Treatment of Rheumatoid Arthritis-Associated Interstitial Lung Disease: A Protocol for the Systematic Review and Meta-Analysis

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Abstract

Background: Rheumatoid Arthritis-Associated Interstitial Lung Disease (RA-ILD) is a significant extra-articular manifestation of rheumatoid arthritis (RA), characterized by progressive lung fibrosis and inflammation, leading to increased morbidity and mortality. While anti-inflammatory therapies have traditionally been used to manage RA-ILD, emerging evidence suggests that antifibrotic therapies may also offer clinical benefits. This protocol outlines a systematic review and meta-analysis to compare the safety and efficacy of antifibrotic versus anti-inflammatory therapies in the management of chronic RA-ILD.

Objective: This study aims to evaluate and compare the impact of antifibrotic and anti-inflammatory therapies on lung function, radiologic progression, clinical outcomes, and safety in patients with chronic RA-ILD.

Methods: A systematic search will be conducted across PubMed, Embase, and the Cochrane Library, following PRISMA guidelines. Eligible studies will include adult patients (?18 years) diagnosed with RA-ILD and treated with either antifibrotic or anti-inflammatory therapies. Primary outcomes include pulmonary function parameters—forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and diffusing capacity of the lungs for carbon monoxide (DLCO). Secondary outcomes include radiological changes (e.g., fibrosis progression on high-resolution computed tomography), clinical endpoints (e.g., disease progression rates, overall survival, quality of life), and safety and tolerability of therapies. Pooled effect estimates will be calculated using random-effects meta-analysis, and heterogeneity will be assessed via Cochran's Q test and I^2 statistic.

Results: This systematic review will identify the comparative efficacy and safety profiles of antifibrotic and anti-inflammatory therapies, providing valuable insights for clinicians managing chronic RA-ILD.

Conclusions: The findings will address critical gaps in the management of RA-ILD, offering evidence-based recommendations for therapeutic decision-making and improving outcomes for patients with this debilitating condition. Clinical Trial: The study protocol has been registered with PROSPERO (CRD42024583847).
Registration Link: https://www.crd.york.ac.uk/prospero/export_details_pdf.php

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Running Title:
RA-ILD Treatment: Systematic Review and Meta-Analysis Protocol

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CONFLICT OF INTEREST*:*
The authors declare no conflict of interest for this article.

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None

DATA AVAILABILITY:
The data analyzed in the study will be available upon request from the corresponding author.

ABSTRACT:

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A systematic search will be conducted across PubMed, Embase, and the Cochrane Library, following PRISMA guidelines. Eligible studies will include adult patients (≥18 years) diagnosed with RA-ILD and treated with either antifibrotic or anti-inflammatory therapies. Primary outcomes include pulmonary function parameters—forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and diffusing capacity of the lungs for carbon monoxide (DLCO). Secondary outcomes include radiological changes (e.g., fibrosis progression on high-resolution computed tomography), clinical endpoints (e.g., disease progression rates, overall survival, quality of life), and safety and tolerability of therapies. Pooled effect estimates will be calculated using random-effects meta-analysis, and heterogeneity will be assessed via Cochran's Q test and I^2 statistic.

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Trial Registration
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ABBREVIATIONS:

1. **AIP** - Acute Interstitial Pneumonia
2. **CI** - Confidence Interval
3. **CINAHL** - Cumulative Index to Nursing and Allied Health Literature
4. **DMARDs** - Disease-Modifying Antirheumatic Drugs
5. **DIP** - Desquamative Interstitial Pneumonia
6. **DLCO** - Diffusing Capacity of the Lungs for Carbon Monoxide
7. **FEV1** - Forced Expiratory Volume in One Second
8. **FVC** - Forced Vital Capacity
9. **HRCT** - High-Resolution Computed Tomography
10. **ILD** - Interstitial Lung Disease
11. **LIP** - Lymphocytic Interstitial Pneumonia
12. **NHLBI** - National Heart, Lung, and Blood Institute
13. **NSIP** - Nonspecific Interstitial Pneumonia
14. **OP** - Organizing Pneumonia
15. **OS** - Overall Survival
16. **PECOS** - Population, Exposure, Comparator, Outcome, Study Design
17. **PFS** - Progression-Free Survival
18. **PRISMA** - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
19. **PROSPERO** - International Prospective Register of Systematic Reviews
20. **RA** - Rheumatoid Arthritis
21. **RA-ILD** - Rheumatoid Arthritis-associated Interstitial Lung Disease
22. **RB-ILD** - Respiratory Bronchiolitis Interstitial Lung Disease
23. **RR** - Risk Ratio
24. **SMD** - Standardized Mean Difference
25. **UIP** - Usual Interstitial Pneumonia
26. **U.S.** - United States

