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Is it time for treat-to-target in antiphospholipid syndrome?

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ABSTRACT

A treat-to-target (T2T) approach aims to the identification of a clinically relevant therapeutic target and applies tight control (periodic visits at prespecified time-points and treatment adjustments) to achieve it with the goal of improving disease outcomes. The application of a T2T strategy appears to be less feasible in APS compared to other autoimmune diseases. This is primarily explicable by the disease's kaleidoscopic clinical presentation, along with the lack of a definitive tool (biomarkers or scoring system) to assess disease activity, making it complex to recognize a singular, effective therapeutic target for APS patients. Nevertheless, the conceptualization of T2T strategies should be considered a key objective when managing APS, aiming to achieve optimal disease control (including lowering the risk for recurrences), to reduce damage accumulation, and, ultimately, to enhance patients' quality of life.

1. Introduction

A treat-to-target (T2T) approach aims to the identification of a clinically relevant therapeutic target and applies tight control (periodic visits at prespecified time-points and treatment adjustments) to achieve this target with the goal of improving disease outcomes. The treatment approach typically adheres to a protocol that adjusts based on the level of disease activity and the patient's response to the therapy.

The principle of T2T was initially applied with success to several high prevalent chronic diseases, to include hyperlipidemia, hyperuricemia, diabetes mellitus, and arterial hypertension, applying predetermined quantitative parameters as targets (such as cholesterol, uric acid levels glycated hemoglobin, blood pressure). Adequately powered randomised clinical trials have shown that the T2T approaches produces better outcomes compared to standard care [1]. Systematically identifying and targeting appropriate therapeutic goals has enhanced patient care and offered valuable guidance for healthcare providers and administrators.

In rheumatologic and systemic autoimmune diseases, the implementation of T2T has been much more multifaceted, as the target cannot be a unique parameter but often is represented by a score computing together multiple clinical and laboratory endpoints, reflecting disease activity control. In this setting, medications are adjusted over time to reach a predetermined treatment goal. The ultimate goal in rheumatic and systemic autoimmune diseases is to achieve remission; however, when fighting a long-standing disease, low disease activity (LDA) is an acceptable goal [2]. A leitmotif in the overarching principles of T2T among the different rheumatologic diseases is that both the target and the way to reach it must be established together with the patient as a shared decision [3–5].

The T2T strategy in for musculoskeletal conditions was initially explored in the management of rheumatoid arthritis (RA) [2]. The connection between achieving a predefined endpoint and improved long-term functional and structural outcomes was first demonstrated in

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the 2003 Tight Control of Rheumatoid Arthritis (TICORA) study. This study utilized a specific definition of low disease activity (LDA) and required mandatory adjustments to therapy if the target was not met during monthly evaluations [6]. This represented a paradigm shift in RA treatment. Since then, various endpoints have been prospectively validated, providing the foundation for RA treatment guidelines [7] and driving a shift in the expected outcomes for patients with RA, which has ultimately led to significant improvements in survival [8]. Although RA is a systemic condition, the T2T strategy's goal—whether remission or a state of low disease activity (LDA)—is primarily determined by the number of affected joints, using criteria such as the 28-joint disease activity score (DAS28) cut-off of 3.2 for LDA and 2.6 for remission, alongside global assessments by both physicians and patients, as well as inflammatory markers [9–16]. Frequency of disease activity assessment ranges from monthly for patients with high activity to every six months or even less for patients with sustained LDA [3].

