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Cyclophosphamide added to glucocorticoids in acute exacerbation of idiopathic pulmonary fibrosis (EXAFIP): a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background The use of cyclophosphamide in patients with acute exacerbation of idiopathic pulmonary fibrosis (IPF) is unknown. Our study was designed to evaluate the efficacy and safety of four cyclophosphamide pulses in addition to high-dose methylprednisolone in this population.

Methods In this double-blind, placebo-controlled trial done in 35 departments across 31 hospitals in France, adult patients (≥ 18 years) with acute exacerbation of IPF and those with suspected acute exacerbation of IPF were randomly assigned in a 1:1 ratio using a web-based system to receive either intravenous pulses of cyclophosphamide (600 mg/m²) plus uromitexan as haemorrhagic cystitis prophylaxis (200 mg/m²) at the time of cyclophosphamide administration and then again, 4 h later, or placebo at days 0, 15, 30, and 60. Random assignment was stratified according to the severity of IPF and was block-balanced with variable block sizes of four or six patients. Patients receiving mechanical ventilation, with active infection, with active cancer, or who were registered on the lung transplant waiting list were excluded. All patients received standardised high-dose glucocorticoids. The investigators, patients, and the sponsor were masked to the treatment assignments. The primary endpoint was 3-month all-cause mortality, analysed by a χ^2 test adhering to an intention-to-treat principle. The trial is now complete and registered with ClinicalTrials.gov, NCT02460588.

Findings Between Jan 22, 2016, and July 19, 2018, 183 patients were assessed for eligibility, of whom 120 patients were randomly assigned and 119 patients (62 [52%] with severe IPF) received at least one dose of cyclophosphamide (n=60) or placebo (n=59), all of whom were included in the intention-to-treat analysis. The 3-month all-cause mortality was 45% (27/60) in patients given cyclophosphamide compared with 31% (18/59) in the placebo group (difference 14.5% [95% CI -3.1 to 31.6]; p=0.10). Similar results were found after adjustment by IPF severity (odds ratio [OR] 1.89 [95% CI 0.89–4.04]). The risk of death at 3 months, independent of the treatment received, was higher with severe than non-severe IPF (OR 2.62 [1.12–6.12]) and was lower with the use of antifibrotic therapy (OR 0.33 [0.13–0.82]). Adverse events were similar between groups by 6 months (25 [42%] in the cyclophosphamide group vs 30 [51%] in the placebo group) and their proportion, including infections, did not differ. Overall infection was the main adverse event and occurred in 20 (33%) of 60 patients in the cyclophosphamide group versus 21 (36%) of 59 patients in the placebo group.

Interpretation In patients with acute exacerbation of IPF, adding intravenous cyclophosphamide pulses to glucocorticoids increased 3-month mortality. These findings provide evidence against the use of intravenous cyclophosphamide in such patients.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease characterised by worsening dyspnoea and a progressive loss of function. With a 5–10% annual incidence, patients with IPF have acute, clinically significant respiratory

deteriorations characterised by new alveolar opacities defining acute exacerbation.¹

Acute exacerbation of IPF is associated with poor outcomes, with an overall 3-month mortality of more than 50% and reaching up to 90% in patients requiring

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Research in context

Evidence before study

We searched PubMed from June 21, 2007, to Jan 1, 2016, for clinical trials and reviews using the search terms “acute exacerbation” in combination with “idiopathic pulmonary fibrosis”. No further exclusion criteria were used, and research was not limited to English language publications. We identified an unmet clinical need in acute exacerbation of idiopathic pulmonary fibrosis (IPF). At the start of the study, only retrospective series were available and this paucity of evidence has led to heterogeneous therapeutic management of patients with acute exacerbation of IPF. Since 2016 and the start of the study, a randomised, placebo-controlled trial evaluating thrombomodulin alfa has been published. This study did not show the efficacy of this treatment and did not change practices. The 2011 international guidelines on IPF recommended the use of glucocorticoids for most patients with acute exacerbation of IPF. Acute exacerbation of IPF was associated with a poor outcome with a short-term mortality of approximately 50%. Some retrospective studies suggested a beneficial effect of cyclophosphamide used mainly in Europe and Asia. These findings provide a compelling rationale to test whether cyclophosphamide added to glucocorticoids will result in improved outcomes for patient with acute exacerbation of IPF.

mechanical ventilation. Moreover, up to 46% of deaths in patients with IPF are preceded by an acute exacerbation.¹ To date, no treatment has been proven effective for acute exacerbation of IPF.

