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Review

Methotrexate Versus Mycophenolate Mofetil as First-Line Therapy in Systemic Sclerosis: Evidence from Clinical Trials and Real-World Studies—A Narrative Review

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Abstract

Systemic sclerosis (SSc) is a heterogeneous autoimmune connective tissue disease characterized by immune activation, vasculopathy and progressive fibrosis of the skin and internal organs. Immunosuppressive treatment is commonly used in early inflammatory disease and in SSc-associated interstitial lung disease (SSc-ILD), yet the optimal first-line agent depends on the dominant clinical phenotype. Methotrexate (MTX) and mycophenolate mofetil (MMF) are two widely used conventional immunomodulatory options. This review summarizes the clinical trial evidence from the last four decades and places it into the context of contemporary guideline recommendations and real-world comparative effectiveness data. Two randomized placebo-controlled trials support a modest role for MTX in early diffuse cutaneous SSc, particularly for skin and musculoskeletal manifestations, but evidence for lung benefit is limited. MMF has stronger evidence for SSc-ILD, principally from the Scleroderma Lung Study II, a randomized double-blind trial showing comparable efficacy to oral cyclophosphamide with better tolerability, and from subsequent pilot, open-label, and real-world studies. Overall, the current evidence supports a phenotype-driven approach: MTX may be considered when skin or joint disease predominates without clinically relevant ILD, whereas MMF is generally preferred for SSc-ILD and systemic inflammatory disease. Direct head-to-head MTX versus MMF trials are lacking and remain an important research priority.

Keywords: systemic sclerosis; scleroderma; methotrexate; mycophenolate mofetil; interstitial lung disease; skin fibrosis

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1. Introduction

Systemic sclerosis (SSc) is a rare multisystem autoimmune disease in which immune dysregulation, microvascular injury and fibroblast activation converge to produce progressive fibrosis. The clinical spectrum ranges from limited cutaneous disease with predominant vascular complications to rapidly progressive diffuse cutaneous SSc (dcSSc) with major organ involvement [1]. Among internal organ manifestations, SSc-associated interstitial lung disease (SSc-ILD) is one of the leading causes of morbidity and disease-related mortality [2].

First-line immunosuppressive treatment selection remains challenging because SSc is not a single therapeutic entity. Skin fibrosis, inflammatory arthritis, myositis overlap, myocardial involvement and ILD may require different therapeutic priorities [3].

Historically, methotrexate (MTX) was one of the first immunomodulatory agents tested in randomized trials for early dcSSc [4]. Mycophenolate mofetil (MMF), and less commonly enteric-coated mycophenolate sodium (EC-MPS), have subsequently become widely used, especially for SSc-ILD, owing to favorable tolerability and accumulating evidence for stabilization of lung function [3,5–7].

Although the term active systemic sclerosis (SSc) is frequently used in clinical practice, there is currently no universally accepted definition. Importantly, disease activity should not be equated with symptom burden alone. Instead, active SSc should refer to objective evidence of ongoing inflammatory and/or fibrotic disease progression that may justify initiation or escalation of immunomodulatory therapy. This concept is consistent with the revised EUSTAR Disease Activity Index, which integrates clinical, laboratory, and functional parameters associated with active disease [8] and might include other features of active disease [1,2,9–12] (Table 1).

Table 1. Suggested clinical features indicating active systemic sclerosis and potential consideration for immunosuppressive therapy. This table represents an author-derived synthesis based on published observational studies, the revised EUSTAR disease activity index and current EULAR recommendations rather than validated treatment criteria.

Domain	Features Suggesting Active Disease
Skin	Increasing mRSS, rapidly progressive skin thickening (<3–5 years disease duration)
Musculoskeletal	Tendon friction rubs, inflammatory arthritis, elevated CK/myositis
Lung	New ILD, HRCT progression, FVC decline $\geq$ 5–10%, DLCO decline $\geq$ 5–10%
Laboratory	Elevated CRP/ESR
Heart	Active myocarditis/pericarditis
Vascular	Recurrent digital ulcers

mRSS: modified Rodnan skin score; CK: creatin kinase; HRCT: high resolution computed tomographie; FVC: forced vital capacity; DLCO: diffusion capacity for carbone monoxide; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate.

