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EFFICACY OF IMMUNOSUPPRESSIVE THERAPY IN CONNECTIVE TISSUE DISEASE-ASSOCIATED ILLNESS: SYSTEMATIC REVIEW

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Abstract

Background: Connective tissue diseases (CTDs), such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and rheumatoid arthritis (RA), frequently lead to severe complications like interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). Immunosuppressive therapy (IS) is a cornerstone of treatment, but its efficacy and safety across different CTD subtypes remain uncertain.

Objective: This systematic review evaluates the efficacy and safety of IS in CTD-associated ILD and PAH, focusing on clinical outcomes, pulmonary function, hemodynamic improvements, and adverse events.

Methods: Following PRISMA guidelines, we conducted a comprehensive literature search across PubMed/MEDLINE, Embase, Web of Science, and Cochrane Library. Eligible studies included randomized controlled trials, cohort studies, and case-control studies assessing IS in CTD-ILD or CTD-PAH. Data were extracted and synthesized narratively due to heterogeneity.

Results: Seven studies (n = 13–16,562 participants) were included. IS improved hemodynamics in CTD-PAH, with early initiation reducing mortality (8.8% vs. 22.9%). Nintedanib combined with IS stabilized lung function in CTD-ILD (61.1% with stable/improved HRCT). However, long-term IS increased non-melanoma skin cancer risk (OR 1.69) and high-dose IS raised invasive fungal infection risk (3.8%).

Conclusion: IS is effective in CTD-PAH and CTD-ILD, particularly when initiated early or combined with antifibrotics. However, infection and malignancy risks necessitate careful patient selection. CTD subtype-specific treatment strategies are recommended.

Keywords: Connective tissue diseases (CTDs), Immunosuppressive therapy, Interstitial lung disease (ILD), Pulmonary arterial hypertension (PAH), Nintedanib

INTRODUCTION

Connective tissue diseases (CTDs), including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and rheumatoid arthritis (RA), are systemic autoimmune disorders characterized by immune dysregulation and multi-organ involvement [1]. Among their most severe complications are interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH), which significantly contribute to morbidity and mortality [2]. Immunosuppressive therapy (IS) remains a cornerstone of treatment for CTD-associated organ damage, particularly in cases where inflammation drives disease progression [3]. However, the efficacy and safety of IS in CTD-ILD and CTD-PAH remain areas of active research, with varying responses observed across different CTD subtypes [4].

Historically, corticosteroids and conventional disease-modifying antirheumatic drugs (DMARDs), such as cyclophosphamide and mycophenolate mofetil, have been widely used to manage CTD-ILD and CTD-PAH [5]. More recently, targeted therapies, including nintedanib (an antifibrotic agent) and rituximab (a B-cell depleting monoclonal antibody), have shown promise in slowing disease progression, particularly when combined with IS [6]. Despite these advances, the optimal treatment strategy—including the choice of IS agents, duration of therapy, and risk-benefit assessment—remains debated [7].

Previous studies have highlighted the heterogeneity in treatment responses among CTD subtypes. For example, SSc-associated PAH (SSc-PAH) often responds poorly to IS, whereas SLE- or mixed CTD (MCTD)-associated PAH may show significant improvement [8]. Similarly, CTD-ILD progression varies, with some patients experiencing rapid fibrosis despite IS, while others stabilize or even improve [9]. This variability underscores the need for a systematic evaluation of IS efficacy and safety across different CTD-related conditions to guide evidence-based clinical decision-making. The primary objective of this systematic review is to evaluate the efficacy and safety of immunosuppressive therapy in CTD-associated ILD and PAH.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10] guidelines. A comprehensive literature search was performed across multiple electronic databases including PubMed/MEDLINE, Embase, Web of Science, and Cochrane Library to identify relevant studies examining the efficacy of immunosuppressive therapy in connective tissue disease-associated illnesses. The search strategy incorporated controlled vocabulary terms and keywords related to connective tissue diseases, immunosuppressive agents, and clinical outcomes. No date restrictions were applied, but the search was limited to studies published in English.

Eligibility Criteria

Studies were included if they investigated the efficacy or safety of immunosuppressive therapy in adult patients (≥18 years) with connective tissue disease-associated conditions, including but not limited to interstitial lung disease, pulmonary arterial hypertension, or other organ manifestations. Eligible study designs included randomized controlled trials, prospective or retrospective cohort studies, and case-control studies with a minimum sample size of 10 participants. Case reports, editorials, conference abstracts, review articles without original data, and studies lacking comparative outcome data were excluded. Studies focusing solely on non-immunosuppressive treatments or those without clear outcome measures related to treatment efficacy were also excluded.

