

The Management of Systemic Lupus Erythematosus (SLE) Patients in Remission

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In recent years, remission has emerged as a key concept in disease management in several autoimmune rheumatic diseases. In systemic lupus erythematosus (SLE), the concept of remission has been extensively discussed, but a generally accepted definition has not been formulated yet [1,2]. Indeed, which disease and treatment variables should be considered and which activity score(s) should be used to define a patient as being in remission have not been established [1,3].

The studies on remission published from 1990 to 2014 used diverse definitions [4–19], and this lack of uniformity prevents a valid way of comparison in most cases [Table 1]. By and large, these studies showed a low percentages of clinical remission in SLE patients. However, it is noteworthy that the majority of these studies were carried out by the Toronto Lupus Cohort. The Toronto Lupus Cohort started almost 50 years ago in 1970, and the results show a scenario that might not be consistent with current disease management, as the therapeutic approach in SLE has greatly changed and improved just in the last 2 decades.

Thus, whether or not remission is still rare or it is an achievable goal in SLE is still not clear.

WHAT IS REMISSION? IS REMISSION STILL RARE IN SLE?

The first important step needed to address these questions was to elaborate a shared definition of remission to apply to different cohorts worldwide.

In 2015, an initiative to achieve consensus on a definition of remission was undertaken by an international task force headed by van Vollenhoven (Definition of Remission in SLE, DORIS) [20]. The DORIS task force first identified four domains that

were considered critical for defining remission in SLE: clinical disease activity, serological activity, treatment, and duration.

Thereafter, through a voting process, the task force agreed on some principles that should guide the further development for the definition of remission. The first principle stated that the absence of clinical activity should be defined as no clinical activity according to the SLE Disease Activity Index (SLEDAI) in patients with a physician global assessment (PGA) lower than 0.5. Second, different subtypes of remission were identified based on serology and the therapies taken by the patients. Thus, remission was defined as clinical or complete, according to the presence or absence of serological abnormalities, and off- or on-treatment, where off-treatments meant free of therapies for SLE apart from

antimalarials, and on-treatment meant a dosage of prednisone \leq 5 mg/day and/or stable immunosuppressive or biologic drugs.

Third, the task force agreed that the most appropriate outcomes for testing the prognostic

value of potential remission definitions were: death, organ damage, disease flare-ups, and measures of health-related quality of life.

Before beginning the DORIS project, Zen et al. [15] carried out a study on prolonged remission in a cohort of Caucasian SLE patients. They defined prolonged remission as a remission \geq 5 consecutive years. Only patients diagnosed with SLE between 1990 and 2009 and quarterly seen from 2009 to 2013 were included. Disease activity was evaluated using SLEDAI-2K and damage by Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) damage index (DI).

Three levels of prolonged remission were defined, based on disease activity and treatment.

- *Complete remission:* no clinical and serologic disease activity according to the SLEDAI-2K in patients who were corticosteroid and immunosuppressant free (antimalarials allowed)
- *Clinical remission, off corticosteroids:* no clinical activity on SLEDAI-2K but active serology in patients who were corticosteroid free (antimalarials and immunosuppressants allowed)

Table 1. Studies on remission in Systemic Lupus Erythematosus (SLE), with different definitions of remission used

