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The Italian Society for Rheumatology guidelines for the treatment of patients with rheumatoid arthritis and interstitial lung disease

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Abstract

Objective. In the absence of national and European guidelines on the treatment of rheumatoid arthritis (RA) with interstitial lung disease (ILD), the Italian Society of Rheumatology decided to develop national clinical practice guidelines on the management of patients with RA-ILD in accordance with the requirements of the National Guideline System of the National Institute of Health.
Methods. The development process included a systematic review of the available evidence and its adaptability to the Italian context, followed by a consultation with experts in rheumatology, respiratory diseases, radiology, and representatives of the health professions and patients.
Results. The panel decided to develop recommendations in three main scenarios. The first section of recommendations is focused on drugs indicated for RA to assess their safety and efficacy in RA-ILD. The second set of recommendations covered the drugs indicated for the treatment of ILD in patients with RA-ILD (to assess their efficacy and safety in patients with RA). The third part of these guidelines dealt with drugs indicated for the treatment of RA-ILD upon first-line failure. Moreover, the lack or absence of scientific evidence in literature on certain topics, such as the value of a multidisciplinary treatment approach and lung transplantation, led to the decision to proceed through expert consensus to develop good clinical practice guidelines.
Conclusions. These guidelines represent a fundamental step towards improving the health management of patients with rheumatological diseases in Italy by providing specific and evidence-based guidelines for the management of RA-ILD. Their use is intended to promote health and reduce the burden of morbidity and mortality in this vulnerable population.

Key words: guidelines, clinical practice, recommendations, rheumatoid arthritis, interstitial lung disease.

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Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory disease that affects approximately 0.5-1% of the adult population in Western countries. It is estimated that at least 350,000 patients are affected in Italy (1, 2).

Although joint inflammation is the main clinical manifestation, extra-articular involvement is not uncommon. The lungs are one of the main extra-articular sites that can be involved in RA, with interstitial lung disease (ILD) being the most common and potentially severe form of respiratory complication (3).

RA-associated ILD (RA-ILD) consists of inflammation with possible fibrotic evolution of the lung parenchyma that can lead to respiratory failure and an increased risk of infections and cardiac complications. Fibroblast hyper-proliferation and epithelial-mesenchymal transition of alveolar epithelial cells are considered the biological processes underlying the fibrotic evolution of RA-ILD (3).

ILD can develop in 10-15% of patients with RA (4), and it is associated with significantly higher morbidity and mortality rates compared to forms without pulmonary involvement (4). The condition entails substantial healthcare costs, both direct, in terms of pharmaceutical costs and management of complications, and indirect, secondary to loss of work capacity and reduced quality of life (5).

Furthermore, the treatment of RA-ILD is challenging due to the heterogeneity of the clinical onset pattern, the course of the pulmonary disease (subclinical, stable, slowly progressive, rapidly progressive), the different radiological patterns and histopathological subtypes of the interstitial disease, and the concomitant presence of RA articular and extra-articular involvements, which in turn are extremely heterogeneous. Therefore, the activity and severity of the articular disease, together with the histopathological/radiological pattern of the ILD, and its severity and progression, are the main factors to be considered for therapeutic decisions (6).

The treatment of ILD does not necessarily coincide with that of arthritis and consists of immunosuppressive and anti-fibrotic treatments. The drugs used to treat RA may also be useful in slowing down the progression of the pulmonary disease. In some cases, however, treatments for arthritis may be ineffective or counterproductive for the concomitant ILD (7, 8). The introduction of anti-fibrotic treatments also for fibrosing ILDs other than the idiopathic forms opened new therapeutic possibilities for progressive forms of pulmonary fibrosis secondary to RA (9-12).

The latest recommendations of the European Alliance of Associations for Rheumatology (EULAR) for the management of RA did not specifically address the treatment of RA-ILD (13).

Recently, the Spanish Society of Rheumatology has produced recommendations for the treatment of patients with RA-ILD, although many of the points addressed remain under discussion (7).

In August 2024, guidelines developed by the American College of Rheumatology (ACR) jointly with the American College of Chest Physicians for the treatment of ILD in patients with systemic autoimmune diseases were published (8). The American guidelines were developed based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, but unlike the Spanish and current recommendations, they provide indications for the treatment of ILD secondary to systemic autoimmune diseases such as systemic sclerosis, idiopathic inflammatory myopathies, mixed connective tissue disease, Sjögren's syndrome, and RA, but without referring to the treatment of joint involvement in this category of patients. Moreover, the different therapeutic indications of several drugs in the United States (US) compared to Italy make the US guidelines not entirely applicable in our Country. In the recommendations specifically dedicated to RA, the first-line use of immunosuppressive drugs is proposed, while pirfenidone and nintedanib are proposed indifferently as second-line drugs, as an alternative to a new course with immunosuppressive drugs, when the first-line immunosuppressant fails. The use of antifibrotics as a first-line option was deeply debated, but the panel did not reach consensus on their possible use as first-line therapy (8).

Several unmet needs in the routine management of patients with RA-ILD, which are not addressed by the available evidence in the literature, suggest the need for shared recommendations on this topic.

Therefore, in the absence of national and European guidelines on the treatment of RA-ILD, the Italian Society of Rheumatology (SIR) decided to develop *de novo* national clinical practice guidelines on the management of patients with RA-ILD in accordance with the requirements of the National Guideline System (NGS) of the National Institute of Health (NIH).

Need for Italian guidance

In Italy, to date, there is no single document with the value of a shared national guideline on the management of patients with RA-ILD.

