Review Article

Acute exacerbation of idiopathic pulmonary fibrosis—a review of current and novel pharmacotherapies

Maya M. Juarez, Andrew L. Chan, Andrew G. Norris, Brian M. Morrissey, Timothy E. Albertson

Division of Pulmonary, Critical Care and Sleep Medicine, University of California, Davis, School of Medicine and VA Northern California Health Care System, Sacramento, CA 95817, USA

Correspondence to: Timothy E. Albertson. Division of Pulmonary, Critical Care and Sleep Medicine, University of California, Davis, School of Medicine and VA Northern California Health Care System, 4150 V Street, Suite 3400, Sacramento, CA 95817, USA. Email: tealbertson@ucdavis.edu.

Abstract: Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive form of lung disease of unknown etiology for which a paucity of therapies suggest benefit, and for which none have demonstrated improved survival. Acute exacerbation of IPF (AE-IPF) is defined as a sudden acceleration of the disease or an idiopathic acute injury superimposed on diseased lung that leads to a significant decline in lung function. An AE-IPF is associated with a mortality rate as high as 85% with mean survival periods of between 3 to 13 days. Under these circumstances, mechanical ventilation (MV) is controversial, unless used a as a bridge to lung transplantation. Judicious fluid management may be helpful. Pharmaceutical treatment regimens for AE-IPF include the use of high dose corticosteroids with or without immunosuppressive agents such as cyclosporine A (CsA), and broad spectrum antibiotics, despite the lack of convincing evidence demonstrating benefit. Newer research focuses on abnormal wound healing as a cause of fibrosis and preventing fibrosis itself through blocking growth factors and their downstream intra-cellular signaling pathways. Several novel pharmaceutical approaches are discussed.

Keywords: Idiopathic pulmonary fibrosis (IPF); acute exacerbation (AE); drug therapy; treatment; clinical trials

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive form of lung disease with an unknown etiology that occurs primarily in adults in their fifties and sixties (1). The annual incidence of IPF in the USA using narrow case definitions has been reported to range from 6.8-16.3 cases per 100,000 population and 0.22-7.4 cases per 100,000 population in Europe (2). The prognosis is poor, with older studies reporting a median survival rate of 2-3 years from the time of diagnosis (3-5). While some patients with IPF will experience a progressive decline in lung function over time (6,7), the clinical course can be highly variable. Some patients experience acute exacerbations of IPF (AE-IPF) resulting in sudden progression of the disease with an up to 85% mortality rate during or immediately after AE-IPF (8,9). Treatment regimens for stable IPF in the past had mainly focused on decreasing inflammation, particularly with high dose steroids, to prevent progression to fibrosis. However, most anti-inflammatory therapies including corticosteroids have shown no significant benefits (6,10,11). Newer research has focused on abnormal wound healing mechanisms as a cause of fibrosis; raising the prevention of fibrosis itself as therapeutic target through the blocking of growth factors and downstream intra-cellular signaling pathways (12-14).

Disease-modifying treatment of IPF has awakened with the publication of results of several phase-3 clinical trials (15-17). King *et al.* (15) reported on the use of pirfenidone, an oral antifibrotic drug, in the Assessment of pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) trial and found that it met its primary

end point of a significant reduction in the one-year rate of decline in forced vital capacity (FVC). However, this trial did not assess effective treatment of AE-IPF. Indeed, one of the adverse events that led to discontinuation of study treatment was a worsening of IPF (15). Richeldi *et al.* (16) studied the effects of nintedanib, an inhibitor of several tyrosine kinases, in the INPULSIS-1 and -2 trials. While nintedanib reduced the decline in FVC in IPF patients, its effect was not consistent when applied to the risk of investigator-reported AE-IPF in these trials (16). The IPF Clinical Research Network evaluated the utility of N-acetylcysteine (NAC) as an IPF therapy in the Prednisone, Azathioprine, and NAC: A Study That Evaluates Response in Idiopathic Pulmonary Fibrosis (PANTHER-IPF) trial, and found that NAC had no positive effect on its primary endpoint of change in FVC after 60 weeks of treatment, or on the frequency of IPF exacerbations as compared to placebo (17). None of these trials reported an improved survival.

Understanding and controlling exacerbations represents a challenge. Given the significant mortality associated with AE-IPF (1,6,7,9,18), research into the pathogenesis, diagnosis and treatment of these exacerbations is imperative. This review highlights current and novel pharmacological therapeutic management approaches for AE-IPF.

Acute exacerbations of IPF (AE-IPF)

An AE-IPF is a sudden acceleration of the disease or an acute injury superimposed on already diseased lung (8,9). This process must be distinguished from other acute events such as infection, pulmonary embolism, pneumothorax, and heart failure, all of which can present in a very similar fashion to that of an AE in patients with IPF (8,9). There is no universal definition of an AE-IPF, but standard criteria proposed by Collard *et al.* (9) help to distinguish AE from conditions that may mimic its presentation. These criteria include a previous or concurrent diagnosis of IPF with unexplained worsening or development of dyspnea within 30 days and new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT). The final requirement is the exclusion of other etiologies including infection, left-sided heart failure, pulmonary embolism, and an identifiable cause of acute lung injury (9).

Epidemiology

Incidence

The incidence of AE-IPF is highly variable in previous studies due to differences in study design as well as the lack of a standard definition for AE. A retrospective review of 461 patients with IPF using the definition of AE-IPF proposed by Collard *et al.* (9) reported a 1- and 3-year incidence of 14.2% and 20.7%, respectively (8). Another retrospective study utilizing the criteria for AE-IPF proposed by Taniguchi *et al.* in 2004 (19) involving 74 patients revealed a 1- and 3-year incidence of 8.6% and 23.9%, respectively (20). Kishaba *et al.*, (21) using a slightly broader definition of AE, which included a sudden aggravation of dyspnea within 30 days associated with new bilateral infiltrates in patients with known IPF, found an incidence of AEs of 9.8% in a cohort of 594 IPF patients over a 10-year period. The time to first incidence of AE-IPF is also highly variable with reports ranging from 3 to 60 months after initial clinic visit (5).

Risk factors and survival

Risk factors for AE-IPF identified by Song *et al.* (8) include lower FVC at baseline (mean of 72.0% of predicted for AE-IPF patients *vs.* 77.6% of predicted for patients without rapid deterioration at initial diagnosis; HR 0.979, P=0.011) as well as never having smoked (HR 0.585, P=0.050). The prevalence of baseline pulmonary hypertension (PH) in patients with IPF is also high, ranging from 32-46% in previous studies (22-25). PH at baseline is also associated with a significant risk of a subsequent AE-IPF (HR 2.217, P=0.041) and the presence of PH is associated with poorer overall survival (HR 4.74, P=0.206) (26). While the incidence of AE in relation to disease severity is unclear, more extensive disease on chest HRCT, including traction bronchiectasis, honeycombing, ground glass opacity and consolidation, is associated with higher mortality in AE-IPF, with a reported 3-month mortality of 80.6% in patients with extensive HRCT disease-stage compared to 54.5% in patients with limited disease-stage (P=0.007) (21). A systematic review of studies reporting 1- and 3-month survival rates after AE-IPF, demonstrated a pooled mortality rate over eight studies of 60% and 67%, respectively (27). Outcomes after AE with rapid deterioration in IPF are also poor, with a reported median survival of only 2.2 months from onset (8). Other smaller AE case series reported mortality rates as high as 85% and mean survival periods of

only 3-13 days (3,28-32). However, again, the definition of AE was not uniform in many of these older studies (33).

