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SPECIAL ARTICLE

Value and goals of treat-to-target in systemic lupus erythematosus: knowledge and foresight

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Treat-to-target is a therapeutic strategy aimed at improving disease outcome through the achievement of shared treatment goals, which has dramatically ameliorated the prognosis of widespread disorders, such as hypertension or diabetes.

Conversely, efforts to delineate treat-to-target in systemic lupus erythematosus (SLE) have failed in pinpointing common goals and treatment strategies, probably because of disease heterogeneity and lack of measurable biomarkers predicting disease course and ensuring a safe treatment tapering during quiescence.

Given the detrimental effects of persistent disease activity and protracted corticosteroid therapy on patients' outcome in lupus, disease remission should be pursued whenever possible. Fortunately, clinical remission is currently realistic for a greater number of patients than it was in the past, yet tight monitoring is required in order for patients to benefit from disease- and corticosteroid-free intervals, while minimizing the risk of disease flares.

In everyday practice, patients should be brought to the lowest level of disease activity ensuring a significant benefit over a persistently active disease, being either clinical remission or low disease activity. *Lupus* (2015) **24,** 507–515.

Key words: Systemic lupus; target; remission; low disease activity; corticosteroid tapering; outcome

Introduction

Treat-to-target may be defined as a therapeutic strategy aimed at treating patients to a goal that is capable of improving disease outcome.[1,2] Attempts are being made to apply treat-to-target to systemic autoimmune rheumatic diseases; however, shared treatment strategies and validated outcome measures that can point to a common goal are still lacking in this field. In fact, unlike metabolic disorders (e.g. diabetes or dyslipidemia), no single measurement is available in systemic autoimmune diseases that faithfully depicts disease course and patient outcome; therefore, single therapeutic targets are hardly pinpointed.

It is worth noting that persistent disease activity worsens the long-term prognosis in prototypic organ-dedicated or multisystemic autoimmune rheumatic diseases, i.e. rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[1,3] Accordingly, a treat-to-target strategy was recently introduced in RA, outlining complete remission as the primary goal and low levels of disease activity as an acceptable benchmark when complete remission is not achievable.[4,5]

In this paper we will discuss the value of treat-to-target in SLE and difficulties that have to be overcome in order to exploit it fully.

Value of treating to target

Abnormal conditions such as hyperlipidemia, hyperglycemia or hypertension can be faithfully monitored through quantifiable laboratory measurements and have definitely benefited from treat-to-target strategy. In fact, discrete values of glycosylated hemoglobin (Hb1Ac), blood pressure and cholesterol levels have been reliably linked to patient prognosis,[6,7] and controlled clinical trials have supported the definition of quantitative thresholds below which life expectancy and organ function are preserved. As an example, Hb1Ac

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lower than 6.5% may halt organ damage in diabetic populations, and lowering blood pressure below 140/90 mmHg reduces the hazard of stroke or myocardial infarction.[7,8] Therefore, clinicians are able to point to a precise target that is universally accepted.

In regards to RA, a few trials have been carried out investigating the value of treating to target versus routine care treatment.[9–12] Three out of four trials[9–11] demonstrated outcome measures were ameliorated in the intensive-treated patient group.

According to the tightly control-based study named Tight Control of Rheumatoid Arthritis (TICORA),[9] patients with early RA who had rapidly been brought to lower levels of disease activity—quantified using the Disease Activity Score (DAS) 28 score—had less radiological progression of bone erosions. However, radiographic progression was not found to be halted in other studies despite clinical improvement,[10,12,13] and one study did not even include radiographic progression among outcome measures,[11] thus suggesting that no shared targets could be unanimously pinpointed that improved prognosis of RA patients.

This notwithstanding, 10 recommendations on RA management have recently been elaborated[5] that take into account improvement in joint function and reduction in inflammatory burden following treat-to-target strategy, suggesting that physicians generally believe in the value of treat-to-target despite weak consensus on treatment strategies, study designs or outcome measures.[14] This may be due in turn to the lack of reassuring surrogate biomarkers that can be easily monitored (such as Hb1Ac in diabetes) and especially to the lack of shared pre-specified treatment objectives that will surely improve patient outcome in RA as well as in SLE.

Treat-to-target in SLE

One big expert panel has been held to define treat-to-target in SLE.[15] Several fair questions have been raised as to what type of response is desirable and how fast it should be achieved. For a few treating objectives to be pinpointed, major determinants have to be found out that significantly influence patients' prognosis.

