Archivos de Bronconeumología xxx (xxxx) xxx–xxx

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

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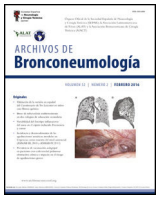

ALAT Voice

Rheumatoid Arthritis-Associated Interstitial Lung Disease (RA-ILD): An Official 2025 ALAT Clinical Practice Guideline

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Abbreviations: ABA, abatacept; ACPA, anticyclic citrullinated peptide antibodies; AZA, azathioprine; CTD, connective tissue diseases; CYC, cyclophosphamide; CTZ, certolizumab; DLco, diffusing capacity of the lungs for carbon monoxide; DMARDs, disease-modifying antirheumatic drugs; bDMARDs, biologic DMARDs; sDMARDs, synthetic DMARDs; csDMARDs, conventional synthetic DMARDs; tsDMARDs, targeted synthetic DMARDs; ETN, etanercept; FVC, forced vital capacity; GC, glucocorticoids; GOLI, golimumab; HR, hazard ratio; IL, interleukin; ILD, interstitial lung disease; INF, infliximab; IPF, idiopathic pulmonary fibrosis; JAKi, janus kinase inhibitors; KL-6, Krebs von der Lungen-6; LE, level of evidence; LDH, lactate dehydrogenase; LEF, leflunomide; MA, meta-analysis; MMF, mycophenolate mofetil; MMP3, matrix metalloproteinase 3; MTX, methotrexate; NSIP, non-specific interstitial pneumonia; NS, not significant; OP, organizing pneumonia; OR, odds ratio; PFT, pulmonary function tests; PPF, progressive pulmonary fibrosis; RA, rheumatoid arthritis; RCTs, randomized controlled trials; RF, rheumatoid factor; RR, relative risk; SR, systematic review; RTX, rituximab; SSZ, sulfasalazine; HRCT, high-resolution computed tomography; TCZ, tocilizumab; TI, incidence rate; TNF, tumor necrosis factor; TNFi, tumor necrosis factor antagonists; UIP, usual interstitial pneumonia.

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https://doi.org/10.1016/j.arbres.2026.04.001
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Please cite this article as: M.L. Alberti, S.J. Auteri, J. Rojas-Serrano et al., Rheumatoid Arthritis-Associated Interstitial Lung Disease (RA-ILD): An Official 2025 ALAT Clinical Practice Guideline, Archivos de Bronconeumología, https://doi.org/10.1016/j.arbres.2026.04.001

ARTICLE INFO

Article history:
Received 14 November 2025
Accepted 8 April 2026
Available online xxx

Keywords:
Interstitial lung disease
Rheumatoid arthritis associated interstitial lung disease
Rheumatoid arthritis
Screening
Disease-modifying antirheumatic drugs
Guidelines
Antifibrotics

ABSTRACT

Rheumatoid arthritis associated interstitial lung disease (RA-ILD) is a serious extra-articular manifestation, being the second cause of death in patients with RA. Usual interstitial pneumonia is the most frequent form of ILD with several factors resembling idiopathic pulmonary fibrosis. Early recognition of ILD through screening could change treatment strategies and prognosis in patients with RA. In this sense achieving articular activity remission included in the treat to target strategy becomes one of the most important factors not only to diminish the risk for developing ILD but also disease progression. Disease-modifying antirheumatic drugs (DMARDs) became the cornerstone for treating patients with RA-ILD together with antifibrotics for those with progressive pulmonary fibrosis. Therefore, this guideline aims to support early recognition and evidence -based management of this condition.

© 2026 SEPAR. Published by Elsevier España, S.L.U. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Rheumatoid arthritis (RA) is one of the most prevalent immune-mediated systemic diseases affecting up to 1% of the world's population [1]. Recent data reveal that 17.6 million (95% CI: 15.8–20.3) people worldwide suffer from RA, with an age-adjusted mortality rate of 0.5 per 100,000 in 2020 [2].

RA-ILD is a serious extra-articular manifestation. In a meta-analysis of 56 studies (11,851 patients) the pooled prevalence was 18.7% (95% CI: 15.8–21.6) [3]. Interstitial lung abnormalities (ILA) considered the mildest forms of ILD occur in 16.9–33% of RA patients and are associated with increased mortality [4–6].

Unlike other autoimmune diseases, it is characterized by a high frequency of usual interstitial pneumonia (UIP) [7,8], which is a risk factor for increased mortality. Other, less frequent forms of interstitial lung involvement included non-specific interstitial pneumonia (NSIP) and organizing pneumonia (OP), among others.

RA-ILD is currently the second leading cause of death in RA [9–11], and increases mortality by 2–10 times [10]. Several factors have been associated with progression and higher mortality in RA-ILD: UIP pattern, male sex, age older than 60 years, smoking, low FVC and/or DLCO, higher CT extent, delayed diagnosis, persistently elevated CRP, and increased Krebs Von den Lungen 6 (KL-6) levels [11–14]. Furthermore, active joint involvement has been identified as a crucial and potentially modifiable factor associated not only with disease progression in RA-ILD but also with an increased risk of ILD development [15–17].

What is the importance of achieving the goals of treat to target (T2T) strategy in RA-ILD?

Achieving articular activity remission, as part of the T2T strategy, represents a fundamental goal in the management of RA, not only from a joint centered point of view, but also for guiding the therapeutic approach of ILD, recognizing RA as a systemic disease. Compliance with the T2T strategy is essential, since patients with RA-ILD and high joint activity have a four fold lower survival [17]. On the other hand, ILD may compromise the T2T strategy by complicating DMARD selection and initiation [18].

Clinical practice guidelines and emerging evidence have provided valuable information for the management of RA ILD. However, some of these guidelines are not fully aligned with the T2T strategy, are unclear regarding the safety and efficacy of certain DMARDs such as methotrexate, and recommend treatments that are not effective for RA including mycophenolate (MMF), cyclophosphamide (CYC), and azathioprine (AZA) [19–22]. Therefore, there is a need to develop specific guidelines to optimize the management and screening of RA ILD.

Methodology

Scope and purpose

This guideline was developed through a collaborative effort convened by the Latin American Thoracic Association's (ALAT) scientific department of ILD, involving pulmonologists and rheumatologists.

Objective

The aim of this document is to resolve controversial issues related to RA-ILD. This is achieved by framing questions using the PICO format and providing answers based on a critical analysis of evidence gathered from a systematic literature search.

Target audience and utility

This document is intended for Latin American respiratory societies and specialist physicians in pulmonology, rheumatology, radiology, internal medicine, and primary care. It serves as a vital tool to facilitate earlier identification and more accurate treatment of this condition.

Group composition, question formulation, and answer drafting

This work involved three distinct groups:

1. **CORE Group:** This team consisted of three pulmonologists (MA, SA, FC) and two methodologists (AA, ES). Their responsibilities included formulating clinical questions using the PICO format and critically analyzing the evidence gathered from the systematic literature search. This group was also responsible for selecting and convening the Panel of Experts to evaluate the formulated questions and answers before they were submitted for the consensus process.
2. **Panel of Experts:** Composed by 22 members of pulmonology (IB, JE, MF, VG, RK, MM, KS, MN, LN, ER, ET) and rheumatology (JR, GC, AB, CC, AC, RG, LM, RM, JR, CT, VW) specialists from various Latin American countries, all with expertise in managing RA-ILD patients. This group participated in a DELPHI consensus process, voting to express their agreement or disagreement with the questions and answers developed by the CORE Group.
3. The document has been submitted for evaluation by an external reviewer (PD).

