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Review of idiopathic pulmonary fibrosis diagnosis and management recommendations in Europe

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Abstract. Increased knowledge of Idiopathic Pulmonary Fibrosis (IPF) led to the development of evidence-based diagnosis and treatment guidelines. A 2011 update of the American Thoracic Society and the European Respiratory Society, together with the Japanese Respiratory Society (JRS) and Latin American Thoracic Association (ALAT) provided new guidance on the diagnosis and treatment of IPF. Although the 2011 statement was a major advance, the application of guideline recommendations has identified limitations. The guidelines focus primarily on 'definite' IPF, most often diagnosed from typical High-Resolution Computed Tomography (HRCT) appearances. The definition of 'probable' and 'possible' IPF is an advance, but there is a lack of management guidance for these highly prevalent clinical scenarios. The integration of HRCT and histological data in assigning of diagnostic likelihood is also important, but does not always meet the needs of some patients in whom a multidisciplinary diagnosis of definite IPF should be made. Moreover, the committee did not find sufficient evidence to support the use of any specific pharmacological therapy for patients with IPF. These issues highlight the need for updating available clinical guidelines. Since 2012, several national European recommendations documents and guidelines have been updated. These generally follow the 2011 guidelines, but reflect more recently available clinical study data. Following the publication of the CAPACITY trials showing positive effects of pirfenidone in IPF and its approval in the European Union, many of these updated guideline documents recommend that patients with mild-to-moderate IPF should be offered this therapy. This review analyses the recently developed European country updates, comparing and contrasting recommendations on the diagnosis and treatment of IPF. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 249-261)*

Key words: IPF, diagnosis, guidelines, recommendations, treatment

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Introduction

Idiopathic Pulmonary Fibrosis (IPF) belongs to a family of over 200 diverse disorders collectively known as diffuse Interstitial (or parenchymal) Lung Diseases (ILDs), many of which are rare or 'orphan' diseases (1,2). IPF is assigned to the subgroup known as Idio-

pathic Interstitial Pneumonias (IIP) differentiated by distinct pathological features and patterns (3). IPF is the most common IIP and defined as "a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathological and/or radiological pattern of 'Usual Interstitial Pneumonia'" (UIP) (4).

The natural history of IPF is typically characterised by progressive fibrosis, increasing respiratory symptoms, worsening Pulmonary Function Test (PFT) parameters leading to death from respiratory failure or complicating comorbidity (4). Symptoms are debilitating and IPF patients have significantly impaired quality of life. The condition is associated with a very poor prognosis (4,5), with an estimated median survival time of between 2 to 5 years from diagnosis which is worse than several types of cancer (5-8). Pharmacological treatments for IPF have been limited with numerous investigational agents evaluated in clinical trials without significant success. However, in 2011, pirfenidone became the first agent to be approved for the treatment of IPF in the European Union (9).

Evolution of IPF Diagnosis and Management Guidelines

Original management recommendations from 2000

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) published the first international consensus statement providing recommendations for the diagnosis and management of IPF in 2000 (10).

This statement proposed four major, and four minor, diagnostic criteria for IPF that together identified a histopathological pattern of UIP (10). Since the original publication, a number of limitations had been identified concerning the four minor criteria of these diagnostic guidelines: the specification of patient age greater than 50 years excludes a patient group, albeit small, in which early diagnosis would be desirable (11). Furthermore, a slow onset of disease does not acknowledge the fact that some IPF patients present initially with acute symptomatic exacerbations (12). Similarly, it is also difficult to define and accurately distinguish IPF from the symptomatic course of patients with a disease duration of at least three months with co-existing pulmonary fibrosis and/or pre-existing smoking-related lung damage. While the presence of crackles on auscultation can facilitate an early diagnosis of IPF, this clinical sign is not specific for IPF and further investigations such as High-Resolution Computed Tomography (HRCT) are required to make a diagnosis (13).

Revised 2011 management guidelines

Since the publication of the ATS/ERS statement on IPF in 2000, diagnostic standards have improved and a considerable number of Randomised Clinical Trials (RCTs) have been published. During 2008–2010, an international collaboration of IPF experts from the ATS, ERS, together with the Japanese Respiratory Society (JRS) and the Latin American Thoracic Association (ALAT), analysed the additional evidence accumulated since the publication of the 2000 ATS/ERS consensus statement to provide evidence-based recommendations for management, which were published in 2011 (4). The main objective was to provide simplified and evidence-based criteria that facilitate a more confident clinical diagnosis of IPF. The recommendations were developed from a thorough review of existing published evidence with the quality of evidence determined according to the GRADE criteria, with the use of expert opinion only when the evidence base was inadequate (4). The 2011 recommendations represent an important advance in the diagnosis of IPF by integrating HRCT with histopathological data in assigning a diagnostic likelihood of IPF i.e. 'definite', 'probable' or 'possible' IPF. As with the original 2000 diagnostic criteria, the revised ATS/ERS/JRS/ALAT guidelines propose that, in an appropriate clinical context, an UIP pattern according to HRCT criteria is sufficient to diagnose IPF without performing a surgical lung biopsy (SLB) and the revised guidelines specifically identify three HRCT patterns for grading the probability of the presence of UIP, namely 'UIP', 'possible UIP' and 'inconsistent with UIP' patterns (4,14).