Throughout this review, the term active systemic sclerosis refers to patients with objective evidence of ongoing inflammatory or fibrotic progression rather than to patients who are symptomatic but clinically stable. This distinction is particularly important because treatment recommendations discussed in this review are intended for patients in whom disease-modifying immunosuppressive therapy is considered appropriate rather than for all patients with systemic sclerosis.

This narrative review focuses on MTX and MMF/EC-MPS as first-line immunosuppressive therapies in SSc. It explicitly separates randomized controlled trials from open-label and observational studies and post hoc comparative effectiveness analysis.

2. Methods

A narrative literature review was performed covering the period from January 1986 to June 2026. Searches were conducted in PubMed using combinations of the following terms: “systemic sclerosis”, “scleroderma”, “methotrexate”, “mycophenolate mofetil”, “mycophenolate sodium”, “interstitial lung disease”, “randomized trial”, “phase II”, “phase III”, “open-label”, and “EUSTAR”. Reference lists of major reviews and guideline documents were screened for additional studies.

Eligible evidence included randomized controlled trials, phase II/III trials, retrospective studies, prospective open-label studies, and large observational or registry analyses evaluating MTX, MMF or EC-MPS in SSc. Studies of other drugs were included only when

MMF or MTX were a comparator, background therapy or real-world treatment arm. Case reports and very small uncontrolled series were not prioritized unless they were historically relevant. Because older SSc trials were often not labeled as phase I/II/III despite randomized design, they are classified by design and evidence level rather than by modern drug-development terminology.

3. Results

3.1. Pathophysiological Rationale for MTX and MMF

SSc pathogenesis involves endothelial cell injury, innate and adaptive immune activation, autoantibody production and profibrotic signaling. In the initial phase of dcSSc, inflammatory infiltrates in the skin and affected organs may precede irreversible fibrosis, providing a therapeutic window for immunomodulation.

MTX and MMF target different aspects of lymphocyte activation and proliferation. Although methotrexate is a folate antagonist that inhibits nucleotide synthesis, its therapeutic efficacy in autoimmune rheumatic diseases is thought to be mediated primarily through immunomodulatory and anti-inflammatory mechanisms, particularly the promotion of extracellular adenosine accumulation, which suppresses inflammatory cell activation and cytokine production [13]. In SSc, its rationale is strongest for inflammatory skin disease and musculoskeletal involvement. MMF is a prodrug of mycophenolic acid (MPA) that inhibits inosine monophosphate dehydrogenase (IMPDH), thereby impairing de novo guanosine nucleotide synthesis, particularly in activated lymphocytes [14]. This mechanism provides a rationale for use in SSc-ILD and active disease.

3.2. Methotrexate: Trial Evidence and Clinical Positioning

Two randomized placebo-controlled trials constitute the core evidence base for MTX in SSc (Table 2). Van den Hoogen et al. performed a 24-week randomized double-blind trial followed by 24 weeks of observation in 29 patients receiving weekly intramuscular MTX or placebo [4]. The study suggested benefit in active SSc, but its small sample size, mixed disease subset composition and short blinded duration limit the certainty of conclusions.

Pope et al. subsequently conducted a larger randomized placebo-controlled trial in dcSSc patients and a disease duration of less than three years. Participants received oral methotrexate at a dose of 15 mg/week for 12 months [15]. MTX showed a trend toward improvement in skin and global disease assessments, supporting a possible disease-modifying effect in early inflammatory dcSSc. However, the magnitude of benefit was modest and evidence for prevention or treatment of ILD was not established.

Clinically, MTX remains most defensible as an early-line option in patients with predominant skin fibrosis or inflammatory musculoskeletal disease and without clinically significant or progressive ILD. It is less attractive when pulmonary disease is already present or when rapid visceral progression is suspected. Standard monitoring includes blood counts, liver enzymes, renal function, infection screening and folic acid supplementation. MTX is contraindicated in pregnancy.

3.3. Mycophenolate Mofetil/Mycophenolate Sodium: Trial Evidence

MMF has become a central agent for SSc-ILD (Tables 2 and 3). The pivotal randomized evidence comes from the Scleroderma Lung Study II (SLS II), which compared two years of MMF with one year of oral cyclophosphamide followed by placebo in symptomatic SSc-ILD [5]. Both treatment strategies were associated with improvement or stabilization in lung function, and MMF had a more favorable tolerability profile. Although SLS II did not prove superiority of MMF over cyclophosphamide for the primary endpoint, the balance

of efficacy and safety strongly supported MMF as a preferred first-line option in many patients with SSc-ILD.

