NEFROPATÍA LÚPICA
INDUCCIÓN DE RESPUESTA

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OBJETIVOS TERAPÉUTICOS

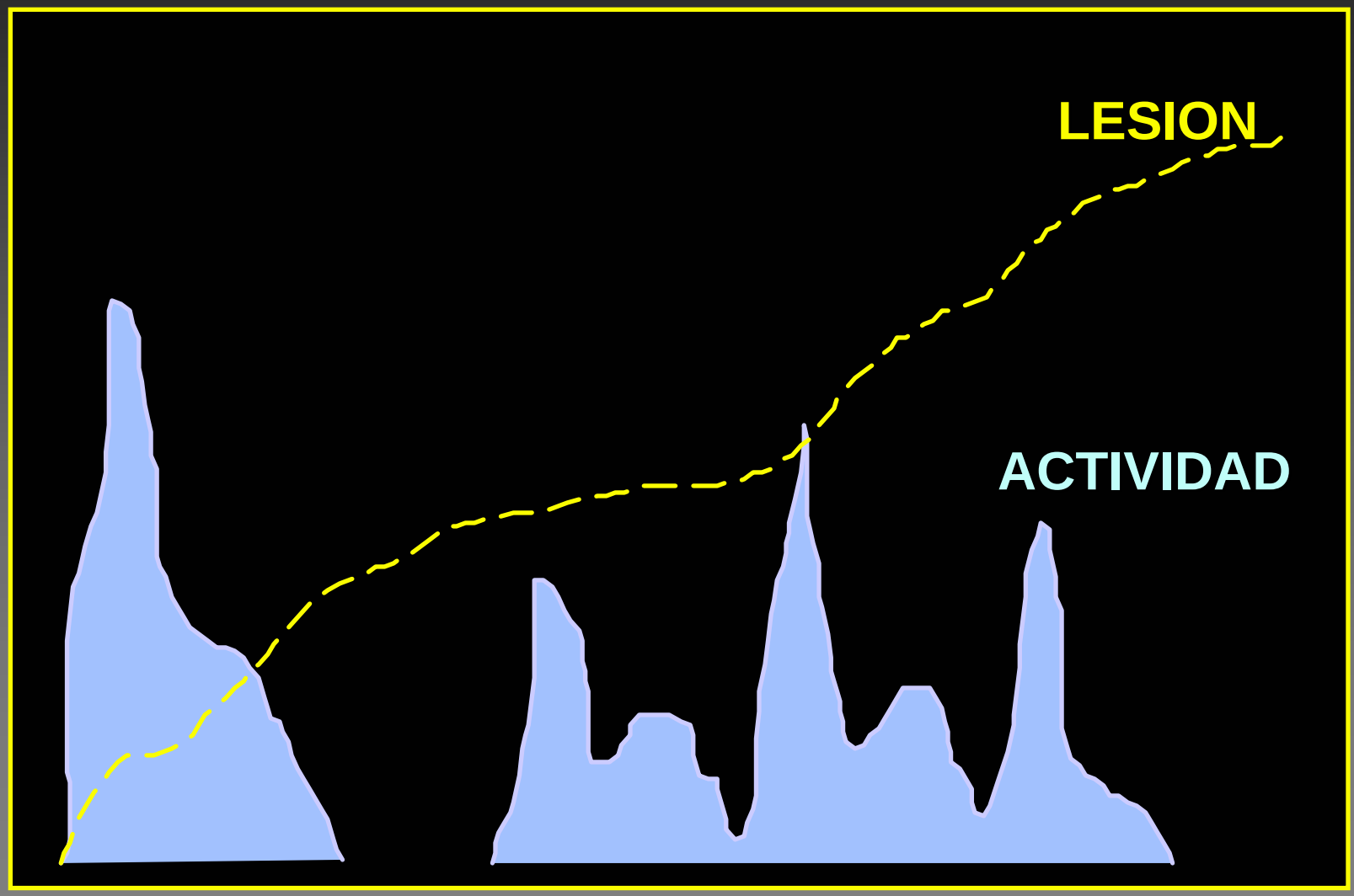
1975 → **Supervivencia en la fase aguda**

1990 ⇒ **Supervivencia a largo plazo con escasos efectos secundarios**

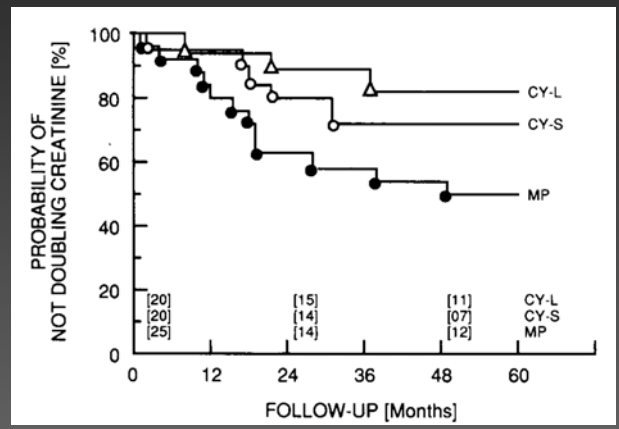
NEFROPATIA LUPICA
Finalidad Terapéutica

- Remisión renal precoz
- Evitar rebrotes renales
- Evitar evolución a cronicidad
- Minimizar la toxicidad

