SEMI

LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

XXXII Congreso Nacional de la SEMI

26-28 Octubre 2011

XIV Congreso de la Sociedad Canaria de Medicina Interna

Costa Meloneras

Palacio de Congresos Expomeloneras
Maspalomas. San Bartolomé de Tirajana
Gran Canaria. Las Palmas

¿Qué dicen los ensayos clínicos en enfermedades autoinmunes en 2011?

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El ponente declara que no presenta ningún conflicto de interés

Métodos

- arámetros de búsqueda (I)

-Pubmed

Randomized clinical trials

Humanos

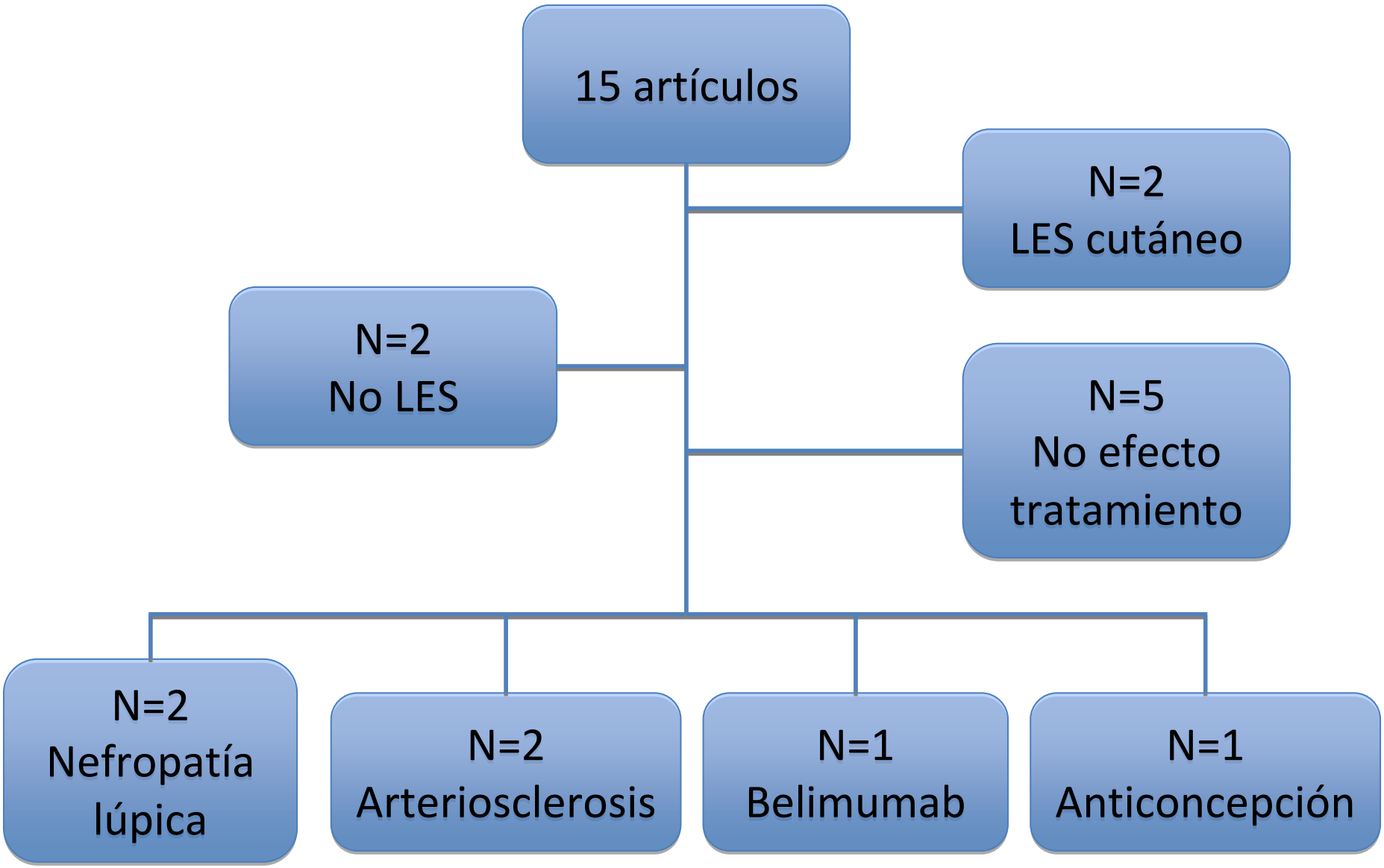
Inglés

01-01-2011 a 15-10-2011

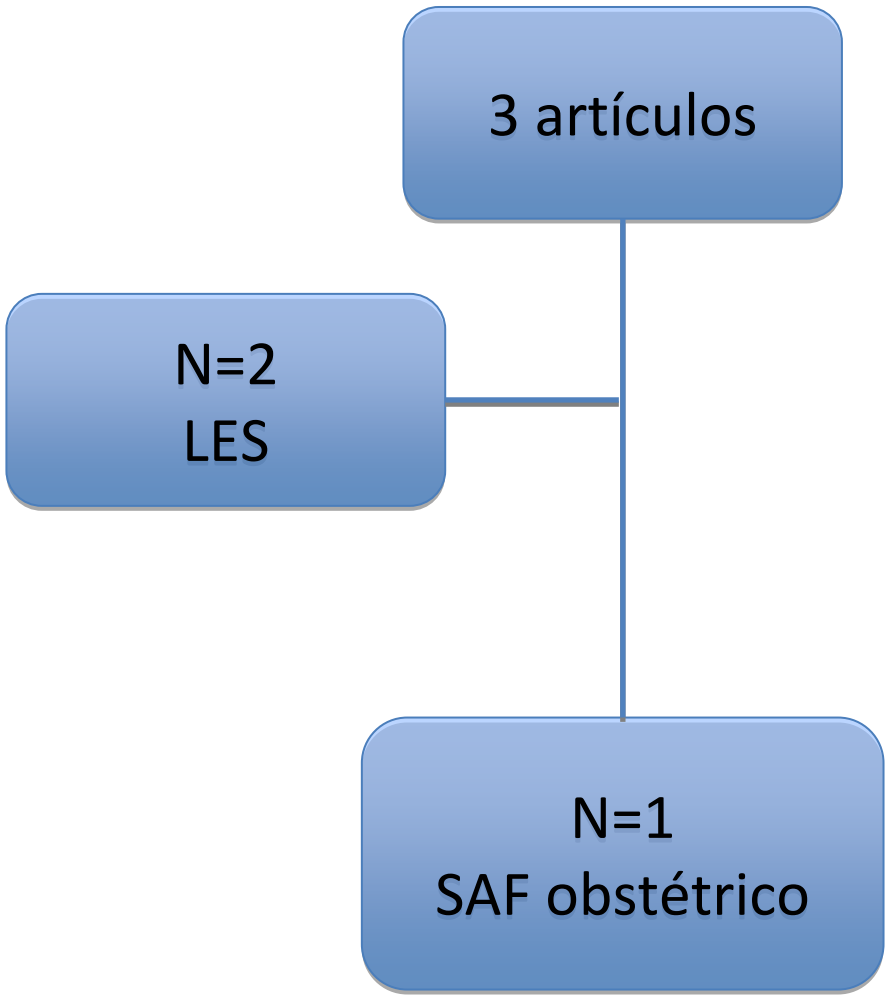
-Palabras clave

Lupus, antiphospholipid, Sjögren syndrome, systemic sclerosis, scleroderma, vasculitis, polymyositis, dermatomyositis

