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ADVANCES IN THE DIAGNOSIS AND TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS - A LITERATURE REVIEW

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease of unknown cause, characterized by irreversible fibrosis of the lung parenchyma, which leads to progressive deterioration of respiratory function, hypoxemia, and eventually respiratory failure and death. The average survival from the time of diagnosis is about 3-5 years, making IPF one of the most fatal chronic respiratory diseases. The disease most often affects men over the age of 60, often smokers or former smokers, and its symptoms - such as chronic dry cough, exertional dyspnea and crackles over the bases of the lungs - are nonspecific, making early diagnosis significantly more difficult. Although advances have been made in the diagnosis and treatment of IPF in recent years, there is still a lack of effective methods to completely stop or reverse the fibrosis process. Currently available therapies - pirfenidone and nintedanib - have been shown to slow the progression of the disease, but do not reverse it. Lung transplantation remains the only causal treatment option, although it is reserved for a limited group of patients. Recent years have seen an intensification of research into new drugs targeting specific molecular mechanisms involved in the pathogenesis of IPF, such as TGF-β, PDGF, VEGF, FGF or inflammatory and epigenetic pathways. In parallel, techniques are being developed to more accurately differentiate disease phenotypes and personalize therapy. The purpose of this paper is to review the current state of knowledge on IPF, with particular emphasis on recent advances in pathogenesis, diagnosis, pharmacological and non-pharmacological treatment, as well as prospects for future research aimed at improving patients' quality of life and prognosis.

KEYWORDS

Idiopathic Pulmonary Fibrosis, IPF, ECM, TGF-B, Pirfenidone, Nintedanib, Lung Transplantation

CITATION

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Introduction.

Idiopathic pulmonary fibrosis (IPF) is a chronic, incurable interstitial lung disease that leads to irreversible fibrosis, chronic inflammation and destruction of lung tissue structure [1,2]. As the disease progresses, extracellular matrix components accumulate, resulting in respiratory failure and death [3]. IPF is one of more than 150 known disease entities in the group of interstitial lung diseases, which are characterized by dyspnea, dry cough, characteristic changes on imaging studies and a restrictive type of ventilatory abnormality, among others [4]. It is estimated that fibrotic conditions account for nearly half of deaths worldwide. Fibrosis refers to excessive deposition of extracellular matrix by activated fibroblasts and myofibroblasts under the influence of cytokines and growth factors, leading to degradation of the architecture of organs such as the lungs, heart, kidneys and liver [5]. Patients with IPF show excessive proliferation of fibroblasts, which synthesize matrix within previously healthy lung tissue, destroying alveoli and impairing gas exchange, ultimately resulting in respiratory failure and death [6]. The first clinical and pathological description of IPF is attributed to Hamman and Rich in 1933 [7]. According to the American Lung Association, IPF is the most common form of idiopathic interstitial pneumonia and one of the most common ILDs [8]. Although IPF is considered a rare disease, the actual incidence may be higher than previously thought [4]. The incidence is estimated at 20-80 cases per 100,000 people, but accurate epidemiological data are difficult to obtain due to non-specific symptoms and late diagnosis - often 1-2 years after the first symptoms [2,4,9]. Globally, IPF affects about 5 million people, with 110,000 cases in Europe [8]. Men with a history of cigarette smoking are most commonly affected [2]. The risk increases significantly after age 70, with a rare occurrence before age 50 [10]. Median survival from diagnosis is only 2-3 years [6]. In 60-70% of patients, death is directly related to IPF, while the remaining deaths are due to comorbidities [11]. Typical complications include pulmonary hypertension, pulmonary embolism and sudden cardiac death [12]. The course of IPF varies from stable for years to rapid progression and acute exacerbations, which occur in about 10% of patients annually and are associated with a high mortality rate within three months [2,13]. Five-year survival is only 20-40% [1], and the annual incidence of acute exacerbations is estimated at 5-10% [14]. Although the etiology of IPF has not been clearly established, a role for genetic factors, environmental factors, aging and epigenetic changes has been suggested [6]. The risk of the disease is increased by age, male gender and smoking, among other factors [10]. IPF can develop as a result of damage to the alveolar epithelial barrier in predisposed individuals [15]. Although IPF primarily affects the lungs, risk factors are common to many other chronic diseases, including the cardiovascular system [16]. It is still debated whether inflammation precedes the fibrotic process [15,17]. In the past, IPF was considered an inflammatory disorder due to the presence of numerous inflammatory cells in the lungs [18], but studies have shown that anti-inflammatory drugs, such as corticosteroids, do not improve and sometimes make the patient worse [15]. An accurate diagnosis of IPF requires the presence of a typical picture of usual interstitial pneumonia (UIP) on HRCT or histology, in the appropriate clinical context and in the absence of a possible cause [16]. Functional studies show reduced vital lung capacity (FVC) and impaired gas diffusion (DLCO) [19]. Treatment of IPF is limited, mainly due to incomplete understanding of the disease mechanisms [9]. Therapy is symptomatic and aimed at delaying fibrosis and improving quality of life, with palliative care in advanced stages [1]. It was only in 2014 that the FDA approved two drugs - pirfenidone and nintedanib - that slow the progression of IPF [19]. Although they limit the progression of the disease, they cannot reverse already existing fibrosis or restore normal lung function [20]. These drugs also carry the risk of side effects, including nausea, diarrhea and fatigue. Lung transplantation remains the only option that offers a chance for a complete cure [12,21], but its availability is limited by a shortage of donors and high costs [20]. New therapies are constantly being researched - especially because of the poor prognosis of patients, whose median survival at the time of diagnosis is estimated at 3-5 years [9]. Until recently, treatment was only symptomatic, and only the introduction of antifibrotic drugs brought a breakthrough. Although nintedanib and pirfenidone are currently the only approved drugs, many other therapies are in various stages of clinical trials [15]. Recent findings suggest that changes in the immune system may provide biomarkers to help monitor the course of IPF and the efficacy of treatment, but the still incomplete knowledge of the disease's pathogenesis is a barrier to further therapy development [20]. Recent years have brought significant advances in understanding the mechanisms of IPF, creating hope for new therapeutic targets [3,22]. The purpose of this paper is to provide an update on the diagnosis, epidemiology, natural course and treatment of IPF in light of recent data and guidelines.