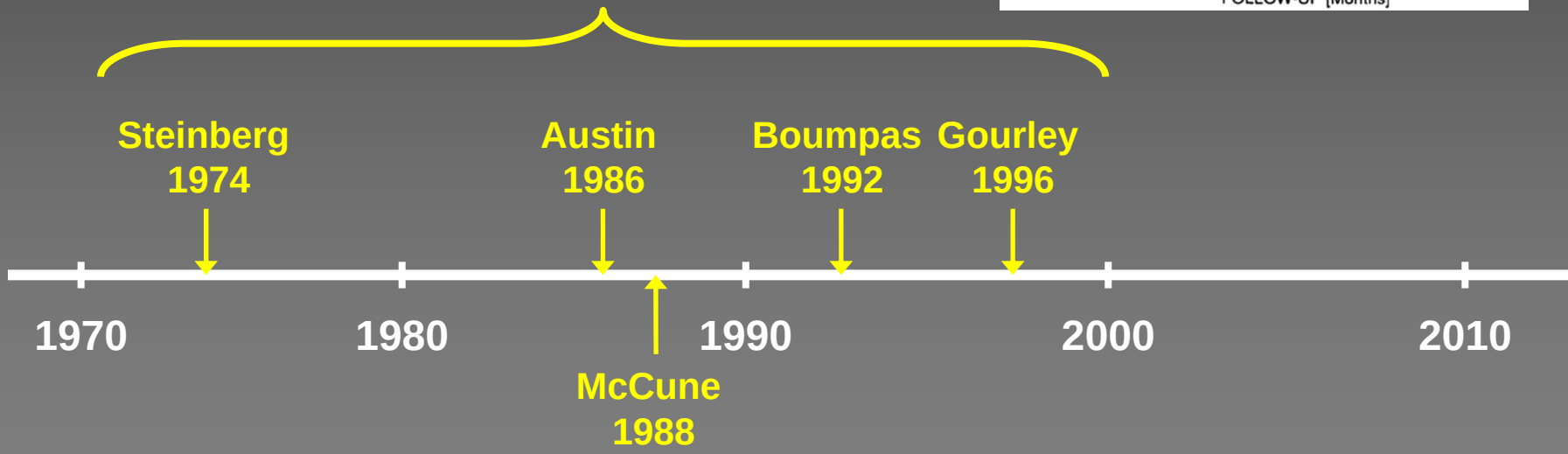
INDICES DE ACTIVIDAD Y LESION



TRATAMIENTO DE LA NEFROPATÍA LÚPICA
EVOLUCIÓN TEMPORAL



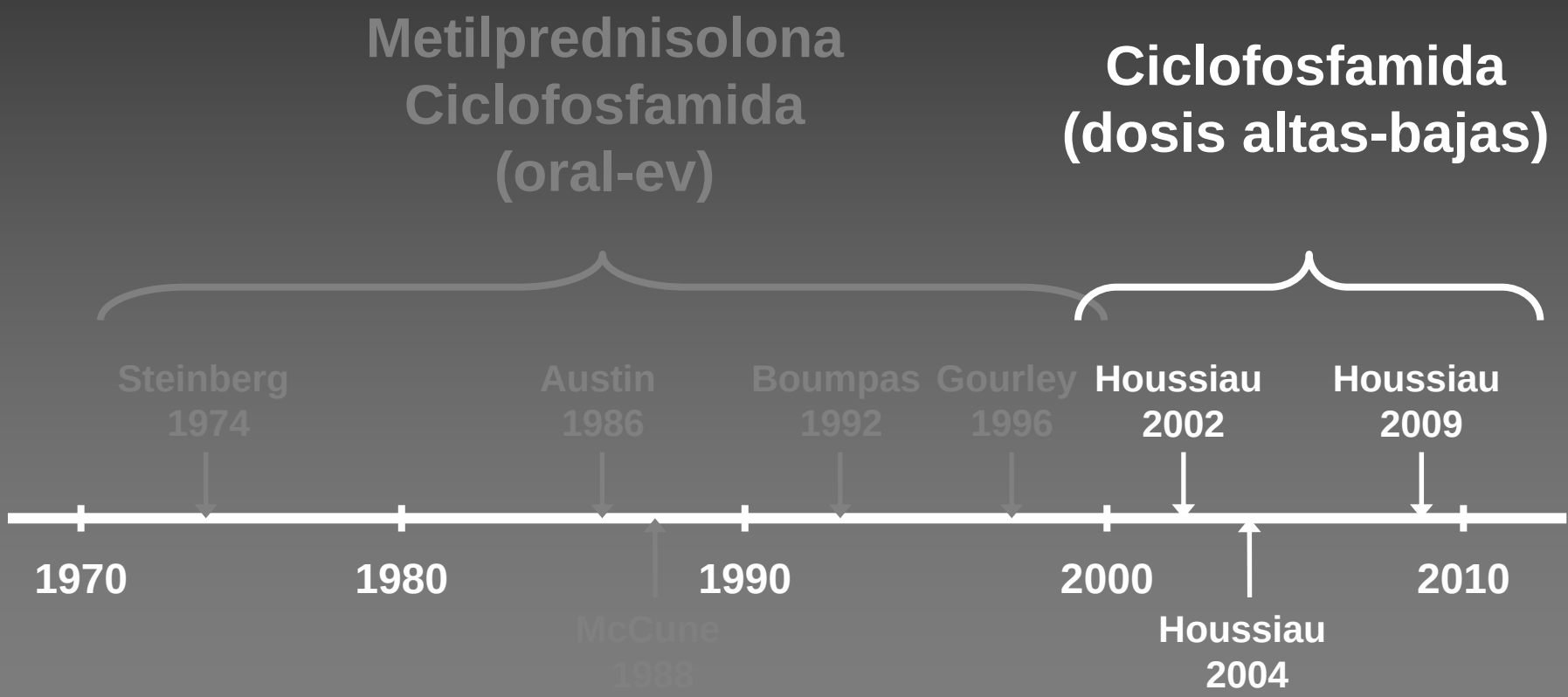
Metilprednisolona
Ciclofosfamida
(oral-ev)



