Perspective

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Treat-to-target in lupus: what does the future hold?

Implementing a 'treat-to-target' (T2T) strategy that aims to improve disease outcomes through achievement of prespecified treatment goals has proven efficacy in chronic medical disorders. An international task force has recommended that treatment in systemic lupus erythematosus patients should aim at prevention of organ damage accrual by achieving the lowest possible disease activity, preventing flares, minimizing glucocorticoid exposure and treating co-morbidities. Notwithstanding the above, application of T2T in routine care remains challenging due to systemic lupus erythematosus complexity, limitations of available activity and damage indices and paucity of validated treatment targets. For the future, we anticipate that accumulating data from clinical studies, together with advances in biomarkers research, will help to resolve these issues and engage the T2T strategy in daily practice.

Keywords: biologics • damage • disease activity • glucocorticoids • lupus nephritis • remission • treatment goals

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In the 1950s, a patient with lupus had a 4-year survival rate of approximately 50% [1]. As a result of significant advances in the understanding of pathophysiology, recognition of milder forms of the disease and optimization of the medical care, survival of patients with systemic lupus erythematosus (SLE) has improved substantially over the past 50 years, reaching a current 10-year survival rate of over 90% in developed countries [2,3]. Likewise, in contemporary trials of lupus nephritis (LN) managed with the standard-of-care, rates of progression to end-stage renal disease (ESRD) are significantly reduced (as low as <5% after a median follow-up of 9 years [4]), although epidemiological studies have suggested stabilization in incidence rates of SLE-ESRD during the last decade [5]. Notwithstanding this progress, lupus patients still carry an increased risk of dying prematurely compared with the general population [6,7]. Moreover, increased morbidity and progressive organ damage accrual due to both the disease *per se* and the potential side effects of medications, contribute – together with other factors – to the reduced health-related quality of life (HRQoL) that SLE patients typically experience [8].

Recently, an international panel of experts introduced the concept of 'treat-to-target' (T2T) in SLE, in other words, a therapeutic strategy aiming to improve disease outcomes through the achievement of prespecified treatment goals [9]. The T2T principle has been introduced in various chronic medical disorders, such as diabetes mellitus and hypertension, but also in the field of rheumatology, where the current treatment paradigm in rheumatoid arthritis (RA) aims for disease remission to prevent long-term structural damage [10].

In this review, we overview the unmet needs and therapeutic targets in patients with SLE in light of the published T2T recommendations. We discuss the feasibility of implementing the T2T strategy in a disease as complex as SLE, highlight challenges and pitfalls, and attempt to provide a practical guide for the physicians caring after lupus patients. We conclude by providing our views on the future steps toward the establishment

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of measurable general and organ-specific targets of disease activity, which will be capable of improving long-term outcomes in patients with SLE.

Unmet needs & therapeutic targets in systemic lupus erythematosus

Progressive accumulation of irreversible organ damage remains the major determinant of mortality in patients with SLE [11,12]. Almost 50% of patients develop increments of the Systemic Lupus International Collaborating Clinics damage index (SDI) after 5–10 years of having the disease [13,14] and a prospective Canadian study showed that patients with early acquisition of damage (within the first year of their disease) had a 3.5-fold higher probability of death over the ensuing 10 years [11]. This was confirmed by recent data from the multicenter Systemic Lupus International Collaborating Clinics cohort (hazard ratio [HR] 1.46 for death per SDI point), which additionally found that development of damage predicts further damage accrual [15]. These data clearly indicate that once irreversible damage ensues in SLE, especially early in the course of the disease, it has a direct impact on prognosis.

Organ damage in SLE may be fueled by increased activity of the disease *per se*, but also from the development of co-morbidities or toxicity of administered medications. Persistent high disease activity, measured with different versions of the SLE Disease Activity Index (SLEDAI) or the British Isles Lupus Assessment Group (BILAG), has been repeatedly correlated with acquisition of damage [16], with HRs ranging from 1.08 to 2.3 [7,17]. Organ systems most responsible for this effect are the musculoskeletal, hematologic, renal and nervous system. Conversely, isolated serologic activity in the absence of clinical activity (i.e., a group of patients with persistently low serum levels of complement C3/C4 and/or high levels of anti-dsDNA antibodies [18]) does not seem to promote damage accrual [19]. Data from large SLE registries suggest that on annual basis, a considerable proportion (10–50%) of patients display persistent (i.e., on at least two consecutive visits) clinical disease activity (SLEDAI–2K $\geq$ 4, excluding serology) despite conventional treatment [7,13,16,20–22].

Along with the detrimental effects of disease activity, both the number and the severity of SLE flares have been correlated with damage accrual. Occurrence of severe (BILAG A) flare corresponds to >18-fold increased risk for damage or death during the next 5 years [23,24]. Notably, even milder flares were associated with increases in SDI in a large multiethnic SLE cohort [25]. Risk factors for flares include African-American descent (odds ratio 1.8), young age (<25 years) at disease onset (HR 2.1), high disease activity and need for glucocorticoids (GCs) or immunosuppressants during the past year (HR 2.4–3.2), and presence of serologic activity (odds ratio 2.2–2.8) [20,21,26,27]. *Post hoc* analysis of the belimumab trials showed that higher baseline levels of clinical (especially active nephritis, CNS disease, vasculitis) and serological activity were significant predictors of severe disease exacerbations during the ensuing 24–52 weeks [28]. In proliferative LN, failure to achieve complete renal response to immunosuppressive treatment and persistence of serological activity, have both been associated with increased risk for subsequent renal flares [29–31]. Together, results from therapeutic trials and observational studies show that, depending on the clinical instrument used, 7 to 74% (typically, 25–35%) of SLE patients will develop at least one flare within a year, the majority (80%) being of mild-to-moderate severity.

Drug toxicity, especially side effects from prolonged GC therapy, constitutes another major unmet need in lupus therapeutics. A validated and practical instrument to document drug toxicity in clinical practice is disappointingly lacking. A recent observational cohort found that average prednisone intake >7.5 mg/day over a period of 4 years resulted in almost tenfold increased risk for damage accrual [32], corroborating earlier data from the Hopkins Lupus cohort linking chronic GC therapy with development of osteoporotic fractures (relative risk [RR] 2.5), coronary artery disease (RR 1.7), cataracts (RR 1.9) and other adverse sequela [33,34]. Other immunosuppressants commonly used in SLE therapy are not associated with an unacceptable toxicity profile, particularly after the substitution of the older high-dose cyclophosphamide (CYC) regimens with low-dose-containing schemes [35] or less gonadotoxic agents, like mycophenolate mofetil (MMF) [36].

