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INVITED REVIEW

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Contemporary Concise Review 2022: Interstitial lung disease

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SUMMARY OF KEY POINTS

- Novel genetic associations for idiopathic pulmonary fibrosis (IPF) risk have been identified. Common genetic variants associated with IPF are also associated with chronic hypersensitivity pneumonitis.
- The characterization of underlying mechanisms, such as pathways involved in myofibroblast differentiation, may reveal targets for future treatments.
- Newly identified circulating biomarkers are associated with disease progression and mortality.
- Deep learning and machine learning may increase accuracy in the interpretation of CT scans.
- Novel treatments have shown benefit in phase 2 clinical trials.
- Hospitalization with COVID-19 is associated with residual lung abnormalities in a substantial number of patients.
- Inequalities exist in delivering and accessing interstitial lung disease specialist care.

KEYWORDS
biomarkers, COVID, fibroblast, idiopathic pulmonary fibrosis, interstitial lung disease

INTRODUCTION

Interstitial lung diseases (ILDs) are a group of conditions in which pulmonary tissue is affected by abnormal cellular processes including inflammation, fibrosis or a combination of both. There may be an identifiable cause or trigger, but in idiopathic pulmonary fibrosis (IPF) the aetiology is unknown. The incidence of IPF, along with prevalence and mortality, increased since the turn of the century in Australia,[1] a pattern which has been observed across all ILDs globally.[2,3] However, more recently trends of increased mortality have slowed or reversed partly due to considerable progress made in the field.[1,2] The past year has seen continued advancements in identifying underlying pathomechanisms, improving diagnosis, managing comorbidities and developing treatments.

PATHOGENESIS

SUMMARY

- Novel genetic associations for IPF risk have been identified. Common genetic variants associated with IPF are also associated with chronic hypersensitivity pneumonitis (HP).
- The characterization of underlying mechanisms, such as pathways involved in myofibroblast differentiation, may reveal targets for future treatments.
- History of inhalational exposure is seen across all fibrotic ILDs.

While no single trigger has been identified in the pathogenesis of IPF, there are known associations and contributory mechanisms. Greater characterization of these factors will bring further clarity in the diagnostic and treatment process.

Genetics

Genetic mutations are a major contributory factor to pulmonary fibrosis, with common variants in the *MUC5B*, *TERC* and *DSP* genes previously identified as associated with IPF risk.[4] These variants are also significantly associated with chronic hypersensitivity pneumonitis (cHP), strengthening the argument for the existence of a shared pathological process between these two conditions.[5] They were again shown to be associated with IPF diagnosis in a whole-genome sequencing (WGS) study alongside newly identified variants in the *TERT* and *RTEL1* genes.[4] Genome-wide association studies (GWAS) involve scanning for genetic variants associated with a trait. Recent GWAS have confirmed 14 previously reported variants and revealed nine novel genetic associations with IPF risk including variants in introns of *KNL1, NPRL3, STMN3* and *RTEL1*,[6] as well as a variant in an antisense RNA gene for *PKN2* with lung function decline[7] and PCSK6 with mortality.[8]

Telomere shortening is associated with poor outcomes in IPF and familial pulmonary fibrosis (FPF) and was recently shown to be associated with risk of developing interstitial lung abnormalities (ILAs).[9] WGS on IPF and FPF patients found that rare telomere-related variants had a significant effect on telomere length and were associated with disease progression and reduced survival.[10]

While the identification of these and other variants (summarized in Table 1) provide clarity on ILD aetiology, genetic testing may have other uses. An international survey of ILD patients, relatives and pulmonologists found that genetic testing can be useful in determining risk, predicting disease course, and influencing diagnostic and therapeutic approach.[14]

Mechanisms and potential novel treatment targets

In vitro and in vivo models of fibrosis have been used to identify mechanisms which may reveal potential targets for future treatments.

