Nuevos fármacos biológicos en LES extrarrenal.

¿Cuándo los utilizamos?

Dra. Nuria Navarrete Navarrete
FEA M. Interna. UEAS H. Virgen de las Nieves. Granada.

XII CONGRESO DE AADEA

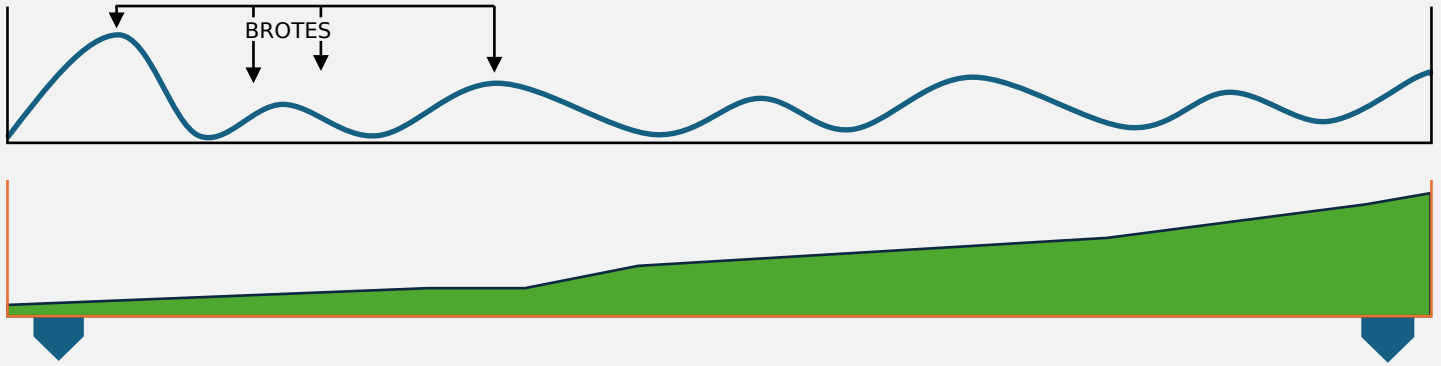
D. Pharmacological interventions are directed by patient characteristics, type and severity of organ involvement, treatment-related harms, comorbidities, risk for progressive organ damage, and patient preferences.

INDIVIDUALIZAR TRATAMIENT

Curso del LES

Actividad clínica

Acumulación daño orgánico



Daño orgánico temprano

Provocado por la actividad persistente de la enfermedad (*manifestaciones renales, pulmonares, gastrointestinales y cutáneas).*

Daño orgánico tardío

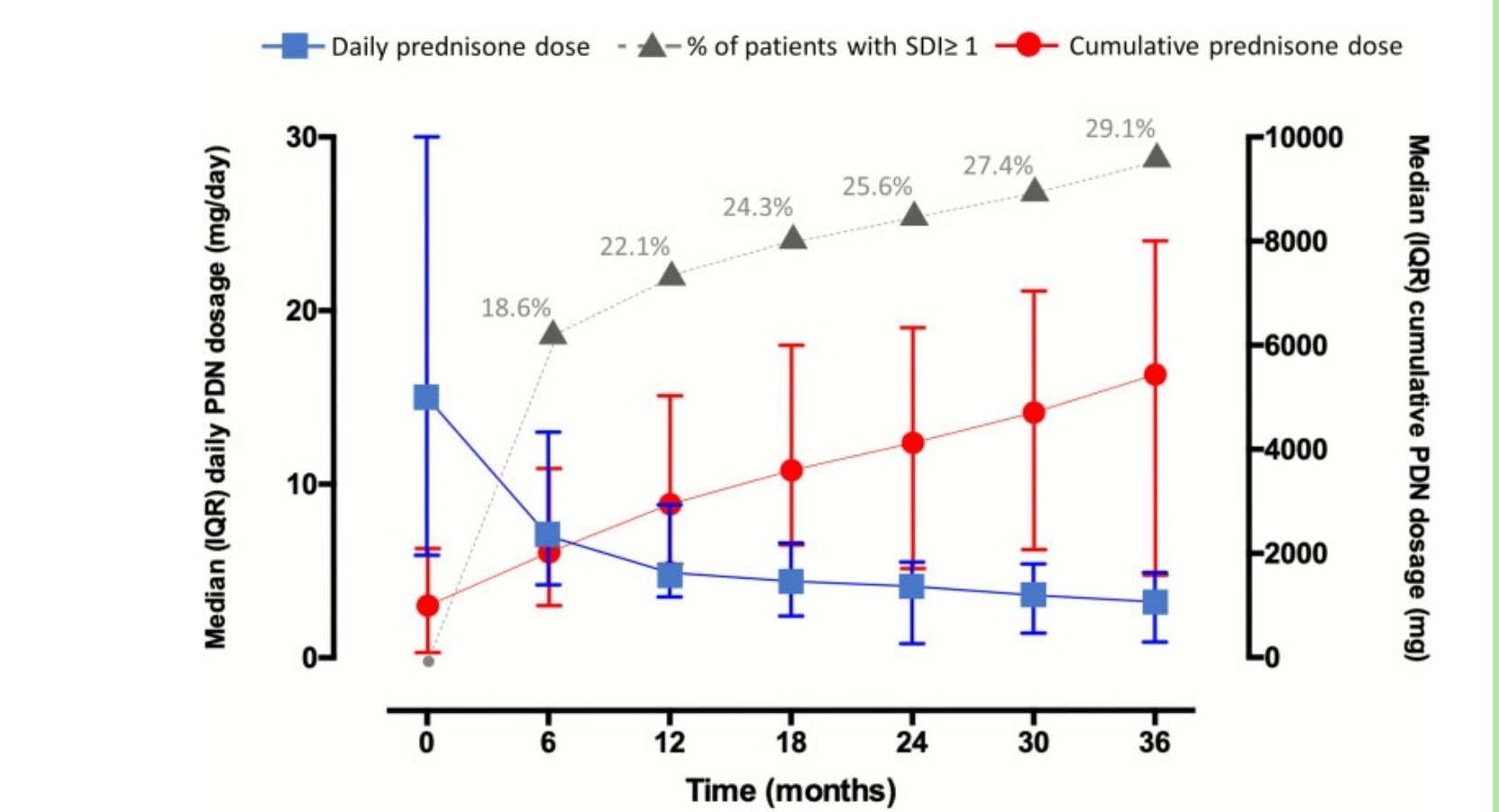
Provocado por los efectos secundarios de fármacos (especialmente la exposición crónica a corticoides).

30–50% de los pacientes con LES presentan daño orgánico después de 5 años

EL DAÑO OCURRE PRECOZMENTE EN EL LES

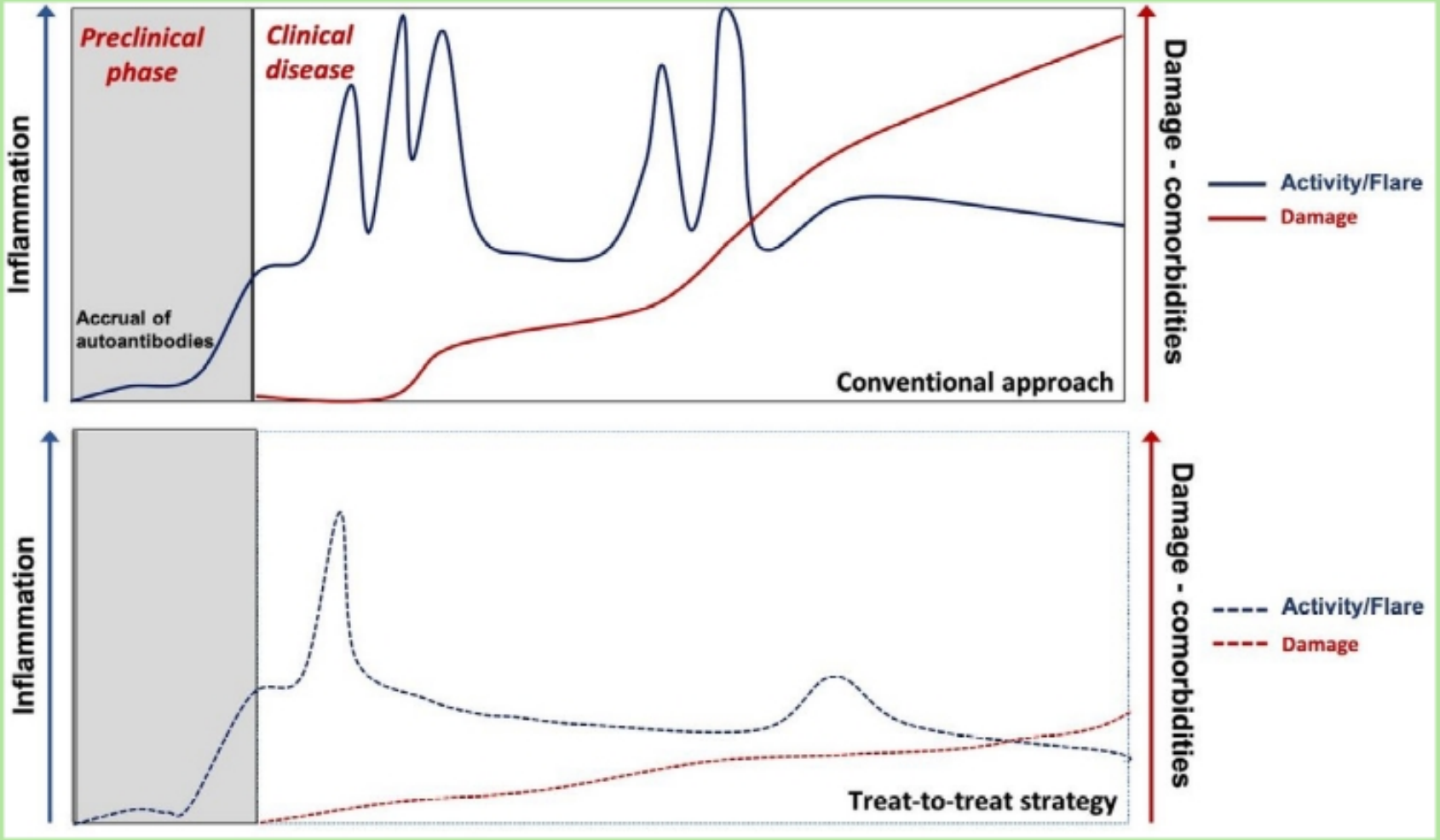
- 230 PACIENTES LES <12 MESES

- MEDIANA SEGUIMIENTO: 27,4 MESES (7,2 – 48)



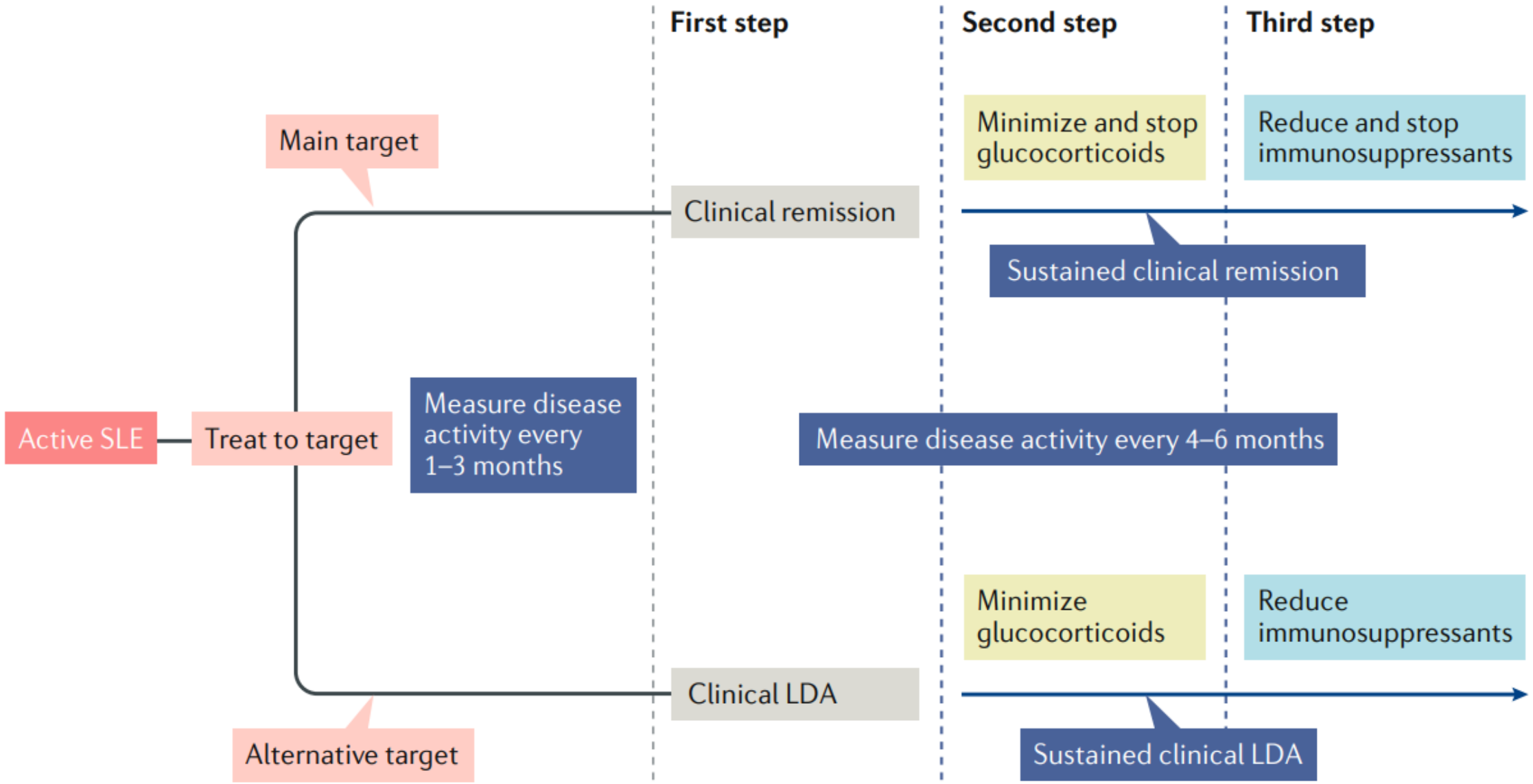
Piga M et al, Risk factors of damage in early diagnosed systemic lupus erythematosus: results of the Italian multicentre Early Lupus Project inception cohort, *Rheumatology*, Volume 59, Issue 9, September 2020, Pages 2272–2281, https://doi.org/10.1093/rheumatology/kez584

Natural history of **SLE** and the potential impact of a treat-to-target strategy.



