In this issue:

- Effect of ambulatory oxygen on quality of life in fibrotic lung disease
- A novel autotaxin inhibitor for treating IPF
- Pirfenidone in the context of multiple disease progression events in IPF
- Nintedanib + sildenafil in IPF
- Australian patients’ experiences of IPF care
- Safety of benzodiazepines and opioids in ILD
- Nintedanib for systemic sclerosis-associated ILD
- Quantitative CT-derived vessel metrics in IPF
- Emphysematous changes in scleroderma-associated ILD

Abbreviations used in this issue

- 6MWD = 6-minute walk distance
- DCO = diffusing capacity of the lung for carbon monoxide
- FVC = forced vital capacity
- ILD = interstitial lung disease
- IPF = idiopathic pulmonary fibrosis

Welcome to this September issue of Respiratory Research Review with the topic of ILD (interstitial lung disease), a field probably big enough to earn its own dedicated review. Following the watershed moment with the publication of the landmark papers 5 years ago (Respiratory Research Review issue 104), pirfenidone and nintedanib are now widely funded for the treatment of IPF (idiopathic pulmonary fibrosis), and we have reached a new steady state. Actually, Wim Wuyts and Vincent Cottin ask in a Eur Respir J editorial “idiopathic pulmonary fibrosis: time for greater expectations?”. The thinking about IPF has changed radically over the last decade. Clinical practice guidelines assist us to adhere to a standardised, evidence-based approach. They also harmonise populations with IPF to allow comparison in outcomes and enrolment in trials, assist regulatory agencies to fund new treatments, and support patients and advocacy groups to understand the natural illness. Last year we commented on the “Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper” (Respiratory Research Review issue 152). The recommendation and conclusion are largely in concordance with the official clinical practice guidelines of the ATS (American Thoracic Society), ERS (European Respiratory Society), JRS (Japanese Respiratory Society) and ALAT (Latin American Thoracic Society) (Am J Respir Crit Care Med). Athol Wells spells it out for us in his editorial. The key clinical change both guidelines agree on is that a probable diagnosis of IPF (likelihood of 70–94%) can be made in the right clinical setting in the absence of classical honeycombing based on basal predominant subpleural reticulation and associated traction bronchiectasis on high-resolution CT. The debate between Vincent Cottin and Athol Wells brought a smile to my face – an argument that Vincent Cottin wins, in my mind, by making the case that pulmonary fibrosis is idiopathic (i.e. an illness in its own right) and not cryptogenic (i.e. an illness caused by a hidden origin). Athol Wells conciliates, quoting Socrates, that clarity of thought is based on the clarity of language and that “the beginning of wisdom is the definition of terms” (Eur Respir J). In time, with all these changes, we have a newly updated factsheet (pdf; 44KB) for our patients written by the European Lung Foundation and European Respiratory Society.

‘The world is failing on silicosis’ is the title of a Lancet editorial pointing out that millions of people develop silicosis, which is entirely preventable via wet-cutting, good ventilation and well-fitted air respirators. Actually, in an opinion piece, Talha Khan Burki links back to the Orwellian tradition of describing the working conditions of so-called ‘small scale mining’ occurring in rural areas with rudimentary tools and makeshift shafts with scant security precautions that are largely unregulated and far away from healthcare facilities. Using the highly corrosion-resistant trace mineral tantalum as an example, which is used in surgical instruments, cell phones, personal computers and cameras, he finishes with a direct quote by George Orwell: “You and I and the editor of the Times and the poets and the Archbishop of Canterbury and Comrade X, author of Marxism and my mind, by making the case that pulmonary fibrosis is idiopathic (i.e. an illness in its own right) and not cryptogenic (i.e. an illness caused by a hidden origin). Athol Wells conciliates, quoting Socrates, that clarity of thought is based on the clarity of language and that “the beginning of wisdom is the definition of terms” (Eur Respir J). In time, with all these changes, we have a newly updated factsheet (pdf; 44KB) for our patients written by the European Lung Foundation and European Respiratory Society.

Finally, we are fortunate in NZ that we can offer patients with IPF the opportunity to participate in randomised controlled trials, which may improve the outlook for our patients with IPF. I would like to acknowledge the persistent hard work of Margaret Wilsher to keep NZ on the horizon. Talk to your local centre, as we are currently recruiting for GALAPAGOS (add-on trial) and GEMINI (add-on trial) in the context of multiple disease progression events in IPF. The debate between Vincent Cottin and Athol Wells brought a smile to my face – an argument that Vincent Cottin wins, in my mind, by making the case that pulmonary fibrosis is idiopathic (i.e. an illness in its own right) and not cryptogenic (i.e. an illness caused by a hidden origin). Athol Wells conciliates, quoting Socrates, that clarity of thought is based on the clarity of language and that “the beginning of wisdom is the definition of terms” (Eur Respir J). In time, with all these changes, we have a newly updated factsheet (pdf; 44KB) for our patients written by the European Lung Foundation and European Respiratory Society.

