AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

American College of Rheumatology (ACR) Guideline for Treatment of Systemic Lupus Erythematosus (SLE)

Project Plan – December 2023

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ORGANIZATIONAL LEADERSHIP AND SUPPORT

This project is led and funded by the American College of Rheumatology (ACR).

BACKGROUND

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder that impacts many different organs. Prevalence rate in the United States is estimated to be between 20-150 cases per 100,000 with a 2-3 fold increased rate among Black individuals. SLE is up to nine times as common in women as in men, with reproductive-aged women being particularly vulnerable. Etiology is multifactorial and includes genetic, immunologic, hormonal, and environmental factors. Disease manifestations range from mild to severe, with renal disease and cardiovascular manifestations causing the greatest morbidity and mortality. Multiple other organ systems can be involved, including but not limited to the skin, lungs, gastrointestinal, hematologic, and nervous systems.

Although mortality and morbidity are improved with earlier diagnosis and current treatment strategies, they are still significantly increased for patients with SLE. Both direct and indirect factors impact patient outcomes. The limited number of targeted biologic medications and inadequate therapeutic strategies allow persistent disease activity, flares, and accrual of damage. Continued dependence on glucocorticoid contributes to multiple comorbidities including cardiovascular disease, diabetes, infection, osteoporosis, and others. Additional important factors influencing disease outcomes are adherence to therapy and limited access to high-quality care, and many patients experience reduced health-related quality of life even with adequate therapy.

The FDA approvals of newer agents have expanded available treatment options for SLE, yet the optimal use of newer agents in combination with, or instead of, standard therapies is uncertain. The safest and most effective treatment strategies for lupus nephritis with our current catalog of therapies remain unclear, including whether standard monotherapy or combination therapy in a step-up or step-down manner is best. An important challenge is the optimal use of glucocorticoid, to benefit from the rapid onset of immunosuppressive effect yet limit the associated long-term morbidities. Therapies for control of lupus may differ depending on organ system involvement, but strategies for extrarenal manifestations are less well explored than for lupus nephritis.

This ACR SLE guideline will be developed and presented in two parts: lupus nephritis and general systemic lupus. The most recent ACR guidelines for the screening, treatment and management of lupus nephritis were published in 2012. For phase 1 of the project, the core oversight team will develop PICO questions on the topic of lupus nephritis screening, treatment and management that will inform the literature review team's selection of articles. The oversight team will develop evidence-based guideline statements that will be voted on by a panel of experts. In phase 2 of the project, the same process will

be used to develop treatment guidelines regarding general manifestations of systemic lupus erythematosus. Topics will include relevant guideline statements for the pediatric population whenever possible.

OBJECTIVES

The objective of this project is to develop a clinical practice guideline that includes evidence-based consensus recommendations for clinicians who care for people with systemic lupus erythematosus (SLE).

Specifically, we aim to:

1. Develop recommendations related to lupus nephritis screening, treatment, and management;
2. Develop recommendations related to the treatment and management of systemic lupus manifestations including hematologic, neuropsychiatric, musculoskeletal, cardiac, cutaneous, and vascular;
3. Develop recommendations and guidance, including good practice statements, on prevention and management of lupus-related comorbidities; and
4. Provide appropriate, directed referral to currently available ACR guidelines with information relevant to treatment of SLE including vaccination guidance, screening and treatment of steroid-induced osteoporosis, and issues regarding reproductive health.

METHODS

Identification of Studies

Literature search strategies, based on PICO questions (Population/patients, Intervention, Comparator, and Outcomes; *see Appendix A*) were drafted by the Core Team and a research librarian. Searches will be performed in OVID Medline (1946 +), Embase (1974 +), and PubMed (mid-1960s +).

The search strategies will be developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for OVID Medline and PubMed; and Emtree terms for Embase. Text words will also be used in OVID Medline, PubMed, and Embase.

Search Limits

Only English language articles will be retrieved.

Literature Search Update

Literature searches will be updated just before the voting panel meeting to ensure completeness.

Inclusion/Exclusion Criteria

Appendix A includes the project's PICO questions, which outline the defined patient population, interventions, comparators, and outcomes. *Appendix B* includes the list of inclusion/exclusion criteria. *Appendix C* includes a more detailed list of outcomes.

Management of Studies and Data

References and abstracts will be imported into bibliographic management software (EndNote) (1), duplicates removed, and exported to Distiller SR, a web-based systematic review manager (2). Screening and data abstraction forms will be created in Distiller SR. Search results will be divided among reviewers, and two reviewers will screen each title/abstract, with disagreements at the title/abstract screening stage defaulting to inclusion for full manuscript review. Following the same dual review process, disagreements at the full manuscript screening stage will be discussed and adjudicated by the literature review leadership, if necessary.

Phases

1. A search for randomized controlled trials and observational studies will be performed to determine existing studies assessing interventions, comparisons and outcomes of interest.
2. Additionally, recently published systematic reviews covering outcomes of interest will also be sought and used for reference cross-checking.
3. Chosen studies will be quality-assessed using validated risk of bias tools
4. Subsequently, evidence will be synthesized and, when feasible, statistical pooling of estimates will be completed using RevMan (3). GRADE evidence summary tables will be developed using GRADE Pro tools (4).

GRADE Methodology

GRADE methodology will be used in this project to grade available evidence and facilitate development of recommendations. The certainty in the evidence (also known as 'quality' of evidence) will be graded as high, moderate, low or very low. The recommendations will have a strength, strong or conditional, and a direction, as in favor or against the intervention. The strength of recommendations will not depend solely on the certainty in the evidence, but also on patients' values, and the tradeoff between benefits and harms in addition to other important decisional factors like feasibility, acceptability and cost/resource and equity implications. A series of articles that describe the GRADE methodology can be found on the GRADE working group's website: www.gradeworkinggroup.org.

Data Analysis and Synthesis

The literature review team will analyze and synthesize data from included studies that address the PICO questions. When feasible, the review team will statistically pool results using Review Manager (RevMan) (4) software. A GRADE evidence profile or Summary of Findings table, when applicable, will be prepared for each PICO question, using GRADEprofiler (GRADEpro) software (4). The Summary of Findings table contains the benefits and harms for each outcome across studies, the assumed and corresponding risk

for comparators and interventions (95% CI), the absolute risk and relative effect (95% CI), the number of participants/number of studies, and the certainty in the evidence for each critical and important outcome (i.e., high, moderate, low or very low).

The evidence profile documents the overall certainty in the evidence for each critical and important outcome across studies and summarizes the rationale of the GRADE criteria for downgrading (risk of bias, inconsistency, indirectness, imprecision, and publication bias), or upgrading the certainty in a body of evidence (large magnitude of effect, dose-response gradient, and all plausible confounding that would reduce a demonstrated effect).

Development of Recommendation Statements

PICO questions will be revised into drafted recommendation statements. Using the GRADE Evidence Profiles and Summaries of Findings tables, the voting panel, consisting of 14 rheumatologists, 1 pediatric rheumatologist, 3 nephrologists, 1 dermatologist, and #TBD patients with lupus, will consider the drafted recommendation statements in two stages. The first assessment will be done individually, and the results will be anonymous to other voting panel members; this vote will only be used to determine where consensus might or might not already exist and develop the voting panel meeting agenda. At the virtual voting panel meeting, chaired by the principal investigator, the panelists will discuss the evidence in the context of their clinical experience and expertise to arrive at consensus on the final recommendations. The voting panel meeting discussions will be supported by the literature review leader/GRADE expert and selected members of the literature review team, who will attend the meeting to provide details about the evidence, as requested. Voting panel discussions and decisions will also be informed by a separately convened patient panel, which will meet in the days before the voting panel meeting, to provide unique patient perspectives on the drafted recommendations based on their experiences and the available literature.

PLANNED APPENDICES (AT MINIMUM)

A. Final literature search strategies
B. Inclusion/Exclusion Criteria
C. Evidence report, including an evidence summary for each PICO question

AUTHORSHIP

Authorship of the guideline will include principal investigator Lisa R. Sammaritano, MD; literature review leader and GRADE expert Reem Mustafa, MD, PhD; content experts Anca Askanase, MD, MPH, Bonnie Bermas, MD, Maria Dall'Era, MD, Ali Duarte-García, MD, MSc, Linda Hiraki, MD, MSC, ScD, Brad Rovin, MD, Mary Beth Son, MD, and Victoria P. Werth, MD. Members of the voting panel and literature review team will also be authors. The PI will determine final authorship, dependent on the efforts made by individuals throughout the guideline development process, using international authorship standards as guidance.

DISCLOSURES/CONFLICTS OF INTEREST

The ACR's disclosure and COI policies for guideline development will be followed for this project. These can be found in the ACR Guideline Manual on this page of the ACR web site, under Policies & Procedures. *See Appendix D for participant disclosures.*

REFERENCES

1. EndNote [software]. https://endnote.com
2. DistillerSR. Ottawa, Canada: Evidence Partners; 2013. http://systematic-review.net/
3. Review Manager [software]. https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman
4. GRADEprofiler [software]. https://gradepro.org/

APPENDIX A – PICO QUESTIONS

Presented in two parts, Lupus Nephritis and SLE Treatment Guidelines, with outlines, PICOs (P1 – P65), good practice statements (GPS) and notes for relevant text discussion.

Lupus Nephritis Treatment Guideline: Outline and PICOs

Brief Outline:

- **A. Introduction to Lupus Nephritis (LN)**
- **B. Renal Biopsy**
- **C. Treatment of LN**
  - **Class II**
  - **Class III / IV (initial and subsequent therapy)**
  - **Class V (initial and subsequent therapy)**
- **D. Therapy for refractory LN**
- **E. Treatment of other lupus-related renal disease**
  - **Lupus podocytopathy**
  - **aPL (+) microangiopathic hemolytic anemia**
- **F. Adjunctive treatments / Considerations for LN patients**
  - **Diet, other medications, infection, vaccines, Mesna, leuprolide**
- **G. Monitoring**
- **H. Renal Replacement Therapy (Dialysis and Transplant)**
- **I. Reproductive Health concerns**
- **J. Pediatric concerns**

A. Introduction to Lupus Nephritis (LN)

Text discussion including definitions of LN, significance of activity and chronicity indices, and definitions of complete renal response (CRR), partial renal response (PRR) and non-response (refractory disease).

B. Renal biopsy:

Good practice statement (GPS): importance of early and ongoing collaboration with nephrology and early biopsy (acknowledging practical limitations)

Text discussion: interpretation of biopsy, importance of biopsy quality; importance of access to care.

Do all SLE patients suspected of having kidney involvement need a kidney biopsy?

P1. In SLE patients with unexplained proteinuria, hematuria, or impaired kidney function, is knowing the renal histology by biopsy associated with better outcomes than not knowing the renal histology?

Population: Patients with SLE with otherwise unexplained

- Proteinuria alone
- Glomerular hematuria with or without proteinuria with normal kidney function
- Impaired kidney function

Intervention: Percutaneous kidney biopsy

Comparator: No percutaneous kidney biopsy
Outcomes:

- Additional or different kidney diagnosis identified (e.g., thrombotic microangiopathic anemia (TMA), acute tubular necrosis (ATN), class change, diabetes mellitus (DM) or arteriosclerosis / arteriolosclerosis.) that impacts decision for and choice of therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Do SLE patients with LN who have achieved at least a partial renal response need a repeat kidney biopsy if a new renal flare is suspected?

P2. In SLE patients with LN who have achieved at least a partial renal response who develop recurrent /worsening proteinuria, hematuria, or impaired kidney function, is knowing the renal histology by biopsy associated with better outcomes than not knowing the renal histology?
Population: LN patients who flare after having achieved a complete or partial renal remission with

- Increased proteinuria alone
- Increased glomerular hematuria with or without proteinuria with stable kidney function
- Worsening kidney function

Intervention: Percutaneous kidney biopsy
Comparator: No percutaneous kidney biopsy
Outcomes:

- Additional or different diagnosis identified (e.g., TMA, ATN, class change, medication effect e.g., calcineurin inhibitor (CNI), DM, or arteriosclerosis / arteriolosclerosis), that impacts decision for and choice of therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Should proteinuria level define which patient with SLE has a kidney biopsy?

P3. In SLE patients with fixed (persistent) unexplained proteinuria with or without glomerular hematuria or impaired renal function, is performing a renal biopsy based on the level of proteinuria associated with better outcomes than not basing biopsy on level of proteinuria?
Population: Patients with SLE who have fixed or persistent proteinuria with or without impaired kidney function and with or without glomerular hematuria.

- 200 – 500 mg/day with or without impaired kidney function and with or without glomerular hematuria
- >500 mg/d with or without impaired kidney function and with or without glomerular hematuria

Intervention: Percutaneous kidney biopsy
Comparator: No percutaneous kidney biopsy
Outcomes:

- Kidney diagnosis identified (e.g., LN vs TMA, ATN, DM, arteriosclerosis / arteriolosclerosis) that impacts decision for and choice of therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Should an SLE patient with LN undergo a for-cause kidney biopsy during treatment if response is inadequate?

P4. In SLE patients with inadequate response to treatment at ≥ 6 months, is knowing the renal histology from a repeat (for-cause) renal biopsy associated with better outcomes than not knowing the renal histology?
Population: Patients with LN on biopsy being treated with appropriate immunosuppression (including changing / more aggressive therapy) in whom proteinuria does not improve or worsens, and/or kidney function does not improve or worsens and/or glomerular hematuria does not improve or worsens.
Intervention: Percutaneous kidney biopsy
Comparator: No percutaneous kidney biopsy
Outcomes:

- Additional or different kidney diagnosis identified on histopathology (e.g., TMA, ATN, class change, medication effect e.g., CNI, DM or arteriosclerosis / arteriolosclerosis) results in a change in therapy
- Reduction of proteinuria
- Preservation of kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy

Should an SLE patient with LN undergo a repeat ("protocol") kidney biopsy during subsequent (maintenance) therapy if they have achieved and maintained a complete or partial renal response?

P5. In SLE patients with LN and complete or partial renal response of at least one year on subsequent (maintenance) therapy (immunosuppressive medication with or without corticosteroids), is knowing the renal histology on a repeat "protocol" biopsy associated with better outcomes than not knowing the renal histology?
Population: Patients with LN diagnosed by a kidney biopsy who have been treated with immunosuppression subsequent (maintenance) therapy, and achieved/ maintained a complete or partial renal response for at least a year

- Complete renal response for at least one year
- Partial renal response for at least one year

Intervention: Percutaneous kidney biopsy
Comparator: No percutaneous kidney biopsy

Outcomes:

- Histopathology results in change and/or continuation of therapy
- Histopathology results in withdrawal of therapy (i.e., no activity seen on biopsy)
- Risk of LN flare
- ESKD
- Adverse effects of biopsy.

C. Treatment of Lupus Nephritis

GPS: institution of treatment as soon as possible; importance of comorbidities and extrarenal symptoms in decision making.

Text discussion: evolution of terminology: induction to initial therapy, maintenance to subsequent therapy; steroid monotherapy (including monthly pulse steroid) presented in historical perspective; emerging importance of genetic variants (including APOL-1 and others) and new biomarkers; dosing issues for pediatric patients.

C1. Class II Lupus Nephritis (in absence of lupus podocytopathy)

C2. Class III/IV Lupus Nephritis

C3. Class V Lupus Nephritis

CI. Class II Lupus Nephritis

Does class II LN without lupus podocytopathy require therapy?

P6. In SLE patients with class II LN without lupus podocytopathy on biopsy and without presence of extrarenal SLE activity requiring therapy, does treatment with renin-angiotensin-aldosterone system inhibitors (RAAS-I) and steroid with or without additional immunosuppressive therapy - versus RAAS-I therapy alone - lead to improved outcomes?

Population: SLE patients with class II LN without lupus podocytopathy on renal biopsy with proteinuria or decreased kidney function, without nonrenal SLE activity, and on treatment with RAAS-I with:

- Proteinuria > 0.5 gm
- Glomerular hematuria with proteinuria > 0.5 gm
- Decreased kidney function with proteinuria > 0.5 gm

Interventions:

- RAAS-I with:
  - Corticosteroid therapy only
  - Corticosteroid therapy plus immunosuppressive therapy
  - Corticosteroid therapy plus CNI therapy

Comparator: RAAS-I therapy only

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of flares
- Cumulative corticosteroid dose

- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

C2. Treatment of class III/ IV Lupus Nephritis

What are the most effective treatment regimens for initial treatment of SLE patients with Class III/IV LN?

P7. In SLE patients with active, newly diagnosed or flare of Class III/IV LN, is treatment with "X" compared to treatment with "Y" for initial therapy (detailed in table) associated with improved outcomes?

Populations:

- Active Class III/IV LN
- Active Class III/IV LN with:
  - Concomitant class V: mycophenolate mofetil/mycophenolic acid (MMF/MPA) vs cyclophosphamide (CYC)
  - Cellular crescents / fibrinoid necrosis (MMF/MPA vs CYC)
  - Decreased kidney function (MMF/MPA vs CYC)
  - In African Americans (MMF/MPA dose, CYC vs MMF/MPA, and monthly IV CYC vs Euro-lupus protocol)
  - In Hispanics (MMF/MPA dose and CYC vs MMF/MPA)
  - In Asians (MMF/MPA dose and CYC vs MMF/MPA)
  - Proteinuria < 0.5 gm/d (RAAS-I question only)
  - Proteinuria ≥ 3 gms/24 hours (MMF/MPA + belimumab vs MMF/MPA + voclosporin)

Not all comparisons will be relevant for all patient groups.

