

## A framework for remission in SLE:

van Vollenhoven, Ronald F.; Gordon, Caroline

DOI:

[10.1136/annrheumdis-2016-209519](https://doi.org/10.1136/annrheumdis-2016-209519)

License:

None: All rights reserved

*Document Version*

Peer reviewed version

*Citation for published version (Harvard):*

van Vollenhoven, RF & Gordon, C 2017, 'A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS)', *Annals of the Rheumatic Diseases*, vol. 76, no. 3, pp. 554-561. <https://doi.org/10.1136/annrheumdis-2016-209519>

[Link to publication on Research at Birmingham portal](#)

### **Publisher Rights Statement:**

van Vollenhoven R, Voskuyl A, Bertsias G, et al A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS) *Annals of the Rheumatic Diseases* 2017;76:554-561.

Final Version of Record available at: <http://dx.doi.org/10.1136/annrheumdis-2016-209519>

Checked 13/12/2016, 9/1/2017

### **General rights**

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

### **Take down policy**

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.

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

The Definition of Remission in SLE (DORIS) task force

## **Corresponding author:**

Ronald van Vollenhoven  
Amsterdam Rheumatology and immunology Center ARC  
Amsterdam, Netherlands  
r.f.vanvollenhoven@amc.uva.nl

## **Authors:**

Ronald van Vollenhoven<sup>1,2</sup>, Alexandre Voskuijl<sup>2</sup>, George Bertias<sup>3</sup>, Cynthia Aranow<sup>4</sup>, Martin Aringer<sup>5</sup>, Laurent Arnaud<sup>1</sup>, Anca Askanase<sup>6</sup>, Petra Balážová<sup>7</sup>, Eloisa Bonfa<sup>8</sup>, Hendrika Bootsma<sup>9</sup>, Dimitrios T Boumpas<sup>10</sup>, Ian N Bruce<sup>11</sup>, Ricard Cervera<sup>12</sup>, Ann Clarke<sup>13</sup>, Cindy Coney<sup>14</sup>, Nathalie Costedoat-Chalumeau<sup>15</sup>, László Czirják<sup>16</sup>, Ronald Derksen<sup>17</sup>, Andrea Doria<sup>18</sup>, Thomas Dörner<sup>19</sup>, Rebecca Fischer-Betz<sup>20</sup>, Ruth Fritsch-Stork<sup>17</sup>, Caroline Gordon<sup>21</sup>, Winfried Graninger<sup>22</sup>, Noémi Györi<sup>1</sup>, Frédéric Houssiau<sup>23</sup>, David Isenberg<sup>24</sup>, Soren Jacobsen<sup>25</sup>, David Jayne<sup>26</sup>, Annegret Kuhn<sup>27</sup>, Veronique Le Guern<sup>15</sup>, Kirsten Lerstrøm<sup>28</sup>, Roger A. Levy<sup>29</sup>, Francinne Machado-Ribeiro<sup>29</sup>, Xavier Mariette<sup>30</sup>, Jamil Missaykeh<sup>31</sup>, Eric Morand<sup>32</sup>, Marta Mosca<sup>33</sup>, Murat Inanc<sup>34</sup>, Sandra Navarra<sup>35</sup>, Irmgard Neumann<sup>36</sup>, Marzena Olesinska<sup>37</sup>, Michelle Petri<sup>38</sup>, Anisur Rahman<sup>24</sup>, Ole Petter Rekvig<sup>39</sup>, Jozef Rovensky<sup>40</sup>, Yehuda Shoenfeld<sup>41</sup>, Josef S. Smolen<sup>42</sup>, Angela Tincani<sup>43</sup>, Murray Urowitz<sup>44</sup>, Bernadette van Leeuw<sup>28</sup>, Carlos Vasconcelos<sup>45</sup>, Victoria P. Werth<sup>46</sup>, Anne Voss<sup>47</sup>, Helena Zakharova<sup>48</sup>, Asad Zoma<sup>49</sup>, Matthias Schneider<sup>20</sup>, Michael Ward<sup>50</sup>.

## **Affiliations**

<sup>1</sup>Karolinska Institutet, Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), D1:00 Karolinska University Hospital, Solna, 171 76 Stockholm, Sweden.

<sup>2</sup> Amsterdam Rheumatology and Immunology Center, VU University Medical Center, Amsterdam, The Netherlands

<sup>3</sup> Rheumatology, Clinical Immunology and Allergy, University of Crete School of Medicine, 2209 Iraklion, Greece

<sup>4</sup> Feinstein Institute for Medical Research, Manhasset, New York, USA

<sup>5</sup> Department of Medicine III, University Medical Center TU Dresden, Dresden, Germany

- <sup>6</sup> New York University, New York, USA.
- <sup>7</sup> LPre SR - Klub Motýlik, Bratislava, Slovakia.
- <sup>8</sup> Rheumatology Division, Faculdade de Medicina da Universidade de São Paulo, Brazil.
- <sup>9</sup> Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands.
- <sup>10</sup> Department of Medicine and Joint Academic Rheumatology Program Medical School, National and Kapodestrian University of Athens, Greece.
- <sup>11</sup> NIHR Manchester Biomedical Research Unit, The University of Manchester and Central Manchester Foundation Trust, Manchester, UK.
- <sup>12</sup> Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Catalonia, Spain.
- <sup>13</sup> Division of Rheumatology The Arthritis Society Chair in Rheumatic Diseases Cumming School of Medicine University of Calgary, Calgary, Alberta, Canada
- <sup>14</sup> Lupus Foundation of America, 2000 L Street, NW, Suite 410, Washington, DC, 20036, USA
- <sup>15</sup> Université Paris-Decartes, Paris, France; AP-HP, Hôpital Cochin, service de médecine interne, centre de référence maladies auto-immunes et systémiques rares, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France
- <sup>16</sup> Institute of Bioanalysis, Institute of Family Medicine, Department of Rheumatology and Immunology, University of Pécs, Pécs and Third Department of Internal Medicine, Semmelweis University, Budapest, Hungary.
- <sup>17</sup> University Medical Center, Dpt. Rheumatology and Clinical Immunology, Heidelberglaan 100, 3584CX Utrecht, The Netherlands.
- <sup>18</sup> Rheumatology Unit, Department of Medicine, University of Padova, Italy.
- <sup>19</sup> Department Medicine/Rheumatology and Clinical Immunology, Charite Universitätsmedizin Berlin, Chariteplatz 01, 10117 Berlin, Germany.
- <sup>20</sup> Policlinic of Rheumatology, Hiller Research Unit, University Clinic Duesseldorf, Heinrich-Heine-University, Germany.
- <sup>21</sup> Rheumatology Research Group, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK.
- <sup>22</sup> Division of Rheumatology, Medical University of Graz, Graz, Austria.
- <sup>23</sup> Service de Rhumatologie, Cliniques universitaires Saint-Luc, Pôle de pathologies rhumatismales inflammatoires et systémiques, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Bruxelles, Belgium.
- <sup>24</sup> The Centre for Rheumatology, Department of Medicine, University College London, UK

