Respiratory Medicine (2014) 108, 376–387

Available online at www.sciencedirect.com

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Outcomes in idiopathic pulmonary fibrosis: A meta-analysis from placebo controlled trials

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Received 7 September 2013; accepted 9 November 2013
Available online 19 November 2013

MESH KEYWORDS
Idiopathic pulmonary fibrosis;
Lung diseases, interstitial;
Meta-analysis

Summary
Background: Most data on outcomes in Idiopathic Pulmonary Fibrosis (IPF) pre-dates current guidelines. Data on rates of infection is sparse; the effect of low-dose corticosteroids and disease severity is unknown.
Methods: We identified randomised-controlled trials of IPF and analysed rates of mortality, lower respiratory tract infections (LRTIs), IPF progression and acute exacerbations from the placebo arms. We standardised event rates and compared differences using incidence rate ratios (IRRs) between subgroups according to disease severity or use of low-dose immunosuppression.
Results: Mortality was lower in trials that recruited patients with mild-moderate disease severities only, as compared to trials where patients with severe disease were allowed (188.6 vs 78.6 deaths per 1000 patient/years, IRR 0.30–0.59, $p < 0.0001$). No statistical difference was seen between trials permitting and excluding low-dose prednisolone use. LRTIs were found to be commoner in trials allowing low dose prednisolone use compared with those that did not (227.1 vs 63.4 infections per 1000 patient/years. IRR 2.56–5.13, $p < 0.0001$), and were less frequent in trials excluding patients with severe disease (153.9 vs 257.8 infections per 1000 patient/years, IRR 0.45–0.81, $p = 0.0003$). Acute exacerbations occurred less frequently in trials excluding severe disease (28.2 vs 122.9 exacerbations per 1000 patient/years, IRR 0.11–0.55, $p < 0.0001$). There was no difference between groups in rates of IPF progression.
Conclusion: Mortality is heterogeneous and dependent on entry criteria. Infection rates were high, both with and without immunosuppression, and were higher in severe disease. Consideration should be given to alternative outcomes to mortality in future IPF trials if severe disease is excluded.
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0954-6111/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.rmed.2013.11.007

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a progressive and incurable form of interstitial lung disease resulting in fibrosis of the parenchyma. Epidemiological data suggests that the incidence is 6.8—16.3 per 100,000 [1], with high mortality [2], though this is based on patients with a diagnostic criteria that precedes current international guidelines from 2000 [3], and the 2011 update [4]. It has also been recently suggested by the European IPF consensus group that mortality in randomised trials studying IPF is much lower than expected, and too low for its use as a primary outcome in future trials [5]. It is therefore unclear if IPF patients enrolled in clinical trials reflect the prognosis and progression of IPF patients seen in the clinic.

The incidence of significant symptoms associated with IPF is not fully known. The incidence of acute exacerbations of IPF is unknown [6] but the proportion of patients suffering this event was calculated to be 8.5% in one year from a study of 147 patients [7]. Bacterial infections may have an important implication in the pathogenesis or prognosis of IPF [8], but frequency of these events is unknown.

In the search for effective treatments, several large randomised, placebo-controlled trials have been performed recently. Although few have shown evidence of benefit (n-acetylcysteine [9], pirfenidone [10] and BIBF-1120 [11]), a pooled analysis of outcomes in the control arms represents a unique opportunity to evaluate the natural history of IPF in a large cohort of patients undergoing rigorous follow-up. A comprehensive synthesis of the well-characterised patients within the RCTs allows quantitative evaluation of a broad range of patient oriented outcomes such as rates of disease progression, acute exacerbations, infections and mortality. In view of previous findings of increased mortality with immunosuppression [12] and the debate about endpoints for clinical trials [5,13], we were interested in the outcomes of studies depending on whether inclusion criteria permitted immunosuppression or stated disease severity.

Methods

Literature search and selection

This review incorporated all double-blind, placebo-controlled RCTs, investigating any pharmacological treatment for IPF. The population of interest was patients with IPF of any severity, diagnosed using radiology or biopsy, who were enrolled in the placebo arms of these trials.

A systematic search was performed of MEDLINE, EMBASE, AMED and Cochrane central. A search was performed using the terms "Idiopathic pulmonary fibrosis" or "IPF" or "Usual interstitial pneumonia" or "UIP," and "Randomised" or "Randomized," and "Placebo". The returned results were screened for appropriate trials by the first author by reviewing each abstract. Trials considered potentially suitable for inclusion were reviewed in full. Bibliographies of relevant articles were reviewed to identify any additional papers.

Data extraction

The pre-specified outcomes of interest were rates of mortality (all-cause and respiratory causes where quoted), lower respiratory tract infections, pneumonia (where reported as a specific and separate event to 'lower respiratory tract infections'), progression of diseases (defined as a reduction in Forced Vital Capacity (FVC) by $\geq$10% or DLco (diffusing capacity of carbon monoxide) by $\geq$15% within the course of the trial), and acute exacerbations of IPF (where listed as a separate entity within trial outcomes and adverse events). Data regarding the outcomes was extracted, as well as baseline characteristics, enrolment criteria for participants, whether immunosuppression was allowed and how many patients were on steroids, and methods of follow-up where available.

Validity assessment

One reviewer rated the methodological quality of each study using the five-point Jadad score for RCTs [14]. Bias was assessed using the 'Risk of Bias' tool provided by the Cochrane collaboration.

Statistical analysis

Standardised event rates were calculated for each outcome. The number of events occurring during follow-up were normalised to give a rate per 1000 patient-years of follow-up. We also conducted random effects meta-analysis of proportion of patients affected per year for each specified outcomes (standardised to rates occurring per 1000 patient/years of follow-up).

For subgroup analysis according to different categories of patients, we classified trials into those including mild-to-moderate disease only, which were defined as trials specifying a lower-limit cut-off value for FVC or DLco at baseline (Table 1), versus those including all severities. The cut-off values are displayed in Table 1. Trials were also classified into those allowing concurrent use of immunosuppression or not. Trials allowing low-dose corticosteroids were defined as those including patients on steady doses of prednisolone not more than 20 mg. One paper [33] was included despite two patients receiving daily prednisolone doses greater than 20 mg. We compared the event rates in different groups of trials by calculated incidence rate ratios (IRRs) and 95% confidence intervals using MedCalc for Windows, version 12.2 (MedCalc Software, Ostend, Belgium).

