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Review

Biologics in Systemic Sclerosis: An Organ- and Manifestation-Specific Reappraisal of What Has Changed, What Has Not, and Why

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Abstract

Systemic sclerosis (SSc) is a heterogeneous autoimmune disease characterized by immune dysregulation, vasculopathy, and progressive fibrosis affecting the skin and internal organs. Although biologic therapies have expanded the therapeutic landscape of immune-mediated diseases, their impact in SSc has been uneven and remains difficult to interpret when viewed only on a drug-by-drug basis. This focused narrative review reappraises biologic therapies in SSc using a manifestation-based framework spanning cutaneous, pulmonary, vascular, gastrointestinal, musculoskeletal, and global or composite outcomes. Published evidence is most developed for selected cutaneous and pulmonary manifestations, particularly through B-cell depletion in selected cutaneous–pulmonary phenotypes and interleukin-6 blockade that attenuates pulmonary function decline in early inflammatory disease, whereas gastrointestinal and vascular manifestations have not yet shown comparable clinical evidence of benefit and remain insufficiently studied. We argue that this asymmetry not only reflects differences in trial design and endpoint selection, but also manifestation-specific pathobiology, disease stage, and the extent to which inflammatory, vascular, and fibrotic processes remain therapeutically modifiable. In particular, vasculopathy may represent an upstream pathogenic layer that constrains the disease-modifying capacity of biologics that primarily improve downstream inflammatory or fibrotic manifestations. We also highlight the relevance of Japanese contributions to the biologics literature in SSc and discuss future priorities, including manifestation-appropriate endpoint selection, early-disease enrichment, and biomarker-informed stratification. Overall, biologics have changed the treatment of SSc in a selective rather than global manner; embracing a manifestation-based view is now essential for both trial design and day-to-day therapeutic decision-making.

Keywords: systemic sclerosis; biologics; rituximab; tocilizumab; interstitial lung disease; skin fibrosis; vasculopathy; manifestation-based review; targeted therapy; precision medicine

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1. Introduction

1.1. Background

Systemic sclerosis (SSc) is a heterogeneous autoimmune disease characterized by immune dysregulation, microvascular injury, and progressive fibrosis affecting the skin and internal organs [1–3]. Clinically, SSc is commonly classified into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) according to the extent of skin involvement, although substantial heterogeneity exists within and across these subsets. In addition to cutaneous thickening, patients may develop interstitial lung disease (ILD), pulmonary vascular disease, gastrointestinal dysfunction, musculoskeletal involvement, and severe vasculopathy manifested by Raynaud's phenomenon and digital ulcers [3–6]. This has long complicated both trial design and therapeutic decision-making [7].

Over the past two decades, advances in the understanding of SSc pathogenesis have supported increasing interest in targeted immunomodulatory strategies, including biologic therapies directed against B cells, interleukin (IL)-6 signaling, T-cell co-stimulation, IL-17/IL-23-related pathways, and other immune mediators [7–14]. This therapeutic shift has occurred alongside a broader conceptual change in SSc management. Rather than viewing SSc as a single uniformly progressive fibrotic disease, current practice increasingly recognizes it as a multi-organ disorder in which inflammatory, vascular, and fibrotic processes interact differently across organs and disease stages.

Among biologic agents, some have already influenced routine practice in selected settings. At the same time, other biologics have shown only preliminary signals, inconsistent efficacy, or manifestation-restricted benefit. In particular, although biologic therapies were initially expected to broadly modify SSc disease course, their impact has proven uneven. This discrepancy raises an important clinical and mechanistic question: have biologics truly changed the treatment of SSc, and if so, in which organ systems, to what extent, and why?

1.2. Why a Manifestation-Based Reappraisal Is Needed

Existing reviews of biologic therapy in SSc have generally emphasized drug classes or specific biological agents, pathogenic pathways or key molecular mediators, or clinical trial summaries [15–17]. Reviews organized by organ system have also been published, but these cover the full range of pharmacological and non-pharmacological treatments rather than isolating biologic agents for dedicated reappraisal [18,19]. While such approaches are valuable, they do not address the question of why biologic therapy has changed SSc management in some organ systems but not others.

Biologic agents in SSc do not behave as a class. Vasculopathy occupies a particularly important position in this regard, as discussed further in Section 4.4 [3,6]. A manifestation-based reappraisal of biologic therapy that incorporates this perspective may therefore clarify not only what has changed in SSc treatment, but why certain successes have been manifestation-restricted rather than broadly disease-modifying.

Accordingly, this focused narrative review reappraises biologic therapies in SSc through a manifestation-based framework, spanning cutaneous, pulmonary, vascular, gastrointestinal, and musculoskeletal manifestations, as well as global and composite outcomes.

This reappraisal also draws particular attention to Japanese contributions to the biologics literature in SSc, as discussed further in Section 4.5.

2. Materials and Methods

This focused narrative review synthesized the available literature on biologic therapies in SSc. The primary objective was not to provide an exhaustive catalog of biologic agents, but rather to explore possible explanations for manifestation-specific differences in response.

We searched PubMed/MEDLINE and Scopus from database inception to 31 May 2026, with the final searches conducted on 18 August 2026, combining terms for systemic sclerosis with the names of the biologic agents considered in this review; the exact, database-specific search strings, filters, and results are provided in Supplementary Table S2. Reference lists of relevant articles and reviews were also screened to identify additional publications. Representative studies were selected on the basis of their clinical relevance to the manifestation-based framework, emphasis on biologic therapies, and contribution to interpreting cutaneous, pulmonary, vascular, gastrointestinal, musculoskeletal, or global/composite outcomes. Where available, randomized or controlled evidence was prioritized over case-based reports for the same manifestation-drug combination.

We included English-language original clinical studies, randomized controlled trials, open-label trials, observational studies, case series, and selected case reports describing the clinical use of biologic therapies in patients with SSc. Narrative and systematic reviews were consulted to provide clinical context, but were not treated as direct efficacy evidence. Studies were interpreted according to the principal outcomes reported for each of these manifestation categories.

