Prevalence and prognosis of unclassifiable interstitial lung disease

To the Editor:

We read with interest the recent article by RYERSON *et al.* [1], describing the prevalence and characteristics of patients with unclassifiable interstitial lung disease (ILD) presenting to a specialist centre. This study is the first to target specifically this newly defined disease category, in parallel with publication of the updated American Thoracic Society/European Respiratory Society classification of the idiopathic interstitial pneumonias (IIPs) [2]. The authors identified 10% of their ILD patient population as having unclassifiable ILD following multidisciplinary discussion (MDD). The major reasons for diagnostic uncertainty related to either inability or unwillingness of the patient to undergo surgical lung biopsy, or inadequacy of the tissue specimen sampled. Only a minority of cases remained ambiguous after a reasonable tissue sample had been obtained.

The study detailed the clinical characteristics of this hybrid group, with many of the mean baseline demographics and disease behaviours falling between the two reference groups of patients with confirmed idiopathic pulmonary fibrosis (IPF) and non-IPF diagnoses. Multivariate analysis revealed low diffusing capacity of the lung for carbon monoxide and high fibrosis scoring on high-resolution computed tomography to be independent predictors of adverse outcomes in the unclassifiable group, as has been shown previously in other ILD populations [3].

We wish to raise our concern about defining these patients with diagnostic uncertainty as a unified entity, given the composite nature of this group. That there will always exist such a group is indisputable. Our fear is that the introduction of ''unclassifiable ILD'' into medical parlance may discourage the pursuit of an accurate and specific ILD diagnosis, thereby limiting timely and appropriate therapy for an increasing number of patients. This would be of particular risk in smaller centres without access to the recognised gold standard, MDD [2, 4]. In Australia and New Zealand, where access to larger specialist centres with MDD is limited, we believe that the temptation to label patients as having unclassifiable ILD without extensive and accurate diagnostic evaluation could become the easier and more common alternative.

While the lack of surgical lung biopsy contributes to the problem, in our experience, complete evaluation of autoimmune serology is not often performed outside specialist settings, in the absence of systemic features. Patients with so-called ''lung-dominant connective tissue disease'' are vulnerable to fall under the umbrella of unclassifiable disease. In diseases such as the antisynthetase syndrome, extrapulmonary manifestations may be subtle or absent [5], and lung disease may also precede systemic features, warranting an ongoing need for detailed clinical assessment and possible revision of the working diagnosis. It would be interesting to determine what proportion of unclassifiable ILD patients in the cohort of RYERSON *et al.* [1] had incomplete autoimmune screening, potentially leading to mislabelling the patient as ''unclassifiable''.

The study by RYERSON *et al.* [1], in fact, confirms that accurate ILD diagnosis is important with regard to prognosis, with IPF having a much poorer outcome compared with other non-IPF ILD [1, 3]. While the cohort of RYERSON *et al.* [1] with unclassifiable ILD had an intermediate prognosis better than IPF and worse than non-IPF ILD, the authors recognise that this group will ultimately be comprised of a spectrum of different specific ILD diagnoses. With recent good evidence demonstrating the harm in giving combination corticosteroids and azathioprine in the IPF subgroup, there is ever more reason to distinguish between those with and without this disease [6]. Similarly, withholding immunomodulatory therapy in patients with inflammatory IIP may also minimise the likelihood of achieving optimal disease control.

The updated IIP guidelines acknowledge that despite extensive investigation and MDD, a proportion of ILD diagnoses will remain obscure. In our own experience within an Australian specialist ILD centre, 9.9% of the patient population (2011–2013; n=232) have unclassifiable disease, despite complete evaluation including MDD. These patients are followed closely and revisited at the MDD if clinical features change. As highlighted in the accompanying editorial by COTTIN and WELLS [7], unclassifiable disease is likely to be relatively rare if strictly confined to patients with no logical first-choice diagnosis following MDD. However, it is likely to increase in prevalence if it is considered to include all patients in whom features are intermediate and only a tentative first-choice diagnosis can be made without diagnostic confidence. It is

important to characterise this level of diagnostic confidence at MDD, thus enabling future research into this patient group.