The increased rate of serious infections in SLE patients during the last 15 years, identified in a recent large population-based study [37], highlighted the importance of co-morbidities that appear as lupus patients grow older, owing to improved life expectancy. Apart from infectious complications, other major co-morbidities include cardiovascular disease, osteoporosis and malignancies. Indeed, SLE patients continue to die mainly from cardiovascular events and infections, despite the fact that active SLE as a major determinant of mortality has subsided [3,6,38]. Additionally, SLE carries a marginally increased risk for overall cancer development (standardized incidence ratio 1.14) [39]. Certain types of malignancies occur more frequently, in particular non-Hodgkin lymphoma, cervical and lung cancer [40]. Both immunosuppressive therapy and the disease *per se* have been implicated for this trend [41].

As a consequence of all the above, SLE has an adverse impact on HRQoL [42–44]. When assessed

with the Short Form–36 index, lupus patients exhibit significant deficits in various components of psychosocial health compared with the general population, including physical function, social function and mental health [45]. In a longitudinal study, both disease activity and damage contributed – albeit modestly – to diminished HRQoL, and progressive accrual of additional damage led to further decline [46]. Other major drivers include fatigue, depression and fibromyalgia, all quite prevalent among SLE patients [44].

Altogether, despite advances in the medical care, there are still significant unmet needs in SLE with a considerable proportion of patients experiencing residual disease activity or flare-ups, adverse effects of administered treatments, development of organ damage and co-morbidities, and diminished HRQoL (Table 1). All of these aspects may represent putative therapeutic targets in SLE with the potential to impact on patients' well-being and long-term outcome.

The concept of treat-to-target in rheumatology: the paradigm of rheumatoid arthritis

Following the establishment of the T2T strategy in chronic metabolic diseases such as diabetes mellitus (target glycosylated hemoglobin [HbA1c]: 6.5%) and hypertension (target blood pressure <140/90 mmHg), RA was the first disease to introduce this concept in the field of rheumatology. Based on the findings of well-designed controlled trials, which showed better long-term functional and structural outcomes with intensive management aiming at achieving a prespecified treatment target compared with usual care [47,48], a paradigm shift in RA has now set target-based therapy as the standard of care. Therapy should aim to achieve remission or, in certain circumstances, low disease activity [10]. Equally important with the 'target' itself, is the concept that a tightly monitored strategy to reach this target may be more important than the individual agents used for this purpose. Indeed, despite lack of consensus regarding the choice of optimal therapy (e.g., with biologics or combination of synthetic disease modifying drugs), the ultimate goal of reducing disease activity as low as possible for prolonged periods of time seems universally accepted in the RA community [49]. Although RA is a systemic disease, the goal of T2T (i.e., remission according to the ACR/EULAR criteria [50] or DAS28 in clinical practice) is essentially based on the number of affected joints and on the patient's own assessment of their disease.

Table 1. Unmet needs in systemic lupus erythematosus.

Medical need	Description and association with adverse outcomes
Increased morbidity and mortality	Major causes of death are infections, cardiovascular diseases and malignancies
Damage accrual	Accumulation of organ damage is the major determinant of mortality in patients with SLE1
	Damage leads to further damage
Co-morbidities	Cardiovascular disease
	Infections
	Malignancies
	Osteoporosis
Residual disease activity	Persistent disease activity leads to organ damage and increased mortality
	Isolated serologic activity does not seem to have long-term adverse sequela
Frequent flares	Number and severity of flares lead to damage accrual
GC toxicity	Daily prednisone doses >6–7.5 mg/day are associated with cardiovascular disease, osteoporotic fractures, cataract and osteonecrosis
Reduced HRQoL	Lupus patients display markedly affected QoL compared with the general population
	Modest correlation with disease activity and damage
	Fatigue, pain and depression are major drivers of reduced HRQoL in SLE

GC: Glucocorticoid; HRQoL: Health-related quality of life; QoL: Quality of life; SLE: Systemic lupus erythematosus.

Treat-to-target recommendations in systemic lupus erythematosus

As discussed above, evidence from observational studies and randomized controlled trials (RCTs) has been useful to identify aspects of SLE care that may serve as therapeutic targets. To this end, an international task force undertook the initiative to develop T2T recommendations for SLE patients following an evidence-based and expert-opinion approach [9]. The task force considered four overarching principles in the management of SLE patients, namely: the importance of shared decisions between the informed patient and the physician(s), the inclusion of multiple – rather than a single – targets of treatment, the importance of multidisciplinary care, and the need for long-term patient monitoring and/or adjustment of treatment [9].

Recommendations regarding the management of SLE patients were also developed, which are summarized in Table 2. Briefly, it was recognized that treatment should aim at remission or low disease activity, prevention of flares and of damage accrual, improvement of HRQoL, minimization of exposure to GCs, prevention of antiphospholipid syndrome-related and other co-morbidities [9]. In addition, early recognition and treatment, as well as long-term maintenance immunosuppression, is recommended for patients with severe lupus manifestations, particularly LN. These recommendations highlight the basic principles for T2T in SLE; yet the question is: how can they be implemented in every-day clinical practice?

Implementation of treat-to-target in systemic lupus erythematosus: practical considerations

Targeting remission or low disease activity

Renal lupus

In patients with LN, a large body of evidence supports that treatment should aim at remission (complete renal response), which is typically defined as very low levels of proteinuria (in the range of ≤0.5 g/24 h) with normal or near-normal renal function. Fulfillment of this goal has been associated with minimal rates of progression to ESRD and improved long-term patient outcomes [30,51]. Conversely, patients with suboptimal response to treatment (i.e., with persistent proteinuria >0.5 to 1 g/24 h) carry a considerably higher risk for progression to ESRD [52,53]. Of note, proteinuria tends to decrease gradually over time and, depending on its offset value, complete resolution may require up to 2 years of immunosuppressive treatment [54,55]. At the same time, early (within the first 3 to 6 months) partial renal response (i.e., ≥50% reduction of proteinuria) has been identified as a predictor of good long-term renal outcome in LN [35,56,57]. *Post hoc* analysis of the MAINTAIN RCT showed that reduction of proteinuria to <1 g/24 h at 12 months had 88% positive predictive value for favorable 10-year renal outcome [58], suggesting that this cut-off of proteinuria could serve as an 'interim' therapeutic target in LN. However, the negative predictive value of this end point was only 64%, indicating that some of the patients who do not achieve this level of proteinuria at 12 months may still preserve their renal function in the long term.