Table 1
Selected clinical questions and outcomes.

Question	Total references selected (type of study)	Recommendation
1) What is the clinical importance of screening for ILD cases in patients diagnosed with RA?	1973, 10 (2 SR [37,38], 6 Cohort studies [39–44] and 2 Case–control [45,46])	1B: There is MODERATE evidence to demonstrate advantages in screening for ILD cases in patients diagnosed with RA. See algorithm Fig. 1.
2) Is there an association between methotrexate use and an increased risk of ILD?	311, 6 (2 SR [54,55], 3 prospective cohort studies [53,56,57] and 1 Case–control [55])	1A: To establish that MTX use is not associated with the risk of developing ILD. 1B: To recommend maintaining MTX use in patients with RA-ILD
3) Is the use of anti-TNF justified in patients with RA-ILD?	610, 2 (1 SR [54] and 1 Cohort study [25])	2B: to consider treatment with TNFi agents in patients with RA-ILD. Given the limited evidence available, we recommend starting another non TNFi DMARDs, especially in elderly patients. Given the limited evidence, the decision to continue treatment with TNFi agents in RA-ILD should be evaluated on a multidisciplinary and individual basis in each case.
4) Could rituximab be a safe and effective alternative for patients with RA-ILD?	1193, 4 (2 SR with MA [59,60], 2 cohort studies [61,62])	2B: to consider RTX treatment as an effective and safe alternative in the treatment of RA-ILD.
5) Could Abatacept be a safe and effective alternative for patients with RA-ILD?	903, 9 (1 SR with MA [66] and 8 observational studies [67–74])	2B: to consider ABA treatment as a safe and effective alternative in patients with RA-ILD.
6) Could anti-Jak drugs be a safe and effective alternative for patients with AR-ILD?	194, 7 (1 SM with MA [66] and 5 observational studies [70,72,76–78] and an open clinical trial [79])	2B: to consider treatment with JAKi in the treatment of RA-ILD in patients receiving other DMARDs
7) In which patients with RA-ILD is the use of antifibrotics justified?	2 SR with MA [80,81], 1 prospective cohort [82], 1 real-life retrospective cohort [83])	1B: for the use of Nintedanib in RA- ILD patients with PPF. 2C: for the use of pirfenidone in patients with RA-associated fibrotic ILD.

Abbreviations: SR: systematic review; MA: meta-analysis; RCT: controlled clinical trials.

Literature search and eligibility criteria

The methodology for this document began by converting all clinical questions into the PICO format (Patient/Problem/Population, Intervention/Exposure, Comparison, and Outcome) to better guide the evidence search [23]. Questions sourced from third parties were deliberately excluded [24].

The literature search was simultaneously conducted in two major metasearch engines: Tripdatabase (PRO version) and PubMed/MEDLINE, employing controlled MeSH terms (SF1 –Table 1). The PRISMA framework was utilized throughout the process.

Study selection process

Initially, all studies were identified for each PICO question. After removing duplicates, two independent reviewers screened the titles and abstracts against the eligibility criteria. Disagreements were resolved through discussion; persistent conflicts required consultation with a third reviewer. The PRISMA flowchart (SF2-Figs. 1–7) illustrates this selection process to each PICO question.

Inclusion criteria and search scope

The search included studies published in Spanish, Portuguese, and English and officially closed in January 2025. However, three highly relevant studies published subsequently were incorporated [25–27]. A summary of the clinical questions and corresponding selected results is provided in Table 1.

Prioritization of evidence

To answer the clinical questions, the selection prioritized the highest levels of evidence: systematic reviews (SRs), randomized controlled trials (RCTs), and meta-analyses (MAs). In the absence of high-level evidence, studies of moderate (observational studies) or low levels (open studies, case series, or consensuses) were selected following the hierarchy of evidence. An algorithmic selection approach was primarily adopted for therapeutic questions [28]. Results from RCTs already included within a systematic review are not selected separately.

Critical analysis and formulation of recommendations

The critical analysis of the selected references utilized the recommendations and templates from the CASPE network (www.redcaspe.org). To classify recommendations and evidence quality, the "ACCP grading system" was adopted. This system classifies recommendations as STRONG (1) or WEAK (conditional) (2), considering the level of evidence, the balance of risk/benefit/cost, and, occasionally, the variability in patient values and preferences.

The quality of evidence is categorized as HIGH (A), MODERATE (B), or LOW (C), based on the study design, consistency of results, and the clarity of the evidence in addressing the PICO question.

Consensus process

The methodology involved conducting sequential Delphi rounds until a consensus was reached on recommendations for managing RA-ILD, derived from a document addressing clinical and therapeutic questions. This process was administered via online surveys.

A total of 8 questions were developed, comprising 7 PICO questions and an evaluation of a proposed algorithm. Participants rated their agreement using a 10-point Likert scale (1 = "totally disagree" to 10 = "totally agree"). Experts provided comments and suggestions, which were integrated before the execution of subsequent rounds.

The results were analyzed using JAMOVI and presented as the median and interquartile range (IQR). Consensus for each question was defined as an agreement median greater than 7 points from more than 70% of the participants. The Delphi rounds were terminated when the IQR for all PICO questions was ≤ 3. Cronbach's α was used to analyze the reliability of the survey (Table 2).

Table 2
Delphi results. Data are expressed as median (interquartile range). Cronbach's α, Round 1: 0.85 Round 2: 0.88.

PICO question	Round 1	Round 2
1: What is the clinical importance of screening for ILD cases in patients diagnosed with RA?	10 (1)	10 (1)
1B: Do you agree with the proposed diagnostic algorithm?	8.5 (3)	10 (1)
2: Is there an association between the use of methotrexate and an increased risk of ILD?	3 (9)	10 (1)
3: Is the use of Anti-TNF justified in patients with RA-ILD?	7.5 (5)	9 (3)
4: Could Rituximab be a safe and effective alternative in patients with RA-ILD?	9 (2)	9 (2)
5: Could Abatacept be a safe and effective alternative in patients with RA-ILD?	8.5 (3)	8.5 (2)
6: Could Anti-JAKs be a safe and effective alternative in patients with RA-ILD?	8 (3)	9 (2)
7: In which patients with RA-ILD is the use of anti-fibrotics justified?	9.5 (2)	9 (1)

Question 1

What is the clinical importance of screening for ILD in patients with RA?

Rationale

The risk of developing ILD is increased in patients with RA compared to the general population [9,29], being the second cause of death in RA after cardiovascular disease. Indeed, patients with RA-ILD have a threefold higher risk of death compared to those with RA without ILD [30]. The clinical presentation of RA-ILD is heterogeneous, with 5–10% of patients showing symptoms and 20–30% remaining asymptomatic [9,31]. Delayed diagnosis of RA-ILD has been associated with increased mortality [14].

The prevalence of RA-ILD depends on the risk factors of the population studied and on the screening method used. The combination of risk factors (male sex, smoking, and seropositivity) has been associated with a higher likelihood of developing RA- ILD [32].

