Acute Exacerbation of Idiopathic Pulmonary Fibrosis

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Idiopathic pulmonary fibrosis (IPF) is a chronic, slowly progressive disease, but abrupt worsening without an identifiable cause, known as acute exacerbation (AE) of IPF, is not uncommon. Recently the significance of AE-IPF has become more and more evident. AE-IPF is a major cause of morbidity and mortality in patients with IPF, accounting for over half of all hospital admissions (Kubo et al., 2005; Song et al., 2011; Teramachi et al., 2018) and 40% of all deaths (Natsuizaka et al., 2014). Autopsy findings have also shown that AE was the most common immediate cause of death in patients with IPF (Daniels et al., 2008). AE usually occurs later in the course of the disease (Kondoh et al., 2010; Song et al., 2011; Collard et al., 2013, 2017; Ohshimo et al., 2014; Schupp et al., 2015), but some patients experiencing AE may not have an established diagnosis of IPF and, thus, AE can be the first manifestation of an underlying preexisting IPF (Kim et al., 2006). Although the real nature of AE including incidence, etiology or pathogenesis is still not clear and there is no proven effective therapy, much progress has been made since the consensus statements were published in 2007, which proposed a clear definition and diagnostic criteria for the first time. The revised definition in 2016 broadened the

inclusion criteria to make the diagnosis of AE-IPF more feasible in clinical practice and to help researchers clarify the nature of AE-IPF and find effective treatment. This article reviews and summarizes the present understanding of AE-IPF.

Definition

In 2007, the National Institutes of Health–sponsored IPF Clinical Network and clinical experts proposed a consensus definition and diagnostic criteria for AE-IPF (Collard et al., 2007). The criteria included a clinical worsening of less than 30 days duration, the presence of new radiologic abnormalities on high-resolution computed tomography (HRCT) with bilateral ground-glass opacification/consolidation, and the exclusion of alternative etiologies. Endobronchial aspirate or bronchoalveolar lavage (BAL) was recommended to exclude potential infectious etiologies and "suspected AE-IPF" was proposed in cases of missing data (Collard et al., 2007). These consensus criteria were originally proposed to standardize the inclusion criteria for future research. However, performing bronchoscopy is often not clinically feasible in patients with significant hypoxemia and even when it is performed, it frequently cannot confidently exclude an underlying infection. Furthermore, the evidence demonstrated that AE-IPF had similar clinical features and prognosis compared with nonidiopathic causes of acute respiratory worsening in IPF (e.g., infection or aspiration) (Song et al., 2011; Collard et al., 2013). Therefore, in 2016, an International Working Group published a revised definition of AE-IPF (Collard et al., 2016). In the current guidelines, AE-IPF is now defined by a clinically significant respiratory deterioration developing within typically less than 1 month, accompanied by new radiologic abnormalities on HRCT such as diffuse, bilateral ground-glass opacification with or without consolidation, and the absence of other obvious clinical causes like fluid overload, left heart failure, or pulmonary embolism. In the revised definition, the term "idiopathic" was omitted to allow for a broader inclusion of exacerbation, including those that may be triggered, thus enabling future researchers to better understand AE-IPF and to find effective therapies for this condition. The clinical scenarios that should be excluded, "fluid overload, left heart failure, or pulmonary embolism," are mentioned because these conditions have a different prognosis and require different therapy compared to AE-IPF. The new definition promotes discrimination between a triggered form of AE-IPF (e.g., infection, postprocedural/postoperative or drug toxicity) and an idiopathic form of AE-IPF, where no trigger is identified (Table 1).

Incidence

The reported incidence of AE is highly variable from less than 1% to almost half of patients with IPF, due to the different criteria and different patient populations studied. As shown in Table 2, the incidence of AE in the placebo arm of most randomized controlled trials (RCT) was low, >1–5%, in contrast to 5–28% 1-year incidence of retrospective cohort studies (Collard et al., 2016). In earlier RCTs, AE was not predefined or listed as a secondary end point, therefore the incidence was mentioned occasionally and only as

Table 1   Comparison of the definition and diagnostic criteria for acute exacerbation of idiopathic pulmonary fibrosis: 2007 vs. 2016.

Definition in 2007 (Collard et al., 2007)	Revised definition in 2016 (Collard et al., 2016)
Acute, clinically significant respiratory deterioration of unidentifiable cause	An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality
Diagnostic criteria	
(1) Previous or concurrent Dx of IPF[a]	(1) Previous or concurrent Dx of IPF[a]
(2) Unexplained worsening or development of dyspnea	(2) Acute worsening or development of dyspnea
● Within 30 days	● typically ,<1 month duration
(3) New bilateral ground-glass abnormality and/or consolidation superimposed on a background of IPF[b]	
(4) No evidence of pulmonary infection by endotracheal aspirate or BAL (should include studies for routine bacterial organisms, opportunistic pathogens, and common viral pathogens)	Deleted
(5) Exclusion of alternative causes, including the following:	(4) Deterioration not fully explained by
● Left heart failure	● Cardiac failure or
● Pulmonary embolism	● Fluid overload
● Identifiable cause of acute lung injury (ALI)	
(Causes of ALI: sepsis, aspiration, trauma, reperfusion pulmonary edema, pulmonary contusion, fat embolization, inhalational injury, cardiopulmonary bypass, drug toxicity, acute pancreatitis, transfusion of blood products, and stem cell transplantation)	
All 5 criteria	All 4 criteria

Patients with idiopathic clinical worsening who fail to meet all five criteria due to missing data should be termed "suspected acute exacerbations."
[a]If the diagnosis of idiopathic pulmonary fibrosis is not previously established this criterion can be met by the presence of radiologic and/or histopathologic changes consistent with usual interstitial pneumonia pattern on the current evaluation.
[b]If no previous high-resolution computed tomography is available, the qualifier "new" can be dropped.

Table 2   Incidence rate of acute exacerbation of idiopathic pulmonary fibrosis reported in randomized clinical trials.

Drug (reference)	Group	No. of patients	Age year	AE (%)	Non-smoker (%)	FVC	DL	Period	Criteria
Pirfenidone									
Azuma (Azuma et al., 2005)	Placebo	35	64.3	14.2	6	78.4	5.7	9 m	JRS
	Tx	72	64	0	11	81.6	57.6		
Taniguchi (Taniguchi et al., 2010)	Placebo	104	64.7	3.8	20.2	79.1	55.2	52 w	JRS
	Tx-low-dose	55	63.9	3.6	21.8	76.2	53.6		
	Tx-high dose	108	65.4	3.7	20.4	77.3	52.1		
CAPACITY-1 (Noble et al., 2011)	Placebo	174	65.7	1.7	29	76.2	46.1	77 w	IPFnet + PaO$_2$
	Tx-low dose	87	68	1.1	31	76.4	47.2		
	Tx-high dose	174	66.3	1.1	32	74.5	46.4		
CAPACITY-2 (Noble et al., 2011)	Placebo	173	67	0.6	37	73.1	47.4	77 w	IPFnet + PaO$_2$
	Tx	171	66.8	1.2	35	74.9	47.8		
Nintedanib									
TOMORROW (Richeldi et al., 2011)	Placebo	85	64.8	15.7	NA	77.6	75	52 w	
	Tx	85	65.4	2.4	NA	78.1	78.3		
INPULSIS-1 (Richeldi et al., 2014)	Placebo	204	67	5.4	25	80	47	52 w	IPFnet
	Tx	309	67	6.1	23	80	48		
INPULSIS-2 (Richeldi et al., 2014)	Placebo	219	67	9.6	32	78	46	52 w	IPFnet
	Tx	329	66	3.6	31	80	47		
N-acetylcysteine									
IFIGENIA (Demedts et al., 2005)	Placebo	64.4	64	1	31	75	74	1 Y	Resp. failure
	Tx	64.4	62	6	39	80	79		
Interferon gamma-1b									
INSPIRE (King Jr. et al., 2009)	Placebo	275	65.9	5.5	31	73.1	47.3		ARF
	Tx	551	66	4.5	28	72.2	47.4	64 w	
Bosentan									
BUILD-1 (King Jr. et al., 2008)	Placebo	83	65.1	3.6	NA	69.5	41.4	12 m	Acute decompensation
	Tx	71	65.3	1.4	NA	65.9	42.3		
BUILD-3 (King Jr. et al., 2011)	Placebo	209	63.2	2.9	32.1	73.1	47.9	20 m	AE (not defined)
	TX	407	63.8	4.7	38.1	74.9	47.7		
Imatinib									
(Daniels et al., 2010)	Placebo	60	67.8	1.7	36	65.6	39.3	96 w	Acute worsening
	Tx	59	66	8.4	28	64.4	39.8		
Sildenafil									
STEP-IPF (Zisman et al., 2010)	Placebo	91	68.2	4	24	58.7	26.7	12 w	IPFnet
	TX	89	70	2	24	55	25.8		