Taken together, and in line with the EULAR/ERA-EDTA recommendations [59], patients with LN should be monitored for attainment of at least partial renal response by 6 (preferably) to 12 months, and of complete renal response by 24 months of immunosuppressive treatment (Figure 1). Failure to achieve these goals, or lack of any improvement within the first 3–4 months of treatment, should evoke the intensification of therapy. In such cases, options include switching immunosuppressive agent (e.g., from CYC to MMF, supported by nonrandomized evidence [60,61]); intravenous pulses of high-dose (0.75–1 g/m^2) CYC; combination of MMF with calcineurin inhibitors; or biological agents (used as add-on or as monotherapy) [59]. In this context, a repeat kidney biopsy can be particularly valuable in demonstrating residual activity (warranting immunosuppression) versus chronicity (irremediable with immunosuppression) lesions. In support of this, a recent study showed that more than half of patients with persistent low-grade (500–1000 mg/24 h) proteinuria or elevated serum creatinine who were on maintenance immunosuppression had no histological activity on repeat kidney biopsy, and therefore would not benefit from therapy intensification [62].

Extra-renal lupus

Unlike the case of LN, the target(s) for extra-renal lupus disease activity are less well-defined, as are the recommended strategies for accomplishing these targets. From a humanistic perspective, treatment should obviously aim at complete resolution of symptoms and signs of the actively involved organ(s). This is also supported by evidence that lupus disease activity (measured by any of the existing validated indices) is incrementally associated with increased risk of damage accrual and other adverse outcomes [17,63]. Thus, depending on the domain (e.g., musculoskeletal, hematological, neurological, etc.) that is actively involved and the severity of the manifestation (for instance, severe, life-threatening vs mild thrombocytopenia), first-line treatment should include a combination of glucocorticoids, hydroxychloroquine (HCQ) and immunosuppressants, reserving CYC for the most severe cases [64].

Table 2. Treat-to-target recommendations for patients with systemic lupus erythematosus.

	Recommendation	Grade of recommendation (A–C)
1	Aim for remission or low disease activity	C (SLE)/A (LN)
2	Prevent flares, particularly major flares	B (SLE)/A (LN)
3	Isolated serology needs no treatment	B
4	Prevent damage	A
5	Control factors associated with HRQoL	B
6	Treat renal involvement early	B
7	Immunosuppressive treatment in LN should be maintained for at least 3 years	B
8	Chronic maintenance treatment should aim for complete withdrawal, or use of the lowest possible GC dosage	B
9	Prevent and treat APS same as primary APS	C
10	Use antimalarials irrespective of the use of other treatments	B
11	Early detection and treatment of co-morbidities	C

APS: Antiphospholipid syndrome; HRQoL: Health-related quality of life; LN: Lupus nephritis; SLE: Systemic lupus erythematosus.
Adapated with permission from [9].

Patients should be monitored regularly for detection of any drug-related harms and assessment of their response to treatment. Frustratingly, for extra-renal lupus manifestations, evidence regarding the specific 'targets' of treatment for each different organ/domain and how quickly these targets should be reached, is less robust and, thus, inconclusive (see the 'Challenges in applying T2T in SLE' section). Early response is typically due to the administered glucocorticoids, since other agents have a slower mode of action and their effect becomes clinically evident after 6 weeks to 4 months of treatment and plateaus afterward. Accordingly, in the case of non-life-threatening manifestations, an initial evaluation of treatment efficacy is usually performed at 3 to 6 months, when the dose of glucocorticoids has been tapered to ≤10 mg/day of prednisone equivalent. Patients who improve on treatment, but still have some residual disease activity, may continue with the same regimen for another 3–6 months, before a more conclusive evaluation is made (Figure 2).

If there is inadequate response to first-line treatment (documented by at least one validated disease activity index and the physician's global assessment), therapy should be adjusted according to the type and severity of manifestation. Current available options include uptitration to the maximum tolerable dose of immunosuppressants; combination of different agents; add-on therapy with belimumab [65,66]; introduction of CYC and off-label use of MMF [67] or rituximab [68]. It should be noted that belimumab is currently not licensed for the treatment of active severe renal or CNS lupus.

For patients with substantial clinical improvement who yet fail to achieve remission (i.e., complete resolution of symptoms and signs) after first- or second-line treatment, and in the absence of strong evidence to suggest that 'low disease activity' is significantly inferior to 'remission', the decision for treatment intensification should be based on the physician's assessment of the disease, the benefit/risk ratio of current and planned treatments and, importantly, the patient's views and assessment of her/his own disease. To illustrate this point, let us consider the case of an SLE patient with predominant arthritis who has been on combination with low-dose prednisone, HCQ and methotrexate (at maximum tolerated dose) for the last 4 months. On follow-up visit, physical examination reveals residual arthritis in four joints, corresponding to a SLEDAI–2K score of 4. The patient reports no fatigue, no significant morning stiffness and only occasional, short-lasting mild arthralgias. Should immunosuppressive therapy be escalated, since this patient is clearly not in remission? Rather, the most prudent decision here is to continue with the same regimen and re-evaluate the patient in 3–4 months. Should the same patient, however, have reported significant joint aches, swelling or stiffness, the physician would probably consider intensification of treatment.