Objective

These guidelines aim to provide up-to-date, evidence-based recommendations on the management of patients with RA-ILD in Italy in accordance with the requirements of the NGS of NIH.

Population target

Adult patients (age ≥18 years old) diagnosed with RA-ILD are the population target.

What is covered

The treatment of patients with RA complicated by chronic ILD with or without signs of progression will be the subject of these guidelines.

Areas that are not covered

These recommendations will not include pediatric patients (<18 years), patients with RA affected by other concurrent forms of primary ILD, or patients with ILD and a rheumatologic diagnosis other than RA. Furthermore, topics related to the diagnosis and monitoring of RA-ILD and acute forms of ILD will not be addressed.

Approach to guideline development and clinical questions

The GRADE-ADOLOPMENT methodology was used to identify existing and relevant guidelines on the topic and to adopt or adapt recommendations in accordance with the methodological manual for developing clinical practice guidelines and the operational manual of the Italian National Center for Clinical Excellence, Quality, and Safety of Care of the NIH (14-16). The guideline topic, activity plan, and resource use were approved, and the project Steering Committee was appointed by the SIR Board of Directors to serve as the Scientific Technical Committee (October 21, 2022). In the absence of reference guidelines, clinical questions were formulated a priori, structured using the PICO method (P,

patient; I, intervention; C, comparator/control; O, outcome). Outcomes (direct, surrogate, or indirect and patient outcomes) were identified, classified, and selected for importance through consultation with panel members and stakeholders. The project was approved by the Steering Committee, and the final protocol for guideline development was approved by the panel (version 2.0, July 16, 2023).

Materials and Methods

Assembly of the working groups

With approval from the Scientific Technical Committee, the Developer (CC) and Co-Developer (NU), along with the Evidence Review Team (EDL, AF, SM, MR) from the SIR Study Center, collaborated with a multidisciplinary and multispecialty panel of clinical experts in rheumatology, pulmonology, and imaging (Executive Committee: MS - Chair, AM - Co-Chair, CAS, FL - Steering Committee; panel members: FA, SLB, RC, MC, GC, LC, LD, GLE, RG, SAH, FI, ALM, MMC, MAM, VP, FS, GDS, CV), a physiotherapist (SS), and a representative (ST) from the National Association of Rheumatic Patients (ANMAR). The panel was chosen under the Chair's and Co-Chair's proposal from Italian rheumatologists with experience in lung involvement in rheumatic diseases, endorsed by the Steering Committee and the executive board of SIR. Pulmonologists and radiologists were proposed by their own Scientific Societies. Discussions were conducted *via* email, web meetings, and online surveys (*via* REDcap®). Participation of at least 75% of the workgroup members was required for discussions and assessments to be considered valid in the development of the final recommendations.

Stakeholder involvement

A multidisciplinary, multi-professional, and nationally representative group of physicians from the SIR Study Groups on Lung and Rheumatoid Arthritis and on Seronegative Arthritis, healthcare professionals from FOR-RHeUMA, and patients' representatives from ANMAR were invited to review and vote on the outcomes and the text of these recommendations. These recommendations were developed without any contribution or collaboration from pharmaceutical or industry companies.

Audience

The document is primarily intended for specialists in rheumatology, immunology and allergology, pulmonology, internal medicine, general practitioners (primary audience), and all healthcare professionals involved in managing patients with rheumatologic disease across primary, secondary, and tertiary care settings, both in community and hospital environments.

Search strategy, selection criteria, data extraction, and synthesis of scientific evidence

Starting from the formulation of clinical questions structured in the PICO format modified and adapted to the Italian context following the ACR Project Plan, the disease outcomes were evaluated by the panel (October 9-23, 2023) and stakeholders (February 1-15, 2024) (17, 18). Outcomes rated as "important and essential" or "important but not essential" were used to guide the systematic search for scientific evidence.

The literature search was based on specifically formulated keywords and search strings to execute a new systematic search aligned with the outcome voting (17). The following databases were queried: Medline (*via* Ovid), Embase (*via* Ovid), and Cochrane Library (*via* Cochrane Central). A *de novo* systematic review was conducted from the historical database inception up to October 9, 2023. The Evidence Review Team selected studies and extracted data (with at least two members independently conducting these steps). Inclusion criteria for the literature search were as follows: English, Italian, or other languages if a translation was available; relevance to the clinical questions; all study designs (including experimental and observational clinical studies, case studies if involving five or more subjects, adjusted during study selection to at least three subjects due to limited available studies). Publications in the form of recommendations, guidelines, or consensus statements, case studies with fewer than three subjects, those in languages for which no translation was available, and those not addressing clinical questions were excluded. The study selection flow is depicted in Figure 1. The results of the data extraction in line with the reference guideline were summarized and reported in synoptic tables (Evidence Profile) divided by PICO (17).

For topics where the panel deemed it appropriate to provide treatment guidance (*e.g.*, lung transplant) but insufficient evidence was available, it was decided to proceed with the development of good clinical practice recommendations in accordance with GRADE criteria for evaluating Good Practice Statements (19).

Critical appraisal of quality

The quality of the evidence identified through systematic search was assessed by the Evidence Review Team in accordance with the GRADE method, analyzing the following domains: limitations (risk of bias quantification), inconsistency, indirectness, imprecision, and publication bias (assessed through funnel plot visualization and Egger's test). Risk of bias was evaluated using the following tools: the Risk of Bias in Non-Randomized Study - of interventions (ROBINS-I) and the Revised Cochrane Risk-of-Bias Tool for randomized trials (RoB 2) for treatment (17, 20, 21). Quality assessment of the evidence also considered three criteria for potentially upgrading observational studies (effect size, dose-response relationship, and consideration of confounding factors). Finally, an overall quality rating was assigned to the evidence using the terms "high", "moderate", "low" and "very low", reflecting the expected impact on confidence in the effect estimate (Table 1).

