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New treatments in idiopathic pulmonary fibrosis

Noi tratamente în fibroza pulmonară idiopatică

Abstract

Idiopathic pulmonary fibrosis is a chronic fibrotic pulmonary disease of unknown origin, with an unfavourable prognosis, leading to death by respiratory failure in most patients within 3-5 years ofdiagnosis. Several drugs were studied for the treatment of this disease, and most of them were not able to stop the relentless evolution of the disease (warfarin, corticosteroids in combination with azathioprine, N-acetylcysteine, ambrisentan, bosentan, sildenafil, antiacids).
Two novel drugs, pirfenidone and nintedanib, proved effective in reducing lung function decline, improving the patient's quality of life, and increasing the patient's probability of survival. These drugs were approved by international health authorities for use in the treatment of IPF patients.
The paper refers also to the status of IPF patients in Romania, where epidemiological data are not known, and where the disease is most likely severely underdiagnosed. Patients are typically diagnosed late, and are therefore in advanced stages of the disease. A proactive attitude, in favour of identification and early diagnosis of IPF patients is highly needed in order to offer to these patients the opportunity of treatment, improved survival, and a better quality of life.
Keywords: idiopathic pulmonary fibrosis, pirfenidone, nintedanib

Rezumat

Fibroza pulmonară idiopatică este o boală pulmonară cronică fibrozantă de cauză necunoscută, cu prognostic nefavorabil, majoritatea pacienților decedând prin insuficiență respiratorie la 3-5 ani de la data diagnosticului. Pentru tratamentul acestei boli au fost studiate numeroase molecule, foarte multe dintre ele nefiind capabile să dovedească o eficacitate în împiedicarea evoluției inexorabile a bolii (warfarină, combinația corticosteroizi – azatioprină, N-acetilcisteină, ambrisentan, bosentan, sildenafil, terapiile antiacide). Două noi molecule, pirfenidona și nintedanib, au reusit să demonstreze o eficacitate în reducerea declinului parametrilor funcționali, ameliorarea calității vieții și creșterea supraviețuirii. Aceste medicamente au fost aprobate de autoritățile medicale pentru tratamentul pacienților cu FPI. Articolul face referire la situația pacienților cu FPI din România, unde datele epidemiologice nu sunt cunoscute, boala este probabil sever subdiagnosticată, iar pacienții sunt diagnosticați tardiv, în stadii severe de boală. Este necesară o atitudine activă pentru identificarea și diagnosticul precoce al pacienților cu FPI în România, pentru a le oferi șansa la tratament, creșterea supraviețuirii și ameliorarea calității vieții.
Cuvinte-cheie:** **fibroză pulmonară idiopatică, pirfenidonă, nintedanib.

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Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic pulmonary disease of unknown cause affecting adults. IPF is one of the most aggressive interstitial diseases, having a progressive, relentless, and relatively rapid evolution towards an invalidating lung fibrosis that induces respiratory failure and premature death, typically within 4 years after diagnosis. From this perspective, IPF is comparable with most aggressive cancers.

IPF is included in the group of idiopathic interstitial pneumonias, according to the classification of the International Committee for IPF[1].

The epidemiology of the disease is difficult to estimate, mainly due to the diagnosis difficulties that lead to underestimation of the disease. IPF can be confused with more common cardiovascular diseases accompanied by shortness of breath, or with other interstitial lung diseases. The frequent changes of the definition, as well as the complex diagnosis algorithm are challenges for epidemiological studies.

Available epidemiological studies suggest a top position of IPF among interstitial lung diseases. In the United States, epidemiological studies based on health insurance reporting according to ICD codes showed a prevalence of 42.7 in 100,000 persons and an incidence of 16.3 in 100,000 persons, with lower numbers if narrow criteria for diagnosis were used (14 %000 and 6.8%000 respectively)[2]. In Europe, the incidence varies between 4.6%000 in United Kingdom, 4.3%000 in Norway, 0.9%000 in Greece and 4.9%000 in Turkey. The prevalence recorded is 23.4%000 in Norway, 16-18%000 in Finland and 3.4%000 in Greece[3].

