Respiratory Research Review™

Making Education Easy

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Abbreviations used in this issue

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

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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 concedes, 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; 442KB) for our patients underwritten 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 for infants – all of us really owe the comparative decency of our lives to poor drudges underground"*.

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 agent to standard therapy), ATLAS (inhaled pirfenidone), and soon for cromolyn for all IPF patients with a persistent cough.

Kind regards,

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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 84 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 on the psychological subdomain. Upper respiratory tract infections were the most common adverse events, with three 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
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

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

Authors: Maher TM et al.

Summary: Nonsmokers aged ≥40 years with IPF 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: This is not the catchiest title for an article; however, the investigative agent called GLPG1690 is causing some excitement in the scientific community (Lancet Respir Med). GLPG1690 is a potent inhibitor of autotaxin, which is responsible for producing lysophosphatidic acid, which is involved in the fibrotic process in the lung. The trial was short and fast and used exploratory outcomes like home spirometry and functional imaging. GLPG1690 was well tolerated; however, only 17 participants received the active agent. **Bottom line: GLPG1690 seems to be a promising new agent to treat IPF. A phase 3 trial is currently open to patients in NZ.**

Reference: Lancet Respir Med 2018;6:627–35
Abstract

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 IPF. 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. 348 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]).

Comment: Pirfenidone is one of the treatments for IPF 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.**

Reference: Chest 2019;155:712–9
Abstract

CLICK HERE to read previous issues of Respiratory Research Review

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_{LCO} 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.

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_{LCO} 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.**

Reference: N Engl J Med 2018;379:1722–31
Abstract

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

Understanding the patient's experience of care in idiopathic pulmonary fibrosis

Authors: Burnett K et al.

Summary: The experiences of 100 patients receiving contemporary care for IPF (FVC 46–106% of predicted) in Australia were captured using semistructured interviews in this qualitative study. Dissatisfaction regarding information received about IPF, particularly at the time of diagnosis, was often reported by the participants. Most participants expressed enthusiasm regarding the benefits of specialist IPF centres, including the prospect of regular monitoring, frequent contact with health professionals and access to clinical trials, although concerns were expressed regarding the burden of travel to specialist centres and treatment costs. Many participants commented that side effects led them to titrate or withhold their antifibrotic therapy, sometimes without consulting their treating team. Well-being was negatively impacted by comorbidities. Participants' perceptions of their responsibilities for self-management included exercise, diet, vaccination and treatment of chest infections, and many thought that this active role should receive more positive emphasis from health professionals.

Comment: Our colleagues in Melbourne interviewed 100 patients with IPF, with this article being freely available. Some of the key findings are summarised by Kathleen Lindell in her accompanying editorial: i) dissatisfaction about information on IPF they received; ii) enthusiasm about specialist care; iii) burden of travel; iv) comorbid conditions, which increase the illness burden they have to manage; and v) side effects of treatment. The same group published a paper about the therapeutic burden of treatment. Kathleen Lindell's title of her editorial is the **bottom line: 'The patients have spoken; now it is time for us to listen…'.**

Reference: Respirology 2019;24:270–7
Abstract

Safety of benzodiazepines and opioids in interstitial lung disease

Authors: Bajwah 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 ratio 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 SENSCIS 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 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.**

Reference: N Engl J Med 2019;380:2518–28
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 between normalised vessel volume (expressed as a percentage of total lung volume) and FVC, D_{LCO}, total lung capacity and a composite physiological index. A correlation was seen between normalised vessel volume and density but not heterogeneity. There was no significant link between quantitatively derived vessel metrics (and artery and vein subdivision scores) and transfer factor for carbon monoxide, and there was only a weak link between these metrics and D_{LCO}. A multivariable linear regression analysis revealed that normalised vessel volume and heterogeneity were both independently associated with D_{LCO}, total lung capacity and the composite physiological index. Artery-vein separation contributed no additional information beyond that captured in the entire vasculature.

Comment: Earlier we reviewed studies trying to address pulmonary hypertension with sildenafil. This is an explorative study of blood vessels in 152 patients with IPF. The authors used a computer algorithm that doesn't focus on the degree of fibrosis. The algorithm can distinguish between pulmonary arteries and veins and can comment on the vessel density, tortuosity and heterogeneity – nonvisible, even to the trained eye. This study produced beautiful pictures based on information created by the computer and demonstrated our **bottom line: the heterogeneity of pulmonary blood vessels correlates to physiological parameters of diffusing capacity and total lung capacity.**

Reference: Respirology 2019;24:445–52
Abstract

Each month we highlight a particularly excellent paper with our butterfly symbol.

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 microvasculature changes in arterioles were seen in 90.5% of the patients with systemic sclerosis-ILD, 85.7% had venules 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: BMC Pulm Med 2018;18:25
Abstract