Results

Literature search

In total, 118 abstracts were screened for suitability. Of these, 20 full-text articles were reviewed for eligibility. Four trials were not placebo controlled and were excluded [9,15—17]. Two trials were excluded because the trials were stopped early and the average length of follow-up was not given [12,18]. One trial was excluded [19] as it predated latest guidelines for IPF diagnosis [3] and the diagnosis of IPF could not be confirmed. In total, thirteen trials were

Table 1 Trial designs and inclusion/exclusion criteria for the randomised controlled trials included in this review.

Trial	Investigated agent	Placebo arm (*n*)	Patient/ years follow-up	Age (yrs) (Mean ± SD)	Male sex (%)	Time since diagnosis (years) (mean ± SD)	FVC baseline (% pred) (mean)	Dlco baseline (% pred) (mean)	Ever smokers (%)	Current smokers (%)	Receiving steroids (%)	Inclusion criteria
Shulgina et al., — 2012 [36,37]	Co-trimoxazole	86	86	70.7 ± 8.6	69.5	2.6 ± 4.7	71.5	39.1	72 (75.8%)	1 (1.1%)	52 (60.5)	Evidence of clinical decline. No restriction; only two patients on >20 mg prednisolone.
Richieldi et al., — 2011 [11]	BIBF-1120	85	85	64.8 ± 8.6	74.1	1.4 ± 1.5	77.6	—	—	—	43 (50.6)	<5 years since diagnosis, FVC >50% pred, DLco 30—79%. Age >40. Prednisolone less than 15 mg daily
King et al., — 2011 [22]	Bosentan (BUILD-3)	209	320	63.2 ± 9.1	63.6	0.5	73.1	47.9	142 (67.9%)	—	36 (17.2)	<3 years since diagnosis. No age limits. Excluded if >5% honeycombing Prednisolone less than 20 mg daily
Noble et al., 2011 [10]	Pirfenidone (CAPACITY)	347	480	60.9	72.6	—	74.6	46.7	232 (66.9%)	17 (5%)	0 (0)	<4 years since diagnosis. Age 40—80. FVC ≥50% predicted, DLco ≥35% predicted. No concomitant immunosuppression
Taniguchi et al., — 2010 [25]	Pirfenidone	104	104	64.7 ± 7.3	77.9	—[a]	79.1	55.2	83 (79.8%)	13 (12.5%)	5 (4.8)	No time limit on diagnosis, Age 20—75. No PFT limits. Prednisolone less than 10 mg daily
IPF research network — 2010 [29]	Sildenafil	91	49	68.2 ± 9.3	82	1.87 ± 1.93	58.73	26.7	69 (76%)	—	0 (0)	DLco ≤35% predicted; advanced IPF only No concomitant immunosuppression
Daniels et al., 2009 [24]	Imatinib	61	113	67.8	64	—	65.6	39.3	38 (64%)	—	0 (0)	<3 years since diagnosis. Age 20—79. FVC ≥55% predicted, DLco ≥35% pred. No concomitant immunosuppression
King et al., — 2009 [23]	Interferon gamma-1b (INSPIRE)	275	407	65.9 ± 7.9	68	—	73.1	47.3	191 (69.4%)	14 (5%)	47 (17.1)	<4 years since diagnosis. Age 40—79. FVC ≥55% predicted, DLco ≥35% pred. Prednisolone less than 0.125 mg/kd/day

King et al., 2008 [21]	Bosentan (BUILD-1)	84	84	65.1 ± 9.1	63	1.1 ± 1.0	69.5	41.4	—	—	11 (13.1)	<3 years since diagnosis. No age limits. FVC >50% predicted, DLco >30% Prednisolone less than 15 mg daily
Raghu et al., 2007 [26]	Etanercept	41	38	65.1 ± 7.1	58.5	1.0 ± 1.1	63.0	36.9	—	—	0 (0)	<2 years since diagnosis. No age limits. FVC >55%, DLco >25% No concomitant immunosuppression
Malouf et al., 2007 [27]	Everolimus	45	90	60.0 ± 9.0	71.1	—	69.0	42.0	—	—	12 (26.7)	No mention of severity of previous decline. Diagnosis of IPF only. Prednisolone less than 10 mg daily
Raghu et al., 2004 [20]	Interferon gamma-1b	168	187	63.4 ± 8.6	66	1.0 ± 0.8	64.1	36.8	—	15 (9%)	77 (45.8)	No maximum length of time of diagnosis. Age 20—79. FVC ≥50% pred, DLco ≥25% Prednisolone less than 15 mg daily
Azuma et al., 2004 [28]	Pirfenidone	35	24	64.3 ± 7.6	94	—	78.4	57.7	32 (92%)	3 (9%)	8 (22.9)	No time limit for diagnosis. Age 20—75. No guidance on PFTs. Prednisolone less than 10 mg daily

Total number of Participants in placebo arms = 1631 Total follow-up across trials = 2067.7 patient/years Total number taking corticosteroids = 266.

[a] No data for average time since diagnosis, though more than a third had IPF for >3 yr.

Table 2 Comparison of baseline characteristics of participants within trials excluding severe disease compared with those including severe disease (2a) and within trials including immunosuppressant use compared with those excluding patients on immunosuppression (2b).

2a		
	Patients with severe disease excluded (9 trials, 1374 patients)	Patients with severe disease included (4 trials, 257 patients)
Age (years)	63.8	67.1
% male	71.2%	80.2%
Time since diagnosis (years)	0.9	2.2
FVC (% predicted)	72.3%	67.5%
Diffusion capacity (% predicted)	45.4%	37.8%
% Ever smokers	68.9%	81.6%
% Current smokers	6.6%	3.3%
% Receiving steroids	15.9%	43.4%
2b		
	Immunosuppressant use (9 trials, 1091 patients)	No immunosuppressant use (3 trials, 449 patients)
Age (years)	64.8	62.2
% male	70.5	75.7
Time since diagnosis (years)	1.1	1.0
FVC (% predicted)	72.2%	70.1%
Diffusion capacity (% predicted)	41.9%	39.8%
% Ever smokers	73.3%	60.1%
% Current smokers	6.9%	5%
% Receiving steroids	26.7%	0%

included in the quantitative meta-analysis, involving 1631 patients, and 2067.7 years of patient follow-up (Tables 1–5).

