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ORIGINAL ARTICLE

Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management

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ABSTRACT

Objective: Some patients with interstitial lung diseases (ILDs) other than idiopathic pulmonary fibrosis (IPF) develop a progressive fibrosing phenotype. We investigated the diagnosis and management of non-IPF ILDs using data from a survey of physicians and from US insurance claims.

Methods: Pulmonologists, rheumatologists and internists in France, Germany, Italy, Japan, Spain, UK and US who had managed ≥10 patients with non-IPF ILDs in the past year, including those with progressive fibrosing ILDs, completed an online survey. Data on US insurance and prescription claims were obtained from a repository that aggregates data on claims routed from providers or pharmacies to payers.

Results: In May–June 2017, 243 pulmonologists, 203 rheumatologists and 40 internists completed an online survey. Respondents estimated that 18–32% of patients diagnosed with non-IPF ILDs develop progressive fibrosis and that time from symptom onset to death in these patients was 61–80 months. Drug treatment was given to 50–75% of patients with non-IPF progressive fibrosing ILDs. Reasons for patients not being treated included that physicians considered patients to have mild or slowly progressing disease, or did not believe that available treatments are effective or well tolerated. Corticosteroids were the preferred first-line treatment for all types of non-IPF ILD. There was considerable heterogeneity in preferences for second- and third-line treatments. US insurance claims data from 3823 patients indicated that, in 2016, 50–75% of patients with ILDs received drug treatment (mostly corticosteroids) for their ILD.

Conclusions: Physicians estimate that 18–32% of patients diagnosed with non-IPF ILDs develop a progressive fibrosing phenotype and that these patients experience significant delays in the diagnosis of ILD and the detection of progressive fibrosis. Between 25% and 50% of patients with progressive fibrosing ILDs do not receive drug therapy. There is an unmet need for effective and well tolerated treatments for progressive fibrosing ILDs.

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Disease management; drug therapy; immunosuppression; pulmonologist; rheumatologist; survey

Introduction

Interstitial lung diseases (ILDs) encompass a large group of parenchymal lung disorders, including diseases of unknown cause, as well as those related to autoimmune diseases and environmental exposures. Idiopathic pulmonary fibrosis (IPF) is an ILD characterized by progressive lung fibrosis, decline in lung function, worsening dyspnea and quality of life[1], and early mortality[2]. Patients with types of ILD other than IPF are also at risk of developing a progressive fibrosing phenotype[3], including those with idiopathic non-specific interstitial pneumonia (iNSIP)[4], unclassifiable idiopathic interstitial pneumonias (IIPs)[5], connective tissue disease-related ILDs (CTD-ILDs) such as those related to rheumatoid arthritis (RA-ILD)[6] and systemic sclerosis (SSc-ILD)[7], chronic sarcoidosis[8], chronic hypersensitivity pneumonitis (HP)[9] and exposure-related diseases such as asbestosis and silicosis[10]. An ATS/ERS statement published in 2013 on the classification of the IIPs proposed a classification, monitoring and treatment strategy based on observed disease behavior[11]. More recently, experts in the field have proposed that IPF be "lumped" with other

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forms of progressive fibrosing ILD that share common pathological pathways and disease behavior for the purposes of addressing the unmet need for evidence-based treatments for these rare diseases[3].

At present, no drugs are licensed for the treatment of ILDs other than IPF, but several clinical trials are ongoing[12,13] or have recently been completed[14]. There are no international treatment guidelines for forms of ILD other than IPF[2,15] and SSc-ILD[16,17]. Treatment decisions are hampered by a lack of high-quality evidence on the efficacy and safety of specific therapies.

Few data are available on current practice in the diagnosis and management of progressive fibrosing ILDs other than IPF. Using data from an online survey of physicians and US insurance claims, we investigated the journey that patients with non-IPF progressive fibrosing ILDs take through diagnosis and management.

Methods

Pulmonologists, rheumatologists and internists in the US, France, Germany, Italy, Spain, UK and Japan were invited via email to complete an online survey. The physicians invited to participate were part of an existing panel that received surveys on various topics. To be eligible to participate in this particular survey, physicians had to spend ≥75% of their professional time managing patients and to have managed ≥10 patients with non-IPF ILDs in the past year, including those with progressive fibrosing ILDs. Progressive fibrosing ILDs were defined in the survey as those with fibrosis detected by high resolution computed tomography (HRCT) (reticular abnormality with traction bronchiectasis with or without honeycombing) that were progressing in terms of worsening of lung function (FVC and/or DL_{CO}) and/or respiratory symptoms and/or chest images. Rheumatologists were asked to respond to questions related to autoimmune ILDs (RA-ILD, SSc-ILD, other CTD-ILDs) only. The survey was completed in May–June 2017.