Intervention (X)	**Comparator (Y)**
Steroid regimen with other therapies:	
Pulse steroid / mod/high dose (0.5 -1 mg/kg)	Pulse steroid / low dose steroid (<0.5 mg/kg) Mod-high dose steroid (0.5 -1 mg/kg) only
Pulse steroid / low dose (<0.5 mg/kg)	Mod - high dose steroid (0.5 -1 mg/kg) only
RAAS-I (<0.5 gm protein pts only)	No RAAS-I (<0.5 gm protein pts only)
CYC:	

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IV monthly CYC (NIH protocol)	Eurolupus CYC Oral CYC
Any (IV) CYC	MMF/MPA (mycophenolic acid)
Any (IV) CYC	MMF/MPA + CNI
Any (IV) CYC	CNI alone
Any CYC plus belimumab	CYC alone
Any CYC plus anti-CD20 therapy	CYC alone
MMF/MPA (mycophenolic acid):	
2 gm/d MMF equivalent	3 gm/d MMF equivalent
MMF/MPA (any dose)	CNI alone
MMF/MPA plus belimumab	MMF/MPA alone (any dose)
MMF/MPA plus CNI*	MMF/MPA alone MMF/MPA plus belimumab CYC plus belimumab
MMF plus anti-CD20 therapy	MMF/MPA alone
Anti-CD 20 plus belimumab	Anti-CD 20 therapy alone

***Eliminated specific CNI names –** but will review literature for any differences among CNIs

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares

- Cumulative steroid dose
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

What are the most effective treatment regimens for subsequent treatment of SLE patients with Class III/IV LN?

P8. In SLE patients who have undergone initial therapy for active Class III/IV LN, is treatment with "X" compared to treatment with "Y" for subsequent therapy (detailed in table) associated with improved outcomes?

Populations:

- Class III/IV LN:
  - Complete response at 6-12 months
  - Partial response at 6-12 months
- Class III/IV LN + Class V (only MMF/MPA alone vs MMF/MPA + CNI after either CYC or MMF/MPA initial therapy)
  - Complete response at 6-12 months
  - Partial response at 6-12 months

Not all comparisons will be relevant for all patient groups.

Intervention (X)	**Comparator (Y)**
Steroid regimen with other therapies:	
Steroid tapered to ≤ 5 mg/d at ≤ 6 mo	Steroid tapered to ≤ 5 mg/d at > 6 mo
Steroid tapered to ≤ 10 mg/d at ≤ 6 mo	Steroid tapered to ≤ 10 mg/d at > 6 mo
Following initial therapy monthly IV CYC:	
Quarterly IV monthly CYC (NIH protocol) for two years	MMF/MPA Azathioprine (AZA)
MMF/MPA	AZA
MMF/MPA plus belimumab	MMF/MPA
MMF/MPA plus CNI	MMF/MPA

MMF/MPA plus anti-CD20 therapy (rituximab or obinutuzumab)	MMF/MPA
Following initial MMF/MPA therapy:	
MMF/MPA	AZA
MMF/MPA plus belimumab	MMF/MPA
MMF/MPA plus CNI*	MMF/MPA
MMF/MPA plus anti-CD20 therapy	MMF/MPA
*MMF, AZA or combination rx. 3-5 yrs.	*MMF, AZA or combination rx. <3 yrs.
*MMF, AZA or combination rx. >5 yrs.	*MMF, AZA or combination rx. 3-5yr

*Time here reflects total duration of LN therapy

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of LN flares
- Cumulative steroid dose
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

C3. Treatment of class V Lupus Nephritis

What are the most effective treatment regimens for initial treatment of SLE patients with Class V LN?

P9. In SLE patients with active, newly diagnosed or flare of Class V LN, is treatment with" X" compared to treatment with "Y" for initial therapy (detailed in table) associated with improved outcomes?

Populations:

- Active Class V LN with:
  - Proteinuria < 0.5 gm/d (RAAS-I question only)

- Proteinuria < 1 gm/d (steroid/immunosuppressive therapy vs no therapy only)
- Proteinuria ≥ 1 gm/d
- Proteinuria ≥ 3.5 gm

Intervention (X)	**Comparator (Y)**
Therapy for proteinuria < 0.5 gm/day	
RAAS-I	No RAAS-I
Therapy for proteinuria < 1 gm/day	
Any steroid and/or immunosuppressive therapy	No steroid and/or immunosuppressive therapy
Therapy for proteinuria ≥ 1 gm/day and for ≥ 3.5 gm/day:	
Corticosteroid monotherapy	
Pulse steroid / mod/high dose	No steroid/immunosuppressive therapy Pulse / low dose steroid (<0.5 mg/kg) Mod/high dose steroid (0.5 - 1 mg/kg)
Mod/high dose steroid (0.5 - 1 mg/kg)	No steroid/immunosuppressive therapy
Corticosteroid regimen with other therapies:	
Pulse steroid / mod/high dose (0.5 - 1 mg/kg)	Pulse steroid / low dose steroid (<0.5 mg/kg mg) Mod-high dose steroid (0.5 -1 mg/kg) only
Pulse steroid / low dose (≤25 mg)	Mod - high dose steroid (0.5 -1 mg/kg) only

CNI:	
CNI	No CNI
CYC:	
IV monthly CYC (NIH protocol)	Eurolupus CYC Oral CYC
Any (IV) CYC	MMF/MPA (mycophenolic acid)
Any CYC plus belimumab	CYC alone
Any CYC plus anti-CD20 therapy	CYC alone
MMF/MPA (mycophenolic acid):	
2 gm/d MMF equivalent	3 gm/d MMF equivalent
MMF/MPA plus belimumab	MMF/MPA alone (any dose)
MMF/MPA plus CNI*	MMF/MPA alone MMF/MPA plus belimumab CYC plus belimumab
MMF plus anti-CD20 therapy	MMF/MPA alone
MMF plus any CNI plus belimumab	MMF/MPA alone
Anti-CD 20 plus belimumab	Anti-CD 20 therapy alone

Any belimumab-containing regimen	MMF/MPA plus CNI
For proteinuria > 3.5 gm/d and/or albumin level of 2.0 g/dL: Anticoagulation	 No anticoagulation

***Eliminated specific CNI names –** but will review literature for any differences among CNIs

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of flares
- Cumulative steroid dose
- Treatment related adverse effects including infection
- Thromboembolic events (for anticoagulation intervention only)
- ESKD (dialysis or transplant)

What are the most effective treatment regimens for subsequent treatment of SLE patients with Class V LN?

P10. In SLE patients who have undergone initial therapy for active Class V LN, is treatment with X compared to treatment with Y for subsequent therapy (detailed in table) associated with improved outcomes?

Population:

- Patients with Class V LN and
  - Complete response at 6-12 months
  - Partial response at 6-12 months

Intervention (X)	**Comparator (Y)**
Corticosteroid regimen with other therapies:	
Steroid tapered to ≤ 5 mg/d at ≤ 6 mo	Steroid tapered to ≤ 5 mg/d at > 6 mo
Steroid tapered to ≤ 10 mg/d at ≤ 6 mo	Steroid tapered to ≤ 10 mg/d at > 6 mo

Following initial therapy monthly IV CYC:	
Quarterly IV monthly CYC (NIH protocol) for two years	MMF/MPA AZA
MMF/MPA	AZA
MMF/MPA plus belimumab	MMF/MPA
MMF/MPA plus CNI (any)	MMF/MPA
MMF/MPA plus anti-CD 20 therapy	MMF/MPA
Following initial MMF/MPA therapy:	
MMF/MPA	AZA
MMF/MPA plus belimumab	MMF/MPA
MMF/MPA plus CNI (any)	MMF/MPA
MMF/MPA plus anti-CD 20 therapy	MMF/MPA
*MMF, AZA or combination rx. 3- 5 yrs.	*MMF, AZA or combination rx. <3 yrs.
*MMF, AZA or combination rx. >5 yrs.	*MMF, AZA or combination rx. 3-5yr

***Time here reflects <u>total duration</u> of LN therapy**

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of flares
- Cumulative steroid dose
- Treatment related adverse effects including infection

- ESKD (dialysis or transplant)

D. Therapy for Refractory Lupus Nephritis

Text to define inadequate response / refractory disease and discuss emerging therapies for the future.

How should LN be treated if it has not responded to adequate initial therapy?

P11. If a LN patient has received adequate/appropriate standard treatment for active LN of any class and has not achieved at least a partial renal response (PRR) to that treatment by 6 months, is treatment with "X" compared to treatment with "Y" (detailed in table) associated with improved outcomes?

Population: LN patients being treated for active LN of any class who have been treated with adequate and appropriate standard therapy and who have been adherent to that therapy but have failed to achieve at least a partial renal response after 6 months of treatment.

Intervention (X)	**Comparator (Y)**
Corticosteroid therapy	
Pulse therapy	No pulse therapy
Increase to high dose oral GC therapy	No increase
Pulse steroid / low dose (<0.5 mg/kg)	Mod - high dose steroid (0.5 -1 mg/kg) only
CYC:	
Change to any (IV) CYC	Continue MMF/MPA
IV CYC plus belimumab	CYC alone
IV CYC plus anti-CD20 therapy	CYC alone
MMF/MPA:	
Increase to 3 gm/d MMF equivalent	Continue 2 gm/d MMF equivalent
MMF/MPA plus belimumab	MMF/MPA alone (any dose)

MMF/MPA plus CNI*	MMF/MPA alone
MMF plus anti-CD20 therapy	MMF/MPA alone
MMF plus any CNI plus belimumab	MMF/MPA alone MMF/MPA plus CNI MMF/MPA plus belimumab
Anti-CD 20 plus belimumab	Anti-CD 20 therapy alone
Any belimumab-containing regimen	MMF/MPA plus CNI
IVIG + any standard therapy	Any standard therapy without IVIG
Leflunomide + any standard therapy	Any standard therapy without leflunomide

***Eliminated specific CNI names –** but will review literature for any differences among CNIs

Outcomes:

- Reduction of proteinuria
- CRR
- PRR
- Preservation of kidney function
- LN Flare rate
- Cumulative steroid dose
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

P12. If a LN patient has received adequate/appropriate initial treatment for active LN of any class and did not achieve at least a partial renal response to that treatment after 6 months*, and then received an alternative standard treatment regimen and did not achieve at least a partial renal response after 6 months* (so now considered to have refractory LN), is treatment with "X" compared to treatment with "Y" (detailed in table) associated with improved outcomes?

***Unless progressive worsening (increased proteinuria or decreasing eGFR) over that 6-month period.**

Need to give enough time to see a response and at the same time be aware of letting time pass with a potentially ineffective treatment; will make very clear in the discussion that if patient is getting worse during those 6 months (increasing UPCR or decreasing eGFR), need to change therapy sooner and not wait the full 6 months.

Population: SLE patients being treated for active LN of any class who have been treated with at least 2 adequate and appropriate standard treatment regimens and who have been adherent to their therapies but have failed to achieve at least a partial renal response after at least 6 months of treatment, and are considered to have refractory LN.

Intervention (X)	**Comparator (Y)**
Pulse methylprednisolone	No pulse glucocorticoids given
Add anti-CD20 therapy	MMF/MPA alone
Add anti-CD20 therapy	CYC alone
Add CNI	MMF/MPA/CYC alone
Add belimumab	MMF/MPA/CYC alone
Add belimumab + CNI	MMF/MPA/CYC alone
Add leflunomide	MMF/MPA/CYC alone
Add IVIG	MMF/MPA/CYC alone
Refer for clinical trial for refractory LN	MMF/MPA/CYC alone

Outcomes:

- Reduction of proteinuria
- CRR
- PRR
- Preservation of kidney function
- LN Flare rate
- Cumulative steroid dose
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

E. Treatment of other lupus-related renal disease:

Text discussion: importance of other renal pathology seen in SLE including renovascular disease (arterial or venous), ATN, medication effects e.g., CNI, non-APL related TMA, DM and ASCVD. (Treatment recommendations for these are beyond our scope.)

E1. aPL-positive TMA
Focus on +aPL TMA here but recognize other causes (e.g., complement-mediated TMA, TTP, and others). GPS: suggest early involvement of hematology specialists and collaborative work-up/ therapy.
E2. Lupus podocytopathy (collapsing glomerulopathy)
Text to discuss that Podocytopathy excludes Class V. If no EM, cannot make a diagnosis of podocytopathy – may be a limitation. However, Class II plus significant proteinuria usually indicates podocytopathy (if EM unavailable).

E1. (+) aPL and thrombotic microangiopathy

In SLE patients with +aPL / APS and thrombotic microangiopathy on renal biopsy, does anticoagulation or aPL-directed immunosuppressive therapies improve outcomes compared to not using these therapies?

P13. In SLE patients with (+)aPL / APS and thrombotic microangiopathy on renal biopsy, do anticoagulation or immunosuppressive therapies compared to no additional medication improve clinical outcomes?

Populations:

- SLE patients with (+)aPL or APS and thrombotic microangiopathy on renal biopsy and concomitant lupus nephritis receiving standard immunosuppressive therapy
- SLE patients with (+)aPL or APS and thrombotic microangiopathy on renal biopsy, without concomitant lupus nephritis

Interventions:

- Anticoagulation
- Anticoagulation plus
    - Anti-CD20 therapy
    - Eculizumab / complement inhibition
    - mTOR inhibitor therapy
    - Plasmapheresis

Comparator:

- No aPL-directed therapy (for anticoagulation)
- Anticoagulation alone (for all others)

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Thromboembolism
- Treatment related adverse effects including infection
- Risk of ESKD

E2. Lupus podocytopathy (collapsing glomerulopathy)

In SLE patients with lupus podocytopathy on biopsy who are already on RAAS-I therapy, does adding corticosteroid with or without immunosuppressive therapy improve outcomes?

P14. In SLE patients with changes of lupus podocytopathy (diffuse epithelial cell foot process -podocyte- effacement) on renal biopsy who are on RAAS-I therapy, does steroid with or without immunosuppressive therapy versus RAAS-I alone improve clinical outcomes?

Population: SLE patients with proteinuria > 0.5 gm with or without decreased kidney function, and changes of lupus podocytopathy (diffuse epithelial cell foot process -podocyte- effacement) on renal biopsy

- Proteinuria > 0.5 gm
- Decreased kidney function with proteinuria > 0.5 gm

Interventions:

- RAAS-I with:
  - Steroid therapy (any dose)
  - Steroid therapy plus any immunosuppressive therapy (including MMF, AZA, CYC, CNI)

Comparator: RAAS-I alone

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function
- Risk of flares
- Treatment related adverse effects including infection
- ESKD (dialysis or transplant)

F. Adjunctive treatments /special considerations for LN patients

GPS/text discussion: Best practices surrounding LN therapy with referral to appropriate guidelines / resources. Including: infection screening and vaccinations; reproductive health issues; cardiovascular health; bone health; renal dosing for medications; pediatric concerns; treatment with RAAS-I and SGLT2-I (reference KDIGO guideline); use of Mesna with CYC (reference oncology guidelines).

F1. HCQ

Should SLE patients with LN be treated with hydroxychloroquine (HCQ) if not already taking this (and if they have no contraindications)?

P15. In SLE patients with presumed or biopsy-confirmed LN, does initiating HCQ (if not already taking and no contraindications) improve clinical outcomes compared to not taking HCQ?

Population: SLE patients with presumed or biopsy-proven LN who are not on HCQ (and have no contraindication to taking)

Intervention: HCQ

Comparator: No HCQ

Outcomes:

- Reduction of proteinuria
- Preservation of kidney function

- Cumulative steroid dose
- Risk of flare
- Treatment related adverse effects (retinal and cardiac toxicity)
- ESKD (dialysis or transplant)

G. Monitoring LN activity

Text: discussion of alternative measures including Cystatin C and others.

Review use of more convenient or alternative urine protein tests compared to using a standard 24-hour urine protein collection: reference renal literature / systematic review /guidelines and include limitations of protein-creatinine ratio versus 24 hour collection. (Ex: Kamińska J, et al. Diagnostic utility of protein to creatinine ratio (P/C ratio) in spot urine sample within routine clinical practice. Critical reviews in clinical laboratory sciences. 2020 Jul 3;57(5):345-64.)

How frequently should urine protein be checked in SLE patients, including those with and without LN?

P16. In SLE patients -with or without presumed or biopsy proven LN – does regularly monitoring urine protein at certain intervals lead to better outcomes than not checking this regularly?

Population: SLE patients

- Without known or suspected nephritis.
- On initial LN therapy
- On subsequent LN therapy
- Who have completed and stopped LN therapy

Intervention: Urine protein testing (any method other than dipstick)

- Every 1 month
- Every 2 months
- Every 3 months
- Every 6 months
- Yearly

Comparator: No regular schedule for urine protein testing

Outcomes:

- Reduction of proteinuria (N/A for no LN hx or those who have had resolution of proteinuria)
- Preservation of kidney function
- LN flare
- Cumulative corticosteroid dose
- ESKD (dialysis or transplant)

How frequently should anti-dsDNA antibody and complement levels be checked in SLE patients with LN?

P17. In SLE patients with presumed or biopsy proven LN does regularly monitoring anti-dsDNA antibody andC3C4 at certain intervals lead to better outcomes than not checking these regularly?