Fallo ovárico: 47%

Infecciones graves: 20%

TRATAMIENTO DE LA NEFROPATÍA LÚPICA
EVOLUCIÓN TEMPORAL

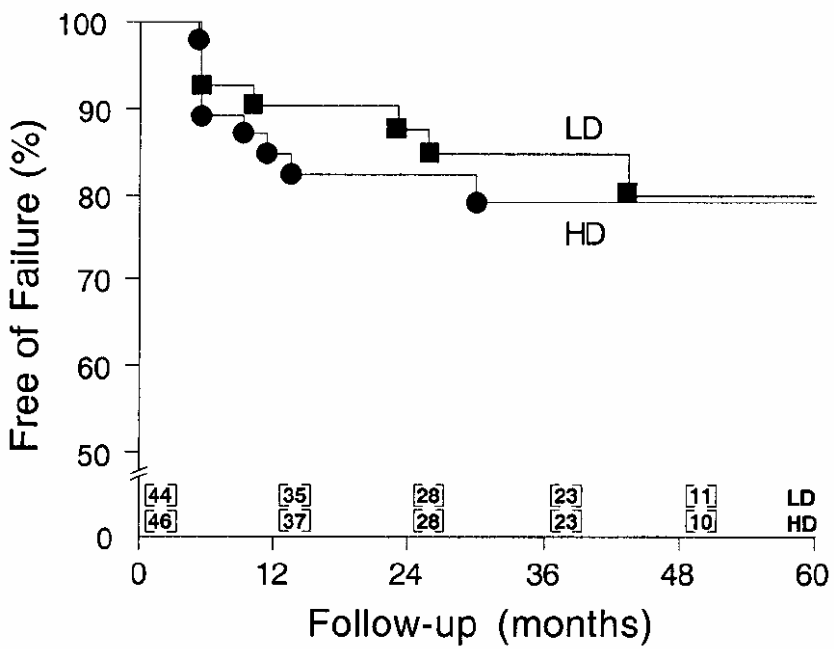


Immunosuppressive Therapy in Lupus Nephritis

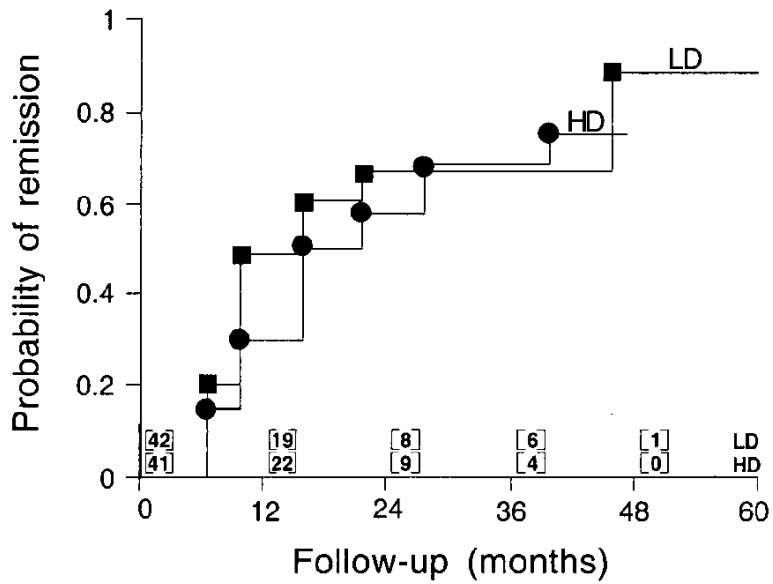
The Euro-Lupus Nephritis Trial, a Randomized Trial of Low-Dose Versus High-Dose Intravenous Cyclophosphamide

