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Rheumatic conditions associated with interstitial lung diseases: real-world outcomes in a secondary care setting

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Abstract

Management of rheumatic conditions associated with interstitial lung disease (r-ILD) requires expertise, often occurring in tertiary referral centers. We set up a combined rheumatology and respiratory service in a district general hospital (DGH) to avoid long patient journeys and improve experience. We evaluated the outcomes of 104 patients managed in this pilot service model.

Referrals were triaged in monthly ILD multidisciplinary team meetings, and appropriate patients were booked into the clinic. All data were recorded electronically with full access to demographics, disease parameters, investigations, and drug management. Of the patients who attended follow-up, 51 (51%) had stable or improved symptoms, 58 (67%) had stable or improved computed tomography imaging, 50 (78%) had stable or improved forced vital capacity, and 40 (77%) had stable or improved diffusing capacity of the lungs for carbon monoxide. There were similar improvements in 6-minute walk tests. A total of 27 patients died, with 33% of these deemed as a direct result of their ILD.

Our report confirms that r-ILD can be successfully managed in a DGH setting, with a large cohort obtaining good comparable clinical outcomes. We show that r-ILD services can be established locally to help overstretched tertiary care while developing local expertise in the management of r-ILD.

Key words: interstitial lung disease, rheumatic diseases, secondary care.

Introduction

Interstitial lung diseases (ILD) comprise a heterogeneous group of distinctive lung disorders characterised by inflammation and ultimately fibrosis of the lungs. Their occurrence in the context of systemic autoimmune rheumatic diseases such as connective tissues diseases (CTD) or rheumatoid arthritis (RA), perhaps as an extra-articular manifestation, carry significant morbidity and premature mortality [1]. Rheumatic conditions associated interstitial lung disease (r-ILD) can have a variable natural history depending on several factors such as disease association and phenotype [2].

Traditionally, given the complexity of these conditions, investigations required as well as specialist management, patients are often referred to tertiary care centres and historically, such complex ILD has been managed solely in such centres. Management of r-ILD requires expertise as the needs of such patients are complex and treatment options limited [3]. Early diagnosis of r-ILD is paramount in order to achieve good clinical outcomes [4]. However, it can be difficult as patients, who may be frail with multiple co-morbidities, often have to travel long distances for investigations and appointments with inevitable delays.

Our large teaching secondary care hospital has a diverse catchment population of 350,000 patients with 40% consisting of other ethnicities. We set up a combined rheumatology and respiratory service in our district general hospital (DGH) to help avoid long journeys, improve overall patient experience with care closer to home, allow local expertise development and help reduce the burden on specialist centres. There is precedent of such services in the hub and spoke model of care provided for pulmonary hypertension.

The aim of our study was to review the natural progression of r-ILD whilst treated in a multi-disciplinary team (MDT) district general hospital (DGH) setting and collect outcomes to ascertain whether such services can achieve results in keeping with published outcomes and potentially provide a foundation for the establishment of secondary care based r-ILD management.

Materials and Methods

A retrospective study was performed of all consecutive 104 patients reviewed in our combined rheumatology-respiratory r-ILD clinic at our large DGH between 23rd February 2016 and 25th November 2019. Sample size was not pre-defined as the intention was to capture real world outcomes for all the patients reviewed during the study period. Referrals were being accepted from any hospital specialist potentially involved in the management of r-ILD and these referrals were triaged by the lead respiratory physician and discussed in monthly ILD MDT meetings.

These meetings comprise a rheumatologist, a respiratory physician, a radiologist and an ILD specialist nurse. Patients were then triaged into the combined clinic, run by the respective

rheumatology and respiratory specialists with an interest in ILD, attracting a multi-specialty tariff.

Demographics were collected prospectively on a database as patients attended the combined clinic. Clinical records were accessed retrospectively through electronic health records, for full data collection and analysis. General practitioners (GPs) were also contacted regarding patients that had died in the community since being reviewed in our clinic, to ensure mortality data was as complete and accurate as possible.

Previous clinic letters, results and investigations as well as imaging were all accessible on a variety of electronic platforms throughout the study period. Data included, but was not limited to, age and ethnicity of the patients, clinic attendance dates, main respiratory diagnoses, main rheumatological diagnoses, pre-and post-treatment symptoms, % predicted FVC, % predicted DLCO, % predicted distance from 6MWT, HRCT imaging results and mortality.

Microsoft Excel was used for data collation and simple statistical analysis.

We had approval for the above research from our local research ethics committee on 6th April 2021.

Results

Patients' demographics

104 patients were included. Results were obtained and analysed up to and including 31st December 2020 (data cut off point). Mean follow up was 20.2 months (0-51 months).

