

Rheumatoid Arthritis Interstitial Lung Disease: Treating the Trajectory, Not the Pattern

Tsvetoslav Georgiev^{1,2}, Stoimen Dimitrov^{1,2*}, Konstantin Batalov^{3,4},
Zguro Batalov^{3,4}, Rositsa Karalilova^{3,4}, Anastas Batalov^{3,4}

1. Clinic of Rheumatology, UMHAT "St. Marina", Varna, Bulgaria
2. Department of Cardiology and Rheumatology, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, Varna, Bulgaria
3. Clinic of Rheumatology, UMHAT "Kaspela", Plovdiv, Bulgaria
4. Department of Propedeutics of Internal Medicine "Prof. Dr. Anton Mitov", Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria

* Correspondence:

Stoimen Dimitrov
Department of Cardiology and Rheumatology, Faculty of Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" – Varna
Varna, Bulgaria
Email: stoimen2000@gmail.com
ORCID: 0009-0007-0559-8506

Running title: RA-ILD: Treating the Trajectory, Not the Pattern

Abstract

Rheumatoid arthritis-associated interstitial lung disease [RA-ILD] requires more than a radiological diagnosis. A usual interstitial pneumonia pattern describes pulmonary architecture, but does not by itself establish whether disease is progressing, which component is modifiable, or how safely treatment can be deferred. This narrative review revisits the disease-behaviour approach and distinguishes susceptibility to ILD, prognosis after ILD develops, and prediction of treatment benefit. It integrates contemporary classification and guidance with evidence from immunomodulatory cohorts, INBUILD, TRAIL1 and FIBRONEER-ILD. We propose a reserve-aware interpretation of trajectory: structural burden and the pace of deterioration should be considered alongside remaining physiological reserve, competing hazards and the likely cost of waiting. This is a clinical reasoning framework, not a validated score. Progressive

Received: Sep 12th, 2026
Accepted: Sep 24th, 2026
Published: Sep 30th, 2026
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How to cite: Georgiev, T., Dimitrov, S., Batalov, K., Batalov, Z., Karalilova, R., & Batalov, A. [2026]. Rheumatoid Arthritis Interstitial Lung Disease: Treating the Trajectory, Not the Pattern. *Rheumatology [Bulgaria]*, 34(3), 249-279. <https://doi.org/10.35465/bvq04536>



pulmonary fibrosis provides a useful operational definition, but should neither be mistaken for proof of an exclusively fibrotic mechanism nor become a prerequisite for treating already consequential lung disease. Molecular advances, including MUC5B, telomere length and protein signatures, illustrate the distance between biological plausibility and treatment selection. Antifibrotic evidence supports slowing functional loss; newer survival analyses require careful separation of overall pulmonary fibrosis populations from RA-specific inference. The therapeutic objective is therefore not to treat an imaging label or normalise an isolated measurement, but to preserve useful lung function while controlling systemic disease and limiting treatment-related harm.

Keywords: rheumatoid arthritis, interstitial lung disease, pulmonary fibrosis, disease progression, antirheumatic agents, precision medicine

1. Introduction

Associated with rheumatoid arthritis (RA) interstitial lung disease (RA-ILD) is among the most severe extra-articular manifestations of RA, encompassing a heterogeneous spectrum of inflammatory and fibrotic parenchymal lung disease with markedly variable clinical trajectories [1,2]. Although high-resolution computed tomography (HRCT) patterns, particularly usual interstitial pneumonia (UIP), retain diagnostic and prognostic importance, morphology alone does not define disease behaviour. This distinction is formalized by the concept of progressive pulmonary fibrosis (PPF), which describes progression in an ILD other than idiopathic pulmonary fibrosis by the development, within one year and without an alternative explanation, of at least two of three domains: worsening respiratory symptoms, physiological progression, and radiological progression [3].

The central challenge in RA-ILD is therefore no longer simply to identify and name an imaging pattern, but to determine which patient is at risk, which lung is truly progressing, and when that trajectory warrants therapeutic intervention. The historical association between RA-ILD and excess mortality established the importance of pulmonary involvement; it did not establish that every interstitial abnormality has the same prognosis or requires the same intervention [4].

A useful starting point predates the current enthusiasm for progressive pulmonary fibrosis. The 2013 American Thoracic Society/European Respiratory Society (ATS/ERS) classification already incorporated disease behaviour, recognising that management sometimes depends on observed

course when a diagnostic label is insufficient. The 2025 ERS/ATS update extends classification beyond idiopathic disease, distinguishes fibrotic from non-fibrotic interstitial disorders and explicitly incorporates diagnostic confidence. These developments refine morphology rather than displace it. A pattern remains indispensable for understanding the lung; it becomes misleading when asked to function as a complete treatment algorithm [5,6].

Three questions must therefore remain separate: what disease is present, what is likely to happen, and what a particular treatment is likely to change. Neither a poor prognostic marker nor a plausible pathogenic mechanism automatically predicts treatment benefit. Current guidance from the American College of Rheumatology/American College of Chest Physicians (ACR/CHEST) and the ERS/European Alliance of Associations for Rheumatology (EULAR) provides a necessary clinical scaffold, but much RA-specific treatment evidence remains conditional and of low or very low certainty. The absence of a simple hierarchy reflects the evidence, not a failure to recognise the correct radiological pattern [7,8].

We use 'treating the trajectory' in a deliberately qualified sense. It means interpreting change in the context of baseline burden, remaining reserve and treatment risk, not waiting for every patient to deteriorate before acting. A severely impaired patient should not have to lose additional lung function merely to make the need for treatment easier to document. Conversely, a fibrotic image in a patient with preserved function and a convincingly stable course is not, by itself, proof that immediate escalation will offer net benefit. The central task is to identify clinically consequential, potentially modifiable disease without confusing vigilance with overtreatment.

2. Beyond UIP and NSIP: What Actually Defines Risk?

Non-specific interstitial pneumonia (NSIP) and UIP describe different morphological organisations of injury, not self-sufficient risk categories. In a cohort of 137 patients with RA-ILD, baseline forced vital capacity (FVC) and its subsequent decline were important mortality predictors, whereas the HRCT pattern did not retain independent prognostic significance in the adjusted model. This does not render UIP unimportant; it shows why physiology and change can substantially modify the information contained in a pattern [9].

