Corticosteroid therapy in fibrotic interstitial lung disease: a modified Delphi survey

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To the Editor:

Fibrotic interstitial lung diseases (fILD) may have features that suggest inflammatory processes that contribute to disease pathogenesis [1]. A recent systematic review shows that the effectiveness and safety of steroid therapy in fILD are still inadequately understood [2], while steroids are potentially harmful in idiopathic pulmonary fibrosis (IPF) [3]. We performed a modified Delphi survey with the objectives of achieving global expert consensus on the indications and role of steroids in treating patients with fILD, and of highlighting future research priorities, while recognising that robust evidence is lacking. This study excluded IPF, systemic sclerosis-associated interstitial lung disease (ILD), sarcoidosis, and ILD treatment in the context of acute exacerbations.

We undertook a qualitative literature review to inform the initial round of the survey, focused on previous definitions of inflammation in fILD, and proposed indications for steroids. The study team then finalised the initial set of statements for inclusion. The surveys were undertaken between August and October 2023. Survey participants were identified from the REMAP-ILD consortium and the Swiss special interest group for ILD and were invited *via* email to complete the surveys. Statements focused on clinical, laboratory, radiological and histological findings that have been proposed to represent inflammation. Statements also focused on the clinical indications for corticosteroids, and dosing, delivery as well as duration of corticosteroids, to treat patients with fILD.

Using a modified Delphi method, participants were provided statements on defining, assessing and treating inflammation in fILD. Each statement was rated on a 5-point Likert scale (strongly disagree, disagree, unsure, agree, or strongly agree). Consensus for agreement required at least 75% agreement (agree or strongly agree), and for disagreement at least 75% disagreement (disagree or strongly disagree). If consensus was not achieved in the first round, statements were revised and reissued with prior round results. Additional statements were generated based on first-round feedback. Two multiple-choice questions on the definition of pulmonary inflammation and defining and predicting steroid responsiveness were added in the second round to contextualise the results. Data were collected and analysed using secure online survey platforms (SurveyMonkey, Momentive Inc.), ensuring participant confidentiality.

In the initial round, 164 participants were invited, of whom 56 (34%) completed the survey. Additional participants were invited to the second round to increase representation: 206 participants were invited, with 67 (33%) completing the survey. Most (95%) were pulmonologists, with two radiologists and one rheumatologist; a large majority of respondents were from Europe (73%), with a minority from North America (18%), South America (3%), Oceania (1%) and Asia (1%). 13 statements were included in the first round, and 10 in the second round. After two rounds of the survey, nine statements met consensus for agreement and one met consensus for disagreement.

As shown in figure 1, participants agreed that clinical signs suggestive of pulmonary inflammation inform their clinical decision-making for steroid therapy. Most participants agreed that high-resolution computed tomography (HRCT) should be performed prior to initiating steroid therapy, and that lung function measurements should be performed at baseline to inform treatment response, but lung biopsies are not required and should not be performed for this reason.

Shareable abstract (@ERSpublications)
The use of steroids in fibrotic interstitial lung diseases is founded on limited evidence. This modified Delphi survey sheds light on current clinical practices. Given the risks of steroids, clinical trials are needed to evaluate efficacy and harm. https://bit.ly/3VkgvbS

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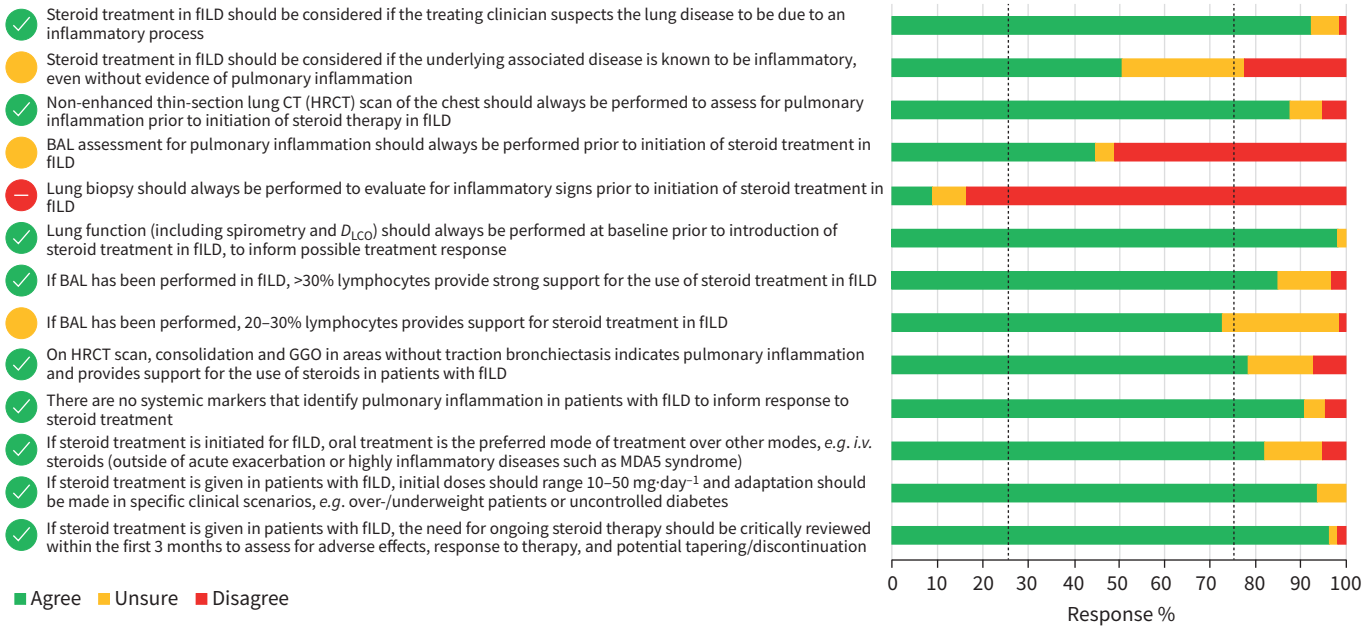