Additional randomized and pilot trial data have explored MMF in earlier or milder ILD, and recent trial designs increasingly use MMF as background standard-of-care therapy. The Scleroderma Lung Study III evaluated whether adding pirfenidone to MMF would provide additional benefit over MMF alone in active SSc-ILD [7]. The study is important methodologically because it reflects the contemporary role of MMF as an anchor therapy against which add-on strategies are tested.

Further randomized evidence was provided by Naidu et al., who investigated MMF in patients with SSc-ILD and only mildly impaired lung function. Although the study did not demonstrate a significant improvement in pulmonary function compared with placebo, a significant improvement in skin involvement was observed, supporting the potential role of MMF in earlier disease stages [16].

Enteric-coated mycophenolate sodium is less extensively studied than MMF although EC-MPS provides delayed intestinal release with overall MPA exposure comparable to equimolar doses of MMF [17] and is thus sometimes discussed as more effective and tolerable in SSc. However, direct comparative studies between EC-MPS and MMF in systemic sclerosis are lacking, and superiority regarding efficacy or tolerability has not been demonstrated. We performed a prospective open-label study in SSc, using EC-MPS and CT histography to monitor pulmonary fibrosis [6]. The study provided early prospective evidence of stabilization of pulmonary fibrosis and highlighted quantitative CT analysis as a potentially sensitive monitoring tool.

More recently, the MINIMISE-Pilot study evaluated MMF in patients with limited cutaneous SSc who would not routinely receive immunosuppressive therapy. Although the study was terminated early because recruitment targets were not achieved and no clinical worsening events occurred during follow-up, it is important because it represents the first randomized, prospective attempt to assess whether MMF may prevent disease progression outside the diffuse cutaneous subset [18].

3.4. Comparative Interpretation: MTX Versus MMF

There are no direct randomized, head-to-head trials comparing MTX with MMF as first-line therapy in SSc. Therefore, therapeutic positioning relies on indirect evidence, organ-specific outcomes and guideline consensus. MTX evidence is concentrated in skin-predominant early diffuse disease, while MMF evidence is strongest in ILD and systemic inflammatory disease with pulmonary risk. Importantly, the overall strength of evidence differs substantially between both agents. Whereas MTX is supported by a limited number of relatively small randomized trials focused primarily on cutaneous disease, MMF has been evaluated across multiple randomized studies, prospective cohorts, long-term observational datasets and comparative effectiveness analyses involving pulmonary, cutaneous and vascular manifestations of SSc.

For a patient with early dcSSc, active skin thickening and inflammatory arthritis but normal CT-scan, preserved pulmonary function and no high-risk lung features, we think MTX remains a reasonable option [3]. For a patient with SSc-ILD, declining FVC or DLCO, inflammatory lung features or high-risk autoantibody/phenotype profile, MMF should generally be preferred. In patients with severe or rapidly progressive disease—especially with risk scores for high mortality—escalation beyond either MTX or MMF may be appropriate, including cyclophosphamide, rituximab, tocilizumab, nintedanib or autologous hematopoietic stem cell transplantation in selected cases [3].

Effective contraception is mandatory before initiation of MTX or MMF. Both drugs are teratogenic and require appropriate counseling before treatment initiation. MMF and MTX carry a particularly high risk of congenital malformations (MMF) and spontaneous abortion (MTX) and should therefore be discontinued well before planned conception according to current regulatory recommendations [19].

3.5. Risk Scores

Several prognostic tools have been developed to support risk stratification in SSc. For SSc-associated ILD, the SPAR (SpO_2 and Arthritis) model predicts progression in patients with mild ILD, and may help identify individuals requiring closer monitoring or earlier treatment [20]. On a broader disease level, EUSTAR-derived models have been developed to predict organ progression and mortality. They identified clinical predictors of disease worsening in dcSSc, and developed a mortality prediction score capable of estimating 3-year survival based on routinely available clinical variables [2]. More recently, the RESIST score has been proposed, a risk model for early mortality in patients eligible for intensive therapies, incorporating factors such as diffuse cutaneous disease, elevated CRP, digital ulcers, impaired DLCO, reduced left ventricular ejection fraction, and higher skin scores [10]. Although these scores are not currently used to determine the choice between MTX and MMF, they may facilitate identification of patients at increased risk of progression who could benefit from earlier immunomodulatory intervention.