The mean age of the patients was 67 years (19-92 years) (Table 1). 36% (n=37) of the patients were male and 64% (n=67) were female. The average number of co-morbidities for the patients was 4 (0-11).

The most predominant ethnicity was white (69%, n=72), followed by Asian (21%, n=22), which included Indian, Pakistani and Chinese whilst the final ethnic category was black (African/Caribbean) (10%, n=10).

Disease demographics

The most predominant high resolution compute tomography (HRCT) pattern was non-specific interstitial pneumonia (NSIP) (n=38, 37%) followed by usual interstitial pneumonia (UIP) (n=27, 26%) (Table 2). Other respiratory diagnoses included sarcoidosis (n=11, 11%) and mixed ILD (n=3, 2.9%) with others including cryptogenic organising pneumonia (COP) (n=4), lymphoid interstitial pneumonia (LIP) (n=2), pulmonary fibrosis (n=2), chronic hypersensitivity pneumonitis (CHP) (n=1), connective tissue disease-related ILD (n=1), vasculitis (n=1) and interstitial pneumonitis (n=1).

35 patients (34%) had arthritis encompassing RA (26 patients), inflammatory arthritis and psoriatic arthritis whilst 36 patients (35%) had CTD including Sjogren's, scleroderma and SLE. 13 of the patients with NSIP (34%) had associated arthritis, with 8 of these patients (30%) having RA specifically. 16 NSIP patients (42%) had associated CTD (*Supplementary Figure 1*). Of the patients with a predominantly UIP pattern on HRCT imaging, 13 (48%) also had associated arthritis (12 patients (44%) had specifically RA) whilst 6 (22%) had related CTD (*Supplementary Figure 2*).

Investigations and drugs

The mean FVC of all patients was 2.66L (0.89-5.83) or 89.5% of predicted (39.7-159.9% predicted), whilst the mean DLCOc was 54.8% of predicted (13.4-99.4% predicted). The mean distance achieved in the 6MWT by patients was 366.92m (30-655m) with the mean % of predicted distance covered 78.9% (7-187%).

80% of patients (n=83) were being treated with at least one medication including either a steroid, disease-modifying antirheumatic drug (DMARD) or biologic, or a combination. Antifibrotic treatment was not routinely prescribed. The most common number of drugs that a patient was taking was 2 drugs (0-5) (Table 3).

73 patients were taking at least one DMARD, 43 were taking steroids and 14 were taking a biologic (Table 4). Side effects and intolerance were monitored regularly and recorded during follow up clinic visits.

Outcomes

Patient outcomes were grouped into one of two categories; either the patient improved/had stable disease or the patient had worsened. For symptoms, this was reported by the patient and documented in a recent clinic letter. For FVC, DLCO and 6MWTs, any value that was more than 10% below their pre-treatment value was deemed as worsened disease and all other values were deemed as stable or improved. For CT imaging, a consultant radiologist report was used to establish whether there was stable/improved or worsening disease since previous imaging. Mortality was split into those who died directly from their ILD and those who had died from other or unknown causes.

Overall outcomes

51% (n=51) of patients who were followed up had stable or better symptoms overall. Of patients with pre- and post-treatment investigations, 78% (n=50) had stable or improved FVC (% predicted), 77% (n=40) had stable or improved DLCO (% predicted) and 60% (n=12) had a stable or improved 6MWT % predicted distance. 67% (n=58) of patients with repeat CT

imaging had stable or improved ILD features after treatment overall. As per 31st December 2020, 26% of patients (n=27) had died, with 33% (n=9) of these patients dying directly from their ILD (*Supplementary Figure 3*).

NSIP

35% (n=13) of patients who were followed up had stable or better symptoms overall. Of patients with pre- and post-treatment investigations, 81% (n=22) had stable or improved FVC (% predicted), 74% (n=17) had stable or improved DLCO (% predicted) and 56% (n=5) had a stable or improved 6MWT % predicted distance. 72% (n=26) of patients with repeat CT imaging had stable or improved ILD features after treatment overall. As per 31st December 2020, 34% of patients (n=13) had died, with 31% (n=4) of these patients dying directly from their ILD (*Supplementary Figure 4*).

UIP

54% (n=14) of patients who were followed up had stable or better symptoms overall. Of patients with pre- and post-treatment investigations, 81% (n=13) had stable or improved FVC (% predicted), 73% (n=8) had stable or improved DLCO (% predicted) and 40% (n=2) had a stable or improved 6MWT % predicted distance. 57% (n=13) of patients with repeat CT imaging had stable or improved ILD features after treatment overall. As per 31st December 2020, 44% of patients (n=12) had died, with 42% (n=5) of these patients dying directly from their ILD (*Supplementary Figure 5*).