US insurance claims were analyzed from the Decision Resources Group (DRG) Real World Evidence Repository, which aggregates data from clearing houses that route claims from providers or pharmacies to payers. This repository includes adjudicated medical claims data from inpatient and ambulatory settings, pharmacy claims data, electronic health records and linkages of patients across these data sets. It represents over two-thirds of US claims and includes data from 98% of US health plans. Patients were categorized as having ILD if they had ≥2 claims with an ILD diagnosis and ≥1 visit to a pulmonologist between 2014 and 2016. Patients were classified into ILD subtypes based on International Statistical Classification of Diseases and Related Health Problems (ICD) codes (see Supplementary Tables S1 and S2). The type of physician who filed the first ILD claim was analyzed in patients who had ILD (as categorized above), whose first ILD claim was made in 2015 or 2016, and who had a claim for any indication ≤180 days prior to the first ILD claim. The latter restriction was included to improve stability of the dataset and increase the likelihood that the claim being analyzed was indeed the first ILD claim. To assess the number of visits to a pulmonologist in a given year, the number of visits in 2014 was analyzed in patients who had ILD (as categorized above) and had ≥1 ILD claim in each of 2014, 2015 and 2016. To assess the number of visits to a rheumatologist in a given year, the number of visits in 2014 was analyzed in patients who had ILD (as categorized above), had ≥1 ILD claim in each of 2014, 2015 and 2016, and who saw a rheumatologist at least once between 2014 and 2016. To assess treatment patterns, the drugs used to treat ILDs in 2016 were analyzed in patients who had ILD (as categorized above), had ≥1 ILD insurance claim in 2016 and had ≥1 pharmacy claim in January–March and October–December 2016 (to ensure they were in the database consistently over the year). The drugs included in the analysis were azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, prednisolone, prednisone, rituximab and tacrolimus. Rituximab was not included in the results as so few patients received it (0.08%). Data are presented descriptively.

Results

The online survey was completed by 486 physicians from the US ($n = 203$), Japan ($n = 80$), Germany ($n = 41$), France ($n = 41$), the UK ($n = 41$), Italy ($n = 40$) and Spain ($n = 40$), of whom 243 were pulmonologists, 203 were rheumatologists and 40 were internists.

Based on US claims data, a total of 113,752 patients were categorized as having ILD. The number of visits to a pulmonologist was analyzed based on claims data from 30,090 patients and the number of visits to a rheumatologist was analyzed based on claims data from 4904 patients. Treatment patterns were analyzed based on US prescription claims from 3823 patients.

Diagnosis of interstitial lung disease

The online survey indicated that an ILD diagnosis is most likely to be made by a pulmonologist, but autoimmune ILDs are also commonly diagnosed by rheumatologists. These findings were similar across countries (Figure 1). Overall, the physicians surveyed estimated that non-IPF ILDs are typically diagnosed 9–12 months after symptoms of ILD develop (Figure 2).

US claims data showed that pulmonologists filed the first claim for ILD in 64% of patients with iNSIP, 55% of patients with HP and 52% of patients with sarcoidosis-related ILD (see Supplementary Figure S1). In patients with autoimmune ILDs, pulmonologists filed the first claim for ILD in 35–39% of patients, radiologists in 12–15%, rheumatologists in 11–15% and internists in 10–14% (see Supplementary Figure S1).

Monitoring and management of interstitial lung disease

Most of the physicians surveyed reported having follow-up visits with patients with ILD every 2–3 months, with some differences observed between countries; 39% of physicians

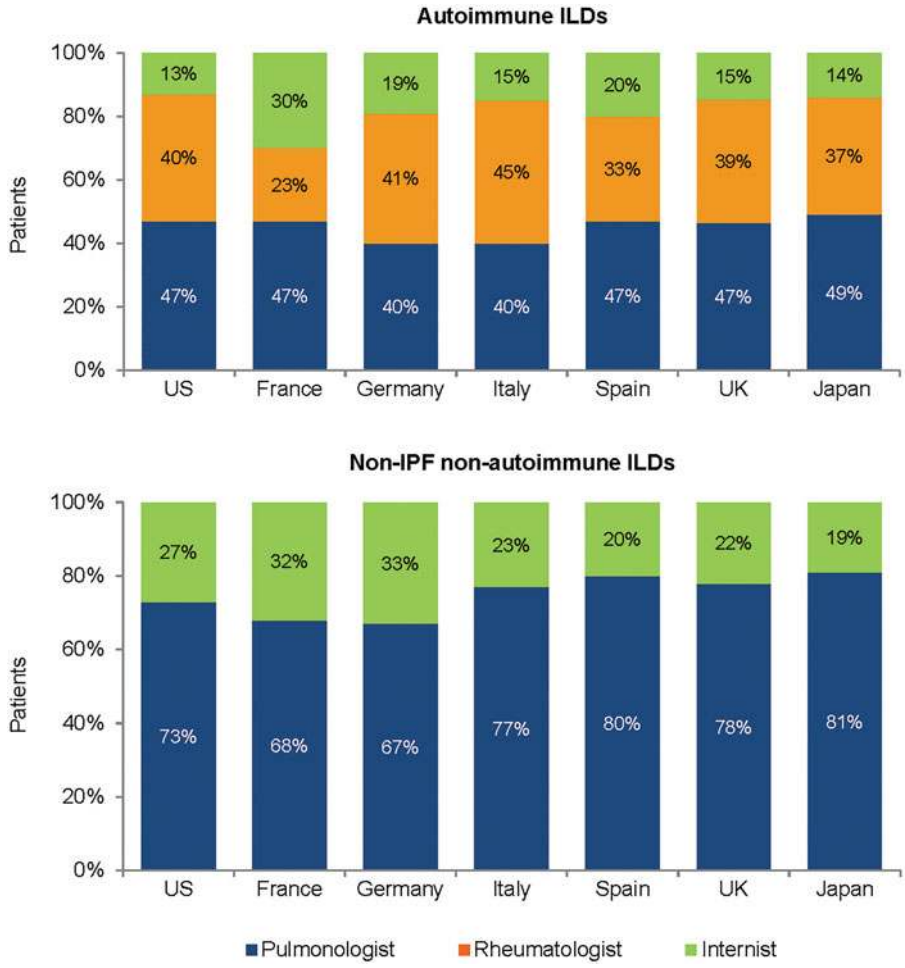
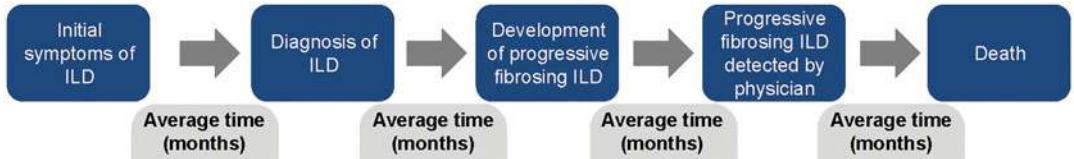