T2T guidelines for axial spondylarthritis (axSpA) and psoriatic arthritis (PsA) were introduced in 2014 [17] and revised in 2017 [5]. As for RA, the ultimate goal is preventing structural damage by repeatedly assessing disease activity and adjusting treatment accordingly [18,19], whereas, unlike RA recommendations, these T2T guidelines include extraarticular manifestations as target and indicate that imaging should also be considered when assessing disease activity, although a specific site to be assessed is not specified [5]. The evidence for T2T in PsA essentially relies on the Tight Control of Psoriatic Arthritis (TICOPA) study [20], which paralleled a tight control group with 4-weekly visits and escalation of treatment (from methotrexate to adalimumab) aiming at minimal disease activity, with a regular assessment every 3 months, showing that tight control almost doubled the odds of achieving the ACR20 response, although with increased rate of adverse events and economic cost. These last aspects are the reason why T2T strategy only received a conditional recommendation in ACR PsA treatment guidelines [21], while being implemented in the EULAR recommendations [22]. To address this issue, the Multicentre Observational Initiative in Treat to target Outcomes in Psoriatic Arthritis (The MONITOR-PsA study is designed to evaluate clinical and patient-reported outcomes, along with the costs linked to the pragmatic, routine implementation of a T2T approach. The study will also compare these outcomes with those observed in the TICOPA trial. The study envisages a three-monthly review of each patient, with a standard step-up care in case of not meeting the outcome (either a reduction in swollen and tender joint count of at least 20 % or achieving minimal disease activity criteria) [23]. On the other hand, the Tight Control of axial Spondyloarthritis (TICOSPA) trial, which analyzed the efficacy of T2T strategy in axSpA with a similar design to TICOPA, showed that T2T was not significantly superior to usual care for the primary outcome (rate of patients with $\geq$30 % improvement in ASAS-Health Index), although showing superiority in several secondary outcomes and, in contrast with TICOPA, in terms of cost-effectiveness [24]. ACR guidelines for axSpA treatment, which were released before the completion of this trial, did not recommend a T2T strategy in axSpA [25], which is instead included in the EULAR recommendations [26]. Both for PsA and axSpA a general concern is the overall low application of T2T in clinical practice [27,28], due to the still limited level of evidence and doubts about cost-effectiveness.

The application of T2T is more challenging in systemic lupus erythematosus (SLE), due to its complexity and heterogeneity, intrinsic to a multisystem disease. The limitations of existing activity and damage indices, along with the scarcity of validated treatment targets, contribute significantly to the recurrent failure of clinical trials in SLE. The lack of well-validated endpoints remains a major challenge in effectively assessing and achieving therapeutic success in this condition [29].

An initial proposal of the T2T approach in SLE was launched by an international task force of experts in the field in 2014 [4]. As in other rheumatologic conditions, the chosen target was achieving remission or, if not feasible, the lowest possible level of disease activity, as high disease activity is associated with increased damage and therefore mortality. However, at the time when recommendations were stated, there was neither accepted definition either for remission nor for low level of disease activity [30]. During the last decade several definitions of remission have been proposed, the most widely accepted one being the DORIS (Definition Of Remission In SLE) definition [31], defined as a clinical SLE disease activity index (SLEDAI) = 0 and a physician global assessment (PGA) < 0.5 with a stable immunosuppressive treatment and low dose corticosteroids (prednisolone $\leq$5 mg/day). In 2016, the Asia-Pacific Lupus Collaboration group proposed and validated the Lupus Low Disease Activity State (LLDAS) definition. This was based on the principle of a "tolerated" or "acceptable" level of disease activity, characterized by a SLEDAI-2 K score of $\leq$4, without major organ involvement, hemolytic anemia, or gastrointestinal involvement. Additionally, there should be no new features of disease activity compared to the previous assessment, and a SELENA-SLEDAI PGA score of $\leq$1. This state must be achieved in a patient on stable immunosuppressive therapy and low-dose corticosteroids (prednisolone $\leq$7.5 mg), with a low likelihood of adverse outcomes [30]. Both the LLDAS and similar targets have been associated with reduced damage accrual [32–35], fewer disease flares, decreased corticosteroid doses [36], and improved quality of life [37,38]. Furthermore, LLDAS demonstrated better performance characteristics when compared to expert opinions not guided by a formal definition [39]. When selecting the target, it must be considered that, even though no study performed a direct comparison between them, the indirect evidence supports the idea that remission implies a more pronounced improvement, especially in terms of damage accrual [34] and corticosteroids doses [40]. On the other hand, although remission is a preferable target, various studies showed that LLDAS is easier to reach [33,41,42]. The LUPUS-BEST trial is designed to compare DORIS remission and LLDAS in order to identify the treatment target that offers the best benefit/risk ratio with respect to attainability, adverse events, and long-term damage [43].

There is presently no consensus about the minimum duration that the chosen target should last. Nevertheless, there is evidence from one of the biggest studies comparing the effect of LLDAS and remission in damage prevention, that even a minor proportion (< 25 %) of time spent in clinical remission on treatment, is associated with a 46 % reduction in damage accrual [34]. Conversely, a prospective study demonstrated that maintenance of LLDAS for at least 50 % of the follow-up, is significantly found to be associated with a reduction of flares and damage accrual [44]. Another study showed that spending at least two years in LLDAS, predisposes to less damage when compared to never achieving this target [33]. Moreover, there is evidence that failure to achieve LLDAS within 6 months from SLE diagnosis is associated to early damage accrual [41].

