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Idiopathic pulmonary fibrosis (IPF) — common practice in Poland before the "antifibrotic drugs era"

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Abstract

Introduction: Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and debilitating lung disease with a median survival time of 3–5 years. For now, pirfenidone (PIR) and nintedanib (NTB) are the only drugs that can slow down the disease's progression. In Poland, these drugs, although registered for legal use, had not been reimbursed for IPF patients until the end of the year 2016. Aim of the study was to assess what was common practice in terms of diagnosis and treatment in the period before antifibrotic drugs became available for IPF patients in Poland.

Material and methods: We performed a survey among participants of two nationwide pulmonological congresses held in 2016.

Results: One hundred and fifty physicians took part in the study. Only 55% of respondents would reach their final diagnosis in collaboration with a radiologist. Just 40% of those sending patients for surgical lung biopsy (SLB) would discuss the case directly with a pathologist. 22% would never refer the patient suspected of having IPF for SLB. 85% believed that bronchoalveolar lavage (BAL) may be useful for diagnosis. 41% of respiratory professionals would not use any drug for the treatment of IPF patients. 23% of physicians would prescribe corticosteroids in high doses (CS), either in monotherapy or in combination with other drugs. Only 43% of respondents would use antacid drugs in case of symptomatic gastro-oesophageal reflux disease (GERD), and only 11% would prescribe these drugs regardless of GERD diagnosis.

Conclusions: The majority of Polish pulmonologists were not supported by radiologists and pathologists in the diagnostic process. Treatment standards were unsatisfactory, mostly due to a lacking of reimbursement regulations. Further education is necessary to improve management of IPF patients in Poland.

Key words: idiopathic pulmonary fibrosis, diagnosis, treatment, international guidelines, Poland

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and debilitating lung disease, with a median survival time of between 3 and 5 years. According to international guidelines, high resolution computed tomography (HRCT) serves as the main diagnostic tool. After exclusion of known causes of interstitial lung disease (ILD), HRCT allows specialists to make a definite diagnosis of IPF in around 40–50% of cases. Patients with a possible UIP diagnosis based on HRCT evaluation should be referred for lung biopsy [1]. A multidisciplinary discussion is necessary in order to reach a diagnosis in patients with a possible UIP pattern or with features inconsistent with UIP [1]. It is recommended that the multidisciplinary team (MDT) includes specialists in radiology and lung pathology as a minimum, alongside the expert pulmonologist, with the condition

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that both specialists are also ILD experts [1]. It is implied that the diagnostic process is to be completed in an ILD reference centre, following the idea that concentration of rare diseases in one institution increases diagnostic potential and reduces the rate of misdiagnosed cases.

An update of clinical practice guidelines was released in 2015, with new recommendations for treatment [2]. According to this document, only two drugs are recommended for IPF treatment, namely pirfenidone (PIR) and nintedanib (NTB) (a weak recommendation has been assigned to both drugs) [2]. Corticosteroids (CS) in high doses, either in monotherapy or in combination with immunosuppressive (IS) drugs, or so called triple therapy — CS, azathioprine and N-acetylcysteine (NAC), are strongly contraindicated. A strong negative recommendation has been also assigned to such treatments as warfarin, ambrisentan, imatinib and other drugs, based on the results of randomized clinical trials [2]. Based on the several suppositions of the potential role of gastroesophageal reflux disease (GERD) in IPF pathogenesis and progression, it is recommended that all patients are treated with antacid therapy (AAT), regardless of whether GERD symptoms are present or not [2]. Non-pharmacological treatments, such as lung transplantation, home oxygen supplementation and rehabilitation were also assigned positive recommendations.

Today PIR and NTB are available and reimbursed in the majority of European countries. The European Medicine Agency (EMA) approved PIR in 2011 and NTB in 2014 [3]. Although both drugs were registered for legal use in Poland, no reimbursement regulations were in place until the end of 2016. This situation is to change in the foreseeable future, as PIR was approved for reimbursement in selected IPF patients [4]. Neither pharmacological nor non-pharmacological treatment standards, nor standardized diagnostic procedures have been established for Polish IPF patients, with regards to the specificity of the national health service system, and specific patients' needs and expectations. This system, for instance, does not favour any high-level reference medical institutions, which clearly contrasts with a recommendation of building-up local ILD reference centres.