Materials and Methods

A comprehensive review of articles published in scientific journals was conducted using online research platforms such as PubMed and Google Scholar. Articles were identified using the following search terms: „Idiopathic pulmonary fibrosis", „IPF", „ECM", „ TGF-β", „pirfenidone", „nintedanib", „lung transplantation".

Discussion

In patients with idiopathic pulmonary fibrosis (IPF), symptoms usually develop gradually, most often in the form of dyspnea occurring during exercise. These symptoms may be accompanied by a chronic, dry cough. In more advanced stages of the disease, hypoxemia at rest is common. Spirometric studies in patients with IPF show a restrictive picture - typically a normal or elevated FEV1/FVC ratio (FEV1/FVC above 70% of the normal value or above the lower limit of normal) is observed, combined with a reduced FVC [4]. Clinical data show that the average annual reduction in FVC in people with mild to moderate pulmonary impairment is about 150-200 ml [23]. A reduction in total lung capacity (TLC) below 80% of normal, as measured by plethysmography, confirms the restrictive nature of the disease. Reduced diffusing capacity of the lungs for carbon monoxide (DLCO) is also common, reflecting impaired gas exchange. Because the greatest blood supply occurs in the lower lungs, where IPF develops most intensively, DLCO is usually more reduced than FVC [4]. Most patients experience a gradual decline in respiratory capacity over time, although some patients experience a sudden clinical deterioration - known as an acute exacerbation - despite previous stabilization of the disease [19]. Although the overall prognosis for patients with IPF is unfavorable, the rate of progression can vary widely between individual patients and is often difficult to predict [16]. Individuals with undiagnosed IPF who report dyspnea and have a history of smoking are often treated empirically with a diagnosis of chronic obstructive pulmonary disease [4]. Significant delays between the onset of symptoms and an accurate diagnosis of IPF have been documented, with an average of 1 to 2 years [23]. There is a strong correlation between deterioration of lung function and reduced quality of life, which can lead to significant psychological burden and increased risk of depression in patients [8].

Epidemiology

Establishing accurate epidemiological data on idiopathic pulmonary fibrosis (IPF) is a significant challenge [18]. The incidence and prevalence of the disease vary widely depending on the geographic region, the diagnostic criteria adopted and the demographic characteristics of the population analyzed. Global estimates indicate that IPF can occur in 1 to 13 people per 100,000, while the incidence rate ranges from 3 to 45 cases per 100,000, with the highest values reported in South Korea, Canada and the United States, among others [23]. There are an estimated 3 million people living with IPF worldwide, and the incidence rate increases markedly with age [18]. With a global aging population, increased awareness of the disease's symptoms, and the increasing impact of risk factors such as environmental pollution, the incidence of IPF is projected to continue to rise worldwide [23].

