Idiopathic pulmonary fibrosis in Sweden: report from the first year of activity of the Swedish IPF-Registry

Giovanni Ferrara\textsuperscript{1,2*}, Lisa Carlson\textsuperscript{1}, Andreas Palm\textsuperscript{3}, Jonas Einarsson\textsuperscript{4,5}, Cecilia Olivesten\textsuperscript{6}, Magnus Sköld\textsuperscript{1,2} for the Swedish Idiopathic Pulmonary Fibrosis Registry Group

\textsuperscript{1}Department of Respiratory Medicine and Allergy, Karolinska University Hospital, Stockholm, Sweden; \textsuperscript{2}Respiratory Medicine Unit, Department of Medicine, Solna and Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden; \textsuperscript{3}Gävle Hospital, Gävle, Sweden; \textsuperscript{4}Skåne University Hospital, Malmö, Sweden; \textsuperscript{5}Department of Respiratory Medicine and Allergology, Skåne University Hospital, Lund University, Lund, Sweden; \textsuperscript{6}Sunderby Hospital, Luleå, Sweden

Background: Idiopathic pulmonary fibrosis (IPF) is an emerging problem in the western world, being related to increasing age and implying significant costs for the diagnosis and management of affected patients. The epidemiology of IPF is not well understood.

Methods: To allow estimates of the problem and eventually to evaluate quality of the care of IPF patients in Sweden, a national IPF Registry was started in the autumn of 2014. Data on criteria used to diagnose IPF, demographics, lung function, and quality of life (measured with the King’s Brief Interstitial Lung Disease Questionnaire, K-BILD) were reported directly to the registry, based at the coordinating centre (Karolinska University Hospital, Stockholm, Sweden) via a web-based platform.

Results: During the first year, the registry was implemented in 11 (33\%) of the 33 respiratory units in the country. Seventy-one patients were registered between October 2014 and October 2015, 50 (70.4\%) males and 21 (29.6\%) females. Median age was 70 (range 47–86). The mean K-BILD score at the first inclusion in the registry was 54.3 $\pm$ 9.5.

Conclusions: The main features of IPF patients in this first Swedish cohort were consistent with data published in the literature in main multinational randomized controlled trials. The K-BILD questionnaire showed that quality of life of patients with IPF and their perception of the disease are quite poor at the time of inclusion in the registry.

Keywords: idiopathic pulmonary fibrosis; registry; quality of life; K-BILD; lung function

Responsible Editor: Riitta Kaarteenaho, Oulu, Finland.

*Correspondence to: Giovanni Ferrara, Department of Respiratory Medicine and Allergy, Karolinska University Hospital, SE-17 176 Stockholm, Sweden, Email: giovanni.ferrara@ki.se

idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosis of unknown cause, occurring primarily in older adults, and limited to the lungs, with a survival of about 3–5 years from the diagnosis (1). A multidisciplinary approach involving specialists with expertise in the field is necessary to differentiate IPF from the other interstitial lung diseases (ILDs) (2). Estimates on IPF prevalence rates are derived from studies carried out with different methodologies mainly in the United States (3), Mexico (4), and England (5), and are still unknown in most of the countries around the world, including Sweden. A national Finnish study estimated the prevalence in Finland around 14–16/100,000 cases (6). Considering the lowest incidence estimates, as many as 432 new cases of IPF should be diagnosed in Sweden every year, with a prevalence of 1,000–1,500 cases.

The Swedish Guidelines for IPF (7), published by a national group of experts from the Swedish Respiratory Society (Svensk Lungmedicinsk Förening, or SLMF), are a first step to uniform and increase the standard of care for patients with IPF in Sweden. Its recommendations are in agreement with major international documents (1).

Two drugs (pirfenidone and nintedanib) are now registered based on large randomised clinical trials (8–11) and are commercially available in Europe and the United States. The high costs (estimated between 28,000 and 38,000 euros/year/patient) (12) and the relatively weak evidence concerning their effect on hard outcomes as mortality (13) have already fuelled a debate on how
resources for patients with IPF should be allocated within
the health-care systems.

