Framework for implementing treat-to-target in Systemic Lupus Erythematosus routine clinical care: consensus statements from an international task force.

Matteo PIGA (MD)[1], Ioannis PARODIS (MD, PhD)[2,3], Zahi TOUMA (MD, PhD)[4], Alexandra LEGGE (MD, PhD)[5], Manuel F. UGARTE-GIL (MD, PhD)[6], Ihsane HMAMOUCHI (MD, PhD)[7], José A. GÓMEZ PUERTA (MD, PhD)[8], Professor Hervé DEVILLIERS (MD, PhD)[9], Margherita ZEN (MD, PhD)[10], Jiacai CHO (MD, PhD)[11,12], Nelly ZIADE (MD, PhD)[13], Johanna MUCKE (MD, PhD)[14,45], Carlos Enrique TORO-GUTIERREZ (MD)[16], Shinji IZUKA (MD)[17], Peter KORSTEN (MD)[18], Baïdy SY KANE (MD)[19], Vera GOLDER (MD, PhD)[20], Benjamin F. CHONG (MD, PhD) [21], Guillermo PONS-ESTEL (MD, PhD)[22], François CHASSET (MD, PhD)[23], Professor Laurent ARNAUD (MD, PhD)[24*].

AFFILIATIONS:

1. Rheumatology Unit, Department of Medical Sciences and Public Health, AOU Cagliari and University of Cagliari. ORCID: 0000-0002-1126-8315
2. Division of Rheumatology, Department of Medicine Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden. ORCID 0000-0002-4875-5395
3. Department of Rheumatology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
4. Krembil Research Institute 60 Leonard Ave, Toronto, ON M5T 0S8, Canada. ORCID: 0000-0001-5177-2076
5. Division of Rheumatology, Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada
6. Grupo Peruano de Estudio de Enfermedades Autoinmunes Sistemicas, Universidad Cientifica del Sur, Lima, Peru and Rheumatology Department, Hospital Nacional Guillermo Almenara Irigoyen-EsSalud, Lima, Peru
7. Health Sciences Research Centre (CReSS), Faculty of Medicine, International University of Rabat (UIR), Rabat, Morocco. ORCID: 0000-0003-4402-5034
8. Rheumatology Department, Hospital Clínic de Barcelona, IDIBAPS and University of Barcelona, Barcelona, Spain ORCID: 0000-0001-8177-702X
9. Internal medicine and systemic disease unit and CIC-EC INSERM 1432, Dijon university Hospital, Dijon, Burgundy France. ORCID: 0000-0003-0679-1029
10. Rheumatology Unit, Department of Medicine, University of Padova, Padova, Italy. ORCID: 0000-0003-0835-1406
11. Division of Rheumatology, Department of Medicine, National University Hospital, Singapore
12. Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore
13. Rheumatology Department, Saint Joseph University and Hotel Dieu de France Hospital, Beirut, Lebanon. ORCID: 0000-0002-4479-7678
14. Department of Rheumatology, Heinrich-Heine University, Duesseldorf, Germany. ORCID: 0000-0001-8915-7837
15. Hiller Research Center for Rheumatology, Heinrich-Heine University, Duesseldorf, Germany
16. Director, Reference Center in Osteoporosis and Rheumatology, Pontificia Javeriana University, Cali, Colombia. ORCID: 0000-0002-6084-7049
17. Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan. Orcid: 0000-0002-9724-4911
18. Department of Rheumatology and Clinical Immunology, St. Josef-Stift Sendenhorst, Sendenhorst, Germany ORCID 0000-0001-6065-5680
19. Department of Internal Medicine, Cheikh Anta DIOP University, Dakar, Senegal.
20. School of Clinical Sciences at Monash Health, Sub Faculty of Clinical and Molecular Medicine, Monash University, Victoria, Australia. ORCID: 0000-0001-5691-4344
21. Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, TX, USA (ORCID: 0000-0002-4092-7658)
22. Grupo Oroño-Centro Regional de Enfermedades Autoinmunes y Reumáticas (GO-CREAR), Rosario, Argentina. ORCID: 0000-0002-0647-929X
23. Sorbonne Université, Faculté de médecine, AP-HP, Service de Dermatologie et Allergologie, Hôpital Tenon, INSERM U1135, CIMI, Paris, France
24. Department of Rheumatology, National Reference Center for Rare Autoimmune Diseases (RESO), Hôpitaux Universitaires de Strasbourg, INSERM UMR-S 1109, Strasbourg, France. ORCID 0000-0002-8077-8394.

***Corresponding author:** Laurent ARNAUD (MD, PhD). Department of Rheumatology, National Reference Center for Rare Autoimmune Diseases (RESO), Hôpitaux Universitaires de Strasbourg, Strasbourg, France. Email: Laurent.arnaud@chru-strasbourg.fr

ABSTRACT

Implementation of Treat-to-Target (T2T) in routine clinical practice remains low in systemic lupus erythematosus (SLE). Real-world data reveal excessive use of glucocorticoids (GCs) and frequently inadequate disease control. Here, an international task force convened to develop a consensus framework for implementing T2T in routine clinical care of adult patients with SLE.

This T2T task force comprised an international panel of 22 physicians involved in the care of SLE and 3 lupus patient research partners. Following a scoping review and online discussions, during which definitions and instruments available for T2T in SLE were examined, the panel developed potential framework statements for implementing T2T in SLE, which were extensively discussed before being agreed upon by Delphi consensus. Additionally, the current challenges of implementing T2T in SLE and how future research may address these issues were analyzed. The framework comprises 5 overarching principles and 11 statements. Despite the absence of formal evidence that T2T offers superiority to conventional SLE management, T2T in SLE has been recommended for over a decade. This task force offers a framework for effectively implementing T2T in SLE from a real-life perspective, informing a wide range of physicians, including those outside the limited circle of lupus specialists.

Keywords: Systemic Lupus Erythematosus, consensus, Treat-to-Target, remission, LLDAS.

