Effect of co-trimoxazole (trimethoprim-sulfamethoxazole) vs placebo on death, lung transplant, or hospital admission in patients with moderate and severe idiopathic pulmonary fibrosis

EME-TIPAC team

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Title: Effect of co-trimoxazole vs placebo on death, lung transplantation, or hospital admission in patients with moderate and severe idiopathic pulmonary fibrosis: a randomized clinical trial

Subtitle: The EME-TIPAC study

Andrew M Wilson MD[1], Allan B Clark PhD[1], Tony Cahn PhD[2], Edwin R Chilvers PhD[3], William Fraser PhD[1], Matthew Hammond MSc[4], David M Livermore PhD[1], Toby M Maher PhD[3], Helen Parfrey PhD[5], Ann Marie Swart MSc[4], Susan Stirling MSc[4], David R Thickett DM[6], Moira Whyte PhD[7] on behalf of the EME-TIPAC team.

List of authors' affiliations:

1. Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, Norfolk, NR4 7TJ
2. Department of Respiratory Medicine, Bedford Hospitals NHS Trust, South Wing, Kempston Road, Bedford, MK42 9DJ
3. National Heart and Lung Institute, Imperial College London, London W12 0NN
4. Norwich Clinical Trials Unit, University of East Anglia, Norwich Research Park, Norwich, Norfolk, NR4 7TJ
5. Royal Papworth Hospital NHS Foundation Trust, Papworth Road, Cambridge Biomedical Campus, Cambridge, CB2 0AY
6. Institute of Inflammation and Aging, University of Birmingham, Edgbaston, Birmingham, B15 2TT

7. MRC Centre for Inflammation Research, University of Edinburgh, Edinburgh EH16 4TJ

Corresponding Author: Professor Andrew M Wilson, Floor 2, Bob Champion Research and Education Building, James Watson Road, University of East Anglia, Norwich Research Park, Norwich, Norfolk, NR4 7TJ. UK. Email: a.m.wilson@uea.ac.uk

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EME-TIPAC team

Nazia Chaudhuri PhD (University Hospital of South Manchester NHS Foundation Trust)

Lisa Spencer MRCP (Aintree University Hospitals NHS Foundation Trust)

Huzaifa Adamali MD (North Bristol NHS Trust)

Simon Hart PhD (Hull and East Yorkshire Hospitals NHS Trust)

Helen Stone MRCP (University Hospitals of North Midlands NHS Trust)

Ian Forrest PhD (The Newcastle Upon Tyne Hospitals NHS Foundation Trust)

John Simpson PhD (Newcastle University)

Andrew Goudie MD (NHS Tayside)

Khaled Amsha FRCP (Sherwood Forest Hospitals NHS Foundation Trust)

Ben Hope-Gill MD (Cardiff and Vale University Health Board)

Stephen Bianchi PhD (Sheffield Teaching Hospitals NHS Foundation Trust)

Rachel Hoyles PhD (Oxford University Hospital NHS Foundation Trust)

Sophie Fletcher MRCP (University Hospital Southampton NHS Foundation Trust)

Timothy Gatheral PhD (University Hospitals of Morecambe Bay NHS Foundation Trust)

Yussef Haider MD (Lancashire Teaching Hospitals NHS Foundation Trust)

Owen Dempsey MD (Aberdeen Royal Infirmary)

Felix Woodhead PhD (University Hospitals of Leicester NHS Trust)

Martin Kelly MD (Western Health and Social Care Trust)

Gareth Walters MD (Heart of England NHS Foundation Trust)

Robert Allcock MRCP (Gateshead Health NHS Foundation Trust)

Gauri Saini PhD (Nottingham University Hospitals NHS Foundation Trust)

Thomas Bongers MD (Blackpool, Fylde and Wyre Hospitals NHS Foundation Trust)

Ahmed Fahim MD (The Royal Wolverhampton NHS Trust)

Raminder Aul MD (St George's University Hospitals NHS Foundation Trust)

Liz Fuller MD (South Tyneside Foundation Trust)

David Parr MD (University Hospitals Coventry and Warwickshire NHS Trust)

Robina Coker PhD (Imperial College Healthcare NHS Trust)

Michael Gibbons PhD (Royal Devon and Exeter NHS Foundation Trust)

George Chalmers MD (NHS Greater Glasgow and Clyde)

Richard Heinink MRCP (The Shrewsbury and Telford Hospital NHS Trust)

Rehan Naseer MRCP (Calderdale and Huddersfield NHS Foundation Trust)

Joanna Porter PhD (University College London Hospitals NHS Foundation Trust)

Stephen O'Hickey MD (Worcestershire Acute Hospitals NHS Trust)

Mark Spears FRCP (NHS Forth Valley)

Key Points

Question: What is the clinical efficacy of co-trimoxazole in idiopathic pulmonary fibrosis in terms of time to death (all causes), lung transplant, or first non-elective hospital admission?

