

Is Janus Kinase Inhibition the Future of the Management of Rheumatoid Arthritis-associated Interstitial Lung Disease?

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Interstitial lung disease is a leading complication of rheumatoid arthritis (RA). However, no drugs are yet available to treat these pulmonary and articular diseases together, although several agents show promise. Janus kinase inhibitors have found increasing favour among rheumatologists in the treatment of active RA because they can rapidly reduce articular disease activity and because they have a simple oral dosing regime and good patient acceptability. There are many plausible reasons to believe that Janus kinase inhibitors may delay the onset and improve the outcomes of RA-associated interstitial lung disease, in tandem with their beneficial articular effects. This editorial describes the rationale for exploring this possibility further.

Keywords

Anti-tumour necrosis factor alpha, interstitial lung disease, Janus kinase inhibitors, non-specific interstitial pneumonia, rheumatoid arthritis, rheumatoid arthritis-associated interstitial lung disease, usual interstitial pneumonia

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Interstitial lung disease (ILD) frequently complicates rheumatoid arthritis (RA).¹ Moreover, it is more common among those who are male, smoke or are seropositive and with increasing age.¹ Emergent risk factors include gain-of-function promoter variants in the *MUC5B* gene and telomere shortening,² the latter possibly mediated by tobacco exposure.³

Among patients with RA, the predominant types of ILD are usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia. UIP due to ILD is phenotypically similar to patients with UIP due to idiopathic pulmonary fibrosis (IPF): both carry a high risk of progressive pulmonary fibrosis and increased short-term mortality. Additionally, some patients with RA and non-specific interstitial pneumonia-type ILD may also develop progressive fibrosis.

RA-associated ILD (RA-ILD) increases morbidity and mortality, and patients with this disease have a median survival of 3–7 years.⁴ However, prognosis has improved in recent years in part due to earlier diagnosis, although the extent of fibrosis inversely relates to survival.⁵ Dry cough and exertional breathlessness may be associated with increasing disability, recurrent exacerbations and increasing hospital admissions,⁶ as well as with excess healthcare costs.⁷

Proven safe and effective therapies abound for RA articular disease, with Janus kinase (JAK) inhibitors a recent addition to the therapeutic landscape. However, until recently, no licensed therapies were available to treat RA-ILD. Historically, such patients often received systemic corticosteroids and azathioprine, which increased mortality in IPF. Alternatively, a recent editorial recommended considering rituximab, mycophenolate or abatacept.⁸ Other agents, such as anti-tumour necrosis factor alpha (TNF α) therapy, may aggravate RA-ILD, although the evidence is inconclusive.⁴ Furthermore, a recent retrospective cohort study suggested that patients exposed to methotrexate might have a lower risk of incident RA-ILD.⁹ However, since methotrexate can cause acute pneumonitis (albeit rarely), clinicians must consider whether individuals with RA-ILD have a sufficient respiratory reserve to tolerate a hypersensitivity reaction should one occur.

Following the results of the recent phase III INBUILD trial, the oral anti-fibrotic agent nintedanib – originally licensed for IPF – has now received regulatory approval in patients with other progressive fibrotic ILDs, including RA-ILD.¹⁰ Nintedanib targets growth factor receptors involved in fibrosis, significantly slows the decline of pulmonary function and may reduce morbidity and mortality.¹⁰ Another anti-fibrotic agent, pirfenidone, has also been shown to reduce the rate of decline of forced vital capacity in a phase II study in patients with RA-ILD.¹¹ However, the results should be interpreted with caution because the study was stopped early and underpowered, preventing it from meeting its composite primary endpoint. Moreover, such anti-fibrotic drugs are expensive, their side effects are often limiting, and they do not improve the underlying articular disease.¹¹ Despite these limitations, they are likely to be increasingly used in patients with RA-ILD patients with a progressive fibrotic phenotype until better options are available.

The observed excess mortality associated with combined immunosuppression in IPF, together with the relative success of anti-fibrotic therapy, has contributed to the present conceptual separation of inflammation and fibrosis.¹² However, this paradigm risks drawing a distinction without a difference, as the processes of tissue injury and subsequent fibrosis are mechanistically linked by the recruitment of inflammatory cells (principally macrophages and T lymphocytes) and the expression of pro-inflammatory and pro-fibrotic cytokines. Together, these factors lead to pathologic phenotypic switches in epithelial cells and fibroblasts.¹³ Even established fibrosis can be seen as a potentially reversible dynamic condition,¹⁴ with a gradual turnover of the abnormal extracellular matrix. Additionally, nintedanib and pirfenidone have mixed anti-inflammatory and anti-fibrotic effects, as does the novel preferential phosphodiesterase 4B inhibitor BI 1015550, recently reported to rapidly stabilize lung function in patients with IPF, with or without concomitant anti-fibrotic treatments.¹⁵ Some treatments for RA, notably JAK inhibitors, may share this dual mode of action, opening the theoretical possibility of suppressing synovitis and parenchymal disease with a single intervention.