Population: SLE patients
- On initial LN therapy
- On subsequent LN therapy
- Who have completed and stopped LN therapy

Intervention: Anti-ds DNA antibody and complement C3 and C4
- Every 1 month
- Every 2 months
- Every 3 months
- Every 6 months
- Yearly

Comparator: No regular schedule for testing

Outcomes:
- Reduction of proteinuria (if applicable)
- Preservation of kidney function
- LN flare
- Cumulative corticosteroid dose
- ESKD (dialysis or transplant)

H. Renal replacement therapy: Dialysis and transplant

What is the impact of renal transplant on patients with LN and ESKD, compared to dialysis?

P.18 In SLE patients with LN with ESKD, does renal transplantation improve clinical outcomes compared to dialysis?

Population: Patients with LN and ESKD

Intervention: Renal transplantation

Comparison: Hemodialysis or peritoneal dialysis

Outcomes:
- Patient survival
- Incidence of infection
- Incidence of CVD
- Quality of life
- Risk of SLE flare
- Disease damage

Is there a difference in clinical outcomes between SLE patients with ESKD using hemodialysis versus peritoneal dialysis?

P19. In SLE patients with LN and ESKD, does use of hemodialysis impact clinical outcomes compared to peritoneal dialysis?

Population: Patients with LN and ESKD

Intervention: Hemodialysis

Comparator: Peritoneal dialysis
Outcomes:

- Patient survival
- Incidence of infection
- Quality of life
- Risk of SLE flare
- Disease damage

Are outcomes improved for SLE patients on renal replacement therapy if they follow regularly with rheumatology in addition to nephrology?

P20. In SLE patients with LN who require renal replacement therapy (RRT), does regular follow up with rheumatology (in addition to nephrology) impact clinical outcomes compared to not following regularly with rheumatology?

Population: Patients with LN on RRT

- On dialysis
- S/p renal transplantation

Intervention: Regular rheumatology follow up
Comparator: No regular rheumatology follow up
Outcomes:

- Patient survival
- Quality of life
- SLE flare
- Hospitalization
- Disease damage

In SLE patients who have undergone renal transplantation does taking/ continuing HCQ following transplantation improve clinical outcomes?

P21. In SLE patients with LN status who are status post renal transplantation, does taking HCQ post-transplant improve clinical outcomes compared to not taking it?

Population: SLE patients with LN s/p renal transplantation
Intervention: HCQ
Comparator: No HCQ
Outcomes:

- Patient survival
- Quality of life
- SLE flare
- Hospitalization

- Disease damage

In SLE patients approaching ESKD, does preemptive renal transplant improve clinical outcomes?

P22. In SLE patients with LN at risk of developing ESKD, does preemptive renal transplant improve clinical outcomes compared to initiating dialysis and no preemptive transplant?

Population: SLE patients with lupus nephritis (LN) at risk of developing ESKD
Intervention: Preemptive renal transplant
Comparator: No preemptive transplant and dialysis
Outcomes:

- Graft survival
- Mortality
- Quality of life
- SLE flare
- Hospitalization

Does high lupus disease activity at the time of renal transplant impact clinical outcomes?

P23. In SLE patients with LN and ESKD, does delaying transplant until clinical or serologic remission, compared to not delaying transplant, impact outcomes?

Population: SLE patients with lupus nephritis (LN) and ESKD
Intervention:

- Transplant with clinical disease activity
- Transplant with serologic activity only

Comparator:

- Transplant with SLE in clinical and serologic remission

Outcomes:

- Graft survival
- Mortality
- Recurrent SLE nephritis in graft

Does addition of anticoagulation improve outcomes in SLE patients with +aPL or APS who are undergoing renal transplant?

P24. In SLE patients s/p renal transplant due to LN and who have +aPL or APS, does anticoagulation with warfarin, compared to no anticoagulation, result in improved outcomes?

Population: Patients who had a renal transplant due to LN with aPL or APS

Intervention: anticoagulation with warfarin
Comparator: no anticoagulation
Outcomes:

- Graft survival
- Mortality
- Vascular (thromboembolic) events
- Bleeding

Does addition of aPL-directed immunosuppressive therapy improve outcomes in SLE patients with +aPL or APS who are undergoing renal transplant?

P25. In patients who had a renal transplant due to LN and who have +aPL or APS, does aPL-directed immunosuppression result in improved outcomes compared to standard of care?
Population: Patients who had a renal transplant due to LN with +aPL or APS
Intervention: immunosuppression (pre and/or post)

- Sirolimus
- Eculizumab
- Anti-CD20 therapy
- Belatacept
- IVIG

Comparison: standard of care
Outcomes:

- Graft survival
- Mortality
- Vascular (thromboembolic) events
- Adverse effects of treatment (bleeding or infection)

SLE Treatment Guideline Outline and PICOs:

A. Diagnosis and Monitoring
B. Comorbidities and risk management (discussion/referral to guidelines/references)

- **Bone health (osteoporosis and avascular necrosis)**
- **CVD risk**
- **Lifestyle (smoking / vaping, diet)**
- **Psychiatric issues**
- **Cancer screening (cervical cancer screening)**
- **Infection risk (vaccines, screening for latent infection e.g., hepatitis B, C and TB, PJP prophylaxis)**
- **Fibromyalgia / central pain syndrome / type 2 SLE (text discussion – beyond scope of this GL)**

C. Medications: risks / special considerations
D. Treatment: guiding principles

- **Goals**
- **Remission/ LDA**

E. Medical management by organ system

- **Constitutional**
- **Hematologic**
- **Neuropsychiatric**
- **Cutaneous/ mucocutaneous**
- **Serositis**
- **Musculoskeletal**
- **Vasculitis**
- **Cardiopulmonary**
- **Renal – Lupus Nephritis GL**
- **Reproductive health**
- **APS: important component of SLE manifestations, beyond the scope of this GL**

F. Non-pharmacologic treatments

A. Diagnosis and Monitoring

GPS: clinical and serologic testing for diagnosis and monitoring of SLE, importance of early diagnosis.
Text discussion addressing issues of access to care, healthcare disparities, utility of classification criteria in clinical care.
Refer to ACR's Quality Measures for SLE:
(https://acrjournals.onlinelibrary.wiley.com/doi/epdf/10.1002/acr.25143)

Does regular use of activity and damage measures improve clinical outcomes for patients with SLE?

P26. In patients with SLE, does use of regular assessment instruments versus not using these instruments impact clinical outcomes?

Population: Patients with SLE
Intervention:

- Disease activity measure at each visit
- Disease damage measure yearly

Comparator: No measures at visits
Outcomes:

- Flare rate
- Disease damage
- Mortality
- Comorbidities
- Quality of life

B. Comorbidities and risk management: GPS and text discussion for most topics here.

B1. Bone health:
Glucocorticoid induced osteoporosis: refer to ACR glucocorticoid-induced osteoporosis guideline (GIOP GL); refer to standard GL for other patients.
Avascular necrosis: Text discussion: importance of risk reduction, screening and referral to/ collaboration with orthopedics and metabolic bone specialists.

B2. Cardiovascular / Metabolic: screening and therapy
GPS regarding increased risk of CVD and necessity of appropriate screening and referral for therapy. Risk factor assessment and modification as responsibilities of the patient's care team, including the primary care physician and/or a preventive cardiologist. Consistent with the 2019 ACC/AHA primary prevention guidelines for the general population, all individuals with SLE between 20-75 years of age should be assessed for traditional risk factors for atherosclerotic cardiovascular disease including hypertension, cigarette smoking, diabetes mellitus, dyslipidemia, and obesity. In addition, all patients should be assessed for "risk-enhancing factors" as defined by the 2018 AHA/ACC guideline on the management of blood cholesterol. Patients should then undergo risk assessment for ASCVD using a risk calculator.

B3. Lifestyle factors
Photoprotection, cessation of smoking and/or vaping, dietary modifications: GPS/Text discussion**B4. Psychiatric comorbidity:**
GPS/ text discussion regarding importance of regular assessment and appropriate referral.

B5. Routine cancer screening
GPS regarding general cancer screening as per general population with exception of cervical cancer screening (text discussion). Systematic reviews on cancer screening specifically for patients with SLE: studies concur that general population screening measures, especially for cervical cancer, are necessary in SLE patients.
Cervical cancer screening: Refer to consensus statement in Guidelines for Cervical Cancer Screening in Immunosuppressed Women Without HIV Infection. Moscicki AB, et al. J Low Genit Tract Dis. 2019;23(2):87.

B6. Infection risk:
Vaccines:
Refer to ACR Vaccine GL, add in comments regarding ACR guidance on Covid vaccines, mention RSV as new option. Pediatric concerns to be included.

Screening for latent infection:
Hepatitis B and Hepatitis C: Follow CDC recommendations**.**
Screening for latent TB: GPS / text discusion, refer to available guidelines
PJP prophylaxis:
When is PJP prophylaxis indicated for patients with SLE on steroid or immunosuppressive therapy?

P27. In patients with SLE for whom immunosuppressive therapy is planned, does prophylactic treatment for PJP reduce risk of infection compared to no prophylactic treatment?

Population: SLE patients for whom immunosuppressive therapy is planned

- With underlying lung disease
- Without underlying lung disease

- Immunosuppressive therapies:
  - Corticosteroid (prednisone ≥ 20 mg/day for ≥ 4 weeks)
  - Methotrexate
  - Azathioprine
  - MMF/MPA
  - CNIs
  - CYC
  - Anti-CD20 inhibitors
  - Belimumab
  - Anifrolumab

Intervention:

- Prophylaxis for PJP
  - Bactrim
  - Atovoquone

Comparator:

- No PJP prophylaxis

Outcomes:

- PJP infection
- Adverse effects of PJP prophylaxis therapy: for Bactrim, rash and allergy; for atovoquone, GI effects and headache.

B7. Non-inflammatory manifestations:

GPS / text discussion: Central sensitization syndromes / fibromyalgia / Type 2 SLE are important determinants of quality of life for SLE patients, but treatment recommendations are beyond our scope.

B8. Pediatric considerations (text discussion as appropriate)

C. Medications: Overview and special considerations

Text discussion and table with relevant dosing concerns / special considerations/ corticosteroid tapering, and pediatric dosing. Lupus-related notes on safe use, adverse effects, specifics for screening /monitoring. Include NSAIDs, corticosteroids, antimalarials, Immunosuppressants, biologics.

Glucocorticoid GPS: The damage from steroids is well documented, emphasize least dose for shortest time as a rule.

In stable SLE patients, does lowering baseline prednisone dose improve clinical outcomes and reduce adverse medication effects compared to maintaining a dose of 10 mg daily?

P28. In patients with stable SLE, what is the impact of lowering prednisone to 2.5, 5 or 7.5 mg daily on clinical outcomes and adverse effects compared to maintaining prednisone 10 mg daily?

Population: Patients with stable SLE on daily prednisone

Intervention: Prednisone daily dose (or equivalent), maintenance (> 6 months)

- 2.5 mg/d
- 5 mg/d
- 7.5 mg/d

Comparator: Prednisone 10 mg/day > 6 months

Outcomes:

- Osteoporosis
- Hypertension
- Fractures
- Cataracts
- T2DM
- Infections
- SDI (disease damage)
- Quality of Life

Does treating SLE patients with an organ-threatening disease flare with pulse steroid followed by oral prednisone taper improve clinical outcomes and reduce adverse medication effects compared to treating with an oral prednisone taper alone?

P29. In patients with organ- threatening SLE, what is the impact of pulse methylprednisolone (250-1000 mg) followed by prednisone taper compared to prednisone taper only on clinical outcomes and adverse medication effects?

Population: Patients with organ threatening SLE flare

Intervention: Pulse therapy (250-1000 mg IV for 1-3 days) followed by prednisone taper

Comparator: Oral prednisone taper only

Outcomes:

- Flare

- Osteoporosis
- Hypertension
- Fractures
- Cataracts
- T2DM
- Infections
- SDI (disease damage)
- Quality of Life

In SLE patients with active SLE (newly diagnosed or flare) being treated with HCQ and prednisone ≥ 20 mg daily for > 4 weeks, does initiating immunosuppressive therapy with a steroid taper result in better clinical outcomes and fewer adverse medication effects?

P30. In patients with active SLE (newly diagnosed or flare) on treatment with HCQ and prednisone ≥ 20 mg daily for > 4 weeks, does initiating immunosuppressive therapy result in better clinical outcomes and fewer adverse medication effects compared to continuing HCQ and prednisone alone at 6 months – 12 months?

Population: Patients with active SLE, newly diagnosed or flare, on HCQ and prednisone ≥ 20 mg for > 4 weeks
Intervention: Initiation of immunosuppression and corticosteroid taper
Comparator: continuing HCQ and prednisone
Outcomes (at 6-12 months):

- Reaching prednisone ≤ 5mg/day
- Stopping GC
- SLE disease activity
- SDI (disease damage)
- Adverse medication effects (infection, cytopenias, diabetes)
- Quality of Life

In SLE patients being treated with HCQ and ≥ 6 months prednisone (> 7.5 mg daily), does initiating immunosuppressive therapy with a steroid taper result in better clinical outcomes and fewer adverse medication effects?

P31. In patients with SLE treated with HCQ and persistent (≥ six months) use of prednisone >7.5 mg daily, does initiation of immunosuppressive therapy with a steroid taper result in better clinical outcomes and fewer adverse medication effects compared to continuing with HCQ and daily prednisone?

Population: Patients with SLE treated with HCQ and persistent (≥six months) prednisone >7.5 mg daily
Intervention: Initiation of immunosuppressive therapy
Comparator: Continuation of current therapy (HCQ and prednisone > 7.5 mg daily)
Outcomes (6-12 months):

- SLE flare

- Osteoporosis
- Hypertension
- Fractures
- Cataracts
- T2DM
- Infections
- SDI (disease damage)
- Quality of Life

In SLE patients in remission on HCQ and prednisone 5 mg daily, does tapering off prednisone result in better clinical outcomes and fewer adverse medication effects?

P32. In SLE patients in remission on HCQ and prednisone 5 mg daily, does tapering off prednisone result in better clinical outcomes and fewer adverse medication effects than continuing the prednisone 5 mg?

Population: Patients with SLE in remission and on HCQ and prednisone 5 mg/d maintenance
Intervention: Full taper to off
Comparator: Continuing 5 mg/d
Outcomes (6-12 months):

- SLE flare
- Osteoporosis
- Hypertension
- Fractures
- Cataracts
- T2DM
- Infections
- SDI (disease damage)
- Quality of Life
- Adrenal insufficiency

Antimalarials:

Text discussion regarding retinal toxicity: Cite ACR/AAO guidance (Rosenbaum, J; PMIDS:33559327) and cardiac toxicity (QTc prolongation and cardiomyopathy): Cite ACR guidance (Desrnairais J;PMID:34697918)

In patients with SLE, does limiting the dose of HCQ to ≤ 5 mg/kg impact clinical effectiveness?

P33. Does HCQ dose of > 5 mg/kg result in better clinical outcomes and control of flares in patients with SLE compared to a dose of ≤ 5 mg/kg?

Population: Patients with SLE taking HCQ

Intervention: HCQ dose of >5 mg/kg
Comparator: HCQ ≤ 5 mg/kg
Outcomes:

- Disease activity
- Flares
- SDI (damage)
- Retinal toxicity
- Cardiac toxicity (Prolonged QTc and/or myopathy)

In patients with SLE on HCQ, does measurement of blood HCQ levels lead to improved clinical outcomes?

P34. In patients with SLE on HCQ, does measuring HCQ blood levels lead to improved clinical outcomes or fewer adverse medication effects than not measuring levels?
Population: Patients with SLE taking HCQ
Intervention: Checking HCQ (whole blood/serum) levels
Comparator: Not checking levels
Outcomes:

- Adherence
- SLE disease activity
- Flares
- Thrombosis,
- Retinal toxicity
- Cardiac toxicity (Prolonged QTc and/or myopathy)

Dermatologic therapies
Discussion in text, Plan table with important topical medications / steroid classes.
Include pregnancy screening for thalidomide, retinoids.

Immunosuppressive and Biologic therapies
Discussion in text, Table with medications.
Include CYC fertility issues (RHGL), contraception for MMF/MPA, TPMT/ NUDT15 for AZA.

D. Guiding therapy principles
GPS: Aim for remission / low disease activity state to improve clinical outcomes.
Being in remission or LDA (regardless of the definition) is associated with improved outcomes in patients with SLE (Ugarte-Gil MF, et al. Lupus Science & Medicine. 2021 Sep 1;8(1):e000542.)
Text discussion regarding goals of therapy: control disease activity, prevent organ damage, improve long term survival, improve QoL, minimize comorbidities, minimize corticosteroid use, minimize medication toxicity

Importance of adherence issues; guiding principles for pediatrics: Minimize steroid exposure (improve bone health, growth and development, and psychosocial outcomes).

Should HCQ be recommended for every patient with SLE unless a contraindication is present?

P35. In patients with SLE, does routine treatment with HCQ (regardless of other therapies), improve clinical outcomes compared to not treating with HCQ?

Population:

- Patients with SLE

Intervention:

- Treating with HCQ (unless a contraindication)

Comparator: Not treating with HCQ

Outcomes:

- Flare risk
- Disease accrual
- Mortality
- Corticosteroid related adverse effects (osteoporosis, infection, diabetes)
- Retinal toxicity
- Cardiac toxicity (Prolonged QTc and/or myopathy)
- Thrombosis
- Quality of life

Can therapy for SLE be tapered off in patients who have achieved clinical remission or a low disease activity state?

P36. In patients with SLE who have achieved remission or low disease activity, does discontinuation of therapy at a particular time point affect clinical outcomes when compared to continuing therapy?