The same distinction is essential when interpreting molecular data. The mucin 5B (MUC5B) promoter variant is strongly associated with susceptibility to RA-ILD, particularly UIP, yet a subsequent RA-ILD cohort

did not establish an association with survival or progression. A susceptibility allele should not quietly become a progression biomarker, still less an indication for antifibrotic therapy. The relevant denominator changes once every patient in the clinic already has ILD [10,11].

Recent biomarkers sharpen, rather than solve, this problem. In a 2025 prospective study of 101 patients, short leukocyte telomeres were associated with more progression events, but the adjusted estimate was imprecise and its confidence interval included unity (odds ratio 2.80; 95% confidence interval 0.99-8.29). A 2026 blood-protein study reported diagnostic discrimination using CXCL9, CXCL13 and TIMP-1, not prospective prediction of progression or treatment response. Neither observation currently supplies a validated molecular rule for choosing immunomodulation over an antifibrotic [12,13].

Disease activity requires equally careful interpretation. Prospective evidence associates greater rheumatoid arthritis activity with incident clinically apparent ILD. This supports attention to systemic inflammation, but it is not equivalent to demonstrating that lowering an articular activity score will reverse established pulmonary fibrosis. Susceptibility, prognosis and treatment responsiveness are related research questions; their endpoints are not interchangeable [14].

2.1 Burden, tempo and reserve

For clinical decisions, the most useful distinction is between the amount of lung already affected, the speed of change and the patient's capacity to tolerate further loss. HRCT defines distribution and structural extent; serial physiology describes functional consequences; symptoms and exercise-related limitations place these measurements in the patient's life. None is sufficient in isolation. We propose considering these domains alongside plausible treatment responsiveness and competing harms (Figure 1). This is an explicit reasoning framework, not a new prognostic score or validated treatment threshold.

A practical decision framework for RA-ILD
Beyond radiologic pattern alone

Domain	Question for the multidisciplinary team	What the answer does not establish
 Structural Burden	How much lung is affected, and by which morphological processes?	A UIP label alone does not establish current progression or treatment responsiveness.
 Tempo	Is deterioration reproducible, attributable to ILD and evident across relevant domains?	A threshold crossing does not identify the mechanism of deterioration.
 Remaining Reserve	How much further functional loss can this patient tolerate?	Low reserve does not distinguish antifibrotic-responsive from immune-responsive disease.
 Modifiability and competing harm	Which component might treatment change, and at what infectious, systemic and tolerability cost?	Biological plausibility and prognostic association do not prove a favourable treatment effect.

Figure 1. A trajectory-based multidisciplinary decision framework for Rheumatoid Arthritis-Associated Interstitial Lung Disease [RA-ILD]. Moving beyond static radiologic classifications, this approach redirects clinical evaluation toward four dynamic domains: structural burden, tempo of disease progression, remaining physiologic reserve, and modifiability versus competing harms. The framework outlines key questions for multidisciplinary teams while explicitly defining the clinical limitations of each domain's assessment, emphasizing that comprehensive disease trajectory - rather than an isolated histopathologic or radiologic pattern - must drive therapeutic decision-making. Abbreviations: RA-ILD, Rheumatoid Arthritis-Associated Interstitial Lung Disease; ILD, Interstitial Lung Disease; UIP, Usual Interstitial Pneumonia; NSIP, Non-Specific Interstitial Pneumonia. Created in BioRender. Dimitrov, S. [2026] <https://BioRender.com/c5xllss>.

A hypothetical comparison illustrates the point. Two patients may both have UIP and the same recent FVC decline, yet the cost of another small loss may differ substantially when one has preserved gas exchange and the other has little functional reserve. Conversely, extensive but stable fibrosis does not prove that additional immunosuppression can recover the missing reserve. Low reserve increases urgency; it does not identify the correct drug. Decisions must address both what is dangerous and what is plausibly modifiable.

Preserved reserve does not justify deferral once progression is objectively documented and not attributable to infection, airway disease or measurement variability (Sections 2.2 and 6.2). Its principal role in timing is confined to marginal, single-domain or technically uncertain change, in which preserved reserve may permit a short, prespecified confirmatory interval and limited reserve favours earlier intervention. Reserve additionally informs treatment intensity and the acceptable level of treatment-related risk.

2.2 Progression is a definition, not a mechanism

The 2022 ATS/ERS/JRS/ALAT definition of progressive PPF, in fibrotic ILD other than idiopathic pulmonary fibrosis (IPF), requires at least two of three domains within the preceding year, without another explanation: worsening respiratory symptoms, physiological progression or radiological progression. The physiological component is an absolute FVC decline of at least 5 percentage points predicted or an absolute decline in haemoglobin-corrected diffusing capacity for carbon monoxide (DLCO) of at least 10 percentage points predicted. A decrease from 80% to 75% predicted is five percentage points, not a 5% relative decline. Two physiological abnormalities still constitute one domain, not two [3].

The one-year interval is an observation window, not a requirement to postpone a decision for twelve months. Nor should the PPF definition be confused with every trial's entry criterion: INBUILD used a different, 24-month progression framework. Validation studies show that deterioration, particularly a relative FVC decline of at least 10%, identifies a poor-prognosis population across non-IPF fibrotic ILDs [15]. Prognostic discrimination, however, is not the same as demonstrating that a threshold uniquely predicts response to a given drug. PPF describes behaviour; it does not establish that inflammation has disappeared or that every competing cause of deterioration is fibrotic [3,16].

2.3 Stability needs a denominator and a time horizon

The 2026 BERTHA cohort provides a useful warning against equating stable average physiology with an event-free course. Among 95 patients with predominantly mild RA-ILD, group-level function and quantitative imaging remained broadly stable over 24 months, yet eight patients died; pulmonary infections accounted for four deaths. These data cannot establish that a particular therapy caused those events, and group averages should not be read as individual trajectories. They do show why infection, hospitalisation and survival must remain visible when a treatment appears successful by FVC alone [17].

