

Is Remission in Systemic Lupus Erythematosus (SLE), a Reality?

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SUMMARY

To date, there are no universally accepted agreed-upon definitions of 'remission' in Systemic Lupus Erythematosus (SLE) because of the heterogeneity of the disease.^{1,2} Most definitions regarding the concept of 'remission' in SLE are multiple. Over the past decades these concepts of remission have emerged as 'nicknames' where one would ideally like to achieve a 'cure'. Cure in clinical terms is 'the ultimate goal of medical intervention', which in reality cannot realistically be hoped for.³ The term remission was originally used in the practice of oncology to describe the total absence of any detectable tumour in patients. In the medical specialties treating autoimmune inflammatory diseases, the concept of remission has gained significant value when evaluating disease activity and in 'treat-to-target' therapies. Three distinct processes regarding the term remission have taken place:

- The idiom of remission was introduced into the language of speciality disciplines so that clinicians, researchers and patients would use this specific term to describe the state they wished to achieve.
- A preliminary definition of remission can specifically be defined for each disease, e.g. Rheumatoid Arthritis (RA). Remission in RA was defined by the American College of Rheumatology (ACR), in 1981.⁴ Subsequently, a definition of remission in RA was promulgated, based on the disease activity score or other disease activity indices.
- Finally, there is the joint ACR and European League Against Rheumatism (EULAR) definition of remission.⁵
- Most notably in RA, remission was codified as the explicit target of therapeutic interventions. Remission has also been expressed in guidelines by the ACR⁶ and EULAR⁷ as well as the 'treat-to-target' work force group⁸ as the goal of therapy for 'most' patients.

These three developments cannot be understated as they strongly influence each other and have made the term

remission a topic of discussion in a multitude of scientific publications and in patient-clinician encounters. In SLE, the concept of remission has also been debated extensively. In this brief review, previous and up-to-date developments regarding remission in SLE were accessed using MEDLINE/PUBMED searches of English language publications using Medical Subject Headings (MeSH). Terms and free text words for the following search keys: systemic lupus erythematosus (SLE), definitions of remission in SLE, quality of life and remission in SLE and patient outcomes and remission in SLE, were used. After reviewing all the articles the most relevant ones were then selected for this brief review.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by a variety of clinical manifestations.^{9,10} The disease has an unpredictable and often fluctuating course with relapses (flares) and remissions over many years. Unfortunately, despite the improvements of SLE prognosis in the last decades, patients with SLE have an increased risk of disease-related complications and premature death.^{1,11} When evaluating disease activity and 'treat-to-target' therapies in several autoimmune rheumatic diseases the concept of remission has gained significant increase.¹² Little information describing long-term remission rates in SLE that are in excess of 15 years exist. There is also inadequate knowledge about predictors of relapse.

No universally accepted agreed-upon definitions of 'remission' in SLE

Remarkably, while remission has been used to describe a favourable clinical state for patients with SLE since the late 70's,¹³ an agreed-upon definition remains elusive. This is substantiated in cohort studies carried out in patients with SLE. These studies highlighted remission, when defined as complete or clinical. However, in reality, this type of remission was uncommon, reported in less than 10% of patients.¹⁴⁻²¹ It is widely understood that remission in SLE is a desirable disease state that should be associated with optimal healthrelated quality of life (HQoL) and favourable prognosis.

Quality of life and patient related outcomes

As previously stated, SLE is a chronic disease that is complex and unpredictable both of which have a direct impact on patient's daily living. Despite advances in the treatment and overall prognosis in SLE, significant improvements in quality of life for the majority of patients are minimal. HQoL is significantly poorer in patients with SLE when compared to the general population. European League Against Rheumatism (EULAR) recommendations

for monitoring SLE patients established that HQoL has to be evaluated at every visit in routine clinical practice, as an independent outcome measure.²² In a recent survey from Lupus UK,²³ almost 75% of its members had problems that limited their ability to carry out routine daily tasks and in addition only 15% of them worked full-time. Many of the patients surveyed stated, 'that they also required day-to-day care and support'. This support chain included a variety of individuals: professional health care workers, partners, family members as well as friends.