INTRODUCTION

The high disease burden of systemic lupus erythematosus (SLE) has been increasingly recognized during the past decades. With the slowly growing number of available treatments and the increasingly recognized toxicity of glucocorticoids (GCs), even when used at low doses, there has been an increased focus on optimizing treatment strategies in SLE, including Treat-to-Target (T2T) and disease modification. A T2T strategy applies tight control (typically through regular visits and sequential treatment adjustment) to reach a predefined and desirable target through a four-step process: 1) defining a specific target; 2) treating with the aim of reaching this target; 3) testing regularly whether the target is achieved or if there was meaningful clinical improvement since the last visit; and 4) if needed, adjusting treatment to better reach the target. The treatment strategy often follows a protocol for treatment adaptations, depending on disease activity and response to treatment [1]. Hence, adequately capturing the latter two is crucial in T2T strategies. This approach has been applied to rheumatoid arthritis [2], psoriatic arthritis [3], and gout [4], enabling significant improvements in treatment outcomes.

The concept of T2T in SLE is not novel and has been recommended in the context of lupus for over a decade. An international panel of rheumatologists [5] agreed that the main goals of SLE treatment should include the following aspects: control of disease activity, prevention of disease flares, minimization of disease- and treatment-related comorbidities, and improvement of health-related quality of life (HRQoL). Accordingly, the 2019 European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of SLE stated that remission is the main treatment target in SLE [6], and this was further confirmed in the 2023 update of these recommendations [7]. In between these updates, the Definitions of Remission in SLE (DORIS) task force has proposed an operational definition of remission in 2021 [8], and the concept of low disease activity (LDA) was refined in several proposals, among which the prevailing one is the Lupus Low Disease Activity State (LLDAS) [9]. Despite these crucial advances, implementation of T2T in routine clinical practice remains low in SLE, with real-world data largely revealing excessive use of GCs and inadequate disease control [10]. This is also due to the fact that no validated T2T strategy has yet shown in a randomized trial that actively treating to target with tight disease control leads to improved outcomes. Here, an international task force of 22 SLE specialists with extensive experience in treating SLE convened to develop a consensus statement about T2T in the routine clinical care of adult patients with SLE. This manuscript does not aim to replace existing therapeutic guidelines in SLE but provides a critical view of the current limitations and best options to effectively implement T2T in SLE from a real-life perspective. Our international consensus underscores the necessity of translating existing

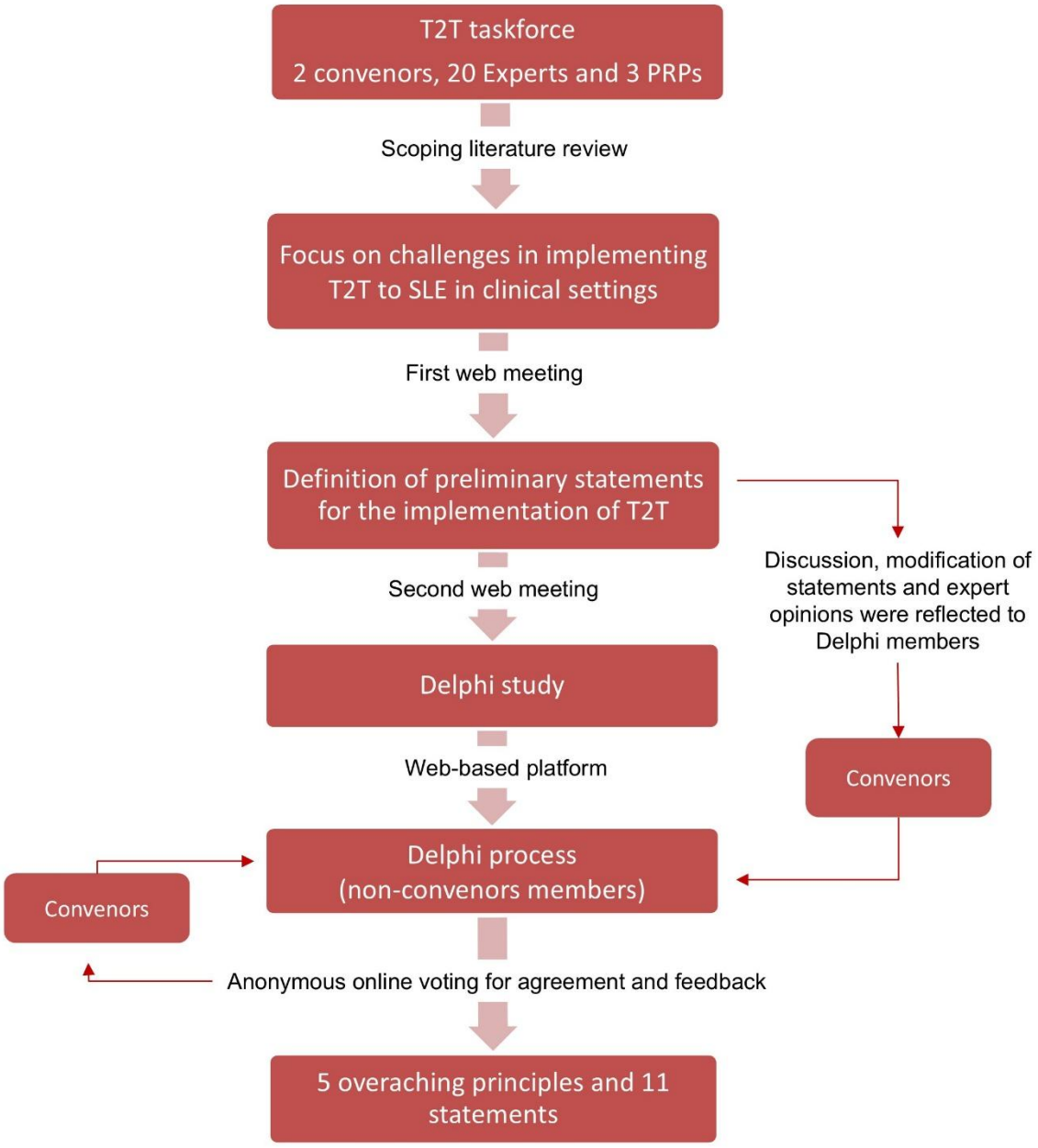
recommendations for SLE management into more practical guidelines. To address these challenges, we advocate for developing a practical framework that clinicians can readily adopt and may inform future research.

METHODS

This T2T task force was headed by 2 convenors (M. Piga, L. Arnaud), a group of 20 physicians involved in the care of SLE, and 3 lupus patient research partners who participated in this work by providing active feedback. The panel's geographical distribution included 9 (40.9%) experts from Europe, 4 (16.5%) from Asia-Pacific, 3 (13.6%) from North America, 3 (13.6%) from Latin America, and 3 (13.6%) from Africa.