Observation should consequently specify both the next assessment and the event that would bring it forward. ACR/CHEST suggests pulmonary function testing every 3-12 months in RA-ILD during the first year, with subsequent frequency tailored to stability; HRCT is appropriate when clinically indicated. Within that range, uncertain or changing disease and limited reserve argue for closer review. An unexpected result should prompt assessment of measurement quality and alternative explanations, not automatic acceptance or dismissal. 'Stable' should mean stable across a defined period and relevant domains, not simply no complaint at the last appointment [18].

3. The Silent Lung: Whom Should We Screen?

ILD represents one of the most frequent and severe extra-articular manifestations of RA, yet it remains notoriously subclinical and insidious during its early stages [19]. A substantial proportion of patients with RA - ranging from 15% in early-onset cohorts up to 50% in established disease - harbor subclinical ILD or interstitial lung abnormalities (ILAs) detectable on HRCT, despite reporting no overt respiratory symptoms [20,21]. This "silent" nature is further compounded by joint pain and functional physical impairment, which frequently mask exertional dyspnea and lead to marked diagnostic delays [22]. Given that established RA-ILD carries a three-fold increase in overall mortality and constitutes a leading cause of non-articular death [23,24], identifying pulmonary involvement before extensive, irreversible fibrotic remodeling occurs has become a paramount clinical goal.

3.1 The Case Against Universal Screening

Despite the high prevalence and substantial prognostic impact of subclinical pulmonary involvement, universal HRCT screening for all unselected RA patients is currently not recommended by international consensus guidelines [25–27]. As emphasized by the French Society of Rheumatology (SFR) guidelines, RA-ILD does not currently fulfill the classical World Health Organization (WHO) criteria for universal screening programs, as there is a lack of high-level evidence demonstrating that early therapeutic intervention in asymptomatic, unselected cohorts improves long-term survival or alters overall disease trajectory [26]. This conservative stance is strongly reinforced by the joint ERS and EULAR clinical practice guidelines, which refrain from universal radiological screening and suggest instead that screening be considered only in RA patients exhibiting specific risk profiles [25]. Longitudinal studies demonstrate that a significant proportion of subclinical ILDs or ILAs remain stationary over extended

follow-up without requiring immediate immunomodulatory or antifibrotic management [20]. Furthermore, unselected radiological screening carries significant drawbacks, including the overdiagnosis of non-progressive or clinically trivial lesions, increased patient anxiety, unnecessary downstream procedures for incidental findings, and substantial economic and radiation burdens on healthcare systems [26].

3.2 Targeted Screening and Risk Stratification

Consequently, current clinical consensus advocates for a risk-stratified, targeted screening approach focused on identifying RA patients at the highest risk for developing progressive ILD [28]. The 2023 ACR]/ CHEST guidelines as well as the joint ERS/EULAR guidelines conditionally recommend screening high-risk individuals, highlighting that screening decisions should be tailored through shared decision-making between rheumatologists and patients [25,27]. This enriched risk profile for RA-ILD encompasses a complex interplay of demographic, clinical, serological, and genetic predictors. Demographically, older age at RA onset (60 years), male sex, and a significant history of cigarette smoking (10-13 pack-years) constitute established non-modifiable and environmental vulnerability factors [20,29]. From a clinical and serological standpoint, risk is strongly driven by high articular disease activity [marked by sustained elevations in DAS28 or CDAI scores, elevated acute-phase reactants (CRP and ESR), high-titer rheumatoid factor (RF), high-titer anti-citrullinated protein antibodies (anti-CCP/ACPA), and the presence of severe extra-articular manifestations such as rheumatoid nodules [30,31]. At the molecular level, genetic predisposition plays a pivotal role, particularly the *MUC5B* promoter gain-of-function variant (rs35705950) - which markedly increases the odds of subclinical ILD and a usual interstitial pneumonia (UIP) pattern - alongside short leukocyte telomeres and elevated serum biomarkers such as Krebs von den Lungen-6 (KL-6), surfactant protein D (SP-D), and matrix metalloproteinase-7 (MMP-7) [32,33].

3.3 Evaluation Modalities: Roles and Limitations

When implementing targeted screening in high-risk or clinically suspicious patients, a multimodal diagnostic strategy is essential to overcome the limitations inherent to any single modality. Clinicians must maintain a high index of suspicion for subtle respiratory complaints, such as dry cough, unexplained exertional dyspnea, or exercise intolerance [19,22]. On physical examination, the presence of fine, dry, inspiratory "Velcro-like" crackles at the lung bases serves as a classic diagnostic clue; however, while highly specific, lung auscultation alone lacks sufficient sensitivity for early

detection [34]. Baseline pulmonary function tests (PFTs) - comprising spirometry, plethysmographic lung volumes, and DLCO - provide vital objective measurements [28]. However, ERS/EULAR guidelines explicitly recommend against replacing HRCT with PFTs alone for screening, as physiological testing frequently misses early subclinical ILD when FVC and DLCO values remain within normal predicted limits despite visible parenchymal involvement on imaging [25].

To address these diagnostic gaps, HRCT stands as the gold-standard modality for detecting, quantifying, and pattern-categorizing RA-ILD [35]. Accordingly, the ACR/CHEST guidelines conditionally recommend combining HRCT with full PFTs over PFTs or clinical examination alone to maximize diagnostic sensitivity in high-risk individuals [27], with low-dose volumetric HRCT protocols increasingly advocated to minimize radiation exposure while preserving diagnostic quality. Furthermore, ERS/EULAR conditionally recommends against replacing HRCT with lung ultrasound (LUS), noting that point-of-care sonography remains highly operator-dependent and non-specific for ILD [25]. Conventional modalities and invasive procedures offer minimal screening value: standard chest radiography exhibits poor sensitivity for early interstitial changes, while routine screening using the 6-minute walk distance (6MWD), ambulatory desaturation testing, bronchoscopy, or invasive lung biopsy is strongly or conditionally discouraged across international guidelines. Indeed, both ACR/CHEST and ERS/EULAR explicitly suggest that lung biopsy has no diagnostic role for routine screening, and restrict bronchoalveolar lavage (BAL) strictly to scenarios where infection, malignancy, or alternative etiologies must be excluded [25,27].