Limitations of Current International Guidelines

Diagnosis

Although the ATS/ERS/JRS/ALAT 2011 management guidelines represent an important con-

sensus on the diagnosis of IPF, a number of experts have identified some limitations in their application in clinical practice. These issues have recently been reviewed by Wells (14) and refer to the application of HRCT and the recommendations for surgical biopsy and Bronchoalveolar Lavage (BAL) in situations where the diagnosis of IPF is less certain. Patients with 'probable' or 'possible' IPF are frequently encountered in clinical practice and often have a differential diagnosis of fibrotic Non-Specific Interstitial Pneumonia (NSIP) or chronic Hypersensitivity Pneumonitis (HP) (14).

A large proportion of patients with suspected IPF may have contraindications to SLB or decline the procedure and thus cannot be diagnosed as 'definite' IPF (14). It has been suggested that a clearer separation between patients who can undergo a SLB with an acceptably low risk and those in whom SLB should be avoided would be helpful to clinicians (14). In addition, a certain proportion of patients may have unclassifiable disease, which has been estimated at approximately 10% of all ILD patients (15). However, this figure may be under-estimated since many patients not classifiable do not undergo SLB and may therefore be a patient group with "unclassifiable clinical/radiological conditions" not evaluated by multidisciplinary discussion (16).

Expert interpretation of HRCT scans is central to the diagnosis of IPF and requires the identification of honeycombing. However, a diagnosis of 'definite' IPF is not usually possible from HRCT alone in approximately one-third of cases (4). In clinical practice, the classification of patients with a predominantly basal and sub-pleural distribution of reticular abnormalities typical of IPF, but without honeycombing on HRCT is relatively common. However, there is no category in the 2011 guidelines that includes this constellation of features that may be seen in patients with 'possible' IPF in clinical practice (14).

Inter-observer variation in the distinction between typical and atypical HRCT appearances of IPF is also substantial among less experienced observers and the current HRCT diagnostic recommendations are not implemented uniformly by the many radiologists (17). Thus, additional diagnostic evaluation is often required in patients with 'possible' IPF in whom there is evidence of peripheral basal reticular change in the absence of honeycombing with other atypical HRCT findings (14).

The weak negative recommendation that BAL cellular analysis should not be performed in the diagnostic evaluation of IPF in the majority of patients, but may be appropriate in a minority of patients has also been debated since this can be applied to two different scenarios – 'definite' IPF (typical clinical and HRCT features of IPF) or 'suspected IPF', in whom the likelihood of IPF is probable or possible but where other differential diagnoses exist, usually HP or NSIP (4,14). Even though the current guidelines reflect the first scenario and BAL may be considered for patients who have uncertain exposures which might be relevant to a diagnosis of HP, it has been shown that BAL lymphocytosis changed the diagnostic perception in a proportion of patients who would otherwise have been misdiagnosed as having IPF without BAL (18). This finding, however, which only applies to a small number of patients, would need to be reproduced in multicentre studies with a larger cohort of patients before major changes in the recommendation are considered.

While the current guidelines reflect the former scenario, they do not adequately account for the latter scenario. It has therefore been proposed that an independent statement for each scenario may be preferable (14).

Treatment guidelines

In the 2011 ATS/ERS/JRS/ALAT guidelines no pharmacological treatment was positively recommended for patients with IPF (Table 1) (4).

The ATS/ERS/JRS/ALAT guidelines include a complicated, evidence-based, treatment matrix which includes weak and strong recommendations for and against specific treatment strategies. This GRADE approach identified all outcomes that are of importance to patients and differentiated the critical outcomes from the important but not critical ones (19). Recommendations depend on the evidence for all patient-important outcomes and the quality of evidence for each of those outcomes. For each question, the committee graded the quality of the evidence available (high, moderate, low, or very low), and made a recommendation for or against the intervention. Recommendations were decided on the basis of majority vote of the 31 voting members of the committee. Recommendations were either 'strong' or 'weak.' The strength of a recommendation

Table 1. Summary of ATS/ERS/JRS/ALAT evidenced-based pharmacological treatment of IPF (4)

Strong positive recommendation Most people in this situation would want the intervention and only a small proportion would not.	**Weak negative recommendation** Most patients would not want the intervention, but many would. Clinicians should spend adequate time with patients to discuss their preferences.	**Strong negative recommendation** Most people in this situation would not want the intervention and only a small proportion would.
• Long-term oxygen therapy in patients with clinically significant resting hypoxemia • Lung transplantation where appropriate	• Combined acetylcysteine, azathioprine and prednisolone* • Acetylcysteine monotherapy • Anti-coagulation* • Pirfenidone	• Corticosteroid monotherapy • Colchicine • Cyclosporine A • Combined corticosteroid and immune-modulator therapy • Interferon gamma 1b • Bosentan • Etanercept

**Subsequent to the publication of the ATS guidelines in 2011 negative results for PANTHER-IPF and ACE-IPF studies were released. The implications of these studies for using triple therapy and anti-coagulation are discussed in more detail later in this document.*

reflected the extent to which one can, across the range of patients for whom the recommendation is intended, be confident that desirable effects outweigh undesirable effects (19). This GRADE system may not be ideally suited to such a rare condition as IPF that has no established current recommended treatment. Indeed, discrepancies between the decisions of the Food Drug Agency (FDA), the European Medicines agency (EMA), and the 2011 International Guideline committee demonstrate that there are different ways to interpret data from RCTs.