In view of the above, the aim of the study was to explore what was common clinical practice amongst Polish pulmonologists regarding IPF diagnosis and treatment, before the change of regulations allowing the wider use of antifibrotic drugs in IPF patients.

Material and methods

The survey was performed during the Polish Respiratory Society (PTChP, Polskie Towarzystwo Chorób Płuc) Congress, held in May 2016, and during the nationwide symposium organized yearly by Warsaw TB and Lung Diseases Research Institute (June 2016). These congresses bring together pulmonologists and other professionals involved in different fields of respiratory medicine. The questionnaires were distributed at the entrance to the lecture room during the ILD sessions and were collected at the end of the session. In order to prevent double-participation, those who completed the questionnaire during the first congress were asked to refrain from completing the survey during the next symposium.

The survey consisted of 20 questions, divided into three parts: 1. Data describing the physicians responding; 2. Diagnostic procedures; and 3. Possible treatment options. The questions asked in the self-prepared questionnaire are available as an on-line supplement.

Data were presented in absolute numbers and as percentages. The sampling distribution for each answer in relation to different characteristics of respondents was checked by Pearson's Chi-squared test with Yates continuity correction. A p-value of < 0.05 was considered to be statistically significant.

Results

Description of respondents

One hundred and fifty physicians took part in the study. 111 (74%) were above 40 years old. 127 (85%) declared having a specialization in pulmonary medicine. 75 physicians (50%) worked in non-academic hospitals, 45 (30%) represented academic centres or research institutions. Ninety (60%) declared being employed, solely or simultaneously, in pulmonological out-patient clinics. Professional experience in pulmonary medicine of 40% of respondents was shorter than 10 years. Only 13 respondents (< 8%) admitted not having been involved in diagnosis and treatment of ILD. From those who were involved in ILD diagnosis and treatment, 52% declared having managed less than 5 IPF patients per year, whereas only 12 respondents (< 9%) were involved in the management of more than 20 IPF patients per year. From those who never or only seldom diagnose ILD patents, 20 out of 79 (25%) referred patients to an institution of a higher reference grade. 58 (73%) decided to perform a chest HRCT, and only when

Table 1. Characteristics of respondents

Question	Answer	n	(%)#
Age [years]	< 30	6	4
	30–40	33	22
	41–50	51	34
	51–60	42	28
	> 60	18	12
Specializations*	None	5	3
	Internal medicine	98	65
	Pulmonary medicine	127	85
	Allergology	11	7
	Family medicine	1	< 1
	Other	4	3
Place of work*	Hospital — academia/research	75	50
	Hospital — non-academic/ /non-research	45	30
	Pulmonary out-patient	90	60
	Family practice	11	7
	Other	8	5
Professional experience in pulmonary medicine (years)	< 5	36	3
	6–10	24	16
	11–20	37	25
	21–30	37	25
	31–40	11	7
	> 40	5	3
Involved in ILD diagnosis and treatment?	Yes	88	59
	Sometimes	49	33
	Never	13	8
If involved — number of IPF patients per year	< 5	71	47
	6–20	61	41
	21–50	11	7
	51–100	1	< 1
	> 100	0	0

*the sum of particular items does not equal 100%; #rounded to a whole number

the suspicion of ILD/IPF was remained did they then refer patients to a higher-grade centre. Those employed in academic centres more often declared having taken care of > 20 IPF patients during last year. The detailed data from this section are shown in Table 1.

IPF diagnosis

144 of 150 (93%) participants considered HRCT as essential for IPF diagnosis, and the rest of the study group would perform this examination in selected patients only. In the opinion of

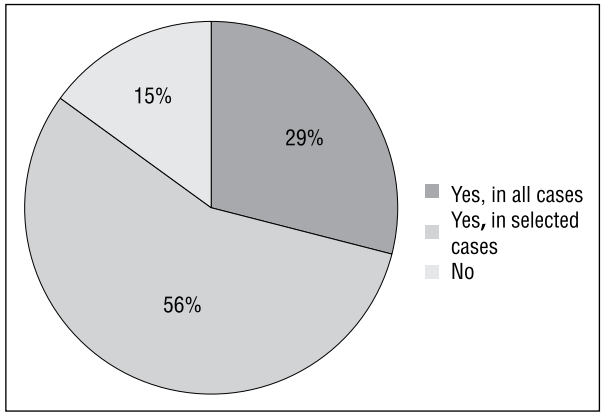

Figure 1. The percentage of answers to the question: Do you agree, that bronchoalveolar lavage (BAL) is necessary in the differential diagnosis of idiopathic pulmonary fibrosis (IPF)?

