



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

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SLEでは寛解の定義が定まっていませんでした。T2Tにおいても寛解がゴールであるとしながらも、寛解の定義には踏み込めなかった。

SLE寛解の定義 by DORIS 2021

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.

≦5mg/day の間違い

Clinical SLEDAI: 補体と抗DNA抗体の結果を除いたSLEDAI

van Vollenhoven RF, *et al.*
Lupus Science & Medicine 2021;8:e000538

Clinical SLEDAIの内容

活動性項目(SLEDAI)		あり	なし	不明		
中枢神経系	痙攣発作	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8点	
	精神症状	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	器質的脳症候群(意識障害を伴う精神症状)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	視力障害(眼底異常所見あり)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	脳神経障害	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	ループス頭痛	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	脳血管障害(新たな出現)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
血管炎	潰瘍・壊死など	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
筋炎、関節炎	筋炎所見	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4点	
	関節炎(2ヶ所以上)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
腎所見	尿円柱(RBC円柱 or 顆粒円柱)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4点	
	赤血球尿(RBC >5/HPF)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	蛋白尿(0.5g/d以上)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	白血球尿(WBC >5/HPF)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
皮膚	新たな紅斑	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2点	
	脱毛	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	粘膜潰瘍	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
漿膜炎	胸膜炎	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2点	
	心膜炎	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
検査所見	低補体血症(C3, C4, or CH50)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2点	
	抗DNA抗体高値(RIA法による)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
	血小板減少(10万未満)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1点	
	白血球減少(3000未満)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
発熱38°C以上	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>			
SLEDAI score					Sum of all points	

これを除いた
ものが
cSLEDAI

Discussion

どのくらいのステロイドを寛解として許容するか
(PSL 5mg/日を超えるものは駄目となった)

Serologyを含めるかどうか

PGA (physician global assessment)を入れる意義

- SLEDAIの欠点を補うため
- 患者さんの視点を反映させるため

寛解は臓器障害の抑制やQOL向上に関連



Table 1 Associations of remission with various outcomes

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

*In these instances, the definition used was based on the clinical SLEDAI; serology was disregarded and some treatments were allowed.⁴
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.

各ステートメントの同意度とエビデンスレベル

Epidemiology and outcomes

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. 血清学的活動性は寛解に含めない	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. 寛解維持期間は含めない	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. 寛解にSLEDAIを用いる (BILAGやECLAMより)	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. 治療中でも寛解としてよい	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. 治験において、LLDASと寛解いずれも用いる	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
	Final recommendation:	97%			9.07
	The task force supports the 2021 DORIS definition of remission in SLE: cSLEDAI=0 and PhGA <0.5, irrespective of serology; the patient may be on antimalarials, low-dose glucocorticoids (prednisolone ≤5 mg/day), and/or stable immunosuppressives including biologics.				

2017年のDORIS

remission

1. Definitions of remission will be worded as follows:
remission in SLE is a durable state characterised by
..... (reference to symptoms, signs, routine labs).
2. For defining remission, a validated index must be used, for example, clinical systemic lupus erythematosus disease activity index (SLEDAI)=0, British Isles lupus assessment group (BILAG) 2004 D/E only, clinical European consensus lupus outcome measure (ECLAM)=0; with routine laboratory assessments included, and supplemented with physician's global assessment.
3. Distinction is made between remission off and on therapy: *remission off therapy* requires the patient to be on no other treatment for SLE than maintenance antimalarials; and *remission on therapy* allows patients to be on stable maintenance antimalarials, low-dose corticosteroids (prednisone ≤ 5 mg/day), maintenance immunosuppressives and/or maintenance biologics.



EXTENDED REPORT

A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS)

- Validationされた活動性指標で活動性なし
例) cSLEDAI=0
BILAG2004ですべてD/E
ECLAM=0
- 血清学的検査を含んでもよい
- Physician's global assessment (PGA)<0.5

治療の有無で寛解を差別化

治療なし寛解では、HCQの治療はOK

治療あり寛解では、PSL 5mg以下、免疫抑制薬、
生物学的製剤はOK

2017年のDORIS寛解（4つの指標）

Table 1 DORIS definitions of remission

	Clinical Remission	Complete Remission	Clinical Remission on treatment	Complete Remission on treatment
cSLEDAI=0	✓	✓	✓	✓
PGA<0.5	✓	✓	✓	✓
Prednisone	0	0	≤5 mg/day	≤5 mg/day
Immunosuppressives	None	None	Allowed	Allowed
Serology negative	×	Yes	×	Yes

Serology includes anti-dsDNA and complement (C3, C4).

cSLEDAI, clinical SLEDAI; DORIS, Definitions Of Remission In SLE; PGA, physician global assessment; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Disease Activity Index.