The cause of acute exacerbation is elusive. Proposed causal factors include the intrinsic acceleration of the underlying fibrotic disease or acute injury in response to external stimuli (ie, infection or micro-aspiration). Although pathological data are scarce, new alveolar opacities, which are widespread in the lungs, are believed to represent essentially acute or organising diffuse alveolar damage, and organising pneumonia superimposed on usual interstitial pneumonia.² Other reported features include acute non-specific inflammation, extensive fibroblast foci, and pulmonary haemorrhage.²⁻⁵ These pathological processes are frequently associated with a biological inflammatory response and might respond to anti-inflammatory therapy. Thus, current guidelines support the use of high-dose glucocorticoids, such as intravenous methylprednisolone pulses.^{6,7}

On the basis of beneficial effects seen in some patients, several research groups also advocate administering other immunosuppressants, especially cyclophosphamide, as either first-line or rescue therapy when glucocorticoids do not work.⁷ An international working group suggested in 2016 that potential immunosuppressive therapy should be studied in randomised controlled trials to better evaluate their possible benefit.¹ In one international survey, approximately 20% of the participating pulmonologists declared

Added value of this study

The EXAFIP study results contribute to the evidence-based treatment of acute exacerbation of IPF. In patients with acute exacerbation of IPF given glucocorticoids, the addition of cyclophosphamide did not improve the short-term or long-term prognosis. The 3-month all-cause mortality was 45% with cyclophosphamide compared with 31% with placebo (difference 14.5% [95% CI -3.1 to 31.6]; $p=0.10$). The 1-year overall survival was 40.5% (95% CI 27.4 to 53.1) in the cyclophosphamide group and 49.5% (36.0 to 61.7) in the placebo group (hazard ratio 1.14 [95% CI 0.59 to 2.22]). The risk of death at 3 months was higher with severe IPF (odds ratio [OR] 2.62 [95% CI 1.12 to 6.12]) and decreased with the use of antifibrotic therapy at baseline (OR 0.33 [0.13 to 0.82]).

Implications of all the available evidence

Cyclophosphamide is the most frequently used immunosuppressive therapy in acute exacerbation of IPF. This is the first trial to show that in patients with acute exacerbation of IPF, cyclophosphamide has no clinical benefit. Our findings provide evidence against the use of intravenous cyclophosphamide in these patients. Notably, baseline antifibrotic therapy decreased the risk of death of patients with acute exacerbation of IPF.

using cyclophosphamide for acute exacerbation of IPF.⁸ Conversely, the PANTHER trial showed that immunosuppression was harmful in patients with stable, mild-to-moderate IPF.⁹ This study found that a three-drug regimen of prednisone, azathioprine, and N-acetylcysteine was associated with increased all-cause mortality at a mean follow-up of 32 weeks, as well as increased occurrence of acute exacerbations compared with placebo. There is therefore an urgent need for trials evaluating the benefit of immunosuppressive therapy in acute exacerbation of IPF.

The EXAFIP study was designed to evaluate the efficacy and safety of four intravenous cyclophosphamide pulses in addition to a standard scheme of high-dose methylprednisolone in a population with acute exacerbation of IPF.

Methods

Study design and participants

The EXAFIP study was a phase 3, investigator-initiated, randomised, double-blind, placebo-controlled trial done at 35 departments across 31 hospitals in France (appendix p 2). The trial was given ethical approval by the Committee for the Protection of Persons of the Hôpital Robert Ballanger and the French National Agency for Medicines and Health Products Safety. The objectives, design, and methods of the trial have been previously reported,¹⁰ and the final protocol, amended in 2019, is available in the appendix (p 9).

Eligible patients were adults (≥ 18 years) with an acute exacerbation of IPF diagnosed by the investigator (all authors) using American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association 2011 international guidelines⁶ and 2007 IPF Clinical Research Network criteria.¹¹ According to the revised definition and criteria, suspected acute exacerbation of IPF, owing to a missing CT or endotracheal aspirate or bronchoscopy data, were included.^{11,12} The main exclusion criteria were patients receiving mechanical ventilation, those with an active infection, with active cancer, or who were registered on a lung transplantation waiting list; a complete list of all inclusion and exclusion criteria is presented in the appendix (p 21). All the patients provided written informed consent.

Randomisation and masking

The investigators enrolled and assigned the participants. Patients were randomly assigned in a 1:1 ratio using a web-based system (CleanWEB) to receive intravenous cyclophosphamide and uromitexan or placebo at days 0, 15, 30, and 60. Random assignment, stratified according to the severity of IPF (as either severe or non-severe), was block-balanced with variable block sizes of four or six patients. Severe IPF was defined by a forced vital capacity (FVC) of less than 50% of the predicted value or a diffuse capacity for carbon monoxide (DLCO) of less than 35% of the predicted value on the last available pulmonary function tests. Patients with inaugural acute exacerbation of IPF occurring in previously unknown IPF were stratified as having non-severe IPF. Cyclophosphamide and uromitexan, and their placebo replacements, were prepared by the pharmacist at each site, and a pharmacy masking was enforced. The investigators, patients, and the sponsor were masked to the treatment assignments.