To provide a platform to address these questions, a
national quality registry for IPF was started in Sweden in
September 2014.

The main objective of this paper is to demonstrate the
feasibility of the implementation of a web-based IPF
registry in Sweden and to report the results of the first
year of activity of the Swedish IPF-Registry.

**Methods**

A web-based platform, already in use in Finland (Granitics
Unify Med, Granitics Ltd, Espoo, Finland), was chosen and
adapted to Swedish healthcare and regulatory standards.
The platform allowed the registration of demographics,
lung function, radiology, quality of life (assessed with the
King’s Brief Interstitial Lung Disease Questionnaire
(K-BILD) questionnaire), and ongoing treatments.

**Table 1.** The Swedish Idiopathic Pulmonary Fibrosis
Registry variables

| Demographics | Gender |
|--------------|--------|
| Date of birth |
| Age |
| Reference hospital |

| Diagnosis (IPF) | Time of diagnosis |
|-----------------|-------------------|
| ICD-10          |
| Base for diagnosis: |
| - Clinical/radiological |
| - Biopsy-proven |
| - Based on MDC |

| Clinical information | Smoking status: |
|----------------------|-----------------|
| Height, Weight, BMI  |
| - Ex-smoker |
| - Current smoker |
| - Never smoker |
| Pack-year |
| Profession, professional/environmental exposure |
| Chronic comorbidities |
| Ongoing treatments |

| Main symptoms and time of onset |
| Clinical findings: |
| - Presence of gastric reflux |
| - Drumstick fingers |
| - Crackles at auscultation |

| Lung function | Lung plethysmography: FEV1, FEV1%, FVC, FVC%, FEV1/FVC, TLC, TLC% |
|---------------|---------------------------------------------------------------|
| Diffusion capacity: DlCO% |
| Pulse oximetry at rest; arterial blood gas analysis |
| 6MWT: saturation at rest and lowest value during/after the test; walk distance |

| Radiology | Chest X-ray |
|-----------|-------------|
| HR CT: |
| - UIP pattern |
| - Possible UIP pattern |
| - Inconsistent with UIP pattern |

| Pathology | BAL: total cell count, cell differentials |
|-----------|----------------------------------------|
| Lung biopsy (open or VATS): |
| - UIP pattern |
| - Probable UIP-pattern |
| - Possible UIP-pattern |
| - Not UIP-pattern |

| Quality of life | K-BILD questionnaire |
|-----------------|----------------------|

| IPF therapy | Date of start, date of stop |
|-------------|----------------------------|
| IPF specific therapies: |
| - Pirfenidone |
| - Nintedanib |
| - NAC |
| - Triple therapy |

**Table 1 (Continued)**

| Best supportive therapy: |
| - Long-term oxygen therapy |
| - Physiotherapy |
| - Psychological support |
| - Palliation (morphine, benzodiazepine) |

| Adverse events: |
| - Date of onset |
| - Type of AE |
| - Severity (according to CTCAE) |
| - Intervention |
| - Suspension/modification of the therapy |

| Outcome | Death: |
|---------|--------|
| - Date of death |
| - Cause of death |

| Transplantation: |
| - Date of transplantation |

| Follow-up: |
| - Lung function testing |
| - Radiology |
| - Quality of life (K-BILD) |

| Outcome | - Ongoing treatments/AEs/modification of IPF-therapies |
|---------|-------------------------------------------------------|

