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REVIEW ARTICLE

Treat to target in systemic lupus erythematosus: a commentary

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Abstract Treat to target (T2T) strategies have proved to be useful in several chronic disorders, including Rheumatoid Arthritis. In systemic lupus erythematosus (SLE), T2T strategy has been proposed in order to control disease activity, improve health-related quality of life, and reduce morbidity and mortality. Remission would be the main target, but a low disease activity state (LDAS) could be an acceptable alternative. However, due to SLE protean manifestations, the operational definitions of both remission and LDAS are still in progress. The definitions of these targets, remission and LDAS, should include a validated disease activity index, the treatments allowed, and the minimum length of time the target should be maintained. Furthermore, achieving these targets should result in better disease outcomes such as reducing damage accrual. This review addresses the current state regarding these possible targets in SLE and the impact of achieving them in intermediate and long-term outcomes of this disease.

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Introduction

Over the last few years, treat to target (T2T) strategies have been proposed as means of improving the management of several chronic diseases and, consequently, their outcome. In 2003, for example, Riddle et al. proposed titrating insulin in patients with diabetes with an inadequate response to oral antidiabetics [1]. Subsequently, several studies have been performed using T2T strategies in order to determine not only their primary efficacy, but also composite endpoints, collateral benefits and safety; in the case of diabetes, a target of glycated hemoglobin to be obtained in all treatment arms was defined; however, a comparison of safety endpoints, such as nocturnal or severe hypoglycemia, may allow establishing the risk-benefit profile of such strategy [2].

In the autoimmune diseases, a T2T strategy was first proposed in rheumatoid arthritis (RA); in this case, the target was remission or low disease activity [3]. T2T strategy has changed the design of clinical trials in RA; before then, new drugs were compared with a standard of care, but in fixed doses. After the introduction of T2T, several trials have been conducted comparing different strategies in order to reach the target; for example, in the BeSt study, patients on the initial combination therapy plus prednisone or the initial combination plus infliximab achieved the target earlier than those on sequential monotherapy or step-up combination strategy; furthermore, these patients had better outcomes in terms of functional capacity and radiographic damage using low disease activity as the target [4].

Based on these results, it would be expected that a T2T strategy could be also quite useful in the management of patients with systemic lupus erythematosus (SLE).

T2T in SLE: defining the target

Despite the fact that the survival of SLE patients has increased during the last 50 years, SLE patients still have a threefold increased risk of death [5], and the risk of death due to cardiovascular disease, infections, and renal disease are significantly increased [5]. Nevertheless, as SLE patients live longer, organ damage increases due to disease activity, comorbidities, and the side effects of therapy [6]. Thus, treatment in SLE should aim at ensuring survival, preventing organ damage, and optimizing health-related quality of life, by controlling disease activity and minimizing comorbidities and drug toxicity [7]. Although the concept of remission in lupus has been around for quite some time, concerted international efforts to define it (as well as the related concept of low disease activity status, LDAS) have only occurred over the last few years. According to the International Task Force named DORIS for Definitions Of Remission In SLE, "the treatment target of SLE should be remission of systemic symptoms and organ manifestations or, where remission cannot be reached, the lowest possible disease activity, measured by a validated lupus activity index and/or by specific organ markers." [7] Similarly, the international group Asia Pacific Lupus Collaboration (APLC) has advanced an operational definition of LDAS. Therefore, it has been proposed that the target should include both remission and LDAS (similar to RA); additionally, immunosuppressive therapy with a low risk of toxic side effects and a dose of glucocorticoids as low as possible should be considered [8]. Furthermore, since SLE is an autoimmune disease with diverse clinical manifestations and organ system involvement, targets could be different depending on the affected organ(s).

We will now discuss several possible targets in SLE:(1) remission; (2) serologically active, clinically quiescent disease (SACQ); (3) minimal disease activity (MDA); and (4) LDAS.

Remission

Remission refers to the absence of disease activity and several definitions have been used over the years. The majority of them include a disease index like the systemic lupus erythematosus disease activity index (SLEDAI), or its variants but other definitions have been also used.

Prior to the development of disease activity indices, remission, defined as the absence of clinical and laboratory activity and no treatment for a median of 75 months, was reported in 4 of 160 patients in the Toronto cohort [9]. Another definition of remission that preceded disease activity indices was the one used in a Mexican cohort which included the absence of clinical activity and medications for at least 1 year but immunological activity was not included. Using this definition, 23.4 % of 667 patients achieved remission during their follow-up [10]; of note, 50 % of those patients who were followed up for 20 years achieved remission for at least 1 year.

