

# 2021 DORIS definition of remission in SLE: final recommendations from an international task force

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## ABSTRACT

**Objective** To achieve consensus on a definition of remission in SLE (DORIS).

**Background** Remission is the stated goal for both patient and caregiver, but consensus on a definition of remission has been lacking. Previously, an international task force consisting of patient representatives and medical specialists published a framework for such a definition, without reaching a final recommendation.

**Methods** Several systematic literature reviews were performed and specific research questions examined in suitably chosen data sets. The findings were discussed, reformulated as recommendations and voted on.

**Results** Based on data from the literature and several SLE-specific data sets, a set of recommendations was endorsed. Ultimately, the DORIS Task Force recommended a single definition of remission in SLE, based on clinical systemic lupus erythematosus disease activity index (SLEDAI)=0, Evaluator's Global Assessment <0.5 (0–3), prednisolone 5 mg/day or less, and stable antimalarials, immunosuppressives, and biologics.

**Conclusion** The 2021 DORIS definition of remission in SLE is recommended for use in clinical care, education, and research including clinical trials and observational studies.

## INTRODUCTION

The optimal approach to treating SLE remains uncertain. An international

## Key messages

### What is already known about this subject?

- ▶ Remission is often stated as the goal for the patient with SLE.
- ▶ Consensus on a definition of remission has been lacking.
- ▶ Previously, an international task force published a framework for such a definition.

### What does this study add?

- ▶ Based on data from the literature and several specific analyses, the Definitions Of Remission In SLE (DORIS) Task Force recommended a single definition of remission in SLE, based on a widely used index (the SLEDAI), the Evaluator's Global Assessment, and allowing certain treatments.

### How might this impact on clinical practice or future developments?

- ▶ It is expected that the 2021 DORIS definition of remission in SLE will be used as an aspirational goal in clinical care, in addition to being valuable in education and research.

task force concluded that the strategy of 'Treating-to-Target (T2T)'—an approach with demonstrated efficaciousness in rheumatoid arthritis,<sup>1</sup> psoriatic arthritis<sup>2</sup> and other

diseases —would most likely be advantageous in SLE, although a formal randomised trial to prove this has not yet been done.<sup>3</sup> The first step in a T2T approach is the selection of an appropriate target, and the same T2T/SLE task force determined that the target of treatment for most patients with SLE should be remission. However, it was recognised that while the concept of ‘remission’ may seem intuitively clear, there was no widely agreed definition of remission for this disease. Therefore, the Definitions Of Remission In SLE (DORIS) Initiative was started in order to provide a framework for defining remission in SLE. The first results of this initiative were published in 2016.<sup>4</sup> Among other topics, the task force recommended a definition of remission that was based on a validated instrument for ascertaining disease activity, and supplemented with the Evaluator’s Global Assessment (EGA) of disease activity. The question whether to include the absence of serological activity in such a definition was left open. In that document, it was recommended to specify remission ‘on-treatment’: allowing some but certainly not all treatments, or ‘off-treatment’. It was also considered possible to specify the duration for which a certain remission definition would have to be maintained in order to be clinically meaningful, and this could also be applied in varying manners to specific research questions.

Since that initial report, considerable work has been performed by many clinician-scientists testing various definitions of remission in a range of settings including observational cohorts, registries and clinical trial data sets. This task force therefore continued the process of gathering information, reviewing the data, and arriving at conclusions more firmly anchored in clinical data and leading to the final recommendations for a definition of remission in SLE.

## METHODS

The DORIS Task Force was first convened in 2015 and consisted of patient representatives and specialists in rheumatology, nephrology, dermatology and clinical immunology. Following the 2016 publication of the framework for such a definition, the full task force was reconvened in 2018 and again in 2020. The steering committee met on several more occasions, and further work by the task force was done through telephone and web conferences and by email.

The task force deliberations were based on systematic literature reviews (SLRs) and specific topical analyses. Data from individual cohorts and registries were reviewed in detail to provide additional information. A typical meeting would begin with such presentations, following which the main topics for further discussion were determined. These were addressed in breakout sessions. The outcomes of these deliberations were used to generate statements that were further discussed and refined, and finally voted on. Statements were considered accepted by the task force if at least 90% of those who voted (not counting abstentions) were in favour. Statements that

achieved a majority but fell short of this bar were discussed and modified, and voted on again.