IPF: idiopathic pulmonary fibrosis; ICD-10: International Statistical
Classification of Diseases and Related Health Problems – Tenth
Revision; MDC: multi-disciplinary conference; BMI: body mass
index; FEV1: forced expiratory volume in 1 s; FEV1%: forced
expiratory volume in 1 s, % of the expected value; FVC: forced
volume capacity; FVC%: forced volume capacity, % of the
expected value; TLC: total lung capacity; TLC%: total lung
capacity, % of the expected value; DlCO%: Diffusion capacity
of carbon monoxide, % of the expected value; 6MWT: 6-min
walking test; HR CT: high-resolution computed tomography;
UIP: usual interstitial pneumonia; BAL: bronchoalveolar lavage;
VATS: video-assisted thoracoscopic; K-BILD: King’s Brief
Interstitial Lung Disease Questionnaire; NAC: N-acetyl-cysteine;
AE: adverse event; CTCAE: Common Terminology Criteria for
Adverse Events.

To provide a platform to address these questions, a
national quality registry for IPF was started in Sweden in
September 2014.

The main objective of this paper is to demonstrate the
feasibility of the implementation of a web-based IPF
registry in Sweden and to report the results of the first
year of activity of the Swedish IPF-Registry.
(K-BILD) (14), ongoing treatments, adverse events according to the Common Terminology Criteria for Adverse Events (15), follow-up and outcomes such as death and lung transplantation at the time of inclusion in the registry and during the follow-up. K-BILD was translated from English to Swedish for the purpose of being included in the registry (16). The K-BILD score measures quality of life on a scale from 0 to 100, with 100 = best health status (14).

To be included in the registry, patients had to fulfil the diagnostic criteria for the diagnosis of IPF according to national and international guidelines (1–7). Table 1 illustrates all the variables collected in the Swedish IPF registry. A registered nurse was hired as registry coordinator with the task to establish contact with other hospitals and to provide on-site training and technical support.

A cross-sectional analysis of the data reported at the time of inclusion in the registry between September 2014 and October 2015 is presented. Continuous variables are presented as mean ± standard deviation of the mean or median and range. Categorical variables are presented as proportions of the total population. Single sample, paired \( t \)-test was used when appropriate, with level of significance at \( p < 0.05 \).

The study was approved in August 2014 by the Stockholm’s Regional Ethical Committee (Ref. No. 2014/1202-31/4). All patients needed to be informed by the case manager at his/her hospital about the aim of the project and to sign a written consent before inclusion in the registry.

Results

The web-based platform was activated at the Karolinska University Hospital, Stockholm, Sweden, and made available for all participating centres in September 2014. The Karolinska University Hospital assumed the role of leading and legally responsible institution for the implementation of the project.

The initiative was made public with annual presentations at the Swedish Respiratory Society Congresses in Malmoe (2014) (17) and in Goteborg (2015) (18) and with thematic articles on IPF and the need of a national registry on the journal of the Swedish Respiratory Society (19, 20) and on local newspapers (21). A web page on the Swedish IPF-Registry was also published on the website of the Swedish Respiratory Society (22).

During the study period, 14 of the 33 (42%) Swedish respiratory disease units were connected to the registry and 11 (33%) started to report data from patients with IPF in the first year of activity of the Swedish IPF-Registry. The hospitals participating in the data collection and the relative number of patients registered for each centre during the study period are reported in Fig. 1.

A total of 71 patients with IPF were recorded in the Swedish IPF-Registry during the first year of activity. Demographics and main features of the patients at the time of registration in the IPF-registry are reported in Table 2.

The diagnosis of IPF was based on clinical–radiological features in 52 (72%) patients, while 10 (14%) underwent a lung biopsy and 14 (20%) received a diagnosis after a multidisciplinary conference.

Thirty-one (44%) of the patients underwent a 6-min walking test at the time of inclusion in the registry; most of them presented a much lower \( \text{SaO}_2 \) during or just after the test compared to the value at rest (95 ± 0.9% at rest vs. 86 ± 2.3% during the test, \( p < 0.05 \)).

The mean value of the K-BILD score was 54.3 ± 9.5, demonstrating a relatively low quality of life at the time of inclusion in the registry.