3.6. Real-World Evidence and Observational Studies

Real-world evidence is essential in SSc because randomized trials are difficult, cohorts are heterogeneous and long-term organ outcomes are clinically decisive (Table 3). The EUSTAR post hoc comparison of tocilizumab, rituximab, MMF and cyclophosphamide in SSc-ILD is particularly relevant [21]. It is not a phase I/II/III trial and should not be interpreted as randomized evidence. Nevertheless, it is a large comparative effectiveness analysis reflecting routine clinical practice. The analysis reported no statistically significant differences in FVC change between the four immunosuppressive treatment groups, while also illustrating contemporary prescribing patterns: MMF and cyclophosphamide were mainly used as first-line immunosuppressive therapies, whereas biologic agents were more often used in later-line settings.

The strengths of the EUSTAR analysis include a large, multinational registry, inclusion of routine-care patients and clinically meaningful pulmonary endpoints. The main limitations are confounding by indication, differences in disease severity and treatment timing, missing data and the post hoc observational design. The study should therefore support, but not replace, randomized evidence. Its value for this review is that it reinforces the current status of MMF as a common first-line real-world comparator in SSc-ILD.

Several observational studies further support the use of MMF in both cutaneous and pulmonary disease. Nihtyanova et al. [22] demonstrated favorable long-term outcomes in diffuse cutaneous SSc, including improved survival and lower progression of pulmonary fibrosis. Le et al., Derk et al., Mendoza et al. and Boulos et al. [23–26] consistently reported improvement in skin scores and stabilization of pulmonary function during long-term MMF treatment. Zamora et al., Simeón-Aznar et al. and Lee et al. [27–29] provided additional evidence supporting stabilization of SSc-associated ILD in routine clinical practice.

More recently, registry-based and translational studies have expanded the potential spectrum of benefits attributable to MMF. Wildt et al. [30] reported an association between MMF exposure and improved nailfold capillary density, suggesting an effect on microvascular disease, while De Lorenzis et al. [31] demonstrated a markedly reduced need for escalation of vasoactive therapy in patients with limited cutaneous SSc treated with MMF.

So experimental and observational data suggest that MMF may exert beneficial effects on vascular inflammation and endothelial activation. However, convincing clinical evidence demonstrating a vascular protective effect in patients with SSc is currently lacking, and this potential mechanism should therefore be regarded as hypothesis-generating rather than clinically established. Observational MMF studies generally support stabilization or improvement of FVC and variable improvement in skin scores [32,33]. Such studies are vulnerable to survivorship bias and regression to the mean, but they are consistent with the overall interpretation of SLS II [5]. For MTX, observational use remains common for arthritis and skin disease, but robust real-world comparative data against MMF are missing.

In a post hoc analysis of the RESOLVE-1 trial of lenabasum (an oral, selective, cannabinoid receptor type 2 (CB2) agonist), outcomes associated with different background immunosuppressive therapies were compared with those of patients who did not receive concomitant immunosuppression [34]. Overall, patients receiving immunosuppressive therapy demonstrated more favorable cutaneous and pulmonary outcomes than those without background immunosuppression. Among the various immunosuppressive agents, MMF showed the most favorable numerical improvements in both skin fibrosis and lung function, whereas outcomes with MTX were generally intermediate. However, these findings were derived from a descriptive post hoc analysis and should not be interpreted as evidence of superiority of MMF over MTX in a prospective head-to-head comparison.

Additional post hoc analyses from the Scleroderma Lung Studies have further strengthened the interpretation of MMF efficacy [35,36]. Analyses of SLS I and SLS II demonstrated clinically meaningful improvements in modified Rodnan Skin Score and identified minimal clinically important differences for both skin thickness and pulmonary function, supporting the clinical relevance of treatment-associated changes observed in MMF-treated patients.