The JAK family has four members (JAK 1, JAK 2, JAK 3 and tyrosine kinase 2), which operate intracellularly in pairs; each pair associates with membrane-bound receptors for specific cytokines and growth factors, and available JAK inhibitors bind preferentially to different isoforms. Receptor–ligand binding activates JAK enzymes, leading to conformational changes in associated signal transducer and activator of transcription (STAT) proteins and to downstream control of gene expression.

Recognition of pathological *JAK-2* gene mutations in specific blood disorders stimulated the rational design of the first successful JAK inhibitors. Further commercial development over the last two decades has yielded a class of drugs characterised by pan-cytokine inhibition and clinically relevant downregulation of pro-inflammatory signalling in patients with diverse inflammatory disorders, including atopic eczema, ulcerative colitis and RA.¹⁶

Licensed oral JAK inhibitors effectively attenuate the clinical expression of joint disease in RA.¹⁷ They are typically well tolerated, rapidly reduce serum C-reactive protein (a marker of systemic interleukin-6 activity) and seem at least as effective as tumour necrosis factor alpha inhibitors in reducing joint disease. Recognized side effects include infection (particularly re-activation of herpes zoster), blood dyscrasias and, possibly, venous thromboembolism, while a recent report suggested that tofacitinib (a JAK1/3 inhibitor) might also increase cardiovascular and cancer risks.¹⁸ Such adverse effects are important, particularly for RA-ILD, which itself increases the risks of infection and cancer.

Whether JAK inhibitors may slow or reverse RA-ILD is not yet known. However, the pathways they block appear important in the development and maintenance of a fibrotic phenotype, both in RA and related autoimmune rheumatic disorders, as well as in other fibrosing lung disorders. Upregulated JAK/STAT signalling occurs in fibrosing disorders of the lung and several other organs, and tofacitinib has been reported to be effective in a mouse model of ILD.¹⁹ Both JAK2 and STAT3 are

over-expressed in fibroblasts isolated in skin biopsies from patients with systemic sclerosis and in lung tissue from patients with IPF. Experimental evidence points to non-canonical JAK/STAT activation by transforming growth factor (TGF)- β 1, driving tissue fibrosis potentially amenable to pharmacological blockade.²⁰ TGF- β 1-dependent JAK1/STAT3 activation has been reported in cultured hepatocytes, and this is also ameliorated by JAK inhibitors or gene silencing.²¹ Taken together, this available evidence suggests that JAK/STAT signalling may be a common pathway mediating fibrotic change in diverse organs in response to aberrant TGF- β signalling.

Clinical support for JAK inhibition in preventing or treating RA-ILD is slowly accumulating. Case reports suggest that pulmonary function can be stabilized or improved with tofacitinib²² and baricitinib.²³ In addition, the overall pulmonary safety of JAK inhibitors in RA is encouraging,²⁴ and the incidence of new RA-ILD appears to be reduced with tofacitinib.²⁵ JAK inhibitors may also benefit other fibrosing lung disorders: tofacitinib has been reported to improve or stabilize ILD (and sometimes other disease characteristics) in patients with dermatomyositis, particularly patients who have anti-melanoma differentiation-associated gene 5 (*MDA5*)-positive antibodies²⁶ and those with anti-synthetase syndromes.²⁷ Baricitinib has been used successfully in patients with type 1 interferonopathy and coatomer protein subunit- α syndrome, and further future applications seem likely.²⁸

Finally, JAK inhibitors also down-regulate the pathological JAK/STAT-mediated cytokine signalling by interferons and interleukin-6 that is observed in acute coronavirus disease 2019 pneumonia: this may explain the clinical benefit of baricitinib in patients with this condition.²⁹ Although not directly comparable with RA-ILD, coronavirus disease 2019 pneumonia may share some pathological mechanisms with this and other systemic rheumatic disorders.³⁰

In conclusion, there are plausible and compelling reasons to suppose that JAK inhibitors may benefit both the joints and lungs of patients with RA-ILD and other similar fibrosing lung diseases. If aberrant JAK/STAT signalling contributes to the pathological deposition of collagen and epithelial–mesenchymal transition, then blocking this signalling may prove effective; therefore, an oral agent able to target joint and pulmonary manifestations simultaneously would be attractive. In addition, the rapid onset and offset of action of JAK inhibitors may prove advantageous in the context of intercurrent infection. There is now a clear rationale and need for well-designed, randomized controlled trials of JAK inhibitors in patients with RA-ILD, ideally with standard-of-care control groups. Indeed, two prospective, interventional trials of tofacitinib, PULMORA (Effects of tofacitinib vs methotrexate on rheumatoid arthritis interstitial lung disease; ClinicalTrials.gov identifier: NCT004311567) and RAILDTo (Tofacitinib in the treatment of rheumatoid arthritis-related interstitial lung disease; ClinicalTrials.gov identifier: NCT005246293), are underway,^{31,32} while a novel JAK1/2 inhibitor, jaktinib, is under evaluation for IPF (Jaktinib dihydrochloride monohydrate in idiopathic pulmonary fibrosis; ClinicalTrials.gov identifier: NCT04312594).³³ The results of these trials will be of great interest to rheumatologists and pulmonologists alike, together with their patients. □

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