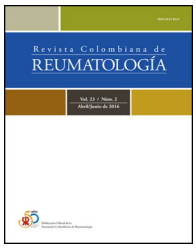
Asociación Colombiana de Reumatología

Revista Colombiana de REUMATOLOGÍA

www.elsevier.es/rcreuma



Review Article

An overview of screening, treatment, and next steps in research in rheumatoid arthritis interstitial lung disease

Scott M. Matson[a,*], *Joyce S. Lee*[b]

[a] *Department of Medicine, Division of Pulmonary, Critical Care and Sleep, School of Medicine, University of Kansas, Kansas City, KS 66103, USA*

[b] *Department of Medicine, Division of Pulmonary Sciences and Critical Care Medicine, School of Medicine, University of Colorado, Anschutz Campus, Aurora, CO, USA*

ARTICLE INFO

Article history:
Received 24 April 2023
Accepted 7 July 2023
Available online 2 September 2023

Keywords:
Rheumatoid arthritis
Interstitial lung disease
Subclinical interstitial lung disease
Immunosuppression
Antifibrotic therapy

ABSTRACT

Rheumatoid arthritis associated interstitial lung disease (RA-ILD) has significant clinical impact on patients due to increased morbidity and mortality. Understanding the progression of ILD in patients with RA from when asymptomatic to clinical progression and the clinical, genetic, and novel markers associated with disease progression is an important step in altering the natural history of ILD in patients with RA. We review the natural history and epidemiology of RA-ILD, with a focus on Latin-American epidemiology in RA-ILD. Additionally, we discuss unique features of RA-ILD compared to other forms of ILD, early disease detection, and current concepts in treatment.

Una visión general del cribado, el tratamiento y los próximos pasos en la investigación de la enfermedad pulmonar intersticial por artritis reumatoide

Palabras clave:
Artritis reumatoide
Enfermedad pulmonar intersticial
Enfermedad pulmonar intersticial subclínica
Inmunosupresión
Terapia antifibrótica

RESUMEN

La enfermedad pulmonar intersticial asociada a la artritis reumatoide (EPI-AR) representa un impacto clínico significativo para los pacientes debido al aumento de la morbilidad y la mortalidad. Comprender la progresión de la EPI en pacientes con AR de progresión asintomática a clínica y los marcadores clínicos, genéticos y novedosos asociados con la progresión de la enfermedad es un paso importante para alterar la historia natural de la EPI en pacientes con AR. Revisamos la historia natural y la epidemiología de la EPI-AR, con un enfoque en la epidemiología latinoamericana en la EPI-AR. Además, discutimos las

* *Corresponding author.*
E-mail address: Smatson@kumc.edu (S.M. Matson).

https://doi.org/10.1016/j.rcreu.2023.07.002

características únicas de la EPI-AR en comparación con otras formas de EPI, la detección temprana de la enfermedad y los conceptos actuales en el tratamiento.

Introduction

Development of rheumatoid arthritis associated interstitial lung disease (RA-ILD) is a significant extra-pulmonary manifestation in patients with RA. Survival from the time of ILD diagnosis is approximately 3 years and is generally worse than other forms of autoimmune ILD.[1–4] There is growing understanding of the genetic profile in RA-ILD, a profile that overlaps with another form of ILD called idiopathic pulmonary fibrosis (IPF).[5,6] These observed clinical and genetic overlap between RA-ILD and IPF contributes to the recent interest in the use of antifibrotic drugs for patients with RA-ILD.[7,8] This review of RA-ILD will discuss several pressing research and clinical areas of focus, including screening, diagnosis, and management of patients with RA-ILD.

Epidemiology and genetic factors of RA-ILD

RA is common affecting 1% of the general population.[9] When screening RA populations for early signs of ILD, approximately 18–21% of patients with RA will have computed tomography (CT) evidence of interstitial lung disease.[6,10] However, clinically significant ILD occurs between 6.8 and 7.7% over the lifespan of patients with RA, depending on method of diagnosis.[1,11] Estimates of the prevalence of ILD from studies performed in recent years appear to be increasing, likely due in large part to more pervasive use of CT imaging for indications such as lung cancer screening.[12]

RA-ILD develops through a concert of genetic and environmental factors. The presence of the minor allele in the *MUC5B* promoter variant has been shown to be associated with both early and established forms of RA-ILD, like observations in early and established forms of IPF.[5,6] Prior to this genetic insight into ILD risk in RA, the most consistent independent predictor of ILD in RA was cigarette smoking,[13–15] although advanced age also has clear associations with RA-ILD.[1,11,13,16–20] As is true for other forms of ILD, the association between age and ILD development in patients with RA is likely due in part to telomere shortening with or without inherited mutations in telomere repair genes such as *TERT, RTEL-1* and *PARN*.[21,22]

Autoantibodies in the development of RA-ILD

RA is caused by the development of pathogenic autoantibodies that react to abnormally citrullinated proteins leading to an acute inflammatory response (antibodies to citrullinated peptides (ACPA)). This inflammatory response is seen in the synovium of RA patients,[23] however the induction of this pathologic citrullination is hypothesized to take place within the lung in response to environmental exposures such as tobacco smoke.[14,15,24–28] Studies have reported anti-CCP activity in lung bronchoalveolar lavage (BAL) fluid prior to serum anti-CCP positivity and prior to the manifestations of RA joint disease.[29,30] Titers of anti-CCP antibodies have also been associated with the development of RA-ILD[31,32] and are therefore thought to play a role in ILD development in RA patients but a direct causative link has not been shown to date.

