Systemic Lupus Erythematosus (SLE): Mainstays of Management and Advances in Treatment

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2021

Yale SCHOOL OF MEDICINE

DISCLOSURES

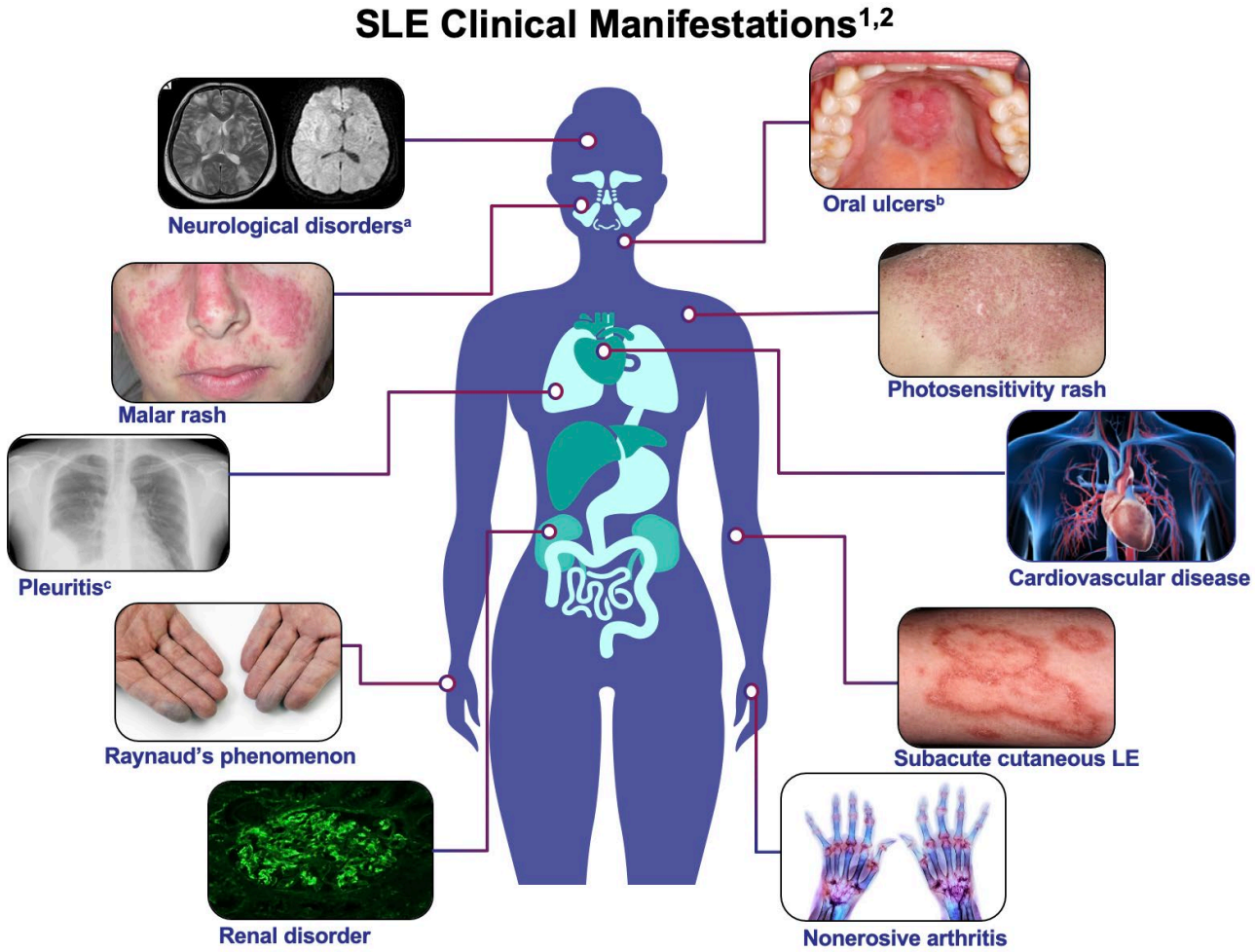
- GSK
- UCB
- AbbVie
- Amgen
- BMS
- LRA
- NIH
- Aurinia

Outline

- When to suspect SLE and making the diagnosis
- Review new guidelines and recommendations for treating SLE
  - Focus on nephritis
- Explore current therapies and recently approved drugs for SLE and lupus nephritis

Lupus is Dangerous

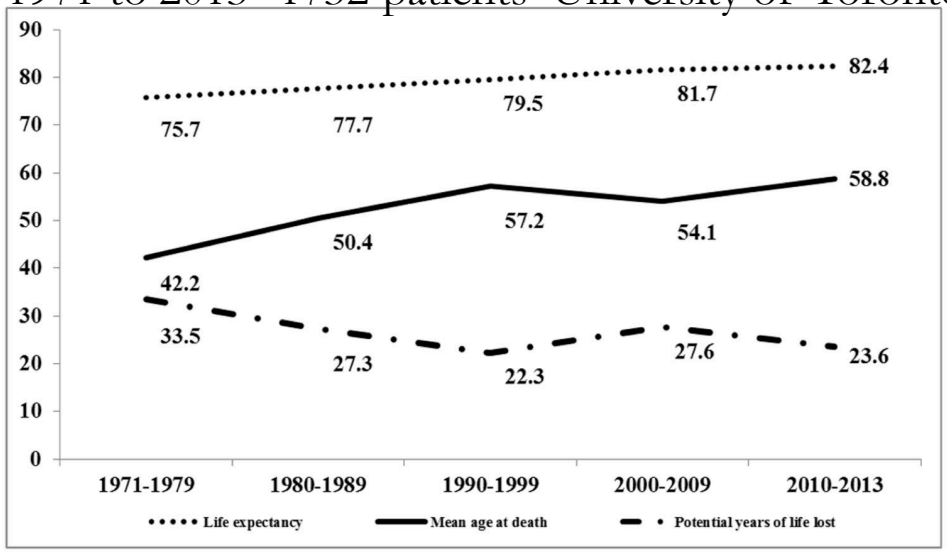
Wide Disease Spectrum



1. Kaul A, et al. *Nat Rev Dis Primers.* 2016;2:16039. 2. Bertsias G, et al. In: Bijlsma J (ed). *EULAR Textbook on Rheumatic Diseases.* London: BMJ Group; 2012:476-505. 3. Izmirly PM, et al. *Arthritis Rheumatol.* 2021;10.1002/art.41632.

Death Rates in SLE: Unmet Need!

1971 to 2013--1732 patients University of Toronto, Canada



Mean age at death of the UTLC patients through the decades (solid line).
The life expectancy of the general Canadian population at the same time points is also depicted (dashed line).

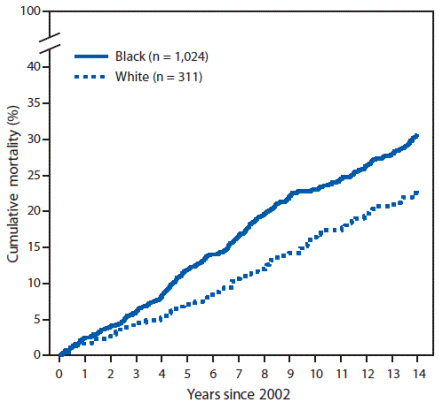
Tselios K, *et al. Ann Rheum Dis* 2019;**78**:802–806. doi:10.1136/annrheumdis-2018

Health Disparity in SLE

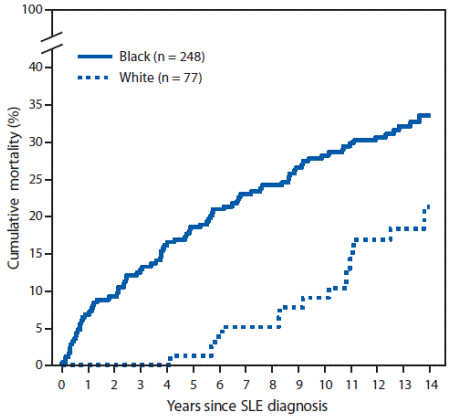
- Despite increasing awareness and advancements in treatment, mortality remains high
  - highest standardized mortality ratio is among black females.

- Racial disparity in mortality is underscored by higher prevalence of SLE in AA
  - 3x vs Caucasians.

Unadjusted SLE Death Rates for White and Black Women in the United States- GA



Cumulative mortality for prevalent SLE cases was calculated using Kaplan-Meier survival analysis to indicate the probability of SLE patients dying at a specified time since 2002.
Diff. p = 0.025, by log rank test.



Cumulative mortality for incident SLE cases was calculated using Kaplan-Meier survival analysis to indicate the probability of SLE patients dying at a specified time since diagnosis.
Diff. p = 0.008, by log rank test.

Lim SS, Helmick CG, Bao G, et al. Racial Disparities in Mortality Associated with Systemic Lupus Erythematosus — Fulton and DeKalb Counties, Georgia, 2002–2016. MMWR Morb Mortal Wkly Rep 2019;68:419–422.

Illustrative Case

A 19 y/o female with SLE is concerned that she has SLE like her mother.

She is a 19 y/o female with no significant history aside from an episode of infectious mononucleosis at age 14 that required no specific therapy. She reports fatigue and joint aches that lasted 3 weeks. She thinks it may be related to vaccines she received in preparation for college, which included the meningococcal vaccine.

ROS otherwise negative. Rare aphthous ulcers.

Exam with spotty posterior LAN, no synovitis. No alopecia. No oral lesions. Chest clear, Cor wnl, abdomen wnl, no pedal edema, skin normal.

Next Steps

- Labs

- Normal CBC, chemistries
- ANA 1:160 homogenous

- Exam normal

- Recommendations
  - Observation vs treatment
  - Cause of joint pain?
    - Meningicoccal vaccine associated with arthralgia

A year later

- The same patient sees you 1 year later for an urgent visit. She is now 20 yrs old. She was vacationing in Florida on Spring Break and developed a rash and body aches. She has changes of her tongue

- Exam with butterfly rash, tongue ulcers vs geographic tongue

Labs

IMMUNOLOGY GENERAL	
Immunoglobulin G	
C3 Complement	95 *
C4 Complement	19 *
ANA Screen, IFA	POSITIVE * !
DNA ds	17 * ▲
Sjogren's Antibody...	
Sjogren's Antibody...	
ANA Titer 1	1:640 * ▲
ANA Pattern 1	HOMOGENEOUS * !
Sm Antibody	
Sm/RNP Antibody	
Histone Ab	
Cardiolipin IgG	
Cardiolipin IgM	
Lupus Anticoagulan...	
B2-Glycoprotein IgA	

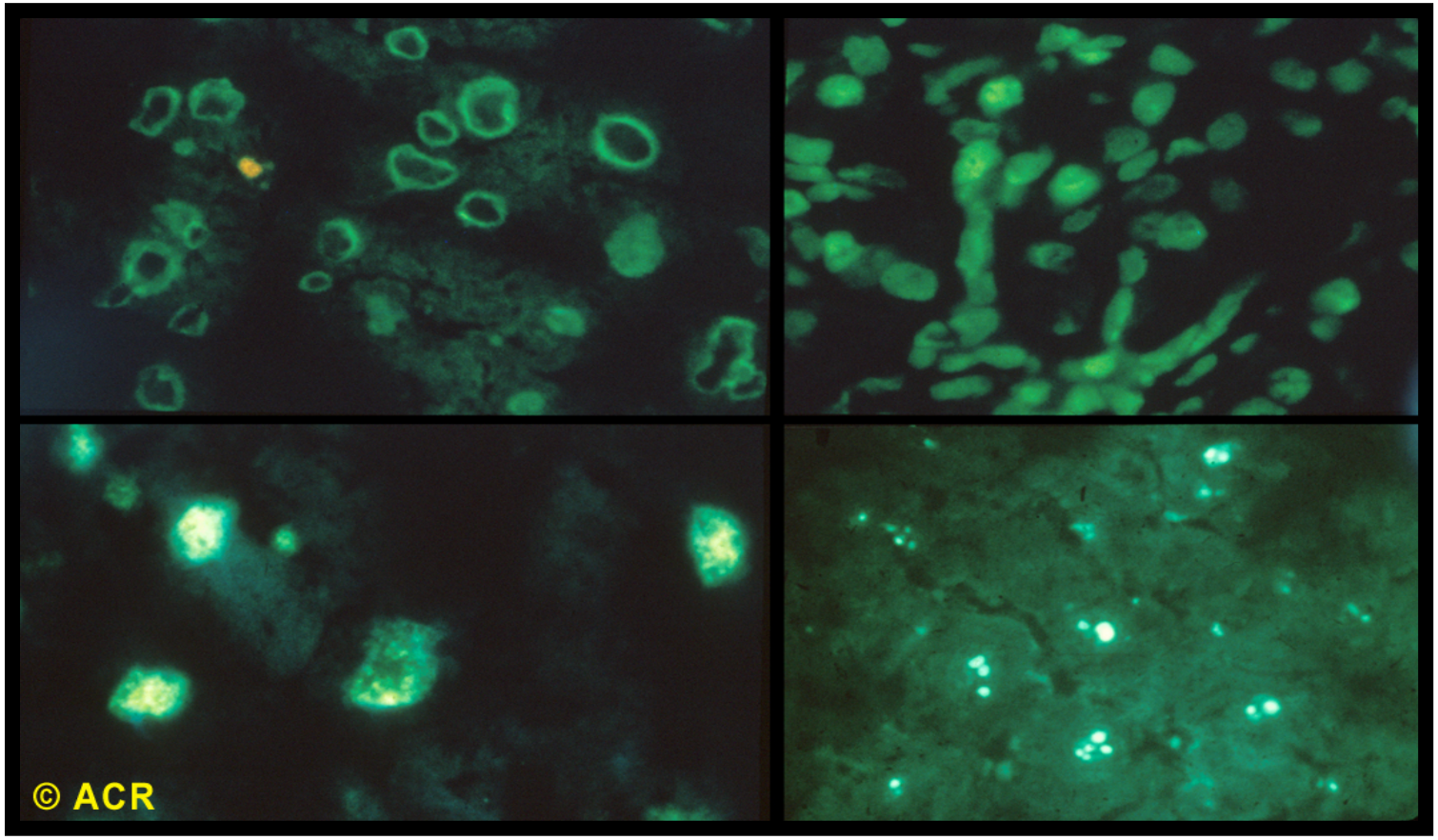
Making The Diagnosis

"I'm sorry, the doctor no longer makes diagnoses."

ANA Patterns Subset with Disease Subtypes

Peripheral or “rim”

Diffuse

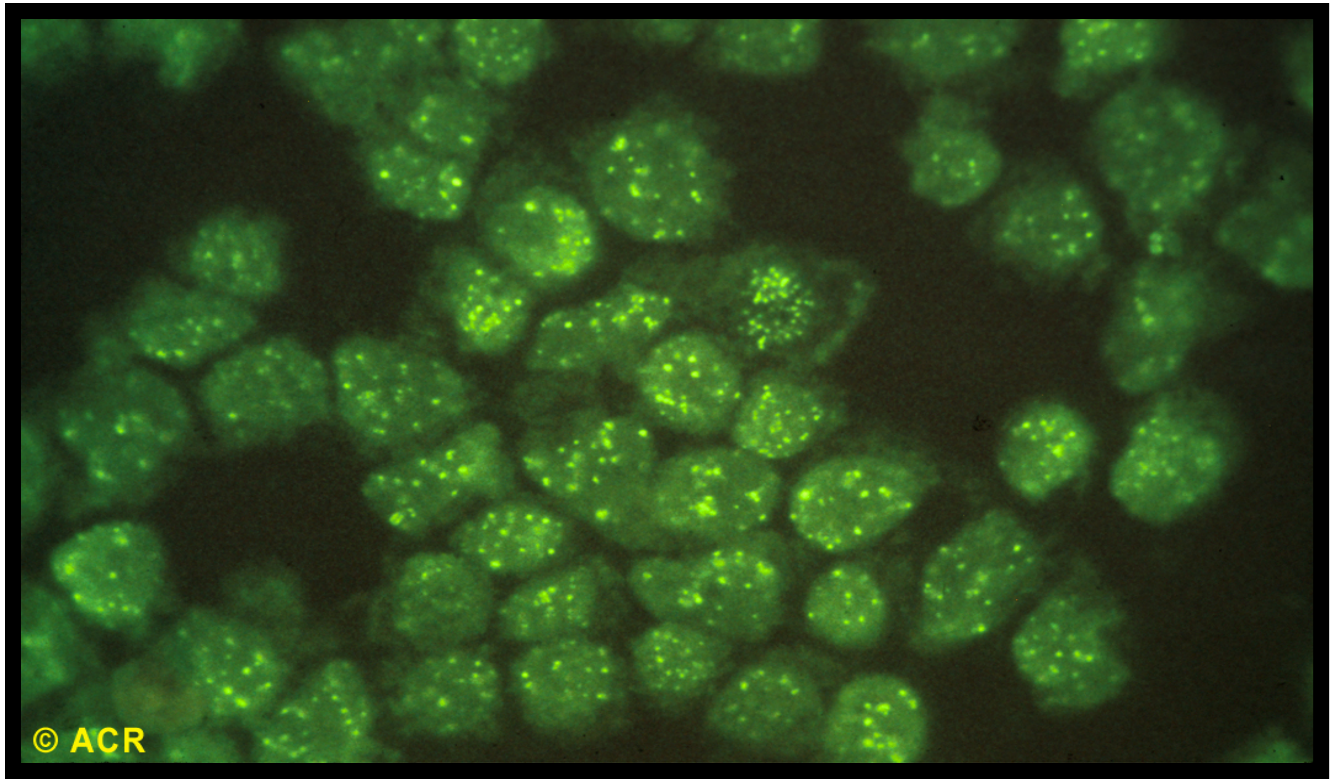


Speckled

Nucleolar

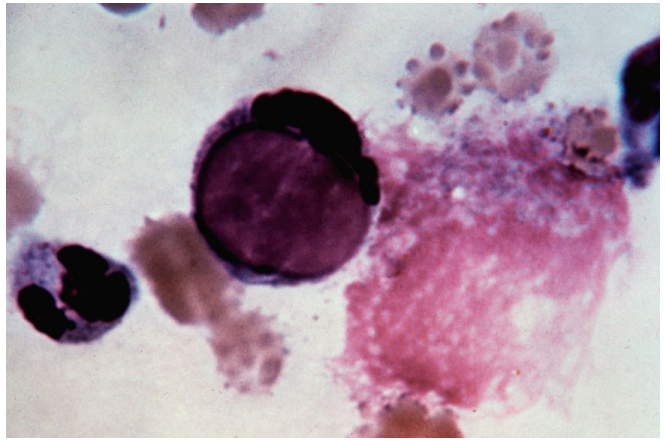
ANA Patterns Subset with Disease Subtypes

Centromere



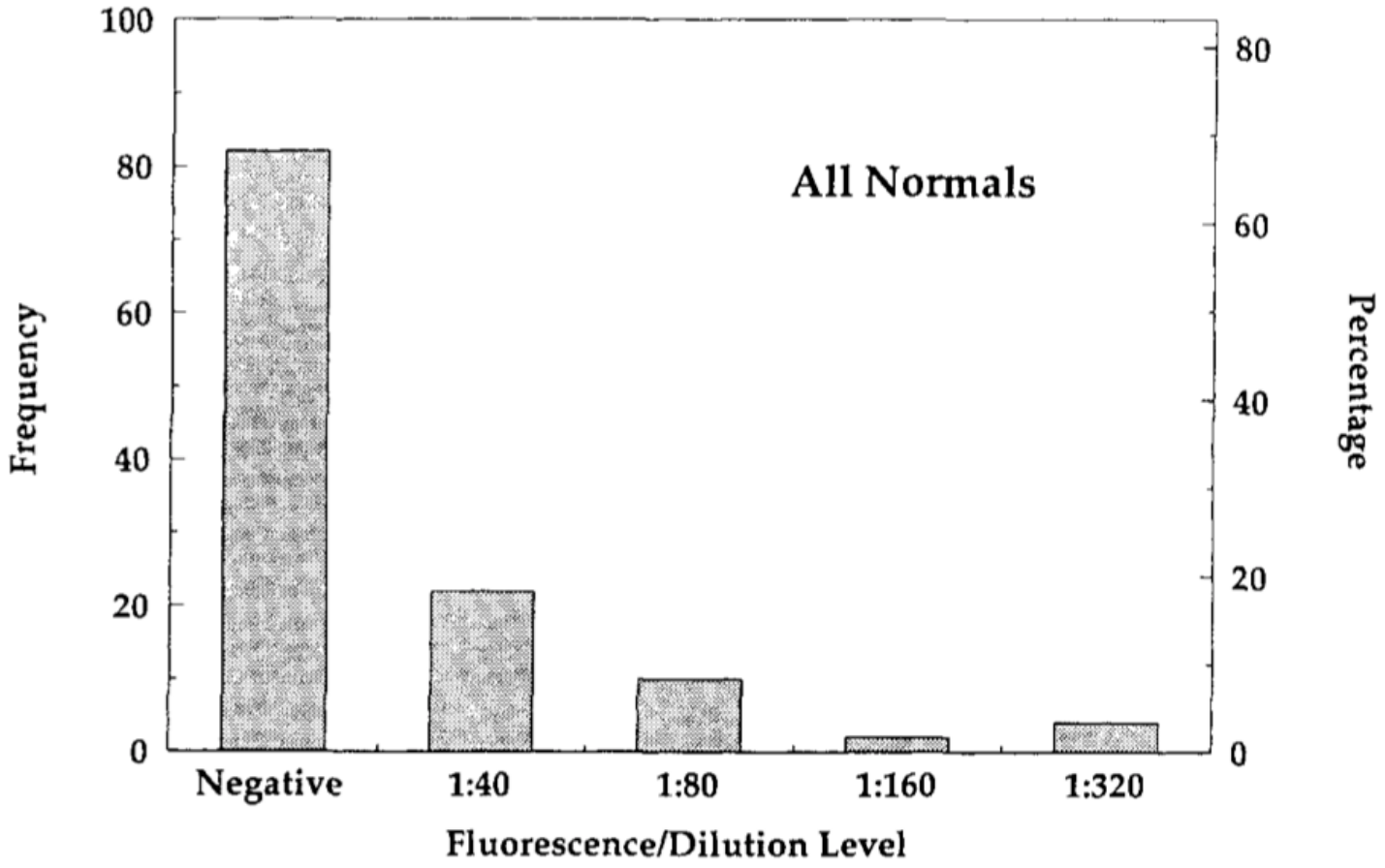
Making the Diagnosis: ANA is Not Specific

- Non- lupus subjects 3%–4%
- SLE 95%–99%
- Scleroderma 95%
- Hashimoto's thyroiditis 50%
- Idiopathic pulmonary fibrosis 50%
- Incidence increases with age, chronic infections, and other chronic conditions
- Up to 30% of normals at low titer
- **Interpret the ANA in context of clinical complaints**
- **ANA+ does not = SLE**



LE cell was the first "anti-nuclear antibody" test.