Etiology

The cause of AE-IPF is unknown. It is possible that AE may constitute a sudden acceleration of the underlying fibrotic disease (as characterized by enhanced epithelial injury and proliferation, and coagulation abnormalities) (34), or it may be triggered by other processes (35). Several possible mechanisms are proposed, including unrecognized infectious etiologies (6,36), and diffuse alveolar damage (DAD) caused by gastroesophageal reflux (GER) -related microaspiration (37-39) and medications such as α-interferon (40).

AE-IPF is associated with invasive procedures. Several case reports point to surgical lung biopsy, lung cancer resection, and bronchoscopy as causes of AE-IPF (41-43). A case series by Ghatol *et al.* suggested that AE-IPF can occur after either pulmonary or non-pulmonary surgery, with one patient experiencing AE-IPF following a total knee replacement (44). The authors postulate that intraoperative exposure to high oxygen concentrations and the high airway pressures or tidal volumes associated with mechanical ventilation (MV) may have been the precipitating factors. During the postoperative period, the parenchymal lung injury resulting from hyperoxia, barotrauma, or volutrauma could enhance the recruitment of circulating fibrocytes to the lung, resulting in worsening fibrosis (44). Although this suggests an association between AE-IPF and surgery, a causal relationship has not been proven.

Because patients with AE-IPF often present with symptoms suggestive of respiratory viral infection, viruses have also been considered a potential cause of AE-IPF. Herpesvirus and transfusion transmitted virus have been found in association with IPF and AE-IPF (45,46); an AE-IPF has also been reported after pandemic influenza A (H1N1) vaccination (47). It has thus been proposed that a considerable proportion of events deemed to be AE-IPF, are likely due to sequelae of infection (48). However, a well-controlled study by Wootton *et al.* found evidence of viral respiratory infection in only 4 of 34 patients who presented with AE-IPF (49). It would appear that viral infections do not play a major role in AE-IPF, however, findings in that study may be limited by the fact that patients may have presented after the initial infection could be detected, as such, viruses cannot be definitely excluded as the cause of AE-IPF (50).

Imaging and histopathology

The most common radiological finding in patients with AE-IPF is new ground-glass opacities superimposed on subpleural reticular and honeycombing densities (51). The pattern of ground glass opacities can be variable in degree and can range in their distribution from peripheral to multifocal to diffuse. Diffuse and multifocal ground glass patterns appear to predict a worse survival in patients with AE-IPF compared with patients peripheral patterns (28,52). In one series, median survival was reported as 16, 240, and 540 days for patients with diffuse, multifocal, and peripheral patterns on HRCT, respectively (OR =4.629; P=0.001 for combined diffuse and multifocal versus peripheral patterns) (52). The histopathology of AE is most commonly described as DAD superimposed on underlying UIP (6,9). It has also been characterized as UIP with organizing pneumonia or other findings not consistent with DAD, including acute lung injury without hyaline membrane formation. Wide distribution of fibroblastic foci away from the established DAD has also been observed (30,36,53).

Treatment of AE of IPF

Consensus guidelines

To date, no blinded, randomized, controlled trials specifically directed at the treatment of AE-IPF have been reported. The management approach currently recommended by international consensus, the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guidelines, includes only the use of supportive care and corticosteroids. Specifically, the recommendation is, "corticosteroids should be used in the majority of patients with AE-IPF, but not using corticosteroids may be a reasonable choice in a minority". This recommendation is weak and based on very low quality evidence, and no specific recommendations regarding the dose, route, and duration of corticosteroid therapy are made. There is consensus that supportive care should be the mainstay of therapy for AE-IPF (1). French practical guidelines for the treatment of AE-IPF state that in addition to their recommendation for the use of supportive care and corticosteroids, "it is possible to use intravenous cyclophosphamide". They also mention that there are "insufficient data regarding the use of low-molecular weight heparin to treat AE of IPF", but that "anticoagulant therapy may be prescribed in the case of

acute worsening of symptoms or if thromboembolic venous disease is suspected", and that "wide-spectrum antibiotics may be used when infection has not been definitely ruled out" (54).

The efficacy of these management strategies is largely untested and mortality continues to be high (8,9). Newer strategies targeting inflammatory mediators, fibrogenic mediators, fibroblast proliferation, and autoimmunity have also been preliminarily examined, and further studies in these areas are ongoing. Approaches for the treatment and prevention of AE-IPF are summarized in *Tables 1* and *2*, respectively.

Corticosteroids

Acute respiratory distress syndrome (ARDS) is typically characterized by DAD, as is AE-IPF. Because the potent anti-inflammatory properties of corticosteroids may offer some benefit in some stages of ARDS (79-81), corticosteroid therapy is often selected to treat AE-IPF despite the lack of clear evidence to support its use for this indication (1,82). Some have reported adverse outcomes in association with corticosteroid use in AE-IPF, and cautioned that support for their use may be unjustified on the grounds that the same evidence used to recommend against corticosteroids in stable IPF, is used to recommend for them in AE-IPF in the absence of a known difference in their pathogenic mechanisms (83,84). Initial reports on the use of corticosteroids in AE-IPF described varying degrees of improvement in chest X-ray findings, pulmonary function, and blood gas values with high dose treatment (1,000 mg daily of methylprednisolone sodium succinate followed by taper) (36). Subsequent retrospective reviews of larger cohorts of patients treated for AE-IPF with corticosteroids in addition to other therapies lacked a uniform definition of AE and showed very high mortality rates. Specifically, for patients treated with steroids as sole immunosuppressive therapy, reported in-hospital mortality was 55% in 65 patients who received methylprednisolone pulse ≥500 mg/day or prednisolone in high (≥0.5 mg/kg) or low doses (≤0.5 mg/kg) (8); 100% in 14 patients in a review in which corticosteroid type and dose was not reported (55); and, 3-month mortality was 82% in 11 patients treated with corticosteroids and corticosteroid pulses (methylprednisolone 1 g/day for 3 days) (6).

Corticosteroids do not appear to prevent AE or reduce overall mortality. A recent meta-analysis of the placebo arms of randomized controlled trials of IPF by Atkins *et al.* demonstrated no statistical difference in mortality between trials that permitted (n=5) or disallowed (n=1) low dose corticosteroid use (11). In fact, the incidence of AE-IPF was lower in a study not permitting immunosuppressants than in those studies allowing corticosteroid therapy, and there were significantly more lower respiratory tract infections in patients receiving corticosteroids. Individual data regarding the dose and time course of corticosteroid use was not presented in this meta-analysis.

Corticosteroids and immunosuppression

Patients with AE-IPF may have elevated erythrocyte sedimentation rates or C-reactive protein (CRP) levels and leukocytosis in the absence of infectious agents. This, along with increased inteleukin-8, α-defensin, and ST2 protein levels (agents involved in fibrocyte recruitment or proliferation), suggests a triggered immune response with an active inflammatory environment rich in activated T cells and neutrophils (9,55,56). Several groups have combined the use of corticosteroids with cytotoxic agents such as cyclosporine or cyclophosphamide, and reported better survival in patients treated with the combination (8,56,58,60). While these studies have been largely retrospective and included small numbers of subjects under various definitions of AE-IPF, this suggests that the use of immunosuppressants in conjunction with corticosteroids is more effective than corticosteroid monotherapy.