RA-ILD in Latin America

Foundational work to understand the risk factors of early ILD in patients with RA was undertaken in Latin-America at the Rheumatology Outpatient Clinic of the Hospital das Clinicas of the University of Sao Paulo, Brazil.[33] In this analysis, 293 patients with RA had a chest CT for clinical purposes (e.g., pulmonary indications (45%), non-pulmonary indications (40%), and unclear indications (15%)). They found that 22% had undiagnosed interstitial lung abnormalities (ILA) or ILD,[33] similar to rates seen in the US and France.[6,10] Interestingly, the authors reported that 56 of these patients with RA had follow-up chest imaging and 21 (37.5%) had radiographic progression upon follow-up.

In addition, the prevalence of RA-ILD across Latin-America has been reported in a large-multicenter analysis of 25 centers across Argentina, Colombia, and Uruguay.[34] In this study, focused on various forms of autoimmune-ILD (AI-ILD, $n = 325$), 31% of the cases were RA-ILD.[34] Like other cohorts of RA-ILD, the radiologic UIP pattern was the most frequent, followed by NSIP. It is interesting to note that in this analysis which spanned 2015–2018, the most common treatment strategy for patients with AI-ILD was a combination of cyclophosphamide and glucocorticoids, followed by azathioprine. While the treatment data were not reported by subtype of AI-ILD, these treatment choices are likely influenced by geographic availability and costs of other commonly used therapies such as mycophenolate mofetil which is typically the first line therapy in these conditions in the US and European countries.[35–39]

Unique features of RA-ILD amongst the autoimmune ILDs

There are several other autoimmune diseases associated with the development of ILD, however, there are unique clinical features, genetic risk factors, and outcomes that set RA-ILD apart from other etiologies of autoimmune ILD. For instance, on average, the median survival for patients with RA-ILD is approximately 3 years from the time of diagnosis, which is worse than other autoimmune ILDs.[1,3] While unconfirmed, this difference in prognosis is thought to be due to a higher

proportion of patients with RA having a usual interstitial pneumonia (UIP) pattern of disease, which generally confers worse prognosis compared to other ILD patterns.[4] Usual interstitial pneumonia is a histologic entity with a well validated radiographic corollary, which has been shown in several studies to identify a group of RA-ILD patients with a poorer prognosis.[40–45] In several prospective cohorts, the proportion of RA-ILD patients with UIP pattern ILD typically makes up a majority of cohort.[43,46] In other autoimmune conditions such as scleroderma, rates of UIP are more commonly a minority (20–30%).[47,48] Other ILD patterns in patients with RA, such as non-specific interstitial pneumonia (NSIP), have clinical outcomes similar to other autoimmune ILDs.[3,4,41]

Another important difference between RA-ILD and other forms of autoimmune ILD relates to sex disparity of those affected. For instance, RA-ILD, and specifically the UIP pattern, is seen more commonly in males, whereas ILD is significantly more common in females in other autoimmune ILD cohorts like scleroderma ILD (SSc-ILD), Sjogren and systemic lupus erythematous associated ILDs.[49–52]

It is also notable that other forms of autoimmune ILD such as scleroderma or myositis lack an association with the *MUC5B* promoter variant, in studies to date.[53,54] It is clear from association studies that the presence of the promoter variant of *MUC5B* has the strongest association with UIP pattern amongst patients with RA-ILD, and therefore, this unique genetic risk for RA-ILD (compared to other types of autoimmune ILD) likely also plays a role in the increased risk of UIP in among those with RA-ILD. There are other genetic risk features that appear to be similar to those identified in other autoimmune ILDs such as scleroderma, including a likely role of telomere dysfunction in the presence of ILD and ILD progression.[21,22,55–58]

Early forms of RA-ILD

There is reason to believe that early recognition of ILD in patients with RA is a promising research endeavor as progressive fibrosing conditions may be the prototypical human pathology where early intervention could alter the natural disease history. For this reason, RA offers researchers and clinicians a unique pre-clinical state for translational study of pulmonary fibrosis development and progression. For instance, we recently prospectively screened 184 patients with RA without known ILD for the presence of interstitial lung disease via high resolution CT scans and we found that 38 (21%) had consensus thoracic-radiologist-determined interstitial lung disease.[6] As discussed briefly already in this review, estimates of lifetime risk for development of clinical ILD within RA cohorts varies, but is described in two studies at 6.8 and 7.7%.[1,11] Given this disparity, where 20% of patients with RA have radiologic findings of ILD, but less than 10% will progress to a clinical form of ILD, there are important, and unknown factors that likely influence and mark risk for ILD progression. Another research group has identified similar rates of early ILD in RA and both studies have demonstrated an association between early RA-ILD and the presence of the *MUC5B* promoter variant.[10]

Another approach to understanding early forms of ILD in patients with RA is the leveraging of population-based or chronic obstructive pulmonary disease (COPD)-based cohorts. For instance, investigators have found within the Multi-Ethnic Study of Atherosclerosis, that autoantibodies associated with RA such as rheumatoid factor and antibodies to cyclic-citrullinated peptides (anti-CCP) are associated with the presence of interstitial lung abnormalities (ILA) and quantitative measures like high attenuation areas on coronary CT scans.[59] These findings indicate the possibility that early ILD changes, such as ILA, are related to the presence of RA autoantibodies. Another investigation underway in COPD Genetic Epidemiology Study (COPDGene) identified RA cases within COPDGene, which enrolled over 10,000 COPD subjects. These RA cases in COPDGene had a higher prevalence of ILA (16.9% vs. 5.0%) than non-RA comparators and perhaps most importantly, the ILA in patients with RA was associated with a 3-fold increased mortality than the presence of RA alone.[60]

Early ILD in RA is an active area of investigation. The outcomes of these multiple approaches to understanding early ILD in RA could inform our understanding of early ILD across multiple etiologies of pulmonary fibrosis, including IPF given the clinical and genetic overlap between RA-ILD and IPF.[61] However, several important and unanswered questions remain in this realm, most notably: does early intervention in early forms of RA-ILD have clinical efficacy and what type of intervention would be most efficacious? Prospective, randomized interventional trials are urgently needed in this space as our understanding of response to therapy, progression, and survival evolves.