Table 2. Randomized or controlled clinical trial evidence relevant to MTX and MMF in SSc. Abbreviations: CYC, cyclophosphamide; dcSSc, diffuse cutaneous SSc; FVC, forced vital capacity; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; MTX, methotrexate; MMF, mycophenolate mofetil; SSc, systemic sclerosis.

Study	Design/Phase	Population	Intervention/Comparator	Main Relevance for This Review
[4] van den Hoogen et al., 1996	Randomized double-blind placebo-controlled trial	29 SSc patients	MTX 15 mg/week intramuscular vs. placebo	53% responders vs. 10% under placebo ($p = 0.03$); significant improvement in skin score and patient well-being.
[15] Pope et al., 2001	Randomized placebo-controlled trial	71 early dcSSc patients	MTX vs. placebo	mRSS −4.3 vs. +1.8 points with placebo ($p = 0.009$); physician global assessment favored MTX.
[5] Tashkin et al. (SLS II), 2016	Randomized double-blind controlled trial	142 SSc-ILD patients	MMF vs. cyclophosphamide	FVC improved +2.19% predicted (MMF) vs. +2.88% (CYC); fewer leukopenia cases (4 vs. 30) and deaths (5 vs. 11) with MMF.
[16] Naidu et al., 2020	Randomized placebo-controlled trial	41 mild SSc-ILD patients	MMF vs. placebo	No significant FVC benefit (−2.7% vs. +1.0%; $p = 0.131$), but mRSS improved −5 vs. −1 points ($p \approx 0.045$).
[18] Denton et al. (MINIMISE-Pilot), 2026	Randomized open-label pilot study	43 lcSSc patients	MMF vs. no immunosuppression	Recruitment feasibility study; 43 randomized (21 MMF, 22 control). No clinical worsening events occurred during follow-up.

Table 3. Prospective open-label, retrospective, post hoc analyses, and observational studies relevant to MMF/EC-MPS and real-world first-line use. Abbreviations: CYC, cyclophosphamide; dcSSc, diffuse cutaneous SSc; FVC, forced vital capacity; HR, hazard ratio; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; MTX, methotrexate; MMF, mycophenolate mofetil; EC-MPS, enteric-coated mycophenolate sodium; immunosuppressive treatment; mycophenolate sodium; SSc, systemic sclerosis.

Study	Design/Phase	Population	Intervention/Comparator	Main Relevance for This Review
[22] Nihtyanova et al., 2007	Retrospective cohort	109 dcSSc patients	MMF vs. other therapies	5-year survival 91.7% vs. 77.8% ($p = 0.012$); pulmonary fibrosis 12% vs. 19%.
[27] Zamora et al., 2008	Retrospective study	17 SSc-ILD patients	MMF 2 g/day	94% stable or improved lung function after 12 months; only 6% worsened.
[24] Derk et al., 2009	Prospective open-label study	15 early dcSSc patients	MMF up to 3 g/day	mRSS improved from 22.5 ± 6.1 to 8.4 ± 4.5 ($p < 0.0001$).
[23] Le et al., 2011	Observational cohort	98 dcSSc patients	MMF	mRSS improved from 24.4 ± 9.5 to 17.5 ± 10.4 ($p < 0.001$); FVC remained stable (79.4% → 80.7% predicted).
[37] Simeón-Aznar et al., 2011	Observational study	SSc-ILD patients	Mycophenolate sodium	Stabilization of pulmonary disease; no major decline in lung function reported.
[25] Mendoza et al., 2012	Prospective observational study	25 recent-onset progressive dcSSc patients	MMF	mRSS improved from 24.6 ± 8.6 to 14.5 ± 10.9 ($p = 0.0004$); affected body surface area 36% → 14% ($p = 0.00001$).
[6] Henes et al., 2013	Prospective open-label study	11 progressive SSc patients	Enteric-coated mycophenolate sodium	mRSS 13.5 → 11; FVC 78% → 85% predicted after 12 months.
[26] Boulos et al., 2017	Long-term cohort	42 dcSSc patients	MMF	mRSS 25.9 → 15.8 after 5 years (−10.5 points); 92% achieved clinically meaningful improvement by year 4.
[29] Lee et al., 2020	Retrospective multicentre study	34 SSc patients	MMF	Median mRSS improved from 17.5 to 10.5 ($p < 0.0001$); FVC remained stable.
[30] Wildt et al., 2024	Prospective cohort	80 SSc patients	MMF exposure vs. no MMF	MMF independently associated with higher capillary density ($\beta = 1.30$, $p = 0.020$) and slower capillary loss ($p < 0.001$).
[21] Yan et al., 2025	EUSTAR post hoc comparative study	955 SSc-ILD patients	MMF vs. CYC vs. RTX vs. TCZ	Mean FVC change +0.98% predicted under MMF; effectiveness comparable to other immunosuppressive therapies.
[34] White et al., 2025	Comparative effectiveness post hoc analysis (RESOLVE-1)	357 dcSSc patients	MMF, MTX, steroids, other IST, no IST	In disease duration ≤ 2 years, mRSS improved −10.8 points with MMF vs. −4.8 without IST; FVC remained stable with MMF but declined by ~160 mL without IST.
[31] De Lorenzis et al., 2026	Registry-based target trial emulation	1435 lcSSc patients (107 matched pairs)	MMF vs. no MMF	Vasoactive treatment escalation: 0.3 vs. 5.4 events/100 patient-years; HR 0.05 (95% CI 0.01–0.38; $p = 0.004$).

