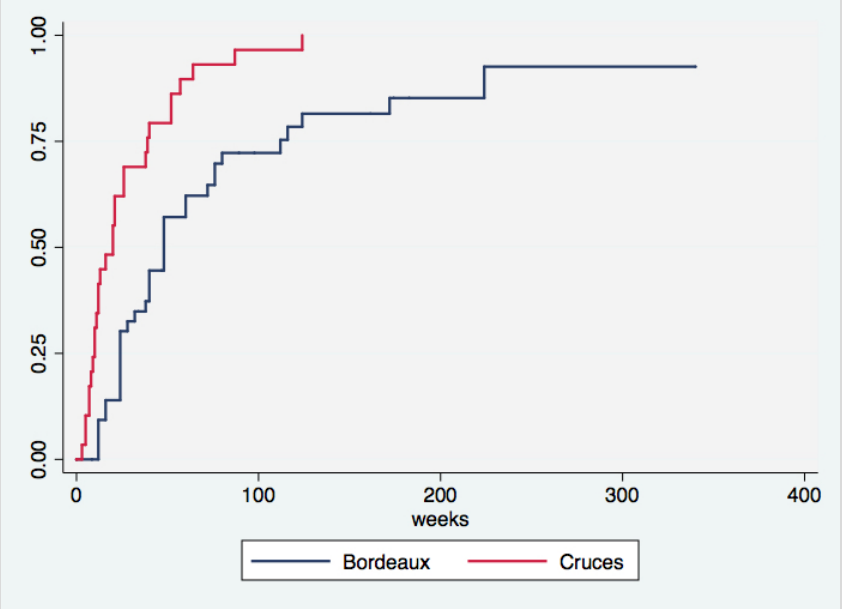
GLUCOCORTICOID TOXICITY





COMPLETE RENAL REMISSION

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	CRUCES (n=29)	BORDEAUX (n=44)	p
CR at 6 months	69%	30%	0.001
CR at 12 months	86%	43%	<0.001
Pr/Cr <0.7 at 12 months	90%	58%	0.013

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Table 4: Pooled analysis of time-dependent therapeutic predictors of complete response

	Initial model HR (95% CI)	Final model HR (95% CI)
Maximum dose of prednisone	1.02 (0.99-1.05)	
Time to prednisone 5 mg/d	0.98 (0.93-1.04)	
Mean prednisone dose at 6 months	0.95 (0.98-1.02)	
N of methyl-prednisolone pulses	1.07 (1.00-1.15)	1.09 (1.03-1.15)
Hydroxychloroquine	1.36 (0.61-3.01)	
Cyclophosphamide	0.58 (0.3-1.01)	
Mycophenolate	0.64 (0.32-1.31)	
Antiproteinuric drugs	0.43 (0.22-0.82)	

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NO HACE FALTA !!


SI SE PUEDE!!
1 mg/kg/d