Level of evidence, strength of recommendation and agreement were determined in standard fashion, the latter by an electronic vote after finalisation of the minutes of the most recent task force meeting.

## RESULTS

### SLR on the influence of remission on health-related quality of life and on damage

The full results of the SLR on the influence of remission on health-related quality of life (HR-QoL) and on damage have been presented<sup>5</sup> and will be published elsewhere. Three studies investigated the association between being or staying in remission (by any definition) and HR-QoL and concluded that remission by any definition was associated with better HR-QoL. This was noted in particular for physical domains. Eight studies investigated the relationship between remission (by any definition) and subsequent damage and concluded that remission was associated with diminished damage accrual.

### SLR on the impact of including serology in the definition of remission

The full results of the SLR on the impact of including serology in the definition of remission will be published elsewhere. Thirty studies examined the longitudinal course of serological markers (in most cases, anti-dsDNA and C3 and C4) in relationship to clinical disease activity. Moderately strong associations were found between these markers and disease activity. Some but not all studies showed that abnormal serology and/or a change in serology predicted (imminent) flare, response to treatment or risk of later relapse. In most studies, abnormal serology was not an independent predictor of damage, late morbidity or mortality.

### Data from individual cohorts and registries

- ▶ Data from the Amsterdam cohort were reviewed (n=268). Prolonged remission was associated with reduced damage accrual.<sup>6</sup> Moreover, Patient Global Assessment (PGA) of disease activity was significantly lower for patients who were in remission by various definitions versus those not in remission. Patients in remission off-treatment had the lowest average global assessment, and remission was associated with marked improvements in short form 36 (SF-36) physical but not mental component score.<sup>7</sup>
- ▶ Data from the two Latin American cohorts GLADEL and Almenara were reviewed. The GLADEL cohort is based on 34 centres and includes 1480 patients with a median length of follow-up of 56.3 months. Data from GLADEL demonstrated that remission (based on SLEDAI and allowing treatment) protects against damage (HR for new damage 0.60, and for severe damage 0.32).<sup>8</sup> Similar results were seen when only non-glucocorticoid-related damage was analysed (HR for new damage 0.51, for severe new damage 0.31).

Furthermore, remission was independently associated with a decreased risk for subsequent hospitalisation (HR 0.46).<sup>9</sup> In Almenara, a cohort of more than 300 mostly mestizo patients from Peru, the same associations were found using the LupusQoL.<sup>10</sup> Data from Almenara also showed that remission was independently associated with decreased risk of subsequent hospitalisation (HR 0.45),<sup>11</sup> and that remission (on-treatment) prevented damage accrual (HR 0.59).<sup>12</sup>

- ▶ Data from the international multiethnic LUMINA cohort were reviewed. The LUMINA cohort includes 640 patients of African American and Hispanic (Puerto Rico) ancestry from three US centres. In LUMINA, disease activity at baseline and a higher dose of prednisone prevented patients from achieving remission or low disease activity (LDA); and having health insurance increased the probability of achieving remission/LDA.<sup>13</sup> Remission and LDA taken together was an independent negative predictor of damage,<sup>14</sup> and more time spent in remission/LDA was associated with better HR-QoL by SF-36.<sup>15</sup>
- ▶ Data from the Hopkins cohort (n=2000) demonstrated that achieving remission for even part of the time was associated with less damage accrual during follow-up. Thus, patients who achieved remission at any time—even if this was the case less than 25% of the time—had a 50% reduction of damage compared with those who never achieved it, and the more time spent in remission, the better the outcome. However, in this large cohort after a median of more than 15 years of follow-up, remission off-treatment was achieved very rarely.<sup>16</sup> These data also showed that remission protects against subsequent cardiovascular (myocardial infarction, cerebrovascular accident) or renal (end-stage renal disease) morbidity, showing a dose–response relationship. No protection was seen against pulmonary hypertension, deep venous thrombosis, malignancy, interstitial lung disease, cognitive impairment or cataracts.<sup>17</sup>
- ▶ In the Padua cohort (N=293), remission was defined based on the SLEDAI, irrespective of PGA and serology, and some treatments were allowed.<sup>18</sup> Notably, 88% of patients achieved at least 1 year of remission and 38% maintained remission for 5 years.<sup>19</sup> There was an inverse relation between duration of remission and damage. Overall, it appeared that 2 years of remission was the shortest duration of remission needed to protect fully against damage accrual. In an Italian multicentre study based on a larger cohort of patients (n=646), the performance of seven different definitions of remission was tested.<sup>20</sup> Clinical SLEDAI=0 had the best performance in terms of protection against damage compared with the other definitions including PGA  $\leq 0.5$  or prednisolone  $\leq 5$  mg/day.
- ▶ Data from the Asia-Pacific Lupus Collaboration cohort were reviewed.<sup>21</sup> In this cohort, serology did not contribute to predicting damage, but in some