4. When Does RA-ILD Need Treatment?

The decision to initiate, defer, or escalate pharmacological therapy for RA-ILD represents a complex clinical challenge, primarily due to the heterogeneous disease trajectory and a historical lack of dedicated randomized controlled trials. Recently, however, expert consensus and the first joint ERS and EULAR clinical practice guidelines have provided a more structured framework for therapeutic triage [25,36]. Treatment decisions must be highly individualized through multidisciplinary discussion, balancing the severity and progression rate of the pulmonary involvement against the activity of the articular disease, while remaining cognizant of the potential pulmonary toxicity or immunosuppressive risks associated with systemic therapies [37]. In contemporary practice, patient

management can be broadly conceptualized into three distinct clinical paradigms: observation, immunomodulation, and antifibrotic escalation.

For a substantial subset of patients with subclinical, mild, or non-progressive RA-ILD, a strategy of watchful observation is considered appropriate. Current guidelines suggest that in the absence of respiratory symptoms, significant physiological impairment, or documented radiological progression, specific pulmonary-targeted interventions may be deferred [25–27]. In these scenarios, the primary therapeutic objective is the strict control of the underlying rheumatoid arthritis, as sustained articular inflammation is an independent predictor of ILD progression [38]. During this observation phase, routine surveillance with pulmonary function tests is mandated, and conventional or targeted synthetic disease-modifying antirheumatic drugs (DMARDs) should be optimized. Notably, historical concerns regarding methotrexate-induced pneumonitis have been largely re-evaluated; recent evidence indicates that methotrexate does not inherently increase the risk of ILD progression and may safely be continued in stable disease [37].

When patients exhibit clinically significant, symptomatic ILD, or manifest a predominantly inflammatory radiological phenotype (such as non-specific interstitial pneumonia or organizing pneumonia), immunomodulatory therapy constitutes the first-line approach [39]. The ERS/EULAR guidelines conditionally recommend immunosuppressive treatment for RA-ILD, though it is explicitly noted that this recommendation rests on a very low certainty of evidence derived mostly from retrospective cohorts and extrapolation from other connective tissue diseases [25]. Glucocorticoids are frequently utilized to induce initial disease control, but their long-term use must be strictly minimized to avert cumulative toxicity and increased infection risk [37]. As a steroid-sparing strategy, biological DMARDs - particularly rituximab and abatacept - are increasingly preferred. Retrospective data and indirect trial evidence suggest these agents can stabilize or modestly improve lung function with an acceptable safety profile, whereas tumor necrosis factor inhibitors (TNFi) are generally approached with caution due to conflicting reports regarding potential pulmonary exacerbations [40]. The role of targeted synthetic DMARDs, such as Janus kinase (JAK) inhibitors, remains an area of active investigation [41]. Conversely, the novel phosphodiesterase-4B (PDE4B) inhibitor nerandomilast has recently demonstrated robust Phase III prospective clinical efficacy in autoimmune disease-related progressive pulmonary fibrosis (autoimmune ILD/PPF) - with RA-ILD as the largest subgroup - significantly slowing FVC decline and reducing mortality risk [42,43].

A critical paradigm shift in the management of RA-ILD involves the recognition and targeted treatment of the PPF phenotype, which closely mimics the relentless trajectory of idiopathic pulmonary fibrosis [44]. For patients demonstrating objective functional or radiological decline despite optimal immunomodulation, or for those presenting with a severe usual interstitial pneumonia (UIP) pattern, the escalation to antifibrotic therapy is warranted [45]. Nintedanib is conditionally recommended by ERS/EULAR for any connective tissue disease exhibiting PPF, largely based on the INBUILD trial which demonstrated a significant 59% reduction in the annual rate of forced vital capacity decline in the RA-ILD subgroup [46]. Similarly, pirfenidone may be considered, particularly for RA-ILD patients with a UIP pattern, drawing upon conditional recommendations and data from the prematurely terminated TRAIL1 study [47]. However, clinical expectations must be managed objectively: antifibrotics serve to decelerate disease progression rather than halt or reverse fibrosis, and their efficacy is frequently compromised by dose-limiting gastrointestinal toxicities [48]. While the concomitant use of antifibrotics and immunomodulators appears safe and is increasingly adopted for severe PPF, the optimal timing for initiation - whether sequentially after immunosuppressant failure or as upfront combination therapy in high-risk UIP - remains a subject of ongoing debate and underscores the critical need for further precision-medicine research.

5. Treating the Joint and the Lung as One Disease

Historically, the clinical management of RA-ILD has been hampered by an artificial and counterproductive dichotomy between "rheumatoid arthritis treatment" and "ILD treatment." Contemporary pathobiological insights and clinical evidence demonstrate that articular inflammation and pulmonary interstitial remodeling are systemic manifestations of a singular autoimmune disease process driven by shared immunological drivers [49]. Consequently, effective management requires a unified approach, where systemic rheumatic disease control is viewed as essential for pulmonary stability.

5.1 Re-evaluating Methotrexate: Dismantling Historical Dogma

For decades, MTX was routinely withheld or discontinued in patients with RA-ILD due to persistent concerns regarding drug-induced pneumonitis and purported fibrogenic pulmonary toxicity [50]. However, rigorous modern epidemiological evidence and prospective cohort studies have comprehensively overturned this long-standing dogma [51]. Current data indicate that MTX use is not associated with an increased risk of incident

RA-ILD; in fact, several large-scale longitudinal analyses suggest that MTX exposure may be linked to a lower incidence of ILD and a delayed onset of pulmonary symptoms [52]. Clinicians must carefully distinguish between rare, acute, hypersensitivity-driven methotrexate pneumonitis (MTX-P) and chronic, progressive RA-ILD, as MTX remains a safe and foundational anchor therapy for the majority of stable RA-ILD patients [53].

5.2 Immunomodulatory Hierarchy: Biologics and Targeted Synthetic DMARDs

Because adaptive immunity and autoantibody-mediated pathways - such as ACPA-driven neutrophil activation and local iBALT formation - fuel both synovial destruction and alveolar remodeling, selecting immunomodulatory agents with targeted pulmonary safety profiles is critical [49,54].