Besides reducing disease activity to the lowest possible level, preventing flares is crucial for damage prevention [45]. However, even though serological parameters, including anti-dsDNA antibodies and C3 and C4, are a useful tool to predict flares in SLE, treatment escalation in serologically active but clinically quiescent patients is not recommended.

Among the different systems that can possibly be involved in SLE, current T2T recommendations focus on renal involvement, stressing on the importance of early recognition of lupus nephritis (through markers such as creatinine clearance, urine sediment, proteinuria and anti-C1q antibodies) and the indication of maintaining treatment for at least three years after induction therapy. There is general agreement that corticosteroids should be reduced at the smallest dose required to control the disease and if feasible, withdrawn completely, to prevent their deleterious side effects and impact on damage accrual. It is generally accepted that a dose $\leq$7.5 mg/day of prednisone is safe and well tolerated in most patients [46], even though some authors suggested a threshold of 5 mg/day to be safer with no increased risk of flares. It is almost universally recognized that antimalarials should be administered to all patients with SLE and never stopped, unless in case of severe side

effects, since the evidence on their efficacy in controlling disease activity, preventing SLE flares, reducing damage and improving survival is quite consistent. Moreover, they have proven effects on thrombosis and infections prevention. Finally, the treatment of associated comorbidities, such as cardiovascular risk, cannot be disregarded in a is known to increase the risk of cardiovascular incidents such as SLE. At same time, prevention of infections and osteoporosis (via vitamin D supplementation) and routine cancer surveillance is warranted.

The T2T approach in SLE still presents several limitations. One challenge is that, except for the renal system—where therapeutic targets like specific proteinuria thresholds have been validated in relation to long-term disease outcomes [47]—there are no widely accepted or validated targets for other areas (such as articular, hematologic, mucocutaneous, lung systems). This raises the question of whether a T2T approach in clinical practice should rely on a set of dissimilar treatment targets for each affected organ or a single, combined lupus activity index. While the use of composed tool is clearly more practical, there remains debate over which index is best suited for SLE, as all existing ones have notable limitations. For example, while the SLEDAI has modest sensitivity to changes in disease activity, the British Isles Lupus Assessment Group (BILAG) index, though more sensitive, is cumbersome to use in daily practice. Despite these limitations, T2T remains the most effective approach for managing complex and multisystem diseases. Recently, a group of lupologists suggested a definition of disease modification in SLE, drawing on experiences from other diseases. They focused on two key aspects: disease manifestations and patient-reported outcomes. Their conclusion was that disease modification in SLE should involve reducing disease activity with the least therapy-related toxicity, while also slowing or avoiding the progression of organ damage [48]. This definition serves as a foundation for harmonizing outcomes in future clinical trials.

2. T2T in antiphospholipid syndrome (APS)

As noted earlier, the T2T strategy seems less suited to APS compared to other chronic conditions, both rheumatological and non-rheumatological. This is primarily related to the disease's variability, along with the absence of a clear marker for disease activity, which makes it difficult to identify a single, effective treatment target for APS. Nevertheless, implementing T2T still represents an important objective in managing APS, with the goals of achieving optimal disease control, preventing damage accumulation, and enhancing patient quality of life. The discovery of specific molecular profiles in APS pathophysiology [48] highlights the potential for precision medicine. Stratifying patients based on specific disease activity markers and predictors of a pro-thrombotic profile (e.g., NETs, IFN signature) [49] could support the successful implementation of T2T. Nevertheless, this approach is not yet widely feasible in routine practice. To make T2T a practical strategy in clinical settings, two key goals must be met: establishing practical and attainable targets and developing therapeutic options that can realistically achieve these targets within specified timeframes.

3. Which target for APS?

In the absence of validated activity index specifically designed for APS, choosing the targets to optimize the management in patients with APS remains, up to now, merely speculative. Nevertheless, several strategic treatment targets have been discussed to manage the disease effectively and mitigate the risk of complications or recurrences.