‘The world is failing on silicosis’ is the title of a Lancet editorial pointing out that millions of people develop silicosis, which is entirely preventable via wet-cutting, good ventilation and well-fitted air respirators. Actually, in an opinion piece, Talha Khan Burki links back to the Orwellian tradition of describing the working conditions of so-called ‘small scale mining’ occurring in rural areas with rudimentary tools and makeshift shafts with scant security precautions that are largely unregulated and far away from healthcare facilities. Using the highly corrosion-resistant trace mineral tantalum as an example, which is used in surgical instruments, cell phones, personal computers and cameras, he finishes with a direct quote by George Orwell: “You and I and the editor of the Times and the poets and the Archbishop of Canterbury and Comrade X, author of Marxism and...
Effect of ambulatory oxygen on quality of life for patients with fibrotic lung disease (AmbOx)

Authors: Visca D et al.

Summary: The prospective, open-label AmbOx study enrolled 64 adults with fibrotic ILD who were not hypoxic at rest but had a decrease in transcutaneous arterial oxygen saturation to ≤88% on a 6MWD test at screening, and who had self-reported stable respiratory symptoms in the prior 2 weeks. In a randomised crossover design, the participants were given and not given 2 weeks of oxygen treatment; 76 participants completed both 2-week trial periods. Compared with no supplemental oxygen, ambulatory oxygen was associated with a significant improvement in mean total King’s Brief Interstitial Lung Disease score (55.5 vs. 51.8 [p<0.0001]), including the breathlessness plus activity and chest symptom subdomains, but with no significant impact among placebo recipients. None of the five serious adverse events recorded during oxygen treatment and one without oxygen treatment. None of the five serious adverse events recorded were considered to be treatment-related.

Comment: This study was published just as I was at the Royal Brompton during my sabbatical period. It is a masterpiece of co-ordination between different services, units and countries. Like all good research, it has increased the awareness of patient suffering, is fuelling debates and has raised many more new questions. Its biggest weaknesses are probably the short timeframe and the lack of a ‘medical air’ control group; nicely considered in the accompanying editorial. The authors’ bottom line: ambulatory oxygen seems to be associated with improvement in health-related quality of life.

Reference: Lancet Respir Med 2018;6:759–70

Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA)

Authors: Muher TM et al.

Summary: Nonsmokers aged ≥40 years with PF who were not receiving pirfenidone or nintedanib were randomised 3:1 to receive the orally administered novel, potent, selective autotaxin inhibitor GLPG1690 600mg (n=17) or placebo (n=6) once daily for 12 weeks in this phase 2a trial, which primarily evaluated safety, tolerability, pharmacokinetics and pharmacodynamics; the study was completed by 20 participants. The respective treatment-emergent adverse event rates among GLPG1690 and placebo recipients were 65% and 67%; most were mild-to-moderate. Only two events among GLPG1690 recipients were considered to be treatment-related, and one GLPG1690 recipient developed cholangiocarcinoma resulting in treatment discontinuation. There were no deaths. GLPG1690’s pharmacokinetic and pharmacodynamic profiles were similar to those previously reported in healthy controls. GLPG1690 administration was associated with consistent decreases in plasma lysophosphatidic acid C18:2 levels, and at week 12, mean change in FVC was 25mL versus –70mL among placebo recipients.

Comment: Pirfenidone is one of the treatments for IFP and is associated with significant side effects such as anorexia, weight loss, nausea, diarrhoea, and skin rash. What should one do if a patient has side effects and disease progression despite treatment? In this post hoc analysis, these researchers pooled data from the CAPACITY and ASCENT trials and documented that events of disease progression were about halved in the treatment group. The key finding of this analysis is in following the patients who progressed on pirfenidone. Bottom line: continued treatment with pirfenidone despite the occurrence of a progression event still conferred significant benefits.


Efficacy of pirfenidone in the context of multiple disease progression events in patients with idiopathic pulmonary fibrosis

Authors: Nathan SD et al.

