Original Article

Latin American Registry of Idiopathic Pulmonary Fibrosis (REFIPI): Clinical Characteristics, Evolution and Treatment

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ABSTRACT

Introduction: Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible and frequently fatal disease. Currently there are national and multinational registries in Europe, United States, Australia and China to better understand the magnitude of the problem and the characteristics of the IPF patients. However, there are no national or regional registries in Latin America, so the objective of this study was to carry out a Latin American registry that would allow the identification of IPF patients in our region.

Methodology: A system consisting of 3 levels of control was designed, ensuring that patients met the diagnostic criteria for IPF according to international guidelines ATS/ERS/ALAT/JRS 2011. Demographic, clinical, serological, functional, tomographic, histological and treatment variables were recorded through a digital platform.

Results: 761 IPF patients from 14 Latin American countries were included for analysis, 74.7% were male, with a mean age of 71.9 ± 8.3 years. In general there was a long period of symptoms before definitive diagnosis (median 1 year). In functional tests, an average reduction of FVC (70.9%) and DLCO (53.7%) was detected. 72% received at least one antifibrotic drug (pirfenidone or nintedanib) and 11.2% of the patients had an acute exacerbation, of which 38 (45.2%) died from this cause.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause. It is usually irreversible, progressive, and fatal within a few years.1,2

IPF presents with different clinical phenotypes, making it particularly difficult to study, even in specialized centres.3 Because of this, national and even regional registries have been developed to gain a clearer understanding of the clinical, radiological, functional and morphological characteristics of IPF.

National registries, each with its own methodology, have now been created in Germany, Sweden, the United Kingdom, Greece, Spain, Australia, India and China.4-12 Multinational registries have only been developed in Europe.10,13 One of the first IPF registries to be created was the Australian Registry, which was compiled between 2012 and 2014 and included 359 patients.7 In the first description of the German registry,1 published in 2014, the authors reported that 34.1% of their 502 incident and prevalent patients required surgical lung biopsy. They also observed that even in a developed country such as Germany, only 2.8% of the study cohort was actually on a lung transplant list, although 58.6% of the patients were potential transplant candidates based on their age (less than 65 years) and disease severity (FVC < 50% and/or DLCO < 40%).

In 2014 Ryerson et al. called for the immediate establishment of a global IPF registry.14 Aware of the pressing need for new registries, we set out to establish the first Latin American IPF registry, the REFIPI (Latin American idiopathic pulmonary fibrosis registry). This registry was created at the initiative of the Department of Interstitial Lung Diseases (ILD) of the Latin American Thoracic Association (ALAT) for the purpose of studying the Latin American population of patients with IPF, supplementing the results of real-world evidence trials on the efficacy and safety of antifibrotic treatments, and comparing our results with other international registries to help create a “global IPF registry”.

The main objective of the REFIPI was to determine the demographic, clinical, functional and radiological characteristics of patients with IPF in Latin America at the time of diagnosis and over the course of their disease, and to record the treatments used, their efficacy and their safety in clinical practice.

Methods

Study design

A central executive committee made up of former directors and the deputy director and director of the ILD section of ALAT was initially formed in 2017 to define the variables to be studied in the REFIPI. A virtual REFIPI platform was then created for uploading patient data (https://alatorax.org/en/login).

An invitation was posted on the ALAT website and also sent by email to all pulmonologists associated with ALAT’s ILD section inviting them to participate freely and voluntarily in the project.

National coordinators were put in charge of promoting the registry in their country and encouraging pulmonologists to upload data from their patients.

Conclusions: Like other registries, we found that there is difficulty in the recognition and excessive delay in the diagnosis of IPF in Latin America. Most of the patients in REFIPI received antifibrotics; these were well tolerated and associated with fewer adverse events than those reported in clinical trials.

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Lung function: Forced vital capacity (FVC % predicted), diffusing capacity for carbon monoxide (DLCO % predicted) adjusted for haemoglobin, and distance achieved in the six-minute walk (6 MW) test. All these variables were mandatory at the time of diagnosis but voluntary during follow-up, with the frequency of testing being decided by each pulmonologist.