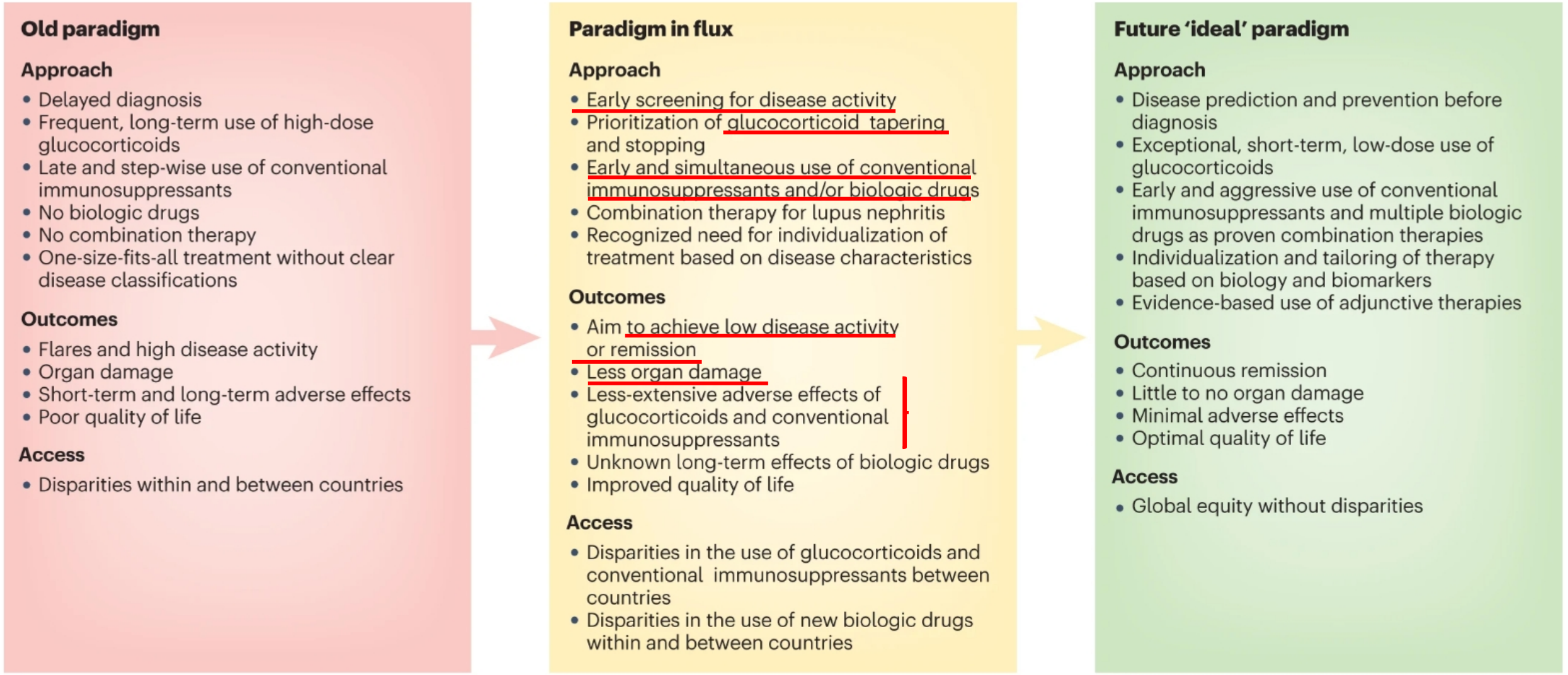
Antonis Fanouriakis et al. Ann Rheum Dis 2021;80:14-25

ARD


First step
Second step
Third step
Main target
Minimize and stop glucocorticoids
Reduce and stop immunosuppressants
Clinical remission
Sustained clinical remission
Active SLE
Treat to target
Measure disease activity every 1–3 months
Measure disease activity every 4–6 months
Minimize glucocorticoids
Reduce immunosuppressants
Clinical LDA
Alternative target
Sustained clinical LDA

EULAR recommendations for the management of systemic lupus erythematosus: 2023 update

Antonis Fanouriakis ,[1] Myrto Kostopoulou ,[1] Jeanette Andersen,[2] Martin Aringer ,[3] Laurent Arnaud ,[4] Sang-Cheol Bae ,[5] John Boletis,[6] Ian N Bruce,[7] Ricard Cervera,[8] Andrea Doria ,[9] Thomas Dörner ,[10] Richard A Furie ,[11] Dafna D Gladman ,[12] Frederic A Houssiau ,[13] Luís Sousa Inês ,[14] David Jayne ,[15] Marios Kouloumas,[16] László Kovács,[17] Chi Chiu Mok ,[18] Eric F Morand ,[19] Gabriella Moroni,[20] Marta Mosca,[21] Johanna Mucke ,[22] Chetan B Mukhtyar ,[23] György Nagy ,[24,25,26] Sandra Navarra,[27] Ioannis Parodis ,[28,29,30] José M Pego-Reigosa,[31] Michelle Petri ,[32] Bernardo A Pons-Estel,[33] Matthias Schneider,[22] Josef S Smolen,[34] Elisabet Svenungsson ,[28,29] Yoshiya Tanaka ,[35] Maria G Tektonidou ,[36] YK Onno Teng ,[37] Angela Tincani ,[38] Edward M Vital ,[39] Ronald F van Vollenhoven ,[40] Chris Wincup ,[41] George Bertsias ,[42] Dimitrios T Boumpas [1,43,44]


Old paradigm
Approach
Delayed diagnosis
Frequent, long-term use of high-dose glucocorticoids
Late and step-wise use of conventional immunosuppressants
No biologic drugs
No combination therapy
One-size-fits-all treatment without clear disease classifications
Outcomes
Flares and high disease activity
Organ damage
Short-term and long-term adverse effects
Poor quality of life
Access
Disparities within and between countries
Paradigm in flux
Approach
Early screening for disease activity
Prioritization of glucocorticoid tapering and stopping
Early and simultaneous use of conventional immunosuppressants and/or biologic drugs
Combination therapy for lupus nephritis
Recognized need for individualization of treatment based on disease characteristics
Outcomes
Aim to achieve low disease activity or remission
Less organ damage
Less-extensive adverse effects of glucocorticoids and conventional immunosuppressants
Unknown long-term effects of biologic drugs
Improved quality of life
Access
Disparities in the use of glucocorticoids and conventional immunosuppressants between countries
Disparities in the use of new biologic drugs within and between countries
Future 'ideal' paradigm
Approach
Disease prediction and prevention before diagnosis
Exceptional, short-term, low-dose use of glucocorticoids
Early and aggressive use of conventional immunosuppressants and multiple biologic drugs as proven combination therapies
Individualization and tailoring of therapy based on biology and biomarkers
Evidence-based use of adjunctive therapies
Outcomes
Continuous remission
Little to no organ damage
Minimal adverse effects
Optimal quality of life
Access
Global equity without disparities

OBJETIVOS DEL TRATAMIENTO EN EL LES EXTRARRENAL

Target

Remission
Clinical SLEDAI=0
HCQ
GC ≤ 5 mg/day

or

Low disease activity
SLEDAI ≤4
HCQ
GC ≤ 5 mg/day

Immunosuppressive or biological agents at stable, tolerated dose

Fanouriakis A, Kostopoulou M, Andersen J, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis. 2024 Jan 2;83(1):15-29. doi: 10.1136/ard-2023-224762. PMID: 37827694.

2. Glucocorticoids, if needed, are dosed based on the type and severity of organ involvement (**2b/C**), and should be reduced to maintenance dose of ≤5 mg/day (prednisone equivalent) (**2a/B**) and, when possible, withdrawn; in patients with moderate-to-severe disease, pulses of intravenous methylprednisolone (125–1000 mg/day, for 1–3 days) (**3b/C**) can be considered.

- USAR DOSIS MÁS BAJA DE CORTICOIDES (PDN ≤ 5 mg/ d) Y RETIRARLO COMPLETAMENTE CUANDO SEA POSIBLE

- LOS CORTICOIDES DEBEN SER USADOS SOLO COMO TRATAMIENTO PUENTE (BRIDGING THERAPY)

EL USO DE PREDNISONA ≥ 5 MG/ DÍA DURANTE LOS 2 AÑOS POSTERIORES AL DIAGNÓSTICO DE LES SE ASOCIA A UN INCREMENTO DEL RIESGO DE MUERTE

RHEUMATOLOGY

Rheumatology 2020;59:524–533
doi:10.1093/rheumatology/kez292
Advance Access publication 3 August 2019

Original article

Damage accrual and mortality over long-term follow-up in 300 patients with systemic lupus erythematosus in a multi-ethnic British cohort

Beatriz Tejera Segura[1], Brett Sydney Bernstein[1], Thomas McDonnell[1], Chris Wincup[1], Vera M Ripoll[1], Ian Giles[1], David Isenberg[1] and Anisur Rahman[1]

- COHORTE MULTICÉNTRICA
- 40 AÑOS SEGUIMIENTO
- "DOSIS ALTAS CORTICOIDES": > 5 mg/ d

- Pacientes con PDN ≥5 mg/día los 2 primeros años: 1,5 veces **más riesgo de padecer daño orgánico**.
- Daño orgánico se asoció con un **aumento del riesgo de mortalidad** (R=8.43; IC95%: 2.64, 26.9; P<0.001)
- Riesgo de mortalidad en pacientes con dosis altas tempranas de corticoides: HR=2,85 (IC 95%: 1,52, 5,34; *P*=0,001)

TABLE 1 Comparison of characteristics of patients with and without damage

	Damage (*n* = 231, 77%)	Non-damage (*n* = 69, 23%)	*P*-value
Age onset SLE, mean (S.D.)	31 (0.71)	30 (1.3)	0.389
Age F-U SLE, mean (S.D.)	40 (10.9)	39 (12.7)	0.494
Time to damage – in months, mean (S.D.)	114 (83.2)	NA	
Mean months F-U with no damage	NA	328 (164.2)	
Female, *n* (%)	217 (93.9)	63 (91.3)	0.441
Ethnicity, *n* (%)			
Caucasian	148 (64.1)	45 (65.2)	0.484
Afro-Caribbean	59 (25.5)	20 (29)	
Asian	24 (10.4)	4 (5.8)	
Skin disease, *n* (%)			
Rash	167 (72.3)	57 (82.6)	0.084
Photosensitivity	99 (42.9)	34 (49.3)	0.346
Alopecia	44 (19)	10 (14.5)	0.387
Mouth ulcers	59 (25.5)	15 (21.7)	0.520
Joint disease, *n* (%)	220 (95.2)	65 (94.2)	0.729
Kidney disease, *n* (%)	97 (42)	11 (15.9)	**<0.001**
Serositis, *n* (%)	115 (49.8)	28 (40.6)	0.179
CNS disease, *n* (%)	70 (30.3)	10 (14.5)	**0.009**
Positive dsDNA, *n* (%)	148 (64.1)	33 (47.8)	**0.016**
Low complement (ever)	106 (45.88)	20 (23)	**0.013**
ENAs, *n* (%)			
SM	27 (11.7)	7 (10.1)	0.723
Ro	79 (34.2)	21 (30.4)	0.561
La	30 (13)	8 (11.6)	0.760
RNP	63 (27.3)	9 (13)	**0.015**
RF	62 (26.9)	15 (21.7)	0.395
APS antibodies, *n* (%)			
Positive	60 (26)	6 (9)	**0.044**
Treatment (ever), *n* (%)			
Steroids (oral, i.v.)	176 (82.5)	34 (58.6)	**<0.001**
HD steroids	121 (70.3)	27 (52.9)	**0.001**
Cyclophosphamide	35 (16.8)	5 (7.6)	0.064
Azathioprine	105 (50.5)	10 (15.2)	**<0.001**
Mycophenolate	48 (23.1)	4 (6.1)	**0.002**
Rituximab	18 (8.9)	1 (1.5)	**0.046**
Hydroxycloroquine	141 (67.8)	36 (54.5)	**0.050**
Early use of HD steroids	103 (59.9)	25 (43.1)	**0.026**
Early use of IS	85 (49.7)	12 (20.7)	**<0.001**

FACTORES PREDICTORES DE DAÑO CRÓNICO

SLEDAI > 6

SDI ELEVADO AL INICIO

CORTICOIDES

USO DE INMUNOSUPRESORES

NMUNOSUPRESORES Y DAÑO

- **TODOS FAVORECEN:**
  - **INFECCIONES**
  - **RIESGO DE NEOPLASIAS (SE RELACIONA CON LA INTENSIDAD Y DURACIÓN DEL TRATAMIENTO)**

- **CFM: FALLO OVÁRICO PRECOZ**

- **INHIB CALCINEURINA: INSUFICIENCIA RENAL**

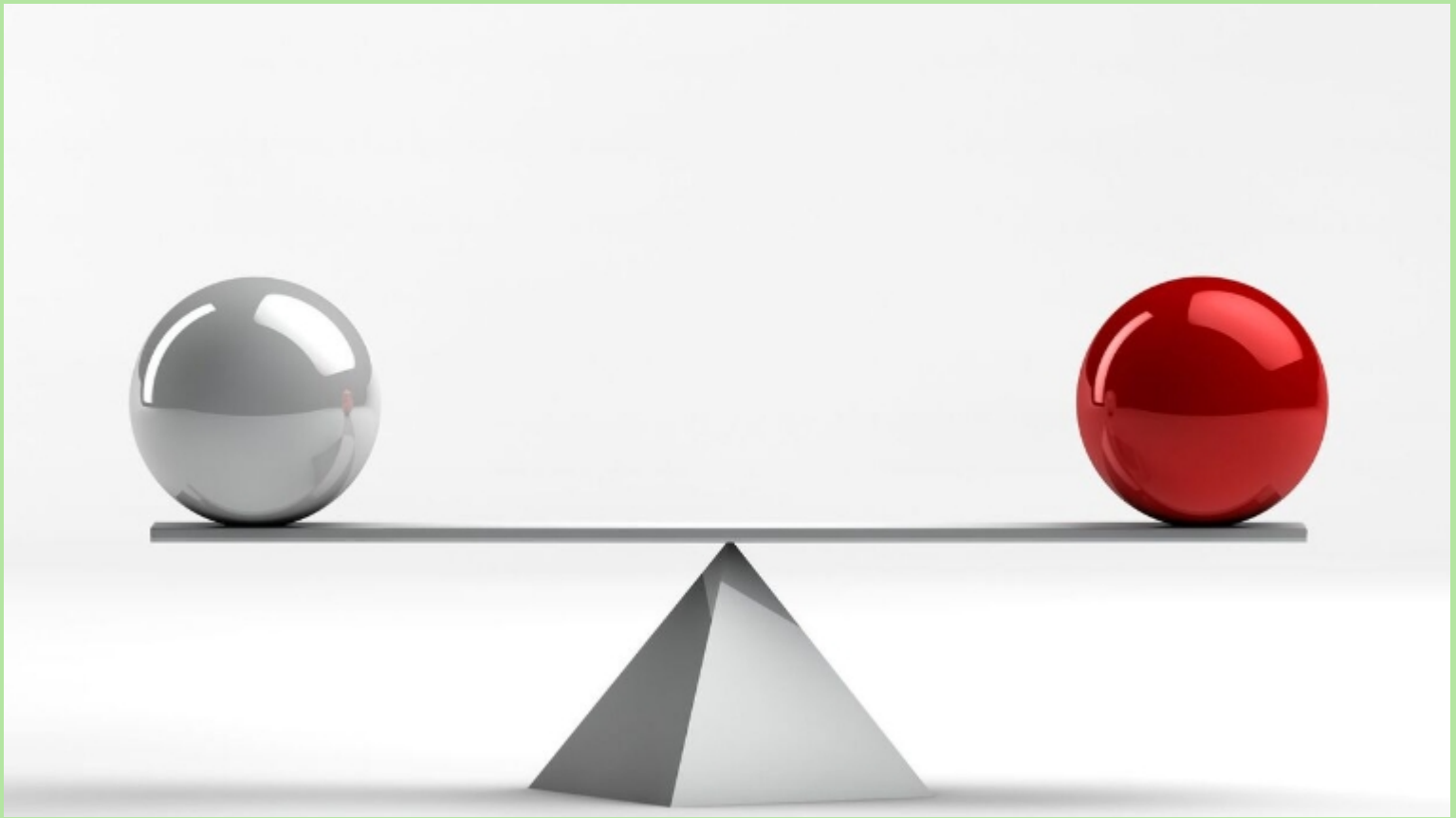
- **TACROLIMUS: DIABETES, ATEROSCLEROSIS (TRASTORNOS METABÓLICOS)**

1er PASO

ACTIVIDAD

2º PASO

CORTICOIDES/ IS



CLINICAL SCIENCE

Withdrawal of low-dose prednisone in SLE patients with a clinically quiescent disease for more than 1 year: a randomised clinical trial

Alexis Mathian ,[1] Micheline Pha,[1] Julien Haroche,[1] Fleur Cohen-Aubart,[1] Miguel Hié,[1] Marc Pineton de Chambrun,[1] Thi Huong Du Boutin,[1] Makoto Miyara,[2] Guy Gorochov,[2] Hans Yssel,[2] Patrick Cherin,[1] Hervé Devilliers,[3] Zahir Amoura[1]

- 124 pacientes lupus quiescente (12 MESES)

- 61 pacientes SIN PDN, 63 CON PDN

- 4/61 (7%) pacientes con PDN vs 17/63 (27%

Table 2 Results for primary and secondary endpoints at 52 weeks

	Maintenance group (n=61)	Withdrawal group (n=63)	Relative risk (95% CI)	P value*
Primary endpoint: any flare according to SFI	4 (7)	17 (27)	0.2 (0.1 to 0.7)	0.003