As the ultimate aim of this task force is not to produce recommendations but to map, identify, and discuss the current limitations and best available options for implementing T2T in SLE, a scoping review was performed by applying a Population/Concept(s)/Context(s) (PCC) framework and searching PubMed and Web of Science to identify pertinent literature addressing T2T strategies in the management of SLE [11]. Our initial search included relevant keywords ('Treat-to-target') and Medical Subject Headings (MeSH) terms (Systemic Lupus Erythematosus, remission induction, treatment outcome, Patient care, planning, disease management) to capture pertinent articles published from inception to May 2023, ensuring a thorough examination of the existing literature pertaining to T2T in SLE (see supplementary file). In addition, task force members were actively engaged in the literature review throughout the duration of the task force, by providing additional references and insights from their respective areas of expertise. This collaborative effort ensured a scoping examination of the literature related to T2T in SLE across various settings. Following informal preliminary discussions and the scoping review, a virtual meeting was held in May 2023, during which the expert panel examined the various concepts, definitions, and instruments available at that time for T2T in SLE, with a special focus on the applicability of these elements outside the specific setting of clinical research. Following additional discussions between the 2 convenors, and based on the insights from the first online meeting, the main authors (M.P. and L.A.) drafted an initial set of statements. A second virtual meeting was organized in November 2023, during which these statements were presented individually to task force members, where they were discussed and modified iteratively based on feedback from physicians and patients. This process continued until a final version was agreed upon and validated by Delphi consensus between December 2023 and January 2024 (Figure 1). The level of evidence (LoE) on which the statements are based is reported according to the Oxford Evidence-Based Medicine criteria.

Figure 1. Flow chart of the T2T-SLE consensus framework



A Delphi survey is a systematic process involving a series of questionnaires and rounds of item generation, data collection, and analysis to derive expert consensus on a topic. This interactive process involved the study team, who were asked to rate a list of statements using a Numerical Rating Scale (NRS) ranging from 1 (strongly disagree) to 10 (strongly agree) during a maximum of three consecutive rounds. At each Delphi round, anonymized and aggregated responses from prior rounds were provided. All experts reviewed the selected statements and provided their level of agreement (LoA).

Statistical analyses

Qualitative data were expressed as numbers and percentages, and quantitative data as median and interquartile range (IQR). According to methodological criteria for reporting Delphi studies, statements scored 7-10 on the NRS by ≥75% of the experts were selected, while those scored 0-3 by ≥75% were rejected. Statements that did not reach these pre-specified levels of agreement were conditionally included in the subsequent Delphi round, together with the comments from the panel, to be re-voted and eventually rejected if ≥75% agreement was not reached. Statistical analyses were performed using the software JMP version 13 (SAS institute, Cary, NC, USA).

RESULTS

The panel agreed upon 5 overarching principles (Table 1) and 11 statements (Table 2). The test accompanying the expert panel's results presents findings from the scoping review.

Table 1. Overarching principles for practical implementation of T2T in SLE routine clinical care.

Overarching principles for T2T in SLE		**LoA Median (IQR)**
A	The T2T strategy should be implemented as early as possible during the course of the disease, ideally starting as soon as the diagnosis of SLE is made.	10 (0)
B	The choice of treatments should follow the latest local / international recommendations.	10 (1)
C	Decisions regarding the implementation of the T2T strategy should be shared between the patient and the medical team (i.e., shared decision-making).	10 (0)
D	Non-pharmacological measures and patient education should be incorporated into the T2T strategy.	10 (0)
E	Telehealth and digitally-supported platforms can be used as additional tools to facilitate the implementation of T2T in SLE.	9 (2)

LoA: level of agreement. T2T: treat to target; SLE: Systemic Lupus Erythematosus.

Overarching principle A: The T2T strategy should be implemented as early as possible during the course of the disease, ideally starting as soon as the diagnosis of SLE is made. (LoA 10)

Prompt T2T strategy implementation offers a chance of achieving remission and reducing organ damage that may occur early in the clinical disease process [12-13]. Failure to achieve remission or LLDAS in the short term can undermine the potential benefits of prompt treatment and could lead to disease progression. Observational studies in newly diagnosed SLE patients revealed that the duration of the disease at the time of diagnosis does not affect the accrual of early damage in the short term, while achieving remission or LLDAS earlier and maintaining them during follow-up independently predicts lower damage accumulation [14,15]. The long-term outcomes in SLE are not only associated with attaining better short-term outcomes but also strongly depend on socioeconomic status and educational level, ethnicity, therapeutic adherence, and accessibility to healthcare. Therefore, T2T requires that socioeconomic, literacy, and accessibility issues be addressed concomitantly for adequate implementation and sustainability over time [16].

Overarching principle B: The choice of treatments should follow the latest local and/or international recommendations. (LoA 10)

The expert panel felt that the task force should focus on the practical implementation of T2T in SLE, while at the same time following current national or international therapeutic recommendations for SLE. The macroeconomic and societal environment is an important determinant of patient pathways and access to treatments, particularly, but not only, biologics and other costly medications [16,17]. In many healthcare systems, SLE patients must pay directly for specialist consultations, laboratory tests and therapies, which is a strong limiting factor in the implementation of T2T [18]. Also, in several low-or-middle income countries (LMICs), access to specialized laboratory tests such as complement levels and anti-dsDNA antibodies is either impractical or can be delayed by several weeks, which may impact the applicability of outcome definitions incorporating lupus serology. Also, treatment of SLE is sometimes executed by general internists, nephrologists, or family physicians, necessitating a standardised local or international guideline to align treatment strategies and outcomes. In the end, the task force highlights the need to follow the latest international recommendations. At the same time, on some occasions, local circumstances and specific regulatory aspects might affect the eventual treatment offered to the patient.

Overarching principle C: Decisions regarding the implementation of the T2T strategy should be shared between the patient and the medical team (shared-decision making). (LoA 10)

Shared decision-making is “a process by which patients and clinicians work together to create a treatment plan that integrates evidence-based information, clinician experience, and patient preferences, values, and goals.” [19]. An OMERACT core domain set for shared decision-making interventions in rheumatology has been recently published [20,21]. Shared decision-making should be incorporated into T2T strategies in SLE, as reflected by the current EULAR recommendations [9]. This is crucial as poor therapeutic adherence is highly prevalent in SLE patients and strongly predicts unfavorable outcomes [22], while shared decision-making [23] has been shown to increase treatment adherence. Importantly, this must be accompanied by patient education to increase self-efficacy [24].