3.7. Guideline Context

The 2023 EULAR recommendations for the treatment of SSc state that MTX, MMF and/or rituximab should be considered for the treatment of SSc skin fibrosis. MTX is the only therapy recommended also for musculoskeletal manifestations, although with very limited evidence [3].

For SSc-ILD, EULAR recommends MMF, cyclophosphamide or rituximab [3]. Nintedanib and tocilizumab are also considered for ILD in appropriate phenotypes. The British and the ERS/EULAR clinical practice guidelines follow the same strategy [9,38]. The recently published German guidelines for the management of systemic sclerosis likewise aim to provide therapeutic recommendations for all disease manifestations. They address cutaneous and musculoskeletal involvement as well as major organ manifestations affecting the lungs, heart, and kidneys [39]. These recommendations align with a phenotype-driven approach rather than a universal first-line algorithm.

The practical implication is that "first-line" in SSc must be organ-specific. For skin fibrosis, both MTX and MMF are acceptable considerations, with MTX supported by older placebo-controlled trials and MMF supported by ILD studies and observational skin outcomes. For ILD, MMF has a substantially stronger evidence base and more favorable long-term usability than cyclophosphamide for many patients.

3.8. Duration of Therapy and Treatment De-Escalation

Evidence regarding the optimal duration of immunosuppressive therapy in systemic sclerosis is limited, as no randomized controlled trial has specifically addressed treatment discontinuation or tapering strategies. Consequently, decisions regarding treatment duration remain individualized and should be guided by disease phenotype, treatment response, tolerability, and the risk of disease progression.

In patients with early inflammatory disease, immunosuppressive therapy is commonly continued as long as objective evidence of disease activity persists. Once sustained clinical stability has been achieved, gradual dose reduction may be considered, although robust evidence supporting a specific tapering strategy is lacking.

The 2024 British Society for Rheumatology guideline recommends considering reduction or discontinuation of immunosuppressive therapy in patients with advanced fibrotic SSc-ILD who experience recurrent infections, particularly in elderly or frail individuals. In such cases, continuation of antifibrotic therapy (e.g., nintedanib) without concomitant immunosuppression may be appropriate. However, these recommendations are based primarily on expert consensus rather than prospective discontinuation studies [9].

At present, there are no evidence-based recommendations defining the optimal duration of methotrexate or mycophenolate mofetil therapy in patients with stable systemic sclerosis. Therefore, treatment decisions should be individualized and regularly reassessed within a multidisciplinary setting.

3.9. Proposed Treatment Algorithm

Based on the literature results above the authors recommmend the following treatent algorithm Figure 1.

