Treat-to-target in systemic lupus erythematosus: where are we today?

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ABSTRACT

Multiple clinical trials performed over twenty years in the treatment of rheumatoid arthritis (RA) have clearly demonstrated that patients have better outcomes if their disease activity at each time-point for follow-up includes a pre-specified target. A European SLE expert panel met in Zurich on May 8, 2012 to discuss whether a treat-to-target approach could be applied in the treatment of systemic lupus erythematosus (SLE) (T2T/SLE), define a research agenda, and establish a plan for moving forward.

In the present paper, observations raised at the meeting and literature data on potential therapeutic targets are reported. The working group on T2T/SLE will continue work over the coming year.

Introduction defining targets for treatment

Until the 1950s, 5-year survival of systemic lupus erythematosus (SLE) patients was around 50%, making patient survival the primary (if not the only) target for treatment. Over the decades a sharp increase of patient survival has been observed, leading to a change in disease characteristics and the emergence of a number of issues that may impact on patient outcomes, such as damage accrual, comorbidities management, patient's quality of life (1-5).

The clinical picture of SLE is heterogeneous, affecting different organs and organ systems with a varying degree of activity, and with a flaring/remitting pattern, damage accrual, comorbidities, and drug toxicity from the perspective of the treating physician, and quality of life form the patient perspective. All these features of disease may present important targets to treatment and should be taken into consideration in clinical trials and in clinical practice (6-10).

Over the past decade, considerable advances have been made in selecting optimal treatment strategies for rheumatoid arthritis (RA). In RA, multiple clinical trials performed over 20 years have demonstrated clearly that patients have better outcomes if their disease activity at each time-point for follow-up is analysed according to a pre-specified target (usually remission or low disease activity, defined quantitatively through a disease activity index), adjusting therapy if the target has not been met. Some of the key clinical trials supporting this concept have been the FinRACO, TICORA, CAMERA, BeSt, and CIMESTRA trials (11-15). These observations have recently been codified by an international expert panel and published as the "treat-to-target" guidelines, a set of recommendations that guides the clinician in terms of treatment strategy (but it does not discuss specific medications) which have been increasingly influential in shaping therapeutic approaches (16).

Similar principles could be evaluated to optimise the treatment of patients with SLE. Therefore, a European SLE expert panel met on May 8, 2012 in Zurich to evaluate and discuss a possible treat-to-target approach in SLE, define a research agenda, and establish a procedure for moving forward.

This review is presented to discuss the literature on treatment targets in SLE, to report on the above panel meeting and to identify a research agenda for a "Treat-to-target in SLE (T2T/SLE)" initiative.

Disease activity

Disease activity refers to clinical or laboratory abnormalities that can be attributed to SLE, interfere with patient well being and/or are linked to the disease outcome, and are likely to be reversible with therapy.

Disease activity in SLE may have different patterns, described in the literature as relapsing-remitting (RR), chronically active (CA) and long quiescent,

the last being least common as 60–85% of SLE patients have either RR or CA courses (17-20). A recent study using SLEDAI 2K as measure of disease activity reported that only 38 (2.4%) out of a cohort of 1613 SLE patients achieved prolonged remission for at least 5 years, defined as serologically inactive (SLEDAI 2K n=0), serologically quiescent or mixed (SLEDAI 2K n=2-4) (21).

In 2010, Nossent *et al*. documented that only a minority of patients were in a state of inactive disease within the first year of follow up, while the remaining had either persistent activity or flares (20). Persistent activity is associated with a higher accrual of damage, lower probability of reaching remission during follow up, and higher corticosteroid dose (20-26). In lupus nephritis, failure to achieve response after 6 months of therapy is associated with a poorer prognosis (27).

In routine clinical practice, disease activity is assessed by the treating physician based on her/his experience. Validated indices have been developed to measure the degree of activity of SLE and these indices are generally used in research and randomised controlled trials. Some recommendations suggest their use also in routine clinical practice (4-6).

Cut-off values have been proposed to classify disease activity and define response to therapy based on these indices (27-29). However no agreement has been reached as yet concerning specific levels as predetermined targets for treatment or a definition of remission (3).

Treatment goals:
control of disease activity

The T2T/SLE panel discussed how disease activity can be used for defining treatment targets. Key issues revolve around the question of *what type of response* should be achieved; *how fast* it should be expected (*i.e*. how soon should *not* meeting the target trigger a treatment change); could rapid control of disease activity at times of flare be a separate target? And how rapid should control be in that case? Finally, should activity be considered globally or separately for each organ system?

The panel also discussed whether, as new therapeutic options are becoming available, to which extent low disease activity would still be "acceptable", and if so, which "level" of activity for which period of time would be acceptable?

Another intuitive target for treatment could be remission. But what is remission? And is that a remission with or without treatment?