Procedures

Patients received intravenous cyclophosphamide (at a dose of 600 mg/m² adapted for age, renal function, and neutrophil count, with a maximum dose of 1.2 g; appendix p 19) and intravenous uromitexan as haemorrhagic cystitis prophylaxis (at a dose of 200 mg/m² at the time of cyclophosphamide administration and 4 h later) or placebo (250 ml of 0.9% NaCl) on days 0, 15, 30, and 60.

All patients received high-dose glucocorticoids therapy (methylprednisolone 10 mg/kg per day for 3 days) followed by a progressive tapering to 10 mg per day for patients weighing more than 65 kg and 7.5 mg per day for those weighing 65 kg or less at month 6. They also received prophylaxis against *Pneumocystis jirovecii* pneumonia with co-trimoxazole or atovaquone. The introduction of pirfenidone or nintedanib was authorised at any point throughout the study.

A direct medical history (review of adverse events, use of concomitant medication, oxygen use, infection, and

admission to hospital), complete physical examination, and clinical laboratory evaluation were done at day 15, 30, and 60, and month 3 and 6. If the patient's clinical status permitted pulmonary function tests, resting blood gas analysis and chest high-resolution CT were done at month 3 and 6. Patients had their last visit at month 6. The mortality status at 1 year was assessed either by phone call to the patient or, in the absence of an answer, via contact with the town council of the patient's birthplace.

Outcomes

The primary outcome was 3-month all-cause mortality. The main secondary outcomes were overall survival at 6 and 12 months. Other outcomes included death from respiratory cause at month 3 and 6, respiratory morbidity between the final results available before acute exacerbation and month 6 (including worsening dyspnoea, worsening in gas exchanges, a decrease in FVC of $\geq 10\%$ of predicted value, or a DLCO of $\geq 15\%$ of predicted value), variation of the extent of interstitial fibrosing features on high-resolution CT between the final results available before acute exacerbation and month 6 (appendix p 3), and analysis of risk factors of mortality at month 3.

Safety was assessed from the first dose to month 6; assessments included clinical evaluations, laboratory measurements, and the recording of adverse events. Serious adverse events were assessed from the first dose to the end of participation at month 12.

Statistical analysis

In a systematic review based on all reported series between 1993 and 2006, the 3-month mortality was estimated to be 67.1% (95% CI 56.2–76.5).¹¹ The treatment strategies varied in the different studies, but in almost all, patients were administered broad-spectrum antibiotics and pulse doses of methylprednisolone (0.5–1.0 g per day). Some studies also used additional immunosuppression with cyclophosphamide and ciclosporin.

We hypothesised that 3-month mortality in the placebo group given only methylprednisolone would be 67%, and that cyclophosphamide pulses would decrease this mortality by 25% (to 42%). With this assumption and a two-sided α risk set at 5%, a sample size of 120 patients would provide 80% power to show the superiority of the cyclophosphamide group.

The primary analysis was done for all patients randomly assigned to receive at least one dose of treatment (the patients in the intention-to-treat population). The primary outcome was compared between groups with a χ^2 test and proportion differences between groups were estimated using the exact method. Missing primary outcome data were replaced with the worst-case (death) imputation method. Sensitivity analyses were done firstly on the per protocol population, defined as all patients without a major protocol violation, and secondly on all patients randomly assigned to receive at least one dose of

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treatment with available data. Furthermore, a sensitivity analysis was done including adjustments by IPF severity with the use of a Mantel-Haenszel statistic. A Breslow-Day test was used to test the homogeneity of odds ratios (ORs) between strata.

The results are presented as counts and percentages for discrete variables and mean (SD) or median (IQR) for continuous variables, according to the distribution.

For secondary outcomes, proportions between groups were compared with the exact method, and median differences were estimated with Mood's method. Patients included and those excluded from the per protocol population were compared. Data concerning worsening dyspnoea with visual analogue scale were missing in most patients and excluded from the analysis.

Survival was estimated with the Kaplan-Meier method considering the time from random assignment to death by any cause, with censoring at the date of transplant or of last follow-up visit. A log-rank test was used to compare survival curves. A stratified Cox proportional-hazards model was used to estimate the hazard ratios and the two-sided 95% CIs of 6-month and 12-month mortality adjusted by IPF severity. The risk proportionality

hypothesis was verified by testing the interaction between the interest variable and time.