Mortality is difficult to assess based on death certificates due to uneven coding. It has values of 5.08%000 in the United States and 5.1%000 in the United Kingdom[3]. The mortality value is similar to the incidence; an increase in mortality is noted in the past decade.

In Romania, epidemiological data for IPF are completely missing. A first attempt to collect these data is currently performed by the use of an on-line national

Table 1 Combined HRCT and histology criteria for the diagnosis of IPF

HRCT pattern	Histology pattern	IPF diagnosis
UIP	UIP	YES
	Probable UIP	
	Possible UIP	
	Nonclassifiable fibrosis	
	Not UIP	NO
Possible UIP	UIP	YES
	Probable UIP	
	Possible UIP	Probable
	Nonclassifiable fibrosis	
	Not UIP	NO
Inconsistent with UIP	UIP	Possible
	Probable UIP	NO
	Possible UIP	
	Nonclassifiable fibrosis	
	Not UIP	

UIP: HRCT and histologic pattern, characteristic for IPF

registry for interstitial lung diseases and sarcoidosis (REGIS), developed by the Working Group for ILD and Sarcoidosis of the Romanian Society of Pulmonology[4].

The cause of the disease is considered unknown. However, there are several risk factors associated with IPF. Advanced age is considered a risk factor by itself due to the fact that IPF is considered more and more as an abnormal aging process of the lungs.

Other relevant risk factors associated with IPF are smoking, gastro-esophageal reflux, and several professional exposures, as metallic dust, cosmetics, agricultural, or wood dust[3].

Genetic factors could have an influence on the development of IPF. Familial IPF represents less than 5% of the cases, but also in sporadic IPF one can assume that a particular response of the lungs against an unknown aggression, leading to fibrosis, might be driven by genetic factors, such as shortened telomeres following several mutations (TERT, TERC, MUC5B)[5].

Diagnosis of IPF is difficult and involves complex investigations. The correct and complete diagnosis is only accessible to well-equipped centers with expertise in the management of patients with ILDs, and should only be confined to these centres.

High resolution computer tomography (HRCT) is currently considered the cardinal test for the diagnosis. The typical pattern for IPF consists in fibrotic changes (traction bronchiectasis and honeycombing) distributed in the subpleural space and in the lower lobes, and in the absence of other inflammatory features (ground glass, infiltrates, nodules). The typical imaging pattern, described as UIP pattern (from the histologic term "usual interstitial pneumonia") is considered the most important diagnostic criterion, even more powerful than lung biopsy.

Lung biopsy is mandatory for the cases where the other diagnostic elements (clinical features, history, HRCT, broncho-alveolar lavage) fail to point to a diagnosis. The typical histology findings suggesting IPF (UIP pattern) consists of an evidence of marked fibrosis, architectural distortion, honeycombing, in a predominantly subpleural or paraseptal distribution, patchy involvement of the lung by fibrosis, presence of fibroblastic foci, and absence of other features suggesting an alternative diagnosis (inflammatory infiltrates, organizing pneumonia, airway centered changes).

The International Committee for IPF designed a diagnosis algorithm based on HRCT and lung biopsy findings in order to obtain the most accurate IPF diagnosis (table 1)[1]. However, this algorithm can be criticized, because some patients will be classified as "probable IPF" or "possible IPF", and these terms do not offer to the clinician an exit from the algorithm towards a well sustained therapeutic attitude.

The evolution of IPF is heterogeneous, but most patients have a progressive aggravation over several months or years, with a mean survival of 3 to 5 years from the moment of the diagnosis[6]. In some patients, the evolution is marked by an acute exacerbation that induces a severe respiratory failure that is fatal in about 80% of the cases[6]. Survival after 10 years is less than 15%. No spontaneous resolution of the disease has been cited.

Major cause of death is respiratory failure, seen in 72% of the cases[7]. Among other causes of death are embolism, cardiac failure, cerebral stroke, and lung cancer[7].

Treatment

The past decades witnessed a great amount of research aiming to identify an efficient treatment for IPF.

