

The patient's perspective: are quality of life and disease burden a possible treatment target in systemic lupus erythematosus?

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Abstract

A few decades ago, the therapy goal of patients with systemic lupus erythematosus (SLE) was survival and the prevention of organ failure. Today, clinical remission and low disease activity are believed to be the optimal therapeutic targets. These aims are difficult to reach for many patients, but they still do not address the health-related quality of life (QoL) that is significantly impaired in SLE patients. Even in the state of remission, QoL and fatigue are insufficiently controlled. Thus, patient-oriented research is essential to design new strategies for the management of lupus patients. The INTEGRATE project analyses the patients' and physicians' perspectives to pave the way to design an innovative therapeutic strategy for lupus and focuses on the multifaceted dimensions of the disease burden. Shared decision making (SDM) could include the patient's perspective of SLE to treatment strategy and consider QoL and the burden of lupus into the process of therapy decision.

Key words: quality of life, QoL, systemic lupus erythematosus, target, therapy, participation

Rheumatology key messages

- Remission and low disease activity are current targets of therapy in SLE.
- Health-related quality of life is not sufficiently considered in current SLE therapy targets.
- Shared decision making can stimulate the integration of QoL aspects in treatment strategies.

Introduction

During the past decades, the lives of patients with systemic lupus erythematosus changed dramatically. Due to improved diagnostics and effective, less toxic drug regimens, the understanding of lupus changed from an acute life threatening disease to a chronic disease with a high disease burden. Thus, the concept of treat-to-target (T2T) is transferred to lupus. Remission as defined by the DORIS (definition of remission in SLE) criteria [1] and the Lupus Low Disease Activity State (LLDAS) [2]

are actually used as targets focusing on disease activity and treatment, but do not address the health-related quality of life or disease burden. SLE patients often feel misunderstood and complain that not all aspects of the disease are addressed by their doctor as described by an analysis of patients recruited by self-help groups in Great Britain and Ireland [3]. Their statements underline the importance of a patient's perspective in treatment decisions, but it is still not accepted as equivalent to the physician's perspective in treatment decisions. Health-related quality of life (QoL) is neither directly nor indirectly captured by disease activity instruments and seems not to be significantly affected by disease activity [4]. Fatigue – the most prominent symptom of lupus, and a major contributor to QoL – is only addressed in some instruments [5]. The relation of QoL and damage, shown in the SLICC cohort [6], may be used as an indicator that the physician's view is also addressing the patient's perspective. Some physicians fear looking at the patient's perspective, because of uncertainties of how to face and treat it [7]. The aim of this review is to

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discuss the integration of QoL and disease burden as therapy targets in SLE. Do we need these additional targets? What would change in the life of lupus patients? How can these targets be addressed?

QoL in SLE

QoL is significantly impaired in SLE patients caused by a high disease burden [8]. Therefore, QoL is a great candidate as a therapy target and, if payers and reimbursement systems would decide about relevance, QoL has clearly the highest impact as target. In lupus patients, all three dimensions of health-related QoL are affected: physical, mental and social health [9]. There is evidence that the physical domain is related to disease activity and may therefore improve with remission. Other aspects like fatigue, sleep and sexual function are not captured by remission state based on clinical activity control. In addition, psychosocial illness, cognitive impairment and anxiety as components of mental health are not affected by DORIS remission status. A German longitudinal study estimated that 60% of the physical component of the Short Form 36 (SF-36) is explained by clinical and laboratory findings in SLE and may therefore follow clinical remission, compared with only 25% of the mental component [10].

Poor physical and mental QoL is often due to pain, fatigue, work or school impairment, skin manifestations and UV sensitivity, distorted body image, inability to do previous activities, and impairment on intimate relationships [11–14]. An analysis of relevant concepts of functioning in daily life identified the same causes [15]. In total, 54% of SLE patients working full or part time scored their QoL significantly higher compared with non-working patients [16]. In addition, work disability in SLE patients is related to the same predictors that influence QoL: pain, fatigue, anxiety and neurocognitive involvement. Other factors are not modifiable, like age, race, education and socioeconomic status [17–19].

One of the major determinants of QoL, functioning and work ability in SLE patients is fatigue [20]. As shown in a European survey, for example, fatigue is not only the most common symptom in SLE, it significantly impairs all domains assessed by SF-36 [21]. To approach the symptom fatigue, instruments like the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) or the Fatigue Severity Scale (FSS) were created and validated [22]. However, they do not allow a clear differentiation of possible causes.