Despite considerable research into its pathophysiology and treatment, IPF has historically been refractory to conventional pharmacological interventions. The vast majority of agents that have been used in the treatment of IPF are not recommended due to the lack of clinical evidence, poor quality data, contradictory results or evidence of potential harmful effects, complications and early morbidity and mortality. Corticosteroids, administered either alone or in combination with immunomodulatory therapy (e.g. cyclophosphamide or azathioprine), have been used for many years in the management of IPF. However, two Cochrane reviews investigating the role of corticosteroids and immunomodulatory agents in IPF failed to find any evidence of benefit (20,21). The 2011 guidelines gave a 'Strong No' against the use of corticosteroids used either alone or in combination with immunomodulatory therapy but only a 'Weak No' against the use of a corticosteroid plus azathioprine in combination with N-acetylcysteine (NAC) based on the results of the IFIGENIA study (4,22).

A clinical study has suggested that anti-coagulation might be of benefit for patients with IPF, particularly during acute exacerbation (23). Based on the available evidence, therefore, anti-coagulant therapy received a 'Weak No' recommendation from the ATS/ERS/JRS/ALAT committee (4). Similarly, other agents including colchicine, cyclosporine A, etanercept, bosentan, and interferon gamma-1b have been shown to have no benefit in the treatment of IPF. These agents have well-described significant toxicities and also have a strong recommendation against their use (4).

Pirfenidone is a small, orally available molecule whose primary anti-fibrotic activity is supplemented by additional anti-inflammatory properties (24). The anti-fibrotic properties of pirfenidone have been demonstrated across multiple animal models, in more than 40 publications and reports (24). To date, four placebo-controlled RCTs have evaluated the treatment of IPF patients with pirfenidone (25-27), including the two CAPACITY (Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes) programme consisting of two concurrent multinational RCTs (Studies 004 and 006) and two studies conducted in Japan (SP2 Phase II and SP3 Phase III studies) (25-27). The primary endpoint in the CAPACITY trials (change in % predicted forced vital capacity [FVC] from baseline to Week 72) was met in study 004 but not in 006. The baseline imbalances, with the intrinsic variability in rates of FVC decline in patients with IPF, could partly account for the attenuated rate of FVC decline in the placebo group in study 006, where the primary endpoint was not met

(25). The primary endpoint analysis of the pooled population showed a pirfenidone treatment effect on percentage predicted FVC at week 72 (-8.5% versus -11%, p=0.005), and a smaller proportion of patients had a decline in FVC of 10% or more in the pooled pirfenidone group (25). The primary endpoint in SP3 (vital capacity [VC] change at Week 52) was met, and although the primary endpoint of SP2 (the difference in the change in the lowest oxygen saturation by pulse) was not met, a significant change in VC was observed (26,27).

The ATS/ERS/JRS/ALAT guideline committee gave a 'Weak No' recommendation for pirfenidone, with high value placed on costs and side effects and low value on the possible reduction in pulmonary function decline (4). It must be noted, however, that the majority of committee members (16/31) abstained from voting on pirfenidone as most were involved in the CAPACITY trials. Under the voting definitions of the GRADE rubric, the panel felt that, while pirfenidone may not be appropriate for the majority of IPF patients, many would want the treatment (4).

A number of non-pharmacological therapies have also been evaluated in patients with IPF including long-term oxygen therapy, lung transplantation and pulmonary rehabilitation (28,29). Although lung transplantation is proven to be an effective treatment in IPF, most IPF patients are ineligible due to their older age, co-morbidities, or severely limited functional status (29).

Update of New clinical study data in IPF

Due to the obvious paucity of clinical study data at the time of publication, the 2011 treatment recommendations were based predominantly on expert opinion and not on evidence (4). New knowledge and evidence-based treatment options for this patient group has impacted in a significant way on how these patients are treated.

Triple therapy

The PANTHER-IPF study is an ongoing study conducted by the US National Heart, Lung and Blood Institute (NHLBI) and is comparing three treatment arms: triple therapy (prednisone, azathioprine, N-acetylcysteine [NAC]), NAC monotherapy and placebo for all three agents. The recently published results of a pre-planned interim analysis of this study revealed that there was an increased risk of mortality, more hospitalisations and more serious adverse events in patients with IPF treated with triple therapy compared to placebo (Figure 1) (30). The precise reasons for the increased rates of death and hospitalisation are unknown and it is difficult to assess which components of the three-drug regimen may be responsible for the observed outcomes. Consequently, the NHLBI discontinued the triple therapy arm of the PANTHER-IPF trial early in October 2011 due to safety concerns. Whilst it is not possible to make a definitive statement on the 'true' efficacy of the combination treatment due to early termination of the study arm, it is expected that the current management of IPF patients will change as this treatment regimen should no longer be used in newly diagnosed patients. The use of NAC antioxidant monotherapy remains inconclusive as the NAC monotherapy and placebo arm of the study is continuing.