Prevention of disease flares

In view of the association between persistent disease activity and risk for future exacerbations, the importance of tight control of SLE activity is further emphasized as a means of preventing flare-ups. Notably, and

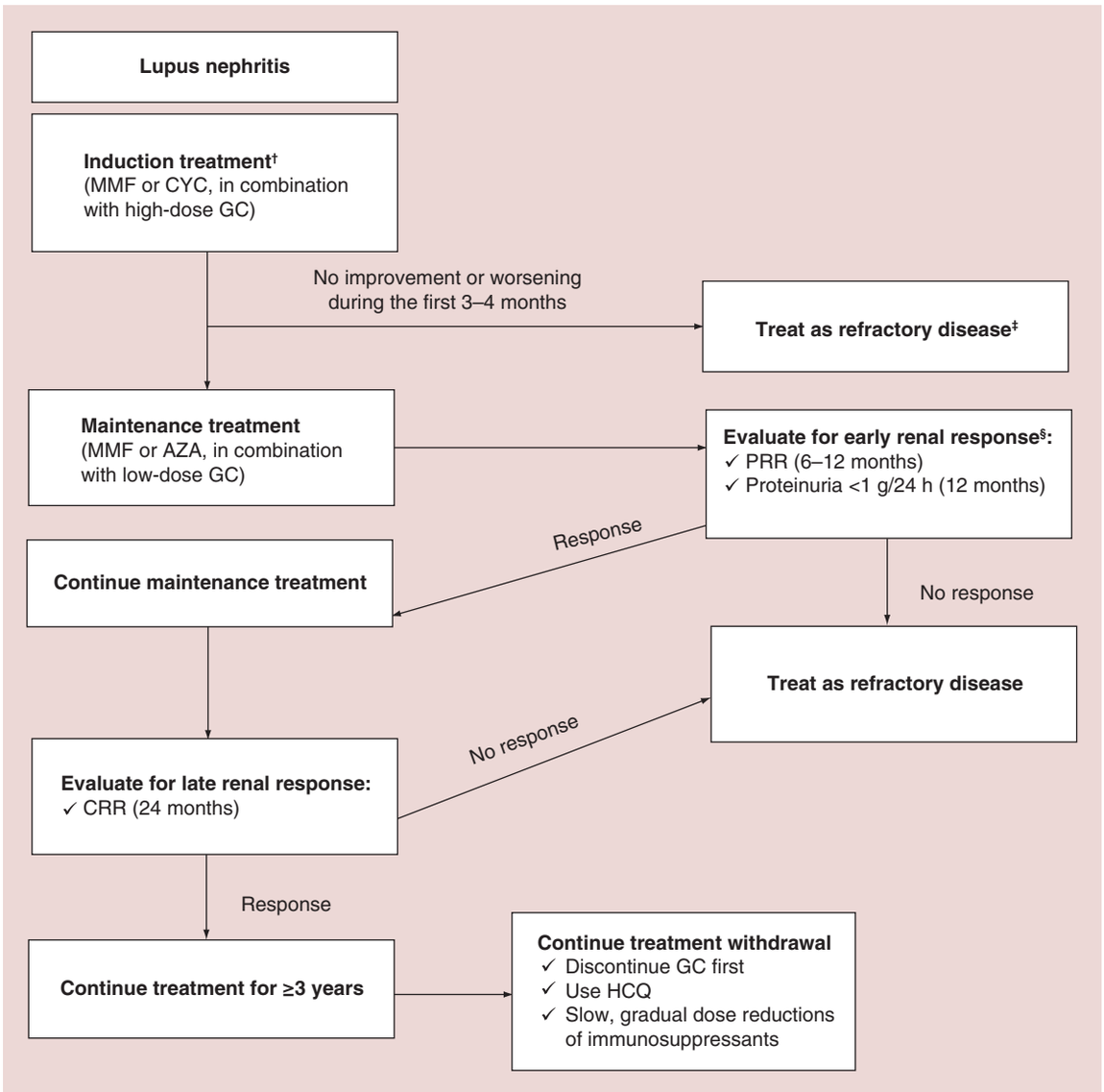

Figure 1. Therapeutic strategy for achieving remission in lupus nephritis.
†Induction regimens include MMF 2–3 g/day for 6 months, low-dose intravenous CYC 3 g over a period of 3 months or monthly pulses high-dose intravenous CYC (0.75–1 g/m^2) for 6 months.
‡Options for refractory lupus nephritis include switching immunosuppressive agent (e.g., from CYC to MMF, or vice versa); intravenous pulses of high-dose (0.75–1 g/m^2) CYC; combination of MMF with calcineurin inhibitors; or biological agents (rituximab used as add-on or as monotherapy). Repeat kidney biopsy may be considered.
§Renal response criteria include partial renal response (defined as ≥50% reduction of initial proteinuria with normal or near-normal renal function) and complete renal response (remission) (defined as proteinuria <0.5 g/24 h with normal or near-normal renal function).
AZA: Azathioprine; CRR: Complete renal response; CYC: Cyclophosphamide; GC: Glucocorticoid; HCQ: Hydroxychloroquine; LN: Lupus nephritis; MMF: mycophenolatemofetil; PRR: Partial renal response.

despite evidence linking serological activity with the risk for flares [26,69,70], it is currently not recommended that treatment be intensified in SLE patients with inactive clinical disease and persistent/stable serological activity (low serum C3/C4 and/or increased anti-dsDNA titers) [9]. Similarly, patients with acute onset serological activity should not receive pre-emptive immunosuppressive treatment, but require close monitoring for prompt identification of clinical features of active disease.

There are very few head-to-head studies of different immunosuppressive agents with regards to their effectiveness in stabilizing lupus and preventing exacerbations. The 10-year follow-up of a trial comparing azathioprine (AZA) and MMF as maintenance therapy in Caucasian patients with proliferative LN who received