- <sup>25</sup> Copenhagen Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Rigshospitalet, DK-2100 Copenhagen, Denmark
- <sup>26</sup> Department of Medicine, University of Cambridge, Cambridge, UK
- <sup>27</sup> Interdisciplinary Center for Clinical Trials (IZKS), University Medical Center Mainz, Mainz, Germany.
- <sup>28</sup> LUPUS EUROPE, co-opted trustee for research, St James House 27-43 Eastern Road Romford, Essex RM1 3NH, UK
- <sup>29</sup> Rheumatology Department at Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Brazil
- <sup>30</sup> Université Paris-Sud; Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris-sud; INSERM U1184, Le Kremlin Bicêtre, France
- <sup>31</sup> Bone Densitometry Unit, Monla Hospital, Tripoli, Lebanon.
- <sup>32</sup> Monash University Faculty of Medicine, Nursing & Health Sciences, Level 3, Block E, Monash Medical Centre, 246 Clayton Road, Clayton VIC 3168, Australia.
- <sup>33</sup> Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy
- <sup>34</sup> Istanbul University, Istanbul Medical Faculty, Department of Internal Medicine, Division of Rheumatology, Capa, Istanbul, Turkey.
- <sup>35</sup> University of Santo Tomas, Manila, Philippines.
- <sup>36</sup> Vasculitis.at, Vienna, Austria
- <sup>37</sup> Department of Connective Tissues Diseases, National Institute of Geriatrics, Rheumatology and Rehabilitation, Warsaw, Poland.
- <sup>38</sup> Johns Hopkins University School of Medicine, Baltimore, USA
- <sup>39</sup> RNA and Molecular Pathology Research Group, Institute of Medical Biology, Health Science Faculty, University of Tromsø, Norway
- <sup>40</sup> National Institute for Rheumatic Diseases, 92101 Piešťany, Slovak Republic.
- <sup>41</sup> Zabłudowicz Center for Autoimmune Diseases, Sheba Medical Center (Affiliated to Tel-Aviv University) Tel-Hashomer 5265601, Israel
- <sup>42</sup> Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, and 2<sup>nd</sup> Department of Medicine, Hietzing Hospital, Vienna, Austria.
- <sup>43</sup> Dipartimento di Scienze Cliniche e Sperimentali, Università degli Studi di Brescia, U.O. Reumatologia e Immunologia Clinica, Spedali Civili di Brescia, Brescia, Italy
- <sup>44</sup> Centre for Prognosis Studies in the Rheumatic Diseases, Senior Scientist Krembil Research Institute, Professor Medicine, University of Toronto, Toronto Western Hospital EW 1-409, Toronto, ON M5T 2S8, Canada

<sup>45</sup> Unidade de Imunologia Clínica, Hospital Santo António, Centro Hospitalar do Porto, UMIB, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal.

<sup>46</sup> Corporal Michael J. Crescenz VA Medical Center (Philadelphia), Philadelphia, Philadelphia, USA. Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, USA

<sup>47</sup> Department of Rheumatology, Odense University Hospital, University of Southern Denmark, Denmark.

<sup>48</sup> Nephrology Unit, City Clinical Hospital n.a. S.P. Botkin, Moscow, Russia.

<sup>49</sup> Lanarkshire Centre for Rheumatology, Hairmyres Hospital, East Kilbride G75 8RG, Scotland, UK

<sup>50</sup> National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, USA

**Keywords:** systemic lupus erythematosus, systematic review, consensus, remission, disease activity

**Word count:** 3679

## **Abstract**

**Objectives.** Treat-to-target recommendations have identified ‘remission’ as a target in systemic lupus erythematosus (SLE) but recognize that there is no universally accepted definition for this. Therefore, we initiated a process to achieve consensus on potential definitions for remission in SLE.

**Methods.** An international task force of sixty specialists and patient representatives participated in preparatory exercises, a face-to-face meeting, and follow-up electronic voting. The level for agreement was set at 90%.

### **Results.**

The task force agreed on eight key statements regarding remission in SLE and three principles to guide the further development of remission definitions:

1. Definitions of remission will be worded as follows: *Remission in SLE is a durable state characterized by .....* (reference to symptoms, signs, routine labs).
2. For defining remission a validated index must be used, e.g., clinical-SLEDAI = 0, BILAG2004 D/E only, clinical ECLAM =0; with routine laboratory assessments included, and supplemented with Physician 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  $\leq 5$  mg/d), maintenance immunosuppressives and/or maintenance biologics.

The task force also agreed that the most appropriate outcomes (dependent variables) for testing the prognostic value (construct validity) of potential remission definitions are: Death, Damage, Flares, and measures of Health-related quality of life.

**Conclusion.** The work of this international task force provides a framework for testing different definitions of remission against longer-term outcomes.