Observational data and systematic reviews consistently position non-TNF biologic agents - specifically the T-cell co-stimulation modulator abatacept and the anti-CD20 B-cell depleting agent rituximab - as superior therapeutic options for RA-ILD [55]. Studies have demonstrated that abatacept, in particular, is associated with stable or improved pulmonary function and radiological markers, and may confer a survival advantage compared to other biologics [56,57]. Rituximab similarly demonstrates efficacy in slowing pulmonary function decline in refractory cases, serving as a pivotal agent in complex management scenarios [58]. In contrast, the role of TNFi in RA-ILD remains a subject of clinical caution. Several observational studies have reported associations between TNFi use and disease exacerbation or higher mortality rates, leading many experts to favor switching to abatacept or rituximab in patients with established or progressive ILD [50,58,59]. Emerging evidence for targeted synthetic DMARDs (tsDMARDs) suggests that JAK inhibitors may possess both anti-inflammatory and potential anti-fibrotic properties [60,61]. Recent comparative data indicate a lower incidence of incident ILD with tofacitinib compared to other biologic classes, and in vitro models suggest an additive effect when combined with MTX in modulating fibrotic pathways like epithelial-mesenchymal transition (EMT) [60–62].

5.3 Integrating Antifibrotic Therapy

When pulmonary fibrosis acquires autonomous momentum and progresses despite optimal immunomodulation, treatment must incorporate targeted antifibrotic therapy [63,64]. Nintedanib has demonstrated robust efficacy in decelerating the annual decline of FVC in patients with PPF, including a distinct subgroup of RA-ILD patients [53,64,65]. Antifibrotics should be

utilized not solely based on a radiological UIP label, but rather as a strategy to arrest an objectively progressive fibrotic trajectory in patients failing first-line immunomodulation [53,66]. Future management strategies will likely rely on a personalized, multidisciplinary framework where the intensity of immunomodulation is calibrated to systemic articular activity, while antifibrotic escalation is triggered by the functional and radiological behavior of the lung.

6. The Clinical Traps

6.1 Not Every Ground-Glass Opacity Is Inflammation

A pervasive clinical misconception in RA-ILD is the automatic conflation of ground-glass opacity (GGO) on high-resolution computed tomography (HRCT) with active, steroid-responsive inflammation. While pure GGO in a non-specific interstitial pneumonia (NSIP) pattern can represent cellular alveolar infiltration, GGO is fundamentally an attenuation marker reflecting non-specific volume averaging of alveolar septal thickening and partial alveolar filling [67]. In patients with pre-existing fibrotic architecture, GGO may represent fine intralobular fibrosis below the threshold of macroscopic resolution, microatelectasis, or traction-induced alveolar collapse rather than active alveolitis [67].

The diagnostic stakes are highest during acute or subacute respiratory worsening, where the emergence of new bilateral GGOs superimposed on chronic reticulation or honeycombing typically heralds an acute exacerbation (AE) of RA-ILD [68]. Pathobiologically characterized by diffuse alveolar damage (DAD) rather than benign inflammatory progression, AE carries a catastrophic in-hospital mortality rates [69]. Because international diagnostic criteria mandate that AE is a diagnosis of exclusion, clinicians must not reflexively treat new GGOs with intensified immunosuppression without first systematically ruling out competing etiologies. In immunocompromised RA cohorts, opportunistic infections - particularly *Pneumocystis jirovecii* pneumonia and respiratory viral infections - present with identical diffuse GGO patterns [49]. Similarly, cardiogenic pulmonary edema, aspiration pneumonitis, and hypersensitivity-driven drug toxicity [such as acute methotrexate pneumonitis] can closely mimic acute interstitial exacerbation [67]. Furthermore, patients with an underlying UIP pattern exhibit a substantially higher vulnerability to developing superimposed DAD and GGO-associated acute deterioration compared to non-UIP phenotypes [68,69]. Consequently, interpreting GGO demands a rigorous multi-tier

evaluation incorporating microbiology, cardiac function assessment, and chronological trajectory rather than an immediate assumption of treatable parenchymal inflammation.

6.2 Not Every FVC Decline Is ILD Progression

FVC is widely regarded as the cornerstone physiological metric for tracking disease behavior and defining PPF [70]. However, in rheumatoid arthritis, reflexively equating a declining FVC with accelerating interstitial parenchymal fibrosis represents a major diagnostic trap [71]. Because RA is a multicompartmental pulmonary disorder, spirometric volume loss is frequently driven by airway pathology, extraparenchymal mechanics, or mixed ventilatory defects rather than pure interstitial fibrotic remodeling [72].

Airway disease is exceptionally prevalent in RA, affecting between 30% and 60% of patients across large series [72]. Distal airway complications - most notably follicular bronchiolitis, constrictive (obliterative) bronchiolitis, and bronchiectasis - cause severe peripheral airflow obstruction, inflammatory luminal plugging, and dynamic hyperinflation [71]. In these scenarios, air trapping and premature airway closure at low lung volumes compress vital capacity, resulting in a spurious FVC decline that masquerades as restrictive disease progression. Similarly, in patients with a history of tobacco exposure, the syndrome of combined pulmonary fibrosis and emphysema (CPFE) introduces complex physiological antagonism: hyperinflation from emphysematous upper lobes counterbalances the volume loss of basilar fibrosis, causing FVC to remain spuriously preserved or to fluctuate unpredictably even as gas exchange (DLCO) deteriorates precipitously [70,72,73].

Extraparenchymal RA manifestations further compromise spirometric reliability. Recurrent rheumatoid pleural effusions, pleural thickening, chest wall restriction from costochondral and thoracic joint involvement, and cricoarytenoid arthritis can each depress FVC independently of parenchymal status [19,72]. Moreover, recent prospective findings from the multicenter BERTHA cohort demonstrate that in mild RA-ILD, group-level FVC and quantitative CT densitometry can remain completely stable over 24 months despite significant mortality from acute pulmonary infections and systemic comorbidities, confirming that fatal events often occur without preceding measurable FVC loss [74]. Conversely, meta-analytic data across targeted therapies (b/tsDMARDs) show overall functional stabilization across broad cohorts [75]. Therefore, an isolated drop in FVC should never trigger an uncritical escalation of antifibrotic or

immunosuppressive therapy; clinicians must first perform plethysmographic lung volume measurements, assess DLCO, and evaluate serial HRCT scans to isolate true parenchymal fibrosis progression from confounding airway or extraparenchymal derangements.