Figure 1. Percentage of patients with ILDs diagnosed by different clinical specialties. Data from online survey of physicians (pulmonologists, $n = 243$; rheumatologists, $n = 203$; internists, $n = 40$). Survey question: "What percentage of patients with the following types of ILDs are diagnosed by the following specialties?" Examples of autoimmune ILDs provided to physicians participating in the survey were RA-ILD, SSc-ILD and other CTD-ILDs. Examples of non-IPF non-autoimmune ILDs provided were iNSIP, HP and sarcoidosis-ILD. Rheumatologists were only asked this question in relation to autoimmune ILDs. Abbreviations. CTD, Connective tissue disease; HP, Hypersensitivity pneumonitis; ILD, Interstitial lung disease; iNSIP, Idiopathic non-specific interstitial pneumonia; IPF, Idiopathic pulmonary fibrosis; RA, Rheumatoid arthritis; SSc, Systemic sclerosis.



	Average time (months)	Average time (months)	Average time (months)	Average time (months)
RA-ILD	11.5	15.2	11.0	41.6
SSc-ILD	9.3	12.3	9.6	33.0
Other CTD-ILDs	11.0	13.9	11.2	38.3
iNSIP	9.3	12.0	8.9	31.1
Unclassifiable IIP	10.3	11.4	9.2	29.7
HP	8.6	13.6	10.4	40.0
Sarcoidosis-ILD	8.8	14.6	11.7	45.2
Other ILDs	9.9	12.7	11.1	33.7

Figure 2. Patient journey in non-IPF progressive fibrosing ILDs. Data from online survey of physicians (pulmonologists, $n = 243$; rheumatologists, $n = 203$; internists, $n = 40$). Survey question: "Please estimate the average duration of the following for the different ILDs: time from symptom onset to diagnosis of ILD; time from diagnosis of ILD to development of ILD that is fibrotic and progressing; time from development of ILD that is fibrotic and progressing to point where fibrotic and progressing ILD is detected by physician; time from point where fibrotic and progressing ILD is detected by physician to patient death". Rheumatologists were only asked this question in relation to RA-ILD, SSc-ILD and other CTD-ILDs. Abbreviations. CTD, Connective tissue disease; HP, Hypersensitivity pneumonitis; IIP, Idiopathic interstitial pneumonias; ILD, Interstitial lung disease; iNSIP, Idiopathic non-specific interstitial pneumonia; IPF, Idiopathic pulmonary fibrosis; RA, Rheumatoid arthritis; SSc, Systemic sclerosis.

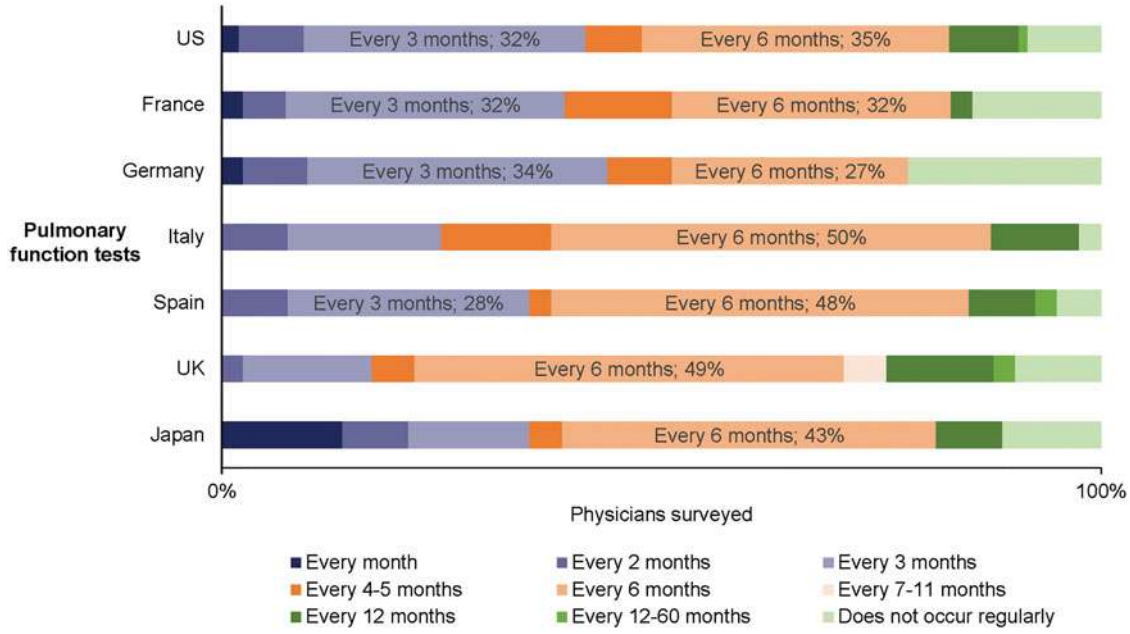


Figure 3. Frequency of pulmonary function tests in patients with ILDs. Data from online survey of physicians (pulmonologists, $n = 243$; rheumatologists, $n = 203$; internists, $n = 40$). Survey question: "In patients with ILD where you manage/help manage the ILD, on average how frequently do you check the status of the patients' ILD based on pulmonary function tests (e.g. FVC, DL_{CO}, 6-minute walk)?" Abbreviations. DL_{CO}, Diffusing capacity of the lungs for carbon monoxide; FVC, Forced vital capacity; ILD, Interstitial lung disease.