116 respondents (77%), body plethysmography and DLCO are indispensable in a clinical work-up of IPF patients, and 4 respondents (< 3%) believe that these examinations are unnecessary. Almost all respondents (148, above 98%) believe that a 6-minute walking test should be carried out, at least in selected patients suspected of IPF. With regards to the use of bronchoalveolar lavage (BAL) examination in the diagnosis of IPF, 43 respondents (29%) would perform BAL in all cases, 85 (56%) in selected patients, and 23 (15%) believe that BAL is unnecessary (Fig. 1).

Almost 23% of respondents never refer patients for surgical lung biopsy (SLB), 108 (72%) would do so for selected patients, and 8 (5%) always refer patients for SLB. 6 respondents (4%) declared that they make diagnoses without consultation with other specialists, 93 (62%) discuss the case with other pulmonologists, and 82 (55%) respondents discuss it with a radiologist (Fig. 2). When the patient was referred for a lung biopsy, only 60 (40%) would discuss the results (in face-to-face or a telephone conversation) with a pathologist. Patients were referred for surgical lung biopsy more often by physicians from academic centres ($p = 0.03$). Physicians from academic centres would also discuss the diagnosis directly with a pathologist more often when a biopsy is performed ($p = 0.03$). Specialists in pulmonary medicine would consult with radiologists experienced in ILD diagnosis more often ($p = 0.01$), as would doctors from academic centres ($p = 0.03$). The group of physicians aged 51–60 years would discuss the IPF diagnosis with other pulmonologists less frequently when compared with the other age groups ($p = 0.02$).

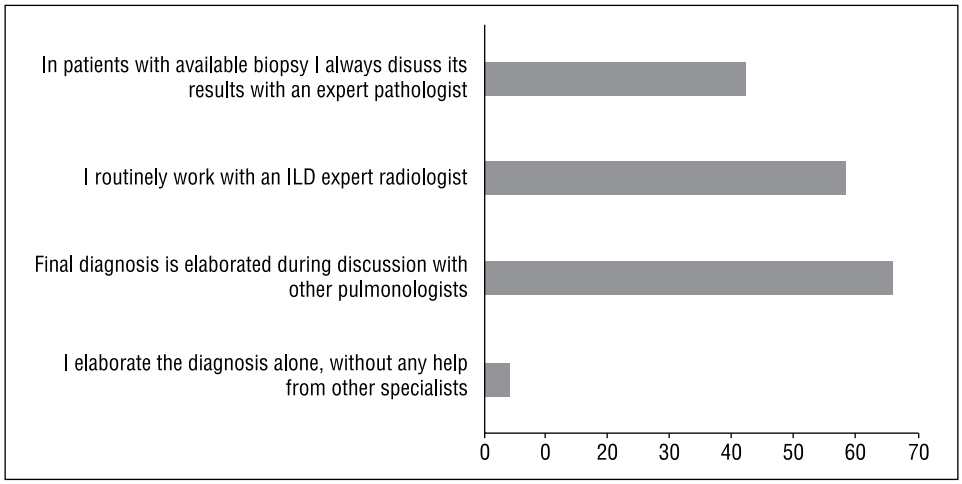

Figure 2. The percentage (x-axis) and number of positive answers (in bars) to the question: Are you assisted by other specialists in the diagnostic process? (multiple choice questions, n = 141)

IPF treatment

Oxygen therapy as an option for IPF patients with signs of chronic respiratory failure at rest would be recommended by 124 (83%) of physicians, and 25 respondents (17%) would recommend oxygen therapy only for those who present hypoxemia with physical effort. Oxygen therapy for patients with exercise hypoxemia would be recommended more often by specialists in pulmonary medicine (p = 0.01). Only 31 respondents (21%) would refer IPF patients to a rehabilitation centre, and 111 (74%) would recommend simple forms of physical activity. 7 respondents (< 5%) would not try to send a patient for rehabilitation due to a lack of rehabilitation units/centres in the close vicinity of their institution (Fig. 3).