INTRODUCTION:

Rheumatoid arthritis (RA) is a prevalent autoimmune inflammatory condition, affecting approximately 0.5 to 1% of the population in the United States (U.S.) and Northern Europe [1]. Interstitial Lung Disease (ILD) is the most common respiratory manifestation of RA and can lead to significant morbidity and increased mortality in some patients with Rheumatoid Arthritis-associated Interstitial Lung Disease (RA-ILD). The prevalence of RA-ILD among individuals with RA ranges from 2-8% [2]. RA-ILD often follows a clinically unpredictable course, with recent studies reporting an increasing prevalence of RA-ILD ranging from 27-67%, a notable proportion of which includes asymptomatic patients [3].
RA-ILD is believed to result from persistent immune activation and inflammation, which leads to excessive fibroproliferation in the lung tissue of individuals with a genetic predisposition [4]. In some cases, the clinical symptoms of ILD may appear before the onset of articular symptoms in patients with RA. One study found that approximately 14% of patients with RA-ILD were diagnosed with ILD 1 to 5 years prior to being diagnosed with RA [5]. Several risk factors for the development of ILD in RA patients have been identified, including older age, male gender, cigarette smoking, and the presence of positive anti-cyclic citrullinated peptide antibodies (anti-CCP) or IgM rheumatoid factor [6][7][8][9].

RA-ILD can be classified into acute, subacute, and chronic forms based on the clinical presentation. In patients with acute RA-ILD, characterized by diffuse alveolar damage, high-dose corticosteroids are typically the first-line treatment. About half of RA patients develop ILD either before or within 5 years of the RA diagnosis [10]. In contrast, the management of chronic RA-ILD focuses on controlling the underlying disease to prevent further progression of ILD. Disease-modifying antirheumatic drugs (DMARDs) have traditionally been used to manage RA-associated symptoms. For RA-ILD specifically, therapies such as corticosteroids, mycophenolate, azathioprine, rituximab, and TNF-alpha inhibitors are commonly employed. Antifibrotic therapies, including Pirfenidone and Nintedanib, have been FDA-approved for idiopathic pulmonary fibrosis (IPF) and are now being explored for RA-ILD [11].

Several clinical trials have demonstrated the safety and efficacy of anti-fibrotic agents in the treatment of ILD [12][13][14]. However, a comprehensive review comparing the safety and efficacy of anti-fibrotic versus anti-inflammatory therapies in patients with chronic RA-ILD remains lacking. In this systematic review and meta-analysis, we aim to compare the safety and efficacy of these two therapeutic approaches in the management of chronic RA-ILD. By examining the comparative benefits and limitations of these treatment strategies, this study aims to provide valuable insights to guide clinical decision-making and improve the management of patients with chronic RA-ILD.

METHODOLOGY:

Ethical Considerations and Guidelines

As this study does not have the direct involvement of human participants, an institutional ethical review will not be warranted. However, to adhere to a strict methodology, the protocol of this systematic review was registered on PROSPERO (CRD42024583847) [15]. PROSPERO is an international database of prospectively registered systematic reviews, which provides a unique permanent registration number to the protocol that prevents duplication, thereby reducing reporting bias. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in conducting and reporting this systematic review to ensure a comprehensive and transparent approach to the evaluation of the available evidence [16].

Review Question

Analyzing the effectiveness of anti-fibrotic compared to anti-inflammatory therapies in improving or stabilizing lung function and clinical outcomes in adult patients with RA-ILD.

Inclusion and Exclusion Criteria

The inclusion criteria for this systematic review were developed using the PECOS (Population, Exposure, Comparator, Outcome, Study Design) framework, ensuring that only studies directly addressing the research question are included (Table 1) [17]. This systematic review contains studies involving adult patients (≥18 years) diagnosed with RA and confirmed IILD through radiological or histopathological findings. Eligible studies must investigate the effectiveness of anti-

fibrotic therapies compared to anti-inflammatory therapies. Studies must report on primary outcomes such as pulmonary function parameters, including forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and diffusing capacity of the lungs for carbon monoxide (DLCO), as well as secondary outcomes like radiological changes on high-resolution computed tomography (HRCT), clinical endpoints, and safety and tolerability.