Table 1. Percentage of US patients who received treatment for non-IPF ILDs in 2016.

	Any treatment[a]	Corticosteroids	Mycophenolate mofetil	Azathioprine	Cyclosporine	Tacrolimus	Cyclophosphamide
RA-ILD	72	69	7	9	5	3	0
SSc-ILD	74	59	29	15	5	4	1
Other CTD-ILDs	67	61	21	15	7	4	0
iNSIP	71	62	15	6	3	3	0
HP	75	74	6	8	2	1	0
Sarcoidosis-ILD	63	62	3	3	2	2	0
Other specified non-IPF ILDs[b]	50	49	3	2	2	1	0
Non-specified ILDs[c]	52	51	3	2	2	2	0

Data from US prescription claims from 3823 patients who had ILD (defined as ≥2 claims with an ILD diagnosis and ≥1 visit to a pulmonologist between 2014 and 2016), had ≥1 ILD insurance claim in 2016, and had ≥1 pharmacy claim in January–March and October–December 2016.
Abbreviations. CTD, Connective tissue disease; HP, Hypersensitivity pneumonitis; ILD, Interstitial lung disease; iNSIP, Idiopathic non-specific interstitial pneumonia; IPF, Idiopathic pulmonary fibrosis; RA, Rheumatoid arthritis; SSc, Systemic sclerosis.
[a]Corticosteroids, mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus or cyclophosphamide.
[b]Acute interstitial pneumonitis, adult pulmonary Langerhans cell histiocytosis, cryptogenic organizing pneumonia, desquamative interstitial pneumonia, idiopathic interstitial pneumonia not otherwise specified, lymphangioleiomyomatosis, lymphoid interstitial pneumonia, respiratory bronchiolitis ILD.
[c]Patients with a generic claim for ILD from which the type of ILD could not be identified.

in the UK reported having visits every 6 months, while 51% of physicians in Japan reported having visits every month (Supplementary Figure S2). Most of the physicians reported performing pulmonary function tests every 3–6 months, although 22% of physicians in Germany reported that pulmonary function tests are not performed regularly (Figure 3). Most of the physicians surveyed reported performing HRCT scans every 6–12 months (Supplementary Figure S2).

Based on US insurance claims data from 2014, approximately 75% of patients with ILDs visited a pulmonologist at least once (mean: 2.3 visits/year) (see Supplementary Figure S3). Approximately 70% of patients with autoimmune ILDs visited a rheumatologist at least once (mean: 2.3 visits/year) (see Supplementary Figure S3). Based on the claims data, 50–75% of patients with ILDs received drug treatment for their ILD in 2016. Most received corticosteroids. The next most commonly used treatment was mycophenolate mofetil, which was given to 29% of patients with SSc-ILD, 7% of patients with RA-ILD, 21% of patients with other CTD-ILDs and 15% of patients with iNSIP (Table 1).

Development of a progressive fibrosing phenotype

Physicians who participated in the online survey estimated that 18–32% of patients diagnosed with non-IPF ILDs will develop a progressive fibrosing phenotype, defined as evidence of fibrosis (reticular abnormality with traction bronchiectasis with or without honeycombing) detected by HRCT, accompanied by worsening of lung function (FVC and/or DL_{CO}) and/or respiratory symptoms and/or chest images (Figure 4). The non-IPF ILDs that physicians believed were most likely to have a progressive fibrosing phenotype were iNSIP, SSc-ILD, unclassifiable IIP and RA-ILD, with 32%, 31%, 29% and 26% of patients with these types of ILD,