In some cases, modifiable causes like anaemia or hypothyroidism may be found, but in most patients, fatigue is unexplained [4]. Disease activity, measured by Patient reported outcomes (PRO) like the Systemic Lupus Activity Questionnaire (SLAQ), is associated with fatigue. In contrast, SLEDAI or BILAG do not correlate with fatigue. This suggests that fatigue has a strong negative impact on the patient perception of the disease. Thus, SLAQ as a target in defining remission would include the patient's burden of the disease. However, this would also include depressiveness in the

assessment of remission, as depressiveness is often associated with fatigue [23].

Another, less good evaluated determinant of QoL in lupus may be the choice of therapy and experienced or expected side effects [10, 24].

Treatment targets in lupus

Classical treatment targets in lupus can be found in the items of disease activity instruments. These are laboratory parameters like levels of complement or proteinuria as well as clinical symptoms like arthritis, erythema and seizures. The control or normalization of these symptoms and laboratory parameters are used for the assessment of disease control. The absence of major symptoms and signs of SLE is the basis of remission, a desirable outcome for patients with SLE [1]. Analyses from several cohorts demonstrate that staying in remission or LLDAS is associated with a favourable outcome [25–29]. Therefore, it is actually the most relevant target of treatment in lupus. It still has to be shown that treating active lupus patients to reach remission is equal to being in remission. In addition, the minimal treatment during remission (off/on immunosuppression) to prevent flares remains unknown.

In clinical trials, the target response is mostly defined by changes in disease activity instruments and physician global assessments [30]. QoL and fatigue are only evaluated as secondary targets, although FDA rules would allow a PRO as primary outcome [31].

Effects of remission on QoL

The physicians' view on lupus dominated the development of remission criteria. It was postulated that a control of disease activity would improve the QoL in SLE. The following data seems to confirm this postulation: Mok *et al.* showed in a Chinese lupus patients cohort that long-term remission is associated with better QoL [32]. Using the SF-36, major effects were seen in the physical component, whereas the mental component was unchanged by remission. In two other cohorts, this effect increased with the time in remission [33, 34]. Interestingly, adjustment for age, depression and fatigue did not change any of the findings [33]. Applying LupusPro, Mok *et al.* demonstrated there was no difference between the remission/non-remission groups in lupus-specific non-health-related domains like desire, social support, coping and satisfaction with medical care [32]. Goswami *et al.* showed in a young Indian population that remission may further improve the physical component (of SF-12), but not the mental component [35]. But, this paper published neither clinical data at the time of observation nor QoL data over time. Data from the Amsterdam cohort postulated that 'disease-related factors are mainly determinants of the physical domain of health-related quality of life' [36] and showed that in a follow-up period over two years, a

change in QoL status was independent of the remission status.

In the LUMINA cohort, with low percentages of remission and LLDAS and low QoL, the mental component increased with the time in remission/LLDAS [34]. Analyses from the Almenara lupus cohort confirmed significant effects of remission/LLDAS on planning and emotional health using the LupusQoL [37]. In a cohort from Thailand, all domains of LupusQoL, mental less than physical, were improved in remission/LLDAS [38].

Although longitudinal data are missing to confirm the impact of clinical remission on QoL in SLE, there is evidence that patients in remission experience a higher QoL. But this relationship is mostly based on physical signs, symptoms and pain.

QoL as target in SLE

Looking at the evidence of PROs for outcome in SLE, it is important to state that PROs were never used as the primary end point in clinical trials. In randomized controlled trials, PROs were often collected and mostly exploratively analysed. There is no evidence that PROs can validly define the above-described status of a controlled disease.

Clinical trial data exhibit that QoL and fatigue may respond to therapy. Although there were some inconsistencies in SF-36 responses to belimumab in RCTs, the detectable response of QoL to belimumab was confirmed in a post-hoc analysis of responders vs non-responders: all SF-36 domains, including the mental, improved significantly and were clinically meaningful in responders [39]. The same was observed for the FACIT-F score from day 56. A similar improvement of fatigue was reported by data analysing the effect of subcutaneous blisibimod and sifalimumab [40, 41]. Six-year follow-up data for belimumab confirmed the positive effect on QoL and fatigue, but exhibited clearly the significant effect on the physical component of SF-36 [42].