Logistic regression was used to estimate the ORs and two-sided 95% CIs to study the risk factors of 3-month mortality. An unadjusted analysis was done to select potential risk factors of clinical interest at the p value threshold of 0.2: sex, age, IPF severity, baseline antifibrotic therapy before acute exacerbation of IPF, C-reactive protein, partial pressure of oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) ratio, high-resolution CT classification of acute exacerbation of IPF, high-resolution CT pattern of new abnormalities in acute exacerbation of IPF (appendix p 3), and time between the first signs and symptoms and administration of treatment (methylprednisolone) for acute exacerbation of IPF. Missing data were imputed as the median when the number of missing data was less than 10% (C-reactive protein and time between first signs and symptoms and administration of methylprednisolone) or handled as a missing data category to keep the maximum number of participants included in the analysis when number of missing data was more than 10% (PaO₂ to FiO₂ ratio). Accordingly, the p values

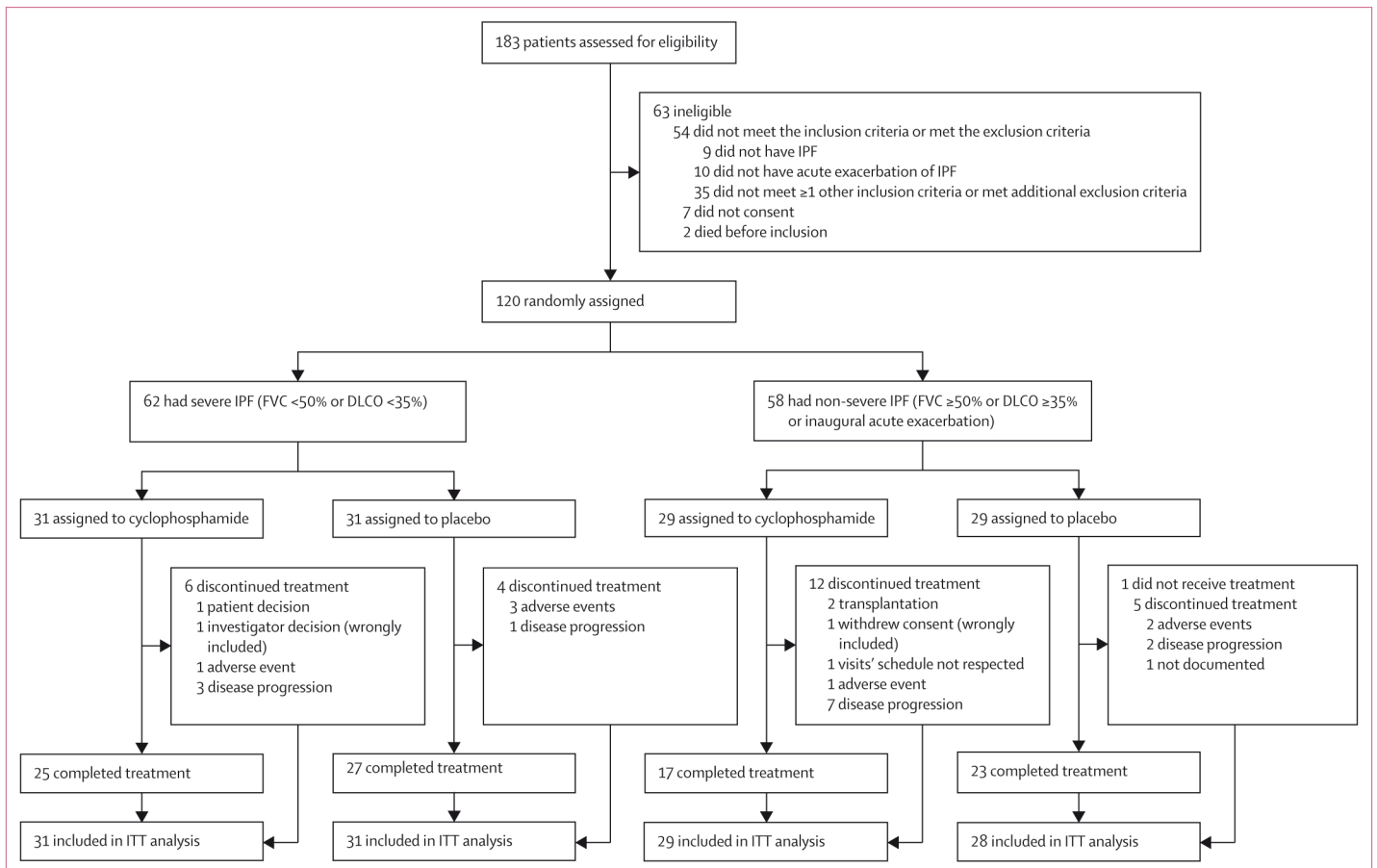


Figure 1: Flow chart of patient selection

DLCO=diffuse capacity for carbon monoxide. FVC=forced vital capacity. IPF=idiopathic pulmonary fibrosis. ITT=intention-to-treat.