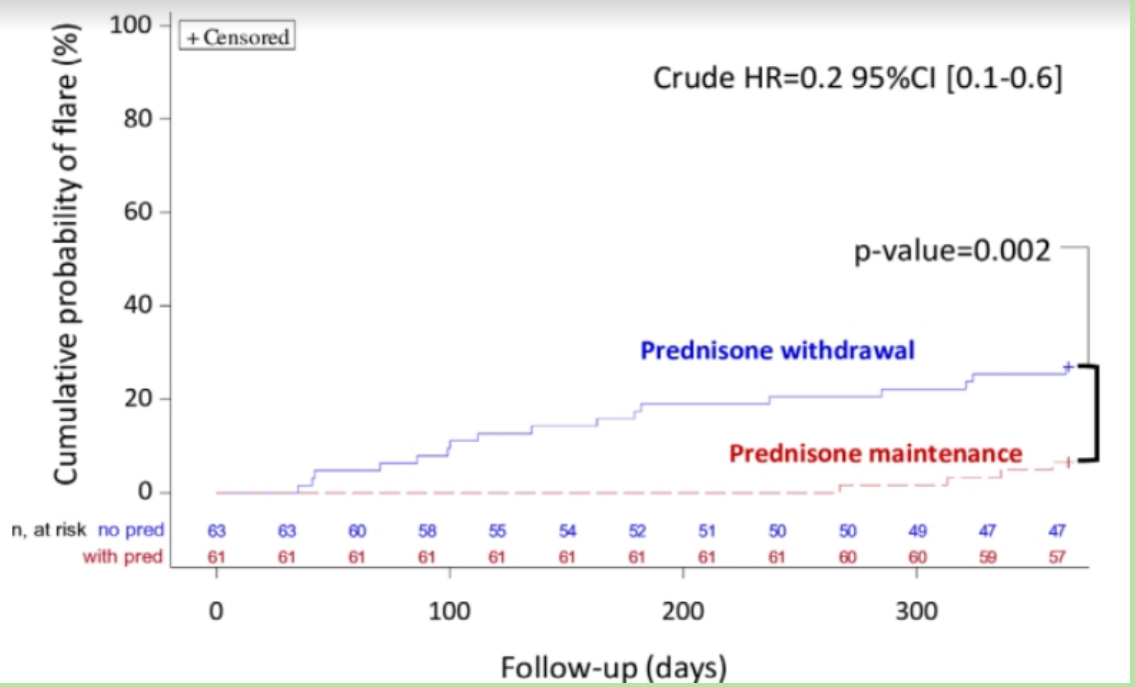


Table 1 Baseline demographic and clinical characteristics of the study subjects

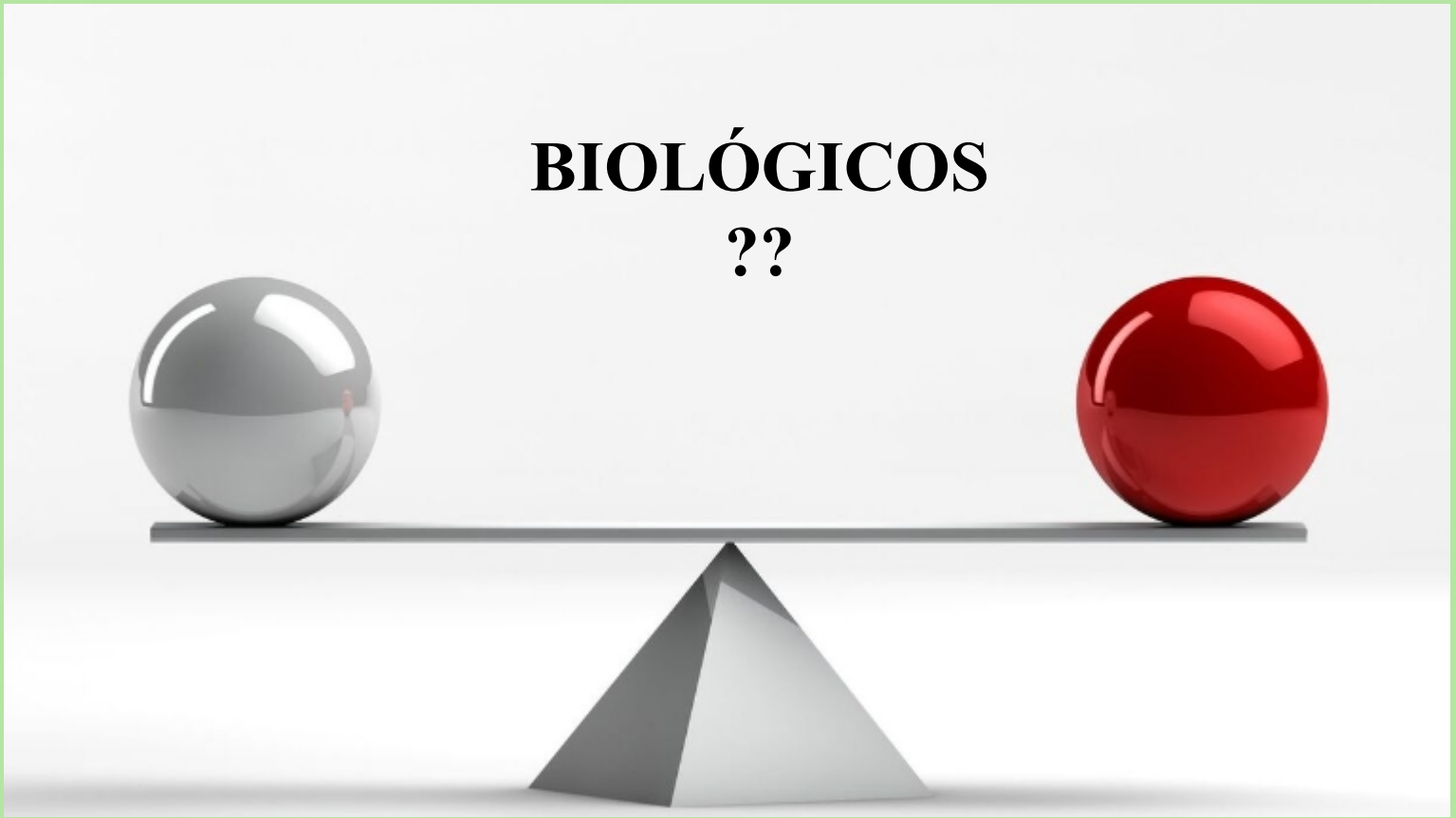
Characteristic	Maintenance group (n=61)	Withdrawal group (n=63)
Age, years	41±1.7	44±1.6
Women	55 (90)	56 (89)
Disease duration, months	147±86	163±96
Quiescence duration, months	56±6	68±7
Mean SELENA–SLEDAI score	1.5±0.2	1.4±0.2
History of		
Lupus nephritis	21 (34)	26 (41)
Neuropsychiatric lupus	4 (7)	8 (13)
Arthritis	43 (71)	55 (87)
Cutaneous lupus	35 (57)	39 (62)
Serositis	15 (25)	17 (27)
SDI score	0.5±0.1	0.7±0.2
Low C3	17 (28)	18 (29)
Increased dsDNA binding	29 (48)	28 (46)
Low C3 and increased dsDNA binding	10 (16)	10 (16)
HCQ use	57 (93)	56 (89)
[HCQ], µg/L	1071±66	953±55
[HCQ]>750 µg/L*	38/56† (68)	38/56† (68)
Corticoid duration, months	137±11	145±13
Immunosuppressive drugs	17 (28)	16 (25)
Methotrexate	10 (16)	3 (5)
Azathioprine	3 (5)	1 (2)
Mycophenolate mofetil	4 (7)	12 (19)

1er PASO

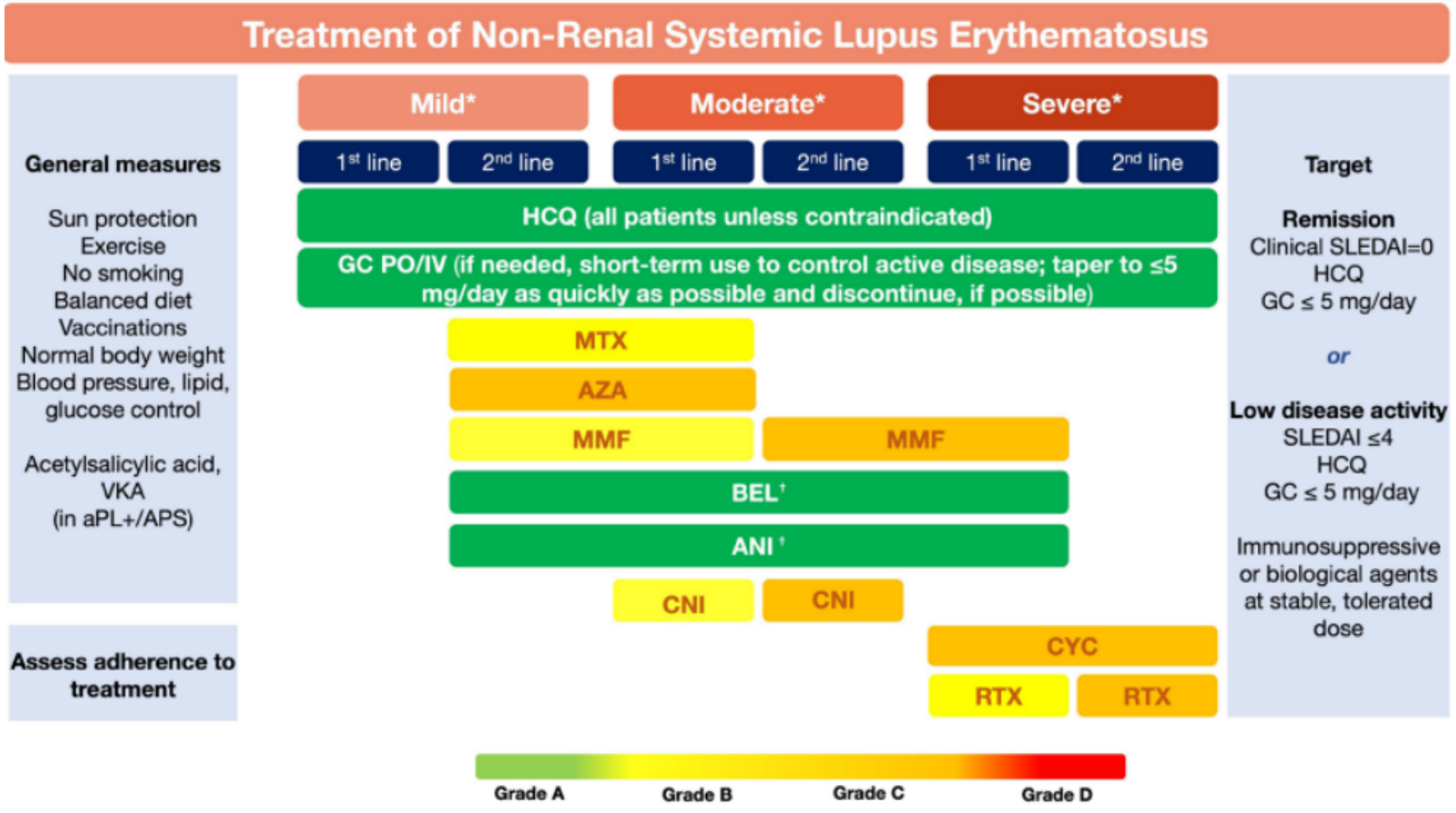
ACTIVIDAD

2º PASO

CORTICOIDES/ IS



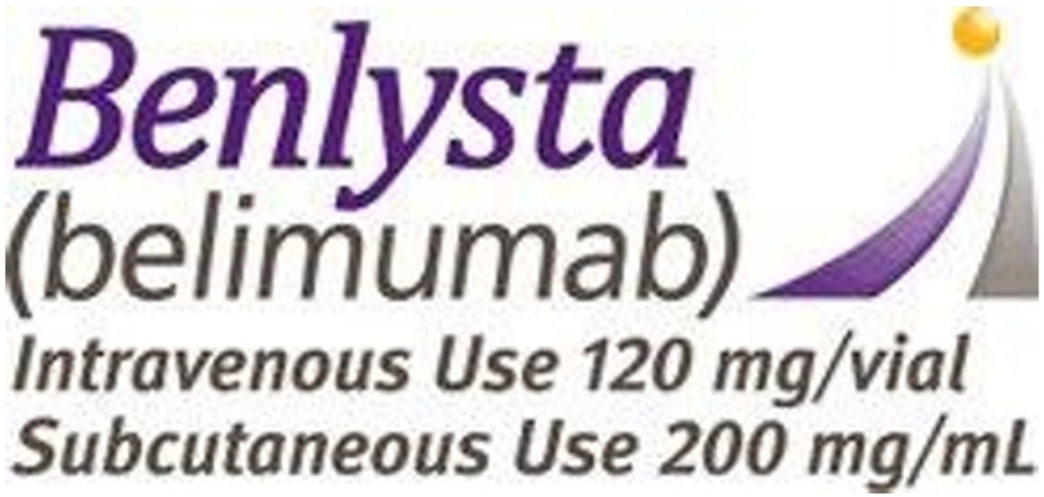
3. In patients **not responding to hydroxychloroquine** (alone or in combination with glucocorticoids) or patients unable to reduce glucocorticoids below doses acceptable for chronic use, **addition of immunomodulating/immunosuppressive agents** (eg, methotrexate (1b/B), azathioprine (2b/C) or mycophenolate (2a/B)) **and/or biological agents** (eg, belimumab (1a/A) or anifrolumab (1a/A)) should be considered.



BIOLÓGICOS EN LES NO RENAL

EN PACIENTES QUE NO RESPONDEN A HCQ +/- GC O SI NO PUEDEN REDUCIR GC: ASOCIAR INMUNOSUPRESORES Y/O BIOLÓGICOS.

Belimumab



- Aprobado por la FDA 2011
- Mecanismo: Anti-BAFF. Bloquea la unión de la forma soluble de BLyS a su receptor en las células B, impidiendo su activación excesiva
- Estudios: BLISS-52 y BLISS-76

Anifrolumab

- Aprobado por la FDA 2021
- Mecanismo: Inhibe IFN1.