Houssiau F, et al. Arthritis Rheum 2002:46:2121-31

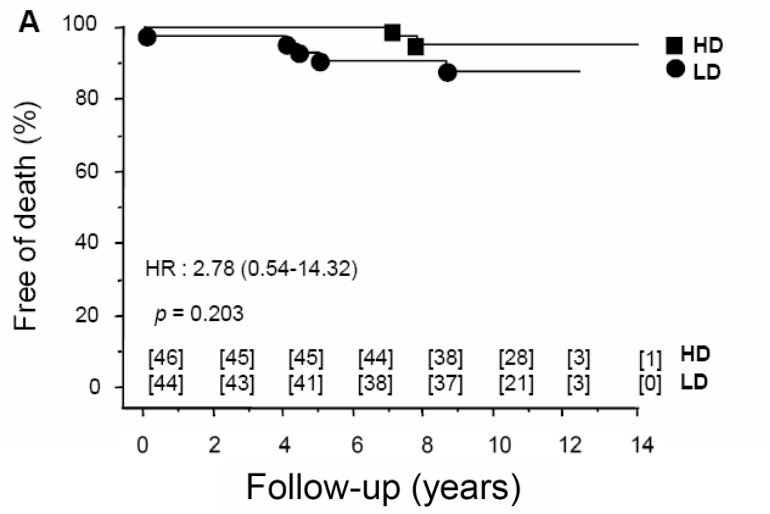
Respuesta al tratamiento

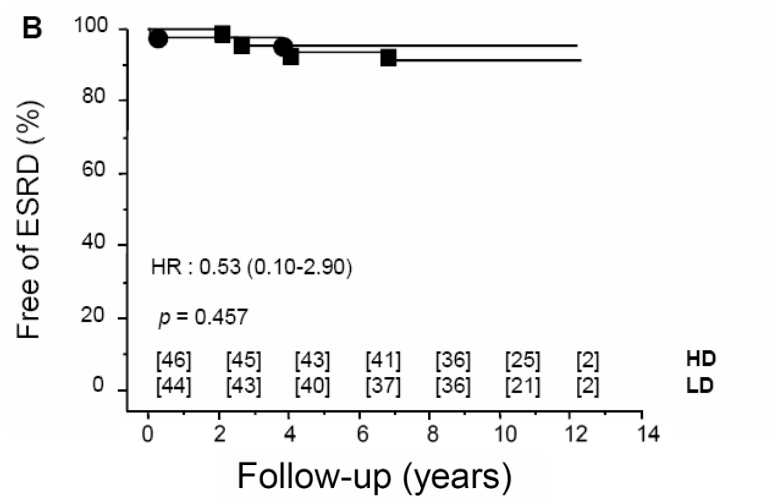


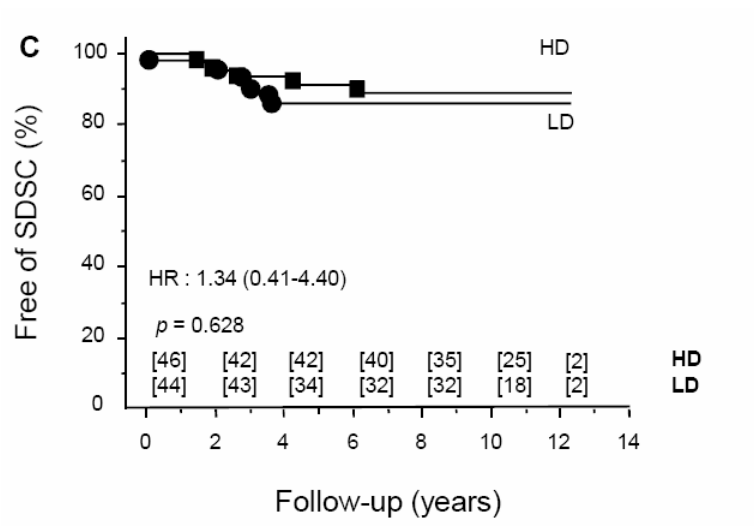
Remisión brote renal



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







Houssiau F, et al. Ann Rheum Dis 2009
doi:10.1136/ard.2008.102533

The Official Journal of the National Kidney Foundation

AJKD American Journal of Kidney Diseases

VOL 43, NO 2, FEBRUARY 2004

THE COCHRANE COLLABORATION®

REVIEWS

Treatment of Diffuse Proliferative Lupus Nephritis: A Meta-Analysis of Randomized Controlled Trials

Robert S. Flanc, MBBS, Matthew A. Roberts, MBBS, Giovanni F.M. Strippoli, MD, MM, Steven J. Chadban, PhD, MBBS, Peter G. Kerr, PhD, MBBS, and Robert C. Atkins, DSc, MBBS

Conclusion: Until future RCTs of newer agents are completed, the current use of cyclophosphamide combined with steroids remains the best option to preserve renal function in patients with DPLN. The smallest effective dose and shortest duration of treatment should be used to minimize gonadal toxicity without compromising efficacy. *Am J Kidney Dis* 43:197-208.

NEFROPATIA LUPICA PROLIFERATIVA

GOLD STANDARD

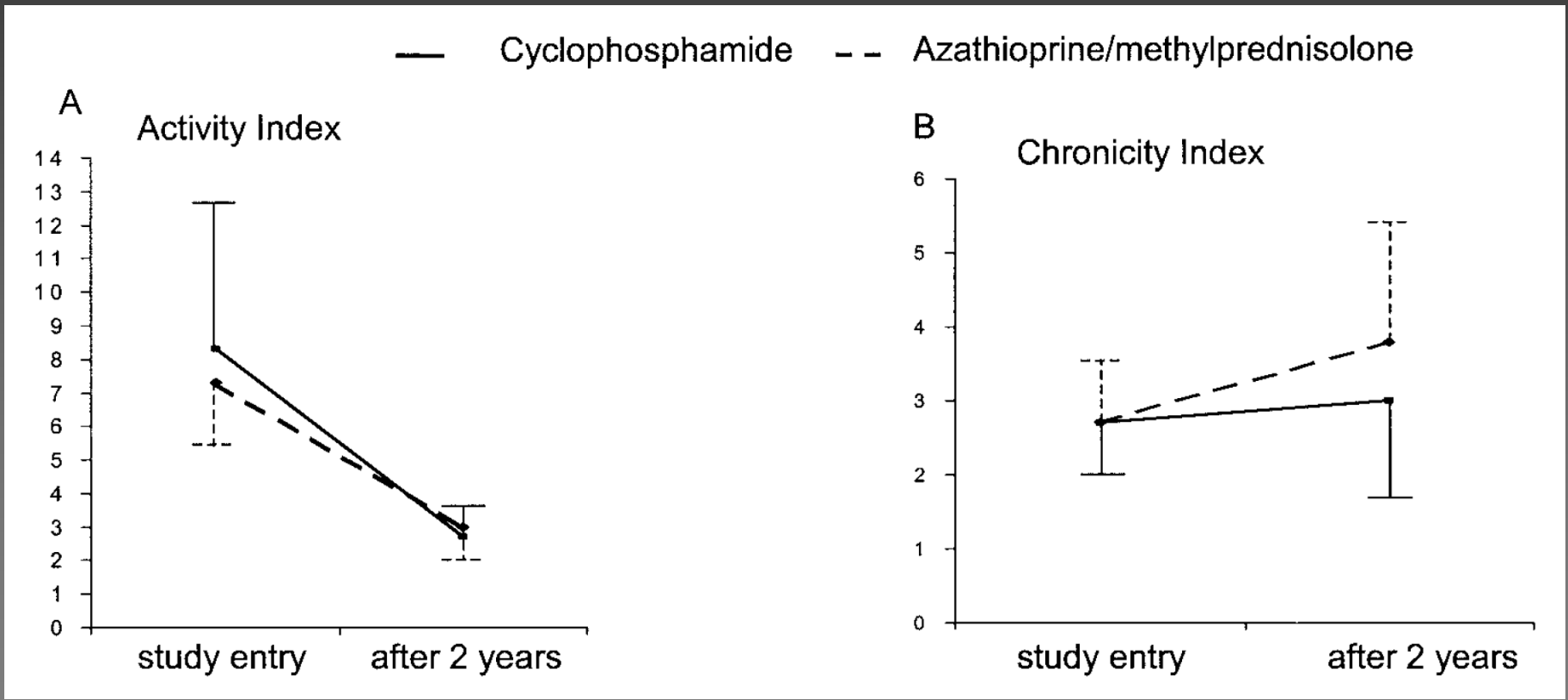
Inducción de la Respuesta

CS + CFM (ev)