BUILD: Bosentan Use in Interstitial Lung Disease. *CAPACITY*: Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes. *IFIGENIA*: Idiopathic Pulmonary Fibrosis International Group Exploring *N*-Acetylcysteine. *INSPIRE*: Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis. *TOMORROW*: To Improve Pulmonary Fibrosis with BIBF 1120. *STEP-IPF*: Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis. *Y*: year.

AE: acute exacerbation; *ARF*: Acute respiratory failure; *d*: day; *DL*: carbon monoxide diffusing capacity; *FVC*: forced vital capacity; *m*: month; *Pirfenidone Low dose*: 1197 mg/day; *High dose*: 2403 mg/day; *Tx*: treatment; *w*: week.

Diagnostic criteria of acute exacerbation:

JRS: Japanese Respiratory Society criteria: manifestation of all of the following: (1) worsening, otherwise unexplained clinical features within 1 month, progression of dyspnea over a few days to less than 5 weeks, (2) new radiographic/high-resolution computed tomography (HRCT) parenchymal abnormalities without pneumothorax or pleural effusion (e.g., new, superimposed ground-glass opacities), (3) a decrease in the PaO$_2$ by 10 mmHg or more, and (4) exclusion of apparent infection based on absence of *Aspergillus* and Pneumococcus antibodies in blood, urine for *Legionella pneumophila*, and sputum cultures.

IPFnet:

(1) previous or concurrent diagnosis of IPF, (2) unexplained worsening or development of dyspnea within 30 days, (3) HRCT with new bilateral ground-glass opacification/consolidation, (4) no evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage, (5) exclusion of alternative causes.

INPULSIS-AE criteria: all of the following criteria: (1) unexplained worsening or development of dyspnea within the previous 30 days; (2) new diffuse pulmonary infiltrates visualized on chest radiography, HRCT, or both, or the development of parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since the preceding visit; and (3) exclusion of any known causes of acute worsening, including infection, left heart failure, pulmonary embolism, and any identifiable cause of acute lung injury, in accordance with routine clinical practice and microbiologic studies.

BUILD-1:

● AE: Not specified but the data are mentioned as acute decompensation

● Acute decompensation (unexplained rapid deterioration over 4 weeks with increased dyspnea requiring hospitalization and oxygen supplementation >5 L/min to maintain a resting oxygen saturation (arterial blood gas; SaO$_2$) > 90% or PaO$_2$ >_55 mmHg (sea level) or 50 mmHg (above 1400 m).

CAPACITY

1) Worsening of PaO$_2$ (>8 mmHg drop from most recent preworsening)

2) Clinically significant worsening of dyspnea

Table 2   (Continued)

3) New superimposed GGO on HRCT in >1 lobe

4) All other causes such as cardiac, thromboembolism, aspiration, or infectious processes have been ruled out.

STEP-IPF: Acute Exacerbations

The following three criteria will define AE in subjects with acute worsening of their respiratory conditions:

1. Clinical (all of the following required): (A) Unexplained worsening of dyspnea or cough within 30 days, triggering unscheduled medical care (e.g., clinic, study visit, hospitalization); (B) No clinical suspicion or overt evidence of cardiac event, pulmonary embolism, or deep venous thrombosis to explain acute worsening of dyspnea; (C) No pneumothorax.

2. Radiologic/Physiologic (only 1 of the following required): (A) New ground-glass opacity or consolidation on computed tomography (CT) scan or new alveolar opacities on chest X-ray. (B) Decline of $\geq 5\%$ in resting room air SpO_2 from last recorded level OR decline of ≥ 8 mmHg in resting room air PaO_2 from last recorded level.

3. Microbiologic (all of the following required): (A) No clinical evidence for infection (i.e., absence of grossly purulent sputum, fever $> 39°C$ orally); (B) No microbiologic evidence of infection (i.e., clinically significant bacterial growth on sputum or endotracheal aspirate cultures, quantitative culture by protected brush specimen ≥ 103 cfu/mL or bronchoalveolar lavage ≥ 104 cfu/mL or the presence of specific pathogens on stains of any of the above).

acute decompensation, acute worsening or acute respiratory failure. Most of the RCTs were performed on mild to moderate severity of IPF without significant comorbidities. In contrast, poor lung function is the most consistent risk factor of AE in the cohort studies. Therefore, the incidence of AE in the RCT may be lower than the incidence in general patient population due to exclusion of IPF patients with more severe disease. Further, the definition of AE is important; in a *post hoc* analysis of the Sildenafil Trial of Exercise Performance in Idiopathic Pulmonary Fibrosis (STEP-IPF) (Zisman et al., 2010), definite AE-IPF occurred in 4 per 100 patient-years, but combining definite and suspected AE-IPF increased the incidence to 20 per 100 patient-years (Collard et al., 2013). The annual rate of AE in a registry-based US study was even lower, 0.13 per patient-year (Fernandez Perez et al., 2010).

Risk Factors

Poor Lung Function, Advanced Disease

Advanced disease with low lung function is the most consistent risk factor of AE-IPF in the majority of the studies, including low forced vital capacity (FVC) (Kondoh et al., 2010; Song et al., 2011; Collard et al., 2013, 2017; Ohshimo et al., 2014; Schupp et al., 2015), low diffusion capacity for carbon monoxide (DLco) (Miyazaki et al., 2008; Collard et al., 2013; Schupp et al., 2015), low total lung capacity (TLC) (Miyazaki et al., 2008; Qiu et al., 2018), lower 6-min walking distance (Collard et al., 2013), impaired baseline oxygenation (Collard et al., 2013, 2017; Kondoh et al., 2015), a recent decline in FVC (Kondoh et al., 2010, 2015; Reichmann et al., 2015), and an increase in dyspnea (Kondoh et al., 2010; Collard et al., 2013). There are some who suggest that advanced disease itself may not increase the real incidence, but increases the chance for recognition due to more symptoms and signs in the patients with already poor physiologic reserve. However, this higher occurrence of AE in the patients with lower lung function was seen not only in cohort studies, but has also been observed in RCTs. In the INPULSIS trials, where AE-IPF was a secondary end point, the 1-year-incidence of AE in patients with a FVC of <70% predicted was 14.9%, but in those with an FVC >70% predicted the incidence was 3.3% (Costabel et al., 2016). Also a meta-analysis of six RCTs showed that AE occurred less frequently in trials excluding severe disease (28.2 vs. 122.9 AE/1000 patient years^{-1}, $P < 0.0001$) (Atkins et al., 2014). In the INPULSIS-ON study (the open-label extension of the INPULSIS trials), a *post hoc* subgroup analysis demonstrated that the progression of disease and fatal events were more frequent in the subgroup of patients with more severe disease (FVC $\leq 50\%$ at the start of the extension phase) than in patients with a less severe disease, although the difference was not statistically significant (Wuyts et al., 2016).

Prior History of Acute Exacerbation

Acute exacerbation was reported to be more common in the patients with previous history of AE (Kubo et al., 2005; Johannson et al., 2014; Reichmann et al., 2015; Sato et al., 2014).