We excluded mechanistic studies without clinical data, studies focused exclusively on non-biologic small molecules, and articles lacking extractable SSc-relevant clinical outcomes. For therapies with extremely limited case-based evidence, such evidence was discussed as exploratory or hypothesis-generating rather than practice-changing. Given the marked heterogeneity of study design, patient population, disease stage, background therapy, and outcome measures, we did not perform a meta-analysis, apply formal risk-of-bias grading, or follow PRISMA reporting standards, reflecting the narrative rather than the systematic scope of this review.

3. Results: A Manifestation-Based Reappraisal of Biologics in Systemic Sclerosis

3.1. Why Biologics in SSc Need to Be Read by Organ System

This apparent inconsistency becomes more understandable when SSc is viewed as a multi-organ disease rather than a single therapeutic entity [3,6].

Cutaneous thickening reflects a dynamic combination of inflammation, stromal activation, extracellular matrix remodeling, and established fibrosis [1,20]. Interstitial lung disease similarly spans inflammatory and fibrotic components, but with different temporal dynamics and clinical urgency [3,6]. Vasculopathy, manifested by Raynaud's phenomenon, digital ulcers, and microangiopathy, may represent an early and central pathogenic process [3,6,21]. Gastrointestinal manifestations often reflect dysmotility and chronic structural dysfunction, while musculoskeletal symptoms may be more closely linked to inflammatory activity in selected patients [3,6,22]. These differences matter because biologics typically target only specific immune or stromal pathways, and their clinical impact depends on whether the relevant biology remains therapeutically modifiable in the organ system.

A biologic associated with stabilization of lung function may have little effect on Raynaud's phenomenon, and even within a single organ, early inflammatory disease may respond differently from late fibrotic disease [3,23].

3.2. Current Clinical Positioning of Biologic Therapies in SSc

Among biologics, not all have contributed equally to current management. At present, IL-6 receptor blockade and B-cell-directed therapy have the most mature evidence base among the biologics considered here (tocilizumab and rituximab, respectively), with tocilizumab based mainly on a secondary pulmonary endpoint in two pivotal trials that did not meet their primary skin endpoint [8,9], and rituximab based mainly on cutaneous

outcomes, with pulmonary evidence that remains more heterogeneous, as detailed in Sections 3.3 and 3.4 [10,11]. In contrast, agents such as abatacept, belimumab, romilkimab, and guselkumab remain of considerable scientific interest but have not yet changed routine management to the same degree [14,24–26].

This distinction reflects the different maturity of the evidence base, the organ system studied, and the disease stage in which a biologic was tested. Some agents may yet prove valuable in enriched populations or in early inflammatory-vascular windows, even if current evidence remains insufficient for broad practice change. Manifestation-specific evidence and current practical interpretation for individual biologics are summarized in Table 1. This manifestation-based therapeutic landscape is further illustrated in Figure 1.