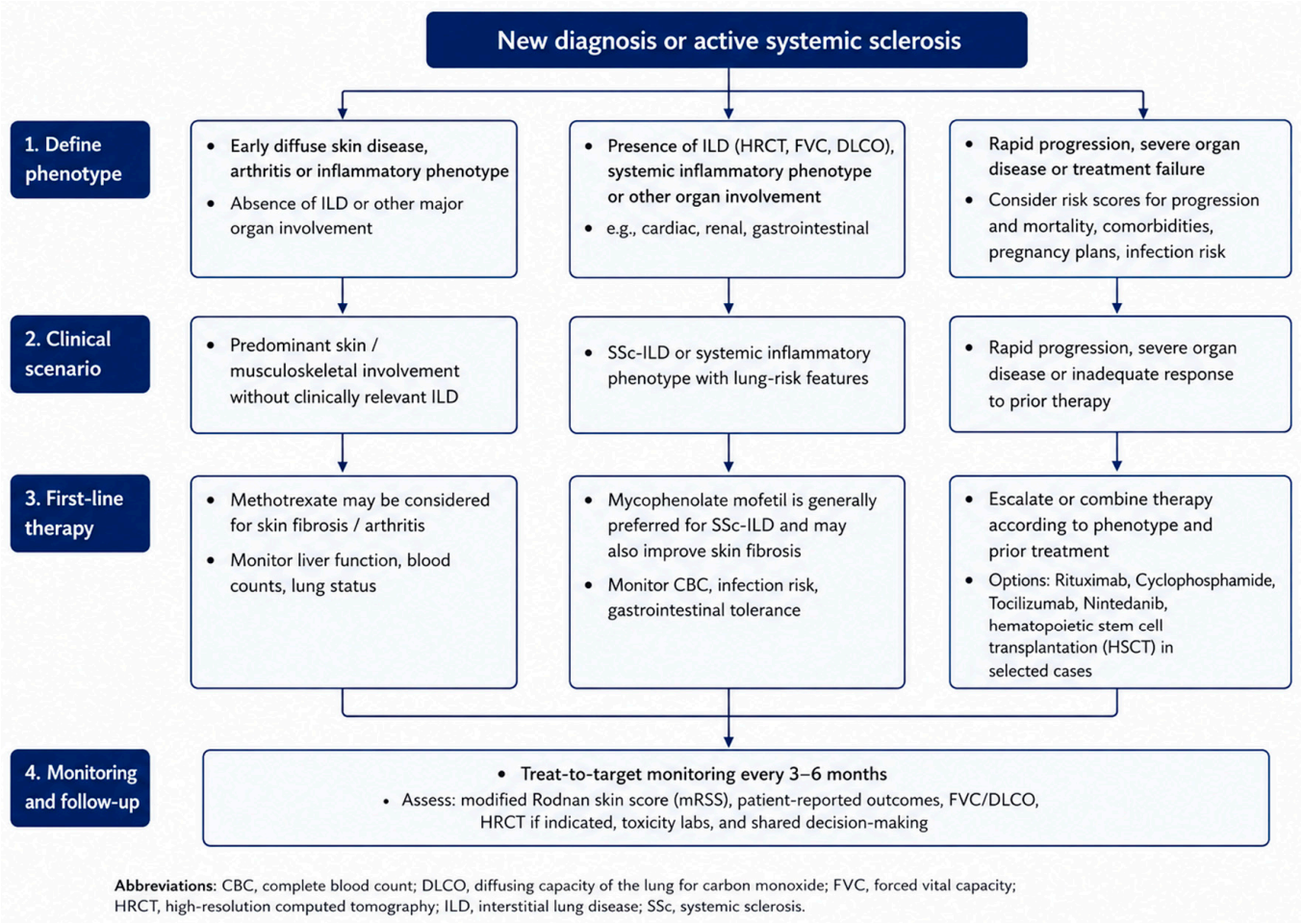


Figure 1. Author-proposed phenotype-based treatment algorithm synthesizing current evidence and international guidelines. MTX is positioned for skin- and musculoskeletal-dominant disease without relevant ILD, whereas MMF is positioned as preferred therapy for ILD. Escalation or combination strategies should be considered for severe, progressive or refractory disease and according to other organ manifestations or comorbidities.

4. Discussion

The available evidence indicates that MTX and MMF should not be viewed as interchangeable first-line therapies for all patients with SSc. Importantly, this review does not compare MTX and MMF based on direct comparative evidence because no head-to-head randomized trials exist. MTX has the advantage of long clinical experience, low cost and randomized placebo-controlled data in early diffuse disease, but its evidence base is limited by small sample size and lack of lung-specific benefit [4,15]. MTX is well known by rheumatologists and has a well-established and well-characterized safety profile with >40 years of evidence [40]. In contrast, MMF has emerged as the preferred immunosuppressive agent for patients with SSc-associated interstitial lung disease, supported by prospective trials demonstrating stabilization or improvement of lung function and additional benefits on skin involvement. As a result, MMF is increasingly used as the preferred background immunosuppressive therapy in patients with SSc-ILD.