definitions it did contribute to predicting the risk of flare. Remission off-treatment was seen very rarely and did not seem to be a pragmatic option. Under most definitions of remission (and LDA), damage accrual and the risk of flare were diminished. The details of each definition subtly changed the strengths of the associations.

- ▶ Data from the University College London cohort showed that 14.5% of patients with lupus achieved a complete remission for 3 years, as defined by British isles lupus assessment group (BILAG) C, D or E in all domains. However, flares were seen to occur beyond 10 years of remission (Isenberg, personal communication).

Thus, both SLRs and in-depth studies from multiple cohorts demonstrate that a state of remission by several definitions is associated with current and future favourable outcomes in multiple domains, supporting the construct validity of these definitions. These results are summarised in [table 1](#).

### Voting session

The task force achieved consensus on five general recommendations (in addition to those published previously), as well as on a final definition of remission ([box 1](#)). These statements were carried by a wide margin (>90% agreed). [Table 2](#) shows these statements, which were generated as the result of substantial reviews of the literature and data from individual registries and clinical trial data sets.

The first recommendation dealt with the inclusion of serology (anti-dsDNA, complement) in the DORIS definition of remission on-treatment. Because the preponderance of the data suggests that this does not meaningfully alter the construct validity of a definition of remission, it is not recommended to include it.

The second recommendation deals with the question of duration and the task force agreed that, while the goal of treatment is sustained remission, a definition of remission should be able to be met at any point in time, so that duration should not be included in the definition.

The third recommendation by the task force was made in observance of the fact that at this time, the SLEDAI-based definitions of remission have been investigated in research studies considerably more extensively than BILAG-based or European consensus lupus activity measure (ECLAM)-based definitions. In view of this, the SLEDAI-based definitions can more confidently be recommended.

The fourth recommendation addresses ‘remission off-treatment’, and while this is the ultimate goal for many patients and care providers, it is achieved very rarely. In clinical research and as an outcome in clinical trials, practical considerations must be weighed in, and therefore the definition for remission on-treatment is recommended.

The fifth recommendation deals with clinical trials; the task force agrees that the lupus low disease activity state (LLDAS) definition for LDA and the DORIS definition of



**Table 1** Associations of remission with various outcomes

Definition of remission	N patients	Association	Cohort (reference)
Various definitions	N/A	Better HR-QoL	3 studies SLR <sup>5</sup>
		Diminished damage accrual	8 studies SLR <sup>5</sup>
DORIS definition*	268	Better HR-QoL	Amsterdam <sup>6,7</sup>
		Diminished damage accrual	
		Lower (better) Patient Global Assessment	
DORIS definition*	1350	Diminished damage accrual	GLADEL <sup>8,9</sup>
	1308	Decreased risk for hospitalisation <sup>9</sup>	
Based on Systemic Lupus Assessment Measure=0	558	Diminished damage accrual	LUMINA <sup>13-15</sup>
	483	Better HR-QoL	
DORIS remission*	243	Better HR-QoL	Almenara Lupus Cohort <sup>10-12</sup>
	308	Decreased risk for hospitalisation	
	281	Diminished damage accrual	
DORIS remission*	2000	Better HR-QoL	Hopkins Lupus cohort <sup>16,17</sup>
		Diminished future cardiovascular and renal comorbidity	
Clinical SLEDAI=0	293	Diminished damage accrual	Padua cohort <sup>18-20</sup>
Various	2160	Diminished damage accrual	Asia-Pacific Lupus Collaboration cohort <sup>21</sup>
		Fewer flares	

\*In these instances, the definition used was based on the clinical SLEDAI; serology was disregarded and some treatments were allowed.<sup>4</sup> DORIS, Definitions Of Remission In SLE; HR-QoL, health-related quality of life; N/A, not applicable; SLEDAI, systemic lupus erythematosus disease activity index; SLR, systematic literature review.

remission on-treatment should both be used as outcomes in such studies.