In the times of "pioneering" in the field of interstitial lung diseases, most cases were treated with high doses of corticosteroids or with associated immunosuppresants. The very non-specific diagnosis of "fibrosis" was typically accompanied by the assumption that a more specific diagnosis is not needed, as long as all these diseases, including in an unstructured bulk IPF, NSIP (non-specific interstitial pneumonia), chronic hypersensitivity pneumonitis, sarcoidosis and other, could be pushed into the "big pot" of diseases treatable with cor-

ticosteroids. However, at that time a perception emerged that some cases improve or are stabilized, while other have a deleterious evolution despite treatment. In 2005, the year when the IFIGENIA study was published, the combination of oral corticosteroids and azathioprine was considered the "standard of care" for IPF patients. This meant that patients were carrying the burden of the side effects of corticosteroids without seeing any improvement of their condition.

In was only in 2012 when it was unequivocally proven that treating IPF patients with a combination of corticosteroids, an immunosuppresant – azathioprine, and N-acetylcysteine (the triple therapy) is worse than inefficient for these patients.

The PANTHER study included IPF patients in three study arms: triple therapy, N-acetylcysteine alone and placebo, and demonstrated that the frequency of exacerbations and mortality were significantly higher in the triple therapy arm as compared to placebo. This led to the premature stop of the study for the triple therapy arm[8].

These findings demonstrated clearly not only the lack of efficiency of immune suppression in IPF, but also its potential harmful effects for these patients.

The decision to prematurely interrupt the study had, of course, a strong ethical reason.However, there are still a few questions that were raised by the study that need answers: was the number of patients sufficient for a significant conclusion? Was there a selection bias, allowing the inclusion of more severe patients in the trial, with a more unfavourable outcome? Even in the triple therapy arm of the study some patients showed a favourable evolution, which raises another question: did all patients have IPF, or were there some with fibrotic NSIP, which could respond well to the aggressive immune suppression?

The conclusions of the PANTHER study imposed the revision of the international guidelines for IPF management, changing the recommendation for triple therapy from "weak against" to "strong against"[9].

The disastrous conclusions of the study strongly highlighted the importance of a sound and confident diagnosis of any interstitial lung disease in everyday practice: away from the old concept of "big pot" of diseases treatable with steroids, it is of maximum importance to define, before any treatment, if an individual patient suffers from IPF (and corticosteroids are contraindicated) or from another confounding interstitial disease (that may benefit from immune suppression).

In the race to find a cure for IPF, many drugs were tested: warfarin, interferon, bosentan, ambrisentan, proton pump inhibitors, N-acetylcysteine, and others.

Based on the findings that a procoagulant status could promote fibrosis, anticoagulant treatment was tested for IPF. A clinical trial initiated in 2011, using warfarin, was prematurely stopped due to lack of any proof of efficacy coupled with a harmful potential, the active treatment arm showed a higher rate mortality than the placebo group at interim analysis[10].

N-acetylcysteine (NAC) was the subject of a large clinical trial, IFIGENIA, published in 2005[11]. The results suggested a significant positive effect of adding NAC to what was considered at the moment "the standard of care", corticosteroids and azathioprine, in IPF patients. A net difference of 9% on forced vital capacity (FVC) and of 24% on alveolar diffusion capacity (DLCO) between the active arm and placebo was recorded. The results strongly encouraged the use of this antioxidant in IPF.

However, if we regard the results from the perspective of the premature stop of PANTHER study due to the deleterious effect of the triple therapy, one can comment that IFIGENIA trial only showed some protective effect of NAC against the negative action of the combination corticosteroids – azathioprine in these patients.

PANTHER study continued with the NAC and placebo arms until it was completed (for 60 weeks) without demonstrating a superior efficacy of NAC in monotherapy versus placebo on vital capacity and DLCO[12].

A high proportion of endothelin receptors ET-A and ET-B were found in the IPF lungs, so it was suggested that endothelin receptor antagonists (ambrisentan, bosentan, macitentan) might help prevent the fibrotic process. A clinical trial with ambrisentan was prematurely stopped because of the higher mortality and disease progression, judged by lung function decline, in patients on the active treatment arm as compared to placebo[13]. The trials testing bosentan or macitentan didn't manage either to prove a higher efficacy than placebo on mortality, disease progression, and lung function decline[9].