It is well known that lupus patients still display a higher standardized mortality rate compared with the general population[3] as well as a poorer quality of life, mostly triggered by accumulating damage.[16–20] In fact, causes of death related to active disease are progressively fading in SLE, while exhausted organ function with intervening infections and cardiovascular events drive the majority of deaths.[3]

We have recently analyzed the effect of different disease activity patterns on damage accumulation,[21] showing that persistent or relapsing-remitting disease activity (RRD) is associated with the greatest damage accrual in follow-up, which is in keeping with previous observations.[22]

Continuative corticosteroid exposure was extensively proven to foster cardiovascular damage, ocular damage and osteoporosis, with premature fractures[23] being responsible for the bulk of late damage accrued by patients.[23,24] The risk of adverse events and damage-related costs are greatly increased as daily steroid intake is increased to high dosage,[25] but it is worth noting that a daily intake of even medium corticosteroid dosage (i.e. $\geq$6.6 mg/day of prednisone or equivalent) is endowed with an increased damage accrual in SLE patients.[18]

This notwithstanding, medium dosage of steroids is currently used in long-term treatment of lupus patients, which is probably due both to past legacies and a lack of reliable tools assessing stability of patients' condition over time.

Taken together, these data show persistent disease activity and protracted corticosteroid treatment to be the major predictors of damage accrual, suggesting that disease activity control and corticosteroid tapering should reasonably represent the utmost targets in SLE management.

Dampening of disease activity together with drug de-escalation do not embody different goals, rather they can be grouped under the definition of disease remission, which should be the major target for treating SLE patients.

Remission in SLE

Remission was previously discussed as an intuitive desirable target;[15] however, a shared definition of remission and treatment strategies is lacking. Remission in SLE should not be intended just as the absence of disease activity (i.e. 0 on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score); rather, the concept of stable remission entails the chance of treatment discharge and especially corticosteroid discontinuation.

Though no validated index exists that is specifically dedicated to measure disease remission in lupus, two main types of remission are commonly

seen in clinical practice, i.e. complete and clinical remission, which may be intended as a clinical-serological healing in patients who are free of any treatment, or as the absence of signs, symptoms, urinary and hematological abnormalities in patients who are at least corticosteroid free, respectively.

Clinical remission may be either complete or partial according to the need of low-dose steroids, hence patients experiencing a clinical quiescence with low-dose steroids (i.e. $\leq$7.5 mg/day prednisone or equivalent) can be reasonably intended as partial clinical remitters.[1,3,18]

One may wonder why patients on immunosuppressants, e.g. azathioprine or mycophenolate, albeit corticosteroid free would be considered in clinical remission, since they are actually on treatment. In contrast to RA, for which corticosteroids were shown to halt radiographic progression, thus emerging as real disease-modifying antirheumatic drugs,[26] continuous corticosteroid intake at low-medium dosage cannot be indicated as a disease-modifying approach in SLE. Indeed, corticosteroids at low-medium dosage do not significantly influence SLE immunological burden and mainly exert an anti-inflammatory effect, being required in case inflammatory manifestations are present. Notably, corticosteroids even at low-moderate dosage contribute to damage accrual in SLE.[23,24] Conversely, a proper immunosuppressant therapy should aim at both the initial dampening of disease activity and subsequent preservation of disease quiescence, as is witnessed by the need for immunosuppressive maintenance therapy following the induction phase in the treatment of lupus nephritis. Thus, the role of immunosuppressants following the acute stage of disease is not to reduce disease activity but to prevent disease relapses, thereby also facilitating corticosteroid tapering in the long term.

Similarly, patients solely on antimalarials may be considered in clinical remission since these drugs were shown to ameliorate patients' survival and prognosis in the long term,[27] thus contributing to an enduring remission.

Recently, Steiman et al.[28] have proposed a widened concept of clinical remission encompassing patients being either serologically and clinically quiescent (SLEDAI = 0 for at least five years), serologically active and clinically quiescent (SLEDAI-2000 (SLEDAI-2 K) = 2 or 4 for at least five years) or who fluctuated from a condition of clinical and serological quiescence to a transient serological activity with no clinical symptoms (mixed remission). Patients were either medication free (except antimalarials) or they were taking corticosteroids or immunosuppressants in order to maintain clinical remission (medication group). In keeping with previous data,[29] the percentage of patients experiencing a prolonged remission was low in both groups (about 2%) with a higher adjusted mean SLEDAI score prior to remission in the medication group.