Randomized and non-randomized clinical trials, case-control, prospective, and retrospective cohort studies will be included. Studies published on human subjects, adult patients aged 18 years or older, and published in the English language between January 1, 1991, and August 1, 2024, and across all geographical locations will be included. Exclusion criteria involve studies focusing on non-human subjects, pediatric populations, or other forms of ILD without specific reference to RA-ILD. Studies not involving anti-fibrotic or anti-inflammatory therapies or that lack quantitative data on lung function or clinical outcomes will be excluded as well. Case studies, case reports, abstract-only studies, reviews, editorials, short communication, and opinion articles will be excluded.

Informational Sources and Search Strategy

A comprehensive search strategy was developed by the study investigators, with guidance from a librarian, to identify relevant articles across multiple databases, including PubMed, Embase, and Cochrane Library. The search was designed to capture studies related to RA-ILD and treatment options involving both anti-fibrotic and anti-inflammatory therapies. The search strategy was refined through preliminary searches in Embase, with additional terms introduced as new concepts were identified. Keywords included combinations of terms such as "Rheumatoid Arthritis," "Interstitial Lung Disease," "Anti-fibrotic therapy," "Anti-inflammatory therapy," "Pirfenidone," "Nintedanib," "Disease-modifying anti-rheumatic drugs (DMARDs)," and "High-resolution computed tomography (HRCT)." These terms were selected to ensure comprehensive coverage of studies addressing the relevant interventions and outcomes in RA-ILD. The search strategy in detail is highlighted in detail in **Appendix 1**.

Screening

All articles will be imported into an intelligent systematic review tool, Rayyan (Rayyan Systems Inc), for screening. After deduplication, the records will be independently reviewed by two reviewers to evaluate eligibility based on predefined inclusion and exclusion criteria. Screening will be conducted systematically and sequentially, starting with titles, followed by abstracts, and then full-text assessments. Reasons for excluding studies will be documented at each step of the screening process to ensure transparency. The study selection process will be visually represented using a PRISMA flow diagram.

Data Extraction and Main Data Elements

Two reviewers will independently extract the relevant data elements from the eligible full texts of the articles and will record these variables in a standardized code book. A double extraction method will be used to ensure accuracy and completeness. After data extraction, disparities will be resolved by consensus and discussion with the third reviewer or a “tie-breaker”. Attempts to contact the corresponding authors of the included articles will be made if more information about the individual study data is needed. The following data elements will be extracted: (1) Study title (2) Authors (3) Year of publication (4) Study design (5) Quality score (6) Total sample size (7) Gender distribution (percentage male/female) (8) Mean age (± standard deviation) (9) Duration of RA diagnosis (mean/median, ± standard deviation) (10) Duration of ILD (mean/median, ± standard deviation) (11) Geographic location (country, region if applicable) (12) Data on comorbidities (e.g., cardiovascular disease, diabetes) (13) Baseline lung function parameters (e.g., FVC, FEV1, DLCO with units and baseline values) (13) Comorbidities (e.g., cardiovascular disease, diabetes, smoking history) (14) Name of the anti-fibrotic drug(s) used (e.g., Nintedanib, Pirfenidone) (15) Name of the anti-inflammatory drug(s) used (e.g., methotrexate, TNF inhibitors) (16) Dosage regimen (17) Treatment duration (18) Adverse events related to therapies (e.g., side effects of anti-fibrotic or anti-inflammatory treatments) (19) Qualitative changes in fibrosis patterns (e.g., ground-glass opacities, honeycombing) (20) Effect sizes for outcomes (e.g., mean differences, hazard ratios, odds ratios) (21) Confidence intervals (CIs) and p-values (22) Clinical endpoints (Overall survival (OS), Progression Free Survival (PFS))

The primary outcomes of this study will focus on pulmonary function parameters to evaluate the impact of interventions

on lung function. These include FVC, FEV1, DLCO. For each parameter, both absolute values and percentages of predicted normal will be assessed, alongside changes from baseline to follow-up.

The secondary outcomes will focus on radiological changes evaluated using qualitative changes in high-resolution computed tomography (HRCT) to assess fibrosis patterns, including ground-glass opacities and honeycombing, and to determine the progression, stabilization, or regression of fibrosis. Additionally, clinical endpoint such as overall survival (OS), measured as the time from baseline to death from any cause, will be studied. Lastly, safety and tolerability will be assessed by monitoring adverse events related to the therapies used in the study. The key primary and secondary outcomes of the study are highlighted in **Table 2**.