Anticuerpo monoclonal humano de tipo inmunoglobulina G1 kappa que se une a la subunidad 1 del receptor del interferón de tipo I (IFNAR1)

- Estudios: TULIP-1 y TULIP-2

QUÉ NECESITAMOS DE LOS BIOLÓGICOS EN LES NO RENAL

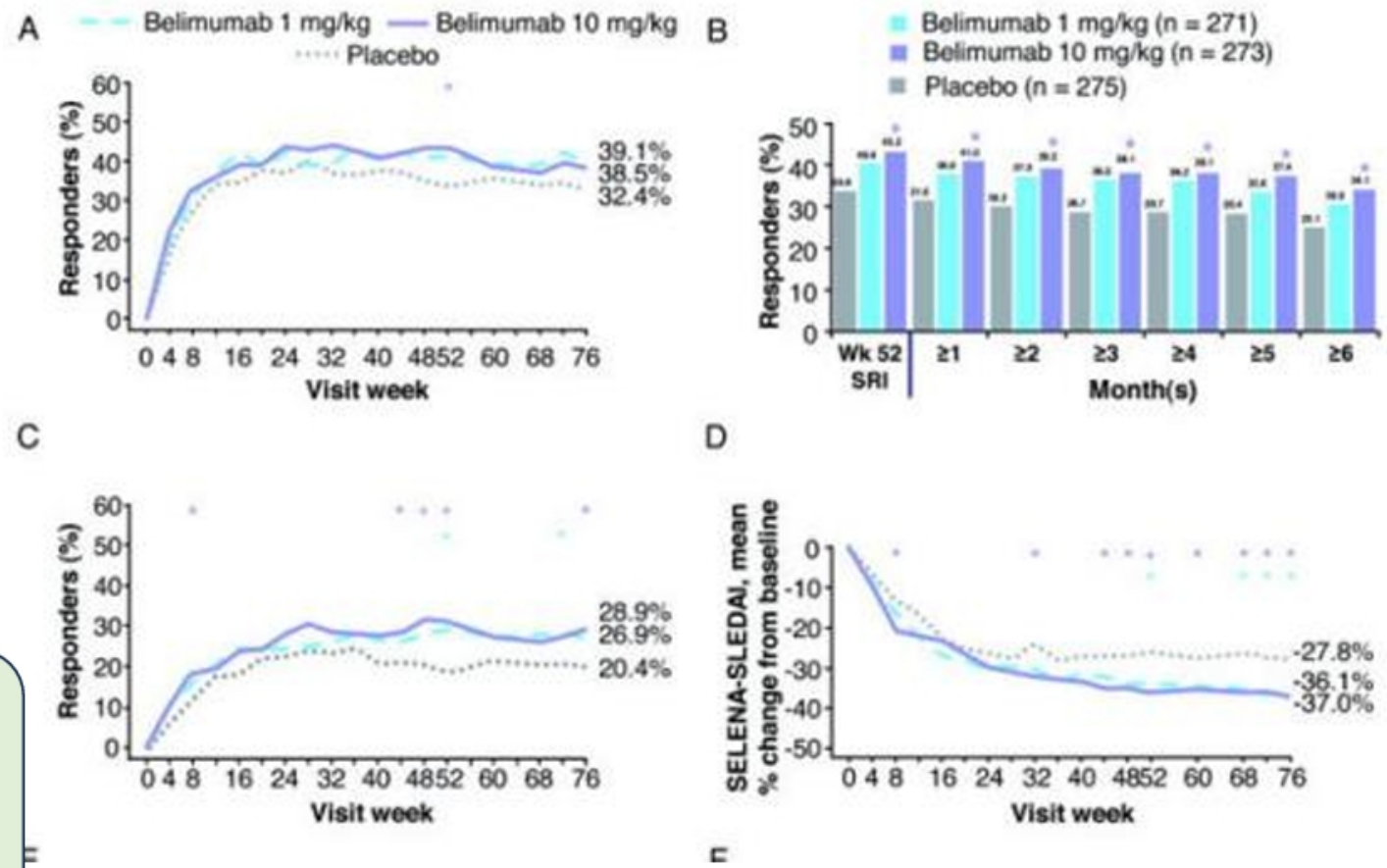
1. EFICACIA COMPROBADA PARA CONTROLAR LA ACTIVIDAD DE LA ENFERMEDAD, REDUCIR LOS BROTES Y PERMITIR LA REDUCCIÓN DE DOSIS DE GC.

Benlysta (belimumab)

Intravenous Use 120 mg/vial

A Phase 3, Randomized, Placebo-Controlled Study of Belimumab, a Monoclonal Antibody That Inhibits BLyS, in Patients With Systemic Lupus Erythematosus

Efficacy parameter	Placebo (n = 275)	Belimumab 1 mg/kg (n = 271)	Belimumab 10 mg/kg (n = 273)
SRI response rate at week 52, n (%)[*]	92 (33.5)	110 (40.6)	118 (43.2)[†]
≥4-point reduction in SELENA-SLEDAI[‖]	97 (35.3)	116 (42.8)	127 (46.5)[‡]
SRI response rate at week 76, n (%)[*‖]	89 (32.4)	106 (39.1)	105 (38.5)
≥4-point reduction in SELENA-SLEDAI[‖]	93 (33.8)	114 (42.1)[†]	113 (41.4)

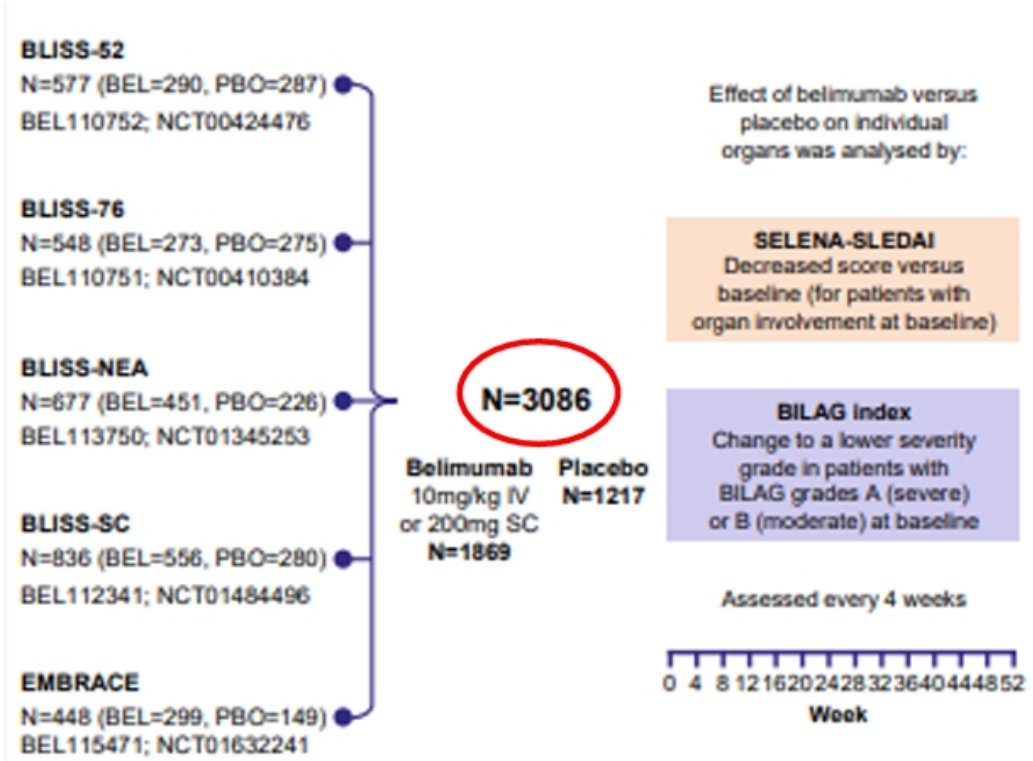


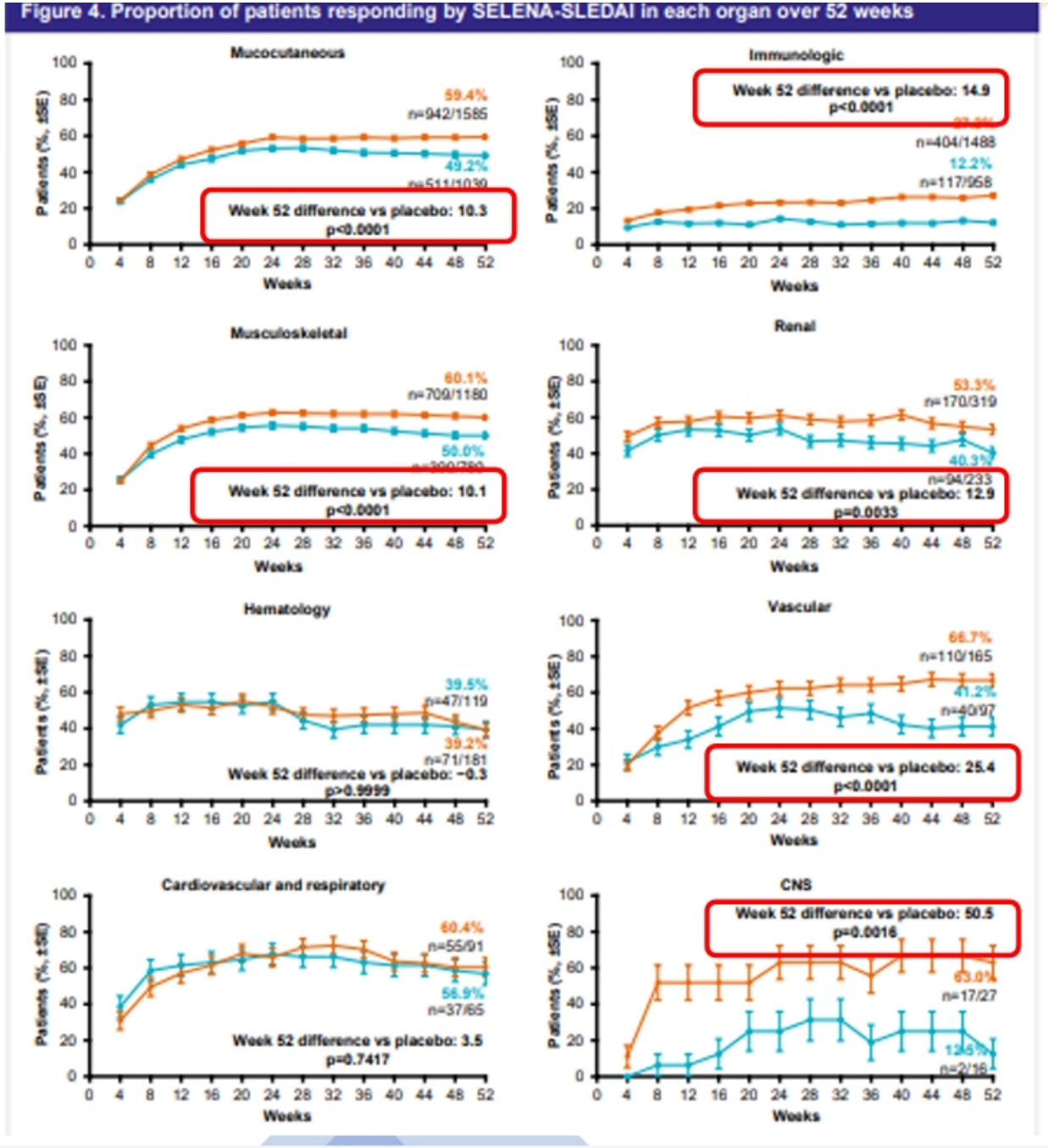
% Reducción del SLEDAI a las 76 semanas:
- Placebo: **–27,8%**
- Belimumab 1mg/kg: **-36,1%**

Lancet. 2011 Feb 26;377(9767):721-31
Arthritis Rheum. 2011 Dec; 63(12): 3918–3930.

Efficacy of Belimumab Across Multiple Organ Domains in Systemic Lupus Erythematosus: Results of a Large Integrated Analysis

This was a pooled analysis of 5 Phase 3, randomized, placebo-controlled belimumab clinical trials: BLISS-52, BLISS-76, BLISS-NEA, BLISS-SC, and EMBRACE (**Figure 1**)





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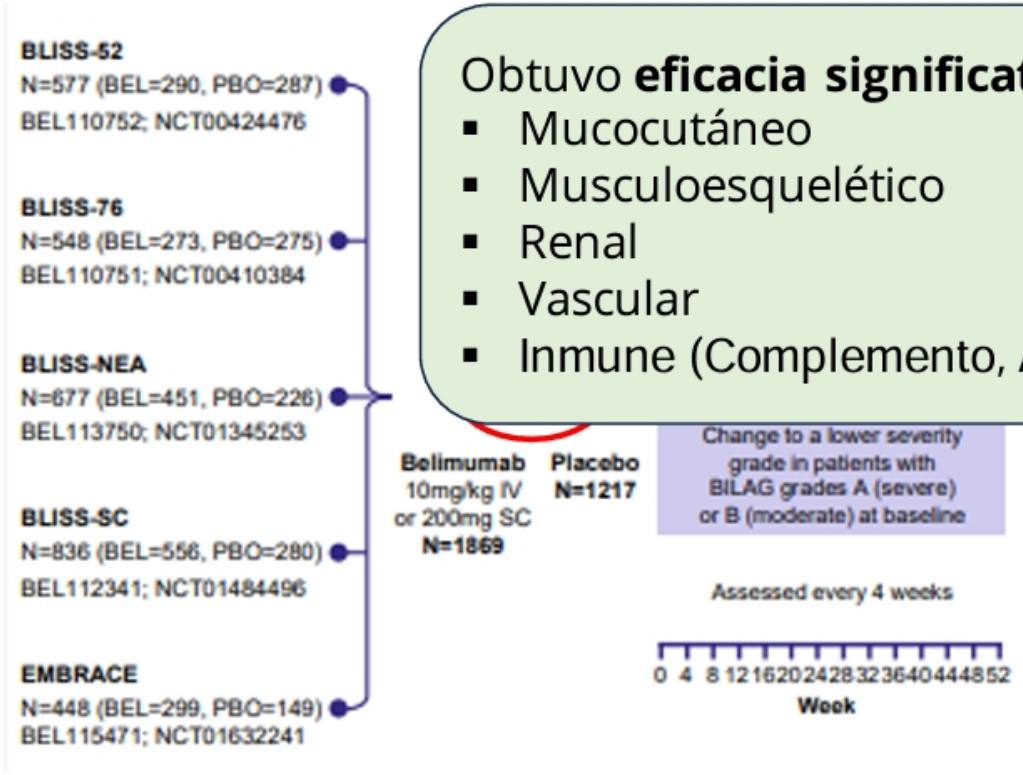
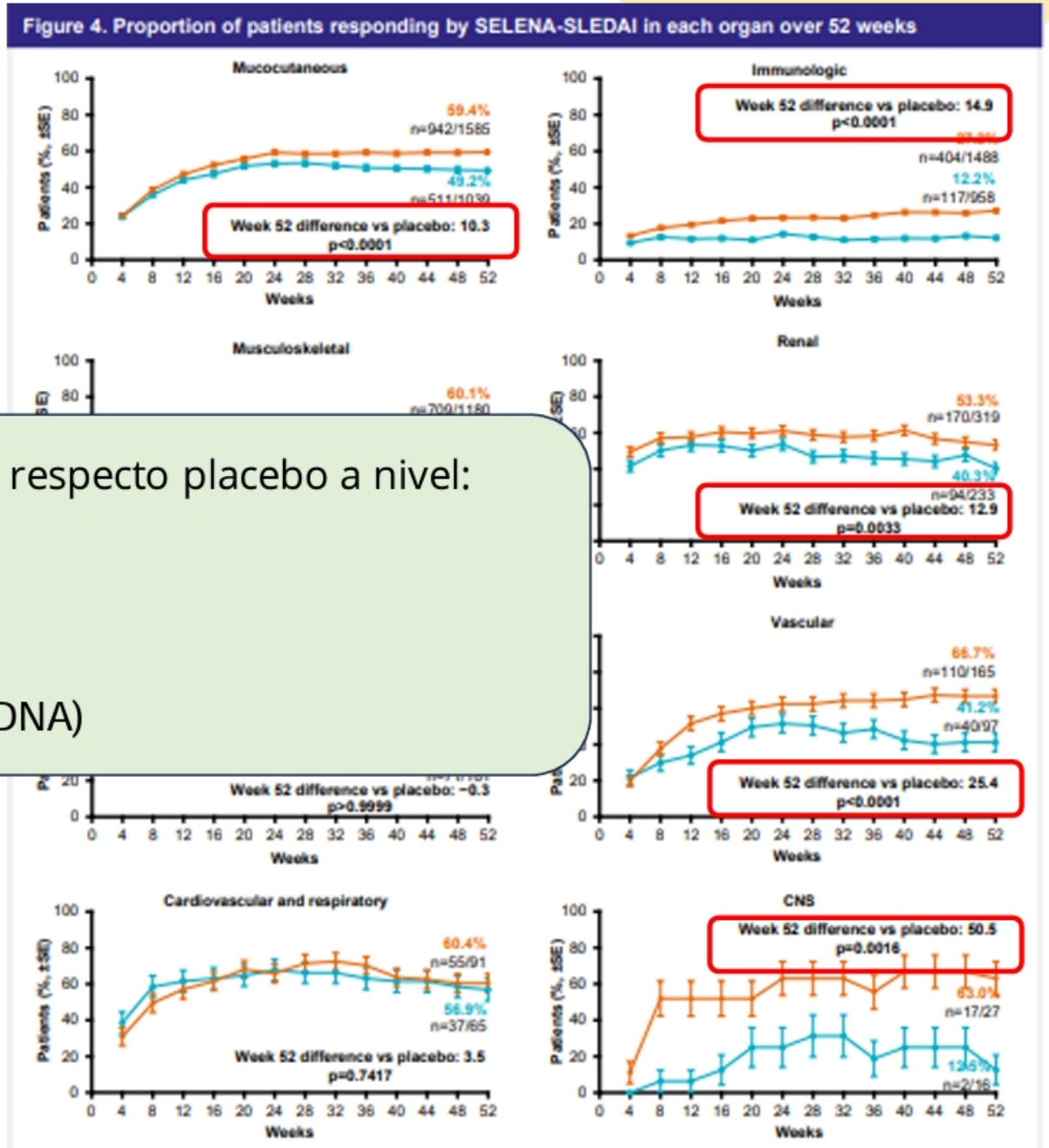