Screening for ILD in patients with RA

Given the lack of clinical data on outcomes with early recognition of ILD in RA, or early intervention in this scenario, there remains no clinical guideline or recommendation to screen for ILD in patients with RA. However, given the clinical importance of the development of ILD as it relates to health-related quality of life and mortality, we believe regular assessment of respiratory symptoms in patients with RA is warranted. It is also important to note that several professional societies have published guidance for screening ILD in other autoimmune diseases such as SSc-ILD and connective tissue disease-ILD writ-large which should inform the nuanced approached to screening in this population.[62,63] RA involvement of the lung can have multiple manifestations, including airways disease[64] and for this reason, a guided history and clinical exam can inform further diagnostic testing if patients with RA have respiratory symptoms. In one study, risk factors for early RA-ILD included four primary characteristics: (1) sex, (2) age at RA onset, (3) RA disease activity (using Disease Activity Score 28-Eyrthrocyte Sedimentation Rate (DAS28-ESR)) and (4) presence of the *MUC5B* promoter variant.[10] These types of risk score systems can improve the sensitivity of screening modalities. However, given the lack of widely available *MUC5B* assays and the lack of data to support improved outcomes with early ILD recognition in patients with RA, these tools remain within the research realm.

Table 1 – Pulmonary toxicities associated with commonly used DMARDs.

Drug	Reported pulmonary toxicity
Methotrexate	Associated with development of an acute hypersensitivity pneumonitis, where most will have peripheral eosinophilia and is commonly associated with broncho-alveolar lymphocytosis[84]
Leflunomide	Associated with low risk of alveolar pneumonitis, especially in those patients with underlying ILD or history of methotrexate-induced lung toxicity[71]
Anti-TNF biologic agents	Direct inflammatory pneumonitis resulting from treatment with biologic agents in RA are reported. However, a direct pathogenic link between the agent and the pneumonitis has not been shown. Given the clinical efficacy of these agents in treating the synovial manifestations of RA there use in autoimmune-ILD patients remains controversial.[78,79,85]
Gold	Although not commonly used in modern eras, a typical but rare pulmonary toxicity was known to be associated with gold administration with fever and an NSIP pattern with lymphocytosis in the lung[86]
Sulfasalazine	Associated with an eosinophilic alveolar infiltrate with fever which is steroid-responsive[87,88]

ILD: interstitial lung disease, RA: rheumatoid arthritis, anti-TNF: anti-tumor necrosis factor, and NSIP: non-specific interstitial pneumonia.

Treatment of RA-ILD

As is the case with most autoimmune ILDs, the primary treatment approach in RA-ILD is derived from randomized, controlled trials (RCTs) in scleroderma ILD (SSc-ILD).[65] In these RCTs, several immunosuppressants have been shown to slow or improve forced vital capacity (FVC) in patients with SSc-ILD.[47,66–68] The scleroderma lung studies (SLSI and SLS II) demonstrated improved health-related quality of life with mycophenolate mofetil and cyclophosphamide.[38,47,65,67,69,70,68] Given the lack of randomized data specific to RA-ILD regarding treatment outcomes from immunosuppression, it is important to consider these differences in genetic, phenotypic, and clinical outcomes in patients with RA-ILD compared to SSc-ILD and other autoimmune ILDs.

However, until additional research is done, the primary treatment strategy in RA-ILD remains the addition of lung-directed immunosuppression to a baseline disease-modifying anti-rheumatic drug (DMARD) regimen.[71–75] Given the clear association between RA disease activity and prevalent and progressive RA-ILD,[19,76,77] we feel an imperative first step in RA-ILD management is adequate baseline joint disease control with DMARDs via collaboration between pulmonary and rheumatology teams.

Another mainstay of management for patients with RA-ILD has been the identification and removal of pharmacotherapies that may contribute to, or exacerbate, underlying ILD.[78–80] There are several DMARD agents which have been implicated in drug induced ILD. This poses a conundrum for physicians when approaching patients with RA with who have joint disease that may be well managed with one of these agents if they develop ILD. Further, there is an association between RA disease activity and ILD prognosis.[76,77] This balance between DMARDs that may be associated with worsening ILD, or a drug induced form of ILD and changing an effective RA disease regimen is an important consideration in an environment that lacks randomized, prospective data to guide treatment decisions. For this reason, we advocate for multi-disciplinary discussions with pulmonologists and rheumatologists with experience caring for patients with ILD to best weigh these options.

One drug that has been controversial in its potential as causing drug-induced pulmonary fibrosis is methotrexate. Methotrexate is an early-line DMARD in patients with RA that is commonly used, either as monotherapy or as a backbone to which other conventional or biologic DMARDs are added.[81] As such, methotrexate is commonly used in the most severe patients with RA and was therefore it has been difficult to differentiate the relationship between methotrexate use, RA disease severity and ILD. For many years, patients with RA-ILD on methotrexate had this medication stopped, and frequently the development of pulmonary fibrosis in patients with RA had been attributed to methotrexate use. However, recently, increasing evidence demonstrates no such association between methotrexate and chronic pulmonary fibrosis, which suggests safety of continuing the drug if it has been effective for treating the RA joint disease.[82,83] However, important caveats remain, including the known development of cellular, acute hypersensitivity pneumonitis from methotrexate. This form of drug toxicity is distinct from fibrotic ILD and can often be differentiated using clinical history, imaging and in some cases, bronchoalveolar lavage is needed in order to help support the diagnosis.[84] While an extensive discussion of DMARD safety is nuanced and beyond the scope of this review, we have summarized known pulmonary toxicities associated with commonly used DMARDs in Table 1.