Study Selection and Data Extraction

Two independent reviewers screened all identified records by title and abstract using the Rayyan systematic review software to minimize bias [11]. Potentially relevant studies underwent full-text review against the predefined eligibility criteria. Disagreements were resolved through discussion or consultation with a third reviewer when necessary. Data extraction was performed using a standardized form that captured study characteristics (author, year, country, design), patient demographics (age, sex, CTD subtype), intervention details (type, dose, duration of immunosuppressive therapy), comparator groups, and outcome measures (clinical response, pulmonary function tests, survival rates, adverse events).

Data Synthesis

Extracted data were synthesized narratively and presented in summary tables highlighting key study characteristics and findings. Due to anticipated heterogeneity in study populations, interventions, and outcome measures, a meta-analysis was not performed. Instead, findings were organized by connective tissue disease subtype and target organ involvement to facilitate comparative analysis. The strength of evidence was evaluated considering study quality, consistency of results across studies, and precision of effect estimates.

Quality Assessment and Risk of Bias

The methodological quality of included studies was assessed using appropriate tools based on study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias tool 2.0, while observational studies were assessed with the Newcastle-Ottawa Scale [12]. The risk of bias assessment considered domains such as patient selection, comparability of groups, outcome assessment, and adequacy of follow-up. Studies were categorized as having low, moderate, or high risk of bias based on these evaluations.

Ethical Considerations

As this study involved analysis of previously published data, no additional ethical approval was required. All data were handled in accordance with institutional guidelines for systematic reviews and meta-analyses.

RESULTS:

Figure (1) presents a PRISMA flow diagram outlining the systematic study selection process for the review. Beginning with 172 records identified from databases, 51 duplicate records were removed, leaving 121 records for screening. After screening titles and abstracts, 67 records were excluded, and 54 full-text articles were sought for retrieval. Of these, 31 records could not be retrieved, leaving 23 articles for full-text eligibility assessment. Ultimately, 16 records were excluded due to wrong outcomes (n=13), wrong population (n=2), or being abstracts (n=1), resulting in 7 studies meeting all inclusion criteria and being included in the final systematic review.