An emerging recommendation is to manage patients according to their disease behaviour, particularly for the subgroup with ill-defined or overlapping diagnostic features. This should not obviate the imperative to pursue a diagnosis where possible, with appropriate means.

While we accept that there is a group of ILD patients in whom a specific ILD diagnosis is not possible, despite all efforts, we wish to encourage respiratory physicians to pursue an accurate ILD diagnosis, rather than accepting a diagnosis of unclassifiable ILD without full and accurate investigation. Although this is a tempting option, particularly in the absence of ready access to MDD, it is associated with more diagnostic and prognostic uncertainty, and ultimately may delay specific treatment options.

@ERSpublications
Physicians should pursue accurate ILD diagnosis, rather than "unclassifiable ILD" without full investigation http://ow.ly/tt8r0

Lauren Troy[1], Ian Glaspole[2], Nicole Goh[3], Chris Zappala[4], Peter Hopkins[5], Margaret Wilsher[6], Yuben Moodley[7] and Tamera Corte[1]
[1]Dept of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Sydney, [2]Dept of Allergy, Immunology and Respiratory Medicine, Alfred Health, Melbourne, [3]Dept of Respiratory and Sleep Medicine, Austin Health, Heidelberg, [4]Dept of Thoracic Medicine, Royal Brisbane and Women's Hospital, Brisbane, [5]Lung Transplant Unit, The Prince Charles Hospital, Brisbane, and [7]Dept of Respiratory Medicine, Royal Perth Hospital, Perth, Australia.[6]Green Lane Respiratory Services, Auckland City Hospital, Auckland, New Zealand.

Correspondence: L. Troy, Dept of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Missenden Rd, Camperdown, Sydney, NSW 2050, Australia. E-mail: ltroy@med.usyd.edu.au

Received: Jan 06 2014 | Accepted: Jan 09 2014

Conflict of interest: None declared.

References

1 Ryerson CJ, Urbania TH, Richeldi L, *et al.* Prevalence and prognosis of unclassifiable interstitial lung disease. *Eur Respir J* 2013; 42: 750–757.
2 Travis WD, Costabel U, Hansell DM, *et al.* An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733–748.
3 Latsi PI, du Bois RM, Nicholson AG, *et al.* Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med* 2003; 168: 531–537.
4 Flaherty KR, King TE Jr, Raghu G, *et al.* Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med* 2004; 170: 904–910.
5 Cottin V. Significance of connective tissue disease features in pulmonary fibrosis. *Eur Respir Rev* 2013; 221: 273–280.
6 Raghu G, Anstrom KJ, King TE Jr, *et al.* Prednisone, azathioprine and *N*-acetylcysteine for pulmonary fibrosis. *N Engl J Med* 2012; 366: 1968–1977.
7 Cottin V, Wells A. Unclassified or unclassifiable interstitial lung disease: confusing or helpful disease category? *Eur Respir J* 2013; 42: 576–579.

Eur Respir J 2014; 43: 1529–1530 | DOI: 10.1183/09031936.00003414 | Copyright ©ERS 2014

Serum CCL18 is predictive for lung disease progression and mortality in systemic sclerosis

To the Editor:

We read with pleasure the article "*Serum CC chemokine ligand-18 predicts lung disease worsening in systemic sclerosis*" [1], published in the *European Respiratory Journal*. Tiev *et al.* [1] demonstrated very nicely that elevated CC chemokine ligand 18 (CCL18) serum levels predict lung disease progression in patients with systemic sclerosis (SSc). In the multivariate analysis, the hazard ratio for lung function worsening or death was 5.36 for SSc patients with serum CCL18 concentration above 187 $ng \cdot mL^{-1}$. They provided clear evidence of this in a French cohort of 83 SSc patients, yet a second affirmation cohort was missing. Recently,