From the evidence profile to the evidence-to-decision framework and the development of the recommendations

The results of the evidence profiles and quality assessments were integrated into the evidence-to-decision (EtD) framework structure, and the recommendations were discussed by the panel *via* web meetings (March 20, 2024; April 4, 2024; and May 2, 2024). Considering the available scientific evidence, as well as the scarcity and heterogeneity of studies, a judgment on the strength of the recommendations was formulated, categorized as strong or conditionally applicable in alignment with the perspectives of patients, clinicians, and policymakers (Table 1).

The panel's considerations on the strength of the recommendations, risks, and benefits, and applicability have been reported in the EtD tables compiled on the basis of the updated evidence (17).

In accordance with the National System of Guidelines Methodological Manual, each recommendation was expressed in formulations of "it is recommended" and "it is suggested" to indicate the recommendation strength as deemed appropriate by the

panel based on the available scientific evidence. Finally, good clinical practice statements were developed through expert panel consensus, taking into account clarity, feasibility, clinical relevance, anticipated favorable health impact, and the time and resource limitations for searching and synthesizing available evidence (19).

The AGREE checklist for guideline publication was used as a framework for the final version of these recommendations (22).

Approval of the recommendations and stakeholders' consultations

The panel members reviewed the draft recommendations *via* an online survey (June 20, 2024 - July 1, 2024; 23 out of 24 complete responses, response rate 95.8%, *via* REDcap®), assigning a score from 1 (worst) to 9 (best). A predefined threshold of an average score above 7 was set for validation and approval of the guide-

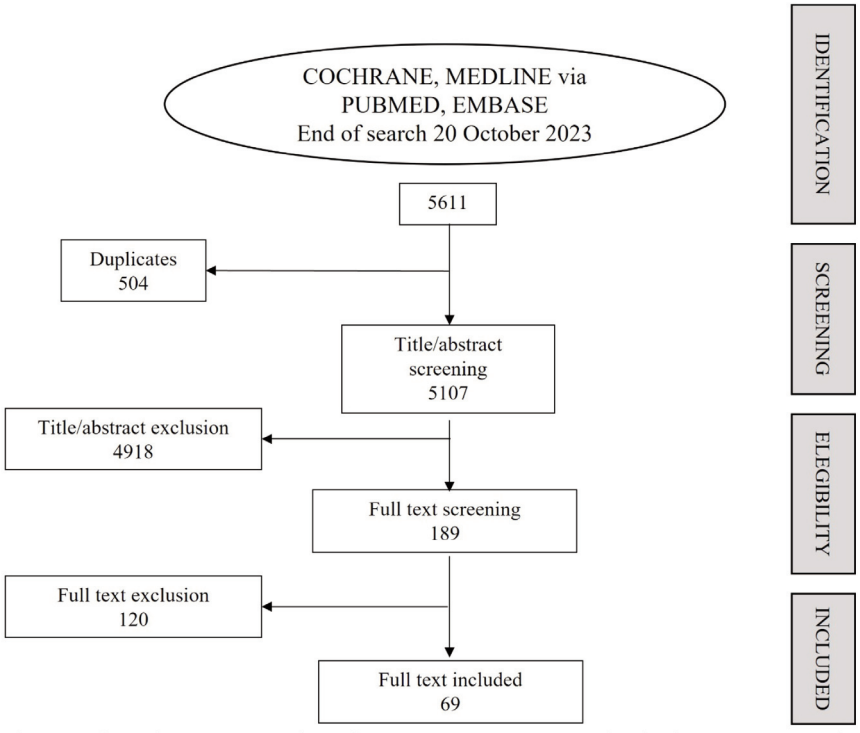

Figure 1. Steps in the systematic reviews on the development of guidelines on rheumatoid arthritis associated with interstitial lung disease.

Table 1. Guidance for the appraisal of the quality of evidence and strength of the recommendations in accordance with the Grades of Recommendation Assessment, Development and Evaluation approach.

Quality of Evidence			
	Expected impact on confidence of the estimate of the effect		
High	"Further research is very unlikely to change our confidence in the estimate of effect"		
Moderate	"Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate"		
Low	"Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate"		
Very Low	"Any estimate of effect is very uncertain"		
Strength and direction of a recommendation			
	Patients	**Clinicians**	**Policy makers**
Strong in favor or against	Most people in this situation would/would not want the recommended course of action and only a small proportion would not.	Most patients should/should not receive the recommended course of action.	The recommendation can/can not be adapted as a policy in most situations.
Conditional in favor or against	The majority of people in this situation would/would not want the recommended course of action, but many would not.	Be prepared to help patients to make a decision that is/is not consistent with their own values.	There is/is not a need for substantial debate and involvement of stakeholders.

Table 2. The final set of recommendations of the Italian Society of Rheumatology on treatment of patients with rheumatoid arthritis and interstitial lung disease.