Findings: In this randomized clinical trial, which included 343 patients with moderate or severe idiopathic pulmonary fibrosis, the incidence of the composite outcome of death, lung transplantation, or non-elective hospitalization among those treated with oral co-trimoxazole 960 mg twice daily vs placebo was 0.45 vs 0.38 per person-year after median follow-up of 1.02 years; the hazard ratio was not statistically significant.

Meaning: Co-trimoxazole did not improve a composite clinical outcome compared with placebo among patients with moderate or severe interstitial pulmonary fibrosis.

Keywords: Idiopathic pulmonary fibrosis, co-trimoxazole, mortality, hospitalisation, cough, randomized controlled trial

ABSTRACT

Importance: Idiopathic pulmonary fibrosis (IPF) has a poor prognosis, and limited treatment options. People with IPF reportedly have altered lung microbiota, with the bacterial burden within the lungs relating to mortality; there is a suggestion of benefit with co-trimoxazole.

Objective: To determine the clinical efficacy of co-trimoxazole in people with moderate and severe IPF.

Design, Setting and Participants: Double-blind, placebo-controlled, parallel, randomized trial of 342 people with IPF, breathlessness (Medical Research Council dyspnea > 1) and impaired lung function (forced vital capacity (FVC) <75% predicted) conducted in 39 UK specialist interstitial lung disease centers between April 2015 and April 2019.

Intervention: Study participants were randomized to receive 960mg twice daily oral co-trimoxazole (n=170) or matched placebo (n=172) for between 12 and 42 months. All patients received 5mg folic acid orally once daily.

Main Outcome and Measures: The primary outcome was time to death (all causes), lung transplantation, or first non-elective hospital admission. Secondary outcomes were the individual components of the primary endpoint, and respiratory-related events. Patient reported outcomes (King's Brief Interstitial Lung Disease questionnaire, EuroQol 5-dimension 5-level (EQ-5D-5L), the Leicester Cough Questionnaire and Cough Score) and lung function (FVC and gas transfer) were

undertaken at baseline and at 12 months.

Results: Among 342 individuals who were randomized (mean age 71.3 years; 46 [13%] female), 283 (83%) completed the trial. The median (interquartile range) duration of follow-up was 1.02 (0.35 to 1.73) years. Events/person year of follow up among participants randomized to the co-trimoxazole and placebo groups were 0.45 (84/186) and 0.38 (80/209) respectively, with a hazard ratio of 1.2 (0.9 to 1.6) (p=0.319). There was no statistically significant difference in other event outcomes, lung function, or patient reported outcomes. Patients in the co-trimoxazole group experienced 696 adverse events (nausea n=89, diarrhea n=52, vomiting n=28, rash n=31) whereas patients in the placebo group experienced 640 adverse events (nausea n= 67, diarrhea n=84, vomiting n=20, rash n=20).

Conclusion and relevance: Among patients with moderate or severe IPF, treatment with oral co-trimoxazole did not reduce a composite outcome of time to death, transplantation, or non-elective hospitalization compared with placebo.

Trial Registration: ISRCTN 17464641

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INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease with a median survival of 5.7 years[1] (European IPF registry, 2018), increasing incidence[2] and limited treatment options. Respiratory tract infection is common in patients with IPF[3] and bronchial washings contain pathogenic bacteria, as identified by quantitative culture[4,5] or non-culture-dependent techniques[6]. Bronchoalveolar lavage studies, from two separate groups, have shown that both a high bacterial load[7,8] and a lung microbiota enriched with *Streptococcus* spp. and *Staphylococcus* spp.[9] predict a poor outcome in IPF. Moreover, innate immune responses may be abnormal in IPF, potentially increasing susceptibility to infection[10,11].

Co-trimoxazole, a broad-spectrum antibiotic, was reported to improve clinical outcomes in IPF in two small randomized controlled trials[12,13] and to be cost-effective[14]. Exploratory analysis suggested an improvement in health-related quality-of-life and oxygen requirements and, in those adhering to the study protocol, a reduction in mortality over a 12-month period; however evidence of a survival benefit was not conclusive[13].