Obtuvo **eficacia significativa** respecto placebo a nivel:

- Mucocutáneo
- Musculoesquelético
- Renal
- Vascular
- Inmune (Complemento, AntiDNA)



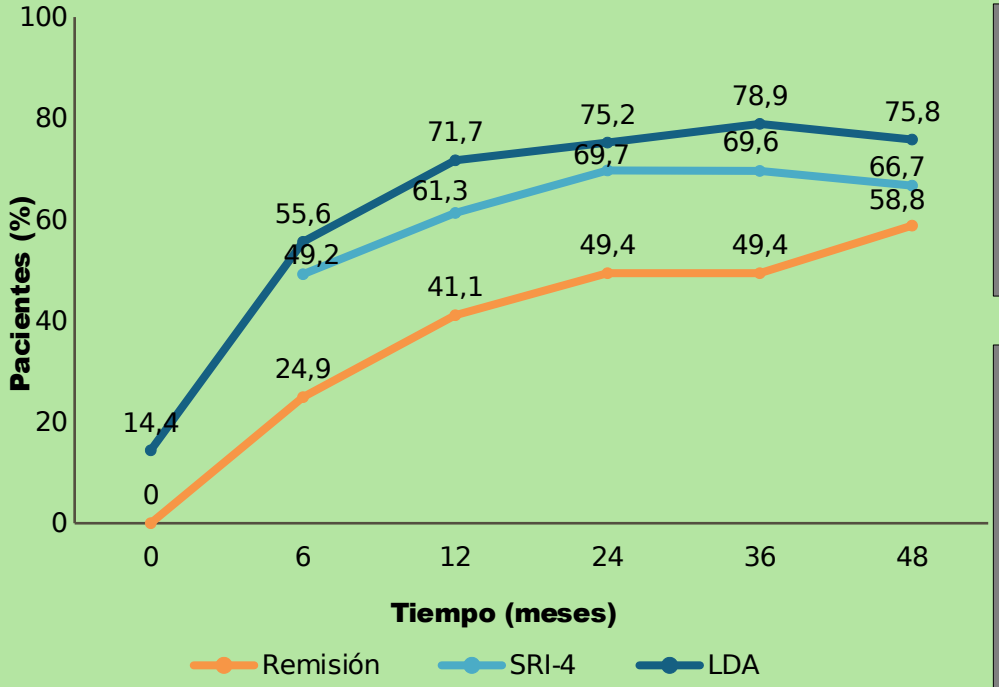
Respuesta SRI-4, LDA y remisión tras el tratamiento con belimumab en el estudio BeRLiSS (N=466) en práctica clínica real (Gatto et al, 2020)

American College of Rheumatology
Empowering Rheumatology Professionals

Arthritis & Rheumatology
Vol. 72, No. 8, August 2020, pp 1314–1324
DOI 10.1002/art.41253
© 2020, American College of Rheumatology

Early Disease and Low Baseline Damage as Predictors of Response to Belimumab in Patients With Systemic Lupus Erythematosus in a Real-Life Setting

Mariele Gatto,[1] Francesca Saccon,[1] Margherita Zen,[1] Francesca Regola,[2] Micaela Fredi,[2] Laura Andreoli,[2] Angela Tincani,[2] Maria Letizia Urban,[3] Giacomo Emmi,[3] Fulvia Ceccarelli,[4] Fabrizio Conti,[4] Alessandra Bortoluzzi,[5] Marcello Govoni,[5] Chiara Tani,[6] Marta Mosca,[6] Tania Ubiali,[7] Maria Gerosa,[7] Enrica Bozzolo,[8] Valentina Canti,[8] Paolo Cardinaletti,[9] Armando Gabrielli,[9] Giacomo Tanti,[10] Elisa Gremese,[11] Ginevra De Marchi,[12] Salvatore De Vita,[12] Serena Fasano,[13] Francesco Ciccia,[13] Giulia Pazzola,[14] Carlo Salvarani,[15] Simone Negrini,[16] Francesco Puppo,[16] Andrea Di Matteo,[17] Rossella De Angelis,[17] Giovanni Orsolini,[18] Maurizio Rossini,[18] Paola Faggioli,[19] Antonella Laria,[19] Matteo Piga,[20] Alessandro Mathieu,[20] Salvatore Scarpato,[21] Francesca W. Rossi,[22] Amato de Paulis,[22] Enrico Brunetta,[23] Angela Ceribelli,[24] Carlo Selmi,[25] Marcella Prete,[26] Vito Racanelli,[26] Angelo Vacca,[26] Elena Bartoloni,[27] Roberto Gerli,[27] Maddalena Larosa,[1] Luca Iaccarino,[1] and Andrea Doria[1]



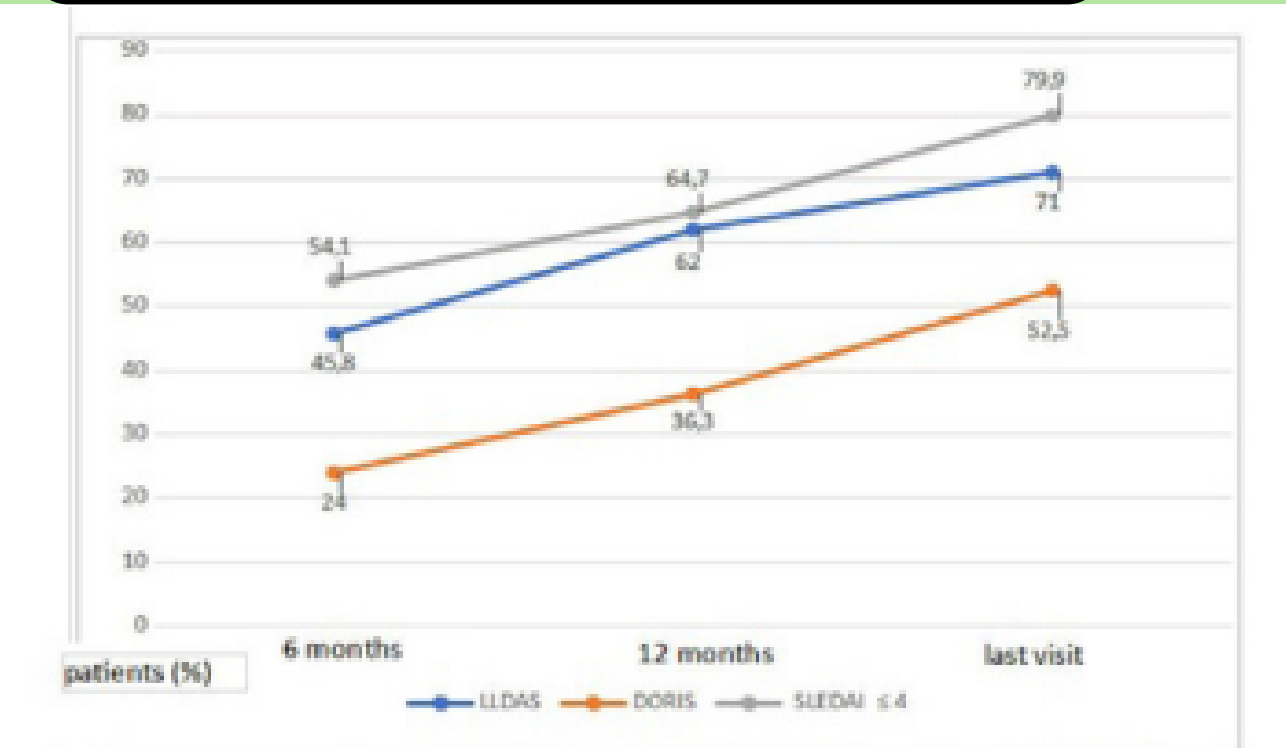
Conclusión: En pacientes con LES activo y daño bajo al inicio del estudio, el tratamiento con belimumab en las primeras etapas de la enfermedad puede conducir a resultados favorables en un entorno de la vida real.

Los pacientes que estuvieron en remisión durante el ≥25% del período de seguimiento (44,3%) o que tuvieron baja actividad de la enfermedad durante el ≥50% del período de seguimiento (66,1%) acumularon un daño significativamente menor (P = 0,046 y P = 0,007).

El índice de respuesta SRI fue del 66,7% a los 48 meses.

Gatto M, Saccon F, Zen M, et al. Early Disease and Low Baseline Damage as Predictors of Response to Belimumab in Patients With Systemic Lupus Erythematosus in a Real-Life Setting. Arthritis Rheumatol. 2020 Aug;72(8):1314-1324.

SLEDAI-2K, LLDAS y DORIS en una cohorte de 324 pacientes (Altabás-González et al, 2023)



El **71%** de los pacientes alcanzaron **LLDAS** (p <0,05) y **más de la mitad (52,5%)** la **remisión** (p<0,05)

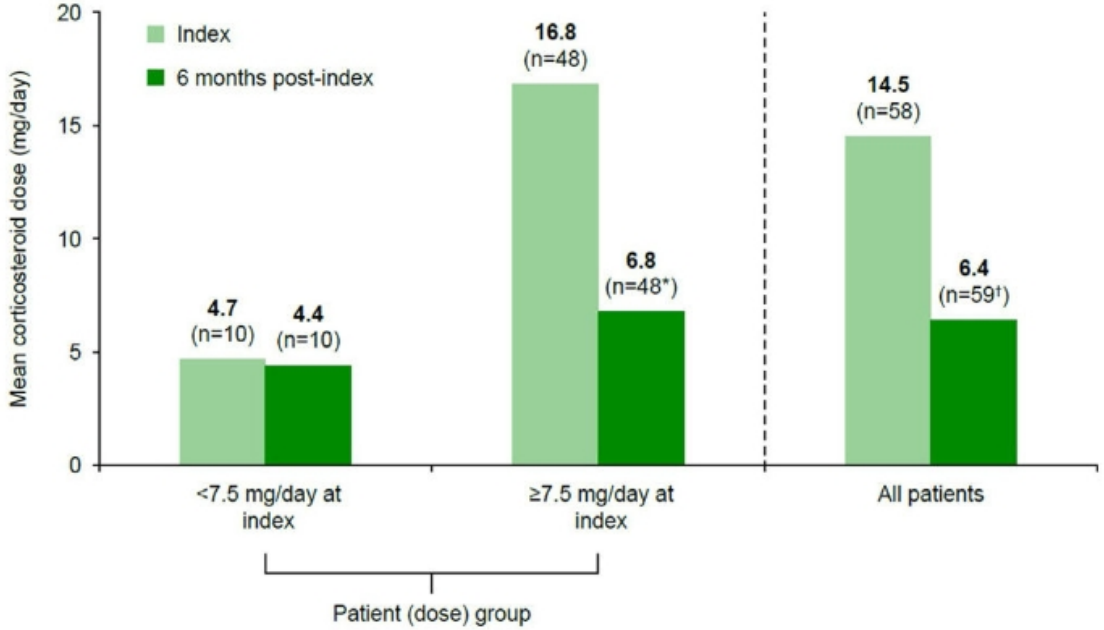
Altabás González I, Pego-Reigosa JM, Mouriño Rodríguez C*, et al* POS1144 EFFECTIVENESS OF BELIMUMAB IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS OF A MULTICENTER SPANISH COHORT *Annals of the Rheumatic Diseases* 2023;**82:**901-902.

Belimumab reduce el riesgo de brotes graves y el uso de corticoides

Brotes extrarrenales en vida real

En el estudio BeRLiSS (N=466) el **64,8% de los pacientes no experimentó ningún brote** y se observó **una reducción significativa vs el período previo a recibir belimumab (p<0,001) (1)**

En el estudio **OBSErve España en práctica clínica real** (n=64), **66,7% de los pacientes** que recibían una dosis alta de GC ≥7,5 mg/día disminuyó la dosis y el **4,2% suspendieron los GC (2)**



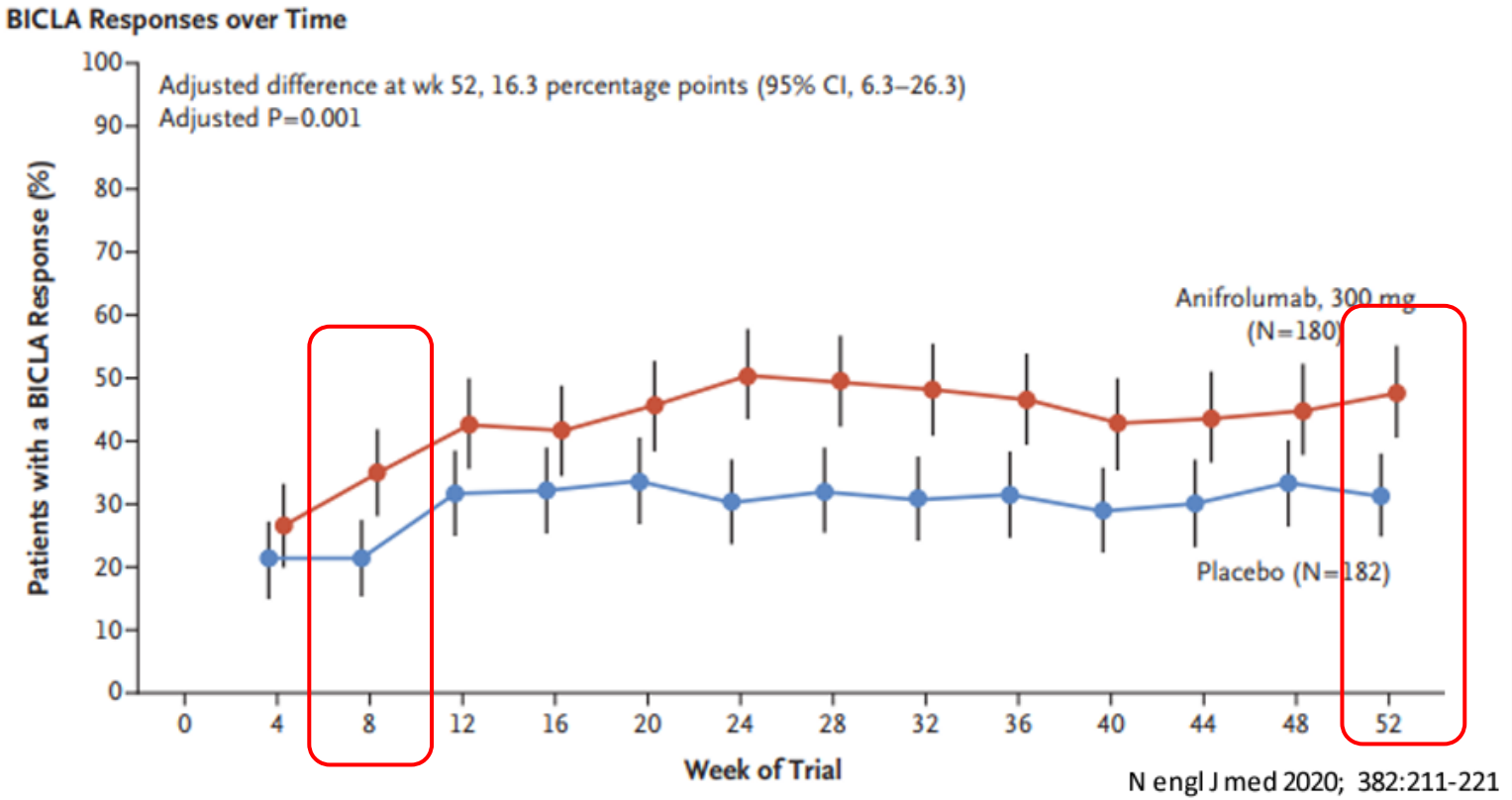
(1) Gatto M, Saccon F, Zen M, et al. Early Disease and Low Baseline Damage as Predictors of Response to Belimumab in Patients With Systemic Lupus Erythematosus in a Real-Life Setting. Arthritis Rheumatol. 2020 Aug;72(8):1314-1324. (2) Cortes-Hernández J. Marras C, Andreu JL, *et al.* Reduction of disease activity, corticosteroids use, and healthcare resource utilisation in patients with systemic lupus erythematosus treated with belimumab in clinical practice settings: OBSErve Spain multicentre study. Reumatología Clínica. 2022.