Factores pronóstico

- **Brotes nefríticos (Illei GG 2002)**
- **Respuesta precoz a los 6 meses (Houssiau FA 2004)**

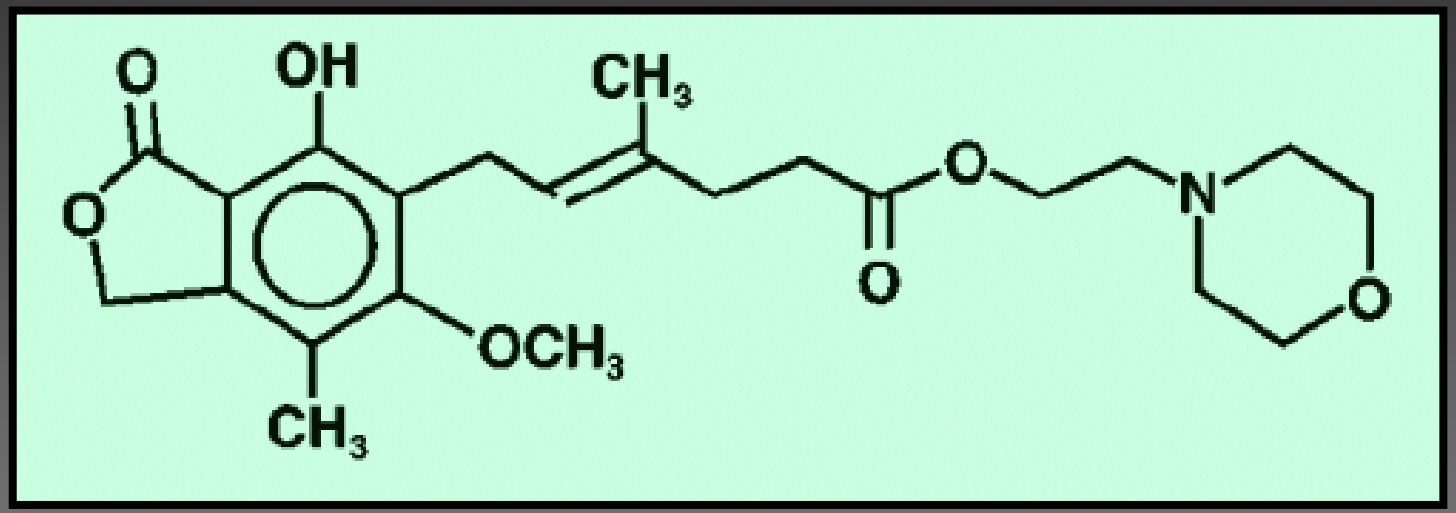
PAPEL DE LA AZATIOPRINA EN LA "INDUCCIÓN DE RESPUESTA"



Grootscholten C, et al. Kidney Int 2006;70:732
Grootscholten C, et al. AR 2007;56:924

NEFROPATIA LUPICA DE RECIENTE DIAGNOSTICO
Finalidad Terapéutica
Luces y Sombras

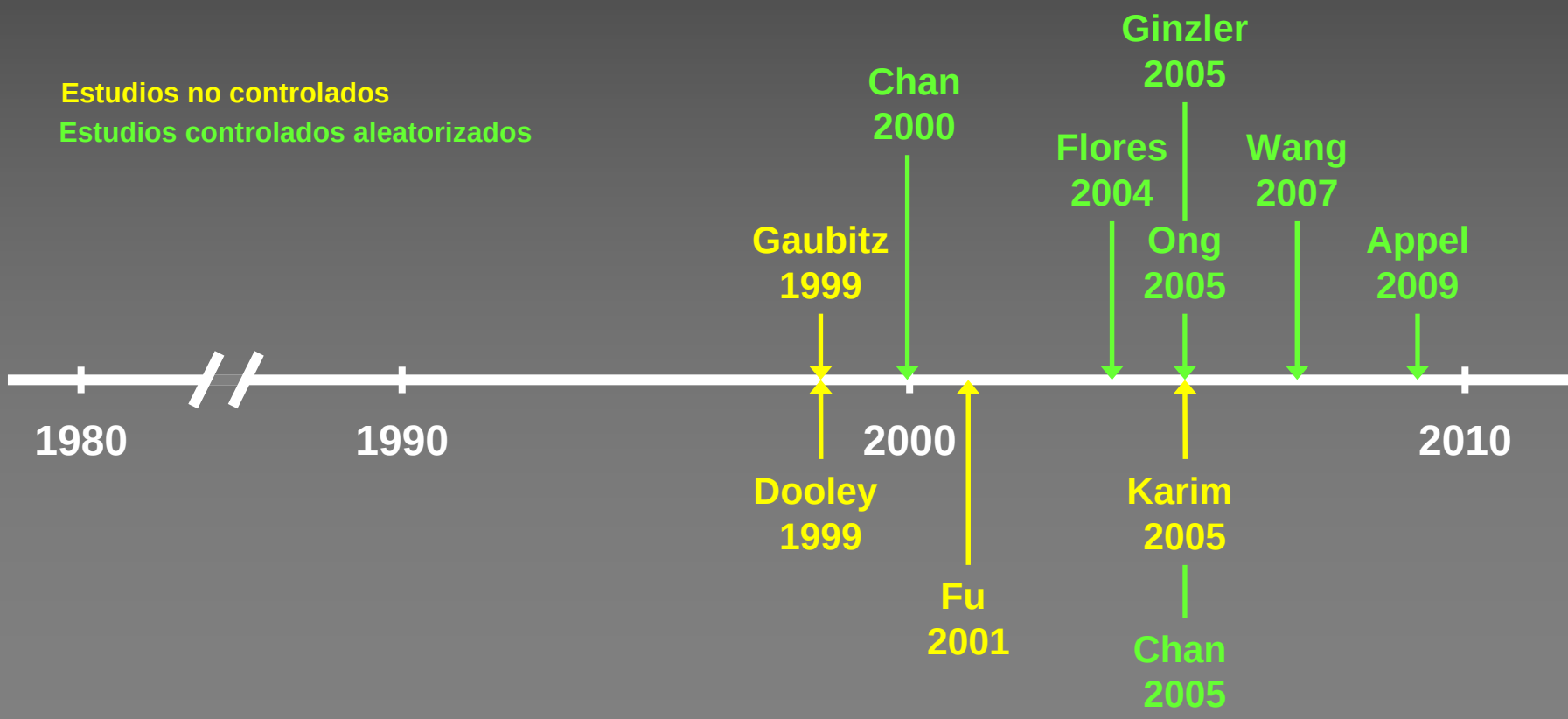
- Remisión renal precoz
  - 80% remisión brote renal
- Evitar rebrotes renales
  - 30% rebrote renal
- Evitar evolución a cronicidad
  - 5-10% IRCT (5-10 años)
- Minimizar la toxicidad