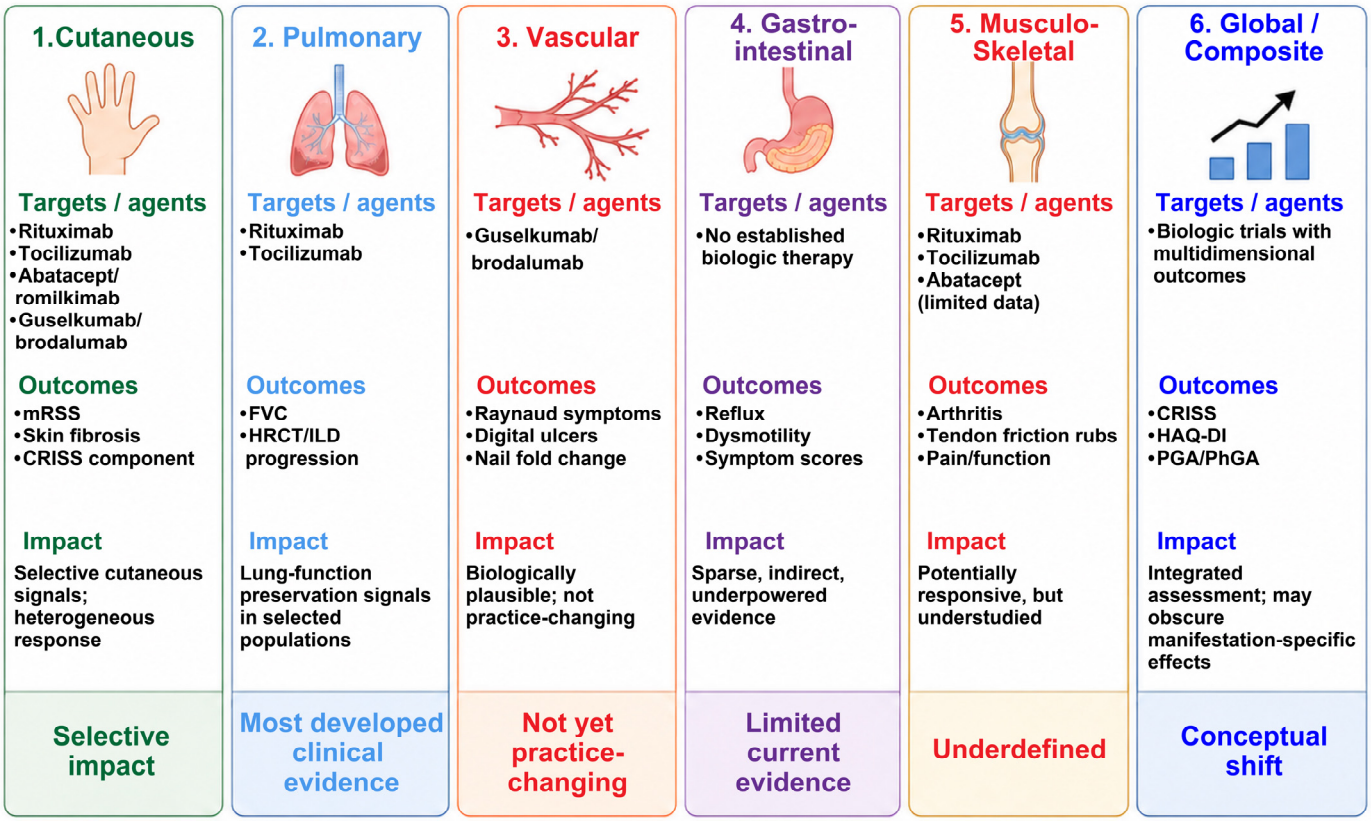


Figure 1. Manifestation-based therapeutic landscape of biologic therapies in systemic sclerosis. This figure summarizes the differential impact of biologic therapies across major clinical manifestations of systemic sclerosis (SSc). Pulmonary involvement has one of the most developed biologic evidence bases, driven mainly by attenuation of FVC decline with tocilizumab in selected early inflammatory populations and more heterogeneous evidence for rituximab, whereas cutaneous evidence is strongest for rituximab. In contrast, vascular and gastrointestinal manifestations remain insufficiently studied, with no comparably established biologic benefit, and musculoskeletal involvement remains underdefined. The apparent strength of this impact should be interpreted in light of differences in trial enrichment, endpoint standardization, and evidence maturity across manifestations. Overall, the figure illustrates the central concept of this review: biologic therapies in SSc should be interpreted according to clinical manifestation rather than as a uniformly effective therapeutic class. Abbreviations: CRISS, American College of Rheumatology Combined Response Index in Systemic Sclerosis; FVC, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; HRCT, high-resolution computed tomography;ILD, interstitial lung disease; mRSS, modified Rodnan skin score; PGA, patient global assessment; PhGA, physician global assessment; SSc, systemic sclerosis.

Table 1. Manifestation-based summary of biologic therapies in systemic sclerosis: what has changed, what has not, and why. Abbreviations: ACR, American College of Rheumatology; BAFF, B-cell activating factor; CD20, cluster of differentiation 20; CHEST, American College of Chest Physicians; dcSSc, diffuse cutaneous systemic sclerosis; EULAR, European Alliance of Associations for Rheumatology; EUSTAR, European Scleroderma Trials and Research; FVC, forced vital capacity; IL, interleukin; lcSSc, limited cutaneous systemic sclerosis; MCTD-ILD, mixed connective tissue disease-associated interstitial lung disease; mRSS, modified Rodnan skin score; OLE, open-label extension; PAO, pustulotic arthro-osteitis; PPP, palmoplantar pustulosis; RCT, randomized controlled trial; SARD-ILD, systemic autoimmune rheumatic disease-associated interstitial lung disease; SSc-ILD, systemic sclerosis-associated interstitial lung disease; Th17, T helper 17. Trial populations and enrichment criteria differed by agent and are detailed in Supplementary Table S1; mRSS was the primary endpoint in several skin-focused trials. Detailed trial-level evidence, effect estimates, evidence certainty, and strength of guideline recommendations are provided in Supplementary Table S1.

Biologic/Target	Main Pathway	Cutaneous Involvement	Pulmonary Involvement (SSc-ILD)	Vascular Manifestations	Gastrointestinal Involvement	Musculoskeletal Manifestations	Key Evidence (Design, *n*)	Guideline Position	Current Practical Interpretation
Rituximab	B-cell depletion (CD20)	Supportive signal; clinically meaningful in selected patients	Secondary RCT and observational signals; heterogeneous evidence	Limited/unclear	Minimal direct evidence	Possible benefit in inflammatory cases	DESIRES: RCT, *n* = 56 (Japan); OLE to 48 wk. EUSTAR: observational, *n* = 63	EULAR: skin, SSc-ILD; ACR/CHEST: SARD-ILD	Best-supported for skin fibrosis; pulmonary evidence more heterogeneous and partly indirect
Tocilizumab	IL-6 receptor blockade	Mixed/modest skin effect	Secondary FVC-preservation signal in selected early inflammatory dcSSc/SSc-ILD populations	Limited	Minimal direct evidence	Secondary/unclear	faSScinate: Phase 2 RCT, *n* = 87. focuSSced: Phase 3 RCT, *n* = 210	EULAR: SSc-ILD; skin (restricted); ACR/CHEST: SSc-ILD/MCTD-ILD	Relevant to attenuation of FVC decline in selected early inflammatory SSc-ILD populations; pulmonary outcome was secondary
Abatacept	T-cell co-stimulation blockade	Exploratory/moderate signal	Limited	Limited	Limited	Possibly relevant in inflammatory subsets	Phase II RCT, *n* = 88 (12-month)	ACR/CHEST: against first-line SARD-ILD	Biologically plausible, but not yet practice-changing
Belimumab	B-cell survival factor (BAFF) inhibition	Early/limited evidence	Limited	Limited	Limited	Limited	Pilot RCT, *n* = 20 (52-week, single-center)	No formal recommendation	Exploratory
Romilkimab	IL-4/IL-13 blockade	Notable skin-focused signal	Limited	Limited	Limited	Limited	Phase II RCT, *n* = 97 (24-week)	No formal recommendation	Promising but not yet established
Guselkumab	IL-23/Th17 axis	Case-based signal; early lcSSc (with PPP/PAO) and diffuse-pattern disease with concomitant psoriasis vulgaris	Very limited	Exploratory microvascular signal	Preliminary	Very limited	Case-based reports; no RCT evidence	No formal recommendation	Hypothesis-generating; mechanistically informative but still exploratory
Brodalumab	IL-17 receptor A antagonism	Open-label phase 1 signal; significant mRSS reduction in early dcSSc	Not assessed	Reduction in digital ulcer count among affected participants	Not assessed	Not assessed	Open-label phase 1 trial; *n* = 8	No formal recommendation	Hypothesis-generating; exploratory, uncontrolled

3.3. Cutaneous Involvement

3.3.1. Biologic Evidence for Cutaneous Involvement

The modified Rodnan skin score (mRSS) has often served as a primary endpoint in biologic trials because skin thickening is closely linked to prognosis in early disease [27,28]. However, changes in mRSS are influenced by disease duration, baseline severity, spontaneous trajectory, and interobserver variability [29–31].