When HRCT is used as a tool for screening, the prevalence can reach up to 55.7% [33,34]. Recently, its use has been recommended in patients with connective tissue diseases (CTD), for the detection of ILA, defined on HRCT as bilateral parenchymal abnormalities in non-dependent zones, including ground glass or reticulations, lung distortion, traction bronchiectasis and/or honeycombing affecting more than 5% of a lung zone [26]. Although HRCT is considered the gold standard for the diagnosis and characterization of ILD, it may not be an appropriate tool in RA patients without respiratory symptoms and risk factors for ILD. In this sense, given its low cost, ease of use and lack of exposure to radiation, lung ultrasound (LUS) has emerged as a screening tool for ILD in different CTD including RA, showing a high negative predictive value [35] and an excellent positive correlation with HRCT findings [36].

Study selection

Two systematic reviews [37,38], six cohort studies [39–44], and two case–control studies [45,46] were included.

Summary of evidence

1) **Risk factors for developing RA-ILD:** A recent systematic review [42], mostly containing retrospective observational studies with notable heterogeneity, summarize the following risk factors associated with ILD: age at RA onset, smoking, ESR, DAS28 score, and rheumatoid factor (RF), KL-6 levels, Anti-citrullinated peptide antibody (ACPA), Surfactant protein D-SP-D, Interleukin 6 (IL-6) [37]. Some studies have aimed to simplify diagnostic suspicion and identify RA patients in whom chest HRCT should be performed. A cohort validated a risk score for subclinical RA-ILD that included four variables (sex, age at RA onset, RA activity using DAS28-ESR, and the MUC5B rs35705950 genetic variant). While the risk score without MUC5B rs35705950 was adequate to discriminate patients with subclinical RA-ILD, the model with determination of the MUC5B variant showed a better performance, suggesting an important contribution of the genetic variant to the overall risk of subclinical RA-ILD [39]. However, its cost and low availability do not make it a clinically useful study for screening. In a multicenter observational case–control study performed as a proof of concept using clinical data collected for 10 years, it was proposed the analysis of 4 risk factors: age (40–70 years: 1 point, >70 years: 2 points), ACPA (weak positive: 8–21 IU/ml: 1 point; Positive > 21 IU/ml: 2 points), RF (weak positive: 15–42: 1 point; Positive > 42: 2 points) and smoking (Smoker or ex-smoker > 17 packs/year: 1 point). Based on these variables, a predictive model for the presence of RA ILD was developed, with a score greater than 5 indicating a high probability of disease (sensitivity: 86%; specificity: 58%) [45]. Another case–control study identified 5 risk factors associated with the development of RA-ILD: male sex, smoking, extra-articular manifestations, CDAI score > 28 and ESR > 80 mm/h. The two-point score showed a sensitivity of 90.38% and a specificity of 63.64%, while the four-point score showed a sensitivity of 51.9% and a specificity of 90.9% [46].

A prospective cohort study that recruited 779 patients over 4 years demonstrated an increased likelihood of ILD related to: Age (>60 years), ESR, DAS28, RF (Positive) and ACPA levels (>7 IU/ml). Additionally, ILD was associated with smoking in individuals carrying the shared epitope of the HLA-DRB1 allele, confirming the epigenetic hypothesis [47]. Another retrospective cohort study, included 128 consecutive RA patients over three years (2020–2023) demonstrating an association between HRCT severity with the DAS28-ESR Activity Score (EC: 0.199; $p = 0.03$) and RF titers (EC: 0.247; $p = 0.01$). When respiratory function variables were added, a significant association was found between the predictive value of FVC and DAS28-ESR Activity Score (CE: 0.23; $p = 0.047$) [48].

2) **Screening tools for ILD screening:** In a cohort of 137 patients with RA who underwent HRCT, breath sounds recorded by an electronic stethoscope had a sensitivity of 93.2% and a specificity of 76.9% to detect ILD. This method was superior over clinical symptoms, physical examination findings, chest X-ray and pulmonary function tests (PFT) [40].

Although the most frequently described respiratory functional abnormalities were decreased DLco and a restrictive spirometric pattern [38], a recent retrospective cohort study confirmed that the presence of an obstructive spirometric pattern (FEV1/FVC < 0.7 post 400 mcg of salbutamol) is an independent risk factor for increased mortality even among patients with ILD [41].

A systematic review of predominantly cross-sectional and heterogeneous studies showed that although HRCT remains the most widely used and sensitive technique for ILD screening in RA, LUS demonstrates a high negative predictive value for the detection of ILD in this population [38]. A prospective study that included 77 RA patients with respiratory symptoms as an inclusion criteria found that LUS had a sensitivity of 82.6% (95% CI: 61.2–95.0%)

and a specificity of 51.9% (95% CI: 37.8–65.7%), corresponding to a positive predictive value of 42.2% (95% CI: 27.7–57.8%) and a negative predictive value of 87.5% (95% CI: 71.0–96.5%) [42]. In another prospective study with a one-year follow-up, including 192 patients with RA of whom 45.3% were asymptomatic respiratory symptoms but had velcro like crackles on auscultation, the number of B lines (>11.5) and the corrected DLco value (<7.13) allowed for better discrimination in the diagnosis of RA-ILD [43]. Finally, in a cohort of 106 patients, the authors reported that the negative predictive value of lung ultrasound was higher (94.7%) than that of LFT (FVC: 70.5% and DLco 85.1%) and velcro like crackles on auscultation (85.1%); with chest X-ray showing the worst diagnostic value (Sensitivity: 64.5% and PPV: 84.7%) [44].

Conclusion and recommendation

Moderate level of evidence and strong recommendation to systematically evaluate the use of multidimensional scores to stratify the risk of developing RA-ILD (1B)

Moderate level of evidence and strong recommendation to recommend the use of HRCT for screening patients with risk factors for developing RA-ILD. (1B)

RCTs are needed to improve the level of this evidence; for example there are still no studies demonstrating the impact of screening on reducing mortality. However, early diagnosis, through the assessment of risk factors and the appropriate use of diagnostic methods, could guide more effective treatment strategies and improve the prognosis of patients with RA. Therefore, we recommend the use of chest HRCT for ILD screening in patients with RA. In asymptomatic patients without risk factors, LUS could be a useful tool given its safety and low cost; thus, we recommend its inclusion in the diagnostic algorithm (Fig. 1). However, in Latin America, improved accessibility and training in LUS for ILD screening are needed. Therefore, if this method is not available in low-risk patients, a HRCT of the chest is recommended.

Question 2

Is there an association between methotrexate (MTX) use and an increased risk of ILD in patients with RA?

Rationale

Methotrexate (MTX) has been the most widely used conventional synthetic DMARDs (csDMARD) in RA. In other autoimmune diseases, no increased risk of ILD has been found with MTX use [49], leading us to believe that the majority of RA-ILDs are not actually linked to MTX use but rather to the activity of the RA itself. We also must consider the possibility of developing methotrexate-induced pneumonitis, which we must differentiate from pre-existing RA-ILD. However, its incidence is very low [50] and usually occurs within the first few months of treatment. Bearing this in mind, methotrexate-induced pneumonitis is frequently confused with pre-existing RA-ILD, which is more common.

Recent Clinical Practice Guidelines have provided inconsistent recommendations regarding the use of MTX in patients with RA-ILD [21,22,51]. Evidence from several studies suggesting an increased risk of lung disease in RA likely reflects a greater awareness and recognition of ILD associated with the disease itself, rather than a direct pulmonary toxicity of methotrexate [52,53].