ANA in General Healthy Population



Indications by expert opinion for ANA

- A patient with signs or symptoms suggestive of SLE
- Assessment of the risk of uveitis in a patient with juvenile idiopathic arthritis
- Assessment of the risk of an underlying connective tissue disease in a patient with Raynaud's Phenomenon

Related connective tissue disease have ANAs

- Sjogren's syndrome- speckled
  - Exocrine gland target, SSA/SSA autoantibodies
- Systemic sclerosis- nucleolar, centromere, speckled
  - ?target, excessive fibroblast activity and collagen deposition, topoisomerase antibodies in diffuse disease
- Dermato(poly)myositis- cytoplasmic, nucleolar
  - T cell predominate muscle inflammation, AutoAb associate
- All (most) have ANA
- All have Raynaud's
- All affect women > men
- Can exist in overlap

ANA in Disease- 1:160 Titer balance point

Table 1. Operating characteristics of antinuclear antibody immunofluorescence assays*

Disease	Cutoff dilution	Sensitivity, %	Specificity, %
SLE	1:40	97.4	68.3
	1:80	97.4	87.6
	1:160	94.7	95.0
	1:320	86.8	96.7
SSc	1:40	100	68.3
	1:80	94.6	86.7
	1:160	86.5	95.0
	1:320	83.8	96.7
SS	1:40	84.2	68.3
	1:80	76.3	86.7
	1:160	73.7	95.0
	1:320	71.1	96.7
RA	1:40	48.6	68.3
	1:80	37.8	86.7
	1:160	13.5	95.0
	1:320	2.7	96.7
STR	1:40	38.5	68.3
	1:80	23.1	86.7
	1:160	7.7	95.0
	1:320	3.8	96.7

Autoimmune Disease

- SLE: 95–100%
- Scleroderma: 60–80%
- Mixed connective tissue disease: 100%
- Polymyositis/dermatomyositis: 61%
- Rheumatoid arthritis: 52%
- Rheumatoid vasculitis: 30–50%
- Sjögren's syndrome: 40–70%
- Drug-induced lupus: 100%
- Discoid lupus: 15%
- Pauciarticular juvenile chronic arthritis: 71%

Nonrheumatic Disease

- Hashimoto's thyroiditis: 46%
- Graves' disease: 50%
- Autoimmune hepatitis: 100%
- Primary autoimmune cholangitis: 100%
- Primary pulmonary hypertension: 40%

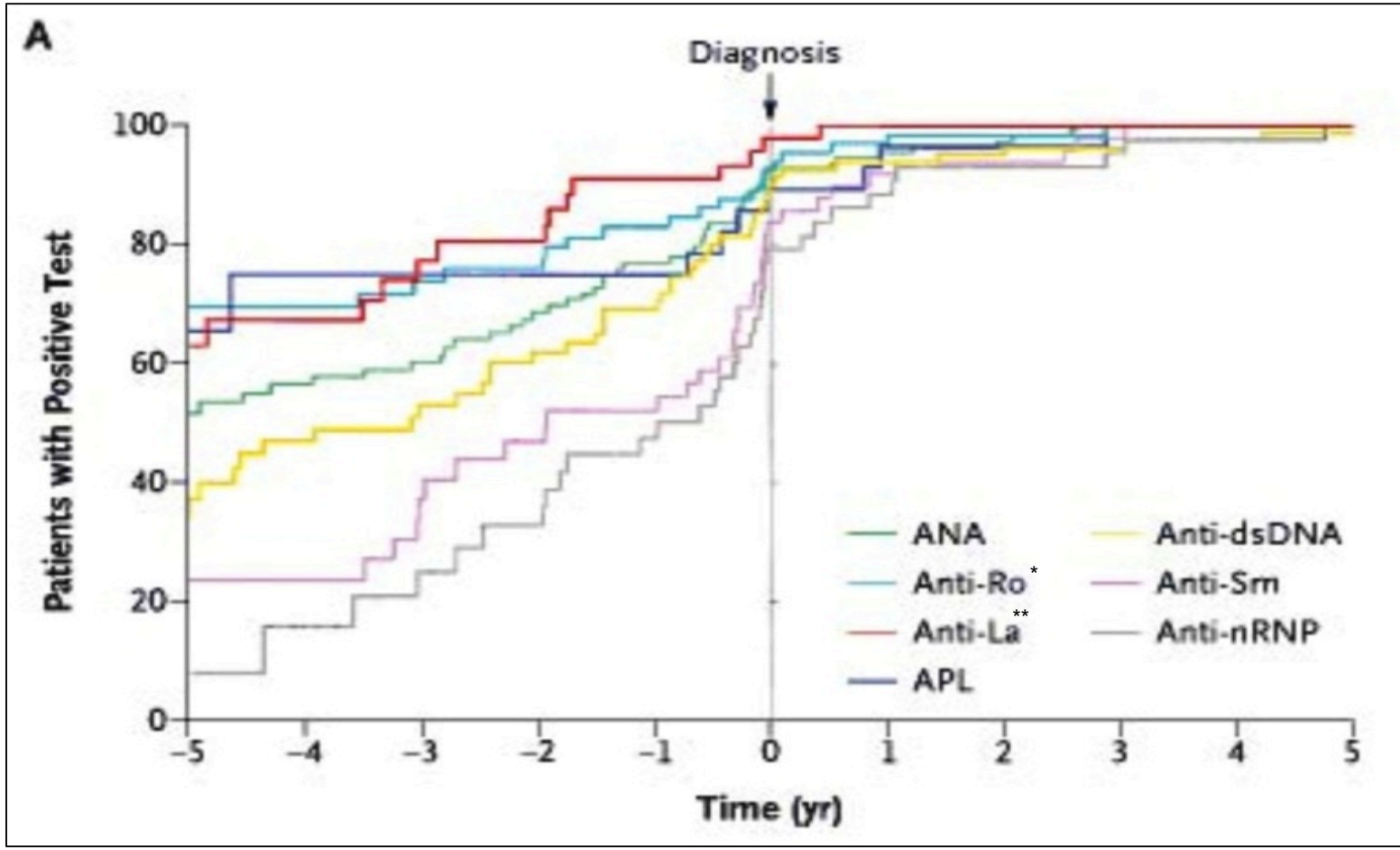
Making the Diagnosis

- Lupus is a variable disease
- Accurate diagnosis depends on a combination of laboratory tests and clinical findings
- New tests are allowing enhanced sensitivity and specificity and disease activity measurement

Making the Diagnosis: Follow your patients

- Autoantibodies precede diagnosis by many years

- Unpredictable
- Military study



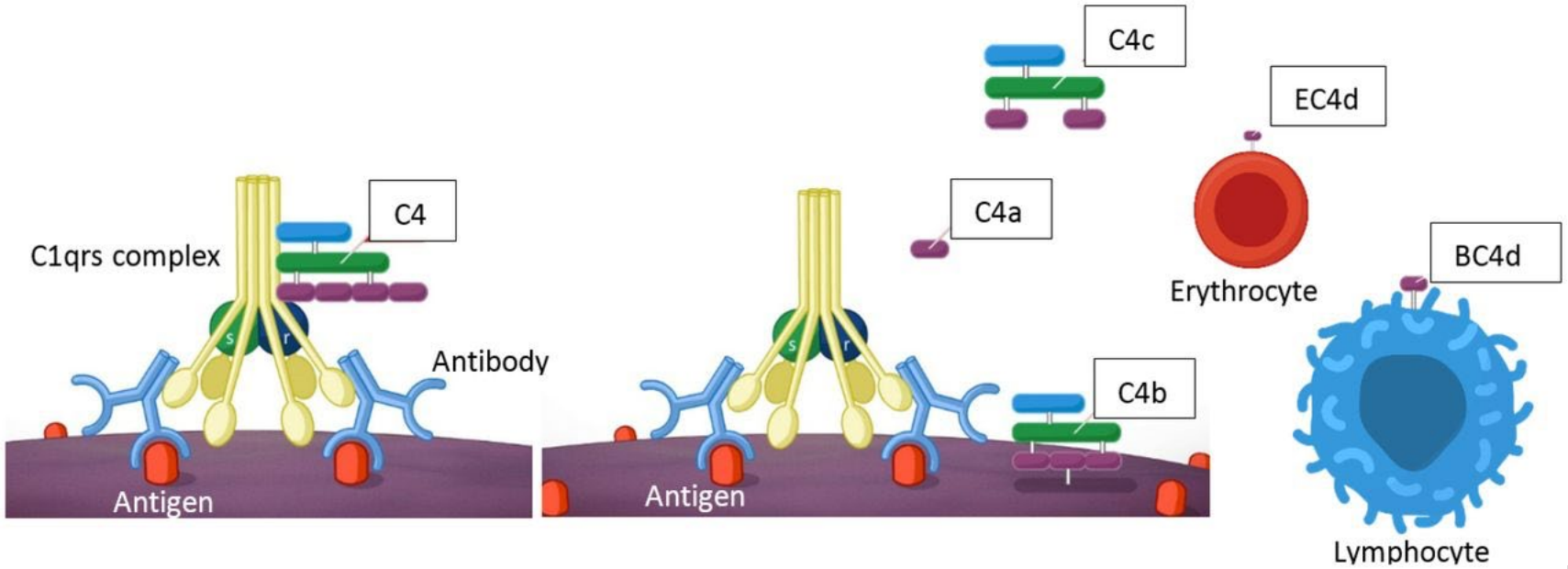
Arbuckle MR, McClain MT, Rubertone MV, et al. *N Engl J Med*. 2003;349:1526-1533.

Unmet Clinical Needs: Diagnosis

Complement activation occurs in patients with probable systemic lupus erythematosus and may predict progression to ACR classified SLE

Rosalind Ramsey-Goldman, Roberta Vezza Alexander, Elena M. Massarotti, Daniel J. Wallace, Sonali Narain, Cristina Arriens, Christopher E. Collins, Amit Saxena, Chaim Putterman, Kenneth C. Kalunian, Tyler O'Malley, Thierry Dervieux, Arthur Weinstein ... See fewer authors

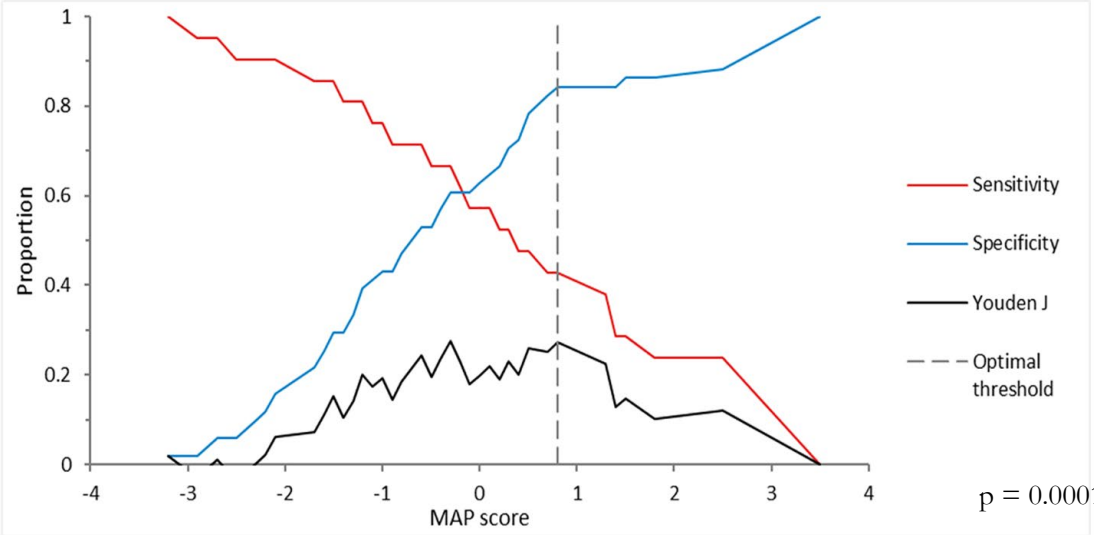
First published: 30 August 2019 | https://doi.org/10.1002/art.41093



Probable SLE Patients Were Positive For CB-CAPS

- 92 pSLE were diagnosed sooner than the 53 established SLE group
  - use of antirheumatic medications was lower

- Of 28% pSLE were positive for CB-CAPs or MAP (40%) vs. low complement (9%) group at time of enrollment
- MAP score > 0.8 at enrollment predicted full (4) ACR criterion within 18 months (HR= 3.11, p<0.01)



p = 0.0001, for each

When To Suspect SLE

Patients **accumulating ≥10 points** are classified.
In the validation cohort,
sensitivity of 96.1%
specificity of 93.4%

compared with:
82.8% sensitivity and 93.4% specificity of the ACR 1997 criteria

96.7% sensitivity and 83.7% specificity of the Systemic Lupus International Collaborating Clinics 2012 criteria

Aringer M, Costenbader K, Daikh D, et al. 2019 Ann Rheum Dis. 2019;78(9):1151-1159.

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

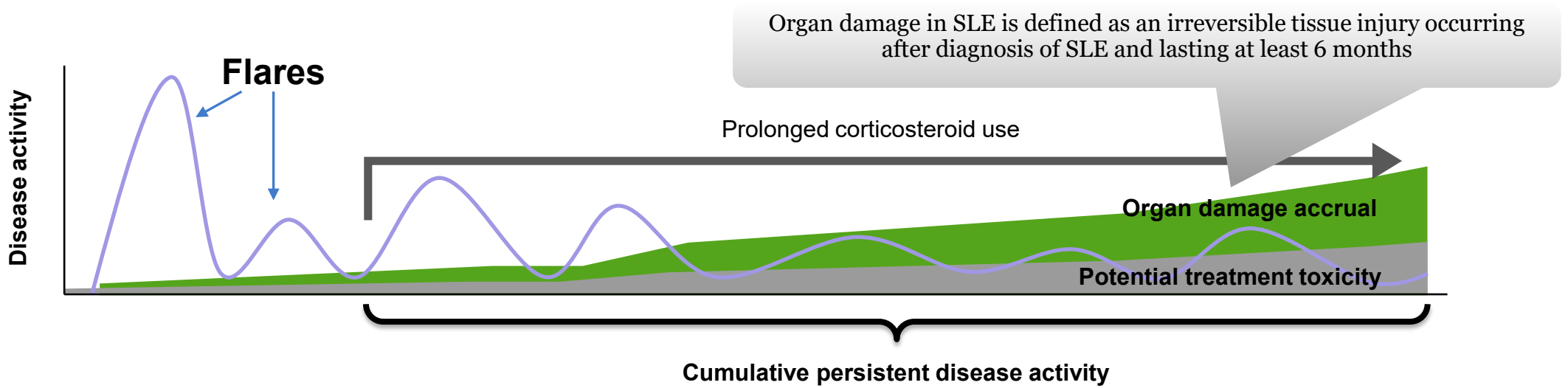
Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

SLE Has an Unpredictable Disease Course

- SLE is characterized by a waxing and waning disease course over time
- Steroids and immunosuppressants are used to manage flares and acute and chronic symptoms
- Prolonged, cumulative use of steroid may lead to negative consequences long-term

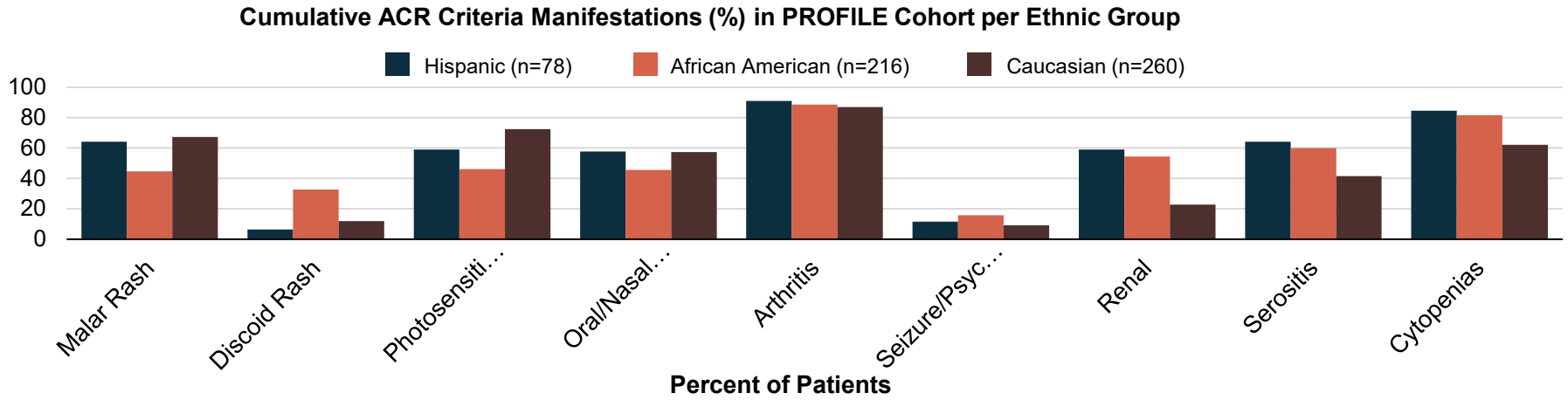


An unmet need exists for treatment options that minimize the long-term consequences of SLE

Bertsias G, et al. *EULAR Textbook on Rheumatic Diseases.* Geneva, Switzerland: European League Against Rheumatism; 2012:476-505. Fanouriakis A, et al. *Ann Rheum Dis.* 2019;78:736-745. Apostolopoulos D, Morand EF. *Rheumatology (Oxford).* 2017;56(suppl 1):i114-i122. Gladman D, et al. *Arthritis Rheum.* 1996;39(3):363-369. Franklyn K, et al. *Ann Rheum Dis.* 2016;75:1615-1621.

Clinical Manifestations Vary by Race

Hispanic and African-American patients tend to have more renal, hematologic, and serosal manifestations following diagnosis



Pooled cohort analysis (University of Alabama at Birmingham, AL; Johns Hopkins University, MD; University of Texas-Houston Health Science Center, TX; Northwestern University, IL) of 568 adults with SLE with a disease duration of <10 years from diagnosis to enrollment. Mean ages were 38-42 years, with 86%, 92%, and 96% female in the Caucasian, African American, and Hispanic patient groups, respectively.