Anifrolumab reduce la actividad de la enfermedad

Table 2. Primary and Key Secondary Efficacy End Points.

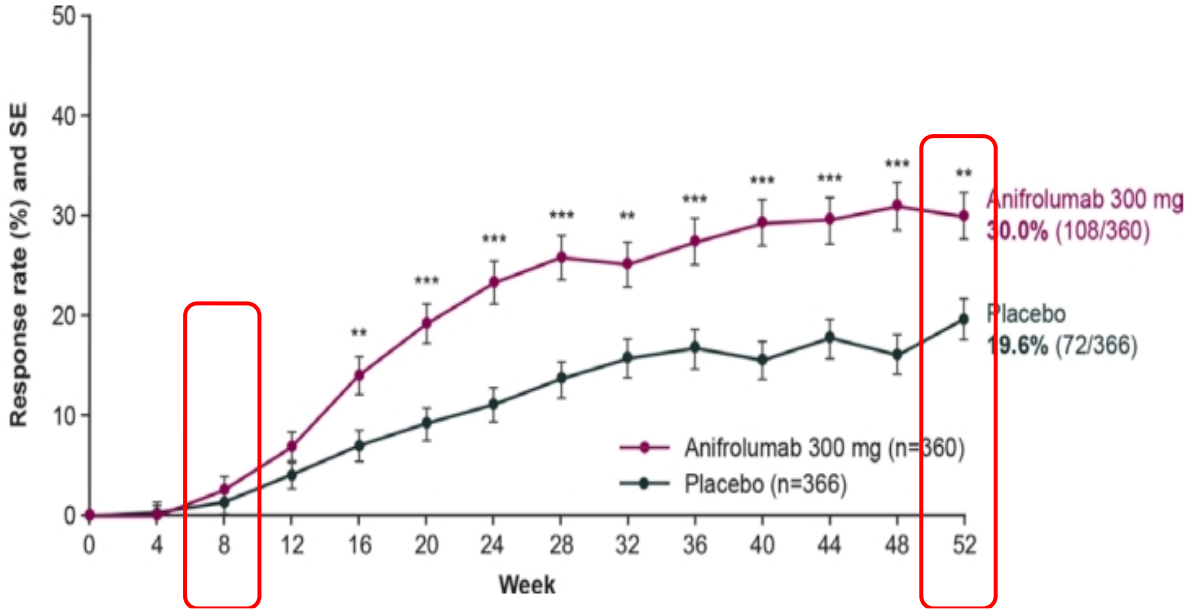
End Point	Placebo (N=182)*	Anifrolumab, 300 mg (N=180)*	Difference (95% CI)*	Adjusted P Value†
	number/total number (percent)		*percentage points*	
Primary end point: BICLA response at wk 52‡	57/182 (31.5)	86/180 (47.8)	16.3 (6.3 to 26.3)	0.001

- **TULIP-2**: Evaluación de respuesta mediante **BICLA** a la semana 52
  - Resultados: Anifrolumab 300 mg vs placebo; Diferencia 16,3 [6,3 to 26,3]; **p=0.001**

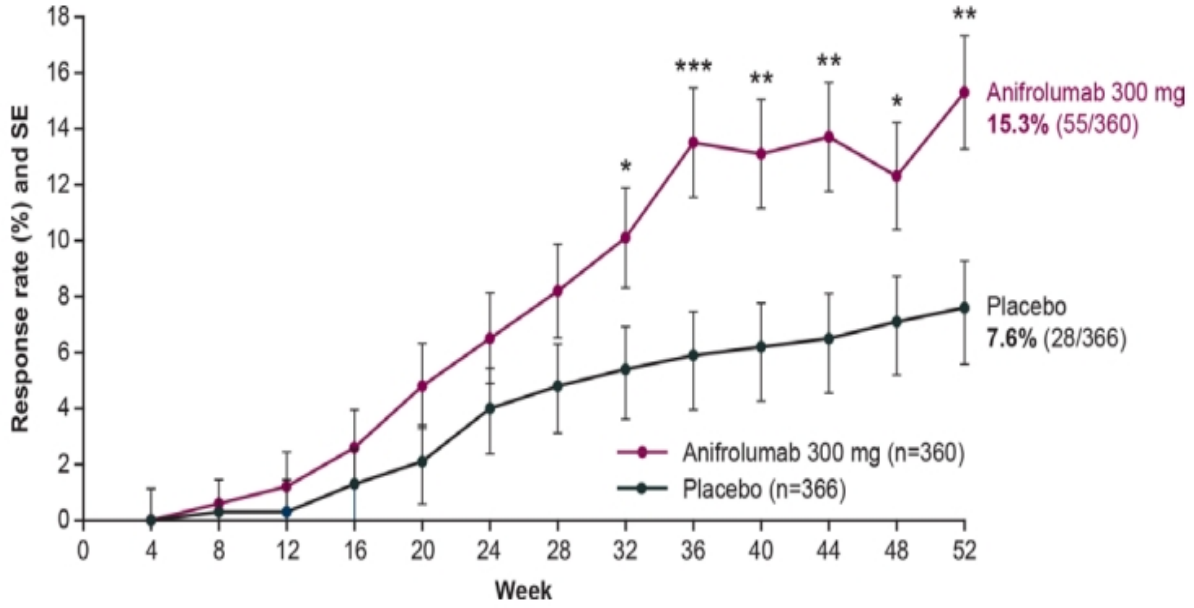


N engl J med 2020; 382:211-221

- 16,3% mejoría BICLA a las 52 semanas respecto placebo
- eficacia a partir de la semana 8



REMISSION



LLADS

⇒ Anifrolumab treatment was associated with earlier, more frequent and more sustained attainment of LLDAS among patients who had active SLE despite receiving standard of care.

⇒ These results highlight the potential utility of anifrolumab in a T2T approach for the management of patients with moderate to severe SLE

Morand E, Abreu G, Furie R, et al. Attainment of the Lupus Low Disease Activity State in response to anifrolumab in 2 phase 3 trials. Arthritis Rheumatol 2021;73 (Suppl 10; Abstract 1459).

ABSTRACT NUMBER: 1828

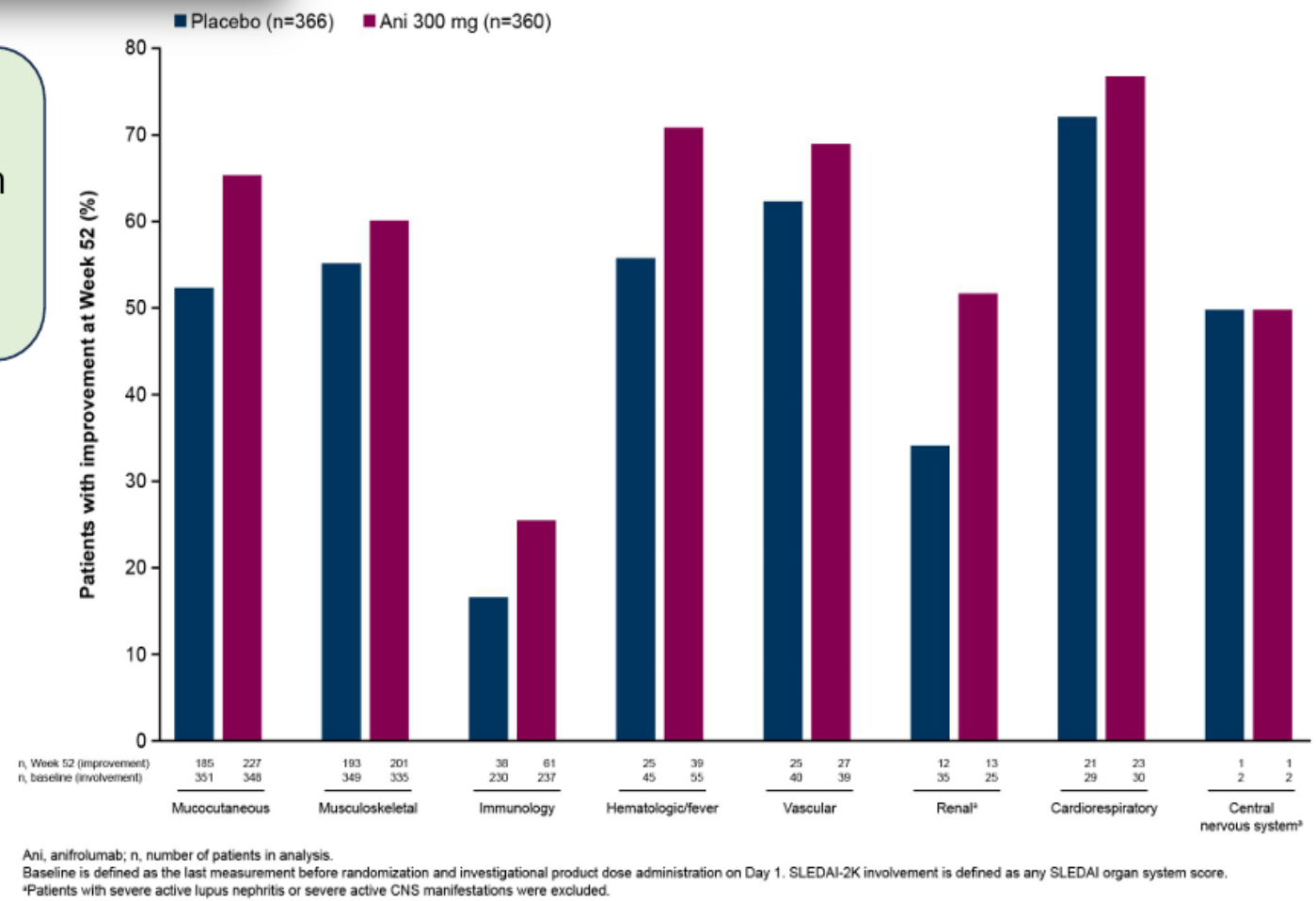
Comprehensive Efficacy of Anifrolumab Across Organ Domains in Patients with Active SLE: Pooled Data from 2 Phase 3 Trials

Estudio **POST-HOC** sobre datos de TULIP-1 y TULIP-2
Subanálisis por órganos de afectación median te SLEDAI-2K Organ a las 52 semanas

NOTA: Pacientes con LN fueron excluidos

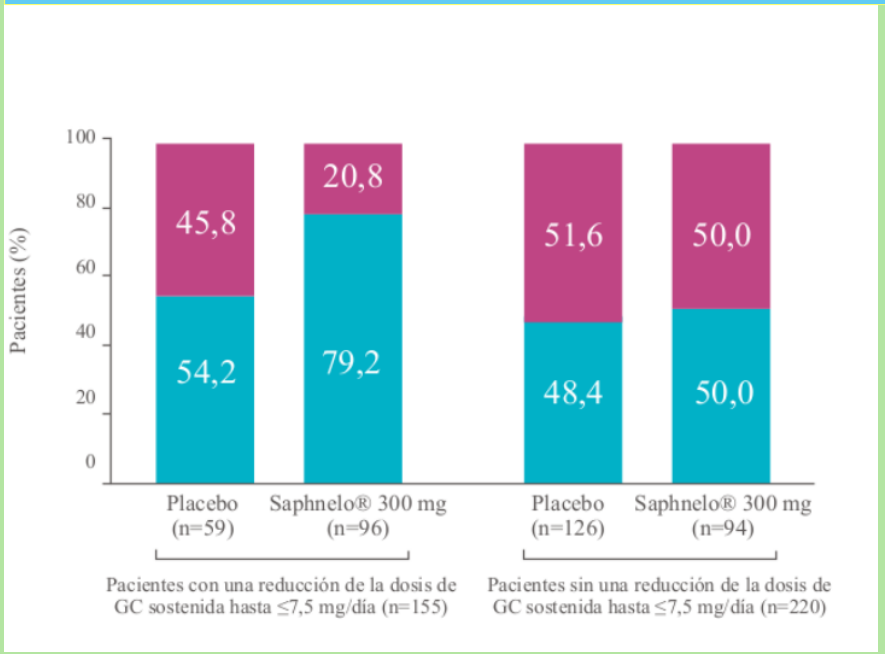
Obtuvo **eficacia significativa** respecto placebo a nivel:

- Mucocutáneo
- Musculoesquelético
- Hematológico
- Inmune (Complemento, AntiDNA)



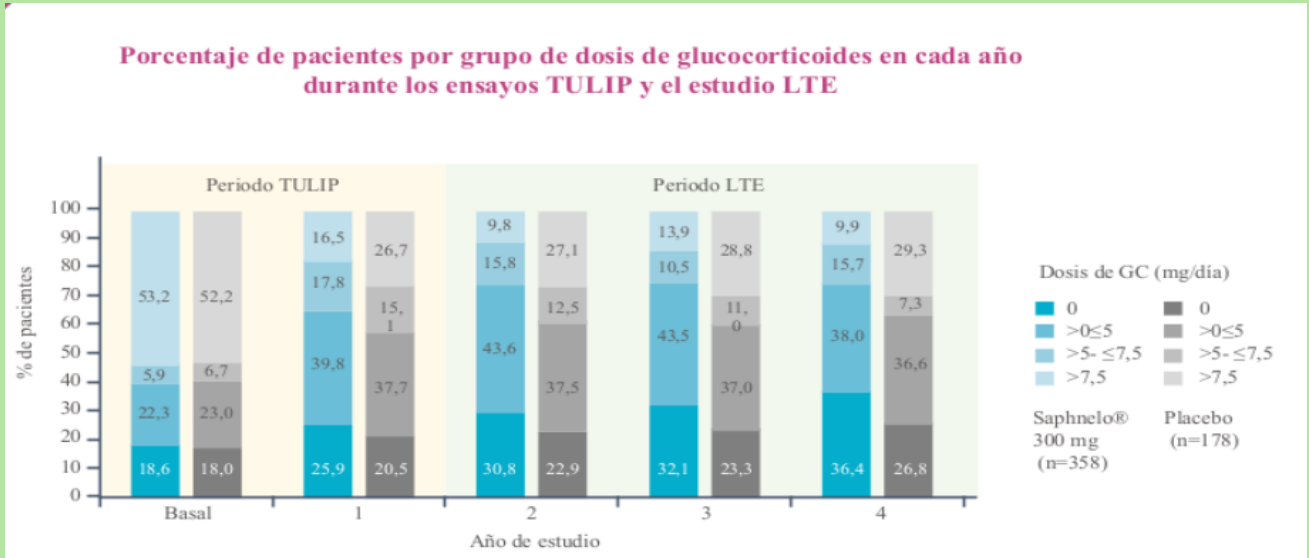
Ani, anifrolumab; n, number of patients in analysis.
Baseline is defined as the last measurement before randomization and investigational product dose administration on Day 1. SLEDAI-2K involvement is defined as any SLEDAI organ system score.
[a]Patients with severe active lupus nephritis or severe active CNS manifestations were excluded.