Mean remission duration was longer in the medication-free group versus the medication group (11.5 years versus 8.5 years) yet not statistically significant. Interestingly, patients in mixed remission showed the longest average remission (nearly 17 years) regardless of serological activity.

No clear-cut period of clinical quiescence has yet been indicated that can classify clinical remission as durable. Urowitz et al. had previously proposed a five-year long disease- and treatment-free interval (also excluding antimalarials) for a complete remission to be defined; this was achieved by a very small percentage of lupus patients in that cohort.[29] As expected, the number of patients in prolonged remission increased as less-stringent definitions of remission were adopted, with a surprising 24.5% remitters when remission was defined as clinical quiescence for one year, yet allowing serological alterations and medications intake including corticosteroids.[29] This least-stringent and provocative definition shows that different definitions may account for different percentages of patients being classified as remitters. This is a point that should be cautiously considered, since patients taking immunosuppressants or even corticosteroids are likely to have their disease suppressed by medications[28] and would not admit a safe treatment tapering. On the other hand, too stringent definitions of remission, e.g. not admitting stable serological alterations, entail the risk of disregarding patients who are likely to persist in a durable clinical quiescence with no need of (over)treatment.

Remission optimizes patients' outcome in SLE

Early remission (within one year from disease onset) was shown to be predictive of a better outcome in SLE in a large multicentric inception cohort of patients prospectively followed up for five years, being associated with significant reduction in disease flares, organ damage and overall cumulative corticosteroid dosage.[30] Conversely, long-term prognosis remained poor in active patients.[30,31] In this regard, a retrospective analysis had shown renal survival to be increased in patients who achieved either complete or partial disease

remission in comparison with persistently active patients, whereas overall survival at 20 years was significantly increased only for those in complete disease remission.[32,33]

Prolonged disease quiescence is intuitively linked with a better prognosis; however, prospective studies supporting this issue are lacking; in any case, premature discontinuation of treatment is associated with disease flares,[34–36] which may per se worsen patients' outcome.

The value of low disease activity (LDA)

Though remission is associated with the best outcome, the matter of LDA is pending in SLE since complete remission and sometimes even corticosteroid-free clinical remission are hard to reach and maintain for a number of patients. In RA, LDA was seen to ameliorate patients' prognosis, ensuring a functional improvement together with halting of long-term joint damage,[37] but whether LDA can be considered a treatment target in SLE has still to be established.

In choosing what degree of disease quiescence is more suitable to any patient, the concept of disutility[38] has to be considered in SLE; indeed, clinicians should go over the issue of what is the real incremental benefit of treating patients to complete remission rather than to clinical remission or LDA. In other words, do benefits connected to additional therapies striving for null disease activity provide a prognostic gain in terms of survival or functional improvement? Do benefits outweigh the risks of medication-related damage? These points were addressed in metabolic disorders such as diabetes, in which the pursuit of very intensive targets for cholesterol levels and blood pressure did not improve the prognoses of patients who had already reduced their risk of cardiovascular events.[39] Similarly, the incremental benefit of additional therapies in RA may be smaller in patients who are already at LDA or in clinical remission rather than in patients with active disease. Accordingly, LDA was posed as the target to be aimed at in most studies testing a treat-to-target approach in RA[9,11,12] but in one study posing remission as the main goal.[10]

Unfortunately, a shared definition of LDA is lacking in SLE, which is primarily due to difficulties in defining a level below which disease activity can be unanimously considered as "low" or "not harmful," and moreover reproducible measures quantifying this condition are lacking. Recently, we have found that a minimal persistent disease activity (MDA) defined as a SLEDAI-2 K equal to 1 in three annual visits does not foster damage accrual more than a long-quiescent disease.[21]

The concept of MDA can partially overlap with that of LDA, suggesting LDA would be an acceptable target for a great number of lupus patients who cannot reach a stable remission. However, LDA encompasses alterations involving diverse organ systems, among which tolerable organ-specific disease activity thresholds minimizing damage accrual are still hard to define.

Treating to a biological or clinical target?

One study on treat-to-target in RA aiming to remission has previously shown that radiographic progression was not steadily halted in the intensive-care patient group despite persistent clinical improvement.[10] In fact, clinical remission may not always reflect a real biological remission in terms of normalization of histological or radiological findings.

With regard to RA, the question was posed whether patients in clinical remission yet displaying unapparent synovitis should be treated to any power Doppler activity. Some evidence suggests they should,[40] since persistent synovial inflammation would herald further erosions and joint damage.