One question that remains in this field, is the role of added immunosuppression in those RA-ILD patients with UIP pattern. This concern primarily arises from increased mortality in RCT data in patients with IPF randomized to an immunosuppressive regimen of prednisone, azathioprine, and N-acetylcysteine compared to placebo.[89] Given the previously mentioned overlaps between IPF and RA-ILD, specifically for RA-ILD with UIP pattern ILD, there is clinical equipoise regarding immunosuppression, which will require randomized, prospective data to fully resolve. However, there are observational studies that support an immunosuppression paradigm in RA-ILD, including patients with UIP pattern ILD. We leveraged a real-world cohort of 212 patients with RA-ILD from 5 ILD centers around the United States and found that added immunosuppression was associated with a statistically significant improvement in FVC and diffusion capacity for carbon monoxide (DLCO) % predicted at 12 months when compared to the pre-treatment trend of pulmonary function

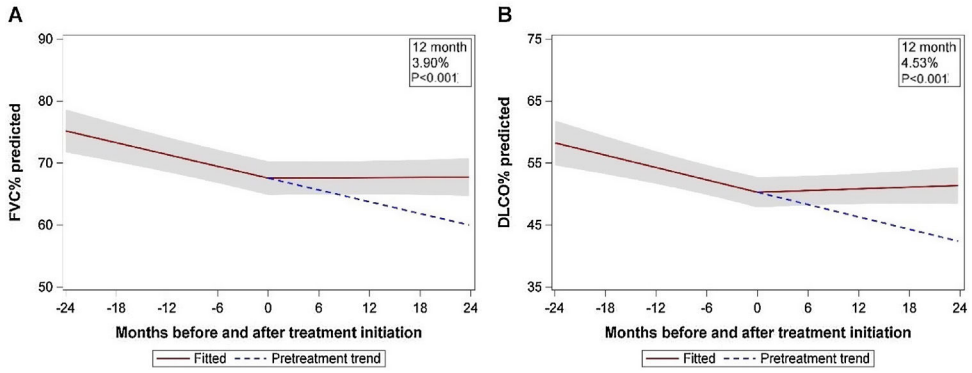


Fig. 1 – (A) Impact of immunosuppression on predicted trajectory of forced vital capacity (FVC) % predicted. The pre-treatment trend in FVC is shown from time −24 months to time 0 when RA-ILD specific treatment was initiated. The pre-treatment trend (blue dotted line) is projected forward from time 0 to +24 months and compared to the observed FVC trend after treatment initiation. After 12 months of treatment, there was a significant increase in FVC % predicted compared to the projected trend without treatment [+3.90, $p < 0.001$; 95% CI: (1.95, 5.84)]. Gray shading indicates 95% confidence intervals. (B) Impact of immunosuppression on diffusion capacity for carbon monoxide (DLCO). There was a significant increase in DLCO % predicted following 12 months of treatment compared to the projected trend without treatment [+4.53%, $p = <0.001$, (2.12, 6.94)]. *Reproduced with permission by Elsevier publishing granted on 2/22/23. Reproduced from CHEST, Matson et al, ISSN: 0012-3692. Copyright Elsevier publishing.*

decline (Fig. 1).[90] In these data we also found that the presence of UIP, as determined by blinded thoracic radiologist consensus, had no significant impact on immunosuppression outcomes, where the presence of definite or probable UIP did not significantly impact treatment response at 12 months for FVC % predicted based on the interaction analysis ($p = 0.506$).[90]

While the standard of care in RA-ILD remains primarily immunosuppression, for those patients with UIP or other fibrotic features, there is increasing interest in the use of the novel antifibrotics. These drugs have been studied in many etiologies of progressive forms of fibrotic ILDs, including RCTs that included patients with RA-ILD.[8,91–93] Outcomes from these trials showed findings like the initial studies in IPF; antifibrotics decrease FVC decline in one-year compared to placebo but fail to improve survival or health-related quality of life.[8,91–93] In 2022, the first RCT dedicated to patients with RA-ILD was published.[7] These data found no statistically significant difference between pirfenidone and placebo in their primary endpoint (proportion of RA-ILD subjects with >10% or more FVC decline from baseline or death).[7] It is notable that FVC decline in TRAIL-1 (secondary endpoint) was similar to trends seen in all other RCTs of antifibrotic therapy, but the study was under-powered and under-recruited for multiple reasons, including the COVID-19 pandemic.[7]

Given the complexities of treating a multi-organ condition, we strongly suggest a multi-disciplinary discussion between rheumatologists and pulmonologists with experience treating these conditions and familiarity with these therapies given the lack of evidence that remains. However, there is hope that collaborative initiatives focused on adaptive trial design in ILD will fill these clinical gaps in knowledge for patients with RA-ILD in the coming years.

Future directions in RA-ILD

RA-ILD is an important condition for patients and clinicians alike. This devastating condition shortens lives and causes significant morbidity. However, there is hope that developing validated, early recognition systems for ILD in patients with RA could alter the natural history of this condition by allowing for study of interventions in earlier forms of the disease and curbing the development of clinically significant ILD. RA joint disease is an apt comparison here where early application of effective DMARD therapy has revolutionized outcomes for these patients. With randomized, prospective studies in both early and established forms of RA-ILD, we will make important progress in the understanding and treatment of RA-ILD.

Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:10.1016/j.rcreu.2023.07.002.

REFERENCES

1. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2010;62:1583–91, http://dx.doi.org/10.1002/art.27405.

2. Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med. 2011;183:372–8, http://dx.doi.org/10.1164/rccm.201004-0622OC.
3. Solomon JJ, Ryu JH, Tazelaar HD, Myers JL, Tuder R, Cool CD, et al. Fibrosing interstitial pneumonia predicts survival in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD). Respir Med. 2013;107:1247–52, http://dx.doi.org/10.1016/j.rmed.2013.05.002.
4. Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2016;47:588–96, http://dx.doi.org/10.1183/13993003.00357-2015.
5. Juge PA, Lee JS, Ebstein E, Furukawa H, Dobrinskikh E, Gazal S, et al. MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. N Engl J Med. 2018;379:2209–19, http://dx.doi.org/10.1056/NEJMoa1801562.
6. Matson SM, Deane KD, Peljto AL, Bang TJ, Sachs PB, Walts AD, et al. Prospective identification of subclinical interstitial lung disease in rheumatoid arthritis cohort is associated with the MUC5B promoter variant. Am J Respir Crit Care Med. 2022;205:473–6, http://dx.doi.org/10.1164/rccm.202109-2087LE.
7. Solomon JJ, Danoff SK, Woodhead FA, Hurwitz S, Maurer R, Glaspole I, et al. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet Respir Med. 2023;11:87–96, http://dx.doi.org/10.1016/S2213-2600(22)00260-0.
8. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med. 2019;381:1718–27, http://dx.doi.org/10.1056/NEJMoa1908681.
9. Gabriel SE, Crowson CS, O'Fallon WM. The epidemiology of rheumatoid arthritis in Rochester Minnesota, 1955–1985. Arthritis Rheum. 1999;42:415–20, http://dx.doi.org/10.1002/1529-0131(1999 04)42:3<415::AID-ANR4>3.0.CO;2-Z.
10. Juge PA, Granger B, Debray MP, Ebstein E, Louis-Sidney F, Kedra J, et al. A Risk score to detect subclinical rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheum. 2022;74:1755–65, http://dx.doi.org/10.1002/art.42162.
11. Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis. 2003;62:722–7, http://dx.doi.org/10.1136/ard.62.8.722.
12. Hess EP, Haas LR, Shah ND, Stroebel RJ, Denham CR, Swensen SJ. Trends in computed tomography utilization rates: a longitudinal practice-based study. J Patient Saf. 2014;10:52–8, http://dx.doi.org/10.1097/PTS.0b013e31829481a.
13. Saag KG, Kolluri S, Koehnke RK, Georgou TA, Rachow JW, Hunninghake GW, et al. Rheumatoid arthritis lung disease determinants of radiographic and physiologic abnormalities. Arthritis Rheum. 1996;39:1711–9, http://dx.doi.org/10.1002/art.1780391014.
14. Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwartz DA. Cigarette smoking and rheumatoid arthritis severity. Ann Rheum Dis. 1997;56:463–9, http://dx.doi.org/10.1136/ard.56.8.463.
15. Hoovestol RA, Mikuls TR. Environmental exposures and rheumatoid arthritis risk. Curr Rheumatol Rep. 2011;13:431–9, http://dx.doi.org/10.1007/s11926-011-0203-9.
16. Assayag D, Lubin M, Lee JS, King TE, Collard HR, Ryerson CJ. Predictors of mortality in rheumatoid arthritis-related interstitial lung disease. Respirology. 2014;19:493–500, http://dx.doi.org/10.1111/resp.12234.
17. Norton S, Koduri G, Nikiphorou E, Dixey J, Williams P, Young A. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. Rheumatology (Oxford). 2013;52:99–110, http://dx.doi.org/10.1093/rheumatology/kes262.
18. Zrour SH, Touzi M, Bejia I, Golli M, Rouatbi N, Sakly N, et al. Correlations between high-resolution computed tomography of the chest and clinical function in patients with rheumatoid arthritis. Prospective study in 75 patients. Joint Bone Spine. 2005;72:41–7, http://dx.doi.org/10.1016/j.jbspin.2004.02.001.
19. Koduri G, Norton S, Young A, Cox N, Davies P, Devlin J, et al. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatology (Oxford). 2010;49:1483–9, http://dx.doi.org/10.1093/rheumatology/keq035.
20. Bilgici A, Ulusoy H, Kuru O, Celenk C, Unsal M, Danaci M. Pulmonary involvement in rheumatoid arthritis. Rheumatol Int. 2005;25:429–35, http://dx.doi.org/10.1007/s00296-004-0472-y.
21. Juge PA, Borie R, Kannengiesser C, Gazal S, Revy P, Wemeau-Stervinou L, et al. Shared genetic predisposition in rheumatoid arthritis-interstitial lung disease and familial pulmonary fibrosis. Eur Respir J. 2017;49:1602314, http://dx.doi.org/10.1183/13993003.02314-2016.
22. Natalini JG, England BR, Baker JF, Chen Q, Singh N, Mahajan TD, et al. Associations between shortened telomeres and rheumatoid arthritis-associated interstitial lung disease among U.S. veterans. Respir Med. 2022;201:106943, http://dx.doi.org/10.1016/j.rmed.2022.106943.
23. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388:2023–38, http://dx.doi.org/10.1016/S0140-6736(16)30173-8.
24. Silman AJ, Newman J, Macgregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis: results from a nationwide study of disease-discordant twins. Arthritis Rheum. 1996;39:732–5, http://dx.doi.org/10.1002/art.1780390504.
25. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006;54:38–46, http://dx.doi.org/10.1002/art.21575.
26. Bongartz T, Cantaert T, Atkins SR, Harle P, Myers JL, Turesson C, et al. Citrullination in extra-articular manifestations of rheumatoid arthritis. Rheumatology (Oxford). 2007;46:70–5, http://dx.doi.org/10.1093/rheumatology/kel202.
27. Ruiz-Esquide V, Gómara MJ, Peinado VI, Gómez Puerta JA, Barberá JA, Cañete Jde D, et al. Anti-citrullinated peptide antibodies in the serum of heavy smokers without rheumatoid arthritis. A differential effect of chronic obstructive pulmonary disease? Clin Rheumatol. 2012;31:1047–50, http://dx.doi.org/10.1007/s10067-012-1971-y.
28. Lee J, Luria A, Rhodes C, Raghu H, Lingampalli N, Sharpe O, et al. Nicotine drives neutrophil extracellular traps formation and accelerates collagen-induced arthritis. Rheumatology (Oxford). 2017;56:644–53, http://dx.doi.org/10.1093/rheumatology/kew449.
29. Deane KD, Norris JM, Holers VM. Preclinical rheumatoid arthritis: identification, evaluation, and future directions for investigation. Rheum Dis Clin North Am. 2010;36:213–41, http://dx.doi.org/10.1016/j.rdc.2010.02.001.
30. Kelmenson LB, Demoruelle MK, Deane KD. The complex role of the lung in the pathogenesis and clinical outcomes of rheumatoid arthritis. Curr Rheumatol Rep. 2016;18:69, http://dx.doi.org/10.1007/s11926-016-0618-4.