Anifrolumab permite reducir corticoides



- 40% pacientes tratados con ANIFROLUMAB redujeron de forma sostenida corticoides ≤ 7,5 mg/ d (1)

- 80% de ellos estuvieron libres de brotes en la semana 52



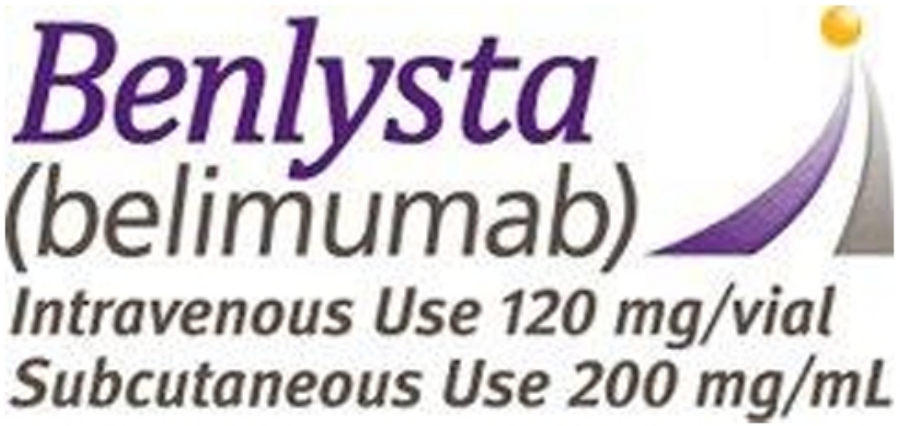
A los 4 años de tratamiento (2):
- 90% tenía corticoides ≤ 7,5 mg/ d
- 36,4%: 0 corticoides
- 74,4 %: ≤ 5 mg/ d

Furie R, Morand EF, Askanase AD, Vital EM, Merrill JT, Kalyani RN, Abreu G, Pineda L, Tummala R. Anifrolumab reduces flare rates in patients with moderate to severe systemic lupus erythematosus. Lupus. 2021 Jul;30(8):1254-1263. doi: 10.1177/09612033211014267. Epub 2021 May 12. PMID: 33977796. (2) Kalunian KC et al. Arthritis Rheumatol 2021; 75 (2): 253-65

BIOLÓGICOS EN LES NO RENAL

2. NO HAY JERARQUÍA EN LA ELECCIÓN ENTRE ANIFROLUMAB Y BELIMUMAB.

3. NO HAY PERFIL CLíNICO DETERMINADO


Benlysta
(belimumab)
Intravenous Use 120 mg/vial
Subcutaneous Use 200 mg/mL

VS


Saphnelo™
(anifrolumab-fnia)
Intravenous Use 300 mg/vial

Benlysta (belimumab)
Intravenous Use 120 mg/vial
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Belimumab versus anifrolumab in adults with systemic lupus erythematosus: an indirect comparison of clinical response at 52 weeks

Binod Neupane,[1] Pragya Shukla,[1] Mahmoud Slim,[1,2] Amber Martin,[3] Michelle Petri ,[4] George K Bertsias ,[5] Alfred H J Kim,[6] Antonis Fanouriakis ,[7] Roger A Levy ,[8] Deven Chauhan,[9] Nick Ballew [10]

Metodología: Meta-regresión de 8 ensayos

- 5 Belimumab (BLISS-52, BLISS-76, NEA, BLISSSC, EMBRACE)
- 3 Anifrolumab (MUSE, TULIP-1, TULIP-2)

Resultados: Belimumab y anifrolumab **fueron comparables** en respuesta **SRI-4** (OR (95% credible interval), **1.04 (0.74–1.45)**

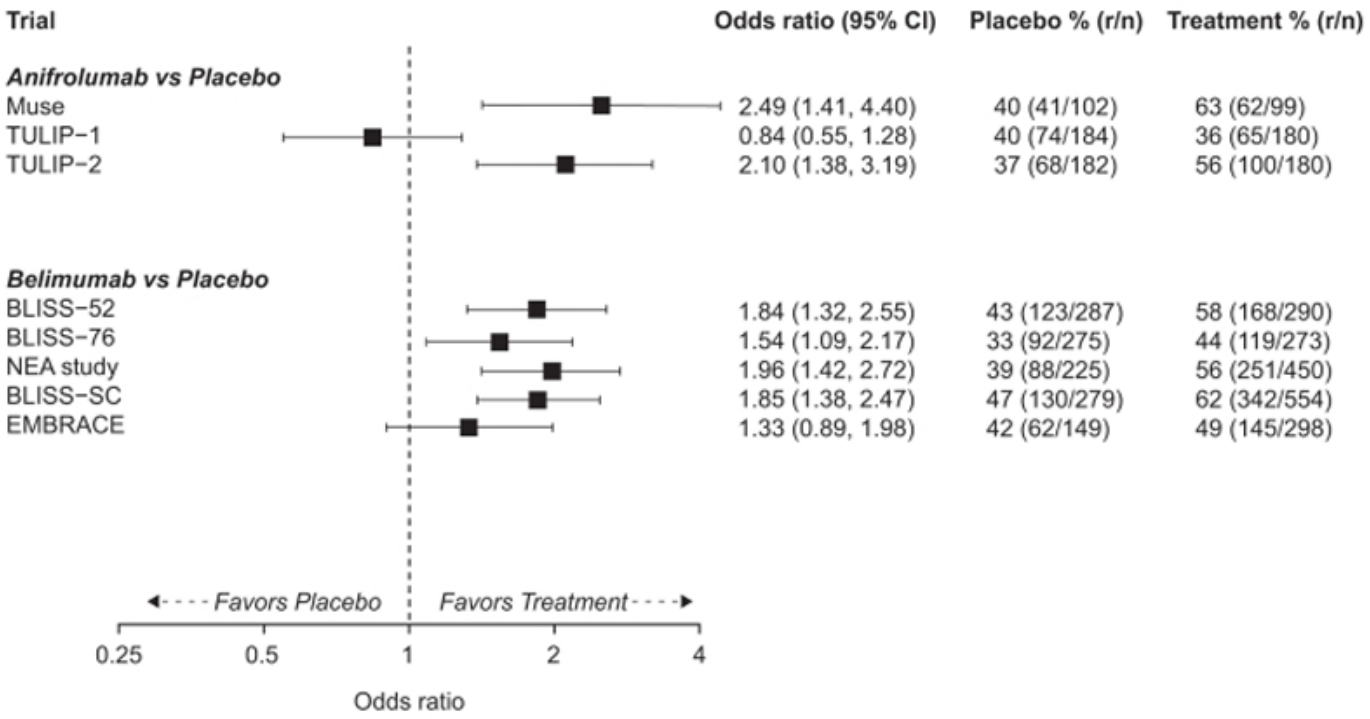

Figure 1 Trial level results that contributed to the ITC for SRI-4 at 52 weeks. ITC, indirect treatment comparison; n, sample size; r, number of responders; SRI-4, SLE Responder Index-4.

Lupus Sci Med. 2023 May;10(1):e000907

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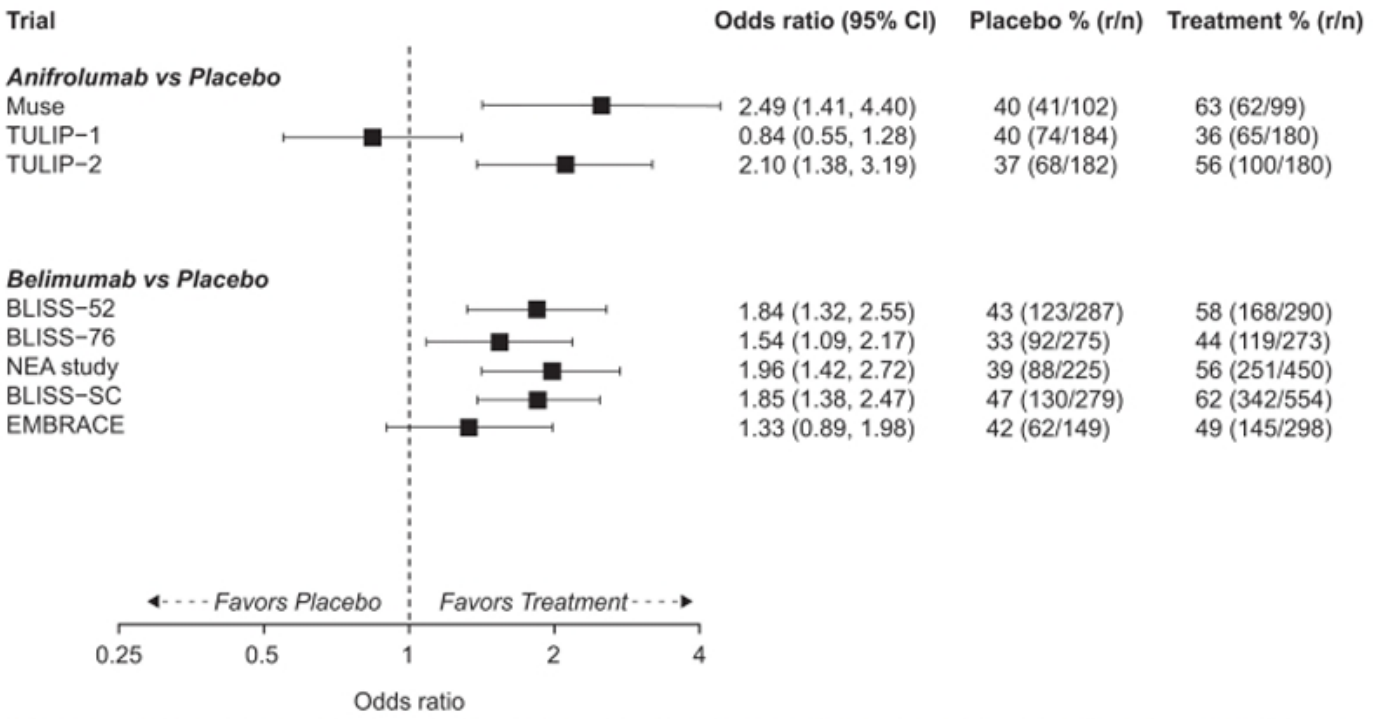

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Lupus Sci Med. 2023 May;10(1):e000907

BIOLÓGICOS EN LES NO RENAL

3. TANTO BELIMUMAB COMO ANIFROLUMAB SON SEGUROS

Belimumab tiene un buen perfil de seguridad

LARGO PLAZO En los estudios **de extensión en abierto de los ensayos fase II (13 años) y fase III (8 años)** de belimumab los datos de seguridad fueron consistentes, l**a incidencia de EAs acumulada en el tiempo se mantuvo estable o se redujo a largo plazo (1).**

Datos estudio BASE: mayor estudio de seguridad en LES (N=4003), con seguimiento a 4 años (2, 3)

Análisis post-hoc combinado del estudio fase II y de cinco ensayos fase III en adultos con LES (4)

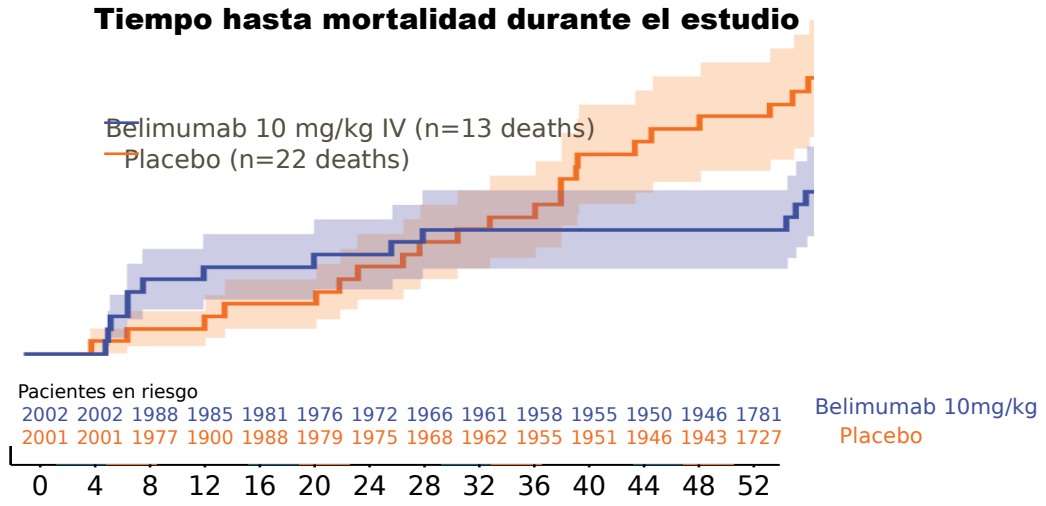


Figura adaptada de Sheikh SZ *et al*. The Lancet Rheumatology. 2021

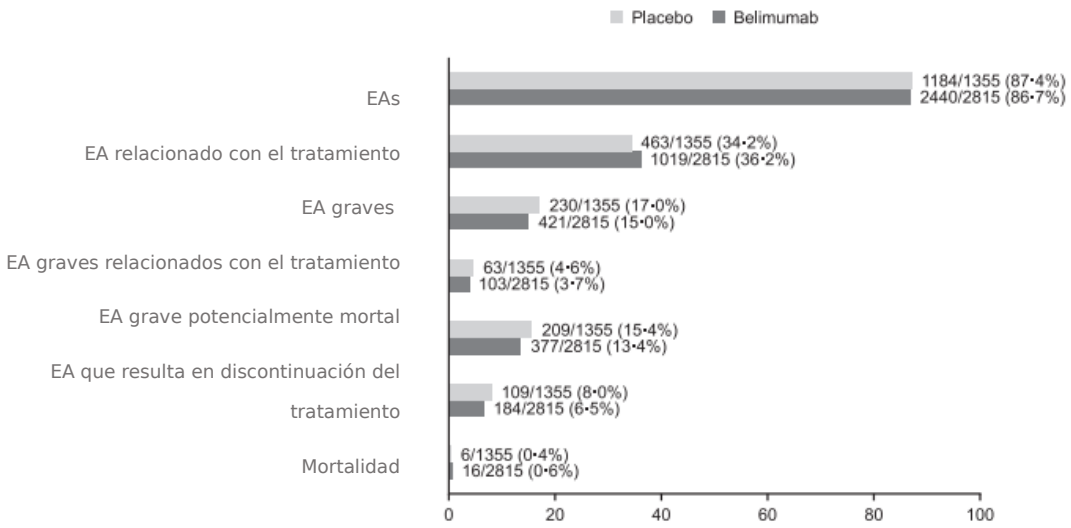


Figura adaptada de Wallace DJ *et al*. Lupus. 2022

Las tasas de infecciones y neoplasias fueron similares entre BELI y placebo y la incidencia de mortalidad fue menor.

Las tasas de EAs, incluyendo mortalidad, fueron similares entre belimumab y placebo (n=4170).

1. Van Vollenhoven R, Navarra S, Levy R, *et al*. Long-term safety and limited organ damage in patients with SLE treated with belimumab: a phase III study extension. Rheumatology (Oxford). 2020 Feb 1;59(2):281-291. **2.** Sheikh SZ, Scheinberg MA, Wei JC *et al*. Mortality and adverse events of special interest with intravenous belimumab for adults with active, autoantibody-positive systemic lupus erythematosus (BASE): a multicentre, double-blind, randomised, placebo-controlled, phase 4 trial. The Lancet Rheumatology. 2021 Feb 1;3(2):e122-30. **3.** Sheikh S, Scheinberg M, Wei JCC, et al. POS0712 year-4 observational follow-up of belimumab safety (mortality and malignancies) in patients with SLE who completed a phase 4, 52-week, randomised, double-blind placebo-controlled safety study. Annals of the Rheumatic Diseases 2022;81:637-638; **4.** Wallace DJ, Atsumi T, Daniels M, Hammer A, Meizlik P, Quasny H, Schwarting A, Zhang F, Roth DA. Safety of belimumab in adult patients with systemic lupus erythematosus: Results of a large integrated analysis of controlled clinical trial data. Lupus. 2022 Nov;31(13):1649-1659.

Seguridad de belimumab en vida real

Riesgo comparativo de infección con belimumab vs IS orales

Estudiar el **riesgo de infección** con BEL vs otros IS orales en el tratamiento del LES

Estudio multicéntrico en **EEUU**

- bases de datos de historias clínicas de pacientes con LES

N = 21486 pacientes (se excluyeron los pacientes con NL)

2011-2021

Inicio de BEL, AZA, MTX, MMF.