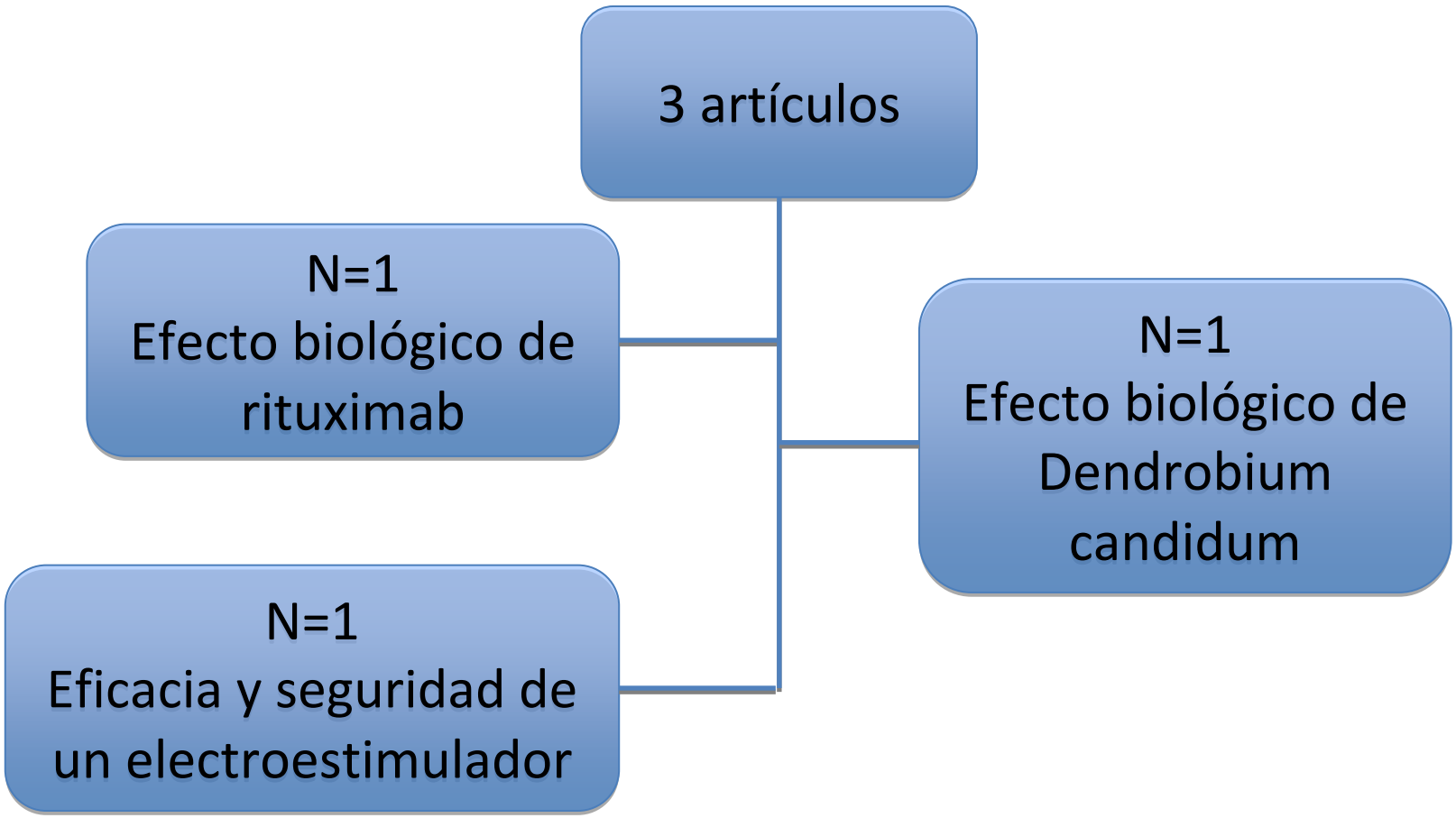
Lupus eritematoso sistémico



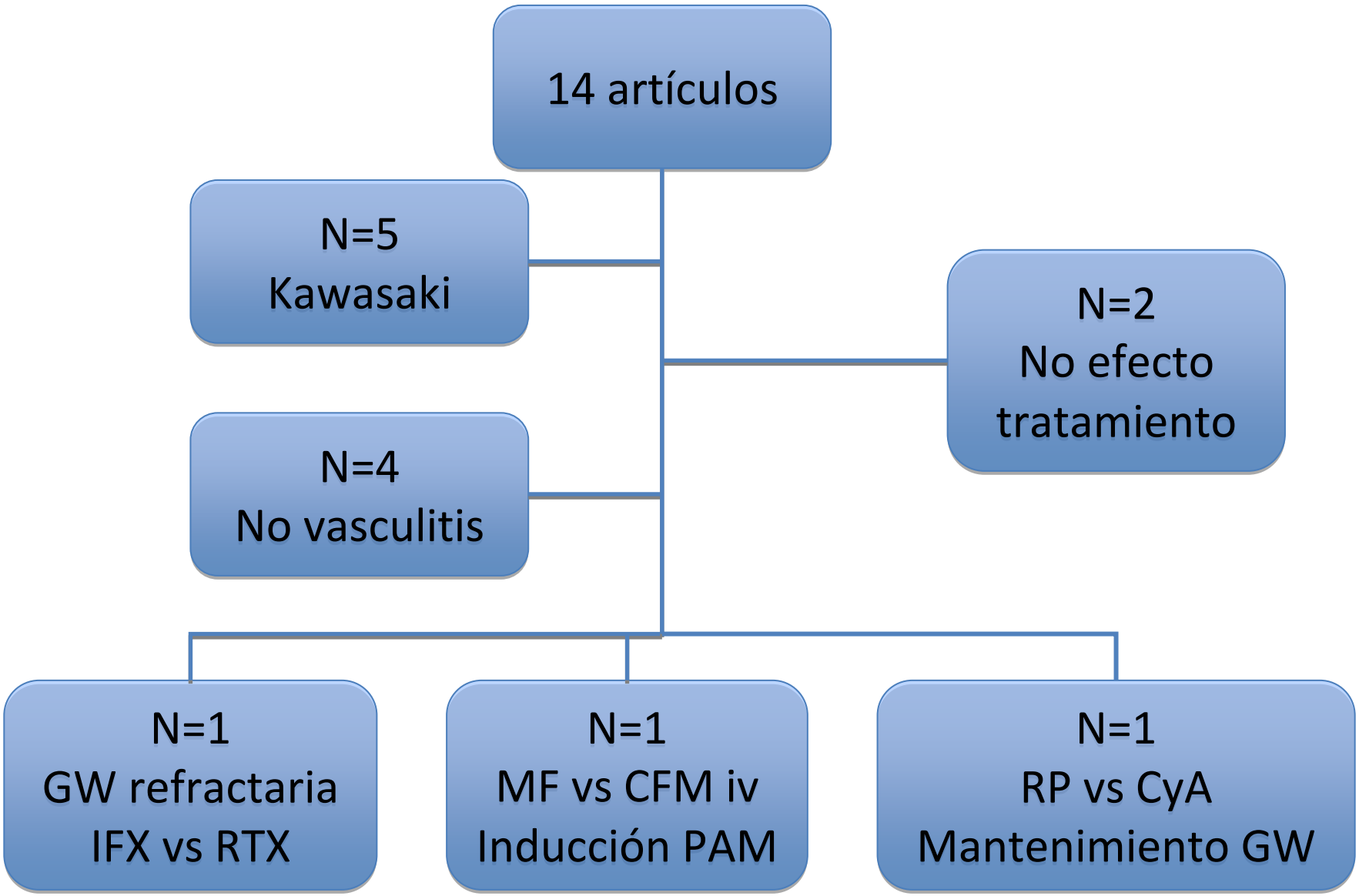
Síndrome antifosfolipídico



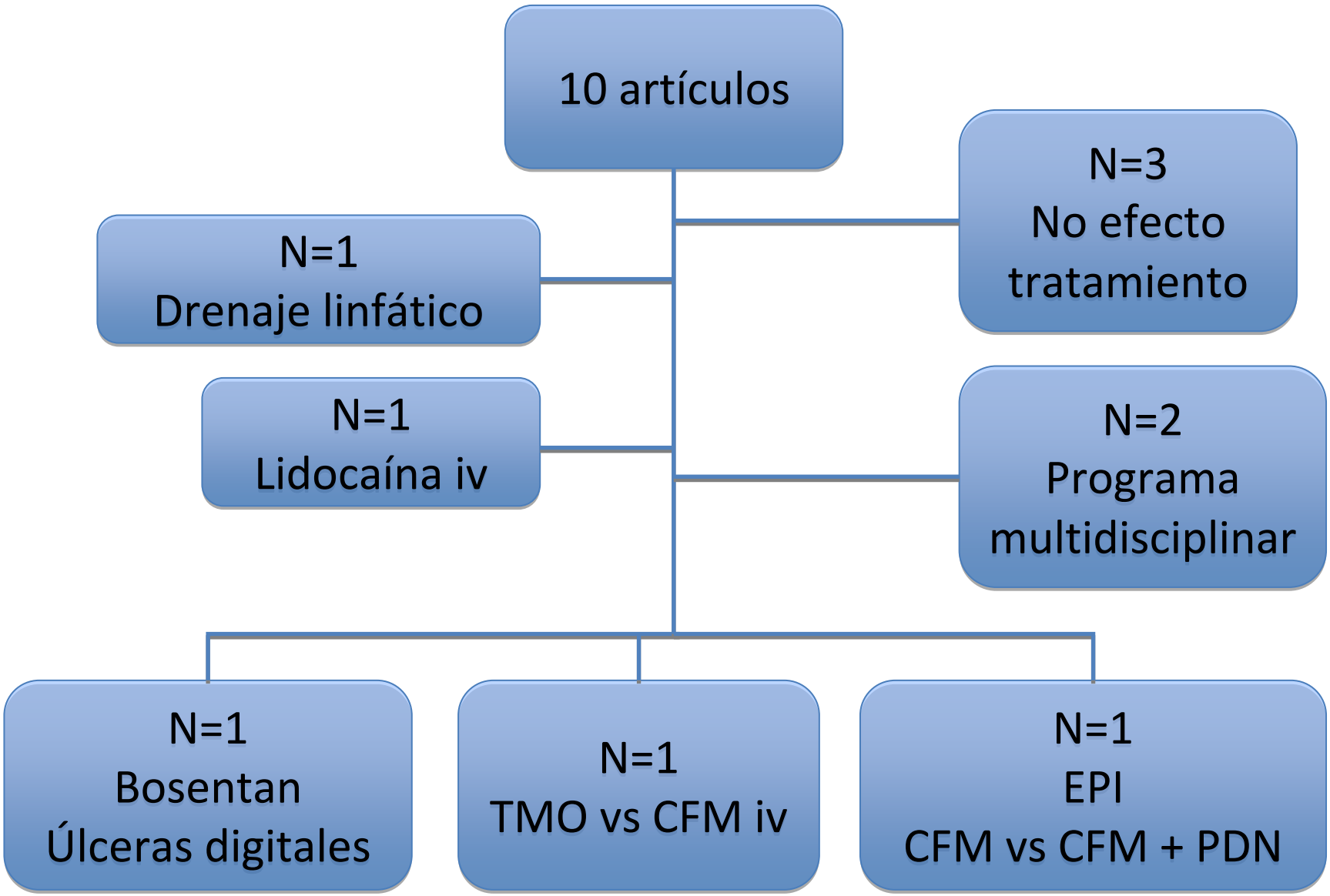
Síndrome de Sjögren



Vasculitis sistémicas



Esclerosis sistémica



Métodos

- arámetros de búsqueda (II)
  - -Rastreo de *abstracts* de últimos congresos
  - -**Criterio del ponente**

Lupus eritematoso sistémico
Nefropatía lúpica

- Mitwalli AH et al. Comparison of high and low dose of cyclophosphamide in lupus nephritis patients: a long-term randomized controlled trial. Saudi J Kidney Transpl 2011;22:935.
- Chen W, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. Am J Kidney Dis 2011;57:235 (NCT 00615173)
- Houssiau FA, et al. Azathioprine versus mycophenolate mofetil for long-term immunosupression in lupus nephritis: results from the MAINTAIN nephritis trial. Ann Rheum Dis 2010;69:2083 (NCT 00204022)
- Dooley MA, et al. Aspreva Lupus Management Study (ALMS): Maintenance results by racial subgroup. Ann Rheum Dis 2011;70(Suppl 3):125 (NCT00377637)

Lupus eritematoso sistémico
Nefropatía lúpica

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LES: Nefropatía lúpica

- Chen W, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. Am J Kidney Dis 2011;57:235.

- Ensayo clínico multicéntrico aleatorizado controlado de no inferioridad.

- Pacientes con nefropatía lúpica clases III, IV, V (ISN/RPS 2003)

- Pacientes excluidos (creatinina >4 mg/dl……..)

Tacrolimus (0,05 mg/kg/d) (N=42)
versus
Ciclofosfamida iv (750 mg/m^2/mes) (N=39)
+
Prednisona 1 mg/kg/d (máx 60 mg/d) en pauta descendente

- **Variable primaria:** Remisión completa a los 6 meses (proteinuria <0,3g/24h, sedimento normal, albúmina sérica ≥ 3,5 g/dl, función renal estable: creatinina normal o no >15% más del valor basal)

- **Variable secundaria:** Respuesta (completa o remisión parcial), cambios en parámetros clínicos, efectos adversos.

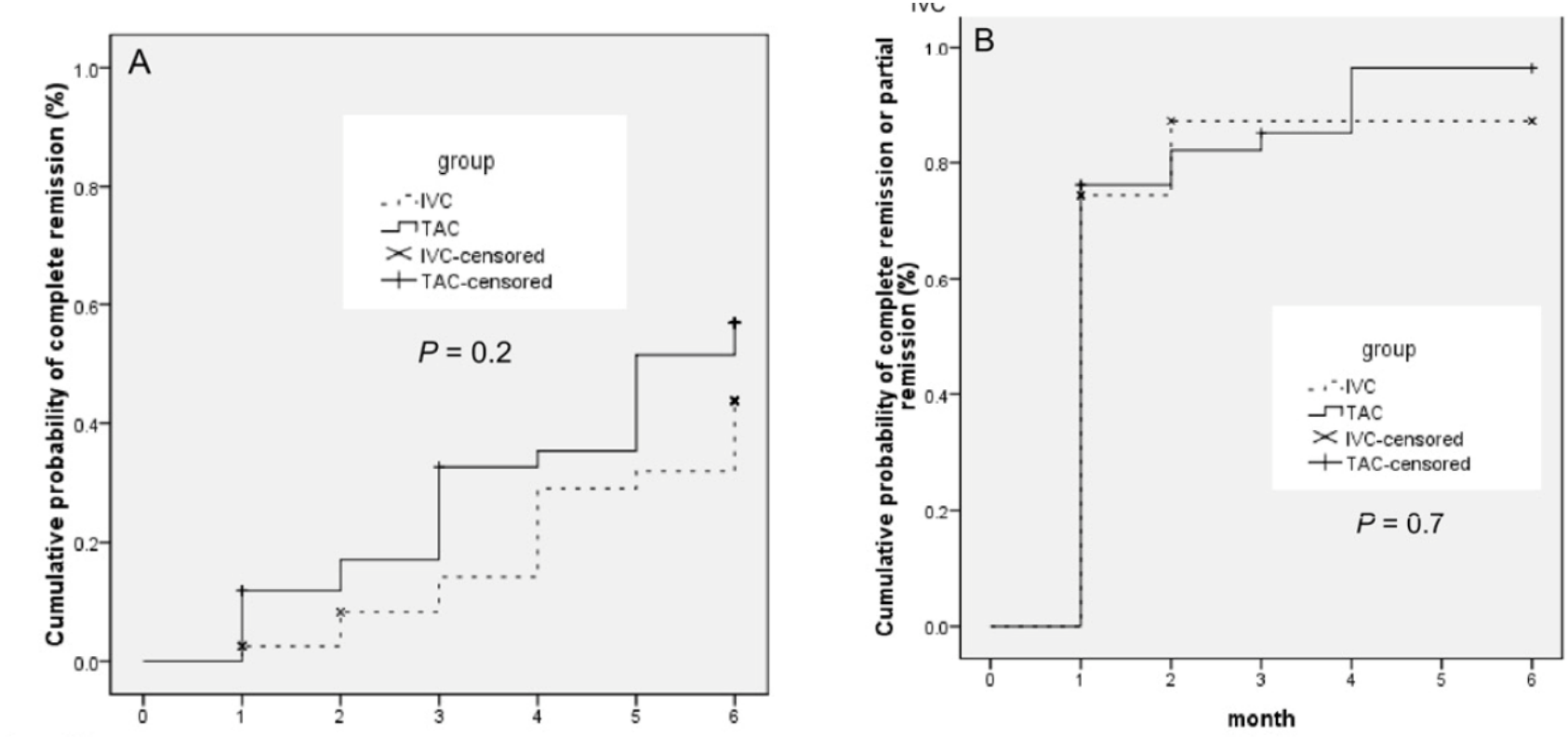
LES: Nefropatía lúpica

- Características basales

	TAC (n=42)	CFM (n=39)	
Proteinuria (g/24h)[a]	0.47 ± 0.35	0.34 ± 0.33	0.1
Proteinuria category			
<2.0 g/24 h	12 (28.6)	16 (41.0)	
2.0-2.99 g/24 h	11 (26.2)	7 (17.9)	
≥3.0 g/24 h	19 (45.2)	16 (41.0)	0.5
Serum albumin (g/dL)[a,b]	0.40 ± 0.13	0.41 ± 0.09	0.7
Serum creatinine (mg/dL)[a,c]	−0.05 ± 0.15	−0.08 ± 0.14	0.5
Serum creatinine category			0.7
<1.0 mg/dL	28 (66.7)	28 (71.8)	
1.0-1.3 mg/dL	8 (19.0)	8 (20.5)	
>1.3 mg/dL	6 (14.3)	3 (7.7)	
MDRD Study eGFR (mL/min)[a]	1.84 ± 0.20	1.85 ± 0.17	0.7
Duration of lupus nephritis (y)	3.8 ± 3.3	3.3 ± 3.1	0.5
Pathologic type			0.9
Class III	2 (4.8)	1 (2.6)	
Class IV	29 (69.0)	29 (74.4)	
Class V	5 (11.9)	4 (10.3)	
Class V+IV or V+III	6 (14.2)	5 (12.8)	
Pathologic active index	7.2 ± 2.3	6.6 ± 1.5	0.3
Pathologic chronic index	1.0 ± 1.6	1.2 ± 1.9	0.5

LES: Nefropatía lúpica

- Resultados



Remisión completa (RC) 6 meses: 22/42 (52,3%) TAC vs. 15/39 (38,4%) CFM

Tiempo hasta RC: 84 días TAC vs. 112 CFM

LES: Nefropatía lúpica

- Resultados

Remisión completa (RC) 6 meses según tipo histológico

Clases III-IV : (n=61)	TAC 58,1%	CFM 50,0%	p=0,5
Clase V (V, V+IV, V+III): (n=20)	TAC 36,3%	CFM 0%	p=0,09

LES: Nefropatía lúpica

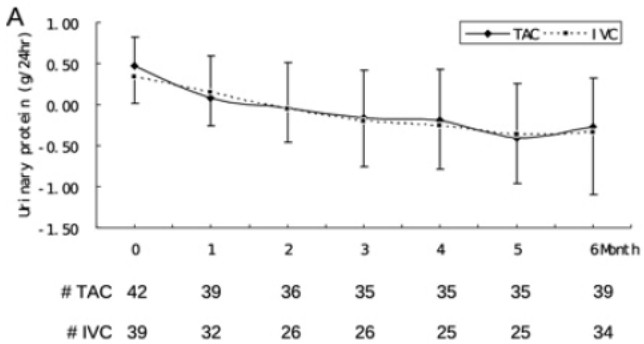
Proteinuria

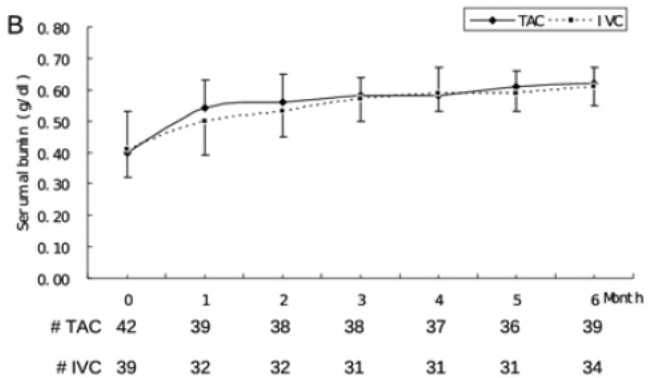
Albúmina

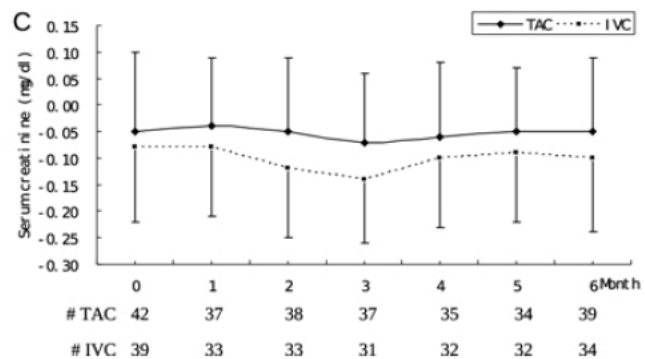
Creatinina

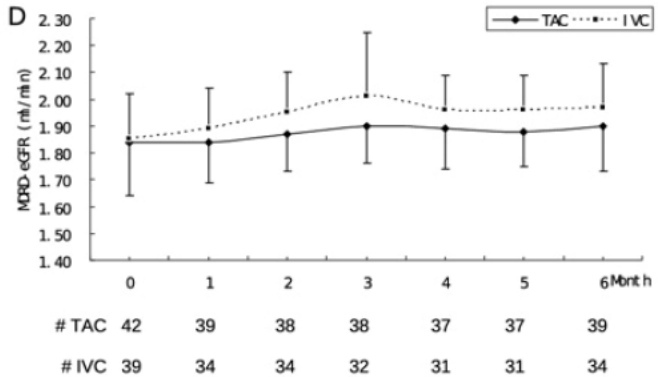
eGFR

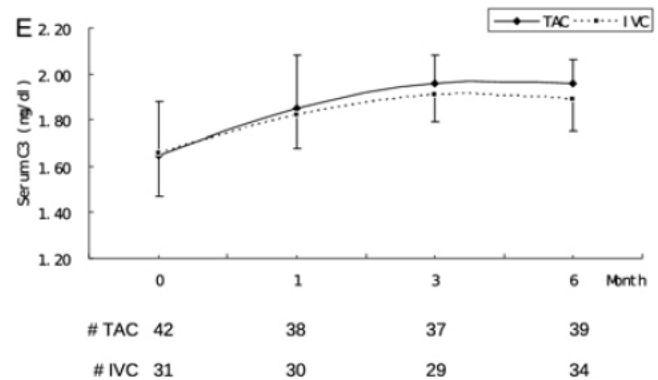
C3











LES: Nefropatía lúpica

Adverse Effects	TAC Group (n = 39)	IVC Group (n = 34)	*P*
Infection			
No. of patients	5	4	0.9
No. of episodes	12	7	0.3
Types of infection			
Upper respiratory tract	3	2	0.9
Pulmonary	1	1	0.9
Urinary tract	3	2	0.9
Herpes zoster	5	2	0.4
Other			
Leukopenia[a]	0	5	0.02
Gastrointestinal symptoms	4	10	0.04
Hair loss	0	3	0.1
Liver function disorder[b]	3	4	0.7
Amenorrhea	0	2	0.2
Hyperglycemia[c]	7	6	0.9
Transient increase in SCr[d]	3	1	0.6
Death	0	1	0.5

Efectos adversos

LES: Nefropatía lúpica
Tacrolimus *vs.* CFM iv

Conclusión:

•En términos de RC o respuesta, TAC es tan eficaz como CFM iv como tratamiento de inducción en pacientes con NL.