Comorbidity

Coexisting pulmonary hypertension (Judge et al., 2012; Qiu et al., 2018) and coronary artery disease (Collard et al., 2013) have been reported as a risk factors for AE-IPF.

Higher Serum Krebs von Lungen-6 (KL-6) Level

Elevated serum levels of KL-6 at baseline have been associated with an increased risk for AE-IPF, after adjustment for clinical features including vital capacity (VC) (Ohshimo et al., 2014). Sato et al. reported that on multivariate analysis, KL-6 along with surgical procedures, history of AE, %VC, and male sex were the independent risk factors for the occurrence of AE in 1235 cases with lung cancer and IPF (Sato et al., 2014). Qui et al. reported that higher serum KL-6, poor pulmonary function, mechanical procedures, and

secondary pulmonary hypertension were associated with increased risks of AE-IPF on meta-analysis of seven studies (Qiu et al., 2018).

High Body Mass Index (BMI)

Kondoh et al. reported that high BMI was a risk factor for AE (Kondoh et al., 2010), but there are some conflicting data (Qiu et al., 2018).

Smoking

There is controversy on the effect of smoking and AE in IPF. Song et al. (2011) and Kishaba et al. reported an increased incidence of AE in never-smoking IPF patients (50% in never-smokers vs. 18.2% in ever-smokers, $P < 0.0001$). However, some studies have observed a higher risk in former smokers (Ohshimo et al., 2014; Collard et al., 2017).

Ethnic Differences

It has been suggested that the East Asian patient population may be at greater risk for AE compared with patients of other races (Saito et al., 2018). However, in the INPULSIS study, the incidence of AE in Asian patients was similar to whites, in both the placebo and nintedanib groups. Among Asians, AE developed in 4.9% of the nintedanib group and 7.6% of the placebo group. In Caucasian patients, AE was reported in 3.6% of the nintedanib group and 6.9% of the placebo group (Taniguchi et al., 2016).

Etiology and Triggering Factors

In most cases of AE-IPF, the cause or triggering factor is not certain. But in some cases, AE develops after a preceding event, such as following surgery or after administration of a pulmonary-toxic medication. The following are triggering factors that have been reported in AE-IPF.

Infection

Fever, "flu-like" symptoms and neutrophilia in BAL fluid specimens implicate an underlying infectious etiology, especially viral. Many studies report that AE occurred more frequently in winter and spring months (Simon-Blancal et al., 2012; Costabel et al., 2016; Oda et al., 2016) and in patients taking immunosuppressive medications. One large study of 220 patients with ILD (100 cases of IPF, 120 cases of non-IPF) showed that 20% of patients were diagnosed with an infection in the setting of an acute respiratory worsening (Moua et al., 2016, #138). Although these accompanying clinical features suggest an infectious etiology, efforts to prove infection in AE-IPF have not been successful. Wootton et al. (2011) tested BAL fluid and serum from patients with AE-IPF, stable IPF, and those with acute lung injury (ALI) without IPF for viral nucleic acid using multiplex polymerase chain reaction testing, pan-viral microarray, and high-throughput cDNA sequencing. Of the 43 patients with AE-IPF, only four had the evidence of a common respiratory virus (parainfluenza, rhinovirus [$n = 2$], and coronavirus). No viruses were detected in the stable IPF patients. Additional pan-viral microarrays revealed evidence of nonrespiratory viruses in 15 patients with AE-IPF: herpes simplex virus, Epstein–Barr virus, and torque teno virus (TTV) ($n = 12$). TTV was found in similar percentages (24%) of patients with ALI. The clinical significance of TTV remains to be determined. Konishi et al. also failed to identify any gene transcription profiles that would be expected in a viral infection, in both patients with AE-IPF and stable IPF (Konishi et al., 2009). In a prospective study of *C. pneumoniae* infection triggering AE-IPF, only two patients had an antibody response (Tomioka et al., 2007), suggesting that *Chlamydophila* is an unlikely trigger for AE-IPF.

Although existing data do not support the role of infection/viruses in all, or even in a majority of cases of AE, it is still possible that infection triggers AE. Due to the relative insidious onset of AE (up to 30 days), any triggering viruses would likely no longer be detectable by the time of clinical presentation of AE, leaving only the acute lung injury pattern with aggravation or acceleration of the underlying interstitial lung disease (ILD). Also, the detection of infection is difficult even with invasive procedures. Autopsy studies found that 28.8% of patients with AE-IPF had a bronchopneumonia (fungal: 13.5%; cytomegalovirus: 11.5%; and bacterial: 9.6%) identified postmortem, but were clinically unsuspected, highlighting difficulties in diagnosing infection in this setting (Oda et al., 2014). A recent study of 119 bronchoscopies performed in 106 ILD patients presenting with acute respiratory failure showed that only 16 of 119 (13%) revealed a potential cause of respiratory worsening (Arcadu and Moua, 2017). Furthermore, identifying infection has not yet been demonstrated to affect outcomes, despite the treatment of microorganisms identified by BAL fluid, a fatal outcome eventually occurred and mortality remained high (Blivet et al., 2001).

Recent studies on the human lung microbiome have shown that changes in number and composition may play an important role in the pathogenesis and progression of lung diseases, including IPF (Han et al., 2014; Molyneaux et al., 2014). Integrated analysis of the host transcriptome and microbial signatures demonstrate an interaction between host and environment in IPF. The response to an altered and more abundant microbiome remains during longitudinal follow-up, suggesting that the bacterial communities of the lower airways may act as a persistent stimulus for repetitive alveolar injury in IPF (Molyneaux et al., 2017b).

In the BAL fluid of AE-IPF, bacterial burden was also increased compared to stable IPF, with an increase in *Campylobacter* sp. and *Stenotrophomonas* sp., as well as a significant decrease in *Veillonella* sp. compared to stable IPF (Molyneaux et al., 2017a). These findings suggest that infection may be an important trigger of AE-IPF even though the presence of a microbial organism is not detected.

Gastroesophageal Reflux (GER) and Microaspiration

Although an increasing number of studies document a high prevalence of GERD (up to 87%) in patients with IPF (Raghu and Meyer, 2012; Lee et al., 2010), there is no direct evidence for causal relationship. Increased pepsin levels in the BAL fluid of the patients with AE-IPF (Lee et al., 2012; Stovold et al., 2007) suggested that GER with aspiration of gastric acid and other nonacid components may trigger the episode of AE. Animal studies have demonstrated that the instillation of acid or gastric juice provoked the diffuse alveolar damage pattern, which is the pathologic pattern of AE-IPF. Further, Lee et al. reported that in the placebo arm of three RCTs (STEP-IPF, ACE-IPF and PANTHER-IPF), patients taking anti-acid therapy at baseline had a slower decline in FVC (over 30-weeks of –0.06 L vs. –0.12 L, $P = 0.05$) and fewer AE (no events versus nine events, $P < 0.01$) during the study period (Lee et al., 2013). Recent studies reported that proton pump inhibitor (PPI) possess anti-inflammatory and anti-fibrotic activities by directly suppressing proinflammatory cytokines, profibrotic proteins, and proliferation of lung fibroblasts (Ghebre and Raghu, 2016).

However, the association is controversial. A small cohort study of *H. pylori* in lung tissue reported no relevant differences in AE events between the gastroesophageal reflux disease (GERD) and non-GERD IPF subgroups (Kreuter et al., 2016a). Also, the recent pooled INPULSIS data showed that the frequency of investigator-reported AE was higher (11.7%) among the patients who were on antacid medication at baseline in the placebo group, compared to no antacid in placebo group (5.0%), and no difference in AE rates on or off antacids in nintedanib group (4.9% vs. 4.8%, respectively) (Costabel et al., 2018).