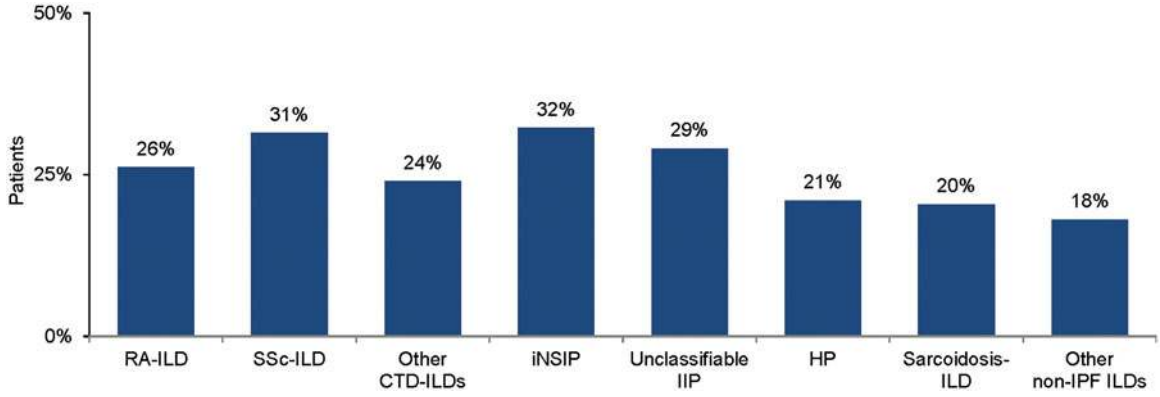


Figure 4. Percentage of patients with non-IPF ILDs who develop a progressive fibrosing phenotype. Data from online survey of physicians (pulmonologists, $n = 243$; rheumatologists, $n = 203$; internists, $n = 40$). Survey question: "For each of the ILD types listed below, among the patients you have seen in the past year, please estimate what percentage of patients had an ILD that (1) had fibrosis detected by HRCT (i.e. reticular abnormality with traction bronchiectasis with or without honeycombing) AND (2) was progressing in terms of worsening of lung function (FVC and/or DL_{CO}) and/or respiratory symptoms and/or chest images". Rheumatologists were only asked this question in relation to RA-ILD, SSc-ILD and other CTD-ILDs. Abbreviations. CTD, Connective tissue disease; DL_{CO}, Diffusing capacity of the lungs for carbon monoxide; FVC, Forced vital capacity; HP, Hypersensitivity pneumonitis; HRCT, High-resolution computed tomography; IIP, Idiopathic interstitial pneumonias; ILD, Interstitial lung disease; iNSIP, Idiopathic non-specific interstitial pneumonia; IPF, Idiopathic pulmonary fibrosis; RA, Rheumatoid arthritis; SSc, Systemic sclerosis.

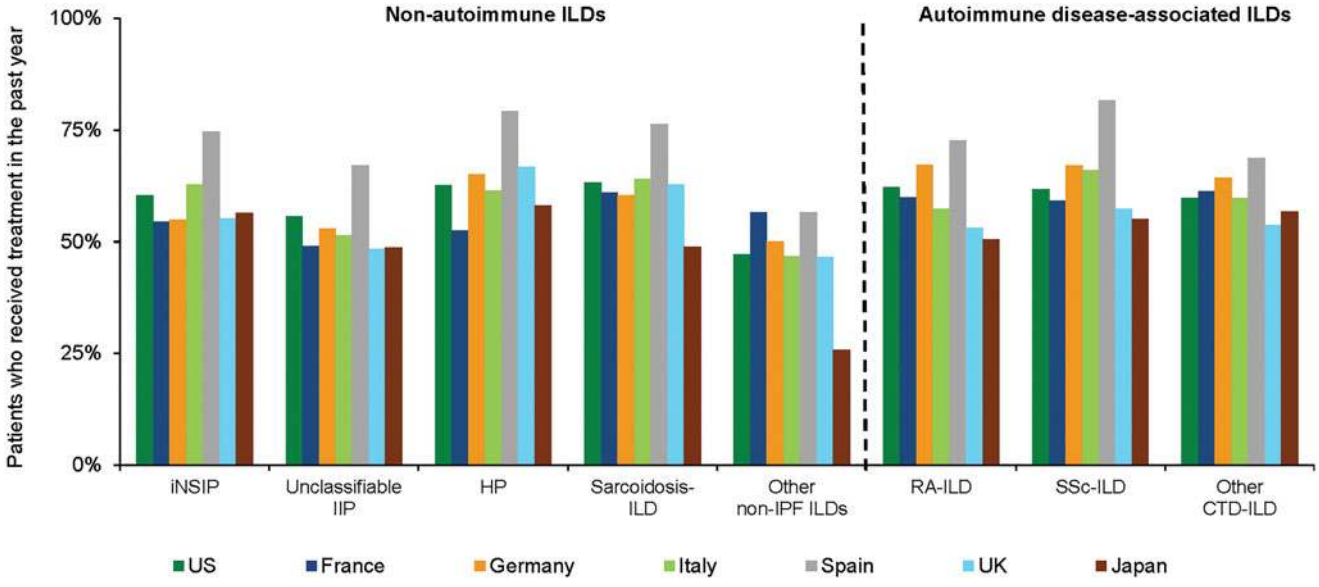


Figure 5. Percentage of patients who received treatment for non-IPF progressive fibrosing ILDs in the past year. Data from online survey of physicians (pulmonologists, $n = 243$; rheumatologists, $n = 203$; internists, $n = 40$). Survey question: "For all non-IPF ILD patients you manage that have fibrosis and progressive disease, what percentage received drug treatment for their ILD in the past year? Examples of treatments include corticosteroids, azathioprine, or other immunosuppressants aimed at treating the ILD". Rheumatologists were only asked this question in relation to RA-ILD, SSc-ILD and other CTD-ILDs. Abbreviations. CTD, Connective tissue disease; HP, Hypersensitivity pneumonitis; IIP, Idiopathic interstitial pneumonias; ILD, Interstitial lung disease; iNSIP, Idiopathic non-specific interstitial pneumonia; IPF, Idiopathic pulmonary fibrosis; RA, Rheumatoid arthritis; SSc, Systemic sclerosis.

respectively, estimated to develop a progressive fibrosing phenotype (Figure 4). Physicians estimated that the time from diagnosis of ILD to development of progressive fibrosing ILD is 11–15 months, and that it takes 9–12 months for physicians to detect this progressive fibrosing phenotype. Estimated time between detection of progressive fibrosis and death was 30–45 months, meaning that the estimated time from onset of symptoms to death in patients with progressive fibrosing ILDs was 61–80 months (Figure 2).

The physicians surveyed believed that pulmonologists take the lead in making treatment decisions in 70–87% of patients with non-autoimmune progressive fibrosing ILDs and 39–58% of patients with autoimmune progressive fibrosing ILDs (see Supplementary Figure S4). Of the pulmonologists surveyed, 79–90% indicated that they would initiate treatment for non-autoimmune progressive fibrosing ILDs without consulting with another physician, except in France and the UK where these proportions were 55% and 60%, respectively (see Supplementary Figure S5). For autoimmune progressive fibrosing ILDs, 50–79% of the pulmonologists indicated that they would initiate treatment without consulting with another physician, except in France where the proportion was 35% (see Supplementary Figure S5). Rheumatologists were split between those who would initiate treatment without consulting with another physician and those who would initiate treatment after consulting with the managing pulmonologist, with some variation across countries (see Supplementary Figure S6).

