Future treatment modalities in IPF / ILD

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AIMS

- Basic pathogenetic mechanisms
- Classical combination therapy
- Treatment of comorbidities
- Drugs in the pipeline
- Non IPF ILD
- Personalised medicine

SUMMARY

Idiopathic pulmonary fibrosis (IPF) is a devastating disease that carries a median survival of 3-4 years after diagnosis. It is characterized by fibroblast proliferation and extracellular matrix remodeling resulting in irreversible damage of the lung architecture. The progressive fibrosis leads to symptoms as there are progressive shortness of breath and dry cough. Pulmonary fibrosis is a group of more than 200 different diseases, of which IPF is the most aggressive and the best studied. IPF is characterized by a fast progressive scarring in the absence of any possible cause (exposure) or underlying disorder [1]. For many years the mainstay of treatment has been corticosteroids often in combination with immunosuppressive agents such as azathioprine. Thereafter the triple therapy was introduced on the basis of the Ifigenia trial showing slower FVC decline when N-Acetylcysteine was added to the combination of corticosteroids and azathioprine [2]. Triple therapy has been the mainstay of treatment for a few years, until the Panther trial has shown that the combination of high dose corticosteroids, azathioprine and N-Acetylcysteine had a higher morbidity and mortality than placebo [3][4]. Several recent trials have investigated therapies directly influencing different pathophysiological mechanisms of the disease. This resulted in 2 antifibrotic agents on the market for IPF: pirfenidone and nintedanib [5][6][7][8]. These drugs significantly slow down the decrease of FVC in patients with mild to moderate IPF and are recently endorsed by the ATS/ERS/JRS and ALAT [9]. However these drugs do not resolve the fibrosis by restoring that has been damaged and moreover they are associated with quite some side effects mainly gastrointestinal of origin. Next to drug treatment there is still the option of lung transplantation, but the outcome is limited and the mortality on the waiting list is still high.
Furthermore age limit is the often the reason why patients with IPF do not have the chance on being candidate for lung transplantation as the disease is more frequent in an older age population. It is clear that there is an urgent need for better treatment, however this is really an endeavor in IPF and interstitial lung diseases as a whole.

Solutions for future therapy can be divided in solutions that can be found on the relatively short term and solutions that require more time. A short term solution might be combination therapy [11]. In this paper it is pointed out that the way forward is combing active drugs as done in other fields like oncology, pulmonary hypertension, diabetes,… There are many reasons why it is thought that combination might be more effective such as tackling different pathways. On the other hand the challenges are huge: pharmacokinetics will be a major hurdle as different drugs can interfere, but also the design of studies should be reviewed [12]. The obvious solution might be the combination of the 2 existing antifibrotic agents. A recent paper has reported the results of a limited amount of patients receiving different dosages of Nintedanib together with Pirfenidone in comparison with patients only receiving Nintedanib. In this study they show that combining Nintedanib with Pirfenidone is feasible as side effects are mild to moderate [13]. Furthermore they found no effect of Nintedanib on Pirfenidone plasma levels, but Pirfenidone would decrease maximum plasma levels of Nintedanib. In their conclusions the authors state that further study is warranted. Other combinations could be a background treatment of antifibrotics with an agent tackling a certain comorbidity. In IPF the best studied comorbidity is pulmonary hypertension [14][15]. The Step IPF trial has shown that Sildenafil in patients with advanced IPF induced some interesting effects on quality of life, there even was a trend on mortality. But the primary endpoint being a 20% increase in 6 minutes walking test was not reached.

The next chapter will deal with solutions on the longer term. This is the development of agents that tackle important steps in the pathogenesis of pulmonary fibrosis as there are agents that block IL-13 and Th2 cytokines [16][17]. Blocking IL-13 ameliorates experimental fibrosis in animal models and several anti-IL-13 monoclonal antibodies are being tested in clinical trials. Another potential target is LPa1, lysophosphatidic acid, which is known to have potent fibroblast chemoattractant activity [18]. Another interesting target is Integrin αvβ6, a known activator of latent TGF-β complexes [19]. Moreover antimicrobials might have a role in future treatment of pulmonary fibrosis. It has already been shown in mice that low dose azithromycin might induced less fibrosis when given in a bleomycin mouse model [20]. This might point to an important role of microbiome in pulmonary fibrosis. Furthermor a randomized controlled trial with cotrimoxazole in 181 patients hasn’t shown a significant effect on pulmonary function decline, but reduced the need for oxygen treatment [21].

Next to IPF another challenge is to discover better treatments for other relentless fibrotic disorders [11]. In this regard traditional drug repositioning should be considered and current antifibrotics should be evaluated on effect in ILD secondary to connective tissue diseases, or chronic hypersensitivity pneumonitis.

With all the new knowledge on pathogenesis and genetics, the ways eems open for personalized medicine, however therefor serious hurdles should still be taken before we will be able to prescribe some tailor made therapy. But is clear that we are already much further than a decade ago.
REFERENCES


EVALUATION

Please provide 3-5 multiple choice questions AND their answers

1. **Combination treatment in IPF means**
   a. Combining 2 anti fibrotic agents
   b. Combining anti fibrotic agents with other agents to treat another feature of the disease
   c. Tackling different pathways in the pathogenesis
   d. All of the above

Answer D

2. **Which is true? Anti microbials in IPF**
   a. Work because of the antimicrobial effect
   b. Work because of an anti-inflammatory effect
   c. Work because of an antifibrotic effect
   d. All of the above

Answer D
3. **In your opinion which answer is correct? In which entities do we need more trials with antifibrotic agents?**
   
   a. IPF  
   b. ILD–SSC  
   c. ILD–RA  
   d. Fibrotic NSIP  
   e. Chronic hypersensitivity pneumonitis  
   f. All of the above  

Answer F