A recent cross-sectional study of patients included in the Swiss SLE Cohort Study²⁴ between April 2007 and June 2016, revealed that the major debilitating symptom was that of increased fatigue, followed by reduced mental health. Serological activity testing in these patients revealed low complement levels and/or the presence of anti-DNA antibodies. Taking this into account a 'treat-to-target strategy' in SLE management can be used in an attempt to achieve remission or a low disease activity state. This is important in avoiding damage accrual in the long-term, in order to improve patient's overall HQoL. In 2017 Golder *et al*²⁵ prospectively evaluated HQoL, by means of the SF-36 (Short Form Health Survey – a 36-item, patient-

Table I. An overview of remission in SLE used in the literature to date

Author(s)	Year	Remission definition (abbreviated)	Serological activity permitted	Duration of remission (i.e. if stated)	Treatments permitted
Dubois ²⁷	1956	Based on rheumatologist's impression	Not specified	No	Not specified
Dubois and Tffanelli ²⁸	1964	Based on rheumatologist's impression	Not specified	No	Not specified
Gladman <i>et al</i> ²⁹	1979	Asymptomatic patient	Yes	No	None
Tozman <i>et al</i> ¹⁶	1982	Absence of clinical manifestations of the disease	No	No	None
Hellar and Schur ¹⁵	1985	Asymptomatic without active organ involvement	No	No	Antimalarials and low-dose glucocorticoids
Waltz LeBlanc <i>et al</i> ³⁰	1994	Clinical SLEDAI=0	Yes	≥3 consecutive clinic visits	Any
Drenkard ³¹	1996	Lack of disease activity permitted SLE treatment withdrawal	Yes	≥1year	None
Barr <i>et al</i> ¹⁴	1999	Clinical SLEDAI=0 or PGA<1.0	Yes	≥1year	Not specified
Fomiga <i>et al</i> ³²	1999	Lack of disease activity permitted SLE treatment withdrawal	Yes	≥1year	None
Swaak <i>et al</i> ³³	1999	Absence of disease-related signs with no need for treatment	Not specified	No	None
Urowitz <i>et al</i> ¹⁷	2005	Clinical SLEDAI=0	Yes	≥5years	None
Nossent <i>et al</i> ³⁴	2010	Physician assessed	Not specified	No	Not specified
Steiman <i>et al</i> ¹⁸	2010	Clinical SLEDAI-2K=0	Yes	≥2years	Antimalarials only
Conti <i>et al</i> ³⁵	2012	Clinical SLEDAI-2K=0	Yes	≥2years	Antimalarials only
Zen <i>et al</i> ¹²	2015	Clinical SLEDAI-2K=0	Yes	≥5years	Antimalarials and low-dose glucocorticoids
Medina – Quiñones <i>et al</i> ³⁶	2016	BILAG Index	Yes	≥3years (study over 32-year period)	Antimalarials only
Mok <i>et al</i> ²⁶	2017	European consensus criteria	Not specified	≥5years	Antimalarials only

PGA, patient global assessment; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus disease activity index; BILAG, British Isles Lupus Assessment Group.

Adapted from Steiman *et al*.¹⁹

reported survey of patient health), in a large cohort of SLE patients. The study found that low disease activity state correlated with better physical component summary (PCS) and mental component summary (MCS) scores and better scores in multiple individual SF-36 domains. In a study of a large cohort of Chinese SLE patients,²⁶ remission (≥ 5 years) was significantly allied with less damage accrual and better HRQoL.

Definitions of remission in SLE

As reviewed by Steiman *et al*¹⁹ there have been a number of *ad hoc* definitions of remission in SLE over the years. These definitions have been used in clinical trials and observational studies (Table I).

Accurately defining remission in SLE would serve multiple purposes:

- (i) to assist in many types of clinical research including epidemiological studies, health economic investigations and in clinical trials. All would lead to standardised cohort descriptions, valid collaborative study comparisons and finally, perhaps better trial outcomes.
- (ii) to facilitate better communication between health providers and patient's.
- (iii) would be useful in education, thereby creating better understanding of the disease.

Agreement on the definition of remission has been drastically hindered by the methods for quantification of disease manifestations. For example, patients in remission or with low disease activity are clinically and perhaps mechanistically more homogeneous than those patients with active disease (i.e. who are more heterogeneous).³⁷ This potentially permits simpler definitions of these clinical states (Figure 1).

Treat to-target (T2T)

In 2014 the treat-to-target for SLE (T2T/SLE) initiative³⁸ established international consensus on an approach to therapy regarding SLE based on:

- identifying an appropriate target for each individual patient;
- directing therapy towards achieving this target goal;
- reassessing the target; and
- if needed, modify treatment regimens.

...defining remission in SLE would serve multiple purposes...

T2T/SLE recommendations identify 'remission of systemic symptoms and organ manifestations' are the key therapy targets in SLE.

The T2T/SLE task force identified that the definition of remission should be a research priority as no generally accepted definition of remission in SLE exists to date. As a result of this lack of clarity an initiative was undertaken to achieve consensus on a definition of remission in SLE by a large multiparty international task force (DORIS – Definition Of Remission In SLE).³⁹ The complete work of this task force was presented at the EULAR congress in 2015 and is an open access publication.