## **Introduction**

Outcomes in systemic lupus erythematosus (SLE) have improved considerably over the past decades. For the most widely studied specific organ involvement in SLE, lupus nephritis, results from clinical trial follow-up studies demonstrate that the long-term renal survival in this condition has now improved to greater than 90%.[1] However, not all outcomes in SLE show the same favorable trends. Most notably the overall health-related quality of life (HR-QoL) for patients with SLE remains reduced.[2]. This and other considerations prompted the initiation of the Treat-to-Target for SLE (T2T/SLE), initiative which over the past several years established an international consensus on the approach to the therapy of SLE based on 1) identifying an appropriate target for each patient; 2) initiating treatment steps to try to achieve this target; 3) assessing the target; and 4) adjusting the therapeutic approach, if necessary. These elaborations led to the T2T/SLE recommendations published in 2014.[3] One of the most significant targets in SLE was identified as “remission of systemic symptoms and organ manifestations”. However, it was recognized by the panel that no generally accepted definition of remission in SLE exists today. Such a definition could be important for basic, clinical and epidemiological studies and clinical trials in lupus, but also for clinical practice. The literature on this topic demonstrates that many clinical trials and observational studies have used a large number of different *ad hoc* definitions of remission; many of these were reviewed in a recent study.[4] Consequently, the T2T/SLE panel identified the definition of remission as a research priority for SLE. In response, an initiative was undertaken in order to achieve consensus in a large multiparty international task force on potential definitions of remission in SLE (DORIS).

## **Methods**

An international task force consisting of rheumatologists, nephrologists, dermatologists, clinical immunologists and patient representatives, totaling 60 individuals, was convened. In March 2014, a

preliminary meeting was held by a steering committee consisting of 15 of these representatives. The steering committee identified four domains critical to further development of remission definitions; ten preliminary statements regarding remission that were felt to be uncontroversial; key controversies; and a set of proposed topics for further discussion. During the following 4-month period, the ten preliminary statements were presented to the full task force electronically, deliberated upon by email, and then subjected to formal electronic voting. High-level agreement was readily achieved for eight of these, whereas two were placed on the agenda for the subsequent consensus conference. Moreover, an additional number of key topics were identified during these deliberations that were to be dealt with more thoroughly at the face-to-face meeting.

In August 2014, a consensus conference took place where a large majority of the full task force was present. The explicit goal of this consensus conference was to establish guiding principles for working towards a definition of remission in SLE and to formulate proposed definitions that would be amenable to scientific testing. During this meeting, formal votes were taken on a range of points. The level for agreement was set at >90%.

The procedure was informed by the results of the systematic literature review that was carried out in the context of the ‘Treat-to-target in SLE’ project [3] and was modified and updated in September 2015. We focused on two of the twelve original topics of interest that were more relevant to the present study, namely topic #2 (“*Have any definitions for low disease activity and remission, -both global and organ-specific-, been validated as surrogates of therapeutic success against damage accrual, mortality, and QoL in SLE?*”) and topic #5 (“*Is sustained reduction of disease activity or prevention of flares, -both general and organ-specific-, an achievable goal in SLE?*”).[3] The literature search was repeated in September 2015 by author GB to include more recently published literature. The PubMed database was searched using index terms and all English-language human studies were evaluated based on the title, abstract and/or full-text. For the purpose of the present

study, we report on the systematic literature review results relevant to remission only, which were published since the year 1990 and included  $\geq 70$  SLE patients.

## Results

Domains considered critical for defining remission in SLE. Four domains critical for defining remission in SLE were identified: clinical disease activity, serological activity, duration, and treatment. Within each of these domains a number of key issues were identified and these form the basis of the work described here.

### Preliminary statements on remission in SLE.

Ten statements, considered highly relevant for developing a definition of remission and expected to be uncontroversial, were prepared by the steering committee and subjected to electronic voting by the task force. Eight of these statements readily achieved a high level of consensus ( $>90\%$ ) and are shown in **table 1**.

	<b>Statement</b>	<b>% in favor</b>
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 <u>not</u> the same as a cure.	100%
4	Remission in SLE is <u>not</u> 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	100%

	anti-DNA antibodies and/or hypocomplementemia.	
7	Treatment with antimalarials <u>does not</u> preclude the patient from being considered to be in remission.	98%
8	Treatment with moderate- or high-dose steroids <u>does</u> preclude the patient from being considered in remission.	98%

Table 1. Preliminary statements on remission in SLE. Out of ten statements selected by the steering committee, eight achieved >90% agreement on electronic voting by the entire task force. Two statements (“A definition of remission SLE must be reasonably consistent with the use of this term in the literature” and “Durability in time can be added to any definition of remission in order to define a ‘durable remission’ but need not be included in the definition of remission itself”) did not achieve consensus and were discussed further at the face-to-face meeting.

Therefore, remission is identified as a desirable outcome for patients with SLE with, -at the very least-, the absence of major symptoms and signs of SLE. Remission is conceived of in terms different from a cure, yet it is also regarded as meaningfully different from a low disease activity state, including the lupus low disease activity state (LLDAS) that has recently been proposed by the Asia-Pacific Lupus Collaboration.[5] Perhaps most critically for future work in this area, it is recognized that remission, like LLDAS, has to be a state that, if sustained, is associated with a low likelihood of adverse outcome. To this end, the systematic literature review identified a number of observational studies in patients with lupus nephritis, which illustrate that attainment of (complete) *renal remission* (or response) (typically defined as a very low level of proteinuria, with normal or stable renal function, with or without inactive urine sediment) is associated with favorable long-term patient and renal outcomes (**Table 2**). Similarly, in general SLE, three retrospective cohort studies

have suggested that patients who achieve disease remission have significantly lower rates of damage accrual or mortality after follow-up.