In the study of asymmetric IPF, the rate of GER was higher in 32 patients with asymmetric IPF (62.5%) than in 64 matched symmetric IPF (31.3%, $P = 0.006$) and similarly AE was significantly more frequent in asymmetric IPF (46.9% vs. 17.2%, $P = 0.004$). In 10 of 15 patients who developed AE (67%), the ground glass opacities (GGO) was virtually unilateral, occurring in the most affected lung by IPF (in most cases, right side). This suggests that loco-regional factors, including GER, may be responsible for both the asymmetry and the occurrence of AE (Tcherakian et al., 2011). However, later, Callahan reported that no statistically significant difference in the number of AE (43% vs. 39%, $P = 0.824$) and GER (both groups 50%) was observed in 14 asymmetric cases of IPF compared to 28 controls (Callahan et al., 2016). These data should be interpreted with caution; the numbers of subjects were smaller and the incidence of AE in symmetric IPF group seemed to be relatively high (39%) compared to most other reports. Only three of 14 patients in the asymmetric group had strictly unilateral involvement and 9 of 14 patients had left lung dominant disease.

Last, WRAP-IPF (Raghu et al., 2018), a phase 2 prospective un-blinded RCT of laparoscopic antireflux surgery in patients with IPF and abnormal acid GER showed that AE (3% vs. 16%, $P = 0.19$), respiratory-related hospitalization (7% vs. 21%, $P = 0.25$) and death (3% vs. 13%, $P = 0.13$) was less common in the surgery group, but did not meet statistical significance. Considering the potential side effects associated with long term PPI use (Freedberg et al., 2017) and an increased risk of infections, including pulmonary infections, observed in many reports (Kreuter et al., 2016b; Costabel et al., 2018), a well-designed, prospective RCT is required to understand the relationship between GER and IPF and also to evaluate the safety and therapeutic efficacy of PPIs/antacids and antireflux surgery for IPF. A recent single-center, double blind RCT of omeprazole in IPF (Dutta et al., 2019) suggested some feasibility for a larger RCT, although the question of a gold standard method for the diagnosis of GER, especially for a large clinical RCT, remains.

Mechanical Procedures

AE-IPF development after the pulmonary resection due to lung cancer has been reported to occur in 3–32% (Watanabe et al., 2008; Sakamoto et al., 2011; Suzuki et al., 2011; Song et al., 2011; Mizuno et al., 2012). AE has been reported to occur after nonpulmonary surgery (Song et al., 2011; Ghatol et al., 2012; Choi et al., 2014) and surgical lung biopsy, although the incidence rate is low (Kondoh et al., 2006; Park et al., 2007; Bando et al., 2009; Samejima et al., 2015). Cases of AE-IPF were also reported following BAL (Hiwatari et al., 1994; Kim et al., 2006; Sakamoto et al., 2012) and cryobiopsy (Casoni et al., 2014; Tomic et al., 2017; Dhooria et al., 2018). The mechanism of AE in this setting is not certain, but may be due to increased susceptibility of additional mechanical stress on an already fibrotic and noncompliant IPF lung.

Drugs

AE-IPF has also been observed in patients receiving chemotherapy for lung cancer, or following radiotherapy (Sakamoto et al., 2011; Goto et al., 2011; Watanabe et al., 2011). Minegishi et al. reported that AE developed after chemotherapy (single drug: 20%, multiple drugs: 42.9%) and radiation therapy (16.7%), but also occurred in 20% of the patients who received only supportive care without any therapy (Minegishi et al., 2009).

Air Pollution

Exposure to increased ozone and nitrogen dioxide levels in ambient air has been reported to be associated with AE-IPF (Johannson et al., 2014).

Pathology

The pathological findings of AE-IPF comprise underlying usual interstitial pneumonia (UIP) with three types of acute lung injury pattern; diffuse alveolar damage (DAD), organizing pneumonia (OP) with or without evidence of organizing DAD, or extensive fibroblastic foci (Churg et al., 2007). The patients with OP pattern and extensive fibroblastic foci appear to have better prognosis (Churg et al., 2007) and Akira et al. reported that the patients with these OP or extensive fibroblastic foci had a peripheral type of GGO on HRCT. The findings on surgical lung biopsies are different from autopsy specimens (Oda et al., 2014). In autopsy specimens, UIP was seen in all, DAD in 78.8%, pulmonary hemorrhage in 28.8%, thromboembolism in 17.8% and lung cancer in 11.5%. In addition, 28.8% showed bronchopneumonia, but OP without DAD was found in only 1.9%, which might be related to better prognosis with an OP pattern and consequently seen less frequent at autopsy. Recently Balestero et al. performed morphometric analysis on explanted lung specimens of 41 patients with IPF, including 11 AE-IPF, and compared pathologic findings with clinical disease progression. Prominent cellular inflammatory infiltrates with a number of both innate (neutrophil, macrophage) and adaptive inflammatory infiltrate (CD4, CD 8, B cell) was significantly higher in the acute exacerbators and rapid progressors compared to the slow progressors. The slow progressors who developed AE showed a more marked increase in overall inflammation (CD45+) than the slow progressors who did not develop AE. Indeed, the degree of inflammation in the rapid progressors who did not exacerbate was similar to that in the acute exacerbator. Interestingly, DAD, that is considered a characteristic feature of AE, was also found to the same extent in rapid progressors who did not exacerbate (Balestro et al., 2016).

Biomarkers

Many blood biomarkers have been reported to have a role in predicting the clinical course and outcomes of AE-ILD, including lactate dehydrogenase: LDH, C-reactive protein: CRP, KL-6, surfactant protein-D: SP-D (Miyazaki et al., 2008; Kishaba et al., 2014; Simon-Blancal et al., 2012; Song et al., 2011), pro-calcitonin (Ding et al., 2013), circulating fibrocytes (Moeller et al., 2009), interleukin-7 (Tachibana et al., 2011), anti-heat shock protein 70 autoantibodies (Kakugawa et al., 2013; Kahloon et al., 2013), alpha-defensin (Sakamoto et al., 2015), ST-2 and decorin (Nikaido et al., 2018), syndecan (Sato et al., 2017). However, none of them have been properly validated in prospective studies and biomarkers currently do not impact clinical decision making in AE (Kondoh et al., 2017). KL-6 is a mucin-like glycoprotein, which is mainly expressed in type II pneumocytes and bronchial epithelial cells (Kohno et al., 1989). It is detected in regenerating type II cells (Kohno et al., 1989) and has been widely used in Japan as a serum marker of predicting the disease course and development of AE-IPF (Ohshimo et al., 2014). Recently, Maher et al. found that SP-D and CA19-9 were the most discriminatory biomarkers in 106 patients with IPF and validated in 206 patients enrolled in a prospective, multicenter, observational cohort study of incident cases of fibrotic interstitial lung disease (PROFILE) study. Baseline values of SP-D (46.6 ng mL^{-1} vs. 34.6 ng mL^{-1}, $P =$.0018) and CA19-9 (53.7 UmL^{-1} vs. 22.2 UmL^{-1}; $P < 0.0001$) were significantly higher in patients with progressive disease than in patients with stable disease, and rising concentrations of CA-125 over 3 months were associated with increased risk of mortality (HR 2.542, 95% CI: 1.493–4.328, $P = 0.00059$), but the association with AE is unknown (Maher et al., 2017).

Treatment

There is no proven, effective treatment for AE-IPF. In clinical practice, high-dose corticosteroids are widely used and current international guidelines have a weak recommendation for its use, solely based on the high mortality of AE-IPF and anecdotal reports of benefit (Raghu et al., 2011). However, there are no controlled trial data supporting the efficacy or safety of corticosteroids in AE-IPF. Some studies have reported a better survival with combination immunosuppressive agents like cyclophosphamide (CTX), cyclosporine-A (CsA), or tacrolimus and auto-antibody reduction therapy with rituximab combined with therapeutic plasma exchange and intravenous immunoglobulin (Donahoe et al., 2015). Other innovative procedures, such as polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) and recombinant human thrombomodulin (rh TM), have been tried, mostly in Japan. However, these studies are often small, retrospective observational cohort studies or controlled studies compared to historical and/or parallel untreated controls, which have obvious or hidden confounding factors, like selection bias or differences in general supportive care.

The results of therapeutic trials in AE-IPF are summarized in Table 3.

Table 3 Summary of treatment studies in acute exacerbation of idiopathic pulmonary fibrosis.