RA

44% (n=11) of patients who were followed up had stable or better symptoms overall. Of patients with pre- and post-treatment investigations, 81% (n=13) had stable or improved FVC (% predicted), 92% (n=11) had stable or improved DLCO (% predicted) and 50% (n=2) had a stable or improved 6MWT % predicted distance. 86% (n=19) of patients with repeat CT imaging had stable or improved ILD features after treatment overall. As per 31st December 2020, 42% of patients (n=11) had died, with 45% (n=5) of these patients dying directly from their ILD (*Supplementary Figure 6*).

CTD

56% (n=19) of patients who were followed up had stable or better symptoms overall. Of patients with pre- and post-treatment investigations, 79% (n=19) had stable or improved FVC (% predicted), 70% (n=14) had stable or improved DLCO (% predicted) and 67% (n=6) had a stable or improved 6MWT % predicted distance. 67% (n=20) of patients with repeat CT

imaging had stable or improved ILD features after treatment overall. As per 31st December 2020, 11% of patients (n=4) had died, with 25% (n=1) of these patients dying directly from their ILD (*Supplementary Figure 7*).

NSIP with RA

25% (n=2) of patients who were followed up had stable or better symptoms overall. Of patients with pre- and post-treatment investigations, 83% (n=5) had stable or improved FVC (% predicted), 80% (n=4) had stable or improved DLCO (% predicted) but no patients had a stable or improved 6MWT % predicted distance. 100% (n=8) of patients with repeat CT imaging had stable or improved ILD features after treatment overall. As per 31st December 2020, 50% of patients (n=4) had died, with 25% (n=1) of these patients dying directly from their ILD.

NSIP with CTD

47% (n=7) of patients who were followed up had stable or better symptoms overall. Of patients with pre- and post-treatment investigations, 83% (n=10) had stable or improved FVC (% predicted), 73% (n=8) had stable or improved DLCO (% predicted) and 60% (n=3) had a stable or improved 6MWT % predicted distance. 73% (n=11) of patients with repeat CT imaging had stable or improved ILD features after treatment overall. As per 31st December 2020, 19% of patients (n=3) had died, with 33% (n=1) of these patients dying directly from their ILD.

UIP with RA

55% (n=6) of patients who were followed up had stable or better symptoms overall. Of patients with pre- and post-treatment investigations, 75% (n=6) had stable or improved FVC (% predicted), 100% (n=5) had stable or improved DLCO (% predicted) and 67% (n=2) had a stable or improved 6MWT % predicted distance. 70% (n=7) of patients with repeat CT imaging had stable or improved ILD features after treatment overall. As per 31st December 2020, 58% of patients (n=7) had died, with 57% (n=4) of these patients dying directly from their ILD.

UIP with CTD

50% (n=3) of patients who were followed up had stable or better symptoms overall. Of patients with pre- and post-treatment investigations, 80% (n=4) had stable or improved FVC (% predicted), no patients had stable or improved DLCO (% predicted) or a stable or improved 6MWT % predicted distance. 50% (n=3) of patients with repeat CT imaging had stable or improved ILD features after treatment overall. As per 31st December 2020, 17% of patients (n=1) had died, with none of these patients dying directly from their ILD.

Discussion

Our study demonstrates that r-ILD can be successfully managed in a secondary care setting with positive outcomes. More than half of all patients had improved or stable symptoms, pulmonary function tests (FVC and DLCO), 6MWT results and CT imaging at their latest follow up, which correlates with outcomes from tertiary centre management of similar patient groups published prior [5].

Other studies to date have also shown that r-ILD patients are complex to manage and require specialist input for successful outcomes [6]. Our study situates itself well within the current body of research, replicating well established demographic findings in that the majority of our patients were female as well as the fact that NSIP was the commonest pattern of ILD in such patients, closely followed by UIP. In addition, it has always been clear that r-ILD disease involving RA carries a worse prognosis [7] and patients in our cohort with RA plus either NSIP or UIP had the highest mortality, with half (50%) of patients with NSIP and RA plus more than half (58%) of patients with UIP and RA deceased by the end of the study.

A quarter of all our patients had died (26%) by the end of our study although not all were directly related to their r-ILD. The successful outcomes of our combined clinic may be in part due to our utilisation of drugs and it is therefore unsurprising that a large proportion of patients were on at least one DMARD at their latest follow up, the most common of which was hydroxychloroquine. This confirms the need to actively treat patients with immunomodulators which can help achieve good outcomes and halt or at least slow down the natural course of inexorable progression [8,9].