6.3 Stable Arthritis Does Not Imply Stable Lung Disease

In clinical practice, achieving articular remission is often falsely equated with complete disease quiescence. However, articular and pulmonary trajectories frequently decouple; patients with mild or oligosymptomatic joint involvement can still harbor significant pleuropulmonary disease [76].

While high systemic inflammatory activity strongly predisposes to interstitial lung involvement in both early and established disease [77], pulmonary damage often develops insidiously within the initial years of arthritis [78]. Longitudinal cohorts show that approximately 50% of RA-ILD patients exhibit progressive fibrotic remodeling on HRCT over 1.5 to 3 years, frequently despite quiescent arthritis [79,80]. This occurs because established pulmonary fibrosis often transitions from an immune-driven phase into an autonomous, self-sustaining fibroproliferative process governed by baseline structural extent and a UIP pattern rather than ongoing joint inflammation [79,80]. Consequently, while controlling synovitis is essential, articular remission alone does not guarantee pulmonary stability, making structured lung surveillance mandatory regardless of joint control.

6.4 UIP in RA Is Not Simply IPF with Arthritis

The radiological and histopathological appearance of UIP in RA has frequently led to the reductionist view that RA-UIP is merely IPF occurring in a patient who happens to have joint disease [81,82]. While both entities share demographic vulnerabilities [older age, male sex, smoking], fibrotic pattern, and specific genetic risks - most notably the *MUC5B* promoter variant [rs35705950] and telomere shortening [83,84] - treating them as biological equivalents ignores fundamental immunopathological divergence.

Histopathologically, RA-UIP exhibits prominent autoimmune features that are absent in IPF, including dense lymphocytic infiltration within myofibroblastic foci, extensive bronchus-associated lymphoid tissue (BALT) hyperplasia, and local immune complex deposition [81,85]. Genome-wide pleiotropy and proteomic profiling confirm that RA-UIP is uniquely driven by shared immune-regulatory loci (such as *IRF5*, *ANKRD55*, and *ALDH2*) and molecular signatures enriched in CD4⁺ effector T-cell

programs and neutrophil-mediated tissue damage [84,86]. Although localized anti-modified protein antibodies (AMPA) and anti-CCP can be detected in the bronchoalveolar lavage of some IPF patients - where they paradoxically delineate a younger, less progressive subgroup [87,88] - RA-UIP is characterized by broad, multivalent systemic autoimmunity [89]. Furthermore, Mendelian randomization demonstrates that alveolar injury in UIP-susceptible lungs actively promotes the breakdown of mucosal immune tolerance to citrullinated antigens, establishing a causal pathogenic link between pulmonary damage and seropositive RA rather than a coincidental overlap [82].

Prognostically, the apparent survival advantage of RA-UIP over IPF is largely driven by earlier diagnostic capture; once adjusted for age and baseline DLCO, fibrotic progression and acute exacerbation risks become comparable [90,91]. Crucially, the therapeutic paradigms remain distinct: while immunosuppression increases mortality in IPF, targeted immunomodulation remains a viable first-line approach in inflammatory or early RA-UIP, with antifibrotics reserved or added sequentially when an autonomous, progressive fibrosing phenotype emerges [81,90]. Equating the two conditions risks withholding effective immunomodulatory therapy in early disease or inappropriately applying IPF-specific treatment algorithms to an autoimmune disorder.

6.5 Observation Without Predefined Follow-Up Is Not a Strategy

Observation or "watchful waiting" is an established and rational clinical approach in patients with mild, subclinical, or seemingly stable RA-ILD, designed to avoid unnecessary or premature therapeutic escalation [92]. However, the clinical challenge arises when observation becomes purely passive - relying solely on the emergence of patient-reported respiratory symptoms or routine physical examination before re-evaluating disease status [93]. Because subclinical interstitial lung changes occur in up to 35% of RA patients, symptom-based questionnaires (such as mMRC or VAS cough) exhibit modest sensitivity (40% to 60%), and conventional chest radiographs miss the vast majority of early fibrotic changes [92,94,95]. Consequently, passive waiting risks undetected functional and anatomical decline before clinical deterioration is recognized.

Because approximately 40% to 55% of RA-ILD patients may eventually develop PPF over their disease course [93,96], recent international recommendations (including ACR/CHEST, SER/SEPAR, and Austrian Delphi consensus statements) emphasize transitioning from passive waiting to structured active surveillance [97–99]. To remain safe and

effective, observation must follow predefined timelines: in confirmed or high-risk RA-ILD, complete PFT - specifically FVC and diffusing capacity DLCO - should be performed every 3 to 12 months during the initial evaluation period and at regular, prespecified intervals thereafter [97]. Furthermore, accessible, radiation-free modalities such as lung ultrasound (which achieves negative predictive values >95%) and low-dose CT protocols are increasingly viable tools to support routine, longitudinal monitoring [94,95].

Most importantly, structured surveillance is only actionable when anchored to predefined progression thresholds. A documented relative decline in FVC of 10% or more, a 5% to 10% FVC decrease accompanied by a declining DLCO, or expanding fibrotic changes on HRCT should systematically trigger a multidisciplinary team (MDT) reassessment to consider adjusting immunomodulatory therapy or introducing antifibrotic agents [96,100]. In this framework, observation is not the absence of management, but a proactive, protocolized monitoring strategy designed to preserve lung function and identify the therapeutic window before irreversible parenchymal loss occurs.

7. When Fibrosis Becomes the Therapeutic Target

The rationale for targeting fibrosis is not that autoimmunity becomes irrelevant, but that extracellular-matrix remodelling may cease to track systemic inflammatory activity closely. Experimental work on lung fibroblasts demonstrates persistence of an activated phenotype after mechanical priming and implicates matrix stiffness-sensitive YAP/TAZ signalling in a profibrotic feedback loop. This provides a plausible account of continuing fibrosis despite improved arthritis. It is mechanistic evidence from experimental systems, not proof that an individual patient's RA-ILD has crossed a measurable boundary into an autonomous phase [101,102].

