Lead Authors' Response to Public Comments on the Project Plan for the American College of Rheumatology (ACR) Guideline for Treatment of Systemic Lupus Erythematosus (SLE)

April 23, 2024

Introduction:

The American College of Rheumatology (ACR) is developing guidelines for the management of patients with systemic lupus erythematosus (SLE) using GRADE methodology. In this methodology, the literature search is based on PICO (Population, Intervention, Comparator, Outcomes) questions in which the populations of interest are defined and the outcomes (benefits and harms) of interventions are compared. The project scope and PICO questions that will inform the literature search were developed by the ACR Lupus Guideline team and were posted for public comment on the ACR website in December 2023.

We appreciate the comments and suggestions submitted by the rheumatology community. Our goal is to provide guidance through formal recommendations, wherever possible. However, there are aspects of care – including some raised through the project plan public comment process – that may be difficult to address due to limitations in project scope and feasibility of the literature review. We plan to offer good practice statements (GPS) and/or specific text discussion regarding important areas that are beyond the scope of this project.

Guideline scope and methodology:

Healthcare disparities and diversity:

We are aware of and plan to address the critical issues of access to care and healthcare disparities in the text; where appropriate, we will consider good practice statements. We will include patient participants that represent the diversity of the U.S. lupus patient population and plan to include diversity in race, ethnicity, type of lupus, age (including childhood-onset), sex assigned at birth, and gender to the best of our ability, based on the patients who express interest in volunteering for the guideline work.

Breadth of guideline team experience:

We appreciate the importance of clinical and research expertise in management of SLE for guideline team participants, including experience with treatment trials and large cohorts. We have included core oversight, literature review, and voting panel members with relevant experience; further, we have striven to include participants with varied clinical experience and training, including adult and pediatric nephrologists, dermatologists, and pediatric and adult rheumatologists.

Age-limited subsets of patients with SLE:

We plan to address and include clinical issues regarding childhood-onset/juvenile SLE, whenever possible. We have two pediatric rheumatologists on the core oversight team and include

pediatric specialists on the literature review and voting panels. We decided against the creation of pediatric-specific PICOs (which drive the literature review) but plan to include pediatric-focused comments and good practice statements (GPS) throughout the guideline. Much of the current state of care for childhood-onset/juvenile SLE is informed by evidence from adult care of patients with SLE. Because children and adolescents comprise a small fraction of all SLE patients, we anticipated that the childhood-onset SLE (cSLE)-specific studies would be fewer in number with fewer participants than studies of adults, and high-quality evidence such as randomized trials would be rare. For these reasons, we decided to not make separate, age-specific formal recommendations, as age ranges and definitions of childhood-onset SLE may differ across studies and be arbitrary. Instead, we will offer special guidance for child/adolescent-specific issues (e.g., growth and development, weight-based medication dosing). Importantly, the literature search will encompass all studies of SLE (i.e., including pediatric studies), and pediatric-specific guidance will be provided, when possible. For similar reasons, although we recognize that SLE in the elderly population – including the issue of polypharmacy raised by one respondent – is an important area of lupus care, we plan to include relevant special comments and guidance in the text without adding separate PICOs.

Lupus nephritis treatment guideline:

Collaboration with other professional societies:
Formal collaboration with the American Society of Nephrology (ASN) is not currently planned. To our knowledge, ASN is not currently publishing (or preparing) formal lupus nephritis guidelines, although this may change in the future; if so, collaboration would be considered for future guideline revisions. To ensure that nephrology clinical and research experience is represented, the ACR SLE guideline team includes nephrologists on the core oversight, literature review and voting panel groups.

Terminology definitions:
We will include relevant definitions for all terminology (including refractory disease, partial renal response, and complete renal response) with text discussion regarding limitations or variations. The calculations of eGFR from creatinine in recent research (over the last 2 years) do not include coefficients for race; however, earlier literature does, and this will be acknowledged in the text discussion.

Kidney biopsy:
We plan to address important aspects of kidney biopsy in the text discussion, including limitations in access to care, as well as issues related to the quality and interpretation of the biopsy. We are only able to include discussion based on peer-reviewed and published renal classification criteria in this evidence-based document but will incorporate any published updates in future guideline revisions.