Epithelium

Although a recently identified role of club cells in IPF suggests that epithelial contribution to fibrosis can occur beyond the alveolar space,[15] alveolar epithelial cell (AEC) injury remains one of the key drivers.[16] Alveolar type 2 cells were previously thought to be able to fully regenerate following injury, but a recent study found that they transdifferentiate into metaplastic basal cells in response to fibrotic signalling.[17] AEC ageing may also contribute to fibrosis, and increased levels of the enzyme CD38 was noted to accelerate this process.[16] Greater CD38 expression was seen in IPF AECs resulting in reduced lung function, and CD38 inactivation counteracted these changes.

TABLE 1 Key findings in publications on genetics in interstitial lung disease.

ILD	Gene	Finding	Method	Study
IPF	*MUC5B, TERC, DSP, TERT*, and *RTEL1*	Variants significantly associated with IPF risk	WGS	4
IPF	*PARN*	Heterozygous mutation associated with IPF risk	Whole exome sequencing	11
IPF	Introns of *KNL1, NPRL3, STMN3* and *RTEL1*. Intergenic variant in 10q25.1	Novel variants associated with IPF risk	GWAS meta-analysis	6
IPF	*PKN2*	Variant in antisense RNA associated with FVC decline	GWAS meta-analysis	7
IPF	*PCSK6*	Variant associated with reduced survival	GWAS	8
IPF and FPF	Rare telomere-related variants	Associated with disease progression and reduced survival	WGS	10
IPF and FPF	*KIF15*	Rare and common variants link nontelomerase pathway of cell proliferation with IPF susceptibility	Gene burden analysis	12
FHP	*MUC5B, IVD, TERC* and *DSP*	Common IPF variants significantly associated with fibrotic HP	Candidate SNP genotyping	5
CHP	*TOLLIP*	Functional changes associated with rapid FVC decline	Candidate SNP genotyping	13
ILA	Mean telomere length	Associated with interstitial lung abnormalities	qPCR and Southern blot analysis	9

Abbreviations: CHP, chronic hypersensitivity pneumonitis; FHP, fibrotic hypersensitivity pneumonitis; FPF, familial pulmonary fibrosis; FVC, forced vital capacity; GWAS, genome wide association studies; IPF, idiopathic pulmonary fibrosis; qPCR, quantitative polymerase chain reaction; SNP, single nucleotide polymorphism; WGS, whole genome sequencing.

Fibroblast activity

Fibroblast activation, differentiation into myofibroblasts and extracellular matrix deposition play a critical role in fibrosis.[18] Checkpoint kinases 1/2 are key components of the DNA damage response, preserving the ability of lung fibroblasts to survive and proliferate. Their overexpression in IPF results in resistance to apoptosis and aberrant parenchymal remodelling.[19] Pharmacological inhibition has antiproliferative and antifibrotic effects.

Pathways involved in myofibroblast differentiation have been explored. The MBD2 protein and TBXAR2 receptor are both highly expressed in IPF fibroblasts.[18,20] Respectively, knockout and inhibition reduced myofibroblast differentiation and profibrotic signalling. Myofibroblast differentiation may also be inhibited by protective growth factors such as fibroblast growth factor 19 (FGF 19) and bone morphogenic protein 4 (BMP4).[21,22]

Immune cells and response to infection

The role of immune cells in fibrosis is less well understood. Mass cytometry and analysis of existing single cell sequencing data from IPF lungs show a reduction in monocyte-like cells and interstitial macrophages, and an increase in alveolar macrophages, dendritic cells and IFN-γ signalling suggesting upregulation of adaptive immunity.[23] Another study found that depletion of plasma cells inhibited fibrosis in murine models.[24]

Triggers and co-morbidities

While there is some understanding of the aetiology of cHP and the connective-tissue disease associated ILDs (CTD-ILDs), triggers for IPF and the other fibrotic ILDs (fILD) are less well established. Recent studies found that in addition to higher risk of IPF diagnosis, smoking history is also associated with shortened survival and honeycombing in FPF.[25,26] Data from the Canadian Registry for Pulmonary Fibrosis showed high prevalence of inhalational exposure in patients with fILD.[27] Although the highest proportion of exposures were seen in HP, surprisingly they were present in more than a third of IPF, CTD-ILD and unclassifiable ILD cases, suggesting a role for these exposures across the fILDs. Inhalational exposure to fine particulate matter and occupational exposure to toxicants are associated with ILD risk in rheumatoid arthritis and forced vital capacity (FVC) decline in systemic sclerosis (SSc), respectively.[28,29] It may therefore follow that there are triggers associated with the development of fibrosis in these conditions beyond the known auto-inflammatory component.