References	Design	Period	No.	Tx.	30 d-SR (%)	3 m-SR (%)	In-hospital SR (%)	Median SR	Remark
Corticosteroid (CS) monotherapy									
Akira et al. (1997)	R. S.		17	CS		47.1			
Tajima et al. (2003)	R. S.		14				0	Mean: 79 ± 99 d	
Parambil et al. (2005)	R. S.	1996–2002	5	CS		20	20		Survived 30 m
Kim et al. (2006)	R. S.	1990–2003	6	CS		18.7			
Song et al. (2011)	R. S.	1990–2009	67	CS			43		
Suzuki et al. (2011)	R. S.	2000–2006	9	CS		100			Postsurgery AE. 3 year-SR: 42%
Tsushima et al. (2014)	Pro. S.	2010–2012	6	CS	17				
Inase et al. (2003)	Cont. R. S.	1990–1999	6	CS (as control group)	83	33			1 year-SR: 11.1%
Sakamoto et al. (2010)	Cont. S.	1994–2004	11	CS (as control group)	82	55		60 d	
Horita et al. (2011)	Cont. R. S.	2001–2010	10	CS (as control group)	60	20	10	38 d	
Corticosteroid (CS) + cyclophosphamide (CTX)									
Ambrosini et al. (2003)	R. S.	2001–2002	5	CS + CTX	20	20			1 year-SR: 20%
Morawiec et al. (2011)	R. S.	2005–	10	CS + CTX	100	55 (suspected AE:100)			1 year-SR of AE + suspected AE: 33%
Simon-Blancal et al. (2012)	R. S.	2002–2009	9	CS + CTX			100		In-hospital SR all 27 patients:73%[c]
Novelli et al. (2016)	R. S.	2009–2013	11	CS + CTX		73	91		1 year-SR: 55%
Akira et al. (2008)	R. S.	1994–2004	58	CS + CTX			56.9		
Tachikawa et al. (2012)	R. S.	2003–2009	13	CS ± CTX ± PMX[b]	31				
Hozumi et al. (2019)	Cont. S[a]	2004–2017	26	CS + CTX ± PMX[b]		76.9			Propensity score matched controlled study
			26	CS ± PMX[b]		84.6			
Corticosteroid + CTX or cyclosporine-A(CsA)									
Hozumi et al. (2019)	R. S.	2004–2017	102	CS (100) + CTX/CsA ± PMX[b]		64.7			1 year-SR: 40.6%
Okamoto et al. (2006)	R. S.	1994–2004	28	CS + CTX/CsA		14		0.9 m	
Yokoyama et al. (2010)	R.S	1998–2004	11	CS + CTX/CsA		45.5		30 d	
Song et al. (2011)	R. S.	1990–2009	90	CS + CTX/CsA		40	50	2.2 m	
Fujimoto et al. (2012)	R. S.	1998–2006	60	CS + CTX/CsA					1 year-SR: 18.3%
Abe et al. (2015)	Pro. Cont.	2014–2014	11 (4 NSIP)	CS + CTX/CsA (control group)	56	10		14 d	

Cyclosporin-A (CsA)

Study	Type	Period	N	Treatment					Outcome
Inase et al. (2003)	Cont. R. S.	1990–1999	7	CS + CsA	85.7	71.4			1 year-SR: 71.4%
			6	CS	83.3	33.3			1 year-SR;11.1%
Homma et al. (2005)	Cont. R. S.	1997–2004	9	CS + CsA		67	9.9 m		1 year-SR: 22.2%
			35	CS (historical control)		2.9	1.7 m		1 year-SR: 2.9%
Sakamoto et al. (2010)	Cont. R. S.	1994–2004	11	CS + CsA	91	80	285 d		
			11	CS	82	55	60 d		
Kataoka et al. (2015)	Cont. S.	2009–2011	20	CS + CsA ± LMWH		53%			Control group for rhTM
Aso et al. (2018)	R. database	2010–2014	7605	CS			74.7		
			384	CS + CsA			76.1		

Tacrolimus

Study	Type	Period	N	Treatment					Outcome
Horita et al. (2011)	Cont. R.	2001–2010	5	CS + Tacro	80	80	80	92 d	AE: none
			10	CS	60	20	10	38 d	AE: 40%

Autoantibody reduction therapy (Therapeutic plasma exchange: TPE) + Rituximab + IVIG (IV Immunoglobulin)

Study	Type	Period	N	Treatment					Outcome
Donahoe et al. (2015)	Pros. historical control	2011–2013	11	CS + TPE	72.7	45.5	60 d: 55 ± 15		Improved gas exchange and symptom. 1 year-SR:46 ± 15%
	2 centers	2009–2011	21	CS			60 d: 20 ± 9		Medical archival record system, no 1 year-SR

Sivelestat

Study	Type	Period	N	Treatment					Outcome
Nakamura et al. (2007)			10	CS ± Sivel All on MV			6 m-SR: 40		Improved PF ratio

Polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP)

Study	Type	Period	N	Treatment					Outcome
Seo et al. (2006)	Pro. Open label		6	CS + PMX + MV	67	67			
Abe et al. (2011)	Pros. Pilot, S.		20	CS + PMX + MV	70	35	35		
Hara et al. (2011)	R. S.	2006–2009	9	CS + PMX ± CsA	55.5	33.3			
Tachibana et al. (2011)	R. S.	2006–2009	19	CS + PMX	47.4	26.3		22 d	IL-7, P/F: improved
Abe et al. (2012)	R. Multi	2004–2008	73	CS + PMX ± anti-coagulant	70.1	34.5			
Oishi et al. (2013)	R. S.	2009–2011	9	CS + PMX ± CTX/CsA		66.7			
Enomoto et al. (2015)	Cont. R. S.	2009–2013	14	CS + PMX ± CTX/CsA + sivel		61.3			1 year-SR: 48.2%. Better P/F ratio
		1997–2012	17	CS ± CTX/CsA ± sivel		65			1 year-SR: 5.9%
Oishi et al. (2016)	Cont. R. S.	2008–2014	27	CS + PMX ± CTX/CsA)	70.4	63		192 d	1 year-SR: 41.7% ($P = 0.04$)
		2006–2008	23	CS ± CTX/CsA	47.9	26.1		29 d	1 year-SR: 9.8%
Ichiyasu et al. (2017)	Cont. R. S.	2007–2015	5	CS + PMX ± CTX/CsA/Tacro ± Sivel		40			Better 90 d-SR in other type of IIP
		2002–2007	7	CS ± CTX/CsA/Tacro ± Sivel		42.9			
Furusawa et al. (2017)	Cont. R. S.	2006–2015	10	CS + PMX ± CTX/CsA/Tacro					Overall SR: 33%. [a]Early induction was better
			14	CS ± CTX/CsA/Tacro				55	Overall SR: 33%

(Continued)

Table 3   (Continued)