The fact that a high percentage of patients have persistently active disease may suggest one of two explanations: that the available drugs are not able to completely control disease activity, or that physicians are keen to accept a compromise between an acceptable level of disease activity and the risk of additional toxicity and probably damage induced by available drugs.

Damage, comorbidities and SLE

With the improvement of long term survival of SLE patients, accrual of damage has gained increasing relevance and attention (1, 3-6, 20-26, 30-37). some evidence of damage is seen within the first 10 years of disease in up to 50% of patients (31). Recently, the SLICC group showed that in an inception cohort of patients followed at referral centres, with a recent onset disease, 50% have accrued damage by the 5th year of follow-up (32).

The Systemic Lupus International Collaborating Clinics (SLICC/ACR) damage index has been developed to assess irreversible damage in SLE patients, independently of its cause, occurring after the disease onset (33-37). It has been widely used in longitudinal studies as well as in clinical trials.

Early accumulation of damage was related with a poor prognosis and increased mortality. Damage accrual has been associated with many variables, the most important being disease activity at disease onset, during early stages of the disease and during follow up, drugs (mainly corticosteroids) and previous damage (20, 23, 24, 26).

Patients with rheumatic diseases, including SLE, are at increased risk of comorbidities, such as cardiovascular disease (CAD), infections, cancer, osteoporosis, which impact on prognosis and survival; however these conditions appear often underdiagnosed in routine clinical practice (4, 5, 38-41). Although recommendations have been developed to specify the appropriate monitoring and treatment that should be adopted in routine clinical practice, evidence exists that the adherence to recommendations is low (4, 5, 41, 42).

Damage, being due to active inflammation as well as to drugs or comorbidities, is an important prognostic factor for death and has a clear impact on the burden of disease for patients (24, 31, 33).

Treatment goals:
reduction of damage accrual

The T2T/SLE panel discussed how damage could be used as a target. An important question is whether the target for damage should be 0, or there is a level of acceptable damage?

It was noted that no clinically meaningful changes in damage have been yet defined. However, it was felt that sufficient data exist that show that damage can be reduced by:

- Controlling disease activity
- Minimising the use of corticosteroids
- Optimising management of comorbidities, including cardiovascular risk factors

In addition, whether disease-related and treatment-related damage should be considered separately will be a matter of further discussion.

Serological targets

Increased anti-dsDNA antibodies, low complement levels as well as other serological abnormalities are associated with SLE disease activity. A number of potential biomarkers have been identified and are being evaluated for their use on clinical practice (43).

Serologically active clinically inactive disease (SACQ) has been defined as a period of 2 years characterised by persistent serologic activity (SLEDAI score 2 or 4 from anti-dsDNA and/or hypocomplementemia) in the absence of clinical activity (44).

Although nearly 60% of these patients flare, these flares occurred over a long term period and, in addition, SACQ patients accrue less damage over 10 years compared to matched controls. These

data support the author's suggestion to monitor patients with SACQ without the need for specific treatment (44, 45).

Patient perspective and quality of life

The existence of a gap between the outcomes that are important for physicians and those that are important for patients has been described in the literature (46-49).

It is well known that patients and physicians have different views of the disease. First of all discordance exists in the rating of disease activity in up to 60% of cases; patients tend to score disease activity higher than physicians and weigh subjective manifestations as more relevant. In a recent report it has been shown that the most common spontaneously reported symptoms by patients are pain (92%), fatigue (86%), skin manifestations (55%) and less commonly depression (27%), kidney problems (32%), hair loss (23%) and stiffness (18%) (47, 48).

Fatigue is a major problem for SLE patients, not necessarily associated with disease activity, damage, or medications (49, 50).

Over the disease course, a large percentage of patients become unemployed, with an important economic impact. Major reasons for work loss are represented by disease activity, joint and neurological involvement, damage accrual, fibromyalgia, age, disease duration and low education level (7, 50).

Patients perspective as treatment target?

The panel discussed the role there is for patient-reported outcomes in defining treatment targets, and what importance should be given to the patient's judgement of disease activity. Since there was broad consensus on the need of including the patient perspective, it has been planned to include patient's representatives in the definition of T2T strategies in SLE.

Conclusions

In summary, the concept of "treating-to-target" appears to hold promise for the treatment of SLE, as it has contributed in a major way to the advancement of treatment in rheumatoid arthritis and other rheumatic diseases (51-56). Specific challenges exist, and considerable work will be required to achieve guidelines. The newly formed working group for T2T/SLE, consisting of the expert panel mentioned above as well as other key stakeholders (including patients), will continue her suing this task over the coming years.

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Competing interests

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T. Dörner has received honoraria for clinical studies as PI, speakers' fees and consultancy honoraria from Roche, UCB, Sanofi, and Medimmune;
A.E. Voskuyl was a member of speakers' bureau of GSK;
R.F. van Vollenhoven has received research support and consultancy honoraria from, Abbott, BMS, GSK, MSD, Pfizer, Roche, and UCB Pharma;
the other co-authors have declared no competing interests.

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