Obesity is commonly associated with IPF.[30] However, in an observational cohort study of fILD patients, raised BMI and obesity were associated with better outcomes, with the highest mortality seen in underweight patients, although this is likely to be due to severe disease promoting weight loss.[31]

DIAGNOSIS, MONITORING AND PROGNOSIS

SUMMARY

- Deep learning and machine learning may increase accuracy in the interpretation of CT scans.
- Newly identified biomarkers may be useful in diagnosis and prognostication.
- Updated clinical practice guidelines now include conditional recommendations for lung cryobiopsy.

Screening

In a retrospective study of patients undergoing lung-cancer screening 1.51% of subjects were diagnosed with ILD and treatment was commenced in eligible patients.[32] Targeted screening programmes for high-risk individuals may result in improved outcomes. Such patients could be identified by calculating the pre-test probability of IPF using a framework compiled by an international working group of ILD specialists, although these risk factors have been designed to be interpreted alongside CT findings.[33]

Imaging

Currently, ILD diagnosis requires consensus between respiratory physicians and radiologists. Deep learning and machine learning involve the creation of algorithms based on previously existing data that can be used to analyse CT scans and formulate a diagnosis. Retrospective analyses found diagnostic accuracy of these methods to be as high as 83.6%[34] and superior to visual analysis in predicting usual interstitial pneumonia (UIP) histology.[35] The application of content-based image retrieval, a method of retrieving and matching similar images from a database, improves diagnostic accuracy and agreement between radiologists.[36]

Biomarkers

Auto-immune screens are part of the diagnostic workup for new ILDs, although the usefulness of these tests may be limited to CTD-ILDs as the presence of rheumatoid factor and anti-CCP in non-CTD ILD is not associated with improved outcomes or treatment response.[37] There is currently no diagnostic blood test for IPF, but newly identified

TABLE 2 Biomarkers and their associations in ILD.

ILD	Marker	Association	Study
Non-CTD fibrotic ILDs	RF and anti-CCP	Not associated with improved outcomes or treatment response	37
IPF	OPN, MMP7, ICAM1, POSTN	Progression and mortality	38
IPF	MMP-7	Worse mortality and disease progression	39
IPF	ccf-dsDNA	Rapid progression of disease. Associated with amino acid, energy and lipid metabolism in IPF	40
IPF	CYFRA 21-1	Localizes to hyperplastic epithelium. Higher in IPF. Predictive of progression and mortality	41
IPF	FUT3	Lower risk of developing IPF	42
PFILD	PLAUR, ITGB6, SPON1, HGF, PRSS8, KRT19 and 11 others	Associated with PFILD	43

Abbreviations: CTD: connective tissue disease; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; PFILD, progressive fibrosing ILD.

biomarkers have the potential to be useful in diagnosis in early disease and prognostication in established disease. A number of circulating biomarkers have been found to be associated with disease progression and mortality, and one with a lower risk of developing IPF (Table 2).[38–42] In non-IPF ILD, 17 biomarkers of the progressive fibrosing phenotype were identified.[43] These were consistent across ILD subtypes suggesting shared pathology and potential targets for treatment.

Biopsy

In the cases where diagnosis cannot be reached from imaging alone, patients may undergo bronchoalveolar lavage (BAL) or lung biopsy. Updated clinical practice guidelines for ILD diagnosis and treatment were produced by the respiratory societies of the USA (ATS), Europe (ERS), Japan (JRS) and Latin America (ALAT).[44,45] In addition to previous recommendations covering CT patterns, BAL and surgical lung biopsy[46] a conditional recommendation was made to regard transbronchial lung cryobiopsy (TBLC) as an acceptable alternative to surgical biopsy for ILD of undetermined type in centres with expertise.