	Cyclophosphamide (n=60)	Placebo (n=59)
Age, year	71.0 (9.0)	73.2 (7.0)
Sex		
Male	49 (82%)	45 (76%)
Female	11 (18%)	14 (24%)
Smoking status		
Former smoker	39 (65%)	40 (68%)
Never smoker	17 (28%)	16 (27%)
Current smoker	3 (5%)	3 (5%)
Missing data	1 (2%)	0
Severe IPF*	31 (52%)	31 (53%)
Previously known IPF	56 (93%)	53 (90%)
Surgical lung biopsy	9 (15%)	7 (12%)
Median time since diagnosis of IPF, years	1.99 (0.73–3.36)	1.93 (0.59–3.62)
Antifibrotic therapy		
Nintedanib	13 (22%)	8 (14%)
Pirfenidone	9 (15%)	14 (24%)
Pulmonary function tests before acute exacerbation of IPF		
Median time since last pulmonary function tests, months	4.0 (2.0–7.0)	3.0 (1.5–6.0)
Median FVC, % predicted value	68.5 (54.0–85.5)	67.0 (58.0–86.0)
Median DLCO, % predicted value	35.0 (24.0–46.0)	32.0 (27.0–42.0)
Missing data	0	1 (2%)
Characteristics at onset of acute exacerbation of IPF		
High-resolution CT pattern		
Definite pattern of usual interstitial pneumonia	33 (55%)	40 (68%)
Probable pattern of usual interstitial pneumonia	9 (15%)	6 (10%)
Indeterminate	12 (20%)	8 (14%)
Alternative diagnosis	3 (5%)	2 (3%)
Missing data	3 (5%)	3 (5%)
High-resolution CT pattern of new abnormalities of acute exacerbation of IPF		
Multifocal	33 (55%)	31 (53%)
Diffuse	12 (20%)	11 (19%)
Peripheral	11 (18%)	14 (24%)
Not evaluable	4 (7%)	3 (5%)

(Table 1 continues in next column)

	Cyclophosphamide (n=60)	Placebo (n=59)
(Continued from previous column)		
Partial pressure of oxygen to fraction of inspired oxygen ratio at acute exacerbation of IPF diagnosis	272.7 (175.5–344.3)	252.7 (171.4–320.8)
Missing data	11 (18%)	9 (15%)
Blood leukocytes, μ L	12 352 (3596.7)	12 103 (4266.2)
Missing data	4 (7%)	0
C-reactive protein, mg/L	22.7 (8.1–66.3)	11.5 (5.0–41.0)
Missing data	4 (7%)	4 (7%)
Bronchoalveolar lavage or tracheal aspirate	18 (30%)	18 (31%)
Time between first signs and symptoms and administration of treatment of acute exacerbation of IPF, days	12.0 (5.0–22.0)	13.0 (5.0–25.0)
Missing data	5 (8%)	4 (7%)

Data are mean (SD), n (%), or median (IQR). DLCO=diffuse capacity for carbon monoxide. FVC=forced vital capacity. IPF=idiopathic pulmonary fibrosis. *Severe IPF was defined by a FVC of less than 50% of the predicted value or a DLCO of less than 35% of the predicted value. Patients with inaugural acute exacerbation of IPF occurring in previously unknown IPF were stratified as having non-severe IPF. Data were missing for one patient in the cyclophosphamide group and one in the placebo group for the median time since last pulmonary function tests; for one patient in the placebo group for FVC and DLCO (who was considered to have severe IPF because they were on oxygen therapy); for two in the cyclophosphamide for DLCO (stratified to the non-severe group with a FVC of 80% and 58%); and for one patient in the placebo group for DLCO (stratified in the non-severe group with a FVC of 81%). 12 patients stratified in the severe group were not able to undergo DLCO (eight in the cyclophosphamide group and four in the placebo group) because of the low inspired volume. Three patients were not able to do high-resolution CT at the onset of acute exacerbation (suspected acute exacerbation) and three other high-resolution CT were not available for reviewing by the two radiologists.

Table 1: Characteristics of patients at baseline

All tests were two-sided and p values of less than 0.05 were considered significant. Statistical analyses were done with SAS 9.4 and R software version 3.6.3.

The data safety monitoring board met every 6 months or every 10 deaths, or both, and in the absence of differences regarding adverse events and deaths between groups, it did not decide to prematurely terminate the study. The trial is closed and completed. This study is registered with ClinicalTrials.gov, NCT02460588.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 22, 2016, and July 19, 2018, 183 patients were assessed for eligibility, of whom 120 patients were randomly assigned. One patient died before he received treatment. 119 (99%) patients received at least one dose of the study medication (60 received intravenous

for each category were preferred for interpretation in place of the overall p value. In cases of violation of linearity in the logit, continuous variables were categorised with quartile values in the model. A multivariable regression model was built using step-wise backward selection (all variables with a p value <0.05 were kept in the final model, except random assignment group and IPF severity, which were forced as adjustment variables).

	Cyclophosphamide (n=60)	Placebo (n=59)	Difference (95% CI)	p value
Death at 3 months in the ITT population*	27/60 (45%)	18/59 (31%)	14.5 (-3.1 to 31.6)	0.10
Death at 3 months in the ITT population with available data	26/59 (44%)	18/59 (31%)	13.6 (-4.1 to 30.7)	0.13
Death at 3 months in the per-protocol population	17/42 (40%)	15/50 (30%)	10.5 (-9.6 to 30.1)	0.29

Data are n/N (%), unless otherwise specified. ITT=intention-to-treat. *The missing data for one patient have been replaced by death.