Summary: These researchers assessed the incidence of multiple events in the same patient over a 12-month period during treatment with pirfenidone for IFP. To do this, they conducted a post hoc analysis of data from phase 3 ASCEND and CAPACITY trial participants who had received pirfenidone 2403 mg/day (n=623) or placebo (n=624). Disease progression events were a relative decline in percent predicted FVC of ≥10%, an absolute decline in 6MWD of ≥50m, hospitalisation for respiratory reasons and death from any cause. The most frequent disease progression events were declines in percent predicted FVC (202 vs. 304 events for pirfenidone versus placebo) and declines in 6MWD (265 vs. 346 events). Compared with placebo recipients, a significantly lower proportion of pirfenidone recipients experienced >1 progression event (17.0% vs. 30.1% [p<0.0001]) or died after experiencing ≥1 such event (2.1% vs. 6.3% [p=0.0002]).

Reference: Chest 2019;155:712–9
Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis

Authors: Kolb M et al., for the INSTAGE Investigators

Summary: Patients with IPF and a $D_{150}$ of ≤35% of predicted ($n=274$) were randomised 1:1 to receive nintedanib 150mg twice daily combined with either sildenafil 20mg or placebo three times daily for 24 weeks. There was no significant difference between nintedanib plus sildenafil versus nintedanib plus placebo for adjusted mean change from baseline in the St. George’s Respiratory Questionnaire total score at week 12 (–1.28 vs. –0.77 points [p=0.72]). Adding sildenafil to nintedanib also provided no benefit in terms of dyspnoea according to a shortness of breath questionnaire. There were no new safety signals reported.


Abstract

Comment: Sildenafil has been approved for treatment for patients with idiopathic pulmonary arterial hypertension but not for patients with pulmonary hypertension secondary to ILD. IPF is associated with fibrotic destruction of the lung vasculature. These researchers explored the hypothesis of combining nintedanib and sildenafil for the treatment of IPF. The authors recruited almost 300 patients with IPF and a $D_{150}$ of <35%. A later subgroup analysis showed some benefit on brain natriuretic peptide level. However, the bottom line: the combination of nintedanib and sildenafil did not provide benefit above nintedanib alone.

Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board. FOR FULL BIO CLICK HERE

Independent Content: The selection of articles and writing of summaries and commentary in this publication is completely independent of the advertisers/sponsors and their products.

Privacy Policy: Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time.

Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Research Review publications are intended for New Zealand health professionals.

We’re looking for a fight with IPF

2.47 additional years*

It’s worth fighting for.

*estimated additional mean years life expectancy, Esbriet compared with best supportive care

Esbriet® Abridged Prescribing Information (API)

Esbriet (pirfenidone) 267 mg oral capsules and 267 mg and 801 mg tablets are Prescription Medicines indicated for the treatment of idiopathic pulmonary fibrosis (IPF). Dosage and Administration: Please see Esbriet Data Sheet for information. Contraindications: Contraindicated in patients with a hypersensitivity to pirfenidone or any of the excipients. Patients taking fluoroquinolones and patients with a history of angioedema with pirfenidone. Precautions: Hepatic Function: Elevations in ALT and AST 3 x ULN have been reported. Liver function tests should be conducted prior to and during treatment. If significant elevations occur the dose of Esbriet should be adjusted, refer to dosage guidelines in Data Sheet. Caution when used in patients with mild to moderate hepatic impairment.

Photosensitivity reaction/rash: exposure to direct sunlight should be minimised during treatment and patients instructed to wear sunblock and protective clothing. Dosage adjustment or temporary discontinuation may be required, refer to dosage guidelines in Data Sheet. Angioedema: patients who develop signs or symptoms of angioedema while taking Esbriet should immediately discontinue treatment. Cigarette smoking and inducers of CYP1A2: exposure to pirfenidone was 50% less in patients who were smokers, concomitant use of strong inducers of CYP1A2 including smoking should be avoided. Pregnancy Cat B3: there are no data on the use in pregnancy. Paediatric: safety has not been established. Renal Impairment: Use with caution in patients with mild, moderate or severe renal impairment.

Drug Interactions: Esbriet is contraindicated in patients taking fluoroquinolone and caution should be taken in patients taking inhibitors of CYP1A2 e.g. e.g. ciprofloxacin, amiodarone, propafenone or inducers of CYP1A2 e.g. simvastatin, rifampicin. Adverse Effects: (Common only): see data sheet for full list. Upper respiratory tract infection; urinary tract infection; weight decreased; decreased appetite; insomnia; diziness; somnolence; dysgeusia; lethargy; hot flush; dyspepsia; cough; productive cough; gastrointestinal reflux disease; vomit; abdominal distension; abdominal discomfort; abdominal pain; abdominal pain upper; stomach discomfort; gastritis; constipation; faecaline ALT increased; AST increased; gamma glutamyl transferase increased; pruritus; erythema; dry skin; rash erythematous; rash macular; rash pruritic; myalgia; arthralgia; asthma; non-cardiac chest pain; sunburn.