Author (ref.)	N	Remission definition(s)	Remission achieved (%)	Association of remission with outcomes
<i>General SLE</i>				
Drenkard [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 [7]	200	Physician judgment (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 [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- Quiñones [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)

### *Lupus nephritis*

Moroni [10]	70	CRR: UPr* <0.2, normal renal function	38.5% (at last follow-up)	CRR was associated with fewer renal flares, better outcome of renal flares
Mok [11]	183	CRR: UPr <0.3, normal SAlb, normal renal function, assessed at the end of first year of therapy	64%	Lack of CRR was associated (RR 9.9) with development of ESRD (mean follow-up 181 months)
Korbet [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%	CRR was associated with reduced risk of progression to ESRD (HR 0.12), increased rates of patient survival at 5 and 10 years (follow-up 120 ± 65 months)
Illei [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%	Lack of CRR was associated with increased risk for severe nephritic flare (LR 5.7) and progression to ESRD (LR 7.0) (median follow-up 116 to 123 months)
Hill [16]	71	CRR: SCr ≤123 μmol/L, UPr ≤0.33	N/D	Lack of CRR was associated with decreased 10-year survival rates from doubling of SCr
Mok [17]	189	CRR: stabilized/improved SCr, UPr <1, improved	55%	Lack of CRR was associated with increased risk (HR

		serum C3 for $\geq 6$ months, assessed at the end of IST		4.5) for development of ESRD (mean follow-up 96.5 months)
Mok [18]	268	Same as in [17]	59%	Lack of CRR was associated with increased risk (HR 4.5) for adverse outcome (doubling of SCr or ESRD or patient death)
Moroni [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)	Lack of CRR was associated (RR 4.3) with development of chronic renal insufficiency (median follow-up 181 months)
Mak [20]	149	CRR: stabilized/improved SCr, improved serum complement, UPr <1, inactive urine sediment for $\geq 6$ months, assessed at the end of first year of therapy	60.4%	Lack of CRR was associated with renal damage (mean follow-up 80 months)
Lee [21]	77	CRR: SCr <1.2 mg/dl, UPr <0.2, inactive urinary sediment, for $\geq 6$ months	52%	Lack of CRR was associated with development of chronic renal insufficiency and/or death (follow-up $8.3 \pm 4.4$ years)
Sun [22]	100	CRR: UPr $\leq 0.4$ , normal urinary sediment, normal SAlb, normal SCr	58%	Lack of CRR was associated with ESRD (median follow-up 60 months)
Ayodele	105	CRR: stable [ $\pm 25\%$ ] renal function, UPr <0.2,	44.8%	CRR was associated with higher mean survival time

[23]		assessed at the end of first year of therapy		
So [24]	117	CRR: SCr $\leq$ 1.4 mg/dl, UPr $\leq$ 0.5, inactive urine sediment, assessed after 6 months of therapy	50.4%	CRR was associated with reduced risk for subsequent renal flares and chronic renal failure (mean follow-up 66–76 months)
Reich [25]	98	CRR: SCr $\leq$ 120 mmol/l (1.4 mg/dl), UPr $<$ 0.3	74.5%	Lack of CRR was associated with faster GFR decline (follow-up $12.4 \pm 8.4$ years)
Alsuwaida [26]	77	CRR: SCr $\leq$ 125 $\mu$ mol/L, UPr $\leq$ 0.33	41.6%	CRR was associated with higher renal survival rate at 10 years. Lower risk for doubling of SCr
Dhir [27]	188	UPr reduction by $\geq$ 50% to $<$ 2, inactive urine sediment, normal SCr ( $\leq$ 1.5 mg/dl), assessed at the end of first year	54.6% <sup>§</sup>	Lack of remission was associated (HR 13.8) with chronic renal failure or death (median follow-up 6 years)
Moroni [28]	103	CRR: SCr $<$ 1.2 mg/dL, stable or 25% increase of baseline CrCl, UPr $<$ 0.2, inactive urine sediment	70.9%	CRR was associated with good renal outcome (no chronic renal insufficiency) (follow-up $156 \pm 105$ months)
Mahmoud [29]	135	CRR: SCr $\leq$ 1.2 mg/dl, and 25% increase of baseline CrCl if abnormal, or stable value if abnormal at	59.3%	Lack of CRR in the first year was associated with adverse outcome (death, ESRD or doubling of SCr)

		baseline, UPr <0.2, inactive urine sediment		
Fernandes das Neves [30]	105	CRR: UPr <0.2, negative anti-dsDNA antibodies, normal C3, and normal SCr, for ≥5 consecutive years	38.1%	CRR was associated with preservation of normal renal function (80% vs. 43%) and reduced mortality (0% vs. 22%) compared to partial/no remission group (follow-up 13.7 ± 14.1 years)
Koo [31]	193	CRR: UPr <0.3, for ≥6 months	42.5%	CRR was associated with reduced risk of mortality and ESRD (follow-up 158 ± 70 months)
Dall’Era [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%	Sensitivity 81% and specificity 78% for favorable long-term (7 years) renal outcome (SCr ≤1.0 mg/dl). The LUNAR study remission criterion (UPr ≤0.5, SCr ±15% of baseline, inactive urine sediment) had 32% sensitivity, 91% specificity
Tamirou [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%	Positive predictive value 92% for achieving good long-term renal outcome (SCr ≤120% of baseline value) after median 110 months
Tamirou [34]	80	Subgroup analysis of [33]. Different sets of response criteria based on a range of cut-offs of	63.8%	Sensitivity 71% and specificity 75% for favorable long-term (7 years) renal outcome (SCr ≤1.0 mg/dl).

UPr, SCr, and RBCs at 3, 6, and 12 months. Best  
criterion was UPr <0.7 at 12 months

---

Table 2. Validation of published definitions of disease remission against outcomes in SLE (studies with  $n \geq 70$  patients).

\* Proteinuria (UPr) assessed by 24-hr urine collection and/or urine protein-to-creatinine ratio

§  $n = 71$  out of 130 with available records

Abbreviations: CRR, complete renal remission (or response); UPr, proteinuria; SCr, serum creatinine; GFR, glomerular filtration rate; CrCl, creatinine clearance; RBCs, red blood cells; HR, hazard ratio; ESRD, end-stage renal disease; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index SLICC group damage index; SAlb, serum albumin; IST, immunosuppressive treatment; HCQ, hydroxychloroquine; N/D, not described.

Specific agreement was also achieved on the definition of “serological activity” where it was agreed that there was sufficient support in the literature pertaining to the presence of anti-DNA antibodies and/or hypocomplementemia (defined as above or below the upper limit of normal value for the local laboratory, respectively), but without reference to other autoantibodies. The task force discussed whether definitions of remission should distinguish patients who are serologically active from those who are serologically inactive, as the former are much more likely to experience subsequent flare.[4, 9] No consensus was reached on that statement and the task force suggested to test each of the clinical criteria with and without serology, in order to determine the usefulness of the latter and whether it adds to the construct validity of each definition.