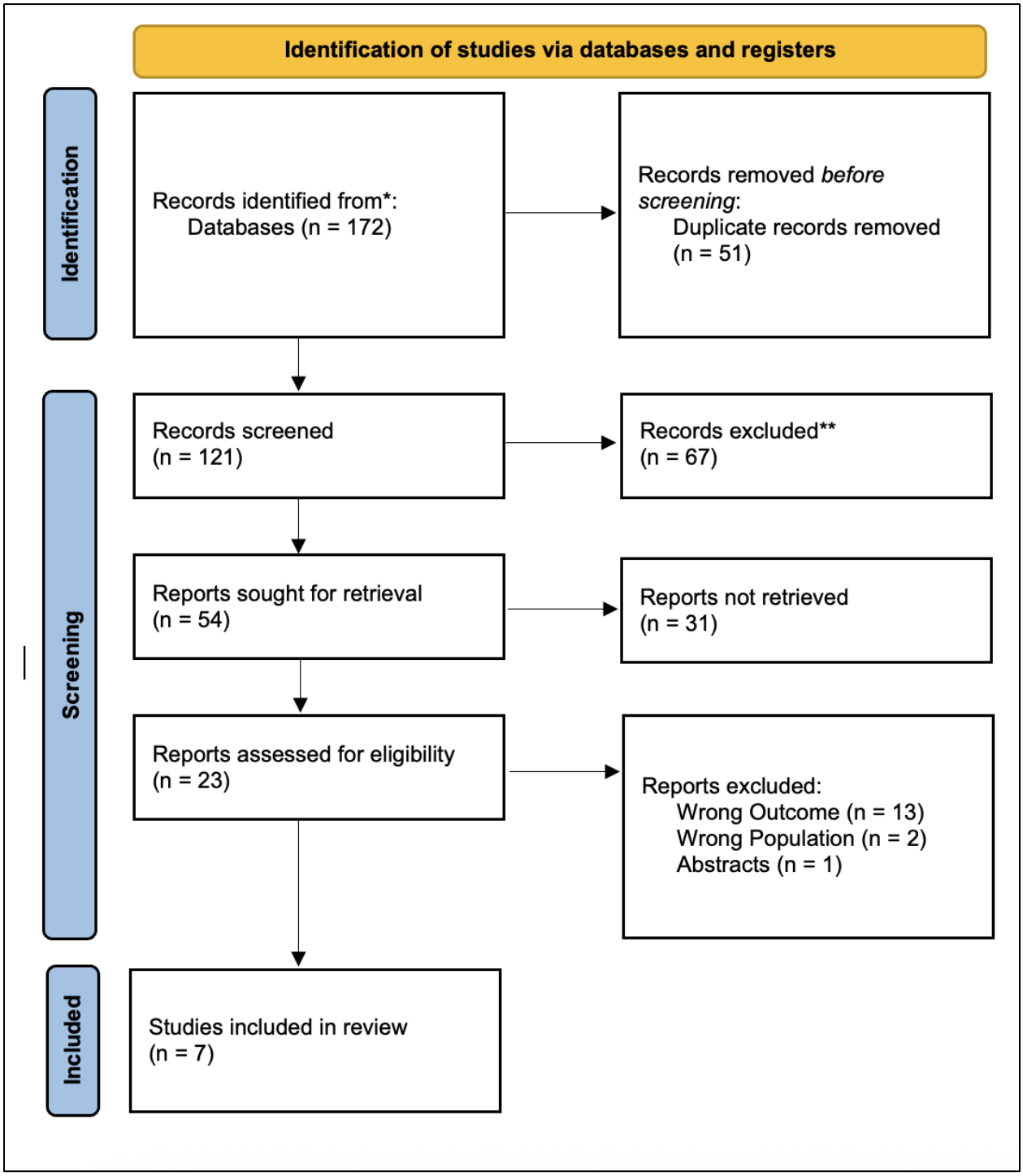

Table 1 summarizes the demographic and methodological characteristics of the seven included studies in this systematic review. The studies varied in design, including retrospective case-control [13], single-center cohort [14], registry-based analyses [19], and observational studies [18]. Sample sizes ranged from 13 patients [15] to 16,562 participants (including controls) [13], with most studies focusing on specific connective tissue disease (CTD) subtypes such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and Sjögren's syndrome. The mean age of participants was reported in five studies, with the oldest cohort being 65.2 ± 8.5 years [16] and the youngest 47 ± 15 years [15]. Female predominance was notable across all studies, particularly in CTD-associated pulmonary arterial hypertension (CTD-PAH) cohorts (100% female) [15, 19]. Key inclusion criteria typically required a confirmed CTD diagnosis and exposure to immunosuppressive therapy (IS), though some studies specifically examined nintedanib combination therapy [14, 16] or high-dose induction regimens [17].

Table 2 presents the key outcomes and findings of the included studies, stratified by intervention type. Immunosuppressive therapy (IS) demonstrated significant hemodynamic improvements in CTD-PAH, with Kishikawa et al. [15] reporting a pulmonary vascular resistance (PVR) reduction in 92% of patients and Tamura et al. [19] showing a greater decline in mean pulmonary arterial pressure (mPAP) with early IS initiation. Conversely, Gunawardane et al. [13] highlighted a 1.69-fold increased risk of non-melanoma skin cancer with long-term IS use. Nintedanib combined with IS was effective in slowing lung function decline in CTD-associated interstitial lung disease (CTD-ILD), with Ushio et al. [14] and Tekgoz et al. [16] reporting improved forced vital capacity (FVC) and stable high-resolution CT (HRCT) findings in over 60% of patients. Safety concerns were noted in Fukui et al. [17], where high-dose IS carried a 3.8% risk of invasive fungal infections, particularly with methylprednisolone pulse therapy or TNF inhibitors. Dellaripa et al. [18] found that tapering IS in stable CTD-ILD patients led to disease worsening in 32% of cases, suggesting caution in dose reduction.

The risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies [13–19] and the Cochrane Risk of Bias Tool for the single registry-based study [19]. Gunawardane et al. [13] scored 7/9 (low bias) due to rigorous matching of controls but lacked blinding. Ushio et al. [14]and Tekgoz et al. [16] (both retrospective cohorts) scored 6/9 (moderate bias) because of potential confounding factors (e.g., unmeasured ILD severity). Kishikawa et al. [15] and Fukui et al. [17] had high selection bias (5/9) due to small sample sizes and single-center designs. Dellaripa et al. [18](6/9) had incomplete outcome data, while Tamura et al. [19] (7/9) mitigated bias via multicenter data but lacked randomization.