Limitaciones:

•Número de pacientes
•Grupo étnico
•Seguimiento a largo plazo

Lupus eritematoso sistémico
Nefropatía lúpica

- Mitwalli AH et al. Comparison of high and low dose of cyclophosphamide in lupus nephritis patients: a long-term randomized controlled trial. Saudi J Kidney Transpl 2011;22:935.
- Chen W, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: a multicenter randomized clinical trial. Am J Kidney Dis 2011;57:235.
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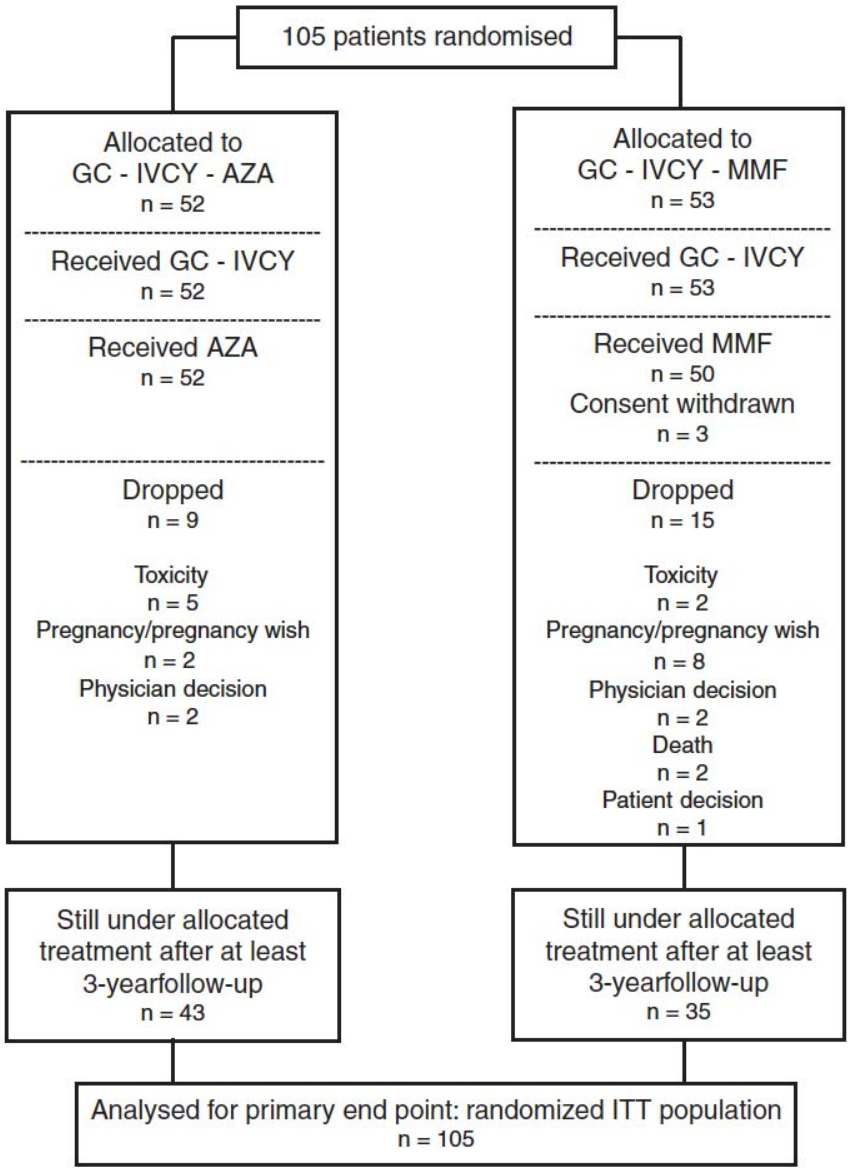
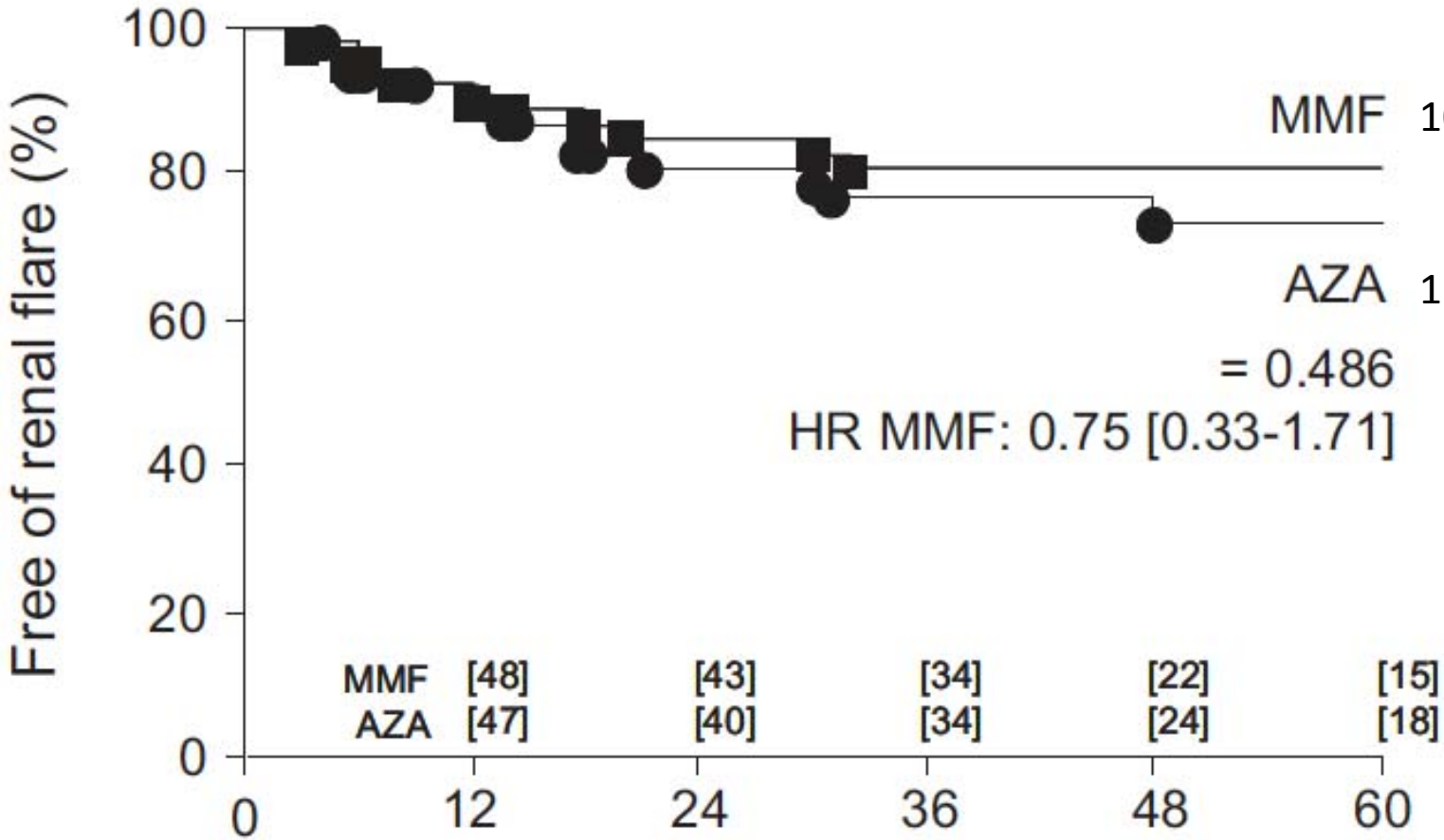
- Dooley MA, et al. Aspreva Lupus Management Study (ALMS): Maintenance results by racial subgroup. Ann Rheum Dis 2011;70(Suppl 3):125.

AZA vs MMF como mantenimiento de NL

LES: MAINTAIN



LES: MAINTAIN



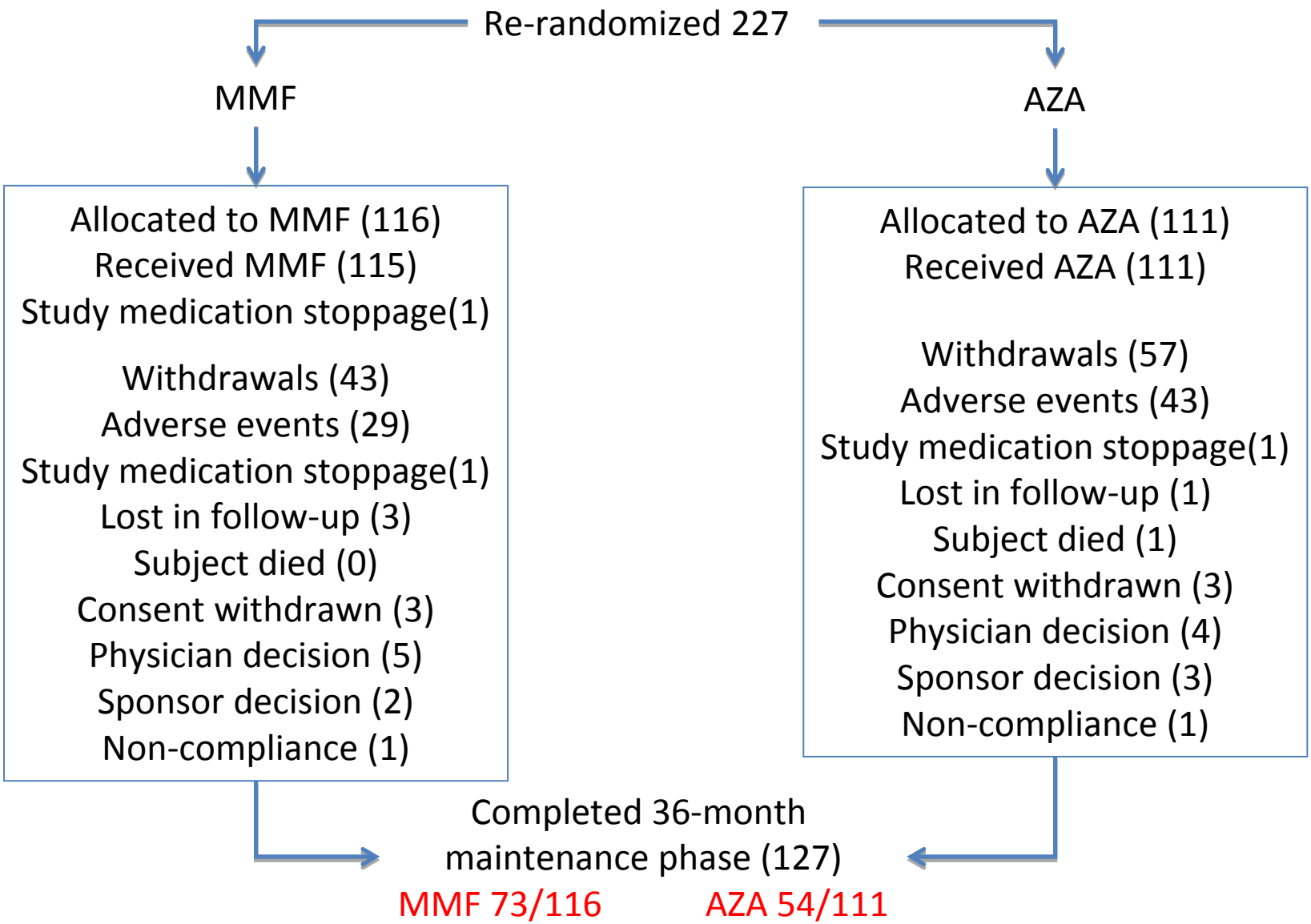
MMF 10/53 (19%)

AZA 13/52 (25%)

Tiempo hasta brote renal

LES: ALMS

(Lupus 2010;19(Suppl):27(CS12.6); Ann Rheum Dis 2011;70(Suppl3):125)



LES: ALMS

(Lupus 2010;19(Suppl):27(CS12.6); Ann Rheum Dis 2011;70(Suppl3):125)

Results: MMF was superior to AZA in time to treatment failure (p=0.003; log-rank test), time to renal flare (p=0.027) and time to rescue therapy (p=0.017; log-rank test).

Patients in each race category who received MMF maintenance therapy had a lower rate and a longer time to treatment failure than patients treated with AZA.

Summary of time to treatment failure and failure rate by race

Race (n)	Failure rate		Hazard ratios	95% CI for HR
	MMF, n/N (%)	AZA, n/N (%)	(MMF/AZA)	
White (99)	9/48 (19)	18/51 (35)	0.512	0.230, 1.139
Black (23)	2/12 (17)	6/11 (55)	0.229	0.046, 1.140
Asian (76)	6/39 (15)	9/37 (24)	0.509	0.181, 1.431
Other (29)	2/17 (12)	3/12 (25)	0.460	0.077, 2.753

The incidence of AEs was similar between MMF and AZA groups. Fewer patients treated with MMF (27/115 [23.5%] than AZA 37/111 [33.3%]) reported at least 1 serious AE.

One death (AZA group, unrelated to treatment) occurred during the study.

MMF was superior to AZA in maintaining renal response and preventing relapse in

NL: MMF vs. AZA en mantenimiento

Conclusión:

- MMF es más eficaz que AZA en mantener la remisión de la NL

Limitaciones:

- Resumen del estudio
- Mayor número de estudios

Lupus eritematoso sistémico

N=2
Aterosclerosis y estatinas

Petri MA, et al. Lupus Atherosclerosis Prevention Study (LAPS). Ann Rheum Dis 2011:70:760 (NCT 00120887)

Mok CC, et al. Effects of rosuvastatin on vascular biomarkers and carotid atherosclerosis in lupus: a randomized, double-blind, placebo-controlled trial. Arthritis Care Res 2011;63:875 (NCT 00371501)

LES: Estatinas

- Petri MA, et al. Lupus Atherosclerosis Prevention Study (LAPS). Ann Rheum Dis 2011:70:760 (NCT 00120887)

- Ensayo clínico aleatorizado, doble ciego, controlado con placebo.

- Pacientes con LES

- Pacientes excluidos: fenómenos ateroscleróticos previos……..

Atorvastatina (40 mg/d) (N=96) versus placebo (N=91)
24 meses

- Variable primaria
Aterosclerosis: Reducción en la progresión de la aterosclerosis subclínica (calcificación arteria coronaria)
Actividad LES: Mejoría en SELENA/SLEDAI

- Variable secundaria
Aterosclerosis: Reducción en la progresión de IMT y de la placa carotidea, marcadores de inflamación y activación endotelial

LES: Estatinas

- Resultados: Cambios en variables de aterosclerosis

Measure	Mean at baseline	Mean after 2 years	Mean change	p Value for change	Difference in change, statin minus placebo(95% CI)	p Value for difference between groups*
Log_e (coronary artery calcium score + 1)						
Atorvastatin	1.16	1.24	0.08	0.52	−0.08 (−0.39 to 0.23)	0.62
Placebo	1.19	1.35	0.15	0.16		
Carotid intima media thickness (mm)						
Atorvastatin	0.59	0.66	0.07	<0.0001	−0.02 (−0.05 to 0.01)	0.24
Placebo	0.57	0.66	0.09	<0.0001		

- Tampoco hubo cambios en las variables de actividad de LES ni en los parámetros de inflamación o marcadores de activación endotelial.

LES: Estatinas

- Mok CC, et al. Effects of rosuvastatin on vascular biomarkers and carotid atherosclerosis in lupus: a randomized, double-blind, placebo-controlled trial. Arthritis Care Res 2011;63:875 (NCT 00371501)

- Ensayo clínico aleatorizado, doble ciego, controlado con placebo.

- Pacientes con LES y aterosclerosis subclínica (IMT carótida o calcificación coronaria)

- Pacientes excluidos: fenómenos ateroscleróticos previos……..

