Treatment targets in SLE: remission and low disease activity state

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Abstract

Treat-to-target strategies have changed the approach to management of many chronic conditions, with improvements in patient outcomes. The key to success of treat to target is the availability of validated treatment endpoints, which have been difficult to derive for SLE, a condition notorious for its heterogeneity. This review will focus on the development and validation of the definitions of remission in SLE framework and the lupus low disease activity state. Lupus low disease activity state is more attainable than remission, with a stepwise concentric relationship between the target states indicating increasing stringency. Both lupus low disease activity state and definitions of remission in SLE remission have been proven to be associated with reduction in disease flares, reduced risk of accrual of irreversible end organ damage, and improvement in patient reported outcomes. These endpoints have therefore provided the key for the development of a treat-to-target approach in clinical practice in SLE and for the design of future clinical trials.

Key words: SLE, treat to target, treatment endpoints, remission, lupus low disease activity state

Introduction

SLE is a chronic multisystem autoimmune disease resulting in significant morbidity and loss of life expectancy. Compared with other rheumatic conditions where new targeted therapies have resulted in high rates of remission or low disease activity, the effect sizes of therapies for SLE have been relatively small [1, 2]. The majority of SLE patients are still treated with chronic glucocorticoids and non-specific immunosuppressants. Despite overall improvement, ten-year mortality from SLE is estimated at up to 1 in 8 for patients with renal involvement [3]; and thus premature death remains a risk for the young women who comprise the majority of patients affected. Those patients that do survive are often burdened with problems of chronic disease, which include not only activity of the disease itself, adverse effects of treatment and complications such as irreversible end organ damage, but also impacts on outcomes such as quality of life, employment and disability.

The adoption of treat-to-target (T2T) strategies have improved patient outcomes in other chronic conditions that follow the paradigm that poor control of the disease process leads to irreversible organ damage. This has been achieved without necessarily the need for new therapeutic agents, such as is the case of tighter control of hypertension or diabetes to prevent ischaemic cardiovascular events [4–7]. This, coupled with the successful implementation of low disease activity and remission as target states in RA, prompted a push for the development of equivalent treatment target states for SLE [8].

The process of developing clinical treatment targets for a complex, multisystem, heterogeneous disease such as SLE has been challenging, and is arguably not entirely complete. Nonetheless, work over the past
several years has seen the emergence of key target states in the form of the lupus low disease activity state (LLDAS) and the definitions of remission in SLE (DORIS) framework; which may, for the first time, allow the adoption of a T2T approach in SLE.

Impact of T2T in other disease
In the clinical context, ‘T2T’ implies a process of initiating and adjusting therapy to achieve and maintain a predefined treatment goal (clinical state, laboratory marker or combination of both). Conceptually these treatment targets or endpoints must have utility (be attainable and sustainable by the majority of patients) and validity (empirical evidence of their association with desired patient outcomes).

T2T approaches have had profound impact in the management of many chronic diseases, especially those in which treatment endpoints are measurable in single organ systems, with resultant substantial reduction in the frequency of complications as well as overall mortality [4–7]. No inflammatory rheumatic condition, perhaps with the exception of uric acid in gout, has a stand-alone biomarker that accurately corresponds to treatment effect or can be undisputedly linked to improved outcomes. Correspondingly, clinical improvement may not necessarily rule out underlying inflammatory activity. As such, composite instruments using both clinical and laboratory measures are relied on to quantify a target state in rheumatology. In RA, T2T approaches, based on the attainment of low disease activity or remission defined by number of inflamed joints, physician and/or patient global assessment and measurement of inflammatory markers, have resulted in dramatically improved outcomes even prior to the introduction of biological therapies [9], and have been adopted in treatment guidelines and the assessment of novel therapies [10]. Moreover, there is evidence that attainment of a target state, rather than measuring treatment response as a change in disease activity from baseline, confers greater protection from accrual of joint damage [11], and as such there is a move to change the primary outcome endpoints in clinical trials of RA to ‘time to’ and ‘time in’ low disease activity and/or remission [10].

Targetable risk factors predicting poor outcomes in SLE
High morbidity in SLE is driven predominantly by poorly controlled disease activity and accrual of irreversible organ damage, both of which impact on health-related quality of life (HR-QoL); thus, making damage and HR-QoL the most frequent outcomes studied in SLE [12]. Damage in SLE refers to the diagnosis of irreversible end organ manifestations such as stroke, end stage renal failure or osteoporosis; it is therefore not surprising that damage accrual increases the likelihood of early mortality [13]. While some predictors of damage are not modifiable, such as older age and non-Caucasian ethnicity [14, 15], there are strong associations of high disease activity levels and glucocorticoid use as independent and modifiable risk factors for damage accrual [16–18].