Predicting prognosis

Just under 60% of IPF and fibrotic HP patients progress after 2 years, and survival in patients with a progressive phenotype is similar in IPF and non-IPF ILDs.[47,48] Accurately predicting progression aids management decisions.

A thorough clinical history may provide useful information. In database analyses features of telomere syndrome (based on clinical history, family history or relevant haematological abnormalities) and cough-specific quality of life were associated with reduced survival in IPF and all ILDs, respectively.[49,50]

Recent studies have sought to clarify the usefulness of pulmonary function testing in predicting progression. Data from clinical trials and a single centre study found that lung function decline at 1 year predicted reduced survival in IPF, fibrotic HP and other PFILDs[51,52] and FVC decline over 3 months was associated with mortality in clinical trial participants.[53] Home spirometry may be useful in increasing patient access to regular monitoring. A study of 82 ILD patients found good adherence and high correlation with hospital spirometry, suggesting the potential for wider usage especially amongst those with limited access to services.[54]

CT imaging is the other key tool for prognostication in ILD and there have been significant developments in this field. Data-driven texture analysis (DTA) was used to quantify the extent of fibrosis of patients registered in the Australian IPF Registry.[55] Baseline DTA score was associated with lung function decline, and extent of fibrosis with worse survival, suggesting that imaging may be able to predict outcomes independent of lung function testing.

MANAGEMENT

SUMMARY

- Promising results were seen in pre-clinical studies and clinical trials assessing novel therapies.
- Phosphodiesterase 5 inhibitors for pulmonary hypertension secondary to ILD is associated with prolonged survival, but needs randomized controlled trial (RCT) validation.
- Emergency lung transplantation may be suitable for selected patients.
- Positive clinical outcomes were seen with pulmonary rehabilitation.

For the benefits of early diagnosis to be truly impactful, more definitive treatment options are needed. Identification

and elimination of the inciting antigen is well established as a key feature of HP diagnosis and treatment.[56] However, these benefits have been seen even in fibrotic HP, with antigen avoidance associated with improved FVC and reduced mortality,[27,57] highlighting the importance of a thorough exposure history in the initial assessment.

Pre-clinical studies

Two studies examined the antifibrotic effects of novel therapies on TGF-β treated human lung fibroblasts (HLFs), bleomycin-induced fibrotic murine models and human precision cut lung slices (hPCLS).[58,59] In the first, the inhibition of Src kinases with saracatinib inhibited profibrotic gene expression and myofibroblast transformation in HLFs. In murine models, epithelial-mesenchymal transition and extracellular matrix organization were attenuated. These findings were validated in hPLCS where fibrosis was ameliorated with saracatinib which was either equal or superior to pirfenidone and nintedanib in all models.[58] The second study generated and examined the effect of MRG-229, a mimic of the micro-RNA miR-29 and found that it reduced fibrosis in HLFs and lung slice culture, and counteracted profibrotic genes in mouse models.[59]

Anti-inflammatory treatment

There is considerable evidence for the use of anti-inflammatories in CTD-ILD,[60] and the past year has seen developments in this area. In the double-blinded randomized controlled phase 2b RECITAL trial, 101 participants with severe or progressive ILD were randomized to treatment with rituximab or cyclophosphamide. Both therapies had a similar positive impact on FVC at 24 weeks, although fewer adverse events and treatment doses make rituximab a viable alternative to cyclophosphamide.[61] A phase 3 RCT assessing skin score in SSc found that tocilizumab slowed FVC decline in a subgroup of patients with SSc-ILD.[62]

Despite the benefits in CTD-ILD, there is evidence of harm in IPF from anti-inflammatory treatment. The most recent example of this was in the EXAFIP study, a phase 3 RCT which found that adding intravenous cyclophosphamide to standard of care glucocorticoid therapy in acute exacerbations of IPF increased 3-month mortality.[63]