Finally, there was consensus in the task force that treatment with anti-malarials does not preclude the patient from being considered to be in remission, even though it is somewhat paradoxical to say “off-treatment” when someone is, in fact, taking a medication. However, this step was strongly supported by the task force in respect of the widely-held view that anti-malarials are often considered long-term maintenance therapy for patients with SLE even if they have achieved remission. Benefits of such treatment are believed to extend beyond flare prevention and disease control, and it was therefore felt incorrect to imply that these medication should be discontinued. The task force does recognize that antimalarials have immunomodulatory effects, and that therefore studies done on patients in remission “off treatment” (by the above definition) may in some instances have to distinguish clearly between those patients who are and who are not taking antimalarials. This would perhaps seem most important for studies of an immunological or pathophysiological nature. A similar arguments does of course also apply to medications that do not fall in the above categories but that have or may have immunomodulatory properties, such as statins and vitamin D.

It was also agreed upon by all that patients who are treated with moderate- or high-dose glucocorticoids cannot be considered to be in remission, even if they would fulfill other criteria for

remission. The main argument for this is the well-established adverse health consequence of long-term moderate- to high-dose glucocorticoid treatment.

Two statements were felt to be uncontroversial by the steering committee but did not achieve >90% agreement in the larger task force. One of these, “A definition of remission in SLE must be reasonably consistent with the use of this term in the literature” was intended by the steering committee as indicating that a definition of remission must be aligned with what historically has been considered to be a remission. However, this statement was felt to be a bit too circular by some, given that the literature is divided on the definition of remission.

The statement “Durability in time can be added to any definition of remission in order to define a ‘durable remission’ – but need not be included in the definition of remission itself.” achieved 86% agreement by pre-meeting electronic voting. Notably, although a few of the published definitions included in Table 2 have incorporated a “duration” component (ranging from 6 months to 5 years), the majority to the studies has not examined the prognostic importance of duration of remission against long-term patient outcomes. When discussed face-to-face by the full task force, an increasing number of delegates were unable to support this statement. After discussion, the vote was 65% in favor – not sufficient to declare consensus. The main arguments for and against this statement, as they were discussed during the meeting, are given in **Table 3**:

<b>In favor of the original statement</b>	<b>Against the original statement</b>
(i.e., the definition of remission does <i>not</i> have to include the duration)	(i.e., the definition of remission <i>does</i> have to include the duration)
<ul style="list-style-type: none"> <li>Definitions of remission in other autoimmune diseases, including</li> </ul>	<ul style="list-style-type: none"> <li>As SLE can be remitting-relapsing,[37] for a patient to be in remission at one</li> </ul>

rheumatoid arthritis [35] and Crohn's disease,[36] do not include durability	specific point in time may not be clinically relevant
<ul style="list-style-type: none"> <li>• Including durability in the definition itself would severely limit the use of the definition as an outcome in clinical trials</li> <li>• Duration can always be added to the analyses in which the definition is used</li> </ul>	<ul style="list-style-type: none"> <li>• Remission for only a short period of time has little relevance in SLE</li> </ul>

Table 3. Arguments for and against the statement “Durability in time can be added to any definition of remission in order to define a ‘durable remission’ but need not be included in the definition of remission itself.”

The framework for a definition.

The task force discussed what form a definition of remission in SLE should take. A literature search on this topic identified many observational studies and clinical trials that used a large number of different *ad hoc* definitions of remission in general SLE (Appendix Table 1) and in lupus nephritis (Appendix Table 2). After extensively reviewing various options, and with particular attention to the discussion described above regarding duration, the following three key principles were agreed upon (summarized in **Table 4**):

<b>Key principles for defining remission in SLE</b>		<b>Agreement</b>
1.	• Definitions of remission in SLE will be worded as follows: <i>Remission</i>	93%

	<p><i>in SLE is a durable state characterized by .....</i></p> <p>(reference to symptoms, signs, routine labs)</p> <ul style="list-style-type: none"> <li>○ Requirement for serology may be added</li> </ul>	(2 abstained)
2.	<ul style="list-style-type: none"> <li>● For defining remission in SLE, a validated index must be used <ul style="list-style-type: none"> <li>○ Suggested indices are: clinical SLEDAI = 0; BILAG 2004 D or E only; clinical ECLAM = 0</li> <li>○ These must be supplemented by the Physician's Global Assessment being below an appropriate threshold (e.g., &lt;0.5 on a 0–3 scale)</li> </ul> </li> </ul>	98%
3.	<ul style="list-style-type: none"> <li>● A distinction will be made between <b>remission off therapy</b> and <b>remission on therapy</b> <ul style="list-style-type: none"> <li>○ <b>Remission off therapy</b> requires the patient to be on no other treatment for SLE than maintenance antimalarials</li> <li>○ <b>Remission on therapy</b> allows patients to be treated with maintenance antimalarials, stable, low-dose glucocorticoids (e.g., prednisone <math>\leq</math>5 mg/day), maintenance immunosuppressives and/or stable (maintenance) biologics</li> </ul> </li> </ul>	100%  (3 abstained)

Table 4. The task force's three key recommendations for defining remission in SLE.

1. The task force achieved consensus (93%) for the principle that remission in SLE will be defined using the following format:

“Remission in SLE is a durable state characterized by .... (followed by a reference indicating the absence of symptoms, signs or abnormal labs)”.

It can be recognized that this definition is to some extent a compromise because it does not specify the length of time during which a remission would have to be sustained in order to qualify. This is a direct result of the fact that no agreement on this could be achieved and that the task force felt that further scientific studies are needed to define the optimal duration for any statement of remission in SLE. A further area of uncertainty was whether the absence of active serology would be required and yet again it was felt that this could be investigated in the future. It should therefore also be recognized that ‘abnormal labs’ in the above statement refers to routine laboratory assessments and not necessarily to anti-DNA antibodies or complement levels.