SLE has a fluctuating nature with periods of relative inactivity contrasted by disease flares, although some patients have persistently active disease despite best efforts at management [19]. There is evidence that both persistent disease activity and disease flares can contribute to irreversible damage [16, 17]; therefore, reduction of overall activity levels and prevention of disease flares are valuable conceptual treatment targets. Disease activity in SLE can be measured as clinical activity (reflecting inflammation in end organs) or serological activity (elevation of antibodies to dsDNA levels or lowering of complement component 3 and/or 4 levels). While there is no doubt that untreated end organ inflammation leads to damage accrual, the role of serological activity in contributing to outcomes is less clear. ‘Serologically active clinically quiescent’ disease is a well-described entity in SLE [20], with some literature suggesting a proportion of serologically active clinically quiescent patients can spend years without emergence of new disease features [21], while others may flare [22, 23]. Certain clinical manifestations, such as lupus nephritis, are more frequent in patients with elevated anti-dsDNA levels. Patients with serologically active disease, particularly the classic markers described above, are more likely to respond to some targeted therapy [24]. The same group of patients were also found to be more likely to flare [25]. Given this potential link between serological activity and disease outcomes, the most stringent target states in SLE, such as DORIS ‘complete’ remission, require the absence of both clinical and serological disease activity (Table 1). In contrast, the more lenient target states such as LLDAS or clinical remission on treatment (CROT) allow for the presence of serological activity, but not together with clinical activity (Table 1).

Despite evidence that prednisolone doses of >7.5 mg are associated with adverse outcomes and independently predict damage accrual [18], glucocorticoids continue to be relied upon in the absence of effective alternate therapies. More recently, glucocorticoids have also been shown to independently contribute to damage not traditionally associated with steroid use in domains other than osteoporosis, avascular necrosis, diabetes mellitus or cataracts [26]. Therefore, use and dosing of glucocorticoids must be considered when thinking about target clinical states in SLE. Perhaps most importantly, it is now known that once damage is established it propagates further damage, irrespective of disease activity control [27], further highlighting the need to control the disease and reduce activity levels early in the treatment course to minimize the risk of damage accrual in the first place.

Challenges of developing and adopting T2T in SLE
The success of the T2T approach in the treatment of hypertension and diabetes is underpinned by the
availability of easily measurable treatment targets (blood pressure and HbA1c, respectively). Such is not the case for SLE, which poses some unique challenges, mainly due to the heterogeneous nature of the disease and incomplete understanding of its pathophysiology.

Because of this clinical heterogeneity, composite measures are used to assess the extent and levels of activity within different organ systems. Several instruments have been developed, of which the SLEDAI 2000 [28], BILAG [29] and ECLAM [30] are amongst the most commonly used. These indices include clinical manifestations and in some cases serological markers of disease activity. The lack of one accepted disease activity index reflects the inability of the available options to optimally express disease activity. The lack of one accepted disease activity index makes this measure less feasible for routine clinical use. However, the absence of disease activity is more attainably measured, as with diminishing activity, patients become more homogeneous and easier to group together and the lack of sensitivity of cutoffs is less impactful. Therefore, defining a state based on low levels or absence of disease activity may be intrinsically more achievable than attempting to quantify active disease across multiple systems. This allows for outcome measurement in a binary fashion – a patient is either in the desired low or absent activity state or not, and ensures that the endpoint or outcome achieved is consistent across all patients.

### Development of remission and LLDAS definitions and their effects on damage and flares

In the treatment of any disease, cure is the ultimate goal. As a cure for SLE does not seem possible in the foreseeable future, attaining remission is the next best disease state that can be envisaged. Remission is usually defined as the absence of disease activity as measured by a chosen disease activity index. Subjective symptoms such as fatigue and pain are not considered in these indices. Previous studies have shown that attaining prolonged drug-free remission is rare. In a Canadian study, in which prolonged remission was defined as a 5-year consecutive period of no disease activity (SLEDAI = 0) and no treatment (corticosteroids, antimalarials or immunosuppressants) allowed, only 1.7% of patients fulfilled the criteria [31]. Thus, even though this stringent form of remission is desirable, it does not seem feasible for the majority of patients.