Tacrolimus and corticosteroids

Tacrolimus is an immunosuppressant used mainly in allotransplantation and collagen vascular disease. Tacrolimus binds to and inhibits the protein phosphatase calcineurin, preventing T cell activation and down regulating interleukin-2 (IL-2) and other cytokines associated with T helper lymphocytes, although it has also been observed to enhance lung injury during the acute inflammatory phase (85). Tacrolimus is also known to prevent immune activation by inhibiting nuclear factor κ-light-chain-enhancer of activated B cells-κB (NF-κB), and to inhibit TGF-β-induced collagen deposition (85,86). Its utility in AE-IPF was addressed in a retrospective review by Horita *et al.* (57). Of 15 patients who received corticosteroids and broad-spectrum antibiotics, 5 also received continuous infusions of tacrolimus for 5-14 days, followed by oral tacrolimus. Target blood levels were 20 and 5 ng/mL for infusion and oral regimes, respectively. Survivors were continued on tacrolimus after

Table 1 Overview of select agents of potential therapeutic utility in AE-IPF

Agents for treatment of AE-IPF*	Potential mechanisms of action	Selected study or retrospective series	Treatment course and dose	Study design and number of AE-IPF subjects	Outcome
Corticosteroids without cytotoxic agents	Suppression of cellular and humoral immunity; reduction of proinflammtory molecules and suppression of neutrophil and leukocyte migration into the lung	Kondoh [1993] (36) Tajima [2003] (55) Parambil [2005] (30) Kim [2006] (6) Sakamoto [2010] (56) Song [2011] (8) Horita [2011] (57) Inase [2003] (58)	Typically, IV MP pulse 500-1,000 mg/day followed by PN in high (≥0.5 mg/kg) or low doses (≤0.5 mg/kg)	Retrospective case reports involving a total of 125 patients treated with corticosteroids (n=3, 14, 5, 11, 11, 65, 10, and 6 patients per series) No controlled trials of corticosteroids for AE-IPF specifically have been reported.	Kondoh: Survival ranged from 5 months to 2.5 years after AE-IPF in 3 patients In-hospital survival in subsequent series involving 84 patients ranged from 0% to 45%: Tajima: 14 of 14 patients died 5 to 274 days post admission Parambil: 5 of 5 patients died 20 to 57 days post admission Song: 36 of 65 patients died after an unspecified in-hospital follow-up period 3-month survival in remaining 38 patients: Kim: 18% Sakamoto: 55% Horita: 20% Inase: 33%
Cyclophosphamide + corticosteroids	Cytotoxic alkylating agent with anti-inflammatory properties	Ambrosini [2003] (29) Parambil [2005] (30) Okamoto [2006] (59) Morawiec [2011] (60)	Ambrosini: IV MP pulses (500-1,000 mg/day for 3 days and then 125 mg/day) and CYP bolus (500 mg/m^2) every 3 weeks Parambil: IV MP pulses 500-1,000 mg/day 3 days followed by PN, CYP 600-750 mg/m^2 every 3 weeks Okamoto: IV MP + CYP Morawiec: 1,000 mg MP pulses on days 1-3 followed by CYP infusion (500 mg) on day 4, increasing by 200 mg every 2 weeks up to 1,500 mg	Retrospective case reports involving a total of 45 AE-IPF (n=5, 2, 28, and 10 patients per series), and 7 SAE-IPF patients	Ambrosini: 1 of 5 patients survived at least 1.5 years until time of review; 4 of 5 died within 1 month. Survival: 1-month 20%, 3-month 20% Parambil: 2 of 2 patients treated after biopsy In-hospital survival: 0% Okamoto: 24 of 28 pts died within 30 days after AE-IPF with cyclophosphamide or cyclosporine A+ corticosteroids (report did not specify whether surviors received cyclophosphamide or cyclosporine A) Survival: 1-month 14%, 3-month 14% Morawiec: 2 of 10 AE-IPF patients 3 of 7 SAE-IPF survived 1 year. Overall 3-month survival was 72% Survival in AE-IPF: 1-month: 100%, 3-month: 50%, 6-month: 40% Survival in SAE-IPF: 1-month: 100%, 3-month: 100%, 6-month: 71%

Table 1 (*continued*)

Table 1 (*continued*)

Agents for treatment of AE-IPF*	Potential mechanisms of action	Selected study or retrospective series	Treatment course and dose	Study design and number of AE-IPF subjects	Outcome
Tacrolimus + Corticosteroids	Inhibitor of calceinurin, NFκB, and TGF-beta-induced collagen deposition	Horita [2011] (57)	Tacrolimus group: continuous IV tacrolimus (target blood level 20 ng/mL) for 5-14 days, followed by oral tacrolimus (target blood level 5 ng/mL), continued after discharge + IV MP pulses (1,000 mg/day for 3 days, tapered to 80 mg/day over 8 days), followed by oral PN (1 mg/kg/day, tapered by 20%/week) Non-tacrolimus comparison group: MP pulses (1,000 mg/day for 3 days) followed by IV or oral glucocorticoid (1 mg/kg/day, tapered by 10 or 20%/week)	Retrospective review of 5 AE-IPF patients treated with tacrolimus and 10 AE-IPF patients not treated with tacrolimus	4 of 5 patients in the tacrolimus group and 1 of 10 patients in the non-tacrolimus group survived their acute exacerbations over the period in review. Survival in tacrolimus (n=5) *vs.* non-tacrolimus group n=10): 1-month 80% *vs.* 60% 3-month 80% *vs.* 20% Median survival time: >92 days for tacrolimus group 38 days for non-tacrolimus group Repeat exacerbation within 6 months: 0 of 4 surviving patients from the tacrolimus group 4 of 10 non-tacrolimus group patients
Cyclosporine A + Corticosteroids	Cytotoxic alkylating agent with anti-inflammatory properties; inhibits calceinurin and TGF-beta-induced collagen deposition	Okamoto [2006] (59) Homma [2005] (61) Sakamoto [2010] (56) Inase [2003] (58)	Okamoto: IV CsA + MP Homma: corticosteroids with or without IV CsA (50-200 mg/day, blood trough: 100-150 ng/mL) Sakamoto: MP pulse (1,000 mg/day 3 days) followed by PN (0.5-1.0 mg/kg, tapered within 4 weeks) with or without CsA (100-150 mg/day) Inase: MP pulse (1,000 mg/day for 3 days) followed by oral PN (40-60 mg/day taper) with or without CsA (1-2 mg/kg/day)	Retrospective case series involving a total of 55 AE-IPF patients (n=28, 9, 11, and 7 patients per series)	Okamoto: 24 of 28 pts died within 30 days after AE-IPF with cyclophosphamide or cyclosporine A+ corticosteroids (available report did not specify whether surviors received cyclophosphamide or cyclosporine A). Survival: 1-month: 14%, 3-month—14% Homma: Mean survival time for CsA (n=7) *vs.* non-CSA group (n=6): 9.9 *vs.* 1.7 months Sakamoto: Survival in CsA (n=11) *vs.* non-CSA group (n=11): 1-month 91% *vs.* 82% (approx.) 3-month 80% *vs.* 55% (approx.) Inase: Survival in CsA (n=7) *vs.* non-CSA group (n=6): 1-month 100% *vs.* 83% 3-month 71% *vs.* 33%

Table 1 (*continued*)