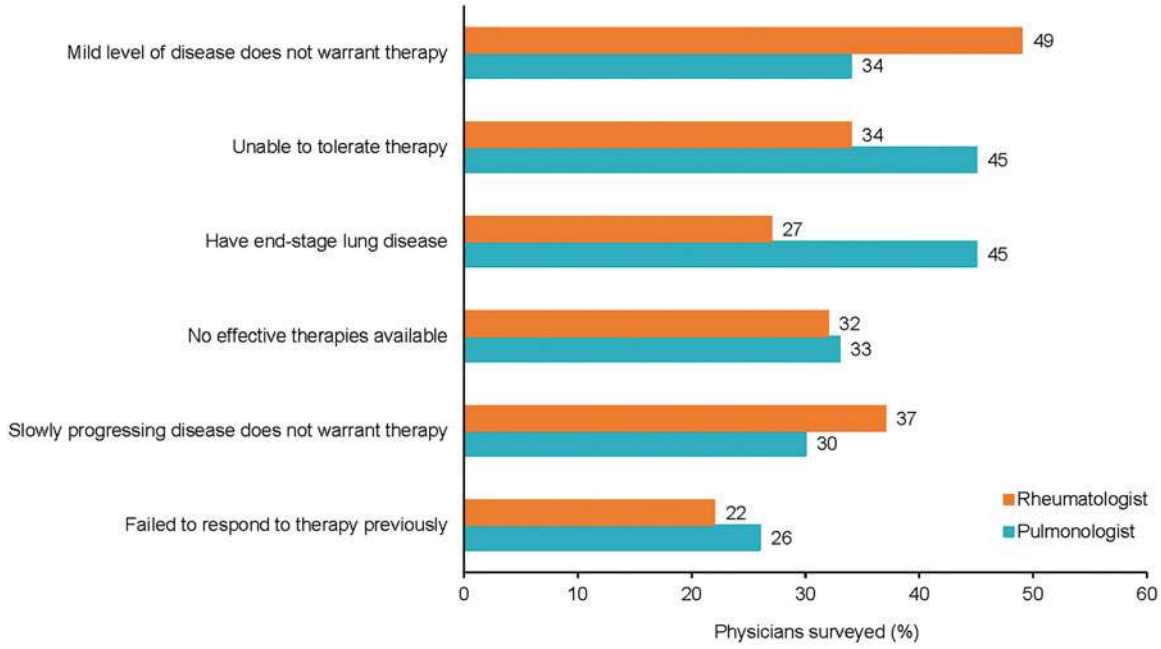


Figure 6. Reasons why patients with non-IPF progressive fibrosing ILDs did not receive treatment. Data from online survey of physicians (pulmonologists, $n = 243$; rheumatologists, $n = 203$). Survey question: "In the previous question, you indicated that some ILD patients that have fibrosis and progressive disease did not receive drug treatment for their ILD in the past year. What are the primary reasons why these patients did not take a therapy?" Abbreviations. ILD, Interstitial lung disease; IPF, Idiopathic pulmonary fibrosis.

Physicians estimated that, of the patients with non-IPF progressive fibrosing ILDs that they have managed, 50–75% received drug treatment in the past year; this was generally similar across countries and types of ILD (Figure 5). The most common reasons given by pulmonologists as to why patients with progressive fibrosing ILDs did not receive drug therapy were that patients had end-stage lung disease (45%) or mild disease (34%), or that the available treatments were not well tolerated (45%) or effective (33%) (Figure 6). The most common reasons given by rheumatologists for patients with progressive fibrosing ILDs not receiving drug therapy were that patients had mild disease (49%), slowly progressing disease (37%), or that the available treatments were not well tolerated (34%) or effective (32%) (Figure 6).

When pulmonologists were asked about the drugs they use to treat fibrotic non-autoimmune ILDs, 63%, 71%, 76% and 77% indicated that they used corticosteroids as first-line therapy for unclassifiable IIP, iNSIP, HP and sarcoidosis-ILD, respectively (Figure 7). Azathioprine was the most commonly used second-line therapy for iNSIP, unclassifiable IIP and HP (used by 33%, 29% and 24% of pulmonologists surveyed, respectively), while methotrexate and azathioprine were the preferred second-line therapies for sarcoidosis-ILD (used by 28% and 21% of pulmonologists surveyed, respectively). The choice of third-line therapies for fibrotic non-autoimmune ILDs was highly heterogeneous (and 19–25% of pulmonologists responded that there is no option for third-line treatment).

When pulmonologists and rheumatologists were asked about the drugs they use to treat fibrotic autoimmune ILDs, 51% and 45% indicated that they used corticosteroids as first-line therapy for fibrotic RA-ILD and SSc-ILD, respectively (Figure 7). Azathioprine, cyclophosphamide and methotrexate were the preferred second-line treatments for RA-ILD, each used by approximately 15% of those surveyed. Cyclophosphamide, azathioprine, and mycophenolate mofetil were the preferred second-line treatments for SSc-ILD, used by 18%, 16% and 13% of physicians surveyed, respectively. Rheumatologists in the US and Europe were more likely to use mycophenolate mofetil as second-line treatment than pulmonologists (see Supplementary Figure S7). Physicians in Japan were more likely to use cyclosporine or tacrolimus and less likely to use mycophenolate mofetil than physicians in the US or Europe (see Supplementary Figure S7). The choice of third-line therapy was highly heterogeneous (Figure 7).