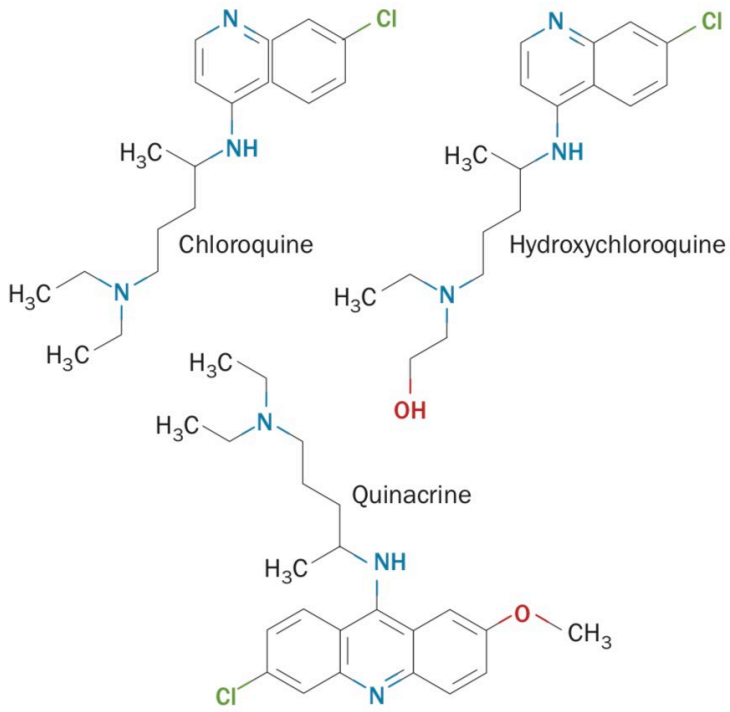
Alarcón GS, et al. *Lupus* 2002;11(2):95-101

Back to the Case

You decide to begin hydroxychloroquine.

What is the evidence?

HCQ can reduce signs and symptoms of disease
Reduces flare risk
Cardioprotective



Our Case-- Does she have SLE?

2019 ACR/EULAR criteria

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Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

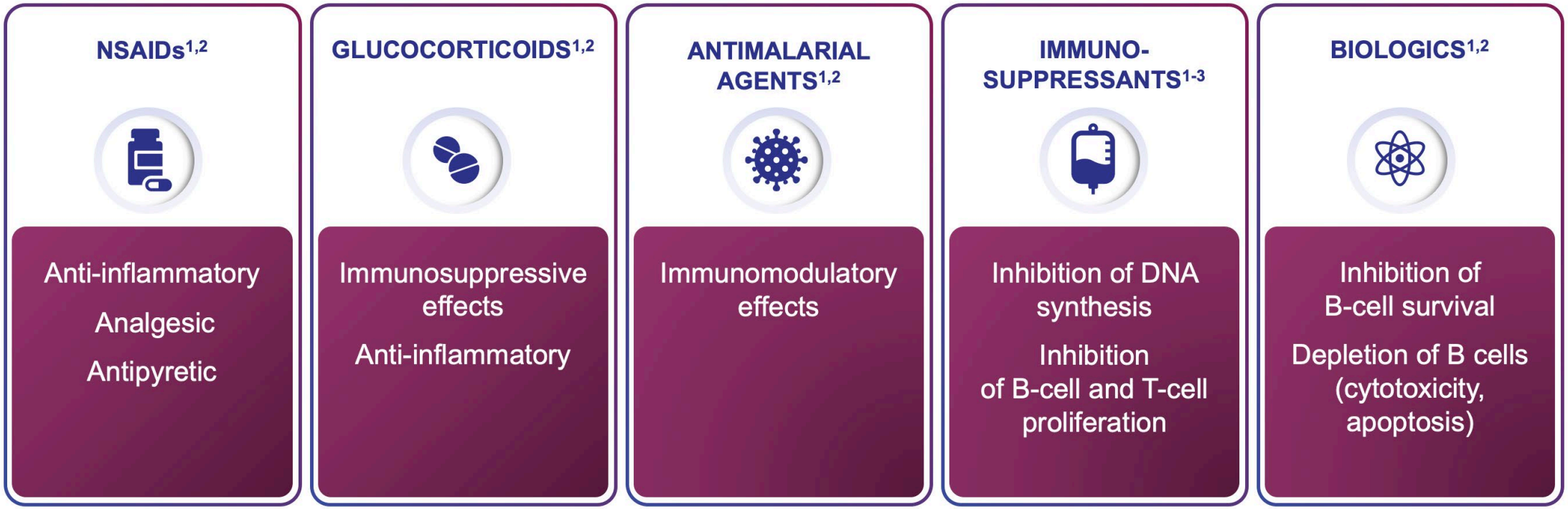
YES

ANA+
Acute LE- 6
dsDNA- 6

Total 12

Aringer M, Costenbader K, Daikh D, et al. 2019 Ann Rheum Dis. 2019;78(9):1151-1159.

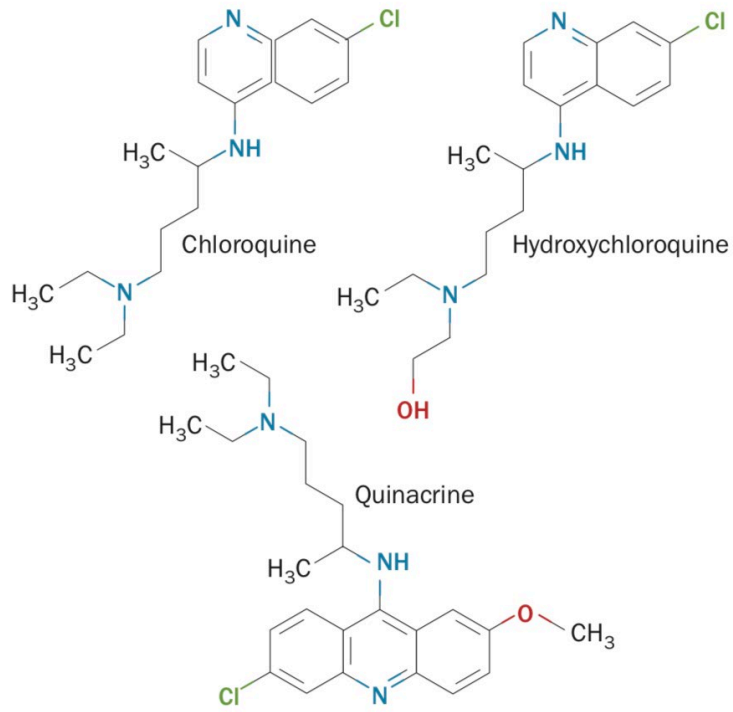
SLE Treatment



ACR treatment guidelines have not been updates in >20yrs

Hydroxychloroquine

- Essential for the management of SLE
  - increases lysosomal pH in antigen presenting cells
  - Reduces TLR signaling (7/9)
    - decreased activation of dendritic cells
    - Reduced INF
- Safe in pregnancy
  - improves pregnancy outcomes

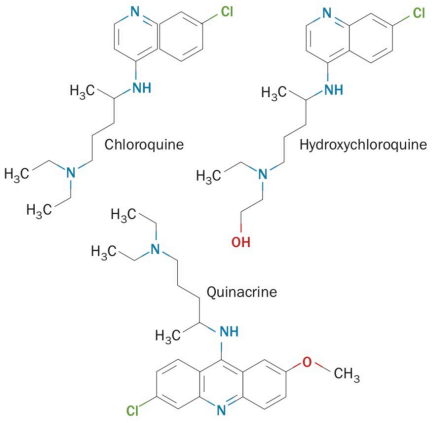


- Effective for mild lupus arthropathy
- Improves fatigue

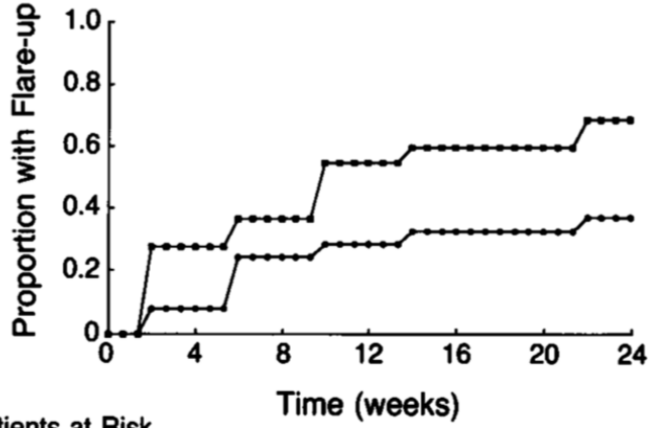
- Levels are unpredictable, but need to measure plasma levels if done

Hydroxychloroquine as background therapy in SLE

- Reduces flares
  - Canadian Hydroxychloroquine Study Group N Engl J Med 1991, 324 150-4
  - Cuhna C et al Nephrol Dial Transplant 2017, 33 1604-10
- Reduces organ damage
  - Fessler BJ et al Arthritis Rheum 2005,52(5) 1473-80
- Lipid favorable
  - Petri M Lupus 1996,5 (Suppl 1)S16-22
  - Wallace DJ et al, Am J Med 1990. 89 322-6
- Triples MMF response in LN
  - Kasitanon N, et al Lupus 2006, 15(6)366-70
- Reduces thrombosis
  - Petri M Curr Rheumatology Rep 2011, 13 77-80
- Improves survival
  - Alarcon GS et al Ann Rheum Dis. 2007. 66 1168-1172
  - Ruiz-Itrastorza, et al Lupus 2006. 15 577-583



HCQ Limits Flares and Flare Severity

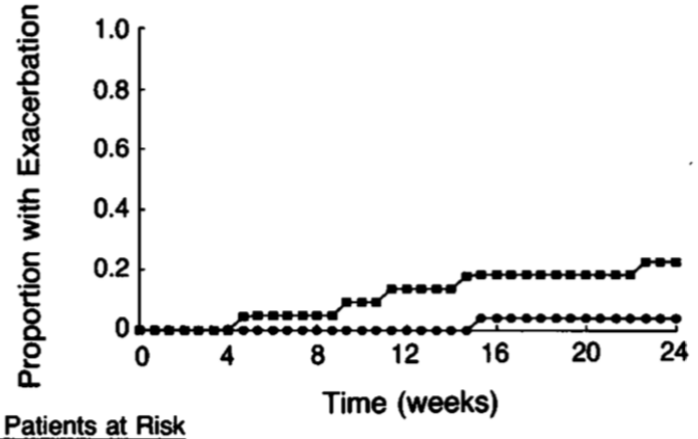


Number of Patients at Risk

Hydroxychloroquine	25	23	18	17	16	16	15
Placebo	22	16	14	10	9	9	6

Figure 1. Life Table of Time to a Clinical Flare-up for Patients Randomly Assigned to Continue Taking Hydroxychloroquine (Circles) or to Receive Placebo (Squares).

The numbers of patients in each treatment group who remained at risk at each four-week interval are shown below the graph. P = 0.02 for the difference between groups.



Number of Patients at Risk

Hydroxychloroquine	25	25	24	24	23	23	23
Placebo	22	22	21	19	18	18	17

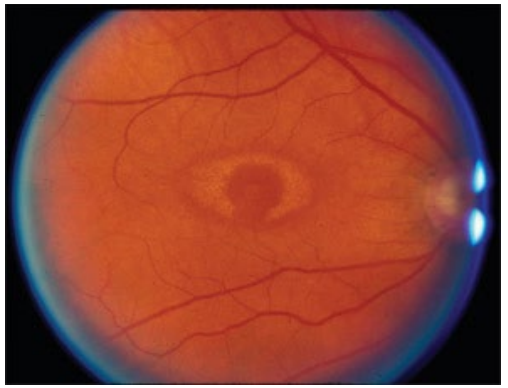
Figure 2. Life Table of Time to a Severe Exacerbation of Disease Activity for Patients Randomly Assigned to Continue Taking Hydroxychloroquine (Circles) or to Receive Placebo (Squares).

The numbers of patients in each treatment group who remained at risk at each four-week interval are shown below the graph. P = 0.06 for the difference between groups.

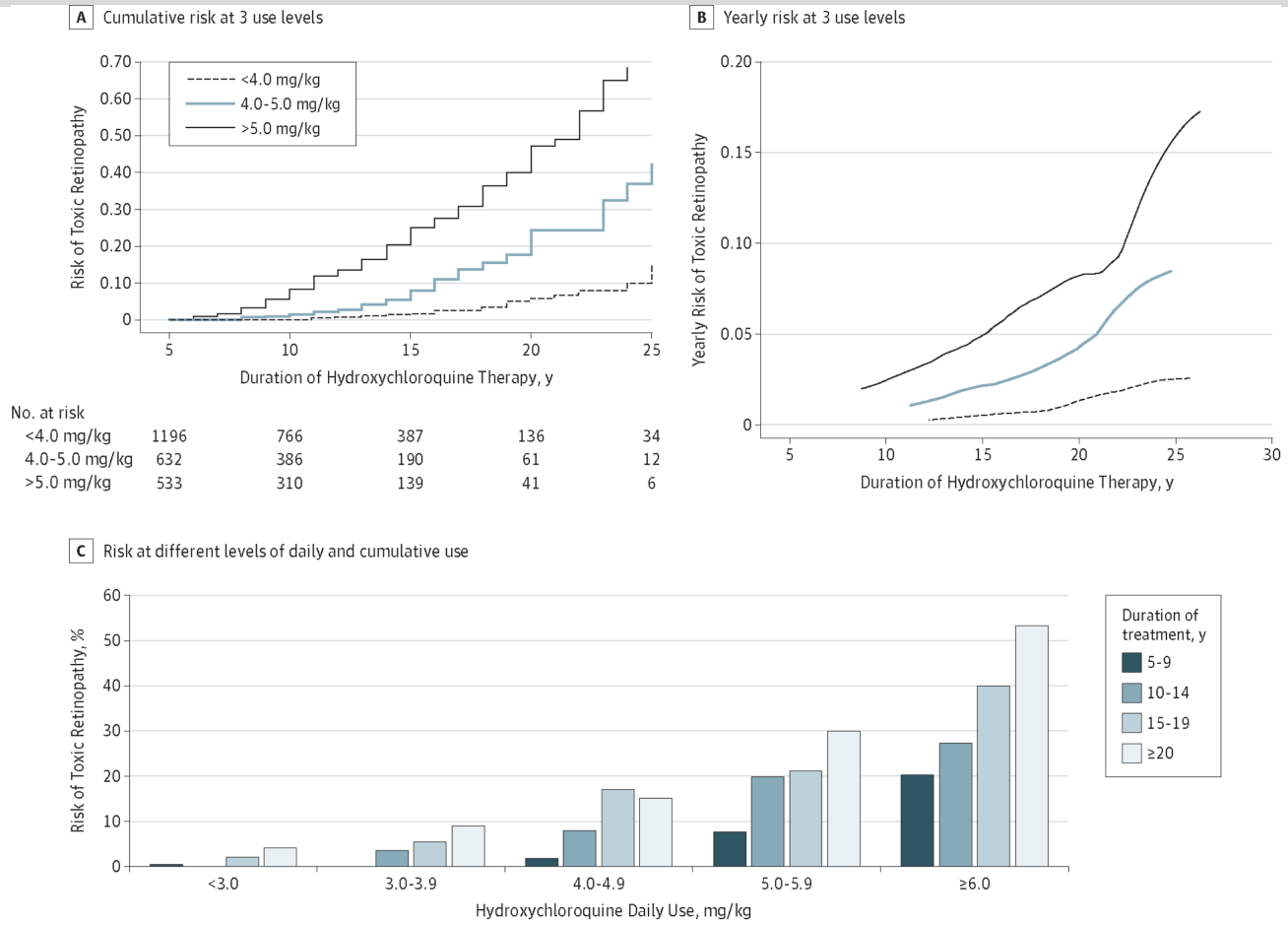
Esdail, eta al, NEJM 1991

HCQ- Retinopathy Risk

- Increased incidence related to increased sensitivity of screening methods
  - OCT
  - inherent limitation
- Limited efficacy as monotherapy for many
- Limited use in severe disease
  - Severe flare can still occur despite adherence to therapy



Retinopathy Risk of HCQ in SLE



JAMA Ophthalmol. 2014;132(12):1453-1460

Case

- In late September your patient calls you after hours and has noted pain in her left>right chest with difficulty breathing, fever and arthritis pain for 4 days, worsening. You send her to the ER.

Pulmonary Manifestations of SLE

- Lung involvement is frequent in SLE
  - Most common CTD that affects the lung
  - Often waxes and wanes
  - Some manifestations can have a chronic course
    - Pleuritis, shrinking lung syndrome, chronic interstitial pneumonitis
  - Some are acute manifestations
    - Diffuse alveolar hemorrhage, acute pneumonitis, acute pulmonary hypertension

Quadrelli SA, Alvarez C, Arce SC, Paz L, Sarano J, Sobrino EM, Manni J.
Pulmonary involvement of systemic lupus erythematosus: analysis of 90 necropsies. Lupus. 2009 Oct;18(12):1053-60.

Case follow up

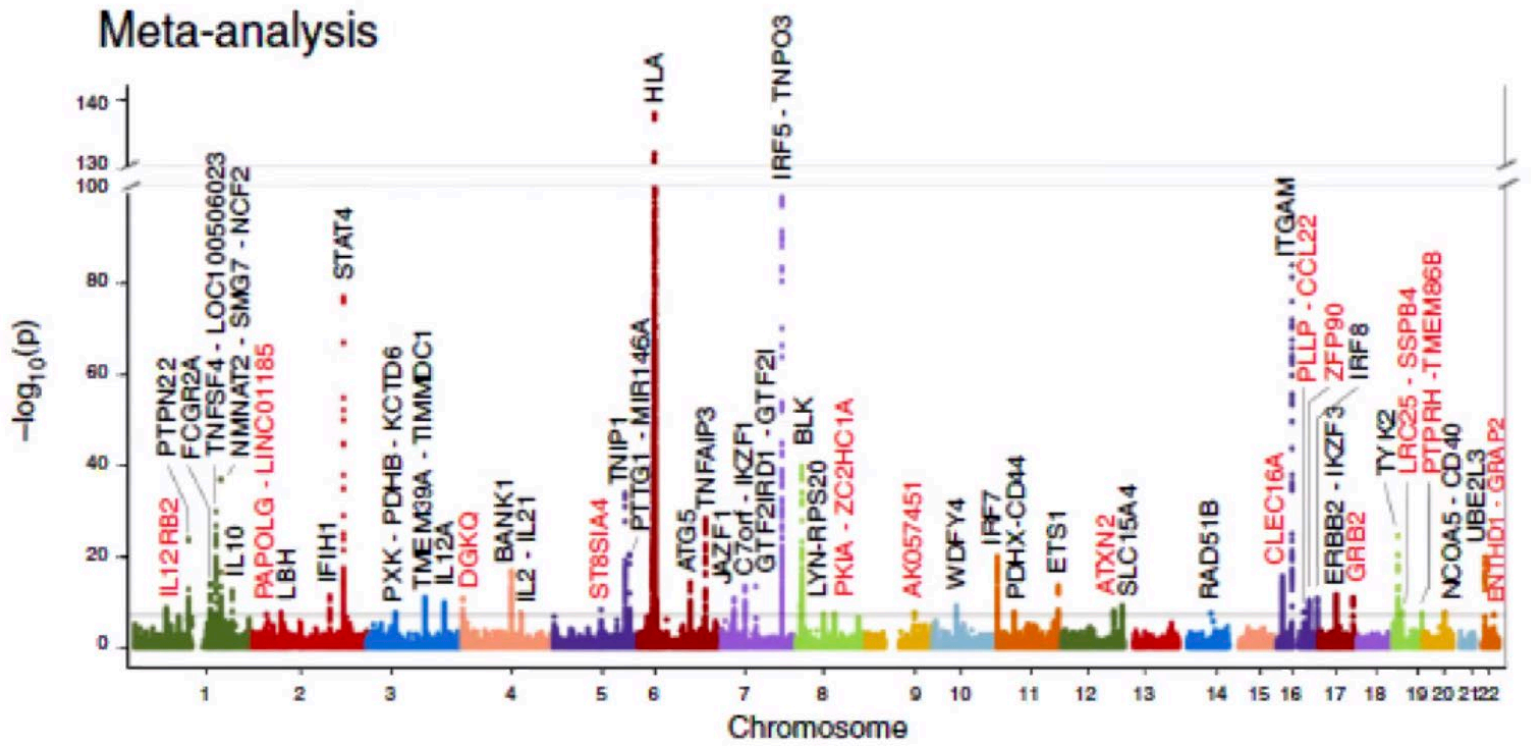
- You decide to add belimumab 200mg s.c weekly
- In 4 months she is feeling well and has tapered off prednisone

Understanding SLE

- Cells
  - Risk is genetic
  - # of genetic variants predict risk
- Signals
  - INF α
- Receptors
  - Nucleic acid handling -- TLR
  - C1, C1q, C2, C4
- Nets