Rituximab has generated some of the most persuasive skin-related evidence in SSc. Across observational cohorts, open-label studies, and randomized evidence, B-cell depletion has repeatedly been associated with improvement or stabilization of skin thickening in diffuse cutaneous disease [10,11,32]. Mechanistically, this is plausible, since B cells participate not only in autoantibody production, but also in antigen presentation, cytokine secretion, and crosstalk with fibroblasts [3]; in early diffuse disease, where immune and stromal activation remain coupled, B-cell depletion may act upstream of established fibrosis. Even so, its apparent benefit in early or active inflammatory cutaneous disease does not necessarily extend to late, fixed, fibrosis-dominant skin disease. In the Japanese literature, rituximab has often been discussed not merely as an experimental biologic, but as a therapy with recognizable relevance in inflammatory skin-lung phenotypes [10]. DESIRES, a Japanese double-blind, placebo-controlled RCT (n = 56), showed a between-group difference in mRSS change at 24 weeks of −8.44 points (95% CI −11.00 to −5.88; $p < 0.0001$) [10]; in its open-label extension, this benefit was sustained to 48 weeks with a second rituximab course [33], though external validity beyond Japanese cohorts remains unconfirmed. Real-world data from a EUSTAR nested case–control study similarly favoured rituximab over matched controls for skin outcomes (n = 63; median follow-up 7 months), but this evidence is non-randomized, unblinded, and potentially confounded by treatment indication [11]; the corresponding pulmonary findings, based on a smaller, shorter-follow-up ILD subgroup within the same analysis, are detailed in Section 3.4.1.

Tocilizumab has also shown cutaneous signals, but its impact has generally been less definitive than its pulmonary relevance, and in clinical practice IL-6 blockade is accordingly framed around SSc-ILD or inflammatory early disease rather than skin-directed modification [7,9]. This was made explicit in the open-label extension of the pivotal phase 3 trial, in which tocilizumab preserved lung function over 48 weeks without a significant effect on skin sclerosis [34]. Earlier suggestions from a small, open-label Japanese study and murine models that IL-6 blockade could also soften cutaneous fibrosis were not confirmed in controlled trials [35,36].

Other biologics remain in earlier stages of evidence. Abatacept and romilkimab have generated interest by targeting plausible upstream immune or profibrotic pathways, but trial-level signals have not yet translated into the same degree of clinical adoption as rituximab or tocilizumab [25,26]. Within the IL-17/IL-23 pathway, two agents have generated preliminary clinical signals in cutaneous SSc, although the nature of the evidence differs. Brodalumab, an IL-17 receptor A antagonist, was assessed in an open-label phase 1 trial of eight patients with early diffuse cutaneous SSc, in which mRSS decreased significantly by week 4 (p = 0.002) and remained significantly reduced through week 52 ($p < 0.001$), with a reduction in digital ulcer count among patients affected at baseline [37]. Guselkumab, an IL-23p19 inhibitor, has been reported in a smaller and more heterogeneous set of cases: one patient with early limited cutaneous SSc and palmoplantar pustulosis, and three patients with skin sclerosis extending from the fingers to the upper arm, complicated by psoriasis vulgaris, a comorbidity that is a potential confounder for the observed skin and composite disease response improvements [12–14]. Neither the uncontrolled brodalumab trial nor the guselkumab case reports can establish efficacy or define a responsive SSc phenotype.

3.3.2. What Has Changed in Cutaneous Involvement

What has changed is more limited but still important: selected biologics, particularly rituximab and in some contexts tocilizumab, have made meaningful cutaneous improvement more plausible in appropriately selected patients, especially in early diffuse or inflammatory-predominant disease. What has not changed is the fundamental heterogeneity of skin response, the challenge of endpoint interpretation, and the persistence of patients in whom biologic modulation remains insufficient.

3.4. Pulmonary Involvement: SSc-Associated Interstitial Lung Disease

3.4.1. Biologic Evidence for Pulmonary Involvement

If cutaneous involvement has historically dominated SSc trial design, pulmonary involvement has increasingly become the area of greatest clinical consequence. SSc-associated interstitial lung disease is a leading cause of morbidity and mortality, and the ability to stabilize lung function has become a major therapeutic benchmark [38–41]. Lung function trajectories are not immune to spontaneous variation, as the regression-to-the-mean pattern discussed in Section 4.3 illustrates. Nonetheless, progressive loss of lung function relates more directly to long-term outcome than does skin thickening [42], so even stabilization, rather than dramatic reversal, may represent an important therapeutic benefit in SSc-ILD.

Among the biologics considered here, tocilizumab has the most developed randomized evidence for attenuation of FVC decline in selected patients with early inflammatory dcSSc and SSc-ILD, although both pivotal trials were designed around skin disease and did not meet their primary mRSS endpoints [8,9,43]. Even when skin endpoints themselves have been mixed or only modestly positive, the pulmonary signal in this same overlapping skin-lung subset has been sufficiently consistent to influence clinical practice in SSc [9,43]. Biological plausibility may partly underlie this selectivity: IL-6 participates in inflammatory amplification, immune-stromal crosstalk, and tissue injury responses relevant to lung disease, and in patients with active or early pulmonary involvement, these processes may remain therapeutically modifiable. Yet, as discussed in Section 4.3, this account is incomplete: pulmonary selectivity is also shaped by trial enrichment and by differences in the reliability of pulmonary versus cutaneous endpoints. Disentangling biological from methodological contributions to this pattern remains an open question.