Rosuvastatina (10 mg/d) (N=36) versus placebo (N=36)
24 meses

- Variable primaria
Aterosclerosis: Cambios en homocisteína, *hsCRP*, *soluble VCAM1*, P-selectina, thrombomodulina

- Variable secundaria
Aterosclerosis: Reducción en la progresión de IMT, fenómenos trombóticos y efectos adversos

LES: Estatinas

- Resultados: Cambios en marcadores de aterosclerosis

Markers	Baseline, median (IQR)	Month 6, median (IQR)	Month 12, median (IQR)	*P*†
Homocysteine, μmoles/liter				
Rosuvastatin	13.6 (9.4)	12.6 (7.1)	13.4 (6.1)	0.48
Placebo	13.1 (4.6)	13.1 (4.8)	13.2 (3.9)	0.40
P‡	0.57	0.99	0.56	
hsCRP, mg/liter				
Rosuvastatin	1.26 (2.3)	0.94 (3.1)	0.88 (1.1)	0.02
Placebo	1.38 (3.0)	1.20 (4.0)	1.28 (4.3)	0.17
P‡	0.73	0.74	0.046	
Soluble VCAM-1, ng/ml				
Rosuvastatin	630 (590)	661 (650)	677 (510)	0.14
Placebo	724 (590)	694 (510)	701 (710)	0.19
P‡	0.26	0.89	0.56	
P-selectin, ng/ml				
Rosuvastatin	44.4 (23)	43.7 (28)	46.8 (23)	0.37
Placebo	44.8 (20)	47.7 (24)	48.7 (25)	0.07
P‡	0.89	0.76	0.66	
Thrombomodulin, ng/ml				
Rosuvastatin	0.91 (1.7)	0.76 (1.1)	0.84 (1.3)	0.04
Placebo	0.80 (0.6)	0.67 (0.6)	0.69 (0.7)	0.06
P‡	0.34	0.73	0.65	

LES: Estatinas

- Resultados: Cambios en IMT carótida

	Month 0, mean ± SD mm	Month 24, mean ± SD mm	Change, %
Right common carotid artery			
Rosuvastatin	0.54 ± 0.15	0.58 ± 0.11	+7.4
Placebo	0.54 ± 0.12	0.60 ± 0.11	+11
Right carotid bulb			
Rosuvastatin	0.65 ± 0.18	0.62 ± 0.14	−4.6
Placebo	0.63 ± 0.22	0.67 ± 0.13	+6.3
Right internal carotid artery			
Rosuvastatin	0.79 ± 0.32	0.72 ± 0.11	−8.9
Placebo	0.78 ± 0.20	0.79 ± 0.13	+1.3
Left common carotid artery			
Rosuvastatin	0.63 ± 0.14	0.66 ± 0.14	+4.5
Placebo	0.59 ± 0.13	0.65 ± 0.12	+10
Left carotid bulb			
Rosuvastatin	0.64 ± 0.13	0.67 ± 0.16	+4.7
Placebo	0.66 ± 0.18	0.71 ± 0.18	+7.6
Left internal carotid artery			
Rosuvastatin	0.80 ± 0.30	0.77 ± 0.12	−3.8
Placebo	0.78 ± 0.21	0.78 ± 0.16	0
Mean intima-media thickness (6 sites)			
Rosuvastatin	0.68 ± 0.20	0.67 ± 0.13	−1.5
Placebo	0.66 ± 0.18	0.70 ± 0.14	+6.1

LES: Estatinas

Conclusión:

- Las estatinas pueden mejorar los marcadores de activación endotelial en pacientes con LES.
- No han demostrado disminuir la actividad del LES ni la progresión de la aterosclerosis subclínica.

Limitaciones:

- Número de pacientes
- Duración del tratamiento
- Dosis de estatinas

Lupus eritematoso sistémico

N=1
Contracepción

Chabbert-Buffet N, et al. Pregnane progestin contraception in systemic lupus erythematosus: a longitudinal study of 187 patients. Contraception 2011:83:229.

Background: Systemic lupus erythematosus (SLE) affects women of child-bearing age. Combined oral contraceptives can worsen the course and increase the risk of thrombosis. The objectives of this study were to provide an alternative contraception and thus evaluate the gynecological tolerability of pregnane progestins (PPs) in SLE patients. Systemic lupus erythematosus disease activity and vascular tolerance were also reported.

Study Design: We used two PP with antigonadotropic potencies, chlormadinone acetate (CMA, 10 mg/day) and cyproterone acetate (CPA, 50 mg/day), administered orally for contraception in 187 SLE patients observed for 46±34.6 months (mean±S.E.), i.e., 6854 women-months.

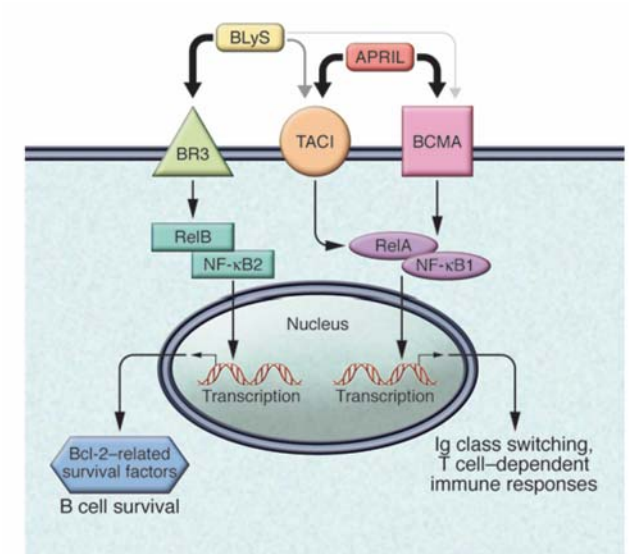
Results: The gynecological tolerability was satisfactory: breakthrough bleeding was reported in 17.7% patients using CPA and 12.6% patients using CMA. No pregnancy was observed in the women followed in this cohort study. One deep vein thrombosis, one myocardial infarction, and one tibial posterior arterial occlusion were observed, giving an incidence for venous thromboembolism of 1.39/year×1000 women (95% CI 0–4.12) and for macroarterial disease an incidence of 2.79/year×1000 women (95% CI 0–6.65). Disease activity was less than before progestins.

Conclusions: Pregnane progestin contraception is effective and well tolerated, thus providing SLE patients an excellent contraceptive alternative to the currently used methods.

Lupus eritematoso sistémico

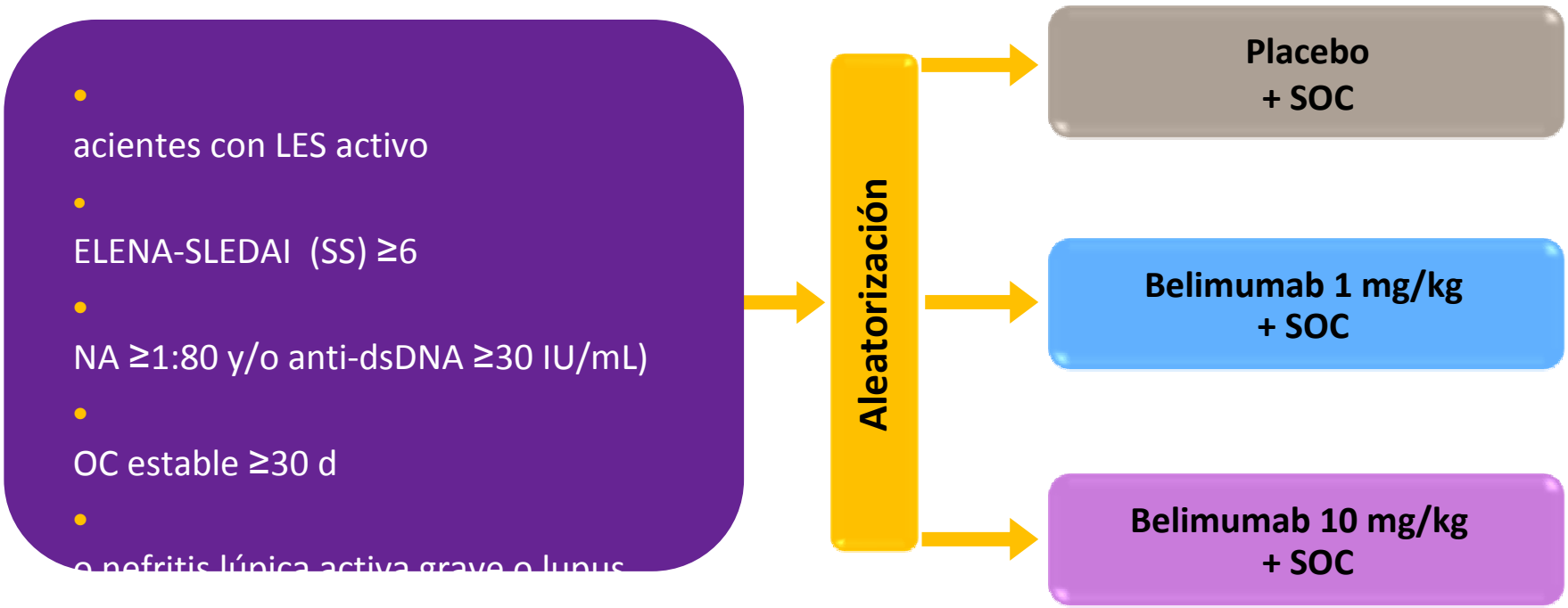
N=1
Belimumab (BLISS 52)

Navarra SV, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011:377:721 (NCT 00424476)



LES: Belimumab (BLISS)

Diseño



- Multicéntrico, aleatorizado, doble ciego, controlado con placebo
- Dosis: d 0, 14, 28, cada 28 d hasta semana 48 con evaluación final semana 52 (BLISS-52; Asia, Sudamérica, Europa del este), o hasta semana 72 con evaluación final semana 52 y semana 76 (BLISS-76; Norteamérica y Europa)
- *Primary endpoint*: SRI en la semana 52 (BLISS-52) y 52 y 76 (BLISS-76)

LES: Belimumab (BLISS)

Diseño

SLE Responder Index (SRI)

≥4-point improvement in SS score

And

No new BILAG 1A/2B flares

And

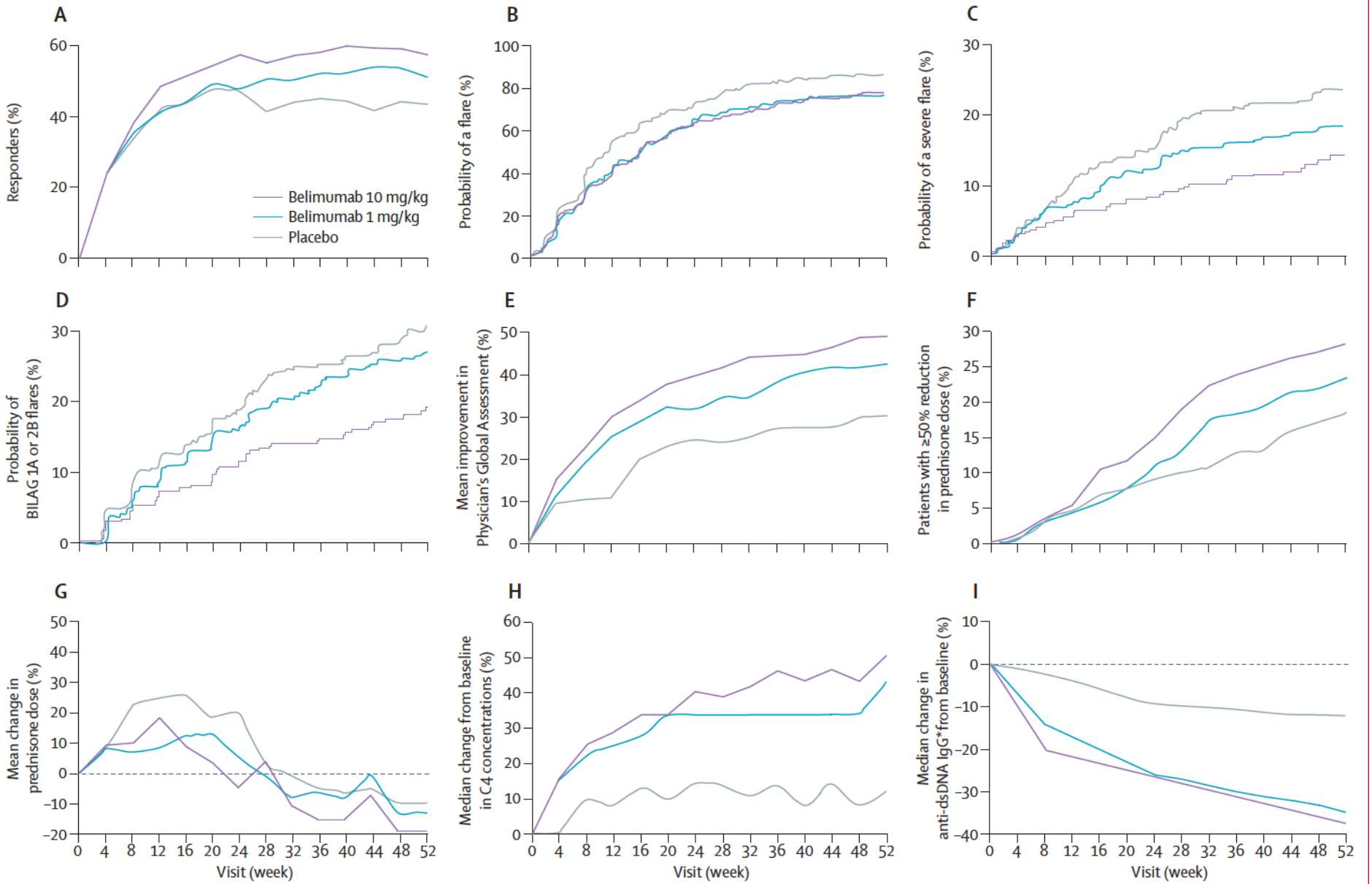
No worsening in PGA (<0.3-point increase)

Furie RA et al. Arthritis Rheum 2009;61:1143-51.

LES: Belimumab (BLISS-52)

Parameter	Placebo (N= 287)	Belimumab 1mg/kg (N=288)	Belimumab 10 mg/kg (N=290)
Primary Endpoint		**n (%)**	
SLE Responder Index Week 52[a]	125 (43.6%)	148 (51.4%) p=0.013	167 (57.6%) p=0.0006
Secondary Endpoints			
4-point reduction in SELENA SLEDAI score	132 (46.0%)	153 (53.1%) p=0.019	169 (58.3%) p=0.0024
No worsening in PGA (≤0.3 pts)	199 (69.3%)	227 (78.8%) p= 0.0078	231 (79.7%) p=0.0048
No new 1A/2B BILAG Organ Domain scores	210 (73.2%)	227 (78.8%) p=0.086	236 (81.4%) p=0.018
Prednisone reduction from >7.5 mg/day by 25% from baseline or to ≤7.5 mg/day during weeks 40-52	23 (12%)	42 (20.6%) p= 0.025	38 (18.6%) p=0.053
Prednisone increased from ≤7.5 mg/day baseline to >7.5 mg/day at week 52	34 (35.8%)	25 (29.8%) p= 0.56	17 (19.8%) p=0.020
		Mean±SE	
Improvement in PGA % change in PGA at week 24	-22.4 ± 2.6%	-29.5 ± 2.2% p= 0.034	-36.8 ± 2.4% p<0.0001
SLE Flares		**Rate (Hazard Ratio)**	
SFI flare[b] Median Time (days) to first SFI flare	80.1% 84	70.5% (0.75) 126 p= 0.0026	70.7% (0.76) 119 p= 0.0036
SFI Severe flare[b]	23.0%	17.7% (0.76) p=0.13	13.8% (0.57) p=0.0055
New BILAG 1A/2B flare[b]	30.0%	26.0% (0.87) p= 0.37	18.6% (0.58) p=0.0016

LES: Belimumab (BLISS-52)



LES: Belimumab (BLISS-52)

	SOC Plus		
Adverse events	**Placebo n=287 (%)**	**1 mg/kg n=288 (%)**	**10 mg/kg n=290 (%)**
All AEs	92	92	92
Serious AEs	13	16	14
Severe AEs	12	13	11
Discontinuation	7	6	5
Death	1	<1%	1
Infections	64	68	67
Severe infections	3	3	2
Malignant neoplasms	0	0	0
Infusion reactions	17	16	17

LES: Belimumab (BLISS-52)

Treatment-emergent adverse events (≥10% of any treatment group)			
Headache	58 (20%)	66 (23%)	76 (26%)
Upper respiratory tract infection	41 (14%)	36 (12%)	47 (16%)
Arthralgia	21 (7%)	33 (11%)	34 (12%)
Urinary tract infection	30 (10%)	26 (9%)	25 (9%)
Influenza	22 (8%)	33 (11%)	25 (9%)
Diarrhoea	28 (10%)	30 (10%)	20 (7%)
Nasopharyngitis	30 (10%)	20 (7%)	23 (8%)
Hypertension	25 (9%)	17 (6%)	30 (10%)
Nausea	16 (6%)	23 (8%)	31 (11%)
Laboratory abnormalities of grade 3 or 4 in >2% of patients given belimumab 10 mg/kg			
White blood cells (<2×10⁹ L)	3 (1%)	12 (4%)	10 (3%)
Neutrophils (<1×10⁹ L)	11 (4%)	11 (4%)	11 (4%)
Lymphocytes (<5×10⁸ L)	80 (28%)	75 (26%)	73 (25%)
Haemoglobin (≤80 g/L)	12 (4%)	5 (2%)	14 (5%)
Prothrombin time (17·25 s) ||	17 (6%)	16 (6%)	12 (4%)
Proteinuria (>2 g/24 h)**	47 (16%)	40 (14%)	51 (18%)
Hypogammaglobulinaemia (<4 g/L)††	0	1 (<1%)‡‡	0
Pregnancy			
All	4 (1%)	11 (4%)	5 (2%)
Spontaneous abortion or stillbirth¶¶	1/3 (33%)	5/9 (56%)	3/5 (60%)