Sildenafil, a phosphodiesterase 5 inhibitor, successfully used in the treatment of pulmonary hypertension, was tested in several small trials on IPF. Their cumulative results suggest a favorable effect of sildenafil on the quality of life, with no influence on mortality, frequency of exacerbations, or disease progression[14].

The use of antacid therapy in IPF patients seems to be a logical option based on the finding that most IPF patients (over 80%) have a gastro-esophageal reflux, asymptomatic in many cases. Acid reflux, associated to micro aspiration of gastric content into the lungs, might favor peripheral lung injuries and aggravate, or even initiate, the fibrotic process of the lung parenchyma.

Several observational studies, including a small number of cases, as well as some case studies, suggested a clear beneficial effect of the use of proton pump inhibitors (PPI) in patients with IPF, due to the fact that it is associated with stabilization of FVC and improved survival[15].

Also, fundoplication was considered as an option for improving the evolution of IPF because it is able to prevent acid and non-acid reflux as well. However, the risks of the surgery and the possible side effects that may impair patient's quality of life need to be considered carefully.

Based on the findings of these trials, the International Committee recommends the use of PPIs in all patients with IPF, regardless of the presence of reflux symptoms[9].

Nevertheless, this recommendation elicits some controversy nowadays. The recommendation is based on small and uncontrolled studies and on anecdotal observations, and doesn't take into account the possible negative effects of long term PPI treatment: favoring infection (including pneumonia) by affecting gut microbiota, possible drug-drug interactions with the novel antifibrotic drugs, influencing their intestinal absorption[16].

None of the drugs tested, mentioned above, showed any significant efficacy when compared with the placebo groups. Moreover, several trials needed to be stopped prematurely due to the unfavorable effect on the IPF patients.

This long list of failed drugs, along with the long time spent with their unfruitful research, seemed to describe IPF as an unlucky disease. Diagnosing a patient with IPF became synonymous with the contemplation of the relentless evolution of the disease, interrupted, maybe, only by the lung transplantation.

Fortunately, two drugs managed to break through this barrier, giving hope to IPF patients: pirfenidone and nintedanib.

Pirfenidone is a small drug with an antifibrotic effect, reducing fibrosis by stopping the production of growth factors and procollagens I and II. The very first trials were performed in Japan on a limited number of subjects[17,18]. Their positive results encouraged the pharmaceutical companies involved (InterMune, later taken over by Hoffmann La Roche) to develop a series of large clinical trials known asthe CAPACITY trials that allowed the drawing of coherent conclusions regarding the efficacy of the drug.

CAPACITY trials 004 and 006 included a total of 779 patients with IPF in 3 continents, receiving pirfenidone 2403 mg/day, or 1197 mg/day, or placebo, for 72 weeks. The parameters evaluated were: FVC and DLCO decline rate, progression-free survival, 6 minute walk test (6MWT), dyspnea, mortality, and adverse effects. The two trials were similar in many aspects so the patients in the two groups (pirfenidone 2403 mg/day and placebo) could be cumulated, leading to more confident and statistically significant conclusions.

Thus, the primary objective, the influence on the FVC decline at 72 weeks, was attained, showing a statistically significant efficacy of pirfenidone (decline of -8.5%) as compared to placebo (-11%) (p=0.005), the effect being noted after the first 24 weeks of treatment.

Pirfenidone 2403 mg/day is able to prolong progression-free survival, with a decrease of 26% of risk of death or disease progression as compared to placebo. A positive effect was also recorded on the 6MWT.

Regarding the global mortality, the results favor pirfenidone, but do not reach the statistical significance threshold (p=0.141 for any cause mortality and p=0.030 for mortality related to IPF).

Adverse effects were present in all patients; the most frequent complaints were nausea and rash, which were encountered more often in the pirfenidone arm than the placebo. From the active treatment group, 15% of patients prematurely interrupted the study due to adverse effects, compared to 9% in the placebo group[19].

The CAPACITY trials were continued in the form of open-label studies, confirming the capacity of pirfenidone to significantly reduce the decline of lung function. In effect, some of the patients initially enrolled in CAPACITY trials, continuing in the open-label trials, had survivals over 10 years on treatment, suggesting for the first time that IPF can be switched from a deadly disease to a chronic disease with long-term evolution[20].