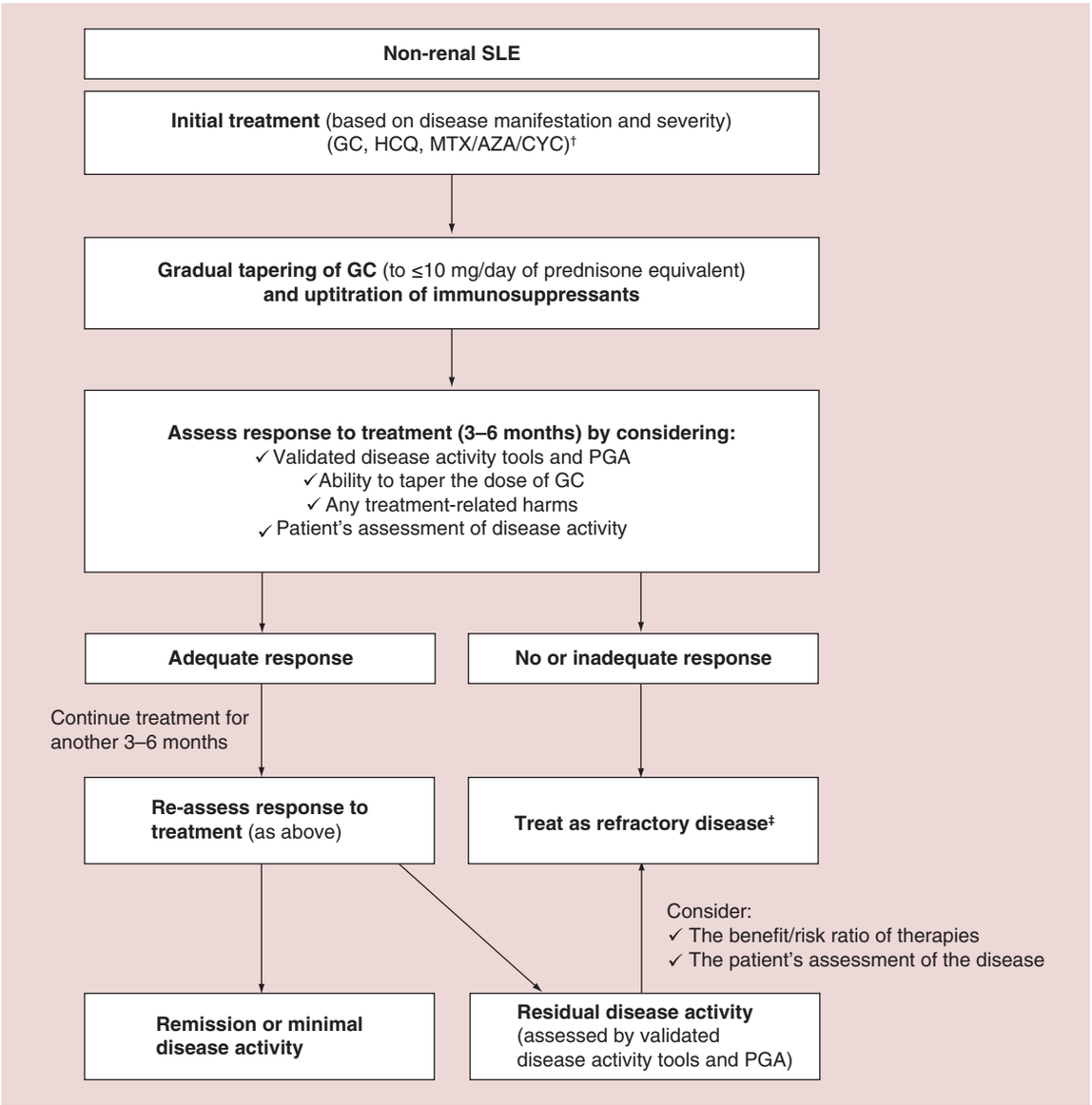

Figure 2. Therapeutic strategy for achieving remission or low disease activity in non-renal systemic lupus erythematosus.

†Initial choice of dose of GC and/or other agent (hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide) is based on the type and severity of the lupus manifestation.

‡Options include uptitration to the maximum tolerable dose of immunosuppressants, combination of different agents, add-on therapy with belimumab, introduction of cyclophosphamide and off-label use of mycophenolatemofetil or rituximab.

AZA: Azathioprine; CYC: Cyclophosphamide; GC: Glucocorticoid; HCQ: Hydroxychloroquine; MTX: Methotrexate; PGA: Physician's global assessment.

induction with low-dose intravenous CYC, reported comparable rates of renal flares and ESRD [4]. In contrast, the Aspreva Lupus Management Study found that in LN patients who responded to initial treatment with either MMF or intravenous CYC, subsequent therapy with MMF was associated with significantly fewer renal relapses compared with AZA over a 3-year period [71]. Ultimately, the choice of maintenance agent depends on a number of factors, including patient's race (MMF preferred in black or Hispanic patients), severity of LN (MMF preferred in most severe cases), induction regimen (MMF preferred if used also as induction treatment) and pregnancy contemplation (AZA preferred). In pure membranous LN, a single RCT found that ciclosporin and intravenous CYC were equally efficacious in reducing proteinuria during the first year but when treatment was withdrawn, CYC was superior in maintaining the response [72].

In general SLE, a 12-month open-label RCT comparing AZA with ciclosporin in active disease requiring ≥15 mg prednisolone/day found comparable effects in terms of reduction in disease activity and frequency of flares [73]. Two other agents, namely HCQ and belimumab, have demonstrated efficacy in preventing major SLE flares in the context of RCTs. Specifically, in the Canadian Hydroxychloroquine Withdrawal Study, patients who were randomized to continue treatment with HCQ had lower risk (HR 0.26) for major renal flares compared with patients who discontinued HCQ [74]. A similar protective effect of HCQ has also been shown in LN [75]. In the BLISS trials, belimumab, when added on top of standard-of-care therapy, led to significantly reduced (by 36%) risk of major SLE flares over a period of 52 weeks [76]. However, the benefits of belimumab should be weighed against its significant cost. In this regard, studies from Italy and Portugal found an acceptable cost–effectiveness profile of the drug [77,78]. In contrast, the UK NIH and NICE recommended against the use of belimumab as add-on therapy based on an almost twofold higher incremental cost–effectiveness ratio (ICER, the cost of the drug in relation to how well it works) per quality-adjusted life years gained compared with the £20,000–30,000 threshold range [79].

In patients who achieve remission or low disease activity following treatment, the optimum timing of immunosuppressive drug withdrawal is important for prevention of flares. In LN, longer duration of immunosuppressive treatment and attainment of renal response for longer time periods are associated with increased odds for successful (i.e., without subsequent disease exacerbation) drug withdrawal or switching to less potent immunosuppressants [75]. Thus, observational studies have shown that discontinuation or switching from MMF to another agent (AZA or calcineurin inhibitor) earlier than 18–24 months after response carries almost twofold increased risk for subsequent renal flare [80,81]. Consequently, although the optimal duration of maintenance therapy in LN has not been definitely established, we generally recommend a period of at least 3 to 5 years. There is even less evidence to guide duration of treatment in non-renal SLE. In these patients, absence of serological activity and gradual tapering (by 25%) of the immunosuppressant(s) have been identified as predictors of relapse-free drug withdrawal [82].

Finally, treating physicians should pay special consideration to any of the drug nonadherence issues and assess potential contributing factors. It is estimated that <25% of SLE patients have an adherence rate ≥80% of the time to HCQ or immunosuppressants [83], and noncompliance to lupus treatment has been associated with increased risk of flare-ups and emergency care utilization [84,85].