An Italian inception cohort demonstrated that despite improvement of nearly all symptoms in the first 12 months in newly diagnosed SLE, mean QoL of the patients worsened [43]. Data from the SLICC cohort exhibited, surprisingly, that despite an excellent recovery from a cerebrovascular event, the patients suffered from consistently limited QoL [44].

Meaningful effects on QoL are seen by physical training, which significantly improves vitality and the physical domain of SF-36 [45–47]. Psychotherapy and cognitive behavioral therapy may improve the mental component score of the SF-36 score, although the data is not consistent [48–50]. In our cohort of patients suffering from disease burden, psychoeducation led to significant and prolonged response in all SF-36 domains but physical function [51].

QoL and burden of lupus mandatory for treat to target and remission

Based on actual recommendations, remission is the target in daily management in SLE patients [52], but QoL and fatigue are insufficiently controlled in the state of remission and despite improvement of disease activity, QoL can remain unchanged over several years [14]. Thus, QoL may be more related to age and damage than activity [53]. However, this may be different for some disease manifestations (e.g. active inflammatory skin manifestations in exposed areas) [54, 55].

We still accept the discordance between the physicians' and the patients' perspective as recently shown by Golder *et al.* [56]: the primary view on organ manifestations vs the inhibited ability to perform in daily life. Why are these two perspectives not integrable? The wellbeing of our patient should be the highest aim in daily practice, not only as an aspect of reimbursement for QUALYs. An explanation for not taking care of the burden of illness is that physicians cannot explain these handicaps, they cannot separate whether they are related to the disease lupus or something else, like fibromyalgia. However, we cannot explain risks for lupus flares, drivers of organ activations, and why some patients respond to medications and others do not, etc. We still treat the disease to the best of our knowledge, perform parallel analyses like proteomics, genomics and epigenetics, and invest in clinical trials. Now it is time to transfer QoL and the burden of lupus to treatment. We need to identify reasons for fatigue, learn to address the causes and perform trials to document the efficacy of specific interventions.

Our actual recommendations do not only call for T2T; shared decision-making (SDM) is also endorsed in the overarching principals [52]. SDM is not yet proven in SLE; it is more than explaining what needs to be done and it must be the basis for every T2T concept. With an integrated SDM, the patient's perspective of SLE will be part of the treatment strategy and consider bringing QoL and burden of lupus into the process of deciding strategy.

Some data suggest that among patients with rheumatic diseases, QoL can be influenced by the nature of interaction of patients with their physician and that the quality of communication with the physician is linked to patient outcomes [57].

Positive patient–physician interactions, such as including the patient in treatment decisions, are associated with higher satisfaction with treatment regimens, a more favourable perception of current health, and being more hopeful about future health [58].

At the onset of disease, patients fall into an unexpected state of emotional, behavioural and cognitive stress. Thereafter, patients should be empowered to be co-producers of their own health to improve its outcome. According to the patient health engagement (PHE) model, patient engagement is a dynamic process in which patients (after the initial denial of the disease) experience

an enhanced awareness of symptoms and finally reach the status of acceptance. Physicians may contribute to this process, supporting patients in understanding the functioning of the disease, the usefulness of prescriptions, and, importantly, sustaining them in maintaining a healthy lifestyle and making new life plans [59].

The answer to what is the most relevant in the management of SLE patients – clinical symptoms, biological information or PROs as target – is: the integration of all important aspects of the disease. This implies more than the statistical evaluation of the best items of these three aspects, it is the active involvement of patients in their care: patient empowerment in SLE, a process in which both the patient and the physician have to learn a lot from and about each other.

Patient-oriented research may be useful to design a new strategy for the management of patients with lupus, based on the integration of patient and physician perspectives.

Thus a pilot EU-funded project (<https://www.integrate-sle.eu>) has been launched by the University of Pisa, University of Duesseldorf and the Scuola Superiore Sant'Anna. Patients and physicians have been called to actively participate in the study to discuss their perspectives through ad-hoc surveys and dedicated focus groups. The results of the INTEGRATE project will pave the way to design an innovative therapeutic strategy for lupus, and more generally for chronic diseases, which focusses on the multifaceted dimensions of the disease burden.

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