References	Design	Period	No.	Tx.	30 d-SR (%)	3 m-SR (%)	In-hospital SR (%)	Median SR	Remark
Human recombinant Thrombomodulin (rhTM)									
Tsushima et al. (2014)	Pro. historical control	2010–2012	20	CS + rhTM + NIV/MV	67		55		
			6	CS + NIV/MV	17				
Isshiki et al. (2015)	R. Control. S.	2006–2013	16	CS + rhTM ± CsA ± LMWH		69		165 d	
			25	CS ± CsA ± LMWH		40		53 d	
Kataoka et al. (2015)	Pros. S. Historical Control	2009–2011	20	CS + rhTM ± CsA + LMWH		70			
		2007–2009	20	CS ± CsA + LMWH		35			
Abe et al. (2015)	Pros. S. Cont. (at different time)	2012–2013	11 (2 NSIP)	CS + rhTM ± CSA/CTX +	82	64		Not reached	
		2014–	11 (4 NSIP)	CS ± CSA/CTX	56	10		14 d	
Hayakawa et al. (2016)	Pro. S. Historical Control	2012–2014	10	CS + rhTM	70	60		153 d	1 year-SR: 40%
		2009–2012	13	CS ± CTX/CsA ± PMX ± Sievel	54	15		48 d	1 year-SR: 8%
Sakamoto et al. (2018)	Cont. S.	2011–2016	45	CS + rhTM ± CSA		67		167 d	
		2006–2011	35	CS ± CSA ± LMWH		37		35 d	
Arai et al. (2019)	Pro. multi. historical Control	2014–2016	39 IIP (12IPF)	CS + rhTM ± AZP/CTX/ CSA ± Pirf ± PMX		67		47.5 d	Propensity score matched control.
		2011–2013	61 IIP (26 IPF)	CS ± AZP/CTX/CSA ± Pirf/Nin ± PMX		47.5		66.7 d	No data on IPF
Antibiotics									
Kawamura et al. (2017)	Cont. R. S.	2012–2016	38	CS + Azithro		60 d SR: 74			
		2005–2012	47	CS + fluoroquinolone ± PMX		60 d SR: 30			
Oda et al. (2016)	R. database	2010–2013	209	MV + CS ± CTX, cotrimox, azithro	44.6	24.6		21 d	Japanese Diagnosis Procedure Combination database
Pirfenidone									
Furuya et al. (2017)	Cont. R. S.	2008–2015	20	Pirf ± CS ± rhTM		55			$P = 0.042$
		2008–2015	27	CS ± rhTM		34			
Supportive care + antibiotics									
Papiris et al. (2015)	Pro. multi. open label	2007–2013	17	No CS, Supportive care + antibiotics	52	45		1.73 m	

AZP: azathioprine; *Azithro*: azithromycin; *Cont*: controlled; *CS*: corticosteroid; *cotrimox*: cotrimoxazol; *CTX*: cyclophosphamide; *CsA*: cyclosporine-A; *d*: day; *IIP*: idiopathic interstitial pneumonia; *LMWH*: low-molecular weight heparin; *m*: month; *multi*: multi-center; *MV*: mechanical ventilation; *Nin*: nintedanib; *NSIP*: nonspecific interstitial pneumonia; *P/F*: PaO$_2$/Fraction of O$_2$ in inspired air; *Pirf*: pirfenidone; *PMX*: Polymyxin B-immobilized fiber column direct hemoperfusion; *Pro*: prospective; *R*: retrospective; *rhTM*: human recombinant thrombomodulin; *S*: single center; *sivel*: sivelestat; *SR*: survival rate; *Tacro*: tacrolimus; *Y*: year; ±: added in some patients.

[a]Propensity score matched controlled study.

[b]Small portion of the patients were treated with PMX-DHP.

[q]In all 27 study subjects including the patients treated with *N*-acetyl-cysteine.

Corticosteroids

Although corticosteroids have been administered to most patients with AE-IPF, actual reported data are limited. There are no placebo controlled studies for corticosteroid use. In 4 controlled studies, a corticosteroid group was used as a control group and the reported outcomes are shown in Table 3 (Inase et al., 2003; Sakamoto et al., 2010; Horita et al., 2011; Tsushima et al., 2002). Other studies have been small, retrospective and in a single center. The reported survival rate is highly variable with a 3-month-survival rate ranging from 18.7% to 100% (100% was the result of acute exacerbation developed after lung resection in nine patients with cancer), but mainly around 50%. The largest study was by Song et al. who reported an in-hospital survival rate of 43.3% in 67 patients treated with variable doses of corticosteroid mono-therapy (Song et al., 2011). The median survival reported in two other studies was 38 days and 60 days (Horita et al., 2011; Sakamoto et al., 2010).

Cyclophosphamide (CTX)

There are no data of cyclophosphamide (CTX) mono-therapy. In all studies, CTX was given with corticosteroids. Ambrosini et al. reported that the 3 month-survival rate was only 20%, but they had only five study subjects (Ambrosini et al., 2003). In the study of Morawiec et al., 55% of patients with AE-IPF survived at 3 months, but in suspected AE-IPF who had slightly delayed onset, all seven patients survived (Morawiec et al., 2011). Another study reported that all nine patients treated with CTX were discharged and the median survival period was 4.2 months (Simon-Blancal et al., 2012). Novelli et al. reported that the 3 month-survival rate was 73% and 55% survived more than 1 year (Novelli et al., 2016). In other studies, either CTX or cyclosporine-A (CsA) was administered with corticosteroids. The reported 3 month-survival rate of corticosteroids + either CTX or CsA was 10–40%, except in the study by Hozumi et al. Hozumi et al. analyzed 102 patients with AE-IPF who were treated with corticosteroids + either CTX or CsA. Their 3 month-survival rate was 64.7%. They also evaluated the efficacy of corticosteroid mono-therapy and corticosteroids + CTX separately using a propensity score-matched method. They compared the outcomes of 26 patients treated with corticosteroids + CTX to that of 26 patients treated with corticosteroid mono-therapy, matched using propensity scores. There was no difference in the 3 month-survival rate between the two groups; corticosteroids + CTX group: 76.9% vs. corticosteroid control group: 84.6%.

Cyclosporin-A (CsA)

The majority of studies on CsA have been controlled studies, however they were all retrospective using a historical control group. As shown in Table 3, the three month-survival of the CsA group was higher than that of a matched corticosteroid control group (71.4% vs. 33.3% in Inase et al., 67% vs. 2.9% in Homma et al., and 80% vs. 55% in Sakamoto et al.) (Inase et al., 2003; Homma et al., 2005; Sakamoto et al., 2010). But in the study of Kataoka et al., where the CsA was a control group for rhTM group, the 3 month-survival was 35%, lower than 70% observed in the rhTM group (Kataoka et al., 2015). Aso et al. compared the outcome of CsA therapy using the Diagnosis Procedure Combination Database in Japan. The in-hospital survival rate of 384 patients treated with CsA was 74.7%, similar to the survival rate of 7605 patients in a corticosteroid control group (76.1%) (Aso et al., 2018).

Tacrolimus

Tacrolimus is an immunosuppressant used mainly to prevent rejection in solid organ transplantation and in the treatment of connective tissue diseases. Tacrolimus inhibits T cell activation and interleukin-2 (IL-2) and other helper T cell cytokines, similar to CsA, but more potent. It also prevents immune activation by inhibiting nuclear factor κB (NF-κB) and TGF-β-induced collagen deposition. Horita et al. compared the effect of tacrolimus in five patients with AE-IPF to a historical control group (10 patients on corticosteroids only). The 3 month-survival rate in the tacrolimus group was 80% with a median survival of 92 days, which was higher than the control group (10%, 38 days). No surviving patients from the tacrolimus group had a reexacerbation for at least 6 months after their initial AE, whereas four of the nontacrolimus group patients died from reexacerbation between 1 and 4.5 months after their initial AE (Horita et al., 2011).

Autoantibody Reduction Therapy

Recent evidence has shown that immune inflammation and auto-antibodies may be involved in IPF progression and AE-IPF (Balestro et al., 2016). Treatments that reduce autoantibodies might be of benefit in a subset of patients with IPF (Kahloon et al., 2013; Feghali-Bostwick et al., 2007). Therefore, autoantibody reduction therapy, including therapeutic plasma exchanges (TPE), corticosteroid pulse, rituximab followed by intravenous immunoglobulin was studied in 11 critically ill patients with AE-IPF. Nine patients (82%) showed improvement in pulmonary gas exchange compared to only one among 20 patients in a historical control group (Donahoe et al., 2015). The 3 month-survival rate of the trial subjects was 45.5% and the 1-year survival was 46 ± 15% vs. 0% among historical controls. As a result of this study, additional trials are ongoing and listed on Clinicaltrials.gov (Therapeutic Plasma Exchange, Rituximab and IV Ig for Severe Acute Exacerbation of IPF Admitted in ICU (EXCHANGE-IPF) NCT03584802 Open-randomized controlled and Phase 2 Autoantibody Reduction for Acute Exacerbations of Idiopathic Pulmonary Fibrosis (STRIVE-IPF) NCT03286556).