In the lupus field, it is likely that patients with no signs of organ compromise may instead display silent alterations either at early stages of disease or during clinical remission,[41,42] hence the question was posed whether such silent abnormalities may be threatening to treatment tapering. Accordingly, a recent retrospective study has suggested that patients with persistent active renal lesions yet without renal abnormalities (i.e. normal serum creatinine, proteinuria <0.5 g/day, no active urinary sediment) would benefit from a longer immunosuppression compared to those displaying both histological and clinical quiescence;[42] however, conclusive data are still lacking.

Though a paired biological-clinical remission would be reassuring (e.g. absence of inflammatory renal lesions after clinical resolution of lupus nephritis), this ideal objective should be founded on the evidence that histological lesions are capable of predicting poor disease course despite a stable clinical remission, which is not yet available in SLE. Unlike synovitis in RA, most of the abnormalities reported to be associated with a higher risk of functional

impairment in SLE did so in patients who concomitantly showed worsening organ function[43] and were doing neither clinically nor biochemically well.

Hence, aiming for a biological remission is likely to entail the risk of overtreating patients with no assurance they are actually pointing to a grounded improvement.

Definition of treatment goals

Based on clinical experience and observational data from longitudinal studies,[29–33] we have recently defined complete remission as the major treat-to-target for SLE patients[1] (Figure 1), which is associated with the best outcome in the long term. However, clinical remission (either complete or partial) can be an effective alternative target as well. SLE patients still displaying minimal signs of disease activity yet doing well in clinical practice fall into a status of LDA that can be set in the third place (Figure 1).

Strategies to treat-to-target

Once treating objectives have been defined, physicians should exploit the most effective tools to achieve the target.

Early diagnosis and early treatment

In lupus, promptness in diagnosis plays a prominent role in leading to early treatment and influencing long-term prognosis. Noteworthy, the optimal lag time to treatment in renal involvement (particularly proliferative lupus nephritis) is likely to range between three and five months;[31,44] indeed, initiation of therapy within five months from onset of clinical manifestations was proven to provide prolonged remission in the long term, which was not applicable if time to treatment was longer than five months.[44]

No other specific windows of opportunity have been pinpointed yet regarding other organ systems; however, the shorter the interval between onset of manifestations and treatment, the better patient

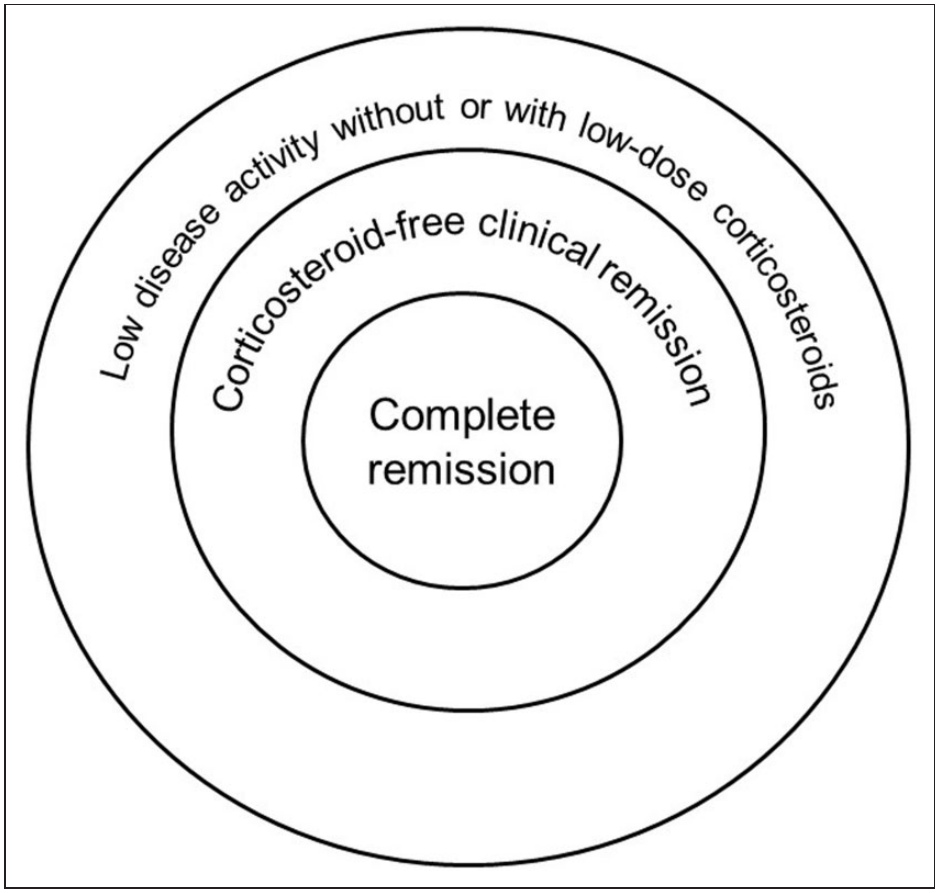

Figure 1 Bulls eye target in lupus.