Since 2012, an international group of SLE experts has developed remission criteria to be used in a T2T approach in SLE. The DORIS taskforce proposed eight potential definitions of remission. All require the absence of any clinical activity as measured by a clinical SLEDAI

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### TABLE 1 Definition of LLDAS, DORIS clinical remission on treatment and DORIS complete remission

| LLDAS | DORIS clinical remission on treatment* | DORIS complete remissionb |
|-------|--------------------------------------|--------------------------|
| SLEDAI-2K \(\leq 4\), with no activity in major organ systems and no new features of activity compared to previous assessment | Clinical SLEDAI = 0 | Clinical SLEDAI = 0 |
| Serological activity allowed (as long as total SLEDAI-2K \(\leq 4\)) | Serological activity allowed | No serological activity |
| SELENA-SLEDAI PGA \(\leq 1\) (scale 0–3) | SELENA-SLEDAI PGA \(\leq 0.5\) (scale 0–3) | SELENA-SLEDAI PGA \(\leq 0.5\) (scale 0–3) |
| Current prednisolone (or equivalent) dose \(\leq 7.5\) mg | Low-dose glucocorticoids (e.g. prednisone \(\leq 5\) mg/day) allowed | No glucocorticoids |
| Standard maintenance doses of immunosuppressive drugs and approved biological agents, excluding investigational drugs | Maintenance antimalarials, immunosuppressives and/or stable (maintenance) biologics allowed | Maintenance antimalarials allowed, but no immunosuppressives and/or biologics |

Serological activity – elevation of antibodies to dsDNA levels above the upper limit of laboratory normal or lowering of complement component 3 and/or 4 levels below the lower limit of laboratory normal. *Most attainable of the eight possible definitions of remission. bLeast attainable of the eight possible definitions of remission. DORIS: definitions of remission in systemic lupus erythematosus; LLDAS: lupus low disease activity state; PGA: physician global assessment; SELENA-SLEDAI: Safety of Estrogen in Lupus National Assessment-SLEDAI; SLEDAI-2K: SLEDAI 2000.
**Table 2** Effect of remission and LLDAS on damage accrual in observational cohorts

| Author          | Year of publication | Number of patients | Clinical remission on/off therapy | LLDAS ≥50% | Association with damage accrual |
|-----------------|---------------------|--------------------|-----------------------------------|------------|-------------------------------|
| *Zen et al.* [32] | 2015                | 224                | 37.4% of patients had ≥5 consecutive years of remission |            | Remission                      |
|                 |                     |                    |                                   |            | Unremitted disease had higher odds of damage accrual (OR 2.53; 95% CI 1.28, 4.99) |
| *Franklyn et al.* [33] | 2016                | 191                |                                    | 33.0% of visits in LLDAS | Patients with LLDAS ≥50% lower risk of damage accrual (RR 0.47; 95% CI 0.28, 0.79) |
| *Tsang-A-Sjoe et al.* [34] | 2017                | 183                | 32.5% of patients had ≥5 consecutive years of remission | 64.5% of patients had ≥50% of visits in LLDAS | Reduced risk of damage accrual for patients ≥5 consecutive years of remission (OR 0.20; 95% CI 0.07, 0.052) |
| *Mok et al.* [35] | 2017                | 769                | 25.1% of patients had ≥5 consecutive years of remission |            | Reduced risk of damage accrual for patients ≥5 consecutive years of remission (OR 0.17; s.d. ± 0.53, P < 0.001) |
| *Ugarte-Gil et al.* [36] | 2017                | 1350               | 11.6% of visits in remission | 10% of visits in LLDAS | Patients in remission had a lower hazard of new damage (HR 0.53; 95% CI 0.38, 0.75). No effect on mortality. |
| *Zen et al.* [37] | 2017                | 293                |                                    | 37.2% of patients in LLDAS ≥5 years | Reduced damage accrual for patients in ≥2 years of LLDAS |
| *Petri et al.* [38] | 2018                | 1356               | 40% of follow-up time was spent in any form of remission | 50% of follow-up time was spent in LLDAS | Longer time spent in remission was associated with lower hazard ratio of damage accrual. Rate of events/10 personyears >0–<25%: 1.01 25–49%: 0.86 50–74%: 0.77 >75%: 0.77 |
| *Tani et al.* [39] | 2018                | 115                | 45% of visits in remission on therapy | 70% of visits in LLDAS | Reduced damage accrual for patients in remission at all visits compared to patients who were not (0.12 vs 0.48 points, P = 0.018) |

