Healthcare utilisation and costs in the diagnosis and treatment of progressive-fibrosing interstitial lung diseases

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Data for ILDs with a progressive fibrosing phenotype are lacking, but the burden and healthcare costs associated with these conditions may be comparable to those reported in IPF http://ow.ly/Eoht30mS4Nx

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ABSTRACT There are over 200 interstitial lung diseases (ILDs). In addition to patients with idiopathic pulmonary fibrosis (IPF), a percentage of patients with other ILDs also develop progressive fibrosis of the lung during their disease course. Patients with progressive-fibrosing ILDs may show limited response to immunomodulatory therapy, worsening symptoms and lung function and, ultimately, early mortality. There are few data for ILDs that may present a progressive fibrosing phenotype specifically, but we believe the burden and healthcare costs associated with these conditions may be comparable to those reported in IPF. This review discusses the burden of ILDs that may present a progressive fibrosing phenotype and the factors impacting healthcare utilisation.

Introduction

In recent years, healthcare utilisation has steadily risen, with estimated annual growth between 1.5% and 5.1% reported in the USA between 2011 and 2017 [1]. This trend towards increased expenditure is expected to continue with the ageing of the population and an increased prevalence of chronic diseases [2–6]. In this review, we will discuss the postulated burden of interstitial lung diseases (ILDs) that may present a progressive fibrosing phenotype, and the factors impacting healthcare utilisation. Healthcare utilisation is defined here as the quantity of healthcare services accessed by a population, quantified by assessing the number of hospital admissions per year, medical procedures or tests, physician visits (primary care or specialist, at inpatient or outpatient facilities), and prescription drug use [4, 7, 8].

Within the various ILDs, a subset of patients develop a progressive fibrosing phenotype. This is characterised by progressive pulmonary fibrosis, worsening respiratory symptoms, declining lung function

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and resistance to immunomodulatory therapies [9]. Progressive-fibrosing ILD (PF-ILD) is a terminology recently used to describe patients with fibrosing ILDs that may present a progressive phenotype [9]. Idiopathic pulmonary fibrosis (IPF) can be considered as the prototype ILD, and almost all patients with this disease show progressive fibrosis. The progressive fibrosing phenotype also occurs in variable proportions of patients with other ILDs, who may share a number of similar characteristics with IPF. In addition to the progressive fibrosing phenotype, other similarities have been identified between these patients and those with IPF, including worsening respiratory symptoms, lung function decline and no response to immunomodulatory therapies, leading to a decreased quality of life and potential early death [9]. Other than for IPF, there are limited data on healthcare utilisation and costs relating specifically to ILDs that may present a progressive fibrosing phenotype. Since ILDs that may present a progressive fibrosing phenotype are hypothesised to behave similarly to IPF, the following discussion relies heavily upon extrapolation from the available data, mostly in the IPF population.

Understanding the burden and assessing healthcare utilisation and costs of ILDs that may present a progressive fibrosing phenotype

For fibrosing ILDs with a progressive phenotype, no study has evaluated the collective disease burden relating to progressive fibrosis for all these ILDs, which include: connective tissue disease-associated ILD; chronic fibrosing hypersensitivity pneumonitis; idiopathic nonspecific interstitial pneumonia; unclassifiable idiopathic interstitial pneumonia; and environmental/occupational lung disease (such as silicosis or asbestosis) or sarcoidosis [9, 10]. We believe that the healthcare utilisation and costs for other ILDs that may present a progressive fibrosing phenotype may be similar to those for IPF and therefore report findings known for IPF as a surrogate for detailed information regarding the collective diseases incorporated as PF-ILD [9, 11]. The combined prevalence and duration of ILDs other than IPF with a progressive fibrosing phenotype are likely to equal or exceed those of IPF [12].

The annual medical cost of IPF to the US healthcare system (excluding medication costs) is estimated to be close to USD 1.8 billion, when considering patients over the age of 65 years [13]. This amount was estimated prior to approval and utilisation of efficacious targeted IPF therapies [13]. These annual direct medical costs for patients with IPF in the USA were estimated to be two-fold higher, USD 20 887 *versus* USD 8932, compared with age- and gender-matched controls in the year following IPF diagnosis, with similar increases observed in medical costs, inpatient and outpatient services [13].

Further studies of ILD patients with various forms of PF-ILDs will allow recruitment of a larger patient population than studies of a specific ILD and provide greater insight into healthcare utilisation within the overall population of patients with ILDs that may present a progressive fibrosing phenotype. It would be valuable to couple such studies with the generation of national or regional registries of patients (as is ongoing in IPF) to better define the burden, impact and healthcare utilisation and costs [14].