outcome in the long term.[31] To date, the mean lag time to lupus diagnosis is about nine months,[31] which greatly overcomes the theoretical window of opportunity shown in studies on glomerulonephritis. Unfortunately, neither serum biomarkers nor new classification criteria are suitable to an early diagnosis,[45] and no reliable prognostic factors exist that predict development of overt SLE in antinuclear antibodies (ANA)-positive patients, for whom a close follow-up looks reasonable.

The question of preventing disease onset is tantalizing to all rheumatologists; however, no prospective observations have been carried out testing a full therapy in asymptomatic people displaying stable serological alterations, e.g. ANA positivity or complement decrease. It is likely that patients displaying new-onset serological abnormalities might benefit from only close monitoring and/or early administration of antimalarials and vitamin D, especially if more specific findings are present (i.e. anti-DNA antibodies), according to the physician's own discretion.

It is worth reporting the limited longitudinal experience analyzing the (bulk) increase in steroid dosage in asymptomatic SLE patients displaying significant changes in serology (e.g. significant fall in complement levels or increased anti-DNA antibody titers) in order to anticipate possible disease flares.[46,47] Patients taking high-dose prednisone (30 mg/day) were shown to avoid disease flares in one study;[47] however, the risk of overtreatment and corticosteroid-related side effects cannot be neglected and should be cautiously considered.

Corticosteroid tapering

Given the positive impact of remission on SLE prognosis, the question is always pending as to how to maintain remission in the long term while tapering corticosteroids and eventually immunosuppressants; indeed, no guidelines could yet pinpoint a minimal span of clinical quiescence beyond which treatment tapering entails no risk of relapse.

Corticosteroid tapering should be aimed at while applying treat-to-target, since avoidance of surplus steroid treatment during stable clinical remission can prevent corticosteroid-related damage accrual. Actually, both the rate and costs of adverse events related to corticosteroid misuse are likely to be greatly increased for medium-to high-dose corticosteroids.[25] On the other hand, no clear cutoff dosage exists abolishing long-term damage in SLE patients, though <6 mg/day of prednisone or equivalent in patients who could not completely get rid of the corticosteroid possibly reduced the burden of corticosteroid-related damage in a previous study.[18] However, observations in our cohort of 225 SLE patients have shown that even low-dose steroids can trigger damage accumulation in patients in clinical remission versus patients who are completely corticosteroid free (Doria A, unpublished observations).

The usefulness of corticosteroid-free intervals was proven in prospective studies enrolling patients with no clinical signs of disease activity yet with active serology.[48] Indeed, the "gray zone" of SLE patients entering in a durable clinical remission with persisting serological abnormalities (serologically active/clinically quiescent patients) was shown not to merit corticosteroid therapy yet maintaining disease quiescence for several years, suggesting that slight serological abnormalities do not effectively predict disease course. Importantly, close patient monitoring is required following corticosteroid-free remission, with a suitable interval of three to four months between visits.[49]

Treating until the target has been achieved: Is it mandatory?

The time required to remission in any single patient cannot be faithfully predicted at baseline, and the question was posed as to how and when to change treatment regimens. In this regard, longitudinal observations on time to proteinuria normalization (<0.5 g/day) in 212 patients with proliferative nephritis showed that the time of recovery is in any case slow and that it is very important not to change treatment strategies in the first six months—which is the current span required to induction therapy—unless a frank worsening occurs in the first three months.[50,51] The latency period to improvement in this study[50] may be due to a carry-over effect of some drugs (e.g. cyclophosphamide) in the early phases of lupus nephritis treatment.

Conversely, one may ask whether patients should be brought to their desirable target with a full treatment or if tapering could be cautiously provided when patients are on their way to remission. To date, it is well known that premature treatment discontinuation can pave the way to disease flares,[33,35,36] and no rule has yet established when early runs the risk of being too early. Therefore, treatment tapering and eventually withdrawal should be reasonably advised only when a stable remission is present.