Discussion

Our report shows that web-based tools can rapidly be implemented and used to address important questions in healthcare at national level. Our experience reinforces previous reports from Australia, showing that technological tools can greatly improve the understanding of rare disease at a national level and overcome quite easily geographical distances and logistic problems (23).

The implementation process is crucial to the success of the project, and many practical and technical issues need to be promptly addressed while connecting the participating centres: to secure that data are correctly entered and timely reported is important to secure accuracy and completeness of the registry; on the other hand, the staff of the respiratory units involved in the project had already a clinical burden of everyday chores to perform in their hospitals. Part of the success of the initial implementation of the Swedish IPF-Registry was to identify committed doctors and motivated staff in the respiratory units. Support of a registry coordinator making regular visits to the participating centres to solve technical and practical issues was crucial to ensure engagement of the users and registered data of high quality. Users were constantly involved in a discussion on how to ease the registration of data, and the national guidelines on IPF served as a valuable source of definitions. Technical, IT, and practical issues (e.g. log in with staff ID, substitution of free text with checklist variables and tips on how to look fast through the journals to collect data) were continuously discussed with the registry coordinator and addressed with the IT company.

The patient cohort presented in this manuscript cannot be considered representative of the whole population of IPF patients in Sweden. Data on the epidemiology of IPF in Sweden are simply not available. One of the aims of starting an IPF-registry was in fact to provide estimates on this disease in Sweden, but this will be possible only if...
the registry covers at least 80% of the country. This goal might be reasonably reached in 2018.

The main features of the patients recorded in the Swedish IPF-Registry seem to resemble the clinical presentation of IPF as reported in multinational multicentre randomised controlled trials (8-11).

Males seem to be more affected than females, as shown in previous studies, as well as the high prevalence of ex-smokers among IPF-patients (24).

The diagnosis was mostly based on clinical–radiological features (according to the criteria identified by national and international guidelines) (1, 7), and only 10% of the patients underwent invasive procedures like lung biopsy in the diagnostic work-out. This is consistent with the data reported in the literature (25).

Interestingly, most of our patients were affected by a mild or moderate form of IPF according to the forced vital capacity (FVC) value. Nevertheless, most of them reported a relatively poor quality of life, with a mean K-BILD of 54.8; this finding supports an ongoing discussion questioning the value of FVC in the assessment and follow-up of patients with IPF. Perhaps total lung capacity and diffusion capacity for carbon monoxide might better correlate to quality of life, but further studies on large cohorts are needed to confirm this hypothesis. Data from the Australian IPF registry, presented at

**Table 2.** Demographics and main clinical features of the patients included in the Swedish Idiopathic Pulmonary Fibrosis Registry

|                        | Men                | Women               | Total               |
|------------------------|--------------------|---------------------|---------------------|
| Patients (N, %)        | 50 (70.4%)         | 21 (29.6%)          | 71 (100)            |
| Age (Median, range)    | 70 (47-86)         | 68.5 (51-84)        | 70 (47-86)          |
| Smoking (N, %)         |                    |                     |                     |
| Never smokers: 12 (24%)|                    |                     |                     |
| Ex-smokers: 30 (60%)   |                    |                     |                     |
| Current smokers: 0 (0%)|                    |                     |                     |
| Missing info: 8 (16%)  |                    |                     |                     |
| Pack-years among ex-smokers (M±SD) | 24.5±14          | 11±11.6             | 20.7±14.6           |
| BMI (M±SD)             | 26.8±3.3           | 27.8±6.8            | 27±4.5              |
| Reflux (N, %)          | 10 (20%)           | 4 (19%)             | 14 (19.8%)          |
| FEV1% of predicted (M±SD) | 77.5±16.9        | 77.5±19             | 77.5±17.3           |
| FVC% of predicted (M±SD) | 70.2±15          | 77.4±20.4           | 72.3±16.9           |
| FEV1/FVC (M±SD)        | 82.2±5.8          | 80±6.2              | 81.5±6              |
| TLC, % of predicted (M±SD) | 64.5±14         | 62.2±12.2           | 70.6±17.3           |
| DlCO%, % of predicted (M±SD) | 50.9±16.9       | 54.5±19.4           | 52.1±17.6           |