Morbidity and mortality

Data to date indicate that the median survival of patients diagnosed with idiopathic pulmonary fibrosis (IPF) ranges from 3 to 5 years after diagnosis. Age and male gender adversely affect patients' life expectancy [23]. Acute exacerbations of the disease often require hospital treatment and are associated with a high mortality rate - the average survival time in such cases is only 3-4 months. For those with stabilized IPF who do not receive antifibrotic treatment or have not undergone lung transplantation, life expectancy is 3 to 4 years [8]. In the past 20 years, improvements in survival rates have been noted, which can be attributed to earlier diagnosis of the disease, reduced use of immunosuppressive drugs and advances in available therapies. Both individual non-randomized studies and pooled analyses of randomized clinical trials have shown a favorable effect of anti-PI treatment on patients' life expectancy. Despite this, the number of IPF-related deaths worldwide continues to rise. The most common cause of death remains progressive lung damage, leading to acute exacerbations and acute respiratory failure, which account for 60-70% of cases. Other causes of death include coronary artery disease, lung cancer, pulmonary infections, pulmonary embolism and chronic obstructive pulmonary disease [23].

Pathogenesis

Although reports of interstitial lung diseases existed as early as the 19th century, the term “idiopathic pulmonary fibrosis” (IPF) was not officially introduced until the late 1960s by Liebow and Carrington, who distinguished “ordinary interstitial pneumonia” (UIP) as a unique histopathologic type within diffuse lung disease [3]. The etiology of IPF still remains incompletely understood, and its mechanisms are likely complex and the result of multiple factors acting simultaneously. The histological picture indicates excessive deposition of extracellular matrix (ECM) components, the presence of fibroblastic foci and areas of fibrosis [1]. It is currently accepted that recurrent microdamage to the follicular epithelium, leading to depletion of AT2 cells, is the main mechanism initiating fibrosis processes [18]. This damage causes disturbances in the normal function of epithelial cells, endothelial cells, macrophages and fibroblasts, and these changes can be observed in the form of altered cytokine and chemokine profiles in both bronchoalveolar lavage fluid (BALF) and tissue material. Numerous mediators, including TGF-β, IGF-1, PDGF, TNF-α, interleukins (IL-1β, IL-4, IL-6, IL-8) and other growth factors, play an important role in fibrosis formation [8]. TGF-β is considered one of the most important promoters of the fibrosis process, by activating collagen synthesis and inhibiting collagen degradation [23]. Patients with IPF show increased levels of TGF-β in BALF, as well as its elevated expression in various types of lung cells - fibroblasts, alveolar epithelium, bronchial cells and macrophages [8]. This cytokine also affects the differentiation of fibroblasts into myofibroblasts, resulting in overproduction of ECM and impaired ECM degradation [20]. Histological studies have also shown an increase in IGF-1 levels in the lung tissue of IPF patients, a factor produced by lymphocytes, macrophages and epithelial cells. IGF-1 promotes epithelial regeneration, stimulates cell migration and differentiation, promotes collagen production and inhibits apoptosis [8]. TNF-α, whose expression is increased, is also involved in the pathogenesis of IPF, although its exact role has not yet been clearly defined. TNF-α may enhance the action of TGF-β1, promote fibroblast proliferation and initiate collagen production [15]. Fibroblast foci (FFs) are clusters of intensely proliferating fibroblasts and myofibroblasts in injured parts of the lung. Compared to fibroblasts found in healthy tissues, cells from FFs are characterized by a higher proliferative potential, a stronger ability to contract, resistance to apoptosis and a different genetic profile [23]. The presence of these foci causes damage to microvascular structures and the vesicle-capillary barrier, leading to destruction of the intervesicular septum [8]. IPF is thought to develop in individuals with a genetic predisposition (e.g., mutations in the telomerase gene, telomere shortening) as a result of repeated damage to follicular epithelial cells [23]. The disease is characterized by a multifaceted interaction between epithelial cells, mesenchymal cells and ECM components [1]. Changes in the structure of the lung interstitium, including the replacement of elastic fibers with collagen, result in decreased tissue elasticity, which increases respiratory effort and leads to a gradual deterioration of ventilation function. Initially, a restrictive type of respiratory distress occurs, and over time, respiratory muscles weaken and vital capacity decreases. As the effective surface area for gas exchange decreases, the dead space volume increases, contributing to increasing respiratory failure. In advanced stages of IPF, pulmonary hypertension can develop, resulting in pulmonary heart (cor pulmonale) [8]. Aging processes also affect the development of IPF by decreasing the number and function of AT2 cells, which are responsible for regenerating the alveolar epithelium after damage [23]. Aging involves a number of mechanisms, such as genetic instability, telomere shortening, epigenetic disorders, loss of protein homeostasis, oxidative stress, deficits in mitochondrial function, cellular aging and disruption of intercellular communication. Environmental factors, such as cigarette smoke, can accelerate cellular aging by activating pathways responsible for permanent cell cycle arrest [16]. An increased risk of IPF is also observed in people with obstructive sleep apnea and diabetes. In the case of the latter, chronic hyperglycemia leads to non-enzymatic protein glycation, which can promote the development of the disease [8]. Eosinophilia, often associated with allergic reactions and inflammatory processes, is also involved in ECM remodeling, especially in cases of allergic pulmonary fibrosis. Macrophages play a central role in the immunopathogenesis of IPF, participating in the regulation of the inflammatory response and fibrosis through the secretion of pro-inflammatory cytokines and growth factors. There are three basic populations of pulmonary macrophages: those derived from monocytes, interstitial macrophages and alveolar macrophages. The oxidative stress generated by these cells is considered an important factor in accelerating the development of fibrosis [20].