Overarching principle D: Non-pharmacological measures and patient education should be incorporated into the T2T strategy. (LoA 10)

Non-pharmacological management should be implemented along with the T2T strategy. Such an approach would be instrumental in the management of common, more subjective manifestations of SLE, such as fatigue and depression [25]. Fatigue is reported by more than two-thirds of SLE patients and severe fatigue by more than one-third, in strong association with anxiety and depression, especially in those with inactive disease [26,27]. Recently, an EULAR task force developed evidence-based recommendations for the non-pharmacological management of connective tissue diseases, including SLE, with a focus on enhancing HRQoL [28]. The task force believed that incorporating non-pharmacological interventions into the T2T strategy requires evaluating their effects over time and modifying the intervention as needed. For example, if a patient participates in a 24-week aerobic exercise program to reduce fatigue and depressive symptoms, its effectiveness should be assessed through patient-reported outcomes (PROs). Additionally, in the T2T strategy, it is important to evaluate smoking habits and the use of UV-protective agents, providing appropriate advice during each visit.

Along with the implementation of lifestyle adjustments, physical activity, patient education, and self-management strategies, T2T in SLE should be centred around patient involvement in the management of their disease and should include a multidisciplinary approach. A particular emphasis should be placed on therapeutic adherence, which should be a key pillar of patient education.

Overarching principle E: Telehealth and digitally-supported platforms can be used as additional tools to facilitate the implementation of T2T in SLE. (LoA 9)

Despite physicians' concerns that teleconsultation and its lack of physical assessment might lead to underestimation of disease activity and subsequently under-treatment, these concerns have been allayed in recent studies showing that teleconsultations are both safe and effective in SLE [29,30]. A video-visiting approach, combining patient self-assessment and Patient-reported outcomes (PROs), helped identify patients with active disease and might support a remotely-based SLE tight-control strategy [31].

Also, telehealth and digital medicine can be instrumental in assessing PROs, which are currently recorded mainly for research purposes, and in most cases on paper during on-site appointments, the inter-visit timeframe being subjected to recall biases. Electronic PROs (ePROs) enable continuous remote monitoring and could improve shared decision-making and implementation of a T2T approach [32]**.** Overall, the development of telehealth, including teleconsultation and tele-expertise, may help in the early detection and management of flares and provide additional understanding of the patient's perspective [33].

Statements for the implementation of T2T in SLE

Table 2 reports the 11 statements regarding the implementation of T2T in SLE. Figure 2 presents an algorithm overview illustrating the general strategy for the practical implementation of T2T in SLE.

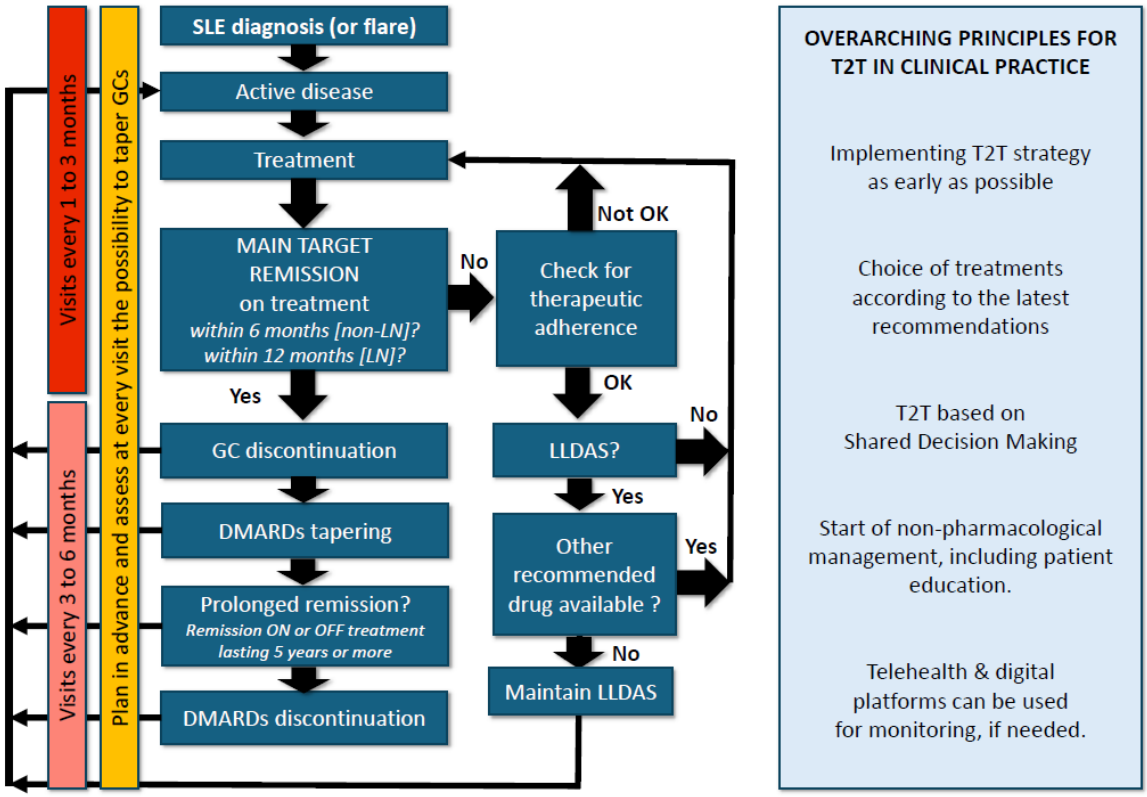
Table 2. Consensus statements for the practical implementation of T2T in SLE routine clinical care.