Table 2: Primary outcomes

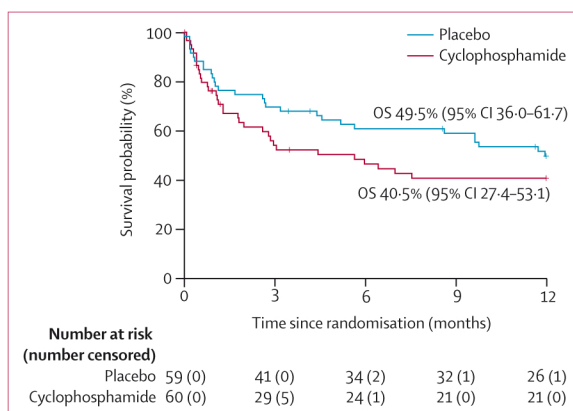


Figure 2: Survival probability over 12 months
OS=overall survival.

cyclophosphamide and 59 received placebo; figure 1). The baseline characteristics of these 119 patients are presented in table 1. The mean age of patients was 72.2 years; 62 (52%) patients had severe IPF, and 25 (21%) were women. There was no difference observed between the patients included and those excluded from the per-protocol population (appendix p 5).

The 3-month all-cause mortality was 45% (27/60, including one patient with missing data) in the cyclophosphamide group and 31% (18/59) in the placebo group (difference 14.5% [95% CI -3.1 to 31.6]; $p=0.10$; table 2). Similar results were found after adjustment by IPF severity (OR 1.89 [95% CI 0.89 to 4.04]). Despite a higher mortality observed in patients with severe IPF in the cyclophosphamide group than in those with severe IPF in the placebo group, there was no significant interaction between the treatment effect and the severity of IPF (non-severe IPF, nine deaths in each group, OR 0.97 [0.45 to 2.07]; severe IPF, 18 deaths in the cyclophosphamide group and nine deaths in the placebo group, OR 2.00 [1.07 to 3.74]; $p=0.10$).

Sensitivity analysis in the randomly assigned intention-to-treat population with available data and in the per-protocol population did not differ significantly between the cyclophosphamide and placebo groups (table 2).

Overall survival in the cyclophosphamide group was 53.9% (95% CI 40.0-65.9) at 3 months, 46.3%

(32.7-58.7) at 6 months, and 40.5% (27.4-53.1) at 12 months. In the placebo group, it was 69.5% (56.0-79.6) at 3 months, 60.7% (46.9-71.9) at 6 months, and 49.5% (36.0-61.7) at 12 months. The hazard ratio between cyclophosphamide and placebo group was 1.14 (95% CI 0.59-2.22; figure 2). Between random assignment and month 12, five patients in the cyclophosphamide group and two in the placebo group had a lung transplantation.

None of the secondary outcomes differed significantly between the two groups (table 3). The causes of death at 3 and 6 months are indicated in the appendix (p 6). At 6 months, 29 (97%) of 30 deaths in the cyclophosphamide group and 22 (96%) of 23 deaths in the placebo group were related to a respiratory cause.

Unadjusted and adjusted analyses of risk factors for 3-month mortality are reported in the appendix (p 7). In the adjusted analysis, independent from the treatment received, severe IPF compared with non-severe IPF was associated with a higher risk of death at 3 months (OR 2.62 [95% CI 1.12-6.12]). Baseline antifibrotic therapy before acute exacerbation of IPF was associated with a lower risk of death at 3 months (OR 0.33 [0.13-0.82]).

Adverse events are reported in table 4. Overall, 25 (42%) patients in the cyclophosphamide group and 30 (51%) in the placebo group had an adverse event by the 6 months follow-up (table 4). Leukopenia, neutropenia, lymphopenia, anaemia, and thrombopenia were present in less than 10% of the patients. No haemorrhagic cystitis was observed in either group. The overall incidence of serious adverse events did not differ notably between groups; 111 serious adverse events occurred in 53 (88%) of 60 patients in the cyclophosphamide group and 135 events in 50 (85%) of 59 patients in the placebo group.

Discussion

In this randomised placebo-controlled trial, intravenous pulses of cyclophosphamide added to high-dose glucocorticoids did not reduce all-cause mortality in patients with acute exacerbation of IPF. Instead, a trend towards increased mortality at 3 months, which was less pronounced at 6 months, was observed in patients receiving cyclophosphamide compared with placebo.