No consensus was reached on the definition of 'serological activity' and whether it should be taken into account to define remission.

This perhaps was the one of the limitations of the task force (i.e. the role of laboratory testing) and their decision to limit serological activity to testing for anti-DNA antibodies and the presence of low complement. Recent research has demonstrated the importance of the entire antinuclear antibody (ANA) profile, since other antibodies such as anti-RNA binding protein antibodies can contribute to SLE pathogenesis. This is possibly through its effects on interferon (IFN) α production⁴⁰ and could be included in future analyses.

Another interest in this regard is biological markers such as Type 1 interferon signature.⁴¹

In further discussions involving experts from DORIS as well as individual patients; four critical domains were highlighted in regard to which definitions of remission are divergent and in addition, where there was no clear consensus (Figure 2).

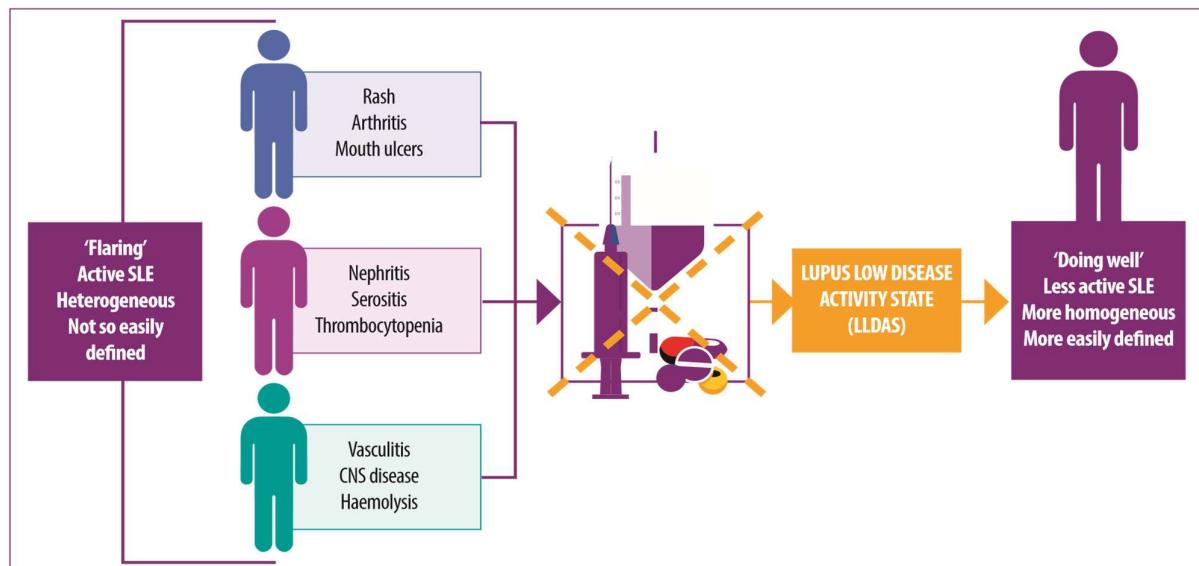


Figure 1. While SLE is an extraordinarily heterogeneous disease, the patients who are in low disease activity or in remission, present with much less heterogeneity. Adapted from Franklyn *et al*.³⁷

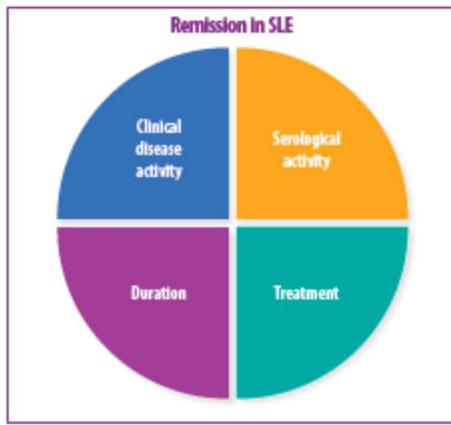


Figure 2. Four domains were considered crucial in defining remission in SLE; clinical disease activity, serological activity, duration and treatment^{3,37}