Statements		**LoA Median (IQR)**
#1	The main goal of the T2T strategy is to achieve remission as early as possible after diagnosis (or a flare), ideally reaching remission on treatment before M6 in non-renal SLE, and before M12 in lupus nephritis, and then to maintain remission for the longest possible duration.	10 (1)
#2	Remission ON treatment is defined by the absence of clinical disease activity AND a maximum dose of 5mg/day of prednisone-equivalent AND stable or decreasing doses of maintenance treatment, if any.	10 (1)
#3	If remission ON treatment is not achieved within the pre-specified time-frame: 1) therapeutic adherence should be assessed; and 2) treatments should be optimized.	10 (0)
#4	In case of active disease, we recommend follow-up visits every 1 to 3 months, based on the type and severity of organ-involvement.	10 (1)
#5	Once Remission ON treatment is achieved, we suggest follow-up visits every 3 to 6 months until prolonged remission is achieved.	9·5 (1)
#6	In case of a suspected flare, a medical consultation should be performed as soon as possible (if needed remotely), and treatment adjusted accordingly after assessing therapeutic adherence.	10 (0)
#7	Prolonged remission is defined as remission* lasting 5 years or more.	9 (3)
#8	Once prolonged remission is reached, we suggest follow-up visits every 3-6 months, based on previous organ involvements (e.g. lupus nephritis).	9 (2·75)
#9	Tapering of GCs should be considered at every visit.	10 (0)
#10	Discontinuation of GCs should be considered in patients in remission ON treatment.	10 (0)
#11	The possibility to taper and then discontinue DMARDs should be assessed in patients in prolonged remission who have previously discontinued GCs	10 (1)

**Remission ON or OFF treatment: As stated elsewhere, not all patients can discontinue GCs. The possibility of discontinuing GCs should be assessed at every visit.*

LoA: Level of Agreement. T2T: treat to target; SLE: Systemic Lupus Erythematosus; M6: Month 6; M12: Month 12; GCs: Glucocorticoids; DMARDs: Disease-modifying antirheumatic drugs.

Figure 2: General strategy for the practical implementation of T2T in SLE



Statement #1: The main goal of the T2T strategy is to achieve remission as early as possible after diagnosis (or a flare), ideally reaching remission on treatment before M6 in non-renal SLE and before M12 in lupus nephritis and then maintaining remission for the longest possible duration. (LoA 10; LoE 2)

As mentioned in the 2023 EULAR recommendations [7] and 2018 GLADEL/PANLAR recommendations [34], management of SLE should aim at remission of disease symptoms and signs, prevention of damage accrual, and minimization of drug side-effects, as well as improvement of HRQoL. Owing to the clinical heterogeneity of SLE, there is still no consensus on the exact definition of remission or low disease activity state globally and in individual organ-systems [35]. However, it is worth mentioning that considerable evidence has been generated regarding the benefits of DORIS-remission [8] and LLDAS [9] (table 3) for prevention of flare and damage, improvement of HRQoL, as well reducing mortality in SLE [36-42]. Observational studies have shown that the achievement of remission or LLDAS within 6 months and further maintenance of these states independently

predicts lower damage accrual [14, 15]. In patients with lupus nephritis, a complete renal response within 12 months and a sustained remission are protective against impaired kidney function [43,44]. Based on the available evidence, the panel agreed to suggest a specific timing for achieving targets in the T2T strategy. The experts agreed that achieving remission should be the primary goal, while LDA states, such as the LLDAS, may serve as an alternative in case of refractory disease, when other therapeutic options are unavailable, or when concurrent conditions restrict treatment escalation.

Table 3. Comparison between the definition of DORIS-Remission and Lupus Low Disease Activity State (LLDAS) in SLE.

	REMISSION (DORIS)	**LLDAS**
SLEDAI-2K	Clinical SLEDAI-2K = 0*	SLEDAI-2K≤4 No activity in major organ systems No new lupus activity
PGA (0-3)	<0·5	≤1
GCs **(equivalent prednisone dose)**	≤5mg/day	≤7·5mg/day
Immunosuppressive treatment	Stable	Standard maintenance dose

* only lupus serology (dsDNA antibodies and complement levels) should be excluded
LLDAS: Lupus Low Disease Activity State; DORIS: Definitions of Remission in SLE; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; PGA: Physician Global Assessment; GCs: Glucocorticoids.

Statement #2: Remission ON treatment is defined by the absence of clinical disease activity AND a maximum dose of 5mg/day of prednisone-equivalent AND stable/decreasing doses of maintenance treatment, if any. (LoA 10; LoE 2-3)

Remission in SLE can be conceptualized as the absence of active clinical manifestations (i.e., no symptoms related to active SLE and clinical examination unremarkable for active disease), including urinary or hematological abnormalities. Accordingly, the expert panel agreed that disease activity and remission should be assessed by validated tools, but no consensus was reached on a single instrument that should be adopted in a real-life clinical setting to evaluate the absence of active clinical manifestations, as no disease activity instrument is universally agreed upon for disease activity monitoring.

In clinical practice, the choice of a disease activity instrument is influenced by the balance between accuracy, ease of use, sensitivity to change, healthcare setting, and alignment with the physician's expertise and specific goals for managing SLE patients. The measurement properties and limitations of the SLE Disease Activity Index (SLEDAI) and other disease activity instruments, such as the SLE Disease Activity Score (SLE-DAS) and British Isles Lupus Assessment Group (BILAG), have been reviewed in depth by others [45], while recent studies investigated the psychometric properties and limitations of the Physician Global Assessment (PGA) in patients

with SLE [46-48]. These validated instruments may all allow for a distinct definition of remission (e.g. clinical SLEDAI =0, clinical SLE-DAS =0, BILAG = D/E in every domain, PGA <0.5) with different characteristics and outcomes [49-51]. However, the necessity for a standardized definition of remission to effectively compare results from various studies has prompted significant efforts in recent years to reach a consensus among researchers. Since the DORIS definition of remission was published, substantial evidence has been gathered regarding the benefits of achieving and maintaining DORIS remission over time [36-42]. While valuable for standardizing research and providing a clear target for disease management, the DORIS remission faces challenges regarding practical implementation in everyday clinical settings on single specific SLE patients. In particular, the instruments used to measure DORIS remission and LLDAS, such as the clinical SLEDAI and the PGA, can be impractical for everyday use. As supporting evidence, 42% of Canadian clinicians used PGA, and only 16% used SLEDAI in everyday clinical practice, with a lower rate of utilization in non-academic settings [52]. Further, there are settings where applying the DORIS definition of remission was reported as impossible [16,53]. In summary, while DORIS remission is a valuable outcome for research, its practical implementation in everyday clinical settings could be hampered by its complexity and the need for more practical assessment tools. In line with this, there is an unmet need to develop accurate and user-friendly definitions of remission for use outside research purposes.