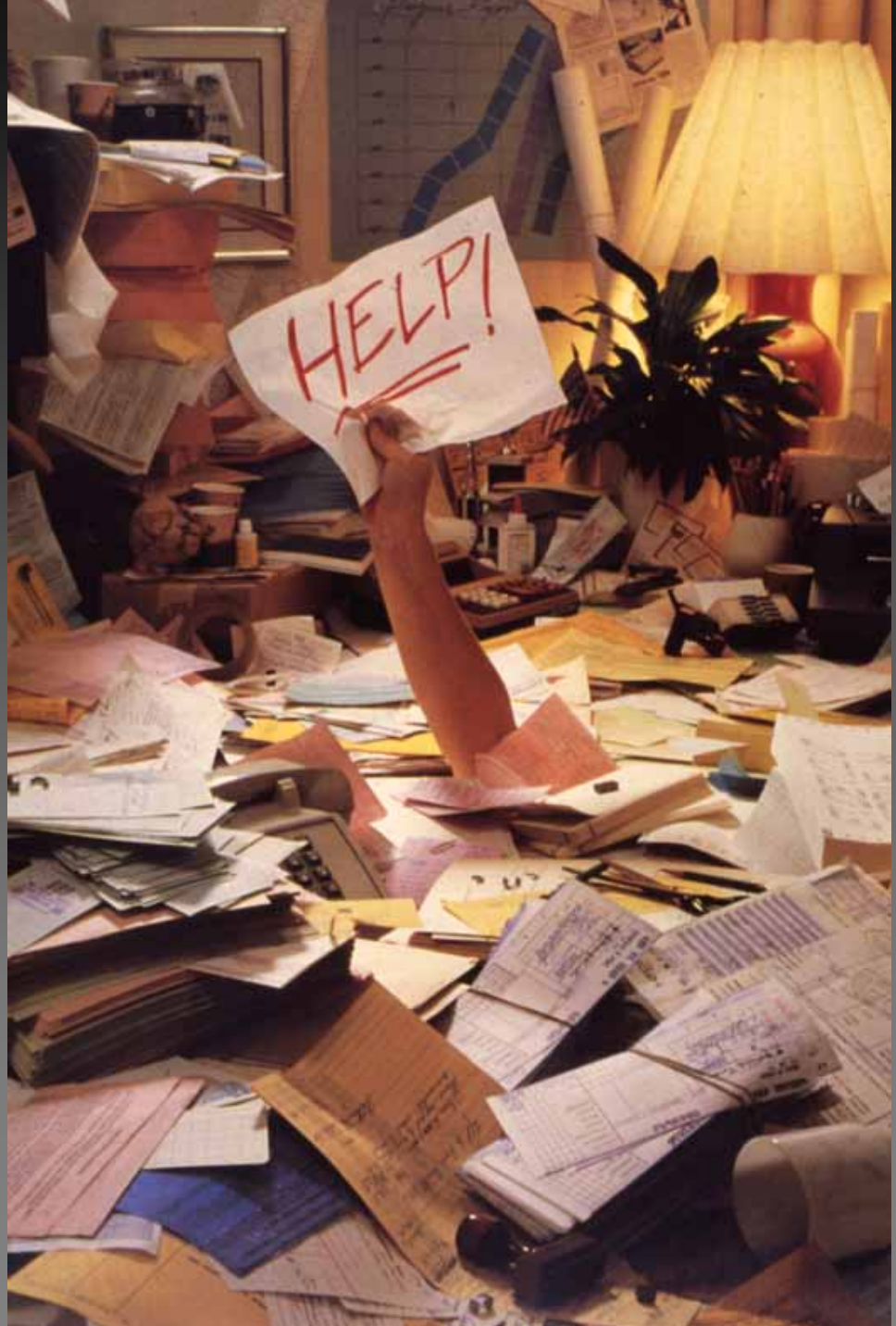


MICOFENOLATO MOFETIL

TRATAMIENTO DE LA NEFROPATÍA LÚPICA
EVOLUCIÓN TEMPORAL

Ciclofosfamida vs
Micofenolato de mofetilo



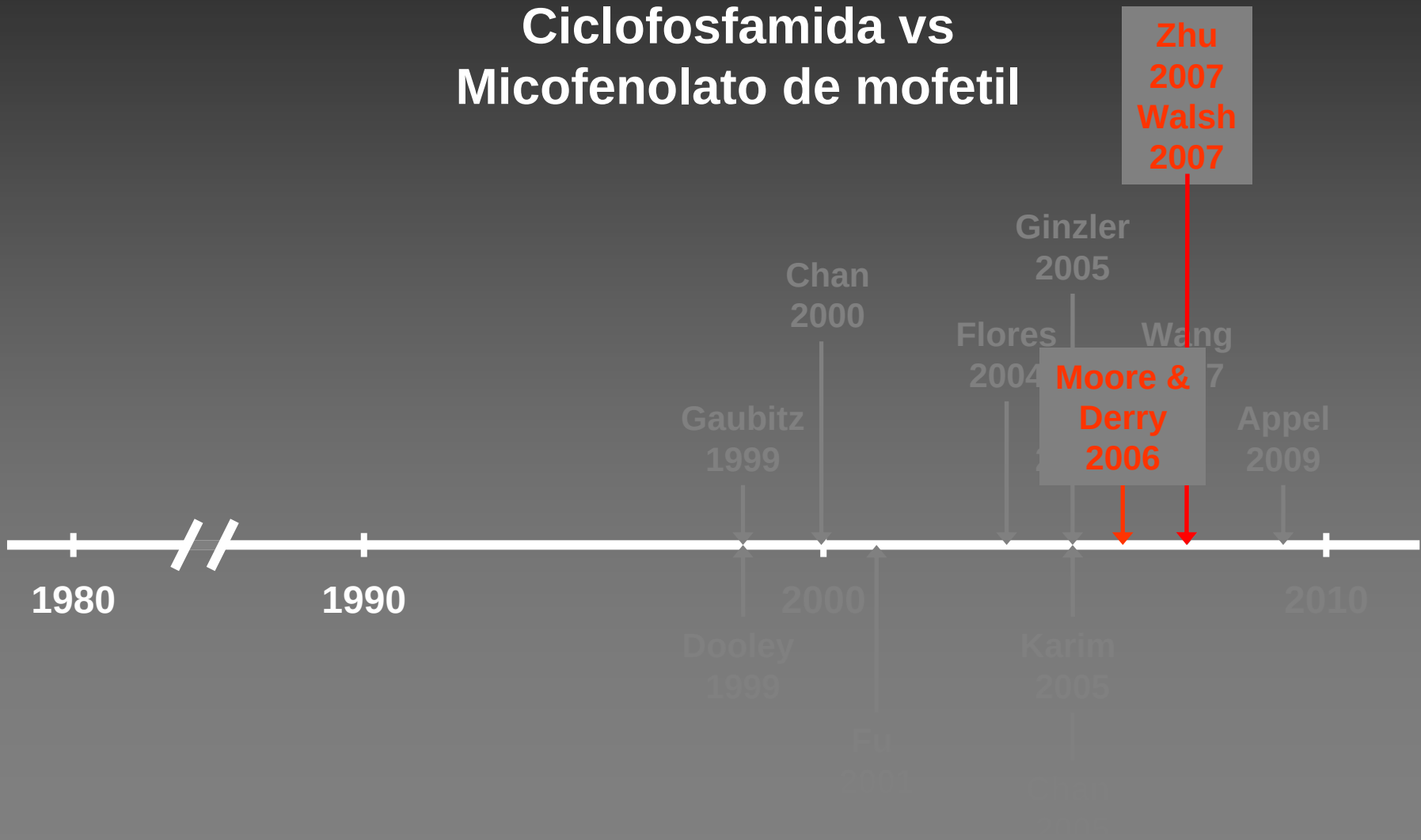

HELP!

Características diferenciales

Study	Number enrolled		Age	Renal pathology type	Renal function	Intervention	Follow-up duration (months)
Ginzler *et al.* [21]	E	71	32.5 ± 10	Class III, IV, V	Ccr > 30 ml/min or Scr < 265 μmol/l	MMF + Pred	36.2 ± 16.9
	C	69	31.0 ± 9.0			IV CYC + Pred	37.2 ± 16.9
Ong *et al.* [22]	E	19	21.8 ± 3.2	Class III, IV, Vb	Scr < 200 μmol/l	MMF + Pred	37.8 ± 7
	C	25	30.5 ± 8.7			IV CYC + Pred	
Chan *et al.* [18]	E	21	36 ± 11	Class IV	Scr < 300 μmol/l	MMF + Pred for 12 mo then AZA	Mean 12
	C	21	39 ± 9			Oral CYC + Pred for 6 mo then AZA	
Chan *et al.* [19]	E	33	38.1 ± 10.2	Class IV	Scr < 400 μmol/l	MMF + Pred for 12 mo then decreased dose of MMF for maintenance	52.2 ± 19.7
	C	31	41.8 ± 8.9			Oral CYC + Pred for 6 mo then AZA for maintenance	63.9 ± 17.6

TRATAMIENTO DE LA NEFROPATÍA LÚPICA
EVOLUCIÓN TEMPORAL

Ciclofosfamida vs Micofenolato de mofetil



Características Metaanálisis

Table 1 Meta-analyses of randomized controlled trials comparing mycophenolate mofetil versus cyclophosphamide as induction therapy in proliferative lupus nephritis.