Pros and cons of treat-to-target in SLE

Treat-to-target in systemic rheumatic diseases was recently blamed for inapplicability, primarily owing to lack of shared strategies aimed at reaching theoretical treatment goals and to real-life impediments in extending the same targets to all patients[14] (Table 1).

Learning from evidence on RA, aiming to prespecified targets can optimize both treatment strategies and disease outcome,[9–12] which is likely to apply to SLE as well. In fact, directing lupus patients toward the lowest reachable level of disease activity they are able to maintain with the lowest effective treatment would probably entail significant prognostic benefits in comparison with a persistently active disease.[21] Even though prospective data are lacking, pointing to the most suitable degree of disease quiescence avoiding overtreatment would provide additional benefits on patient outcome in terms both of organ function and life quality, reasonably outweighing the risks of disease- and drug-related damage.[38]

Definition of achievable targets (e.g. LDA in spite of complete or clinical remission) would also help less-experienced rheumatologists in exploiting the most adequate therapeutic strategy to that goal.

In addition, delineating a grounded pathway to be pursued by clinician and patient together would increase patients' adherence to treatment. Indeed, treat-to-target strategy may be influenced by patients' point of view because of the risk of poor compliance and/or patients' fear of losing control of their disease while changing treatment regimens.[14] As an example, some lupus patients feel more comfortable on low-dose steroids rather than stopping them completely, even when experiencing disease quiescence.[36] Taking into account such issues in clinical trials on RA (even in case of long-lasting disease) led to the evidence that patients achieving a reachable target tend to optimize adherence to treatment and minimize treatment discontinuations,[52] which seems applicable to SLE as well.

One of the major cons that was raised in treat-to-target applied to SLE is that not all lupus patients tend to complete remission, and currently no clear hierarchy could be established among surrogate goals that can stand for remission.[2] Moreover, patients from different ethnicities may be more or less likely to achieve remission, with SLE being usually less severe in the white Caucasian population.[53]

Actually, lupus patients tend to different degrees of disease quiescence, ranging from complete or clinical remission to LDA, and the most suitable goal for each patient should be indicated taking into account the specific disease activity pattern, prominent disease manifestations, accrued damage and burden of medications. Moreover, treatment goals may not only change among different patients, but also they can vary along one patient's history because of changing disease activity patterns. Accordingly, patients suffering from a RRD or a chronic active disease (CAD)[21,54] need to be treated differently to have their flares prevented during disease quiescence (RRD) or they are brought to a stable degree of remission (CAD); in turn, clinical remission also requires an effective continuative treatment in order to be maintained in the long term, avoiding disease flares.

The question was also posed whether clinical or biological remission or both should represent the ideal target of a successful therapeutic strategy;[42] currently there is no evidence that a biological remission would improve patients' prognosis significantly more than a prolonged clinical remission, even though a paired clinical and biological remission with no acute or chronic lesions would suggest the complete recovery of organ function. Actually, the risk of overtreatment is intimately linked with the effort of treating patients to biological remission; on the other hand, pointing toward loose treatment goals entails the risk of patients' undertreatment and flares.

Table 1 Pros and cons of treat-to-target in SLE

Pros	*Cons*
Pointing to a pre-specified target can optimize treatment strategies thus improving SLE outcome.	Pointing to a precise target is hard owing to SLE heterogeneity.
Definition of a few effective treatment goals will help experienced and less experienced physicians in SLE management.	Treatment goals can vary according to different phases of disease course and/or pattern of disease activity.
Pointing to a reachable target improves patients' compliance.	Pointing to non-appropriate treatment targets entails the risk of patients' overtreatment or undertreatment.
	Clinical and biological targets may diverge in SLE.

SLE: systemic lupus erythematosus.

Concluding remarks

Growing knowledge of lupus course and drawbacks of inadequate treatment schemes should compel physicians to pursue therapeutic targets capable of improving patients' outcome. Treatment strategies should be primarily founded on the need to influence patients' prognosis in the long term. In this regard, control of persistent disease activity and reduction of corticosteroid burden should be aimed at for all patients. At the same time, complete remission, clinical remission or LDA are not to be seen as different treatment goals, rather they should be read as different scores of the same lupus ''bulls eye target'' aiming to the highest degree of disease quiescence that can be applied to any patient (Figure 1).

Despite intrinsic obstacles, treating to a target may render lupus patients more confident and rheumatologists more forward-seeing, probably representing the right approach for lupus to be steadily tamed and not indefinitely chased.

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Conflict of interest statement

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