Domains of healthcare utilisation of ILDs that may present a progressive fibrosing phenotype: gaps and unmet needs

High healthcare utilisation among patients with ILDs, probably inclusive of the PF-ILD phenotype, is attributable to multiple factors including the number of tests needed to reach a diagnosis, disease monitoring, acute exacerbations and comorbidities (figure 1).

Diagnosis and prognosis

The diagnosis of fibrotic ILDs can be challenging [11]. Accurate diagnosis requires a multidisciplinary approach with incorporation of clinical, pathophysiological, immunological and imaging information. This comprehensive testing contributes to the cost of healthcare [15–20]. It has been reported that up to 34% of ILD patients do not receive a final diagnosis for ⩾2 years during which time we anecdotally observe repetition of diagnostic tests and consultations. Despite this, up to 25% of patients remain unclassifiable following extensive investigation, which can be due to conflicting radiological or histopathological data or the unavailability of a lung biopsy [17, 21–24]. The epidemiology of ILDs that may present a progressive fibrosing phenotype is reviewed in [12]. Despite these shortcomings, the avoidance of invasive diagnostic procedures has been advocated where alternative diagnostic approaches are available, and this has the potential to reduce the use of healthcare resources.

Treatment

In general, therapeutic options for ILDs that may present a progressive fibrosing phenotype include anti-inflammatory, immunosuppressive and antifibrotic agents. For IPF there are two approved antifibrotic drugs (nintedanib and pirfenidone), while for other ILDs, unapproved treatment with anti-inflammatory drugs and immunosuppressants is used empirically in the absence of data to confirm the effectiveness of these drugs in patients with a progressive phenotype [25–27]. Other treatment

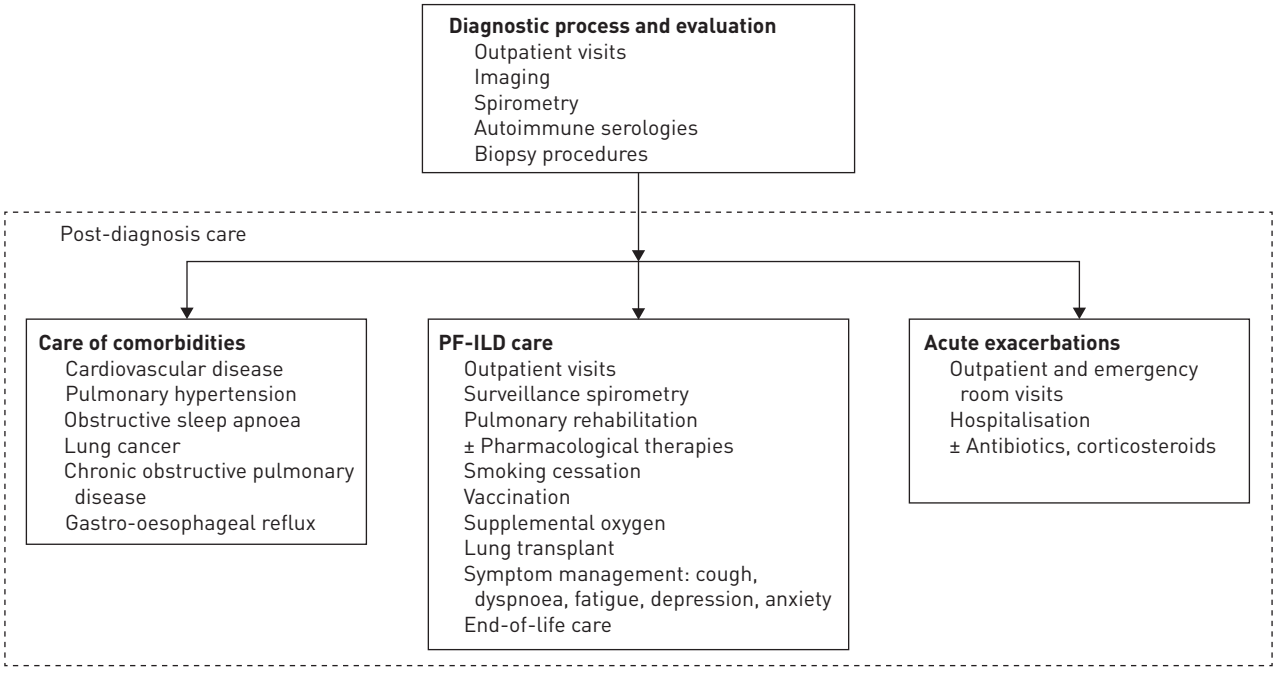

FIGURE 1 Healthcare utilisation for patients with fibrosing interstitial lung diseases (ILDs) with a progressive phenotype. PF-ILD: progressive-fibrosing ILD.