No paper scored less than 3 points using the Jadad score, indicating good methodological quality. Assessment of bias suggested low risk of bias through study design, with only two trials judged as 'unclear' for sequence generation, as found in the Jadad score. Publication bias was not felt to be an issue due to the use of placebo arms of trials only.

Nine trials included only mild-to-moderate disease severity [10,11,20–26], three trials included all disease severities [8,27,28], and one trial [29] included severe disease only. Nine trials included patients who were concurrently taking immunosuppression [8,11,20–23,25,27,28], three did not [10,24,26] and one did not specify [29]. In total, 291 patients within these trials (26.7%) were taking corticosteroids.

Outcomes

We included thirteen trials with a total of 1631 patients, and 2067.7 years of patient follow-up. Baseline characteristics for the pooled patient groups are shown in Table 2a (comparing trials excluding severe disease with those enrolling all disease severities) and Table 2b (comparing trials allowing concurrent use of low-dose immunosuppression and those not allowing immunosuppression). There were no major baseline differences in patients enrolled in trials allowing and excluding prednisolone use. Baseline differences between trials excluding severe disease and those including all severities showed that those including severe disease were older (67.1 yrs vs 63.8 yrs), had been diagnosed for longer (2.2 vs 0.9 yrs), had lower baseline FVC and DLco values, and were more likely to have already commenced immunosuppression (43.4% vs 15.9%).

There were a total of 190 fatalities in the placebo arms of the trials, thus giving a standardised mortality rate of 91.9 deaths per 1000 patient/years follow-up. The relative proportions of patients dying per year by study are shown in Fig. 1. All but one of the trials stated how many patients died from respiratory problems, which totaled 142 patients from twelve trials, thus giving a standardised event rate of 70.3 deaths per 1000 patient/years due to respiratory events.

The mortality rate was significantly lower overall in trials that only included mild and moderate disease severities as compared to trials where severe patients were included (IRR 0.42, 95% CI 0.30–0.59,$p < 0.0001$). The overall standardised mortality rate was 78.6 deaths per 1000 patient/years in eight trials that recruited only patients with mild-to-moderate disease as compared to 188.6 fatalities per 1000 patient/years overall in four trials that included patients with severe disease (Table 5). The proportion of fatal events per year in each trial and the pooled average from the random effect meta-analysis are shown in Figs. 1 and 2. Key features illustrated in the Forest plots are the extent of heterogeneity between studies, and the difference between studies that recruited only mild to moderate disease (annual proportion of fatalities 8%; 95% CI 5.2%–12%) as compared to those that included patients with severe disease (annual proportion of fatalities 15.4%; 95% CI 9.1%–23.1%).

We observed that trials permitting concomitant use of low dose immunosuppression had higher rates of death compared to those where participants were not taking immunosuppression alongside placebo (Table 4). All-cause mortality rates were 95.8 deaths per 1000 patient/years overall in ten trials allowing immunosuppression, compared with 72.9 deaths per 1000 patient/years overall in three trials enrolling those not on immunosuppression (IRR 1.31, 95% CI 0.93–1.88).

In studies reporting infective events, the standardised rate of lower respiratory tract infections was 172.5 events per 1000 patient/years in ten trials reporting the outcome, whereas the overall standardised rate of pneumonia was 45.6 events per 1000 patient/years across eight studies (Fig. 3). Six of the studies allowing concurrent use of low-dose steroids and three of the studies not allowing steroid use reported infective events. Incidence of lower respiratory tract infections was significantly higher in the group that allowed immunosuppression, at 227.1 respiratory infections per 1000 patient/years, compared with rates in the non-immunosuppressant group of 63.4 per 1000 patient/years ($p < 0.0001$, IRR 3.58, 95% C.I. 2.56–5.13). A similar

Table 3 Standardised event rates.

Trial	Investigated agent	Lower respiratory tract infections		Pneumonia (if listed separately)		Death(All cause mortality)		Death (respiratory cause mortality)		Acute exacerbations		IPF progression	
		Actual events (%)	Events per 1000 patient/ years	Actual events (%)	Events per 1000 patient/ years	Actual events (%)	Events per 1000 patient/ years	Actual events (%)	Events per 1000 patient/ years	Actual events (%)	Events per 1000 patient/ years	Actual events (%)	Events per 1000 patient/ years
Shulgina et al., — 2012 [8]	Co-trimoxazole	46 (53.5)	534.9	8 (9.3)	93.0	19 (22.1)	220.9	16 (18.6)	186.1	No data	—	No data	—
Richieldi et al., — 2011 [11]	BIBF-1120	11 (12.9)	129.4	—	—	12 (14.1)	141.2	8 (9.4)	94.1	No data	—	37 (44)	435.3
King et al., — 2011 [22]	Bosentan (BUILD-3)	64 (30.6)	200.0	12 (5.7)	37.5	6 (2.9)	18.8	3 (1.4)	9.4	6 (2.9)	18.8	82 (36.4)	256.3
Noble et al., 2011 [10]	Pirfenidone (CAPACITY)	22 (6.3)	45.8	15 (4.3)	31.2	34 (9.8)	70.8	28 (8.1)	58.3	No data	—	106 (31)	220.6
Taniguchi et al., — 2010 [25]	Pirfenidone	—	—	—	—	4 (3.8)	38.5	1 (1.0)	9.6	4 (3.8)	38.5	58 (55.8)	557.7
IPF clinical research network — 2010 [29]	Sildenafil	2 (2.2)	40.8	1 (1.1)	20.4	11 (12.1)	224.5	—	—	4 (4.4)	81.6	5 (5.5)	102.0
Daniels et al., 2009 [24]	Imatinib	7 (11.5)	62.2	7 (11.5)	62.1	10 (16.4)	88.8	7 (11.5)	62.2	1 (1.6)	8.9	19 (25.3)	168.7
King et al., — 2009 [23]	Interferon gamma-1b (INSPIRE)	76 (27.6)	186.6	13 (4.7)	31.9	39 (14.2)	95.8	32 (11.6)	78.6	15 (5.5)	36.8	21 (8)	51.6
King et al., — 2008 [21]	Bosentan (BUILD-1)	—	—	—	—	8 (9.5)	95.2	8 (9.5)	95.2	3 (3.6)	35.7	30 (36.1	357.1
Raghu et al., 2007 [26]	Etanercept	11 (26.8)	290.7	—	—	2 (4.9)	52.9	2 (4.9)	52.9	No data	—	22 (53.6)	581.3
Malouf et al., 2007 [27]	Everolimus	10 (22.2)	111.1	10 (22.2)	111.1	16 (35.6)	177.8	13 (28.9)	144.4	No data	—	14 (31.1)	155.6
Raghu et al., 2004 [20]	Interferon gamma-1b	60 (35.7)	320.2	13 (7.7)	69.4	28 (16.7)	149.4	23 (13.7)	122.7	No data	—	87 (52)	464.3
Azuma et al., 2004 [28]	Pirfenidone	—	—	—	—	1 (2.9)	41.3	1 (2.9)	41.3	5 (14.3)	206.3	No data	—
Overall		309	172.5[b]	79	45.6[b]	190	91.9[b]	142	68.7[b]	29	26.3[b]	481	245.7[b]
Percentage of Patients suffering event		21.9%[a]	—	6.2%[a]	—	11.6%	—	9.2%[a]	—	3.4%[a]	—	31.9%[a]	—