Risk factors

One of the key features of idiopathic pulmonary fibrosis (IPF) is the lack of a clearly defined cause. According to current diagnostic recommendations, other possible causes of interstitial lung disease (ILD), such as environmental factors, connective tissue disease (CTD) or drug toxicity, should be ruled out before making a diagnosis of IPF [18]. Both genetic and environmental factors play an important role in the development of IPF [23]. As in other lung diseases, smoking has been shown to be significantly associated with IPF. Despite this, the mechanisms by which tobacco smoke affects the initiation and progression of the disease are still incompletely elucidated. Studies indicate that smoking may overexpress genes related to the epithelial-mesenchymal transition (EMT) and fibroblast-like phenotype, and accelerate telomere shortening. Nicotine, the main addictive ingredient in tobacco, can directly increase the production of TGF-β, one of the key factors promoting fibrosis [12]. Importantly, the risk of lung damage persists even after smoking cessation. Individuals with IPF who have smoked in the past show a worse prognosis compared to non-smoking patients [24]. The disease is more often diagnosed in older people, with the highest incidence observed in patients over 60. Men account for about 70% of IPF cases [23]. Studies in animal models suggest that male sex hormones may promote fibrosis, while estrogen may have a protective effect [12]. Occupations involving exposure to inhalation agents, such as mineral dust, asbestos and wood dust, have also been shown to correlate with the incidence of IPF [12,23]. Common associated diseases include gastroesophageal reflux disease (GERD), sleep apnea, diabetes, and viral infections. Chronic microaspiration of gastric contents resulting from GERD may contribute to lung tissue damage and promote the development of IPF [12]. The role of genetic predisposition in the development of IPF has been well documented, with hereditary factors accounting for about one-third of the risk of developing the disease [21]. IPF is associated with a variety of genetic features, including both gene mutations and changes in transcriptional regulation that lead to loss of epithelial integrity. The familial form of interstitial pneumonia (FIP) is diagnosed when the disease affects at least two members of the same family. FIP is inherited in an autosomal dominant manner with varying degrees of penetrance and accounts for 2% to 20% of IPF cases [24]. Genes associated with susceptibility to IPF are currently classified into four main groups: (1) those responsible for alveolar stability (SFTPC, SFTPA1, SFTPA2); (2) those affecting accelerated cellular aging through telomerase dysfunction (TERT, TERC, DKC1, PARN, RTEL1); (3) those involved in the body's defense mechanisms (MUC5B, TOLLIP); and (4) those affecting epithelial barrier integrity (DSK) [5,12].