Esbriet is a funded medicine for patients with IPF who meet pre-defined criteria. Prescription and doctors’ fees may apply.

For more information, please go to www.medsafe.govt.nz

We’re looking for a fight with IPF

2.47 additional years*

It’s worth fighting for.

*estimated additional mean years life expectancy, Esbriet compared with best supportive care

Esbriet® Abridged Prescribing Information (API)

Esbriet (pirfenidone) 267 mg oral capsules and 267 mg and 801 mg tablets are Prescription Medicines indicated for the treatment of idiopathic pulmonary fibrosis (IPF). Dosage and Administration: Please see Esbriet Data Sheet for information. Contraindications: Contraindicated in patients with a hypersensitivity to pirfenidone or any of the excipients. Patients taking fluoroquinolones and patients with a history of angioedema with pirfenidone. Precautions: Hepatic Function: Elevations in ALT and AST 3 x ULN have been reported. Liver function tests should be conducted prior to and during treatment. If significant elevations occur the dose of Esbriet should be adjusted, refer to dosage guidelines in Data Sheet. Caution when used in patients with mild to moderate hepatic impairment.

Photosensitivity reaction/rash: exposure to direct sunlight should be minimised during treatment and patients instructed to wear sunblock and protective clothing. Dosage adjustment or temporary discontinuation may be required, refer to dosage guidelines in Data Sheet. Angioedema: patients who develop signs or symptoms of angioedema while taking Esbriet should immediately discontinue treatment. Cigarette smoking and inducers of CYP1A2: exposure to pirfenidone was 50% less in patients who were smokers, concomitant use of strong inducers of CYP1A2 including smoking should be avoided. Pregnancy Cat B3: there are no data on the use in pregnancy. Paediatric: safety has not been established. Renal Impairment: Use with caution in patients with mild, moderate or severe renal impairment.

Drug Interactions: Esbriet is contraindicated in patients taking fluoroquinolone and caution should be taken in patients taking inhibitors of CYP1A2 e.g. e.g. ciprofloxacin, amiodarone, propafenone or inducers of CYP1A2 e.g. simvastatin, rifampicin. Adverse Effects: (Common only): see data sheet for full list. Upper respiratory tract infection; urinary tract infection; weight decreased; decreased appetite; insomnia; diziness; somnolence; dysgeusia; lethargy; hot flush; dyspepsia; cough; productive cough; gastrointestinal reflux disease; vomit; abdominal distension; abdominal discomfort; abdominal pain; abdominal pain upper; stomach discomfort; gastritis; constipation; faecaline ALT increased; AST increased; gamma glutamyl transferase increased; pruritus; erythema; dry skin; rash erythematous; rash macular; rash pruritic; myalgia; arthralgia; asthma; non-cardiac chest pain; sunburn.

Esbriet is a funded medicine for patients with IPF who meet pre-defined criteria. Prescription and doctors’ fees may apply.

For more information, please go to www.medsafe.govt.nz
Safety of benzodiazepines and opioids in interstitial lung disease

Authors: Bajwa S et al.

Summary: Relationships between benzodiazepine and opioid use and the risks of hospitalisation and death were explored in this prospective population-based longitudinal cohort study of 1603 patients starting long-term oxygen therapy for fibrotic ILD in Sweden; benzodiazepines were used by 196 of the patients and opioids were used by 254. No association was seen between benzodiazepine or opioid use and increased hospital admission. High-dose (but not low-dose) benzodiazepine use was associated with increased mortality (subdistribution hazard rate 1.46 [95% CI 1.08, 1.98]). Neither low- nor high-dose opioid use was significantly associated with increased mortality.

Comment: Kathleen Lindell also co-authored the accompanying editorial for this article. She points out that 70–98% of patients with fibrotic lung disease experience breathlessness, 60–95% cough and up to 50% report depression. This population-wide study identified 1600 patients, with about 12% using benzodiazepines and 15% low-dose opioids to manage their breathlessness. This matches the findings from the previous studies in Australia; that patients have unmet needs of symptom control. The good news from this article is the bottom line: low-dose benzodiazepines and opioids were not associated with increased hospital admission or mortality.