[a] Percentage of patients from trials reporting this outcome.
[b] Averages (means) are weighted relative to the size of each study.

Table 4 Comparison of trials permitting immunosuppression vs no immunosuppression allowed.

Trial	Investigated Agent	Death (All cause mortality)		Death (Respiratory cause mortality)		Acute exacerbations		Lower Respiratory Tract Infections		Pneumonia		IPF Progression	
		Actual Events (%)	Events per 1000 patient/ years	Actual Events (%)	Events per 1000 patient/ years	Actual Events (%)	Events per 1000 patient/ years	Actual Events (%)	Events per 1000 patient/ years	Actual Events (%)	Events per 1000 patient/ years	Actual Events (%)	Events per 1000 patient/ years
Immunosuppression Permitted (1388 patient/years follow up)													
Shulgina et al., — 2012 [8]	Co-trimoxazole	19 (22.1)	220.9	16 (18.6)	186.1	—	—	46 (53.5)	534.9	8 (9.3)	93.0	No data	—
Richieldi et al., — 2011 [11]	BIBF-1120	12 (14.1)	141.2	8 (9.4)	94.1	—	—	11 (12.9)	129.4	—	—	37 (44)	435.3
King et al., — 2011 [22]	Bosentan (BUILD-3)	6 (2.9)	18.8	3 (1.4)	9.4	6 (2.9)	18.8	64 (30.6)	200.0	12 (5.7)	37.5	82 (36.4)	256.3
Taniguchi et al., — 2010 [25]	Pirfenidone	4 (3.8)	38.5	1 (1.0)	9.6	4 (3.8)	38.5	—	—	—	—	58 (55.8)	557.7
King et al., — 2009 [23]	Interferon gamma-1b (INSPIRE)	39 (14.2)	95.8	32 (11.6)	78.6	15 (5.5)	36.8	76 (27.6)	186.6	13 (5)	31.92	21 (8)	51.6
King et al., — 2008 [21]	Bosentan (BUILD-1)	8 (9.5)	95.2	8 (9.5)	95.2	3 (3.6)	35.7	—	—	—	—	30 (36.1)	357.1
Malouf et al., 2007 [27]	Everolimus	16 (35.6)	177.8	13 (28.9)	144.4	—	—	10 (22.2)	111.1	10 (22)	111.1	14 (31.1)	155.6
Raghu et al., 2004 [20]	Interferon gamma-1b	28 (16.7)	149.4	23 (13.7)	122.7	—	—	60 (35.7)	320.2	13 (8)	69.4	87 (52)	464.3
Azuma et al., 2004 [28]	Pirfenidone	1 (2.9)	41.3	1 (2.9)	41.3	5 (14.3)	206.3	—	—	—	—	No data	—
Overall		133	95.84	105	75.66	33	35.1	267	227.1	56	51.4	329	257.5
Immunosuppression Not Permitted (631 patient/years follow up)													
Noble et al., 2011 [10]	Pirfenidone (CAPACITY)	34 (9.8)	70.8	28 (8.1)	58.3	—	—	22 (6.3)	45.8	15	31.2	106 (31)	220.6
Daniels et al., 2009 [24]	Imatinib	10 (16.4)	88.8	7 (11.5)	62.2	1 (1.6)	8.9	7 (11.5)	62.2	7	62.1	19 (25.3)	168.7
Raghu et al., 2007 [26]	Etanercept	2 (4.9)	52.9	2 (4.9)	52.9	—	—	11 (26.8)	290.7	—	—	22 (53.6)	581.3
Overall		46	72.9	37	58.6	1 (1.6)	8.9	40	63.4	22	37.1	147	233.0
Incidence rate ratio (comparing groups)			1.31 (0.93—1.88, $p = 0.11$)		1.29 (0.88—1.93, $p = 0.18$)		3.93 (0.65—159.95, $p = 0.14$)		3.58 (2.56—5.13, $p < 0.0001$)		1.39 (0.83—2.38, $p = 0.19$)		1.11 (0.91—1.35), $p = 0.31$

Table 5 Comparison of trials including mild and moderate disease severities only with those permitting all disease severities.