Authors	Definition of remission	Serological activity allowed	Treatment(s) allowed	Duration of remission	Number of patients	% of patients achieving remission
Heller et al. 1985 [4]	Asymptomatic patients, with no active organ involvement	No	Antimalarials and low-dose glucocorticoids	Not required	305	4.0
LeBlanc et al. 1994 [5]	Clinical SLEDAI = 0	Yes	Any	≥ 3 consecutive clinic visits	609	13.0
Drenkard et al. 1996 [6]	Lack of disease activity	Yes	None	≥ 1 year	667	23.4
Barr et al. 1999 [7]	Clinical SLEDAI = 0 or PGA < 1.0	Yes	Not specified	≥ 1 year	204	44 (PGA) or 28 (SLEDAI)
Formiga et al. 1999 [8]	Lack of disease activity	Yes	None	≥ 1 year	100	24.0
Swaak et al. 1999 [9]	Absence of disease-related signs with no need for treatment	Not specified	None	Not required	187	0
Urowitz et al. 2005 [10]	Clinical SLEDAI = 0	Yes	None	≥ 1 years, ≥ 5 years	703	2.8; 14.5
Urowitz et al. 2005 [10]	SLEDAI = 0	No	None	≥ 1 years, ≥ 5 years	703	6.5; 1.7
Nossent et al. 2010 [11]	According to physician assessment	Not specified	Not specified	Not required	200	27.5
Steiman et al. 2010 [12]	Clinical SLEDAI-2K = 0	Yes	Antimalarials only	≥ 2 years	924	6.1
Conti et al. 2012 [13]	Clinical SLEDAI-2K = 0	Yes	Antimalarials only	≥ 2 years	45	2.2
Steiman et al. 2014 [14]	Clinical SLEDAI-2K = 0	Yes	Antimalarials only	≥ 5 years	1613	2.4
Zen et al. 2015 [15]	Clinical SLEDAI-2K = 0	Yes	Antimalarials, stable IS, 1–5 mg prednisone daily	≥ 5 years	224	38.0
Medina-Quiñones et al. 2015 [16]	BILAG scores of C, D or E only	No	Antimalarials only	≥ 3 years	532	14.5
Medina-Quiñones et al. 2015 [16]	BILAG scores of C, D or E only	Yes	Antimalarials only	≥ 3 years	532	23.0
das Chagas Medeiros et al. 2016 [17]	Absence of any clinical manifestation or laboratory finding indicating active disease	Not specified	Not specified	Not required (disease remission evaluated upon the last consultation)	338	57.4
Zen et al. 2016 [18]	Clinical SLEDAI-2K = 0	Yes	Antimalarials, stable IS, 1–5 mg prednisone daily	1, 2, 3, 4, ≥ 5 consecutive years	294	1 year 9.6 2 years 16 3 years 15.4 4 years 8.9 ≥ 5 years 38.6
Wilhelm et al. 2016 [19]	Clinical SLEDAI-2K = 0 AND PGA < 0.5	Yes	Remission on-treatment: stable IS, ≤ 5 mg prednisone daily, antimalarials. Remission off-treatment: antimalarials	1, 2, 5, 10 years	2307	1 year 9.3–13.4 2 years 3.6–5.6 5 years 0.6–1.2 10 years 0.4–1.3

SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index, SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000, PGA = physician global assessment, IS = immunosuppressives, BILAG = British Isles Lupus Assessment Group

- *Clinical remission, on corticosteroids:* no clinical activity on SLEDAI-2K, with or without active serology in patients treated with a daily dose of prednisone ≤ 5 mg (antimalarials and immunosuppressant allowed)

In this study, 7% of patients achieved a prolonged complete remission, 15% prolonged clinical remission off corticosteroids and 16% prolonged clinical remission on corticosteroids. The other 62% did not achieve a prolonged remission, which means they achieved a remission either earlier than 5 years or their disease persisted in a chronic active or relapsing remittance.

Recently, Wilhelm et al. [19] evaluated prolonged remission in their cohort and found an opposite result, that is, that durable remission is rare in SLE. The authors tested the DORIS definition of remission in 2307 patients who entered the cohort from 1987 to 2014 and were seen quarterly thereafter. Patients not in

remission at cohort entry were followed prospectively. The percentage of patients with durable remission at 2, 5 and 10 years was very low (e.g., 5 year remission ranged from 0.7 to 2.0% according to subtypes of DORIS definitions of remission). The percentage of patients with durable remission was so low that the authors did not analyse the effect of remission on disease outcomes, such as damage accrual.

Although this study is an important contribution to this topic, its result is a little bit disturbing: indeed, only a minority of lupus patients could maintain a durable remission, which means that according to this study remission is not a suitable target for SLE treatment.

Nevertheless, some considerations have to be made before considering remission an unsuitable target for SLE treatment. More than 40% of Wilhelm’s patients were Black, only 35–37% of the patients were anti-double stranded DNA-positive at

baseline, approximately 25% had low complement fraction C3 and 20% low C4, and less than 20% had renal activity. More interestingly, the authors considered only the first period of remission achieved by each patient in the disease course, and not the longest one, as was done in the study by Zen et al [15]. Last, approximately 20% of patients who did not satisfy Wilhelm's [19] definitions of remission at study entry had a PGA < 0.5 and 40% had a clinical SLEDAI score equal to 0. Thus, a discrepancy between clinical SLEDAI and PGA could prevent the fulfilment of the definition of remission in their study. Thus, other studies are needed to shed light on this topic.