Treatment recommendations:

Respondents raised concerns regarding the inclusion of race/ethnicity in lupus nephritis Class III/IV subpopulations; comments ranged from recommending against any mention of racial/ethnic groups due to the substantial genetic, ancestry and disease heterogeneity between individuals within groups, to suggesting the addition of specific PICO questions on variation in treatment according to race. We recognize the multiple challenges posed by this topic; we've elected to keep the subpopulations as currently listed and examine available evidence, even if limited. There are ancestral populations that have not been studied to the extent of the listed groups, another concern in this area. We do not anticipate making specific guideline recommendations regarding race/ethnicity given the limitations of this construct; rather, we plan to address race/ethnicity as a special consideration in the text, since it is a common question raised by practicing rheumatologists.

Respondents also emphasized the importance of comparing a broad spectrum of therapies, including multidrug regimens. We plan to make these comparisons and have expanded the combinations in initial (induction) therapy, as suggested for the relevant PICOs. We have also clarified that, for subsequent (maintenance) therapy, this patient population includes patients who have been on initial therapy for 6 - 12 months and achieved a partial or a complete renal response. We have included clinical trials as an option for therapies for patients who do not achieve at least partial renal remission, and we plan to discuss relevant directions for future research in the text.

Other lupus-related kidney disease:
The spectrum of other lupus-related kidney disease is broad and will be addressed through relevant PICOs, text discussion, and referral to other published ACR guidelines. Severe patient populations are included as subpopulations for the class III/ IV therapy PICOs. Antiphospholipid-related kidney disease issues, including treatment and transplant issues, are addressed with relevant PICOs. Pregnancy-related questions were discussed in the ACR reproductive health guideline, and additional lupus nephritis-specific PICOs are planned for the next reproductive health guideline revision.

Adjunctive treatments and special considerations for lupus nephritis patients:
We plan a best practice discussion surrounding adjunct treatments and considerations including referral to published guidelines and resources, good practice statements, and text discussion. Topics include infection screening and vaccinations, reproductive health issues (referencing the ACR reproductive health guideline); cardiovascular health; bone health (referencing the ACR glucocorticoid-induced osteoporosis guideline); renal dosing for medications; pediatric concerns; treatment with RAAS-I and SGLT2-I medications (referencing the 2024 KDIGO lupus nephritis guideline); and use of Mesna with cyclophosphamide therapy (referencing oncology guidelines).

Monitoring lupus nephritis activity:
Respondents suggested alterations in PICOs addressing monitoring of anti-dsDNA antibodies, complement levels and proteinuria that included eliminating the PICOs and instead issuing a

good practice statement, or expanding the PICOs to include additional analytes and biomarkers such as cell-bound activation products and anti-C1q antibodies.

We agree it may be difficult to obtain clear data on anti-dsDNA antibodies and complement levels but decided to retain the current PICOs in hopes of identifying evidence to support a formal recommendation on these frequently ordered and easily available disease activity markers. Data may be limited; our goal is to provide evidence-based guidance either through a formal recommendation or a good practice statement. We acknowledge that cell bound activation products and anti-C1q antibodies are important emerging biomarkers; if these become more accessible to general rheumatologists and their patients, we would include specific PICOs in a future guideline revision.

Renal replacement therapy:
Respondent concerns surrounding kidney transplant and dialysis for patients with lupus nephritis included optimal timing to begin evaluation for and to perform kidney transplant, whether dialysis risks differ for patients with SLE vs. non-SLE end stage kidney disease (ESKD), and whether a recommendation regarding the importance of rheumatology follow up post-transplant could be supported. As rheumatologists, we generally defer to our nephrology colleagues regarding timing for transplant; we plan to discuss the critical importance of close collaboration with nephrologists in the text. Transplant outcomes may differ when transplant is done pre-emptively compared to once the patient is dialysis-dependent, and this may guide decision-making. Concern regarding outcomes of peritoneal dialysis versus hemodialysis in SLE relates to the degree of immunosuppression in patients with SLE, and the resulting potential for increased infection risk. We realize that evidence showing better outcomes in post-transplant patients with SLE who continue regular follow up with their rheumatologist in addition to their transplant team may be limited.

<u>SLE Treatment guideline:</u>

Diagnosis and monitoring in patients with SLE:
Even though the guideline scope focuses on treatment of SLE, we plan to briefly address general aspects of care for patients with SLE with good practice statements or text discussion regarding diagnosis and monitoring of SLE, benefits of early diagnosis, access to care, healthcare disparities and socioeconomic factors, variations in clinical response, and outcome measures.