More than half of respondents (57%) would refer a patient with IPF for lung transplantation in case of rapid deterioration, and 2 respondents would refer all patients as soon as the IPF diagnosis is confirmed. As many as 46 respondents (31%) would never refer a patient for lung transplantation because, in their opinion, the access to transplantation centres in Poland is too limited. 6 respondents (4%) do not believe in the effectiveness of this treatment approach, or they do not refer their patients to transplantation centres due to their own religious or ideological concerns (Fig. 4). Doctors from academic centres would refer their patients for transplantation more often (p = 0.00519).

Still, 13 respondents (9%) declared having treated patients with high doses of CS, 16 (11%) recommended CS with immunosuppressive drugs, and 6 (4%) declared having recommended triple therapy (CS+AZA+NAC). Low doses of CS were recommended by 28 respondents (19%),

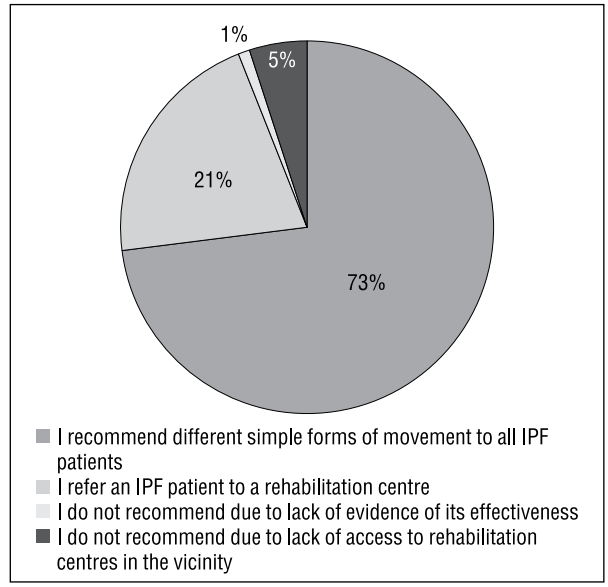

Figure 3. Proportions of answers to the question about pulmonary rehabilitation

mostly as symptomatic treatment for cough. Steroids in monotherapy or in different combinations were recommended by 43% of respondents. Sixty-five (43%) of respondents would use AAT, but only 11% would prescribe this therapy exclusively for patients with symptomatic GERD. 62 (41%) would not use any treatment, mainly because effective drugs are not available (Fig. 5).

Only 17 respondents had ever met a patient treated with pirfenidone, and in all cases the drug was used as part of a clinical trial. Only two respondents had ever met a patient treated with nintedanib.

Academic physicians declared more often than not that they would recommend some type of treatment (p = 0.003).

Discussion

The idea of performing this survey was prompted by the 2013 Advancing IPF Research (AIR) survey arranged by Vincent Cottin, whose results were published in 2014 [3]. The aim of this survey was to assess current approaches to the diagnosis and treatment of idiopathic pulmonary fibrosis (IPF) by experienced physicians. The author confirmed a high level of multidisciplinary team involvement in both diagnosis and management amongst Western European pulmonologists, however it also showed that some improvement in early diagnosis is needed. There was also a follow-up survey showing improvement in the adherence to guidelines, mainly with a significant decrease of the use of steroids, increase in the proportion of patients treated with pirfenidone, and more frequent involvement of multidisciplinary teams in the diagnostic process [4].

