II Reunión en Enfermedades Autoinmunes Sistémicas

Bilbao 2009 25-26 junio

Daño orgánico en el LES: causas y consecuencias

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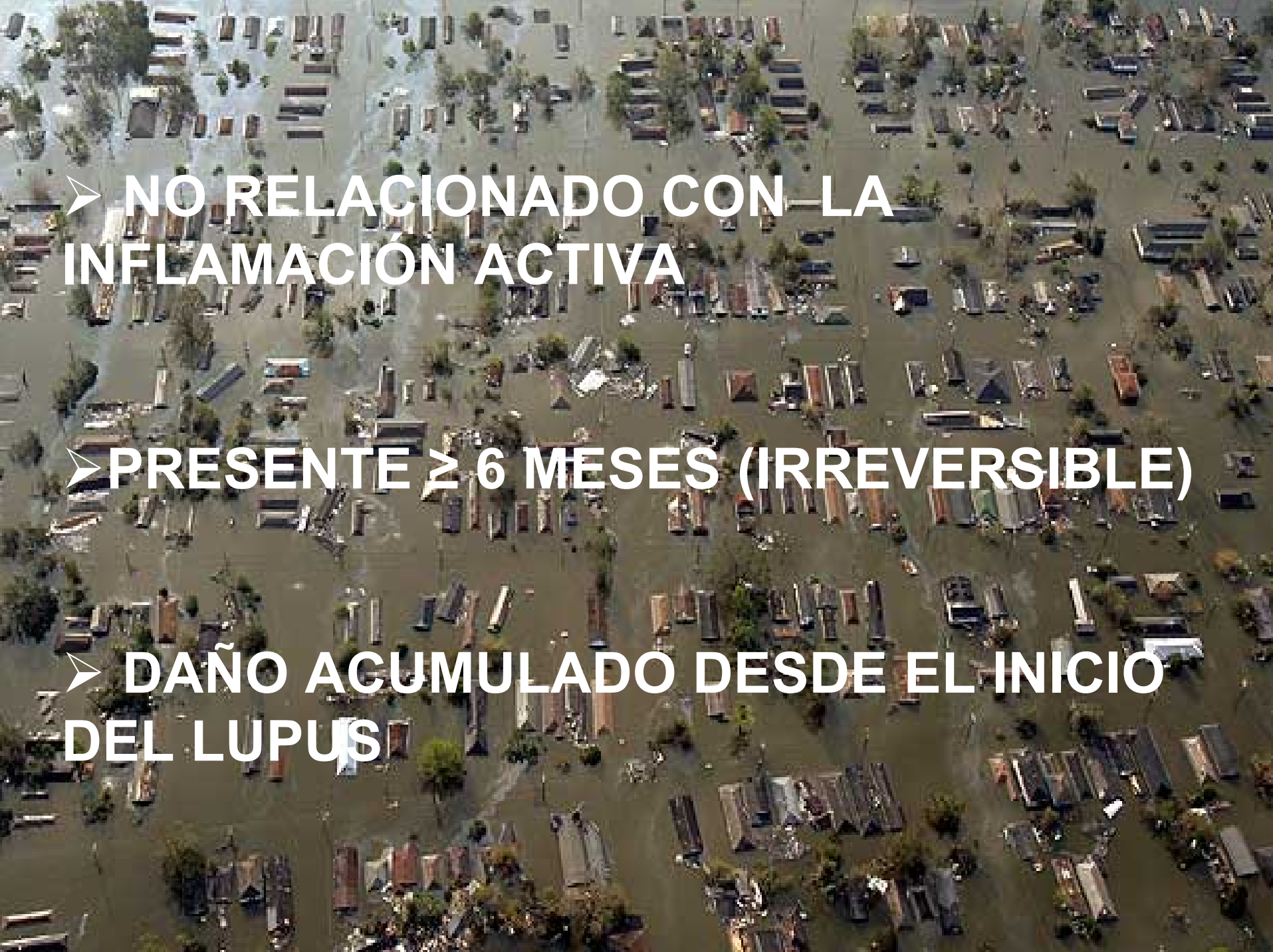
ACTIVIDAD LÚPICA


DAÑO ORGÁNICO

- **NO RELACIONADO CON LA INFLAMACIÓN ACTIVA**

- NO RELACIONADO CON LA INFLAMACIÓN ACTIVA

- PRESENTE ≥ 6 MESES (IRREVERSIBLE)



- NO RELACIONADO CON LA INFLAMACIÓN ACTIVA
- PRESENTE ≥ 6 MESES (IRREVERSIBLE)
- DAÑO ACUMULADO DESDE EL INICIO DEL LUPUS

ARTHRITIS & RHEUMATISM
Vol. 39, No. 3, March 1996, pp 363–369

THE DEVELOPMENT AND INITIAL VALIDATION OF THE SYSTEMIC LUPUS INTERNATIONAL COLLABORATING CLINICS/AMERICAN COLLEGE OF RHEUMATOLOGY DAMAGE INDEX FOR SYSTEMIC LUPUS ERYTHEMATOSUS

DAFNA GLADMAN, ELLEN GINZLER, CHARLES GOLDSMITH, PAUL FORTIN, MATTHEW LIANG, MURRAY UROWITZ, PAUL BACON, STEFANO BOMBARDIERI, JOHN HANLY, ELAINE HAY, DAVID ISENBERG, JOHN JONES, KENNETH KALUNIAN, PETER MADDISON, OLA NIVED, MICHELLE PETRI, MARTIN RICHTER, JORGE SANCHEZ-GUERRERO, MICHAEL SNAITH, GUNNAR STURFELT, DEBORAH SYMMONS, and ASAD ZOMA

SLICC/ACR Damage Index for SLE

Ocular
Catarata, retinopatía, atrofia óptica

Neuropsiquiátrico
Alteraciones cognitivas, convulsiones, ACV, neuropatía periférica o PC, mielitis transversa

Renal
TFG<50%, prot ≥3.5 g/d, IRCT

Pulmonar
HTP, fibrosis pulmonar o pleural, pulmón encogido, infarto pulmonar

Cardiovascular
Card isquémica, cardiomiopatía, valvulopatía, pericarditis

Vasculatura periférica
Claudicación intermitente, pérdida tisular, trombosis venosa

Gastrointestinal
Infarto o resección intestinal, hepática, esplénica, vesicular, insuf. mesentérica, peritonitis, estenosis o cirugía TGI

Musculoesquelético
Atrofia o debilidad muscular, artritis erosiva o deformante, fractura vertebral osteoporótica, ONA, osteomielitis

Cutáneo
Alopecia cicatricial, placas cicatriciales cutáneas extensas, atrofia panículo adiposo, cuero cabelludo o pulpejos

Fallo gonadal prematuro

Diabetes

Neoplasias

Adaptado de Gladman DD, et al A&R 1996; 39: 363-9

CAUSAS DEL DAÑO ORGÁNICO EN EL LUPUS ERITEMATOSO SISTÉMICO

SLICC/ACR Damage Index for SLE

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Catarata, retinopatía, atrofia óptica

Neuropsiquiátrico
Alteraciones cognitivas, convulsiones, ACV, neuropatía periférica o PC