The aim of this study was to determine the clinical efficacy of co-trimoxazole in patients with moderate-severe IPF (defined as FVC≤75% predicted), in terms of the time to death (all-cause), lung transplantation, or first non-elective hospital admission. Secondary aims were to assess the effects on respiratory-related outcomes, patient-reported outcomes (in terms of health-related quality of life, cough and breathlessness) and lung function.

METHODS

This was a phase III double blind, placebo-controlled, parallel, randomized multi-center study of oral co-trimoxazole added to standard care. The protocol has been published[15] and the final protocol, amendments and statistical analysis plan are available in supplement 1.

Patients were treated from randomization until withdrawal, death, first non-elective admission (for any reason), lung transplantation or the end of the study follow-up, with a minimum duration of 12 months and maximum of 42 months. The study was conducted in 43 specialist interstitial lung disease (ILD) centers, or in sites affiliated with them, from all regions in the UK.

The study was conducted according to Good Clinical Practice, and the study protocol received ethical approval (14/LO/1800). All participants provided written informed consent. Participants were randomized between April 2015 and April 2018 and follow-up was completed in April 2019. In May 2016, modifications removed an exclusion of participants diagnosed more than 2 years before randomization and increased the permitted FVC% predicted value from 70% to 75% to improve recruitment. An optional bronchoscopy sub-study was discontinued in June 2017.

Patients were recruited into the study if they had IPF diagnosed according to contemporaneous international guidelines[16] and had a modified Medical Research Council (MRC) dyspnea score >1. They could receive licensed medication for IPF at a stable regimen. Patients were excluded if they had FVC >75% predicted, a significant co-existing respiratory or other comorbidity, or a respiratory tract infection

during the preceding 4 weeks or were receiving immunosuppression.

Patients were randomized on a 1:1 basis to receive either oral co-trimoxazole 960 mg twice daily (as 2 tablets of 480 mg each) or 2 matched placebo tablets. The treatment allocated was generated via a computer code using minimisation for site, current use of antifibrotic therapy and involvement in bronchoscopy sub-study, under the supervision of the study statistician. All patients received 5mg folic acid orally once daily. Treatments were given in addition to standard care as defined by National Institute for Health and Clinical Excellence (NICE) guidelines (www.nice.org.uk/CG163).

A reduction of the dose to 2 tablets (i.e. 960 mg co-trimoxazole or 2 placebo tablets daily) plus 5 mg folic acid three times weekly was permitted if a participant developed gastrointestinal side effects or rash, grade 1 hyperkalemia, or any other adverse event requiring dose reduction in the view of the Principal Investigator.

Outcomes

The primary outcome was the time to death (all causes), lung transplantation, or first non-elective hospital admission for any reason. These data were obtained at each site, until the date of withdrawal or the end of the study, by screening hospital records and capturing details of out-of-hospital death from Primary Care records, if required. The primary outcome was censored at the date of withdrawal if patients withdrew consent to be followed up. Secondary outcomes included the individual components of the primary outcome. Respiratory-related events, determined by an independent committee, were analyzed separately. The King's Brief Interstitial Lung

Disease (K-BILD) questionnaire[17], modified MRC dyspnea scale[18], Euroqol 5-dimension 5-level (EQ-5D-5L) questionnaire[19], Leicester Cough Questionnaire (LCQ)[20] and cough score (captured on visual analogue scale, ranging from 0mm “I have not been bothered by my cough at all” to 100mm “My cough has been the worst it can be”) were undertaken at baseline, at 3 and 6 months, then 6-monthly throughout the study, including a final assessment at the end of the study. Spirometry[21] and gas transfer[22] were captured at baseline, 6 and 12 months. Sputum was obtained, where clinically relevant, and sent for local microbiological culture and antibiotic susceptibility testing. Blood was taken for full blood count, urea and electrolytes and liver function at baseline, 6 weeks, 3, 6, 9 and 12 months then 6-monthly for the duration of the study. Adverse events were captured at each visit and assessed for severity. Blood biomarker analysis is not reported here.

Statistical analysis

The trial was designed to have 80% power (two-sided test, significance level of 5%) to show a change in hospitalization-free survival from a median value of 28.8 months in the placebo group to 51.1 months in the co-trimoxazole group (hazard ratio (HR) of 0.56) over this study period, assuming 330 patients were randomized and 20% withdrew from the study. This was based on a sensitivity analysis of patients from the previous study[13] with reduced lung function (FVC<70% predicted) using an intention-to-treat analysis.