Prevention of damage accrual

Since a number of different factors contribute to development of damage in SLE, strategies for its prevention should be multifaceted. First, disease activity should be adequately controlled, since this will halt inflammation-driven tissue injury and subsequent dysfunction. Although observational studies have illustrated a near-linear association between disease activity (quantified by any of the existing validated instruments) and damage accrual, [7,16,17,63] only a few SLE treatments have demonstrated direct effect on prevention of organ damage. In LN, a Cochrane Review and meta-analysis of RCTs showed that only the combination of CYC with glucocorticoids is better than glucocorticoids alone in preventing chronic renal damage [86]. Although MMF is at least as efficacious as CYC in the short-term, long-term data on renal damage accrual are still very limited [87]. CYC has also exhibited efficacy in patients with acute severe neuropsychiatric lupus [88], although long-term follow-up data relevant to damage are lacking.

With regards to general SLE, there is mounting evidence from cohort studies to suggest that HCQ use is associated with reduced risk for accrual of organ damage irrespective of other contributing factors [89]. Accordingly, the T2T recommendations emphasize the need to consider antimalarials in all SLE patients, unless contraindicated or not tolerated, regardless of the use of other treatments [9]. Recent data from the prospective follow-up of patients who were treated with belimumab in the context of two trials suggested lower rates of damage accrual over a period of 5 years [90]. However, the lack of a placebo-treated control group precludes any definitive conclusions, as both groups also received standard-of-care.

A final consideration is that lupus medications *per se*, aside from their effect on controlling disease activity, can sometimes cause significant harms and irreversible organ dysfunction. In this regard, excessive exposure to glucocorticoids (see below) is a major contributor to organ damage in SLE. Also, CYC can cause permanent gonadal toxicity, that is both age- and dose-dependent [91]. Consequently, judicious use of these treatments is warranted to avoid damage accrual, while maintaining their therapeutic properties.

Minimization of exposure to glucocorticoids

Glucocorticoids exert potent anti-inflammatory properties and have the advantage of rapid onset of action. They are generally considered as the mainstay of treatment for moderately severe or very severe lupus mani-

festations, wherein they are usually prescribed at moderate (0.3–0.5 mg/kg/day of prednisone equivalent) to high (>0.5 mg/kg/day) doses, together with an immunosuppressive or biological agent. Glucocorticoids are also used at lower doses in milder manifestations or flares. Initial management of severe lupus frequently includes one to three pulses of intravenous methylprednisolone administered on consecutive days [92]. The benefits of this regimen include the more potent and faster anti-inflammatory effects of the intravenous route and the possibility to prescribe lower initial doses of oral glucocorticoids (0.5 vs 1.0 mg/kg/day) [93]. Notably, studies have suggested that damage accrual in SLE is related to the cumulative dose of oral steroids, but not of intravenous pulses of methylprednisolone [32,34]. Moreover, no consensus exists regarding the optimal dose of intravenous pulse methylprednisolone, although most experts recommend 0.5–1 g/pulse.

Following initial high-dose treatment, the dose of glucocorticoids should be gradually tapered to ≤10 mg/day (prednisone equivalent) within a period of 1 (if mild-to-moderate disease) to 4 (if moderate-to-severe disease) months. This process may be facilitated by the introduction and/or uptitration of immunosuppressive or biological agent(s) due to their steroid-sparing effect [68,76,94]. In routine practice, SLE patients who are started on oral glucocorticoids should be given a dose-tapering diary, be monitored regularly for the identification of associated harms or compliance issues, and for possible re-evaluation of their dosage/tapering scheme. Only doses <7.5 mg/day of prednisone equivalent are considered acceptable for long-term maintenance treatment [32,33]. Intriguingly, efforts are currently underway to develop 'steroid-free' regimens for induction treatment of active LN [95].

Prevention of co-morbidities

Prevention of co-morbid conditions in SLE patients requires a multi-targeted approach that entails lowering of lupus disease activity, minimization of drug-related harms and modification of any general, non-SLE-specific risk factors. Accordingly, preventive strategies for cardiovascular disease should involve adequate control of the disease, limiting the dose of glucocorticoids, smoking cessation, management of hypertension, dyslipidemia and diabetes mellitus, as well as promotion of physical activity/exercise [96]. Special consideration should also be given to initiating or continuing (if already prescribed) HCQ, based on evidence for its atheroprotective effects [97]. Prophylactic antiplatelet treatment is currently recommended for patients with persistently positive antiphospholipid antibodies and those at high risk for cardiovascular events, as in the general adult population. To reduce the burden of infectious complications, patients with SLE should be monitored for prompt tapering of GC dosage and of other immunosuppressive or biological treatments [98]. In addition, immunizations should be offered according to existing recommendations. Basic hygiene measures including frequent hand washing should not be overlooked. Osteoprotection and vitamin D supplementation are essential measures, especially for patients who are on glucocorticoids. Finally, SLE patients should undergo routine cancer surveillance, as recommended for the general population. Existing evidence suggests that human papilloma virus (HPV) immunization is both safe and efficacious in patients with stable or inactive disease [99].

Is treat-to-target beneficial to systemic lupus erythematosus patients?

Undisputedly, the effectiveness of a therapeutic intervention or strategy can only be judged in terms of its impact on patient survival, preservation of organ function and HRQoL (the latter used as an indirect measure of the patient 'well-being'). Any potential gains in employment or disability issues, as well as in direct and indirect medical costs, should also be considered. To date, there has been no formal appraisal of the T2T strategy in SLE, ideally by means of a controlled study comparing 'usual care' versus 'T2T' strategy. Nevertheless, preliminary results from the Asia-Pacific Lupus Collaboration observational study offer some proof-of-concept for the T2T strategy in SLE. In this study, the researchers developed a consensus definition of 'low disease activity state' (LDAS) that encompassed: descriptors of low SLE activity (assessed both objectively and according to physician global assessment); use of glucocorticoids at a dose ≤7.5 mg/day prednisone equivalent; and well-tolerated standard maintenance doses of immunosuppressive or biologic agents [100]. They also tested the aforementioned definition in 192 SLE patients who were followed-up for an average of 3.6 years. Notably, patients who attained the LDAS for >245 days had 20% reduced risk (HR 0.80; 95% CI: 0.66–0.97) for damage accrual compared with patients with LDAS for shorter time period [100]. Further confirmation of these findings in larger longitudinal studies will be required.