mielitis transversa

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pericarditis

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LES

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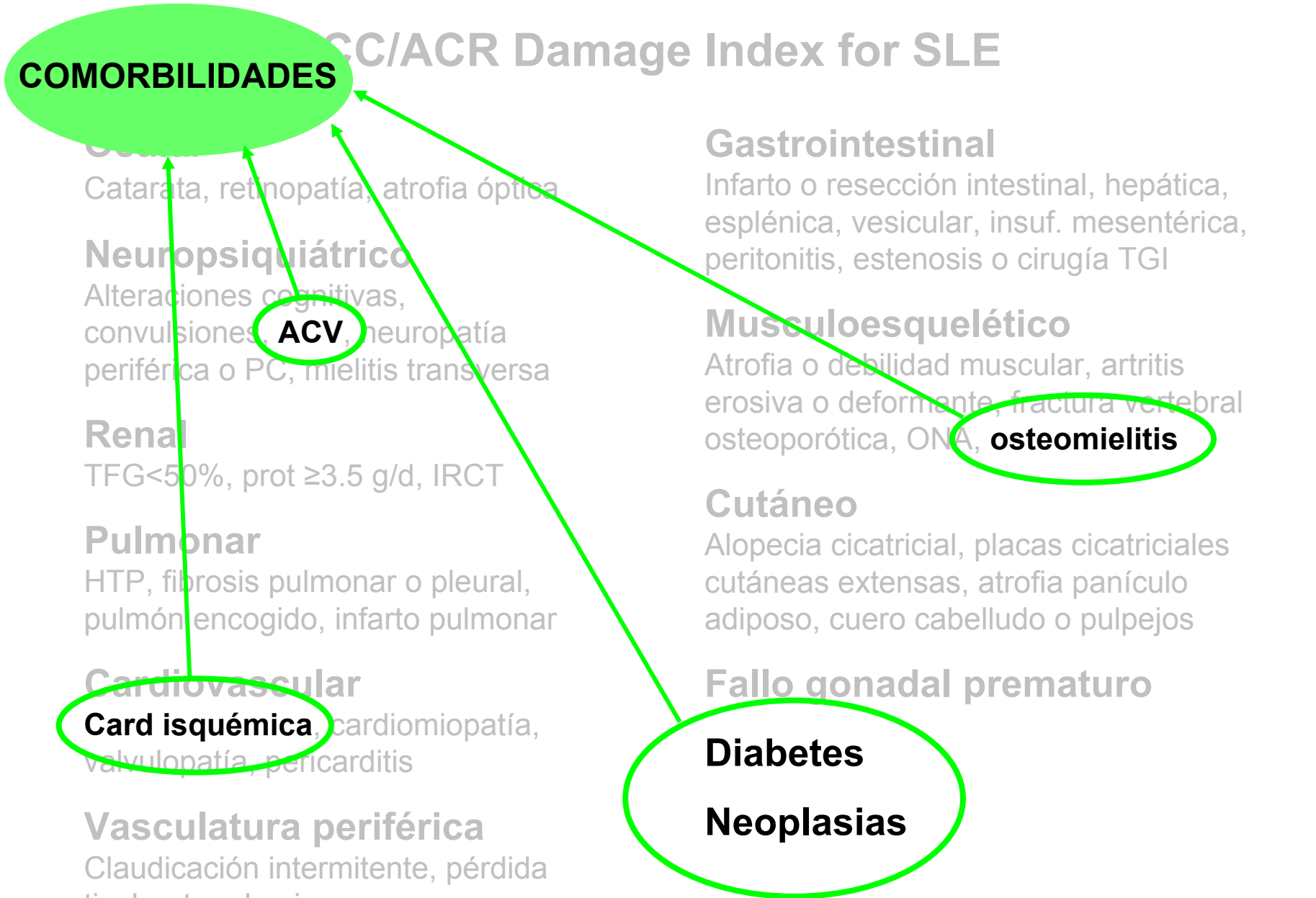
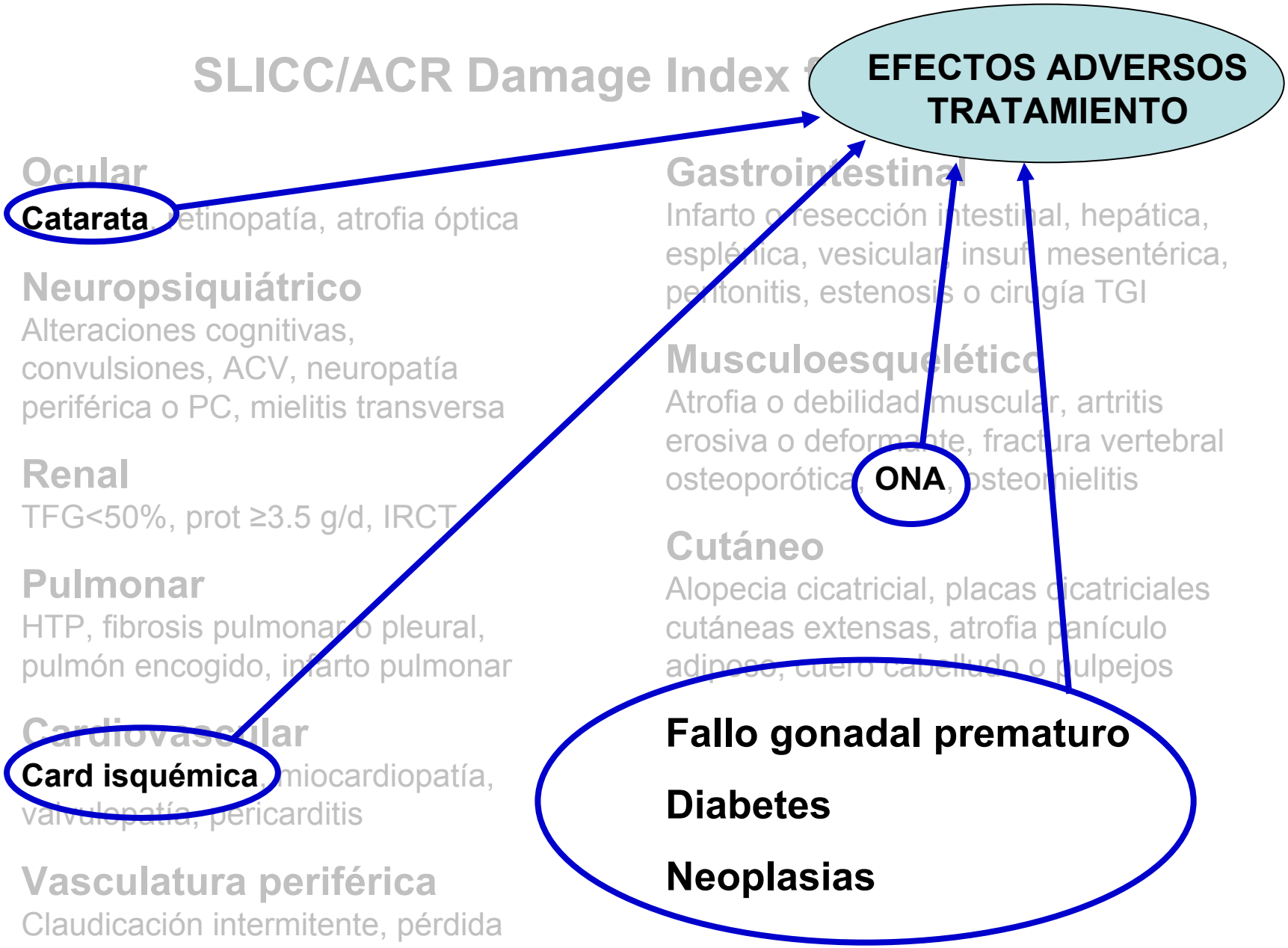


Adaptado de Gladman DD, et al A&R 1996; 39: 363-9



Adaptado de Gladman DD, et al A&R 1996; 39: 363-9

SLICC/ACR Damage Index for SLE

COMORBILIDADES

Ocular
Catarata, retinopatía, atrofia óptica

Neuropsiquiátrico
Alteraciones cognitivas, **convulsiones**, ACV, neuropatía periférica o PC, mielitis transversa

Renal
TFG<50%, prot ≥3.5 g/d, IRCT

Pulmonar
HTP, fibrosis pulmonar o pleural, pulmón encogido, infarto pulmonar

Cardiovascular
Card isquémica, cardiomiopatía, **valvulopatía**, pericarditis

Vasculatura periférica
Claudicación intermitente, pérdida tisular, trombosis venosa

Gastrointestinal
Infarto o resección intestinal, hepática, esplénica, vesicular, insuf. mesentérica, peritonitis, estenosis o cirugía TGI

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Alopecia cicatricial, placas cicatriciales cutáneas extensas, atrofia panículo adiposo, cuero cabelludo o pulpejos

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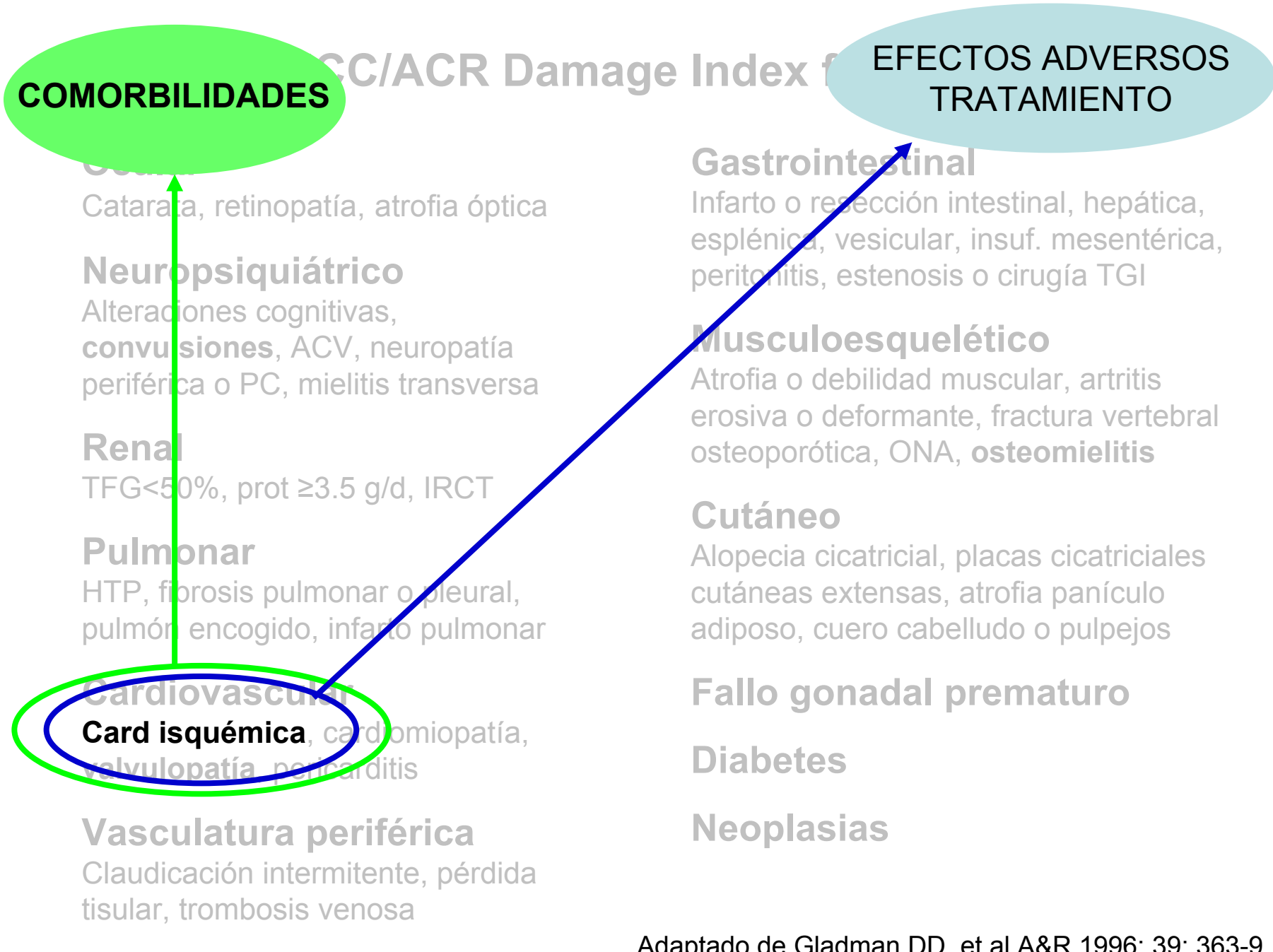