Histology: The histology pattern was categorized according to the ATS/ERS/JRS/ALAT 2011 guidelines as typical usual interstitial pneumonia (UIP), probable UIP, possible UIP, and inconsistent with UIP.

Treatment: Variables related to treatment for gastroesophageal reflux (GER), use of corticosteroids and/or immunosuppressants, and treatment with pirfenidone and/or nintedanib were recorded. Tolerance of antifibrotics was evaluated on the basis of the different antifibrotic–related adverse events recorded from the date the drug was started until the last visit, death or suspension of the drug. Significant elevation of liver enzymes was defined as ≥3 times the normal value in patients who reported symptoms, or ≥5 times in those without symptoms.

Disease progression: Date and cause of death or lung transplantation and acute exacerbation according to recent criteria were recorded. Follow-up was defined as the time elapsed from the date of diagnosis to the date of the last consultation or the date of death/transplantation, as appropriate.

Statistical analysis

For the descriptive analysis, quantitative variables were reported as mean ± standard deviation or median with interquartile ranges 25–75, depending on the distribution of the sample. The distribution of the variables was analysed using histograms and skewness and kurtosis values. Categorical variables were described as absolute and relative frequencies (proportion). Qualitative variables were analysed using Fisher’s exact test or the Xi squared test, as appropriate. Logistic regression models were used to adjust for possible confounders. The odds ratio (OR) and confidence interval (95% CI) were reported for the variables used in the final models. Goodness of fit was evaluated using the Hosmer–Lemeshow test. Finally, all statistical calculations were performed using STATATA 13.0 (Stata Corporation, College Station, TX, USA).

Results

One hundred and forty six doctors from 14 Latin American countries took part in the registry between November 2017 and November 2019. A total of 974 cases were uploaded to the platform (tier 1), of which 761 were approved and included in the final analysis: 189 cases were rejected by country coordinators (tier 2) and 24 cases were rejected by the ALAT central committee (tier 3), and were therefore excluded from the final analysis.

Of the total number of patients included, 569 (74.7%) were men with a mean age of 71.9 (±8.3) years. Approximately half (52.3%) were former smokers. The median time from onset of symptoms to diagnosis was 12 months (IQR 6–24); no differences were found between participating countries (Fig. 2). Median follow-up was 14 months (IQR: 5–30). The principal study variables are described in Table 1. Autoimmune tests showed that 23 (3%) patients were positive for RF and 80 (11%) for ANA, the fine speckled IIF pattern being the most frequent (42.5%). Specific IIF patterns were only described in 15 cases (8 cytoplasmic, 6 nuclear, and 1 centromere). The following systemic signs and symptoms were observed: xerophthalmia 16/753 (2.1%), xerostomia 32/753 (4.2%), joint symptoms 29/753 (3.8%), muscle weakness 27/753 (3.6%), and Raynaud’s phenomenon 6/753 (0.8%).

In the respiratory function test, the average baseline FVC and DLCO was 70.9% and 53.7%, respectively. No differences in baseline FVC % were observed among countries (Fig. 3).

Regarding treatment (Table 2), 553 patients (72%) received at least 1 antifibrotic drug, 375 (67.8%) received pirfenidone, 103 (18.6%) received nintedanib and 75 (13.5%) received both antifibrotics in succession. Regarding other treatments, 24 (4.1%) patients received triple anti-inflammatory/immunosuppressive therapy (azathioprine + corticosteroids + N-acetylcysteine).

![Fig. 2. Box-and-whisker plot showing the time from symptom onset to diagnosis in months, according to participating country.](image-url)