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Agents for treatment of AE-IPF*	Potential mechanisms of action	Selected study or retrospective series	Treatment course and dose	Study design and number of AE-IPF subjects	Outcome
Sivelestat + Corticosteroids	Inhibition of neutrophil elastase	Nakamura [2007] (13)	Sivelestat and MP therapy for 3 days, followed by prednisone (0.5 mg/kg/day)	Retrospective review of 10 patients treated with sivelestat	6-month survival: 40%
Azathioprine + Corticosteroids	Cytotoxic agent inhibiting leading to selective lymphocyte dysfunction. Suppresses natural killer cell activity, antibody production, and antibody-dependent cellular cytotoxicity	Shishido [1992] (62)	AZA (15 mg/kg) + MP pulse followed by PN (0.8 mg/kg)	Single AE-IPF case report	Patient survived >6 months after treatment. Tapering of immunosuppression led to a recurrence 3 months later, calling into question the diagnosis of IPF
Procalcitonin-guided antibiotic use	Tool for detecting of bacterial inflammation to guide initiation and discontinuation of antibiotics	Ding [2013] (63)	PCT level threshold of 0.25 ng/mL	Randomized controlled trial of PCT-guided antibiotic use (n=33 *vs.* routine antibiotic therapy (n=35)	PCT group *vs.* control group: Mean antibiotic treatment duation: 8.76.6 *vs.* 14.25.2 days Number of patients exposed to antibiotics: 79% *vs.* 100% No difference in outcome with respect to: Treatment success, mortality rate, days of hospitalization and duration of mechanical ventilation
Thrombomodulin + Corticosteroids	Anticoagulation by increased activation of protein C	Tsushima [2014] (64)	MP pulse (1,000 mg/day 3 days) followed by PN (1 mg/kg/day) + thrombomodulin (0.06 mg/kg/day 6 days)	Prospective open-label study using retrospective cohort of patients not treated with thrombomodulin for comparison	Thrombomodulin group *vs.* historical control group 28-day survival: 65% *vs.* 17%, P=0.048

Table 1 (*continued*)

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Agents for treatment of AE-IPF*	Potential mechanisms of action	Selected study or retrospective series	Treatment course and dose	Study design and number of AE-IPF subjects	Outcome
Hemoperfusion with polymixin B-immobilized fiber column	Removal of endotoxins, reactive oxygen species, activated neutrophils, and proinflammatory, proangiogenic, and profibrotic cytokines (IL-9, IL-12, IL-17, PDGF and VEGF), amongst other substances	Seo [2006] (65) Noma [2007] (66) Tachibana [2011] (67) Abe [2012] (68) Oishi [2013] (69)	Seo: PMX-DHP (80-100 mL/min) 1-5 times for 2-6 hours over a variable time period, in combination with PN, CYP, or NAC Noma: PMX-DHP over 3 days + MP pulse (1,000 mg/day 3 days) followed by CYP (500 mg/day) followed by PN (30 mg/day and AZA (150 mg/day) maintenance. Tachibana: PMX-DHP (80-100 mL/min) + high-dose corticosteroids Abe: PMX-DHP (80-100 mL/min) once per day for 2 successive days + high-dose corticosteroids Oishi: MP pulse (1,000 mg/day 3 days) followed + PMX-DHP (80-100 mL/min) over 2 successive days	Seo: open label pilot (n=6) Noma: case report (n=1) Tachibana: retrospective review (n=19) Abe: restrospective multi-center review (n=73) Oishi: prospective case series (n=9)	Seo: 1-month survival: 67%; Noma: survived until discharge 44 days after treatment Tachibana: 1-month survival: 47.4%; 3-month survival: 26.3% Abe: 1-month survival: 70.1%, 3-month survival: 34.4% Oishi: 3-month survival: 66.7% Typically, respiratory status and P/F ratio improved after first treatment, although not always sustained; cytokine and activated neutrophil levels in BALF decreased after therapy
Plasma exchange + rituximab + corticosteroids	Autoantibody removal by plasma exchange (PEX). Immunoglobulin load reduction through B-cell depletion by rituximab	Donahoe [2013—abstract] (70)	MP (1,000 mg/day 1 day, then tapered from 40 mg/day over 4 weeks) + 5 PEX (1.5 plasma volume) over 6 days followed by IV rituximab (1,000 mg once per week for 2 weeks)	Two open-label studies are being conducted (NCT01266317 and NCT01524068). The results of one open-label study of 6 patients have been published as an abstract	4 of 6 patients died within 38 days; 2 of 6 patients survived >60 days. 2 deaths were not directly attributable to AE-IPF These findings have not been peer-reviewed

*Therapeutic agents in this table were usually administered in combination with antibiotics and various supportive care measures. AE-IPF, acute exacerbation of IPF; AZA, azathioprine; BALF, bronchoalveolar lavage fluid; CsA, cyclosporine A; CYP, cyclophosphamide; IL, interleukin; IV, intravenous; MP, methylprednisolone; NAC, N-acetylceysteine; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; PCT, Procalcitonin-guided antibiotic use; PDGF, platelet-derived growth factor; PEX, Plasma exchange; P/F, arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2); PMX-DHP, Hemoperfusion with polymixin B-immobilized fiber column; PN, prednisolone; SAE-IPF, sub-acute exacerbation of IPF; TGF-beta, transforming growth factor beta; VEGF, vascular endothelial grow.

Table 2 Overview of select agents of potential therapeutic utility for the prevention of AE-IPF

Agents for prevention of AE-IPF	Potential mechanisms of action	Selected study or retrospective series	Dose	Study design and number of subjects	Outcome
Corticosteroids	Suppression of cellular and humoral immunity; reduction of proinflammtory molecules and suppression of neutrophil and leukocyte migration into the lung	Atkins [2014] (11)	Typically, PN in low doses (≤20 mg/day)	Meta-analysis of placebo arms of eight randomized, controlled trials of various therapies in stable IPF; six trials reported on AE-IPF events Total patients in placebo arm n=1,631, total patients taking corticosteroids n=266	No difference in the rate of AE-IPF in trials permitting corticosteroid use *vs.* trials not allowing immunosuppression (IRR 3.93, P=0.14). Higher rate of AE-IPF in trials including patients with severe disease (IRR =0.23, P<0.0001); higher rate of use of low-dose immunosuppression in this group use may increase risk of AE-IPF. Incidence of respiratory infection was significantly higher in patients on corticosteroids (IRR 3.58, P<0.0001)
Azathioprine + Corticosteroids + N-acetylcysteine	Cytotoxic agent inhibiting leading to selective lymphocyte dysfunction. Suppresses natural killer cell activity, antibody production, and antibody-dependent cellular cytotoxicity	IPF Net [2012] (71)	Prednisone (0.5-0.15 mg/kg/day) + AZA (1.0-2.0 mg/kg/day) + NAC (600 mg 3 per day)	Prospective, double-blinded, randomized placebo-controlled trial of triple therapy (n=77) *vs.* NAC (n=81) *vs.* placebo (n=78) in stable IPF	Triple therapy arm was stopped early, after interim analysis. Triple therapy group *vs.* placebo group: Deaths: 8 *vs.* 1 (mostly due to respiratory causes) Hospitalizations: 23 *vs.* 7 AE-IPF events: 5 *vs.* 0 Serious adverse events: 24 *vs.* 0
Systemic anticoagulants + corticosteroids	Systemic anticoagulation via inhibition of vitamin K reduction	Kubo [2005] (72) Noth [2012] (73) Tomassetti [2013] (74)	Kubo: PN (0.5 to 1.0 mg/kg/day for 4 weeks, with subsequent tapering of the dose to 10 to 20 mg/day over a 1-month period) + Warfarin with targed INR between 2.0 to 3.0 Noth and Tomassetti: Warfarin with targed INR between 2.0 to 3.0	Kubo: randomized open label trial prednisolone + warfarin/low molecular weight heparin(n=23) *vs.* prednisolone + placebo (n=33) in stable IPF Noth: ACE-IPF trial: double-blind, randomized, controlled trial of warfarin (n=72) *vs.* placebo (n=73) in stable IPF Tomassetti: retrospective review of stable IPF patients on anticoagulant (n=23) *vs.* not taking anticoagulants (n=79)	Kubo: Mortality from AE-IPF in warfarin *vs.* placebo groups: 18% *vs.* 71% (2 in 11 AE-IPF *vs.* 15 in 21 AE-IPF, P=0.008) Noth: Incidence of AE-IPF in warfarin *vs.* placebo: n=8.3% *vs.* n=2.7%, respectively, P=0.17 Tomassetti: No significant difference in incidence of AE-IPF in anticoagulant *vs.* non-anticoagulant groups: 22% *vs.* 23% (5 of 23 *vs.* 18 of 79 patients) No significant difference in AE-IPF mortality rate: 60% *vs.* 66%, (3 of 5 *vs.* 12 of 18 patients)