Trial	Investigated Agent	Death (All cause mortality)		Death (Respiratory cause mortality)		Acute exacerbations		Lower Respiratory Tract Infections		Pneumonia		IPF Progression	
		Actual Events (%)	Events per 1000 patient/ years	Actual Events (%)	Events per 1000 patient/ years	Actual Events (%)	Events per 1000 patient/ years	Actual Events (%)	Events per 1000 patient/ years	Actual Events (%)	Events per 1000 patient/ years	Actual Events (%)	Events per 1000 patient/ years
Patients with severe disease excluded (1818.5 patient/years follow-up)													
Richieldi et al., — 2011 [11]	BIBF-1120	12 (14.1)	141.2	8 (9.4)	94.1	—	—	11 (12.9)	129.4	—	—	37 (44)	435.3
Noble et al., 2011 [10]	Pirfenidone (CAPACITY)	34 (9.8)	70.8	28 (8.1)	58.3	—	—	22 (6.3)	45.8	15 (4.3)	31.2	106 (31)	220.6
King et al., — 2011 [22]	Bosentan (BUILD-3)	6 (2.9)	18.8	3 (1.4)	9.4	6 (2.9)	18.8	64 (30.6)	200.0	12 (5.7)	37.5	82 (36.4)	256.3
Taniguchi et al., — 2010 [25]	Pirfenidone	4 (3.8)	38.5	1 (1.0)	9.6	4 (3.8)	38.5	—	—	—	—	58 (55.8)	557.7
King et al., — 2009 [23]	Interferon gamma-1b (INSPIRE)	39 (14.2)	95.8	32 (11.6)	78.6	15 (5.5)	36.8	76 (27.6)	186.6	13 (5)	31.92	21 (8)	51.6
Daniels et al., 2009 [24]	Imatinib	10 (16.4)	88.8	7 (11.5)	62.2	1 (1.6)	8.9	7 (11.5)	62.2	7 (11.5)	62.1	19 (25.3)	168.7
King et al., — 2008 [21]	Bosentan (BUILD-1)	8 (9.5)	95.2	8 (9.5)	95.2	3 (3.6)	35.7	—	—	—	—	30 (36.1)	357.1
Raghu et al., 2007 [26]	Etanercept	2 (4.9)	52.9	2 (4.9)	52.9	—	—	11 (26.8)	290.7	—	—	22 (53.6)	581.3
Raghu et al., 2004 [20]	Interferon gamma-1b	28 (16.7)	149.4	23 (13.7)	122.7	—	—	60 (35.7)	320.2	13 (8)	69.4	87 (52)	464.3
Overall		143	78.6	112	61.6	29	28.2	251	153.9	60	39.1	462	254.1
Patients with severe disease included (249.2 patient/years follow-up)													
Shulgina et al., — 2012 [8]	Co-trimoxazole	19 (22.1)	220.9	16 (18.6)	186.1	—	—	46 (53.5)	534.9	8 (9.3)	93.0	No data	—
IPF clinical research network — 2010 [29]	Sildenafil	11 (12.1)	224.5	—	—	4 (4.4)	81.6	2 (2.2)	40.8	1 (1.1%)	20.4	5 (5%)	102.0
Malouf et al., 2007 [27]	Everolimus	16 (35.6)	177.8	13 (28.9)	144.4	—	—	10 (22.2)	111.1	10 (22)	111.1	14 (31.1)	155.6
Azuma et al., 2004 [28]	Pirfenidone	1 (2.9)	41.3	1 (2.9)	41.3	5 (14.3)	206.3	—	—	—	—	No data	—
Overall		47	188.6	30	149.8	9	122.9	58	257.8	19	96.4	19	136.7
Incidence rate ratio			0.42 (0.30—0.59) $p < 0.0001$		0.41 (0.27—0.64) $p < 0.0001$		0.23 (0.11—0.55) $p < 0.0001$		0.60 (0.45—0.81) $p = 0.0003$		0.41 (0.24—0.72) $p = 0.004$		1.86 (1.18—3.12), $p = 0.007$

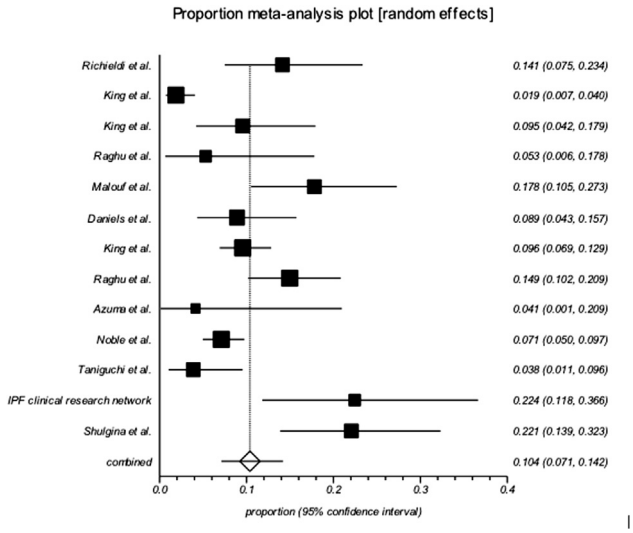

Figure 1 Forest plot showing proportion of mortality per year across all studies.

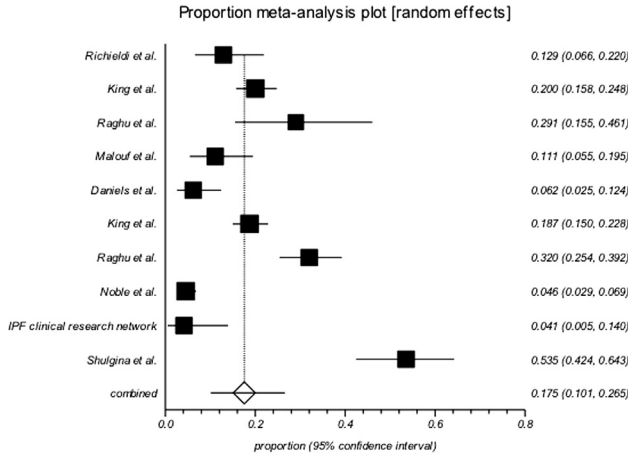

Figure 3 Forest plot showing proportion of patients suffering lower respiratory tract infection per year (all studies).

trend was seen with the incidence of pneumonias, with an average incidence in the six trials permitting immunosuppression of 51.4 pneumonias per 1000 patient/years, compared with 37.1 pneumonias/1000 patient/years in two trials not allowing immunosuppression, although the higher rate in the trials allowing low-dose immunosuppression was not statistically significant (IRR 1.39, 95% C.I. 0.83—2.38). The proportion of lower respiratory tract infections per year in each trial and the pooled average from the random effects meta-analysis are shown in Figs. 3 and 4, clearly displaying the heterogeneity between studies.