## DISCUSSION

The DORIS Task Force on definition of remission in SLE, an ad hoc task force comprised of patient representatives and medical specialists with varying backgrounds, undertook a multiyear process in order to arrive at a definition of remission in SLE for use in patient care, education and research including clinical trials. This initiative resulted in a framework published several years ago and, in the current report, the final recommendations including the proposal for the 2021 DORIS definition of remission in SLE.

Multiple cohort studies done in recent years support several aspects of the validity of the proposed definition of remission. Thus, the data demonstrating that various DORIS remissions are associated with lower PGA

(Amsterdam cohort), as well as with better concurrent HR-QoL (Amsterdam, LUMINA, Almenara), support the *face validity* of DORIS remissions. Similarly, the association of DORIS remission with less damage (GLADEL, LUMINA, Hopkins, Padua, Almenara) and fewer hospital admissions (GLADEL, Almenara) supports the *construct* (or *predictive*) *validity* of this definition.

The effort of this task force was evidence based to the greatest possible degree, with SLRs and analyses of suitable data sets being the starting points for all deliberations. Nonetheless, practical considerations also applied. Thus, it was found that definitions of remission that would require the patient to be on no treatment (other than, possibly, antimalarials) would be achieved too rarely for such a definition to be meaningful in analyses, and the concern was raised that in some settings, overly zealous efforts to achieve remission off-treatment could lead to the withdrawal of needed therapies with negative consequences for the patient.

Some may feel that the proposed definition is more lenient than other definitions that were considered, and this was certainly a major discussion in the task force. It is of importance to emphasise that the task before the group was to find the definition that would be most useful to be deployed operationally to correspond with the intuitive concept of remission. Inasmuch as even the concept itself is subject to variety of interpretations (meaning that even thoughtful experts may have somewhat differing

### Box 1 The 2021 DORIS definition of remission in SLE

- ▶ Clinical SLEDAI=0.
- ▶ Physician Global Assessment <0.5 (0–3).
  - Irrespective of serology.
  - The patient may be on antimalarials, low-dose glucocorticoids (prednisolone <5 mg/day), and/or stable immunosuppressives including biologics.

**Table 2** Statements, generated as the result of substantial reviews of the literature and data from individual registries and clinical trial data sets, and supported by the DORIS Task Force

	Vote in favour	LoE	GoR	Agreement
1. Inclusion of serology (anti-DNA, complement) in the DORIS definition of remission on-treatment does not meaningfully alter the construct validity and therefore it is not recommended to include it.	90%	2a	B	8.38
2. While the goal of treatment is sustained remission, a definition of remission should be able to be met at any point in time; therefore, duration should not be included in the definition.	100%	5	C	9.02
3. To date, the SLEDAI-based definitions of remission have formally been investigated more extensively than BILAG-based or ECLAM-based definitions. The SLEDAI-based definitions can therefore more confidently be recommended.	91%	2a	B	9.25
4. Remission off-treatment, while the ultimate goal for many patients and care providers, is achieved very rarely. In clinical research and as an outcome in clinical trials, the definition for remission on-treatment is recommended.	92%	2a	B	9.52
5. In clinical trials, the LLDAS definition for low disease activity and the DORIS definition of remission are both recommended as outcomes.	100%	5	C	9.25
<b>Final recommendation:</b> <b>The task force supports the 2021 DORIS definition of remission in SLE: cSLEDAI=0 and PhGA &lt;0.5, irrespective of serology;</b> the patient may be on antimalarials, low-dose glucocorticoids (prednisolone $\leq 5$ mg/day), and/or stable immunosuppressives including biologics.	97%			9.07

Agreement=the average of individual task force members' agreements with the statement on a scale of 1–10.

Note that GoRs were not easily applied to recommendations 2 and 5; we considered these consensus statements to be 'extrapolations from level 2 or 3 studies', yielding a GoR of C.

BILAG, British isles lupus assessment group; cSLEDAI, clinical SLEDAI; DORIS, Definitions Of Remission In SLE; ECLAM, European consensus lupus activity measure; GoR, grade of recommendation; LLDAS, lupus low disease activity state; LoE, level of evidence; PhGA, Physician Global Assessment; SLEDAI, systemic lupus erythematosus disease activity index.

opinions on what remission really is), it was inevitable that both stricter and more lenient definitions were considered. The final decision was based, not solely on practical considerations, but also on considerations of validity and studies demonstrating the performance characteristics of this definition.