**Table 1** Baseline characteristics of the REFIPi cohort (n = 761).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>569 (74.7)</td>
</tr>
<tr>
<td>Age, years, mean (SD)</td>
<td>71.9 (±8.3)</td>
</tr>
<tr>
<td>Onset of symptoms to diagnosis, median (IQR)</td>
<td>12 (6–24)</td>
</tr>
<tr>
<td>Dyspnœa Grade 0 mMRC, n (%)</td>
<td>60 (7.9)</td>
</tr>
<tr>
<td>Grade 1 mMRC, n (%)</td>
<td>228 (30.3)</td>
</tr>
<tr>
<td>Grade 2 mMRC, n (%)</td>
<td>300 (39.8)</td>
</tr>
<tr>
<td>Grade 3 mMRC, n (%)</td>
<td>133 (17.6)</td>
</tr>
<tr>
<td>Grade 4 mMRC, n (%)</td>
<td>32 (4.2)</td>
</tr>
<tr>
<td>Non-smokers, n (%)</td>
<td>341 (45.3)</td>
</tr>
<tr>
<td>Former smokers, n (%)</td>
<td>394 (52.3)</td>
</tr>
<tr>
<td>Current smokers, n (%)</td>
<td>18 (2.4)</td>
</tr>
<tr>
<td>Family history of fibrosis, n (%)</td>
<td>63 (8.4)</td>
</tr>
<tr>
<td>ANA+, n (%)</td>
<td>80 (11.1)</td>
</tr>
<tr>
<td>Rheumatoid factor+, n (%)</td>
<td>23 (3.1)</td>
</tr>
<tr>
<td>PASP, median mmHg (IQR)</td>
<td>942 (24–39.5)</td>
</tr>
<tr>
<td>Finger clubbing, n (%)</td>
<td>315 (41.8)</td>
</tr>
<tr>
<td>Velcro crackles, n (%)</td>
<td>732 (97.2)</td>
</tr>
<tr>
<td>GER symptoms, n (%)</td>
<td>283 (37.6)</td>
</tr>
<tr>
<td>% FVC, mean (SD) [n = 744]</td>
<td>70.9 (±9.8)</td>
</tr>
<tr>
<td>% DLCO, mean (SD) [n = 477]</td>
<td>53.7 (±45.4)</td>
</tr>
<tr>
<td>HRCT typical UIP, n (%)</td>
<td>511 (67.8)</td>
</tr>
<tr>
<td>HRCT possible UIP, n (%)</td>
<td>230 (30.5)</td>
</tr>
<tr>
<td>HRCT inconsistent with UIP, n (%)</td>
<td>12 (1.6)</td>
</tr>
<tr>
<td>Histology typical UIP, n (%)</td>
<td>124 (16.3)</td>
</tr>
<tr>
<td>Histology probable UIP, n (%)</td>
<td>114 (91.9)</td>
</tr>
<tr>
<td>Histology possible UIP, n (%)</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Histology no UIP, n (%)</td>
<td>4 (3.2)</td>
</tr>
</tbody>
</table>

and 337/573 (58.8%) received anti-gastro-oesophageal reflux treatment.

Antifibrotic-related adverse events were observed in 169 patients (30.5%), 117 (31.2%) of which were related to pirfenidone and 35 (33.9%) to nintedanib. The comparative analysis showed no statistically significant difference between nintedanib and pirfenidone in terms of the proportion of patients with adverse events (Table 3). Logistic regression analysis showed no association between adverse events adjusted for various variables, such as age, sex, baseline FVC %, baseline DLCO %, or smoking.

During follow-up, 84/746 patients (11.2%) presented an acute exacerbation, 38 (45.2%) of which died as a result. The usual treatment used for acute exacerbation was corticosteroids in 76 patients (90.5%), and corticosteroids and immunosuppressants in 2.4% of patients. No specific treatment was reported in 6 patients (7.1%). Thirty-three patients (4.3%) were included in the lung transplant list and only 11 (1.4%) were transplanted during the study period: 1 in Argentina, 1 in Mexico and 9 in Chile. A total of 88 (11.5%) deaths were reported over the 2 years of the registry, all of them related to IPF – 38 (43%) due to acute exacerbation and 50 (57%) to disease progression.

**Discussion**

REFIPI is the first Latin American IPF registry, and so far one of the largest multinational registries in terms of participating countries and number of patients. One hundred and forty six doctors from 14 different countries participated in this first stage of the project, and 761 patients were included in the final analysis (Fig. 4). The 3-tier verification system used to confirm diagnosis and central analysis of all the chest CT scans adds robustness to the study and increases the diagnostic certainty of IPF. This system allowed us to exclude 111 patients (11.4%) with an alternative diagnosis at the 2nd and 3rd tiers, and highlights the difficulties involved in diagnosing IPF in Latin America, even among specialists.