2. The task force spent much time on finding correct formulations for defining the absence of clinical signs and symptoms for use in a definition and agreed, in the end, that for this a validated index must be used (98% agreement). The task force specifically suggests that the following can be considered: clinical SLEDAI = 0; BILAG 2004 D or E categories only; or clinical ECLAM = 0. Furthermore, it is recommended that each of these indices is supplemented with the requirement for the Physician’s Global Assessment (PhGA) to be below a certain level: in the case of a PhGA ranging from 0 to 3 that should be < 0.5. Note that in all instances the term “clinical” for SLEDAI and ECLAM refers to symptoms, signs and routine laboratory testing and disregarding only the points that can be given for the presence of anti-DNA antibodies and/or low complement. The task force also discussed the possibility of defining remission in terms of specific symptoms and signs, such as was done for the proposed definition of remission in pediatric SLE, where certain symptoms and signs are “allowed” for patients with SLE who are nevertheless considered to be in remission.[38] Although a minority of participants favored this

approach, there was a more widespread feeling that *not* using validated indices would to some extent be retrograde, and that practice in various research settings would also increasingly be dominated by the use of such indices.

3. The task force recommends that a distinction should be made between “remission off therapy” and “remission on therapy” (100% agreement). These two descriptors were chosen in preference to many other suggested terms, some of which are: “complete” versus “partial” remission; “complete” versus “clinical” remission; “remission” versus “lupus under control” or “inactive disease”. *While there are subtle nuances differentiating between these possibilities, it was considered important to simplify this matter and to strictly limit the number of definitions to two levels of remission.*

In this regard, it is also important that “off-therapy” will mean that the patient is on no other immunomodulatory treatment for SLE than possibly anti-malarials. As pointed out earlier, for some studies, in particular mechanistic investigations, the immunomodulatory properties of antimalarials must be considered, and in general accurate recording of all medications is recommended.

“Remission-on-therapy” will allow some, but not all medications. Specifically, stable immunosuppressives, including biological immunomodulators, are allowed within this level of remission. It was noted that definitions of remission in other autoimmune diseases, including rheumatoid arthritis[35] and Crohn’s disease[36], do not exclude the chronic use of specific antirheumatic medications, immunosuppressives, or biologics. Likewise, these definitions do not limit the use of glucocorticoids. However, in SLE a major contributor to long-term damage and other adverse outcomes is the chronic use of glucocorticoids, and the task force felt that for the patient to be declared in “remission-on-treatment” the highest allowable dose of glucocorticoids

is 5 mg/day prednisone (or equivalent). Prednisone dose thresholds associated with protection from treatment-related harm are currently being studied by several groups and data from those studies should further inform the selection of a threshold glucocorticoid dose in a definition of remission-on-therapy.

Further development of the most appropriate definition of remission. The task force discussed in what manner a future definition of remission in SLE could be most thoroughly established.

It was agreed upon by voting that for testing the construct validity of each potential remission definition the most appropriate outcomes are death, damage, lupus flares, and HR-QOL measures (100% agreement).

Thus, the task force indicated that any definition of remission in SLE must be tested in terms of the degree to which it correctly identifies patients whose future disease course will be better in these four outcomes. Though mortality remains a key outcome, it is unlikely that many studies will be able to identify this as a differentiating factor. Damage as measured by the SLICC damage index (SDI) [39] will most likely be the most effective way of ascertaining the construct validity of a definition of remission, as has been provisionally demonstrated for the definition of LLDAS. However, the occurrence of flares, especially severe flares, that can be measured by a variety of instruments,[40-42] and measures of HR-QoL will also be important in determining which potential definition of remission in SLE has the greatest validity.

Other points of discussion.

Patient's Global Assessment. There was controversy about the role of the Patient's Global Assessment (PGA) in a remission definition. A majority felt that PGA cannot currently be included

pending further research, and specifically that such research is needed to validate PGA as an outcome in reference to remission. Many felt that a better instrument to capture the patient's perspective may be needed. However, patient representatives (authors KL, CC, BvL) were concerned that the patient perspective was omitted. Indeed, in the T2T recommendations for SLE, both overarching principles and specific recommendations advocate including the patient's perspective in decision-making. However, there is no fully validated measure for the patient's perspective at this time. It was remarked that the PhGA can reflect patient perspective, and it was proposed to emphasize that PhGA should pay careful attention to patient symptoms, or conversely, that PGA could be a longer-term outcome used in the testing of remission definitions; but in formal votes no consensus was reached on these points.

Inclusion of validated skin score. The dermatologists in the task force (authors AK and VPW) suggested to supplement the definition of remission with a validated skin score.

Definition based only on symptoms. A rheumatologist (author MW) pointed out that in as much as the task force is developing *possible* definitions of remission, a definition based only on symptoms and *without* the use of an index could also be tested.

Plans for further work and research agenda. The task force agreed upon a plan of work that would include the use of longitudinal datasets from clinical trials, observational studies, registries etc. to test each of the definitions of remission. Likewise, definitions of remission “on treatment” and “off treatment” will be tested separately against the pre-specified dependent outcomes indicated above, and different durations of these definitions will also be tested. Moreover, studies done on patients “off treatment” will also record the use of antimalarials and analyze the extent to which this makes a difference. As always, findings in such subanalyses may inform future changes in the proposed definitions.

Proposed durations to be analyzed include 6 months, 12 months, 2 years, and 5 years.

In addition to this continued work, the task force also recommends specific research to investigate whether definitions of remission are applicable irrespective of genetic backgrounds and/or ethnicity.

## Discussion

An international task force consisting of patient representatives and specialists in clinical immunology, dermatology, nephrology and rheumatology was convened and achieved high-level agreement on eight statements, three key principles, and a set of outcomes relating to remission in SLE, thereby providing a road-map for further work towards a generally applicable definition.

Remission was approached as a global state, whereas it is recognized that remission can be defined, and has in some instances been defined, at the individual organ system level.