However, the apparent superiority of MMF in contemporary treatment algorithms should not lead to the conclusion that MTX has become obsolete in SSc. The two drugs address different clinical scenarios and should be considered complementary rather than competing therapeutic options. MMF is generally favored in patients with established or progressive ILD, or broader systemic inflammatory involvement. MTX remains attractive because of its extensive rheumatologic experience spanning more than four decades, its low

cost, ease of administration, and favorable long-term safety profile. In patients with early inflammatory diffuse cutaneous disease, inflammatory arthritis, tendon friction rubs, or overlap manifestations without clinically significant interstitial lung disease, MTX continues to represent a reasonable first-line therapeutic option. Rather than representing alternative approaches, MTX and MMF occupy distinct positions within the therapeutic spectrum of SSc, and treatment selection should be guided by the dominant clinical phenotype, pattern of organ involvement, and individual risk profile [3,10,41,42].

Conversely, the increasing recognition of SSc-ILD as the major cause of disease-related morbidity and mortality has substantially shifted treatment paradigms toward MMF. The evidence generated by SLS II and subsequent observational studies has positioned MMF as the preferred first-line immunosuppressive agent for patients with pulmonary involvement [5]. Importantly, MMF has evolved beyond a therapeutic option for ILD and has become the background standard-of-care therapy against which novel antifibrotic and biologic strategies are being tested. This role as an "anchor therapy" further emphasizes its central position in current SSc management.

Another important observation emerging from the literature is that treatment decisions in SSc are increasingly phenotype-driven rather than disease-driven. The historical distinction between limited and diffuse cutaneous subsets alone is insufficient to guide therapeutic decisions. Instead, the presence and progression of organ involvement, particularly pulmonary disease, inflammatory activity, autoantibody status, and individual risk profiles should determine treatment selection. Such an approach is reflected in contemporary international and national guidelines and is supported by real-world evidence from large observational cohorts [3,9,38,39].

Nevertheless, several important knowledge gaps remain. First, no prospective head-to-head trial comparing MTX and MMF has ever been conducted. Consequently, treatment recommendations are based on indirect comparisons, organ-specific evidence, and expert consensus. Second, biomarkers capable of predicting treatment response are lacking. It remains unclear whether distinct molecular signatures, autoantibody profiles, or imaging phenotypes could identify patients who preferentially respond to MTX or MMF. Third, the optimal duration of immunosuppressive treatment and the appropriate timing of escalation to biologic or antifibrotic therapies remain poorly defined.

The future of SSc treatment will likely move toward precision medicine approaches integrating clinical phenotype, molecular profiling, and individualized risk stratification. Emerging therapies, including rituximab, tocilizumab, and antifibrotic agents such as nintedanib, are increasingly incorporated into treatment algorithms and may be used sequentially or in combination with conventional immunosuppression. Rather than replacing MTX or MMF, these agents are likely to complement established therapies and further refine phenotype-specific treatment strategies.

Taken together, the available evidence supports a pragmatic and organ-based approach to first-line therapy in systemic sclerosis. MTX may primarily be considered for patients with skin- and musculoskeletal-dominant disease without clinically relevant ILD, whereas MMF may be considered in patients with inflammatory organ involvement (e.g., SSc-ILD) or progressive fibrotic disease. However, this recommendation is based largely on indirect evidence and extrapolation from organ-specific studies rather than direct comparative trials [3]. Several recommendations discussed in this review extend beyond the available randomized evidence and are necessarily based on indirect organ-specific studies, observational cohorts, expert consensus, and current international recommendations. Consequently, the proposed positioning of MTX and MMF should be interpreted as a pragmatic synthesis of the current literature rather than evidence of comparative superiority. Future prospective comparative studies and biomarker-driven trials are urgently needed to op-

timize treatment selection and to establish truly personalized therapeutic algorithms in systemic sclerosis.

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