31. Giles JT, Danoff SK, Sokolove J, Wagner CA, Winchester R, Pappas DA, et al. Association of fine specificity and repertoire expansion of anticitrullinated peptide antibodies with rheumatoid arthritis associated interstitial lung disease. Ann Rheum Dis. 2014;73:1487–94, http://dx.doi.org/10.1136/annrheumdis-2012-203160.
32. Rocha-Munoz AD, Ponce-Guarneros M, Gamez-Nava JI, Olivas-Flores EM, Mejia M, Juarez-Contreras P, et al. Anti-cyclic citrullinated peptide antibodies and severity of interstitial lung disease in women with rheumatoid arthritis. J Immun Res. 2015;2015:151626, http://dx.doi.org/10.1155/2015/151626.
33. Kawano-Dourado L, Doyle TJ, Bonfiglioli K, Sawamura MVY, Nakagawa RH, Arimura FE, et al. Baseline characteristics and progression of a spectrum of interstitial lung abnormalities and disease in rheumatoid arthritis. Chest. 2020;158:1546–54, http://dx.doi.org/10.1016/j.chest.2020.04.061.
34. Vivero F, Campins F, Lancellotti D, Malfante P, Babini S, Sebastiani J, et al. Autoimmune interstitial lung disease in Latin-America. Clin Immunol. 2019;199:52–6, http://dx.doi.org/10.1016/j.clim.2018.12.013.
35. Au K, Khanna D, Clements PJ, Furst DE, Tashkin DP. Current concepts in disease-modifying therapy for systemic sclerosis-associated interstitial lung disease: lessons from clinical trials. Curr Rheumatol Rep. 2009;11:111–9, http://dx.doi.org/10.1007/s11926-009-0016-2.
36. Fischer A, Brown KK, Du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Perez ER, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol. 2013;40:640–6, http://dx.doi.org/10.3899/jrheum.121043.
37. Papiris SA, Kagouridis K, Papadaki G, Kolilekas L, Manali ED. Treating CTDs related fibrotic ILDs by immunosuppressants: "facts and faults". Lung. 2014;192:221–3, http://dx.doi.org/10.1007/s00408-013-9532-y.
38. Volkmann ER, Tashkin DP, LeClair H, Roth MD, Kim G, Goldin J, et al. Treatment with mycophenolate and cyclophosphamide leads to clinically meaningful improvements in patient-reported outcomes in scleroderma lung disease: results of Scleroderma Lung Study II. ACR Open Rheumatol. 2020;2:362–70, http://dx.doi.org/10.1002/acr2.11125.
39. Rahaghi FF, Hsu VM, Kaner RJ, Mayes MD, Rosas IO, Saggar R, et al. Expert consensus on the management of systemic sclerosis-associated interstitial lung disease. Respir Res. 2023;24:6, http://dx.doi.org/10.1186/s12931-022-02292-3.
40. Yousem SA, Colby TV, Carrington CB. Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis. 1985;131:770–7, http://dx.doi.org/10.1164/arrd.1985.131.5.770.
41. Lee HK, Kim DS, Yoo B, Seo JB, Rho JY, Colby TV, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest. 2005;127:2019–27, http://dx.doi.org/10.1378/chest.127.6.2019.
42. Kim EJ, Collard HR, King TE Jr. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest. 2009;136:1397–405, http://dx.doi.org/10.1378/chest.09-0444.
43. Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J. 2010;35:1322–8, http://dx.doi.org/10.1183/09031936.00092309.
44. Assayag D, Elicker BM, Urbania TH, Colby TV, Kang BH, Ryu JH, et al. Rheumatoid arthritis-associated interstitial lung disease: radiologic identification of usual interstitial pneumonia pattern. Radiology. 2014;270:583–8, http://dx.doi.org/10.1148/radiol.13130187.
45. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis An Official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198:e44–68, http://dx.doi.org/10.1164/rccm.201807-1255ST.
46. Yunt ZX, Chung JH, Hobbs S, Fernandez-Perez ER, Olson AL, Huie TJ, et al. High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: relationship to survival. Respir Med. 2017;126:100–4, http://dx.doi.org/10.1016/j.rmed.2017.03.027.
47. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006;354:2655–66, http://dx.doi.org/10.1056/NEJMoa055120.
48. Goldin JG, Lynch DA, Strollo DC, Suh RD, Schraufnagel DE, Clements PJ, et al. High-resolution CT scan findings in patients with symptomatic scleroderma-related interstitial lung disease. Chest. 2008;134:358–67, http://dx.doi.org/10.1378/chest.07-2444.
49. Gabriel SE. The epidemiology of rheumatoid arthritis. Rheum Dis Clin North Am. 2001;27:269–81, http://dx.doi.org/10.1016/S0889-857X(05)70201-5.
50. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics – a large multicentre UK study. Rheumatology (Oxford). 2014;53:1676–82, http://dx.doi.org/10.1093/rheumatology/keu165.
51. Hyldgaard C, Hilberg O, Pedersen AB, Ulrichsen SP, Løkke A, Bendstrup E, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis. 2017;76:1700–6, http://dx.doi.org/10.1136/annrheumdis-2017-211138.
52. Kawano-Dourado L, Glassberg MK, Assayag D, Borie R, Johannson KA. Sex and gender in interstitial lung diseases. Eur Respir Rev. 2021;30:210105, http://dx.doi.org/10.1183/16000617.0105-2021.
53. Borie R, Crestani B, Dieude P, Nunes H, Allanore Y, Kannengiesser C, et al. The MUC5B variant is associated with idiopathic pulmonary fibrosis but not with systemic sclerosis interstitial lung disease in the European Caucasian population. PLoS One. 2013;8:e70621, http://dx.doi.org/10.1371/journal.pone.0070621.
54. Johnson C, Rosen P, Lloyd T, Horton M, Christopher-Stine L, Oddis CV, et al. Exploration of the MUC5B promoter variant and ILD risk in patients with autoimmune myositis. Respir Med. 2017;130:52–4, http://dx.doi.org/10.1016/j.rmed.2017.07.010.
55. Fujii H, Shao L, Colmegna I, Goronzy JJ, Weyand CM. Telomerase insufficiency in rheumatoid arthritis. Proc Natl Acad Sci U S A. 2009;106:4360–5, http://dx.doi.org/10.1073/pnas.0811332106.
56. Lee JS, La J, Aziz S, Dobrinskikh E, Brownell R, Jones KD, et al. Molecular Markers of telomere dysfunction and senescence are common findings in the usual interstitial pneumonia pattern of lung fibrosis. Histopathology. 2021;79:67–76, http://dx.doi.org/10.1111/his.14334.
57. Tomos I, Karakatsani A, Manali ED, Kottaridi C, Spathis A, Argentos S, et al. Telomere length across different UIP fibrotic-interstitial lung diseases: a prospective Greek case–control study. Pulmonology. 2022;28:254–61, http://dx.doi.org/10.1016/j.pulmoe.2020.11.005.
58. Liu S, Chung MP, Ley B, French S, Elicker BM, Fiorentino DF, et al. Peripheral blood leucocyte telomere length is associated with progression of interstitial lung disease in systemic sclerosis. Thorax. 2021;76:1186–92, http://dx.doi.org/10.1136/thoraxjnl-2020-215918.