Rates of infection were also seen to be higher in studies including patients with severe disease. In the three trials reporting rates of lower respiratory tract infections, the event rate was 257.8 per 1000 patient/years, compared with 153.9 per 1000 patient/years in those including mild and moderate disease severities only (IRR 0.60, 95% C.I. 0.45—0.81, $p = 0.0003$).

Acute exacerbation rates were captured in six trials, with a weighted average of 41 acute exacerbations per 1000 patient/years overall. No difference was observed between trials permitting immunosuppression with those not (incidence rate ratio 3.93. 95% C.I. 0.65—159.95), though only one trial not permitting immunosuppressant use [10] quoted rates of acute exacerbations. The study not permitting immunosuppression use did show the lowest rates of acute exacerbations of any of the trials. Rates of acute exacerbations were much lower in trials that excluded patients with severe disease as compared to trials where severe patients were included (IRR 0.23, 95% C.I. 0.11—0.55, $p < 0.0001$).

Progression of disease was similar between trials allowing immunosuppression and those that did not (257.5 vs 233.0 per 1000 patient/years). Although rates were higher in trials excluding severe disease compared with those including all disease severities (254.1 vs 136.7 events per 1000 patient/years), only two trials including all disease severities captured data regarding disease progression, which included only 136 patients in total and 139 patient/years of follow-up.

Discussion

From analysis of the placebo arms of clinical trials, we have shown that there was considerable variation in the mortality rate between trials. Mortality rates were significantly

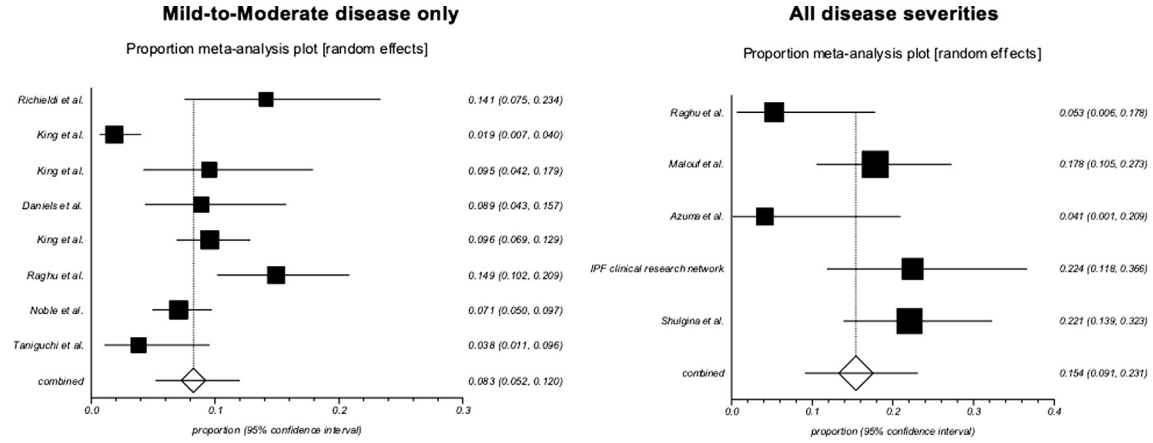

Figure 2 Forest plot showing proportion of mortality per year (studies including mild-to-moderate disease severity only vs all disease severities included).

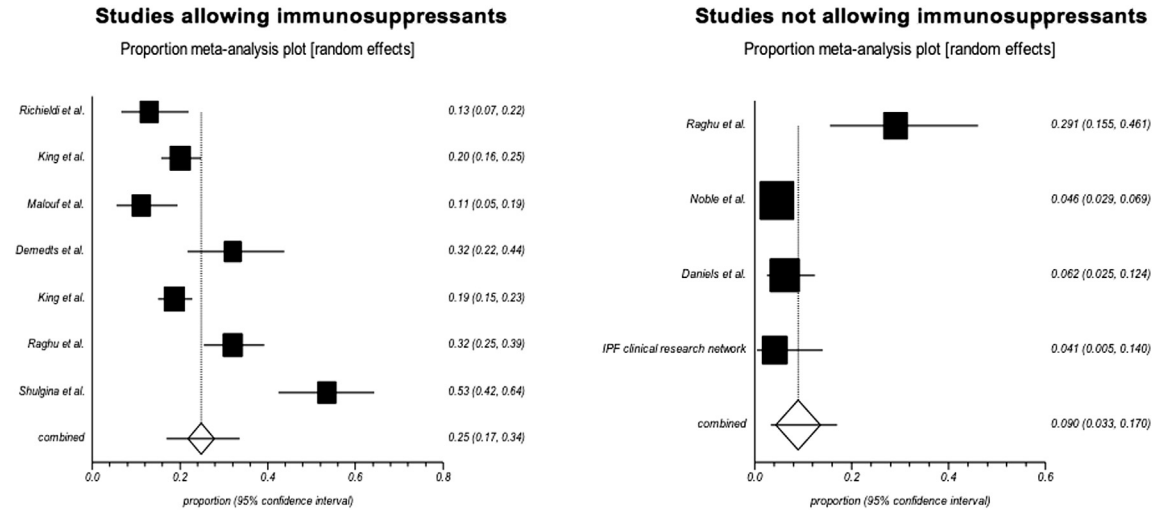

Figure 4 Forest plot showing proportion of patients suffering lower respiratory tract infections per year (trials allowing immunosuppression vs those allowing no concurrent immunosuppression).

lower in trials excluding severe disease compared to those including all disease severities. There were significantly higher rates of infection in those studies permitting the use of low-dose corticosteroids versus those not allowing use of any immunosuppressants. However, rates of infection were still high in patients not receiving any form of immunosuppression. Although reporting of acute exacerbations was limited, our meta-analysis also suggests that the risk of these events is increased in patients taking corticosteroids and in patients with severe disease.