Diagnosis

Early diagnosis of idiopathic pulmonary fibrosis (IPF) poses a significant diagnostic challenge, as the initial symptoms - mainly dyspnea and dry cough - are nonspecific and often resemble those of other respiratory diseases [1]. It takes an average of 0.6 to 2.3 years from the onset of symptoms to diagnosis. Studies show that a delay in diagnosis of more than 12 months adversely affects patients' quality of life, hospitalization rates and progression-free survival [18]. The typical patient suspected of having IPF is a person in his or her 60s whose imaging studies (chest X-ray or CT) show bilateral pulmonary fibrosis of unclear etiology. These patients are often former or current smokers and may have a history of occupational or environmental exposure [23]. Symptoms such as lower extremity edema and jugular venous dilatation may be indicative of developing pulmonary hypertension at an advanced stage of the disease. Pulmonary function tests are essential not only in the diagnostic context, but also for assessing prognosis and monitoring the progression of IPF. The typical picture includes a restrictive pattern with reduced FVC, TLC and DLCO values. FVC is the best documented predictor of mortality - its relative decline of ≥10% and absolute decline of >5% are considered criteria for disease progression [22]. The Six-Minute Walk Test (6MWT) is another important functional assessment tool to determine exercise-induced hypoxemia and the distance covered by the patient, which also helps predict prognosis [4]. Despite advances in the quality of high-resolution computed tomography (HRCT) imaging, the diagnosis of ILD, including IPF, can still be problematic - even with modern tools like deep learning analysis and interdisciplinary data evaluation [13]. Early identification of IPF is important for initiating therapy as soon as possible. HRCT performed in the supine position during full inspiration remains the primary diagnostic tool [8,19]. The image typical of UIP on HRCT is a strong indicator of IPF. Characteristic changes include opaque vitreous, reticularity, bronchial dilatation, and the presence of so-called “honeycombing” - that is, cystic air spaces 0.3-1 cm in diameter, usually located subpleurally [7]. Radiologists classify the pattern of UIP on HRCT as typical, possible or inconsistent. If the image meets all UIP criteria and does not contain any features of alternative pathology, a confident diagnosis can be made. In inconclusive situations (possible/inconsistent UIP), histopathological verification by surgical lung biopsy is necessary [4]. Biopsy is usually performed from two or three lung lobes, due to the heterogeneous distribution of lesions. However, before proceeding, the risk

must be carefully assessed - especially in elderly patients with advanced respiratory failure or comorbidities such as pulmonary hypertension or heart failure [5,7]. Confirmation of the histopathologic pattern of UIP is necessary to make the diagnosis of IPF [8]. The preferred method of biopsy is surgical technique - preferably minimally invasive video-assisted thoracoscopy, which allows for shorter hospitalization and faster recovery [4]. The gold standard for diagnosing ILD, including IPF, remains multidisciplinary meetings involving pulmonologists, radiologists and pathologists. Evaluation should be performed at specialized ILD centers. A prerequisite for a diagnosis of IPF is the exclusion of known causes of ILD, such as drugs, hypersensitivity to environmental antigens (fHP) or connective tissue diseases. In case of uncertainty or the need to consider other diagnoses, histopathological examinations provide additional information [22]. Although bronchoscopy and bronchoalveolar lavage (BAL) can be helpful in the diagnosis of ILD (e.g., chronic hypersensitivity pneumonia), their role in the diagnosis of IPF is limited. The 2018 guidelines recommend performing BAL in situations where HRCT images do not clearly indicate UIP [9]. A complete diagnosis of a patient with suspected ILD should include a thorough environmental history (e.g., contact with mold, birds, drugs) and a search for extrapulmonary symptoms (joint pain, dry syndrome, skin lesions) that may suggest connective tissue disease (CTD). Serological tests - RF, ANA or antibodies to citrullinated peptide - are also useful in the differential diagnosis [7]. The presence of consolidation may indicate organizing inflammation, and cysts may indicate LIP or LAM. Upper lobe fibrosis is atypical of UIP and suggests other diagnoses such as sarcoidosis or fHP [19]. Although the symptoms of entities such as fHP or sarcoidosis resemble IPF (e.g., dyspnea, dry cough, restrictive nature of PFTs), they are usually associated with a more favorable prognosis and better response to immunosuppressive therapy [7].