Table 2 (*continued*)

Table 2 (*continued*)

Agents for prevention of AE-IPF	Potential mechanisms of action	Selected study or retrospective series	Dose	Study design and number of subjects	Outcome
Azithromycin	Macrolide antibiotic with antiinflammatory qualities, inhibits some Gram-positive bacteria, some Gram-negative bacteria, and many atypical bacteria	Liu [2011] (75)	Azithromycin (oral, dose not available)	Randomized controlled trial of azithromycin (n=50) *vs.* placebo (n=60) for 12 weeks in stable IPF	After 12 weeks: Decreased TGF-beta1 level in azithromycin group patients AE-IPF admissions: 8% *vs.* 22% in azithromycin group *vs.* control group
Nintedanib (formerly BIBF1120)	Angiokinase inhibitor targeting proliferative growth factors in fibroblasts (FGFR, PDGFR, VEGFR)	Richeldi [2014] (16)	Nintedanib 150 mg/day	Two randomized, double-blind, multi-center, placebo-controlled trials in stable IPF: INPULSIS-1 nintedanib group n=309; placebo group n=204 INPULSIS-2 nintedanib group n=329; placebo group n=219 Pooled data nintedanib group n=638; placebo group n=423	Inconsistent results with respect to incidence of and time to first AE-IPF between the 2 trials Time to first AE-IPF INPULSIS-1: no difference between nintedanib *vs.* placebo group (HR =1.15, P=0.67) INPULSIS-2: longer time to first AE-IPF in nintedanib group (HR 0.38; P=0.005) Frequency of AE-IPF in nitedanib *vs.* placebo groups INPULSIS-1 nintedanib *vs.* placebo groups: 3.6% *vs.* 9.6% INPULSIS-2 nintedanib *vs.* placebo groups: 6.1% *vs.* 5.4% Pooled data on time to first AE-IPF No difference in time to first AE-IPF in nintedanib group *vs.* placebo group (HR=0.64, P=0.08) Smaller proportion of patients with AE-IPF in nintedanib group (4.9% *vs.* 7.6% in placebo group)

Table 2 (*continued*)

Table 2 (*continued*)

Agents for prevention of AE-IPF	Potential mechanisms of action	Selected study or retrospective series	Dose	Study design and number of subjects	Outcome
Pirfenidone	Inhibition of TGFβ, anti-inflammatory, antioxidant	Azuma [2005] (14) Taniguchi [2010] (76) Noble [2011] (77) King [2014] (15)	Azuma: pirfenidone (titrated from 600 up to 1,800 mg/day) or placebo Taniguchi: pirfenidone (1,200 or 1,800 mg/day) or placebo Noble: Study 004: pirfenidone (1,197 or 2,403 mg/day) or placebo Study 006: pirfenidone (2,403 mg/day) or placebo	Azuma: randomized, double-blind trial of pirfenidone (n=72) *vs.* placebo (n=35) in stable IPF Taniguchi: randomized, double-blind trial of pirfenidone in high dose (n=110) *vs.* low-dose (n=56) *vs.* placebo (n=109) for stable IPF Noble: two randomized, double-blind trials of pirfenidone	Azuma: incidence of AE-IPF significantly lower in pirfenidone group *vs.* placebo group (0% *vs.* 14%; P=0.0031). Trial is stopped early for this reason. Taniguchi: no significant difference in the incidence of AE-IPF in high dose *vs.* low dose *vs.* placebo groups (5.6% *vs.* 5.5% *vs.* 4.8%) Noble: no significant difference in time to worsening IPF (including AE-IPF, death, transplant, or respiratory hospitalization) King: did not assess effect on AE-IPF
N-acetylcysteine	Repletion of glutathione stores to restore natural oxidant/anti-oxidant balance	IPF Net [2014] (17)	NAC 600 mg 3 per day	Prospective, double-blinded, randomized placebo-controlled trial of NAC (n=133) *vs.* placebo (n=131) in stable IPF over 60 weeks	Incidence of AE-IPF in NAC *vs.* placebo groups: 2.3% *vs.* 2.3%, P>0.99
Anti-acid therapy	Prevention of microaspiration due to acid reflux	Lee [2013] (78)	Routine use of anti-acid therapy (PPI or H2B)	Analysis of placebo arms of 3 randomized, controlled trials of various therapies in stable IPF Total patients in placebo arms n=242; total patients taking anti-acids at baseline, before randomization into trial n=124 (PPI, n=113; H2B, n=11)	Incidence of AE-IPF in anti-acid *vs.* no-anti-acid groups*: 0% *vs.* 7.6%, P<0.01 Patients with GER diagnosis in anti-acid *vs.* no-anti-acid groups*: 89% *vs.* 25%

*94% of patients in antacid group continued this therapy throughout the study and 16% of patients in the no-antacids group started anti-acid therapy during the study. ACE-IPF, anticoagulant effectiveness in idiopathic pulmonary Fibrosis; AE-IPF, acute exacerbation of IPF; AZA, azathioprine; FGFR, fibroblast growth factor receptor; GER, gastroesophageal reflux; H2B, histamine-2 blockers; INPULSIS, Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients; IRR, incidence rate ratio; NAC, N-acetylceysteine; PDGFR, platelet derived growth factor receptor; PN, prednisolone; PPI, proton pump inhibitors; TGF-beta, transforming growth factor-beta; VEGFR, vascular endothelial growth factor receptor.

discharge. Four of the five patients in the tacrolimus group and one of the ten patients in the non-tacrolimus group survived their initial or subsequent AE during the review period (57). Median survival in the tacrolimus group was significantly longer than in the non-tacrolimus group (>92 *vs.* 38 days, respectively, P<0.05). In contrast to the fact that no surviving patients from the tacrolimus group had a repeat exacerbation from at least 3 and up to 6 months after their initial AE, four of the non-tacrolimus group patients died from re-exacerbation between 1 to 4.5 months after their initial AE. The authors postulate that tacrolimus may restrain the fibrotic phase of DAD that is characterized by remodeling, thereby averting subsequent exacerbations. Larger, multi-centered randomized studies are needed to fully understand the efficacy of tacrolimus in the treatment of AE-IPF.