Challenges in applying treat-to-target in systemic lupus erythematosus

Although there is strong rationale for introducing a T2T approach in the management of SLE, there are still a number of challenges and caveats to be considered. First, owing to the disease heterogeneity, different treatment 'targets' for each affected organ will

have to be defined. With the exception of the renal system, for which specific proteinuria thresholds have been introduced as therapeutic targets and have been validated against long-term disease outcomes (see above), there are no universally accepted or validated targets for other domains, such as the skin, joints, hematologic, pulmonary, etc. As an example, no evidence exists to support that treatment of lupus thrombocytopenia should aim at a platelet count of 50,000, 80,000 or 150,000/μl. This is important, because aiming for 'full remission' (e.g., normal platelet count) might carry the risk of overtreating patients and causing drug-related harms. In Table 3, we outline our suggestions for the minimum acceptable targets of treatment for selected extrarenal SLE manifestations. Obviously, these definitions will have to be tested against damage accrual and/or other outcomes in prospective cohort studies.

Pertinent to the previous is the issue of whether the application of T2T in clinical practice should be based upon a battery of different treatment targets (i.e., one for each different organ) or a single, composite lupus activity index. Obviously, the latter may be more practical, since it could assist physicians to implement the T2T strategy by targeting an easy-to-remember disease activity score, similar to the clinical utility of the DAS28 cut-off values for remission or low disease activity in RA. However, in contrast to RA, where DAS28 has been established as the single most reliable and accurate disease activity index, there is still debate about the best index to use for monitoring SLE patients. In fact, all existing indices have inherent shortcomings; the SLEDAI has modest sensitivity to disease activity changes, whereas the BILAG is cumbersome to use in daily practice [101]. Also, general SLE activity indices may overlook some important aspects of disease activity (e.g., neurological domain). Importantly, there is no evidence to suggest a specific cut-off value of any activity index, to be considered as a therapeutic target. This is further complicated by the fact that in global activity indices such as the SLEDAI, the same score can result from different manifestations or organs, which however, are likely to have different prognostic impact (e.g., a score of 4 in the SLEDAI can be due to arthritis or due to proteinuria).

To provide a practical and realistic guide for routine clinical practice, we propose application of the SLEDAI (2K version) coupled with the physician's global assessment [102]. Inclusion of the physician's global assessment ensures consideration of SLE manifestations that are not listed in the SLEDAI (e.g., myelitis) and the severity of organ involvement in a similar way with the – more comprehensive, yet complex – BILAG instrument. For assessment of arthritis in particular, swollen and tender joint counts are probably more clinically important than the mere presence or absence of synovitis in >2 joints, as defined in the SLEDAI. Although the same principle could apply to other manifestations, it is not yet known whether organ-specific instruments, such as the Cutaneous Lupus Erythematosus Disease Area and Severity Index [103], may be more appropriate in implementation of T2T in SLE.

Since lupus is characterized by a waxing and waning course and relapses tend to occur frequently, a time constituent has been proposed to be included in the T2T definitions of low disease activity or remission. For instance, some experts would consider a patient to be in remission only if (s)he endures a state of absent disease activity for a period of at least 6 months. In fact, the Asia-Pacific Lupus Collaboration observational study showed that only SLE patients who attained LDAS over a certain time period had significantly lower risk for damage accrual [100].

Finally, considering that organ damage and disability in SLE may be caused by excessive exposure to glucocorticoids and/or immunosuppressants, it has been argued that low disease activity or remission should be reserved for cases in which acceptable, maintenance doses of these treatments are being used. To this end, an international task force will try to address some of the above-mentioned issues by testing combinations of definitions of SLE remission against disease outcomes in trial- and registry-derived data [104].

Novel therapies

A number of novel biological therapies are currently under trial for the treatment of SLE. These include – but are not limited to – drugs that target B-cell surface molecules or survival factors (epratuzumab, tabalumab), or agents directed against cytokines such as type I interferon (rontalizumab, sifalimumab) [105]. Preliminary findings suggest efficacy of some of these drugs when added to 'standard-of-care' as manifested by reductions in clinical and serological activity, glucocorticoids dose and prevention of flares. Confirmation in phase III studies could lead to their approval for SLE. Hopefully, inclusion of these novel agents in the therapeutic armamentarium of SLE will enable a proportion of patients with active/flaring disease in spite of conventional therapy to meet (some of) the previously discussed therapeutic targets. A hypothetical alternative strategy could involve the use of biological agents at earlier disease stages in order to minimize exposure and potential harms caused by conventional therapies and possibly alter the natural history of the disease.

To this end, the success of belimumab and presumably of other biologicals has triggered efforts to identify patient subsets that would benefit the most from specific therapies (instead of a 'one-size-fits-all' approach) and accurate response measures to capture improvement of the disease. In addition, upcoming treatment agents should be tested for their effects on different organ domains, flare prevention, induction or maintenance regimens; furthermore, response to therapy should take into account various parameters, including clinical and composite measures, patient-reported outcomes, flares and damage, as well as pharmacoeconomic considerations [106].

Conclusion

Despite improvements in overall survival rates, there are still numerous unmet needs in the care of SLE patients. A considerable proportion of patients will accrue damage early or later in the course of the disease, as a result of residual/flaring disease activity and exposure to high doses of potentially harmful agents, particularly glucocorticoids. Similar to other chronic diseases, implementation of a T2T strategy in SLE will hopefully enable physicians to realize the disease aspects that impact significantly on long-term outcomes and, consequently, apply a more holistic care plan to their patients. At the same time, however, additional work will be needed to improve existing clinical tools for the assessment of SLE activity and damage, set specific and measurable treatment targets, and define the best approach to accomplish them. For the future, we remain optimistic that utilization of data from large RCTs and patient registries will yield answers to some of these issues, and that translational research will identify reliable biomarkers to be incorporated into the T2T strategy. Importantly, lupus has entered the era of biologic therapies and novel agents have shown signs of efficacy and exert positive effects, not only on disease activity, but also on other aspects of the T2T strategy, such as prevention of flares, reduction of GC dosage and improvement of HRQoL in SLE patients.

Future perspective

Despite the challenges in the management of SLE, owing to heterogeneity of the disease, its unpredictable course and the complex interplay between activity, therapies and organ damage/co-morbidities, it is encouraging that the community has reached consensus about the importance of introducing the T2T principle in clinical care and the disease aspects that constitute major therapeutic goals (e.g., prevention of damage accrual). However, controversy exists with regards to specific treatment targets and the optimal approach to reach them. To resolve some of these issues, we eagerly wait for additional evidence from the analysis of large cohorts of patients who are included in RCTs and well-characterized registries. Sophisticated statistical approaches will be helpful to 'dissect' the individual effects of demographic factors, different disease patterns and severity, serological profile, exposure to lupus medications and co-existing medical conditions on disease outcomes, such as major flares and damage accrual. Although this is certainly a herculean task, it will provide insights about the prognostic role of individual components of disease activity and will help the community to specify therapeutic targets for each different affected organ.