Comorbidities

Recent systematic studies confirm that patients with idiopathic pulmonary fibrosis (IPF) are significantly more likely to suffer from various comorbidities than those in the general population. The results of one study analyzed showed that about 60% of people with IPF had one to three comorbidities, 30% suffered from four to seven, and only 10% reported no additional conditions. These data underscore the clinical importance of comorbidity in IPF and its impact on life expectancy [16]. The median survival of patients varied according to the number of comorbidities - 66 months in those without comorbidity, 48 months in patients with 1-3 comorbidities, and 35 months in those with 4-7 comorbidities, respectively. Cardiovascular diseases and lung cancer had a particularly unfavorable impact on prognosis [11]. Some comorbidities, such as lung cancer, COPD and cardiovascular disease, share risk factors with IPF - especially smoking. There are also medical conditions that can contribute to the development of IPF. For example, diabetes - through hyperglycemia and associated inflammation - may play a role in the initiation or progression of fibrosis [11,16]. A common complication of IPF is pulmonary hypertension (PH), which has long been associated with a worsened prognosis [22]. PH is defined as mean pulmonary artery pressure (mPAP) at rest ≥ 20 mmHg [11]. Symptoms of PH in patients with IPF are nonspecific, often leading to delayed diagnosis. Clinical features may include increased dyspnea, low DLCO values, rapid exercise desaturation, elevated BNP, and signs of right heart failure [16]. A study involving more than 6,500 patients showed that even mild PH increased mortality among patients with IPF. Currently, there are no approved targeted therapies for PH coexisting with IPF [11,16]. Although various pulmonary vasodilators have been tested, they have not been proven effective in modifying the course of the disease [22]. Thus, these patients remain a population with a large and unmet need for new therapeutic options [11]. Obstructive sleep apnea (OSA), defined as an AHI index > 15 events/hour, is common in patients with IPF, with a prevalence of up to 50-90% [16,22]. Sleep-disordered breathing in these patients can range from simple snoring to full-blown apnea episodes. Due to the high prevalence of OSA, polysomnography is recommended at the time of IPF diagnosis to allow early detection [11]. CPAP therapy can significantly improve quality of life and reduce mortality in patients with IPF and concurrent OSA [16]. The progressive nature of IPF and its impact on deteriorating respiratory capacity often lead to the development of depressive symptoms and anxiety [11]. Increasing dyspnea, worsening pulmonary function tests and hypoxemia correlate most strongly with these disorders. The percentage of patients with IPF suffering from anxiety and depression is about 31% and 23%, respectively. Treatment may include cognitive-behavioral therapy and antidepressant pharmacotherapy [16,22]. Deconditioning - that is, a decline in physical and/or mental performance - is a phenomenon that often accompanies chronic illnesses, including IPF. Limited physical activity negatively affects the functioning of many body systems, impairing quality of life and the ability to function independently [11,16,22]. Sarcopenia - defined as loss of muscle mass and strength - is common in IPF and is associated with functional decline, reduced quality of life and higher risk of death.

Retrospective data indicate that low muscle mass in this group of patients may be a significant risk factor for death from any cause [11,22]. A significant proportion of patients with IPF are current or former smokers, which favors emphysema or chronic obstructive pulmonary disease. Approximately 30% of patients with IPF have concurrent emphysema, which can lead to the diagnosis of CPFE, a phenotype that combines features of emphysema and fibrosis [11,16]. Gastroesophageal reflux (GER) is a common finding in patients with IPF, with a prevalence as high as 70-90%. GER can be acidic or non-acidic, depending on the pH of the contents [16]. When it leads to symptoms or complications, we speak of GERD. It is believed that GERD may contribute to acute exacerbations of IPF through a microaspiration mechanism. Although the use of antisecretory drugs to treat GERD in patients with IPF has shown promising results in observational studies, their effectiveness in preventing IPF progression remains controversial [11]. Patients with IPF also have a significantly higher risk of developing lung cancer than the general population, regardless of age, gender and smoking history. The incidence of cancer increases with the duration of the disease, from 3.3% at one year to more than 50% at 10 years after diagnosis [11]. Symptoms are nonspecific, and radiological changes can be difficult to distinguish from fibrotic lesions. Oncologic treatment should be tailored individually, taking into account the patient's overall condition and prognosis resulting from IPF [16]. IPF patients are also at particular risk for complications after thoracic surgery, including lung cancer resection. Approximately 10 percent of them have a postoperative exacerbation of IPF, which is associated with an approximately 50 percent short-term mortality rate [16].