Sivelestat

Due to the implication of neutrophils in AE-IPF, the efficacy of a neutrophil elastase inhibitor, sivelestat, in combination with corticosteroids was examined in 10 mechanically ventilated patients with AE-IPF. Four of 10 patients survived to day 180 and in the survivors, the PaO_2/FiO_2 (arterial oxygen tension/fraction of inspired oxygen), C-reactive protein, and positive end-expiratory pressure (PEEP) levels were improved (Nakamura et al., 2007).

Polymyxin B-Immobilized Fiber Column Direct Hemoperfusion (PMX-DHP)

PMX-DHP was originally developed for the removal of endotoxins from gram-negative bacteria based on the potential of columns to absorb endotoxins, plasma proinflammatory, profibrotic and proangiogenic cytokines, reactive oxygen species, and activated neutrophils. The use of PMX-DHP columns has been studied in patients with acute respiratory distress syndrome (ARDS) and improvements in oxygenation have been observed with therapy (Cruz et al., 2009). After the open label pilot trial of PMX-DHP in six patients with AE-IPF demonstrated a 3 month-survival rate of 67% (Seo et al., 2006), several more retrospective cohort studies were performed and reported 3 month survival rates between 27–67% (Table 3). The biggest study was by Abe et al., who performed PMX-DHP on 160 patients with interstitial pneumonia including AE-IPF (73 patients) and other types of interstitial pneumonia, such as nonspecific interstitial pneumonia (NSIP) or organizing pneumonia (OP), which might respond to high doses of corticosteroids. All patients had been given corticosteroids. Therefore, the response may not be solely due to PMX-DHP. In this study, the 3 month-survival of AE-IPF was 34.5% (Abe et al., 2012).

There have been four controlled trials using PMX-DHP. Two studies were performed only in AE-IPF patients and both studies reported a better survival in PMX-DHP group. In Enomoto's trial, the three month-survival rate of the PMX-DHP group was similar to controls (61.3%, 65% respectively), but the 1 year-survival rate was significantly better in PMX-DHP group (48.2% vs. 5.9%) (Enomoto et al., 2015). However, these data should be interpreted with caution because all severe patients, such as age over 85 years, severe comorbidities, or cardiovascular instability, were excluded from the PMX-DHP group and put in the control group. Oshi et al. also reported better survival in the PMX-DHP group. They reported a 3 month and 1-year survival rate of 63% and 41.7%, respectively, in contrast to 26.1% and 9.8% in the control group. The other two studies include various types of interstitial pneumonias. Furthermore, in addition to corticosteroids, other agents, such as CTX, CsA, tacrolimus, sivelestat or anticoagulants, were administered during the study period (Furusawa et al., 2017; Ichiyasu et al., 2017). Itchyasu reported that among patients with AE-IPF, there was no difference in 3 month survival between PMX-DHP (40%) and control group (42.9%). However, when all types of IIP were included in the analysis, survival was better in the PMX-DHP group (Ichiyasu et al., 2017). Similarly, in the study by Furusawa et al., among the patients with AE-IPF, there was no difference in overall survival between the PMX-DHP (33%) and the control group (50%) (Furusawa et al., 2017). Therefore, in order to determine the effect of PMX-DHP in AE-IPF, double blind randomized controlled study is required.

Thrombomodulin

Thrombomodulin is a thrombin receptor on the endothelial cell surface and recombinant human thrombomodulin (rhTM) forms a reversible complex with thrombin, which activates plasma protein C and exhibits antiinflammatory, anticoagulant, and antifibrinolytic properties. Collard et al. studied the plasma biomarker profile of AE-IPF and found that mechanical ventilation and log change in thrombomodulin were both significant predictors of survival in AE-IPF (Collard et al., 2010). Due to the hypercoagulable state in AE-IPF, Tsushima et al. prospectively tried rhTM and reported that the 30-day survival was higher in 20 patients with AE-IPF compared to six historical controls (67% vs. 17%). Several retrospective studies using historical controls or parallel untreated controls showed promising results with a 3 month-survival rate around 60%, better than what was observed in the control group (Table 3). However, they were all small studies and other medications like N-acetylcysteine (NAC), CTX, CsA, anticoagulants, and even PMX-DHP, were administered to the study subjects during the trial. Therefore, a Phase 3 placebo controlled randomized trial (NCT02739165) was recently performed and finished recruitment.

Antibiotics

Macrolides accelerate apoptosis of neutrophils and the removal of cell debris by macrophages. Azithromycin also has a modulating effect on the TH1/TH2 fate as well as the TH17/iTreg lineage (adaptive immunity) (Wuyts et al., 2010). Azithromycin inhibits the production of aberrant proinflammatory cytokines by alveolar macrophages in a dose-dependent way (Cai et al., 2013), suggesting a potential role in the treatment of IPF. Azithromycin was evaluated in a retrospective study and 60-day survival of 38 AE-IPF patients was significantly better (74%) compared to 47 fluoroquinolone-treated historical controls (30%, $P < 0.001$) (Kawamura et al., 2017).

Using the Japanese Diagnosis Procedure Combination (DPC) database, Oda et al. performed a retrospective epidemiologic and prognostic analysis on 209 patients with IPF receiving mechanical ventilation and high-dose corticosteroids with or without CTX or cotrimoxazole. They found that treatments with cotrimoxazole and macrolides were significantly associated with a better prognosis and high-dose cyclophosphamide was significantly associated with a poor prognosis. The 3 months-survival rate was 24.6% and median survival time was 21 days.

Antifibrotic Drugs

Pirfenidone and nintedanib have been shown to reduce the progression of IPF and they may be useful in AE-IPF. Furuya et al. found that among 47 cases of AE-IPF (all treated with high dose corticosteroid and some with NAC, CTX/CsA or rhTM), the 3 month-survival rate was significantly better in 20 patients receiving pirfenidone than in 27 patients not receiving pirfenidone (55% vs. 34%, $P = 0.042$). Among the patients receiving rhTM ($N = 22$), pirfenidone did not make significant difference in the outcome (80% vs. 42%, $P = 0.067$) (Furuya et al., 2017). In univariate analysis, nonuse of rhTM was a potential risk factor for death (hazard ratio [HR], 3.717; $P = 0.035$). In all patients, nonuse of pirfenidone was a potential risk factor for death (HR: 6.993; $P = 0.043$). Recently Vianello et al. reported improved median survival time of pirfenidone group (137 days) compared to nine retrospective control patients (16 days, $P = 0.0009$) (Vianello et al., 2019). However, the study had many limitations including a small number of the patients and older age and lower lung function in a historical control group.

Nonsteroidal Approach

The PANTHER trial reported a harmful effect with the combined use of corticosteroids, NAC, and azathioprine (Raghu et al., 2012). Therefore a nonsteroidal approach with immediate cessation of immunosuppressive therapy (if any), best supportive care and broad-spectrum antimicrobials and thorough evaluation to detect reversible causes of deterioration was tried and resulted in at least comparable survival rates (45% at 3 months and 40% in 1 year, median survival time, 1.73 month). Furthermore, a history of immunosuppressive therapy, including corticosteroids before AE, exerted a less favorable prognosis (Papiris et al., 2015).

As reviewed above, there are no proven effective drugs for the treatment of AE-IPF, but some agents have potential and randomized controlled trials are on-going.