The Spanish Society of Rheumatology (SER) and the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) guidelines propose different scenarios regarding the use of MTX in patients with RA-ILD. The authors proposed that if ILD is present at the time of RA diagnosis, MTX use should be individualized due to the risk of pneumonitis, the use of another csDMARD is preferred to minimize risks. In another scenario, they recommended temporarily discontinuing MTX if ILD is diagnosed or if it worsens during the first year of treatment until it is clarified whether or not a causal relationship exists. In the last scenario, they recommended that MTX can be continued if patients who have been on treatment for more than one year are diagnosed with ILD, since there is no evidence to justify its discontinuation [21].

The American College of Rheumatology (ACR) and the American College of Chest Physicians (CHEST) largely propose a unified therapeutic approach for CTD ILD. This guideline recommends maintaining MTX use in patients receiving it for extrapulmonary manifestations, but suggests that it should be discontinued if pneumonitis is suspected; moreover, some panelists prefer to stop MTX if ILD develops [22]. Finally, the 2021 ACR guidelines on the treatment of RA [22,51] conditionally recommend MTX over other csDMARD for patients with moderate to severe joint activity, who have mild, stable lung disease – including airway or parenchymal involvement – because the risk of lung disease worsening with MTX remains uncertain. The recommendation favors MTX given its central role as a first line therapy for RA, while it is conditional because some specialists prefer another therapeutic option rather than accepting the risk of pulmonary toxicity.

Due to the notable differences in recommendations for the use of MTX in patients with RA-ILD, we decided to evaluate the current evidence on this question.

Study selection

Two systematic reviews [54,55], three prospective cohort studies [53,56,57], and one case–control study [55] were included.

Summary of evidence

A systematic review addresses aspects related to the onset, progression, and mortality from MTX-associated ILD. The authors conclude that no association was found between MTX and the onset of ILD; in fact, they suggested that its use could delay the onset and improve survival. Additionally, they reported that patients receiving MTX do not have an increased risk of respiratory or infectious complications or respiratory-related mortality compared to other csDMARDs or biologics [54]. Another systematic review of 15 cohort studies, reported decreased mortality in patients with RA (HR = 0.59; 95% CI 0.50–0.71; $p < 0.001$) and specifically in RA-ILD patients (HR = 0.44; 95% CI 0.20–0.95; $p = 0.037$) with the use of MTX [55]. A study analyzing data from 30,512 patients diagnosed with RA from the Danish DANBIO registry and the Danish national patient registry found no association between MTX use and ILD, both at 1 year [HR 1.03 (95% CI 0.71, 1.48)] and at 5 years follow-up [HR 1.00 (0.78, 1.27)] [53].

A prospective cohort from two studies (ERAS: 1986–2001 and ERAN: 2002–2012) that included 2701 RA patients, identified 92 cases with ILD. Among them, 39 of 1578 MTX-exposed patients (2.5%) and 53 of 1114 unexposed patients (4.8%) developed ILD, showing no association between MTX exposure and ILD (OR = 0.85; 95% CI 0.49–1.49; $p = 0.58$). Moreover, MTX exposure was significantly associated with a reduced likelihood of developing ILD (OR = 0.51; 95% CI: 0.32– 0.79; $p = 0.001$) [56]. Recently, another multicenter prospective cohort study evaluated 143 RA-ILD patients, from 2015 to 2018, observing progression of ILD in 64 patients. No association was found between ILD progression and MTX use (adjusted HR: 1.75; CI95: 0.8–3.46) or tacrolimus (adjusted HR: 0.94; CI95: 0.52–1.72), but deterioration of respiratory function was observed with the use of leflunomide (adjusted HR: 8.42; CI95: 2.61–27.5) [57]. Similarly, in a

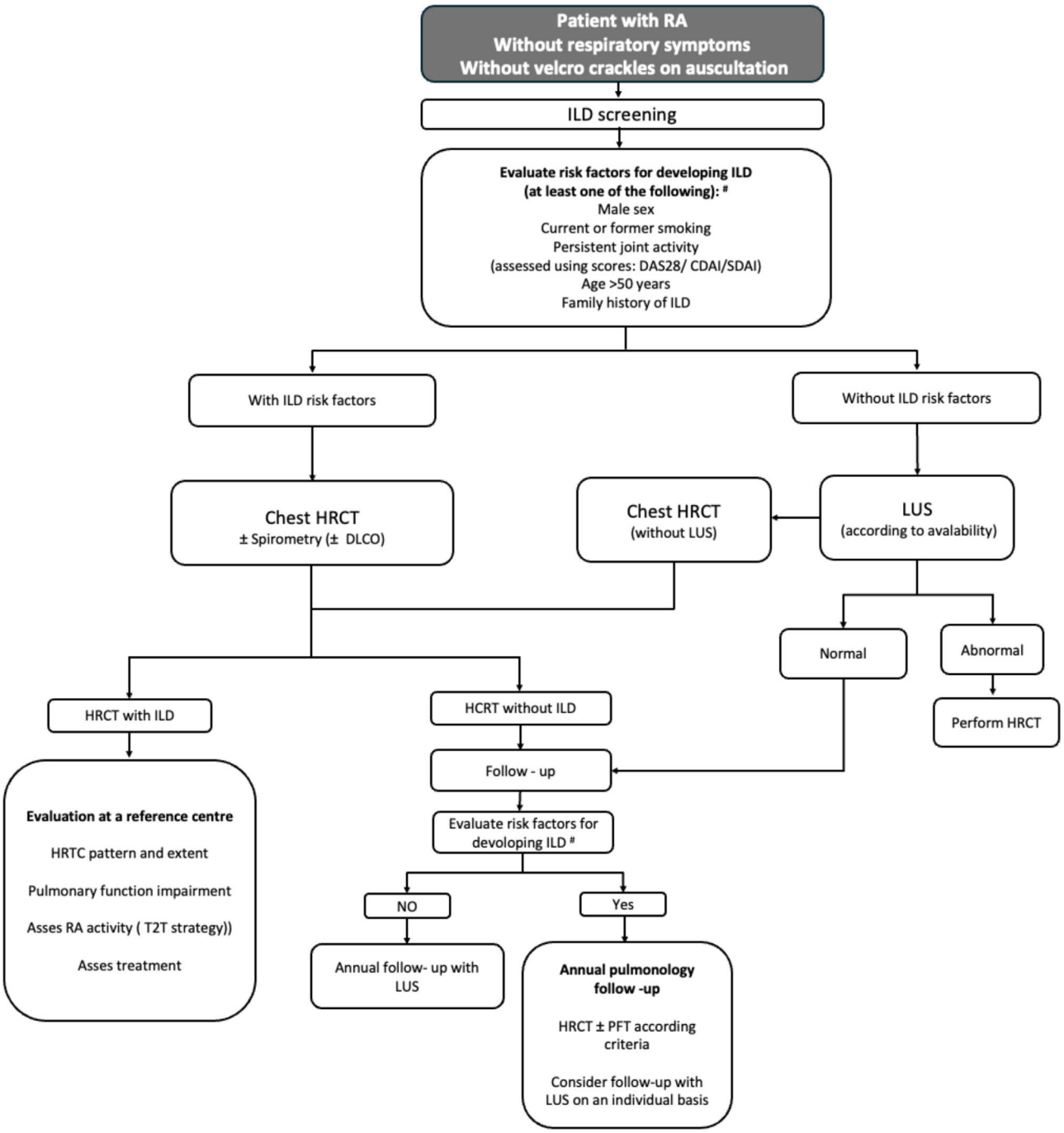

Fig. 1. Algorithm for RA-ILD screening. RA, rheumatoid arthritis; ILD, interstitial lung disease; HRCT, high-resolution computed tomography; LUS, lung ultrasound; T2T, treat to target.

multiethnic case–control study comparing 413 patients with RA-ILD and 673 patients with RA without ILD, MTX was not associated with an increased risk of ILD (adjusted OR = 0.46; 95% CI: 0.24–0.90; $p = 0.022$). Moreover, MTX use was associated with a delayed onset of ILD in this study [55].