2019 294 (continued)
| Author          | Year of publication | Number of patients | Clinical remission on/off therapy | LLDAS ≥50%                                                                 | Association with damage accrual                                                                 |
|-----------------|---------------------|--------------------|-----------------------------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Fasano et al.   | 2019                | 558                | 44.5% of patients had ≥5 consecutive years of remission | Patients in remission for 5 consecutive years had a greater overall cardiovascular event-free rate. HR 0.11 (95% CI 0.02, 0.47) |                                                                                                     |
| Alarcón et al.  | 2019                | 558                | 1.8% of visits in remission       | 15.1% of visits in LDAS                                                                                       | Time spent in combined remission/LDAS was associated with reduced damage accrual. Rate ratio 0.18 (95% CI 0.12, 0.26) |
| Golder et al.   | 2019                | 1707               | 47.9% of visits in LLDAS         | Attainment of LLDAS at any timepoint was associated with reduction in damage accrual (hazard ratio 0.59; 95% CI 0.45, 0.76). Patients in LLDAS ≥50% reduced risk of damage accrual (HR 0.54; 95% CI 0.42, 0.70) and flare (HR 0.41; 95% CI 0.35, 0.48) |                                                                                                     |
| Golder et al.   | 2019                | 1707               | 35.8% of visits in remission (definition 3) | Patients in ≥50% visits in remission (definition 3) reduced risk of damage accrual (HR 0.49; 95% CI 0.38, 0.65) | LLDAS more attainable (47.9% of visits) with similar risk reduction (HR 0.54; 95% CI 0.42, 0.70) |
| Floris et al.   | 2019                | 116                | 21.6% clinical remission 6 months after diagnosis | 42.2% LLDAS 6 months after diagnosis                                                                 | Reduced damage accrual for patients in LLDAS after 6 months (OR 0.20; 95% CI 0.05, 0.50) |
| Sharma et al.   | 2020                | 69                 | 33.5% of patients LLDAS ≥50% of visits |                                                                                                     | Patients in LLDAS ≥50% reduced risk of damage accrual (HR 0.37; 95% CI 0.19, 0.73) and mortality (HR 0.31; 95% CI 0.16, 0.62) |

*Disease activity measured with SLAM. HR: hazard ratio; LDAS: low disease activity score according to individual study criteria; LLDAS: lupus low disease activity score; OR: odds ratio; RR: relative risk as defined by Franklyn et al. [46]*
of 0 and a physician global assessment \( \leq 0.5 \) on a scale of 0–3, but vary in allowing for serological activity, use of immunsuppression and prednisolone of up to 5 mg. Out of the eight possible definitions of remission according to the DORIS framework, the least stringent and therefore the one with the most practical use is the definition based on the clinical SLEDAI=0, irrespective of serology and allowing for certain treatments (antimalarials, low-dose glucocorticoids, and immunosuppressives including biologics), sometimes also referred to as CROT (Table 1). Observational studies from Northern and Southern America, Europe and Asia applying these criteria showed an association with reduced damage accrual for patients in DORIS remission consistently (Table 2) [32, 34–36, 40, 41, 47]. Prolonged remission on treatment according to DORIS criteria is more attainable than strict remission (off treatment) and was seen in between 25% and 37% of patients. Furthermore, there was an association between the duration of remission and the reduction in damage accrual [38, 41, 48]. The variables associated with likelihood of attaining remission are those indicative of less severe disease, such as lower disease activity at diagnosis, lower damage index at the start of observation or absence of lupus nephritis [34, 35, 49].

Whilst remission should remain the key target state in any inflammatory disease, in SLE the stricter forms of remission are seldom attained or sustained with currently available therapies. As such, the need for a more attainable target that is still associated with protection from adverse outcomes became apparent [8, 46]. In response to this, the Asia Pacific Lupus Collaboration (APLC) embarked on a series of studies to define and validate the LLDAS. Like DORIS remission, LLDAS is a composite outcome measure that includes activity and treatment-related domains, derived using Delphi consensus methods [33]. Intuitively, the cut-offs for these are more lenient than remission, such as a SLEDAI \( \leq 4 \) and physician global assessment \( \leq 1 \), as well as prednisolone \( \leq 7.5 \) mg/day; but with the additional criteria of no new activity (clinical or serological) since the previous patient assessment (Table 1) [33]. Over the course of 6 years, the APLC has completed face, content, construct and criterion validity studies of LLDAS, with the overall conclusion that LLDAS is an attainable treatment target that is associated with reduced disease flares and damage accrual, as well as improved patient-reported outcomes (Table 2) [33, 42, 50–52].