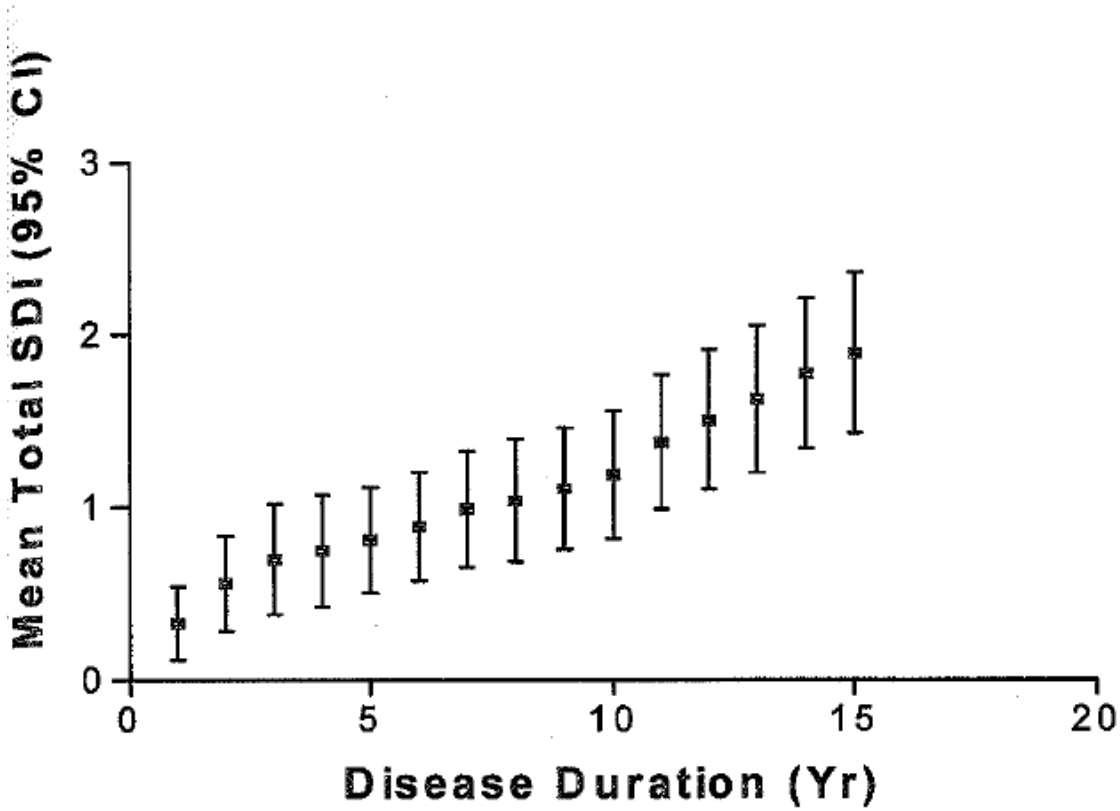
Adaptado de Gladman DD, et al A&R 1996; 39: 363-9

Adaptado de Gladman DD, et al A&R 1996; 39: 363-9

FACTORES ASOCIADOS AL DAÑO ORGÁNICO

- 1. Duración del LES

Daño orgánico y duración de la enfermedad



Gladman DD et al. J Rheumatol 2003;30:1955

10%

Category	Year 1 (232 patients)	Year 5 (232 patients)	Year 10 (232 patients)	Year 15 (143 patients)	Year 20 (75 patients)	Year 25 (6 patients)
Neuropsychiatric	6 (2.6)	26 (11.2)	34 (14.7)	18 (12.5)	12 (16.0)	1 (16.7)
Seizures	1	6	7	6	2	0
Cerebrovascular accident	3	4	5	2	5	1
Cognitive impairment or major psychosis	1	14	19	7	3	0
Cranial/peripheral neuropathy	1	2	2	3	1	0
Transverse myelitis	0	0	1	0	1	0
Ocular	0 (0)	0 (0)	3 (1.3)	3 (2.1)	1 (1.3)	0 (0)
Cataracts	0	0	2	2	1	0
Retinal change	0	0	1	1	0	0
Renal	1 (0.4)	16 (6.9)	30 (12.9)	20 (14.0)	10 (13.3)	2 (33.3)
GFR < 50%	0	11	15	10	4	1
Proteinuria > 3.5 g/24 h	0	2	8	4	2	0
End-stage renal disease	1	3	6	6	4	1
Pulmonary	0 (0)	0 (0)	8 (3.4)	7 (4.9)	3 (4)	0 (0)
Pulmonary hypertension	0	0	3	2	1	0
Pulmonary fibrosis	0	0	2	2	1	0
Shrinking lung	0	0	1	0	0	0
Pleural fibrosis	0	0	1	1	0	0
Pulmonary infarction	0	0	1	2	1	0
Cardiovascular	1 (0.4)	4 (1.7)	11 (4.7)	11 (7.7)	7 (9.3)	2 (33.3)
Angina or coronary bypass	1	3	5	5	4	0
Myocardial infarction	0	0	3	4	1	1
Valvular disease	0	1	2	2	2	1
Pericarditis	0	0	1	0	0	0
Peripheral vascular	2 (0.9)	8 (3.4)	11 (4.7)	12 (8.4)	7 (9.3)	2 (33.3)
Venous thrombosis	1	4	6	6	4	1
Claudication	0	2	3	3	1	1
Minor tissue loss	0	1	1	2	1	0
Significant tissue loss	1	1	1	1	1	0
Gastrointestinal	4 (1.7)	6 (2.5)	8 (3.4)	8 (5.6)	9 (12)	1 (16.7)
Resection of bowel	4	4	5	5	6	1
Upper gastrointestinal tract surgery	0	2	3	3	3	0
Musculoskeletal	5 (2.2)	13 (5.6)	28 (12.1)	31 (21.7)	19 (25.3)	2 (33.3)
Muscle atrophy or weakness	0	4	7	10	6	1
Deforming/erosive arthritis	3	6	15	15	9	1
Osteoporosis with fracture	1	1	2	2	2	0
Avascular necrosis	1	2	4	4	2	0
Skin	5 (2.2)	9 (3.9)	12 (5.2)	5 (3.5)	5 (6.7)	0 (0)
Scarring alopecia	2	5	6	3	3	0
Scarring of panniculum	0	0	0	0	1	0
Skin ulceration	3	4	6	2	1	0
Premature ovarian failure	0 (0)	0 (0)	1 (0.43)	3 (2.1)	1 (1.3)	0 (0)
Endocrine (diabetes)	0 (0)	0 (0)	1 (0.4)	1 (0.7)	1 (1.3)	0 (0)
Malignancy	0 (0)	2 (0.9)	5 (2.2)	5 (3.4)	8 (10.7)	2 (33.3)

Chambers SA, et al. Rhematology 2009;48:673

10% 51%

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Chambers SA, et al. Rhematology 2009;48:673