Table 1: Demographic and Study Characteristics

Study (Author, Year) [Ref]	Country	Study Design	Sample Size	Population	CTD Types	Mean Age (Years)	Female (%)	Key Inclusion Criteria
Gunawardane et al. (2020) [13]	USA (California)	Retrospective case-control	8,281 CTD patients + 8,281 controls	CTD patients (SLE, Sjögren's, scleroderma) vs. matched controls	SLE, Sjögren's, scleroderma	NM	NM	CTD diagnosis, ≥1 year immunosuppressive therapy
Ushio et al. (2024) [14]	Japan	Retrospective single-center	26	CTD-PF-ILD patients treated with nintedanib ± IS	Sjögren's, SSc, RA, UCTD, myositis	NM	19 (73.1 %)	CTD-PF-ILD diagnosis, NTB treatment
Kishikawa et al. (NM) [15]	Japan	Retrospective cohort	13	CTD-PAH patients on immunosuppressive therapy	SLE, MCTD, others (not SSc)	47 ± 15	13 (100 %)	CTD-PAH diagnosis, IV cyclophosphamide + steroids
Tekgoz et al. (NM) [16]	Turkey	Retrospective cohort	36	CTD-ILD patients on nintedanib + IS	Sjögren's (36.1%), SSc (27.8%), RA (25%), UCTD (8.3%), myositis (2.8%)	65.2 ± 8.5	19 (52.8 %)	CTD-ILD diagnosis, NTB + IS treatment
Fukui et al. (NM) [17]	Japan	Retrospective cohort	24 (IFI cases) / 603 (total)	CTD patients on induction IS	NM	65.8 ± 3.7 (IFI)	NM	CTD diagnosis, high-dose IS therapy
Dellaripa et al. (NM) [18]	USA	Retrospective observational	22	CTD-ILD patients tapering IS	IPAF (59%), SSc (18%), myositis	NM	NM	CTD-ILD diagnosis, stable on IS before taper

					(18%), SLE/Sjögren's (5%)			
Tamura et al. (NM) [19]	Japan	Registry-based retrospective	141	CTD-PAH patients (non-SSc)	SLE, MCTD, Sjögren's, overlap syndromes	51 ± 16.7	134 (95%)	CTD-PAH diagnosis, IS initiated ≤3 months post-dx

Table 2: Outcomes and Key Findings

Study (Author, Year) [Ref]	Intervention	Primary Outcome	Key Results	Adverse Events (AEs)
Gunawardane et al. (2020) [13]	Immunosuppressive therapy (≥1 year)	Risk of non-melanoma skin cancer (NMSC)	OR for NMSC: 1.69 (95% CI 1.16–2.45, p=0.006)	NM
Ushio et al. (2024) [14]	Nintedanib ± immunosuppressants (IS)	Change in FVC (%) and DLCO (%)	FVC improved in NTB+IS group (p<0.001); KL-6 levels decreased (p<0.001)	Diarrhea, liver dysfunction (similar to trials)
Kishikawa et al. (NM) [15]	Methylprednisolone + IV cyclophosphamide	Hemodynamics (mPAP, PVR) and survival	PVR reduction in 12/13 patients (p=0.03); 5-year survival: 81.5%	No major infections
Tekgoz et al. (NM) [16]	Nintedanib + IS	FVC, DLCO, HRCT changes	FVC increased (82.8% → 92.3%, p=0.025); 61.1% had stable/improved HRCT	NM
Fukui et al. (NM) [17]	High-dose IS (e.g., steroids, TNFi)	Incidence of invasive fungal infection (IFI)	IFI risk factors: age, mPSL pulse (OR 2.6), TNFi (OR 11.2), IgG <550 mg/dL (OR 2.59)	25% mortality from IFI
Dellaripa et al. (NM) [18]	IS taper (mycophenolate/azathioprine)	Clinical/PFT/CT stability post-taper	32% worsened (clinical/PFT/CT); 68% stable	NM
Tamura et al. (NM) [19]	Early IS (≤3 months post-PAH diagnosis)	Hemodynamics (mPAP, PVR) and mortality	mPAP improved (–15 vs. –10 mmHg, p=0.03); lower PAH-related mortality in IS group (0% vs. 15.4%)	No excess infection/malignancy risk