Genetic risk and sufficient Ag promote autoantibody production

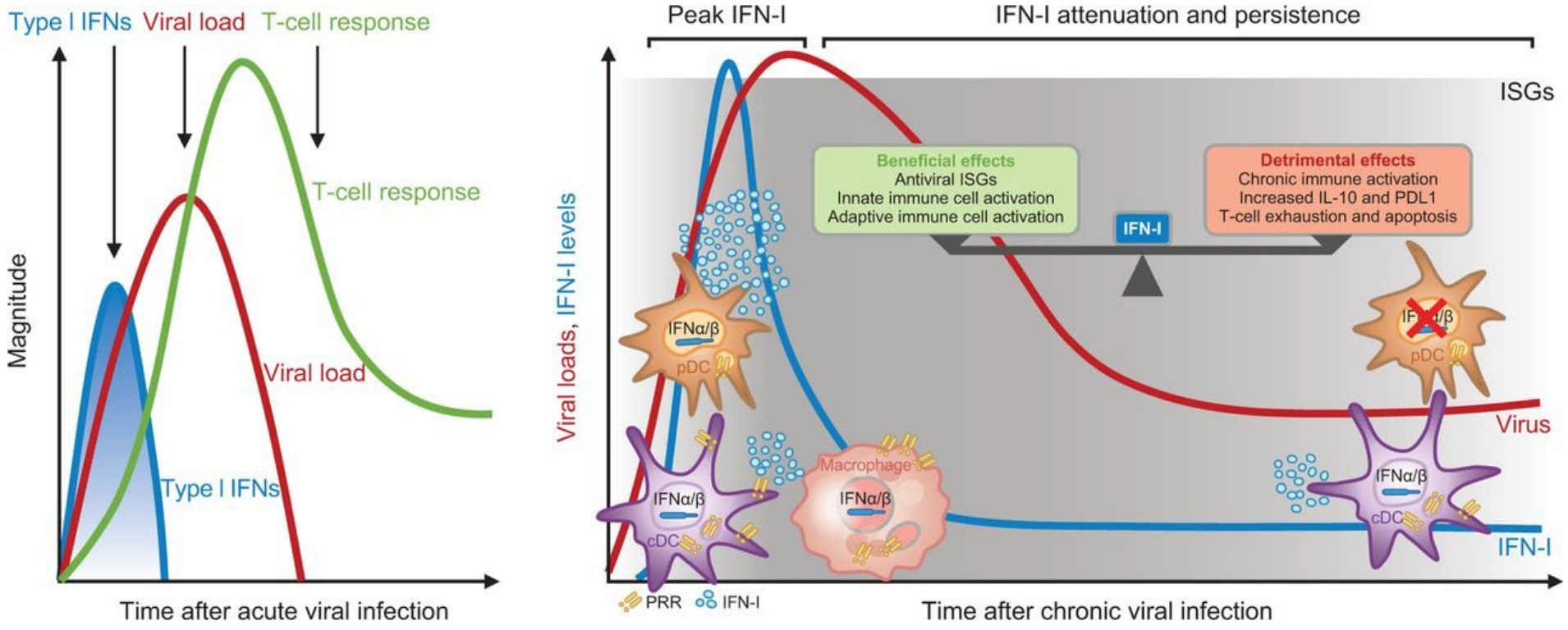
Genome-wide associations in SLE



Analysis of 27,574 SLE cases and controls

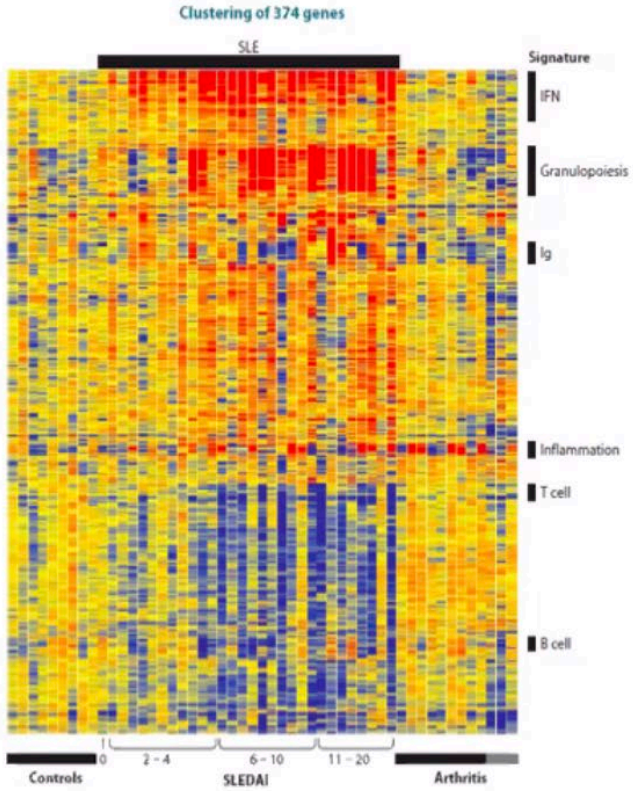
Langefeld KD, et al. Nature Communications, 8:16021, 2016

Interferons and Plasmacytoid Dendritic Cells



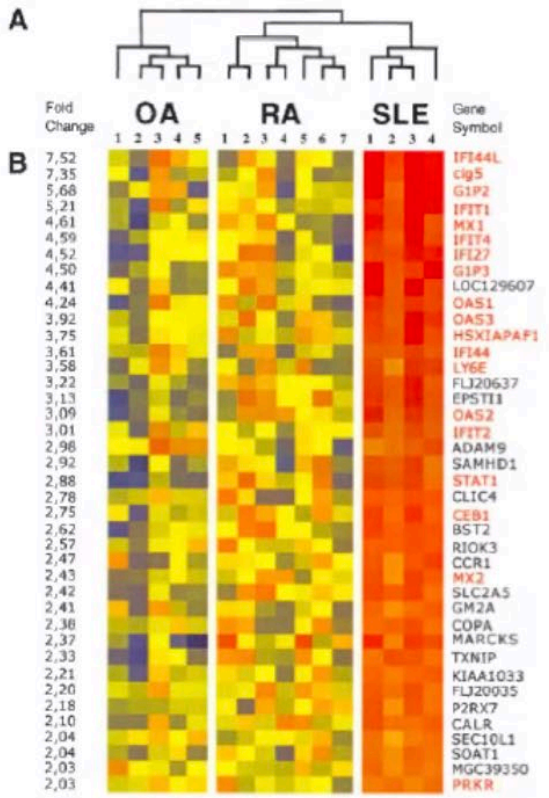
Crow 2018

Type I interferon-induced gene transcripts in lupus blood and tissue (the "Interferon Signature")



Lupus Blood

Bennett et al, JEM, 2003



Lupus Synovial Tissue

Toukap AN et al. Arthritis Rheum 56:1569, 2007

Assessment Tools in SLE

Disease Activity and Flares

- **BILAG** - British Isles Lupus Assessment Group
- **SLEDAI** - SLE Disease Activity Index
- **PGA** - Physician's Global Assessment
- **LLDAS** - Lupus Low Disease Activity State
- **CLASI** - Cutaneous Lupus Erythematosus Disease Area and Severity Index

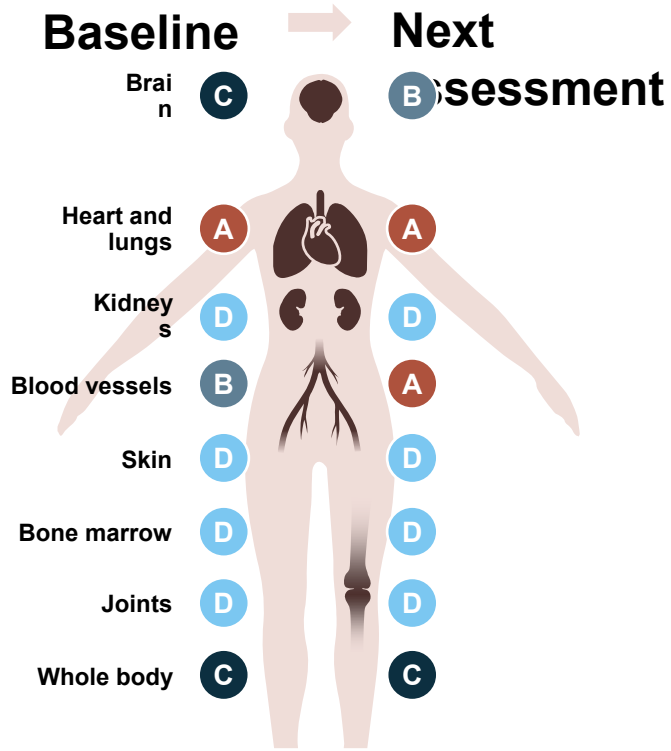
Organ Damage

- **SDI** - Systemic Lupus International Collaborating Clinics (SLICC) Damage Index

BILAG: Disease Activity and Flares

Each organ domain assigned a category of A through E

A	Requires prednisone >20 mg/day or immunosuppressive
B	Requires antimalarials, NSAID or prednisone <20 mg/day
C	Mild, stable disease
D	Domain previously affected, currently inactive
E	Domain never involved



Hay EM, et al. *Q J Med* 1993;86:447-458

SLEDAI: Disease Activity and Flares

- SLE Disease Activity Index (SLEDAI) assesses 24 manifestations of SLE
- Each given a score weighted 1, 2, 4, or 8
- Manifestations are either present or absent
  (i.e., improvement or worsening not measured)
- Maximum score of 105, few score higher than 45
  - Low score = less active SLE
  - High score = more active SLE

Weight	Check if Present	Descriptor
8	☐	Seizure
8	☐	Psychosis
8	☐	Organic brain syndrome
8	☐	Visual disturbance
8	☐	Cranial nerve disorder
8	☐	Lupus headache
8	☐	CVA
8	☐	Vasculitis
4	☐	Arthritis
4	☐	Myositis
4	☐	Urinary casts
4	☐	Hematuria
4	☐	Proteinuria
4	☐	Pyuria
2	☐	Rash
2	☐	Alopecia
2	☐	Mucosal ulcers
2	☐	Pleurisy
2	☐	Pericarditis
2	☐	Low complement
2	☐	Increased DNA binding
1	☐	Fever
1	☐	Thrombocytopenia
1	☐	Leukopenia

Bombardier C, et al. *Arthritis Rheum* 1992;35:630-640

PGA: Disease Activity and Flares

- The Physician's Global Assessment (PGA)[1]
  - Assesses the patient's overall condition
  - A 10-cm visual analog scale ranging from 0 to 3 (higher score = more severe disease activity)[2]

Petri M, et al. Lupus 1999;8:685-691.
Furie RA, *et al. Arthritis Rheum* 2009;61(9):1143-1151

LLDAS: Treat to Target

- **LLDAS Definition: patient must meet all 5 criteria to be considered as having achieved a low disease activity state**
  - **SLEDAI-2K ≤4**, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity
  - **No new features** of lupus disease activity compared with previous assessment
  - SELENA-SLEDAI physician global assessment **(PGA, scale 0-3) ≤1**
  - Current prednisolone (or equivalent) dose **≤7.5 mg daily**
  - Well-tolerated **standard maintenance doses** of immunosuppressive drugs and approved biological agents, excluding investigational drugs

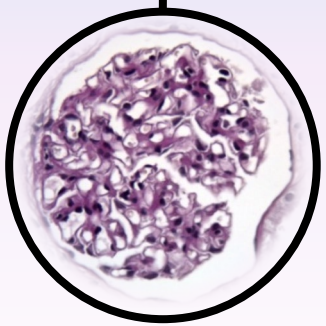
Franklyn K, et al. *Ann Rheum Dis* 2016;75:1615-1621.

Case Continues

- The mother, your patient, now 48y/o, calls worried about leg edema and that she has nephritis since we stopped her low dose prednisone 8 months ago.
  - She had Type III nephritis at her disease onset which was 20 years ago shortly after the delivery of her child, who also developed SLE

ISN/RPS Lupus Nephritis Classification System and Prevalence (In Those Biopsied)

Class I

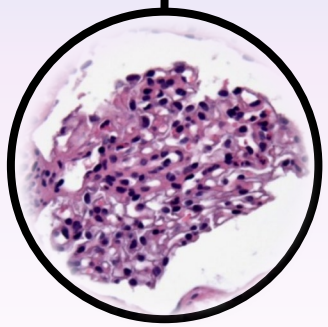


Minimal mesangial LN[1,2]

- Normal glomeruli[1]
- Mesangial immune deposits[1]

Prevalence:
0.4%[3,*]

Class II

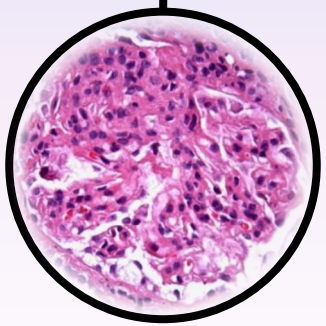


Mesangial proliferative LN[1,2]

- Mesangial hypercellularity and/or matrix expansion[1]
- Mesangial immune deposits[1]

Prevalence:
11.1%[3,*]

Class III

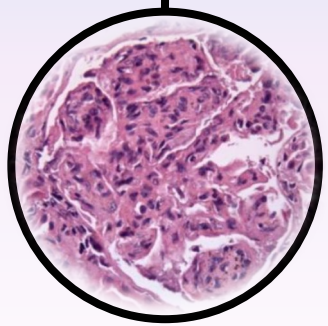


Focal **proliferative** LN[1,2]

- <50% glomeruli involved, endocapillary hypercellularity[1,4]
- Active, chronic, and/or active/chronic lesions[5]

Prevalence:
25.1%[3,*]

Class IV

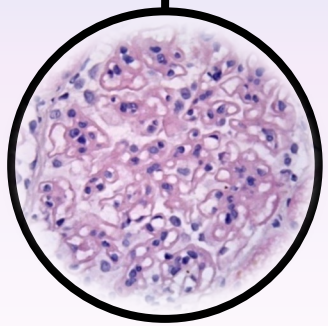


Diffuse **proliferative** LN[1,2]

- IV-S – diffuse segmental LN; IV-G – diffuse global LN[1,2]
- ≥50% glomeruli involved, subendothelial deposits[1]; endocapillary hypercellularity[4]
- Active, chronic, and/or active/chronic lesions[5]

Prevalence:
53.1%[3,*]

Class V



Membranous LN[1,2] with global or segmental, continuous, granular, subepithelial immune deposits

- Subepithelial deposits[1]
- Active or chronic glomerular lesions (Class III + V/IV + V)[1]

Prevalence:
10.3%[3,*,†]

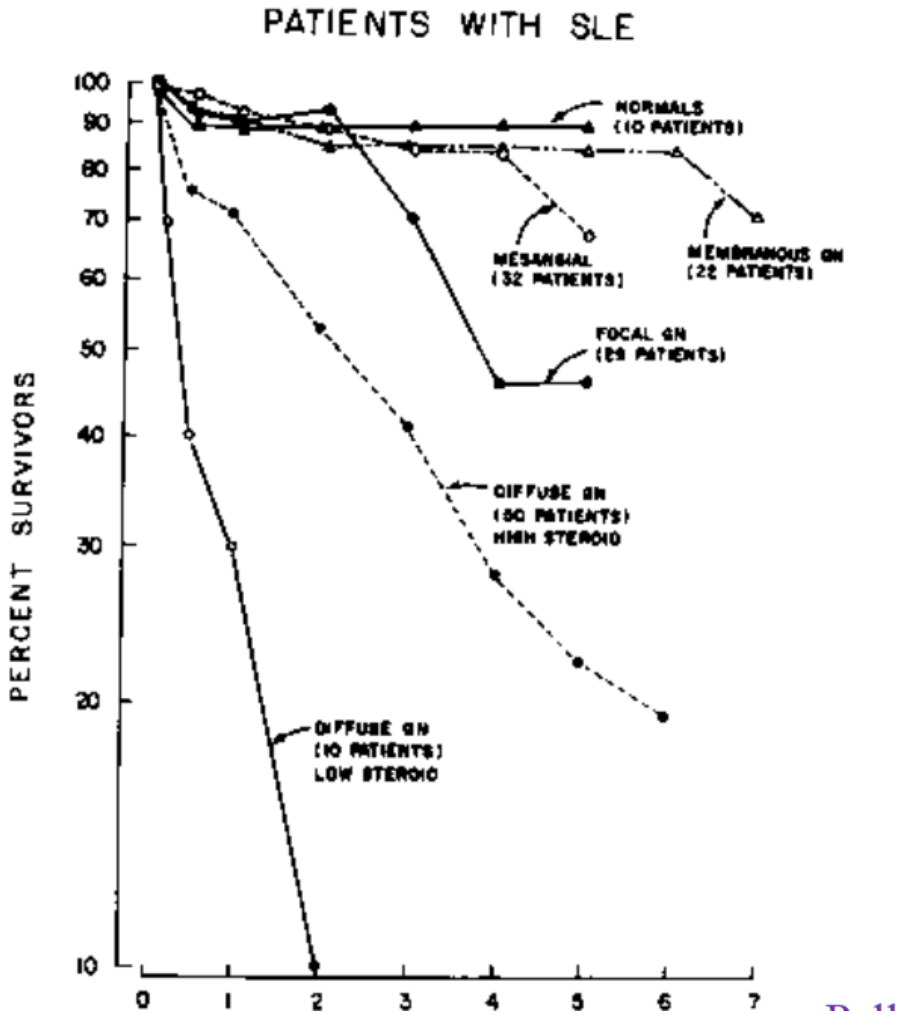
*From a study involving 2355 patients with SLE and LN from the database of the Rheumatology Research Center, Tehran University of Medical Sciences. †Class V alone.
ISN/RPS = International Society of Nephrology/Renal Pathology Society; IV-G = class IV global; IV-S = class IV segmental; LN = lupus nephritis; SLE = systemic lupus erythematosus.

1. Kiremitci S, Ensari A. *ScientificWorldJournal.* 2014;2014:580620. doi: 10.1155/2014/580620. **2**. Hahn BH, et al. *Arthritis Care Res (Hoboken).* 2012;64(6):797-808.
3. Faezi S, et al. *Rheum Res.* 2017;2(2):51-59. **4**. Bajema IM, et al. *Kidney Int.* 2018;93(4):789-796. **5**. Markowitz GS, D'Agati VD. *Kidney Int.* 2007;71(6):491-495.

Serologic worsening correlates with flares

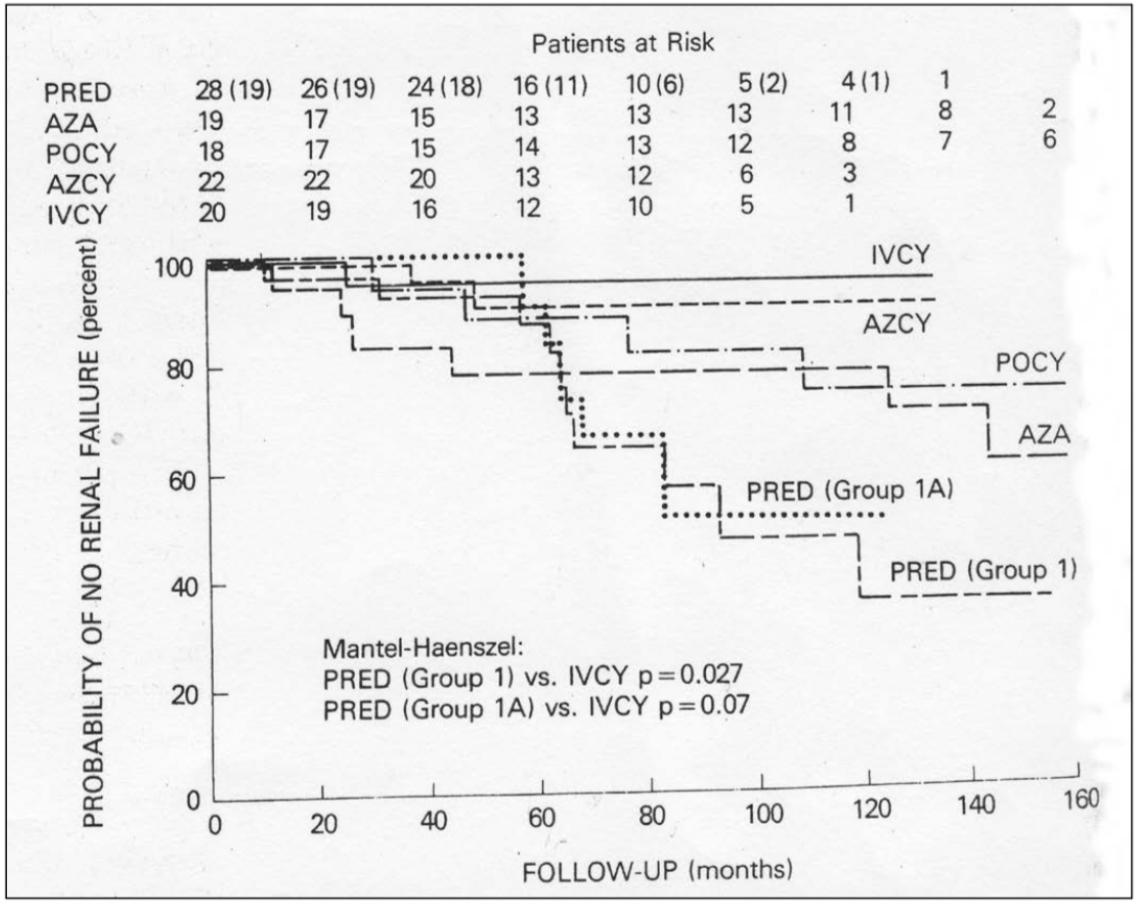
IMMUNOLOGY GENERAL					
Creatinine, Urine,...	158	156 *	229 *	265	265
C3 Complement	65 ↓	58 * ↓	61 * ↓		100
C4 Complement	10 ↓	9 * ↓	7 * ↓		12 ↓
dsDNA Ab	925.2 * ↑	734.4 * ↑			84.1 * ↑
dsDNA Ab, IgG			211.0 * ↑		