Little data on disease management during remission are available; however, in remitted patients an attempt to withdraw or reduce prednisone to the lowest effective dosage should be considered

consecutive years remission, irrespective of the level of remission, that is if they were in complete remission or in clinical remission on or off corticosteroids. Of interest, when the level of remission was considered in the analysis, no differences in the median increase in SDI were observed in patients with 1, 2, 3, and 4 consecutive years remission for each duration of remission; by contrast, a significant difference was observed among patients with ≥ 5 consecutive years remission, where patients in clinical remission on corticosteroids had more damage than those in remission off corticosteroids. This means that the absence of SLE clinical activity is more relevant than low-dose corticosteroid intake in hindering damage progression in the short-term, while in the long-term even low-dose corticosteroids can contribute to organ damage

At multivariate analysis, 2 consecutive years remission was the shortest duration of remission which was protective against damage.

CAN REMISSION IMPROVE DISEASE OUTCOMES?

Data available this topic suggest that remission can positively impact disease outcomes.

It has been shown that patients who achieved early remission compared to those with chronic active disease had less disease activity, less disease relapses and less damage, and took a lower cumulative dose of corticosteroids over time [11]. Accordingly, Steiman et al. [21] analysed damage accrual in patient with and without prolonged (> 2 years) serologically active clinically quiescent disease and found that after 3 and 10 years of follow-up the mean damage increase was significantly lower in the former compared with the latter. Similar findings were shown in lupus glomerulonephritis, as renal survival or survival without renal insufficiency were significantly higher in patients who achieved a complete remission compare to those with partial or no remission [22,23].

In the study on prolonged remission by Zen et al. [15], the increase in organ damage from baseline to the end of the observational period was more common in patients who did not achieve prolonged remission and progressively lower in those with clinical remission on corticosteroids, clinical remission off corticosteroids and complete remission. Accordingly, unremitted disease and high dose corticosteroid intake were independent risk factors for damage accrual in multivariate analysis. As the durability of remission varied from study to study, how long the remission should last to yield significant benefits on patient outcome has not been fully elucidated yet.

Only recently this question was assessed in a study by Zen et al. [18], where the authors evaluated the effect of damage on different levels and durations of remission, namely 1, 2, 3, 4, and ≥ 5 consecutive or cumulative years.

The increase in SDI as well as the proportion of patients with an increase in SDI from the baseline to the end of follow-up were significantly more common in unremitted patients and progressively less common in patients with 1, 2, 3, 4 and ≥ 5

Remitted patients should be assessed every 3 to 4 months

Previous studies identified immunosuppressives and high dose corticosteroid therapy as relevant risk factors for organ damage in SLE [24-26].

It is known that corticosteroids are associated with many side-effects and complications [15,26] and thus, in remitted patients a decrease and/or withdrawal from prednisone should be attempted. The results obtained in the study by Zen et al. [18] support this statement. Steiman et al. [21] evaluated patients with a 2 year clinical remission free of therapy including corticosteroids, and found that when corticosteroids were reintroduced due to a disease flare, patients who experienced flair-ups tended to accumulate corticosteroid related damage to a lesser extent compared with control patients with persistent clinical disease activity, who had continued corticosteroids during the entire follow-up. Thus, achieving a treatment free clinical remission, although for a limited period of time, is an advantage in terms of damage, since it can slow down damage progression.

There is little data on the risk of corticosteroid tapering in SLE patients are available. In a study from Petri et al. [24], carried out in patients who were prescribed a prednisone dose of 5 mg/day and were prospectively followed, 668 out of 866 patients tapered the dosage below 5 mg/day, and 377 of them (55%) had a successful tapering, defined as the prednisone tapering to less than 5 mg/day for at least 1 year. Interestingly, the tapering was more frequently successful after the year 2000, in patients with lower disease activity, and in patients without musculoskeletal or cutaneous activity [27].