Anticoagulation therapy

ACE-IPF evaluated the effect of warfarin versus placebo in a well-designed randomised, controlled trial (31). After an interim analysis, a low probability of benefit and an increase in mortality was observed in subjects randomised to warfarin (14 versus 3 placebo deaths; p<0.005) and the study was terminated in 2011 after 145 of the planned 256 subjects were enrolled (Figure 2). In ACE-IPF, warfarin (coumadin) was as-

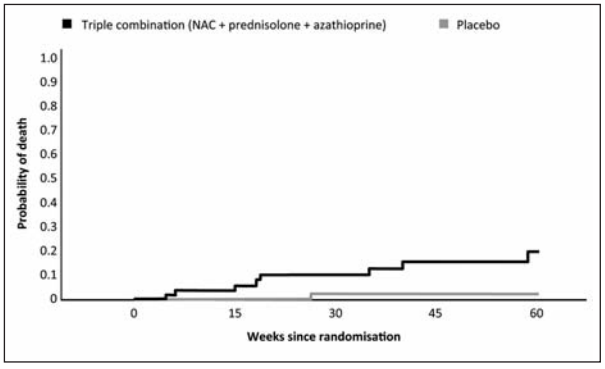

Fig. 1. PANTHER-IPF Study: mortality rates for triple therapy versus placebo. From N Engl J Med. Raghu G, Anstom JA, King Te Jr., Lasky JA, Martinez FJ. Prednisone, Azathioprine, and N-Acetylcysteine for Pulmonary Fibrosis. 2012; 366:1968-77 (30). Copyright©(2012) Massachusetts Medical Society. Reprint with permission from Massachusetts Medical Society.

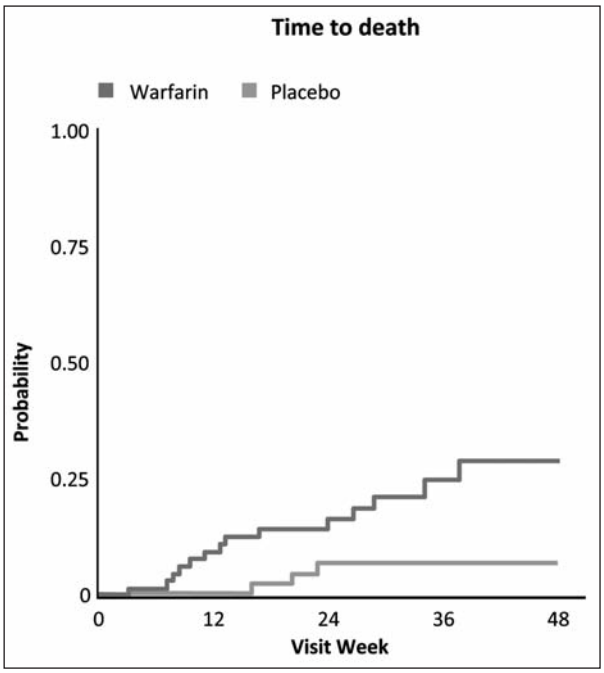

Fig. 2. Mortality rates in the ACE-IPF study. Reprinted with permission of the American Thoracic Society. Copyright© 2013 American Thoracic Society. Noth I, Anstrom KJ, Calvert SB, et al. 2012 A placebo controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2012; 186: 88-95 (31).

sociated with an increased risk of mortality in an IPF population who lacked other indications for anticoagulation (31). The study did not reveal if warfarin had any efficacy in IPF, but due to the considerable number of serious adverse effects, the use of anticoagulation treatment for IPF is discouraged unless patients have other reasons to be on these drugs.

Novel anti-fibrotic agents

IPF is characterised by formation and proliferation of fibroblast foci. Endothelin-1 acts on the Endothelin A (ET_A) receptor to modulate lung fibroblast proliferation and contraction (32). Selective and dual Endothelin Receptor Antagonists (ERAs) have therefore been investigated as novel treatments in IPF. Macitentan (ACT-064992) is an orally active, non-peptide dual endothelin (ET_A) and (ET_B) receptor antagonist effective in pulmonary arterial hypertension that was studied in the MUSIC (Macitentan Use in an Idiopathic Pulmonary Fibrosis Clinical Study) trial (33). Unfortunately, this trial did not meet the primary endpoint of change in FVC from baseline. Ambrisentan, which is also a selective ET_A antagonist, was studied in ARTEMIS-IPF (A Randomized, Placebo-Controlled Study to Evaluate Safety and Effectiveness of Ambrisentan in IPF). As with MUSIC, the ARTEMIS-IPF trial was stopped as an interim analysis indicated a low likelihood of showing efficacy for the endpoint by the scheduled end of the study and safety concerns (32). Investigation into other treatments continues with a number of Phase II and III ongoing studies. Imatinib has been studied in a small Phase II RCT but demonstrated no benefit regarding the primary outcome, time to disease progression, and no benefit in secondary outcome parameters (34). Nintedanib (BIBF 1120) is a triple kinase inhibitor that has been evaluated in a Phase II trial (35) at varying doses ranging (50 mg q.i.d., 50 mg b.i.d., 100 mg b.i.d., or 150 mg b.i.d.) versus placebo. In the group receiving 150 mg b.i.d., FVC declined by 0.06 litres per year, as compared with 0.19 litres per year in the placebo group (p=0.06) as well as a reduction in acute exacerbations. The 150 mg b.i.d. regimen was associated with gastrointestinal symptoms which led to more discontinuations than in the placebo group and increases in levels of liver aminotransferases. This treatment is currently being studied in Phase III trials.

Since the ATS/ERS/JRS/ALAT guidelines were prepared, additional evidence for pirfenidone has become available and the CAPACITY data published (25). Pooled data from both data sets of the CAPACITY studies provides strong evidence that pirfenidone reduces decline in lung function, the primary endpoint. Significant effects were also seen in secondary outcomes including reduced decline in the 6-Minute Walking Test (6MWT) distance and improvement in progression-free survival. A significant reduction in the proportion of patients who experienced a decline in FVC of 10% or more and in IPF-related mortality was also observed (Figure 3) (25). A Cochrane meta-analysis of pirfenidone including three clinical trials eligible for analysis, i.e. the Japanese SP3 trial and the two large, international, CAPACITY (004 and 006) trials showed that treatment with pirfenidone reduced the risk of disease progression disease progression or death by 30% (HR 0.70, 95% CI 0.56 to 0.88, p=0.002) (Figure 4) (26,27,36). Pirfenidone is the only drug to date to have shown a significant effect on progression-free survival (PFS) compared with placebo in patients with IPF.