The primary outcome, and secondary event measurements, were analysed using a Cox proportional hazards model adjusted for the baseline variables, licensed IPF medication use and site as a random effect. The proportionality assumption was

assessed using the global test with Schoenfeld residual. This had a test statistic of 1.58 and a p-value of 0.45, thus providing no evidence that the assumption was violated. The results are presented as the Kaplan-Meier estimate with median time to outcome. The MRC Breathlessness Score was analyzed using a Mann-Whitney test; other questionnaires and lung function measurements were analyzed using linear mixed models to compare the mean values between the treatment and placebo groups adjusted for the baseline variables, licensed IPF medication use and site as a random effect. A repeated measures model was fitted for each outcome with a fixed term for licensed IPF medication, randomization arm and time, random effects were included for site and the person identification number.

All analyses were two sided at the 5% level of significance and were undertaken as pre-specified, including all participants analyzed in the group to which they were randomized. Additionally, pre-specified per-protocol ($\geq$80% adherence to study medication) and modified-per-protocol (those who adhered to the high-dose regimen) analyses were undertaken.

The missing endpoints at 12 months were imputed using the iterative chained equations approach[23]. The outcomes at 12 months and baseline were included in the equations, along with randomization arm, body mass index and gender. As the rate of missing data was high, a total of 45 imputations were created and the results model estimates combined using Rubin's equations. The analysis was conducted using Stata/MP 16. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory.

The adverse event analysis was based on all patients who received at least one dose of drug or placebo. Data were analysed for event rates and percentage of patients with at least one adverse event and coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Safety blood measures were compared at 12 months.

RESULTS

A total of 1305 participants were screened at 43 sites; 349 meet the inclusion criteria and 342 were randomized from 39 sites (Figure 1). Of these, 58 (17%) withdrew from the intervention, 32 (19%) from the co-trimoxazole group and 26 (15%) from the placebo group. One participant, randomized to the intervention (co-trimoxazole) group, was randomized in error and their data were not analysed. A total follow-up of 395-person years was assessed with 164 events. The mean (standard deviation (SD)) patient age was 71.3 (7.5) years, with a mean FVC of 2.25 (0.56) liters (L) or 55.7 (9.4) % predicted. Baseline characteristics and other factors were balanced between the two treatment groups, other than for gender and the presence of diabetes (Table 1).

The mean (SD) compliance in the co-trimoxazole group was 81.4 (22.8) %, compared with 85.5 (21.7) % in the control (placebo) group. The percentage of participants who met the 80% treatment threshold was 120 (71.9%) in the co-trimoxazole group compared with 125 (72.1%) in the placebo group. Dose reduction occurred in 47 (18%) individuals: 16 (9%) in the placebo group and 32 (19%) in the co-trimoxazole group (eTable 1 in supplement 2).

Primary Outcome

A total of 164 primary outcome events occurred (Figure 2). The incidence of events was 0.45 (84/186) per person-year in the co-trimoxazole group and 0.38 (80/209) in the placebo group. The HR was 1.2 (0.9,1.6) for both the unadjusted analysis and adjusted analysis. The median (inter quartile range (IQR)) survival was 1.45 (1.28, 1.78) years in the co-trimoxazole group and 1.94 (1.48,2.84) in the placebo group.

The site could not be included in this model due to model instability; a robust variance method gave HR 1.2 (0.8,1.6), p=0.37 and with stratification gave HR 1.2 (0.9,1.7), p=0.24. There were no statistically significant differences between the two groups for the per-protocol or modified per protocol analyses (eTable 2 in supplement 2) for event outcomes.

Secondary Exploratory Outcomes

The individual components of the primary outcome are shown in Figure 2 and eTable 1 in supplement 2. There was no statistically significant difference in all-cause mortality (HR = 1.5 (0.8, 2.8), p=0.17), respiratory related deaths (HR = 1.4 [0.7, 2.6], p=0.34), all cause (HR = 1.1 [0.7,1.5], p=0.75) or respiratory related (HR = 1.0 [0.7,1.6] p=0.83) hospitalizations (all cause: HR = 1.1 [0.7,1.5], p=0.75; respiratory related: HR = 1.0 [0.7,1.6] p=0.83) between the two groups. There were no statistically significant differences between the two groups for the per-protocol or modified per protocol analyses (eTable 2 in supplement 2) for event outcomes.