	Recommendation	Quality of evidence	Strength and direction of recommendation	Level of agreement
1. Recommendations for drugs indicated for rheumatoid arthritis to assess their safety and efficacy in RA-ILD				
1.a	It is suggested to use methotrexate, when indicated for the treatment of arthritis, even in patients with RA-ILD.	Low	Conditional in favor	8.3 (1.2)
1.b	As an alternative to methotrexate, in patients with RA-ILD, it is suggested to consider treatment with other csDMARDs for arthritis management, following current guidelines applied to patients without ILD.	Low (calcineurin inhibitors, leflunomide), very low (azathioprine)	Conditional in favor	7.9 (1.1)
1.c	In patients with RA-ILD, it is suggested to avoid using TNFα inhibitors for arthritis treatment.	Low	Conditional against	7.5 (1.6)
1.d	In patients with RA-ILD, when clinically indicated, it is suggested to use abatacept for arthritis treatment.	Very low	Conditional in favor	8.1 (0.9)
1.e	In patients with RA-ILD, when clinically indicated, it is suggested to use rituximab for arthritis treatment.	Very low	Conditional in favor	8.0 (1.0)
1.f	In patients with RA-ILD, it is suggested to use IL-6 receptor antagonists for arthritis treatment, adopting an individualized approach.	Low	Conditional in favor	8.0 (0.9)
1.g	In patients with RA-ILD, it is suggested to use JAK inhibitors for arthritis treatment, adopting an individualized approach.	Very low	Conditional in favor	7.9 (1.0)
2.0 Recommendations on drugs indicated for the treatment of interstitial lung disease in patients with RA-ILD (to assess their efficacy and safety in patients with RA)				
2.a	In patients with RA-ILD, it is suggested to consider immunosuppressive agents (azathioprine, cyclophosphamide, and mycophenolate mofetil) as one of the therapeutic options for treating ILD.	Very low	Conditional in favor	7.7 (0.9)
2.b	In patients with RA-ILD, it is suggested to avoid the use of TNFα inhibitors for the treatment of ILD.	Low	Conditional against	7.7 (1.7)
2.c	In patients with RA-ILD, it is suggested to consider biologic agents (abatacept and rituximab) as one of the therapeutic options for treating ILD.	Very low	Conditional in favor	7.9 (0.8)
2.d	In patients with RA-ILD, it is suggested to use glucocorticoids in short courses, adopting an individualized approach, as one of the therapeutic options for treating ILD.	Very low	Conditional in favor	8.0 (1.0)
2.e	In patients with RA-ILD classifiable as progressive pulmonary fibrosis, regardless of DMARD treatment, it is suggested to use nintedanib as one of the therapeutic options for managing ILD	Low	Conditional in favor	8.4 (0.9)
2.f	In patients with RA-ILD and with progressive pulmonary fibrosis, regardless of the cs/b/tsDMARD treatment, it is suggested not to use pirfenidone as a first-line therapy for treating progressive pulmonary fibrosis.	Low	Conditional against	8.0 (1.0)
3.0 Recommendations on drugs indicated for the treatment of RA-ILD upon first-line failure				
3.a	In patients with RA-ILD and progressive pulmonary fibrosis who have not responded to first-line ILD treatment, it is suggested to use nintedanib as one of the subsequent therapeutic options.	Low	Conditional in favor	8.0 (1.7)
3.b	In patients with RA-ILD who have not responded to first-line ILD treatment, it is suggested not to use TNFα inhibitors as salvage therapy for pulmonary disease following the failure of alternative treatments.	Very low	Conditional against	7.7 (1.8)

Key:

Strong in favor

Conditionally in favor

Conditionally against

Strong against

RA-ILD, rheumatoid arthritis associated with interstitial lung disease; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; TNF, tumor necrosis factor; IL-6, interleukin-6; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs.

line for clinical practice use. The outcome of the second voting round for each recommendation is provided in the final document (17). In cases where a panel member disclosed a specific potential conflict of interest, the associated vote was excluded from the calculation of the average score for approval.

Stakeholders were consulted to provide comments and rate (also on a scale of 1 to 9) the preliminary version of the recommendations through an online survey (July 10-26, 2024, *via* REDcap®). Comments from respondents were considered in developing the final version of the recommendations. When available, these comments were included in the section "from evidence to recommendation" (17).

Results

Key to understanding the guidance

Each recommendation is reported with the quality of evidence, strength of the recommendation, and level of agreement between the members of the panel (Table 2). The text supporting each recommendation is structured as follows: i) supporting evidence – list of the evidence; ii) from evidence to recommendation – panel's discussion based on the evidence and the clinical experience used to develop the recommendation. A summary of all recommendations is presented in the NIH document (17).

Recommendations

Table 2 reports the final set of recommendations of SIR on the treatment of patients with RA and ILD.

Recommendations for drugs indicated for rheumatoid arthritis to assess their safety and efficacy in rheumatoid arthritis associated with interstitial lung disease

Supporting evidence to recommendation 1.a

Evidence is derived from studies that evaluated the reduction of forced vital capacity (FVC) under methotrexate and from observational studies that explored mortality during therapy with this drug (23-25). A retrospective case-control study and a cross-sectional observational study were also considered (26, 27).

From evidence to recommendation 1.a

In patients with RA-ILD who are taking methotrexate therapy, the panel suggests an individualized approach. In patients in whom ILD is occasionally found in a well-controlled RA on stable methotrexate therapy, the panel suggests continuing methotrexate therapy, while in patients with new findings of ILD or who experience ILD progression, it is suggested to consider discontinuing methotrexate. The temporal relationship between the start of treatment with methotrexate and the diagnosis of ILD should represent the most important factor for the therapeutic decision if continuing or withdrawing the drug, particularly in the occurrence of acute onset or symptomatic ILD.

Supporting evidence to recommendation 1.b

The considerations supporting this recommendation derive mainly from evidence from observational studies of low quality for leflunomide and cyclosporine A and very low quality for evidence on the use of azathioprine (23, 28, 29).