A heated and ongoing debate has arisen inside the task force around the opportunity to suggest a practical and operational definition of remission, based on a physician's judgment alone, as the primary goal of the T2T strategy in SLE. While relying solely on a physician's decision to define remission in SLE might enhance the implementation of T2T strategies, it introduces several risks. These risks include subjectivity, variability in patient care, inconsistent application of T2T protocols, and delays in making necessary treatment adjustments. Research has demonstrated that using validated measurements for remission is significantly more reliable than relying on physician judgment alone [54], particularly among those who are not experts in SLE. Therefore, this task force strongly suggests using validated outcomes for assessing disease activity and remission, without depending on a single definition.

Finally, differentiating between remission “on treatment” and “off treatment” reflects what happens in daily care, as the patients will first reach remission on treatment, then initiate the tapering phase, and ideally maintain remission without glucocorticoids and immunosuppressants (Figure 2). The panel felt that remission ON treatment could be considered only in patients in whom ‘maintenance’ treatment (i.e. conventional immunosuppressive agents and/or biologics) was not being increased. By contrast, remission OFF treatment is defined by the absence

of clinical disease activity AND no other drugs for SLE than a stable maintenance dosage of hydroxychloroquine. The task force believes this differentiation acknowledges the disease's natural history and the importance of inducing remission and tapering glucocorticoids and immunosuppressive agents, if possible, which are key to aiding clinicians across the different phases of patient management in real-world practice.

Statement #3: If remission on treatment is not achieved within the pre-specified time frame: 1) therapeutic adherence should be assessed; and 2) treatments should be optimized. (LoA 10; LoE 3).

Therapeutic adherence

Poor therapeutic adherence in SLE patients is associated with higher disease activity, risk of flares, hospitalizations and poor renal outcome [55]. The panel strongly agreed on the need to actively assess adherence to treatment, especially if remission is not achieved, to prevent the incorrect interpretation of lack of remission achievement as an inadequate response to treatment. Several methods can be used to assess poor adherence, but many are highly subjective and inaccurate [56].

Unscheduled assays of hydroxychloroquine (HCQ) levels in whole blood are considered a reliable, simple and objective method for identifying severely non-adherent SLE patients [57]. HCQ is the mainstay of SLE treatment, due to the accumulating numerous benefits in the SLE population, including a significant reduction of flare risk, organ damage, and death [58]. For the first time, the 2023 EULAR recommendations suggest the use of blood level monitoring to help individualize the dose [7]. Monitoring blood levels is useful to detect non-adherent patients, but we must highlight that no randomized controlled clinical trial (RCT) has formally confirmed the value of HCQ monitoring [59]. However, HCQ blood level monitoring is not available in every country or clinical setting. Therefore, physicians should also investigate both unintentional (e.g. incorrect understanding of the prescription) and intentional non-adherence to treatment using alternative methods such as evaluating the refilling approach from the pharmacy or the use of electronic medical records [56],

Once poor adherence to treatment has been identified, physicians should actively engage patients, responding to their specific concerns in an open and non-blaming approach, suggesting pragmatic strategies to improve adherence (e.g., by simplifying the regimen, using reminders, providing education, etc.) [60].

Treatment optimization

In case of failure to achieve treatment target within the prespecified timeframe, dose optimization or the addition/change of immunosuppressant treatments and/or biologics, as necessary, should be considered. However, unlike in RA, treatments readily available for therapeutic switching in SLE are limited, and the optimal drug or

drug combination is not clearly identified at the organ-level, except for lupus nephritis (LN), where more than a dozen RCTs have helped to determine the optimal treatment strategy over the last decades [61]. High-grade evidence about the use of conventional immunosuppressants is limited to a few RCTs showing the efficacy of methotrexate and the superiority of mycophenolic acid derivatives over azathioprine [62]. On the other hand, in a post-hoc analysis of the belimumab trials (BLISS-52 and BLISS-76), LLDAS was able to discriminate active drug from placebo [63]. In a more recent post-hoc analysis of the anifrolumab phase III trials (TULIP 1 and 2), significantly more patients in the treatment group attained and sustained remission and LLDAS compared to placebo [64,65]. These results suggest that the availability of belimumab and anifrolumab in the T2T strategy will increase the rate of remission and LLDAS in SLE patients. Importantly, the 2023 revised EULAR recommendations for SLE state that the addition of immunosuppressive agents and/or biological agents such as belimumab or anifrolumab should be considered in patients not responding to hydroxychloroquine, alone or in combination with glucocorticoids [7].

No formal RCT has yet assessed the benefits of T2T in lupus, but a German trial is underway (NCT05714930) [66]. In this cluster-randomised trial, SLE centres will be assigned 1:1 to standard of care (SoC) therapy or T2T DORIS-remission. Per arm, 303 patients who are not in remission, will be included, and the study duration will be 120 weeks using change in damage and HRQoL as major outcomes. Patients in the T2T arm are reassessed every six weeks. In the case of stable remission, they switch to three-monthly visits but can re-enter tight control in case of flares. Treatment decisions in the T2T arm will be based on shared-decision-making, for which the study personnel will be specifically trained. In the SoC arm, patients receive their usual three- to six-month control visits and treatment adjustments at the physician's discretion. The primary endpoint will be damage accrual at 120 weeks, as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Importantly, the US Federal Drug Administration and the European Medicines Agency have not approved remission and LLDAS as main endpoints in RCTs, despite emerging evidence about the role of new therapies in the attainment of these states [67].

Statement #4: In case of active disease, we recommend follow-up visits every 1 to 3 months, based on the type and severity of organ-involvement (LoA 10; LoE 4).

AND

Statement #5: Once Remission ON treatment is achieved, we suggest follow-up visits every 3 to 6 months until prolonged remission is achieved (LoA 9.5; LoE 4).

AND

Statement #6: In case of a suspected flare, a medical consultation should be performed as soon as possible (if needed remotely), and treatment adjusted accordingly after assessing therapeutic adherence (LoA 10; LoE 4).

No RCT has been conducted to compare follow-up visits every three to six months to any other approach in SLE. Therefore, the panel relying on personal experience suggested follow-up visits within well-defined but distinct intervals, depending on the disease activity and the type and severity of organ involvement. Timely access to lupus specialist care to reassess disease activity, especially in case of a suspected flare, is crucial [68]. Importantly, studies in LN showed the importance of complement normalization and proteinuria improvement ≥25% after eight weeks of induction treatment [69] as well as of targets, such as reaching proteinuria <0·7-0·8g/24h at one year, as markers of favorable prognosis [70]. However, there are no comparable time point targets for follow-up visits in other organ-specific involvement, representing a knowledge gap that needs to be addressed in future research. Moreover, while the principal goal of LN therapy is preventing renal function worsening, agreement upon outcome measures and clinically meaningful short- and long-term targets of LN therapy have yet to be determined.