Glucocorticoids for Lupus Nephritis



Pollak, V 1961

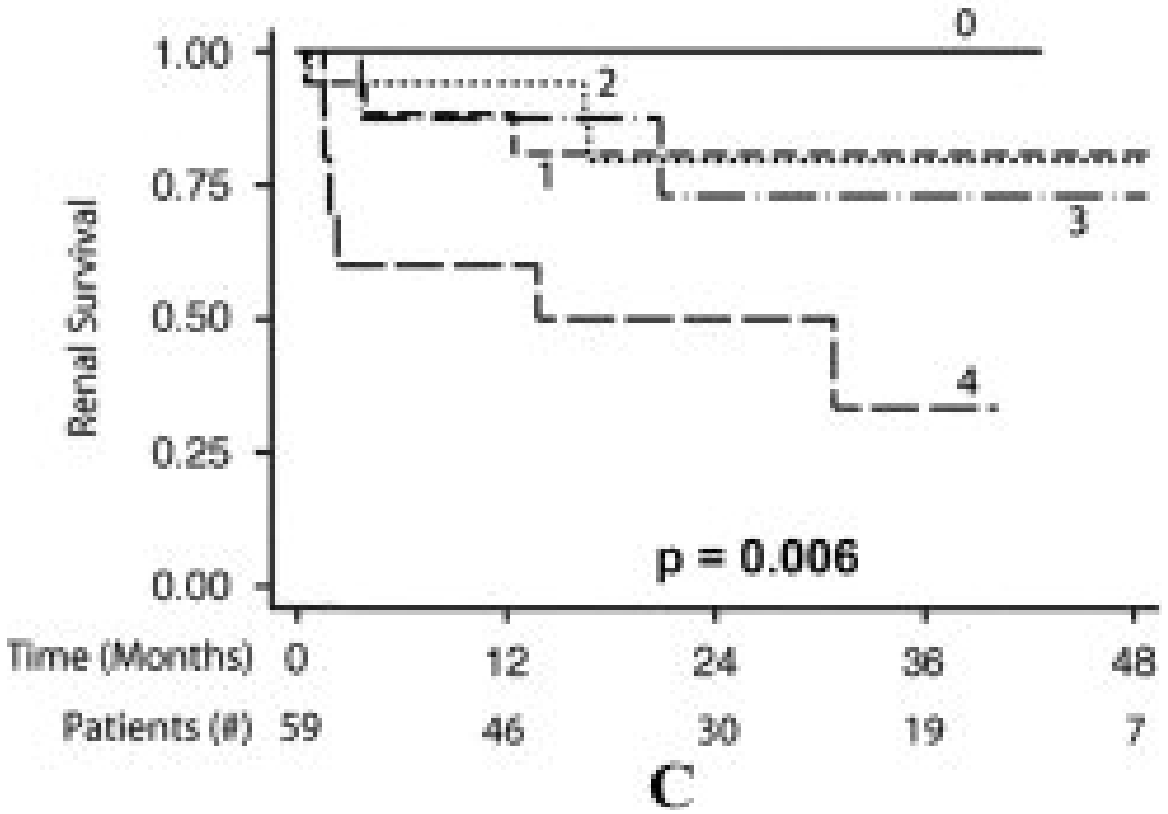
CYC for LN- Combination Therapy- Induction



Austin HA et al. NEJM 1986; 314:614-619

Predicting Outcomes of Lupus Nephritis

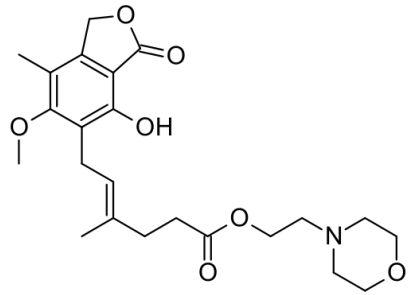
Tubulointerstitial inflammation and scarring important predictor



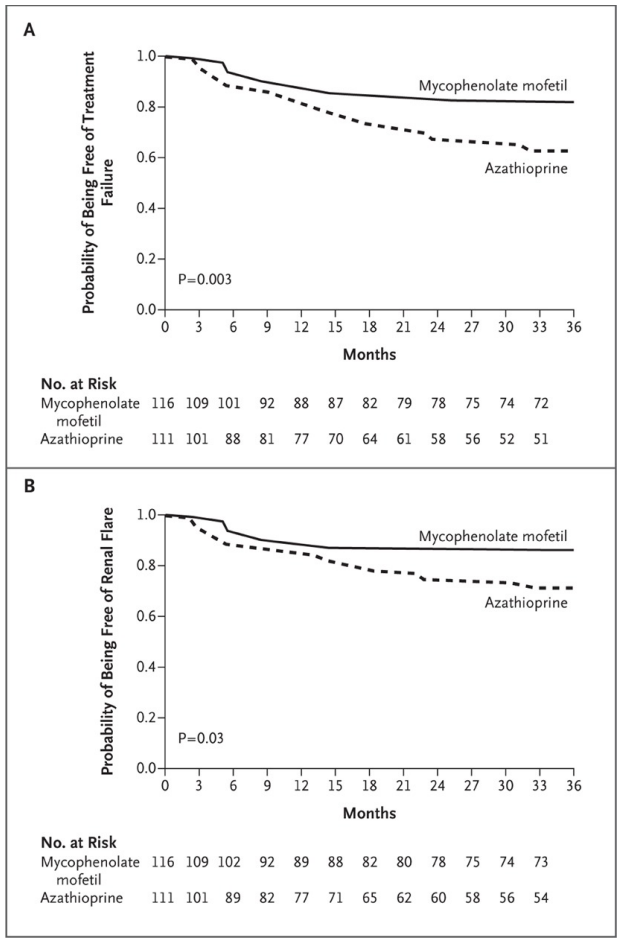
Hsieh *et al.*. *Arth. Res.Therapy* 63:865, 2011

Mycophenolate Gains Acceptance

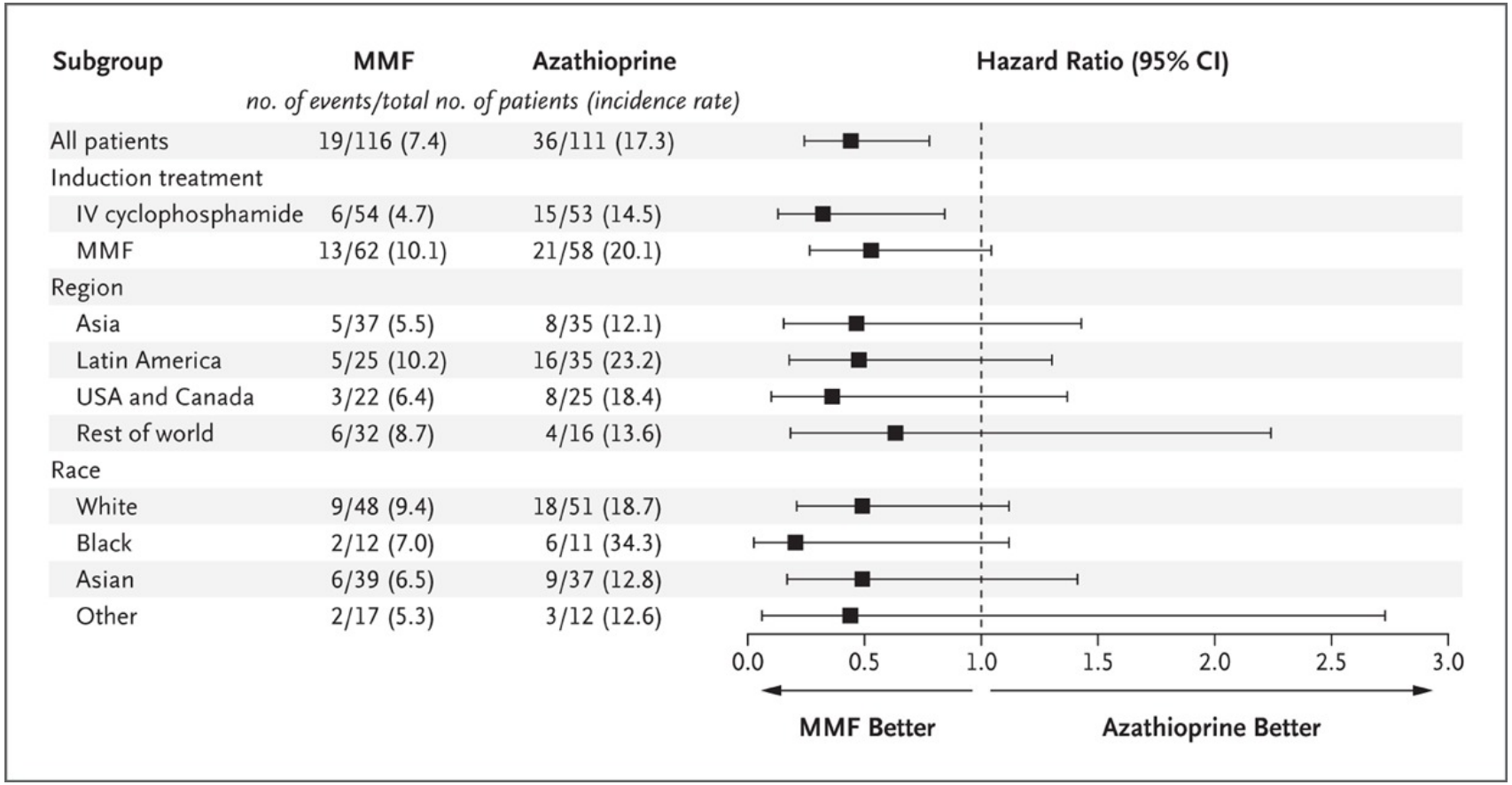
- Mycophenolate mofetil
  - pro-drug of mycophenolic acid
  - inhibits inosine monophosphate dehydrogenase
    - rate-limiting enzyme in *de novo* synthesis of guanosine nucleotides
- Similar efficacy to cyclophosphamide but better toxicity profile
- 1st line for lupus nephritis
- Slow acting therapy
  - response rates 50% at 12 mos



Lupus Nephritis- Maintenance of Remission



Time to Treatment Failure and Time to Renal Flare



Treatment Failure Risk

Dooley et al., NEJM 2011

Treatment

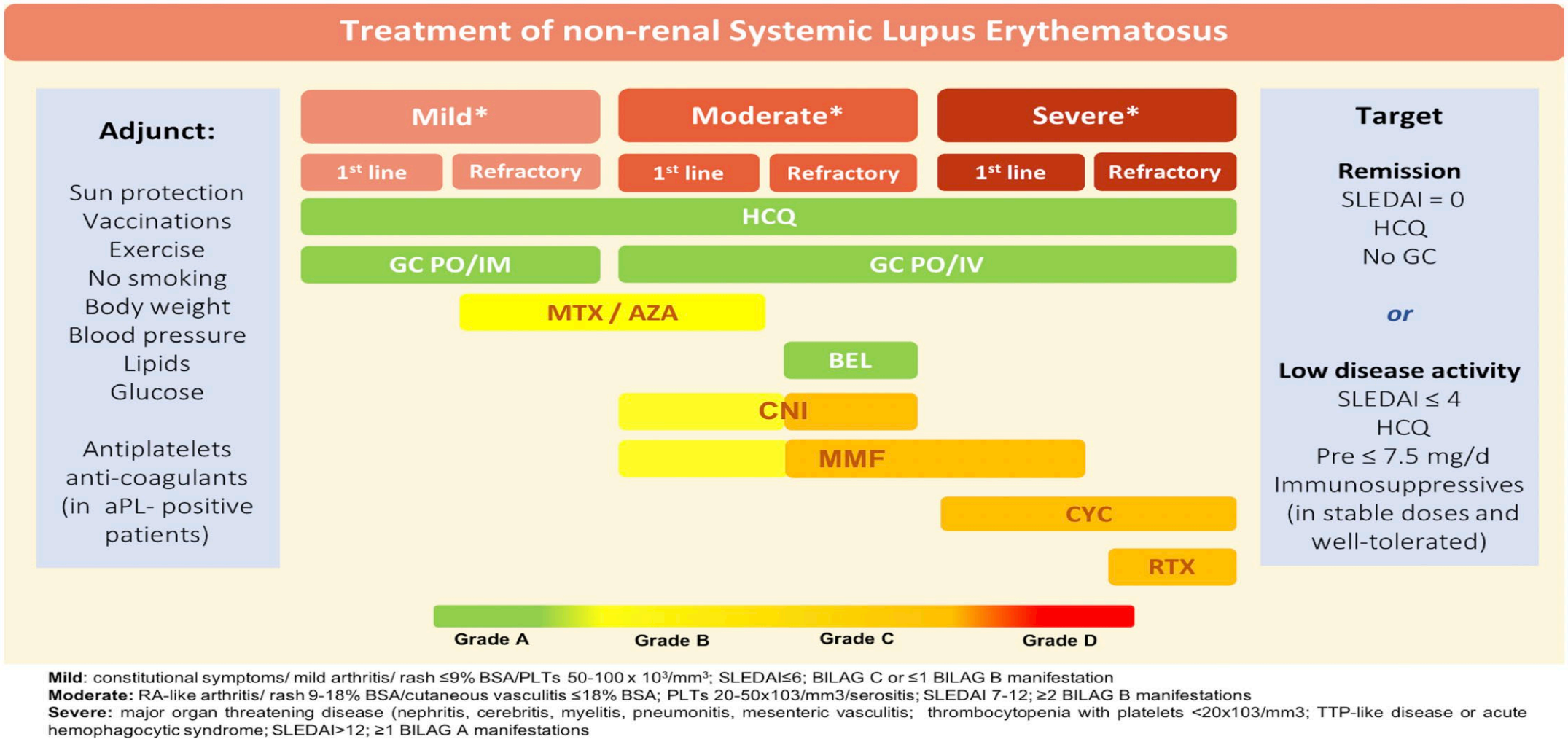
Treatment Recommendations for SLE: EULAR

Table 1 Recommendations for the management of patients with systemic lupus erythematosus

Overarching principles
► SLE is a multisystem disease—occasionally limited to one or few organs—diagnosed on clinical grounds in the presence of characteristic serological abnormalities.
► SLE care is multidisciplinary, based on a shared patient-physician decision, and should consider individual, medical and societal costs.
► Treatment of organ-threatening/life-threatening SLE includes an initial period of high-intensity immunosuppressive therapy to control disease activity, followed by a longer period of less intensive therapy to consolidate response and prevent relapses.
► Treatment goals include long-term patient survival, prevention of organ damage and optimisation of health-related quality of life.

Fanouriakis A, Kostopoulou M, Alunno A, *et al*
2019 update of the EULAR recommendations for the management of systemic lupus erythematosus
Annals of the Rheumatic Diseases 2019;**78:**736-745.

Treatment Recommendations for SLE: EULAR



Mild: constitutional symptoms/ mild arthritis/ rash ≤9% BSA/PLTs 50-100 x 10^3/mm^3; SLEDAI≤6; BILAG C or ≤1 BILAG B manifestation
Moderate: RA-like arthritis/ rash 9-18% BSA/cutaneous vasculitis ≤18% BSA; PLTs 20-50x103/mm3/serositis; SLEDAI 7-12; ≥2 BILAG B manifestations
Severe: major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis; thrombocytopenia with platelets <20x103/mm3; TTP-like disease or acute hemophagocytic syndrome; SLEDAI>12; ≥1 BILAG A manifestations

Fanouriakis A, Kostopoulou M, Alunno A, *et al* 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus *Annals of the Rheumatic Diseases* 2019;**78:**736-745.

Treatment Recommendations for Lupus Nephritis

Initial treatment	
4.3 For patients with class III or IV (±V) LN, MMF(target dose: 2 to 3 g/day, or MPA at equivalent dose)	1a/A
or low-dose intravenous CY (500 mg every 2 weeks for a total of 6 doses)	1a/A
in combination with glucocorticoids, are recommended as they have the best efficacy/toxicity ratio.	
4.4 Combination of MMF (target dose: 1 to 2 g/day, or MPA at equivalent dose) with a CNI (especially TAC) is an alternative, particularly in patients with nephrotic-range proteinuria.	1a/B
4.5 Patients at high risk for kidney failure (reduced GFR, histological presence of crescents or fibrinoid necrosis or severe interstitial inflammation) can be treated as in 4.3–4.4,	2b/B
but high-dose ntravenous CY (0.5–0.75 g/m^2 monthly for 6 months) can also be considered.	1a/B
4.6 To reduce cumulative glucocorticoid dose, the use of intravenous pulses methylprednisolone (total dose 500–2500 mg, depending on disease severity) is recommended, followed by oral prednisone (0.3–0.5 mg/kg/day) for up to 4 weeks, tapered to ≤7.5 mg/day by 3 to 6 months.	2b/C
4.7 In pure class V nephritis, MMF (target dose 2 to 3 g/day; or MPA at equivalent dose),	2a/B
in combination with pulse intravenous methylprednisolone (total dose 500–2500 mg, depending on disease severity) followed by oral prednisone (20 mg/day, tapered to ≤5 mg/day by 3 months)	2b/C
is recommended as initial treatment due to best efficacy/toxicity ratio.	
4.8 Alternative options for class V nephritis include intravenous CY,	2b/B
or CNIs (especially TAC) in monotherapy	2b/B
or in combination with MMF/MPA, particularly in patients with nephrotic-range proteinuria.	1b/B
4.9 HCQ should be coadministered,	2a/B
at a dose not to exceed 5 mg/kg/day and adjusted for the GFR.	3b/C

Fanouriakis A, Kostopoulou M, Cheema K, et al 2019 Update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritisAnnals of the Rheumatic Diseases 2020;79:713-723.

Treatment Recommendations for SLE: EULAR

Subsequent treatment

4.10 If improvement after initial treatment is achieved, subsequent immunosuppression is recommended with either MMF/MPA (dose: 1 to 2 g/day)—especially if it was used as initial treatment—	**1a/A**
or AZA (2 mg/kg/day)—preferred if pregnancy is contemplated—in combination with low-dose prednisone (2.5–5 mg/day) when needed to control disease activity.	**1a/A**
4.11 Gradual withdrawal of treatment (glucocorticoids first, then immunosuppressive drugs) can be attempted after at least 3 to 5 years therapy in *complete clinical response*. HCQ should be continued long-term.	**2b/C**

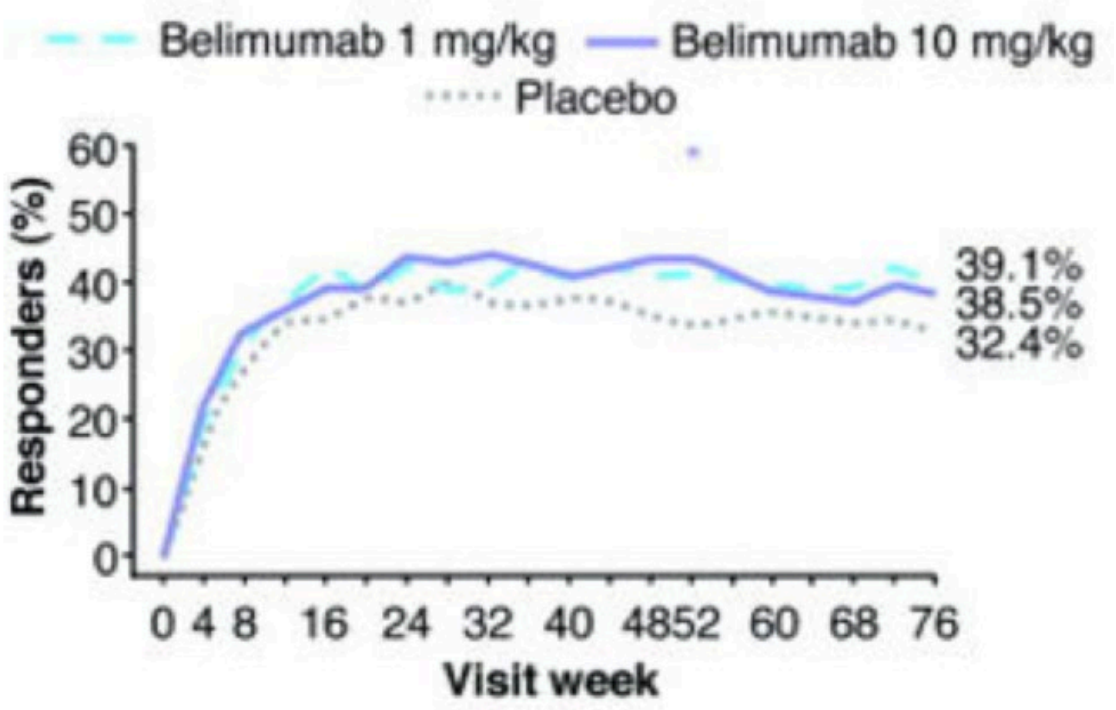
Fanouriakis A, Kostopoulou M, Cheema K, et al
2019 Update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis
Annals of the Rheumatic Diseases 2020;79:713-723.