Rituximab has also accumulated evidence in SSc-ILD, though this evidence is more heterogeneous and largely observational than its cutaneous evidence. DESIRES, whose primary endpoint was skin thickening rather than lung function, nonetheless found a significant secondary improvement in %predicted FVC at 24 weeks in the rituximab group compared with placebo (0.09% versus −2.87%; difference 2.96%, 95% CI 0.08–5.84; $p = 0.044$) [7,10,11]. This finding contrasts with RECITAL, a broader trial in connective-tissue-disease-associated ILD, in which rituximab was not superior to cyclophosphamide for its primary 24-week FVC endpoint (difference −40 mL, 95% CI −153 to 74; $p = 0.49$) [44]. Real-world evidence from a EUSTAR nested case–control analysis is similarly supportive but limited: in a small matched subgroup of patients with ILD ($n = 9$), rituximab prevented further FVC decline relative to controls (0.4% versus −7.7%; $p = 0.02$) over a median follow-up of only 6 months; this was an observational analysis limited by residual confounding by indication, partly retrospective data collection, and some residual imbalance in baseline characteristics despite matching [7,10,11]. As discussed in Section 3.3.1, Japanese randomized evidence has nonetheless been particularly important in establishing rituximab's relevance across combined cutaneous-pulmonary disease.

For most other biologics, pulmonary data remain limited, inconsistent, or secondary. Trials of agents such as abatacept, belimumab, and romilkimab were primarily designed around cutaneous or global disease outcomes rather than SSc-ILD-specific efficacy, and

pulmonary observations have generally been exploratory or supportive rather than practice-changing [24–26]. Similarly, guselkumab, targeting IL-23p19, remains at an early stage, with insufficient evidence to define a pulmonary role [14]. Some studies provide reassurance against major pulmonary worsening, without demonstrating a therapeutic effect. Overall, tocilizumab and rituximab are the two biologics that have most often informed pulmonary decision-making in practice, though this reflects a secondary pulmonary endpoint for tocilizumab and predominantly observational evidence for rituximab, rather than a dedicated pulmonary indication for either agent.

These biologic findings should also be read alongside established non-biologic treatments for SSc-ILD: cyclophosphamide and mycophenolate mofetil have each shown clinically meaningful, comparable improvements in FVC in placebo-controlled and head-to-head trials, respectively, and nintedanib slows FVC decline independent of concomitant mycophenolate use [40,41,45]. Biologic therapy for SSc-ILD therefore represents an addition to, or alternative within, an already-active non-biologic treatment landscape rather than a comparison against no treatment.

3.4.2. What Has Changed in Pulmonary Involvement

Pulmonary involvement is among the manifestations for which biologics have generated the most developed clinical evidence, although the nature and certainty of that evidence differ by agent. Tocilizumab attenuated FVC decline versus placebo as a secondary endpoint in selected early inflammatory dcSSc populations, whereas pulmonary evidence for rituximab is more heterogeneous and includes secondary and observational analyses, with no superiority to cyclophosphamide in RECITAL [7–10,44].

3.5. Vascular Manifestations

3.5.1. Biologic Evidence for Vascular Manifestations

Vasculopathy is one of the earliest and most defining features of SSc pathogenesis [21,46]. Raynaud's phenomenon, digital ulcers, nailfold microangiopathy, and later pulmonary vascular complications all reflect the central role of endothelial injury and microvascular dysfunction in the disease [1,3,6,21]. Conceptually, this should make vascular manifestations an attractive target for biologic therapy. In practice, however, biologics have not reshaped routine management of Raynaud's phenomenon, digital ulcer prevention, or structural microangiopathy to the same extent as they have influenced cutaneous or pulmonary involvement [7,21].

Several factors may account for this discrepancy. First, vascular manifestations in SSc are shaped not only by immune activation but also by structural vascular loss, endothelial dysfunction, altered vasoreactivity, platelet activation, and chronic tissue ischemia [21,47,48]. By the time clinically overt vascular complications are established, some elements of the process may no longer be easily reversed by targeted immune modulation alone. Second, vascular outcomes are highly sensitive to environmental and behavioral influences, making signal detection more difficult [47,48]. Third, many biologic studies in SSc have not prioritized vascular endpoints as primary outcomes.

This progression toward structural entrenchment, discussed further in Section 4.4, may explain why biologics are most likely to show vascular benefit in very early disease or in microangiopathic rather than ulcerative endpoints [46].

That said, vasculopathy should not be dismissed as biologically unresponsive. Case-based and exploratory studies have described improvements in Raynaud's symptoms and nailfold capillaroscopic findings with guselkumab [12–14], and reduced digital ulcer counts with brodalumab [37]. These observations are provocative because they suggest that at least some early vascular manifestations may retain an inflammatory and therefore

targetable component. However, the evidence remains preliminary: in the guselkumab cases, concomitant psoriasis vulgaris is a potential confounder, since resolution of psoriatic inflammation could itself account for part of the observed vascular changes. Nailfold capillaroscopic improvement, while interesting, does not yet establish the prevention of clinically meaningful vascular outcomes such as new digital ulcers, ischemic progression, or long-term structural vascular preservation.

3.5.2. What Has Changed in Vasculopathy

What has changed is more modest but still important: these early signals have made biologic modulation of vasculopathy more plausible, and they have exposed the need for better vascular trial design. Thus, vascular manifestations currently represent not a success story, but a frontier in which biologic therapy remains biologically plausible yet clinically underrealized.

3.6. Gastrointestinal Involvement

3.6.1. Biologic Evidence for Gastrointestinal Involvement

Gastrointestinal involvement is common in SSc and contributes substantially to symptom burden and quality of life [22,31]. However, it is particularly challenging from the standpoint of biologic intervention. Esophageal reflux, dysmotility, bloating, malabsorption, constipation, and pseudo-obstructive phenomena reflect a mixture of neuromuscular dysfunction, smooth muscle involvement, connective tissue remodeling, vascular injury, microbial factors, and chronic structural change [22,49], a multifactorial biology that makes it difficult to expect a targeted immunologic therapy to produce dramatic or uniform gastrointestinal benefit, especially in established disease.

At present, evidence for biologics in gastrointestinal SSc is limited and largely indirect [22,49]. In case-based reports of guselkumab, reflux-related symptoms and global patient-reported measures improved alongside other disease outcomes in patients with concomitant psoriasis vulgaris [12–14], although observations are difficult to interpret. Symptom improvement may reflect reduced systemic inflammation, better overall well-being, resolution of the comorbid psoriatic disease, concomitant supportive care, or fluctuations unrelated to direct gastrointestinal disease modification, and endpoints in SSc trials are often secondary, heterogeneous, and underpowered [49,50]. No biologic, including guselkumab, can currently be said to have altered gastrointestinal management in SSc in a meaningful way [7].