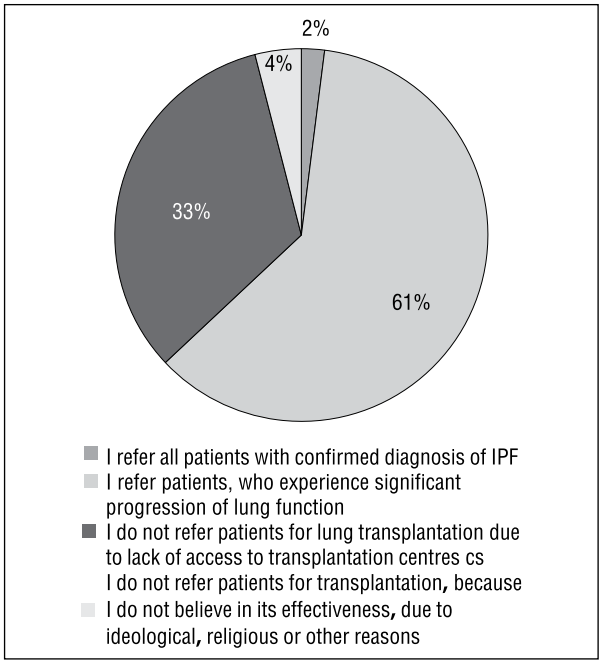

Figure 4. Proportions of answers to the question about lung transplantation

Our survey was designed to answer the question of how Polish physicians (mostly specialists) deal with the diagnosis and treatment of IPF in the specific situation where neither PIR nor NTB were available for IPF patients due to a lack of reimbursement regulations, regardless of positive recommendations from international guidelines. In the first part of the survey, we confirmed that proper diagnostic tools are used for the IPF diagnosis and clinical work-up. The percentage of respondents indicating BAL as an important diagnostic tool seems to be high. Although IPF international guidelines do not recommend BAL in the majority of IPF patients, placing a high value on the additional risk and cost of BAL in patients with IPF and a low value on possible improved specificity of diagnosis, this trend is in line with many reports pointing out the necessity of differentiation between IPF and chronic hypersensitivity pneumonitis (cHP), where higher lymphocyte percentage is observed [1, 5].

As many as 72% of respondents refer selected patients for SLB, which is in line with international recommendations [1], which prompts one to consider surgical lung biopsy not only in patients with a pattern inconsistent with UIP but also in those with a possible UIP pattern (when there is

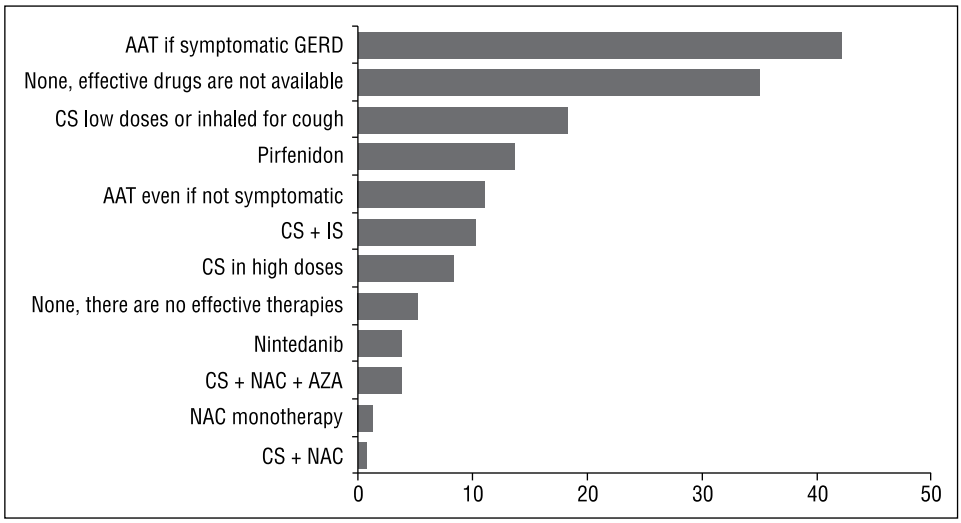

Figure 5. The percentage of answers to the question: What drugs do you use in the treatment of idiopathic pulmonary fibrosis (IPF)? (multiple choice questions). AAT — antacid therapy; AZA — azathioprine; CS — corticosteroids; GERD — gastroesophageal reflux disease; IS — immunosuppressive drugs; NAC — N-acetylcysteine

no honeycombing, but all other criteria for UIP are met).