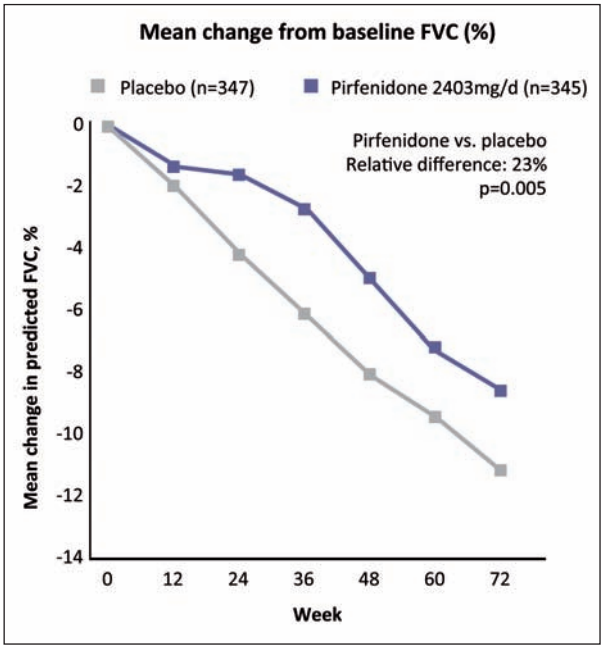

Fig. 3. Pooled analysis showed an overall treatment effect for pirfenidone on FVC. Reprinted from The Lancet. Noble PW, Albera C, Bradford WZ et al. CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. 2011; 377: 1760-9 (25) Copyright© (2011) with permission from Elsevier.

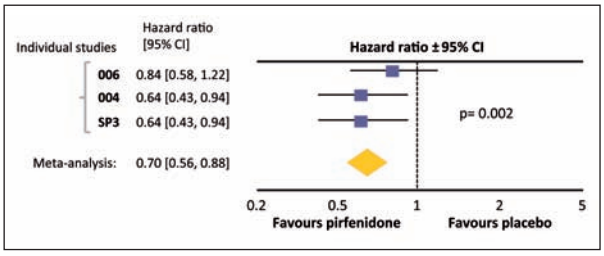

Fig. 4. An independent Cochrane review supports pirfenidone efficacy in IPF. Adapted from Spagnolo P, Del Giovane C, Luppi F, et al. Non-steroid agents for idiopathic pulmonary fibrosis. Cochrane Database Syst Rev 2010; (9): CD 003134 (36). Copyright© 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

An extension phase of the CAPACITY studies (RECAP) was designed to assess the safety of pirfenidone beyond the duration of the Phase III studies. Data from the RECAP extension study were highly consistent with those in pirfenidone-treated patients in the two previous randomised, controlled Phase III CAPACITY studies and confirm the tolerability of pirfenidone (37).

Further evidence for pirfenidone is awaited from an ongoing, randomised, multi-centre, double-blind, placebo-controlled Phase III trial (ASCEND) which is being conducted in the United States, Mexico, South America, Australia and New Zealand. This study is examining the efficacy of pirfenidone in IPF patients enrolled with more disease progression than in the CAPACITY trials, i.e. a forced expiratory volume in 1 second FEV_1/FVC ratio ≥0.80, %FVC upper limit of 90% and diffusing capacity of the lung for carbon monoxide DL_{CO} with a lower limit of 30%.

Update of national European Recommendations

The results of PANTHER-IPF and ACE-IPF have not yet been incorporated into the 2011 ATS/ERS/JRS/ALAT consensus guidelines (4), but it is anticipated that the results will change the 'weak against' recommendation for triple therapy and anticoagulants to a 'strong against' recommendation. In the meantime, several national European recommendation documents have been, or are being, updated, reflecting more recent evidence (Table 2).

Germany

A 'consensus conference' attended by German IPF experts was held in December 2011 with the aim of integrating the 2011 international guidelines and more recent data into the German Health System and facilitating the implementation of the guidelines in Germany (38,39). Representatives of the German Association for Pneumology and Respiratory Medicine (DGP), the German Association for Pathology (DGP) and the Working Group of Scientific Medical Associations (AWMF) participated in developing the guidelines which used the GRADE methodology despite its acknowledged limitations (38).