approaches (*e.g.* oxygen therapy or pulmonary rehabilitation) mainly target symptoms and exercise tolerance without altering disease progression [25, 27, 28]. Lung transplantation is an option for certain patients but availability of, and enthusiasm for, this option is limited by eligibility criteria, organ supply, post-transplant survival and a significant post-transplant care burden [15, 29]. Early palliative care appears to increase the likelihood of death occurring at the patient's preferred location (*i.e.* at home or in a hospice) [27, 30]. Palliative care has been advocated as a means of increasing quality of life in the wider population of patients with ILDs [27], and therefore should be considered in those with a progressive fibrosing phenotype.

Many patients with a progressive fibrosing phenotype respond minimally to the currently available therapies resulting in a heterogeneously reduced survival duration [9]. In IPF, median survival rates below 5 years have been observed [15, 31–33].

The targeted antifibrotic therapies, nintedanib and pirfenidone, have shown efficacy in the context of IPF [34–37], further details on pharmacological management of ILDs that may present a progressive fibrosing phenotype are discussed in [38]. Preclinical and clinical data with nintedanib and pirfenidone in IPF have highlighted their efficacy in slowing disease progression [36, 39–44]. Current, ongoing clinical trials of nintedanib and pirfenidone will provide greater insight into the potential benefit of these treatments in ILDs other than IPF that may present a progressive fibrosing phenotype [9, 27]. It is hoped that these treatments will limit disease progression as other ILDs that may present a progressive fibrosing phenotype often share similar clinical, radiographic and histological pulmonary features with IPF. The effect of introducing efficacious therapies for other ILDs that may present a progressive fibrosing phenotype on healthcare utilisation is unknown.

Acute exacerbation

Similar to IPF, acute exacerbation in other ILDs that may present a progressive fibrosing phenotype is proposed to be an acute, clinically significant, respiratory deterioration radiologically characterised by a new widespread alveolar abnormality typically occurring within 1 month in the absence of an apparent clinical cause (*e.g.* pneumothorax, pleural effusion or cardiac overload) [45]. Kolb *et al.* [46] provide a detailed discussion of acute exacerbations. Acute exacerbations occur infrequently, with typical annual incidences between 5% and 15% in IPF [47]. However, they are serious events that have a high impact on patients and on costs; hospitalisation is often required, and the associated in-hospital mortality rates can be up to 50% [45, 48]. Acute exacerbations are associated with similar morbidity in patients with IPF and other ILDs that may present a progressive fibrosing phenotype [48].

Comorbidities

The likely elevation of healthcare utilisation in patients with ILD arises in part from comorbidities in patients with ILD that include cardiovascular disease, malignancy, sleep apnoea and pulmonary hypertension (PH), and contribute to hospitalisations, physician visits and medication use [6, 49, 50]. Again, using the example of IPF, in a recent analysis of healthcare costs and utilisation in patients covered by Medicare in the USA, it was estimated that the total annual medical costs in 2000–2011 were up to USD 3 billion, of which USD 1.8 billion was attributable to IPF and associated comorbidities [13]. For example, World Health Organization group 3 PH is associated with substantially higher healthcare resource use than in control disease-matched patients, particularly in the number of prescription claims, outpatient visits and physician office visits [49]. Prevalence rates of comorbidities in IPF have been published with wide ranges, for example: PH 8–84%; cardiac disease 60%; lung cancer 4.4–10%; and sleep apnoea, 60–90% [49, 50]. Based on a small number of results, rates of comorbidities in patients with other progressive-fibrosing ILDs may be similar to those in IPF.

Conclusions

Healthcare utilisation and costs of ILDs that may present a progressive fibrosing phenotype may be inferred from the similarities shared with IPF, but further studies are needed to clearly establish the burden and healthcare impact of this disease spectrum. Increased recognition of ILDs at risk of a progressive fibrosing phenotype should help advance our understanding. The current therapeutic approaches utilised in patients with progressive-fibrosing ILDs are not well defined; however, antifibrotic therapies could demonstrate potential to address the unmet therapeutic need in these patients. Additional studies are required to further define this distinctive group of patients and to assess the impact of therapies, their effect on disease progression and subsequently on healthcare utilisation.

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