M, mean; SD, standard deviation; BMI, body mass index; FEV1%, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC: total lung capacity; DICO%: diffusing capacity of the lung for carbon monoxide.
Acknowledgements

Thanks to a grant from the Swedish Heart and Lung Foundation (Ref. No. 20130706). We thank the Karolinska University Hospital, the Karolinska Institutet and the Quality-Registry-Centre Stockholm (QRC-Stockholm) for the technical support, and the Department of Respiratory Medicine and Allergy at the Karolinska University Hospital for supporting the project by providing resources to hire the registry coordinator. Boheringer Ingelheim contributed with a supporting grant in 2015 and Interunique/Roche supported the translation in Swedish of the K-BILD questionnaire. We thank Dr. Surrinder Birring for allowing the use of K-BILD and for the technical help he offered in implementing K-BILD in our registry. A special thanks to Helène Blomqvist, Margitha Dahl, Gunnell de Forest, Henrik Ryftenius, and Lise-Lotte Ladenfelt Gestrè for their help in the implementation of the registry at the headquarter of Karolinska University Hospital, Solna, Sweden.

The Swedish Idiopathic Pulmonary Fibrosis Registry Group: Stockholm: Giovanni Ferrara, Magnus Sköld, Lisa Carlson, Maria Diakopoulos, Valentina Yasinska, Henrik Ryftenius, Lise-Lott Landenfelt Gestrè, Gunnell de Forest, Margitha Dahl, Helene Blomqvist, Ingrid Gerhardsson, Olov Andersson. Göteborg: Anders Thylen, Kärtist Bystrom; Umeå: Kenneth Nilsson, Lena Granbom, Ala Muula. Uppsala: Shumi Omar, Carl-Axel Karlsson, Inger Dahlen. Gävle: Andreas Palm, Anna Svensson, Kristina Forsberg, Anna Bergengren, Carl Blomberg, Eva Branden, Johan Isaksson, Hirsh Koiy, Johanna Roos, Stefan Soneberg. Falun: Pierre Sobrino, Anders Pettersson, Anders Birkehug, Jon Goenechea, Wolfgang Greger, Gabriel Lundberg, Saba Raouf. Helsingborg: Rolf Rosin, Charlotte Berling, Lars Danielsson, Lena Eldh, Mats Lagerstedt. Lund: Jonas Einarsson, Helena Jonsson, Hillevi Larsson. Linköping: Lennart Persson, Ewa Pettersstedt, Christel Bergström, Antje Kühlmann, Maria Sege. Sandby: Dirk Albrecht, Christos Belias, Cecilia Dahlen. Örebro: Lennart Nilsson, Lena Granbom, Ala Muula. Umeå: Kenneth Nilsson, Lena Granbom, Ala Muula. Upsala: Shumi Omar, Carl-Axel Karlsson, Inger Dahlen. Göteborg: Anders Thylen, Kärtist Bystrom; Umeå: Kenneth Nilsson, Lena Granbom, Ala Muula.

Conflicts of interest and funding

Giovanni Ferrara received honoraria for lectures from Roche. Magnus Sköld received honoraria for advisory board/lectures from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Meda, Novartis, Mundipharma, Sandoz, Chiesi, Almirall, Interunique, Roche and research grants from Boehringer Ingelheim, Roche and Sandoz. None of the other authors has CoI to declare.