Evidence of effective treatments for patients with acute exacerbation of IPF is scarce and only includes retrospective series; therefore, therapeutic management of these patients is heterogenous.⁸ The 2011 international guidelines on IPF recommended the use of glucocorticoids for most patients with acute exacerbation of IPF;⁶ however, it was a weak recommendation based on expert opinion. Most pulmonologists, mainly in Europe and Asia, who use immunosuppressive therapy to treat acute exacerbation of IPF, use intravenous cyclophosphamide.⁸

A beneficial effect of cyclophosphamide had been hypothesised based on its anti-inflammatory effects, but the results of retrospective studies are controversial.¹⁴⁻¹⁸

However, given its mechanism of action, an increased risk of infection could be expected. The results of this study are consistent with those of the PANTHER trial,⁹ with a non-significant higher mortality at 3 months in patients who received cyclophosphamide for acute exacerbation of IPF, especially in those with severe IPF. However, respiratory insufficiency due to the progression or recurrence of acute exacerbation of IPF was the main cause of death in both placebo and cyclophosphamide groups, with no difference in the incidence of all infectious-related serious adverse events. Taken together, these findings suggest that cyclophosphamide might have a deleterious effect on the progression of fibrosis in IPF. Of note, accumulating evidence links IPF progression with lung dysbiosis,^{19,20} and Molyneaux and colleagues²¹ showed that acute exacerbation of IPF is associated with an increased bacterial burden of bronchoalveolar lavage compared with stable IPF. Trials have not shown an efficacy of co-trimoxazole or doxycycline in patients with IPF, but this finding does not disprove the hypothesis that the lung microbiome influences disease progression.^{22,23} It is conceivable that immunosuppressive therapy increases the susceptibility of the pulmonary epithelium to injury or that it alters the microbiome in a negative way.

The 3-month mortality in both groups of our trial were lower than previously reported.¹ This finding might be explained by the fact that the patients were in a clinical study setting, which might enable earlier diagnosis and treatment than in a real-life setting. Another possible explanation is the exclusion of patients receiving mechanical ventilation. Finally, the standard care administered to both groups could have been beneficial. However, compared with the randomised placebo-controlled trial by Kondoh and colleagues,²⁴ the 3-month mortality of the EXAFIP study was higher. The study by Kondoh and colleagues evaluated the efficacy and safety of thrombomodulin alfa, used for its anticoagulant and anti-inflammatory effect in acute exacerbation of IPF.²⁴ Thrombomodulin alfa did not improve the 90-day survival rate (72.5% in the thrombomodulin alfa group and 89.2% in the placebo group). The difference in 3-month mortality between the two studies might be explained by the inclusion of patients with more severe IPF (52.1% in EXAFIP) and fewer patients on baseline antifibrotic therapy (48.1% vs 37.0%). The analysis of the independent risk factor of death in our study showed that the severity of IPF and baseline antifibrotic therapy were associated with a decreased risk of death.

The strength of this study is that it involved a broad range of patients with acute exacerbation of IPF, with few exclusion criteria, making the results clinically relevant to most patients with this condition.

Notable limitations include the exclusion of patients with mechanical ventilation, thus our data might not apply to such patients. Among the patients alive at 6 months, there was no difference in respiratory morbidity

	Cyclophosphamide (n=60)	Placebo (n=59)	Difference (95% CI)
Death at 3 months	26 (43%)	18 (31%)	..
Death related to respiratory cause at 3 months	25 (96%)	17 (94%)	1.7 (-14.8 to 23.7)
Death at 6 months	30 (50%)	23 (39%)	..
Death related to respiratory cause at 6 months	29 (97%)	22 (96%)	1.0 (-14.3 to 18.8)
Morbidity at 6 months			
Patients who are alive and have not undergone a transplantation	24 (40%)	34 (58%)	..
At least one respiratory morbidity at 6 months of the available data	15/16 (94%)	27/29 (93%)	0.6 (-23.4 to 18.7)
Missing data	8 (33%)	5 (15%)	..
Worsening in gas exchanges at 6 months of the available data*	12/20 (60%)	19/29 (66%)	-5.5 (-33.7 to 21.9)
Missing data	4 (17%)	5 (15%)	..
Decrease in FVC ≥10% of the predicted value at 6 months of the available data†	4/17 (24%)	8/27 (30%)	-6.1 (-32.0 to 23.4)
Missing data	7 (29%)	7 (21%)	..
Decrease in DLCO ≥15% of the predicted value at 6 months of the available data†	3/12 (25)	7/23 (30)	-5.4 (-34.7 to 29.4)
Missing data	12 (50%)	11 (32%)	..
Median variation of global extent of interstitial fibrosing features‡‡	10.0% (5.0 to 15.0)	15.0% (7.0 to 19.0)	-5 (-10.0 to 5.0)

Data presented as n (%) or median (IQR). DLCO=diffuse capacity for carbon monoxide. FVC=forced vital capacity. IPF=idiopathic pulmonary fibrosis. *Initiation of oxygen supplementation or increased need of supplemental oxygen to 3 L per min or more to obtain a SpO₂ of more than 90% or a decrease in PaO₂ of 10 mmHg or more with the same rate of flow supplemental oxygen in patients with known IPF before acute exacerbation. †In patients with known IPF before acute exacerbation. ‡Between the final results available before acute exacerbation and month 6. Data were available for ten patients in the cyclophosphamide group and 17 in the placebo group for the final row in the table.