Study	Number of studies	Number of patients	Outcome measures (MMF vs CY)[a]	Toxicity profile (MMF vs CY)[a]	Comments
Zhu *et al.* (2007)[12]	3	123 (MMF), 125 (CY)	CR 37% vs 24% (RR 1.8; 0.7–4.7) PR 29% vs 27% (RR 1.1; 0.7–1.6) ESRD 6% vs 10% (RR 0.6; 0.2–1.7)	Amenorrhea 0% vs 6% (RR 0.2; 0.0–1.2) Gastrointestinal 39% vs 30% (RR 1.3; 1.0–1.8) Leucopenia 21% vs 39% (RR 0.6; 0.4–1.0) Infections 36% vs 54% (RR 0.7; 0.5–0.8) Herpes zoster 6% vs 8% (RR 0.8; 0.3–2.0)	One of the studies was the long-term follow-up of the original trial with additional randomized patients
Walsh *et al.* (2007)[11]					When ne original l trial were s were not One study in abstract form
Moore and Derry (2006)[10]	5	152 (MMF), 154 (CY)	CR 36% vs 23% (RR 1.5; 1.1–2.1) CR+PR 66% vs 54% (RR 1.2; 1.0–1.4) Relapse 27% vs 34% (RR 0.8; 0.4–1.4) Death 1% vs 8% (RR 0.2; 0.1–0.7)	Amenorrhea 2% vs 12% (RR 0.2; 0.1–0.6) Diarrhea 16% vs 4% (RR 4.0; 1.5–10) Leucopenia 2% vs 25% (RR 0.1; 0.0–0.5) Infections 39% vs 73% (RR 0.5; 0.4–0.7) Serious infections 4% vs 15% (RR 0.3; 0.1–0.6)	As above. One of the included studies was not an induction trial; rather it compared MMF vs CY as maintenance regimens

[a]Data are presented as RR; 95% CI. Abbreviations: CR, complete response; CY, cyclophosphamide; ESRD, end-stage renal disease; MMF, mycophenolate mofetil; PR, partial response; RR, relative risk.

El tratamiento con MMF se asocia a mayor frecuencia de respuestas completas o parciales y a menos complicaciones

Bertsias G, Boumpas DT. Nat Clin Pract Rheumatol 2008;4:464

MMF

CFM

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LIMITACIONES
Metaanálisis

- Diferentes tipos histológicos de NL
- Diferente grado de disfunción renal
- Diferente origen étnico de los pacientes
- Diferentes pautas terapéuticas
- Sesgo de publicación
- No datos de evolución a largo plazo

Aspreva Lupus Management Study (ALMS)

MMF 3gr/d vs CFM ev (24 semanas)

	MMF (%)	CFM (%)	p
Pacientes (n)	185	185	
Respuesta	56	54	NS
Remisión completa	8,6	8,1	NS
Efectos adversos graves	28	23	NS
Infecciones	69	62	NS

Dooley MA, et al. Lupus 2008;17:455
Appel et al. J Am Soc Nephrol 2009;20:1103

Aspreva Lupus Management Study (ALMS)

MMF 3gr/d vs CFM ev (24 semanas)

	MMF (%)	CFM (%)	p
Todas	56	53	0,575
Caucásica	56	54,2	0,834
Asiática	53,2	63,9	0,236
Otras (negra/mestizas)	60,4	38,5	0,033
Hispanic	60,9	38,8	0,011

Dooley MA, et al. Lupus 2008;17:455
Appel et al. J Am Soc Nephrol 2009;20:1103

…y qué hay de la relación coste/efectividad?

Modelo Teórico

MMF is likely to result in better QoL and be less expensive than IVC

Wilson ECF et al. Rheumatology 2007;46:1096-101.

Modelo Práctico

While the cost of MMF is much higher compared with CTX-AZA, the increased drug cost is partially offset by savings from the reduced incident of complications.

Tse k, et al. J Rheumatol 2009;36:76-81.

NL (III / IV) 2009

Manejo en unidades especializadas
Diagnóstico precoz, Biopsia renal

Inducción de la respuesta

GOLD STANDARD

CS + **CFM ev 3-6 meses**
MMF

“Tratamiento Individualizado”

Datos de la biopsia renal
Elevado índice de actividad
Datos clínicos (IR, proteinuria >3g/d)
Deseo gestacional
Etnia


CFM
MMF

	CFM	MMF
•No Caucásica/No Asiática *(ALMS)*		X
•Deseo gestacional		X
•Dudas del cumplimiento terapéutico	X	
•Disponibilidad del tratamiento	X	

Houssiau FA, Ginzler EM. Lupus 2008:17:426-30

Medidas no inmunodepresoras

	Objetivo	Tratamiento
TENSIÓN ARTERIAL PROTEINURIA	*TA ≤130/80 mmHg* *Proteinuria <0,5-1 g/d*	IECA y/o ARA II por sus efectos antihipertensivos y antiproteinúricos. Se puede asociar diuréticos de asa, antagonistas del calcio o betabloqueantes. *Si no respuesta:* asociar pentoxifilina
HÁBITO TABÁQUICO	Supresión	En algunos casos, valoración por unidades especializadas
RIESGO VASCULAR	Minimizar	AAS (síndrome nefrótico, ECV) ACO (AAF, síndrome nefrótico)
DISLIPEMIA	*LDL ≤80-100 mg/dl*	ESTATINAS (a las dosis habituales)
OSTEOPOROSIS	Evitar	Aporte de calcio y vitamina D
HIDROXICLOROQUINA (mantener)		
EDUCACIÓN SANITARIA (asegurar cumplimiento)		
CONTROL PERIÓDICO (3 meses)		

…..y si todo esto falla?

- Micofenolato si inducción con CFM o viceversa
- Rituximab
- Ciclosporina
- Tacrolimus
- Micofenolato + Tacrolimus
- Leflunomida


AG