Pharmacological treatment

In recent years, there have been significant developments in the pharmacological treatment of idiopathic pulmonary fibrosis (IPF) [18]. In 2014, the US Food and Drug Administration (FDA) approved two drugs, pirfenidone and nintedanib, for the treatment of IPF, basing the decision on the results of phase III clinical trials. The two drugs are now staples of IPF treatment, with a good safety profile and acceptable tolerability. Their action is to slow the progression of the disease and limit further pulmonary fibrosis, but they do not lead to a complete cure [12]. Numerous studies have shown that the use of pirfenidone and nintedanib is associated with a reduction in mortality compared to placebo, as well as a reduction in the rate of lung volume loss [8,23]. Both drugs have also shown efficacy in treating other progressive fibrotic lung diseases [5].

Pirfenidone

Pirfenidone is a small-molecule chemical compound that acts by reducing fibroblast proliferation and collagen synthesis [2]. Although its mechanism of action is not yet fully elucidated, it is known to inhibit the activity of fibrosis mediators, myofibroblast differentiation and fibroblast proliferation, mainly by affecting TGF-β-related signaling pathways. The standard therapeutic dose is 267 mg taken three times a day [22]. The substance is characterized by rapid absorption from the gastrointestinal tract and a half-life of about 3 hours. Pirfenidone exerts both anti-inflammatory and antifibrotic effects [15]. The most commonly observed side effects are skin lesions, photo-sensitivity reactions and gastrointestinal complaints, particularly nausea and vomiting [22]. It is recommended to evaluate liver enzyme levels before starting therapy, and then monitor them monthly for six months, and every three months thereafter. The drug should not be used in patients with severe liver impairment (Child-Pugh class C) or those requiring dialysis [12].

Nintedanib

Nintedanib is a tyrosine kinase inhibitor that interacts with several receptors, including FGFR and VEGFR, the receptors responsible for fibroblast and vascular endothelial growth. The recommended dosage is 150 mg twice a day. The most commonly reported side effects include gastrointestinal symptoms, particularly diarrhea - which occurs in about 60% of those treated. Because of the potential for hepatotoxicity, regular monitoring of liver enzymes is necessary [22]. Caution is also advised in patients with recent cardiovascular incidents and with concomitant use of anticoagulants, due to the risk of clotting disorders and bleeding resulting from the drug's mechanism of action [4]. As with pirfenidone, in the event of adverse effects or liver damage, temporary discontinuation, dose reduction, or slow re-increase after resolution of symptoms is acceptable [12]. To date, no direct comparative studies have been conducted on the efficacy and tolerability of pirfenidone and nintedanib. For this reason, the decision to choose a drug should be made on an individual basis, taking into account patient preference, potential side effects, therapeutic benefits and the presence of comorbidities [4]. For example, nintedanib is more often recommended as an alternative to pirfenidone in patients with dermatoses or in those who are unable to avoid sunlight [12].

Lung transplantation

More than 4,600 lung transplants are performed worldwide each year, nearly half of which involve patients with interstitial lung disease [18,25]. Compared to other therapies, lung transplantation stands out because as the only treatment option it can improve both the quality of life and the length of survival of patients [1]. Lung transplantation (LungTx) represents a potential opportunity to prolong life in patients with advanced or rapidly progressive fibrotic interstitial lung disease (ILD), including idiopathic pulmonary fibrosis (IPF), which is currently the most common indication for this type of surgery worldwide [18]. The main factors that qualify a patient to be placed on the transplant waiting list include a rapid decline in vital lung capacity (FVC) or diffusion of carbon monoxide (DLCO), exercise-induced hypoxia, a shortened distance covered during the 6-minute walk test, the onset of pulmonary hypertension, complications such as pneumothorax or acute deterioration of respiratory function requiring hospitalization [1]. Although the number of transplants performed for IPF is steadily increasing, the waiting time for an organ remains relatively long. The average life expectancy after lung transplantation is 4 to 6 years, with about 80% of patients surviving the first year after surgery. About half of patients live at least five years after transplantation. The procedure can be performed as a unilateral or bilateral lung transplant [26].Single-lung transplantation is associated with shorter waiting times, a less complicated surgical course and a lower risk of perioperative complications, and allows two people to have their organs transplanted from a single donor. Nevertheless, better survival outcomes are usually reported in patients who have undergone bilateral lung transplantation [8].