Table 3: Other secondary outcomes

	Cyclophosphamide (n=60)	Placebo (n=59)
Any adverse event between month 0 and month 6	25 (42%)	30 (51%)
Haemorrhagic cystitis	0	0
Leukopenia	1 (2%)	0
Neutropenia	3 (5%)	0
Lymphopenia	0	1 (2%)
Anaemia	1 (2%)	0
Thrombopenia	0	2 (3%)
Nausea or vomiting	4 (7%)	3 (5%)
Diarrhoea	7 (12%)	4 (7%)
Newly developed diabetes	0 (0%)	1 (2%)
Newly developed hypertension	2 (3%)	2 (3%)
Infectious disease	20 (33%)	21 (36%)
Any serious adverse event between 0 and 12 months	53 (88%)	50 (85%)
Serious adverse event excluding progression of IPF between 0 and 12 months	26 (43%)	29 (49%)
Serious infectious disease	9 (15%)	15 (25%)
Cardiac disorder	6 (10%)	10 (17%)

IPF=idiopathic pulmonary fibrosis.

Table 4: Adverse events and serious adverse events

or a variation in the extent of interstitial features on high-resolution CT between the cyclophosphamide and placebo groups, suggesting the absence of a benefit of cyclophosphamide even in this subgroup of patients. However, missing data in these last two criteria (respiratory morbidity and interstitial features on high-resolution CT) limit their interpretability. The median time between the onset of signs and symptoms and administration of treatment of acute exacerbation of IPF was 12 days in the cyclophosphamide group and 13 days in the placebo group. It might be argued that these lengths of time were too late to show a difference. However, in the unadjusted and adjusted analyses of risk factors associated with 3-month mortality, time to the administration of treatment of acute exacerbation of IPF did not influence the 3-month mortality. Moreover, cyclophosphamide was added to glucocorticoids and we cannot conclude on the usefulness of glucocorticoids. We did consider at the time of EXAFIP conception that the acceptability by patients and by pulmonologists of a placebo-controlled trial of corticosteroids would probably be low, given their broad routine use for this condition and the published recommendations in favour of this treatment. One reported retrospective cohort found no evidence that glucocorticoids improve outcomes in patients with acute exacerbation of IPF,²⁵ therefore, because no good evidence is available to support their use in acute exacerbation of IPF, future research should encompass randomised controlled trials to address the efficacy and safety of glucocorticoids in this indication.

In conclusion, the results of this EXAFIP trial showed that the addition of intravenous pulses of cyclophosphamide to high-dose glucocorticoids did not confer a survival benefit in patients with acute exacerbation of IPF. The higher mortality with cyclophosphamide than with placebo suggests a potential deleterious effect, and the findings of this study provide evidence against its use in such patients. Notably, baseline antifibrotic therapy decreased the risk of death of patients with acute exacerbation of IPF.

Contributors

AT, AC, AN, AGo, A-SG, AP, AB, AGi, ALB-K, CC, CL, DI-B, EBl, EBe, EG, FL, F-XB, FG, FR, GP, GB, JP, JT, LP, LW-S, MK, M-CD, M-PD, MR-G, MD, NB, OF, PB, PYB, RB, SH, SD, SJ, SM-A, SL, TD, J-MN, HN, MC, LB, AR, TS, BC, JC, VC, and DV verify that this study was done per protocol and vouch for data accuracy and completeness, and contributed to drafting the article, provided final approval for publication, and agree to be accountable for all aspects of the article. J-MN, HN, MC, LB, AR, and TS had access to the raw data. J-MN, HN, TS, BC, JC, VC, and DV contributed to the design of the study. J-MN, HN, TS, MC, and AR contributed to the development of methods. J-MN, MC, LB, AR, and TS contributed to data collection. J-MN, HN, MC, AR, and TS contributed to data analysis and interpretation. J-MN, MC, and HN contributed to the drafting of the article. J-MN, HN, MC, AR, and TS verified the data.

Declaration of interests

J-MN reports grants from the French Ministry of Health and Roche, during the conduct of the study; personal fees from AstraZeneca and Boehringer Ingelheim; and non-financial support from Boehringer Ingelheim. SJ reports personal fees from Actelion, Association pour les Insuffisants Respiratoires de Bretagne, AstraZeneca,

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Data sharing

Qualified researchers can request access to the deidentified patient data set, study protocol, and statistical analysis plan. These data will be available after the publication of the main results of our study. This access will be available to researchers whose proposed use of the data are approved by the EXAFIP steering committee for sub-studies and ancillary analysis with scientific merit that can be approached in a valid manner with EXAFIP data. Data will be made available after request by email: jmnacache@gbpsj.fr.

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