LES: Belimumab (BLISS-76)

	SOC Plus		
	Placebo n=275 (%)	**Belimumab 1 mg/kg n=271 (%)**	**Belimumab 10 mg/kg n=273 (%)**
Primary endpoint SRI at wk 52	33.5	40.6 p = 0.089	43.2 p = 0.017
Components of SRI			
≥4-point improvement in SS score	35.3	42.8 p = 0.087	46.5 p = 0.006
No worsening in PGA (<0.3 points)	62.9	72.7 p = 0.012	69.6 p = 0.13
No new BILAG 1A/2B organ domain scores	65.5	74.9 p = 0.013	69.2 p = 0.32

Arthritis Rheum 2011 (in press)

LES: Belimumab (BLISS-76)

	SOC Plus		
	Placebo n=275 (%)	**Belimumab 1 mg/kg n=271 (%)**	**Belimumab 10 mg/kg n=273 (%)**
Primary endpoint SRI at wk 76	32.4	39.1 p = 0.11	38.5 p = 0.13
Components of SRI			
≥4-point improvement in SS score	33.8	42.1 p < 0.05	41.4
No worsening in PGA (<0.3 points)	58.2	65.7	63.0
No new BILAG 1A/2B organ domain scores	58.9	69.0 p < 0.05	63.4

Arthritis Rheum 2011 (in press)

BLISS-76: Response Rates

	BLISS-76/Wk 52 SOC Plus			BLISS-76/Wk 76 SOC Plus		
	Placebo n=275 (%)	1 mg/kg n=271 (%)	10 mg/kg n=273 (%)	Placebo n=275 (%)	1 mg/kg n=271 (%)	10 mg/kg n=273 (%)
SRI 4[a]	33.8	40.6	43.2	32.4	39.1	38.5
p value		0.104	0.017		0.11	0.13
SRI 5[b]	20.4	31.0	32.6	21.8	28.4	30.8
p value		0.004	0.001		0.081	0.014
SRI 6[b]	18.9	28.8	30.8	20.4	26.9	28.9
p value		0.007	0.001		0.075	0.015
SRI 7[b],[c]	13.4	19.4	21.2	13.9	21.7	21.8
p value		0.088	0.028		0.027	0.017

[a] Primary end point at Week 52; [b] SRI modified based on 5–7-point reduction in SS. [c] Among subjects with SS score ≥7 at baseline.

LES: Belimumab (BLISS-52 + BLISS-76)

	SOC Plus		
	Placebo (n=476) (%)	**Belimumab 1 mg/kg (n=496) (%)**	**Belimumab 10 mg/kg (n=495) (%)**
Primary endpoint SRI at wk 52	43.6	51.4 p = 0.013	57.6 p = 0.0006
Prednisone reduction by ≥25% to ≤7.5 mg/d during wk 40-52	12	20 p = 0.0097	18 p = 0.045
Severe flares/patient/year from wk24-52	0.24	0.15	0.16
Prednisone reduction by ≥25% to ≤7.5 mg/d during wk 40-52	6	11 p = 0.017	14 p = 0.0013
Severe flares from wk24-52	39	46 p=0.006	50 p<0.0001

Ann Rheum Dis 2011;70(Suppl3):321

LES: Belimumab

D. D'Cruz, et al. **Belimumab reduced disease activity across multiple organ domains in patients with SLE: combined results from BLISS-52 and BLISS-76**
Conclusions: Belimumab reduced overall disease activity in patients with SLE and was associated with improvement and less worsening across several SS and BILAG domains. Ann Rheum Dis 2011;70(Suppl3):318

R. van Vollenhoven, et al. **Durability of response in SLE patients treated with belimumab in the phase 3 BLISS-52 and BLISS-76 studies**
Conclusions: SRI response rate was higher among patients who received belimumab plus routine SLE therapy vs placebo plus routine SLE therapy. Among SRI responders, belimumab-treated patients were more likely to maintain a durable response by any of several criteria vs placebo. Ann Rheum Dis 2011;70(Suppl3):321

D. Wallace, et al**. Safety profile of belimumab in patients with active SLE: pooled phase 2/3**
Data Conclusions: Overall, belimumab plus routine SLE therapy had a favorable safety profile for its intended use. As with all immunomodulatory treatments, diligence in monitoring patients during treatment is required. Ann Rheum Dis 2011;70(Suppl3):318

M. Petri, et al. **Six-year experience with belimumab in patients with SLE - poster**
Tours Conclusions: Belimumab added to routine SLE therapy was well tolerated in pts remaining on treatment over 6 y. Seropositive pts treated with belimumab showed sustained improvement in disease activity and a decline in BILAG and SFI flares over 6 y accompanied by reductions in corticosteroid use and autoantibody levels. Ann Rheum Dis 2011;70(Suppl3):314

LES: Belimumab

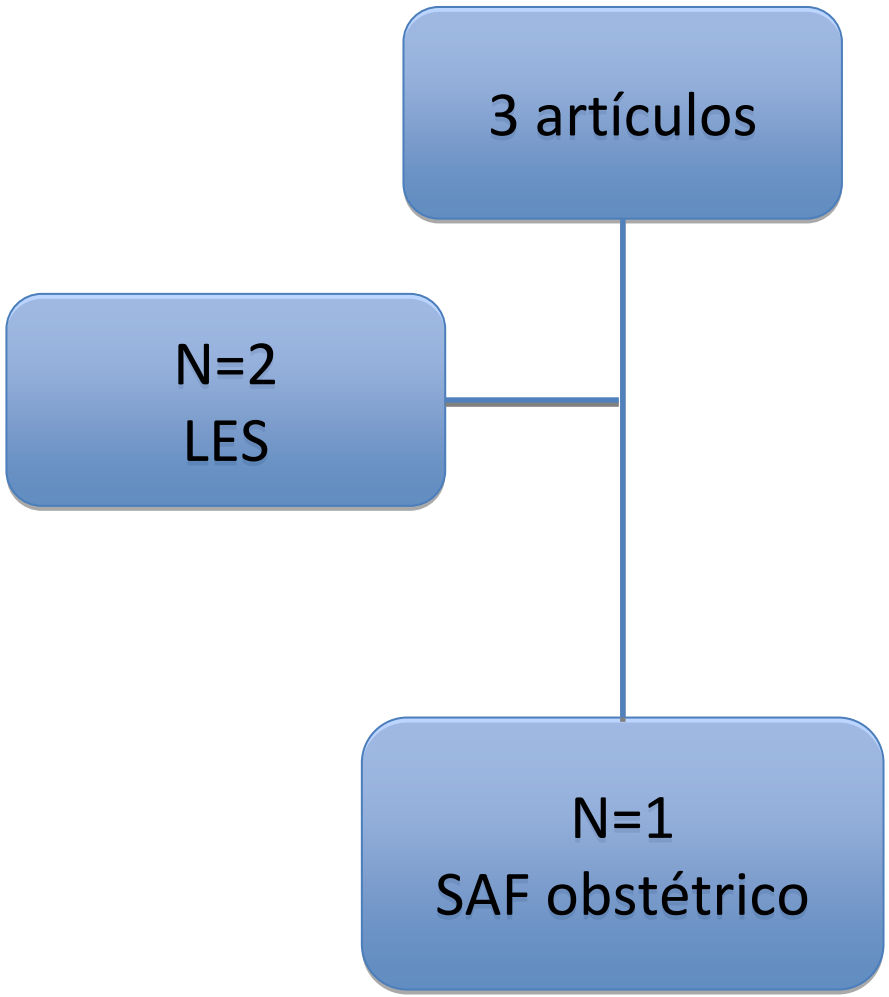
El Futuro

	SOC Plus		
	Placebo (n=476) (%)	**Belimumab 1 mg/kg (n=496) (%)**	**Belimumab 10 mg/kg (n=495) (%)**
Primary endpoint SRI at wk 52	43.6	51.4 p = 0.013	57.6 p = 0.0006

¿Una diferencia de <15% es suficiente para justificar el uso de Belimumab?

¿Qué pacientes se pueden beneficiar de Belimumab?

Síndrome antifosfolipídico



Síndrome antifosfolipídico

N=1
SAF obstétrico

- Fouda UM, et al. Enoxaparin versus unfractioned heparin in the management of recurrent aboprtion secondary to antiphospholipid syndrome. Int J Gynaecol Obstet 2011;112:211 (NCT 01051778)

- Ensayo clínico aleatorizado
- Embarazadas con SAF obstétrico (3 abortos antes de la 10ª semana de gestación)

UFH (5000 U/12h) + LDA (n=30)		vs. Enoxaparin 40 mg + LDA (n=30)	
RN vivos	66.67%	80%	p=0.243

No diferencias respecto a complicaciones del embarazo o morbilidad neonatal.
No casos de sangrado grave, trombocitopenia o fracturas espontáneas.

Síndrome antifosfolipídico

- Criterio del ponente

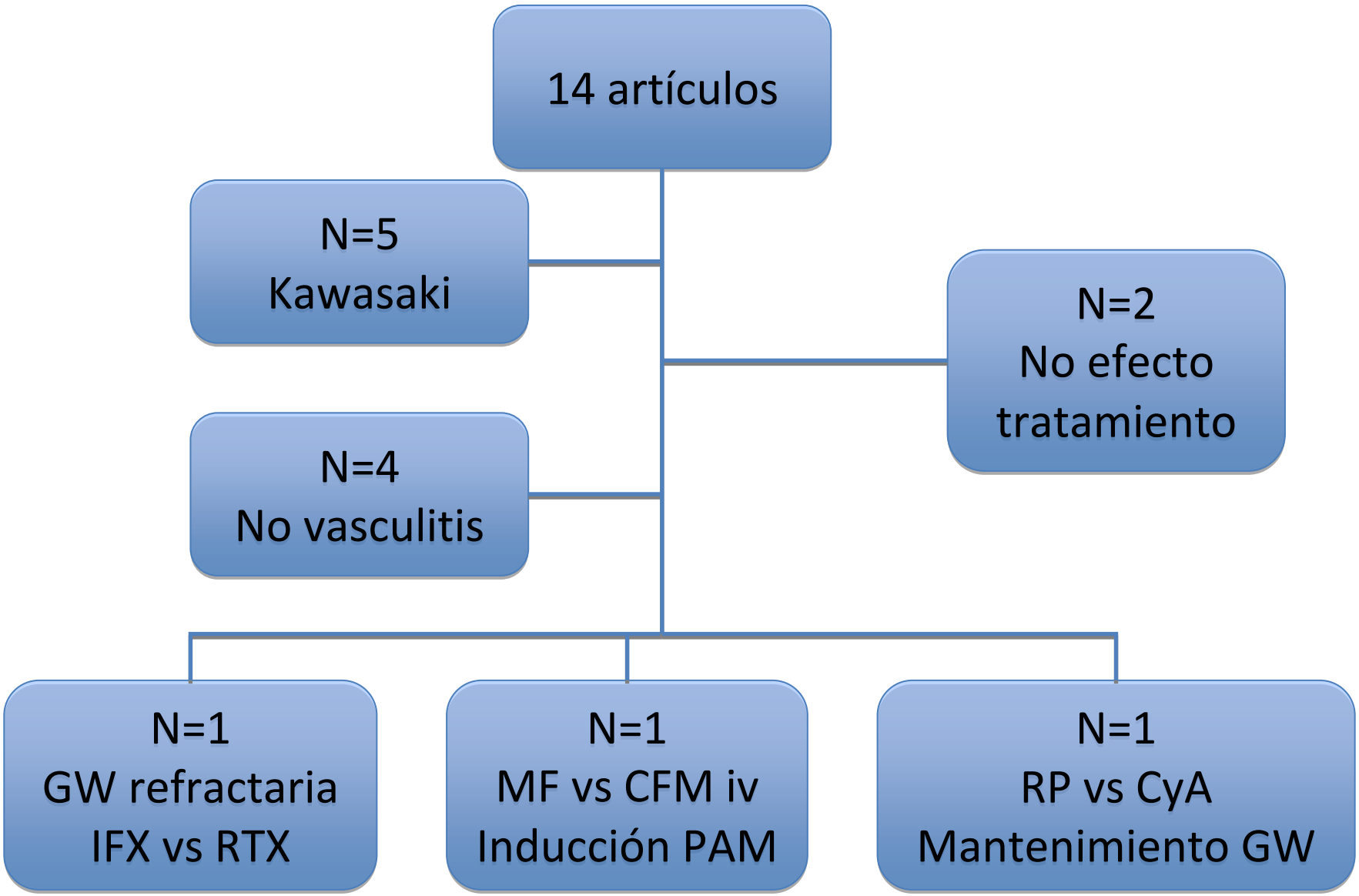
- Fouda UM, et al. Efficacy and safety of two doses of low molecular weight heparin (enoxaparin) in pregnant women with a history of recurrent abortion secondary to antiphospholipid syndrome. J Obstet Gynaecol 2010;30:842.

- Ensayo clínico aleatorizado
- Embarazadas con SAF obstétrico (3 abortos antes de la 10ª semana de gestación)

Enoxaparina 40 mg + LDA (n=30) vs. Enoxaparin 20 mg + LDA (n=30)			
RN vivos	76.67%	70%	p=0.559

No diferencias respecto a complicaciones maternas, obstétricas o del RN.
No casos de sangrado grave, trombocitopenia o fracturas espontáneas.