10% 51% 100%

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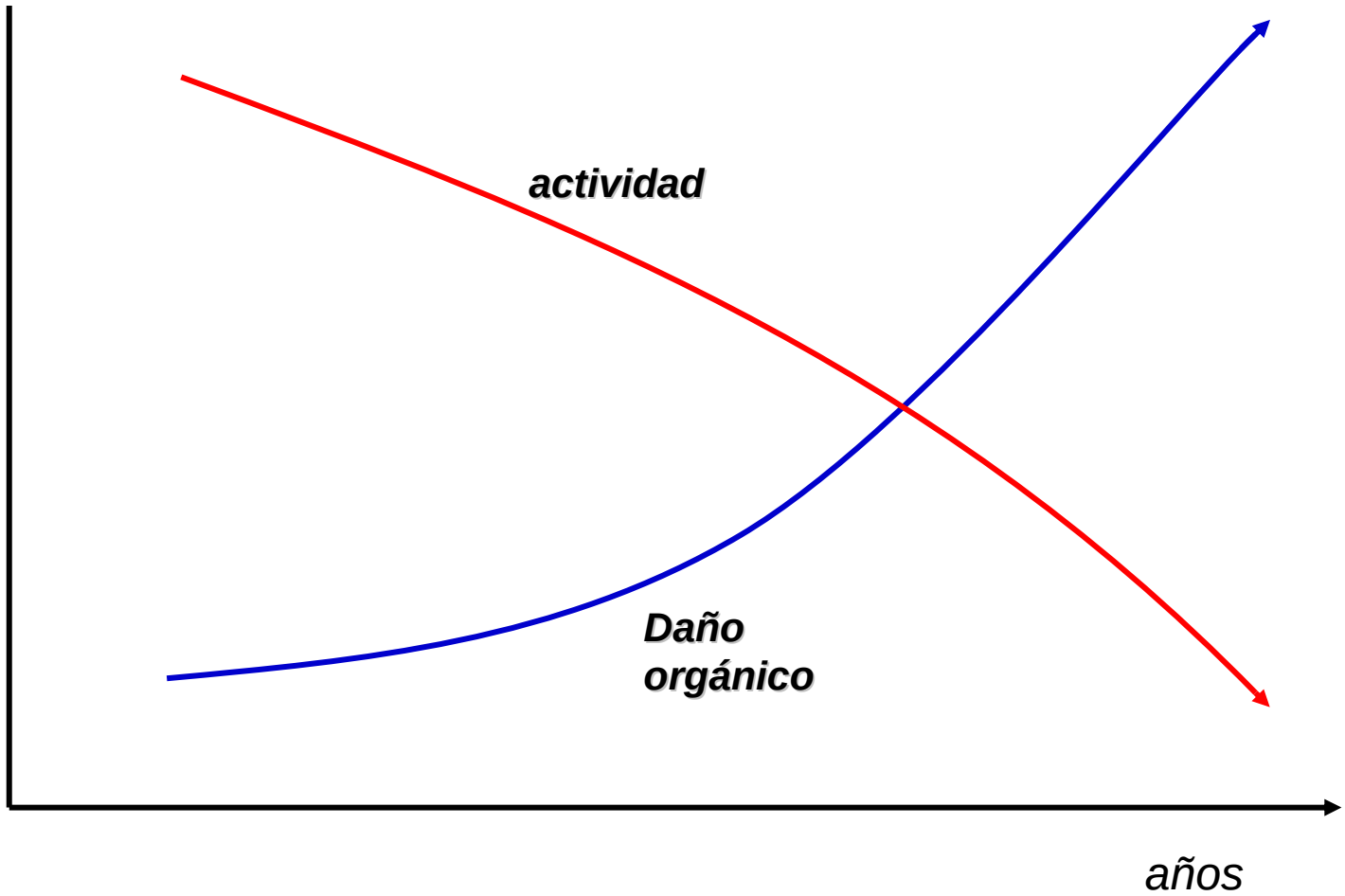
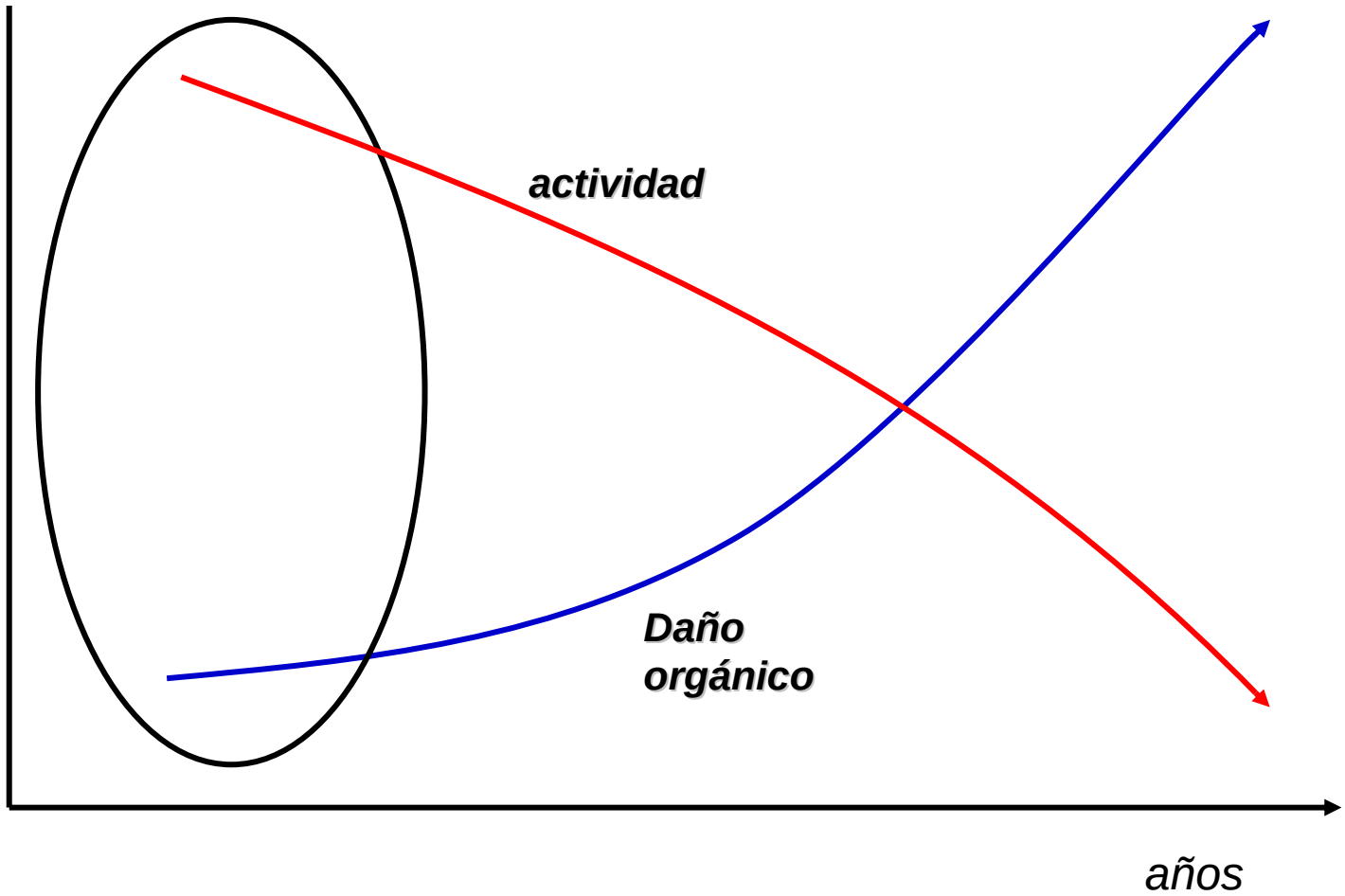


Duración del LES



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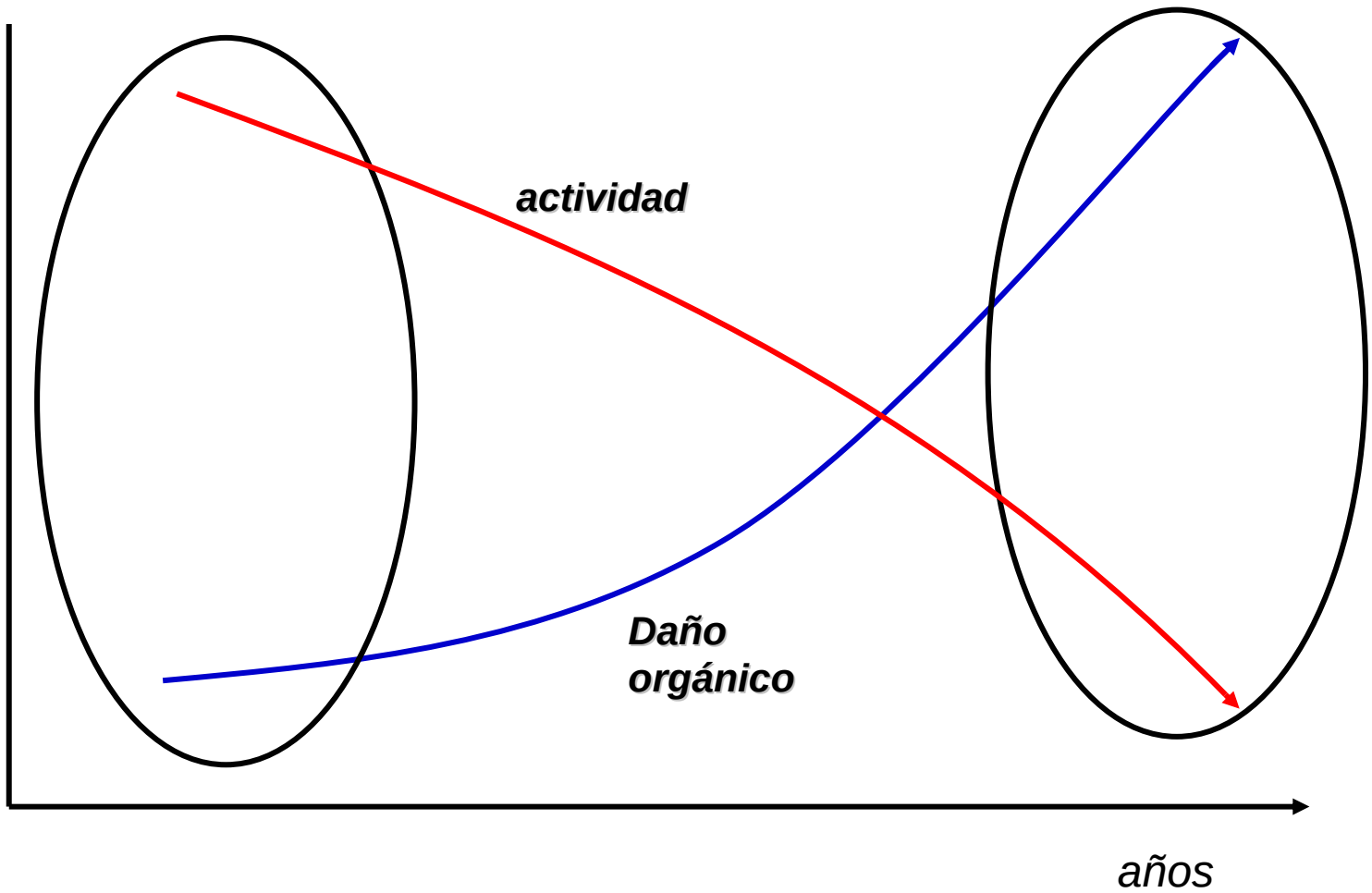

Duración del LES

- Duración del LES
- Actividad del LES

La actividad del LES determina más daño orgánico

TABLE 3. Prediction of death or increase in total damage score 5 yr after inclusion ($n = 135$) when disease activity was described using the average of the total BILAG scores (per visit)

Disease variable	Odds ratio	95% C.I.	*P*
Total BILAG score (average per encounter)	1.623	1.219–2.161	0.001***
Initial mental health (SF-20+)	1.029	1.003–1.056	0.029*
Disease duration	1.063	0.988–1.144	0.104
Physical functioning (SF-20+)	0.987	0.968–1.006	0.167

Stoll T et al. Rheumatology 2004;43:1039

La actividad lúpica inicial del LES determina el desarrollo posterior de daño orgánico

Table 5. Comparison of baseline demographic and disease variables between patients with and without 2 year increase in organ damage. Mean (SD) for continuous, number (%) for categorical variables.

	Increased Damage, n = 24	No Change, n = 67	p*
Women	22 (92)	60 (90)	0.77
Age	46.6 (15.5)	45.5 (15.5)	0.78
Disease variables			
Disease duration, yrs	7.9 (7.9)	5.5 (4.9)	0.17
Disease activity (SLEDAI)	9.1 (6.3)	5.5 (5.1)	0.02
Organ damage (SDI)	3.4 (2.9)	1.5 (1.7)	0.01

Gilboe IM, et al. J Rheumatol 2001;28:266

La actividad lúpica inicial del LES determina el desarrollo posterior de daño orgánico

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Age	46.6 (15.5)	45.5 (15.5)	0.78
Disease variables			
Dise			
Dise			
Orga			

Para evitar la aparición de daño orgánico es preciso tratar precoz e intensivamente la actividad al inicio de la enfermedad

Daño orgánico y actividad lúpica

Table 2. Disease activity and disease damage in different categories of sedimentation rate and of anti-dsDNA antibody reactivity.