Nonpharmacological treatment

Effective management of patients with idiopathic pulmonary fibrosis (IPF) also includes treatment of comorbidities, with a particular focus on pulmonary problems such as obstructive sleep apnea and pulmonary hypertension [8,25]. In addition to pharmacological therapy, non-pharmacological methods play an important role, which significantly support patients in their daily functioning and help keep their quality of life as high as possible. In smokers, one of the priorities should be to give up tobacco completely [18]. Maintaining good physical condition, regular activity and a balanced diet are important elements in slowing the deterioration of respiratory function. In patients with advanced respiratory failure, home or portable oxygen therapy is recommended [8,27]. Indications for the use of ambulatory oxygen therapy often coincide with criteria adopted for chronic obstructive pulmonary disease - these include a saturation below 88% on ambient air or a value of 88-90% in combination with polycythemia vera and/or pulmonary hypertension - but data on the efficacy of this approach in IPF are limited [22]. Shortness of breath, as one of the most troublesome symptoms, can be relieved with opioids (e.g., morphine), assisted by oxygen therapy and rehabilitation programs, if available. Additional non-pharmacologic techniques, such as learning to breathe effectively, use of a hand-held ventilator, individualized activity counseling, or access to a dyspnea clinic, have shown efficacy in refractory patients [22]. The use of oxygen improves exercise tolerance and reduces dyspnea during physical activity [18]. Another significant symptom is persistent cough, which can be very troublesome in some cases. Opioids are also used to treat it, with codeine more often preferred to morphine. Treatment of comorbid conditions such as gastroesophageal reflux disease (GERD) or rhinitis can also be helpful [22]. Early data suggest that microaspiration associated with pathologic reflux may increase the risk of IPF, justifying recommendations for aggressive treatment of GERD, although these are based on limited evidence [4]. Among the non-pharmacological experimental approaches being considered for the treatment of IPF is mesenchymal stem cell (MSC) therapy. These cells, which are multipotent and undifferentiated in nature, show the ability to modulate fibrotic processes and participate in the regeneration of damaged lung tissue [1,28]. MSCs can be easily obtained from various sources, including adipose tissue, bone marrow, peripheral blood or umbilical cord. Preclinical data indicate their potent anti-inflammatory, anti-fibrotic, and immunomodulatory effects due to both paracrine signaling and their ability to differentiate. Studies have shown that MSC administration led to attenuation of TGF-β pathway activity and lung histopathologic improvement [21].

Biomarkers

Assessment of the course of IPF based on functional and imaging parameters is sometimes unreliable and does not accurately predict further disease progression. The most commonly used monitoring method is to analyze changes in FVC values over a 12-month period, where a decrease of at least 10% is considered clinically significant and indicates progression. Unfortunately, so far it has not been possible to develop unambiguous blood biomarkers that are widely used in clinical practice. The search for such indicators is one of the main directions of research, as it could significantly improve the diagnostic process and the evaluation

of treatment efficacy. Among the potential biomarkers being analyzed in the context of IPF is the receptor for advanced glycation products (RAGE), which is found in type I follicular epithelial cells. In patients with IPF, its levels are significantly reduced in the lungs, and lower levels of circulating RAGE correlate with worsening lung function. Other biomarkers under consideration include type I and III collagen turnover, which may reflect increased fibrosis in the lungs [1,13]. However, there is still a clear need to identify markers to predict response to therapy and the rate of disease progression [13,29].

Conclusions

Idiopathic pulmonary fibrosis (IPF) remains one of the most difficult interstitial lung diseases to treat and diagnose. Despite significant advances over the past two decades - including the development of antifibrotic drugs and diagnostic guidelines - the disease continues to be characterized by high mortality rates, poor quality of life for patients, and a lack of effective therapies for a complete cure. This paper discusses a number of issues crucial to understanding IPF, ranging from the pathogenesis involving follicular epithelial activation, fibroblast and myofibroblast recruitment, to the processes leading to excessive extracellular matrix production. Contemporary diagnostic capabilities, including the use of high-resolution computed tomography (HRCT), lung biopsy and molecular methods, as well as the importance of early differentiation of IPF from other interstitial diseases, are also covered. Current therapeutic strategies were also highlighted: drug treatment based on nintedanib and pirfenidone, which slow the progression of the disease but do not treat its cause. The need for multidisciplinary patient care was pointed out, taking into account not only drug treatment, but also rehabilitation, psychological support, treatment of comorbidities and preparation for possible lung transplantation. Current research directions include the development of targeted drugs, the study of combination therapies and the use of molecular biomarkers. The conclusion of the paper is the need to further improve knowledge of the mechanisms of the disease and to develop more effective therapies that will not only slow the course of IPF, but make it possible to stop or reverse it. It is also necessary to increase awareness of IPF among GPs and to implement integrated models of care for patients with interstitial lung disease.

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