Closer towards a definition of remission

1. Clinical disease activity
2. Serological activity
3. Duration
4. Treatment

1. A 'true' definition of remission may well require a complete absence of clinical disease activity without *any* signs or symptoms that are suggestive of SLE. Alternatively, a certain amount of symptomatology may be accepted. An example of this is in the proposed definition of remission in paediatric SLE⁴² that permits symptoms such as: mild fatigue, mild myalgia and mild alopecia. A technique that has dominated the literature over the past decade has been that of a practical approach, using validated indexes to define the clinical disease activity of SLE i.e.:
 - a. Systemic lupus disease activity index (SLEDAI)⁴³ <2
 - b. 'Clinical SLEDAI'44 (i.e. disregarding serology) = 0
 - c. European Consensus Lupus Activity Measurement (ECLAM)⁴⁵ = 0
 - d. British Isles Lupus Activity Group (BILAG)^{46,47} categories D and E only
- e. SLE-DAS,⁴⁸ a new continuous global score to assess disease activity in SLE. The SLE-DAS provides a more accurate identification of clinically meaningful changes over time, with a much higher sensitivity as compared with SLEDAI-2K and similar specificity
2. Included in some definitions of remission, is serological activity where one can demonstrate anti-doublestranded DNA (anti-dsDNA) antibodies and/or hypocomplementaemia due to complement activation. A serological activity state with clinical quiescence (SACQ) has been defined where serological activity alone is permitted in a patient who is not on any therapy apart from antimalarials. Persistent SACQ has been associated with improved outcomes.²¹

3. The duration of remission is contentious issue with no consensus having been reached to-date. This is mainly because of the relapsing-remitting patterns seen in SLE,

in contrast to the other chronic autoimmune diseases.¹⁴ van Vollenhoven *et al*³ suggests that omitting a pre-specified duration from a definition of remission would allow the effects of various durations to be studied. This would hopefully lead to the identification of threshold duration of remission, which could have a positive impact on the outcomes of the disease.

4. The last component of a remission definition is treatment. Obviously, patients that are still receiving moderate-dose or high-dose corticosteroids cannot be considered to be in remission even if they fulfil all the criteria. On the other hand patients being treated with antimalarial medications as long term maintenance therapy will not be precluded of being considered to be in remission.

Recent clinical application of the T2T approach

Medina-Quiñones *et al*³⁶ (Table I highlighted) presented interesting all new insights into the questions surrounding remission in SLE. The principal aim of their comprehensive study was to identify the number of SLE patients achieving a 'complete' remission. This was implied that for 3 years there were no clinical or serologic characteristics. Additionally, no therapies with corticosteroids or immunosuppressive drugs were permitted, only antimalarials and non-steroidal anti-inflammatory drugs were allowed. Of a single cohort of 624 patients a total of 532 met the strict inclusion criteria and were followed for a 32 year period from 1978-2010. In addition the authors identified patients in clinical but not serologic remission (SACQ) and were particularly interested in determining factors associated with complete remission. The authors chose to apply the following remission criteria:

- The definition of a complete remission was a minimum 3-year consecutive period of no disease activity i.e. patients who had a score of C, D or E on the BILAG index^{46,47} and also fulfilled the treatment criteria: not taking steroids and immunosuppressant drugs (antimalarials being the exception); had normal laboratory results (no dsDNA antibodies and normal serum C3 complement levels); no recurrence or any reason for treatment failure before time-point of interest.
- The definition of clinical remission or SACQ i.e. patients who had a score of C, D or E on the BILAG index^{46,47} and also fulfilled the absence of steroids and immuno-suppressant's (antimalarials being the exception).

Persistent serologic activity: positive anti-dsDNA antibodies and/or hypocomplementaemia at each clinic visit for a period of at least 3 consecutive years.

- The definition of serologic remission i.e. patients who demonstrated normal C3 complement and anti-dsDNA antibody levels. Persistent clinical activity score of A or B on the BILAG index^{46,47} and or treatment with steroids or immunosuppressant's for at least 3 consecutive years.
- The definition of a clinical flare (or relapse) was the development of a score of A or B on the BILAG index^{46,47} with or without a low C3 complement serum levels or positive anti-dsDNA antibodies. The definition of a serologic flare (or relapse) was a low level of C3 complement and/or positive anti-dsDNA antibodies in the group of patients who achieved only serologic remission but remained clinically symptomatic (Figure 3).

Zen *et al*¹² chose to apply a definition of remission based on the SLEDAI-2K three levels system, with additional stringent requirements. Despite these requirements, prolonged remission in their cohort of patients was not unusual, 37% achieving at least a 'clinical remission on corticosteroids'. In contrast, a complete remission using one of the three levels (i.e. no clinical activity, no serological activity and no treatment) was more unusual, in that it was only seen in 7.1% of patients. Each definition of prolonged remission required that the patient achieved this state for the full 5 years of follow-up.