There was no statistically significant difference for the LCQ, cough score, or other patient-related outcomes (Table 2). In the unadjusted per-protocol analysis there were no statistically significant differences between co-trimoxazole or placebo groups for any of the patient reported outcomes other than for the chest domain of the K-BILD, which favoured co-trimoxazole (eTable 3 in supplement 2). In the adjusted per-protocol analysis, co-trimoxazole therapy resulted in a statistically significant ($p<0.05$) benefit in terms of the total score and physiological and social domains of the LCQ and the chest domain of the KBILD but not for other domains of the LCQ, total KBILD or other domains of KBILD, cough score, MRC breathlessness

score or EQ-5D-5L (eTable 3 in supplement 2). There was no statistically significant difference between the groups for any of the lung function measures (Table 2 and eTable 3 in supplement 2). The modified per protocol analysis is shown in eTable 4 in supplement 2. The model assumptions were assessed visually by plotting the residuals, which were all approximately normally distributed.

Further analysis

When reviewing the data at all time-points, there was a statistically significant (p=0.02) difference in cough score (15.0 [1.2, 28.8] mm) at 18 months in favor of the co-trimoxazole group, and, overall, the differential between the groups was statistically significant (p=0.04), with a mean difference of 5.7 (0.1, 11.2) (eTable 5 in supplement 2). There were no statistically significant differences for the LCQ and KBILD total scores or sub-domains, MRC score, or lung function measurements between the groups and no overall treatment effect.

Adverse events

There were 696 adverse events (18 SAEs) in the co-trimoxazole group and 640 (16 SAEs) in the placebo group (Table 3).There were more reports of nausea in the co-trimoxazole group (89/157) compared to placebo (67/163), whereas diarrhea was reported more frequently in the placebo group (52/157 vs 84/163). There were more episodes of hyperkalemia (24/157 vs 14/163), vomiting (28/157 vs 20/163) and rash (31/157 vs 20/163) with co-trimoxazole (Table 3). There was no difference in the 12 months safety blood analysis between the two groups (eTable 6 in supplement 2) except for creatinine which was statistically significantly higher in the co-trimoxazole group.

Seventeen sputum samples and one nasal swab were obtained in total for all patient visits. Only three of these grew possible relevant microbiological agents on culture: *Staphylococcus aureus* (n=1), *Haemophilus influenzae* (n=1) and “yeasts” (n=1).

DISCUSSION

This double-blind, randomized, placebo-controlled clinical trial found that there was no improvement in all-cause mortality, hospitalisation or lung transplantation whether considered together or as discrete events with co-trimoxazole in people with moderate-severe IPF. The findings were the same when the outcomes were restricted to respiratory-related events and when analysis was confined to those who adhered to high dose treatment throughout the trial.

In contrast to the previous smaller study[13], there was no reduction in mortality with co-trimoxazole. In this previous study, nearly 60% of people were taking prednisolone (mostly at high dose) and 30% were taking azathioprine whereas in the current trial, those receiving immunosuppression other than low-dose corticosteroids (6% of individuals) were excluded. It is therefore plausible that, in the previous study[13], co-trimoxazole prevented infection-related adverse outcomes that were contingent on immunosuppression, which is known to result in poor outcomes in IPF[24]. Furthermore, antifibrotic therapy (pirfenidone and nintedanib) was not available at the time of the previous study[13], whereas 75% of people the current study were receiving this treatment. Pirfenidone, for example, has been estimated to improve IPF life expectancy by 2.47 years[25]. Overall, the changes between the two studies resulted in a doubling of the hospital-free survival (mean 23.3 months versus 12.8 months). In addition, inclusion in the current study was restricted to people with moderate to severe IPF, as defined by a FVC <75% predicted, whereas no such restriction pertained in the previous study. However, it is unlikely that co-trimoxazole would have been more effective in a less severe population, as there was no

subgroup effect of baseline disease severity in the previous study[13], and neither bacterial burden[26] nor response to antifibrotic therapy[27,28] is related to FVC in IPF.

The benefit of co-trimoxazole in terms of the cough score, LCQ and the chest symptom domain of the KBILD questionnaire (which captures chest tightness, air hunger and wheeze) only met clinical relevant thresholds at 18 months but support the previously-identified clinical benefit of co-trimoxazole[13] in respect of the 'symptom' domain of the SGRQ[29] (which captures cough, sputum, breathlessness and wheeze). However, given the number of endpoints, any potential improvement in cough should be considered as hypothesis-generating only.

The results of this study do not disprove the hypothesis that the "lung microbiome" influences disease progression and outcomes in IPF[7,9,26]. Indeed, a potential antibacterial benefit of co-trimoxazole may have been lost owing to widespread bacterial resistance, despite in-therapy selection of resistance being rare for co-trimoxazole[30] and acquired resistance, whilst not uncommon, unlikely to have been so universal as to overwhelm a positive effect. Furthermore, the possibility of an unrecognised IPF-associated co-trimoxazole-resistant pathogen cannot be entirely dismissed, though there is no positive evidence to support such a hypothesis; an ongoing randomised open-label trial of co-trimoxazole or doxycycline vs standard care may provide further insight[31]. However, a study of explanted lungs yielded very few bacterial 16S rRNA gene reads in the IPF interstitium compared with the airways of IPF patients and healthy controls. It is, therefore, possible that airway and lung tissue compartments are separate in IPF, with different microbiota[32].