Nintedanib, developed by Boehringer Ingelheim, was initially used in oncology in the therapeutic schemes for non-small lung cancer. It is an intracellular inhibitor of several tyrosine-kinases, targeting the receptors of some growth factors: vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR), and platelet derived growth factor receptor (PDGFR). The mechanism of action involves the inhibition of the pathways leading to the development of pulmonary fibrosis.

The first large clinical trial on nintedanib[21] used different daily dosages (50, 100, 150 and 300 mg/day versus placebo), being able to prove for all doses a similar efficacy over mortality, FVC decline rate, and frequency of exacerbations proved to be significantly better than placebo. The adverse effects, mainly digestive, were more frequent in the active arm, but without statistical significance.

INPULSIS-1 and INPULSIS-2 trials[22] included a total of 1,066 patients, treated with nintedanib 150 mg bid versus placebo for 52 weeks. These trials demonstrated significant favorable effects on lung function decline, with a mean annual decline of FVC of 114.7 ml as compared to 239.9 ml in the placebo group. The effects on mortality and frequency of exacerbations were no longer as obvious as in the first trial. The adverse effects were more frequent in the active group than in the placebo group, and were primarily nausea and diarrhea. For the management of digestive symptoms, temporary reduction of daily dosage to 100 mg bid was tried, with a positive response in the majority of cases.

INPULSIS trials were continued through INPULSIS-ON trial, which is still ongoing. All patients participating in INPULSIS trials were invited to continue an open-label nintedanib treatment, 150 mg bid. This study had a more flexible inclusion criteria, which allowed the evaluation of patients with a FVC < 50% predicted at inclusion. It was noted that the reduction of the lung function decline was similar to that already demonstrated in the INPULSIS trials[23].

The two drugs were approved by the international authorities (FDA and EMA) for the treatment of IPF and were marketed in Europe and the United States, and are available under several trade names. For pirfenidone:

Esbriet (Europe, Canada and United States), Pirespa (Japan), Pirfenex (India), Etuary (China). For nintedanib: Ofev or Vagatef (for lung cancer).

Undoubtedly, the emergence of active drugs for IFP is good news. Nevertheless, the clinical trials dedicated to their study demonstrate overall only their efficacy in reducing the decline of functional parameters, but they do not show a return to the patient's initial state of health or even an improvement in the patient's condition. This can lead to an unfavorable subjective perception for the patients: after starting the treatment, they don't feel better than before; they continue to complain of exercise dyspnea, and vital capacity continues to deteriorate. Patients can only trust their physician, who assures them that without treatment it would be even worse.

Another significant problem with these drugs is the very high cost. Both pirfenidone and nintedanib are too expensive to be bought directly by the patient from pharmacy on a long term. A prescription reimbursed by the health authorities or health insurances is needed, based on guidelines that respect strictly the diagnosis criteria for IPF.

Currently, no studies are available regarding the efficacy of these drugs in other lung fibrosing diseases (fibrotic NSIP, chronic hypersensitivity pneumonitis, systemic sclerosis with lung involvement etc.).

CAPACITY and INPULSIS trials only included patients with mild and moderate IPF, with CV > 50% predicted and DLCO > 35% predicted. It is not yet clear what would be the effect of the drugs in patients with severe IPF.

Considering that both pirfenidone and nintedanib only manage to slow the progression of the disease, it is essential that the diagnosis of IPF should be established as early as possible, and treatment started when the patient still has a preserved ventilatory function. It is very likely they will need the treatment for the rest of their lives.

In Romania, the status of IPF patients seems to be even worse. Patients with IPF seem to be difficult to find, as experienced recently by the author, who had some difficulties in recruiting IPF patients for a clinical trial. In the past two years a national electronic registry was created in order to include the patients with various interstitial lung diseases from all over the country. The registry (REGIS)[4] is based on the voluntary inclusion of cases by the physicians that are caring for ILD patients in the main expertise centers in Romania (Bucharest, Timisoara, Constanta, Cluj).