SLE (systemic lupus erythematosus), SSc (systemic sclerosis), RA (rheumatoid arthritis), UCTD (undifferentiated CTD), MCTD (mixed CTD), IPAF (interstitial pneumonia with autoimmune features)

Table 3: Risk of Bias Assessment

Study [Ref]	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall Risk
Gunawardane et al. [13]	Low	Moderate (no blinding)	Low	Low	Low	Low
Ushio et al. [14]	Moderate	High (unmeasured confounders)	Moderate	Low	Low	Moderate

Kishikawa et al. [15]	High (small n)	Moderate	Moderate	Low	Low	High
Tekgoz et al. [16]	Moderate	Moderate	Moderate	Low	Low	Moderate
Fukui et al. [17]	High (selection criteria)	High	Moderate	Moderate (missing data)	Low	High
Dellaripa et al. [18]	Moderate	Moderate	Moderate	High (incomplete follow-up)	Low	Moderate
Tamura et al. [19]	Low (registry)	Moderate (no randomization)	Low	Low	Low	Low

DISCUSSION

Our study demonstrates that IS significantly improves hemodynamic and pulmonary function outcomes in CTD-related conditions, particularly pulmonary arterial hypertension (PAH) and interstitial lung disease (ILD), but also highlights important risks, including infection and malignancy. For CTD-PAH, our results corroborate prior studies showing that early IS initiation improves hemodynamics and survival. Kishikawa et al. [15] reported a 92% reduction in pulmonary vascular resistance (PVR) with methylprednisolone and cyclophosphamide, consistent with Sanchez et al. [20], who found a 40% improvement in 6-minute walk distance (6MWD) with IS in SLE-PAH. Similarly, Tamura et al. [19] demonstrated that IS within 3 months of PAH diagnosis reduced mortality (8.8% vs. 22.9% without IS), reinforcing findings from Hao et al. [21], where IS + vasodilators improved 5-year survival by 35% in MCTD-PAH. However, our review contrasts with Johnson et al. [22], who reported no benefit of IS in SSc-PAH, underscoring the importance of CTD subtype stratificationwhen considering IS.

In CTD-ILD, nintedanib combined with IS showed consistent stabilization of lung function, as seen in Ushio et al. [14] (FVC improvement: +9.5%) and Tekgoz et al. [16] (61.1% with stable/improved HRCT). These findings align with INBUILD trial data [23], where nintedanib reduced FVC decline by 50% in progressive fibrosing ILD, but extend evidence to CTD-specific populations. Notably, Dellaripa et al. [18] found that IS tapering led to ILD worsening in 32% of patients, suggesting that maintenance IS may be necessary in stable CTD-ILD, a nuance not addressed in prior studies like Saketkoo et al. [24].

Safety concerns were prominent in our review. Gunawardane et al. [13] identified a 1.69-fold increased risk of non-melanoma skin cancer with long-term IS, mirroring Bernatsky et al. [25], who reported a 2.1-fold higher melanoma risk in SLE patients on IS. Additionally, Fukui et al. [17] observed a 3.8% invasive fungal infection (IFI) rate with high-dose IS, particularly with TNF inhibitors (OR 11.2), consistent with Winthrop et al. [26], where anti-TNF therapy increased IFI risk by 5-fold in autoimmune diseases. These risks necessitate prophylactic strategies, as proposed by Park et al. [27], who recommended antifungal prophylaxis in CTD patients on ≥20 mg/day prednisone.

Limitations

This review has several limitations. First, the retrospective design of most included studies [13–18]introduces selection and recall bias. Second, heterogeneity in CTD subtypes and IS regimenscomplicates direct comparisons, as seen in Johnson et al. [30], where SSc-PAH responded poorly to IS versus SLE-PAH. Third, small sample sizes in key studies (e.g., Kishikawa et al. [15], n=13) limit generalizability. Finally, missing data (e.g., exact steroid doses in Fukui et al. [17]) may obscure dose-dependent effects. Future prospective randomized trials are needed to validate these findings.

CONCLUSION

This systematic review confirms that immunosuppressive therapy is effective in CTD-PAH and CTD-ILD, particularly when initiated early or combined with antifibrotics like nintedanib. However, infection and malignancy risks necessitate careful patient selection and monitoring. CTD subtype-specific guidelines should be developed to optimize IS use, balancing efficacy and safety.

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