Conclusions and recommendations

HIGH evidence and STRONG recommendation. MTX is not associated with a risk of developing ILD. RECOMMENDATION 1A.

In patients with RA-ILD, we recommend initiating or continuing MTX treatment. RECOMMENDATION 1B.

Question 3

Is the use of TNF inhibitors (TNFi) justified in patients with RA-ILD?

Rationale

Because TNF-alpha plays a central role in the pathogenesis, the use of TNFi was initially proposed in RA patients who developed ILD; however, several clinical studies have reported unfavorable safety outcomes. This question evaluates recent evidence with the aim of clarifying their role of TNFi in RA-ILD.

Study selection

1 Systematic Review [54] and 1 Cohort [25] were included.

Summary of evidence

A systematic review demonstrated higher mortality in patients with RA-ILD treated with TNFi agents versus rituximab (RTX) as the first biologic or when compared with csDMARDs (21% vs. 7%). However, no difference was found in the incidence of ILD when TNFi therapy was initiated in RA patients without ILD [54]. The studies included in this review analyzed the onset or worsening of ILD in RA patients treated with TNFi agents compared with non-TNFi biologics. TNFi were implicated in 85% of the ILD events detected. Adverse events and mortality were associated with older age and concomitant use of AZA. Moreover, they found that RA-ILD patients treated with TNFi may be at higher risk of adverse events and mortality from ILD than those treated with abatacept (ABA) or RTX, particularly among older individuals and those with pre-existing ILD [54]. This systematic review included an analysis of a cohort study that evaluated the risk of ILD onset or exacerbation associated with TNFi use. The cohort comprised 163 RA patients who initiated biologic therapy (102 with TNFi and 51 with non-TNFi agents), including 58 with pre-existing ILD and 105 without. After one year of follow-up, ILD developed in 17 patients (10%), occurring more frequently among those treated with TNFi [58]. After 1 year of follow-up, the rate of exacerbation of prior ILD was higher for TNFi versus non-TNFi biologic DMARDs (bDMARDs) ($p = 0.024$) [58]. However, these studies are limited by disease onset bias and severity was not comparable in patient recruitment.

Conclusions and recommendations

MODERATE evidence and WEAK recommendation for considering TNFi therapy in patients with RA-ILD. Given the limited available evidence of TNFi in RA-ILD, we recommend initiating a non-TNFi DMARD, particularly in elderly patients. The decision to continue TNFi therapy in RA-ILD should be multidisciplinary and individualized. RECOMMENDATION 2B

RCTs are needed to clarify the potential association between TNFi therapy and an increased incidence of ILD and mortality in patients with RA.

Question 4

Is Rituximab (RTX) a safe and effective therapy in patients with RA-ILD?

Rationale

Rituximab (RTX), a monoclonal antibody that specifically targets the CD20 antigen, has emerged as a promising therapeutic option for patients with RA-ILD. This is based on the observation of B-cell follicular hyperplasia and interstitial plasma cell infiltrates in lung biopsy specimens [54]. This question summarizes the efficacy and safety of RTX in patients with RA-ILD.

Study selection

Two systematic reviews with meta-analyses of observational studies [59,60] and two retrospective cohort studies were included [61,62].

Summary evidence

A systematic review with meta-analysis that included 15 studies (4 prospective and 11 retrospective) with 314 patients showed that 88% of patients with RA-ILD experienced stabilization or improvement of their ILD after treatment with RTX (95% CI: 0.76–0.96; $p = 0.02$). Stabilization or improvement in FVC was observed in 85% of cases (95% CI: 0.62–0.99), with an average increase of 7.43% in the percentage predicted of FVC (95% CI: 1.14–13.72%). However, the sensitivity analysis did not show a significant improvement in the percentage predicted DLCO values. Regarding safety, only two studies reported data on 87 patients, among whom 18 (20%) experienced serious adverse events and 10 (8.7%) died [59].

Another systematic review with meta-analysis evaluating the safety of RTX in the treatment of ILD associated with CTD, including 238 out of 827 RA patients (28%), reported a prevalence of adverse events of 29.7% (95% CI: 0.17–0.42). Infections occurred in 20.7% of cases (95% CI: 0.15–0.27), and all-cause mortality was 11.6% (95% CI: 0.08–0.16) [60].

In addition, a retrospective, multicenter, real-world cohort study, evaluated 212 patients with RA-ILD treated with RTX, AZA or MMF. After one year of treatment, a significant improvement was observed in FVC% and DLco% compared with the response predicted by a mathematical model without treatment. However, no significant differences were found in any of the evaluated outcomes when comparing RTX, AZA, and MMF individually, and all therapies showed a good safety profile [61].

Data from the Spanish NEREA registry indicate that patients with RA-ILD treated with RTX had an incidence of respiratory deterioration (5% decline in FVC at one year of follow-up) of 23.5 per 100 patients – semesters, 50% of these patients experienced functional decline at 1.75 years after the diagnosis of RA-ILD. Finally, in the multivariate analysis, treatment with RTX was associated with a lower risk of respiratory functional deterioration (HR 0.51; 95% CI: 0.31–0.85) [62].

Conclusions and recommendations

MODERATE evidence and WEAK recommendation to consider RTX as an effective and safe treatment for RA-ILD patients. RCTs are needed to clarify this recommendation. RECOMMENDATION 2B.

Question 5

Is Abatacept a safe and effective treatment for patients with RA-ILD?

Rationale

Abatacept (ABA) is a biologic drug belonging to the class of T-cell co-stimulation modulators. Similar to RTX, and based on its mechanism of action and the pathophysiology of RA, ABA may represent another promising therapeutic alternative for the treatment of RA-ILD [63,64].

In this context, we questioned whether the use of ABA could represent a therapeutic option for patients with RA-ILD, given its favorable safety and efficacy profile [65].

Study selection

One systematic review with meta-analysis of observational studies [66] and eight observational studies [67–74] were included.

Summary evidence

A prospective cohort of 57 patients treated with ABA and followed for 27 months, observed an improvement of pulmonary disease in 71% of cases, while 22.8% experienced worsening. In addition, 10.5% of patients developed adverse events and 5.3% died [67]. Several retrospective cohort studies have compared the efficacy and safety of ABA treatment compared to other DMARDs. Fernández-Díaz et al. reported that ABA therapy, whether used as monotherapy, in combination with methotrexate (MTX), or with another non-MTX DMARD, was equally effective in achieving stabilization and/or improvement of pulmonary function, symptoms, radiologic findings, and RA activity; while maintaining a favorable safety profile [68]. A subanalysis of this cohort evaluating the efficacy of ABA treatment in 190 patients according to the HRCT pattern of ILD (UIP: 106 patients and NSIP: 84 patients) reported stability of lung function, with stabilization and/or improvement in HRCT (UIP: 73.1%; NSIP: 72.9%) and dyspnea (UIP: 90.5%; NSIP: 94.6%) [69]. On the other hand, Mochizuki et al. reported no significant differences in HRCT progression among 84 patients treated with ABA vs JAK inhibitor (JAKi) (ABA: 10.5%; JAKi: 18.2%; $p = 0.61$) [70].