3.6.2. What Has Changed in Gastrointestinal Involvement

In practical terms, very little has changed. Nonetheless, a manifestation-based reading is still valuable because it prevents overinterpretation. A biologic may improve skin or lung disease while leaving gastrointestinal dysfunction largely unchanged; this should not be misread as global treatment failure, but rather as evidence of manifestation-specific therapeutic limitation.

3.7. Musculoskeletal Manifestations

Musculoskeletal manifestations of SSc, including arthralgia, inflammatory arthritis, tendon friction rubs, myalgia, and reduced function related to skin and fascial involvement, occupy an intermediate position in current biologic evidence [51–53]. This area may contain a relatively inflammation-sensitive component: signals relevant to pain, function, or inflammatory musculoskeletal features have been reported in selected studies, particularly where broader improvement in inflammatory disease activity is evident [10,11,25]. Musculoskeletal outcomes are often difficult to disentangle from pain, disability, skin tightening, edema, and global disease activity [51,53], and the evidence base remains less

mature than that for cutaneous or pulmonary involvement. The phase 2 tocilizumab trial stratified randomization by joint involvement and reported a numerically greater reduction in tendon friction rub with tocilizumab than placebo at 24 and 48 weeks, without reaching significance; joint-specific outcomes were not carried forward into the phase 3 trial [8,9]. Musculoskeletal benefit is therefore more often regarded as a supportive or secondary advantage than as a primary reason to choose a biologic, and this has not yet translated into a clear change in practice standards.

3.8. Global and Composite Outcomes

The Appeal and Limits of Composite Measures

Composite outcomes are attractive in SSc because they attempt to capture multidimensional disease response rather than isolated organ changes. Measures such as the Combined Response Index in Systemic Sclerosis (CRISS) were developed in part to address the complexity of SSc trials and to create a more integrated assessment of improvement [54]. In theory, biologics with distributed but modest effects across several manifestations may be better captured through composite endpoints.

However, composite outcomes also present interpretive challenges. Because different manifestations contribute differently to the final score, an apparent global response may be driven by change in one major component while masking non-response in others. Conversely, clinically meaningful improvement in a specific high-priority area, such as ILD stabilization, may not always translate into a dramatic composite signal. Thus, composite measures are helpful but do not eliminate the need for manifestation-specific analysis.

These limitations are compounded by CRISS's origin: the index was developed and validated specifically in early diffuse cutaneous SSc [54], and its final model includes no gastrointestinal item and only an indirect vascular signal—digital ulcers, tested but found near-chance in predictive value, were excluded. CRISS also classifies a patient as not improved, regardless of improvement elsewhere, if pulmonary arterial hypertension, renal crisis, or substantial FVC decline develops, which limits its interpretation in patients with predominant ILD or vascular involvement.

4. Discussion: What Has Changed, What Has Not, and Why

4.1. The Main Reappraisal

The main conclusion of this review is that biologics have changed therapeutic expectations, but only in a manifestation-restricted and biologically uneven way [7–14,24–27]. This represents neither therapeutic failure nor broad therapeutic success. Rather, it reflects the reality that SSc is not a single disease process expressed uniformly across organs, but a syndrome in which immune activation, vascular injury, tissue remodeling, and established fibrosis interact differently depending on clinical manifestation and disease stage. These manifestation-specific differences are examined below.

4.2. Why Manifestation-Specific Responses Differ

Several explanations likely account for these differences.

First, the relative contribution of inflammation versus fixed structural damage differs by manifestation. Biologics are most likely to succeed where inflammatory and immune-stromal interactions remain active and at least partly reversible [1–3,6,20]. This may partly explain why early active skin disease and selected SSc-ILD phenotypes show more tractable signals than long-standing vasculopathy or advanced gastrointestinal dysmotility [21,22,49]. Thus, lack of efficacy of a biologic in later disease does not necessarily invalidate the pathway; it may instead reflect treatment outside the optimal biological window.

Second, endpoint choice strongly shapes perceived efficacy, as detailed in Section 4.3. A biologic may fail one endpoint while remaining clinically relevant in another. Manifestation-based interpretation therefore provides a more faithful account of biologic performance than broad success/failure labeling.

Third, patient heterogeneity remains substantial. Autoantibody profile, disease duration, degree of inflammatory activity, extent of fibrosis, and dominant organ involvement likely all influence biologic responsiveness. One reason the field sometimes appears contradictory is that "SSc" in trial populations often encompasses biologically distinct states.

Taken together, these considerations suggest that the apparent efficacy of biologic therapy in SSc depends not only on the agent being used, but also on the disease phase, endpoint selection, and patient heterogeneity. This conceptual relationship is summarized in Figure 2.