From evidence to recommendation 1.b

The expert panel members emphasized that the treatment of RA should be consistent with the latest guidelines on the management of RA (13, 30, 31), including for patients with associated ILD. For the treatment of arthritis in patients with RA-ILD, as an alternative to methotrexate, identified as the drug of first choice, the use of leflunomide, cyclosporine A, or azathioprine may be considered in patients in whom methotrexate is contraindicated or has been discontinued due to side effects.

Supporting evidence to recommendation 1.c

The evidence supporting this recommendation is derived from observational studies and retrospective studies, such as case-series or cohort studies (32-35).

From evidence to recommendation 1.c

The discussion of this recommendation did not reach complete agreement of the panel of experts; however, the final wording of the recommendation was agreed upon with some specifics that are detailed below. Evidence from literature suggests a possible deleterious effect of tumor necrosis factor (TNF) α inhibitors on ILD, mainly regarding an increased risk of acute exacerbation (35), but without confirmation in controlled studies. Therefore, the panel members emphasized that, in patients with RA-ILD who are taking TNFα inhibitor therapy, an individualized approach is necessary. Indeed, in patients with RA who are taking TNFα inhibitors for the treatment of RA, in whom a diagnosis of non-symptomatic ILD is made, discontinuation of therapy is not suggested. Whereas in those patients with RA on TNFα inhibitors for the treatment of RA, in whom clinically significant ILD is documented, the panel suggests discontinuing anti-TNFα inhibitor treatment. Finally, in those patients with RA-ILD who are already on TNFα inhibitors for the treatment of RA, in whom a progression of ILD is observed, the panel members do not suggest the continuation of therapy with TNFα inhibitors.

Supporting evidence to recommendation 1.d

The expert panel made this recommendation based on uncontrolled studies, both retrospective and prospective, with a very low level of evidence (36-42). In retrospective, uncontrolled studies, the largest amount of data did not raise any safety concern on this drug for patients with joint involvement in RA-ILD patients. Recently, abatacept confirmed its safety on RA-ILD in a small longitudinal study from Korea (43).

From evidence to recommendation 1.d

The expert panel emphasizes that abatacept could be used in monotherapy, without methotrexate, if clinically necessary.

Supporting evidence to recommendation 1.e

The formulation of this recommendation derives from the discussion of very low-quality evidence, which mainly refers to uncontrolled, non-randomized studies (44-49). In many cases, data is derived from studies including both RA and connective tissue diseases patients.

From evidence to recommendation 1.e

Similar to recommendation 1.d, the expert panel points out that the use of rituximab is not necessarily to be referred to in combination with methotrexate, as it considers rituximab monotherapy possible, if clinically appropriate. The expert panel suggests that the infectious risk should be carefully evaluated on an individualized basis when choosing rituximab as therapy for arthritis.

Supporting evidence to recommendation 1.f

The evidence supporting this recommendation comes from non-randomized, controlled studies (23), and from non-randomized, non-controlled studies (50, 51), and refers to interleukin (IL)-6 receptor antagonists for the treatment of arthritis, *i.e.*, tocilizumab and sarilumab.

From evidence to recommendation 1.f

The expert panel considered, based on the available evidence, recommending the use of IL-6 receptor antagonists in patients with RA-ILD, maintaining an individualized approach.

Supporting evidence to recommendation 1.g

The evidence supporting this recommendation is of very low quality and comes from non-randomized, non-controlled retrospective, case-controlled studies (42, 52, 53).

From evidence to recommendation 1.g

The panel formulated this recommendation on Janus kinase (JAK) inhibitor drugs for the treatment of arthritis, namely tofacitinib, baricitinib, upadacitinib, and filgotinib. The individualized approach is recommended, according to the most recent guidelines on the management of RA (7, 8, 13, 31).

Recommendations on drugs indicated for the treatment of interstitial lung disease in patients with rheumatoid arthritis associated with interstitial lung disease (to assess their efficacy and safety in patients with rheumatoid arthritis)

Supporting evidence to recommendation 2.a

The studies supporting the use of azathioprine are based on retrospective, non-randomized, and uncontrolled data (29), similarly to the studies supporting the use of mycophenolate mofetil (29, 54). Evidence for the use of cyclophosphamide comes from a non-randomized controlled study on the survival of RA-ILD patients treated with cyclophosphamide and a retrospective study (55, 56).

From evidence to recommendation 2.a

The panel was in favor of intervention with immunosuppressants (azathioprine, cyclophosphamide, or mycophenolate mofetil), albeit conditionally due to the low or very low quality of the evidence supporting the recommendation. The panel emphasizes that attention should be paid to the safety profile of azathioprine and cyclophosphamide, especially regarding the infectious risk of the latter, and stresses the need for an individualized approach. Furthermore, in a holistic approach to the patient, the lack of effectiveness of these immunosuppressants in RA-related joint involvement should be taken into account. In such cases, a combination therapy with a disease-modifying antirheumatic drug (DMARD) should be considered, inducing a further increase in the infectious risk, already augmented in RA-ILD subjects.

Supporting evidence to recommendation 2.b

This recommendation is based on evidence from studies with a low strength of evidence. Specifically, it refers to a non-randomized, controlled study (27), that evaluated functional decline in RA-ILD patients treated with TNFα inhibitors and a non-randomized controlled study that observed no reduction in survival for RA-ILD patients on TNFα inhibitors (57). On the other hand, case series and case reports suggested an increased risk of acute exacerbation of ILD in patients treated with TNFα inhibitors, mainly infliximab (58). Additionally, the panel's evaluations considered a retrospective study and a case series on the use of infliximab in formulating this recommendation (32, 33).