The REFIPI supplements the results reported in other studies and randomized clinical trials and, like other registries, includes a higher proportion of elderly male patients. On physical examination, 97.2% of patients were found to have Velcro crackles, highlighting the importance of this sign as a tool for the early detection of IPF. It is interesting to note that 8.4% of patients included in the REFIPI had a family history of pulmonary fibrosis. Although this finding was not corroborated by genetic studies, it suggests that about 1 in 10 patients with apparently sporadic IPF may have familial pulmonary fibrosis.

The main diseases included in the differential diagnosis of IPF are fibrotic hypersensitivity pneumonitis and autoimmune diseases. In terms of the latter, 10% of patients tested positive for autoantibodies, and only 15 presented a specific IF ANA pattern; however, our 3-tier verification system confirmed that none of these cases met the criteria for a defined autoimmune disease or an interstitial disease with autoimmune features. Fibrotic hypersensitivity pneumonitis may often be indistinguishable from IPF, and is mainly diagnosed on the basis of inhaled antigens, the imaging pattern, and bronchoalveolar lavage tests. In the REFIPI, 12% of patients reported some exposure to inhaled antigens, mainly avian. All these cases, however, presented a typical or probable pattern of UIP on HRCT, and this, in the opinion of a multidisciplinary team, formed the basis for a reliable definitive or provisional diagnosis in each case. In terms of the HRCT pattern, only 12 (1.6%) patients presented a pattern inconsistent with UIP, but in all these cases lung biopsy was consistent with UIP.

Surgical lung biopsy was performed in 124 patients (16.3%) – less than the percentage found in most registries, such as the German (34.1%) and EurIPFreg (32%) registries. This could be due to the fact that these European registries were carried out prior to publication of the Fleischner Society recommendations, and the guidelines in force at that time recommended that patients with possible UIP on HRCT should undergo surgical biopsy for a firm diagnosis. In our study, surgical lung biopsy was performed on all patients who presented HRCT findings consistent with UIP, and in 112 of 230 patients (48.7%) who presented HRCT findings of possible UIP. This shows that half the time, specialists in Latin America do not perform lung biopsy on patients with possible UIP due to an exposure history within the appropriate clinical context, and rely instead on a provisional high confidence diagnosis (70%-90%) for IPF, as recommended by the Fleischner Society.

Moreover, most of the pulmonologists participating in the REFIPI are affiliated with the ILD section of ALAT and specialise in treating patients with this type of disease (participation bias). This could have led them to include mostly patients with a firm clinical diagnosis.

Regarding the delay in diagnosis, patients had experienced symptoms for a median of 12 months before diagnosis. This period, however, varied widely among participating countries, and is evidence of the considerable delay that characterizes the diagnosis of this disease. Nevertheless, it is interesting to note that our median delay was shorter than that observed in most multinational
registries published to date. For example, in the eurlIPFreg and EMPIRE registries, mean time from onset of symptoms to diagnosis was 21.8 and 19.2 months, respectively. In the REFIG, the delay in diagnosis was similar to that reported in the United States registry (IPF-PRO), namely 13.6 months, although in half of all registry patients the delay was greater than 1 year. Delays in the diagnosis of IPF have been associated with worse survival, and our results together with those reported in other regions underscore this problem of vital global importance.

In terms of treatment, it is important to draw attention to the low proportion of patients who were treated with corticosteroids and immunosuppressives (4.2%). This treatment has been associated with a higher rate of hospitalization and mortality in patients with IPF. Similar results emerged from the EurIPFreg registry where less than 10% of patients received anti-inflammatory/immunosuppressive treatment over the same period as the REFIG. In contrast our results, the German INSIGHT registry contained a high proportion of patients (26.1%) receiving corticosteroids. The same was true of a survey conducted in France and several randomized controlled clinical trials.

A significant proportion of patients (72%) in the REFIG were receiving some type of antifibrotic drug. This could be due to the aforementioned participation bias, as all participating pulmonologists were affiliated with the ILD section of ALAT and, given their extensive experience with IPF, would have been more likely to prescribe antifibrotics to their patients. Most of these patients received pirfenidone (49.3%) compared to nintedanib (13.5%).