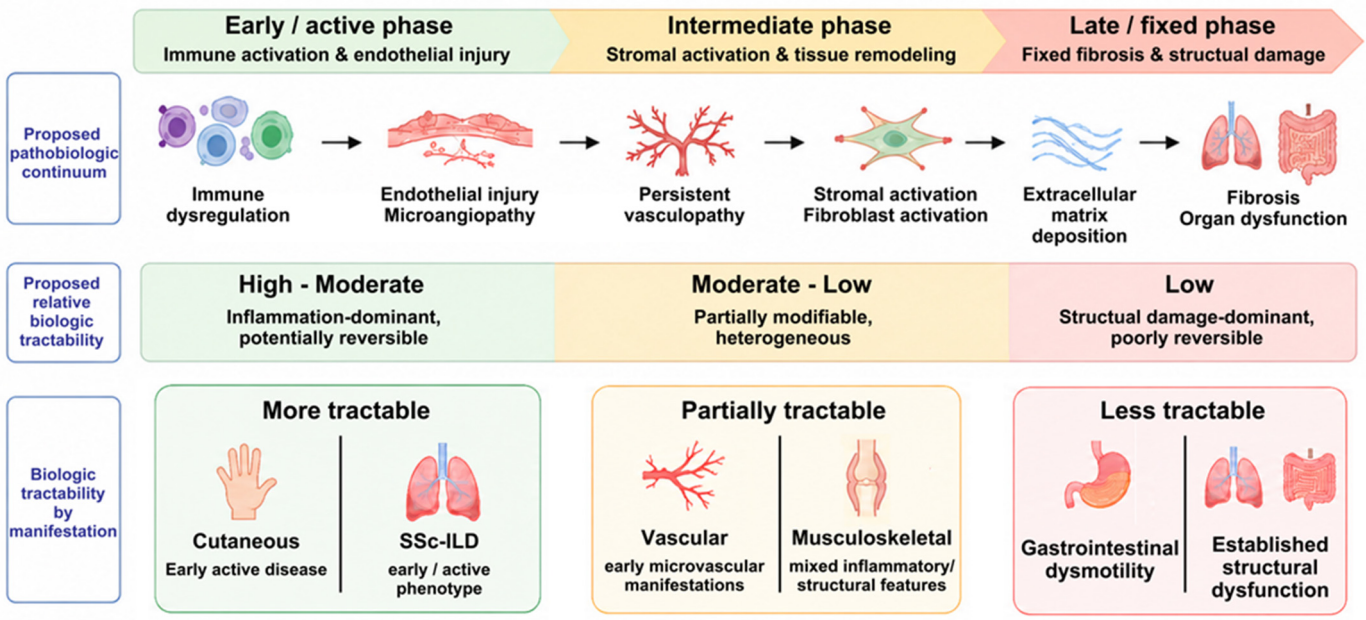


Figure 2. Proposed mechanism underlying manifestation-selective biologic efficacy in systemic sclerosis. This figure illustrates a conceptual framework linking disease phase, pathobiologic progression, and manifestation-level biologic tractability in systemic sclerosis (SSc). Biologic therapies may be more likely to show clinically detectable effects in early or active inflammatory phenotypes, such as early active cutaneous disease and selected SSc-associated interstitial lung disease, whereas established structural dysfunction and gastrointestinal dysmotility may be less biologically tractable. Vascular disease is positioned as an early and persistent pathogenic layer; early microvascular manifestations may remain partially tractable. This framework emphasizes that biologic efficacy in SSc should be interpreted according to disease manifestation, disease stage, and reversibility. Abbreviations: SSc-ILD, systemic sclerosis-associated interstitial lung disease.

4.3. Differences in Trial and Endpoint Maturity Across Manifestations

The manifestation rankings summarized above should not be read as a direct measure of underlying disease biology alone. They are also shaped by how mature, standardized, and well-resourced the clinical trial infrastructure is for each manifestation—a factor that is conceptually distinct from, and potentially confounded with, the disease-stage and reversibility arguments discussed above.

Pulmonary involvement illustrates how enrichment can amplify an apparent treatment effect, and this enrichment was skin-defined: focuSSced and faSScinate enrolled patients according to progressive skin sclerosis (mRSS 10–35 and 15–40, respectively; both with disease duration $\leq$ 60 months) rather than pulmonary criteria [7,9]. When the en-

richment criteria used in focuSSced were applied to a large real-world EUSTAR cohort, they identified only 1.6% of the SSc-ILD population, and this small subset was already declining substantially faster than the unselected cohort (−3.7% versus −0.1% change in FVC over 12 months) [55]. This same analysis, however, found no significant association between enrichment criteria and ILD progression overall, and the focuSSced-enriched subset showed numeric improvement in lung function during the second year of observation. This pattern is more consistent with regression to the mean than with a stable, enrichment-defined disease trajectory. Consistent with this, in a broader, non-enriched real-world population, tocilizumab no longer showed a statistically significant effect on either skin or lung outcomes, although the direction of effect still favored treatment [56]. Endpoint properties may compound this effect: an ex vivo substudy of the faSScinate trial found that tocilizumab profoundly reversed the profibrotic gene expression profile of dermal fibroblasts, yet this molecular change showed little correlation with the clinical skin score after correction for multiple testing [57].

Vasculopathy illustrates the converse problem. Rather than a single, large, enriched trial comparable to focuSSced, biologic and vasoactive development in this area has relied on numerous small, heterogeneous studies using inconsistent outcome measures: patient-reported symptom diaries confounded by pain, coping strategies, and season; digital ulcer definitions with poor inter-rater reliability among experienced clinicians; and thermographic and laser-based perfusion imaging methods for which no preferred endpoint has yet emerged [58–61]. As one review notes, the paucity of approved treatments for cutaneous vascular manifestations of SSc relates as much to challenges in trial design and endpoint reliability as to an absence of therapeutic options [62].

These observations do not invalidate the manifestation-based framework used throughout this review; rather, the manifestation-level comparisons summarized in Figure 1 and Table 1 should be interpreted with this additional source of variation in mind.

4.4. Vasculopathy as an Upstream Constraint on Disease Modification

Trial and endpoint limitations alone are unlikely to fully explain vasculopathy's therapeutic refractoriness. As noted above, vascular manifestations in SSc are shaped by chronic tissue ischemia that, once established, may not be readily reversible regardless of how outcomes are measured [21,47,48]. With this caveat in mind, a manifestation-based reappraisal also raises a broader pathophysiological question. In SSc, vasculopathy should not be viewed merely as one clinical manifestation among others, but as an early and upstream pathogenic layer that may shape downstream tissue injury, immune-stromal activation, fibrotic remodeling, and organ dysfunction [1–3,6,21,46], proposed here as a conceptual model rather than an established mechanism. This does not imply a simple linear model in which vascular injury alone causes fibrosis. Rather, persistent microvascular dysfunction may act as an upstream constraint that interacts with immune activation and stromal remodeling, thereby limiting the extent to which downstream inflammatory or fibrotic manifestations can be fully modified by biologic therapy [1,20,21].

This may help explain why some biologics yield measurable benefit in skin or lung outcomes, while broader transformation of SSc remains limited: partial control of downstream inflammation or fibrosis may not necessarily translate into interruption of the vascular pathology that helps sustain disease progression.