Variable	SLAM Score, mean (SD)	p	PGA Score, mean (SD)	p	SDI Score, mean (SD)	p
At baseline						
ESR (mm/hr)						
< 25	6.5 (4.5)	< 0.001	1.7 (1.7)	< 0.001	0.8 (1.3)	< 0.001
25–50	8.5 (4.6)		2.4 (1.8)		1.0 (1.3)	
51–75	9.6 (5.5)		2.5 (1.8)		1.3 (1.9)	
> 75	11.3 (6.2)		3.8 (2.6)		1.4 (1.8)	
Anti-dsDNA						
Negative	7.3 (4.7)	0.013	1.9 (1.8)	< 0.001	0.9 (1.3)	0.035
Positive	9.4 (5.2)		3.0 (2.1)		1.3 (1.8)	
All visits						
ESR (mm/hr)						
< 25	6.3 (3.9)	< 0.001	1.7 (1.7)	< 0.001	1.1 (1.6)	< 0.001
25–50	7.8 (4.2)		2.3 (1.8)		1.4 (1.7)	
51–75	10.0 (5.2)		2.8 (2.0)		2.0 (2.2)	
> 75	11.1 (5.4)		3.6 (2.4)		2.1 (2.3)	
Anti-dsDNA						
Negative	6.3 (3.9)	< 0.001	1.7 (1.7)	< 0.001	1.1 (1.6)	< 0.001
Positive	8.8 (4.8)		2.6 (2.0)		1.6 (2.0)	

SLAM: Systemic Lupus Activity Measure (ESR score excluded from total SLAM score). PGA: Physician's Global Assessment. SDI: Systemic Lupus International Collaborating Clinics Damage Index.

Vilá LM, et al. LUMINA. J Rheumatol 2005;32:2150

- Duración del LES
- Actividad del LES
- Daño orgánico previo

El daño orgánico predice el desarrollo de más daño orgánico

TABLE 3. Multivariable generalized estimating equation analyses of damage accrual in LUMINA patients

Variable	Parameter estimate	*Z* score	*P*
Age	0.0154	2.87	0.0041
SLAM score	0.0705	5.46	< 0.0001
Prior SDI	0.0687	4.81	< 0.0001
Corticosteroids (maximum dose)	0.4897	2.82	0.0048
Time	–0.0335	–0.93	0.3532

***Conclusions*. Once damage occurs in SLE, further damage is expected to occur.**

Alarcon GS, et al Rheumatology 2004;43:202

El daño orgánico predice el desarrollo de más daño orgánico

TABLE 3. Multivariable generalized estimating equation analyses of damage accrual in LUMINA patients

Variable	Parameter estimate	*Z* score	*P*
Ag			
SL			
Pri			
Co			
Ti			

Concl occur.

Una manera de EVITAR el daño orgánico es PREVENIR su aparición

Alarcon GS, et al Rheumatology 2004;43:202

- Duración del LES
- Actividad del LES
- Daño orgánico previo
- LES de inicio tardío

Daño orgánico e inicio del LES

Table 4. Variables independently associated with late-onset lupus by multivariable analysis*

Variable	OR	95% CI	P†
Neurologic involvement	2.82	1.12–6.79	0.020
Renal involvement	0.24	0.09–0.63	0.004
Arterial vascular events	5.53	1.22–24.99	0.026
SLAM-R at enrollment	0.84	0.74–0.95	0.008
SDI at last visit	3.70	1.36–9.99	0.010
Anti-Sm antibodies	0.23	0.07–0.73	0.013
Hypertriglyceridemia	1.01	1.00–1.01	0.001
High levels of HDL cholesterol	2.40	1.00–5.79	0.050
Abnormal illness-related behaviors	0.89	0.82–0.95	0.003
Deceased	33.87	5.00–229.40	<0.001

* Variables were adjusted for sex. OR = odds ratio; 95% CI = 95% confidence interval; SLAM-R = revised Systemic Lupus Activity Measure; SDI = Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; HDL = high-density lipoprotein.
† Only variables with $P \leq 0.05$ are shown.

Bertoli AM et al. A&R 2006;54:1580

Daño orgánico e inicio del LES

Table 4. Variables independently associated with late-onset lupus by multivariable analysis*

Variable	OR	95% CI	P†
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Menor uso de corticoides y de inmunosupresores

Bertoli AM et al. A&R 2006;54:1580

Daño orgánico e inicio del LES

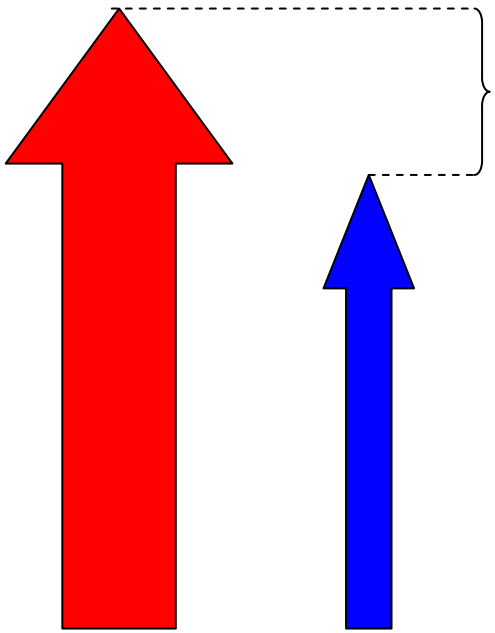
Table 2. Cumulative clinical features of LUMINA patients according to age at disease onset*

Feature	Late-onset lupus (n = 73)	Early-onset lupus (n = 144)	P†
Total disease duration, months	63.4 ± 42.1	62.7 ± 41.6	
Disease onset type, % acute	23	25	
No. of ACR criteria at diagnosis	5.2 ± 1.1	5.6 ± 1.2	0.014
Organ system involvement, %			
Integument	69	55	0.058
Musculoskeletal	74	64	0.089
Cardiopulmonary	33	20	0.046
Neurologic	53	32	0.003
Hematologic	51	49	
Renal	29	56	<0.001
Comorbidities, %			
Arterial thrombotic events	25	6	<0.001
Venous thrombotic events	7	6	
Hypertension	59	39	0.006
Hypothyroidism	22	6	<0.001
Diabetes mellitus	8	6	
Osteoporosis	7	1	0.017

Bertoli AM et al. A&R 2006;54:1580

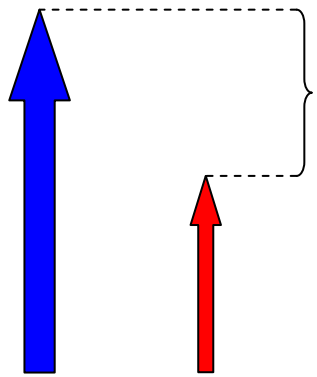
- Duración del LES
- Actividad del LES
- Daño orgánico previo
- LES de inicio tardío
- Corticoides

EFECTO DOSIS-DEPENDIENTE DE LOS CORTICOIDES



Efecto deletéreo: dislipemia, HTA, obesidad, diabetes

Efecto beneficioso



Dosis elevadas

Dosis bajas

EFECTO DE LOS CORTICOIDES SOBRE EL DAÑO ORGÁNICO

Cumulative Average Dose (mg/mo)		Unadjusted Model HR	95% CI	Conventionally-Adjusted Model* HR	95% CI	Weighted Model* HR	95% CI
0		Ref		Ref		Ref	
0–180	< 6 mg/dl	1.58	1.00, 2.50	2.01	1.11, 3.63	1.16	0.54, 2.50
180–360	6-12	2.10	1.24, 3.55	2.46	1.17, 5.16	1.50	0.58, 3.88
360–540	12-18	3.04	1.67, 5.53	3.54	1.55, 8.12	1.64	0.58, 4.69
> 540	>18	4.19	2.35, 7.47	4.10	1.74, 9.65	2.51	0.87, 7.27

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

Conclusion. Our results suggest that low doses of prednisone do not result in a substantially increased risk of irreversible organ damage.

Thamer M, et al. J Rheumatol 2009;36:560

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*A ovariates.

DOSIS MÍNIMA EFICAZ

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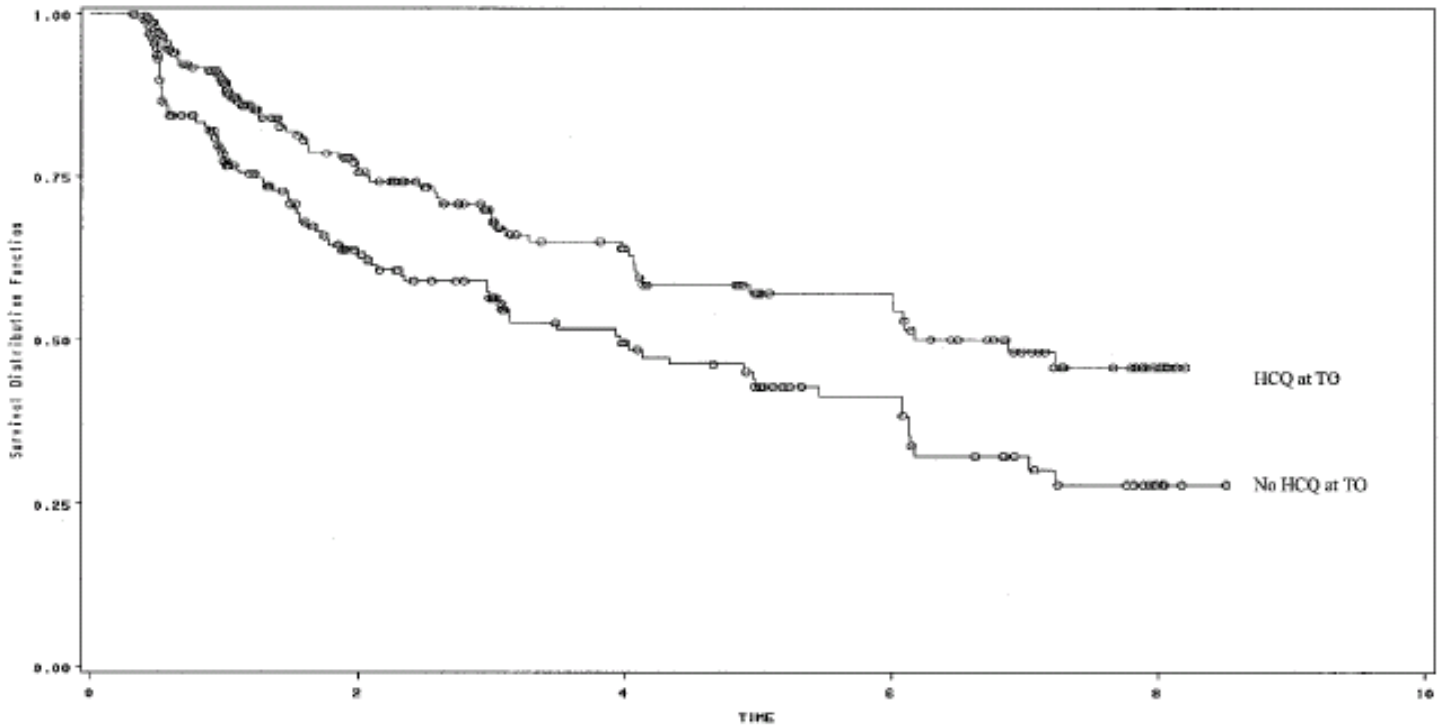
Thamer M, et al. J Rheumatol 2009;36:560