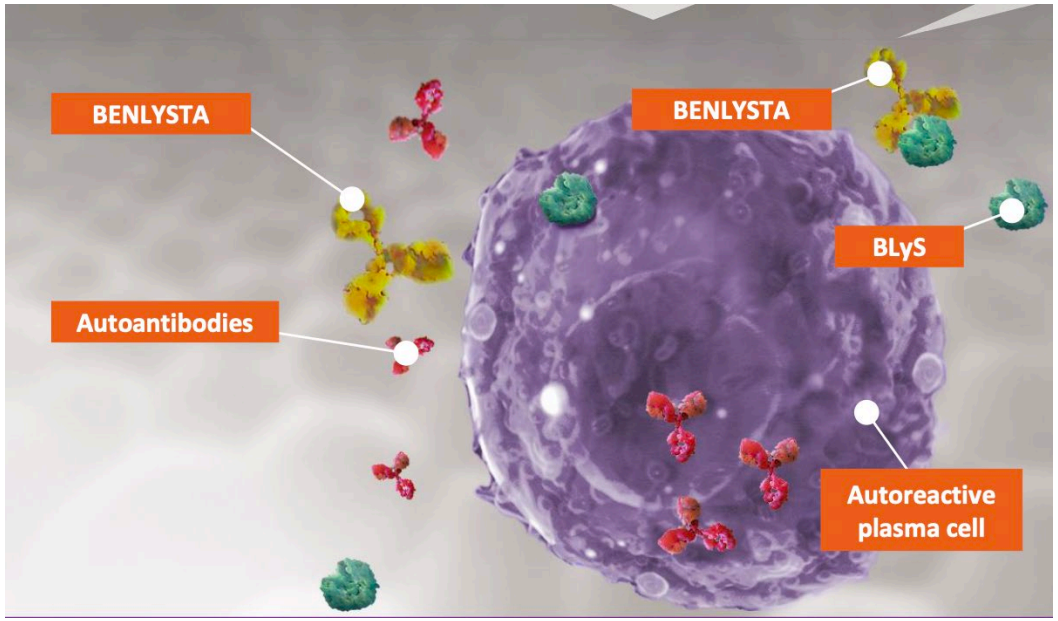
5. Adjunct treatment		
5.1 Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are recommended for all patients with UPCR >500 mg/g or arterial hypertension.	**5/D**	**9.84 (0.37)**
5.2 Statins are recommended on the basis of lipid levels and estimated 10-year cardiovascular disease risk using the Systematic Coronary Risk Evaluation or other validated tools.	**5/D**	**9.52 (0.75)**
5.3 Bone protection (calcium/vitamin D supplementation and/or antiresorptive agents) and immunizations with non-live vaccines may reduce treatment-related and disease-related comorbidities and are recommended.	**5/D**	**9.68 (0.61)**
5.4 If aPL (defined as in the international consensus statement for definite antiphospholipid syndrome classification criteria) are positive, and based on aPL profile, acetyl-salicylic acid (80–100 mg/day) may be used after balancing benefits and bleeding risk.	**2a/C**	**9.28 (1.25)**
5.5 Anticoagulant treatment should be considered in cases of nephrotic syndrome with serum albumin <20 g/L.	**5/D**	**9.76 (0.43)**
5.6 Belimumab may be considered as add-on treatment, to facilitate glucocorticoid sparing, control extra-renal lupus activity and decrease the risk for extra-renal flares.	**2a/C**	**8.48 (1.92)**

Fanouriakis A, Kostopoulou M, Cheema K, et al
2019 Update of the Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) recommendations for the management of lupus nephritis
Annals of the Rheumatic Diseases 2020;79:713-723.

New Agents for LN

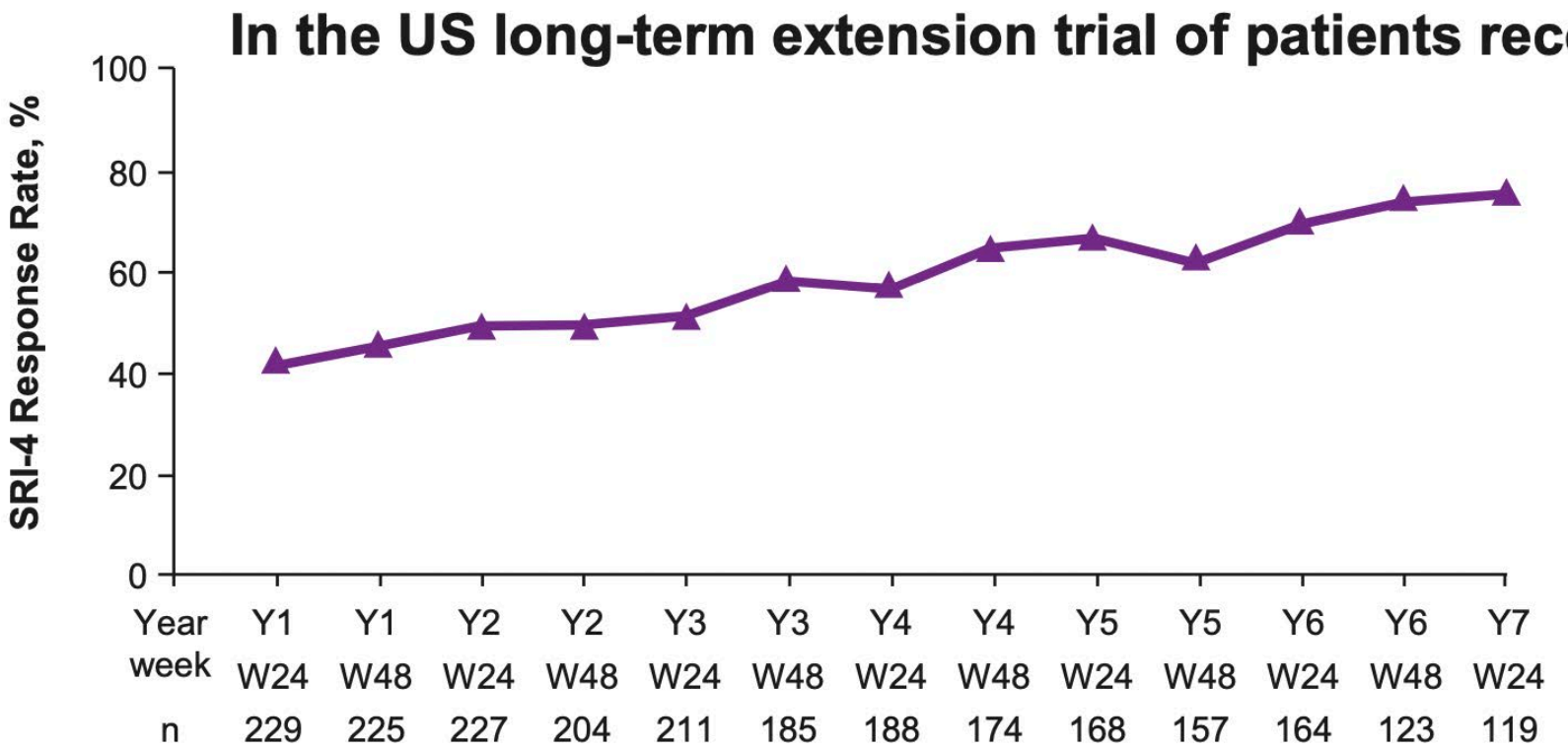
Targeted Therapy in SLE- BAFF inhibitor: Belimumab for SLE and LN





Wallace DJ, et al. Arthritis and rheumatism. 2009;61(9):1168-1178.

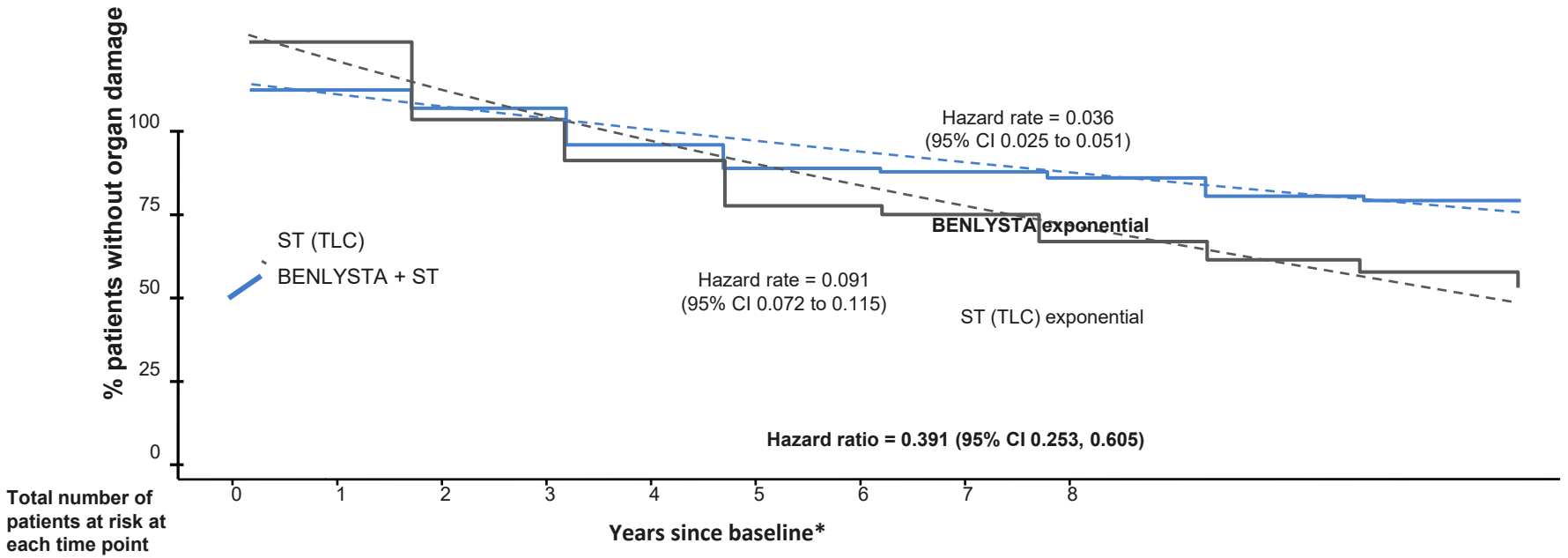
Targeted Therapy in SLE- BAFF inhibitor: Belimumab for SLE



75.6% patients were observed to achieve an SRI-4 response at 7-years

Furie RA, et al. *Arthritis Rheumatol.* 2018;70(6):868-877.

Belimumab + ST Was Associated With Slowed Annual Rate of Organ Damage Accrual in a Post hoc PSM Analysis

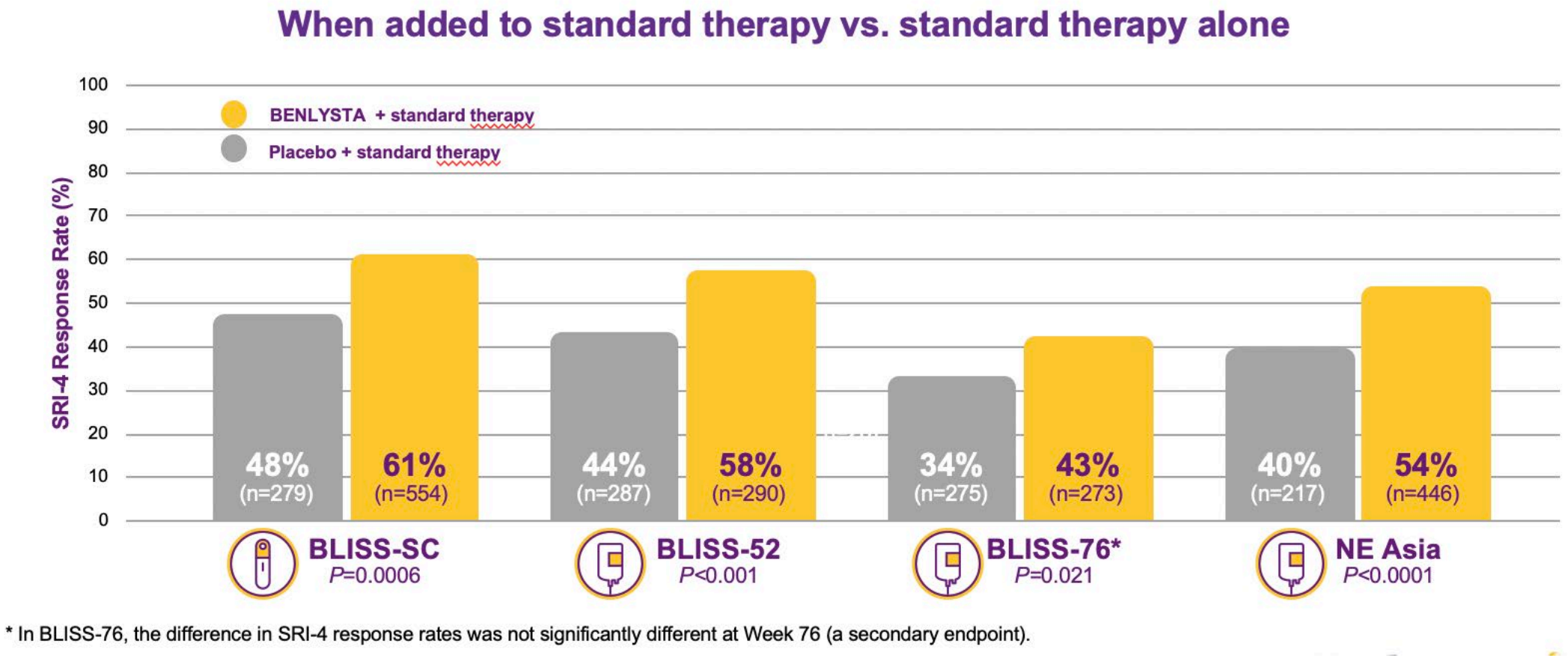


Total number of patients at risk at each time point

BENLYSTA	179	166	137	121	112	88	65	31	0
ST (TLC)	179	135	111	83	71	57	44	30	28

Urowitz MB, et al. *Ann Rheum Dis*. 2019;78(3):372-379.

Belimumab + ST Was Effective Across Clinical Trials



Stohl W, et al. *Arthritis Rheum.* 2017;69(5):1016-1027.Navarra S, et al. *Lancet.* 2011;377(9767):721-731. Furie R, et al. *Arthritis Rheum.* 2011;63(12):3918-3930. Zhang F, et al. *Ann Rheum Dis.* 2018;77:355-363

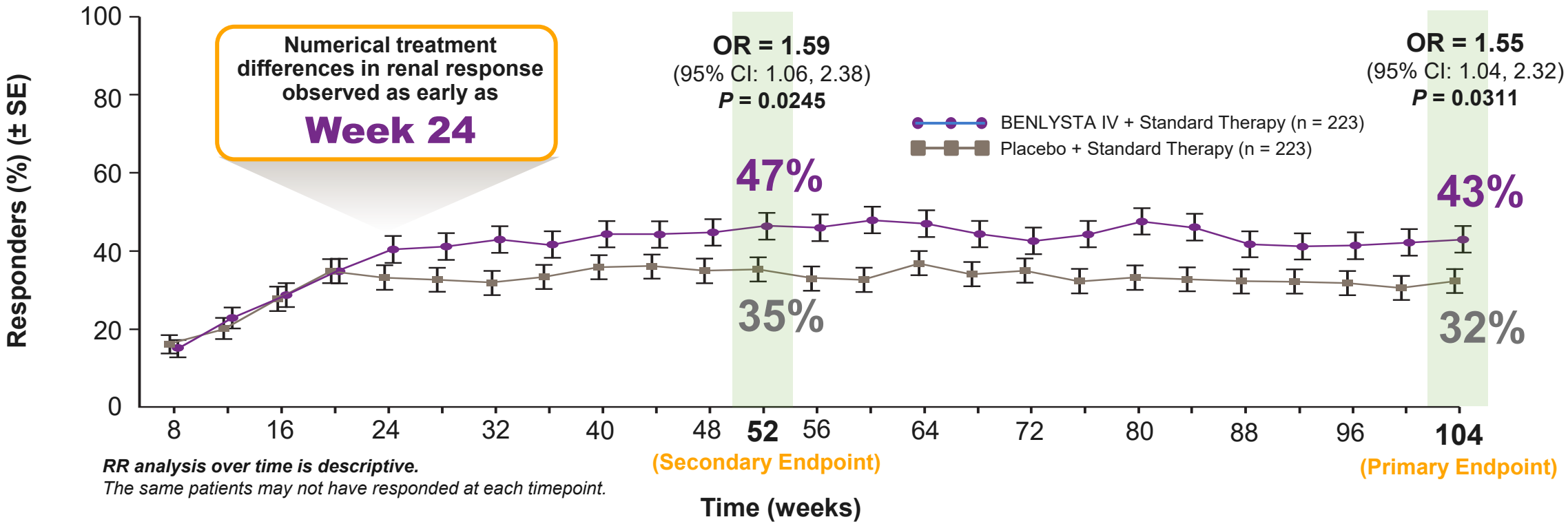
SLE Organ Domains in Belimumab Trials

Organ Domain*	BLISS-SC[1] N=836	BLISS-52[2] N=865	BLISS-76[3] N=819	NE Asia[4] N=677
Mucocutaneous (%)	88	82	82	82
Immunology (%)	76	85	74	90
Musculoskeletal (%)	79	59	73	32
Renal (%)	12	20	11	32
CV and respiratory (%)	6	4	9	1
CNS (%)	1	2	3	0.4
Vascular (%)	8	7	6	14
Hematological and fever (%)	8	7	12	10

Stohl W, et al. *Arthritis Rheum.* 2017;69(5):1016-1027.Navarra S, et al. *Lancet.* 2011;377(9767):721-731.
Furie R, et al. *Arthritis Rheum.* 2011;63(12):3918-3930. Zhang F, et al. *Ann Rheum Dis.* 2018;77:355-363

BENLYSTA + ST: Significantly More Patients Achieved Renal Response at Weeks 52 and 104 Compared With ST Alone

Renal Response Over Time[1-3,*]



RR analysis over time is descriptive.
The same patients may not have responded at each timepoint.

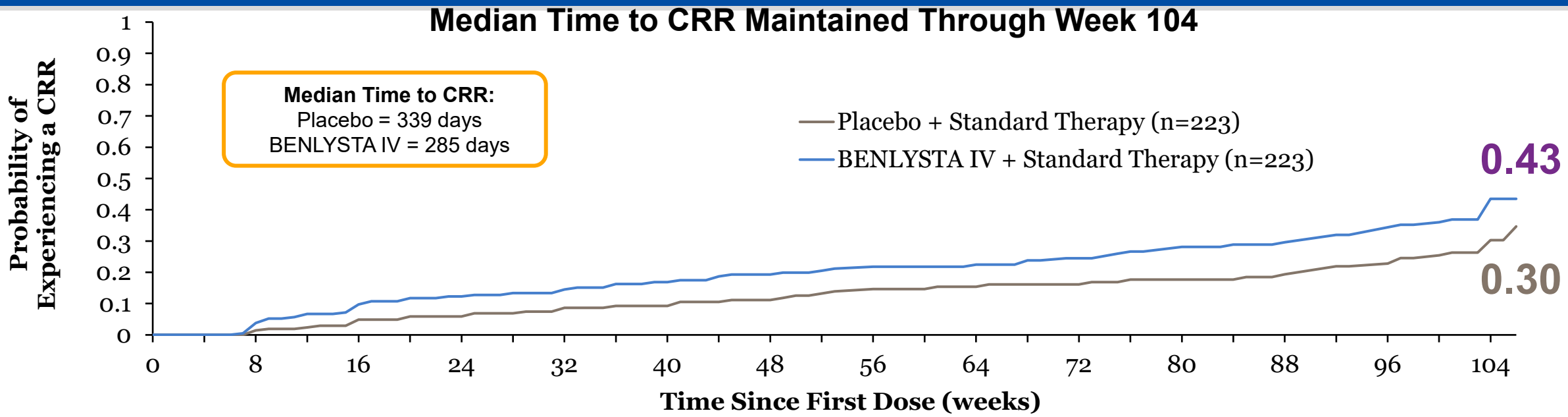
For the RR endpoint, patients receiving prohibited medications were considered as treatment failures.
For these endpoints, in order to be considered a responder, steroid treatment for renal events had to be reduced to ≤10 mg/day from Week 24.

Standard Therapy = Mycophenolate mofetil (MMF) + glucocorticoids OR cyclophosphamide/azathioprine + glucocorticoids

*Renal response was defined as eGFR ≥ 60 mL/min/1.73m^2 or eGFR no worse than 20% below the pre-flare value; and uPCR ≤0.7; and not a treatment failure.
eGFR = estimated glomerular filtration rate; OR = odds ratio; RR = renal response; SE = standard error; ST = standard therapy; uPCR = urinary protein:creatinine ratio.