4.5. Distinctive Contributions of This Reappraisal

As introduced in Section 1.2, this manifestation-based framing more closely mirrors clinical decision-making: physicians do not treat "SSc in general" in the abstract; they treat a patient with progressive ILD, inflammatory early diffuse skin disease, recurrent digital

ischemia, or severe reflux and dysmotility. A drug-centered rather than manifestation-centered reading may therefore underestimate both the real progress and the real limitations of current therapy.

In practice, agent selection should follow both the manifestation and the nature of the supporting evidence: rituximab has the strongest direct randomized evidence for skin fibrosis and is guideline-supported for SSc-ILD, whereas tocilizumab is most relevant to SSc-ILD in selected early inflammatory dcSSc, where the observed benefit is attenuation of FVC decline rather than reversal of fibrosis. Vascular, gastrointestinal, or musculoskeletal effects should not currently serve as primary indications for biologic selection.

Current guidelines independently converge on this same pattern. The 2023 EULAR recommendations endorse rituximab for both skin fibrosis and SSc-ILD (evidence level 1a, grade A) and tocilizumab for SSc-ILD (evidence level 1b, grade B), though tocilizumab's skin fibrosis recommendation is weaker and restricted to early inflammatory diffuse disease (grade C)—a formal grading hierarchy distinct from the trial-enrichment reasoning emphasized in Section 4.3—yet neither agent appears among the recommended options for vascular, gastrointestinal, or musculoskeletal manifestations [7]. The 2023 ACR/CHEST ILD guideline requires similar qualification: rituximab is conditionally recommended as one of several first-line options for the broader category of SARD-ILD, rather than for SSc-ILD specifically, while tocilizumab is conditionally recommended specifically for SSc-ILD and MCTD-ILD; the certainty of the underlying evidence is graded very low for both [63].

Safety receives comparatively limited attention in this and much of the literature, despite its clinical relevance. A concise drug-specific framework separates pre-treatment screening from ongoing monitoring: for rituximab, pre-treatment screening includes hepatitis B and C serology and latent tuberculosis testing, and ongoing monitoring includes complete blood count with differential at baseline and every 2–4 months, given the risks of infection, cytopenias, hypogammaglobulinemia, and hepatitis B reactivation, together with a black-box warning for progressive multifocal leukoencephalopathy [10,11,33,63]; for tocilizumab, pre-treatment screening includes latent tuberculosis testing, and ongoing monitoring includes complete blood count with differential, liver function tests, and lipid panels at baseline, every 4–8 weeks for the first 6 months, and every 3 months thereafter, given the risks of transaminitis, hyperlipidemia, and bowel perforation [8,9,34,56,63]. Age-appropriate vaccination is recommended before starting either agent, given their immunosuppressive effect [63].

A Japanese perspective is particularly valuable in this context. Japanese investigators have contributed notably to the biologics literature in SSc, especially through randomized evidence for rituximab and mechanistically oriented reports on emerging cytokine pathways, including IL-17/IL-23-related strategies such as brodalumab and guselkumab [10,12–14,37]. The Japanese evidence is also notable for its emphasis on phenotypic context, early disease evaluation, and translational linkage between mechanism and clinical observation [2,10,12–14].

4.6. Future Directions

Several priorities emerge from this reappraisal.

First, future trials should be designed with explicit manifestation-specific logic. Biologic trials in SSc should avoid assuming that efficacy in one manifestation predicts benefit in another. Instead, they should specify the manifestation being targeted and select outcomes accordingly.

Second, earlier disease windows deserve greater trial attention, as noted in Section 4.2, before irreversible structural damage predominates.

Third, biomarker-informed stratification is likely essential, building on the "early active disease" concept already used to enrich pivotal trials—typically operationalized as

short overall disease duration (e.g., ≤60 months) combined with elevated acute-phase reactants and evidence of recent skin progression [9]. Immune phenotype, autoantibody profile, degree of inflammatory activation, B-cell transcriptional signatures, nailfold capillaroscopic pattern, and pulmonary function trajectory may all help identify biologic-responsive subgroups, although no such biomarker has yet been prospectively validated for biologic selection. A post hoc analysis of focuSSced found that male sex, anti-topoisomerase antibody positivity, shorter disease duration (<2 years), and younger age (<65 years) predicted greater tocilizumab benefit on lung function, whereas elevated baseline IL-6—the drug's own therapeutic target—did not; these associations require prospective confirmation [64]. Precision-medicine approaches—molecular subsetting of SSc, biologic-antifibrotic combination therapy, and adaptive trial designs that adjust for these subsets—represent a further, related research priority.

Fourth, vascular and gastrointestinal manifestations require more thoughtful biologic development. Their limited apparent efficacy to date may reflect not only true biological refractoriness, but also inadequate endpoint selection and insufficient enrichment for early or inflammation-linked phenotypes.

Fifth, trial results should be interpreted alongside the maturity of each manifestation's endpoint infrastructure (Section 4.3): enrichment that maximizes detection of a treatment effect can limit generalizability, and future trials should report how representative their population is of real-world practice.

5. Conclusions

Biologics have changed therapeutic expectations and clinical decision-making in systemic sclerosis, but not in a uniform or disease-wide manner, with the most substantial evidence base in selected pulmonary and cutaneous populations and more limited change elsewhere.

A manifestation-based reappraisal helps reconcile what otherwise appears to be a contradictory literature. Biologics have not broadly solved SSc, but neither have they failed wholesale: SSc treatment response is instead distributed unevenly across manifestations, disease stages, and patient subsets. The key challenge moving forward is not only to develop more biologics, but to determine which biologic should be used in which manifestation, at which stage, and in which patient.

If future studies combine manifestation-appropriate endpoints, early-disease enrichment, and biomarker-informed stratification, biologics may yet have a broader impact on SSc management. For now, however, the clearest lesson is that in SSc, what has changed depends on what one chooses to measure.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/sclerosis4030028/s1. Table S1: Detailed trial characteristics, effect estimates, and guideline positioning for biologic therapies in systemic sclerosis; Table S2: Database-specific search strings and results (searched 18 August 2026).

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