In a prospective APLC study that followed 1707 SLE patients for a mean of 2.2 years, LLDAS was attained in just under half of all visits, with almost 80% of the cohort being able to attain LLDAS on at least one occasion, demonstrating the utility of LLDAS as a feasible target state. In the same study, even a single visit in LLDAS resulted in a 30–40% reduction in subsequent disease flare and damage accrual [42]. Furthermore, the magnitude of the protective effect increased incrementally with increasing durations of time spent in LLDAS, with almost a 90% reduction in risk of damage in patients who sustained LLDAS for 12 months or more. Similar associations of attainment of LLDAS with significant reduction in damage accrual have been found in other cohorts, with a ‘dose-dependent’ relationship between time spent in LLDAS and reduction in risk of damage. In particular, studies of three separate cohorts have shown that 50% of observed time in LLDAS corresponds to a \( \sim \)50% reduction in damage accrual [34, 38, 45]. In a longer follow-up study of 200 Norwegian patients with SLE, not only was \( \geq 50\% \) observed time spent in LLDAS protective against damage accrual, it was also associated with an almost 70% reduction in mortality [45].

Several studies have compared the effects of DORIS remission and LLDAS on flares and damage accrual (Table 2) [34, 37–39, 43, 44]. While both LLDAS and remission were associated with reduced flares and damage [34], less time was needed in remission to see significant associations (<25% observed time for remission vs 25–50% observed time for LLDAS), suggesting a stronger protective effect of the deeper remission states [38]. On the other hand, the stricter definitions of

Adapted with permission from Golder et al [49], 1707 SLE patients were followed for a mean of 2.2 years, totalling 12 689 observed visits. Of these, 6,081 visits (47.9%) fulfilled criteria for LLDAS, 4,546 visits (35.8%) fulfilled criteria for DORIS CROT and 581 visits (4.6%) fulfilled criteria for DORIS complete remission. CROT: clinical remission on treatment; DORIS: definitions of remission in systemic lupus erythematosus; LLDAS: lupus low disease activity state.

**Fig. 1 Stepwise concentric attainment of LLDAS and DORIS remission**
remission were difficult to achieve [47] and to maintain for more than a single visit (7.1% of patients in complete remission for ≥2 consecutive visits) [43]. In all but one study, LLiDAS was more attainable and sustainable than any remission definition; the exception was described in a monocentric prevalent cohort of Caucasian patients with unusually high rates of remission [37]. In contrast, in an inception cohort of newly diagnosed SLE, LLiDAS was attained in twice as many patients compared with clinical remission within 6 months of treatment (42.2% vs 21.6%) [44]. In the APLC cohort, all eight DORIS definitions of remission and LLiDAS were compared side by side. LLiDAS and remission were shown to be concentric stepwise target states, such that patients who fulfill the criteria for the stricter forms of remission also fulfilled criteria for LLiDAS, but not vice versa (Fig. 1) [43]. Interestingly, a small proportion of patients fulfilled the criteria for CROt but not LLiDAS, based on new serological activity from previous assessment (new elevation of antibodies to dsDNA or lowering of complement levels), which is not allowed in LLiDAS and not accounted for in CROt (Fig. 1). Likewise, each increase in the stringency of a target state resulted in a reduction in attainability, with sufficient separation between LLiDAS and remission (tested by assessing only those visits meeting criteria for LLiDAS but not for remission) to demonstrate the usefulness of LLiDAS and remission as individual stepwise targets.

Effect of LLiDAS and remission on patient-reported outcomes

The negative impact of SLE on HR-QoL is comparable to other chronic diseases such as chronic heart failure, coronary artery disease, end-stage airways disease, human immunodeficiency virus and RA [53–55]. From a patient’s perspective, HR-QoL is an important outcome parameter, as it reflects aspects of the burden of disease not captured in physician measures.

In two studies of different cohorts, prolonged remission (≥5 years) was associated with higher HR-QoL as measured by both SF-36 and LupusPRO [35, 56]. No association was found with the mental component, which was also shown in a separate Italian study [57]. Likewise, two large cohort studies assessing the relationship between LLiDAS and HR-QoL have demonstrated that LLiDAS is associated with improved HR-QoL, as measured with both a generic (SF-36) and an SLE-specific (SLEQOL) instrument [51, 58]. These observations further support the use of clinical remission or LLiDAS as a target of SLE. While the more lenient definitions of remission and the LLiDAS definition of low disease activity may perform similarly from a measurement standpoint, it is important to note the conceptual difference between a disease state that is defined as the complete absence of clinical symptoms and a state that allows for a certain low level of disease activity.