The therapeutic implication is coexistence rather than an obligatory sequence of inflammation followed by fibrosis. In a multisite observational study of 212 patients treated with mycophenolate, azathioprine or rituximab, post-treatment pulmonary function was better than the trajectory projected from pretreatment measurements; UIP did not show a statistically significant differential treatment association. The study cannot supply an untreated randomised counterfactual or prove equal efficacy across patterns. It does, however, argue against using UIP as a reason to dismiss the possibility of an immunomodulatory benefit [103].

7.1 Nintedanib: a defensible indication and a defined evidence boundary

INBUILD enrolled patients with fibrotic ILD affecting more than 10% of lung volume and evidence of progression within the previous 24 months despite management considered appropriate in clinical practice. Its results therefore concern an enriched progressive population, not all CT-detected fibrosis. In the overall trial, nintedanib reduced the annual rate of FVC loss. The study was not a randomised comparison of an antifibrotic-first strategy against an immunomodulation-first strategy [15].

The RA-ILD subgroup comprised 89 patients. Annual FVC decline was -82.6 mL with nintedanib and -199.3 mL with placebo, a difference of 116.7 mL/year (95% confidence interval 7.4-226.1; nominal $p=0.037$). This is the basis of the frequently quoted 59% relative reduction in decline. It is not a 59% reduction in death, and it does not demonstrate restoration of lost lung. As a subgroup estimate, its precision and ability to address mortality are limited [104].

The most directly supported candidate is consequently a patient with established fibrotic RA-ILD and attributable, objectively documented progression despite otherwise appropriate management. ACR/CHEST includes nintedanib among options after progression on first-line ILD treatment, but did not reach consensus on its first-line use in RA-ILD [7]. 'Appropriate management' should not be interpreted as a requirement to expose every patient to several ineffective or contraindicated immunosuppressants before considering an antifibrotic. The decision should instead document disease tempo, fibrotic burden, plausible inflammatory activity, previous treatment and why further waiting is acceptable or hazardous [7].

7.2 Pirfenidone and the limits of a pattern-independent argument

TRAIL1 is particularly relevant because it was a dedicated RA-ILD trial. Recruitment stopped early, with 123 participants, and the primary composite of FVC decline of at least 10% or death was not significantly different between groups: 7 of 63 versus 9 of 60 participants ($p=0.48$). The estimated annual FVC decline nevertheless favoured pirfenidone (-66 versus -146 mL; $p=0.0082$). The positive secondary result is clinically informative, but does not erase the unsuccessful primary endpoint or the consequences of under-recruitment [105].

A strictly pattern-blind interpretation would also misrepresent current guidance. ERS/EULAR conditionally suggests pirfenidone in RA-ILD with

UIP, while ACR/CHEST conditionally supports adding it in RA-ILD progressing despite first-line treatment. Morphology therefore remains relevant to the discussion. A conditional recommendation resting on limited evidence should not be transformed into proof that every stable RA-UIP patient benefits, or that UIP is a validated predictive biomarker. The defensible principle is not to ignore pattern, but to resist allowing it to decide alone [7,8].

7.3 Nerandomilast: new evidence without subgroup inflation

FIBRONEER-ILD extends treatment evidence beyond conventional antifibrotic agents. In 1176 patients with PPF, the preferential phosphodiesterase-4B inhibitor nerandomilast reduced 52-week FVC loss; 43.5% were receiving background nintedanib. At 18 mg twice daily, the adjusted difference from placebo was 67.2 mL (95% confidence interval 31.9-102.5); at 9 mg twice daily it was 81.1 mL (46.0-116.3). These results establish an effect in the trial's PPF population, not superiority of the lower dose or comparative superiority over nintedanib [106].

The subsequent survival evidence deserves inclusion, not dismissal. Whole-trial follow-up reported a mortality hazard ratio of 0.51 (95% confidence interval 0.34-0.78) for each nerandomilast dose versus placebo. A later pooled analysis of FIBRONEER-IPF and FIBRONEER-ILD also supported a survival signal [107]. These analyses extend beyond the primary 52-week FVC endpoint; the original trials had not met their key secondary composite endpoints, and the hierarchy and multiplicity of later analyses matter. Neither analysis establishes a separately powered, RA-specific mortality benefit. Evidence for the broad progressive phenotype must not be relabelled as definitive evidence for every constituent autoimmune disease [107,108].

The broader lesson is methodological. A drug can act on overlapping inflammatory and fibrotic pathways without the trial demonstrating control of rheumatoid synovitis, permitting withdrawal of an effective disease-modifying antirheumatic drug, or defining the optimum sequence of combined therapy. RA-specific treatment decisions still require attention to the underlying trial population and concomitant-treatment restrictions. The size of a subgroup is not a substitute for its estimate and uncertainty.

7.4 Add, switch or combine?

In mixed inflammatory-fibrotic disease, adding a lung-directed agent may be more coherent than replacing treatment that is successfully controlling systemic autoimmunity. Conversely, apparent progression during poorly

tolerated or inadequately delivered immunomodulation warrants reassessment of the whole regimen. These are different problems, and neither is solved by a universal 'antifibrotic next' rule. For a patient without progression on mycophenolate, ACR/CHEST conditionally recommends against routine antifibrotic addition; its recommendations should not be read as endorsing indiscriminate upfront combination therapy [7].

New combination reports have not closed the RA-specific evidence gap. A 2026 pooled real-world study of nintedanib with dual immunosuppression included 28 patients with RA-ILD and 36 with systemic sclerosis-ILD, but longitudinal pulmonary function was unavailable for the RA subgroup. Functional findings from the systemic sclerosis participants cannot therefore be presented as evidence of efficacy for triple therapy in RA-ILD. Feasibility, tolerability, efficacy and optimal sequencing remain separate claims [109].

7.5 The endpoint is preserved function, not a motionless FVC

A patient may continue to lose FVC while benefiting from a treatment that makes the decline slower than it would otherwise have been (Table 1). Because that untreated individual trajectory is unobservable, residual decline is neither proof of failure nor permission to disregard worsening disease. It should trigger review of adherence, adverse effects, alternative causes, radiological change and the need for additional intervention. Clinical success should include useful activity, symptoms, oxygen requirements, hospitalisations and treatment burden, rather than a forced choice between 'stable FVC' and 'no benefit'.