Antifibrotic therapy

Antifibrotic therapy remains the mainstay of treatment in IPF, and the updated ATS/ERS/JRS/ALAT guidelines now suggest nintedanib for PPF patients who have failed standard management.[44] However, the benefits of antifibrotic therapy require ongoing review in other ILDs. The 2019 INBUILD trial was a double-blind, placebo-controlled phase 3 trial which demonstrated a reduced rate of FVC decline with nintedanib over 52 weeks in non-IPF progressive fibrosing ILDs (PFILDs).[64] Further analysis of data from this study has shown that nintedanib has a similar adverse event profile in PFILD as it does IPF, reduces the risk of events indicative of disease progression and that the effect on lung function decline is consistent across subgroups based on the different elements of criteria for ILD progression.[65–67] This effect on lung function was also seen in a subgroup of patients with progressive fibrosing autoimmune disease-related ILDs, with an average FVC decline of −75.9 mL/year in comparison with −178.6 mL/year with placebo.[68] Pirfenidone also slowed lung function decline in rheumatoid arthritis associated ILD in a phase 2 trial of 123 patients, further justifying the role of antifibrotic treatment across the spectrum of fibrosing ILDs, although the study did not reach its primary endpoint because it was terminated early and therefore underpowered.[69]

Clinical trials of novel treatments

Established IPF treatments slow lung function decline rather than reverse fibrosis,[70,71] necessitating further research into novel therapeutic options. A multi-centre phase 2, double-blinded placebo-controlled trial examined the effects of inhibition of PDE4, an enzyme with anti-inflammatory and profibrotic effects due to its role in cAMP release.[72] As it is highly expressed in lung tissue, the PDE4B subtype was targeted to avoid side effects associated with PDE4 inhibition such as gastrointestinal symptoms and suicidal ideation. Twice daily administration of BI 1015550 was associated with lung function stability over 12 weeks in comparison with placebo in patients with and without concurrent antifibrotic treatment. Despite the selective targeting, however, 24% of patients suffered with GI symptoms and 13% discontinued the trial due to adverse events, with a higher proportion seen in those on concurrent antifibrotic treatment. The phase 3 programme is currently underway to explore the efficacy, safety and tolerability of the drug in IPF and PF-ILD (ClinicalTrialsgov Identifier: NCT05321069). Another phase 3 RCT will assess the effect of inhaled treprostinil over a year on FVC, exacerbation frequency and survival in IPF, having had beneficial effects on FVC in subjects with pulmonary hypertension (PH) secondary to this condition.[73]

Other trials had less favourable outcomes. A monoclonal antibody targeting $\alpha_v\beta_6$ integrins in IPF was associated with physiological and radiological progression, resulting in the termination of development for the drug BG00011.[74] A phase 2B study assessing the effects of inhaled cromolyn sodium did not show any beneficial effects in the treatment of chronic cough in IPF.[75]

Managing and preventing comorbidities

ILD frequently presents with comorbidities which may require tailored management. PH is a common sequala of ILD and management has historically involved treatment of the underlying cause. However, patients treated with

phosphodiesterase 5 inhibitors (PDE5i) for PH secondary to ILD survived longer than those who did not receive treatment in a cohort study, although RCTs are required to validate this finding.[76] Post hoc analysis of the INCREASE study examining the effect of inhaled Treprostinil (a prostacyclin analogue) in PH due to ILD found that patients in the treatment arm were less likely to experience disease progression events.[77]

The risk of developing lung cancer is increased in IPF, but a multicentre retrospective study found that antifibrotic therapy in IPF was associated with a significantly reduced lung cancer incidence and prevalence, suggesting potential benefits beyond slowing disease progression.[78]

Transplant

Lung transplantation had previously been thought to be associated with poor outcomes in acute exacerbations of ILD (AE-ILD) in comparison with those performed on patients with stable disease. However, in a single centre analysis patients undergoing transplant during AE-ILD had similar 1-year survival to those with stable disease suggesting that emergency lung transplantation may suitable for selected patients.[79] It may be beneficial to withhold antifibrotic treatment at the time of transplantation, as chest wall dehiscence was seen earlier and 1-year survival was worse in patients on treatment, although there was no significant difference in overall incidence of dehiscence or survival at other time points (30 days, 90 days and 3 or 5 years).[80]