The role of T2T endpoints in clinical trials

When compared with other rheumatic diseases, there has been a considerable lag in the development of effective targeted therapies for treatment of SLE. Of the multiple potential therapeutic agents in the clinical trial pipeline, only two have managed to hit Phase III trial primary endpoints in the last 8 years. Belimumab, an antibody blocking B-lymphocyte stimulation, reached statistical significance in two Phase III trials, particularly in serologically active patients with musculoskeletal and mucocutaneous disease [1, 2]. However, the absolute effect size of belimumab over placebo as measured by the SLE responder index (SRI) appears to be small, suggesting both the need for a more robust endpoint to better discriminate responders from non-responders and the need for therapies with different mechanisms of action. Anifrolumab, an antibody to the type I interferon receptor, achieved the primary endpoint of the British Isles Composite Lupus Assessment (BICLA) in a second pivotal Phase III trial [59].

The reasons for the lacklustre results in SLE trials are multifactorial, including complex immunopathogenesis, clinical and biological disease heterogeneity, debate about optimal trial design with criticisms regarding the dose of concomitant glucocorticoids and immunosuppression allowed, and, most importantly, endpoint measures that may have hindered the ability to differentiate responders from non-responders [49, 60]. The use of historical endpoints that lack sufficient validation for use as primary outcome measures for clinical trials in SLE is a state of affairs recently described as a ‘crisis’ [61]. And yet, in the absence of other options, these historical endpoints have continued to be used as a priori primary outcomes.

In this setting, LLiDAS is now being tested as an outcome measure in clinical trials of existing and novel therapies. In a head-to-head superiority comparison of mycophenolate and azathioprine in patients with active SLE, LLiDAS was assessed as a secondary discriminant outcome measure, with more patients in the mycophenolate treatment group attaining and sustaining LLiDAS compared with patients treated with azathioprine (79% vs 57% at 12 months, respectively) [62]. In studies of novel therapies including belimumab, atacicept, baricitinib and anifrolumab, LLiDAS was able to discriminate responders to active drug from placebo [63–66]. Moreover, LLiDAS was a more stringent discriminator compared with currently used responder indices such as SRI and BICLA [63–65]. In the post-hoc analysis of the anifrolumab Phase IIb trial, 74–87% of patients in LLiDAS at week 52 were also SRI/BICLA responders; on the other hand, only 47–51% of SRI/BICLA responders reached LLiDAS [64]. Compared with placebo, patients treated with anifrolumab were two to three times more likely to attain LLiDAS at 52 weeks. The implications of this for design of future Phase III trials is enormous, as a more discriminatory endpoint may enable trials with more robust findings.
In contrast, DORIS remission has been harder to achieve in the clinical trial setting, thus far only studied in relation to belimumab, with the lack of discrimination between placebo and active treatment using remission as an endpoint potentially reflecting the result of combining moderate efficacy of drug with a higher stringency outcome measure [67].

Conclusions and future directions

The body of work giving rise to and validating DORIS remission and LLDAS has, for the first time, provided feasible and validated treatment targets for the adoption of T2T strategies in SLE. Several key steps need to occur to build on existing studies prior to the approval of these target states by regulatory agencies, and hence use as primary endpoints in clinical trials; or the adoption into clinical guidelines, and hence use in routine patient care.

As with any study arising from an observational cohort, there are inherent limitations to the conclusions on the causal relationship between remission or LLDAS and improved disease outcomes. In order to test this, an interventional trial is needed using a T2T approach with non-attainment of LLDAS or remission as an inflection point for treatment escalation, compared with conventional management, as has been done for RA [9]. Not only will such a study address causal impact on patient outcomes, it may also address the deployability of LLDAS or remission with assessment of the resources required for use in clinical practice. DORIS remission requires refinement of criteria, particularly pertaining to immunosuppression and glucocorticoids, using data from longer follow-up prospective cohorts, allowing narrowing from eight framework definitions to one or two, in order to have utility in routine practice or clinical trials.

In summary, LLDAS and DORIS remission represent tangible and concentric clinical target states, shown to be associated with a reduction in adverse outcomes including disease flares and damage accrual, as well as improvement in patient-reported measures such as HR-QoL. With some further work, these endpoints have the potential to allow the adoption of a T2T approach in routine patient care, and provide robust and discriminative outcome measures for use in clinical trials.

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