The need for a multidisciplinary team, consisting of a pulmonologist, a radiologist and a pathologist is emphasized in the guidelines [1]. All these specialists should have vast experience in the field of ILD. In our survey only about 55% of respondents had the option of consulting the IPF diagnosis during discussion with an experienced radiologist, and only 40% of those who refer their patients for lung biopsy (either always or in selected cases) discuss the results with a pathologist. These results show the necessity of building up the real multidisciplinary teams in Polish pulmonary centres, which aspire to achieve the reference standard. This process may take a long time, as it usually takes a few years to gain enough experience in this area.

Given that the survey was performed before antifibrotic drugs were available for Polish IPF patients, it is obvious that Polish pulmonologists could not comply with the recommendation for the use of antifibrotic drugs in the treatment of IPF.

In total, 24% of respondents still used high doses of steroids or other immunosuppressive agents, which was clearly against guidelines. This percentage was even higher in the first AIR survey, reaching 49 % in total [3]. Increased availability of antifibrotic drugs in France and other Western European countries has reduced the use of other therapies in follow-up to 7% [4]. AAT is recommended for all patients with IPF, regardless of whether the disease is symptomatic or not. This recommendation was sustained in a document updated in 2015 [2]. Although the role of recurrent microaspirations due to GERD in the pathogenesis of IPF and its progression is not fully explained, there are strong data supporting this hypothesis [6, 7]. Therefore, due to the vast availability of these drugs, low costs and possible protection against the progression of lung fibrosis, these drugs should be used more widely. In our survey only 43% of physicians prescribed AAT, and only 11% did so in patients without gastrointestinal symptoms.

Where non-pharmacological treatment is concerned, home oxygen therapy, pulmonary rehabilitation and lung transplantation are recommended for IPF patients who meet specific indications [1, 2]. Oxygen in those with significant resting hypoxemia is indicated (strong recommendation, very low-quality evidence), but specific criteria in terms of PaO_2 threshold or duration of supplementation (hrs per day) have not been established in IPF. In practice, general criteria for home oxygen therapy are used, which are elaborated based on the population of COPD patients. Although there are no clear data showing that oxygen supplementation in IPF patients improves survival rates, it may improve exercise tolerance [8]. There is an assumption that exercise tolerance and quality of life may be improved by the use of mobile oxygen sources during exercise, especially in those with significant exertional hypoxemia, but strong evidence supporting this opinion is lacking. Nevertheless, although the majority of respondents would recommend oxygen supplementation in IPF patients with resting hypoxemia, only 83% of those patients with doubtless indications for oxygen therapy would be prescribed domiciliary oxygen.

Pulmonary rehabilitation is also recommended in IPF patients by international guidelines (weak recommendation, low-quality evidence) [1, 2]. There are a few studies showing improvement in walking distance, symptoms and quality of life [9, 10]. Pulmonary rehabilitation clearly exceeds "simple forms of physical activity" and involves aerobic conditioning, strength and flexibility training, educational lectures, nutritional interventions, and psychosocial support. IPF warrants easier access to dedicated rehabilitation centres, but this condition is difficult to meet due to a lacking of such centres (the authors are aware of a maximum of 3–5) in Poland. The results of our survey reflect this poor state of Polish rehabilitation, as only 21% of respondents would send the patient to a rehabilitation centre and the majority would recommend simple forms of physical activity.

It is of note that lung transplantation is recommended by international experts for appropriate patients [1]. Referral for transplantation is encouraged in appropriate patients at the time of diagnosis, and detailed evaluation for lung transplantation should occur in a timely manner at the first sign of any deterioration [1], for instance in those with > 10% decrease in FVC in the last 6 months or after experiencing acute exacerbation. In our study as many as 31% of respondents would not refer patients for lung transplantation due to poor access to transplantation centres. This problem requires further detailed analysis.

In conclusion, the majority of Polish physicians who are involved in the diagnosis and treatment of IPF patients are aware of the most important international guidelines' recommendations. The survey shows that the involvement of other specialists in the process of differential diagnosis is insufficient. Treatment standards were not met, mainly due to a lack of access to

antifibrotic therapies. Further education is indicated to improve treatment standards. The authors would like to follow-up on the situation in this field by the use of a repeated survey in the future.

Conflict of interest

This study was supported by Boehringer-Ingelheim, Poland.

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