Supportive treatment

Supportive care is crucial for symptom control but may also have an effect on clinical outcomes. Pulmonary rehabilitation (PR) programmes are structured exercise regimes aimed at improving physical and psychological deficits in patients with respiratory disease. A retrospective multinational cohort study of fILD patients found that frequent participation in PR and improvement in exercise capacity was associated with lower mortality.[81] Similar results were seen in a prospective study of IPF patients, with greater one-year mortality in patients who did not complete the course.[82] However, causality was difficult to establish in both studies, with confounding factors such as comorbidities and exacerbations liable to affect engagement in PR and survival outcomes equally. Regardless, PR should be offered to all patient with fILD who are able to safely participate.

Oxygen therapy is commonly used in ILD for hypoxia, but there is limited high quality evidence to guide best practice.[83] A blinded randomized control trial found that treating supplemental oxygen with pulsed inhaled nitric oxide was associated with an improvement in breathlessness in fILD, with a phase-3 trial underway.[84] A smaller open-label randomized crossover trial found that oxygen delivered via high flow nasal cannulae increased exercise tolerance in IPF patients with exercise-induced hypoxia in comparison to delivery via a Venturi mask.[85]

IMPACT OF THE COVID-19 PANDEMIC

SUMMARY

- For patients who were hospitalized with COVID, 11% were estimated to have residual lung abnormalities.
- Low dose prednisolone was found to be equivalent to high dose in patients with residual change.
- IPF mortality increased during the pandemic.

Patients with severe COVID may be vulnerable to developing fibrotic change as there is positive genome-wide genetic correlation between risk of IPF and severe COVID.[86] The multicentre UKILD Post-COVID study aims to determine the prevalence of residual lung abnormalities after COVID infection. In an interim analysis 11% of patients were estimated to have persistent changes after hospitalization.[87] A meta-analysis of 46 studies found that fibrotic sequelae were estimated in 29% of scans following hospitalization at a median follow-up time of 12 months, although significant study heterogeneity should be noted.[88] Given the range of time points seen across these studies it remains difficult to predict the burden of disease following COVID-19 infection. However, it is likely that many of the abnormalities will resolve over time given the physiological improvements seen over 6 months in a prospective multi-centre study.[89]

Glucocorticoids are commonly prescribed for the management of residual lung abnormalities.[90] A single-centre study found no significant difference in radiological, physiological or quality of life outcomes between 6 weeks of high dose versus low dose prednisolone, although a trend was seen in the majority of parameters in favour of higher dose therapy.[90]

The pandemic also had an impact beyond those infected with the virus. An increase in IPF mortality was seen during the second wave, thought to be mostly related to the burden placed on respiratory services.[91] In a small subset of patients with IPF, COVID-19 vaccination may trigger acute exacerbation, although benefits of vaccination significantly outweigh these risks.[92]

INEQUALITIES IN ACCESSING CARE AND CONCLUSION

SUMMARY

- Inequalities exist in delivering and accessing ILD specialist care. Greater effort is required to address these inequalities and positively impact ILD prognosis.

For these advances to have a significant impact, it is crucial that delays in ILD diagnosis and treatment are

minimized.[93] A multicentre prospective cohort study found that patients in the USA with fILD in areas with greatest disadvantage had the highest mortality risk, and that IPF patients in these areas had the lowest odds of lung transplantation.[94] A number of retrospective studies validate these findings, observing that socioeconomic disadvantage and distance from specialist services can be associated with delayed presentation, reduced antifibrotic use, lower likelihood of lung transplantation and greater risk of death.[95–98] Regional respiratory physicians in Australia reported barriers to treatment related to staffing and inadequate access to clinical trials and funding.[99] Greater effort is required to address these inequalities and positively impact ILD prognosis.

Although prognosis remains poor in many cases, the above developments represent significant progress in the field of ILD research and it is to be hoped that the outlook will continue to improve.

CONFLICT OF INTEREST STATEMENT

None declared.

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