FIGURE 1 Overview of the survey statements that were evaluated by the participants. fILD: fibrotic interstitial lung diseases; CT: computed tomography; HRCT: high-resolution CT; BAL: bronchoalveolar lavage; D_{LCO}: diffusing capacity of the lung for carbon monoxide; GGO: ground glass opacity; MDA5: melanoma differentiation-associated protein 5.

Participants agreed that bronchoalveolar lavage (BAL) and HRCT findings might suggest pulmonary inflammation. BAL fluid lymphocytosis >30%, radiological findings of ground glass opacity (GGO), consolidation or GGO in areas without traction bronchiectasis could indicate steroid responsiveness.

Participants agreed that if steroid treatment is initiated in patients with fILD, the oral route is preferred, initial doses being proposed at 10–50 mg·day^{-1}, adapted to comorbidities and risk profile. Participants suggested steroid therapy should be reviewed within the first 3 months to assess for adverse effects, response to therapy, and potential tapering/discontinuation.

In this international modified Delphi survey, consensus was achieved on three domains: 1) clinical indicators that may represent pulmonary inflammation, 2) how clinicians anticipate response to steroid therapy, and 3) how steroids are prescribed and managed in patients with fILD. That consensus was achieved for several statements highlights the desire for clinicians to treat potentially treatable traits despite an absence of evidence. While consensus represents agreement in the three domains, it does not replace the need for robust objective data, and the findings herein highlight heterogeneity in clinical practice with the urgent need for prospective randomised clinical trials to address these questions.

Despite the unclear definition of pulmonary inflammation, our survey found that clinicians consider it a potentially treatable trait. According to our survey results, participants agreed that pulmonary inflammation is suggested by the presence of GGO on HRCT, although it can represent alveolar oedema, air trapping, haemorrhage and fine reticulation. Similarly, BAL lymphocytosis was considered a reason for treatment with steroids in the absence of high-quality evidence that BAL lymphocytosis reflects a specific steroid-responsive cellular subpopulation. Limitations of available data that currently guide decision-making include their retrospective non-randomised study designs and considerable residual confounding [4–7]. However, use of BAL lymphocytosis as a marker is supported by recent data showing that elevated BAL lymphocytes were associated with lower probability of disease progression in patients with limited fibrosis or lack of usual interstitial pneumonia pattern on HRCT [8]. While systemic blood biomarkers for inflammation may be identified in patients with fILD [9], none are sufficiently validated to justify clinical implementation.

HRCT was suggested as a mandatory test prior to steroid treatment, suggesting that radiological findings strongly inform management decisions despite the broad differential for the radiological features considered to associate with inflammation. Previous studies used radiological HRCT patterns to identify steroid-sensitive patients in connective tissue disease-associated ILD (CTD-ILD) [10]. Participants did not

agree on performing BAL, although, if performed, lymphocytosis was considered to support steroid responsiveness [6, 7]. There was, however, agreement that lung biopsies do not predict treatment response and, given their risk profile, should be considered judiciously.

Steroid treatment is often prescribed first-line in patients with progressive fILD other than IPF [11, 12], such as hypersensitivity pneumonitis [13] and CTD-ILD, based on limited evidence, but when the fibrotic component of the ILD predominates, no effect of corticosteroid treatment has been shown [6, 14]. There is no support for steroid use in IPF patients, and even potentially harmful effects [3]. If used in non-IPF fILD, the dose regimens vary widely, with limited evidence of low certainty [2]. There are no protocols or international recommendations regarding dosage and administration for fILD patients, although steroid treatment is suggested for various subtypes [15]. Despite the lack of high-quality evidence, our survey suggests that most experts agree on the use of moderate doses of steroids in fILD suspected to be inflammatory, with re-evaluation after 3 months. This highlights that steroids are being broadly used despite absence of evidence and, given the known harms of this therapy, a clinical trial is urgently required.

No consensus was achieved on whether steroids would be appropriate in the absence of pulmonary inflammation, even when the associated underlying disease is known to be inflammatory (*e.g.* CTD-ILD), whether BAL should always be performed prior to steroid initiation, and whether BAL lymphocytosis of 20–30% provides support for steroid treatment in fILD. The lack of consensus highlights important areas for future research to define pulmonary inflammation more accurately and to establish the role of BAL to inform management decisions.

This study has limitations. Most participants responding to the survey were from Europe, potentially limiting generalisability. The relatively low response rate may introduce selection bias. Nuances of steroid therapy, including individual case management, could not be ascertained and these results present a general overview of expert opinion. Most importantly, consensus through the Delphi process does not replace the need for objective evidence. Each topic presented herein should be further evaluated in the context of prospective randomised controlled trials, to robustly inform effectiveness and safety. Additional stakeholder views including those of rheumatologists, radiologists and patients should be explored in future work.

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