This was an adequately-powered, multi-centered academic clinical trial using a clinically-relevant outcome with high follow-up rates and long timescales. It over-recruited and evaluated 342 individuals from 39 geographically diverse sites, of varying sizes, for up to 3 years. The primary endpoint included (i) unplanned hospital admission, which is financially and socially costly, with a high frequency of death, and (ii) all-cause mortality, which is the most clinical meaningful primary endpoint[33]. The study was aligned to clinical care, minimizing the research burden for patients. The event rate (164 events) was higher than anticipated (99 events), so the study had adequate power to detect a meaningful difference in the primary endpoint. The findings are, therefore, robust, and a larger study would be unlikely to generate a different outcome.

Limitations

This study has several limitations. First, there was a lack of evaluation of the lung microbiome, or quantitation of the influence that co-trimoxazole had on its composition and ecology, including antimicrobial resistance. However, given the lack of efficacy, it is questionable whether any such analysis would have been clinically meaningful. Second, it is not possible to tell whether co-trimoxazole reduced infection-related events, as the numbers of respiratory tract infections *per se* were not captured; rather “respiratory related” events were assessed, encompassing all events related to the respiratory system. Assessing whether respiratory infection is present or not during acute exacerbations or other clinical settings is challenging[34]. Third, a protocol exclusion was allergy to co-trimoxazole and although few people were reported to have this allergy (Figure 1) this, and the FVC criteria, may have limited the generalizability of the study. Fourth, the entry criteria were modified, by

removing the exclusion of subjects diagnosed more than 2 years before randomization as well as increasing the permitted FVC% predicted value from 70% to 75%. Fifth, our agreed analysis plan did not include adjustment for gastroesophageal reflux disease or proton pump inhibitor usage, however the occurrences of these were similar in both groups (Table 1), and an exploratory post hoc analysis, adjusting for them, did not change the conclusion of the study.

Conclusions

Among patients with moderate or severe IPF, treatment with oral co-trimoxazole did not reduce a composite outcome of time to death, lung transplantation, or non-elective hospitalization compared with placebo. The findings do not support the prophylactic use of co-trimoxazole in people with IPF.

Conflicts of Interest and Financial Disclosures

The following authors have nothing to disclose: Allan Clark, Tony Cahn, Edwin Chilvers, William Fraser, Matthew Hammond, Helen Parfrey, Ann-Marie Swart, Susan Stirling, David Thickett, Moira Whyte.

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Access to data

Andrew Wilson, Allan Clark and Sue Stirling had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Role of Funder/Sponsor

The funding and sponsoring organisations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript and decision to submit the manuscript for publication. In addition they had no right to veto publication or to control the decision regarding to which journal the paper was submitted

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Data sharing statement: See supplement 3

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Contribution of Authors

Andrew M Wilson: (Professor of Respiratory Medicine) was the Chief Investigator and oversaw the delivery of the study. He contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report

Allan B Clark (Senior Trial Statistician) oversaw the statistical analysis and contributed to the design of the trial. He was responsible for statistical analysis, and contributed to the interpretation of results and writing/editing the report

Dr Tony Cahn (Consultant physician) provided expertise in clinical trial design and delivery. He contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

Edwin R Chilvers (Professor of Medicine) provided expertise in ILD and lung inflammation. He contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

William Fraser (Professor of Medicine) oversaw the biochemical analyses. He contributed to the conception and design of the trial, the interpretation of results and writing/editing the report, with particular emphasis on the biochemical analysis.

Matthew Hammond (CTU Deputy Director) was responsible for the day-to-day management of the trial, and contributed to the interpretation of results and writing/editing the report.

David M Livermore (Professor of Medical Microbiology) provided expertise in the microbiological aspects of the study. He contributed to the conception and design of

the trial, the interpretation of results and writing/editing the report, with particular emphasis on the microbiological aspects.

Toby M Maher (Professor of Respiratory Medicine) provided expertise in ILD and clinical trial methodology. He contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

Helen Parfrey (Consultant Physician) provided expertise in ILD. She contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

Ann Marie Swart (CTU Director) was responsible for the day-to-day management of the trial. She contributed to the interpretation of results and writing/editing the report.