Tolerability is part of effectiveness. In the RA-ILD INBUILD analysis, diarrhoea occurred in 61.9% with nintedanib and 27.7% with placebo over the whole trial; adverse events led to permanent discontinuation in 23.8% and 17.0%, respectively. Shared planning for gastrointestinal symptoms, liver-function monitoring, dose adjustment or interruption, and competing comorbidities is therefore essential. A treatment that cannot be sustained may offer little practical protection, however persuasive the average trial effect [15, 104].

Nintedanib should therefore be viewed not as a treatment for the radiological label of RA-UIP, but as a strategy to slow an objectively progressive fibrotic trajectory.

Table 1. Three treatment programmes: the supported inference and its boundary.

Evidence	What was demonstrated	What should not be inferred
INBUILD: RA-ILD subgroup; 89 patients [20]	Nintedanib reduced annual FVC loss by 116.7 mL versus placebo; 95% CI 7.4-226.1.	No demonstrated reversal of fibrosis or adequately powered RA-specific survival benefit.
TRAIL1: dedicated RA-ILD trial; 123 patients [21]	Primary composite not significant; a secondary FVC slope analysis favoured pirfenidone.	Not a positive primary-endpoint trial; no mandate to treat all stable UIP.
FIBRONEER-ILD: PPF; 1176 treated patients [22, 23, 24]	Reduced 52-week FVC loss; subsequent broader-population analyses support a survival signal.	Not a separately powered RA-ILD trial, a head-to-head comparison or proof of arthritis control.

The populations, entry criteria and endpoints differ. The numerical results must not be used for an indirect ranking of the drugs. FVC, forced vital capacity; PPF, progressive pulmonary fibrosis; UIP, usual interstitial pneumonia; CI, confidence interval.

8. Strengths and Limitations

This is a critical narrative review, and the proposed reserve-aware framework should be viewed as a clinically oriented synthesis rather than a validated decision tool. Its interpretation is constrained by the underlying RA-ILD literature, particularly the predominance of observational data for immunomodulatory therapy and the limited size and generalisability of RA-specific subgroups in antifibrotic trials [103,110]. Prospective validation is therefore needed before such a framework - or any molecular stratification strategy - can be used to guide treatment allocation. For now, “precision” in RA-ILD should refer to the quality of the clinical decision rather than to a level of biological certainty the evidence does not yet support.

9. Conclusion

The practical objective is to preserve usable lung while controlling rheumatoid disease and avoiding preventable harm. That requires separate attention to systemic immune activity, pulmonary progression, competing causes of deterioration and treatment tolerability. When fibrosis is demonstrably progressing, antifibrotic treatment has a defensible role; when mechanisms overlap, combination may be reasonable without being assumed optimal. The decision to observe, add or switch should have an explicit target and a scheduled test of whether that target is being met.

The pattern is where the discussion begins. The trajectory, interpreted in the context of reserve and modifiability, is what should keep changing the decision.

Declarations

Author Contributions

TG, AB conceived the article and its overarching conceptual framework, developed the trajectory- and reserve-based approach to RA-ILD, drafted the Introduction and the sections on risk stratification, antifibrotic therapy, strengths and limitations, and conclusions, and integrated and critically revised the final manuscript. SD drafted the sections on screening, indications for treatment, integrated articular and pulmonary management, and major clinical pitfalls, and contributed to the interpretation and critical revision of the manuscript. AB contributed to the conceptual development and clinical interpretation of the review and critically revised the manuscript for important intellectual content. R.K., K.B. and Z.B. contributed to the appraisal and interpretation of the evidence and critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. Generative AI (Claude, Opus 5, Anthropic Inc.) was used as a language-editing and formatting assistant during manuscript preparation. It helped refine English phrasing, improve clarity, and align the structure with Rheumatology (Bulgaria) formatting requirements. No AI tools were used for data generation, analysis, interpretation, or reference fabrication. All scientific content, interpretation, and conclusions are entirely the authors' own. The authors take full responsibility for the accuracy and integrity of the submitted work.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

No new data has been generated in the preparation of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Интерстициална белодробна болест, асоциирана с ревматоиден артрит: лечение, насочено към траекторията, а не към модела на засягане

Резюме

Интерстициалната белодробна болест, асоциирана с ревматоиден артрит (РА-ИББ), изисква повече от рентгенологична диагноза. Моделът на обичайна интерстициална пневмония описва белодробната архитектура. Сам по себе си обаче той не показва дали заболяването прогресира, кой компонент е модифицируем и доколко безопасно може да се отложи лечението. Настоящият наративен обзор преразглежда подхода, основан на поведението на заболяването, и разграничава три въпроса: предразположението към ИББ, прогнозата след развитието на ИББ и предвиждането на ползата от лечението. Обзорът интегрира съвременните класификации и препоръки с доказателства от кохорти, лекувани с имуномодулиращи средства, и от проучванията INBUILD, TRAIL1 и FIBRONEER-ILD. Предлагаме тълкуване на траекторията, съобразено с белодробния резерв. Структурната тежест и темпът на влошаване трябва да се преценяват заедно с оставащия физиологичен резерв, конкуриращите рискове и вероятната цена на изчакването. Това е рамка за клинично мислене, а не валидиран скор. Прогресиращата белодробна фиброза е полезна операционална дефиниция. Тя обаче не бива да се приема като доказателство за изцяло фибротичен механизъм, нито да се превръща в предварително условие за лечение на вече клинично значимо белодробно заболяване. Молекулярните постижения, включително MUC5B, дължината на теломерите и протеиновите профили, показват колко голяма е дистанцията между биологичната правдоподобност и избора на лечение. Доказателствата подкрепят ролята на антифибротичната терапия за забавяне на функционалната загуба. По-новите анализи на преживяемостта обаче изискват внимателно разграничаване между данните от общите популации с белодробна фиброза и изводите, специфични за РА. Следователно терапевтичната цел не е да се лекува образен етикет или да се нормализира отделен показател. Целта е да се запази полезната белодробна функция, като едновременно се контролира системното заболяване и се ограничава вредата, свързана с лечението.

Ключови думи: ревматоиден артрит, интерстициална белодробна болест, белодробна фиброза, прогресия на заболяването; антиревматични средства, прецизна медицина