Cyclosporine A and corticosteroids

Like tacrolimus, cyclosporine A (CsA) binds to and inhibits calcineurin, restricting lymphocyte proliferation by down regulating transcription of IL-2, IL-3 and IL-4, tumor necrosis factor (TNF)-alpha, CD40 ligand, granulocyte-macrophage colony-stimulating factor, and interferon-gamma (87,88). *In vitro*, however, these effects of CsA are 100 times less powerful than those exhibited by tacrolimus (57). The usefulness of CsA in AE-IPF has been evaluated in a few small non-randomized retrospective studies. Inase *et al.* (58) evaluated thirteen patients with AE-IPF, seven of whom received CsA (1.0-2.0 mg/kg per day) after treatment with corticosteroids (pulse therapy with methylprednisolone 1,000 mg per day for 3 days followed by oral prednisone 40-60 mg per day and maintained for 4 to 8 weeks). They reported a survival of between 60 and 208 weeks in 4 of 7 AE-IPF patients treated with CsA. In contrast, all six patients who did not receive CsA died within sixty-six weeks after the onset of AE-IPF. Homma *et al.* (61) reported that while 34 of 35 AE-IPF patients in a historical comparative cohort had died within 4 months of the exacerbation, 6 of 9 AE-IPF patients treated with CsA (50-200 mg/day combined with corticosteroids for at least 7 days) survived from 7 up to 35 months after the event. A more recent study also reported a better mean survival for AE-IPF patients treated with CsA (low dose 100-150 mg/day) and corticosteroids (pulse therapy with methylprednisolone 1,000 mg per day for 3 days followed by maintenance dosage 0.5-1.0 mg/kg) (285 days, n=11) than those received corticosteroids alone (60 days, n=11) (56). Large randomized multi-centered studies are still needed to understand the potential role of CsA in the treatment of AE-IPF.

Cyclophosphamide and corticosteroids

Cyclophosphamide is an immunomodulatory alkylating agent used in preventing graft-*vs.*-host disease and thought to spare regulatory T cells (89). Recent cancer research has focused on therapies that ablate the immunocompetent cells found in many tumors that convey immunosuppressive activity in a microenvironment that is consistent with the end of wound healing (90,91). Cyclosphosphamide is one such agent. A few case series involving different definitions of AE-IPF document the use of cyclophosphamide (as single intravenous bolus of 500-750 mg/kg) and corticosteroids (pulsed methylprednisolone from 0.5-1 g/day) in addition to various supportive care measures for AE-IPF (29,30,59). These case series report mixed results, most commonly no significant association between this therapy and significantly improved outcomes. More recently, Morawiec *et al.* (60) retrospectively evaluated the utility of combined pulse methylprednisolone therapy followed by pulse cyclophosphamide therapy in ten AE-IPF patients and seven IPF patients with sub-acute exacerbation (SAE-IPF, with an onset of symptoms as between 30-90 days prior to treatment). Treatment consisted of 1,000 mg methylprednisolone on days 1-3 followed by a cyclophosphamide infusion (500 mg) on day 4, increasing by 200 mg every 2 weeks up to 1,500 mg. The authors reported a 3-month survival of 50% in AE-IPF patients and 100% in SAE-IPF patients, and a 6-month overall survival of 56%, promising some benefit of this combination therapy (60).

Sivelestat and corticosteroids

Neutrophils have been implicated in the pathogenesis of bleomycin-induced pulmonary fibrosis (92), and resistance to bleomycin-induced pulmonary fibrosis has been observed in neutrophil elastase knockout mice (93). The utility of a neutrophil elastase inhibitor, sivelestat, in combination with corticosteroids was examined in a small non-randomized study of ten mechanically ventilated patients with AE-IPF (13). All patients were followed for 180 days and treated with sivelestat and methylprednisolone pulse therapy for 3 days, with subsequent maintenance therapy with prednisone (0.5 mg/kg/day). Four of ten patients survived to day 180. In

these survivors, the arterial oxygen tension (PaO_2)/inspiratory oxygen fraction (FiO_2) (P/F ratio), peak end expiratory pressure (PEEP) levels, and the values of peripheral white blood cell number and CRP were significantly improved on day 7 as compared to baseline. Larger, multi-centered studies are still clearly needed to determine whether sivelestat is of clinical and survival value in AE-IPF.

Azathioprine and corticosteroids

Azathioprine, a widely used cytotoxic drug that blocks the function of proliferating cells such as T cells and B cells and also decreases the number of circulating monocytes and granulocytes (94), can be used as a steroid-sparing agent in AE-IPF, although there is a dearth of data to support this. A single case report of the use of azathioprine in the treatment of AE-IPF has been published (62). The patient received pulse therapy with methylprednisolone followed by prednisolone (0.8 mg/kg) and azathioprine (15 mg/kg). The patient had marked improvement in hypoxia and chest X-ray findings after five weeks. Azathioprine use in stable IPF, however, is not associated with prevention of AE-IPF. The PANTHER-IPF trial (NCT00650091) (17,71), demonstrated that patients treated with triple therapy with prednisone, azathioprine, and NAC experienced significantly more AE-IPF events than those on placebo.

Antibiotics

The role of the respiratory microbiome has been only scantily investigated in AE-IPF (45). In studies looking at treatment and outcomes in AE-IPF, the vast majority of people received empiric antibiotics in addition to corticosteroids despite the absence of any controlled study demonstrating a benefit with empiric treatment (27). The use of antibiotics in patients with AE-IPF is largely based on the fact that many patients present with fever, flu-like symptoms, and have elevated neutrophil counts in BAL fluid when bronchoscopy is performed (6,36). Unfortunately, this typically leads to prolonged antibiotic courses in patients with AE-IPF in whom no pathogens have been identified, an approach that has been associated with increased risk for subsequent fungal infections and a higher incidence of drug-resistant organisms (95). Procalcitonin, a peptide more abundantly present in the setting of microbial toxins and bacterial proinflammatory molecules, is useful in detecting whether the cause of inflammation is bacterial in origin and in guiding the initiation and discontinuation of antibiotics in patients with acute respiratory infections (96,97). A recent study evaluated the utility of procalcitonin values to guide the use of antibiotics in AE-IPF (63). Antibiotic therapy guided by a procalcitonin threshold of 0.25 ng/mL resulted in a reduction of antibiotic treatment duration (8.7±6.6 *vs.* 14.2±5.2 days, P<0.001) as well as fewer patients being exposed to antibiotic treatment (26 of 33 procalcitonin group patients *vs.* 35 of 35 standard care group patients, P<0.001), in the absence of significant differences in treatment success or mortality rates. The specific antibiotics used in these trials were unfortunately not reported, although many were described as broad-spectrum. Azithromycin, an antibiotic known for its anti-inflammatory qualities, has been evaluated for the treatment of IPF. It demonstrated a significant reduction in both fibrosis and restrictive lung function pattern in a bleomycin induced pulmonary fibrosis mouse model (98). Although azithromycin use in IPF patients was reportedly associated with a lower rate of AE-IPF admissions in one study (75), no formal clinical trials examining the use azithromycin in patients with AE-IPF have been reported to date. It appears that antibiotics therapy during the treatment of AE-IPF is best guided by clinical findings and procalcitonin level monitoring.