Regarding the route of administration of ABA, data from the Spanish national registry including 397 patients found no differences in lung function, clinical symptoms, progression of HRCT and safety when comparing the subcutaneous versus intravenous routes of administration [71].

A case–control study comparing the effectiveness of ABA ($n = 45$) with JAKi ($n = 26$) treatment found no significant differences between groups in treatment persistence at two years, pulmonary complications, HRCT fibrosis score, and prednisolone dose reduction. However, an improvement in HRCT ground-glass score was seen in the JAKi group [72].

A real-life study investigated the risk of mortality in patients with RA-ILD treated with ABA compared with TNFi. After propensity score matching, 895 patients per treatment arm were retrospectively evaluated, showing that those treated with ABA had higher overall mortality (HR: 1.296; 95% CI: 1.006–1.671). However, the retrospective design of this study did not allow for assessment of ILD subtype or severity, RA activity level, or causes of death or mechanical ventilation. Moreover, the potential influence of residual confounding factors, despite statistical adjustments, may have increased bias and limited the interpretation of the results [73].

Data from a Korean registry that studied 125 patients with RA-ILD followed for 26 months who received ABA showed a treatment retention rate of 30.5%, which was better than TNFi but lower than JAKi (log-rank $p = 0.020$), with no differences in the discontinuation rate between groups [74].

Conclusions and recommendations

MODERATE evidence and WEAK recommendation to consider ABA treatment as a safe and effective therapeutic option for patients with RA-ILD. RCTs are needed to clarify this recommendation. RECOMMENDATION 2B.

Question 6

Is Janus kinase inhibitors a safe and effective treatment in patients with RA-ILD?

Rationale

Janus kinase inhibitors (JAKi) have proven to be a novel, safe, and effective alternative as monotherapy or in combination for the treatment of RA. Due to their mechanism of action and potential antifibrotic effect [75], JAKi could be promising drugs in RA-ILD. However, there is limited information on their efficacy and safety in the treatment of RA-ILD. For these reasons, it is worth exploring whether sufficient evidence exists to justify the use of JAKi in patients with RA-ILD.

Study selection

One systematic review with meta-analysis of observational studies [66], five observational studies [70,72,76–78], and one open clinical trial [79] are included.

Summary evidence

A systematic review with meta-analysis of observational studies evaluating the efficacy of JAKi in the treatment of RA-ILD showed no significant changes in FVC and DLco decline with tofacitinib or baricitinib. However, the rate of non-progression of RA-ILD on HRCT among patients treated with JAKi was statistically significant (0.839; 95% CI: 0.66–0.94). Other outcomes such as quality of life or mortality were not assessed [66].

In RA-ILD patients with UIP HRCT included in a prospective cohort, the combination of tofacininib plus iguratimod showed significant improvement in FVC (84.7 ± 14.7 ml vs. 90.7 ± 15.4 ml; $p = 0.031$) and HRCT fibrosis score (7.3 ± 3.4 vs. 7.0 ± 5.6; $p = 0.015$) compared with csDMARDs. However no significant differences in either FVC% or DLco% [76]. In a case–control study comparing the safety and efficacy of JAKi versus ABA, no significant differences were found in the 2-year drug persistence rate, pulmonary complication rate, or HRCT fibrosis assessment scores [72]. Kalyancu et al. observed that patients treated with tofacitinib followed for one year showed stability in FVC after treatment (FVC: 79.8% vs. 82.8%; $p = 0.014$) with disease worsening in only 11.1% of patients [77]. In a Japanese cohort study, the rate of radiologic worsening was similar between patients treated with ABA and those receiving JAKi (4.2% vs. 5.6%; $p = 0.847$) [70]. Venerito et al. showed a significant reduction in DLco (Mean difference from baseline 3.44 ± 7.18; $p = 0.02$) with stability in FVC and HRCT in a cohort with a mean follow-up of 19 months [78].

Finally, data published from a randomized, open-label, non-inferiority trial including 1455 patients receiving tofacitinib 5 mg twice daily, 1456 receiving tofacitinib 10 mg twice daily, and 1451 receiving TNFi (adalimumab and etanercept) with a median follow-up of 4 years, observed higher incidences of major cardiovascular events (3.4%, n:98 patients) and cancer (4.2%, n:122 patients) in the tofacitinib versus TNFi group (2.5%, n:37 patients and 2.9%, n:42 patients, respectively); with no non-inferiority criteria met for tofacitinib [79].

Conclusions and recommendations

MODERATE level of evidence and WEAK recommendation to consider JAKi therapy for the treatment of RA-ILD patients already receiving other DMARDs. RECOMMENDATION 2B.

RCTs are needed to further clarify this recommendation.

In patients aged ≥65 years with a history of smoking, cardiovascular disease, malignancy risk factors, and/or thromboembolic events, we recommend a careful, multidisciplinary, and individualized assessment before initiating JAKi therapy.

Question 7

Which patients with RA-associated ILD may be appropriate candidates for antifibrotic therapy?

Rationale

As previously discussed, UIP pattern is one of the most frequent HRCT findings in patients with RA-ILD and is associated with a prognosis similar to that of IPF.

The use of pirfenidone or nintedanib has been shown to be effective in reducing lung function decline and disease progression in patients with IPF. Additionally, these results are further supported by the recently published findings of a phase 3 RCT evaluating a new antifibrotic (nerandomilast) in IPF and progressive pulmonary fibrosis (PPF) [27].

Due to the lack of evidence in the treatment of RA-ILD, pathophysiologic similarities with IPF, and the emerging concept of PPF, there has been growing interest in the use of antifibrotic agents in RA-ILD patients. Therefore, it is important to investigate whether evidence exists to justify the use of antifibrotic therapy in patients with RA-associated ILD (RA-ILD).

Study selection

Two systematic reviews with meta-analyses of RCTs were included [80,81], one prospective cohort study [82], and one real-life retrospective cohort study [83].

Summary evidence

In a systematic review with meta-analysis that included two randomized clinical trials. In one study (TRAIL1), pirfenidone significantly reduced the annual decline in FVC in patients without PPF criteria compared with placebo (pirfenidone: −66 ml/year vs. placebo: −146 ml/year; $p = 0.0082$). However, the primary composite endpoint (≥10% decline in FVC or death) was not met, primarily due to recruitment limitations related to the COVID-19 pandemic, which increased the risk of bias in the study results. In another study (INBUILD) that include patients with RA-ILD who meet PPF criteria, a subanalysis showed that nintedanib significantly reduced the change in FVC compared with placebo at 52 weeks of follow-up [Nintedanib vs. placebo: 82 ml/year vs. 199 ml/year (SD = 36.2)]. The meta-analysis revealed that antifibrotic agents showed a significant reduction in FVC decline compared to placebo in patients with RA-ILD (mean difference, 88.30; 95% CI, 37.10–139.50). No differences in all-cause mortality were observed between the groups (RR = 0.82; 95% CI: 0.37–1.81; $p = 0.62$), and the safety profiles of both agents were comparable [80]. These findings are consistent with those reported by another systematic review with meta-analysis of RCTs that evaluated the effect of antifibrotics in 827 patients with ILD associated with CTD, of whom 238 had RA-ILD [81].