References: 1. Benlysta [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2020. **2.** Furie R, et al. *N Engl J Med.* 2020;383(12):1117-1128.
3. Data on File. GSK.

Complete Renal Response Maintained to Week 104



Number of patients at risk

Placebo + ST	209	196	183	156	143	132	120	115	108	102	95	90	62
BENLYSTA IV + ST	211	184	169	150	138	131	126	118	106	101	92	85	58

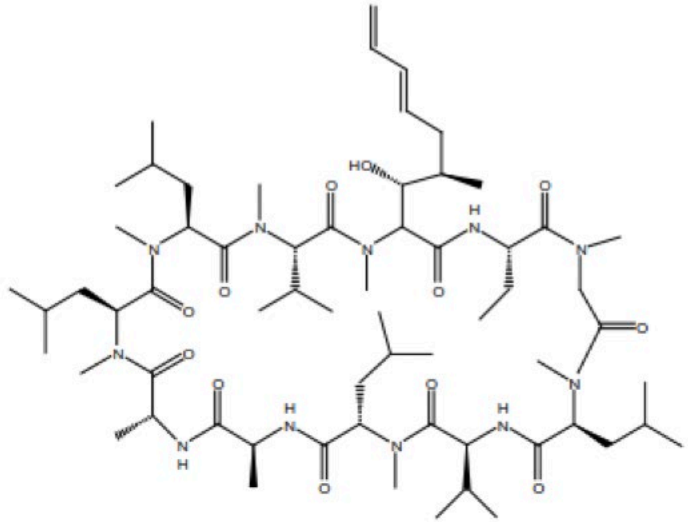
Compared with standard therapy alone, patients on BENLYSTA IV had a 58% [HR (95% CI)= 1.58 (1.08, 2.31)] increased likelihood at any time of achieving a complete renal response that would be maintained to Week 104

Standard Therapy = Mycophenolate mofetil (MMF) + glucocorticoids OR cyclophosphamide/azathioprine + glucocorticoids

*Complete renal response was defined as eGFR ≥ 90 mL/min/1.73m^2 or eGFR no worse than 10% below the pre-flare value; and uPCR <0.5; and not a treatment failure. Furie R, et al. *N Engl J Med.* 2020;383(12):1117-1128.

Meeting The Unmet Clinical Needs for Lupus Nephritis

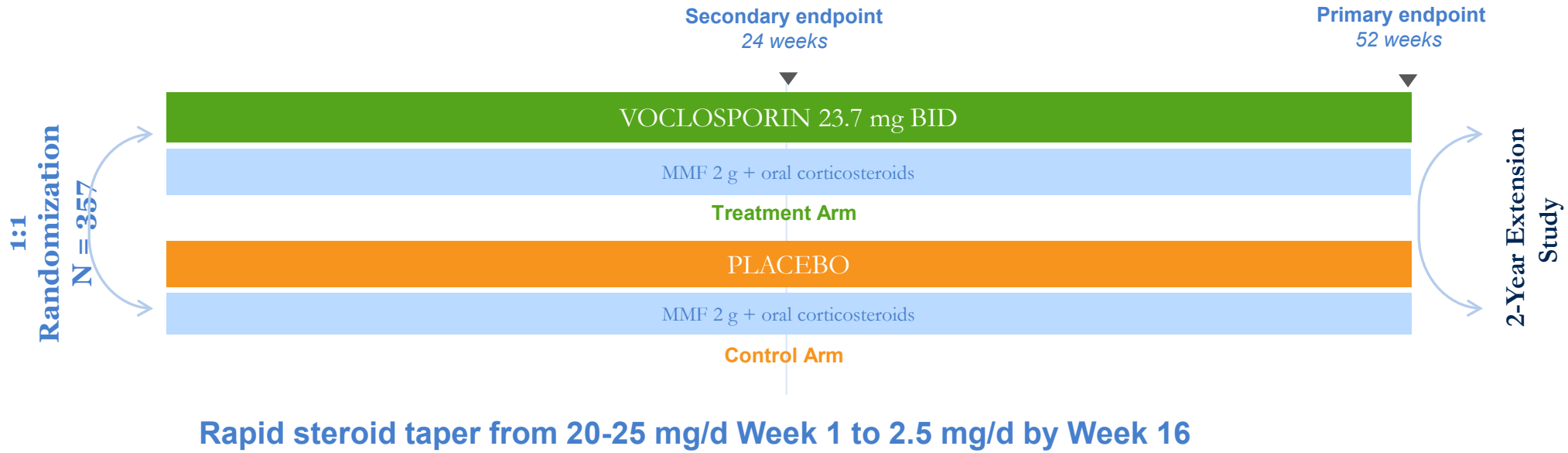
- Voclosporin approved for lupus nephritis
  - best-in-class calcineurin inhibitor
  - more predictable PK/PD



  - increased binding to calcineurin with increased immunosuppressive activity relative to CsA
  - Studies demonstrate efficacy across racial groups

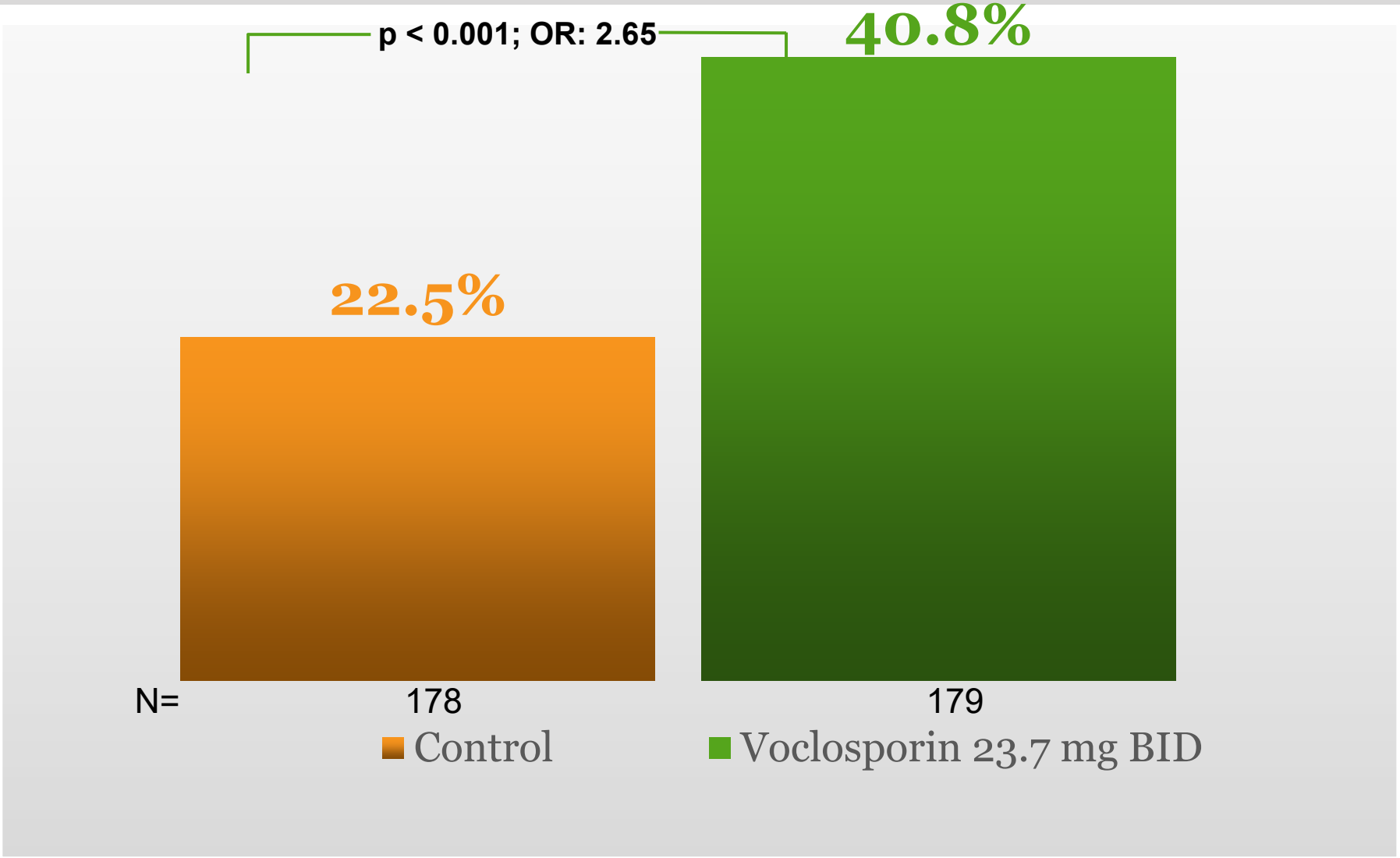
Voclosporin Phase 3 Study Design

- UPCR of ≤0.5 mg/mg
- eGFR ≥60 mL/min/1.73m^2 or no confirmed decrease from baseline in eGFR of ≥20%
- ≤10mg pred. from Week 44-52)
- No rescue medications



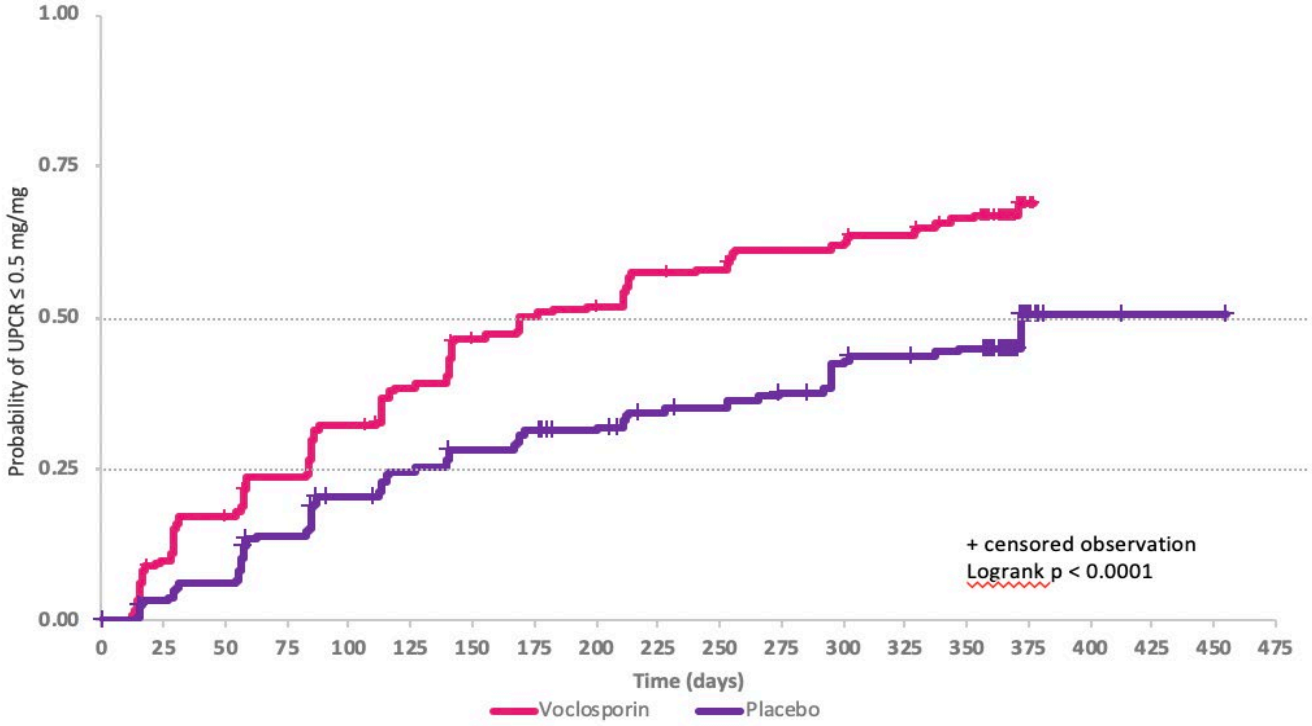
Abbreviations: BID = twice a day ; MMF = mycophenolate mofetil

Voclosporin Primary Efficacy Endpoint: Week 52 Renal Response (ITT)



NNT 5.4

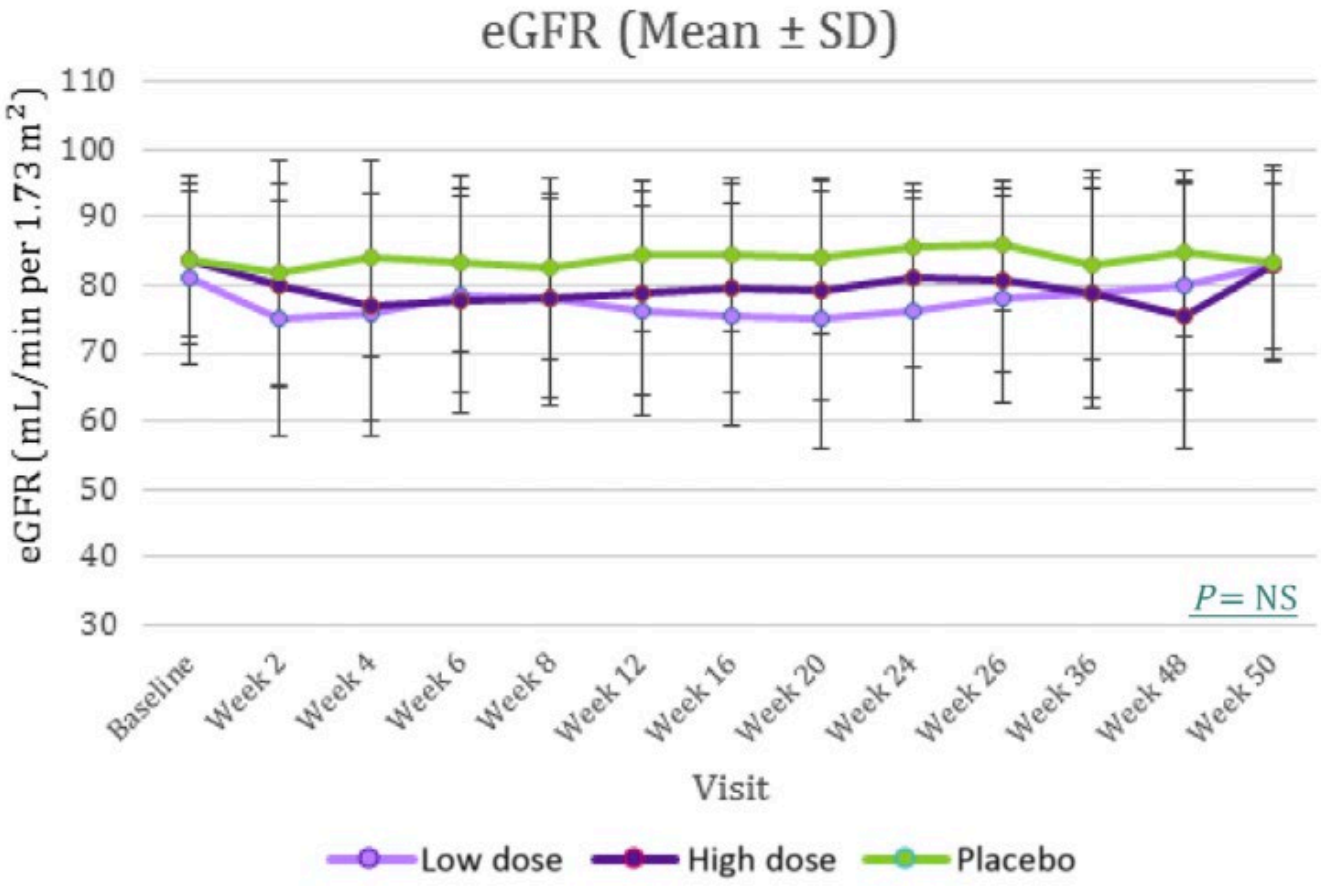
Probability to Reach UPr/Cr <0.5mg/dL Over Time



Measure	Result (Days)	p-value
Median Time (50%) to UPCR ≤ 0.5 mg/mg	Voclosporin:169 Control: 372	< 0.001
Median Time (25%) to UPCR ≤ 0.5 mg/mg	Voclosporin: 84 Control: 127	< 0.001

Rovin *et al.*, *Lancet* 397: 2070-2080, 2021 doi.org/10.1016/S0140-6736(21)00578-X

Voclosporin Did Not Significantly Alter eGFR In Most



Rovin, B., Kidney-International. 2018

Table 1: Adverse Reactions in ≥3% of Patients Treated with LUPKYNIS 23.7 mg Twice a Day and ≥2% Higher than Placebo in Studies 1 and 2

Adverse Reaction	LUPKYNIS 23.7 mg twice a day (n=267)	Placebo (n=266)
Glomerular filtration rate decreased*	26%	9%
Hypertension	19%	9%
Diarrhea	19%	13%
Headache	15%	8%
Anemia	12%	6%
Cough	11%	2%
Urinary tract infection	10%	6%
Abdominal pain upper	7%	2%
Dyspepsia	6%	3%
Alopecia	6%	3%
Renal Impairment*	6%	3%
Abdominal pain	5%	2%
Mouth ulceration	4%	1%
Fatigue	4%	1%
Tremor	3%	1%
Acute kidney injury*	3%	1%
Decreased appetite	3%	1%

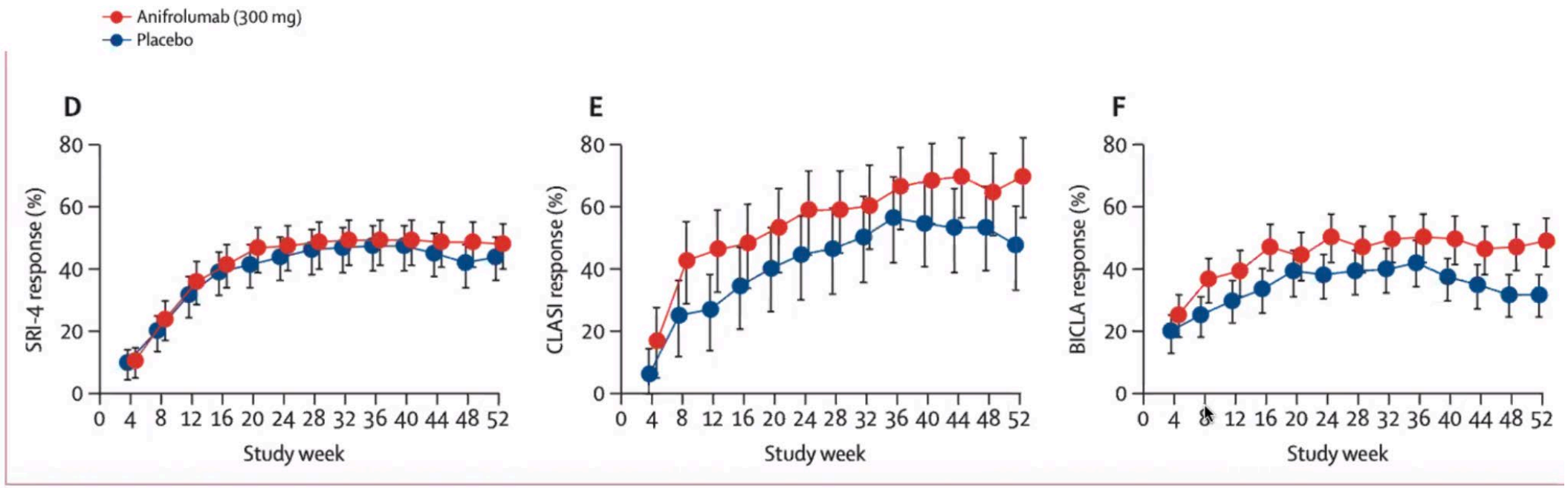
**See Specific Adverse Reactions below (Nephrotoxicity)*

Anifrolumab: an INF-α Rc antibody

- 2 phase III studies TULIP I/II
- Showed different positive results
- SRI vs BICLA
  - TULIP I met SRI $
  - TULIP II met BICLA
  - During TULIP II primary end point was changes to BICLA based in TULIP I data of BICLA (a secondary endpoint)