References

1. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011; 183: 788–824.
2. Thomeer M, Demedts M, Behr J, Buhl R, Costabel U, Flower CDR, et al. Multidisciplinary interobserver agreement in the diagnosis of idiopathic pulmonary fibrosis. Eur Respir J. 2008; 31: 585–91.
3. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2006; 174: 810–6.
4. Coutlas DB, Zunwald RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med. 1994; 150: 967–72.
5. Griibbin J, Hubbard RB, Le Jeune I, Smith CJP, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax. 2006; 61: 980–5.
6. Hodgson U, Laitinen T, Tukiainen P. Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: evidence of founder effect among multiplex families in Finland. Thorax. 2002; 57: 338–42.
7. Svensk Lungmedicinsk Förråning. Vårdförrånd program för idiopatisk lungfibros [Internet]. Svensk Lungmedicinsk förärling; 2012. Available from: http://www.slmf.se/sites/default/files/VPIL_2013_web_final.pdf [cited 19 January 2016]
8. King TE, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370: 2083–92.
9. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011; 377: 1760–9.1.
10. Richeldi L, Costabel U, Elman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med. 2011; 365: 1079–87.
11. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370: 2071–82.
12. Tandvårds och Läkemedelsförsäkringsverket. Underlag för beslut om subvention – Esbriet (pirfenidone). Available from: http://www.tlv.se/UploadBeslut_2015/underlag-beslut-esbriet.pdf [cited 19 January 2016]
13. Raghu G, Collard HR, Anstrom KJ, Flaherty KR, Fleming TR, King TE, et al. Idiopathic pulmonary fibrosis: clinically meaningful primary endpoints in phase 3 clinical trials. Am J Respir Crit Care Med. 2012; 185: 1044–8.
14. Patel AS, Siegert RJ, Brignall K, Gordon P, Steer S, Desai SR, et al. The development and validation of the King’s Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax. 2012; 67: 804–10.
15. National Cancer Institute. Common terminology criteria for adverse events. National Cancer Institute, US National
16. Wapenaar M, Patel AS, Birring SS, van Domburg R, Bakker E, Sköld M, et al. The King’s Brief Interstitial Lung Disease (K-BILD) questionnaire: the development of Dutch, French, Italian and Swedish versions. [under submission]
17. Ferrara G, Andersson O, Sköld M. Ett svenskt kvalitetsregister för idiopatisk lungfibros (IPF). Lung Allergi Forum. 2014; 4: 67.
18. Ferrara G, Carlsson L, Sköld M. Det nationella Lungfibrosregistret: framsteg och implementering. Lung Allergi Forum. 2015; 4: 53.
19. Sköld M, Ferrara G, Carlson L. Register lanserat för idiopatisk lungfibros. Lung Allergi Forum. 2015; 4: 59–61.
20. Carlson L, Ferrara G. Lungfibrosregistret, ett år! Lung Allergi Forum. 2015; 3: 39.
21. Ferrara G, Carlson L. Nytt register gynnar patienter med lungfibros. Dagens Medicin. 2015; 22: 1.
22. Lungfibrosregistret. Available from: http://www.slmf.se/lungfibrosregistret [cited 19 May 2015].
23. Moodley Y, Goh N, Glaspole I, Macansh S, Walters EH, Chapman S, et al. Australian Idiopathic Pulmonary Fibrosis Registry: vital lessons from a national prospective collaborative project. Respiratory. 2014; 19: 1088–91.
24. Fernández Pérez ER, Daniels CE, Schroeder DR, St Sauver J, Hartman TE, Bartholmai BJ, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. Chest. 2010; 137: 129–37.
25. Kaunisto J, Kelloniemi K, Sutinen E, Hodgson U, Piilonen A, Kaarteenaho R, et al. Re-evaluation of diagnostic parameters is crucial for obtaining accurate data on idiopathic pulmonary fibrosis. BMC Pulm Med. 2015; 15: 92.
26. Glaspole I, Goh N, Hopkins P, Moodley Y, Reynolds PN, Walters EH, et al. Quality of life of patients with idiopathic pulmonary fibrosis (IPF): what can the Australian IPF registry tell us? Amsterdam, Netherlands: ERS. p. OA4964.