Statement #7: Prolonged remission is defined as remission* lasting 5 years or more (LoA 9; LoE 3).

**Remission ON or OFF treatment. Not all patients can discontinue GCs. According to statement #9, the possibility of discontinuing GCs should be assessed at every visit.*

Several definitions of remission, including the one by DORIS, do not allow for any clinical disease activity, but prednisone at an equivalent dose of ≤5 mg per day and stable doses of antimalarial, immunosuppressive or biological drugs are allowed within the definitions [72]. Of note, no minimal duration for defining stability is explicitly described. Also, although indirectly implied, de-escalating treatment is not explicitly included in the DORIS definition. More extended remission periods are linked to a reduced risk of flare [73]. The panel debated on the minimum duration to define prolonged remission and whether remission on GCs could be defined as prolonged remission. Since the literature lacks consistent evidence about prolonged remission duration, with some studies suggesting a timeframe of 3 years and others 5 years as associated with a lower risk of relapse, the panel voted to set a minimum of 5 years for defining prolonged remission as the time window allowing tapering and discontinuation of immunosuppressants with lower risk of flare (see also statement #11). An observational study

reported that damage was similar among patients achieving <5 years remission, irrespective of being treated with prednisone ≤ 5 mg/day or not, whereas among patients achieving ≥5 years remission, damage was higher in those in clinical remission on GCs [74]. Moreover, GC-free remission offers a higher protection against mortality than LLDAS and remission on GC [36]. Accordingly, some experts suggested excluding treatment with low GCs from the definition of prolonged remission to avoid considering prolonged remission on and off GC as equal in terms of prognosis. Following extensive discussion, the task force finally agreed that not every patient with SLE is suitable for GCs discontinuation within 5 years of remission achievement. For example, patients with more severe disease (e.g., renal involvement), those on long-term GCs treatment, or those who previously experienced severe flares after GC discontinuation. In the end, after heated debate, the final agreement among the expert panel was to define prolonged remission as either ON or OFF treatment lasting 5 years or more and evaluate patients for tapering and discontinuing of GCs at every visit using a shared decision-making approach (see statement #9).

Statement #8: Once prolonged remission is reached, we suggest follow-up visits every 3-6 months, based on previous organ involvements (e.g. lupus nephritis). (LoA 9; LoE 4)

The panel debated whether suggesting a longer interval between follow-up visits after prolonged remission is achieved would be desirable, but in the end, suggested follow-up visits every 3-6 months. Although the task force agreed that prolonged remission is associated with a lower risk of flare [73], this was not considered sufficient to suggest longer intervals between follow-up visits, especially given the absence of supporting evidence. Flares of lupus nephritis may be asymptomatic; therefore, urinary sediment, proteinuria, and glomerular filtration should be monitored every 3 months to identify any early changes [7,75]. Visits every 3 to 6 months are necessary to evaluate for tapering and/or discontinuation of GCs and immunosuppressants thereafter, monitor drug safety, and assess for adherence to treatment and comorbidities. Nevertheless, the panel agreed that, in patients with less severe organ involvement and stable remission OFF treatment, follow-up visits up to every 12 months could be considered.

Statement #9: Tapering of GCs should be considered at every visit. (LoA 10; LoE 3)

There is broad consensus that GCs should be tapered to the lowest possible dose and possibly discontinued to minimize the detrimental effects of their chronic exposure [7], particularly the increased risk of irreversible organ damage. Initial dosing guided by organ involvement and disease severity is now recommended by EULAR [7]. This is particularly critical for the initial treatment of LN, where the starting dose recommended by EULAR was

0.3-0.5mg/kg/day of prednisone-equivalent [75], while the 2023 KDIGO recommendations now suggest using 0.5-1 mg/kg/day instead [61]. The initial dose of GCs is key in a T2T strategy, as higher initial GC doses are associated with longer time to GC tapering [76]. This is crucial as the DORIS definition of remission and the LLDAS incorporate GC thresholds of 5 and 7.5 mg/day of prednisone equivalent, respectively. The GULP study, a sub-analysis of the multicentre Early Lupus inception cohort, revealed that tapering prednisone below 5 mg/day yields a monthly reduction of the damage incidence rate ratio by 4 % without escalating the risk of short-term disease flare [77]. Of note, modifying the remission glucocorticoid threshold (<5 mg/day prednisolone) was more protective against mortality than current remission definitions, and glucocorticoid-free remission was the most protective [36]. However, physicians can rely only on their experience to taper and discontinue GC [78], which can hinder the T2T strategy. Indeed, no formal tapering strategy is recommended, except for the KDIGO recommendations, in which three tapering schemes are suggested [61].

The task force strongly agreed that it is crucial to consider the tapering of GCs at every visit. The tapering scheme should aim at a ≤5 mg/day prednisone equivalent dose while targeting clinical remission within 6 months in non-renal SLE and 12 months in LN. Once remission is achieved, GC tapering should still be considered at every visit to reach the lowest possible dose below 5 mg/day of prednisone and possibly discontinue GCs. Notably, the panel agreed that the dose-dependent nature of most GC-related side effects justifies the need to taper GCs to the lowest possible dose that will still control the disease. The tapering scheme should be discussed with the patient according to a shared decision-making approach and tailored to the patient's characteristics, including the type of organ involvement, disease severity, initial and cumulative prednisone dose, and comorbidities (e.g., infections)..

The use of intravenous methylprednisolone pulses, which supposedly engage the rapid non-genomic effects of GCs, is included among the potential therapeutic options recommended by EULAR [6,7]. However, the available evidence is limited to retrospective observational studies and indirect comparisons [79], and the literature about the non-genomic effects of GC is scarce [80].

Statement #10: Discontinuation of GCs should be considered in patients in remission on treatment (LoA 10; LoE 3).