- Antiphospholipid antibody (aPL) levels: triple aPL-positive results or persistently high aPL titers have been correlated with an increased risk of thrombotic events [49,50,51]. One could speculate the opposite: should we include among the primary aims of T2T in APS the reduction of aPL levels? While regular monitoring of aPL can be considered a cornerstone of thrombotic risk stratification, only anecdotal cases of therapy-induced aPL seroconversion have been reported [52]. One clinical trial is currently ongoing exploring the use of belimumab in primary APS [53]. Among the secondary outcomes of the BLAST trial, an open-label, prospective, phase II descriptive pilot trial of belimumab therapy for refractory and/or non-criteria manifestations of antiphospholipid syndrome, the aPL titer reduction has been introduced. Among others, results from this study will help us to understand if aPL seroconversion is an actionable target to optimize the management of patients with APS.
- Prevention of thrombosis recurrence and thromboprophylaxis: one of the cornerstones of APS management is the prevention of new thrombotic recurrences. This is typically achieved through anticoagulant therapies, mainly vitamin K antagonists. Therefore, preventing recurrent thrombotic episodes could be considered a critical target and thromboprophylaxis should be adjusted accordingly.
- Management of non-thrombotic manifestation: given that APS is an autoimmune disorder, patients may experience systemic symptoms beyond thrombosis. These range from fatigue and cutaneous manifestations to life threating clinical scenarios (e.g., neurological manifestations such as transverse myelitis). The effective management of these symptoms to enhance prognosis and the patient's quality of life is heterogenous and should reflect the clinical presentation. It can range from the use of steroids or immunosuppressive agents and biologics (e.g., to control hematological manifestations such as thrombocytopenia and hemolytic anemia) to therapeutic educational programs to reduce the impact systemic symptoms such as fatigue.
- Pregnancy management: for individuals with aPL or APS who are pregnant or planning pregnancy, one additional target could be to achieve a successful and uncomplicated gestation. This necessitates meticulous monitoring, appropriate adjustment of anticoagulant therapy, and prevention of pregnancy-related complications [49,50,54].
- Expanding therapeutic targets by incorporating the 2023 ACR/EULAR classification criteria: the recent update to the classification criteria for APS introduces six clinical domains to enhance patient classification. These domains are: (1) macrovascular – venous thromboembolism, (2) macrovascular – arterial thrombosis, (3) microvascular – including manifestations such as livedo racemosa, livedoid vasculopathy, aPL nephropathy, pulmonary hemorrhage, myocardial disease, adrenal hemorrhage, and microthrombosis, (4) obstetric APS, (5) cardiac valve – including valve thickening or vegetations, and (6) hematology – thrombocytopenia. While thrombotic and obstetric manifestations are thoroughly assessed when suspecting APS, a systematic screening for the previously called "non-criteria" manifestations could improve patient characterization and ultimately support efforts to control disease activity.
- Reduction of organ damage: APS can precipitate organ damage, including renal impairment and valvular heart disease. The therapeutic target is to prevent further damage and manage these complications through appropriate medical interventions.

The Damage Index for APS (DIAPS) was designed to measure damage accumulation in thrombotic APS and comprises 37 items across 10 organ-specific domains, with 22 items adapted from the SLE International Collaboration Clinics/American College of Rheumatology Damage Index (SDI). The initial study introducing DIAPS evaluated it in 156 thrombotic APS patients from several countries in Latin America, including Mexico, Venezuela, El Salvador, and the Dominican Republic. The DIAPS was validated, showing content, criterion, and construct validity, and it significantly correlated with health-related quality of life (HR-QoL), as assessed by the EuroQol 3-level 5-domain HR-QoL scale (EQ-5D-3L). Since its first description, the use DIAPS has been validated in different cohorts, supporting its potential role as a promising tool when considering T2T approaches in APS [55–58]. It is noteworthy to consider that patients with APS exhibit a distinct pattern of chronicity compared to those with SLE.

Specifically, APS patients tend to show higher DIAPS scores early in their disease course [59]. Additionally, research has shown that patients who test positive for aPL may develop damage even before experiencing a vascular event, suggesting that aPL should be considered an independent vascular risk factor. These aspects should be evaluated when considering reducing the damage accrual as a therapeutic target in APS [60]