- Duración del LES
- Actividad del LES
- Daño orgánico previo
- LES de inicio tardío
- Corticoides
- Uso de hidroxicloroquina

Efecto protector de la HCQ sobre el daño orgánico



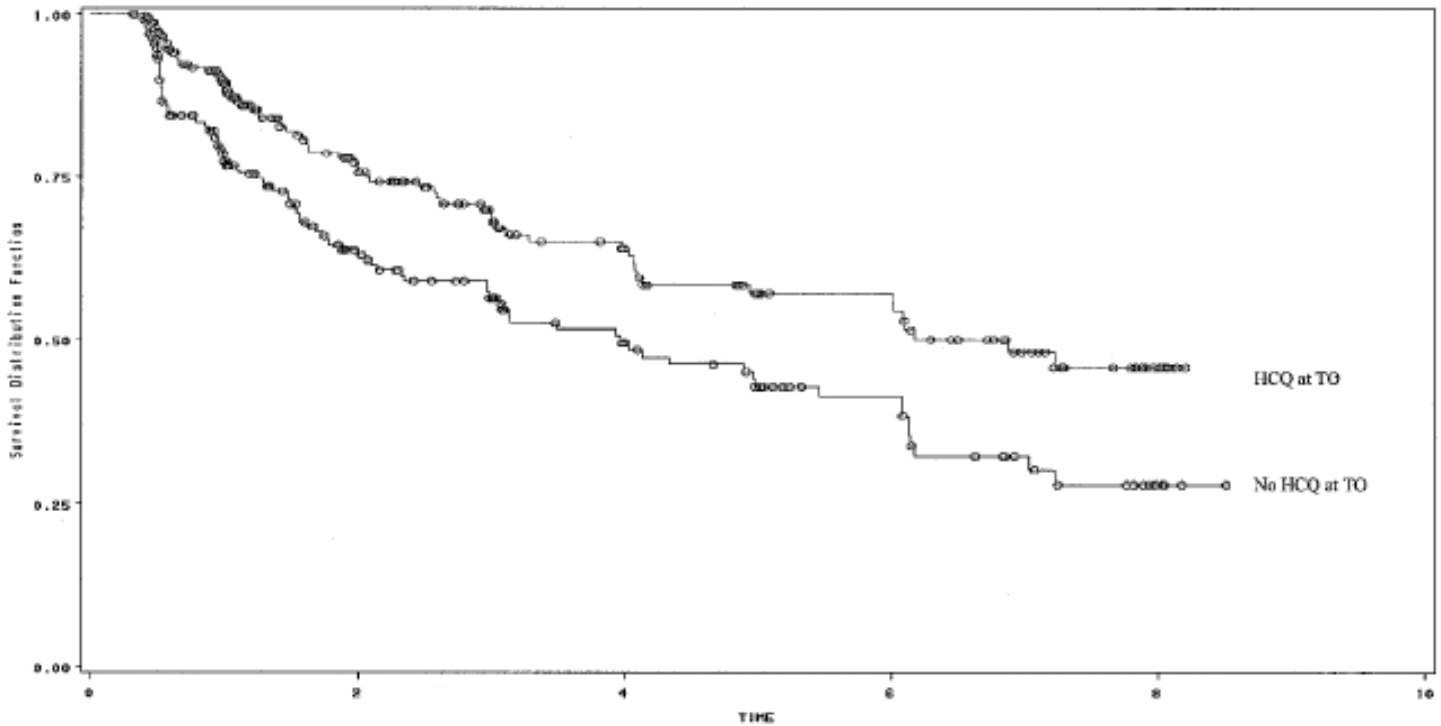
Time (years)	0	2	4	6	8	10
HCQ at T0	297	105	57	41	9	0
No HCQ at T0	229	83	48	28	4	0

Figure 1. Time to accrual of new damage (unadjusted for propensity score) in systemic lupus erythematosus patients who were and those who were not treated with hydroxychloroquine (HCQ) at time 0 (T0).

Conclusion. **These findings indicate that, after adjustment for propensity to receive HCQ, HCQ usage is independently associated with a reduced risk of damage accrual in SLE patients who had not yet accrued damage at the time of treatment initiation.**

Fessler BJ, et al. A&R 2005;52:1473

Efecto protector de la HCQ sobre el daño orgánico



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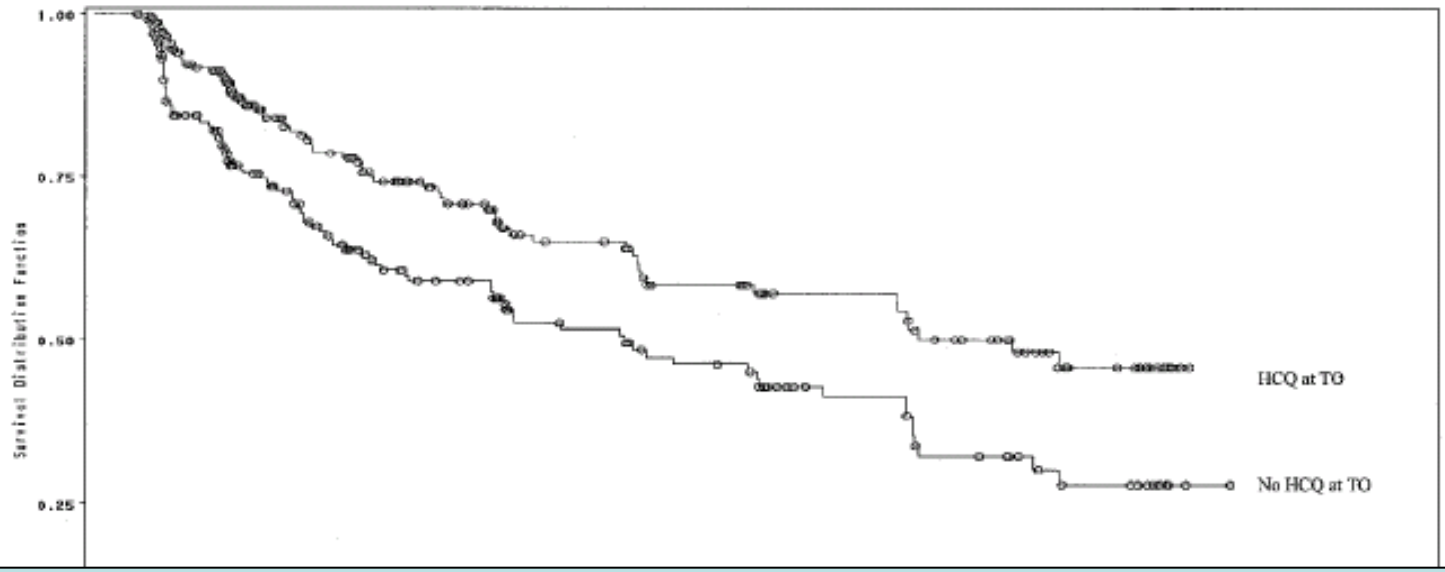

INTRODUCCIÓN PRECOZ DE LA HIDROXICLOROQUINA EN EL TRATAMIENTO DEL LUPUS ERITEMATOSO SISTÉMICO

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Fessler BJ, et al. A&R 2005;52:1473

EFECTOS BENEFICIOSOS DE LA HCQ

(diferente grado de evidencia)

- Prevención de brotes lúpicos
- Ahorrador de corticoides
- Efecto antitrombótico
- Previene pérdida de masa ósea (?)
- Efecto beneficioso sobre el perfil lipídico proaterogénico (?)
- Efecto hipoglucemiante (?)
- Previene arteriosclerosis subclínica (?)
- Protección contra el cáncer (?)