The finding of raised rates of infection was striking. The suspension of the triple therapy arm of the PANTHER-IPF trial [12] had previously shown that, patients receiving high dose prednisolone (0.5 mg/kg), azathioprine and n-acetylcysteine were at an increased risk of death (11% vs 1%) and hospitalisation (29% vs 8%), but no difference in the rates of infective events between arms (6% vs 1%, $p = 0.12$). Unexpectedly, in this meta-analysis rates of respiratory infections were significantly higher even in trials permitting low-dose prednisolone. The association between low dose immunosuppression and infection is likely to be stronger than suggested here as not all patients enrolled in the trials permitting low-dose prednisolone were on immunosuppression, or the events may not have been picked up during the course of trial follow-up.

Although a higher rate of infection may have been expected in the trials allowing concurrent use of immunosuppressive drugs [30], a high frequency of lower respiratory tract infections and pneumonias was also observed in patients who were enrolled in trials not allowing immunosuppressant medications. For comparison with another chronic respiratory disease, the incidence of pneumonias in patients not taking immunosuppression was similar to that previously seen in a cohort with severe COPD [31]. This suggests that IPF itself is a risk factor for the development of pulmonary infections. The results also suggest a possible correlation between susceptibility to infection and underlying disease state. The higher rate of infections seen in the trials where severe disease was captured indicates that infections may become increasingly problematic in the natural course of the disease as it progresses.

The findings are in keeping with data from a post-mortem study of IPF patients which reported that bacterial pneumonia (23% of cases) was the commonest cause of death and significantly more common than age matched controls [32], suggesting infections become more frequent as the disease progresses, and are commonly a terminal event. Previous research has shown alveolar macrophages in IPF patients are able to phagocytose bacteria, but expressed little bacteriocidal or bacteriostatic activity, leaving them unable to kill facultative intracellular bacteria [33]. These alveolar macrophages normally clear the air spaces of infectious particles [34], and a loss of function could predispose to infections.

From epidemiological data, the median survival of IPF patients is 3.9 years, with a mortality rate of 180 deaths per 1000 patient/years follow-up [35]. This is in stark contrast to the overall mortality rate seen in the placebo arms of the clinical trials (91.9 deaths per 1000 patient/years of follow-up). Separating trials into those including all disease severities had a mortality rate almost identical to that from epidemiological data (188.6 deaths per 1000 patient/years), whereas studies excluding these patients had a much lower mortality rate (78.6 deaths per 1000 patient/years). It is clear that the mortality rate is highly variable and dependent on disease severity. Indeed markers of severity, in particular FVC, are key components to predictors of mortality The low overall mortality rate seen in the placebo arms would suggest that it would be difficult to see a significant difference in this outcome when investigating a new agent in patients with mild-to-moderate disease [5]. However, the high rates of mortality in unselected studies or studies of more severe disease suggest that mortality might be an appropriate outcome measurement in trials including these patients. Nevertheless, the frequency of fatal events may not increase in a strictly linear fashion with time, and so extension of the duration of clinical trials of IPF patients to 2- or 3-year duration may yield different findings or potentially higher rates than

which might be expected through simple extrapolation from one-year (or shorter) duration studies. Disease progression over this time could potentially have a significant impact on the mortality rate in a placebo group, but this would need to be evaluated in an actual clinical trial. Regardless, these data highlights the importance of selecting the outcomes of clinical trials of therapeutic entities in light of the entry criteria.

Poor reporting of rates of acute exacerbations prevent a clear picture of whether immunosuppression use or disease severity increases the risk of these potentially fatal events [7]. However the incidence rate was lower in the study not permitting immunosuppressants than in those permitting corticosteroid therapy. Incidence rates of acute exacerbations were substantially higher in trials enrolling all disease severities, which may suggest that these events become more frequent as the disease advances, or could be related to the higher rates of low-dose immunosuppression use in these trials.

No difference was seen in rates of disease progression (as defined by a reduction in FVC $\geq$10% or DLco $\geq$15% during the trials) between trials allowing and excluding low-dose corticosteroid use, suggesting that although steroids do not prevent disease progression, they do not increase the likelihood of the disease progressing. When comparing trials including all disease severities with those only including mild and moderate severities, only two trials reported rates of IPF progression in the former group, making it very difficult to accurately draw any conclusions about whether progression of disease is more common in trials including more severe disease. As clinical trials are now tending to focus on rates of progression (given the previously mentioned issues with mortality) [5], understanding how frequently patients in the placebo arms will suffer progression is clearly important.

The weakness of this review is the absence of individual patient data. When analysing the frequency of adverse events and infective events in studies including patients on corticosteroids, we do not have information on the duration of corticosteroid use, nor the exact dose (though less than 20 mg of prednisolone). No differences were observed between the baseline characteristics of patients enrolled in trials permitting low-dose prednisolone compared with trials not permitting any immunosuppression (Table 2b) to account for the differences observed between these groups. Although there were some differences in baseline characteristics between studies permitting all disease severities and those excluding severe disease (Table 2a), the most important explanation of the mortality and infection rate differences seem to be time since diagnosis, poor pulmonary function and use of immunosuppression. Nevertheless, we recognise that infectious complications and survival outcomes in IPF may be associated with a diverse range of patient or treatment variables, and that no single trial may have sufficient sample size to enable statistical evaluation of all these important variables. Hence, a comprehensive analysis examining outcomes in key subgroups may only be possible through individual patient meta-analysis, as demonstrated in recent research on attributable mortality in ventilator-associated pneumonia where the initial systematic review was subsequently followed-up by an individual patient data analysis [36,37].

This study provides important information for the design of future clinical trials in IPF. Future studies should consider the issue of sample size based upon their defined entry criteria. If patients with severe disease are excluded then the mortality rate should be expected to be low, and an alternative primary outcome, such as change in FVC, should be considered. Further research is needed to look specifically at rates of respiratory infections and possible risk factors for LRTIs and pneumonias in IPF patients. There may also be benefit in identifying strategies that may help reduce the frequency of these infective events.

Disclosures

This work was not funded or contributed to in any way by external parties (e.g. pharmaceutical companies), nor was it produced for profit in any way.