In 2005, Urowitz *et al*¹⁷ reported that only 12 of 703 patients (1.7%) satisfied all the criteria for prolonged complete remission (SLEDAI score = 0) after 5 years without therapy.

CONCLUSION

In future studies, it may be worthwhile to look at the predictive effect of a range of durations of remission on outcomes. It makes sense that remission maintained for a longer duration is superior to that achieved only for a short period of time. But, it would be useful if the latter (i.e. achieving remission of 1-2 years) is also associated with a significantly better outcome, regarding the overall profile of SLE. As an example, the use of shorter

durations could be useful in implementing studies of remission in SLE in clinical research.

As seen in this brief review of the literature the definitions of remission in SLE are somewhat conflicting. However, they also illustrate a sound approach in testing the impact that these various definitions have on 'hard' long term outcomes such as damage accrual. Other possibilities would be further studies on lupus flares and death as an allegory to the study of Medina-Quiñones *et al*.³⁶ Whatever transpires, a suitable study protocol for each analysis would have to be developed. This would include appropriate inclusion criteria (perhaps an entire ANA profile), well defined frequency and quality of follow-up.

It makes sense that remission maintained for a longer duration is superior to that achieved only for a short period of time

In summary, with the existence of numerous definitions in literature regarding remission in SLE there is a dire need for unification in future research, perhaps even accessing registries such as those in Padova and Madrid to aid analysis. This will enable enhanced studies and as a result, better understanding, treatments and outcomes for this somewhat elusive disease. Long-term remission in SLE is indeed a reality. However, follow-ups are mandatory and HRQoL has to be evaluated at every visit in routine clinical practice, as an independent outcome measure.⁴⁹

Conflict of interest

The author has no conflict of interest regarding this brief review.

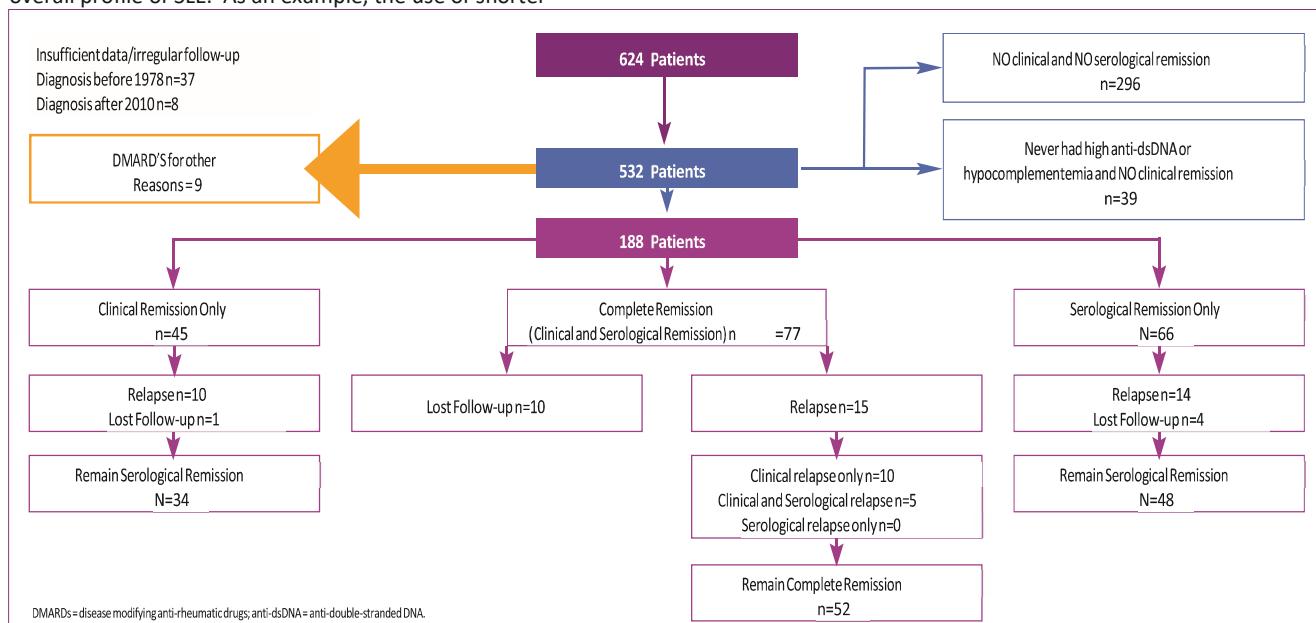


Figure 3. Frequency of patients fulfilling the different types of remission and also those showing no remission. Adapted from Medina-Quiñones *et al*.³⁶

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FURTHER REFERENCES ARE AVAILABLE ON REQUEST.