Discussion

Despite growing clinical and research interest in progressive fibrosing ILDs[3,13,18–20], few data are available on the journey that patients with non-IPF ILDs take through diagnosis and management. Our data from an online survey of 486 physicians who manage patients with progressive fibrosing ILDs suggest a period of 9–12 months between onset of symptoms and diagnosis of ILD. Similar delays to diagnosis have been observed in patients with IPF[21,22] and likely reflect the non-specific symptoms of ILDs and the low awareness of ILDs among primary care physicians. Interestingly, although US claims data showed that pulmonologists were the clinical specialty most likely to file the first claim for ILD, specialties other than a pulmonologist or radiologist filed the first claim for ILD in approximately a third of patients with HP or sarcoidosis-ILD and almost a quarter of patients with iNSIP. Further, US claims data showed that in 35–40% patients with CTD-ILDs, the first claim for ILD was filed by a clinical specialty other than a pulmonologist, rheumatologist or

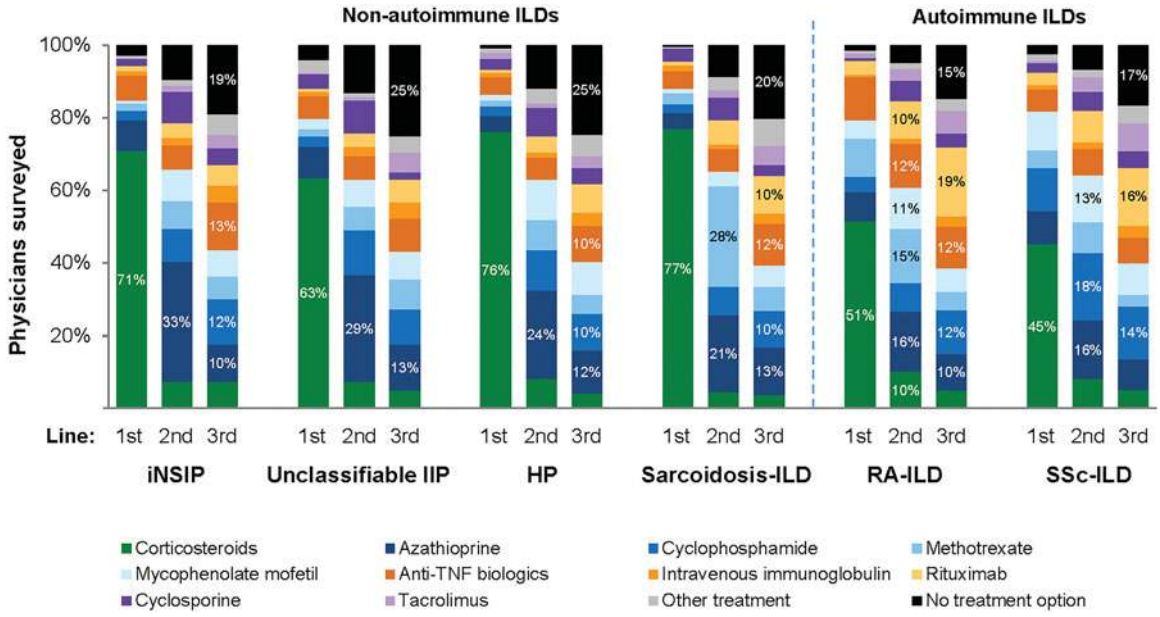


Figure 7. Agents used as first-, second- and third-line treatments for fibrotic ILDs. Data from online survey of physicians (non-autoimmune ILDs: 243 pulmonologists; autoimmune ILDs: 243 pulmonologists and 203 rheumatologists). Survey question: "For the following types of ILDs where patients also have lung fibrosis, please indicate your preferred first, second, and third line treatments for the respective ILD". Rheumatologists were only asked this question in relation to RA-ILD and SSc-ILD. Abbreviations. HP, Hypersensitivity pneumonitis; IIP, Idiopathic interstitial pneumonias; ILD, Interstitial lung disease; iNSIP, Idiopathic non-specific interstitial pneumonia; RA, Rheumatoid arthritis; SSc, Systemic sclerosis.

radiologist. The results of the online survey suggested that a higher proportion of cases of ILD were diagnosed by pulmonologists or rheumatologists, possibly because most of the respondents came from one of these specialties, but still that 20–30% of patients of patients with ILDs were diagnosed by another clinical specialty. These findings suggest that there is no established pathway for the referral and diagnosis of patients with suspected ILDs, leading to delays in the diagnosis, follow-up and management of progressive fibrosing ILDs.

Our data suggest that patients with non-autoimmune ILDs are managed mainly by pulmonologists, while patients with autoimmune ILDs tend to be co-managed by pulmonologists and rheumatologists. Such a cross-disciplinary approach is believed to be important to optimize the management of autoimmune ILDs[23]. Most of the physicians surveyed performed pulmonary function tests every 3–6 months, and HRCT scans every 6–12 months, in their patients with ILDs. A decline in FVC or an increase in fibrotic changes on HRCT in patients with ILDs reflects disease progression and is predictive of mortality[24–29]. Thus regular monitoring is important for the early detection of patients with a progressive phenotype and could inform management decisions and patient counseling. While no guidance on the appropriate frequency of follow-up in patients with non-IPF ILDs has been issued by professional associations, the frequency of pulmonary function tests reported by physicians in our survey appears to be in line with expert opinion on best practice in the management of CTD-ILDs[30,31].