Nintedanib

Nintedanib inhibits three tyrosine kinase receptor families including platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF) (12). It has been proposed that these growth factors activate signal transduction cascades that result in the development of fibrosis and therefore pose an intriguing target for therapy in IPF (99-101). In the Phase IIb TOMORROW trial (NCT00514683), treatment with nintedanib was associated with slower decline in lung function, decrease in the frequency of AE-IPF and improvement in quality of life (12). In one of two subsequent randomized placebo-controlled Phase III clinical trials performed simultaneously (INPULSIS-1 and -2, NCT01335464, NCT01335477), significantly fewer patients treated with a target dose of 150 mg twice daily of nintedanib experienced an AE-IPF event as compared to those receiving placebo (3.6% *vs.* 9.6%, respectively), and patients treated with nintedanib had a significant delay in time to first exacerbation (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005). When data from the two trials

were pooled, nintedanib treatment was associated with a significantly longer time to adjudicated AE. However, because these effects were not observed in the other study, it is unclear whether nintedanib may serve to prevent exacerbations or significantly delay the time to first exacerbation. Nintedanib has not been formally investigated as a therapy for AE-IPF.

Anticoagulants

Inflammation and vascular injury, including the loss of epithelial cell integrity, have been demonstrated in fibrotic lung disease and therefore the presence of thrombosis in the pulmonary vasculature may also be present (72). In addition, the coagulation cascade is thought to marshal subsequent inflammatory and fibroproliferative responses during normal wound healing (102). The coagulation, inflammation, fibroproliferation and tissue remodeling associated with normal wound healing response may, as a result of repeated tissue injury or aberrant repair mechanism in IPF lungs, result in excessive deposition of extracellular matrix proteins (102). Treatment of IPF with anti-coagulants has produced mixed results. An initial study examined the effects of treatment with corticosteroids alone or in combination with anticoagulant therapy (72). The authors reported better survival in those receiving anticoagulation, due in large part to improved survival in subjects with AE-IPF. The mortality from AE-IPF in the anticoagulant group, (18%, 2 in 11 AE) was significantly reduced compared to that of the non-anticoagulant group (71%, 15 in 21 AE). This study, however, has been criticized based on low subject retention rate, high incidence of AE overall, and lack of blinding (18,103). A follow up double-blind, randomized, placebo-controlled trial of warfarin, the ACE-IPF trial, showed warfarin to be ineffective and potentially harmful as a therapy for patients with IPF and AE-IPF (73). AE of IPF were noted to occur in a greater number of subjects in the warfarin group compared with the placebo group (n=6 *vs.* n=2, respectively, P=0.17), and there were no significant treatment effects observed in the secondary endpoints (FVC, 6-minute walk distance, and carbon monoxide diffusion). The trial was ended early due to the low probability of benefit and an increase in mortality in the warfarin group. Another retrospective cohort study by Tomassetti *et al.*, demonstrated that patients with IPF treated with anticoagulants had worse survival and shorter interval to disease progression (74).

More recently, increased deposition of total lung collagen in an animal model of viral exacerbation of pulmonary fibrosis in which the extrinsic coagulation cascade was upregulated has been reported in an abstract (104). The authors suggest that, when taken together with the failure of the studies employing systemic anticoagulants described above, coagulation activity may be both harmful and beneficial in pulmonary fibrosis and that anticoagulant interventions should thus be targeted toward specific profibrotic processes.

Thrombomodulin, a protein expressed by epithelial cells, functions as a cofactor that binds to thrombin to greatly increase the activation of protein C. Recombinant human thrombomodulin (rhTM) is approved as a treatment for disseminated vascular coagulopathy in Japan. After confirming that AE-IPF patients in a historical cohort exhibited signs of hypercoagulability, Tsushima *et al.* (64) prospectively evaluated the utility of rhTM in 20 patients with AE-IPF. Six historical cases of AE-IPF patients not treated with rhTM were used for comparison. All patients received methylprednisolone pulse therapy (1 g/day for three days) followed by prednisolone (1 mg/kg/day), and were on positive pressure ventilation. The patients in the treatment group also received 0.06 mg/kg/day rhTM for 6 days). The 28-day mortality was significantly higher in untreated patients as compared to those receiving rhTM (83% *vs.* 35%, P=0.048). The authors also reported improved SpO_2/FiO_2 and a reduction in the degree of intravascular coagulation disturbance in association to rhTM administration (64). These results are encouraging and merit further exploration to define the role of thrombomodulin in the treatment of AE-IPF.

Pirfenidone

Pirfenidone has demonstrated anti-oxidant, anti-inflammatory, and antifibrotic effects in experimental models of pulmonary fibrosis (14). An initial prospective trial involving a group of 107 IPF patients was completed in Japan (14). Patients received either pirfenidone or placebo in a dose-titration schedule (from 600 up to 1,800 mg/day). While the study did not reach its primary endpoint of improvement in the lowest oxygen saturation during 6-minute exercise testing, a positive treatment effect in the secondary endpoints of change in vital capacity at 9 months and a lower incidence of AE-IPF events in the treatment group was observed, with all five episodes of AE-IPF at the 6 months interim analysis occurring in the placebo group. This study was discontinued in favor of pirfenidone based largely on the notion that

it could prevent AE-IPF. Unfortunately, larger follow-up trials (Taniguchi *et al.*, and the CAPACITY-1 and -2 studies NCT00287729 and NCT00287716) did not confirm the reduction in incidence of AE-IPF (dosing of pirfenidone in the latter trials ranged from 1,197 to 2,403 mg/day) (76,77). Another subsequent phase 3 trial, the ASCEND study (NCT01366209), documented improvement in stable IPF, but did not assess effective treatment of AE-IPF (15). Currently there are no compelling data to support the use of pirfenidone in AE-IPF.

Hemoperfusion with polymyxin B-Immobilized fiber column

One potential therapy for AE-IPF currently under study is direct hemoperfusion with a polymyxin B (PMX)-immobilized fiber column (PMX-DHP). PMX-DHP columns absorb endotoxins and reactive oxygen species (ROS), amongst other substances, and also selectively remove activated neutrophils, reducing the ability of circulating cells to cause endothelial damage (105-107). The use of PMX-DHP columns has been studied in patients with ARDS, which, like AE-IPF, is characterized by DAD, and improvement in oxygenation has been observed after therapy (108,109). The use of PMX-DHP for AE-IPF has been explored in Japan. An open-label pilot study and a case report including a total of seven AE-IPF patients indicate that therapy is safe and might be of benefit (65,66). In addition, a retrospective review of 19 AE-IPF subjects reported a median survival of 22 days after diagnosis of AE in polymyxin-treated patients. Survival rates after diagnosis of AE were 47%, 32% and 26% at 1, 2, and 3 months, respectively. Serum levels of IL-7, an inhibitor of fibroblast TGF-β production and signaling were significantly increased in the surviving subjects, possibly indicating an anti-fibrotic mechanism in the action of PMX-DHP (67,110). A larger retrospective study of 160 patients with interstitial pneumonia (IP), that included 73 patients with IPF demonstrated that, in patients with AE-IPF, P/F ratio was significantly improved after treatment with PMX-DHP compared to pre-PMX-DHP (173.9±105.4 to 195.2±106.8 Torr, respectively, P=0.003) (68). A subsequent study examined the possible mechanism of action of improvement in oxygenation by PMX-DHP by examining the cytokine profile adsorbed onto the PMX-DHP fibers (69). They found a significant reduction in serum levels of cytokines including IL-9, IL-12, IL-17, PDGF and VEGF, with IL-12 and VEGF the most significantly reduced. The authors postulate that the observed therapeutic effects of PMH-DHP are based on the adsorption of proinflammatory, profibrotic, and proangiogenic cytokines by PMX-DHP-fibers. Specifically, the removal of VEGF may contribute to the improvement in oxygenation by suppressing vascular permeability in the lung. Finally, a recent abstract reported that the 3-month survival of patients treated with PMX-DHP was better than those not receiving this treatment (72% of 14 patients *vs.* 48% of 18 patients, respectively, HR 0.33, P=0.04) (111). Although direct hemoperfusion with PMX-DHP therapy is promising, larger, randomized multicenter trials are still needed to determine its role in AE-IPF.