- Enhancement of quality of life: a key objective of APS treatment is to improve overall quality of life by alleviating symptoms, reducing thrombotic risk, and minimizing the impact of APS on daily activities. To date, no APS-specific tool has been developed for this condition and the assessment of Quality of Life mainly relies on scoring systems used in the general population or in other rheumatic diseases.
- Available scoring systems for risk stratification in APS as tools to guide T2T: a fundamental aspect of health and clinical research is the identification of individuals at high risk of adverse outcomes within a certain timeframe, enabling early intervention through preventative strategies and potential treatments. Numerous predictive models have been developed, particularly for cardiovascular diseases, often targeting stroke or ischemic heart events [61–62]. More recently, scoring systems have been created specifically for APS to assess the risk of thrombosis and obstetric complications [63–64]. These systems aid physicians in risk stratification of patients. The initial scores concentrated on the profiles of antiphospholipid antibodies (aPL), whereas the latest, known as the Global APS Score (GAPSS), additionally incorporates cardiovascular risk factors and autoimmune profiles into its risk assessment. GAPSS has been validated in prospective cohorts [65–66], showing that patients who experienced vascular events during the follow-up showed a significant increase in their GAPSS over time. More specifically, the risk increased when the GAPSS rose by more than 3 points. Shifting from a qualitative to a quantitative approach in risk prediction might aid the implementation of specific targets in APS.

4. From SLE to APS: can we translate what we have learned in SLE to speculate a T2T adaptation for APS?

Translating T2T strategies from SLE to APS could involve adapting the lessons learned in SLE management to formulate specific, actionable recommendations for APS. Table 1 includes a speculative adaptation for patients with APS of the T2T recommendations suggested for SLE proposed by an international task force [4]. T2T can be inspired by those in SLE, particularly when considering tailoring treatment to reduce the risk of thrombotic events, manage symptoms, and stabilize the patient's condition. Nevertheless, some intrinsic differences, mainly related to the different pathophysiology of the two conditions, limit a fully transability.

International efforts are needed to design and validate T2T strategies in APS. In the meantime, one could only speculate potential overarching principles guiding the process.

Firstly, in the management of APS, a nuanced approach is employed, beginning with risk stratification. Patients are categorized based on their thrombotic risk, which guides the intensity and nature of their treatment regimen. This stratification is pivotal as it tailors therapy to individual needs, ensuring that each patient receives the most appropriate level of care. As previously discussed, central to the treatment strategy in APS are the target goals. Potential target only partially overlaps with those suggested for SLE. Additional targets considering the unicity of APS should be explored. These include the prevention of thrombotic episodes, the control of cardiovascular risk factors, and the control of any comorbid conditions. Additionally, achieving a seronegative status for aPL can be considered an exploratory target. Although the practical relevance of this goal is still being evaluated through ongoing research, it represents a potential marker for adjusting treatment strategies and measuring their success. Finally, the treatment process requires diligent

Table 1
From SLE to APS: Can we translate what we have learned in SLE to speculate T2T recommendations for APS?

	T2T SLE recommendations[63]	T2T APS adaptations
Recommendation 1	The treatment target of SLE should be remission of systemic symptoms and organ manifestations or, where remission cannot be reached, the lowest possible disease activity, measured by a validated lupus activity index and/or by organ-specific markers	The treatment target of APS should be remission of systemic symptoms and organ manifestations or, where remission cannot be reached, the lowest possible disease activity, measured by organ-specific markers or available stratifications scoring tools.
Recommendation 2	Prevention of flares (especially severe flares) is a realistic target in SLE and should be a therapeutic goal.	Prevention of thrombosis is a realistic target in APS and should be a therapeutic goal.
Recommendation 3	It is not recommended that the treatment in clinically asymptomatic patients be escalated based solely on stable or persistent serological activity.	Thromboprophylaxis strategies should consider both the aPL profile and the previous medical history, including concomitant risk factors.
Recommendation 4	Since damage predicts subsequent damage and death, prevention of damage accrual should be a major therapeutic goal in SLE.	Since damage predicts subsequent damage and death, prevention of damage accrual should be a major therapeutic goal in APS.
Recommendation 5	Factors negatively influencing health-related quality of life, such as fatigue, pain and depression should be addressed, in addition to control of disease activity and prevention of damage.	Factors negatively influencing health-related quality of life, such as fatigue, pain and depression should be addressed, in addition to control of the occurrence of new manifestations and prevention of damage.
Recommendation 6	Early recognition and treatment of renal involvement in lupus patients is strongly recommended.	Early recognition of organ involvement (e.g., cardiac, neurological) in APS is strongly recommended.
Recommendation 7	For lupus nephritis, following induction therapy, at least 3 years of immunosuppressive maintenance treatment is recommended to optimize outcomes.	If not contraindicated, renal involvement in APS should be confirmed by kidney biopsy. For patients on antithrombotic agents, careful management—such as appropriately timing the suspension of antiplatelet therapy and/or bridging VKAs with heparin—is essential to reduce bleeding risk.
Recommendation 8	Lupus maintenance treatment should aim for the lowest glucocorticoid dosage needed to control disease, and if possible, glucocorticoids should be withdrawn completely.	For those aPL-related manifestations requiring the use of glucocorticoids, maintenance treatment should aim for the lowest glucocorticoid dosage needed, and when possible, glucocorticoids should be withdrawn completely.
Recommendation 9	Prevention and treatment of antiphospholipid syndrome (APS)-related morbidity should be a therapeutic goal in SLE;	When associated to another CTD, including SLE, the optimization of CTD-comorbidity should be a therapeutic goal in APS.
Recommendation 10	Irrespective of the use of other treatments, serious consideration should be given to the use of antimalarials.	Consideration should be given to the use of antimalarials in selected cases (i.e. recurrent pregnancy morbidity besides SoC)
Recommendation 11	Relevant therapies adjunctive to any immunomodulation should be considered to control comorbidity in SLE patients.	Relevant therapies adjunctive to any anticoagulation (e.g., statins) should be considered to control comorbidity in APS patients.