Population:

- Patients with SLE who have achieved remission
- Patient with SLE who have achieved low disease activity

Intervention:

- Discontinuation of immunosuppressive therapy at (from time of complete remission or low disease activity)
  - One year
  - > One year but ≤ 3 years
  - > 3 years
- Discontinuation of HCQ at (from time of complete remission or low disease activity)
  - ≤ 5 years
  - 5-10 years
  - > 10 years

Comparator: Not discontinuing therapy

Outcomes:

- Flare risk
- Disease accrual
- Mortality
- Corticosteroid related adverse effects of osteoporosis and diabetes
- Immunosuppressive therapy related adverse effects of infection and cytopenias for immunosuppressive therapy
- HCQ related adverse effects of retinal toxicity and cardiac toxicity (prolonged QTc and myopathy) for HCQ therapy
- Quality of life

E. Treatment by organ system / medical management

E1. Constitutional symptoms

GPS / text discussion regarding importance of ruling out endocrine, infectious, oncologic, and psychological causes which would demand alternative therapies.

Stress importance of multifactorial etiology (e.g. Arnaud L, et al. Predictors of fatigue and severe fatigue in a large international cohort of patients with systemic lupus erythematosus and a systematic review of the literature. Rheumatology. 2019 Jun 1;58(6):987-96; del Pino-Sedeño T, et al. Effectiveness of nonpharmacologic interventions for decreasing fatigue in adults with systemic lupus erythematosus: a systematic review. Arthritis Care & Research. 2016 Jan;68(1):141-8.

E2. Hematologic manifestations

Text discussion of life-threatening heme diagnoses such as MAS.

In SLE patients with leukopenia, does treatment with immunosuppressive therapy improve or worsen clinical outcomes compared to no immunosuppressive therapy?

P37. In SLE patients with leukopenia, does adding, changing, or discontinuing immunosuppressive therapy improve clinical outcomes?

Population: SLE patients (may be on HCQ)

- Leukopenia not on immunosuppressive medication.
- Leukopenia on immunosuppressive medication (AZA, MMF/MPA, MTX or biologic therapy)

Intervention:

- For non-immunosuppressed patients: addition of
  - Azathioprine
  - MMF/MPA
  - Glucocorticoid
- For patients on immunosuppressants:
  - Stopping or lowering immunosuppressive therapy

Comparator:

- No treatment (or HCQ alone) (for patients not on immunosuppressive medications)
- Continuing therapy at same dose (for patients on immunosuppressive medications)

Outcomes:

- WBC count (increase, decrease or no change)
- Infection
- Mortality
- Disease damage
- Disease flare

Does chronic asymptomatic thrombocytopenia in patients with SLE require medical therapy?

P38. In SLE patients with thrombocytopenia that is chronic and asymptomatic, does addition of immunosuppressive medication impact clinical outcomes compared to not adding medication?

Population: SLE patients with thrombocytopenia (on HCQ or no therapy) that is chronic and asymptomatic:

- >50,000
- 10,000-50,000
- <10,000

Intervention:

- Glucocorticoid therapy
- Immunosuppressive therapy
- Biologic therapy

Comparator:

- No therapy or HCQ alone

Outcomes:

- Life-threatening bleeds
- Mortality
- Treatment related adverse effects of infection
- Disease damage
- Disease flare

In patients with SLE and acute progressive thrombocytopenia, does treatment with glucocorticoid and immunosuppressive therapy (or surgery) lead to improved clinical outcomes compared to glucocorticoid alone?

P39. In SLE patients with acute and progressive thrombocytopenia on HCQ or no therapy, does addition of immunosuppressive therapy (or surgery) to glucocorticoid therapy lead to improved clinical outcomes compared to glucocorticoid therapy alone?

Populations: SLE patients with thrombocytopenia (on HCQ or no therapy), that is acute, progressive and symptomatic:

- >50,000
- 10,000 – 50,000

- <10,000

Intervention:

- Glucocorticoid therapy (high dose) plus
  - Immunosuppressive therapy
    - AZA
    - MMF/MPA
    - Cyclosporine
  - Anti-CD20 therapy
  - Splenectomy
  - IVIG

Comparator:

- Glucocorticoid therapy

Outcomes:

- Life-threatening bleed
- Mortality
- Treatment related adverse effect of infection
- Disease damage
- Disease flare

In SLE patients with autoimmune hemolytic anemia, does addition of immunosuppressive therapy (or surgery) to glucocorticoid therapy lead to improved clinical outcomes?

P40. In SLE patients with autoimmune hemolytic anemia on HCQ or no therapy, does the addition of immunosuppressive therapy or surgery to glucocorticoid therapy improve clinical outcomes compared to glucocorticoid therapy alone?

Populations: SLE patients with autoimmune hemolytic anemia on HCQ or no therapy

Intervention:

- Glucocorticoid therapy (high dose) plus
  - Immunosuppressive therapy
    - AZA
    - MMF/MPA
    - Cyclosporine
  - Anti-CD 20 therapy
  - Splenectomy
  - IVIG

Comparator: Glucocorticoid therapy alone

Outcomes:

- Mortality
- Disease damage
- Treatment related adverse effect of infection

- Disease flare

E3. Neuropsychiatric manifestations

GPS: Endorse multi-disciplinary approach including co-management with neurology and/or psychiatry for evaluation/ treatment with consideration of the use of non-SLE therapies that are directed toward the specific manifestation (e.g. anti-seizure therapy, anti-psychotic therapy, therapy for movement disorders, PT/OT, etc.)

Perform thorough evaluation for alternative etiologies of neuropsychiatric symptoms/ signs; Rule out metabolic abnormalities, infection, hypertension, PRES, mimicking immune-mediated diseases such as MS, NMOSD, MOGAD.

What is the most effective therapy for lupus myelitis?

P41. In patients with active, newly diagnosed or flare of lupus myelitis*, what is the impact of the listed medical therapies on clinical outcomes compared to standard therapy of pulse steroid with or without CYC?

*Text to include rational for using this term - we are treating inflammatory (and not purely ischemic) lesions.

Population: SLE patients with active, newly diagnosed or flare of lupus myelitis

Interventions: Pulse IV glucocorticoid followed by high dose glucocorticoid and:

- MMF/MPA
- Anti-CD20 therapy
- Anifrolumab
- CYC + anti-CD20 therapy
- CYC + PLEX (plasmapheresis)
- CYC + IVIG
- CYC + PLEX + IVIG
- CYC + anti-CD20 therapy + PLEX + IVIG
- Antithrombotic regime + immunosuppressive regimen

Comparators:

- Pulse IV glucocorticoid followed by high dose glucocorticoid (no additional immunosuppressive)
- Pulse IV glucocorticoid followed by high dose glucocorticoid and IV CYC.

Outcomes:

- Disease activity
- Disease flares
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for lupus-related optic neuritis?

P42. In patients with active, newly diagnosed or flare of optic neuritis secondary to SLE (not NMO)*, does the addition of immunosuppressive therapy to glucocorticoid lead to improved clinical outcomes compared to glucocorticoid with or without CYC?

*Optic neuritis: 1999 ACR nomenclature refers to this entity as "neuropathy, cranial." For the purposes of our recommendations, we are referring to optic neuritis of inflammatory etiology and NOT optic neuropathy of ischemic etiology.

Population: SLE patients with active, newly diagnosed or flare of optic neuritis
Interventions: Pulse IV corticosteroid followed by high dose corticosteroid and:

- MMF
- Anti-CD20 therapy
- Anifrolumab
- CYC + anti-CD20 therapy
- CYC + PLEX
- CYC + IVIG
- CYC + PLEX + IVIG
- CYC + anti-CD20 therapy + PLEX + IVIG
- Antithrombotic regimen + immunosuppressive regimen

Comparators:

- Pulse IV glucocorticoid followed by high dose glucocorticoid (no additional immunosuppressive)
- Pulse IV glucocorticoid followed by high dose corticosteroid +3IV CYC

Outcomes:

- Disease activity
- Disease flares
- Optic nerve damage
- Vision
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias

What is the most effective therapy for lupus-related seizures (occurring in the absence of stroke) in addition to standard antiseizure therapy?

P43. In patients with active, newly diagnosed or flare of lupus seizure in the absence of stroke, does glucocorticoid therapy with or without immunosuppressive or antithrombotic therapy improve clinical outcomes compared to anti-seizure therapy alone?

Population: SLE patients with active, newly diagnosed or flare of lupus seizure in the absence of stroke

Interventions: Anti-seizure medication and addition of:

- Glucocorticoid therapy
- Glucocorticoid therapy +
  - IV CYC
  - MMF/MPA
  - AZA
  - Anti-CD20 therapy
  - Anifrolumab
  - Belimumab
  - Antithrombotic regimen + immunosuppressive regimen

Comparator:

- Appropriate anti-seizure therapy alone.

Outcomes:

- Seizure activity
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective medical therapy for acute confusional state due to SLE?

P44. In patients with acute confusional state secondary to active SLE, does glucocorticoid with additional (listed) therapies improve clinical outcomes compared to glucocorticoid with or without CYC?

*Note of clarification: per the 1999 ACR nomenclature and case definitions for neuropsychiatric lupus, “acute confusional state” is equivalent to “delirium.” Neurologists often use the term “encephalopathy” to describe the same clinical state. No treatment option of anti-thrombotics in acute confusional state because the mechanism of acute confessional state is inflammatory and the issue of anti-thrombotics is usually not relevant. These questions pertain to acute confusional state in the absence of stroke**.**

Population: SLE patients with acute confusional state secondary to active SLE

Interventions: Pulse IV glucocorticoid followed by high dose glucocorticoid and:

- MMF
- Anti-CD20 therapy
- Anti-CD20 therapy + PLEX

- Anifrolumab
- Belimumab
- CYC + anti-CD20 therapy
- CYC + PLEX
- CYC + IVIG
- CYC + PLE + IVIG
- CYC + anti-CD20 therapy + PLEX + IVIG

Comparators:

- Pulse IV glucocorticoid followed by high dose glucocorticoid (no additional immunosuppressive)
- Pulse IV glucocorticoid followed by high dose glucocorticoid + IV CYC

Outcomes:

- Disease activity
- Resolution of acute confusional state
- Neurologic damage
- Mortality
- Improvement in quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for lupus-related psychosis in addition to standard antipsychotic therapy?

P45. In patients with active, newly diagnosed or flare of lupus psychosis in the absence of stroke, does glucocorticoid with or without additional (listed) therapies improve clinical outcomes compared to antipsychotic therapy alone?

Population: SLE patients with active, newly diagnosed or flare of lupus psychosis

Interventions: Antipsychotic therapy and addition of:

- Glucocorticoid therapy alone
- Glucocorticoids plus:
  - IV CYC
  - MMF/MPA
  - AZA
  - Anti-CD20 therapy
  - Anifrolumab
  - Belimumab
  - IVIG

Comparators: Antipsychotic therapy alone

Outcomes:

- Resolution of psychosis
- Prevention of recurrent psychosis

- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for active mononeuritis multiplex in patients with SLE?

P46. In patients with active, newly diagnosed or flare of mononeuritis multiplex secondary to active SLE, does glucocorticoid with additional (listed) therapies improve clinical outcomes compared to glucocorticoid with or without CYC?

Population: SLE patients with active, newly diagnosed or flare of mononeuritis multiplex

Interventions: Pulse IV glucocorticoids followed by high dose glucocorticoid and:

- MMF/MPA
- Anti-CD20 therapy
- Anifrolumab
- Belimumab
- CYC + anti-CD20 therapy
- CYC + PLEX
- CYC + IVIG
- CYC + PLE + IVIG
- CYC + anti-CD20 therapy + PLEX + IVIG
- Antithrombotic regimen + immunosuppressive regimen

Comparator:

- Pulse IV glucocorticoid followed by high dose glucocorticoid (no additional immunosuppressive)
- Pulse IV glucocorticoid followed by high dose glucocorticoid + IV CYC

Outcomes:

- Resolution of mononeuritis multiplex
- Prevention of recurrent mononeuritis multiplex
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for polyneuropathy secondary to active SLE? **– eliminate since most severe (mononeuritis) and most common (small fiber) are addressed.**

What is the most effective therapy for small-fiber neuropathy secondary to SLE?

P47. In patients with small-fiber neuropathy secondary to active SLE, does addition of glucocorticoid or immunosuppressive therapy to symptomatic (non-immunosuppressive nerve-directed) therapy improve clinical outcomes compared to symptomatic therapy only?

*Note of clarification: small-fiber neuropathy refers to damage to the small diameter somatic and autonomic unmyelinated C-fibers and/or thinly myelinated A-delta fibers. In conjunction with a neurologist, confirmation of the diagnosis via skin biopsy demonstrating decreased intra-epidermal nerve fiber density is strongly recommended. However, it is important to note that skin biopsies have imperfect sensitivity for the diagnosis. Other diagnostic tests such as QSART testing may also be considered.

Population: Patients with small-fiber neuropathy secondary to active SLE
Interventions:

- Glucocorticoid therapy
- MMF/MPA
- AZA
- Anifrolumab
- IVIG
- Belimumab

Comparator: Non-immunosuppressive, symptomatic, nerve-directed therapy alone
Outcomes:

- Improvement of small-fiber neuropathy
- Prevention of recurrent small-fiber neuropathy
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g. Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for cognitive dysfunction or decline secondary to SLE?

P48. In patients with cognitive dysfunction or decline secondary to active SLE in the absence of stroke, does addition of glucocorticoid or immunosuppressive therapy to cognitive rehabilitation therapy improve clinical outcomes compared to cognitive rehabilitation therapy only?

*Note of clarification: per the 1999 ACR nomenclature and case definitions for neuropsychiatric lupus, cognitive dysfunction is defined as significant deficits in any or all of the following cognitive functions: simple of complex attention, reasoning, executive skills, memory, visual-spatial processing, language, and psychomotor speed. Neuropsychological testing should be performed for documentation of cognitive deficits. Decreased academic performance/school function can be an informative sign in childhood/adolescence.

Population: Patients with cognitive dysfunction or significant cognitive decline secondary to active SLE.
Interventions: Cognitive therapy and addition of:

- Corticosteroid therapy
- MMF/MPA
- AZA
- Anti-CD20 therapy
- Anifrolumab
- Anti-thrombotic therapy

Comparator: Cognitive rehabilitation therapy
Outcomes:

- Further decline in cognitive ability
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

What is the most effective therapy for ischemic stroke in aPL-negative SLE patients?

P49. In SLE patients with ischemic stroke in the absence of aPL who have received acute stroke-directed therapy and/or procedure-based intervention, does addition of glucocorticoid, immunosuppressive therapy, or anticoagulation to antiplatelet therapy improve clinical outcomes compared to antiplatelet therapy only?

Population: Patients with SLE and ischemic stroke in the absence of aPL who have received acute stroke-directed therapy and/or procedure-based intervention, if indicated.
Interventions:

- Anticoagulation
- Corticosteroid therapy
- MMF/MPA
- AZA

Comparator: Antiplatelet therapy alone
Outcomes:

- Improvement of the stroke
- Prevention of recurrent stroke
- Neurologic damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment-related adverse events of infection and cytopenias for steroid and immunosuppressive therapies, bleeding for anticoagulation
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)

E4. Cutaneous/ mucocutaneous

Tables for guidance on use of 1) Sunscreens and 2) Topical steroid preparations.
GPS regarding referral to dermatologist; importance of collaboration and early diagnosis (include access of care issues);
GPS regarding education and encouragement for patients on use of sunscreen / photoprotection to reduce risk of rash as well as potential disease flare.

In SLE patients with acute cutaneous lupus despite HCQ and topical steroid therapy, what is the most effective additional therapy for persistent rash?

P50. Among SLE patients with active acute cutaneous lupus despite treatment with topical steroid and HCQ, does additional therapy , compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with active ACLE on HCQ and topical steroid therapy
Interventions: Continued HCQ and topical steroid therapy with addition of

- Chloroquine
- Quinacrine
- MTX
- AZA
- MMF/MPA
- Belimumab
- Anifrolumab
- Anti-CD-20 therapy

Comparator:

- HCQ and topical steroid therapy

Outcomes:

- Disease activity
- Flares
- Disease damage
- Mortality
- Quality of life

- Adverse impact of medications - for immunosuppressives including biologics: infection and cytopenias; for antimalarials: retinal toxicity and cardiac toxicity (prolonged QTc and myopathy).

In SLE patients with subacute or chronic cutaneous lupus despite HCQ and topical steroid therapy, what is the most effective additional therapy for persistent rash?

P51. Among SLE patients with active SCLE or DLE on HCQ and topical steroid therapy, does the addition of listed therapies, compared to no additional therapy, improve clinical outcomes?

Population: SLE patients with SCLE or DLE on HCQ and topical steroid therapy

Interventions: Continued HCQ and topical steroid therapy and addition of:

- Chloroquine
- Quinacrine
- Dapsone
- Retinoids
- MTX
- AZA
- MMF/MPA
- Thalidomide /Lenalidomide
- Belimumab
- Anifrolumab
- Anti-CD-20 therapy
- JAK-I

Comparators:

- HCQ and topical steroid therapy for Dapsone, Retinoids, MTX, ASA, MMF/MPA
- HCQ, topical steroid therapy and immunosuppressive therapy (with MTX, MMF/MPA or AZA) for thalidomide /lenalidomide, belimumab, anifrolumab, anti-CD-20 therapy and JAK-I

Outcomes:

- Disease activity
- Flares
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications for immunosuppressives including biologics and small molecules: infection and cytopenias; for antimalarials: retinal toxicity and cardiac toxicity (prolonged QTc and myopathy); for thalidomide and lenalidomide: neuropathy and GI effects; for retinoids: liver toxicity

In SLE patients with bullous lupus, what is the most effective therapy?