寛解の条件 (by DORIS 2017)

Table 1 Preliminary statements on remission in SLE

Statement	% in favour
1 Remission is a desirable outcome for the patient with SLE.	100
2 Remission in SLE includes, at the very least, the absence of symptoms and signs of SLE.	100
3 Remission in SLE is <i>not</i> the same as a cure.	100
4 Remission in SLE is <i>not</i> the same as low disease activity.	93
5 Remission is a state that, if sustained, is associated with a low likelihood of adverse outcome.	100
6 'Serological activity' in SLE generally refers to the presence of anti-DNA antibodies and/or hypocomplementemia.	100
7 Treatment with antimalarials <i>does not</i> preclude the patient from being considered to be in remission.	98
8 Treatment with moderate-dose or high-dose steroids <i>does</i> preclude the patient from being considered in remission.	98

1. 寛解が目標

2. 寛解は疾患に関連した症状のないこと

3. 寛解と治癒は異なる

4. 低疾患活動性とは異なる

5. 継続するとよい結果が得られる状態

6. 血清学的活動性とは抗DNA抗体と補体

7. HCQ内服していても寛解としてよい

8. 中等度以上のPSL内服中は寛解ではない

過去のRemission定義 (general SLE)

Table 2 Validation of published definitions of disease remission against outcomes in SLE (studies with n ≥70 patients)

Author (ref.)	N	Remission definition(s)	Remission achieved (%)	Association of remission with outcomes
<i>General SLE</i>				
Drenkard <i>et al</i> ⁶	667	≥1 year of clinically inactive disease (serological activity allowed) that permitted withdrawal of all lupus drugs	23.4%	12.5-fold reduced risk for death (follow-up 11.6 ±6.0 years), after controlling for effects of renal disease and thrombocytopenia
Nossent <i>et al</i> ⁷	200	Physician judgement (not otherwise specified), assessed during the first year of disease	27.5%	Lower annual relapse rates, lower average SLEDAI, lower cumulative SDI scores at the end of 5-year follow-up
Zen <i>et al</i> ⁸	224	≥5 years complete remission with SLEDAI-2K=0 (HCQ allowed) or clinical remission with clinical SLEDAI-2K=0 (serological activity allowed) off-steroids or on low-dose steroids (HCQ/ISTs allowed)	7.1% (complete remission), 14.7% (off-steroids), 15.6% (on steroids)	Damage accrual rates (end of 5-year follow-up): 18.8% (complete remission), 18.2% (off-steroids), 37.1% (on steroids) and 51.4% (no remission)
Medina-Quñones <i>et al</i> ⁹	532	≥3 years with BILAG C, D or E, no serological activity, off-steroids, off-immunosuppressives (HCQ/NSAIDs allowed)	14.5%	Lower mortality rates (5.2% vs 13.4%; median follow-up 12 years)

過去のRemission定義 (ループス腎炎)