While most of the recommendations of the international guidelines were upheld, a number of important amendments were incorporated. Regarding the diagnosis of IPF, BAL was recommended in cases of suspected IPF for differential diagnosis and reflects common practice in Europe. However, it was not recommended to conduct a cellular BAL analysis in the diagnostic investigation of IPF. Amended treatment recommendations included upgrading the recommendation for pirfenidone from a 'weak negative' to a 'weak posi-

Table 2. Summary of national IPF treatment recommendations issued since 2011

Country	Type	Publication date	Treatment recommendation
Denmark	Guideline	2012	• Pirfenidone in patients with FVC >50% or DLco >35% • Strong recommendation against triple therapy in newly diagnosed patients • NAC monotherapy should be continued until new data become available
Ireland	Position statement	2012	• Pirfenidone weakly recommended (FVC <80% ≥50%; DLco >35%) • New patients should not be initiated on regimens containing prednisolone and azathioprine
Germany	Guideline	2013	• Pirfenidone weakly recommended • Triple therapy strongly disadvised in definitive IPF
Spain	Guideline	2013	• Pirfenidone first line for all patients with FVC >50% • In patients who progress, there is the possibility of designing pirfenidone combination regimens (4)
Sweden	Guideline	2013	• Pirfenidone is the first choice in patients with disease progression and FVC 50–80% and DLco >35% • Triple therapy should not be offered to any new patients • NAC monotherapy to be considered as an alternative in selected patients
Austria	Expert statement	2013	• Pirfenidone is the standard of care in mild-to-moderate IPF (FVC >50%, DLco >35%) • Triple therapy should not be offered to any new patients
UK	Health technology assessment	2013	• Pirfenidone recommended for idiopathic pulmonary fibrosis in patients with predicted FVC 50–80%
France	Practical management guidelines	2013	• Pirfenidone in patients with mild-to- moderate disease and FVC 50–80% and DLco >35% • NAC monotherapy to be considered in patients not eligible for pirfenidone or clinical trials • Triple therapy should not be offered to any new patients • Anti-coagulants, ERA not recommended

Abbreviations: DLco: diffusing capacity of the lung for carbon monoxide; ERA: endothelin receptor antagonist; FEV_1: forced vital capacity; NAC: N-actetylcysteine.

tive' for patients with low and moderate degrees of severity, based on the results from the CAPACITY trials and the Cochrane meta-analysis. The recommendations for treatment with anticoagulants and triple therapy for patients with IPF were downgraded to 'strong negative' based on the recent evidence (38,39).

Spain

The ATS/ERS/JRS/ALAT statement prompted the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) to publish revised guidelines for IPF diagnosis and treatment in 2013 (40). Pirfenidone is recommended as first-line treatment for mild-to-moderate IPF (FVC >50%, DL_{CO} >35%), while NAC's true efficacy as monotherapy cannot be elucidated until data from the PANTHER clinical trial are available. Evidence-based recommendation propose NAC monotherapy for selected patients. Anticoagulant use and triple therapy with NAC were listed in the 'not recommended' section (Figure 5) (40).

Denmark

In Denmark there is a regular review of guidelines to take into account new clinical data and relevant recommendations for clinical practice and the Danish Society of Respiratory Medicine reviewed