A recent unpublished study (the graduation paper in 2016 of a medical student in Bucharest) analyzed the ILD cases included in the registry in 2015. Only 27.94% patients were diagnosed with IPF, fewer than sarcoidosis. The analysis of the profile of these patients brings many concerns: more than half of the patients were diagnosed after more than 12 months from the onset of symptoms, which suggests that meanwhile they were considered as having a different heart or lung disease. Some of them had complex cardiologic investigations, including heart catheterization, and even in the absence of a cardiologic diagnosis, they were not referred to a respiratory specialist. The lung function in most of the patients was severely altered at the date of diagnosis, with a mean vital capacity of 58.12% of predicted (between 17 and 87%) and a mean DLCO of 39.98% (between 9 and 62% of predicted value). The mean DLCO is actually at the limit for lung transplantation indication.

One can assume that for this patient profile the newly emerged treatments may have limited value, most likely only managing to maintain for a longer time a ventilatory status already severely damaged, and with a deeply altered quality of life.

Another feature revealed by the study is that most IPF patients presented with typical symptoms and clinical findings: all had dyspnea on exercise without orthopnea. All patients had crackles at the bases of the lungs and more than half presented with clubbing of the fingers. A 6 minute walk test was performed in only one third of the patients, all showing a significant desaturation of at least 6%.

Although IPF might be a disease that is mostly ignored in our country, this behaviour isn't without justification: it is a rare disease, not well acknowledged among general practitioners or cardiologists, both categories of physicians most likely have the tendency to allocate the most prominent symptom, exercise dyspnea, to one of the more frequent diagnostics: COPD or cardiac failure.

Among pulmonologists there is also a tendency to confuse IPF for other more frequent diseases, or simply to allocate these findings to the general term "lung fibrosis", without extending the investigations and without offering any treatment. This situation is quite frequent and difficult to explain, as the interstitial lung diseases have long been included in the educational curricula of any pulmonologist.

The status of these patients is even more dramatic due to the fact that access to lung transplantation is nonexistent in Romania at this point in time, and referring a patient to a centre outside the country involves considerable efforts for the patient and their physician.

The emergence in the medical panel of these two new drugs, efficient for IPF, need to change this situation radically. The IPF cases need to be brought to light as early as possible, because now these patients can have the benefit of a treatment! The earlier the diagnosis is defined and the earlier the treatment is started, the higher the probability of a longer and better quality survival are.

Two aspects are equally important: the initial suspicion of an interstitial lung disease, which is the responsibility of the primary care physician, and the establishment of a specific diagnosis of ILD, which is the task of pulmonologists in the centres of expertise.

Currently, IPF is also recognized as a political priority, as of July 11th 2016 the European Parliament

recorded a declaration signed by 388 members of the EU parliament: "Written declaration, under Rule 136 of Parliament's Rules of Procedure, on idiopathic pulmonary fibrosis". Among the statements in this declaration we can find: "Diagnosis and treatment are often delayed owing to insufficient information and an absence of diagnostic pathways." "Many patients lack timely access to pharmacological and non-pharmacological treatment because of funding delays and the exclusion of IPF from national health baskets." "Few IPF patients are eligible for lung transplants owing to inequality in the existing eligibility criteria in Europe." "The Commission is called upon to work in cooperation with Member States to enable access for IPF patients to orphan drugs and new medication approved by EMA."[24].

Based on the findings of the analysis of IPF cases included in REGIS, one can draft a ***"minimal practical guideline"*** for suspicion of IPF from the very first presentation. So, a patient presenting with the following features should be referred for supplemental tests to a centre with the capability for diagnosis of interstitial lung diseases:

- Dyspnea at exercise, with progressive aggravation and without orthopnea or wheezing
- Physical examination finds crackles at both bases of the lungs, without wheezes
- Clubbing
- Decrease of oxygen saturation at exercise

IPF is a real challenge for the clinician, due to diagnostic difficulties and severe prognosis. The emerging opportunity for an efficient treatment should be a motivation for every effort towards an early diagnosis and start of efficient treatment, aiming to offer the patient the chance for a longer life and a better quality of life. ■

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