Current therapy of idiopathic pulmonary fibrosis:

primum non noccere!

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The last decade we witness a significant progress in our understanding the pathogenesis and the natural history of idiopathic pulmonary fibrosis (IPF). This progress has been translated into novel investigational agents, and big clinical trials with the enrollment hundreds of patients, with the approval by the European Medicines Agency (EMEA) the first drug for IPF[1-3].

Interestingly, last year published the evidence-based guidelines[4] that replace the previous consensus statement[5]. The new guidelines, is a product of 3 years of tremendous work of a panel of experts from the ATS, ERS, and JRS. The committee reviewed and evaluated the existing medical literature according to GRADE system[6]. The result of the voting of the panel is: A "**strong yes"** recommendation for the use of long-term oxygen therapy and lung transplantation in appropriate patients. A "**weak yes"** for the use of corticosteroids for acute exacerbation of IPF, for the treatment of asymptomatic gastro-oesophageal reflux and pulmonary rehabilitation. A "**strong no"** for the use of monotherapy with corticosteroids, colchicine, cyclosporine A, combined corticosteroid and immune modulator therapy, interferon-γ -1b, bosentan and etanercept. A "**weak no"** for the monotherapy with NAC, pirfenidone, pulmonary hypertension associated with IPF and the use of mechanical ventilation in patients with respiratory failure due to IPF **(Table 1)**.

After the conclusion of the works of the committee and under the light of the publication of two new randomized controlled trials with negative results regarding the triple therapy with prednisone, azathioprine, and N-acetylcysteine (PANTHER trial),[7] and the negative results of the trial with warfarin (ACE-IPF trial),[8] the week no for the use of them changed from "weak no" to "strong no".

In consequence, the continuation of the common practice treating patients with the triple therapy is no more validated as making more harm than good! The Hippocratic aphorism *"ασκέειν, περί τα νουσήματα, δύο, ωφελέειν, ή μη βλάπτειν", (Above All, Do No Harm!)* should be followed strictly according to good clinical practice rules, avoiding ethical and legal consequences.

The PANTHER trial[7] was a randomized, double-blind, placebo-controlled trial in patients with IPF who had mild-to-moderate lung-function impair-

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TABLE 1. Treatment options for idiopathic pulmonary fi brosis

Pharmacological agents

Strong no recommendation
- monotherapy with corticosteroids; colchicine; ciclosporin A
- combined corticosteroid treatment and immune modulating treatment;
- interferon gamma-1b; bosentan; and etanercept
- triple therapy (prednisone, azathioprine, and N-acetyl cysteine)*
- warfarin (anticoagulation)*

**[needs to be updated on the basis of new evidence]*

Weak yes recommendation
- corticosteroids for acute exacerbations
- treatment for asymptomatic gastro-oesophageal refl ux

Weak no recommendation
- monotherapy with N-acetyl cysteine
- pirfenidone
- treatment of pulmonary hypertension associated with the disorder

Other considerations
- Participation in clinical trials
- Long-term oxygen treatment for patients with clinically significant resting hypoxaemia (strong yes)
- Lung transplantation in suitable patients (strong yes)
- Pulmonary rehabilitation (weak yes)
- Mechanical ventilation in patients with respiratory failure due to idiopathic pulmonary fi brosis (weak no)
- Palliative care: symptom control (cough, dyspnoea) and comfort care
- Treatment of comorbidities (eg, sleep apnoea, gastro-oesophageal reflux, pulmonary embolus or deep venous thrombosis, pulmonary hypertension, emphysema, obesity, respiratory infection, pneumothorax, lung neoplasm, diabetes mellitus, atrial arrhythmia).

*Modified from reference 4.

ment receiving a combination of prednisone, azathioprine, and NAC (triple therapy), NAC alone, or placebo in a 1:1:1 ratio. The primary outcome was the change in longitudinal measurements of forced vital capacity during a 60-week treatment period. The interim analysis revealed that patients in the combination-therapy group, as compared with the placebo group, had an increased rate of death (10% vs. 1%, p=0.01), hospitalization [(23 (30%) vs. 7 (9%), p<0.001)] and serious adverse events (31% vs. 10%, p=0.001). These observations, prompted the independent data and safety monitoring board to recommend termination of the combination-therapy group at a mean follow-up of 32 weeks. The authors conclude that the increased risks of death and hospitalization observed in patients who were treated with a combination of prednisone, azathioprine, and NAC, as compared with placebo provide evidence against the use of this combination in such patients.

Last year the European Medicines Agency (EMEA) approved pirfenidone, as the first ever drug, for the treatment of IPF. Pooled analysis of primary end-point data from two RCT (CAPACITY) showed that pirfenidone significantly reduced the decline in per cent predicted FVC compared to placebo (p<0.005)[9]. Pirfenidone was generally well tolerated, with the most common side-effects being gastrointestinal discomfort and photosensitivity. According the aforementioned data, pirfenidone monotherapy can be viewed as "a rationale" therapeutic approach for IPF[10,11]. However, FDA is waiting the results of ongoing clinical trial for its approval.

Therapies without recommendation by the committee, as RCT published subsequent to final formal face-to-face discussion, include the drugs imatinib (negative study), sildenafil (negative study), and BIBF 1120. Interestingly, it has been published that BIBF 1120 at a dose of 150 mg twice daily, as compared with placebo, was associated with a trend toward a reduction in the decline in lung function, with fewer acute exacerbations and preserved quality of life[12]. A new trial is ongoing to further explore these results.

In conclusion, and under the light of the existing evidence, encouraging the patients to participate in clinical trials and scientists to intensify the research into the role of gene and stem cell therapy, clinicians should abolish the so far common practice of using harmful treatments, including corticosteroids and triple therapy[13-15]!

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