As a conceptual starting-point remission was identified as a desirable outcome for patients with SLE with at the very least the absence of major symptoms and signs of SLE. Remission is considered distinct from a cure and it is also regarded as meaningfully different from a state of low disease activity in SLE such as the lupus low disease activity state (LLDAS) that has recently been developed by the Asia-Pacific Lupus Collaboration.[5] However, the latter definition does not solely *require* the presence of low disease activity and does therefore, in fact, include both patients who have a low level of disease activity and also those who are in remission.

Perhaps most critically for future work in this area, it is recognized that remission has to be a state that, if sustained, is associated with a low likelihood of adverse outcome.

Regarding treatment, there was consensus that treatment with antimalarials does not preclude the patient from being considered to be in remission, in respect of the recommendation that anti-malarials should be considered as long-term maintenance therapy for patients with SLE even if they

have achieved remission.[3] It was also agreed upon by all that patients who are treated with moderate- or high-dose glucocorticoids cannot be considered to be in remission even if they would fulfill other criteria for remission. It is well established that glucocorticoids may suppress signs of disease, but will not achieve *bona fide* disease control, and also constitute one of the major risk factors for negative outcomes in SLE.

In contrast to these areas of agreement, no consensus could be achieved on two important issues.

First, it transpired that the inclusion of ‘duration’ in a definition of remission was controversial. Some argued that definitions of remission in other disease areas do not have this requirement, and that utility of a definition in clinical studies including clinical trials will be significantly limited if duration is explicitly required. Others argued that remission achieved on only one given point in time lacks clinical relevance in a disease that can be relapsing and remitting. Following lengthy discussion, the task force was able to agree on a compromise using the wording “Remission is a durable state characterized by ....” and also clearly identified the need for studies linking the duration of any definition of remission with longer-term outcomes.

Second, the task force did not agree on the precise role of the Patient Global Assessment (Patient GA) in a remission definition. This issue was debated at considerable length. Several task force members including patient representatives were concerned that the patient perspective was not explicitly included in the definition, and emphasized the importance of a definition of remission that ‘resonates’ with the patient. However, a majority of the task force felt that while the patient’s perspective is critically important in the patient-physician interaction, when it comes to a definition of remission for the purposes of clinical and epidemiological studies and clinical trials more work is needed in order either to validate Patient GA as an outcome, or more likely to develop a better instrument to capture the patient’s perspective. It was pointed out that the physician, when assessing disease activity, is expected to weigh in the patient’s perspective.

Additionally, the task force agreed on the definition of “serological activity” but no consensus was reached regarding whether the latter should be taken into account to define remission. The task force agreed upon the use of longitudinal datasets to determine whether serology adds to the construct validity of each definition.

Nomenclature for remission in SLE was extensively discussed. Many terms were proposed, including “complete remission”, “partial” remission”, “clinical remission”, “serological remission”, “lupus under control”, “inactive disease” etc., many of which were overlapping. In order to simplify matters and achieve consistency the task force recommends that only one distinction is made between “remission off therapy” and “remission on therapy”, where “off-therapy” must mean that the patient is on no systemic treatments for SLE other than anti-malarials. While “remission-on-antimalarials-only” would be the most accurate term for this state, “remission off-therapy” was chosen for brevity and convenience, even though it does allow antimalarial therapy. As stated previously, it will be necessary in future studies to account for the actual use of antimalarials in this group of patients, and subsequent analyses of patients who are and who are not on antimalarials may lead to further distinctions in these categories.

“Remission-on-therapy” will allow stable immunosuppressives, including biologics, and low-dose glucocorticoids. It is of interest to note that the latter type of definition is the more usual in other autoimmune diseases, such as RA and Crohn’s disease, and would also allow investigators to use the definition in clinical trials.

One limitation of the approach taken by the task force is the decision to limit serological activity to anti-DNA antibodies and low complement. Recent research shows the importance of antibodies to RNA binding proteins (RBPs) to the formation of immune complexes that can stimulate interferon production. Further research may show that, unless these antibodies are assayed, the serological assessment is incomplete.

Finally, the task force recommends a clear research agenda of testing the construct validity of potential remission definitions against death, damage, lupus flares, and HR-QOL measures as outcomes (dependent variables) in suitable cohorts of patients. Several task force members have conducted or are conducting such studies. This approach will establish which definition(s) of remission in SLE optimally identifies patients with a better disease course in these four outcomes.

**In summary, a set of statements and key principles relevant to remission in SLE were established by an international task force. This work provides a pathway for testing individual definitions against longer-term outcomes in order to arrive at a definition of remission in SLE.**

## **Acknowledgments**

The authors wish to acknowledge Ms Lisbeth Löfstrand, Administrator at Karolinska Institutet for her invaluable help during the organization of the DORIS meetings as well as for manuscript preparation.

## **Competing Interests**

**Ronald van Vollenhoven** reports having received Research Support and Grants from AbbVie, Amgen, BMS, GSK, Pfizer, Roche, UCB, and Consultancy or honoraria from AbbVie, Biotest, BMS, Celgene, Crescendo, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, Vertex.

**Laurent Arnaud** reports having received travel grants, consultancy or honoraria from Adelphivalues, Amgen, Eli Lilly, GSK, LFB, Menarini France, MSD, Raison de santé.

## **Funding**

No funding declared

## References

- 1 Houssiau FA, Vasconcelos C, D'Cruz D, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 2010;1:61-4.
- 2 Bexelius C, Wachtmeister K, Skare P, et al. Drivers of cost and health-related quality of life in patients with systemic lupus erythematosus (SLE): a Swedish nationwide study based on patient reports. *Lupus* 2013;8:793-801.
- 3 van Vollenhoven RF, Mosca M, Bertias G, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014;6:958-67.
- 4 Steiman AJ, Urowitz MB, Ibanez D, et al. Prolonged clinical remission in patients with systemic lupus erythematosus. *J Rheumatol* 2014;9:1808-16.
- 5 Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis* 2015.
- 6 Drenkard C, Villa AR, Garcia-Padilla C, et al. Remission of systematic lupus erythematosus. *Medicine (Baltimore)* 1996;2:88-98.
- 7 Nossent J, Kiss E, Rozman B, et al. Disease activity and damage accrual during the early disease course in a multinational inception cohort of patients with systemic lupus erythematosus. *Lupus* 2010;8:949-56.
- 8 Zen M, Iaccarino L, Gatto M, et al. Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. *Ann Rheum Dis* 2015;12:2117-22.
- 43 Medina-Quinones CV, Ramos-Merino L, Ruiz-Sada P, et al. Analysis of Complete Remission in Lupus Patients over a period of 32 years. *Arthritis care & research* 2015.
- 9 Moroni G, Quaglini S, Maccario M, et al. "Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis. *Kidney Int* 1996;6:2047-53.
- 10 Mok CC, Wong RW and Lau CS. Lupus nephritis in Southern Chinese patients: clinicopathologic findings and long-term outcome. *Am J Kidney Dis* 1999;2:315-23.
- 11 Korbet SM, Lewis EJ, Schwartz MM, et al. Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group. *Am J Kidney Dis* 2000;5:904-14.