Vasculitis sistémicas



VS-ANCA

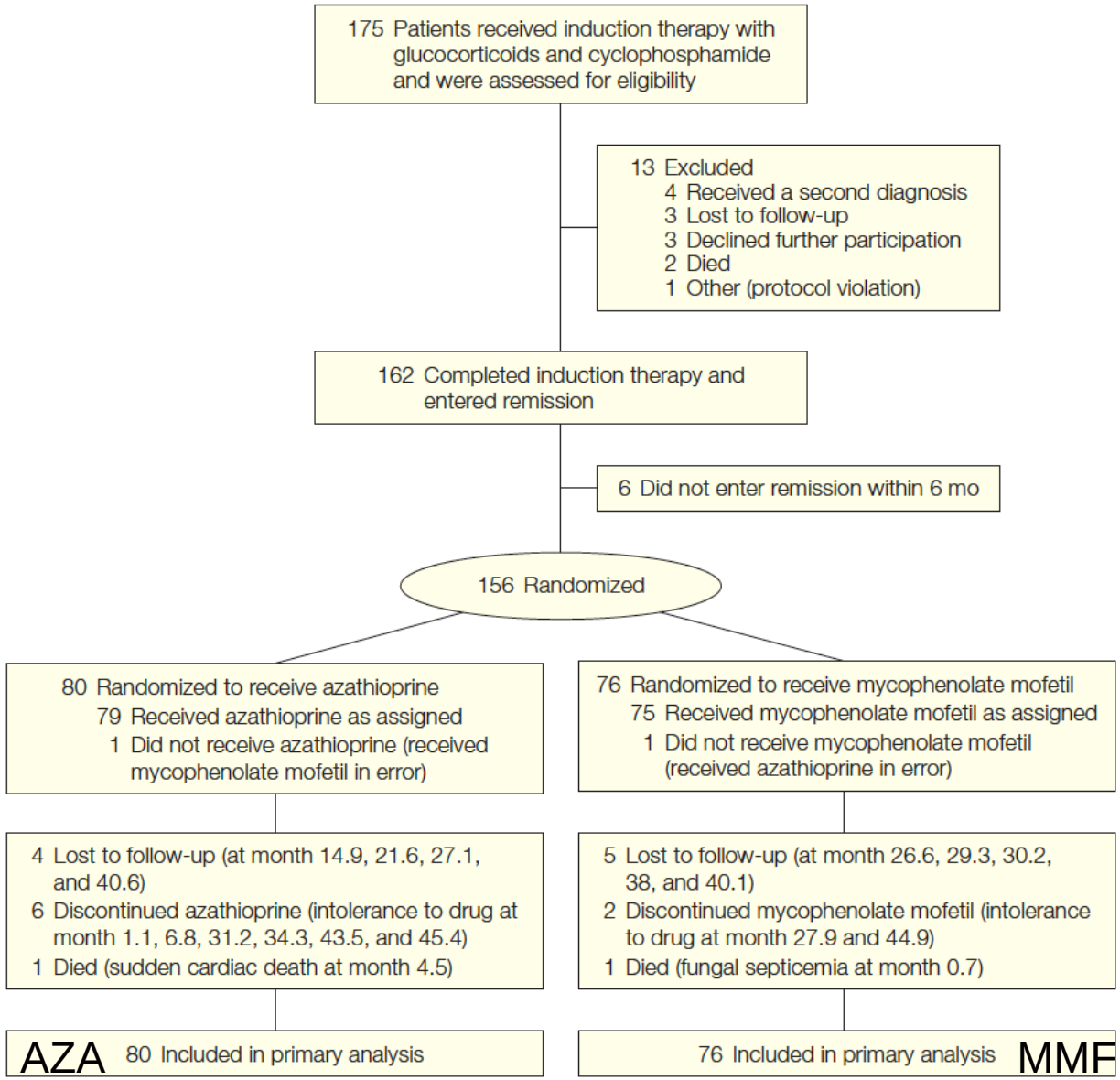
- Criterio del ponente

Mycophenolate Mofetil vs Azathioprine for Remission Maintenance in Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

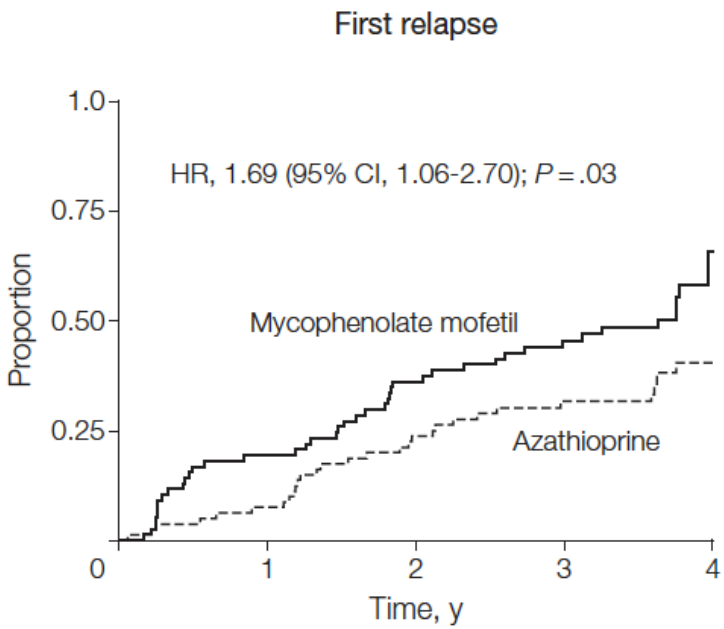
A Randomized Controlled Trial (IMPROVE)

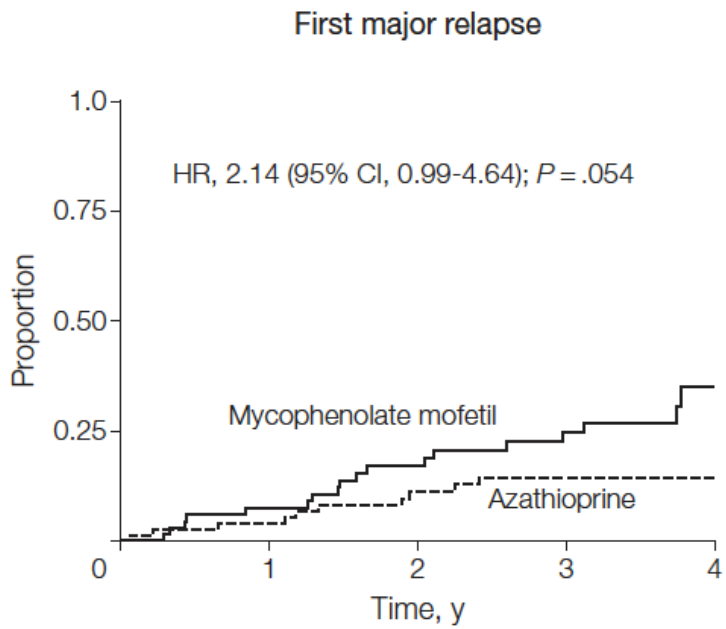
JAMA 2010;304:2381

VS-ANCA: MMF vs. AZA



VS-ANCA: MMF vs. AZA





No. at risk					
Azathioprine	80	72	57	46	6
Mycophenolate mofetil	76	60	47	37	4

Relapses:	AZA	MMF
All	30/80	42/76
Major	18	24
Minor	10	20

V-ANCA: MMF vs. AZA en mantenimiento

- MMF es más eficaz que AZA en LES
- MMF no es más eficaz que AZA en vasculitis-ANCA

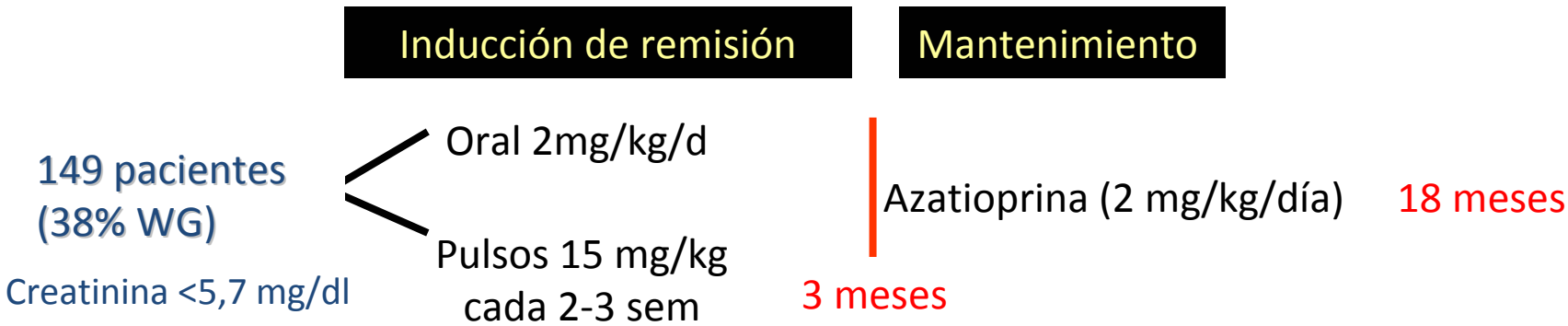
VS-ANCA

- Criterio del ponente
- Evolución a medio y largo plazo de los ensayos clínicos de EUVAS

15th International Vasculitis & ANCA Workshop
Chapel Hill, NC
Clin Exp Immunol 2011;164 (Suppl1):50-67

VS-ANCA: Estudio CYCLOPS

CICLOFOSFAMIDA: pulsos ev/1-4 semanas vs. vía oral/día



- Tiempo hasta la remisión clínica similar
- Remisión a los 9 meses (67% pulsos vs. 64% oral)
- Tasa de rebrotes (13% pulsos vs. 6% oral)
- Efectos adversos igual (77%)
  - Menor leucopenia en pulsos (26% vs. 45%)
  - Menor dosis acumulada en pulsos (8 gr vs 16 gr)

de Groot K et al. Ann Intern Med 2009

VS-ANCA: Estudio CYCLOPS

Seguimiento a largo plazo

134 pacientes. Seguimiento medio 4,3 años

Muertes: CYC oral 12 / CYC pulsos 13

Rebrotes 29 CYC pulsos / 15 CYC oral

CYC oral > tiempo hasta el rebrote

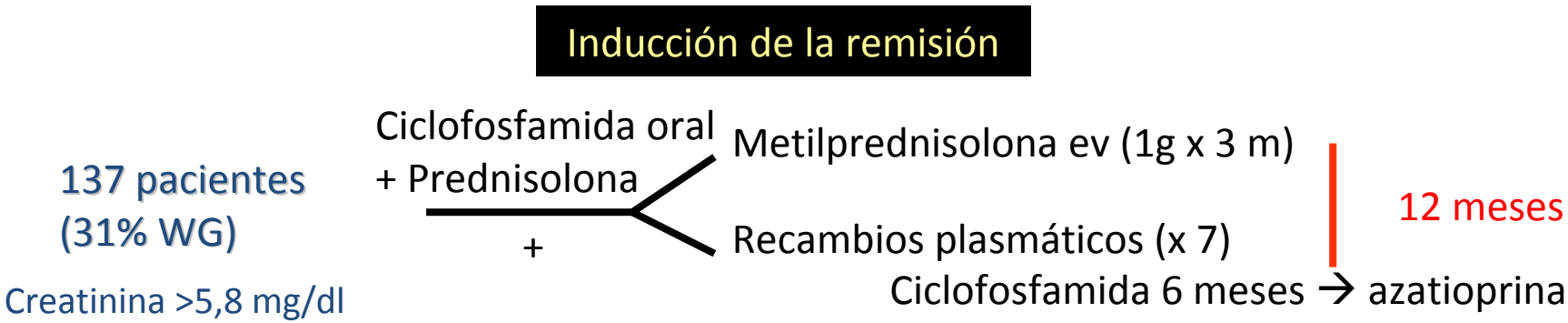
PR3 + > rebrotes

Función renal y efectos adversos: no diferencias

- En el tratamiento de inducción a la remisión, la CYC en pulsos está asociada a un mayor nº de rebrotes que la CYC oral a largo plazo
- No influencia en función renal ni muertes

Harper L *et al*. *Clin Exp Immunol* 2011;164(Suppl 1):56

VS-ANCA: Estudio MEPEX



137 pacientes con ANCA-vasculitis de debut con:

- confirmación histológica (biopsia renal)
- creatinina > 5.8 mg/dl

Resultados

- A los 3 meses: No diálisis: 69% RP vs. 49% MPDN (p= 0,02)
- A los 12 meses: No diálisis: 59% RP vs. 43% MPDN
  Progresión a IRC: 14% RP vs. 33% MPDN
  Supervivencia: 73% RP vs. 76% MPDN
  Efectos adversos graves: 50% RP vs. 48% MPDN

Jayne D et al. J Am Soc Nephrol 2007

VS-ANCA: Estudio MEPEX

Seguimiento a largo plazo

137 pacientes. Seguimiento medio 4 años

IRT: 70 (51%)

Muertes: 56 (41%)

Rebrotes: (≥ 1) 26 (19%)

NO DIFERENCIAS ENTRE GRUPOS

No beneficio a largo plazo de los RP respecto a MPDN en relación a IRT, muerte ni rebrotes

Casian A. Clin Exp Immunol 2011;164(Suppl1):52

VS-ANCA: Estudio CYCAZAREM

155 pacientes
(61% WG)

Creatinina <5,7 mg/dl

Ciclofosfamida oral + PDN

3 meses

Remisión

MANTENIMIENTO

Azatioprina (2 mg/kg/día)

Ciclofosfamida

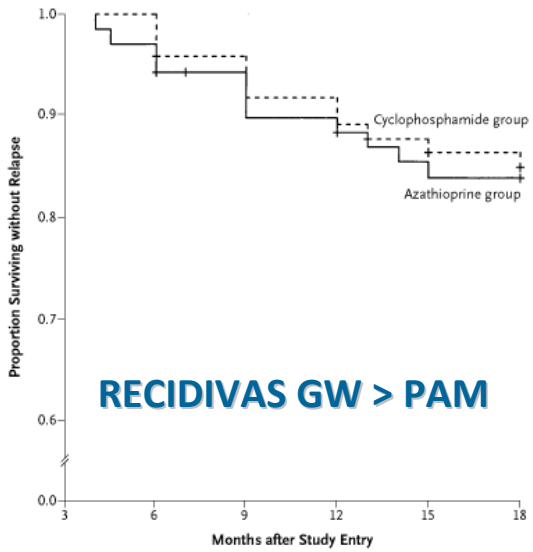
18 meses

93% remisión

Similar:

-Recidivas (15,5% AZA vs. 13,7% CFM)

-Efectos adversos graves (11% AZA vs. 10% CFM)



Jayne D et al. NEJM 2003

VS-ANCA: Estudio CYCAZAREM

Seguimiento a largo plazo

130 pacientes. Seguimiento 7±3 años

IRT: CYC 6/65 (9%) / AZA 8/65 (12%)

Único predictor de IRT en el seguimiento: función renal basal

Mantenimiento de la remisión AZA=CYC en la preservación de la función renal a largo plazo

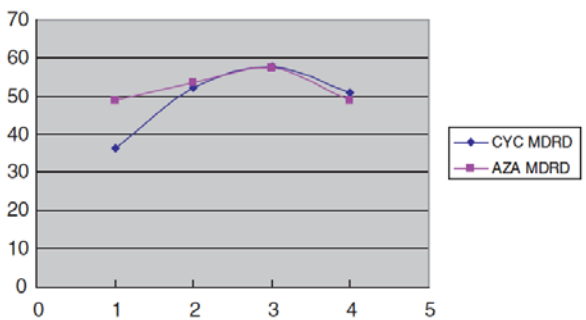
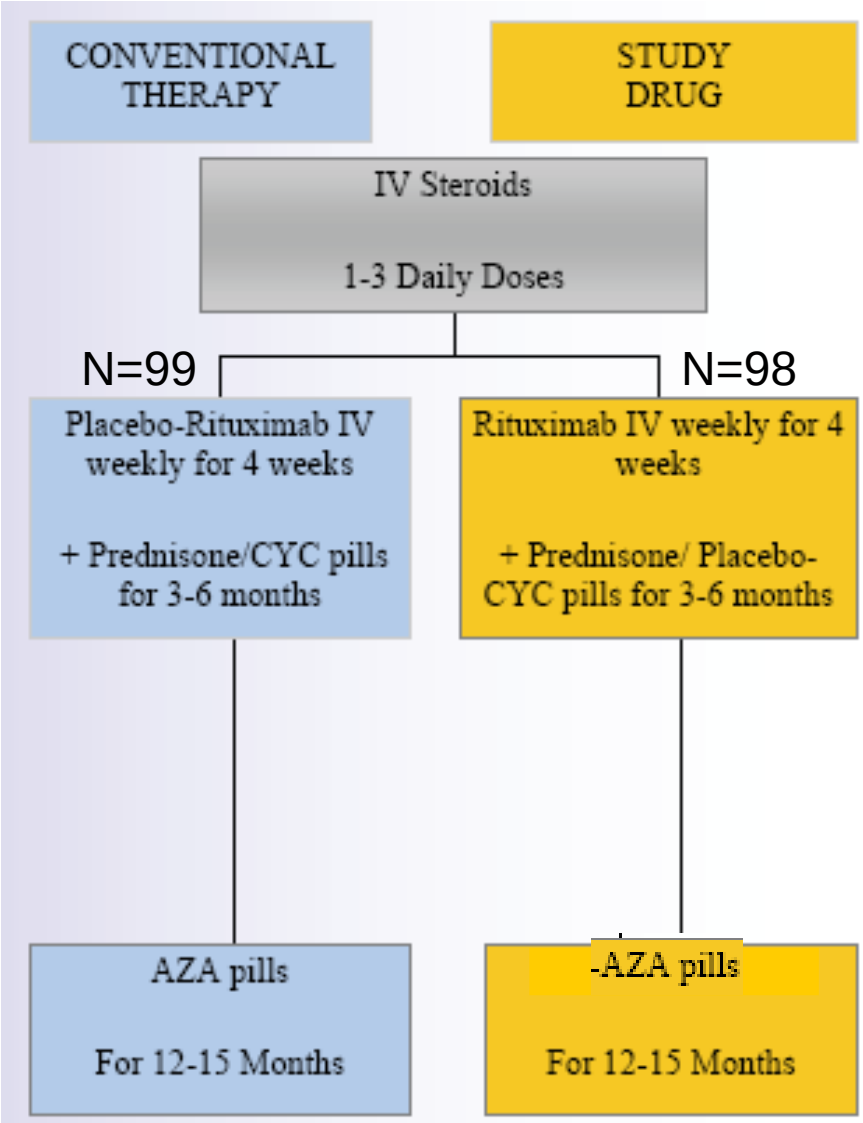


Figure 1. Points 1, 2, 3 and 4 represent, respectively, mean eGFR at baseline/remission/18 months/5-year follow-up.