P52. In SLE patients with bullous lupus, what is the impact of listed medical treatments compared to steroids alone on clinical outcomes?

Population: SLE patients with bullous LE

Interventions:

- Dapsone
- Colchicine
- Corticosteroids
- Corticosteroids plus:
  - MTX
  - AZA
  - MMF/MPA
  - Anti-CD-20 therapy

Comparators:

- HCQ (for all except anti-CD 20 therapy)
- Oral glucocorticoids
- Stable background meds (including corticosteroid and immunosuppressive medications) for anti-CD 20 therapy

Outcomes:

- Disease activity
- Flares
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications: infection and cytopenias (for corticosteroids and immunosuppressives/ biologics); GI upset with dapsone; cytopenias and GI upset with colchicine

In SLE patients with lupus panniculitis, what is the most effective therapy?

Eliminate – uncommon manifestation.

In SLE patients with chilblains, what is the most effective therapy beyond symptomatic measures?

P53. In SLE patients with chilblains, does addition of the listed medical treatments compared to symptomatic measures (with or without topical therapies) lead to improved clinical outcomes?

Population: SLE patients with chilblains

Interventions: Symptomatic therapy and

- Topical steroid
- Topical calcineurin inhibitors
- HCQ
- Chloroquine
- Dapsone
- Calcium channel blockers
- Retinoids

- MTX
- AZA
- MMF/MPA
- Thalidomide
- Lenalidomide
- Belimumab
- Anifrolumab

Comparators:

- For topical steroid and topical calcineurin inhibitors, no therapy other than gloves/socks/warmers (symptomatic)
- For HCQ and chloroquine: symptomatic therapy, topical steroid therapy and topical calcineurin inhibitors
- For all others: symptomatic therapy, antimalarials, topical steroid therapy and topical calcineurin inhibitors

Outcomes:

- Disease activity
- Flares
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications: Adverse impact of medications: retinoids: liver toxicity; immunosuppressives: infection and cytopenias; thalidomide/lenalidomide: neuropathy and GI effects; antimalarial: retinal and cardiac toxicity; dapsone and colchicine: GI effects; calcium channel blockers: lightheadedness.

In SLE patients with cutaneous vasculitis, what is the most effective therapy?

P54. In SLE patients with cutaneous vasculitis, what is the impact of listed medical treatments compared to topical steroids alone or other standard therapy on clinical outcomes?

Population: SLE patients with cutaneous vasculitis

Interventions:

- Topical steroid
- Topical calcineurin inhibitors,
- HCQ
- Chloroquine
- Dapsone
- Colchicine
- Retinoids
- Pentoxyfylline
- MTX
- AZA
- MMF/MPA
- Thalidomide

- Lenalidomide
- Belimumab
- Anifrolumab

Comparators:

- For topical steroid and topical calcineurin inhibitors: no therapy as comparator
- For HCQ and chloroquine: topical steroid therapy and topical calcineurin inhibitors as comparators
- For all others: antimalarials plus topical steroid therapy and topical calcineurin inhibitors
- For Thalidomide, lenalidomide, belimumab and anifrolumab: also compare to antimalarials, topical steroid, topical calcineurin inhibitors and immunosuppressives (MTX, AZA, MMF/MPA)

Outcomes:

- Disease activity
- Flares
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications: retinoids: liver toxicity; immunosuppressives including biologics: infection and cytopenias; thalidomide/lenalidomide: neuropathy and GI effects; antimalarial: retinal and cardiac toxicity; dapsone, pentoxifylline, colchicine: GI effects

In SLE patients with focal alopecia due to CLE or SLE, does addition of topical therapies to systemic therapy improve clinical outcomes?

P55. In SLE patients with focal active alopecia due to CLE or SLE, does the addition of topical treatment to systemic therapies, compared to no topical treatment, improve clinical outcomes?

Population: Patients with SLE and focal alopecia on systemic therapy (HCQ and/or immunosuppressives)

Interventions:

- Intralesional Kenalog with systemic treatment
- Intralesional Kenalog alone
- Topical steroid

Comparators:

- Antimalarials
- Immunosuppressives

Outcomes:

Rate and amount of improvement

In SLE patients with severe oral ulcers, does topical therapy improve clinical outcomes?

P56. In patients with oral ulcers due to SLE does the addition of targeted local therapies to standard systemic therapies, compared to no targeted local therapies, improve clinical outcomes?

Population: Patients with SLE and mouth ulcers on systemic therapy (HCQ and/or immunosuppressives)

Interventions:

- Intralesional Kenalog
- Topical steroids.

Comparators:

- Antimalarials
- Immunosuppressives.

Outcomes:

- Rate and amount of improvement

E5. Serositis

In SLE patients with pericarditis, what is the most effective therapy?

P57. In SLE patients with pericarditis what is the impact of listed medical therapies or pericardectomy versus baseline therapy alone on clinical outcomes?

Population: Patients with lupus and pericarditis

Intervention:

- NSAIDs
- Colchicine
- Glucocorticoid therapy alone
- Methotrexate
- Azathioprine
- MMF/MPA
- Cyclophosphamide
- Belimumab
- Anifrolumab
- Anti-CD20
- Anti IL-1therapy
- Pericardiectomy

Comparator:

- Hydroxychloroquine and/or NSAIDs
- Colchicine with HCQ (for all but HCQ, NSAID and colchicine)
- HCQ / NSAID / colchicine
- Corticosteroid (for MTX, AZA, MMF/MPA, CYC, biologics and pericardectomy)

Outcomes:

- Resolution of pericarditis
- Prevention of pericarditis flares

- Prevention of pericardiectomy
- Prevention of chronic pericarditis (≥6 mo)
- Improvement in quality of life
- Cumulative GC
- Adverse treatment events: immunosuppressives including biologics, infection and cytopenias; colchicine and NSAIDs: GI symptoms; steroid alone: osteoporosis and infection
- Mortality
- Disease damage

In SLE patients with pleuritic pain and/or pleural effusion, what is the most effective therapy?

P58. In patients with SLE and pleural disease what is the impact of medical therapy versus baseline therapy alone on clinical outcomes?

Population: Patients with lupus and pleural disease (pleuritic pain, effusion)

Intervention:

- NSAIDs
- Colchicine
- Glucocorticoid therapy alone
- Methotrexate
- Azathioprine
- MMF/MPA
- Cyclophosphamide
- Belimumab
- Anifrolumab
- Anti-CD20
- Anti IL-1 therapy

Comparator:

- Hydroxychloroquine and/or NSAIDs
- Colchicine with HCQ (for all but HCQ, NSAID and colchicine)
- HCQ / NSAID / colchicine
- Corticosteroid (for MTX, AZA, MMF/MPA, CYC, biologics)

Outcomes:

- Resolution of pleural disease
- Prevention of pleural disease flares
- Prevention of shrinking lung syndrome
- Prevention of fibrothorax
- Improvement in quality of life
- Cumulative GC

- Adverse treatment events: immunosuppressives including biologics, infection and cytopenias; NSAIDs and colchicine: GI effects; steroid alone: osteoporosis and infection
- Mortality
- Disease Damage

E6. Musculoskeletal

Is there a benefit to imaging symptomatic joints in SLE patients with arthritis?

P59. In patients with SLE and lupus arthritis or tendonitis, does imaging with US or MRI compared to not doing this imaging improve clinical outcomes?

Population: Patients with lupus arthritis or tendonitis

Intervention:

- Ultrasound
- MRI

Comparator: PE alone

Outcomes:

- Diagnosis of subclinical arthritis
- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Disease activity
- SLE flares
- Joint damage
- Disease damage
- Quality of life
- Functional status

In SLE patients with arthritis, what is the most effective therapy?

P60. In patients with SLE and lupus arthritis, does treatment with listed medical therapies compared to no treatment impact clinical outcomes?

Population: SLE patients with active lupus arthritis

Intervention:

- HCQ and other antimalarials (AM)
- NSAIDs
- Glucocorticoid-containing regimens
- Immunosuppressants
    - MTX
    - MMF/MPA
    - AZA

- Leflunomide
- CNI

- Biologics
  - Anti-CD20
  - Belimumab
  - Anifrolumab
  - Abatacept

Comparator:

- No treatment (for HCQ and NSAIDs)
- HCQ alone (for all other options)
- HCQ +steroid (for all other options)

Outcomes

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Joint damage
- Disease damage
- Quality of life
- Treatment-related adverse events: immunosuppressives and biologics: infection and cytopenias; steroids: osteoporosis and infection; NSAIDs: GI side effects; Antimalarials: retinal and cardiac effects (prolonged QTc and myopathy)

In SLE patients with chronic persistent arthritis on HCQ with or without corticosteroid, what is the most effective therapy?

P61. In patients with SLE and chronic persistent lupus arthritis on HCQ and steroid, does treatment with listed medical therapies compared to no added treatment impact clinical outcomes?

Population:

- SLE patients with chronic persistent lupus arthritis on HCQ and steroid
- SLE patients with chronic persistent lupus arthritis on HCQ, steroid and standard immunosuppressives

Intervention:

- Immunosuppressants (for HCQ/steroid group)
  - MTX
  - MMF/MPA
  - AZA
  - Leflunomide
  - CNI

CYC

- Biologics (for HCQ/steroid group and for HCQ/steroid/immunosuppressant group)
  - Anti-CD20
  - Belimumab
  - Anifrolumab
  - Abatacept
  - Tocilizumab
- Jak-I (for HCQ/steroid/immunosuppressant group only)

Comparator:

- HCQ and steroids alone
- HCQ, steroid and standard immunosuppressive therapy (for biologics and JAK-I)

Outcomes:

- Arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Disease activity
- SLE flares
- Joint damage
- Disease damage
- Quality of life
- Treatment-related adverse events: immunosuppressives and biologics: infection and cytopenias; steroids: osteoporosis and infection; NSAIDs: GI side effects; Antimalarials: retinal and cardiac effects (prolonged QTc and myopathy)

In SLE patients with Jaccoud's arthropathy, does addition of medical therapy to standard of care (PT/OT and/or surgery) improve clinical outcomes?

P62. In SLE patients with chronic Jaccoud's arthropathy, what is the impact of medical therapy or surgery vs PT/OT on clinical outcomes?

Populations: SLE patients with Jaccoud's arthropathy

Interventions:

- Hand arthroplasty
- Immunosuppressive therapy (MMF, AZA, MTX, or other standard immunosuppressives)

Comparator: PT/OT including splinting

Outcomes:

- Function of affected joints (hand function measure)
- Functional status as measured by a validated tool (e.g., Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Quality of life
- Treatment-related adverse events: infection and cytopenias for immunosuppressive therapies; surgical complications of hand arthroplasty for surgery adverse outcomes

E7. Renal: **refer to Lupus Nephritis Guideline**

E8. Vasculitis (non-cutaneous)

In SLE patients with (non-cutaneous) vasculitis, what is the most effective therapy?

P63. In patients with SLE with vasculitis (not including cutaneous vasculitis) on HCQ and steroid, what is the impact of adding listed therapies versus not adding additional therapy on clinical outcomes?

Population: SLE patients with vasculitis (not including cutaneous vasculitis) on HCQ/steroid.

Interventions:

- High dose glucocorticoid-containing regimens – pulse followed by high dose
- Immunosuppressants
  - MTX
  - MMF
  - AZA
  - CNI
  - Cytoxan
- Biologics
  - Anti-CD20
  - Belimumab
  - Anifrolumab
- IVIG
- Plasmapheresis

Comparator: HCQ and steroid

Outcomes:

- Vasculitis activity
- Disease activity
- SLE flares
- Disease damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment -related adverse events: steroids: infection and osteoporosis; immunosuppressives including biologics and small molecules: infection and cytopenias; IVIG: headache; plasmapheresis: low blood pressure

E9. Cardiopulmonary

Rarer complications to be noted in text but not addressed in PICOs.

In SLE patients with myocarditis, what is the most effective therapy?

P64. In patients with lupus myocarditis what is the impact of listed therapies vs no therapy or HCQ alone on clinical outcomes?

Population: SLE patients with lupus myocarditis

- Acute and worsening
- Chronic and persistent

Interventions:

- Glucocorticoid-containing regimens
- Immunosuppressants
  - MMF/MPA
  - AZA
  - CYC
- Biologics
  - Anti-CD20
  - Belimumab
  - Anifrolumab
- IVIG

Comparator: No therapy or HCQ alone

Outcomes:

- Reduction of myocarditis activity
- Overall disease activity
- Disease damage
- Mortality
- Quality of life
- Cumulative glucocorticoid dose
- Treatment -related adverse events: steroids: infection and osteoporosis; immunosuppressives including biologics and small molecules: infection and cytopenias; IVIG: headache

In SLE patients with Libman-Sacks endocarditis, what is the most effective therapy?

P65. In SLE patients with lupus Libman-Sacks endocarditis, does treatment with listed medical therapy vs HCQ treatment alone impact clinical outcomes?

Population: SLE patients with Libman-Sacks endocarditis defined as sterile vegetations on the valve surface or a thickened valve or valvulitis with or without vegetation (with or without aPL/APS, and with or without low complement levels).

Interventions:

- Anticoagulation
- Steroids
- Traditional Immunosuppressants and approved biologics (Belimumab, Anifrolumab)

- B-cell depletion (anti-CD-20 therapy)
- Surgical intervention (valvular surgery)

Comparators:

- Anticoagulation (AC) with vit K antagonists vs. no AC as comparator
- Steroid therapy vs. AC alone
- Steroid+ AC vs AC alone
- Immunosuppression + steroids vs AC
- Immunosuppression + steroids + AC vs AC
- B cell depletion therapy + steroids vs AC
- B cell depletion therapy + steroids + AC vs AC
- No surgical intervention vs (any) medical management

Outcomes:

- Size of the vegetations
- Valvular dysfunction requiring valve replacement / surgery
- Embolic disease (including stroke and TIA)
- Disease damage
- Mortality
- Quality of life
- Adverse impact of medications: bleeding for anticoagulation, infection and diabetes for steroid, infection and cytopenias for immunosuppressive medications.

F. Alternative treatments:

F1. Supplements – Address as GPS or text discussion

F2. Nonpharmacologic therapies – Address as GPS or text discussion

G. Other

- **Pregnancy / other reproductive health issues** – refer to reproductive health guideline
- **APS:** Text discussion, refer to recent relevant publications, emphasize importance in SLE, beyond scope of this GL

APPENDIX B – INCLUSION/EXCLUSION CRITERIA

POPULATIONS

Include

- All age groups (no age limit)
- All SLE patients

Exclude

- Patients with SLE as part of overlap syndrome

INTERVENTIONS

Include

Diagnosis:

- Percutaneous renal biopsy and histopathology report

LN class II therapy:

- RAAS-I therapy with: corticosteroid, corticosteroid plus immunosuppressives (MMF/MPA, AZA, CYC) or corticosteroid plus CNI

LN classes III/IV or V initial therapy:

- Pulse dose steroid followed by moderate-high dose corticosteroid
- Pulse dose steroid followed by low dose corticosteroid
- Cyclophosphamide (CYC) alone: Monthly IV or Eurolupus
- IV CYC plus belimumab
- IV CYC plus anti-CD 20 therapy
- Mycophenolate mofetil (MMF) / mycophenolic acid (MPA) at 2 gms daily MMF-equivalent
- MMF/MPA (any dose) alone
- MMF/MPA plus belimumab
- MMF/MPA plus anti-CD 20 therapy
- MMF/MPA plus CNI
- Anti CD 20 therapy plus belimumab

LN classes III/IV or V subsequent therapy:

- Steroid tapered to $\leq$ 5 mg/d at $\leq$ 6 mo
- Steroid tapered to $\leq$ 10 mg/d at $\leq$ 6 mo
- Quarterly IV monthly CYC (NIH protocol) for two years
- MMF/MPA alone or with CNI, belimumab, or anti-CD 20 therapy after initial IV CYC therapy
- MMF/MPA alone or with CNI, belimumab, or anti-CD 20 therapy after initial MMF/MPA therapy
- MMF, AZA or combination rx. 3-5 yrs.
- MMF, AZA or combination rx. >5 yrs

Refractory LN therapy:

- Pulse steroid therapy

- Moderate-high dose oral corticosteroid
- Pulse therapy followed by low dose oral corticosteroid
- IV CYC
- CYC plus belimumab
- CYC plus anti-CD 20 therapy
- MMF.MPA 3 gm daily
- MMF/MPA plus belimumab
- MMF/MPA plus CNI
- MMF/MPA plus anti-CD 20 therapy
- MMF/MPA plus CNI plus belimumab
- Anti-CD 20 therapy plus belimumab
- Any belimumab containing regimen
- IVIG plus any standard therapy
- Leflunomide plus any standard therapy
- Addition of any of the following to current therapy:
    - Pulse steroid therapy
    - Anti-CD 20 therapy
    - CNI
    - Belimumab
    - Belimumab plus CNI
    - Leflunomide
    - IVIG
- Referral to clinical trial

Other lupus-related kidney disease:

- Anticoagulation
- Anticoagulation plus:
    - Anti-CD20 therapy
    - Eculizumab / complement inhibition
    - mTOR inhibitor therapy
    - Plasmapheresis
- RAAS-I with:
    - Steroid therapy (any dose)
    - Steroid therapy plus any immunosuppressive therapy (including MMF, AZA, CYC, CNI)

Monitoring LN:

- Regular interval urinary protein testing (every 1,2,3, 6 or 12 months)
- Regular interval dsDNA antibody and C3C4 testing (every 1,2,3, 6 or 12 months)
- Alternate measures of urinary protein measurement including:
    - Random UPCR
    - 12-hour urine protein (overnight sample)
    - 24-hour urine protein with UPCR on same sample

- First void urine UPCR
- Random urine albumin (or microalbumin) to creatinine ratio

Renal replacement therapy:

- Renal transplantation
- Hemodialysis
- Regular rheumatology follow-up
- HCQ
- Pre-emptive kidney transplant
- Kidney transplant with clinical disease activity
- Kidney transplant with serologic disease activity
- Anticoagulation
- Sirolimus
- Eculizumab
- Anti-CD20 therapy
- Belatacept
- IVIG

Diagnosis and monitoring of SLE:

- Disease activity measure at each visit
- Disease damage measure yearly

Comorbidities and risk management:

- Sulfamethoxazole and trimethoprim PJP prophylaxis
- Atovaquone PJP Prophylaxis

Medications:

- Prednisone 2.5, 5, or 7.5 mg prednisone for > 6 months
- Pulse therapy followed by oral prednisone taper
- Initiation of immunosuppressive therapy with oral prednisone taper
- Taper of prednisone to off
- Once daily prednisone dosing
- HCQ dose $\leq$ 5 mg/kg
- Monitoring HCQ levels
- HCQ
- Discontinuation of immunosuppressive therapy at (from time of complete remission or low disease activity)
  - One year
  - > one year but $\leq$ 3 years
  - > 3 years
- Discontinuation of HCQ at (from time of complete remission or low disease activity)
  - $\leq$ 5 years
  - 5-10 years
  - > 10 years

Treatment:

- Low dose glucocorticoid
- Moderate to high dose glucocorticoid
- Immunosuppressive medication (any)
- Biologic therapy (any)
- Azathioprine
- MMF/MPA
- Glucocorticoid
- For patients on immunosuppressants: Stopping or lowering immunosuppressive therapy
- Cyclosporine
- Anti-CD20 therapy
- Splenectomy
- IVIG
- CYC
- MMF/MPA
- Anti-CD20 therapy
- Anifrolumab
- Belimumab
- CYC plus anti-CD20 therapy
- CYC plus PLEX (plasmapheresis)
- CYC plus IVIG
- CYC plus PLEX plus IVIG
- CYC plus anti-CD20 therapy plus PLEX plus IVIG
- Antithrombotic regime (any) plus immunosuppressive regimen
- Antiseizure medication with glucocorticoid alone or with (any) immunosuppressive or biologic therapy.
- Antipsychotic medication with glucocorticoid alone or with (any) immunosuppressive or biologic therapy.
- Non-immunosuppressive, symptomatic, nerve-directed therapy with glucocorticoid alone or with (any) immunosuppressive or biologic therapy.
- Cognitive therapy with glucocorticoid alone or with (any) immunosuppressive or biologic therapy.
- Anti-platelet therapy and anticoagulation, corticosteroid therapy, MMF/MPA, or AZA
- HCQ and topical steroid therapy with addition of Chloroquine, Quinacrine, MTX, AZA, MMF/MPA, Belimumab, Anifrolumab, Anti-CD-20 therapy, Dapsone, Retinoids, Thalidomide /Lenalidomide, or JAK-I
- Corticosteroids plus MTX, AZA, MMF/MPA, Anti-CD20 therapy
- Symptomatic therapy with gloves, socks, warmers, plus addition of Topical steroid, Topical calcineurin inhibitors, HCQ, Chloroquine, Dapsone, Calcium channel blockers, Pentoxifylline, Retinoids, MTX, AZA, MMF/MPA, Thalidomide/ Lenalidomide, belimumab, or anifrolumab
- Immunosuppressive or biologic therapy with addition of Intralesional Kenalog or Topical steroid
- NSAIDs, Colchicine, Glucocorticoid therapy, Methotrexate, Azathioprine, MMF/MPA, Cyclophosphamide, Belimumab, Anifrolumab Anti-CD20, Anti IL-1 or Pericardiectomy
- Immunosuppressants (for HCQ/steroid group) including MTX, MMF/MPA, AZA, leflunomide, CNI, CYC

- Biologics (added to HCQ/steroid group or HCQ/steroid/immunosuppressant group) including anti-CD20 therapy, belimumab, anifrolumab, abatacept or tocilizumab
- Jak-I added to HCQ/steroid/immunosuppressant group
- PT/OT and splinting for Jaccoud's arthropathy plus surgical or medical therapy
- Steroid and anticoagulation with or without immunosuppressives and/ or biologics and/or anti-CD 20 therapy
- Surgical intervention (valve surgery)

Exclude

- Vaccines: refer to 2022 ACR vaccine guideline
- Hepatitis B and C screening: refer to CDC recommendations
- Latent TB screening: refer to outside recommendations
- Glucocorticoid-induced osteoporosis screening and treatment: refer to upcoming ACR GIOP guideline
- Cardiovascular screening and therapies (refer to appropriate cardiology guidelines)
- Pregnancy, contraception, assisted reproductive technology, menopause interventions: refer to 2020 ACR reproductive health guideline
- Fibromyalgia treatment (beyond scope)
- Antiphospholipid syndrome treatment (beyond scope)

COMPARATORS

Include

Diagnosis:

- No percutaneous biopsy / histopathology

LN Class II therapy:

- RASSI-I therapy alone

LN Class III/IV or V initial therapy:

- Pulse steroid followed by low-dose corticosteroid
- Moderate-high dose oral corticosteroid
- CYC alone: Eurolupus or oral
- MMF/MPA alone
- MMF/MPA plus CNI
- CNI alone
- MMF/MPA at 3 gms/day
- MMF/MPA plus belimumab
- IV CYC plus belimumab
- Anti-CD20 therapy alone

LN Class III/IV or V subsequent therapy:

- Steroid tapered to $\leq$ 5 mg/d at > 6 mo
- Steroid tapered to $\leq$ 10 mg/d at > 6 mo
- MMF/MPA
- AZA

- MMF, AZA or combination rx. <3 yrs.
- MMF, AZA or combination rx. 3- 5yrs.

Refractory LN therapy:

- No pulse therapy
- No increase in oral corticosteroid
- MMF/MPA
- CYC
- MMF/MPA 2 gm/day
- MMF/MPA plus CNI
- MMF/MPA plus belimumab
- Anti-CD 20 therapy
- Any standard therapy without IVIG
- Any standard therapy without leflunomide

Other lupus-related kidney disease:

- No anticoagulation
- Anticoagulation without additional therapy
- No RAAS-I therapy

Adjunctive treatments/considerations for LN

- No RAAS-I therapy
- No SGLT2-I
- RAAS-I alone without SGLT2-I
- No HCQ

Monitoring LN:

- No regular schedule for urinary protein monitoring
- No regular schedule for dsDNA antibody and C3C4 monitoring

Renal replacement therapy:

- Hemodialysis or peritoneal dialysis
- No regular rheumatology follow up
- No HCQ
- No pre-emptive kidney transplant
- Transplant with no clinical and serologic activity
- No anticoagulation
- Standard of care for kidney transplant

Diagnosis and monitoring of SLE:

- No regular disease activity measure or damage index

Comorbidities and risk management:

- No PJP prophylaxis

Medications:

- Prednisone 10 mg/day for > 6 months
- Oral prednisone taper

- Continued prednisone and HCQ
- Continuing prednisone 5 mg/day
- Twice daily prednisone dosing
- HCQ >5 mg/kg
- Not monitoring HCQ levels
- No HCQ
- No discontinuation of immunosuppressive or HCQ therapy

Treatment:

- HCQ alone
- No treatment (or HCQ alone)
- Continuing therapy at same dose (for patients on immunosuppressive medications)
- Glucocorticoid therapy alone
- Pulse IV glucocorticoid followed by high dose glucocorticoid (no additional immunosuppressive)
- Pulse IV glucocorticoid followed by high dose glucocorticoid plus IV CYC.
- Antiseizure therapy alone
- Antipsychotic therapy alone
- Non-immunosuppressive, symptomatic, nerve-directed therapy alone
- Cognitive therapy alone
- Anti-platelet therapy alone
- HCQ and topical steroid therapy alone
- HCQ, topical steroid therapy and immunosuppressive therapy (with MTX, MMF/MPA or AZA) for thalidomide /lenalidomide, belimumab, anifrolumab, anti-CD-20 therapy and JAK-I additional treatment.
- Stable background meds (including corticosteroid and immunosuppressive medications) for anti-CD20 therapy
- Symptomatic therapy with gloves, socks, warmers, alone or plus Topical steroid or Topical calcineurin inhibitors
- Immunosuppressive or biologic therapy without addition of Intralesional Kenalog or Topical steroid
- HCQ with or without NSAIDs, Colchicine, Glucocorticoid therapy, or immunosuppressives and without biologic therapy or pericardiectomy
- No anticoagulation
- Anticoagulation alone
- No surgical intervention (valve surgery) with medical therapy (Steroid and anticoagulation with or without immunosuppressives and/ or biologics and/or anti-CD 20 therapy)
- PT/OT and splinting for Jaccoud's arthropathy without surgical or medical therapy

APPENDIX C: OUTCOMES

Kidney biopsy:

- Additional or different kidney diagnosis identified (e.g., TMA, ATN, class change, DM or arteriosclerosis / arteriolosclerosis) that impacts decision for and choice of therapy
- Level of proteinuria
- Kidney function
- ESKD (dialysis or transplant)
- Adverse effects of biopsy (separate literature search for general meta-analysis or systematic review)
- Histopathology results in change and/or continuation of therapy
- Histopathology results in withdrawal of therapy (i.e., no activity seen on biopsy)
- LN flare

LN Treatment:

- Level of proteinuria
- Kidney function
- LN flares
- Cumulative corticosteroid dose
- ESKD (dialysis or transplant)
- Treatment related adverse effects for RAAS-I: cough and hypotension (RAAS-I therapy alone only)
- Treatment related adverse effects for steroid monotherapy: DM, infection
- Treatment related adverse effects for immunosuppressive regimens: infection and cytopenias
- Treatment related adverse effects for anticoagulation regimens: bleeding
- Thromboembolic events (for anticoagulation intervention only)
- CRR (complete renal response)
- PRR (partial renal response)
- Treatment related adverse effects for HCQ / antimalarials: retinopathy and cardiac toxicity (prolonged QTc and myopathy)

Monitoring LN activity:

- Level of proteinuria (N/A for no LN hx or those who have had resolution of proteinuria)
- Kidney function
- LN flare
- Cumulative corticosteroid dose
- ESKD (dialysis or transplant)

Renal replacement therapy:

- Incidence of infection
- Incidence of cardiovascular disease (CVD)
- Quality of life

- SLE flare
- Disease damage
- Hospitalization
- Graft survival
- Recurrent SLE in renal graft
- Mortality
- Vascular (thromboembolic) events
- Bleeding
- Adverse effects of therapy of immunosuppressive therapy: infection and cytopenias
- Adverse effects of therapy with IVIG: headache and hypersensitivity

Extrarenal SLE

Diagnosis and monitoring:

- SLE Flare
- Disease damage
- Mortality
- Comorbidities
- Quality of life

Comorbidities and risk management:

- Quality of life
- Need for joint arthroplasty
- Flare of rash
- SLE Flare
- Disease damage
- Quality of life
- Mortality
- Cardiovascular disease
- PJP infection
- Adverse effects of PJP prophylaxis therapy with sulfa: rash, other allergic reaction
- Adverse effects of PJP prophylaxis therapy with atovaquone: GI effects, headache

Medication overview and considerations:

- Osteoporosis
- Hypertension
- Fractures
- Cataracts
- T2DM
- Infections

- Disease damage
- Quality of Life
- SLE Flare
- Reaching prednisone ≤ 5mg/day
- Stopping steroid therapy
- SLE disease activity
- Adverse medication effects for corticosteroid: infection and DM
- Adverse medication effects for immunosuppressive: infection and cytopenias
- Glucocorticoid-induced adrenal insufficiency
- Retinal toxicity
- Thrombosis
- Cardiac toxicity (prolonged QTc and/or myopathy)
- Adherence to therapy with HCQ

Guiding principles:

- Disease damage
- Mortality
- Corticosteroid related adverse effects: Osteoporosis, T2DM
- Other medication related adverse effects: Infection, cytopenias
- Retinal toxicity
- Cardiac toxicity (prolonged QTc and/or myopathy)
- Thromboses
- Quality of life

Organ system treatment:

- Level of Fatigue
- Quality of life
- Cumulative GC dose
- Treatment related adverse events of steroid: infection and DM for steroid
- Treatment related adverse effects of immunosuppressives and biologics: infection and cytopenias
- WBC count (increase, decrease or no change)
- Infection
- Mortality
- Disease damage
- SLE flare
- Life-threatening bleeds
- Mortality
- SLE disease activity
- Prevention of neurologic damage

- Functional status as measured by a validated tool (e.g. Health Assessment Questionnaire Disability index, Health Assessment Questionnaire-II, Multidimensional Health Assessment Questionnaire)
- Prevention of optic nerve damage
- Preservation of vision
- Improvement in seizure activity / prevention of further seizures
- Adverse effect of antithrombotic regimen only: bleeding
- Resolution of acute confusional state
- Prevention of flares of psychosis
- Resolution of mononeuritis multiplex
- Prevention of mononeuritis multiplex
- Resolution or improvement of small-fiber neuropathy
- Prevention of small-fiber neuropathy
- Further decline in cognitive ability
- Prevention of cognitive dysfunction
- Improvement of the stroke
- Prevention of stroke
- Cutaneous disease activity
- Panniculitis: Disease activity (if induration improves, lesions don't expand, no new lesions)
- Adverse impact of medications: retinoids: liver toxicity; immunosuppressives: infection and cytopenias; thalidomide/lenalidomide: neuropathy and GI effects; antimalarials: retinal and cardiac toxicity
- Rate and amount of improvement of alopecia
- Rate and amount of improvement, oral ulcers
- Resolution of pericarditis
- Prevention of pericarditis flares
- Prevention of pericardiectomy
- Prevention of chronic pericarditis ($\geq$6 mo)
- Resolution of pleural disease
- Prevention of pleural disease flares
- Prevention of shrinking lung syndrome
- Prevention of fibrothorax
- Reduction of arthritis activity (improvement in joint pains, joint stiffness, joint swelling, and function)
- Joint damage
- Function of affected joints (hand function measure)
- Reduction of vasculitis activity
- Reduction of myocarditis activity
- Pain level
- Fatigue
- Low bone density
- Fracture
- Size of the valvular vegetations
- Valvular dysfunction requiring valve replacement

- Embolic disease related to vegetations (including stroke and TIA)

STUDY DESIGN (includes only studies published in English language)

For all PICO questions, we will include randomized or non-randomized controlled trials (this includes case-control studies). To capture adverse events, we will also consider open-label extension studies of RCTs or other longitudinal observational studies that focus on safety and tolerability. For PICO questions that focus on assessing the accuracy of screening tools, we will also include studies without an independent control group, specifically cohort and cross-sectional studies. We will also include existing systematic reviews and guidelines from other societies **only** to confirm that we have included all relevant references.

Include

- RCTs, including:
  - Open-label extensions of RCTs with placebo involved
- Non-randomized controlled studies, including
  - Case-control studies
- Cohort studies
- Cross-sectional studies
- Longitudinal studies (focusing on safety and tolerability)
- Systematic reviews and Guidelines from other societies

[NOTE: If there has been a recently done, well-done systematic review on the exact PICO that ACR is asking, then that systematic review could be considered for use in the guideline; primary study data would still need to be pulled in the ACR's database, though.]

Exclude

- Abstracts
- Case reports
- Narrative reviews
- Prevalence studies
- Economic studies, e.g., cost-effectiveness studies
- Drug adherence studies
- Studies of risk factors
- Foreign language studies
- Studies with irrelevant population, interventions, or outcomes
- Animal studies

American College of Rheumatology (ACR) Guideline for Treatment of Systemic Lupus Erythematosus (SLE)

Project Plan – December 2023

APPENDIX D: DISCLOSURES

Participant Disclosures - American College of Rheumatology (ACR) Guideline for Systemic Lupus Erythematosus (SLE)
In order for the College to most effectively further its mission and to otherwise maintain its excellent reputation in the medical community and with the public, it is important that confidence in the College's integrity be maintained. The cornerstone of the ACR's Disclosure Policy is disclosure of actual and potential conflicts so that they can be evaluated by the College in order to avoid undue influence of potential conflicts. The purpose of the ACR's Disclosure Policy is identification of relationships which may pose actual or potential conflicts. These actual or potential conflicts can then be evaluated by the College so that adjustments can be made that will avoid any undue influence. This policy is based on the principle that, in many cases, full disclosure of the actual or potentially conflicting relationship will of itself suffice to protect the integrity of the College and its interests.