From evidence to recommendation 2.b

The panel, based on currently available evidence, suggests that TNFα inhibitor drugs should not be used for the treatment of ILD.

Supporting evidence to recommendation 2.c

This recommendation is based on very low-quality evidence. For abatacept, the supporting evidence primarily comes from non-randomized, uncontrolled, retrospective cohort studies (37, 39-41), and non-randomized, uncontrolled prospective studies (37, 39, 59). Recently, a prospective Korean study showed a slower progression of ILD in RA-ILD patients treated with abatacept compared to conventional DMARDs (43). The panel also noted a meta-analysis supporting this recommendation (60). Evidence for the use of rituximab is derived from non-randomized, uncontrolled retrospective studies (44-46, 49), and open-label prospective studies (48).

From evidence to recommendation 2.c

In patients with RA-ILD, according to currently available evidence, the panel suggests the use of bDMARDs, such as abatacept and rituximab, as one of the therapeutic options for the treatment of ILD.

Supporting evidence to recommendation 2.d

The panel formulated these recommendations based on very low-quality evidence. This includes non-randomized controlled studies on the use of oral glucocorticoids in relation to pulmonary function decline, assessed *via* FVC (23), and retrospective cohort studies on the use of high-dose prednisone in patients with RA-ILD (61).

From evidence to recommendation 2.d

The expert panel advises clinicians to use glucocorticoids with an individualized approach. Specifically, they suggest glucocorticoids use in acute-subacute forms, with rapidly progressive onset, and in inflammatory patterns other than usual interstitial pneumonia (non-UIP). The panel, in alignment with stakeholder feedback, highlights the importance of immunosuppressants in preventing and reducing the side effects of chronic glucocorticoid therapy, helping to lower their dosages and, in some cases, facilitating their discontinuation. In case of glucocorticoids use, the panel suggests using the minimum possible dosage and to discontinue as rapidly as possible A short course could be defined as a therapy of 3 months or shorter. Furthermore, in managing RA-ILD, therapeutic options are limited, especially given the impact of the condition on prognosis. Therefore, the risk-benefit ratio of steroids in RA-ILD treatment should be assessed on an individual basis.

Regarding the use of glucocorticoids for the treatment of RA-ILD, the expert panel points out that it is important to refer to the guidance provided in the latest EULAR recommendations on RA management (13), and the SIR recommendations (31).

Supporting evidence to recommendation 2.e

The recommendation on the use of nintedanib was made considering the data from the post-hoc analysis of the INBUILD randomized controlled trial (11). The effect of nintedanib in terms of a smaller decline in FVC in the treated group compared to placebo was reported, achieving statistical significance, particularly in

patients with a UIP-like fibrotic pattern on high-resolution computed tomography (HRCT) imaging, as opposed to other fibrotic patterns in a basket trial including 89 patients with RA-ILD. Additional evidence for nintedanib comes from non-randomized controlled studies that evaluated its effects on respiratory function (measured by FVC), incidence of lung disease exacerbations, hospitalization rate, as well as its safety profile (measured by 52-week mortality, respiratory infections, number of serious adverse events, and toxicity leading to drug discontinuation) (62).

From evidence to recommendation 2.e

Based on the evidence provided, the panel suggests considering nintedanib as a therapeutic option for progressive fibrosing ILD. In particular, the panel suggests considering this drug in patients with UIP patterns.

Supporting evidence to recommendation 2.f

The panel formulated the recommendation based on low-quality data coming from two randomized controlled trials (12, 63).

From evidence to recommendation 2.f

The panel, based on low-quality evidence, suggests limiting the consideration of pirfenidone to patients who cannot use nintedanib, particularly those with a UIP pattern. The phase 2 RCT TRAIL1 did not meet its composite primary endpoint due to early termination from low recruitment rates during the COVID-19 pandemic. However, compared to the placebo group, patients in the pirfenidone group showed a slower rate of decline in the estimated annual change in absolute FVC (key secondary endpoint). Pirfenidone demonstrated a more pronounced slowing of FVC decline in both the overall population and in the subset with a UIP pattern. This recommendation reflects considerations regarding the limited evidence of efficacy, potential adverse effects, and costs. Currently, pirfenidone is not indicated for the treatment of ILD other than idiopathic pulmonary fibrosis in Italy and Europe.

Commentary on the recommendations section for drugs indicated for the treatment of rheumatoid arthritis to evaluate their efficacy and safety on interstitial lung disease

Regarding the use of JAK inhibitors or IL-6Ra for the treatment of RA-ILD, there is no data to support their use, but neither is there any data to contraindicate them.

Recommendations on drugs indicated for the treatment of rheumatoid arthritis associated with interstitial lung disease upon first-line failure

Supporting evidence to recommendation 3.a

The evidence supporting this recommendation is based on the post hoc analysis of the INBUILD randomized controlled trial (11).

From evidence to recommendation 3.a

The panel highlights that, depending on the clinical scenario, combining nintedanib with an immunosuppressive agent may be considered, as the safety profile has been investigated in previous RCTs on systemic sclerosis and as suggested in recently published recommendations for systemic sclerosis-associated ILD (64, 65). Recently, a registry-based Italian study suggested the safety of nintedanib also in combination with conventional and biologic DMARDs (66).

Supporting evidence to recommendation 3.b

Evidence supporting this recommendation comes from a non-randomized, controlled study that documented a significant decline in lung function expressed as a ≥10% reduction in FVC in patients treated with anti-TNFα drugs (23). Similarly, another non-randomized controlled study showed a shorter survival in RA-ILD patients treated with TNFα inhibitors (57).