Reference: Eur Respir J 2018;52:1801278

Abstract

Nintedanib for systemic sclerosis-associated interstitial lung disease

Authors: Distler O et al., for the SENSICS Trial Investigators

Summary: Patients with ILD associated with systemic sclerosis (evaluable n=576) were randomised 1:1 to receive oral nintedanib 150mg or placebo twice daily. Compared with placebo, nintedanib recipients had a smaller adjusted rate of decline in FVC (primary endpoint; −52.4 vs. −93.3 mL/year [p=0.04]; the p values were 0.06–0.10 in sensitivity analyses based on multiple imputation for missing data). There was no significant between-group difference for change from baseline in the modified Rodnan skin score or for total St. George’s Respiratory Questionnaire score at week 52.

Comment: It is logical to explore the effects of our antifibrotic agents in other diseases besides IPF. These authors managed to recruit almost 600 patients with scleroderma-related fibrotic lung disease into a randomised controlled trial, which in itself is an achievement. About half of the patients were already taking mycophenolate mofetil. Seventy-five percent of patients on nintedanib developed diarrhoea. Fifteen percent of the patients in the nintedanib arm and 8% in the placebo group withdrew from the study. Bottom line: a year's treatment with nintedanib reduced the loss of vital capacity by 40mL; however, no improvements in patient-related outcomes were observed.


Abstract

Quantitative CT-derived vessel metrics in idiopathic pulmonary fibrosis

Authors: Jacob J et al.

Summary: This structure-function study sought to determine if quantitative lung vessel morphology, as determined by analysis of CT images by a fully automated algorithm, was associated with functional indices in 152 patients with IPF. Separate quantitation of pulmonary arterial and venous metrics was undertaken in 106 patients, and the results were evaluated against lung function test readouts. A univariable linear regression analysis revealed moderate but significant correlations of emphysematous changes. They found that pathologica pulmonary emphysema was the most frequent complication in 76.2% of patients with or without a smoking history (62.5% were never-smokers). High-resolution CT revealed a low attenuation area within interstitial abnormalities in 31.3% of the patients. Patients who had pathological pulmonary emphysema with systemic sclerosis-ILD had lower D_LCO values, a greater disease extent on high-resolution CT and more intimal/medial thickening in muscular pulmonary arteries; however, FVC was well preserved regardless of the presence of pathological pulmonary emphysema. Pulmonary microvascular changes in arterioles were seen in 90.5% of the patients with systemic sclerosis-ILD, 85.7% had haeus and 81.0% had interlobular veins.

Comment: This last article is essentially a 'note to self', something I had overlooked and my colleagues at The Brompton had to point out to you. We have touched on the relationship between fibrosing lung disease and vascular pathology already. Some patients with scleroderma-related ILD develop small-vessel vasculitis; this may destroy the alveolar walls, which may cause emphysematous changes. In this paper, a group of Japanese researchers carefully reviewed the radiology and histology of 21 patients with scleroderma-related ILD. My personal bottom line: about a third of never-smoker patients with scleroderma-related ILD can have features of emphysema.


Abstract

Emphysematous change with scleroderma-associated interstitial lung disease: the potential contribution of vasculopathy?

Authors: Yamakawa H et al.

Summary: These authors retrospectively reviewed the records of 21 consecutive patients presenting with systemic sclerosis-ILD diagnosed by surgical lung biopsy, focussing on radio-pathological correlations of emphysematous changes. They found that pathological pulmonary emphysema was the most frequent complication in 76.2% of patients with or without a smoking history (62.5% were never-smokers). High-resolution CT revealed a low attenuation area within interstitial abnormalities in 31.3% of the patients. Patients who had pathological pulmonary emphysema with systemic sclerosis-ILD had lower D_LCO values, a greater disease extent on high-resolution CT and more intimal/medial thickening in muscular pulmonary arteries; however, FVC was well preserved regardless of the presence of pathological pulmonary emphysema. Pulmonary microvascular changes in arterioles were seen in 90.5% of the patients with systemic sclerosis-ILD, 85.7% had haeus and 81.0% had interlobular veins.

Comment: This last article is essentially a ‘note to self’, something I had overlooked and my colleagues at The Brompton had to point out to you. We have touched on the relationship between fibrosing lung disease and vascular pathology already. Some patients with scleroderma-related ILD develop small-vessel vasculitis; this may destroy the alveolar walls, which may cause emphysematous changes. In this paper, a group of Japanese researchers carefully reviewed the radiology and histology of 21 patients with scleroderma-related ILD. My personal bottom line: about a third of never-smoker patients with scleroderma-related ILD can have features of emphysema.

Reference: Eur Respir J 2018;52:1801278

Abstract

New Zealand Research Review subscribers can claim CPD/CME points for time spent reading our reviews from a wide range of local medical and nursing colleges. Find out more on our CPD page.