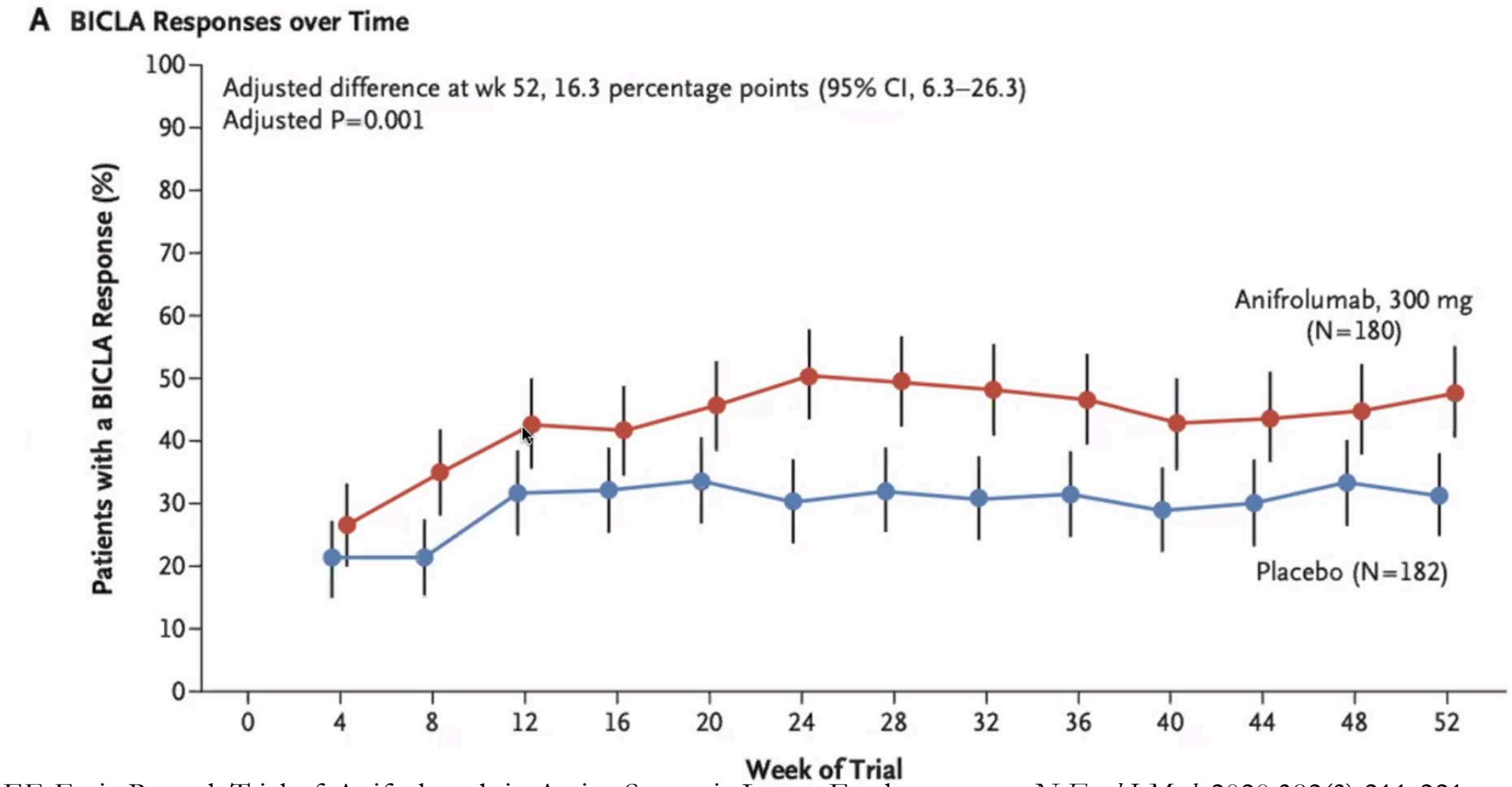
Anifrolumab for SLE- TULIP I

SRI-4, CLASI, and BICLA responses in anifrolumab 300 mg groups compared to placebo



Furie RA, Morand EF, Bruce IN, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. Lancet Rheumatol 2019;1(4):e208-e219.

Anifrolumab for SLE- TULIP II

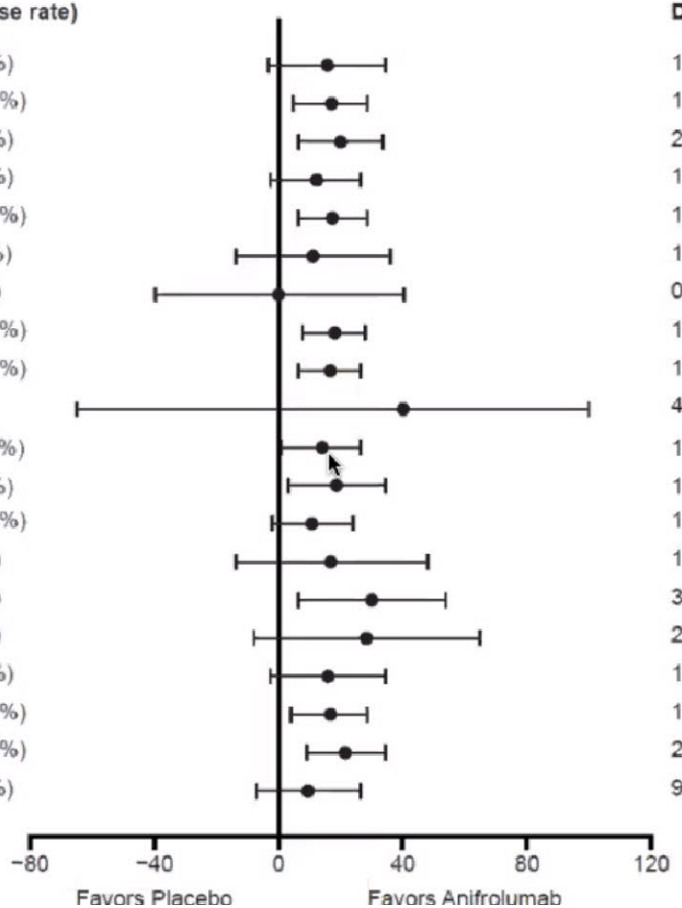


Morand EF, Furie R, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med.* 2020;382(3):211-221

Anifrolumab for SLE- TULIP II

Figure S5. BICLA Response Rates at Week 52 by Patient Subgroups*

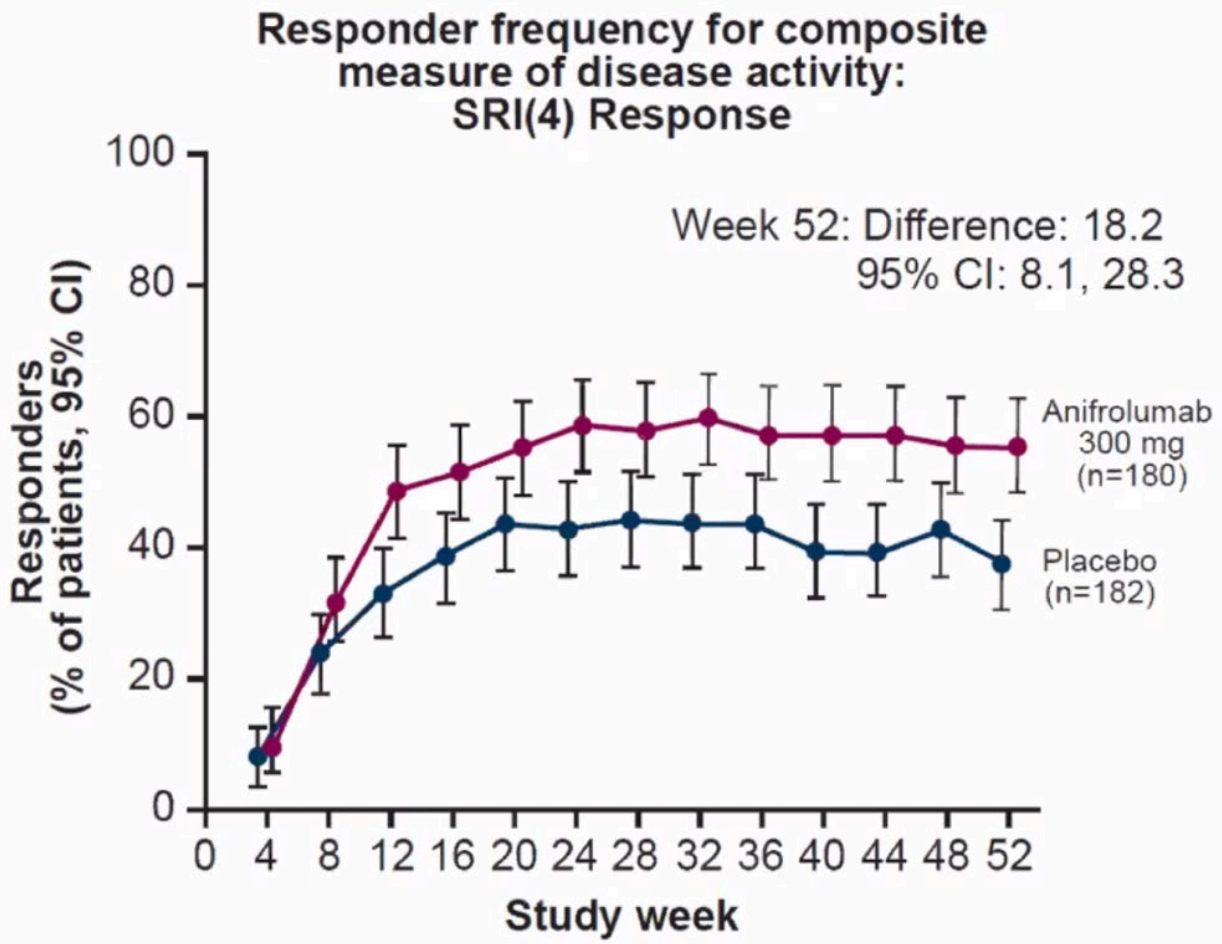
Subgroup	Anifrolumab 300 mg n/N (response rate)	Placebo n/N (response rate)	Difference [95% CI]
SLEDAI-2K score at screening <10	28/54 (51.8%)	19/52 (36.5%)	15.3 [−3.3, 33.9]
SLEDAI-2K score at screening ≥10	58/126 (46.2%)	38/130 (29.5%)	16.7 [4.9, 28.5]
Glucocorticoid dosage at baseline <10 mg/day	46/93 (49.5%)	29/99 (29.4%)	20.1 [6.5, 33.7]
Glucocorticoid dosage at baseline ≥10 mg/day	40/87 (45.8%)	28/83 (33.8%)	12.0 [−2.5, 26.6]
Result of type 1 IFN test high	72/150 (48.0%)	46/151 (30.7%)	17.3 [6.5, 28.2]
Result of type 1 IFN test low	14/30 (46.7%)	11/31 (35.5%)	11.2 [−13.5, 35.8]
Sex: male	6/12 (50.0%)	6/12 (50.0%)	0.0 [−40.0, 40.0]
Sex: female	80/168 (47.7%)	51/170 (30.0%)	17.7 [7.4 27.9]
Age ≥18 to 65	84/175 (48.0%)	57/181 (31.7%)	16.3 [6.3, 26.4]
Age ≥65	2/5 (40.0%)	0/1	40.0 [−65.4, 100]
BMI ≤28 kg/m^2	51/107 (47.5%)	38/114 (33.6%)	13.9 [1.1, 26.6]
BMI >28 kg/m^2	35/73 (48.0%)	19/68 (29.3%)	18.7 [3.0, 34.4]
Race: White	49/110 (44.6%)	36/107 (33.8%)	10.8 [−2.2, 23.8]
Race: Black or African American	9/17 (52.9%)	9/25 (36.0%)	16.9 [−13.5, 47.4]
Race: Asian	15/30 (50.0%)	6/30 (20.0%)	30.0 [6.5, 53.5]
Race: Other	8/15 (53.3%)	3/12 (25.0%)	28.3 [−8.1, 64.8]
Ethnicity: Hispanic/Latino	30/54 (55.9%)	22/54 (40.1%)	15.8 [−2.9, 34.4]
Ethnicity: Non-hispanic/Latino	51/118 (43.2%)	32/120 (26.8%)	16.4 [4.3, 28.5]
Baseline anti-dsDNA, C3 and C4: At least one positive/abnormal	60/122 (49.2%)	28/101 (27.9%)	21.3 [8.8, 33.9]
Baseline anti-dsDNA, C3 and C4: All negative/normal	26/58 (44.9%)	29/81 (35.7%)	9.2 [−7.5, 25.8]



Morand EF, Furie R, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med.* 2020;382(3):211-221

Anifrolumab for SLE- TULIP II

Figure S4. Percentage (95% CI) of Patients With SRI(4) Response Over Time*



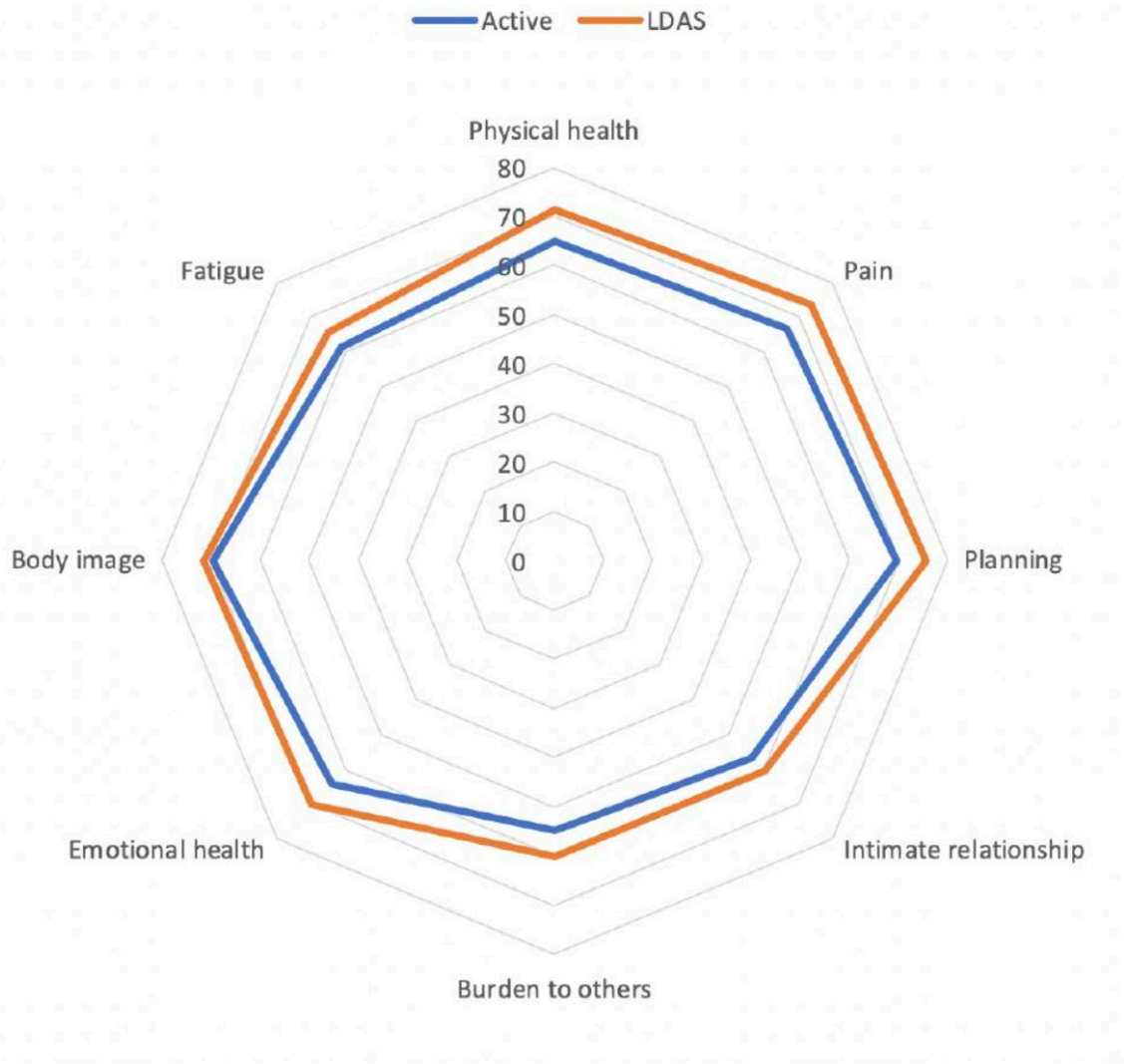
Morand EF, Furie R, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. *N Engl J Med.* 2020;382(3):211-221

Low Lupus Disease Activity State: Treat to Target

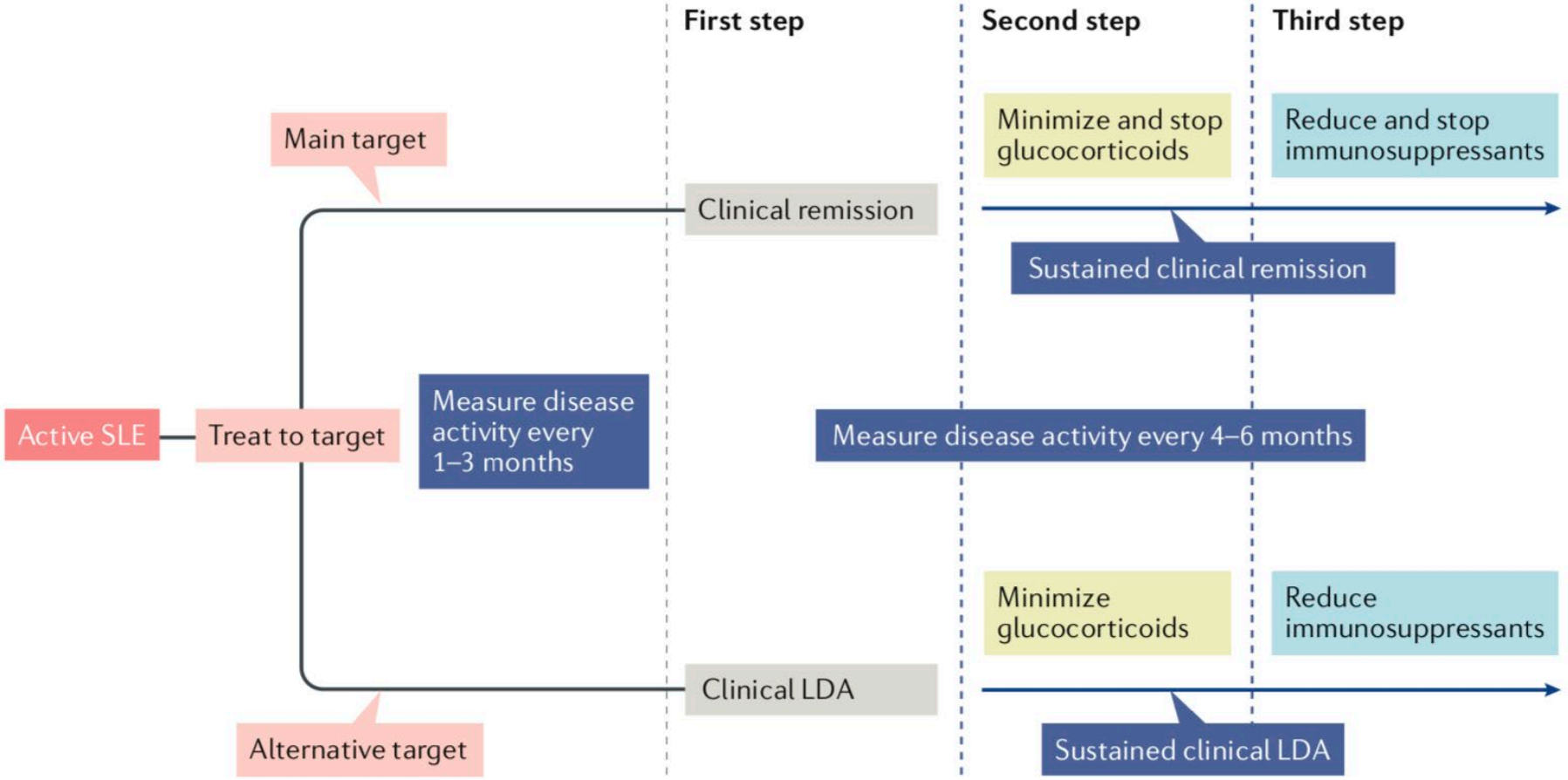
- **LLDAS Definition: patient must meet all 5 criteria to be considered as having achieved a low disease activity state**
  - **SLEDAI-2K ≤4**, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity
  - **No new features** of lupus disease activity compared with previous assessment
  - SELENA-SLEDAI physician global assessment **(PGA, scale 0-3) ≤1**
  - Current prednisolone (or equivalent) dose **≤7.5 mg daily**
  - Well-tolerated **standard maintenance doses** of immunosuppressive drugs and approved biological agents, excluding investigational drugs

Franklyn K, et al. *Ann Rheum Dis* 2016;75:1615-1621.

HRQoL as a Function of Being Active or on LDAS



Proposed Model for SLE management in Phases



Gatto, et al., Nature Reviews Rheumatology. Voll 15, pages30–48 (2019)

Summary

- SLE is multisystem
- SLE is a spectrum disease
- Heath disparities seen in SLE
- Nephritis is main reason for morbidity and mortality in SLE
- Combination therapies are essential to reduce GC use and damage accrual

THANK YOU

Fotios Koumpouras
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Yale Lupus Program



A model of comprehensive care for patients with lupus, providing access to groundbreaking clinical therapeutics, scientific research, and education for patients and their families.

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