A prospective cohort study including 111 patients with ILD associated with CTD, 17 of whom had RA-ILD, evaluated the effect of pirfenidone combined with glucocorticoids and/or immunosuppressants. In the RA-ILD subgroup receiving pirfenidone, an increase in DLCO of 7.40% (2.18–14.00%) ($p = 0.002$) was observed overall, and particularly in patients with a non-UIP HRCT pattern ($p = 0.047$) [82].

Finally, a real-world retrospective cohort study [83] including 74 patients with RA-ILD who initiated antifibrotic therapy (40 with nintedanib and 34 with pirfenidone) and had a median follow-up of 89 weeks, showed a significant improvement in the estimated rate of FVC decline after antifibrotic treatment (−0.3% per year post-treatment vs. −6.2% per year pre-treatment).

Conclusions and recommendations

MODERATE level of evidence and STRONG recommendation for the use of nintedanib in RA-ILD patients with PPF. RECOMMENDATION 1B.

LOW level of evidence and WEAK recommendation for the use of pirfenidone in RA-ILD patients with fibrotic ILD. RECOMMENDATION 2C.

The use of pirfenidone may be determined by drug accessibility in each country. Further RCTs specifically in RA- ILD patients are essential to clarify this recommendation.

Treatment approach

Management of RA-ILD requires a multidisciplinary approach involving both rheumatologists and pulmonologists. Assessment of articular disease activity, the pattern of interstitial lung involvement and the degree of functional impairment is essential to guide therapeutic decision-making (Fig. 2).

Data from several RA-ILD cohorts suggest the possibility of distinct phenotypes defined by ILD patterns in combination with clinical characteristics, degrees of joint activity, biomarkers, and other factors. One phenotype, predominantly inflammatory, characterized by the presence of non-UIP patterns on HRCT, such as NSIP and/or OP. This phenotype more commonly affects younger females patients and is associated with persistently high articular disease activity [15,16,84,85]. Conversely, a predominantly fibrotic phenotype characterized by the presence of a UIP-like pattern, which typically affects older males (over 60 years) with a history of smoking and variable degrees of articular disease activity [17,32,86,87]. This phenotype shares several features with IPF including male gender, older age, UIP pattern, genetic profile and higher mortality which may have therapeutic implications [8,86,87].

The goal of DMARD therapy is to achieve articular activity remission while stabilizing or improving ILD, particularly in terms of functional outcomes, as radiological improvement is uncommon except in inflammatory phenotypes. No single optimal DMARD strategy exists for RA-ILD; therefore, treatment should be individualized according to patient phenotype, comorbidities, articular disease activity, HRCT pattern, and drug availability. Treatment response should be periodically assessed through clinical evaluation, laboratory tests, joint activity assessment, respiratory symptoms, pulmonary function tests, and HRCT when appropriate. Persistent joint activity and/or progression of the inflammatory interstitial component should prompt reconsideration of DMARD therapy.

Immunosuppressive agents such as MMF, AZA, and CYC are also widely used in daily clinical practice for the treatment of ILD secondary to other autoimmune diseases. However, given the low level of evidence supporting their use in the context of RA-ILD [88,61], and the fact that they are not considered DMARDs for achieving articular remission [89,90], these agents have not been included in this guideline for the treatment of RA-ILD. Their indication should be exceptional, and always based on a multidisciplinary and individualized evaluation, while prioritizing the use of DMARDs as the mainstay of treatment.

During follow-up, a proportion of patients with fibrotic ILD develop PPF. Although the exact proportion of RA-ILD patients who develop PPF has not yet been fully established, one cohort study reported that 36.6% of patients exhibited this behavior [91]. According to the ATS/ERS/JRS/ALAT guidelines, PPF is defined by the presence of at least two of the following three criteria within one year of follow-up: (1) worsening dyspnea without .another explanatory cause; (2) physiological progression defined as an absolute decline in FVC ≥ 5% and/or DLCO ≥ 10%; and (3) radiological evidence of fibrotic progression on CT [92]. Another study reported CT progression in 51% of patients [93].

In this scenario, initiation of antifibrotic therapy—preferably with nintedanib or nerandomilast (if available)—should be considered, along with reassessment of the patient's joint disease activity.