59. Bernstein EJ, Barr RG, Austin JHM, Kawut SM, Raghu G, Sell JL, et al. Rheumatoid arthritis-associated autoantibodies and subclinical interstitial lung disease: the multi-ethnic study of atherosclerosis. Thorax. 2016;71:1082–90, http://dx.doi.org/10.1136/thoraxjnl-2016-208932.
60. McDermott GC, Hayashi K, Yoshida K, Moll M, Cho MH, Doyle TJ, et al. Prevalence and mortality associations of interstitial lung abnormalities in rheumatoid arthritis within a multicenter prospective cohort of smokers. medRxiv. 2022;2022, http://dx.doi.org/10.1101/2022.12.17.22283610.
61. Matson S, Lee J, Eickelberg O. Two sides of the same coin? A review of the similarities and differences between idiopathic pulmonary fibrosis and rheumatoid arthritis associated interstitial lung disease. Eur Respir J. 2020;57:2002533, http://dx.doi.org/10.1183/13993003.02533-2020.
62. Hoffmann-Vold AM, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. Lancet Rheumatol. 2020;2:e71–83, http://dx.doi.org/10.1016/S2665-9913(19)30144-4.
63. Jee AS, Sheehy R, Hopkins P, Corte TJ, Grainge C, Troy LK, et al. Diagnosis and management of connective tissue disease-associated interstitial lung disease in Australia and New Zealand: a position statement from the Thoracic Society of Australia and New Zealand. Respirology. 2021;26:23–51, http://dx.doi.org/10.1111/resp.13977.
64. Matson SM, Demoruelle MK, Castro M. Airway disease in rheumatoid arthritis. Ann Am Thorac Soc. 2022;19:343–52, http://dx.doi.org/10.1513/AnnalsATS. 202107-876CME.
65. Matson SM, Griffith M, Lee JS. FocuSSced on the target in systemic sclerosis-interstitial lung disease: another arrow in the quiver? Am J Respir Crit Care Med. 2022;205:608–10, http://dx.doi.org/10.1164/rccm.202111-2587ED.
66. Weaver AL, Divertie MB, Titus JL. Pulmonary scleroderma. Dis Chest. 1968;54:490–8, http://dx.doi.org/10.1378/chest.54.6.490.
67. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4:708–19, http://dx.doi.org/10.1016/S2213-2600(16)30152-7.
68. Khanna D, Lin CJF, Furst DE, Goldin J, Kim G, Kuwana M, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2020;8:963–74, http://dx.doi.org/10.1016/S2213-2600(20)30318-0.
69. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet. 2016;387:2630–40, http://dx.doi.org/10.1016/S0140-6736(16)00232-4.
70. Tashkin DP, Volkmann ER, Tseng CH, Roth MD, Khanna D, Furst DE, et al. Improved cough and cough-specific quality of life in patients treated for scleroderma-related interstitial lung disease: results of Scleroderma Lung Study II. Chest. 2017;151:813–20, http://dx.doi.org/10.1016/j.chest.2016.11.052.
71. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum. 2006;54:1435–9, http://dx.doi.org/10.1002/art.21806.
72. Assayag D, Lee JS, King TE Jr. Rheumatoid arthritis associated interstitial lung disease: a review. Medicina (B Aires). 2014;74:158–65.
73. Iqbal K, Kelly C. Treatment of rheumatoid arthritis-associated interstitial lung disease: a perspective review. Ther Adv Musculoskelet Dis. 2015;7:247–67, http://dx.doi.org/10.1177/1759720X15612250.
74. Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. BMJ. 2016;352:h6819, http://dx.doi.org/10.1136/bmj.h6819.
75. Brito Y, Glassberg MK, Ascherman DP. Rheumatoid arthritis-associated interstitial lung disease: current concepts. Curr Rheumatol Rep. 2017;19:79, http://dx.doi.org/10.1007/s11926-017-0701-5.
76. Sparks JA, He X, Huang J, Fletcher EA, Zaccardelli A, Friedlander HM, et al. Rheumatoid arthritis disease activity predicting incident clinically apparent rheumatoid arthritis-associated interstitial lung disease: a prospective cohort study. Arthritis Rheumatol. 2019;71:1472–82, http://dx.doi.org/10.1002/art.40904.