Plasma exchange, rituximab, and corticosteroids

The pathogenesis of AE-IPF has also been linked to antibody-driven autoimmunity leading to epithelial cell apoptosis (112). A variety of unconventional IgG autoantibodies have been observed in as many as 80% of IPF patients, and some, like anti-heat shock protein 70, are associated with increased mortality and pulmonary function deterioration (113,114). Reducing the presence of antibodies or deposition of immune complex could therefore be of benefit in AE-IPF. Two studies to test the feasibility of autoantibody removal by plasma exchange (PEX) together with immunoglobulin load reduction by B-cell depletion with rituximab, in combination with or without anti-inflammatory corticosteroids for the treatment of AE-IPF are currently being conducted (NCT01266317 and NCT01524068). Recently, the outcomes of six AE-IPF subjects treated with PEX and rituximab were published in abstract form. All received intravenous methylprednisolone (1 g), then an oral taper from 40 mg/day over 4 weeks and 5 PEX (1.5 times plasma volume) over six days, followed by rituximab (1 g intravenously, repeated after 1 week) (70). Results of these studies will help to guide larger, multicenter trials to ascertain the therapeutic utility of autoantibody reduction in AE-IPF.

Anti-acids

Microaspiration of gastroesophageal refluxate could be one of the key insults to the delicate lung parenchyma that leads to IPF and/or the cause of AE-IPF. The prevalence of GER in IPF patients is high, and pepsin has been found in the bronchoalveolar lavage fluid of patients with AE-IPF (37,115). An analysis of the placebo arms of three prospective, randomized, controlled trials of various therapeutic agents in stable IPF found that patients taking

antacids routinely (proton pump inhibitors or histamine-2 blockers at baseline, prior to randomization into a trial), were less likely to develop AE-IPF than patients not taking anti-acids (0 of 124 patients on anti-acids *vs.* 9 of 118 patients not on anti-acids) (78). Although further prospective study is warranted, this analysis suggests that control of gastroesophageal reflux with anti-acid therapy could be useful in preventing AE-IPF.

N-acetylcysteine (NAC)

NAC, an antioxidant, has been studied as a potentially therapeutic agent in IPF with the expectation that it could prevent the oxidative injury that precedes fibroproliferation by restoring the natural oxidant/antioxidant balance. In the PANTHER-IPF trial (17) (NCT00650091), oral NAC therapy (1,800 mg/day) did not result in a reduction in the incidence of AE-IPF. Patients talking NAC were in fact significantly more likely to develop a cardiac adverse event as compared to patients on placebo (6.8 % in the NAC group *vs.* 1.5% in the placebo group, P=0.03). NAC has not been considered as a therapy for use during an AE-IPF.

Non-invasive ventilation

Previous studies have suggested that there is no benefit to MV in patients with IPF presenting with acute respiratory failure and should be restricted to those patients who can have lung transplantation within several days of initiating MV (116). Given the high mortality rate associated with invasive MV, a small study involving 11 patients was performed to describe the outcomes in patient with AE-IPF who received noninvasive ventilation (NIV) (117). Five patients were able to avoid intubation and survived more than 3 months after their AE. Of the six patients who failed NIV, four required intubation and all died within 3 months. This suggests there may be a role for NIV in AE-IPF but further study is clearly needed.

Intraoperative management for AE-IPF prevention

Postoperative exacerbation of IPF (PAE-IPF) is a recognized complication after pulmonary resection and carries a high mortality rate (43,118,119). Appropriate intraoperative management of these patients is therefore profoundly important to prevent PAE-IPF and improve mortality. One area of interest is intraoperative fluid balance. Mizuno *et al.* retrospectively analyzed 52 patients with clinical IPF who underwent pulmonary resection for primary lung cancer (120). The incidence of PAE-IPF was 13.5% (7 of 52 patients), with six of the seven patients dying of respiratory failure. The authors reported an increased amount of intraoperative fluid infused (7.71±3.11 *vs.* 10.0±3.66 mL/kg/h, P=0.049) and intraoperative fluid balance (4.99±2.86 *vs.* 8.00±4.21 mL/kg/h) in the patients who developed PAE-IPF. A multivariate logistic analysis of all patients showed that increased intraoperative fluid balance was a prognostic factor for PAE-IPF (OR 1.312, P=0.026).

The influence of intraoperative oxygen delivered in patients with IPF has also been discussed as a potential risk factor in development of PAE-IPF. It has been suggested that AE-IPF is similar to acute lung injury/ARDS in that pulmonary injury is closely related to ROS (121). More specifically, high concentrations of oxygen stimulate the release of inflammatory cytokines including TNF-α, IL-8, IFN-gamma and IL-6 which can injure pulmonary endothelium and alveoli and can lead to pulmonary hemorrhage, lung edema, hyalinization and increased alveolar thickness (121). Ventilator-induced lung injury may also result from barotrauma or volutrauma, resulting in increased recruitment of circulating fibrocytes to the lung and worsening fibrosis (44). High pressure ventilation and inhalation of high oxygen concentrations should therefore be considered with caution in patients with IPF undergoing surgical procedures.

Conclusions

The AE-IPF is a severe and life threatening event that carries a high mortality rate and results in significantly reduced median survival. Current mainstays of AE-IPF treatment are limited and involve supportive care with the addition of corticosteroids, broad spectrum antibiotics and sometimes additional immunosuppression, even though little data exists to support this approach. Novel therapies targeted at inflammatory and fibrogenic mediators, autoimmunity, and fibroblast proliferation have shown promise in decreasing the incidence of AE-IPF or improving mortality from AEs. The combined use of tacrolimus and corticosteroids, removal of select immune system cells and mediators with PMX-DHP, and procalcitonin-guided antibiotic use are amongst the most promising. While these studies are encouraging, it is unfortunately not clear at this time whether treatment with any of the therapies discussed in this review will ever prove efficacious for AE-IPF under

the gold standard of a prospective, randomized, controlled clinical trial. This is mainly due to the great challenge that conducting such a trial would represent in this rare disorder that lacks a simple or uniform diagnostic method. Nevertheless, there is evidence to suggest that the prompt initiation of oxygen therapy, corticosteroids, antibiotics, and/or cyclophosphamide, is associated with a better prognosis (122). Given the likely complex pathophysiology of AE-IPF, it is also possible that a therapeutic approach involving multiple therapeutic modalities will result in better treatment outcomes. Advances in the development of new therapeutic agents for stable IPF are hoped to translate into a better understanding of the pathogenic mechanisms of AE-IPF, and subsequently to result in improved therapeutics and prognosis for this devastating condition.

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