Lupus nephritis

Moroni et al ¹⁰	70	CRR: UPr* <0.2, normal renal function	38.5% (at last follow-up)
Mok et al ¹¹	183	CRR: UPr <0.3, normal SAlb, normal renal function, assessed at the end of first year of therapy	64%
Korbet et al ¹²	86	CRR: SCr ≤1.4 mg/dL, UPr ≤0.33, attained within 5 years of entering the study. See also refs 13, 14	43%
Illei et al ¹⁵	145	CRR: SCr <130% of the lowest level during treatment, UPr <1, inactive urine sediment, off IST (HCQ and prednisone ≤10 mg/day allowed), for ≥6 months	50.3%
Hill et al ¹⁶	71	CRR: SCr ≤123 μmol/L, UPr ≤0.33	ND
Mok et al ¹⁷	189	CRR: stabilised/improved SCr, UPr <1, improved serum C3 for ≥6 months, assessed at the end of IST	55%
Mok et al ¹⁸	268	Same as in ¹⁷	59%
Moroni et al ¹⁹	93	CRR: SCr <1.2 mg/dL, stable or 25% increase of baseline CrCl, UPr <0.2, inactive urine sediment	82% (63.4% at last follow-up)
Mak et al ²⁰	149	CRR: stabilised/improved SCr, improved serum complement, UPr <1, inactive urine sediment for ≥6 months, assessed at the end of first year of therapy	60.4%
Lee et al ²¹	77	CRR: SCr <1.2 mg/dL, UPr <0.2, inactive urinary sediment, for ≥6 months	52%
Sun et al ²²	100	CRR: UPr ≤0.4, normal urinary sediment, normal SAlb, normal SCr	58%
Ayodele et al ²³	105	CRR: stable (±25%) renal function, UPr <0.2, assessed at the end of first year of therapy	44.8%
So et al ²⁴	117	CRR: SCr ≤1.4 mg/dL, UPr ≤0.5, inactive urine sediment, assessed after 6 months of therapy	50.4%

Author (ref.)	N	Remission definition(s)	Remission achieved (%)
Fernandes das Neves et al ³⁰	105	CRR: UPr <0.2, negative anti-double stranded DNA antibodies, normal C3 and normal SCr, for ≥5 consecutive years	38.1%
Koo et al ³¹	193	CRR: UPr <0.3, for ≥6 months	42.5%
Dall'Era et al ³²	76	Different sets of response criteria based on a range of cut-offs of UPr, SCr and RBCs at 3, 6 and 12 months. Best criterion was UPr <0.8 at 12 months	59.2%
Tamirou et al ³³	104	Different sets of CR criteria based on levels of UPr, SCr and urinary RBCs at 3, 6 and 12 months. Best criterion was UPr ≤0.5 at 12 months	49.0%
Tamirou et al ³⁴	80	Subgroup analysis of ³³ Different sets of response criteria based on a range of cut-offs of UPr, SCr and RBCs at 3, 6 and 12 months. Best criterion was UPr <0.7 at 12 months	63.8%
Reich et al ²⁵	98	CRR: SCr ≤120 mmol/L (1.4 mg/dL), UPr <0.3	74.5%
Alsuwaida et al ²⁶	77	CRR: SCr ≤125 μmol/L, UPr ≤0.33	41.6%
Dhir et al ²⁷	188	UPr reduction by ≥50% to <2, inactive urine sediment, normal SCr (≤1.5 mg/dL), assessed at the end of first year	54.6%†
Moroni et al ²⁸	103	CRR: SCr <1.2 mg/dL, stable or 25% increase of baseline CrCl, UPr <0.2, inactive urine sediment	70.9%
Mahmoud et al ²⁹	135	CRR: SCr ≤1.2 mg/dL, and 25% increase of baseline CrCl if abnormal, or stable value if abnormal at baseline, UPr <0.2, inactive urine sediment	59.3%

低疾患活動性の定義 (LLDASが現実的?)

Clinical and epidemiological research

EXTENDED REPORT

Definition and initial validation of a Lupus Low Disease Activity State (LLDAS)

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LLDAS

1. SLEDAI-2K \leq 4 (かつ重要臓器に活動性なし)
2. 新たな活動性所見がないこと
3. PGA \leq 1 (0-3 scale)
4. PSL \leq 7.5mg/日
5. 免疫抑制薬、生物学的製剤はOK

Table 1 LLDAS definition

Domain and items	Mean agreement score* in Delphi Round 2
<i>Disease activity</i>	
1. SLEDAI-2K \leq 4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no haemolytic anaemia or gastrointestinal activity	5.0
2. No new features of lupus disease activity compared with the previous assessment	4.7
3. SELENA-SLEDAI physician global assessment (PGA, scale 0-3) \leq 1	4.8
<i>Immunosuppressive medications</i>	
4. Current prednisolone (or equivalent) dose \leq 7.5 mg daily	4.5
5. Well tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs	4.5

*Scale 1 to 5, where 1=strongly disagree, 2=disagree, 3=unsure, 4=agree, 5=strongly agree.

CNS, central nervous system; LLDAS, Lupus Low Disease Activity State; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.