monitoring and flexible adjustment of therapies. This is accomplished through regular clinical assessments and laboratory testing. Based on these evaluations, treatments—such as anticoagulants and immunosuppressive agents—are adjusted to align with the patient's current health status and response to therapy.

Implementing T2T in APS could also help rationalize the use of glucocorticoids and immunosuppressants for this condition. Currently, their use is largely guided by the treating physician's judgment and is primarily aimed at controlling non-thrombotic manifestations (e.g., hematologic complications or, less frequently, neurological or renal involvement). Similarly, hydroxychloroquine is often considered in cases with systemic symptoms, such as arthralgia, or mild thrombocytopenia, and more rarely as an add-on to Vitamin K antagonists (VKAs) for refractory thrombotic events. Its role in obstetric APS is also currently under investigation.

A dynamic approach could ensure that treatment remains effective and responsive to the evolving nature of APS, ultimately aiming to mitigate the disease's impact on the patient's health.

5. Barriers for the implementations of T2T approach in APS and possible solutions

Several barriers may hinder the implementation of T2T in APS. The first challenge is the lack of clear understanding regarding the appropriate treatment targets and the strategies to achieve them. For example, while a six-month timeframe has been suggested for monitoring disease activity in the T2T strategy for SLE [67], it remains uncertain whether this timing is optimal for APS. Additionally, defining remission in APS is particularly challenging. Some clinical manifestations of APS are binary (such as thrombosis), while others are continuous (such as thrombocytopenia). Critical questions arise, including: What is the appropriate timeframe to consider reaching the target? Does this vary across available therapies or APS clinical features? How often should patients be assessed to determine if the target is achieved or if treatment adjustments are necessary? What is the balance between effective disease control and minimizing drug toxicity? Moreover, striving for the complete absence of clinical manifestations in APS (e.g., livedo reticularis) may be unrealistic due to the presence of some comorbidities and the absence of an ideal treatment. Similarly, the identification of laboratory parameters to differentiate between concomitant disease manifestations and those directly related to aPL/APS will be a critical milestone in implementing T2T strategies.

In order to advance the T2T approach, involving patients in the decision-making process is also essential [68,69]. This not only aims to improve adherence to therapy but also addresses a significant issue of treatment failure due to non-adherence. Studies have shown that up to 75 % of patients may be non-adherent, and up to 33 % discontinue therapy after five years [70]. Enhancing patient understanding of the disease and the benefits of prescribed therapies through effective communication is crucial.

Furthermore, there is no unanimous agreement on the best methodologies to achieve consensus when defining T2T strategies or applicable tools (e.g., disease activity indexes). While the Delphi methodology is frequently used, the rapidly growing application of artificial intelligence in clinical decision-making—such as analyzing patient data and predicting disease progression—could further support the optimization of care pathways for chronic disease patients.

Finally, it remains to be proven that a T2T approach is clearly advantageous in autoimmune diseases, in terms of facilitating the achievement of clinical outcomes, enhancing quality of life, and reducing healthcare costs.

6. Conclusions

The available evidence suggests that implementing a T2T approach in APS is feasible, though it does face certain obstacles. It is likely that many specialized centers are already hypothesizing this strategy, although standardized protocols have yet to be established. With patients experiencing better disease management in recent years, adopting and applying T2T strategies could further improve the overall outcome of APS patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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