Berden A et al. Clin Exp Immunol 2011;164(Suppl1):51

VS-ANCA: RTX, Estudio RAVE



Objetivo primario:

Remisión a los 6 meses sin PDN

RTX 64% vs CYC 53% (p<0.001)

WG: RTX 63% vs CYC 50% (p=0.11)

MPA: RTX 67% vs CYC 62% (p=0.76)

Objetivos secundarios:

Remisión completa + PDN<10mg/d

RTX 71% vs CYC 62% (p =0.10)

Eficacia en inducción de remisión en enfermedad recidivante

RTX 67% vs CYC 42% (p = 0.01)

Pacientes con ≥1 efecto adverso

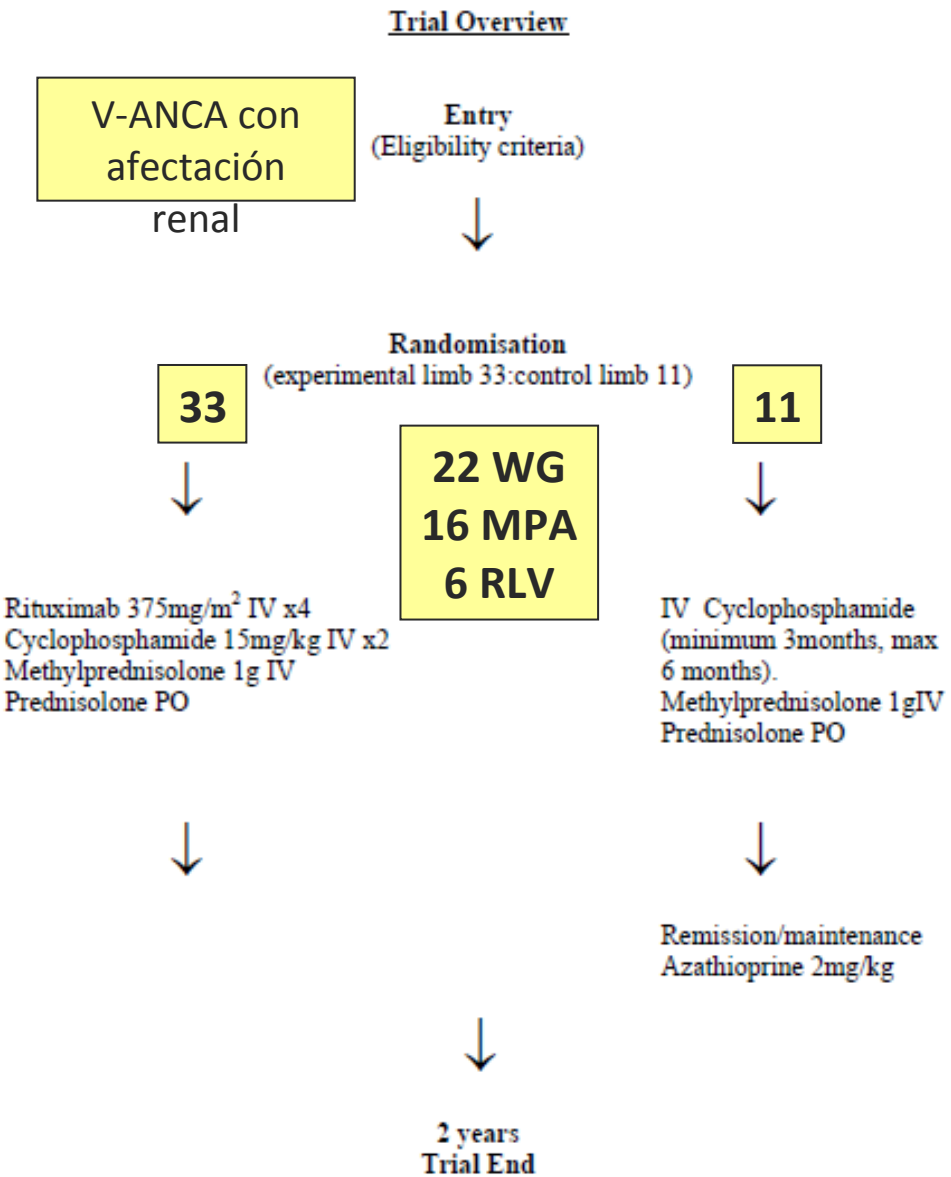
RTX 22 vs CYC 32 (p=0.01)

No diferencias en rebrotes ni en la respuesta en pacientes con afectación renal/pulmonar grave

No inferioridad respecto a la ciclofosfamida en la inducción de la remisión.
Efectos adversos menores.

Stone JH et al. NEJM 2010

VS-ANCA: RTX, Estudio RITUXVAS



Objetivo primario:
Remisión a los 12 ms
RTX 76% vs CYC 82% (p=0,68)

Objetivos secundarios:
Pacientes con efectos adversos graves
RTX 42% vs CYC 36% (p=0,77)

No diferencias en el tiempo para alcanzar la remisión, en recuperación renal ni en muertes

No inferioridad respecto a la ciclofosfamida en la inducción de la remisión.
Similar porcentaje de efectos adversos

Jayne D et al. NEJM 2010

VS-ANCA: RTX
Estudio RAVE, RITUXVAS

Clara alternativa a CFM en pacientes con enfermedad refractaria

Posible alternativa a la CFM como tratamiento inicial, sobre todo en pacientes con enfermedad renal

¿A MEDIO Y LARGO PLAZO?

VS-ANCA: Estudio RAVE, RITUXVAS

RAVE — 1,5 años

Objetivo primario:
Remisión SIN corticoides
- *12 meses*: **RTX 42% vs CYC 38% (p=ns)**
- *18 meses*: **RTX 36% vs CYC 31% (p=ns)**

-*18 meses*: No diferencias en
- -Nº de rebrotes / pacientes >1 rebrote
  Rebrotes PR3 > MPO
- -Dosis acumulada de corticoides
- -Efectos adversos

Un único ciclo de RTX es igual de eficaz que la CYC como tratamiento de inducción y de mantenimiento durante los primeros 18 meses

Specks U Clin Exp Immunol 2011:164(Suppl1):65

RITUXVAS — 2 años

Objetivo primario:
Rebrote, muerte o IRT (combinado)
RTX 42% vs CYC 36% (p=1)

Rebrote	RTX 21% vs CYC 18% (p=1)
Muerte	RTX 18% vs CYC 27% (p=0,671)
IRT	RTX 6% vs CYC 0% (p=0,57)

Efectos adversos graves:
RTX 61% vs CYC 36% (p=0,64)
Función renal: No diferencias

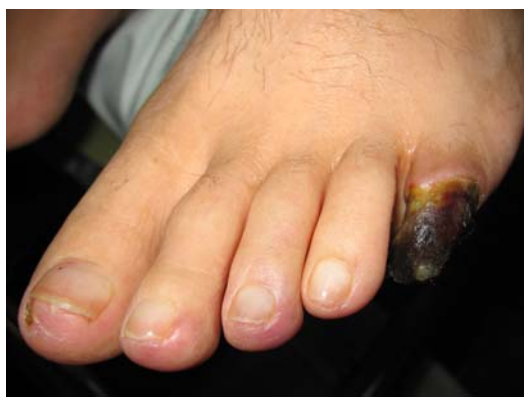
El RTX como inducción a la remisión es eficaz pero no superior a la CYC en rebrote, mortalidad y evolución a IRT durante los primeros 2 años