CPA has no disclosures or conflicts of interest.

YKL has no disclosures or conflicts of interest.

AMW has attended a meeting with funding from intermune.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.11.007.

References

[1] Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006 Oct 1;174(7):810—6.

[2] Bjoraker JA, Ryu JH, Edwin MK, Myers JL, Tazelaar HD, Schroeder DR, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998 Jan 1;157(1):199—203.

[3] American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000 Feb;161(2 Pt 1):646—64.

[4] Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011 Mar 15; 183(6):788—824.

[5] Wells AU, Behr J, Costabel U, Cottin V, Poletti V, Richeldi L. Hot of the breath: mortality as a primary end-point in IPF treatment trials: the best is the enemy of the good. Thorax 2012 Nov;67(11):938—40.

[6] Hyzy R, Huang S, Myers J, Flaherty K, Martinez F. Acute exacerbation of idiopathic pulmonary fibrosis. Chest 2007 Nov;132(5):1652—8.

[7] Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby T. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. Eur Respir J 2006 Jan;27(1):143—50.

[8] Shulgina L, Cahn AP, Chilvers ER, Parfrey H, Clark AB, Wilson ECF, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. Thorax 2013 Feb;68(2):155—62.

[9] Demedts M, Behr J, Buhl R, Costabel U, Dekhuijzen R, Jansen HM, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2005 Nov 24;353(21):2229—42.

[10] Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011;377(9779):1760—9.
[11] Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, et al. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. N Engl J Med 2011 Sep 21; 365(12):1079—87.
[12] Raghu G, Anstrom KJ, King Jr TE, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012 May 24;366(21):1968—77.
[13] Raghu G, Collard HR, Anstrom KJ, Flaherty KR, Fleming TR, King Jr TE, et al. Idiopathic pulmonary fibrosis: clinically meaningful primary endpoints in phase 3 clinical trials. Am J Respir Crit Care Med 2012 May 15;185(10):1044—8.
[14] Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996 Feb;17(1):1—12.
[15] Kubo H, Nakayama K, Yanai M, Suzuki T, Yamaya M, Watanabe M, et al. Anticoagulant therapy for idiopathic pulmonary fibrosis. Chest 2005 Sep;128(3):1475—82.
[16] Douglas WW, Ryu JH, Swensen SJ, Offord KP, Schroeder DR, Caron GM, et al. Colchicine versus prednisone in the treatment of idiopathic pulmonary fibrosis. A randomized prospective study. Members of the Lung Study Group. Am J Respir Crit Care Med 1998 Jul;158(1):220—5.
[17] Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block LH. A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. N Engl J Med 1999 Oct 21;341(17): 1264—9.
[18] Noth I, Anstrom KJ, Calvert SB, De Andrade J, Flaherty KR, Glazer C, et al. A placebo-controlled randomized trial of warfarin in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2012 Jul 1;186(1):88—95.
[19] Raghu G, Depaso WJ, Cain K, Hammar SP, Wetzel CE, Dreis DF, et al. Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: a prospective double-blind, randomized, placebo-controlled clinical trial. Am Rev Respir Dis 1991 Aug;144(2):291—6.
[20] Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 2004 Jan 8;350(2):125—33.
[21] King Jr TE, Behr J, Brown KK, Du Bois RM, Lancaster L, De Andrade JA, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008 Jan 1;177(1):75—81.
[22] King Jr TE, Brown KK, Raghu G, Du Bois RM, Lynch DA, Martinez F, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011 Jul 1;184(1):92—9.
[23] King Jr TE, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, et al. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. Lancet 2009 Jul 18;374(9685):222—8.
[24] Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR. Imatinib treatment for idiopathic pulmonary fibrosis: randomized placebo-controlled trial results. Am J Respir Crit Care Med 2010 Mar 15;181(6):604—10.
[25] Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, et al. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010 Apr;35(4):821—9.
[26] Raghu G, Brown KK, Costabel U, Cottin V, Du Bois RM, Lasky JA, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. Am J Respir Crit Care Med 2008 Nov 1;178(9):948—55.
[27] Malouf MA, Hopkins P, Snell G, Glanville AR. An investigator-driven study of everolimus in surgical lung biopsy confirmed idiopathic pulmonary fibrosis. Respirology 2011 Jul;16(5): 776—83.
[28] Azuma A, Nukiwa T, Tsuboi E, Suga M, Abe S, Nakata K, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2005 May 1;171(9):1040—7.
[29] Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, Hunninghake GW. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010 Aug 12; 363(7):620—8.
[30] Buttgereit F, Straub RH, Wehling M, Burmester G- R. Glucocorticoids in the treatment of rheumatic diseases: an update on the mechanisms of action. Arthritis Rheum 2004;50(11): 3408—17.
[31] Müllerova H, Chigbo C, Hagan GW, Woodhead MA, Miravitlles M, Davis KJ, et al. The natural history of community-acquired pneumonia in COPD patients: a population database analysis. Respir Med 2012 Aug;106(8):1124—33.
[32] Araki T, Katsura H, Sawabe M, Kida K. A clinical study of idiopathic pulmonary fibrosis based on autopsy studies in elderly patients. Intern Med 2003 Jun;42(6):483—9.
[33] Savici D, Campbell PA, King TE. Bronchoalveolar macrophages from patients with idiopathic pulmonary fibrosis are unable to kill facultative intracellular bacteria. Am J Respir Crit Care Med 1989 Jan 1;139(1):22—7.
[34] Sibille Y, Reynolds HY. Macrophages and polymorphonuclear neutrophils in lung defense and injury. Am Rev Respir Dis 1990 Feb;141(2):471—501.
[35] Gribbin J, Hubbard RB, Le Jeune I, Smith CJP, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax 2006 Nov;61(11):980—5.
[36] Melsen WG, Rovers MM, Koeman M, Bonten MJM. Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. Crit Care Med 2011 Dec; 39(12):2736—42.
[37] Melsen WG, Rovers MM, Groenwold RHH, Bergmans DCJJ, Camus C, Bauer TT, et al. Attributable mortality of ventilator-associated pneumonia: a meta-analysis of individual patient data from randomised prevention studies. Lancet Infect Dis 2013 Aug;13(8):665—71.