Participants	Role	Primary Employer	Interest Held By	Interest Type	Entity/Licensee	Additional Information	Start from Date	End Date	Value
Lisa R. Sammaritano, MD	Core Team - PI	Hospital for Special Surgery	Nothing to disclose	Independent Contractor - Editorial Board	Best Practice and Clinical Rheumatology				
Anca Askanase, MD, MPH	Core Team/Content Expert	Columbia University	Self	Independent Contractor - Consultant - Author	GlaxoSmithKline		7/15/2022	Ongoing / No known end date	$4,995.00
			Self	Grant / Contract	Eli Lilly and Company	per patient payment	4/30/2019	6/22/2022	$36,000.00
			Self	Independent Contractor - Member	Lupus Foundation of America		1/1/2014	Ongoing / No known end date	
			Self	Grant / Contract	Genentech	Per patient	12/2/2022	Ongoing / No known end date	$0.00
			Self	Independent Contractor - Study PI	SANOFI PASTEUR INC.		9/22/2022	Ongoing / No known end date	
			Self	Grant / Contract	UCB	Per patient	9/18/2021	Ongoing / No known end date	$100.00
			Self	Independent Contractor - Consultant - EULAR presentation	AstraZeneca	4950	6/1/2022	6/2/2022	$4,950.00
			Self	Independent Contractor - Consultant - POETYK - SLE trial	Bristol Myers Squibb Company		1/30/2023	Ongoing / No known end date	$4,000.00

			Self	Grant / Contract	Pfizer	Not yet started, expected per patient	3/15/2020	Ongoing / No known end date	$20,000.00
			Self	Independent Contractor - Data And Safety Monitoring - DSMB Panel Member	Amgen		1/1/2022	Ongoing / No known end date	$4,950.00
			Self	Grant / Contract	Celgene Corporation	per patient payment	6/14/2018	3/2/2022	$19,679.00
			Self	Grant / Contract	SANOFI PASTEUR BIOLOGICS LLC	Not determined yet	9/22/2022	Ongoing / No known end date	$100.00
			Self	Independent Contractor - Consultant - UCB Trial	UCB		10/19/2022	Ongoing / No known end date	$4,950.00
			Self	Grant / Contract	AstraZeneca	per patient	1/20/2023	Ongoing / No known end date	$100.00
			Self	Grant / Contract	Lupus Research Alliance		1/1/2017	Ongoing / No known end date	$40,000.00
			Self	Grant / Contract	Idorsia	per patient	10/22/2020	8/24/2022	$100.00
Bonnie L. Bermas, MD	Core Team/Content Expert	UT Southwestern Medical Center	Self	Intellectual Property - Other Intellectual Property	UptoDate	I receive Royalty fees twice a year			
Maria Dall'Era, Md	Core Team/Content Expert	University of California, San Francisco	Self	Independent Contractor - Consultant	Aurinia		1/1/2021	Ongoing / No known end date	$4,000.00
			Self	Independent Contractor - Consultant	AstraZeneca		2/1/2020	Ongoing / No known end date	$6,000.00
			Self	Independent Contractor - Data And Safety Monitoring - DMB member	Janssen Biotech		3/1/2020	Ongoing / No known end date	$5,000.00
			Self	Independent Contractor - Data And Safety Monitoring - DMC member	Pfizer		4/2/2021	Ongoing / No known end date	$5,000.00

			Self	Independent Contractor - Consultant	GlaxoSmithKline		1/1/2019	Ongoing / No known end date	$6,000.00
Alí Duarte-García, MD, MSc	Core Team/Content Expert	Mayo Clinic	Nothing to disclose						
Linda Hiraki, MD, MSCScD	Core Team/Content Expert	University of Toronto	Self	Independent Contractor - Consultant	Janssen Research & Development, LLC		8/5/2022	Ongoing / No known end date	$4,500.00
			Self	Grant / Contract	Childhood Arthritis & Rheumatology Research Alliance (CARRA)		3/1/2021	Ongoing / No known end date	$100,000.00
			Self	Grant / Contract	Lupus Research Alliance		9/1/2021	Ongoing / No known end date	$100,845.00
			Self	Grant / Contract	U.S. Department of Defense		9/30/2022	Ongoing / No known end date	$299,994.00
Reem Mustafa, MD, PhD	Core Team/Lit Review Team Leader & GRADE Expert	University of Kansas	Self	Grant / Contract	World Health Organization		1/1/2022	11/1/2022	$9,979.00
			Self	Other Professional Activities - Consultant - Methodologist	Evidence Foundation		1/1/2014	Ongoing / No known end date	
			Self	Grant / Contract	National Institute of Diabetes and Digestive and Kidney Diseases		7/1/2020	Ongoing / No known end date	$965,620.00
			Self	Other Professional Activities - Chair of the Midwest Comparative Effectiveness Public Advisory Council (CEPAC)	Institute For Clinical and Economic Review		1/1/2021	Ongoing / No known end date	
			Self	Employment - Associate Professor of Internal Medicine	University of Kansas Medical Center		2/28/2017	Ongoing / No known end date	
			Self	Grant / Contract	American Society of Hematology		6/1/2023	Ongoing / No known end date	$650,000.00

			Self	Other Professional Activities - Board member	Evidence Foundation		1/1/2014	Ongoing / No known end date	
			Self	Other Professional Activities - Data And Safety Monitoring	National Institute of Health		1/18/2022	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant - Methodologist	American Academy of Sleep Medicine		1/1/2022	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant - Methodologist	Infectious Diseases Society of America		6/1/2020	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant - Methodologist	American Academy of Pediatrics		10/28/2022	Ongoing / No known end date	
			Self	Other Professional Activities - Methodologist	Kidney Disease: Improving Global Outcomes		8/9/2019	Ongoing / No known end date	
			This is funding that is received by the University and I do not receive any of it and it does not support my salary	Grant / Contract	Boehringer Ingelheim		1/1/2019	9/1/2022	$474,836.00
Brad Rovin, MD	Core Team/Content Expert	Ohio State University	Self	Other Professional Activities - Consultant/Advisory Board/Clinical Trial PI	Genentech USA, Inc.		1/1/2016	Ongoing / No known end date	$0.00
			Self	Other Professional Activities - Consultant/Advisory Board/Clinical Trial PI	AstraZeneca		11/24/2022	Ongoing / No known end date	$2,000.00

			Self	Other Professional Activities - Consultant	Sana		7/1/2023	Ongoing / No known end date	$0.00
			Self	Other Professional Activities - Consultant/Advisory Board/Clinical Trial PI	Kyverna		1/1/2021	Ongoing / No known end date	$2,000.00
			Self	Other Professional Activities - Consultant/Advisory Board/Clinical Trial PI	Biogen Idec		3/2/2022	Ongoing / No known end date	$1,000.00
			Self	Other Professional Activities - Consultant/Advisory Board/Clinical Trial PI	Aurinia Pharmaceuticals Inc.		8/1/2021	8/2/2022	$2,000.00
			Self	Other Professional Activities - Consultant	Gilead Sciences Inc		1/1/2023	10/1/2023	$2,500.00
			Self	Other Professional Activities - Consultant - Co-Chair Consultant Meetings (2), Virtual Advisory Board (1), Virtual Committee includes 2 WebEx cal	GlaxoSmithKline		7/1/2022	Ongoing / No known end date	$2,500.00
			Self	Member	HiBio		1/1/2022	Ongoing / No known end date	$5,000.00
			Self	Other Professional Activities - Consultant - Scientific Advosor Board	Lupus Foundation of America		1/1/2016	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Artiva		7/1/2023	Ongoing / No known end date	$2,000.00
			Self	Other Professional Activities - Consultant - Clinical Trial PI	LuCin		7/1/2022	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant/Advisory Board/Clinical Trial PI	Novartis		1/1/2019	Ongoing / No known end date	$2,500.00
			Self	Other Professional Activities - Consultant/Advisory Board/Clinical Trial PI	Kezar		1/1/2020	Ongoing / No known end date	$1,500.00

Mary Beth Son, MD	Core Team/Content Expert	Boston Children's Hospital	Self	Intellectual Property - Other Intellectual Property	UpToDate				$5,000.00
Victoria P. Werth, MD	Core Team/Content Expert	University of Pennsylvania	Grant to Penn	Grant / Contract	Argenx		7/4/2022	Ongoing / No known end date	$50,000.00
			Self	Other Professional Activities - Consultant	Merck		9/15/2021	Ongoing / No known end date	
			Self	Grant / Contract	Gilead Sciences (aka Gilead Foundation)	Site for lupus clinical trial	6/22/2023	Ongoing / No known end date	$60,000.00
			Self	Other Professional Activities - Consultant	Inmagene		10/6/2022	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	SANOFI US SERVICES INC.		11/1/2020	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Nuvig		4/19/2023	Ongoing / No known end date	
			Self	Grant / Contract	Celgene Corporation		2/4/2020	5/3/2023	$100,000.00
			Self	Other Professional Activities - Consultant	Bristol-Myers Squibb Company		3/12/2019	Ongoing / No known end date	Forthcoming
			University of Pennsylvania	Grant / Contract	Bristol-Myers Squibb Company	PI for iberdomide trial	6/2/2020	5/10/2023	$150,000.00
			Self	Other Professional Activities - Consultant	AstraZeneca		11/3/2020	Ongoing / No known end date	Forthcoming
			Self	Other Professional Activities - Consultant	EMD Serono		1/10/2018	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Horizon Therapeutics plc		7/30/2021	Ongoing / No known end date	Forthcoming

			Self	Other Professional Activities - Consultant	Janssen Biotech, Inc.		2/19/2015	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Manta Medicines		4/26/2023	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	AbbVie		10/2/2019	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Alpine Immune Sciences		10/5/2022	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	XENCOR		5/4/2021	Ongoing / No known end date	$450.00
			Self	Other Professional Activities - Consultant	GlaxoSmithKline		3/9/2021	Ongoing / No known end date	Forthcoming
			Self	Other Professional Activities - Consultant	Biogen, Inc.		1/7/2013	Ongoing / No known end date	Forthcoming
			Self	Other Professional Activities - Consultant	Cabaletta		1/21/2019	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Cugene		1/5/2020	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Argenx		6/18/2019	Ongoing / No known end date	
			Self	Grant / Contract	Biogen, Inc.	Trial site for Litifilimab for Cutaneous Lupus Erythematosus	5/11/2023	Ongoing / No known end date	$100,000.00

			Self	Other Professional Activities - Consultant	Amgen Inc.	$4500/hour, approved by supervisor, consulted on trial design.	9/15/2021	Ongoing / No known end date	Forthcoming
			Self	Other Professional Activities - Consultant	Lumanity		4/3/2023	Ongoing / No known end date	
			Outcome measure for CLE	Intellectual Property - Copyright		Instrument licensed for multiple lupus trials			
			Self	Other Professional Activities - Consultant	Alumis		8/2/2022	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Eli Lilly and Company		2/19/2019	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Gilead Sciences (aka Gilead Foundation)		4/19/2017	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Genentech USA, Inc.		8/21/2012	Ongoing / No known end date	Forthcoming
			Grant to Penn	Other Professional Activities - Consultant - Grant	Pfizer		6/1/2016	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Sanofi		11/3/2020	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Pfizer		4/12/2021	Ongoing / No known end date	Forthcoming
			Self	Other Professional Activities - Consultant	Kyowa Hakko Kirin		11/1/2020	Ongoing / No known end date	

Jane Kang, MD, MS	ACR Board of Directors Liaison	Columbia University Medical Center	Self	Employment - Associate Professor of Medicine, Rheumatology Fellowship Program Director	Columbia University Medical Center		10/1/2009	Ongoing / No known end date	
			Self	Other Professional Activities - Fellow	GE2P2		9/1/2020	Ongoing / No known end date	
			Self	Grant / Contract	National Institutes of Health		8/1/2019	5/31/2022	$100,000.00
			Self	Grant / Contract	Rheumatology Research Foundation		7/1/2018	6/30/2023	$180,000.00
Christie Bartels, MD, MS	Lit Review Team	University of Wisconsin	Self	Employment - Associate Professor, Division Chief	School of Medicine and Public Health, University of Wisconsin-Madison	Division Chief UW Rheumatology			
			Self	Independent Contractor - Medical Scientific Advisory Council	Lupus Foundation of America	Medical Scientific Advisory Council Member	1/1/2019	Ongoing / No known end date	$3,000.00
			Self	Co-Chair, ACR Lupus Measures Project & RHIT; Consultant	American College of Rheumatology	Contracted, with two payments of $1,000/yr, to co-chair the ACR/CDC Lupus Measures project; $2k as committee Chair 2023. Additionally, unpaid ACR committee roles with rare annual meeting travel support.			$250,000.00
Ashira D. Blazer, MD, MSCI	Lit Review Team	Hospital for Special Surgery Weill Cornell Medicine	Self	Independent Contractor - Consultant - Disparities advisory counsel	Novartis				$3,000.00
			Self	Independent Contractor - Consultant - Medical educators network	GlaxoSmithKline				$4,000.00
Maria Cuellar-Gutierrez, MD	Lit Review Team	Mayo Clinic	Nothing to disclose						

Joanne S. Cunha, MD	Lit Review Team	Warren Alpert Medical School of Brown University	Nothing to disclose						
Kimberly DeQuattro, MD	Lit Review Team	University of Pennsylvania	Self	Other Professional Activities - Sub-investigator	Kyverna	Start and End dates are estimates. Role as sub-investigator is potential as clinical trial is planned but not yet approved/started.	8/1/2023	Ongoing / No known end date	$0.00
			Self	Employment - Assistant Professor of Medicine, Division of Rheumatology	University of Pennsylvania		9/15/2021	Ongoing / No known end date	
Titilola Falasinnu, PhD	Lit Review Team	Stanford University	Nothing to disclose						
Andrea Fava, MD	Lit Review Team	Johns Hopkins University	Self	Other Professional Activities - Consultant	UCB	Consultant	9/1/2023	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	AstraZeneca	Consultant	9/1/2023	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant	Annexon Bio	Consultant	5/1/2023	5/1/2023	
			Self	Other Professional Activities - Consultant	SANOFI PASTEUR INC.	I provided expert opinion in the potential development of a novel treatment for lupus nephritis - Advisory Board (Sanofi)	4/20/2022	4/20/2022	$2,585.00
			Self	Other Professional Activities - Consultant	Lupus Foundation of America	Editorial Board	10/1/2021	Ongoing / No known end date	

			Self	Intellectual Property - Patent		No current application, no commercially available tool, no royalties, no income expected from this IP in the upcoming 3-5 years			
Gabriel Figueroa-Parra, MD	Lit Review Team	Mayo Clinic	Nothing to disclose						
Shivani Garg, MD, MS	Lit Review Team	Univerrsity of Wisconsin	Self	Intellectual Property - Copyright	HCQ-SAFE Decision Aid Tool for Clinical Use to Improve Adherence				
			Self	Grant / Contract	Foundation for the National Institutes of Health	Research career development award, renewed on annual basis. 2 years supported by the NIH and 2 years supported by UW ICTR's funds	8/1/2022	6/30/2023	$150,000.00
Lais Gomes, MD	Lit Review Team	University of Pennsylvania	Nothing to disclose						
Jessica Greco, MD	Lit Review Team	Ohio State University	Nothing to disclose						
Priyanka Iyer, MD, MPH	Lit Review Team	University of California Irvine Medical Center	Self	Independent Contractor - commitee member	Southern California Rheumatology Society		1/1/2022	Ongoing / No known end date	
Andrew S. Johannemann	Lit Review Team	Carolina Arthritis Center	Nothing to disclose						

April Jorge	Lit Review Team	Massachusetts General Hospital	Self	Grant / Contract	Bristol Myers Squibb Company	This has not yet started and the grant amount has not yet been determined, but the amount listed is the anticipated award amount per patient costs. This is an anticipated disclosure within the next 12 months.	1/27/2023	Ongoing / No known end date	$38,724.00
Shanthini Kasturi, MD, MS	Lit Review Team	Tufts Medical Center	Self	Employment - Attending Physician	Tufts Medical Center		1/1/2019	Ongoing / No known end date	
			Self	Other Professional Activities - SLE Medical Educators' Network	GlaxoSmithKline	Provide expert advice on the development of non-product related SLE disease educational materials for a physician audience as part of an educational advisory board.	3/18/2021	12/31/2023	$2,500.00
			Self	Other Professional Activities - Consultant	Voluntis		1/3/2023	12/31/2023	$1,300.00
			Self	Other Professional Activities - Ad hoc scientific reviewer	U.S. Department of Defense		10/19/2023	10/20/2023	$375.00
Hassan Kawtharany, MD	Lit Review Team	Kansas University Medical Center	Nothing to disclose			Nothing to disclose			

Kyriakos A. Kirou, MD, DSc	Lit Review Team	Hospital for Special Surgery Weill Cornell Medicine	Self	Independent Contractor - Clinical Trial	Novartis	Re: "SELUNE STUDY": "A 2 year, phase 3 randomized, double-Blind parallel group, placebo controlled trial to evaluate the safety , efficacy & tolerability of 300 mg sc secukinumab versus placebo, in combination with SOC therapy in patients with active lupus nephritis"	9/20/2022	Ongoing / No known end date	$14,550.00
			Self	Independent Contractor - Scientific Advisory Board	Aurinia Pharmaceuticals		10/15/2022	10/15/2022	$2,640.00
			Self	Independent Contractor - Clinical Trial	Amgen	re: AMG 570 Study 20170588: Phase 2 Dose Ranging Study to Evaluate Efficacy & Safety of AMG 570 in subjects with Active SLE with inadequate response to SOC therapy	1/1/2021	Ongoing / No known end date	$18,655.00
			Self	Independent Contractor - Scientific Advisory Board	AMPEL Bio Solutions LLC	hourly rate	11/12/2022	11/12/2022	$1,000.00
			Self	Independent Contractor - Clinical Trial	Lupus Therapeutics	CLINICAL TRIAL NETWORK INFRASTRUCTURE GRANT	6/1/2016	Ongoing / No known end date	$60,000.00