In the upcoming years, we expect additional efforts toward improvement of the existing tools for assessment of SLE patients. Although the SDI is considered a reliable measure of irreversible organ damage and has been consistently validated against patient survival, it still suffers from limitations, the major being the inability to discriminate between disease- or treatment-related damage. Activity indices would also benefit from modification toward a better coverage of all possible disease manifestations and an enhanced sensitivity to longitudinal changes of disease activity; this, however, should ideally not come at the expense of their simplicity and user-friendliness.

Intensive efforts are currently underway for the identification of accurate serological, genomic or other biomarkers of disease activity and severity in SLE. While some of these results are indeed encouraging, further confirmation and validation in large patient cohorts will be required. Ideally, some of the tested biomarkers will help us further toward understanding disease heterogeneity and will prove useful in assisting diagnostic (e.g., urinary biomarkers for active LN) and therapeutic decisions by means of risk stratification, prediction of response to different regimens and monitoring disease activity. One could even envision the inclusion of any of these biomarkers in the T2T algorithm as surrogates of disease activity, predictors of future damage or co-morbidities, or as an integral part of the therapeutic targets.

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Executive summary

Unmet needs & therapeutic targets in systemic lupus erythematosus

- Despite improvements in life expectancy during the past decades, systemic lupus erythematosus (SLE) patients still experience nearly threefold increased mortality rates when compared with the general population.
- Irreversible organ dysfunction (damage) develops in almost 50% of SLE patients after 5–10 years of disease. Damage is a powerful predictor of further damage accrual and mortality.
- Organ damage may be fuelled by persistent disease activity, which is encountered in 10–50% of SLE patients who are receiving conventional treatment.
- Flares of disease activity are frequent (up to 74% within 1 year) in SLE patients. Both major and mild-to-moderate flares contribute to organ damage accrual.
- Chronic glucocorticoid intake – especially at dosage ≥7.5 mg/day of prednisone equivalent – is a major driver of organ damage in SLE.
- Infectious complications, cardiovascular disease, osteoporosis and malignancies represent the most prevalent co-morbidities in SLE patients.
- As a result of these factors and also, due to pain, fatigue and depression, SLE patients experienced reduced health-related quality of life.

The concept of treat-to-target in rheumatology: the paradigm of rheumatoid arthritis

- Implementing a 'treat-to-target' (T2T) strategy, in other words, a therapeutic strategy aiming to improve disease outcomes through achievement of prespecified treatment goals, has proven efficacy in chronic medical disorders, such as diabetes mellitus and hypertension.
- In rheumatoid arthritis, well-designed controlled trials have shown improved long-term functional and structural outcomes with intensive management aiming at achieving a prespecified treatment target compared with usual care.

Treat-to-target recommendations in systemic lupus erythematosus

- An international task force has recently developed T2T recommendations for SLE patients, following an evidence-base and expert-opinion approach. A high level of agreement among experts was reached.
- It is recommended that treatment in SLE should aim at remission or low disease activity, prevention of flares and damage accrual, improvement of health-related quality of life, minimization of glucocorticoid exposure, prevention of antiphospholipid syndrome-related and other co-morbidities.
- Early recognition and treatment as well as long-term maintenance immunosuppression is recommended for patients with lupus nephritis.

Implementation of treat-to-target in systemic lupus erythematosus: practical considerations

- In lupus nephritis, immunosuppressive treatment should aim at partial renal response (defined as ≥50% reduction in proteinuria with [near-] normal renal function) by 6–12 months, and at complete renal response (proteinuria <0.5 g/24 h) by 24 months. Failure to achieve these goals, or lack of any improvement within the first 3–4 months of treatment should evoke discussions for treatment intensification.
- In extra-renal lupus, therapeutic goals are less well defined; nonetheless, treatment should aim at remission or the lowest possible disease activity. The decision for treatment intensification should take into account the physician's assessment of the disease, the benefit/risk ratio of current and planned treatments, and the patient's views and assessment of her/his own disease.
- Strategies for prevention of SLE flares include tight control of disease activity, careful tapering and withdrawal of immunosuppressants following response to treatment, special consideration for drugs capable of stabilizing response (hydroxychloroquine, belimumab), and ensuring patient adherence to medications.
- Prevention of damage accrual involves tight control of disease activity, use of hydroxychloroquine and minimization of exposure to harmful agents, particularly glucocorticoids. Cyclophosphamide is efficacious in preventing renal damage but its prolonged administration has been linked to irreversible gonadal toxicity.
- In moderately severe or severe SLE manifestations, initial treatment with three consecutive pulses of intravenous methylprednisolone (0.5–1 g/pulse) allows for the use of lower dosage of oral glucocorticoids (0.5 mg/kg/day). In chronic maintenance treatment, prednisone should be used at <7.5 mg/day.
- Prevention of co-morbid conditions requires lowering of lupus disease activity, minimization of drug-related harms and control of any general, non-SLE-specific risk factors.

Challenges in applying treat-to-target in systemic lupus erythematosus & future perspective

- Owing to disease heterogeneity, measurable treatment targets for each different affected organ (with the exception of kidneys) remain to be defined.
- In extra-renal lupus, there is currently no evidence to suggest that targeting remission leads to significantly better outcomes when compared with low disease activity.

Executive summary (cont.)

Challenges in applying treat-to-target in systemic lupus erythematosus & future perspective (cont.)

- It is not yet clear whether application of T2T in routine practice should be based upon a battery of different treatment targets (i.e., one for each different organ) or a single, composite lupus activity index.
- Existing clinical tools for assessment of disease activity and damage suffer from inherent shortcomings and need optimization.
- As a practical approach, we recommend the use of SLE Disease Activity Index coupled with the Physician Global Assessment (PGA) in routine assessment of SLE patients.
- For the future, we remain optimistic that additional studies and utilization of large randomized controlled trials and patient registries will yield answers to some of the above-mentioned issues, and that translational research will identify reliable biomarkers that could be incorporated into the T2T strategy.

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