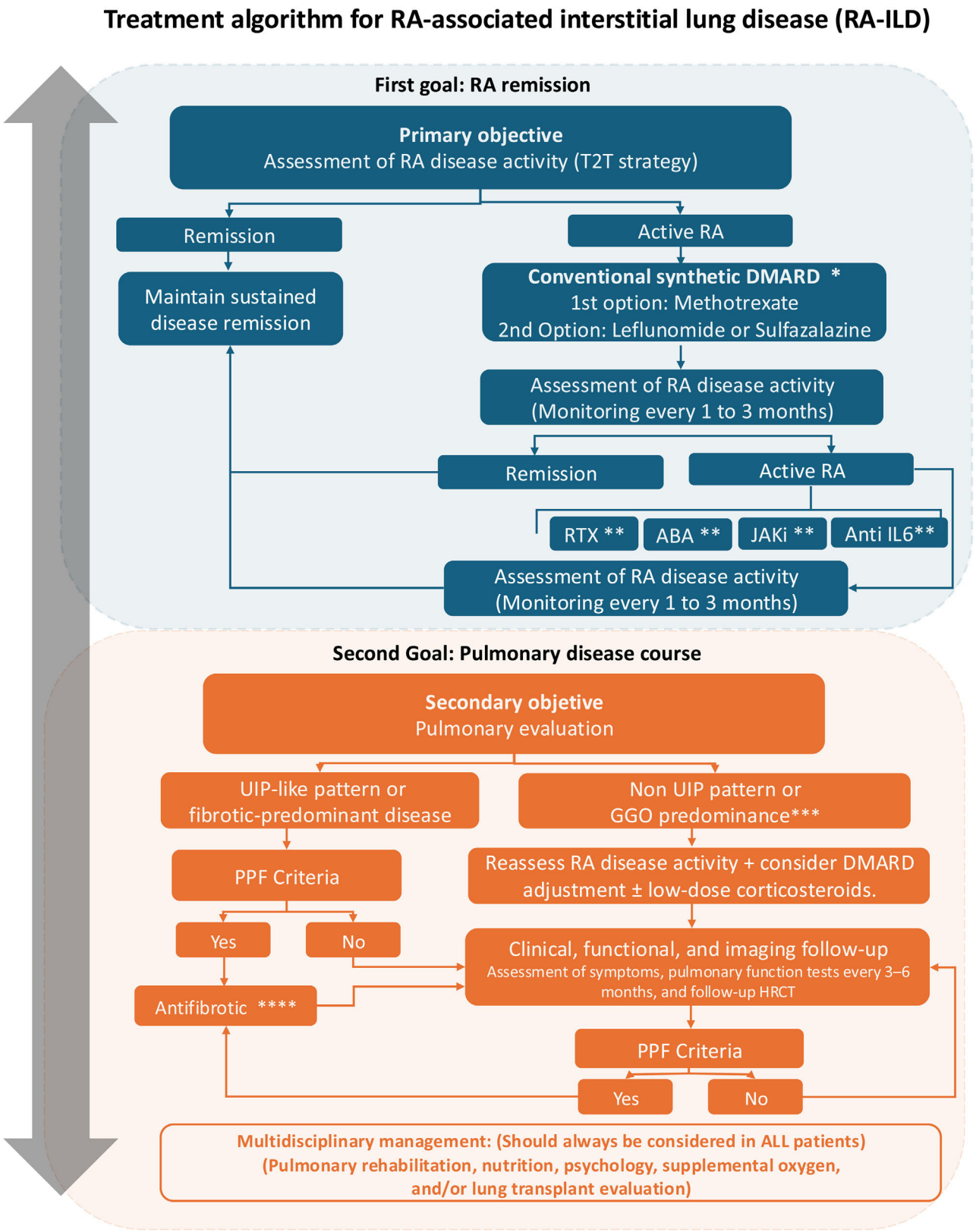

Fig. 2. Treatment algorithm for RA-associated interstitial lung disease (RA-ILD). RA, rheumatoid arthritis; ILD, interstitial lung disease; HRCT, high-resolution computed tomography; T2T, treat to target; DMARD, disease-modifying antirheumatic drugs; RTX, rituximab; ABA, abatacept; JAKi, janus kinase inhibitors; UIP, usual interstitial pneumonia; GGO, ground glass opacities; PPF, progressive pulmonary fibrosis. * In patients with MTX intolerance, LFN or SFZ should be considered. ** Evaluate the use of monotherapy versus combination therapy with methotrexate. *** Non-UIP patterns: OP, AFOP with airway predominance, or NSIP with airway predominance, or a combination of the above. **** Consider nintedanib as a first-line option, depending on availability in each country. Consider pirfenidone only if the former are not available. "This figure was developed by the authors to summarize the treatment approach described in the text and was not part of the formal Delphi voting process.".

Finally, as part of non-pharmacological management, smoking cessation, pulmonary rehabilitation, oxygen therapy when indicated, vaccination, appropriate nutrition, psychology support and evaluation for lung transplantation when appropriate should also be considered.

Conclusions

As previously mentioned, RA is the most prevalent autoimmune disease worldwide, and ILD is the second leading cause of death in this population. Therefore, one of the purposes of this document has been to provide a diagnostic strategy that allows for early identification of ILD, especially in patients with risk factors for ILD. Through appropriate screening, we can offer timely, adequate, and early treatment to improve patient outcomes.

The available evidence regarding the use of DMARDs for the treatment of RA-ILD has been extensively analyzed, considering that achieving articular remission remains the primary goal, not only for reducing the risk of ILD development but also for disease progression.

As a limitation of these guidelines, although they were developed as a practical tool for daily clinical practice, the available evidence for the management of this condition remains limited. Therefore, the diagnosis and treatment of patients with RA-ILD should always consider an individualized, specialized, and multidisciplinary approach. Another limitation of these recommendations is the absence of patient perspectives and/or input from patient associations regarding the applicability of the recommendations.

Unlike other guidelines, we emphasize the central role of DMARDs such as MTX, ABA, RTX, and/or JAKi. Also, we analyze the use of nintedanib and pirfenidone across different scenarios of fibrotic RA-ILD. Although the therapeutic approach to RA-ILD is not standardized, we propose a treatment algorithm that focuses on both achieving articular remission and treating ILD.

Artificial intelligence involvement

Partially for correction of the English translation.

Funding of the research

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

- Maria Laura Alberti – Speaker, Advisory activities or academic support from Boehringer Ingelheim, Adium, Bago, Tuteur. Financial competing interest: none.
- Santiago Jose Auteri – Speaker, Advisory activities or academic support from Adium, Boehringer Ingelheim, Bago, Tuteur. Financial competing interest: none.
- Jorge Rojas-Serrano – Speaker and consultant of Boehringer Ingelheim, Pfizer y Bristol Myers Squibb.
- Gustavo Citera – Advisor, investigator or speaker: Abbvie, Addium, Bagó, BioSidus, Boheringer Ingelheim, Bristol Myers Squibb, GSK, Johnson & Johnson, Pfizer, Sandoz.
- Ivette Buendía-Roldan – the authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Alejandra Babini – the authors declare not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Carlos Vinicio Caballero-Uribe – the author declares not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Antonio Cachafeiro – the author declares not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Juan Ignacio Enghelmayer – Investigator in clinical trials (Boehringer Ingelheim); research sponsorships (Boehringer Ingelheim, Adium, Elea); educational activities and speaker (Boehringer Ingelheim, Bagó, Adium, Tuteur, Grupo Knight, Finadiet, Elea, Aspen, BMS, Roche, Gador); scientific advisor (Boehringer Ingelheim, Bagó, Adium, Roche, Aspen, Gador, Tuteur).
- Matias Florenzano – the author declares not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Rodrigo García-Salinas – AbbVie/Abbott, Adium, Amgen, Biogen, Bristol-Myers Squibb(BMS), Eli Lilly, Janssen, Novartis, Pfizer, Raffo, Roche, UCB, Boehringer Ingelheim.
- Vicente Girón Atoche – Speaker Boehringer Ingelheim.
- Licia Maria Henrique da Mota – Received personal or institutional support from Abbvie, Janssen, Pfizer and Roche; has delivered speeches at events related to this work and sponsored by Abbvie, Boehringer Ingelheim, GSK, Janssen, Libbs, Lilly, Novartis, Pfizer, Roche, Sandoz, and UCB. Financial competing interest: none. Non-financial competing interest: none.
- Ronaldo Adib Kairalla – Participation in scientific events and assistance with conferences: Boehringer Ingelheim. Participation in scientific events: Sun Pharma.
- Agustín Acuña Izcaray – He received professional fees for the development and implementation of methodological aspects of these guidelines through Medsolid.
- Efraín Sanchez – He received professional fees for the development and implementation of methodological aspects of these guidelines through Medsolid.
- Ricardo Machado Xavier – Speaker/Consultant/Clinical investigator: Abbvie, Amgen, Biogen, Astra Zeneca, Johnson&Johnson, Novartis, EMS, Roche.
- Mayra Mejía – the author declares not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Karin Mueller Storrer – the author declares not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- María Belen Noboa-Sevilla – the author declares not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Lorena Noriega-Aguirre – Speaker Boehringer Ingelheim. Vice President of ALAT.
- Emily Rincon- Alvarez – the author declares not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Javier Rosa – the author declares not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Esther Tavera – the author declares not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Carlos Enrique Toro Gutierrez – Advisory Board and Speaker: AbbVie, Boehringer Ingelheim, BMS, Biopas, Johnson & Johnson, Pharmalab, Pfizer.
- Verónica Wolff – the author declares not to have any conflicts of interest that may be considered to influence directly or indirectly the content of the manuscript.
- Philippe Dieudè – Medical writing support from Bristol Myers Squibb. Grants or contracts from Bristol Myers Squibb, Boehringer

Ingelheim Pharmaceuticals Inc., Astrazeneca. Consulting fees from Bristol Myers Squibb, Pfizer, Boehringer Ingelheim. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Bristol Myers Squibb, Boehringer Ingelheim Pharmaceuticals, Pfizer. Participation on a Data Safety Monitoring Board or Advisory Board: Bristol Myers Squibb, Boehringer Ingelheim Pharmaceuticals, Pfizer.

- Fabian Matías Caro – Speaker, Advisory activities or academic support from Boehringer Ingelheim, Adium, Bago, Tuteur and Ferrer. Financial competing interest: none.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2026.04.001.

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