Additionally, very low-quality data from the literature, including case series and retrospective cohort studies (28, 29), did not provide definitive conclusions regarding the use of this drug class.

From evidence to recommendation 3.b

Based on the evidence available to date, the panel suggested against the use of anti-TNFα drugs for the treatment of ILD as rescue therapy after the failure of alternative therapies.

Further comments concerning the recommendations section for medications indicated for interstitial lung disease treatment upon first-line failure

The available literature is limited regarding progressive ILD forms that do not respond to first-line treatment, both for fibrotic and inflammatory ILD subtypes. For fibrotic forms, the panel did not issue a recommendation on the potential use of pirfenidone as a second-line therapeutic option for ILD, as the currently available evidence was deemed insufficient to formulate a statement. Data from the RELIEF study were considered (67), suggesting that in patients with worsening fibrotic ILDs other than idiopathic pulmonary fibrosis, adding pirfenidone to existing treatment might slow disease progression, measured by reduced FVC decline. Additionally, a double-blind, randomized phase 2 study on subjects with progressive unclassified ILD was reviewed as indirect evidence (68), though it was not conducted on the target population of these guidelines, focusing instead on progressive fibrosing ILD of unclassifiable types.

Similarly, the panel did not make a recommendation on the use of abatacept and IL-6Ra in RA-ILD patients PPF following first-line treatment due to a lack of supporting literature. Likewise, the panel recognizes that no evidence is currently available for rituximab use in this context, as existing data relate solely to its use in inflammatory lung disease, particularly in acute cases, with no data available for chronic fibrosing forms, with the exception of a small number of patients described in the retrospective study by Matson (29). Similarly, based on available evidence, the expert panel refrained from making a statement on the use of intravenous immunoglobulins in patients with progressive RA-ILD unresponsive to first-line treatment, although a potential role is acknowledged in ILD patients with a high infection risk and as add-on therapy in patients with rapidly progressive ILD associated with connective tissue diseases (8) (Figure 2).

Good clinical practice in the management of patients with rheumatoid arthritis associated with interstitial lung disease

The significant prognostic impact of ILD in patients with RA has necessitated the development of clinical guidance for managing these patients. However, the scarcity or absence of scientific evidence in literature on certain topics, such as the value of a multidisciplinary treatment approach and lung transplantation, led to the decision to proceed through expert consensus to develop good clinical practice guidelines. These good clinical practice statements aim to provide support in these areas not covered by

the previous recommendations. The good clinical practice statements are detailed in Table 3. Regarding lung transplant indications, the panel emphasizes the importance of adhering to current national guidelines for organ transplantation (69) (Table 3).

Discussion and Conclusions

To date, there are no single, comprehensive national recommendations in Italy for the management of RA-ILD. An updated