The first time the SLEDAI was used to define remission (SLEDAI = 0) was in the Toronto cohort; in this study, glucocorticoids and immunosuppressive drugs could not have been used, but antimalarials were allowed. Using this definition, only 1.7 % of 703 patients achieved this outcome for 5 years, whereas 10.2 % achieved it for 1 year [11]. However, if glucocorticoids and/or immunosuppressive drugs regardless of their dosage were allowed, 1.8 % achieved remission for 5 years and 18.9 % for 1 year [11]. A similar definition (SLEDAI = 0, no immunosuppressives, no glucocorticoids, but antimalarials allowed, for at least 5 years) was used in an Italian cohort; in this study, 7.1 % of 224 patients achieved remission [12]. A variation of this definition (SLEDAI = 0 for at least 1 year, without medication and abnormalities in the laboratory) was used in a Spanish cohort; in this study, 24 % of 100 patients achieved remission [13].

In 2015, DORIS defined remission by consensus as a durable state characterized by the absence of symptoms, signs, and abnormal laboratory results. They noted that remission could be achieved off therapy (only antimalarials) or on therapy (prednisone ≤5 mg/day, maintenance immunosuppressive drugs and/or maintenance biologics) [14]. An operational definition of remission was developed by the Lupus Clinical Trials Consortium (LCTC) group based on the work of DORIS and APLC: SLEDAI = 0 and physician global assessment (PGA) ≤0.5 which could be achieved on- or off therapy. Based on this definition, 7.6 % of 1228 patients in this registry achieved remission on therapy and 5.4 % achieved remission off therapy for at least 1 year [15].

Using a similar definition of remission (SLEDAI = 0 and physician global assessment (PGA) ≤0.5, prednisone ≤5 mg/day without immunosuppressive drugs), 16 % of 1555 patients from the Hopkins Lupus cohort were found to be in remission for at least 1 year, and 2 % for at least 5 years [16]. If instead four categories of remission were used [1. complete remission (clinical, serological, PGA) on therapy (prednisone ≤5 mg/day and maintenance immunosuppressive drugs); 2. same, off therapy; 3. clinical remission (regardless of immunological activity) on therapy; and 4. same, off therapy], the median duration of remission was 3 months and it was similar for all groups; antimalarials were allowed in all groups [17].

In the GLADEL (*Grupo Latino Americano de Estudio de Lupus*) cohort, remission (SLEDAI = 0), on therapy (prednisone ≤5 mg/day and/or maintenance immunosuppressive drugs), and off therapy (only antimalarials allowed) were achieved in the 9.7 and 1.9 % of the intervals examined in

1355 patients. In these analyses, interval was defined as the time between two SLEDAI measures which, per protocol, was ascertained every 6 months.

In the University College London Lupus cohort, remission defined using the British Isles Lupus Assessment Group (BILAG) scores of C, D, or E, absence of immunological activity, and neither glucocorticoids nor immunosuppressive drugs, but allowing antimalarials, 14.5 % of 532 patients achieved remission for at least 3 years, and 4.7 % for at least 10 years [18].

Serologically active, clinically quiescent (SACQ)

The concept of SACQ disease was defined by the Toronto group and includes patients with immunological (low complement and/or the presence of antidsDNA antibodies) but no clinical activity [11]. Since these laboratory findings suggest some level of disease activity, the use of prednisone, was theorized, could prevent disease flares; indeed SACQ patients treated with a tapering course of prednisone starting at 30 mg/day experienced fewer severe flares than those not treated with such a course [19, 20]; however, this practice is no longer recommended given the increased recognition of damage accrual associated with the use of glucocorticoids [7].

According to this definition, 1.4 % of 703 patients in the Toronto cohort achieved SACQ status for at least 5 years, and no longer required glucocorticoids or immunosuppressive drugs; 11.5 % achieved such status for at least 1 year; antimalarials were allowed [11]; however, when the definition of SACQ is less restrictive and all drugs are allowed, 24.5 % of the patients achieved SACQ for at least 1 year, and 4.7 % for at least 5 years [11]. And in an Italian cohort, 14.7 % of 224 patients achieved SACQ when immunosuppressive drugs but not glucocorticoids were allowed; when both were allowed (glucocorticoids not higher than 5 mg/day of prednisone), the percentage increased to 30.3 % [12].

Minimal disease activity (MDA)

MDA has been defined as a clinical SLEDAI-2K = 1 in at least one annual visit, excluding serology, and not higher in the subsequent of visits. In the aforementioned Italian cohort, and with 7 years of follow-up, MDA was found in 5.9 % (68/1155) of the patient-years of follow-up; 9.1 % (18/165) patients had at least one period of MDA [21].