There is little data available on therapy discontinuation in non-renal lupus. Three studies, two randomized controlled trials and one prospective study, evaluated the discontinuation of azathioprine (one study) and hydroxychloroquine (two studies) [28-30]. These studies demonstrated that discontinuation was associated with an increased risk of disease relapse. In the two study on hydroxychloroquine, the relative risk of flare-up after drug withdrawal was 2.5 and 6.1, respectively.

More recently, Nalotto et al. [31] found that among 104 patients who discontinued corticosteroids due to remission achievement, only 21% experienced flare-up after a mean 20 ± 13 months. However, it has to be pointed out that all these studies included a low number of patients.

Some more data on discontinuation of immunosuppressants and prednisone in patients with glomerulonephritis are available. In different studies, characterized by a low number of patients, different time elapsed between remission and discontinuation as well as different follow-up time after therapy discontinuation, the frequency of glomerulonephritis relapses was substantially low, ranging from 4 to 15.6 per 100 patients per year [32-37].

In the study by Moroni et al. [37], out of 52 patients who discontinued the treatment, 20 developed a glomerulonephritis relapse. Patients who did not flare after therapy withdrawal had a significantly longer duration of treatment before withdrawal (98 vs. 30 months) as well as a longer duration of remission before withdrawal (52 vs. 12 months) and were more commonly treated with antimalarials compared with those who flared.

HOW OFTEN SHOULD WE ASSESS REMITTED PATIENTS?

According to ACR guidelines, patients should be assessed every 3–6 months [38], while according to the European recommendations, patients should be monitored every 6–12 months [39], and according to a recent study from a Canadian group every 3–4 months [40].

This last suggestion was based on the observation that the follow-up every 3–4 months in a cohort of 515 SLE patients allowed the identification of renal, serologic, hematologic asymptomatic abnormalities in 25% of patients. In some cases these abnormalities led to therapeutic changes or a more tight control [40].

CONCLUSIONS

In conclusion, we can state that remission is now more common than in the past and it can be considered a suitable target in SLE management since it seems to improve disease outcomes, especially in halting accrual of organ damage.

Very little is known on disease management during remission; however, in remitted patients, prednisone should be reduced at the lowest effective dosage or even withdrawn. The discontinuation of hydroxychloroquine and immunosuppressants can jeopardize patient health and should be considered

only in selected cases. Remitted patients should be assessed every 3–4 months.

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Capsule

Targeting senescence to combat osteoarthritis

During senescence, cells remain in a state of growth arrest. Accumulation of similar nonfunctional cells has been linked to chronic inflammatory diseases and degenerative disorders. Inflammation after joint injury is a common sequela. Jeon et al. sought to understand whether senescence was involved in the development of osteoarthritis by using a model of anterior cruciate ligament surgery. Senescent cells assembled

in the traumatized knee joint and triggered development of osteoarthritis and cartilage erosion in mice. By injecting a drug that caused the specific removal of these cells, the arthritis symptoms were alleviated, and cartilage regeneration and recovery were improved.

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Capsule

Dectin 1 activation on macrophages by galectin 9 promotes pancreatic carcinoma and peritumoral immune tolerance

The progression of pancreatic oncogenesis requires immune-suppressive inflammation in cooperation with oncogenic mutations. However, the drivers of intratumoral immune tolerance are uncertain. Dectin 1 is an innate immune receptor crucial for anti-fungal immunity, but its role in sterile inflammation and oncogenesis has not been well defined. Furthermore, non-pathogen-derived ligands for dectin 1 have not been characterized. Daley and co-authors found that dectin 1 is highly expressed on macrophages in pancreatic ductal adenocarcinoma (PDA). Dectin 1 ligation accelerated the progression of PDA in mice, whereas deletion of *Clec7a*, the gene encoding dectin 1, or blockade of dectin 1 down-

stream signaling was protective. The authors found that dectin 1 can ligate the lectin galectin 9 in mouse and human PDA, which results in tolerogenic macrophage programming and adaptive immune suppression. Upon disruption of the dectin 1-galectin 9 axis, CD4+ and CD8+ T cells, which are dispensable for PDA progression in hosts with an intact signaling axis, become reprogrammed into indispensable mediators of anti-tumor immunity. These data suggest that targeting dectin 1 signaling is an attractive strategy for developing an immunotherapy for PDA.

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