Ruiz-Irastorza G, et al. Ann Rheum Dis 2009; Jun 4

Hidroxicloroquina y síndrome metabólico

Variables associated with metabolic syndrome in patients with SLE, using logistic regression

Explanatory variable	*Odds ratio*	*95% confidence interval*	P
Educational level	0.835	0.749–0.930	<0.001
Triglycerides	1.024	1.011–1.036	<0.001
HDL cholesterol	0.936	0.906–0.968	<0.001
C3	1.017	1.001–1.032	0.032
Hydroxychloroquine use	0.192	0.061–0.605	0.003

Sabio JM, et al. Lupus 2008; 17: 849

Tesis doctoral de la Dra Mónica Zamora

SLICC/ACR Damage Index for SLE

Ocular
Catarata, retinopatía, atrofia óptica

Neuropsiquiátrico
Alteraciones cognitivas, convulsiones, **ACV**, neuropatía periférica o PC, mielitis transversa

Renal
TFG<50%, prot ≥3.5 g/d, IRCT

Pulmonar
HTP, fibrosis pulmonar o pleural, pulmón encogido, **infarto pulmonar**

Cardiovascular
Card isquémica, cardiomiopatía, valvulopatía, pericarditis

Vasculatura periférica
Claudicación intermitente, pérdida tisular, trombosis venosa

Gastrointestinal
Infarto o resección intestinal, hepática, esplénica, vesicular, insuf. mesentérica, peritonitis, estenosis o cirugía TGI

Musculoesquelético
Atrofia o debilidad muscular, artritis erosiva o deformante, **fractura vertebral osteoporótica**, ONA, osteomielitis

Cutáneo
Alopecia cicatricial, placas cicatriciales cutáneas extensas, atrofia panículo adiposo, cuero cabelludo o pulpejos

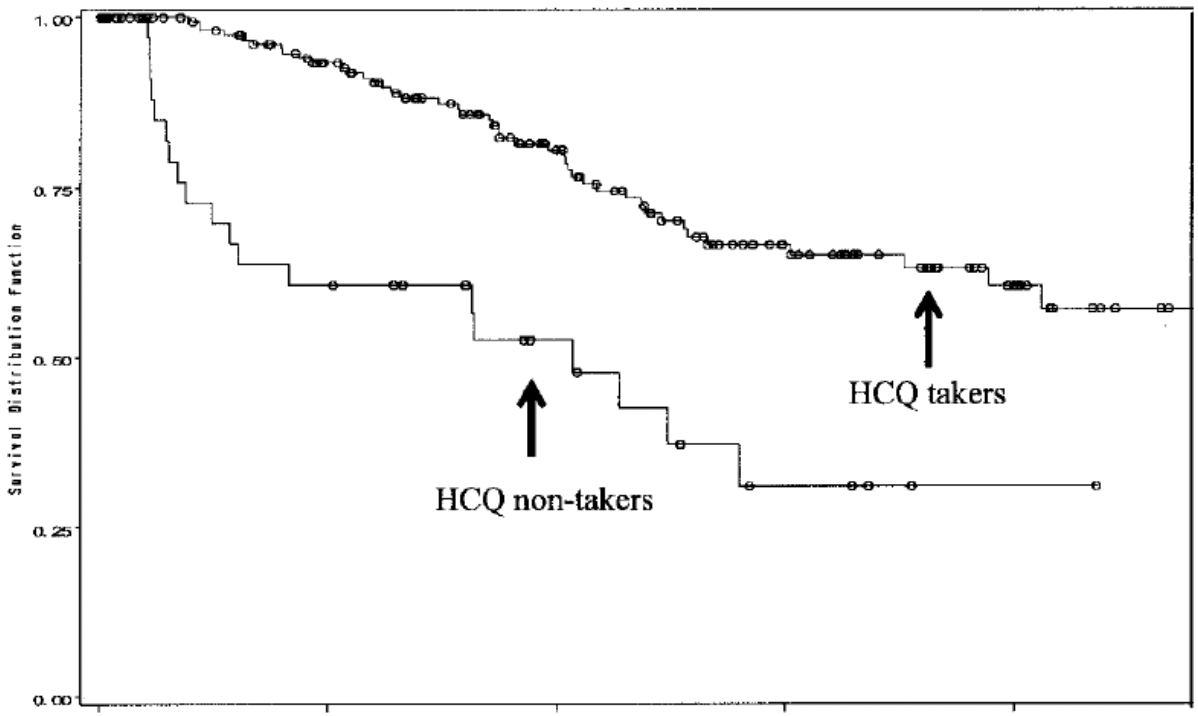
Fallo gonadal prematuro

Diabetes

Neoplasias

Adaptado de Gladman DD, et al A&R 1996; 39: 363-9

Cumulative probability of developing renal damage in LUMINA

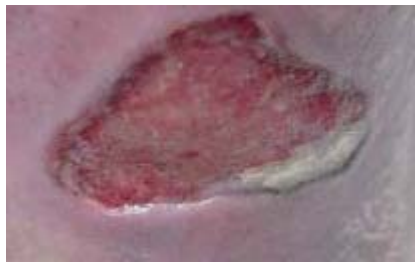


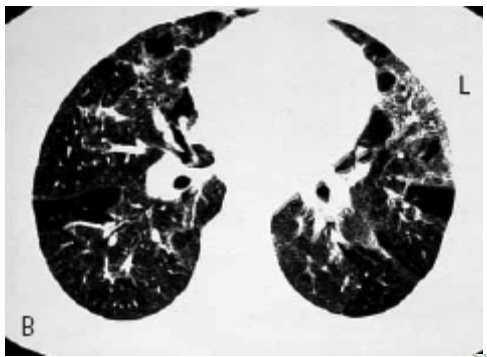
Time (years)	0	2.5	5	7.5	10
Hydroxychloroquine (HCQ) takers	161	131	83	45	20
Hydroxychloroquine non-takers	42	20	11	4	1

Conclusion. **After adjusting for possible confounding factors, the protective effect of hydroxychloroquine in retarding renal damage occurrence in systemic lupus erythematosus is still evident.**

Pons-Estel G, et al. LUMINA Arthritis Rheum 2009;28:266

CONSECUENCIAS DEL DAÑO ORGÁNICO

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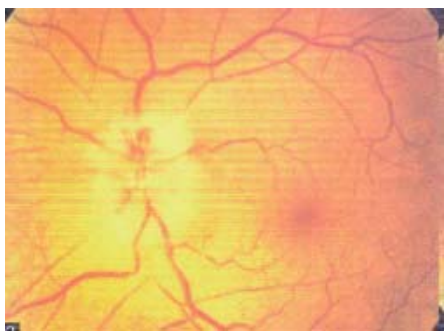
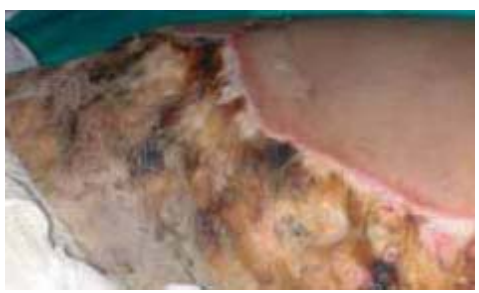
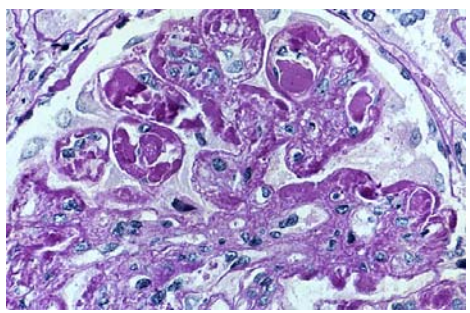
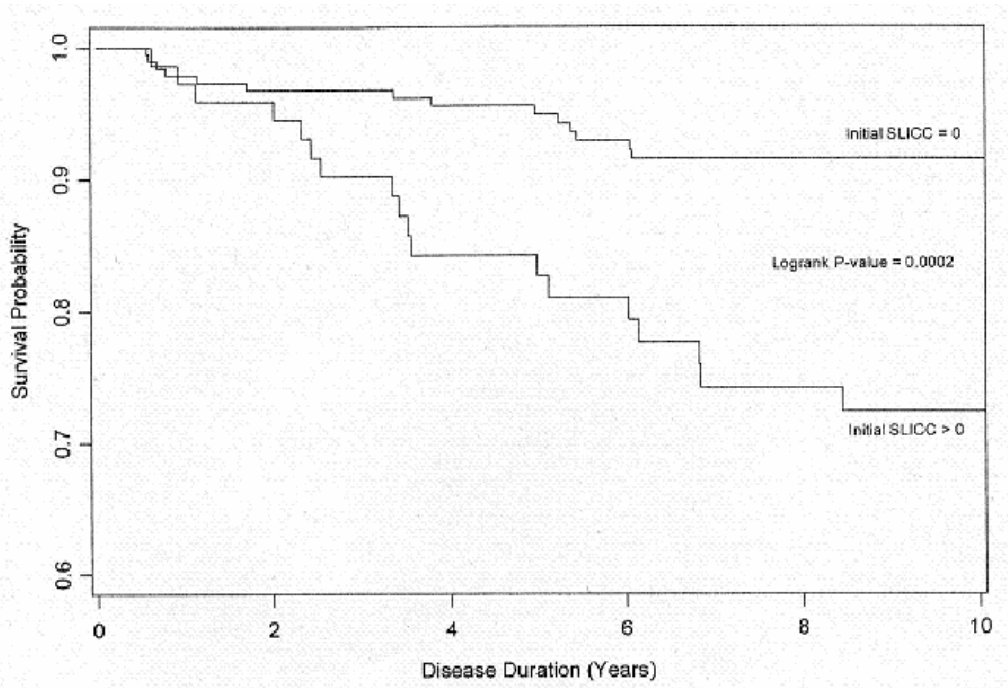