Similarly, the inclusion of duration in the definition of remission was discussed at great length, but would have diminished the value of the definition for various practical applications. Thus, the task force decided not to include duration in the definition itself, but to consider it a parameter that can be added to the definition based on the context. In clinical trials, most outcomes are 'landmark' outcomes that are assessed at one point in time. It is relevant that the SLEDAI assesses disease activity over the previous 30 days in most clinical trials. Moreover, a definition of remission that is agnostic to duration allows future studies examining effects of duration. For example, studies can be done to determine the minimum remission time capable of achieving outcomes such as improved HR-QoL or reduced damage. Thus, the DORIS Task Force feels that the current definition represents the best possible balance between scientific rigour and practical considerations.

Major discussions took place over the issue of whether to 'allow' any glucocorticoids in the definition, especially since some studies suggest how even low doses of

glucocorticoids have (long-term) risks (of course, the data are not fully conclusive, since residual bias in these studies cannot be excluded completely). For this very reason, many task force members expressed the same view that a remission without glucocorticoids is preferable for the patient. However, the question before the task force was not so much what the preferred state of the patient should be, but what definition would be most useful to be deployed operationally to correspond with the concept of remission. It is also relevant that in most disease areas, remission definitions do not consider treatment at all. Turning it around, the task force had to decide how much glucocorticoids would *disqualify* the patient from being in remission, and that choice was ultimately set at any dose over 5 mg daily.

The task force debated extensively whether the definition of remission should include a requirement for normal serology (ie, absence of anti-DNA antibodies and normal levels of complement). As the SLR had revealed, many studies have documented associations between these biomarkers and clinical disease activity. However, associations between these markers and later events, including subsequent flares, the response to treatment, the risk of relapse, later morbidity and mortality, were less clear, with some studies providing moderately strong evidence for and others against such a predictive property. Moreover, the studies in which abnormal serology

predicted subsequent events did not always prove that this was independent of other disease characteristics. In addition, it was recognised by the task force that methodological issues complicate matters: testing for anti-DNA can be done by various methods, each having its own set of characteristics, and abnormally low complement can result from immune activation and also from known genetic complement defects in SLE. Finally, a requirement for serological testing in ascertaining remission would create serious constraints due to cost in less privileged health-care environments.

The need for including the Physician Global Assessment (PhGA or EGA) as part of the definition was discussed at length. The main reasons to include the PhGA in the definition were twofold: (1) the SLEDAI has certain limitations ('holes') and it is conceivable that a patient would have significant activity in a domain that is not covered by the SLEDAI. Although this is a rare situation, it is important to ensure the face validity of the remission definition. (2) The patient's perspective is not explicitly included in the definition of remission. In order to do justice to the patient's perspective, it was previously decided that the physician/evaluator should include the patient's perspective in the overall assessment.

The question could be asked what additional benefit the proposed remission definition provides compared with the existing definition of LLDAS. Indeed, some studies investigated both patients who were in remission (by any definition) and those who had LDA (usually by LLDAS), and in most cases similar results were obtained. This is not surprising, as the patients in remission comprise a major subset of those who are considered to have LDA, since the LLDAS does not have a lower bound. The focus of the current task force was not to form an opinion on whether remission or LDA is a more useful target for treatment, or a better outcome for research including clinical trials. The essential defining difference between remission and LDA in the context of this task force is the face validity: the state of remission from the patient's perspective being fundamentally different from having an LDA (but not remission). Remission as a desired goal of treatment is strongly supported by patients and physicians, and is conceptually distinct from LDA. So for the state of being in remission, and accepting the premise that it is useful to have a definition for a desirable clinical state, a definition different from LLDAS is therefore needed on conceptual grounds.

In addition, it would seem that the jury is not completely out on the question whether remission is better than LDA in terms of future damage accrual and prognosis: some studies have failed to show additional benefit, but other studies have indeed suggested that, in the end, the patient is better off being in remission than 'merely' attaining LDA.

Thus, it is clear that both definitions, DORIS and LLDAS, serve unique important purposes, and the task force feels that both should be used in clinical practice and research settings including clinical trials.

In summary, a large international task force consisting of patients and specialists recommends a single definition of remission in SLE for use as an aspirational goal in clinical care, a key concept in education and an outcome in research including clinical trials.

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