77. Rojas-Serrano J, Mejía M, Rivera-Matias PA, Herrera-Bringas D, Pérez-Román DI, Pérez-Dorame R, et al. Rheumatoid arthritis-related interstitial lung disease (RA-ILD): a possible association between disease activity and prognosis. Clin Rheumatol. 2022;41:1741–7, http://dx.doi.org/10.1007/s10067-021-06040-8.
78. Perez-Alvarez R, Perez-de-Lis M, Diaz-Lagares C, Pego-Reigosa JM, Retamozo S, Bove A, et al. Interstitial lung disease induced or exacerbated by TNF-targeted therapies: analysis of 122 cases. Semin Arthritis Rheum. 2011;41:256–64, http://dx.doi.org/10.1016/j.semarthrit.2010.11.002.
79. Nakashita T, Ando K, Kaneko N, Takahashi K, Motojima S. Potential risk of TNF inhibitors on the progression of interstitial lung disease in patients with rheumatoid arthritis. BMJ Open. 2014;4:e005615, http://dx.doi.org/10.1136/bmjopen-2014-005615.
80. Hallowell RW, Horton MR. Interstitial lung disease in patients with rheumatoid arthritis: spontaneous and drug induced. Drugs. 2014;74:443–50, http://dx.doi.org/10.1007/s40265-014-0190-z.
81. Fraenkel L, Bathon JM, England BR, Clair St, Arayssi EW, Carandang TK, et al. 2021 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheum. 2021;73:1108–23, http://dx.doi.org/10.1002/art.41752.
82. Juge PA, Lee JS, Lau J, Kawano-Dourado L, Rojas Serrano J, Sebastiani M, et al. Methotrexate and rheumatoid arthritis associated interstitial lung disease. Eur Respir J. 2020:2000337, http://dx.doi.org/10.1183/13993003.00337-2020.
83. Mehta P, Redhead G, Nair A, Sparks JA, Porter JC. Can we finally exonerate methotrexate as a factor in causing or exacerbating fibrotic interstitial lung disease in patients with rheumatoid arthritis? Clin Rheumatol. 2022;41:2925–8, http://dx.doi.org/10.1007/s10067-022-06245-5.
84. Schnabel A, Richter C, Bauerfeind S, Gross WL. Bronchoalveolar lavage cell profile in methotrexate induced pneumonitis. Thorax. 1997;52:377–9, http://dx.doi.org/10.1136/thx.52.4.377.
85. Panopoulos ST, Sfikakis PP. Biological treatments and connective tissue disease associated interstitial lung disease. Curr Opin Pulm Med. 2011;17:362–7, http://dx.doi.org/10.1097/MCP.0b013e3283483ea5.
86. Tomioka R, King TE Jr. Gold-induced pulmonary disease: clinical features, outcome, and differentiation from rheumatoid lung disease. Am J Respir Crit Care Med. 1997;155:1011–20, http://dx.doi.org/10.1164/ajrccm.155.3.9116980.
87. Goodwin SD, Glenny RW. Nonsteroidal anti-inflammatory drug-associated pulmonary infiltrates with eosinophilia: review of the literature and Food and Drug Administration Adverse Drug Reaction reports. Ann Intern Med. 1992;152:1521–4, http://dx.doi.org/10.1001/archinte.152.7.1521.

88. Parry SD, Barbatzas C, Peel ET, Barton JR. Sulphasalazine and lung toxicity. Eur Respir J. 2002;19:756–64, http://dx.doi.org/10.1183/09031936.02.00267402.
89. Raghu G, Anstrom KJ, King TE Jr, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366:1968–77, http://dx.doi.org/10.1056/NEJMoa1113354.
90. Matson SM, Baqir M, Moua T, Marll M, Kent J, Iannazzo NS, et al. Treatment outcomes for rheumatoid arthritis associated interstitial lung disease; a real-world, multisite study of the impact of immunosuppression on pulmonary function trajectory. Chest. 2023;163:861–9, http://dx.doi.org/10.1016/j.chest.2022.11.035.
91. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071–82, http://dx.doi.org/10.1056/NEJMoa1402584.
92. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med. 2019;380:2518–28, http://dx.doi.org/10.1056/NEJMoa1903076.
93. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2083–92, http://dx.doi.org/10.1056/NEJMoa1402582.