Jones R Clin Exp Immunol 2011;164(Suppl1):57

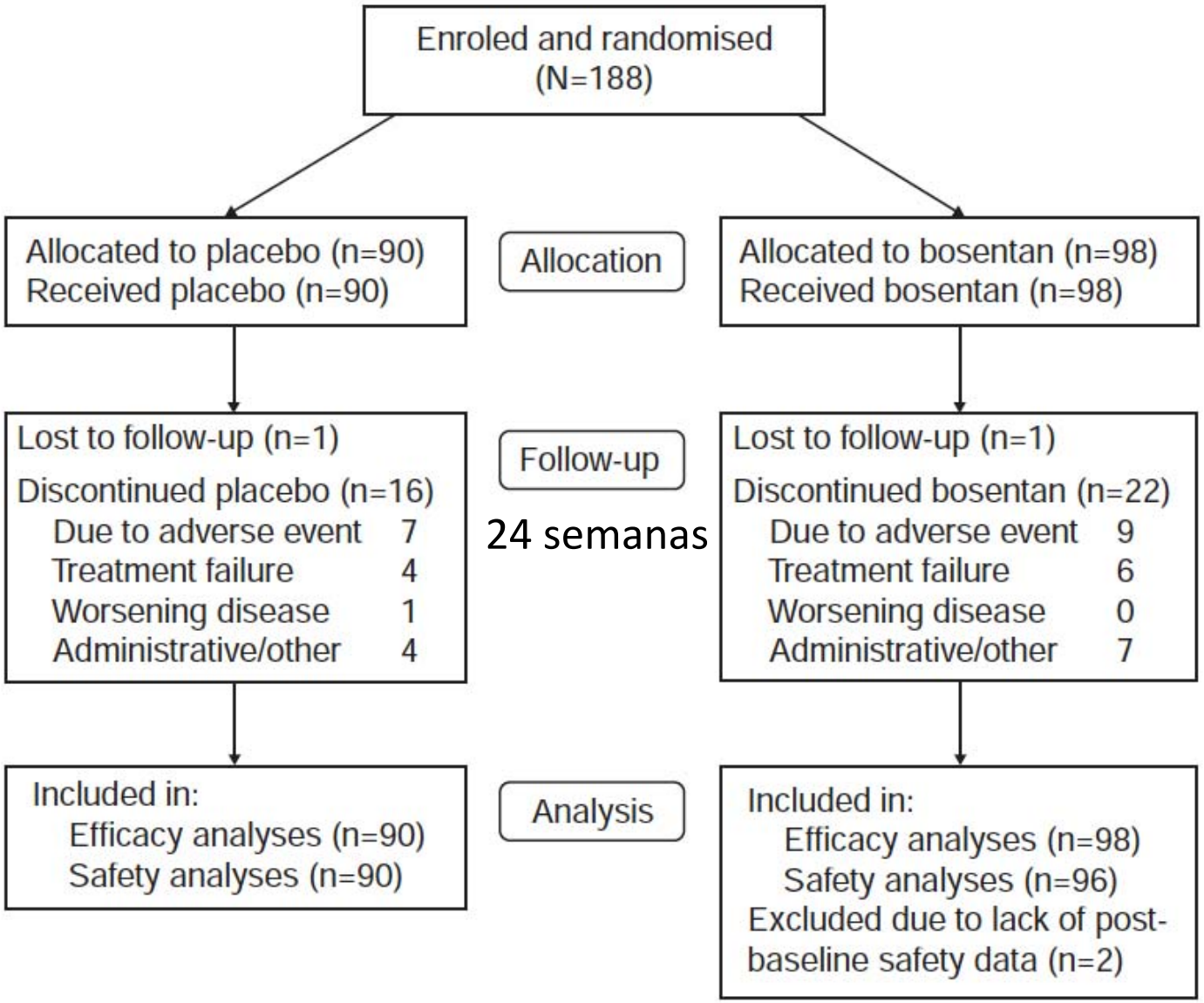
Esclerosis sistémica

Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial

Matucci-Cerinic M, et al. Ann Rheum Dis 2011;70:32

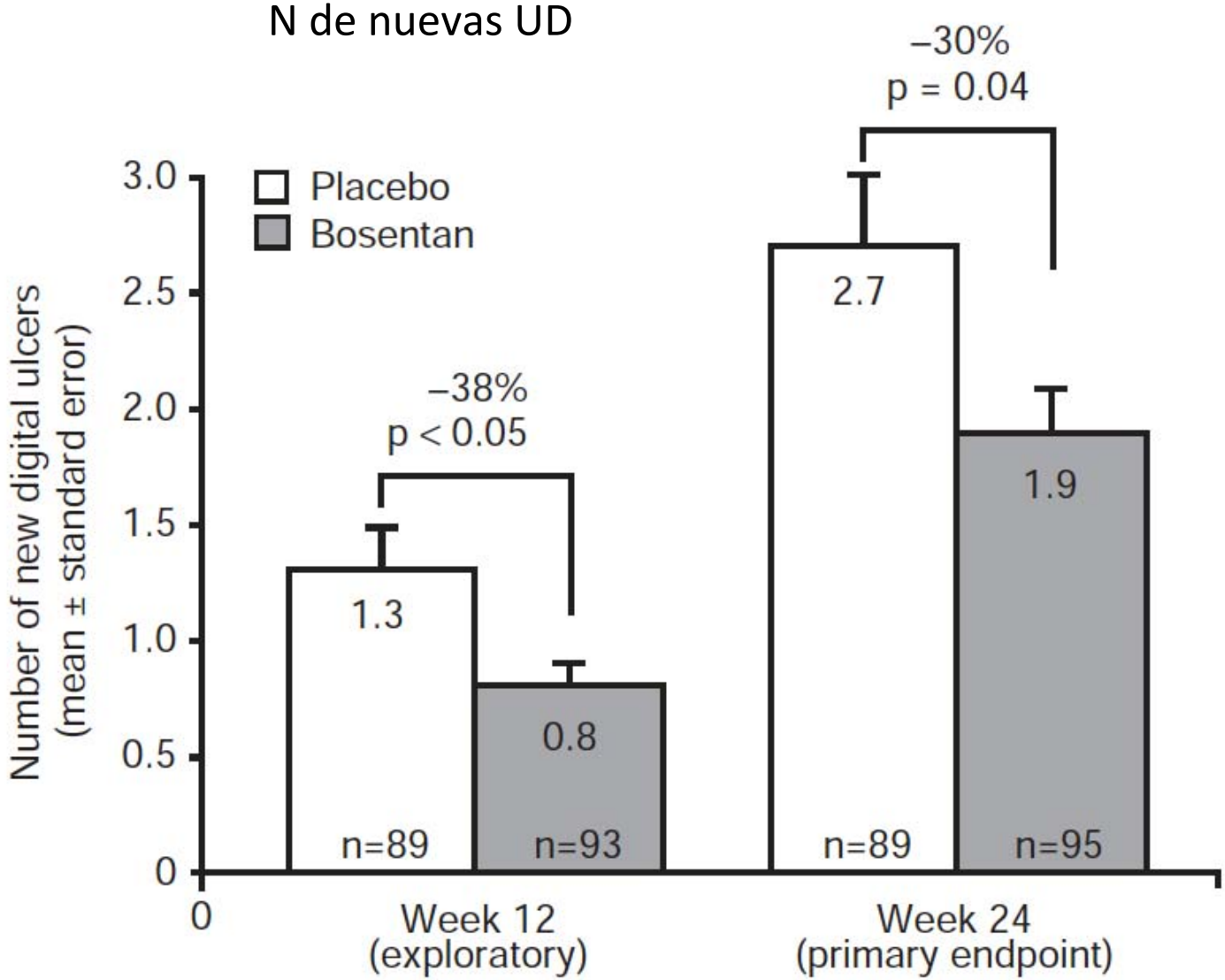


ES: RAPIDS-2

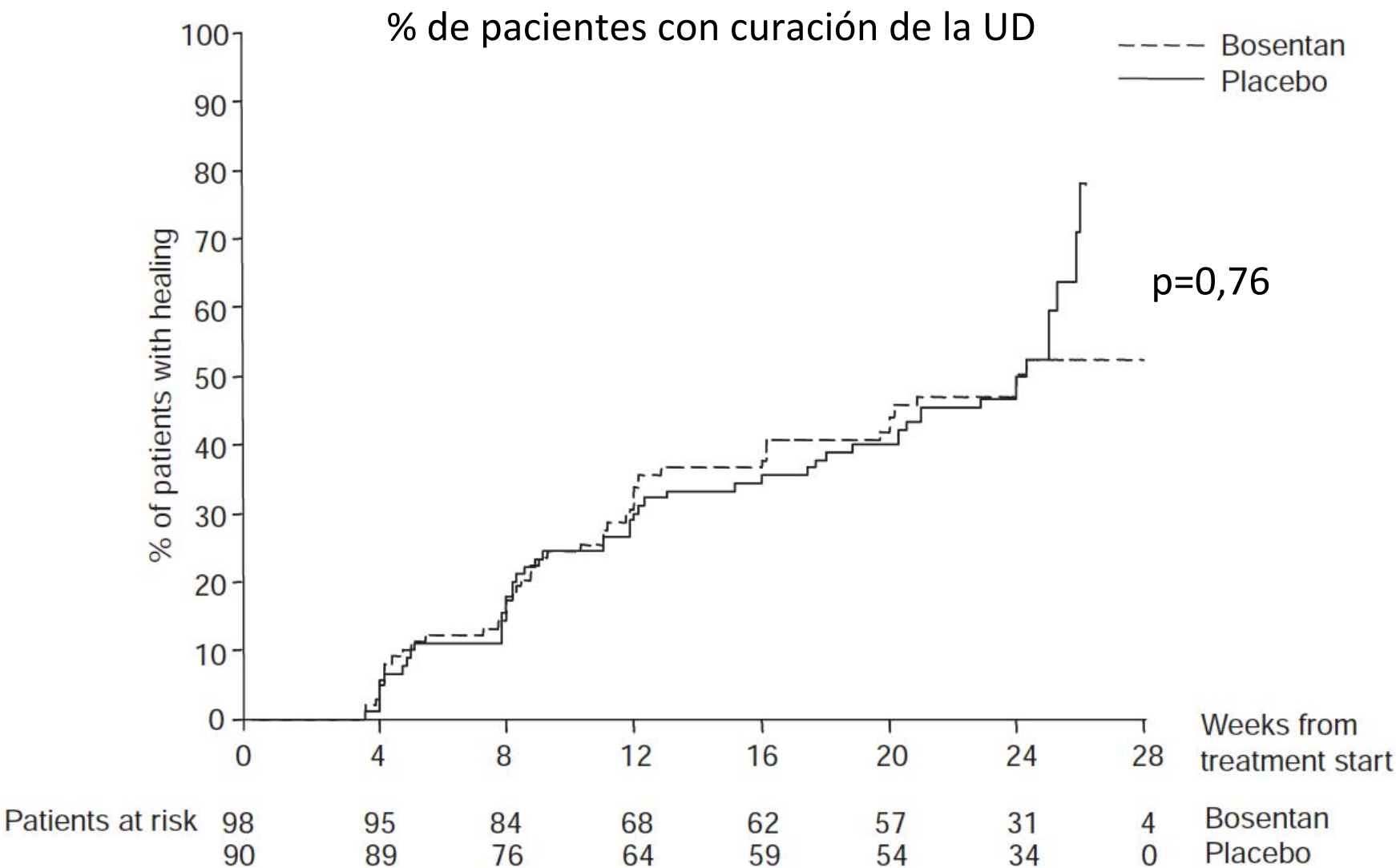

Enroled and randomised
(N=188)
Allocated to placebo (n=90)
Received placebo (n=90)
Allocation
Allocated to bosentan (n=98)
Received bosentan (n=98)
Lost to follow-up (n=1)
Discontinued placebo (n=16)
Due to adverse event 7
Treatment failure 4
Worsening disease 1
Administrative/other 4
Follow-up
24 semanas
Lost to follow-up (n=1)
Discontinued bosentan (n=22)
Due to adverse event 9
Treatment failure 6
Worsening disease 0
Administrative/other 7
Included in:
Efficacy analyses (n=90)
Safety analyses (n=90)
Analysis
Included in:
Efficacy analyses (n=98)
Safety analyses (n=96)
Excluded due to lack of post-baseline safety data (n=2)

ES: RAPIDS-2

N de nuevas UD



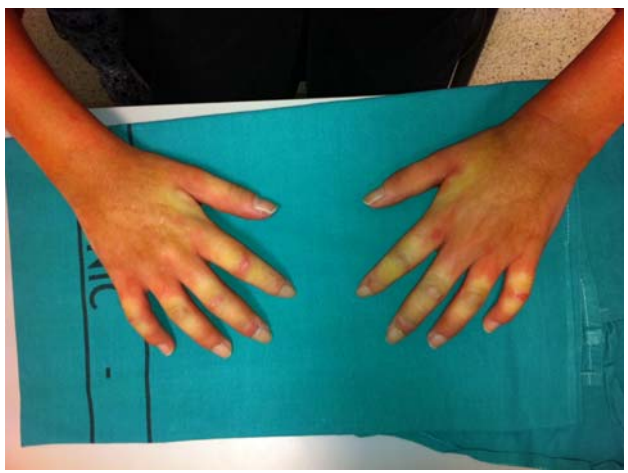
ES: RAPIDS-2

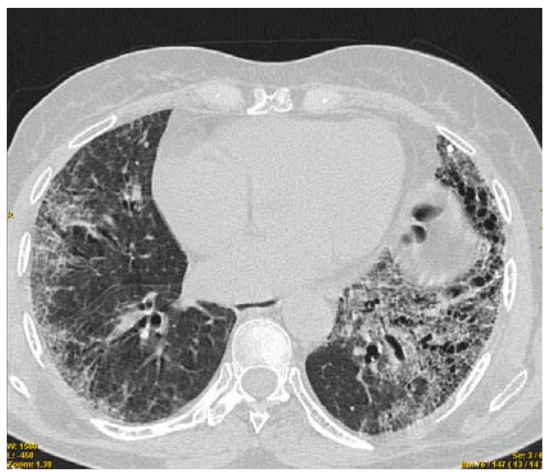

% de pacientes con curación de la UD
Bosentan
Placebo
p=0,76
% of patients with healing
100
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
28
Weeks from treatment start
Patients at risk
98
95
84
68
62
57
31
4
Bosentan
90
89
76
64
59
54
34
0
Placebo

Esclerosis sistémica

Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial

Burt RK, et al. Lancet 2011;378:498





Esclerosis sistémica: HSCT vs. CFM iv

- Ensayo clínico abierto, aleatorizado, controlado en fase 2

- Pacientes con ES difusa con mRSS >14 y afectación órgano interno (DLco <80% o disminucion de FCV>10% en los 12 meses previos, TCAR con EPI, ECG alterado o afectación GI). Pacientes con mRSS <14 con afectación pulmonar.

- Pacientes excluidos: TLC < 45%, FE < 40%, afectación cardiaca clínica, duración de la ES > 4 años, insuficiencia renal, PAPs >40 mmHg o PAPm >25 mmHg.

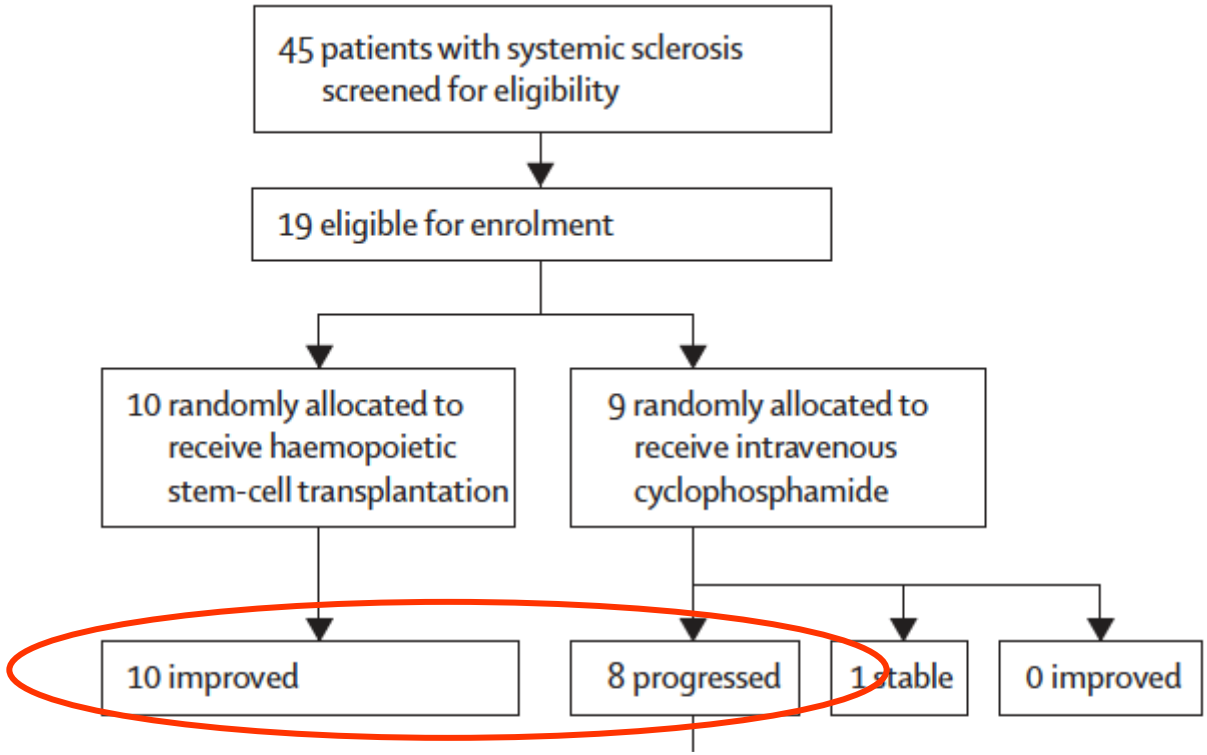
HSCT (N=10) versus CFM iv (N=9)
12 meses

- Variables

Mejoría: disminución del 25% del mRSS (si mRSS >14) o aumento mayor del 10% en la FVC

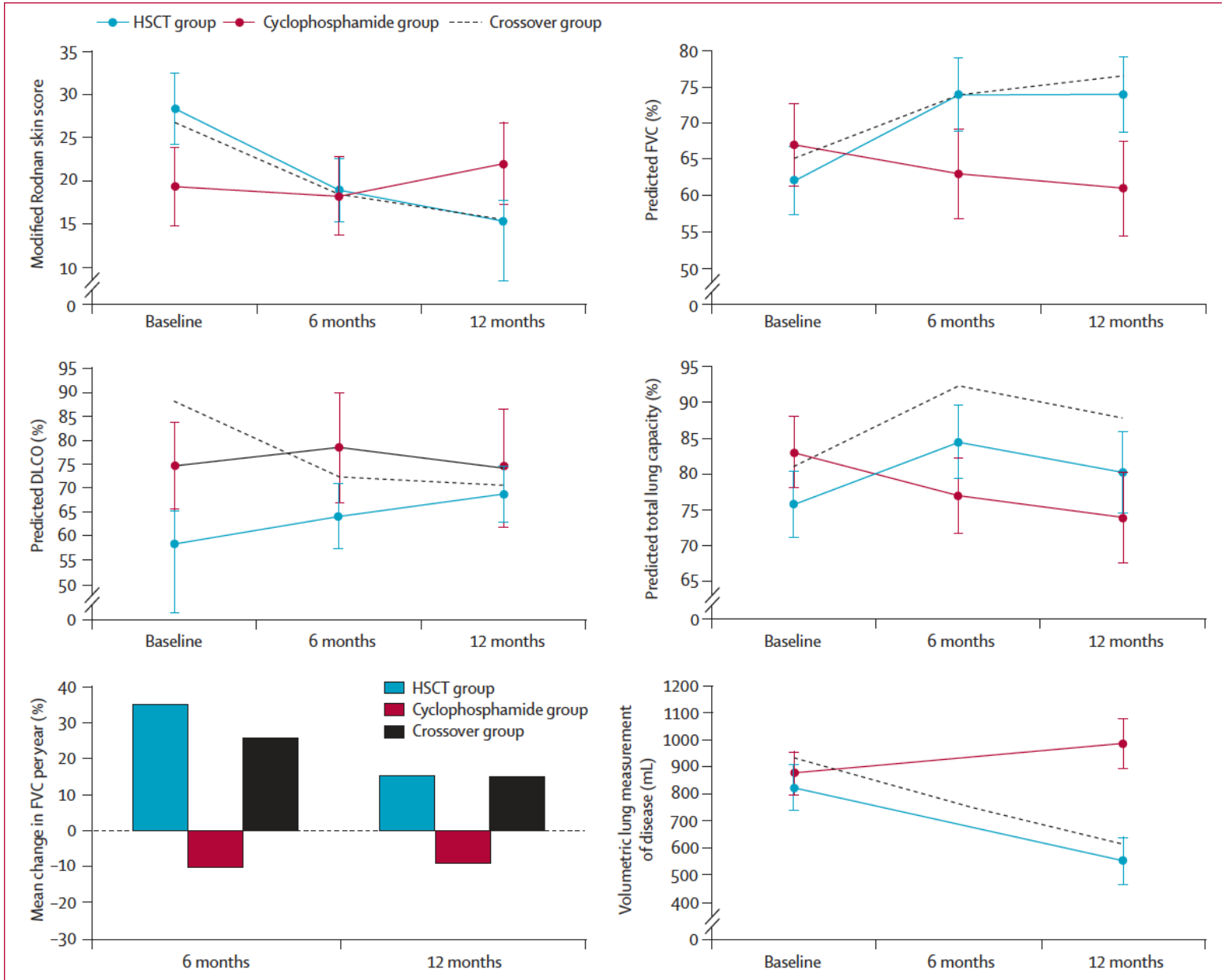
Progresión: Aumento del 25% del mRSS (si mRSS >14) o disminución del 10% en la FVC

Esclerosis sistémica: HSCT vs. CFM iv



OR 110, 95% CI 14.04-∞
p=0.00001

Esclerosis sistémica: HSCT vs. CFM iv



Esclerosis sistémica: HSCT vs. CFM iv

	Before switch to transplantation				
	Cyclophosphamide group (n=9)		Transplant group (n=10)		p value
	Baseline	1 year	Baseline	1 year	
Predicted forced vital capacity (%)					
Mean (SD)	67% (17·0)	61% (19·8)	62% (15·0)	74% (15·7)	0·004
Median (range)	78% (43–84)	69% (35–83)	62% (36–85)	82% (52–96)	..
Rate of change (%)†	..	–9%	..	15%	0·006
Predicted total lung capacity (%)					
Mean (SD)	83% (14·8)	74% (18·7)	76% (14·6)	80% (17·9)	0·005
Median (range)	89% (59–99)	69% (45–95)	73% (57–102)	72% (62–104)	..
Predicted DLCO corrected for haemoglobin (%)					
Mean (SD)	75% (27·5)	74% (37·0)	58% (21·8)	69% (18·6)	0·36
Median (range)	80% (29–111)	73% (28–120)	58% (29–94)	67% (33–90)	..
Volume diseased lung (mL)‡					
Mean (SD)	877 (240·6)	985 (277·1)	823 (268·9)	551 (277·1)	0·001
Median (range)	961 (462–1195)	858 (808–1189)	850 (359–1095)	546 (240–1118)	..
Modified Rodnan skin score					
Mean (SD)	19 (13·7)	22 (14·2)	28 (13·6)	15 (7·9)	0·0004
Median (range)	16 (6–45)	22 (3–44)	30 (6–47)	16 (2–29)	..

Esclerosis sistémica: HSCT vs. CFM iv

Efectos adversos:

HSCT:
Infección por *Clostridium difficile* (1)
Bacteriemia por microccus (1)
Arritmias (TPSV y AcxFA) (2)
Sobrecarga de volumen (2)
Reactivación de CMV (1)

CFM iv
Celulitis (1)
Intolerancia GI (2)

Conclusiones

- TAC como posible tratamiento de inducción de NL
- MMF superior a AZA en mantenimiento de NL
- Papel de las estatinas en la progresión de la aterosclerosis en LES
- Belimumab es superior a placebo en pacientes con LES activo
- AZA es superior a MMF en mantenimiento de vasculitis-ANCA
- RTX como alternativa eficaz a CFM iv en inducción y mantenimiento de vasculitis-ANCA
- Bosentan previene la aparición de úlceras digitales en SSc
- El trasplante de progenitores hemopoyéticos como alternativa más eficaz que la CFM iv en SSc grave