AE: adverse events.

**Fig. 4.** Map of countries participating in the REFIG. The shade of green indicates the number of patients included by each country. Doctors: the number of physicians contributing patients, by country.
This is understandable in Latin America, where pirfenidone was marketed before nintedanib in most countries in the region. The same trend was observed in the Spanish registry, where 51.9% of patients received pirfenidone versus 17.9% receiving nintedanib, one reason being that pirfenidone was available 2 years prior to nintedanib in Spain.\(^9\)

The same pirfenidone- and nintedanib-related adverse events as described in the initial ASCEND\(^{22}\) and INPULSIS/TOMORROW\(^{26,28}\) clinical trials were observed in the REFIPI, although in a lower proportion, insofar as adverse events were only reported in 31.2% and 33.9% of patients taking pirfenidone and nintedanib, respectively. The most common adverse events associated with pirfenidone were nausea, hyporexia/anorexia and photosensitivity in 25.1%, 20.2% and 8.5%, respectively. In the case of nintedanib, the most frequent adverse events were diarrhoea and hyporexia in 33.9% and 15.5% of patients, respectively.

The SEPAR registry also describes a lower rate of adverse events (23.4%), although the proportion of patients with nausea, anorexia and photosensitivity (9.5%, 7.8% and 5.7% respectively) was lower than that reported in REFIPI.\(^9\)

Interestingly, the proportion of patients with photosensitivity in REFIPI (8.5%) and in the Spanish SEPAR registry\(^8\) (5.6%) was significantly lower than that found in the ASCEND (28.1%) study, even though a significant proportion of Latin American countries are located in latitudes with a high ultraviolet radiation index. This finding could be due to the different phototypes found in our region and a more widespread use of sunscreen.\(^{25}\)

In the TOMORROW/INPULSIS trials investigating nintedanib, 61.5%, 11.2%, and 24.3% of patients reported diarrhoea, anorexia, and nausea, respectively.\(^{27,28}\) In the REFIPI, we observed a significantly lower rate of diarrhoea (33.9%). Although this could be underestimated due to the different study methodologies used, similar results were found in other real-world experience studies with nintedanib.\(^{29}\)

Finally, only 8% of our population receiving pirfenidone and 10.6% receiving nintedanib had to suspend treatment due to adverse events. This contrasts with the findings of the pivotal ASCEND and INPULSIS/TOMORROW clinical trials, in which treatment had to be suspended in 14.4% and 20.6% of cases, respectively.\(^{26,28}\) The same trend has been reported in other international registries, and shows that both drugs are well-tolerated in clinical practice.

The REFIPI has both strengths and weaknesses. On the one hand, it is the first multinational, unsponsored, Latin American IPF registry, and has the backing of a recognized scientific society (ALAT). The 3-tier verification system and independent HRCT pattern analysis increases the level of confidence in the diagnosis of IPF. A large number of specialists from many different countries participated in the REFIPI, making it a good example of collaboration and a true representation of IPF in Latin America. The results of the REFIPI have given us the chance to identify and correct some major problems in the management of patients with IPF in Latin America: misdiagnosis of IPF (11.4% of cases were excluded for this reason), delay in diagnosis (12 months), and poor access to lung transplantation (only 1.4% of patients were transplanted).

This study has limitations that are typical of any registry, namely, case selection bias and intervention bias on the part of participating physicians. The number of cases contributed by each country also differs significantly, and is proportional to the number of inhabitants (Fig. 4). This is mainly due to lower adherence to the registry in some countries and/or delays in joining the REFIPI due to delays by some institutional review boards in approving the registry protocol. Finally, it is important to clarify that the REFIPI is not a prevalence study but a real-world observational study of data from IPF patients submitted voluntarily from countries across Latin America.

Conclusions

The REFIPI is the first Latin American IPF registry. Like other registries, we observed difficulties and excessive delays in IPF diagnosis in Latin America. Most patients in the REFIPI received antifibrotics, which were well tolerated and associated with a lower rate of adverse events than reported in clinical trials.

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Conflict of interests

The authors have no conflict of interest to declare.

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