Bongartz *et al*. (2010) demonstrated similar findings in a large longitudinal study in the USA [10]. Mortality was three times higher in an RA patient with associated ILD than without, with a median survival of less than 3 years. We mirror similarly poor prognosis and although the highest mortality overall in our study was in patients with UIP, patients with RA followed next. However, congruent to other studies it is the combination that results in poor prognosis. It is clear there is work to be done in this group of patients and their complexity should not be underestimated. Our results were not similar for CTD, suggesting a better prognosis or response to treatment, although the numbers were smaller in our cohort.

Currently, there is limited data from district general hospital r-ILD clinics, given their relative inexistence and so we believe we are a unique service in the UK. We aim to prove that a successful model can be implemented in such hospitals, developing local expertise whilst also saving time and money for patients who may have to travel long distances for specialist input. We envisage more district general hospitals constructing clinics not dissimilar to our own, possibly with support from tertiary centres, in a model similar to that used in pulmonary

hypertension clinics and other MDT services that are now trialling specialised clinics at differing locations, bringing expertise more locally for patients, but also medical colleagues, to access. For obvious reasons it is also in the interest of tertiary referral centres to support such clinics, given the waiting times and burdens placed on their own services, with district general hospital models aiming to remove some of the pressure.

Finally, there are a number of strengths and limitations to this study. We have analysed data from 104 patients, and this large cohort increases the validity of our results and allows strong conclusions to be drawn from the data. In addition, the patients were followed up over a long period of time, given the retrospective nature of the study. This allowed a large number of medication trials to be analysed as well as accurate mortality and morbidity data to be obtained. In addition to mortality data, further detailed information was obtained regarding the causes of mortality for most of the patients that had passed away, avoiding an under or over-estimation of mortality secondary to r-ILD in this patient group.

In contrast to this, there are limitations to our study. This was a single-centre retrospective study and so further studies would be needed from differing centres to further validate our findings. Other drawbacks comprised missing data such as patients not attending repeat lung function testing or 6MWTs and this therefore reduced the number of patients for which a pre- and post-treatment analysis could be carried out. There were also 6 patients for which we were unable to ascertain a cause of death, which may mean we are in fact under or over-estimating our mortality figures.

Conclusions

This real-world study confirms the utility of a combined specialist service in a district general hospital. Nearly half of this complex and resource intensive patient cohort had good clinical outcomes and derived benefit from the expertise in one room. Feedback from both patients and referrers was unanimously positive. No patient required tertiary centre referral and all could be managed adequately in the clinical setting. Our report confirms that r-ILD can be managed in a DGH setting with a stream-lined service offering clear benefits to patients. We would argue that an r-ILD service, congruent to satellite pulmonary hypertension clinics in secondary care with hub-and-spoke model liaison with tertiary centres, can be established on similar principles and could help over-stretched tertiary care with repatriation of services whilst helping develop local expertise in the management of chronic ILD.

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Online supplementary material:
Supplementary Figure 1. Non-specific interstitial pneumonia patients.
Supplementary Figure 2. Usual interstitial pneumonia patients.
Supplementary Figure 3. Outcomes overall.
Supplementary Figure 4. Outcomes for patients with non-specific interstitial pneumonia.
Supplementary Figure 5. Outcomes for patients with usual interstitial pneumonia.
Supplementary Figure 6. Outcomes for patients with rheumatoid arthritis.
Supplementary Figure 7. Outcomes for patients with connective tissue diseases.

Table 1. Age breakdown.

Age range	Number of patients
20-39	4
40-59	24
60-79	57
80+	19

Table 2. Respiratory and rheumatological demographics.

Respiratory		Rheumatological	
NSIP	38	Arthritis	35
UIP	27	Scleroderma	12
Sarcoidosis	11	Sjogren's	8
Mixed ILD	3	SLE	6
Other	12	Other CTD	10
No ILD	13	Other rheumatological issues	4
		No rheumatological issues	29

CTD, connective tissue disease; ILD, interstitial lung disease; NSIP, non-specific interstitial pneumonia; SLE, systemic lupus erythematosus; UIP, usual interstitial pneumonia.

Table 3. Number of drugs.

Number of drugs	Number of patients
0	21
1	25
2	33
3	21
4	3
5	1

Table 4. Drug breakdown.

Steroids		DMARDs		Biologics	
Prednisolone	42	Hydroxychloroquine	57	Rituximab	8
Methyl-prednisolone	1	Methotrexate	21	Abatacept	2
		Mycophenolate	17	Etanercept	1
		Sulfasalazine	9	Tocilizumab	1
		Azathioprine	5	Baricitinib	1
		Leflunomide	4	Seculinumab	1
		Cyclophosphamide	1		

DMARDs, disease-modifying anti-rheumatic drugs.