Table 1: PECOS Criteria for Systematic Review on RA-ILD Therapies

PECOS Criteria	Details
Population (P)	Adult patients (≥18 years) diagnosed with Rheumatoid Arthritis (RA) and confirmed Interstitial Lung Disease (ILD) via radiological or histopathological findings.
Exposure (E)	Anti-fibrotic therapy for the treatment of RA-associated ILD.
Comparator (C)	Anti-inflammatory therapy for the treatment of RA-associated ILD.
Outcomes (O)	Change in lung function parameters (e.g., forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], and diffusing capacity for carbon monoxide [DLCO]), and changes observed on high-resolution computed tomography (HRCT).
Study Design (S)	Included: Studies that compare the efficacy of anti-fibrotic versus anti-inflammatory therapies, including randomized controlled trials (RCTs), cohort studies, and observational studies. Excluded: Case studies, case reports, abstract-only studies, reviews, editorials, short communication, and opinion articles

Table 2: Key Primary and Secondary Outcomes of the Study

Outcome Type	Outcome	Details
Primary Outcomes	Pulmonary Function Parameters	- Forced Vital Capacity (FVC) - Forced Expiratory Volume in 1 Second (FEV1) - Diffusing Capacity for Carbon Monoxide (DLCO)
Secondary Outcomes	Radiological Changes (HRCT)	- Evaluate fibrosis regression, stabilization, or progression through high-resolution computed tomography (HRCT) scans.
	Clinical Endpoints	- Disease progression rates - Frequency of exacerbations - Overall survival - Quality of life measures
	Safety and Tolerability	- Adverse events related to the therapies

Quality or Risk of Bias Assessment

The quality of the included studies will be assessed using the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool [18]. Two independent reviewers will evaluate the full texts and score them separately. Inter-rater agreement will be measured using Kappa statistics. The NHLBI tool consists of 14 checklist items that cover all key components of original research studies. Based on the tool's guidelines, the quality will be rated as poor (0–4 out of 14), fair (5–10 out of 14), or good (11–14 out of 14).

Statistical Plan

The initial results of all the studies ultimately included in the analysis will be summarized in a concise table. The pooled effect estimates, along with their 95% confidence intervals (CIs), will be calculated using Comprehensive Meta-Analysis software (version 3.0; Biostat). Given the expected heterogeneity across the included studies, a random-effects model will be used to compute the pooled estimates, as it provides a more robust approach by accounting for variability between studies.

To evaluate heterogeneity, both Cochran's Q test and the I^2 statistic will be applied. These measures will help determine the extent of variability that is due to true differences across studies, rather than being attributable to random chance. Cochran's Q test will assess the overall heterogeneity, while the I^2 statistic will quantify the proportion of total variation across studies that is due to differences in study outcomes.

If a sufficient number of studies are available, subgroup analyses will be performed to examine the influence of moderator variables such as sociodemographic factors, country, and types of interventions on the outcomes. Additionally, sensitivity analyses will be conducted to determine if any individual studies have an outsized effect on the pooled estimates.

To assess publication bias, a funnel plot will be created, and Egger's linear regression test will be conducted. The significance level for all tests will be set at a two-sided p-value of < 0.05. In the meta-analysis, effect sizes will be presented using standardized mean differences (SMDs) for continuous outcomes and risk ratios (RRs) for dichotomous outcomes. SMDs will allow for the comparison of effect sizes across studies with different measurement scales, while RRs will quantify the likelihood of an outcome occurring in the treatment group relative to the control group. Forest plots will be utilized to visually represent the effect estimates and their associated confidence intervals, providing a clear depiction of the pooled results.