			Self	Independent Contractor - Clinical Trial	Novartis	Re: CYTB323G12101 study entitled "An open-label, multi-center, phase ½ study to assess safety, efficacy and cellular kinetics of YTB323 in participants with severe, refractory autoimmune disorders"	1/10/2023	Ongoing / No known end date	$0.00
			Self	Independent Contractor - Clinical Trial	UCB	Re: A Randomized placebo-controlled study to evaluate the efficacy and safety of dapirolizumab pegol in study participants with moderately to severely active systemic lupus erythematosus	5/1/2021	Ongoing / No known end date	$20,470.00
			Self	Independent Contractor - Clinical Trial	AstraZeneca	RE: A Multicenter, Randomized, Double-blind, Placebo-Controlled Phase 3 Extension Study to Characterize the Long-term Safety and Tolerability of Anifrolumab in Adult Subjects with Active Systemic Lupus Erythematosus.	8/8/2018	9/1/2022	$66,213.00

			Self	Independent Contractor - Clinical Trial	NIH Clinical Center	Re: NIAID trial ITN091AI: "A Phase 2a Randomized Placebo-Controlled Double-Blind Multicenter Trial of VIB4920 for Active Lupus Nephritis"	1/1/2022	Ongoing / No known end date	$0.00
			Self	Independent Contractor - Clinical Trial	Lupus Therapeutics	Re; A novel Phase 2 double-blind, randomized, controlled clinical trial to evaluate the efficacy of centrally acting, non-toxic ACE inhibition in cognitive impairment associated with SLE	10/1/2020	Ongoing / No known end date	$5,200.00
Alex Legge, MD. MSc	Lit Review Team	Dalhousie University	Self	Independent Contractor - CRA Guidelines Committee Member	Canadian Rheumatology Association	Member on the CRA Guidelines committee, which oversees and provides support for clinical guideline initiatives led by CRA members. I do not have any current involvement or knowledge of any CRA initiatives related to the topic of this ACR project.	7/1/2020	Ongoing / No known end date	
			Self	Independent Contractor - CRA Rheumatoid Arthritis Guidelines Panel	Canadian Rheumatology Association		7/1/2022	Ongoing / No known end date	

			Self	Independent Contractor - CRA Annual Scientific Meeting (ASM) Program Committee Member	Canadian Rheumatology Association		7/1/2020	Ongoing / No known end date	
Kelly V. Liang, MD, MS	Lit Review Team	Kansas University Medical Center	Self	Other Professional Activities - Observational Registry Study	Aurinia Pharmaceuticals	$0	8/25/2022	Ongoing / No known end date	
			Self	Other Professional Activities - Clinical Trial	Novartis	$0	1/13/2023	Ongoing / No known end date	
Kimberly P. Liang	Lit Review Team	University of Kansas Health System	Self	Other Professional Activities - Clinical Trial	Novartis	$0	1/13/2023	Ongoing / No known end date	
Megan M. Lockwood, MD	Lit Review Team	Georgetown University Hospital	Nothing to disclose						
Alain Sanchez-Rodriguez, MD	Lit Review Team	Mayo Clinic	Nothing to disclose						
Marat Turgunbaev, MD	Lit Review Team	American College of Rheumatology	Nothing to disclose						
Jessica N. Williams, MD, MPH	Lit Review Team	Emory University	Self	Independent Contractor - Research and Publications Subcommittee Member	American College of Rheumatology		10/1/2020	10/1/2023	
			Self	Employment - Assistant Professor of Medicine, Division of Rheumatology	Emory University		8/1/2021	Ongoing / No known end date	
			Self	Independent Contractor - Steering Committee Member	Lupus Research Alliance		4/29/2022	4/29/2025	$15,000.00
			Self	Grant / Contract	Genentech		1/1/2022	Ongoing / No known end date	$1,780.63
			Self	Independent Contractor - Consultant - Medical Consulting	CVS		3/17/2022	3/16/2025	$0.00
			Self	Grant / Contract	Bristol-Myers Squibb Foundation		10/15/2021	1/6/2024	$240,000.00

Anthony Alvardo, MD	Voting Panel	Kaiser Permanente	Self	Employment	Kaiser Permanente	salary physician - nephrologist	8/3/2020	Ongoing / No known end date	
			Self	Other Professional Activities - Clinical trial	Vertex Pharmaceuticals Incorporated	compensation is based on hourly rate - Clinical trial	5/1/2023	Ongoing / No known end date	
Cynthia Aranow, MD	Voting Panel	Feinstein Institutes for Medical Research	Self	Independent Contractor - Consultant	AstraZeneca	One 4 hour (meeting with preparation and follow-up @ $537/hour) unclear if this program will continue	5/26/2022	Ongoing / No known end date	$2,148.00
			Self	Independent Contractor - Advisory Committee Member	Bristol-Myers Squibb	$528/hour	8/17/2022	Ongoing / No known end date	$528.00
			Self	Grant / Contract	GlaxoSmithKline	PI of a multi-site study	12/20/2018	Ongoing / No known end date	$1,500,000.00
April Barnado, MD, MSCI	Voting Panel	Vanderbilt University	Self	Grant / Contract	National Institutes of Health	K08 career development grant to risk stratify SLE patients using electronic health record data	5/4/2018	4/30/2023	$816,882.00
			Self	Independent Contractor - Annual Planning Meeting Committee	American College of Rheumatology		2/1/2021	Ongoing / No known end date	
			Self	Independent Contractor - Committee Member	American College of Rheumatology		3/1/2021	Ongoing / No known end date	$500.00
			Self	Grant / Contract	National Institutes of Health	Principal investigator for R01 grant looking at patients with positive antinuclear antibodies	4/1/2022	2/28/2027	$2,479,962.00

Anna Broder, MD	Voting Panel	Hackensack University Medical Center	Nothing to disclose						
Hermine I. Brunner, MD, MSc, MBA	Voting Panel	University of Cincinnati	Self	Other Professional Activities - Consultant - Dr.	EMD Serono, Inc.	compensation goes to CCHMC - Dr. Brunner's employer	1/1/2015	Ongoing / No known end date	$16,430.00
			research collaboration and RCT site; also I am receiving for my NIAMS R (PLUMM Study) MMF study drug free of charge from 2023-2028	Other Professional Activities - Consultant - Dr.	Genentech	research collaboration and RCT site; also I am receiving for my NIAMS R)! (PLUMM Study) MMF study drug free of charge from 2023-2028	1/1/2008	Ongoing / No known end date	$0.00
			Self	Other Professional Activities - Consultant - Dr.	Novartis	compensation goes to CCHMC - Dr. Brunner's employer	1/1/2010	Ongoing / No known end date	$6,762.00
			Self	Other Professional Activities - Consultant - Dr.	Janssen Biotech, Inc.	compensation goes to CCHMC - Dr. Brunner's employer	5/4/2023	Ongoing / No known end date	$100,000.00
			Self	Other Professional Activities - Data And Safety Monitoring - Dr.	Johnson & Johnson Medical Devices & Diagnostics Group - Latin America, L.L.C.	compensation goes to CCHMC - Dr. Brunner's employer	3/1/2022	Ongoing / No known end date	$10,000.00
			PI	Grant / Contract	Pfizer		1/1/2017	Ongoing / No known end date	$693,592.00
			Editorial and committee work	Other Professional Activities - Associate Editor & Committee Chair	American College of Rheumatology Research and Education Foundation		1/1/2013	Ongoing / No known end date	$0.00

			Self	Other Professional Activities - Consultant - Dr.	Johnson & Johnson Medical Devices & Diagnostics Group - Latin America, L.L.C.	compensation goes to CCHMC - Dr. Brunner's employer	5/1/2023	Ongoing / No known end date	$10,000.00
			Self	Other Professional Activities - Consultant - Dr.	Eli Lilly and Company	compensation goes to CCHMC - Dr. Brunner's employer	1/1/2013	Ongoing / No known end date	
			Self	Other Professional Activities - Consultant - Dr.	Bristol-Myers Squibb		1/1/2010	Ongoing / No known end date	$64,200.00
			Self	Other Professional Activities - Consultant - Dr.	AstraZeneca	compensation goes to CCHMC - Dr. Brunner's employer	1/1/2014	Ongoing / No known end date	$27,000.00
			Self	Other Professional Activities - Dr.	Genentech	Site investigator for Obinutuzumab study in adolescents and adults with lupus nephritis compensation goes to CCHMC - Dr. Brunner's employer	4/1/2023	Ongoing / No known end date	$704.00
			Self	Other Professional Activities - Consultant - Dr.	Pfizer	compensation goes to CCHMC - Dr. Brunner's employer	1/1/2016	Ongoing / No known end date	$7,087.00
			Self	Other Professional Activities - Consultant - Dr.	Janssen Biotech, Inc.	compensation goes to CCHMC - Dr. Brunner's employer	1/1/2008	Ongoing / No known end date	$16,090.00
Benjamin Chong, MD	Voting Panel	UT Southwestern Medical Center	Self	Intellectual Property - Other Intellectual Property		The name of Intellectual Property is CLEQoL			$24,667.00
			Self	Other Professional Activities - Consultant - Adjudicator	Bristol Myers Squibb Company		7/2/2021	Ongoing / No known end date	$23,725.00
			Self	Travel	Amgen Inc.		5/6/2023	8/11/2023	$6,000.00

			Self	Other Professional Activities - Consultant	Lupus Research Alliance		3/1/2023	Ongoing / No known end date	$1,400.00
			Self	Other Professional Activities - Consultant - Steering Committee	Biogen, Inc.		9/13/2022	Ongoing / No known end date	$725.00
			Self	Other Professional Activities - Consultant	EMD Serono, Inc.		12/1/2022	12/31/2023	$300.00
			Self	Other Professional Activities - Member of Committee on Education and Programs	Medical Dermatology Society		8/1/2021	7/31/2024	
			Self	Other Professional Activities - Consultant - Adjudicator	Horizon Therapeutics plc		4/1/2023	Ongoing / No known end date	$2,500.00
Vaidehi Chowdhary, MD, MBBS, DM	Voting Panel	Yale University School of Medicine	Self	Independent Contractor - International Editor	International Journal of Rheumatic Diseases		1/1/2006	Ongoing / No known end date	
			Self	Independent Contractor - International editorial board member	Indian Journal of Rheumatology		1/1/2019	Ongoing / No known end date	
Gabriel Contreras, MD, MPH	Voting Panel	University of Miami	Self	Other Professional Activities - Data And Safety Monitoring - Chair of independent data monitoring committee	Genentech	The compensation is based on hours worked reviewing adverse events and safety reports, attending and coordinating quarterly meetings with sponsor and other members of the iDMC.	6/1/2021	Ongoing / No known end date	

			Self	Other Professional Activities - Data And Safety Monitoring - Chair of independent data monitoring committee	Genentech	The compensation is based on hours worked reviewing adverse events and safety reports, attending and coordinating quarterly meetings with sponsor and other members of the iDMC.	8/6/2020	Ongoing / No known end date	
Elizabeth D. Ferucci, MD	Voting Panel	Alaska Native Medical Center	Self	Employment- Phtsician - Rheumatologist	Alaska Native Tribal Health Consortium		10/1/2003	Ongoing / No known end date	
Keisha L. Gibson, MD, MPH	Voting Panel	University of North Carolina	Self	Independent Contractor - Consultant	Travere Therapeutics, Inc.				$1,500.00
			Self	Fiduciary Officer - Nephrology Councilor	Society of Pediatric Research				
			Self	Fiduciary Officer - Treasurer	American Society of Nephrology				
			Self	Independent Contractor - Clinical Trial--Inshore Study	Genentech				Forthcoming
			Self	Independent Contractor - Clinical Trial--Vocal Study	Aurinia Inc				Forthcoming
			Self	Employment	UNC Kidney Center				
Aimee O. Hersh, MD	Voting Panel	The University of Utah	Spouse/Partner	Fiduciary Officer	Pediatric Infectious Diseases Society - Board Member		7/1/2019	6/30/2023	

			Self	Independent Contractor - Consultant	GlaxoSmithKline - Medical Educator	The money was paid at an hourly rate, I did not participate in any public speaking events, the money was not personal compensation but was paid to our institution to support division research activities.	1/1/2022	12/31/2022	$2,000.00
			Spouse/Partner	Fiduciary Officer	Pediatric Infectious Diseases Society - Editorial Board Member		7/1/2015	Ongoing / No known end date	
Peter M. Izmirly, MD	Voting Panel	NYU Langone Health	Self	Stock	Biogen, Inc.	Our money is managed under a discretionary account by a money manager to comply with my wife's job as a corporate lawyer. We have absolutely no say on what to purchase and when to sell. The numbers provided are aggregate for my family with the earliest date purchased.	10/17/2022	Ongoing / No known divestment date	$10,081.00

			Self	Stock	Novartis Pharmaceuticals Corporation	Our money is managed under a discretionary account by a money manager to comply with my wife's job as a corporate lawyer. We have absolutely no say on what to purchase and when to sell. The numbers provided are aggregate for my family with the earliest date purchased.	7/30/2020	Ongoing / No known divestment date	$80,533.00
			Self	Stock	Amgen Inc.	Our money is managed under a discretionary account by a money manager to comply with my wife's job as a corporate lawyer. We have absolutely no say on what to purchase and when to sell. The numbers provided are aggregate for my family with the earliest date purchased.	2/3/2009	Ongoing / No known divestment date	$63,044.00

			Self	Stock	Bristol Myers Squibb Company	Our money is managed under a discretionary account by a money manager to comply with my wife's job as a corporate lawyer. We have absolutely no say on what to purchase and when to sell. The numbers provided are aggregate for my family with the earliest date purchased.	1/4/2013	Ongoing / No known divestment date	$158,512.00
			Self	Stock	Pfizer Inc.	Our money is managed under a discretionary account by a money manager to comply with my wife's job as a corporate lawyer. We have absolutely no say on what to purchase and when to sell. The numbers provided are aggregate for my family with the earliest date purchased.	4/13/2020	Ongoing / No known divestment date	$78,318.00
Kenneth Kalunian, MD	Voting Panel	University of California, San Diego	Self	Independent Contractor - Data And Safety Monitoring - Committee member	Genentech USA, Inc.		2/3/2020	Ongoing / No known end date	$1,500.00

			Self	Independent Contractor - Consultant	Biogen		1/1/2017	Ongoing / No known end date	$2,000.00
			Self	Independent Contractor - Data And Safety Monitoring - Committee member	Novartis		1/2/2023	Ongoing / No known end date	Forthcoming
			Self	Independent Contractor - Consultant	Aurinia Pharmaceuticals		2/5/2020	Ongoing / No known end date	$2,496.00
			Self	Independent Contractor - Lupus consultant	Genentech USA, Inc.		1/1/2020	Ongoing / No known end date	$1,000.00
			Self	Independent Contractor - Consultant	Idorsia		4/1/2023	Ongoing / No known end date	$3,000.00
			Self	Independent Contractor - Consultant	GlaxoSmithKline, LLC.		5/3/2021	Ongoing / No known end date	$3,200.00
			Self	Independent Contractor - Consultant	Bristol-Myers Squibb		4/8/2020	Ongoing / No known end date	$3,000.00
			Self	Independent Contractor - Consultant	RemeGen		3/8/2023	Ongoing / No known end date	$1,500.00
			Self	Independent Contractor - Consultant	AstraZeneca		4/3/2018	Ongoing / No known end date	$4,000.00
			Self	Independent Contractor - Consultant	UCB SA		2/2/2020	Ongoing / No known end date	$2,000.00
Diane Kamen, MD	Voting Panel	Medical University of South Carolina	Self	Independent Contractor - Scientific Advisory Board Member	Vera Therapeutics	One-time participation for 3 hours in an advisory board for clinical trial design input			$1,500.00

			Self	Independent Contractor - Scientific Advisory Board Member	Aurinia Pharmaceuticals	Limited to a one day meeting participation			$2,600.00
			Self	Independent Contractor - Data And Safety Monitoring - Committee member	Alpine Immune Sciences	$500 / hour for review of study data and participation in meetings			$1,500.00
			Self	Independent Contractor - Data And Safety Monitoring - Chair	Equillium	$400 / hour rate for data review and meeting attendance			$500.00
Banjamin J. Smith, DMSc, PA-C	Voting Panel	Florida State University	University	Grant / Contract	Health Resources and Services Administration		7/1/2019	Ongoing / No known end date	$3,750,000.00
			Self	Fiduciary Officer - Member, Board od Directors	National Commission on Certification of Physician Assistants		1/1/2020	Ongoing / No known end date	
			Self	Other Professional Activities - Voting Panel Member, RA, gout, and vaccine guidelines	American College of Rheumatology		1/1/2019	Ongoing / No known end date	
			Self	Employment - PD, Associate Dean, School of Physician Assistant Practice, FSU College of Medicine	Florida State University		10/3/2016	Ongoing / No known end date	
			Self	Fiduciary Officer - Member, Board of Directors	nccPA Health Foundation		1/1/2021	Ongoing / No known end date	
Asha Thomas, MD	Voting Panel	JPS Hospital	Nothing to disclose						
Homa Timlin, MD, MSc	Voting Panel	Johns Hospital University	Nothing to disclose						
Daniel J. Wallace, MD	Voting Panel	Cedars-Sinai	Self	Other Professional Activities - Consultant	AstraZeneca	unbranded talks	6/1/2022	6/15/2023	$5,000.00
Michael Ward, MD	Voting Panel	National Institutes of Health	Self	Independent Contractor - Member, Editorial board	Annals of the Rheumatic Diseases		1/1/2004	Ongoing / No known end date	

			Self	Independent Contractor - Member, editorial board	J Rheumatology		1/1/2007	Ongoing / No known end date	