Se diseñaron ensayos hipotéticos para estimar la incidencia acumulada y el cociente de **riesgo de infección grave** y **hospitalización por infección grave** comparando BELI vs inmunosupresores orales

TRES BRAZOS DE COMPARACIÓN INDIRECTA

- BEL vs AZA
- BEL vs MTX
- BEL vs MMF

N = 3.955 BEL
N = 6.957 AZA
N = 8.917 MTX
N = 8.617 MMF

1 **Variable principal:** infección severa*

2 **Variable secundaria:** hospitalización por infección severa

*Bacteriemia, neumonía, infección de piel/tejidos blandos, osteomielitis, meningitis e infección gastrointestinal

Materne E, Choi H, Zhou B, Costenbader KH, Zhang Y, Jorge A. Comparative Risks of Infection with Belimumab versus Oral Immunosuppressants in Patients with Non-Renal Systemic Lupus Erythematosus. Arthritis Rheumatol. 2022

Seguridad de belimumab en vida real

Riesgo comparativo de infección con BELIMUMAB vs IS orales

Incidencia acumulada de INFECCIONES GRAVES a 5 años[1]:

Belimumab vs. Azatioprina

30,2% **34,9%**

HR=0,81 (IC del 95%: 0,72-0,92)

Belimumab vs. Metotrexato

27,2% **30,4%**

HR=0,87 (IC del 95%: 0,76-0,98)

Belimumab vs. Micofenolato

32,2% **41,2%**

HR=0,68 (IC del 95%: 0,61-0,77)

Incidencia acumulada de HOSPITALIZACIÓN por infección a los 5 años[1]:

Belimumab vs. Azatioprina

8% **10,4%**

HR=0,73 (IC del 95%: 0,57-0,94)

Belimumab vs. Metotrexato

6,7% **6,6%**

HR=1,04 (IC del 95%: 0,79-1,35)

Belimumab vs. Micofenolato

9,8% **15,8%**

HR=0,55 (IC del 95%: 0,43-0,71)

En comparación con AZA y MMF, **Belimumab se asoció a un menor riesgo de infección grave y hospitalización por infección.**

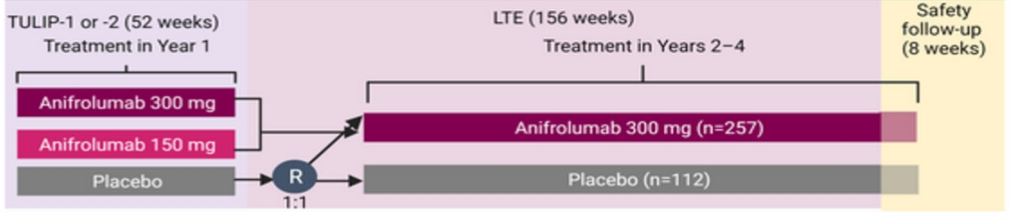
Materne E, Choi H, Zhou B, Costenbader KH, Zhang Y, Jorge A. Comparative Risks of Infection with Belimumab versus Oral Immunosuppressants in Patients with Non-Renal Systemic Lupus Erythematosus. Arthritis Rheumatol. 2023.

Anifrolumab tiene un buen perfil de seguridad

A Randomized, Placebo-Controlled Phase III Extension Trial of the Long-Term Safety and Tolerability of Anifrolumab in Active SLE

OBJECTIVE: To evaluate the long-term safety and tolerability of anifrolumab 300 mg versus placebo in patients with moderate-to-severe SLE receiving standard therapy who completed the first year of treatment in a TULIP trial

STUDY DESIGN

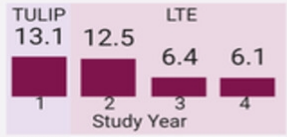


SAFETY

Primary safety during the LTE period

	Anifrolumab 300 mg	vs	Placebo
	EAIRs per 100 PY		
AEs	33.1	vs	37.6
SAEs	8.5	vs	11.2
Deaths	0.4	vs	0.4
DAEs	2.5	vs	3.2
Non-opportunistic serious infections	3.7	vs	3.6
Herpes zoster	3.4	vs	2.8
Malignancy	0.3	vs	0.8
	Event rates (adjusted from start of COVID-19) per 100 PY		
COVID-related AEs	15.5	vs	9.8

SAE event rates per 100 PY decreased over time



Most COVID-related AEs occurred during the first 6 months of the pandemic, prior to the availability of vaccinations or treatments for COVID-19

CONCLUSIONS

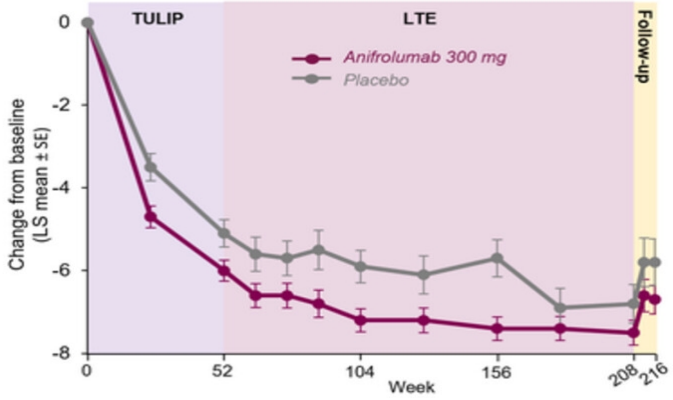
Treatment with anifrolumab was well tolerated and no new safety findings were identified in the LTE; this study shows an acceptable safety profile of anifrolumab while maintaining reductions in disease activity and GC dosing/use

Collectively, these results support a favorable benefit–risk profile of anifrolumab as a long-term treatment in patients with moderate to severe SLE

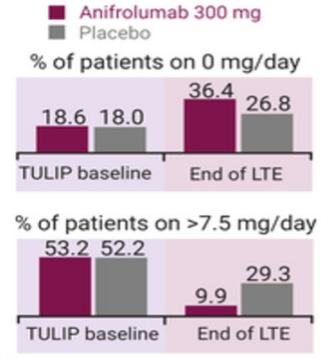
EFFICACY

Mean SLEDAI-2K reduction was achieved in parallel with mean GC dose reduction over time; disease activity and GC use were lower with anifrolumab vs placebo

Mean SLEDAI-2K score decreased during the TULIP+LTE period

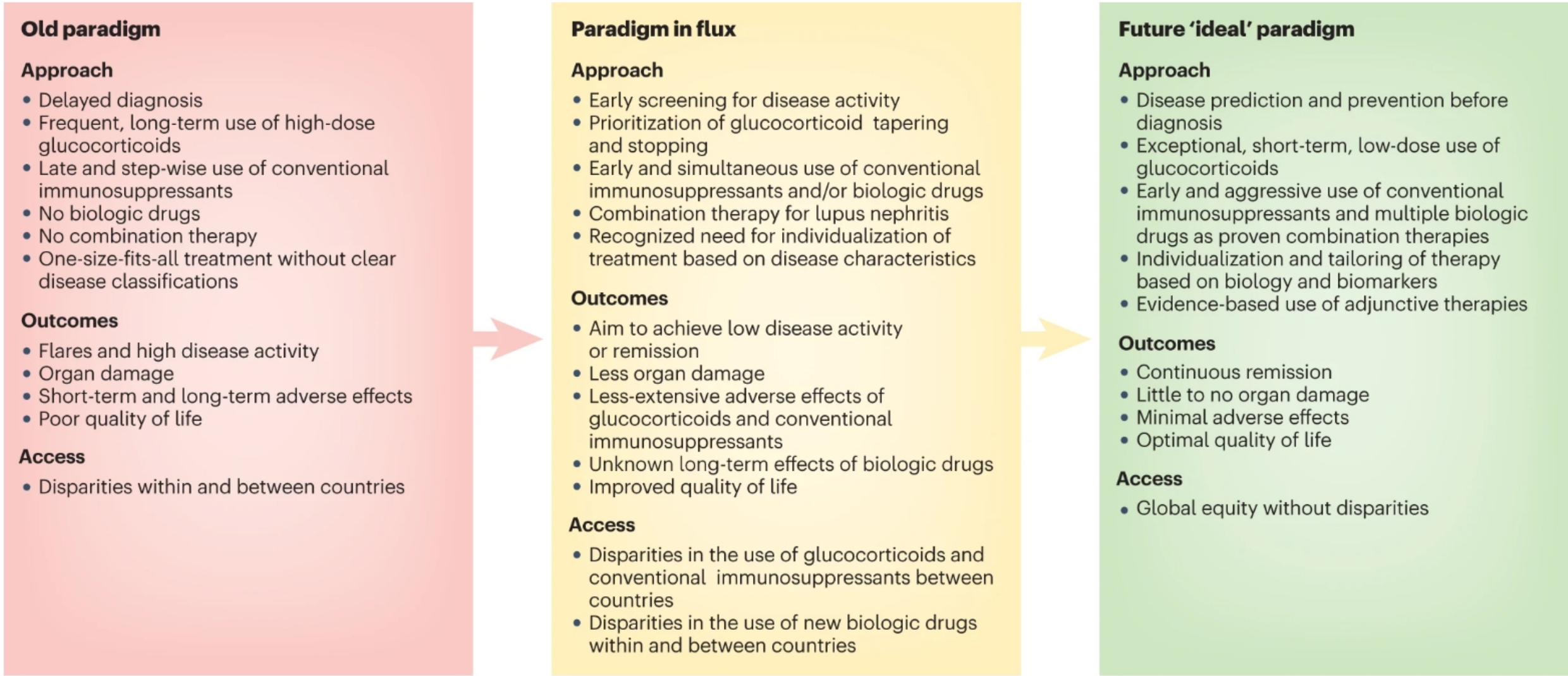


GC dose during the TULIP+LTE period



Kalunian KC, Furie R, Morand EF, et al. A randomized, placebo-controlled phase III extension trial of the long-term safety and tolerability of anifrolumab in active systemic lupus erythematosus. Arthritis Rheumatol 2023.

Arthritis & Rheumatology ACR American College of Rheumatology


Old paradigm
Approach
• Delayed diagnosis
• Frequent, long-term use of high-dose glucocorticoids
• Late and step-wise use of conventional immunosuppressants
• No biologic drugs
• No combination therapy
• One-size-fits-all treatment without clear disease classifications
Outcomes
• Flares and high disease activity
• Organ damage
• Short-term and long-term adverse effects
• Poor quality of life
Access
• Disparities within and between countries
Paradigm in flux
Approach
• Early screening for disease activity
• Prioritization of glucocorticoid tapering and stopping
• Early and simultaneous use of conventional immunosuppressants and/or biologic drugs
• Combination therapy for lupus nephritis
• Recognized need for individualization of treatment based on disease characteristics
Outcomes
• Aim to achieve low disease activity or remission
• Less organ damage
• Less-extensive adverse effects of glucocorticoids and conventional immunosuppressants
• Unknown long-term effects of biologic drugs
• Improved quality of life
Access
• Disparities in the use of glucocorticoids and conventional immunosuppressants between countries
• Disparities in the use of new biologic drugs within and between countries
Future 'ideal' paradigm
Approach
• Disease prediction and prevention before diagnosis
• Exceptional, short-term, low-dose use of glucocorticoids
• Early and aggressive use of conventional immunosuppressants and multiple biologic drugs as proven combination therapies
• Individualization and tailoring of therapy based on biology and biomarkers
• Evidence-based use of adjunctive therapies
Outcomes
• Continuous remission
• Little to no organ damage
• Minimal adverse effects
• Optimal quality of life
Access
• Global equity without disparities

Future 'ideal' paradigm

Approach

- Disease prediction and prevention before diagnosis
- Exceptional, short-term, low-dose use of glucocorticoids
- Early and aggressive use of conventional immunosuppressants and multiple biologic drugs as proven combination therapies
- Individualization and tailoring of therapy based on biology and biomarkers
- Evidence-based use of adjunctive therapies

Outcomes

- Continuous remission
- Little to no organ damage
- Minimal adverse effects
- Optimal quality of life

Access

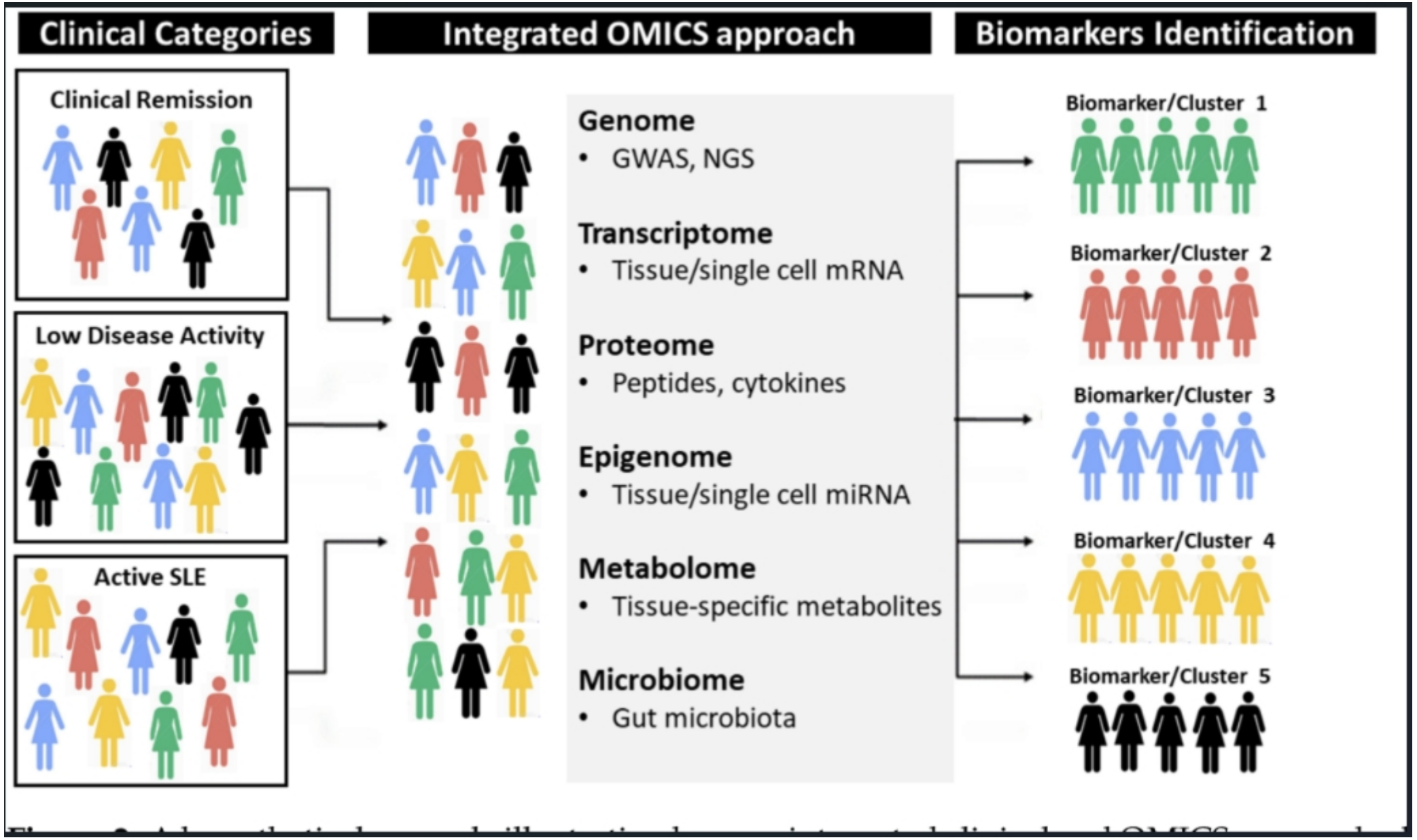
- Global equity without disparities

¿ES LA FIRMA DEL IFN UN BIOMARCADOR ÚTIL DE ACTIVIDAD?

1. Una firma génica de IFN tipo1 elevada se puede asociar a mayor actividad y gravedad.
2. Estudios longitudinales demuestran datos contradictorios, se necesita más investigación para demostrar su valor.
3. La firma del IFN se utiliza como marcador farmacodinámico.

¿ES ÚTIL LA CANTIDAD DE BlySS?

Mayor respuesta en pacientes con expresión elevada de ARNm y/o proteína BlySS al inicio.


Clinical Categories
Integrated OMICS approach
Biomarkers Identification
Clinical Remission
Low Disease Activity
Active SLE
Genome
• GWAS, NGS
Transcriptome
• Tissue/single cell mRNA
Proteome
• Peptides, cytokines
Epigenome
• Tissue/single cell miRNA
Metabolome
• Tissue-specific metabolites
Microbiome
• Gut microbiota
Biomarker/Cluster 1
Biomarker/Cluster 2
Biomarker/Cluster 3
Biomarker/Cluster 4
Biomarker/Cluster 5


Gracias