Low disease activity status (LDAS)

There are at least two definitions of LDAS; one has been proposed by APLC and includes a SLEDAI-2K ≤4, no activity in any major organ, no new features of disease activity, PGA ≤1, prednisone dose ≤7.5 mg/day and maintenance dose of immunosuppressive drugs [22]. According to this definition, 88.5 % of 191 patients achieved at least once of LDAS, and the cumulative duration of LDAS was 41 % of the total period of observation (patients had been followed for a mean of 3.9 years) [22]. The second definition has been proposed by LCTC and is based on both the APLC definition of LDAS and the definition of remission by the DORIS consensus panel: SLEDAI ≤4, PGA <1, prednisone daily dose ≤7.5 mg/day, and maintenance dose of immunosuppressive drugs. According to this definition, 14.9 % achieved LDAS for at least 1 year; additionally, 12.9 % achieved remission (on or off therapy) [15]. Using this LDAS definition (but excluding the PGA), 10.0 % of the intervals in patients from the GLADEL cohort met this status.

The proposed targets are depicted in Table 1.

Impact of T2T on the outcome of SLE patients

In order to determine if remission, SACQ, MDA, or LDAS are good enough for preventing damage or improving survival, several studies have been and are being performed.

In the Toronto cohort, SACQ patients accrued less damage over 10 years than those with active disease (1.3 vs 2.3; $p = 0.001$) [23]. In the same cohort, those patients who achieved remission off therapy accrued less damage than those with active disease (1.1 vs 1.6; $p = 0.03$). Additionally, damage accrual among patients on remission either off- or on therapy was similar [24].

In the Italian study, patients with unremitted disease had a two-time higher risk of accruing damage compared to those

Table 1 Definition of proposed targets (T2T) in SLE

	Complete remission off therapy	Complete remission on therapy	Clinical remission off therapy	Clinical remission on therapy	LDAS
Clinical activity	No	No	No	No	Yes, but global SLEDAI ≤4
Serological activity	No	No	Yes	Yes	Yes, but global SLEDAI ≤4
Prednisone	No	≤5 mg/day	No	≤5 mg/day	≤7.5 mg/day
Immunosuppressive drugs	No	Yes	No	Yes	Yes
Antimalarials	Yes	Yes	Yes	Yes	Yes

LDAS low disease activity state

on remission. Remission groups included complete remission (SLEDAI = 0, and without glucocorticoids and immunosuppressive drugs) and clinical remission (with or without serological activity) with immunosuppressive drugs with or without glucocorticoids (not higher than 5 mg/day of prednisone) for at least 5 years. Furthermore, among patients with remitted disease, those on prednisone had a higher frequency of developing glucocorticoid-related damage than those not on; that was not the case for damage unrelated to glucocorticoid use which was similar in all groups of remitted disease [12].

In a study from the APLC, patients who stayed more than 50 % of the observation time on LDAS experienced a twofold reduction in the risk of accruing new damage, compared to those patients with LDAS for less than 50 % of the time [22].

In the GLADEL cohort, we found that remission on/off therapy prevented the occurrence of new damage (defined as an increase of at least one point in the SDI) and severe new damage (defined as an increase of at least three points in the SDI); LDAS prevented the occurrence of severe new damage. Mortality was not associated with either state which probably relates to the small number of deaths in this cohort.

Conclusions

Although T2T is a promising strategy in the management of SLE, it still has a long way to go. First, the definition of the target has shown to be more complex than with any other disease, since it must include multiple variables, such as different biological responses to treatment depending on the affected organ; because of that, operationalizing the target is more difficult with lupus. Alternative targets may include SACQ disease which is associated with lower flare rates or LDAS, which is also probably associated with lower flare rates, although this has not been determined yet. Other considerations such as ethnicity, age, and number of flares (as monocyclic or polycyclic activity) may need to be considered.

Second, the time to reach the target may be different depending on the organ system affected and this will need to be defined. Third, the precise doses of immunosuppressive drugs and glucocorticoids allowed (less than 5 or 7.5 mg of prednisone?) should be defined for both remission and LDAS. It is, however, clear that antimalarials are allowed in all scenarios. Fourth, like in RA, the patients' global assessment of disease activity and quality of life and the relationship between them and disease activity, damage accrual, and flares need to be considered. Finally, the impact of T2T in the intermediate and final outcomes of lupus need to be assessed in other lupus populations across the world.

Certainly, in the years to come, we expect that the community of rheumatologists dedicated to the care of patients with lupus and to the advancement of our knowledge about this disease will provide the guidance necessary to set these targets, to assess their impact and thus improving the management and outcomes of patients afflicted with this cruel disease.

Compliance with ethical standards

Disclosures None.

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