Regular use of activity and damage measures are included as PICO interventions to determine whether there is published evidence that this improves outcomes. Suggested additions from respondents included a specific PICO on quality of life, as well as the inclusion of regular monitoring of patient reported outcome measures (PROMs) as an intervention. We include quality of life (as defined by specific studies) as an outcome measure in almost all therapy PICOs and so did not feel an additional PICO would add to this. We focused on validated activity and damage assessment instruments as guided by the ACR's 2023 publication on quality measures

for SLE (to be discussed in the text). We plan to refer to and discuss the recent ACR publication on PROMs for SLE (doi: 10.1002/acr.25301. Epub ahead of print. PMID: 38225171.

Corticosteroid tapering and other treatment considerations:
We will discuss tapering of steroids for patients with stable SLE, including patients who are in a state of low disease activity and/or remission. Stable SLE will also include patients who are not experiencing a disease flare and who are on maintenance therapies, including a low dose of prednisone. We will be more specific after reviewing the literature, as there will likely be various definitions used.

We have clarified definitions for immunosuppressive therapy in all PICO questions where specific agents are not listed. Immunosuppressive therapy not otherwise specified will include both conventional and biologic therapies. Monitoring and adverse effects of therapies will be summarized in the text, including retinal toxicity (ACR/American Academy of Ophthalmology guidance) and cardiac toxicity, both QTc prolongation and cardiomyopathy (ACR guidance) related to antimalarial therapy. Further, we intend to review the evidence supporting measurement of hydroxychloroquine (HCQ) levels with a specific PICO; a recommendation will be made, if appropriate.

Treatment goals will be reviewed in the text, including control of disease activity, prevention of organ damage, improvement in long-term survival, improvement in quality of life, minimizing comorbidities, minimizing corticosteroid use, and minimizing medication toxicity. Remission and low disease activity will be emphasized, and standard definitions reviewed, compared, and discussed. Guiding principles for pediatric patients will be reviewed, including importance of adherence issues and impact of corticosteroids on bone health, growth, and development, as well as psychosocial outcomes. We do not plan a separate PICO for low disease activity because we are assessing disease activity as an outcome in almost all the PICO questions, and we expect low disease activity will be captured in this way. We plan to address the important evolving concept of disease modification in the text.

Treatment by organ system:
We have included comparators we believed were appropriate for the severity of the organ manifestations addressed within the project scope, including corticosteroids and cyclophosphamide for severe manifestations. We will comment on the history of previous cyclophosphamide therapy in the text discussion. We will emphasize that decisions for treatment will be influenced by various factors, and previous cyclophosphamide may be one such factor.

Several respondents suggested the addition of PICOs to evaluate therapies for constitutional symptoms. We had included PICOs regarding constitutional symptoms in earlier versions of the project plan and agree fatigue and other constitutional symptoms are common and often debilitating for SLE patients. We removed them for two reasons: we were constrained by the limits of our literature review team and time (i.e., numbers of references we would be able to review), and, given the multifactorial nature and complexity of these symptoms, we prioritized

the more clearly inflammatory/immune-mediated aspects of SLE such as hematology manifestations, pleuritis, and others. We plan to include discussion (or GPS) related to constitutional symptoms. We will stress the importance of ruling out endocrine, infectious, malignant, psychological, and other causes for these and other symptoms that would demand alternative therapies, as well as the importance of consideration of multifactorial etiologies. As we better understand the biological mechanisms underlying these different symptoms, we hope to make formal recommendations in future guideline revisions.

Definitions for leukopenia, thrombocytopenia and hemolytic anemia will be those from EULAR/ACR classification criteria.

There was a suggestion that we include depression and suicidality as a PICO question; we did not include this due to limitations in literature review feasibility and the likelihood of multiple confounding etiologies. In addition, we elected to not consider belimumab or anifrolumab as therapy options for neuropsychiatric questions because the focus is on initial, acute management only.

Another suggestion was to add a PICO question to investigate the impact of systemic treatment interventions (e.g., HCQ, immunosuppressants, and biologics) on SLE-associated alopecia. It is true that alopecia is distressing to patients, but alopecia may be due to a variety of etiologies, including disease activity, non-lupus conditions such as androgenetic alopecia, or scarring from damage. It is difficult, at times, to determine the exact attribution of hair loss (i.e., lupus or not lupus). Cutaneous lupus therapy specifically – including the scalp – is addressed in other PICO questions.

PICOs on additional SLE manifestations including lupus myopathy and gastrointestinal manifestations were suggested. Given that these are uncommon manifestations, early PICOs on these topics were dropped due to practical limitations in the literature review process. We plan to briefly discuss these in the text.