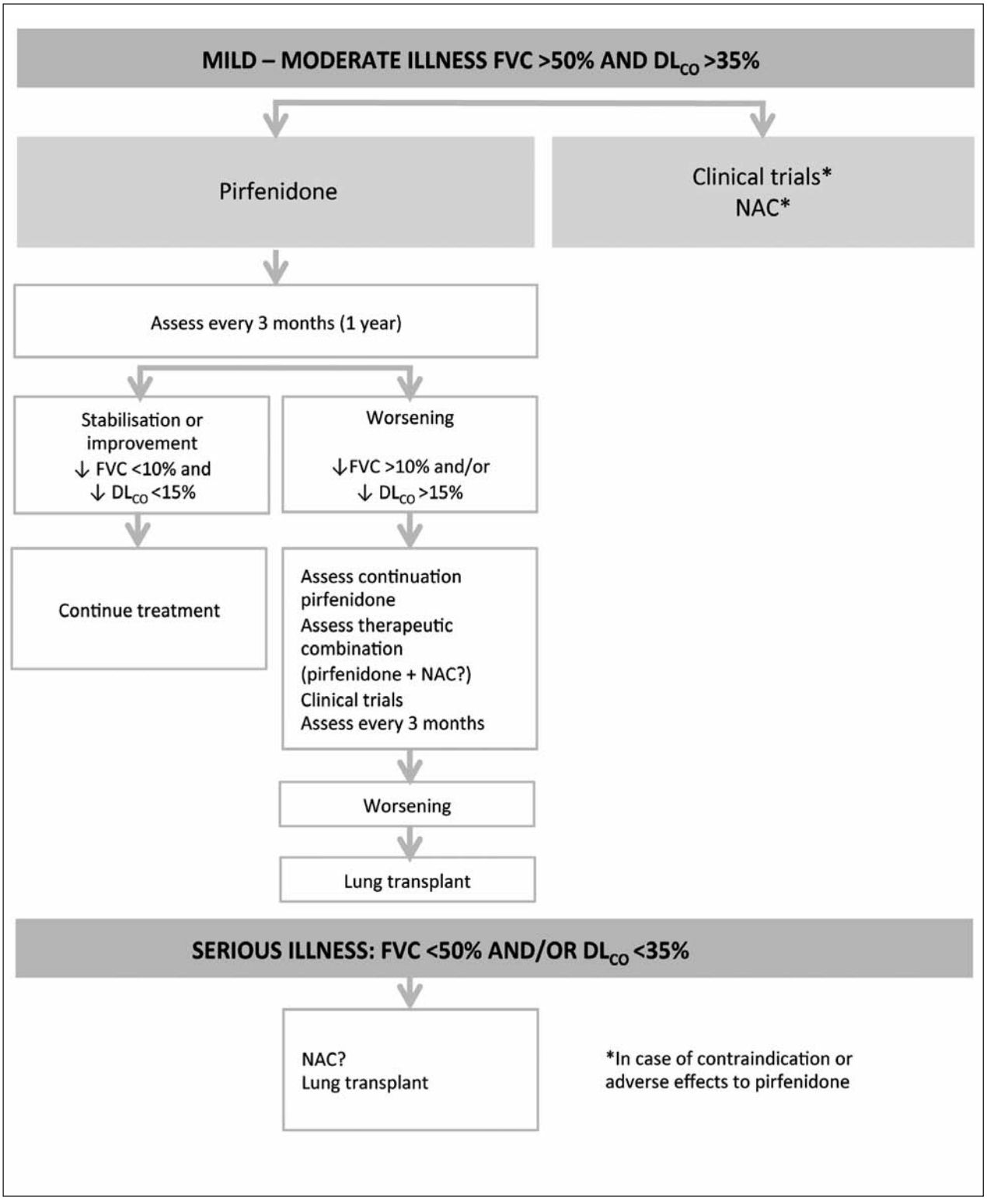

Fig. 5. Summary of pharmacological recommendations for IPF in the Spanish Guidelines for Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis. Adapted from Xaubet A, et al. Arch Broncopneumol 2013; 49: 343-53 (40).

their IPF guidelines in 2012 (41). The guidelines refer to the interim results from the PANTHER-IPF study and strongly recommend avoiding triple therapy in patients newly diagnosed with IPF. It is also recommended that patients on triple therapy are well informed about the results and that discontinuation of azathioprine and prednisolone may be considered. Use of NAC monotherapy should be continued until results from the NAC only arm of the PANTHER-IPF study become available. Treatment with pirfenidone was recommended for those with mild-to-moderate IPF and should be continued even when there is disease progression. Pirfenidone is not recommended for patients with more severe IPF (FVC <50% or transfer factor of the lung for carbon monoxide [TL_{CO}] <35%) (41).

Ireland

In recognition of the new evidence that has emerged, the Irish Thoracic Society (ITS) issued a 'Position Statement' in the form of an update to their existing guidelines (42). This statement carried a recommendation for pirfenidone in patients with mild-to-moderate IPF; however, it was highlighted that pirfenidone should be excluded in patients with evidence of airflow obstruction (FEV_1/FVC ratio of 0.7). In establishing this position for pirfenidone, the Irish Thoracic Society cited 'results from two large, pivotal, international, placebo-controlled, randomised clinical trials along with supporting data from two Japanese clinical trials and the Cochrane meta-analyses'. Consistent with the PANTHER-IPF study findings, triple therapy with NAC was not advised for new patients diagnosed with IPF and no immediate decision has been made on NAC monotherapy (42).

Sweden

The Swedish Respiratory Society published an update of the 'Care Programme for IPF' in 2012 in line with newly available evidence (43). The revised document begins by renaming idiopathic fibrosing alveolitis to IPF, reflecting current opinion that inflammation is no longer thought to be the main pathogenic driver of this condition. The Swedish guidelines also point out that evaluation of patients for treatment should also always include the possibility of lung transplantation. While mentioning that triple therapy with NAC was originally recommended on the basis of IFIGENIA trial results, the society has now withdrawn this recommendation in light of the PANTHER-IPF triple therapy arm termination. Anticoagulant therapy for IPF was not recommended for patients unless there was another indication for this treatment. Treatment with pirfenidone is reviewed in the document and referral made to the Swedish Dental and Pharmaceutical Benefits Agency (TLV) indication for pirfenidone in patients with mild-to-moderate IPF, specifying an upper limit of FVC <80% predicted and progressive disease. Pirfenidone is the first treatment of choice in symptomatic patients with an IPF diagnosis and a predicted FVC of 50% or more. Patients with advanced disease (FVC <50%) have not been studied and treatment with pirfenidone cannot be recommended for this patient group until further data becomes available (43). It is recommended that treatment with pirfenidone should be given for at least six months, and patients should be clinically monitored initially every three months. If lung function remains stable after six months, or if it is judged that the decline in lung function has leveled off, treatment may continue. An alternative treatment, in selected patients, may be NAC monotherapy (43).

Austria

An Austrian 'expert statement' on IPF diagnosis and treatment was developed in March 2013 (44). The Austrian expert recommendations are based on the revised 2011 ATS/ERS consensus statement but also incorporate recommendations from the German guidelines. Regarding the diagnosis of IPF, BAL was recommended in cases of possible UIP or HR-CT patterns which are inconsistent with UIP for differential diagnosis and included in the diagnostic algorithm. Pirfenidone is recommended for patients with mild-to-moderate IPF based on a review of the data from CAPACITY, RECAP and the Cochrane meta-analysis. Triple therapy with NAC is not recommended in newly diagnosed patients with IPF based on PANTHER-IPF study findings. Furthermore, patients who are already treated with this triple therapy should be re-evaluated.

UK

The British Thoracic Society (BTS) published guidelines for the management of interstitial lung

disease in 2008 (45). This has been updated based on the results of the PANTHER-IPF study and now recommends that new patients with definite IPF should not be initiated on a regimen containing prednisolone plus azathioprine. In patients with definite IPF already receiving combination prednisolone/azathioprine/NAC therapy, it is recommended that azathioprine therapy in particular should be withdrawn if there is evidence of disease progression (declining lung function). In patients established on triple therapy with 'stable' disease, the decision to withdraw should be on a case-by-case basis. The interim results have no immediate implications on the use of NAC in IPF.