Discontinuation of GC therapy in SLE patients remains controversial [81]. Yet, GC tapering remains generally desirable, and the latest EULAR recommendations suggest complete GC withdrawal as one of the main objectives [7]. However, in an open-label randomized trial, the proportion of patients experiencing a flare after one year of disease quiescence was significantly lower in patients maintaining 5 mg/day of prednisone compared with the

group that abruptly stopped GCs [82]. Conversely, gradual GC withdrawal was safe in SLE patients with two consecutive years of clinically quiescent disease and was associated with fewer clinical flares and less damage accrual at 24 months [83]. Observational studies consistently showed that a longer duration of remission, HCQ use, and a slower tapering protocol (i.e., ≥ 6 months) are associated with a reduced risk of flare after GCs discontinuation [84-87]. According to this evidence, the task force agreed to prioritize discontinuing GCs for patients in remission and on stable HCQ treatment. Starting at a dose of prednisone 5 mg daily, the discontinuation process should consider a slow tapering protocol lasting at least 6 months.

Recent data show that GC tapering from ≤7·5 mg/day is feasible in clinically quiescent but serologically active patients, with no increase in the risk of flare and resulting in lower damage [86]. On the other hand, some authors reported that increasing anti-dsDNA titers and hypocomplementemia are independent risk factors for flares after GC tapering and withdrawal [87]. There is an urgent need for RCTs designed to investigate these issues.

Statement #11: The possibility to taper and then discontinue DMARDs should be assessed in patients in prolonged remission who have previously discontinued GCs (LoA 10; LoE 2-3)

An investigator-initiated RCT reported higher relapses of LN and more extrarenal flares in patients discontinuing mycophenolate mofetil (MMF) or AZA after 2–3 years of therapy in LN [88]. Conversely, an open-label RCT reported that MMF withdrawal is not inferior to MMF maintenance after ≥2 years of stable therapy in LN and ≥1 year for non-renal SLE [89]. Also, observational studies showed conflicting results on renal and non-renal flare risk after immunosuppressant withdrawal. However, more recent reports are consistent in reporting a lower risk of flares after immunosuppressive withdrawal in patients with more prolonged remission while receiving HCQ [90-91], but no univocal results on the optimal remission duration are available. The panel agreed that a five-year remission would be associated with the lowest risk of flare [39]. A prospective observational study involving more than 3000 patients reported tapering in complete (clinical and serological) remission offers stronger protection against flare than LLDAS and clinical remission [92].

Based on this emerging, although not definitive, evidence and considering the risk of opportunistic infections, bone marrow toxicity, and malignancy associated with long-term immunosuppressant therapy, the task force agreed that the opportunity to taper and then discontinue DMARDs should be considered in SLE patients with renal and non-renal involvement after prolonged remission is achieved. This decision should be made using a shared decision-making approach. Nonetheless, the task force recognized that evidence-based strategies for

DMARDs tapering/withdrawal are needed. As of today, the exact tapering strategy for both immunosuppressive agents and biologics, particularly the exact sequence for tapering remains a matter of debate and should be considered on an individual case basis.

Serological markers such as anti-double stranded (ds)DNA antibodies and complement fractions C3/C4 are integral components of disease activity assessment in patients with SLE. However, it remains uncertain whether treatment should aim at restoring serological abnormalities because existing evidence indicates a modest association between active serology and risk for flare in patients with clinically quiescent/inactive SLE [93-95]. Most authors currently agree that serologically active but clinically quiescent disease should not trigger a pre-emptive change in treatment. Altogether, these findings provide limited support for inclusion in the T2T approach and suggest an urgent need for further research.

4. CONCLUSION

Although the concept of T2T is widely acknowledged within the SLE community, its operationalization in daily clinical practice remains notably limited, and none of the available recommendations or recent publications actually advise how to implement T2T in real-world clinical practice. Moreover, accumulating data highlights the importance of early attainment and maintenance of remission to limit damage accrual and mortality in SLE, but no RCT has prospectively demonstrated the relevance of T2T in SLE. This framework aims to provide guidance on how to implement T2T in everyday care settings and to reach a broad audience of physicians even outside the restricted core of lupus specialists. This consensus framework differs significantly from current international recommendations (e.g., EULAR and GLADEL/PANLAR) dealing with detailed therapeutic strategies at the organ manifestation level. On the other hand, the task force acknowledged that international recommendations should be followed but can, if needed, be modulated by national recommendations or local circumstances. This was agreed upon to increase the generalizability of the T2T framework in various settings, such as LMICs. Furthermore, the task force prompts various innovative points as overarching principles of the T2T strategy, including non-pharmacological measures, patient education, and telehealth. Despite significant discrepancies in the perception of active disease between patients and physicians, digital tools may be useful for capturing disease states between visits and enabling early detection of flares.

Along with these novelties, the importance of promptly achieving remission after diagnosis is highlighted, while LLDAS emerged as a valuable alternative target when remission cannot be achieved and maintained or when no other recommended drugs are available. The task force acknowledged that disease activity, remission, and LDA

should be assessed by validated tools. Still, it recognized that the limitations of existing disease activity measures result in a restriction towards implementing T2T in routine clinical care, beyond the narrow group of ultra-specialized lupus clinics. Therefore, the task force pragmatically suggested not relying on a single definition of remission in clinical practice but adopting the validated definition that could better suit diverse clinical settings that might impact T2T applicability. Finally, the task force proposed time intervals between visits, distinguished by disease activity status, along with tapering and possible discontinuation of treatments. There was a firm agreement to gradually reduce prednisone to 5 mg/day within a specific time frame while aiming for remission and evaluating the tapering and possible discontinuation of glucocorticoids at each visit for patients in remission. While this framework may represent a significant advancement in the application of the T2T strategy in SLE clinical practice, the task force acknowledged the need for further studies to strengthen the evidence supporting T2T implementation and identified priority research areas. (Figure 3) .

In conclusion, despite the absence of formal evidence that T2T offers superiority to conventional SLE management, the framework suggested by the task force offers a path forward to effectively implementing T2T in SLE. It bridges theory and practice to provide pragmatic answers to implementing T2T into daily clinical practice and highlights gaps in knowledge that need to be addressed in future research. Advancing knowledge on T2T in SLE will necessitate ongoing updates to this framework, which can function as a platform for future recommendations.

Figure 3: Research priority areas for implementing T2T in SLE routine clinical care.


Protocols for treatment adaptations
Standardizing intervals between visits
Tools for assessing adherence
Strategies for drugs tapering and discontinuation
Role of lupus serology in T2T strategy
Treatment response measure
Research priority domains

Authors' contributions

Matteo PIGA and Laurent ARNAUD designed the study, collected the data, performed the statistical analysis and wrote the draft manuscript. All authors reviewed the manuscript for significant intellectual content. All authors approved the final manuscript.

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