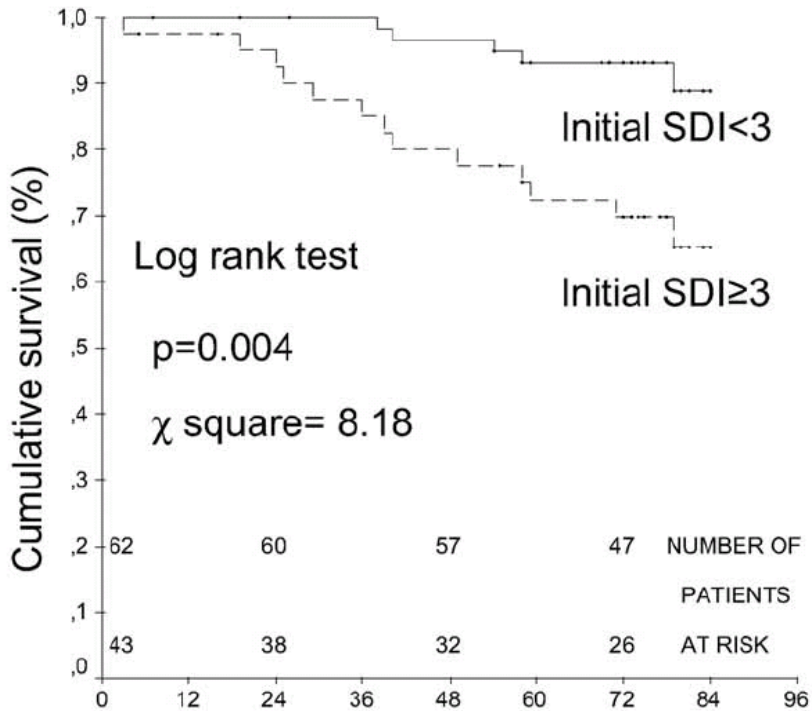




DAÑO ORGÁNICO Y SUPERVIVENCIA

Daño orgánico precoz y mortalidad

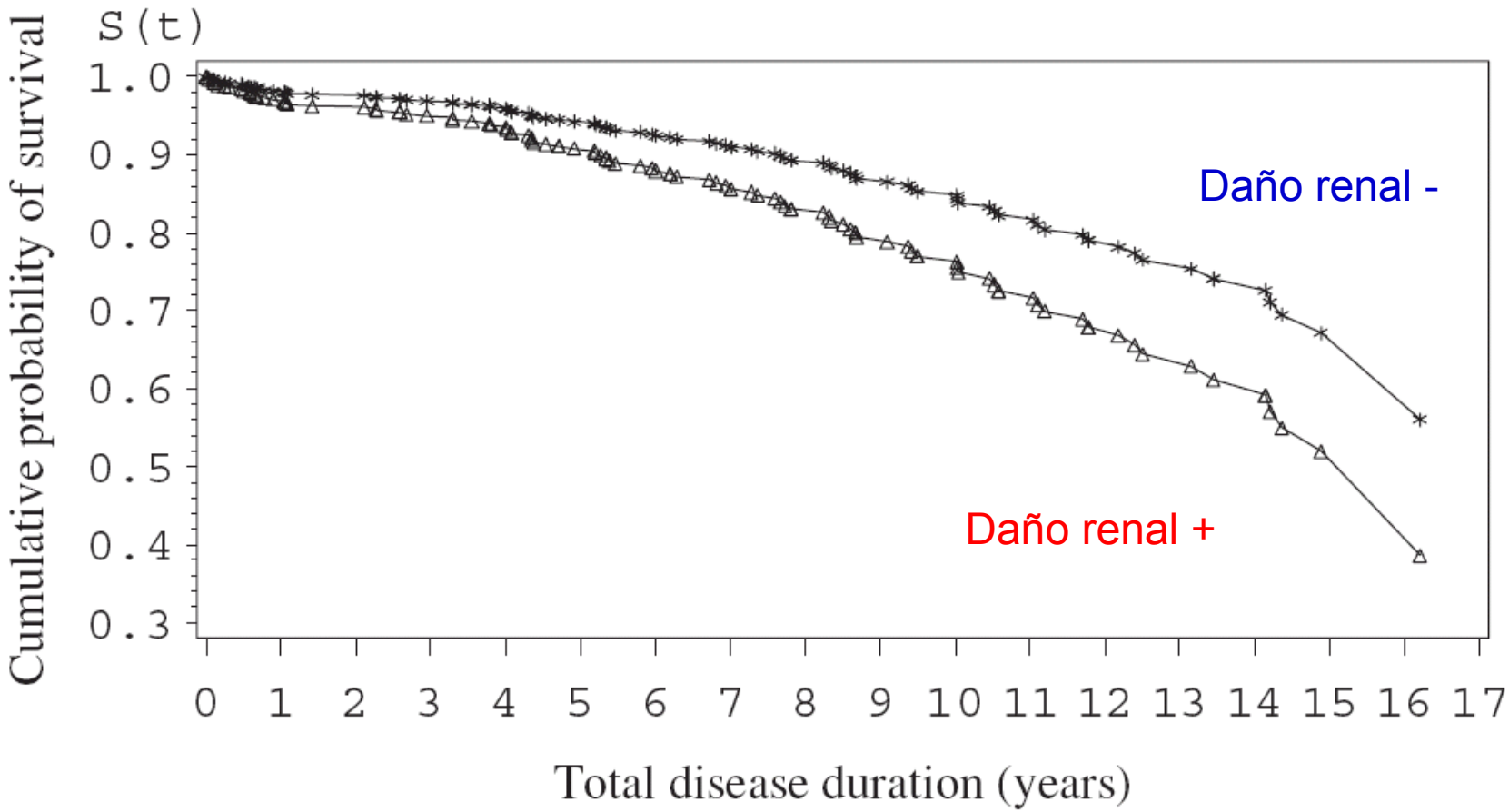




Rahman P ,et al. Lupus 2001;10:93

Cardoso C, et al. Lupus 2008;17:1042

El daño renal es el dominio que mejor predice la mortalidad en LES



Danila MI, et al LUMINA. Rheumatology 2009;48:542

Calidad de vida y daño orgánico

- ✓ Mok CC, et al. Scand J Rheumatol 2009;38;121-7
- ✓ Abu-Shakra M, et al. Lupus 2006;15:32-7
- ✓ Wang C, et al. J Rheumatol 2001;28:525-32

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- ✓ Wang C, et al. J Rheumatol 2001;28:525-32

NO o DÉBIL:

- ✓ Hanly JG. Lupus 1997;6:243-7
- ✓ Stoll T et al. J Rheumatol 1997;24:309-13

LIMITACIONES ÍNDICE SLICC/ACR SDI

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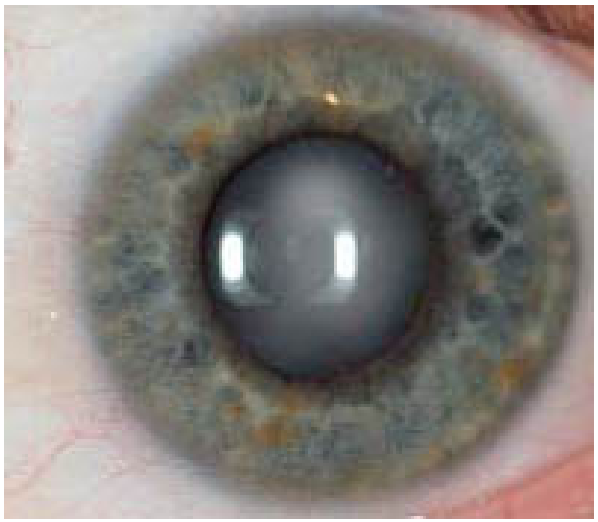

SDI 1

LIMITACIONES ÍNDICE SLICC/ACR SDI

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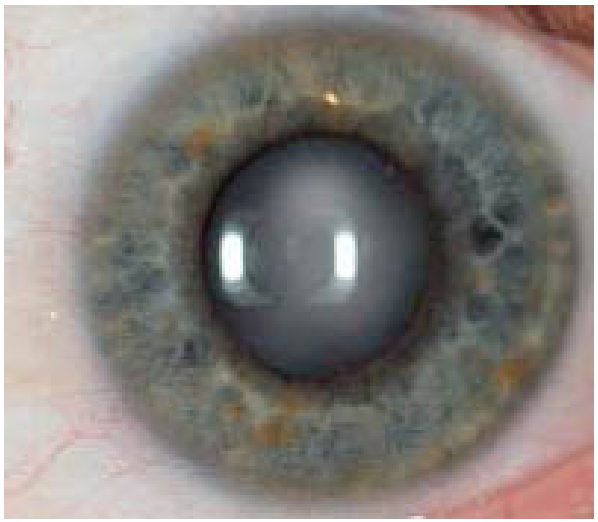

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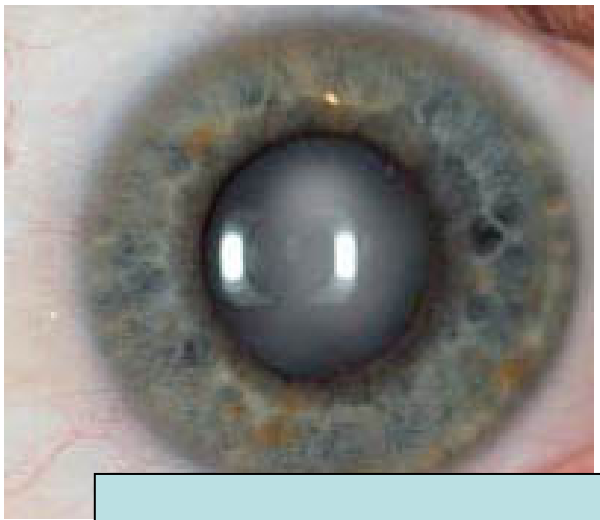
LIMITACIONES ÍNDICE SLICC/ACR SDI



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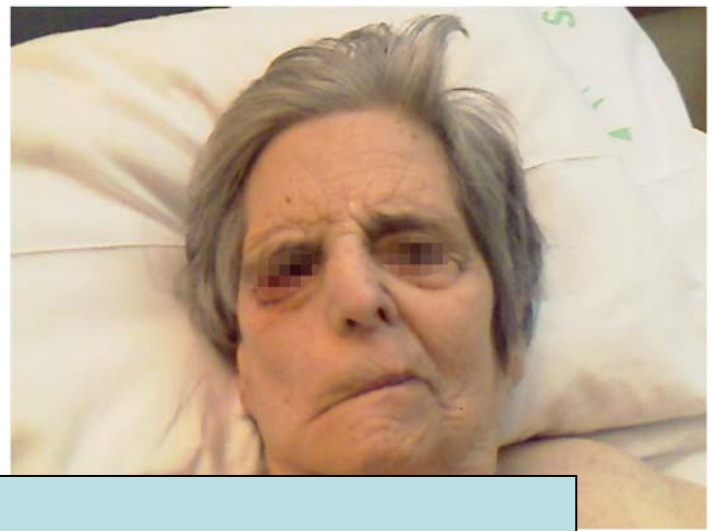

Para el cálculo del daño orgánico (índice SLICC) debería tenerse en cuenta el peso relativo de cada lesión

Estrategias para disminuir el daño orgánico

1. Diagnóstico precoz
2. Tratamiento precoz y adecuado
3. Control de la actividad lúpica y prevención del daño orgánico
4. Uso adecuado de corticoides (dosis mímima eficaz)
5. Uso precoz de la HCQ
6. Control estrecho y prevención de los efectos adversos de los fármacos
7. Control de comorbilidades: por ejemplo FRCV
8. Uso de nuevos inmunosupresores (MFM *vs* CFM)


GRACIAS