The National Institute for Health and Care Excellence (NICE) in the UK published recommendations on IPF in June 2013, and in addition to making revisions to treatment recommendations, emphasises the need for early diagnosis of IPF (46). NICE recommends against the use of endothelial receptor antagonists bosentan and ambrisentan for patients with IPF. The NICE committee recommended pirfenidone for the treatment of mild-to-moderate IPF (FVC 50%–80%) but cautioned that further long-term data was needed beyond efficacy at 72 weeks. It is noteworthy that this guidance sets an upper limit for the use of pirfenidone in patients with FVC less than 80% predicted, citing that the full trial population had milder IPF and fewer comorbidities than typically seen in UK clinical practice (45,46).

France

The *Commission de Transparence* of the *French Haute Autorité de Santé* (CT) recently specified the labeled indication for pirfenidone in patients with mild-to-moderate IPF defined as FVC ≥50% and DL_{CO} ≥35%. The CT stated that no other treatment had the same level of clinical evidence for IPF as pirfenidone and issued *an Amélioration du Service Médical Rendu* (ASMR) rating of level IV for this drug corresponding to a weak rating of added value in comparison with existing therapies.

Practical management guidelines for IPF have been developed independently by French expert centres under the auspices of the *Société de Pneumologie de Langue Francaise* (SPLF) for a variety of diagnosis and treatment issues, including pharmacological therapy (47). The SPLF recommended pirfenidone as first-line therapy in patients with mild-to-moderate IPF as defined by FVC ≥50% of predicted value and DLco ≥35% of predicted value. Triple therapy with NAC was strongly discouraged, while NAC monotherapy was considered an option after individual evaluation of the risk to benefit ratio in patients not eligible for pirfenidone or for inclusion into clinical trials. Corticosteroids, anticoagulants and ERAs were not recommended.

Summary of IPF treatment recommendations in European country guideline documents

Following the recent publication of data from the ACE-IPF and PANTHER-IPF clinical trials and further clinical evidence for pirfenidone in mild-to-moderate IPF, several key amendments have been consistently made to national recommendations for many European countries. The formerly widely accepted role of combined therapy of corticosteroids and an immunosuppressive agent (e.g. azathioprine) plus high-dose oral NAC is now strongly discouraged in patients newly diagnosed with IPF although the role for NAC monotherapy awaits completion of the monotherapy arm in PANTHER-IPF. Key changes in treatment recommendations for IPF therefore commonly include:

- Strong negative recommendations for triple therapy, anti-coagulation and ERA
- Recommendation for pirfenidone as first-line treatment for patients with mild-to-moderate IPF.

A further theme common to all management documents is that IPF patients should be managed and treated in designated specialist centres with the support of a multidisciplinary team. Investigations of ILD are often complex and include several examinations that need to be considered together in order to reach a reasonable diagnosis (48). In many cases this is only a probability diagnosis that must sometimes be reviewed when new information is obtained, such as responses to laboratory investigations or disease progression and treatment response. A multidisciplinary approach is proven to increase diagnostic certainty, and should therefore be a core component of the diagnosis and follow-up (4,48).

ERS expert statement on IPF

In addition to revisions in several national recommendation documents, an update of the ERS statement is also in progress. In contrast to the 2011 guidelines, the ERS statement will be developed using a modified Delphi technique – a structured method which is focused on the achievement of a consensus in the voting process (49). It is anticipated that this statement will be available in 2014.

Conclusions

The 2011 ATS/ERS/JRS/ALAT guidelines are more focused than the original guidelines published in 2000 for the diagnosis and treatment of IPF. Although this represents an advance, several limitations have been noted during the clinical application of these guidelines.

The 2011 guidelines focus primarily on 'definite' IPF, and while the definition of 'probable' and 'possible' IPF is an advance, there is a lack of management guidance for these highly prevalent clinical scenarios. Another issue is the ongoing ambiguity regarding the role of BAL; the importance of BAL in the diagnostic algorithm is no clearer than in the 2002 ATS/ERS Consensus Classification (4). While HRCT is central in the diagnostic pathway, the challenges associated with interpretation of HRCT appearances remains significant. Finally, the lack of a recommendation for a single pharmacological treatment highlights the need for improving treatment options and updating these guidelines in future. The recommendation ratings from the 2011 guidelines stemmed, partly, from the use of the GRADE system in evidence quality assessment, but also from the limited evidence available at the time the guidelines were developed – significant data have since emerged.

This mixed appraisal of the 2011 ATS/ERS/JRS/ALAT guidelines is apparent in the revisions that have been made, or are taking place, in several European national recommendation documents. While maintaining the many positive aspects of the 2011 guidelines, such as the use of HRCT without biopsy for the diagnosis of 'definite IPF', they have also made several updates. These revisions predominantly focus on treatment recommendations rather than diagnostic recommendations. Several consistent key revisions have been made across the guidelines of several European countries. In response to the new evidence which has emerged since the 2011 guidelines, strong negative recommendations have now been made for triple therapy, anticoagulants and ERAs such as macitentan and ambrisentan. In addition, pirfenidone, which has the highest grade of evidence supporting its use, has now been upgraded to a 'Weak Positive' in an increasing number of European countries and is now widely recommended as first-line treatment for mild-to-moderate IPF.

Results from recent studies have underlined the need for clear and unambiguous guidelines for IPF management. In addition to revisions in several European countries, an update of the ERS statement is also underway and amendments of the international guidelines are also expected in the future.

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