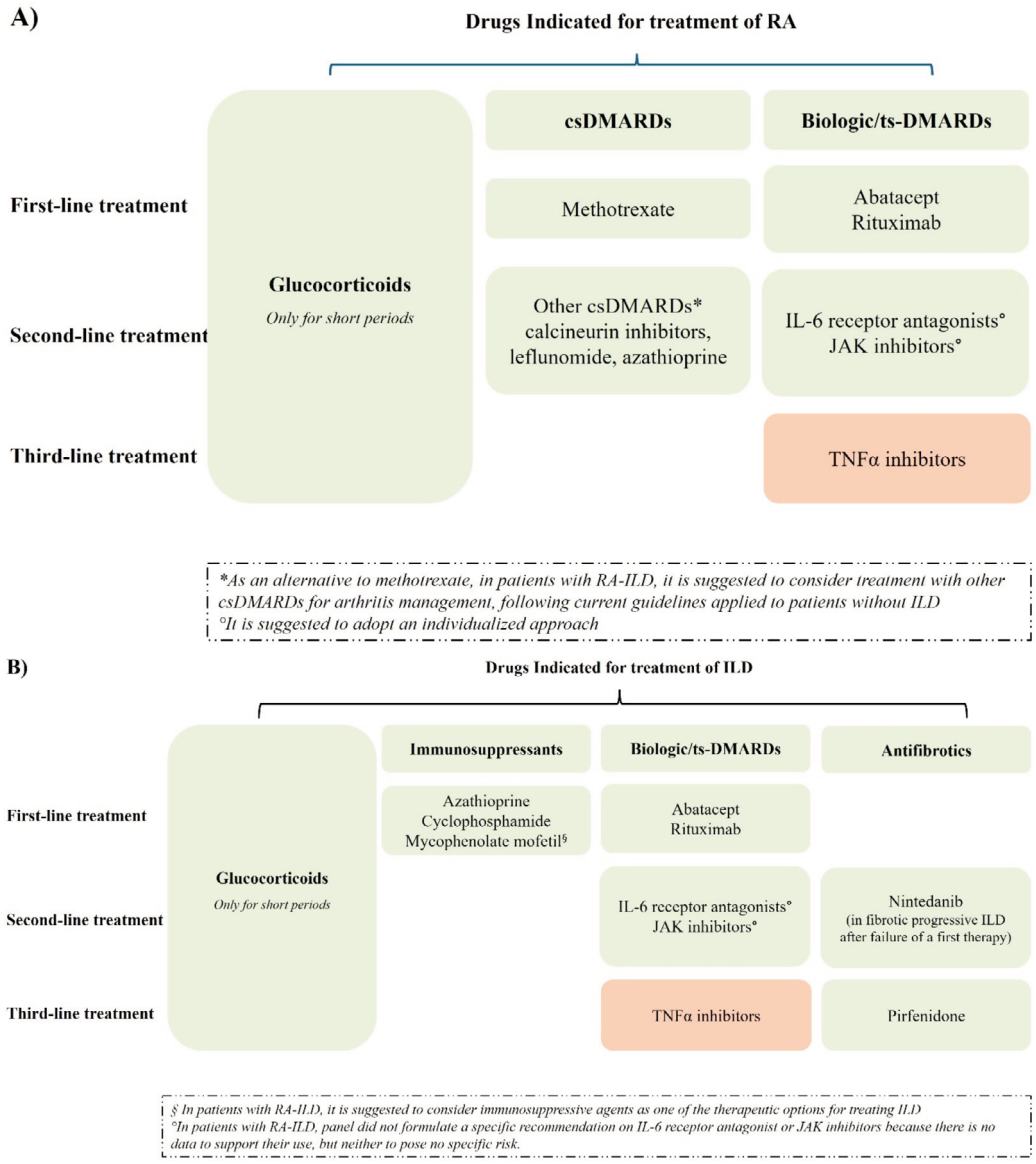

Figure 2. Flow chart on drugs indicated for treatment of rheumatoid arthritis (RA) [exploring safety on interstitial lung disease (ILD)-RA] (**A**) and on drugs indicated for treatment of ILD (**B**). csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; IL-6, interleukin-6; JAK, Janus Kinase; TNF, tumor necrosis factor.

Table 3. Good clinical practice statements on the treatment of patients with rheumatoid arthritis associated with interstitial lung disease.

	Good clinical practice statements
1.1	A multidisciplinary approach is recommended for the treatment of patients with RA-ILD.
1.2	In patients with RA and severe and/or treatment-refractory progressive fibrosing ILD, referral to a transplant center is suggested to assess eligibility for potential lung transplantation

RA-ILD, rheumatoid arthritis associated with interstitial lung disease.

national guideline on this topic is an essential clinical tool to achieve and maintain the highest standards of care and support for patients across Italy.

The present recommendations were formulated *de novo* and, by decision of the panel, had the treatment of RA-ILD as the predominant topic. It was decided to split the recommendations into three macro-areas of intervention (drugs indicated for the treatment of RA in patients with ILD, drugs indicated as first-line for RA-ILD, and drugs indicated for the treatment of RA-ILD upon failure of a first-line intervention).

Indeed, it is striking that, despite the significant prevalence of RA within the general population and the abundance of studies focusing on joint involvement, there remains a lack of data on immunomodulatory treatments for RA-ILD. This document clarifies the safety profile of methotrexate, biologic DMARDs such as abatacept and rituximab, IL-6 receptor antagonists, and JAK inhibitors. A particularly noteworthy remark is the safety of methotrexate in RA-ILD patients, a drug that maintains its role as a potential anchor drug for RA treatment within this subset.

Abatacept and rituximab are suggested as first-choice biologic agents in these patients due to their favorable safety profiles in the RA-ILD context. Similarly, JAK inhibitors currently appear to pose no specific risk in this population. Conversely, while there are no strong or consistent signals indicating significant negative pulmonary outcomes with TNFα inhibitor treatment, many case reports suggest an increased risk of acute exacerbation of RA-ILD (70); therefore, further research is essential to confirm their safety. For now, the panel has issued a conditional recommendation against initiating TNFα inhibitors for joint involvement in patients with established RA-ILD. Nevertheless, in RA patients on TNFα inhibitors for arthritis treatment who are diagnosed with asymptomatic ILD, discontinuing the treatment is not advised, especially if good control of joint disease activity has been achieved.

Despite the low to very low quality of the available evidence, an increasing number of open studies suggest that abatacept and rituximab may be beneficial in managing RA-ILD, stabilizing or even improving respiratory function and HRCT findings. Notably, there is a significant knowledge gap regarding the potential role of systemic glucocorticoids; particularly, the panel considered short courses of GCs as a potential therapeutic option for RA-ILD. However, the panel strongly emphasizes the necessity of an individualized approach to avoid chronic treatments and their associated well-known toxicities.

Recently, nintedanib has been added to the therapeutic arsenal for treating fibrosing forms of progressive RA-ILD, as indicated by a post-hoc analysis of the INBUILD trial, focusing on the RA-ILD subgroup. Conversely, due to inconclusive data from studies on the second antifibrotic currently available, pirfenidone is suggested only for patients ineligible for nintedanib (*e.g.*, those experiencing significant adverse events).

The present document also includes important Good Practice Statements aimed at providing support in these essential areas. Statements emphasizing the critical importance of a multidisciplinary approach and the option of transplant referral in very select cases were ultimately proposed.

A multidisciplinary approach, requiring at least a rheumatologist, pulmonologist, and chest radiologist, should be required for the management of RA-ILD. The therapeutic choice should be tailored to the patient according to the articular disease activity, the severity of ILD, including radiologic pattern and the progression over time, but also other RA extra-articular manifestations and comorbidities, that could influence the treatment response and safety (71). During the guideline development, the guidelines of the ACR were also published, which were not readapted, but provided an additional tool to support panelists with evidence (8).

These recommendations have some limitations. Firstly, the most recent literature search is restricted to publications available up to October 20, 2023, and studies published after this date were not included in the evidence discussion. Secondly, most recommendations are based on low or very low-quality evidence, primarily derived from retrospective studies and, at times, indirect evidence. Lastly, no included studies specifically addressed healthcare economics. However, when feasible, considerations on the efficiency of specific strategies were included to enhance applicability within the Italian healthcare context.

Update plan

The need for updating will be re-evaluated after 3 years. In case of significant scientific novelties published in the literature, a partial or complete revision of these guidelines will be considered.

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