RESULTS:

Table 3: Timeline for Systematic Review and Meta-Analysis Tasks

Tasks	Aug 2024	Sep 2024	Oct 2024	Nov 2024	Dec 2024	Jan 2025	Feb 2025	Mar 2025	Apr 2025	May 2025	Jun 2025	Jul 2025	Aug 2025
Initial design and searches	✓	✓											
Screening of duplicates and titles			✓	✓									
Screening of abstracts					✓	✓							
Screening of full-text articles							✓	✓					
Search references of									✓				

included studies													
Data extraction										✓	✓		
Synthesis and risk of bias assessment											✓	✓	
Analysis												✓	
Abstract and manuscript drafting													✓
Submission to conferences and peer-reviewed journals													✓

DISCUSSION:

Overview

RA-ILD represents a complex and challenging aspect of managing patients with RA. This systematic review and meta-analysis aims to comprehensively assess the efficacy of anti-fibrotic and anti-inflammatory therapies in patients with chronic RA-ILD, highlighting the comparative benefits and limitations of these therapeutic strategies. The prevalence of RA-ILD is significant, and its clinical presentation varies widely. Given the complexity and heterogeneity of RA-ILD, it is imperative to tailor treatment strategies based on the underlying pathophysiology and patient characteristics.

Diagnostic Imaging in RA-ILD:

RA-ILD can be diagnosed based on the histopathologic and imaging features. The most common subtype of RA-ILD is usual interstitial pneumonia (UIP), which is characterized by fibrosis and is associated with poor prognosis. There is growing evidence to support differentiating UIP from non-UIP pattern in patients with RA-ILD due to differences in clinical outcomes [19][20]. The prognosis of RA-ILD patients with UIP pattern is poorer than patients with non-UIP patterns [21]. RA-ILD patients with UIP tend to be older individuals and seem to be less responsive to conventional treatment compared to patients without RA-ILD [22][23]. HRCT serves as a reliable tool for accurate identification of the histopathologic UIP pattern, with a positive predictive value of 95% (19 out of 20 cases) [24]. The presence of definite HRCT UIP pattern characterized by basal and subpleural interstitial reticulations, fibrosis, traction bronchiectasis, and honeycombing exhibit a specificity of 96% (26 out of 27 cases) and a sensitivity of 45% (19 out of 42 cases) in relation to histopathologic UIP pattern [24]. Nonspecific interstitial pneumonia (NSIP) is also common in some patients with RA-ILD. NSIP is characterized by parenchymal inflammation and has a better prognosis compared to UIP. Other less common RA-ILD subtypes include lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonia (AIP), organizing pneumonia (OP), desquamative interstitial pneumonia (DIP), and respiratory bronchiolitis ILD (RB-ILD) [25]. In most cases, radiographic imaging in the form of HRCT is sufficient to identify the underlying fibrosis pattern, and surgical biopsy is reserved only for patients in whom radiographic imaging is not diagnostic [26].

Strengths and Limitations

This systematic review has several strengths, including a comprehensive evaluation of the literature and rigorous methods to assess study quality and minimize biases. However, limitations exist. One major challenge is the heterogeneity among the studies, stemming from differences in methodologies, settings, interventions, diets, and outcome measures, which may impact the consistency of findings. Reviewer bias is another concern, but we will address this by using standardized risk of bias tools for each study and conducting sensitivity analyses to assess the impact of low-quality studies on the overall results. To further ensure objectivity, we will seek input from subject matter experts and maintain transparency throughout the process.

Another limitation is the potential for missing relevant studies despite a broad search strategy developed with the help of a medical librarian. This risk could affect the completeness of the review. Additionally, publication bias may skew

results, as studies with positive outcomes are more likely to be published. To address this, we will assess publication bias through funnel plots and Egger's regression test, helping to ensure a balanced and accurate interpretation of the evidence.

Dissemination Plan

The findings from this systematic review will be disseminated through a peer-reviewed journal article and presentations at academic conferences.

Conclusions

This study will provide a comprehensive review comparing the anti-fibrotic and anti-inflammatory therapies in the management of chronic RA-ILD. This study will include data on treatment efficacy, patient outcomes, radiologic progression, symptom burden, and quality of life for patients with RA-ILD comparing anti-fibrotic and anti-inflammatory therapies, and thereby, offering insights for the management of chronic RA-ILD.

ACKNOWLEDGEMENTS*:*

We would like to acknowledge Ana Coral, librarian at the Kirk Kerkorian School of Medicine at the University of Nevada (UNLV) Library for her support in formulating the search terminology for database search.

CONFLICT OF INTEREST*:*

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FUNDING:

None

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DATA AVAILABILITY:
The data analyzed in the study will be available upon request from the corresponding author.

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Supplementary Files

Multimedia Appendixes

Research Query For Database Search.
URL: http://asset.jmir.pub/assets/b5efe2f5f3abfd55a8a3e8de31a27e38.docx

Prisma-P Checklist.
URL: http://asset.jmir.pub/assets/3f9e27228d56cde813c91da684fa0d7e.docx