- 12 Najafi CC, Korbet SM, Lewis EJ, et al. Significance of histologic patterns of glomerular injury upon long-term prognosis in severe lupus glomerulonephritis. *Kidney Int* 2001;6:2156-63.
- 13 Chen YE, Korbet SM, Katz RS, et al. Value of a complete or partial remission in severe lupus nephritis. *Clin J Am Soc Nephrol* 2008;1:46-53.
- 14 Illei GG, Takada K, Parkin D, et al. Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term followup of a cohort of 145 patients participating in randomized controlled studies. *Arthritis Rheum* 2002;4:995-1002.
- 15 Hill GS, Delahousse M, Nochy D, et al. Outcome of relapse in lupus nephritis: roles of reversal of renal fibrosis and response of inflammation to therapy. *Kidney Int* 2002;6:2176-86.
- 16 Mok CC, Ying KY, Tang S, et al. Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. *Arthritis Rheum* 2004;8:2559-68.
- 17 Mok CC, Ying KY, Ng WL, et al. Long-term outcome of diffuse proliferative lupus glomerulonephritis treated with cyclophosphamide. *Am J Med* 2006;4:355 e25-33.
- 18 Moroni G, Quaglini S, Gallelli B, et al. The long-term outcome of 93 patients with proliferative lupus nephritis. *Nephrol Dial Transplant* 2007;9:2531-9.
- 19 Mak A, Mok CC, Chu WP, et al. Renal damage in systemic lupus erythematosus: a comparative analysis of different age groups. *Lupus* 2007;1:28-34.
- 20 Lee BS, Cho HY, Kim EJ, et al. Clinical outcomes of childhood lupus nephritis: a single center's experience. *Pediatr Nephrol* 2007;2:222-31.
- 21 Sun HO, Hu WX, Xie HL, et al. Long-term outcome of Chinese patients with membranous lupus nephropathy. *Lupus* 2008;1:56-61.
- 22 Ayodele OE, Okpechi IG and Swanepoel CR. Predictors of poor renal outcome in patients with biopsy-proven lupus nephritis. *Nephrology (Carlton)* 2010;4:482-90.
- 23 So MW, Koo BS, Kim YG, et al. Predictive value of remission status after 6 months induction therapy in patients with proliferative lupus nephritis: a retrospective analysis. *Clin Rheumatol* 2011;11:1399-405.
- 24 Reich HN, Gladman DD, Urowitz MB, et al. Persistent proteinuria and dyslipidemia increase the risk of progressive chronic kidney disease in lupus erythematosus. *Kidney Int* 2011;8:914-20.

- 25 Alsuwaida A, Husain S, Alghonaim M, et al. Strategy for second kidney biopsy in patients with lupus nephritis. *Nephrol Dial Transplant* 2012;4:1472-8.
- 26 Dhir V, Aggarwal A, Lawrence A, et al. Long-term outcome of lupus nephritis in Asian Indians. *Arthritis Care Res (Hoboken)* 2012;5:713-20.
- 27 Moroni G, Quaglini S, Gravellone L, et al. Membranous nephropathy in systemic lupus erythematosus: long-term outcome and prognostic factors of 103 patients. *Semin Arthritis Rheum* 2012;5:642-51.
- 28 Mahmoud GA, Zayed HS and Ghoniem SA. Renal outcomes among Egyptian lupus nephritis patients: a retrospective analysis of 135 cases from a single centre. *Lupus* 2015;3:331-8.
- 42 Fernandes das Neves M, Irlapati RV and Isenberg D. Assessment of long-term remission in lupus nephritis patients: a retrospective analysis over 30 years. *Rheumatology (Oxford)* 2015;8:1403-7.
- 29 Koo HS, Kim S and Chin HJ. Remission of proteinuria indicates good prognosis in patients with diffuse proliferative lupus nephritis. *Lupus* 2016;1:3-11.
- 30 Dall'Era M, Cisternas MG, Smilek DE, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. *Arthritis Rheumatol* 2015;5:1305-13.
- 31 Tamirou F, D'Cruz D, Sangle S, et al. Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. *Ann Rheum Dis* 2015.
- 32 Tamirou F, Lauwerys BR, Dall'Era M, et al. A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. *Lupus Sci Med* 2015;1:e000123.
- 33 Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;3:404-13.
- 34 Best WR, Beckett JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;3:439-44.
- 35 Barr SG, Zonana-Nacach A, Magder LS, et al. Patterns of disease activity in systemic lupus erythematosus. *Arthritis Rheum* 1999;12:2682-8.
- 36 Mina R, Klein-Gitelman MS, Ravelli A, et al. Inactive disease and remission in childhood-onset systemic lupus erythematosus. *Arthritis care & research* 2012;5:683-93.

- 37 Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis and rheumatism* 1996;3:363-9.
- 38 Gordon C, Sutcliffe N, Skan J, et al. Definition and treatment of lupus flares measured by the BILAG index. *Rheumatology (Oxford)* 2003;11:1372-9.
- 39 Merrill J, Buyon J, Furie R, et al. Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER). *Lupus* 2011;7:709-16.
- 40 Isenberg DA, Allen E, Farewell V, et al. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. *Ann Rheum Dis* 2011;1:54-9.