Supportive care, ventilatory support

At present, supportive care is the mainstay of therapy in these critically ill patients, including palliation of symptoms and correction of hypoxemia with supplemental oxygen. The current IPF guidelines state that while the majority of patients with respiratory failure due to IPF should not receive mechanical ventilation, it may be a reasonable in a minority (weak recommendation, low-quality evidence) and that noninvasive ventilation (NIV) may be appropriate in some (Raghu et al., 2011). This is based on the high in-hospital mortality observed in AE-IPF, up to 90% (Mallick, 2008). Because the fibrotic noncompliant lung is more susceptible to ventilator-induced lung injury, a protective ventilation (i.e., low tidal volume) strategy, NIV (Mollica et al., 2010; Tomii et al., 2010; Vianello et al., 2014), or high-flow nasal cannula oxygen (Koyauchi et al., 2018; Faverio et al., 2018) may reduce the risk. Rush et al. analyzed data from the Nationwide Inpatient Sample from the United States, and found that invasive mechanical ventilation (IMV) had a higher in-hospital mortality rate compared to NIV (51.6% with IMV vs. 30.9% in NIV, $P < 0.0001$) among 2481 patients with IPF (Rush et al., 2016). In Japan, among 209 patients receiving IMV, the 30 day- and 90-day survival rates were 44.6% and 24.6%, respectively. (Oda et al., 2016)

Lung Transplantation

Lung transplantation is the last resort and is recommended by the international guidelines for highly selected patients with AE-IPF. Extracorporeal membrane oxygenation (ECMO) may be used as a bridge to transplantation as it may minimize the risk of ventilator induced lung injury and the "triggering" of fatal deterioration of the underlying fibrotic process (Moerer and Quintel, 2016). Recent advances in the technique has enabled ambulatory ECMO or awake, spontaneous breathing ECMO as a bridge to lung transplantation and have shown encouraging results (Garcia et al., 2010; Hakim et al., 2018). Because ECMO cannot reverse the original prognosis, it is appropriate to consider ECMO only for the lung transplantation candidate (Trudzinski et al., 2016). Even with ECMO, the prognosis of these patients is worse than that of lung transplantation in stable IPF patients. Therefore, it is recommended that eligible patients with IPF need to have transplant evaluations early in the course of their disease, before an episode of AE-IPF.

Prognosis

Previously, the in-hospital mortality of AE-IPF was reported to be over 50%, and in the patients on mechanical ventilation, the in-hospital mortality is 87% with an overall mortality of 94% among 135 cases reported (Mallick, 2008). However, more recent studies suggest a slightly better survival, with 1 month-survival rate of 66% (range: 47–85%), 3 month rate of 41% (range: 0–54%), and survival to hospital discharge of 44% (4–77%) (Kondoh et al., 2017). For patients treated with IMV or NIV, in-hospital survival rates have been reported to be 49.4% with IMV and 69.1% with NIV, in the United States (Rush et al., 2016) and a 30 day-survival rate of 44.6% and 3 month-survival rate of 24.6% in Japan (Oda et al., 2016). The median survival of patients with IPF who experience an AE is approximately 3–4 months (Leuschner and Behr, 2017). Recently Aso et al. reported that the in-hospital survival rate of 7989 patients treated with CsA or high dose corticosteroids was over 70% in Japan (Aso et al., 2018).

Prevention

Prevention is more effective than medical treatment of AE and avoiding triggering factors is important. Vaccination for influenza virus and Pneumococcus has been shown to be effective in preventing respiratory infection, an important triggering factor for AE. Vaccinations, along with hand washing and avoidance of sick contacts, especially in the winter season, is recommended.

GERD is another important risk factor for AE and the use of pharmacological and nonpharmacological therapy to reduce GER is an appropriate preventive measure. However, a recent study reported that antacid therapy increased the risk of overall and pulmonary infections in patients with advanced IPF (i.e., FVC < 70%). Therefore, the risk/benefit ratio should be carefully evaluated in individual patients until a large double blinded RCT is performed.

Avoidance of airborne irritants or pollutants, and strategies to minimize mechanical ventilator-induced lung injury should be considered in patients with IPF.

Pharmacological Prophylaxis

Antifibrotic drugs

Therapies beneficial for the treatment of IPF itself may reduce the risk of AE-IPF.

Nintedanib

Acute exacerbation was a key secondary endpoint in all three placebo-controlled clinical trials of nintedanib. A phase 2 trial of nintedanib in the treatment of IPF (TOMORROW) demonstrated a lower incidence of investigated-reported AE-IPF (2.4 vs. 15.7 per 100-patient years, risk ratio, 0.16, $P = 0.02$) and a delay in the time to first investigator-reported AE-IPF (Richeldi et al., 2011). In the subsequent phase 3 trials, the time to first AE-IPF was significantly delayed in INPULSIS-2 (hazard ratio: 0.38, $P = 0.005$) but not in INPULSIS-1 (hazard ratio: 1.15, $P = 0.67$) (Richeldi et al., 2014). However, a prespecified sensitivity analysis of pooled data from INPULSIS-1 and INPULSIS-2 demonstrated that nintedanib significantly delayed the time to first adjudicated AE-IPF (either confirmed or suspected) compared to placebo (hazard ratio: 0.32, $P = 0.001$). A separate pooled analysis of all three trials (TOMORROW and INPULSIS-1 and 2) demonstrated a reduction in centrally adjudicated confirmed or suspected AE-IPF with nintedanib therapy (5.9% on placebo vs. 2.2% on nintedanib, $P = 0.01$) (Collard et al., 2017). However, these results need to be interpreted with caution as the number of events was relatively small and no significant differences in mortality were observed between investigator reported AE, adjudicated AE and adjudicated as not-AE (other forms of acute respiratory worsening) (Collard et al., 2017). The time to first adjudicated AE-IPF in the prespecified pooled analysis (INPULSIS-1 and 2) and the time to first investigator-reported AE-IPF in a separate pooled analysis of all three trials (TOMORROW and INPULSIS-1 and 2) demonstrated a delay in those randomized to nintedanib.

Pirfenidone

The phase 2 trial of pirfenidone performed in Japan was terminated early because of a statistically significant reduction in AE in the subjects receiving pirfenidone (Azuma et al., 2005). Episodes of AE-IPF occurred exclusively in the placebo group (3/35 subjects) and in none of the pirfenidone group during the 9 months ($P = 0.0031$). However, a subsequent trial on 275-subjects in Japan did not replicate these results, with AE occurring in 3.6–3.7% in both the pirfenidone and control groups (Taniguchi et al., 2010). The subsequent multinational phase 3 clinical trials of pirfenidone performed in Western countries (CAPACITY-1, CAPACITY-2 and ASCEND Trial) did not include AE as an end-point. Recently Ley et al. analyzed pooled data of three RCTs (2 CAPACITY and ASCEND) and found that pirfenidone was associated with a lower risk of respiratory-related hospitalization compared to placebo (7% vs. 12%, HR: 0.52; $P = 0.001$), but all-cause (HR: 0.91; $P = 0.528$) or non–respiratory-related hospitalization (HR: 1.3; $P = 0.145$) was not associated with treatment (Ley et al., 2017).

Pirfenidone has also been suggested to reduce the risk of AE postoperatively. Iwata et al. reported that the incidence of postsurgery AE in patients with lung cancer and IPF was lower in the pirfenidone pretreated group compared to the nontreated group (3.2% vs. 21.1%) (Iwata et al., 2016a). He also performed a phase 2 clinical trial and found reduced incidence of AE (Iwata et al., 2016b). Although these studies had several limitations, including a small number of subjects and single-arm design, it suggested a potential role for prevention with use of perioperative pirfenidone.

It is not clear whether either of these agents should be withheld or continued during an exacerbation event (Richeldi et al., 2018).

Macrolide

Kuse et al. reported a reduced incidence of AE in patients treated with a macrolide in addition to conventional drugs (13.8%) during a 36 month follow-up period compared to patients not given a macrolide (34.8%). Further, the AE-free survival rate of the macrolide group was significantly better than the nonmacrolide group ($P = 0.047$), suggesting a potential beneficial effect of macrolide therapy on prevention of AE (Kuse et al., 2016).

Conclusion

With the first consensus statement in 2007 and the revised statement in 2016, AE-IPF has been better defined and progress in the knowledge about the incidence, risk factors and triggering factors has been made. The prognosis is more favorable, although it is still associated with a high-mortality rate and there is no proven effective therapy. Several new innovative therapies have been studied and suggest a potential benefit in the treatment of AE-IPF, resulting in the initiation of several double blind randomized clinical trials. Prophylactic measures are now better defined and emerging data suggest efficacy of antifibrotic drugs in the prevention of AE-IPF.

Acknowledgment

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