Physicians who participated in the online survey estimated that 18–32% of patients diagnosed with non-IPF ILDs will develop a progressive fibrosing phenotype. Previous studies have reported a wide range of figures for the prevalence of progressive disease in patients with ILDs, reflecting the different cohorts studied and the variety of criteria used to define progression. However, it is clear that a sizeable minority of patients with CTD-ILDs, chronic HP, iNSIP, sarcoidosis-ILD and unclassifiable IIP develop a progressive fibrosing phenotype characterized by decline in lung function, worsening symptoms and premature death[4,5,7,25,27,28,32–35]. The physicians who participated in this survey estimated that patients with non-IPF progressive fibrosing ILDs die approximately 4–5 years after initial diagnosis of ILD. This is similar to the mortality of patients with IPF prior to the availability of therapies that slow disease progression[36,37].

Data from our physician survey suggested that 25–50% of patients with progressive fibrosing ILDs did not receive any drug therapy in the past year. These findings are in line with data from an online survey of 290 European physicians managing patients with IPF conducted in February–March 2016 that indicated that 54% of patients with IPF, and 71% of those with IPF considered to be mild, were not treated with an approved antifibrotic agent[38]. Approximately a third of the pulmonologists and nearly half of the rheumatologists included in our online survey indicated that a primary reason for not initiating therapy in patients with progressive fibrosing ILDs was that patients were considered to have a "mild" level of disease. That rheumatologists were more likely than pulmonologists not to initiate treatment for this reason may reflect pulmonologists having a better understanding of the unpredictable course of ILDs and the poor prognosis associated with disease progression. Approximately a third of pulmonologists and rheumatologists indicated that the reason for not initiating therapy was a lack of effective therapies, while similar numbers indicated that the reason was that

patients were unable to tolerate therapy, presumably referring to the side-effects of immunosuppressants.

By far the most commonly used first-line therapy for all the non-IPF fibrosing ILDs we studied was corticosteroids. This is consistent with recent data from the EXCITING-ILD registry in Germany, which showed that prednisone was used by two-thirds of patients with ILD[19]. Corticosteroids are commonly used treatments for several types of ILD and may lead to short-term improvements in lung function, but no randomized clinical trials have evaluated their efficacy in patients with progressive fibrosing lung disease. Corticosteroids are commonly used in the treatment of SSc-ILD[39] but there is very little evidence to support their use in these patients and they are not recommended in international treatment guidelines[17] or in a treatment algorithm recently issued by an expert consensus group[40]. Cyclophosphamide and mycophenolate mofetil, which have shown efficacy in clinical trials in SSc-ILD[41,42], were named as preferred first-line treatments for fibrosing SSc-ILD by only 12% and 11%, respectively, of the physicians who completed the online survey. This is lower than suggested by other studies[40,43] and the reasons for this are unclear. The online survey revealed great heterogeneity in the drugs used as second- and third-line therapies for all the ILDs studied, reflecting the lack of evidence available to guide therapeutic decision-making.

To our knowledge, this is the first large survey of physicians and the first study of US insurance claims to investigate current practice in the diagnosis and management of patients with non-IPF progressive fibrosing ILDs. Strengths of our analyses include the recruitment of physicians with experience in managing patients with ILDs to participate in the online survey, the large sample size, and the systematic collection of data based on US insurance claims. Limitations include the inherent biases in individuals who choose to respond to online surveys and possible differences in the way that respondents interpreted concepts such as worsening of lung function and "progressive" ILD in their answers. We do not know if physicians interpreted ILD to be progressive only if patients did not respond to immunosuppressive treatment. The survey required physicians to distinguish between the time at which fibrotic and progressing ILD developed and the time at which fibrotic and progressing ILD was detected by a physician. It is not known how physicians estimated the first of these time points but it may have been the last time-point before disease progression was observed. The survey question related to estimated survival in patients with progressive fibrosing ILDs did not account for the presence of comorbidities, such as pulmonary hypertension, which are common in patients with ILDs and can significantly affect survival[44]. Patients with autoimmune-disease-related ILDs managed solely by a rheumatologist were not covered in the analysis of US insurance claims data. We did not investigate the reasons for physicians using (or not using) particular treatments for ILDs. Physicians' preferred treatments for ILDs are influenced by the availability and insurance coverage of drugs in their country or region, so data collected in specific countries may not apply to other countries.

Conclusions

Physicians who treat patients with ILDs estimate that 18–32% of patients diagnosed with non-IPF ILDs develop a progressive fibrosing phenotype. The journey for these patients includes delays in the initial diagnosis of ILD and in the detection of progressive fibrosis. Physicians estimate that post-diagnosis survival time in patients who develop other progressive fibrosing ILDs is similar to that of patients with IPF prior to the availability of antifibrotic therapies. Over a quarter of patients with non-IPF progressive fibrosing ILDs do not receive any drug treatment. There is a high unmet need for effective and well tolerated treatments for progressive fibrosing ILDs.

Transparency

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Author contributions

C.D.W. contributed to the design of this study and the analysis of the data. B.M., L.Z.L. and M.Q. contributed to the design of the questionnaire used in the online survey. M.W., M.K., A.O., A.F., E.B., C.D.W., C.P.D., B.M., L.Z.L., M.Q. and V.C. contributed to the interpretation of the data and the development of the manuscript. All authors have approved the final manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, were fully responsible for all content and editorial decisions, were involved at all stages of development and have approved the final version.

Declaration of financial/other relationships

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Compliance with ethics guidelines

No ethics committee approval was required for physicians to complete a survey for which the results were anonymized. No ethics approval was needed for an analysis of healthcare claims data. Patients did not participate in this research.

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Data availability

The datasets used and/or analyzed during the current study are not publicly available but are available from Boehringer Ingelheim on reasonable request.

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