Susan Stirling (Trial Statistician) undertook the statistical analysis. She contributed to the interpretation of results and writing/editing the report

David R Thickett (Professor of Respiratory Medicine) provided expertise in ILD. He contributed to the conception and design of the trial, conduct of the trial, recruitment and follow-up of participants, the interpretation of results and writing/editing the report.

Moira Whyte (Professor of Respiratory Medicine) provided expertise in ILD. She contributed to the conception and design of the trial, the interpretation of results and writing/editing the report.

The EME-TIPAC team contributed to the data collection of the study and the editing of the manuscript.

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REFERENCES

1. Guenther A, Krauss E, Tello S, et al. The European IPF registry (eurIPFreg): baseline characteristics and survival of patients with idiopathic pulmonary fibrosis. Respir Res. 2018;19(1):141.
2. Navaratnam V, Fleming KM, West J, et al. The rising incidence of idiopathic pulmonary fibrosis in the UK. Thorax. 2011;66(6):462-467.
3. Atkins CPL, Y.;Wilson,A.M.;. Outcomes in idiopathic pulmonary fibrosis: a meta-analysis from placebo controlled trials. Thorax. 2013;68 (Suppl 3):A11.
4. Richter AG, Stockley RA, Harper L, Thickett DR. Pulmonary infection in Wegener granulomatosis and idiopathic pulmonary fibrosis. Thorax. 2009;64(8):692-697.
5. Vidal S, de la Horra C, Martin J, et al. Pneumocystis jirovecii colonisation in patients with interstitial lung disease. Clin Microbiol Infect. 2006;12(3):231-235.
6. Garzoni C, Brugger SD, Qi W, et al. Microbial communities in the respiratory tract of patients with interstitial lung disease. Thorax. 2013;68(12):1150-1156.
7. Molyneaux PLC, M.J.;Mallia,P.;Johnston,S.L.;Moffatt,M.F.;Cookson,W.O.C.;Maher,T.M. The role of the respiratory microbiome in idiopathic pulmonary fibrosis. Thorax. 2013;68 (Suppl 3):A22.
8. Hilty M, Burke C, Pedro H, et al. Disordered microbial communities in asthmatic airways. PLoS One. 2010;5(1):e8578.

9. Han MKE-D, Y.; Zhou, Y.; Tayob, N.; Murray,S.; Flaherty, K.R.; Huffnagle,G.B.; Martinez, F.J.;. The IPF Microbiome: Analysis from the COMET study. Am J Respir Crit Care Med. 2013;187:A3769.
10. Savici D, Campbell PA, King TE, Jr. Bronchoalveolar macrophages from patients with idiopathic pulmonary fibrosis are unable to kill facultative intracellular bacteria. Am Rev Respir Dis. 1989;139(1):22-27.
11. Samara KD, Antoniou KM, Karagiannis K, et al. Expression profiles of Toll-like receptors in non-small cell lung cancer and idiopathic pulmonary fibrosis. Int J Oncol. 2012;40(5):1397-1404.
12. Varney VA, Parnell HM, Salisbury DT, Ratnatheepan S, Tayar RB. A double blind randomised placebo controlled pilot study of oral co-trimoxazole in advanced fibrotic lung disease. Pulmonary Pharmacology & Therapeutics. 2008;21(1):178-187.
13. Shulgina L, Cahn AP, Chilvers ER, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: a randomised controlled trial. Thorax. 2013;68(2):155-162.
14. Wilson EC, Shulgina L, Cahn AP, et al. Treating idiopathic pulmonary fibrosis with the addition of co-trimoxazole: an economic evaluation alongside a randomised controlled trial. Pharmacoeconomics. 2014;32(1):87-99.
15. Hammond M, Clark AB, Cahn AP, et al. The Efficacy and Mechanism Evaluation of Treating Idiopathic Pulmonary fibrosis with the Addition of Co-trimoxazole (EME-TIPAC): study protocol for a randomised controlled trial. Trials. 2018;19(1):89.
16. Raghu G, Collard HR, Egan JJ, 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;183(6):788-824.

17. Patel AS, Siegert RJ, Brignall K, et al. The development and validation of the King's Brief Interstitial Lung Disease (K-BILD) health status questionnaire. Thorax. 2012;67(9):804-810.

18. Manali ED, Lyberopoulos P, Triantafillidou C, et al. MRC chronic Dyspnea Scale: Relationships with cardiopulmonary exercise testing and 6-minute walk test in idiopathic pulmonary fibrosis patients: a prospective study. BMC Pulm Med. 2010;10:32.

19. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-1736.

20. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax. 2003;58(4):339-343.

21. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338.

22. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26(4):720-735.

23. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30(4):377-399.

24. Raghu G, Anstrom KJ, King TE, Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366(21):1968-1977.
25. Fisher M, Nathan SD, Hill C, et al. Predicting Life Expectancy for Pirfenidone in Idiopathic Pulmonary Fibrosis. J Manag Care Spec Pharm. 2017;23(3-b Suppl):S17-S24.
26. Invernizzi R, Barnett J, Rawal B, et al. Bacterial burden in the lower airways predicts disease progression in idiopathic pulmonary fibrosis and is independent of radiological disease extent. Eur Respir J. 2020;55(4).
27. Nathan SD, Costabel U, Albera C, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis and more advanced lung function impairment. Respir Med. 2019;153:44-51.
28. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377(9779):1760-1769.
29. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321-1327.
30. Lacey RW, Lord VL, Gunasekera HK, Leiberman PJ, Luxton DE. Comparison of trimethoprim alone with trimethoprim sulphamethoxazole in the treatment of respiratory and urinary infections with particular reference to selection of trimethoprim resistance. Lancet. 1980;1(8181):1270-1273.
31. Anstrom KJ, Noth I, Flaherty KR, et al. Design and rationale of a multi-center, pragmatic, open-label randomized trial of antimicrobial therapy - the study of clinical efficacy of antimicrobial therapy strategy using pragmatic design in

Idiopathic Pulmonary Fibrosis (CleanUP-IPF) clinical trial. Respir Res. 2020;21(1):68.

32. Jenkins G. A big beautiful wall against infection. Thorax. 2018;73(5):485.

33. 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;67(11):938-940.

34. Collard HR, Ryerson CJ, Corte TJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med. 2016;194(3):265-275.

Figure Legends

Figure 1 Enrolment, randomization and follow-up of participants

Consort diagram showing the flow of participants throughout the study. FVC = Forced vital capacity [a] A reduction of the dose to 2 tablets (i.e. 960 mg co-trimoxazole or 2 placebo tablets daily) plus 5 mg folic acid three times weekly was permitted if a participant developed gastrointestinal side effects or rash, grade 1 hyperkalemia, or any other adverse event requiring dose reduction in the view of the Principal Investigator.

Figure 2 Kaplan-Meier estimate for the primary endpoint

Kaplan-Meier estimates for time to event for primary endpoint (death (all causes), lung transplantation or first non-elective hospital admission) analysed according to the group to which participants were randomised. There was no significant difference between the co-trimoxazole and placebo groups. The graph is truncated at 30 months.

Table 1 Baseline characteristics of the randomized participants

	Co-trimoxazole	Placebo
Baseline characteristics		
Number in group [a]	169	172
Male participants: n (%)	138 (81.7)	157 (91.3)
Female participants: n (%)	31 (18.3)	15 (8.7)
Age in years: mean (SD)	71.9 (7.8)	70.7 (7.1)
Smoking status: never smoked: n (%)	59 (34.9)	56 (32.6)
ex-smoker: n (%)	109 (64.5)	114 (66.3)
current smoker: n (%)	1 (0.6)	2 (1.2)
Comorbidities[b]		
Gastroesophageal reflux disease: n (%)	69 (40.8)	62 (36.1)
Ischaemic heart or angina: n (%)	38 (22.5)	44 (25.6)
Diabetes mellitus: n (%)	40 (23.7)	25 (14.5)
Anxiety or Depression: n (%)	17 (10)	23 (13.4)
Pulmonary hypertension: n (%)	13 (7.7)	10 (5.8)
Osteoporosis: n (%)	11 (6.5)	11 (6.4)
COPD: n (%)	6 (3.6)	6 (3.5)
Bronchiectasis: n (%)	2 (1.2)	7 (4.1)[1]
Medications[c]		
PPI	87 (51.5%)	78 (45.3%)
Pirfenidone	71 (42.0%)	66 (38.4%)

Nintedanib	56 (33.1%)	61 (35.5%)
Prednisolone	12 (7.1%)	10 (5.8%)
N-Acetyl cysteine	8 (4.7%)	7 (4.1%)
Other antioxidant	3 (1.8%)	5 (2.9%)
Lung Function Tests[d]		
Absolute value		
FVC, mean (SD)	2.2 (0.6)	2.3 (0.5)
FEV1, mean (SD) [N]	1.9 (0.5)	1.9 (0.4) [171]
FEV1/FVC ratio, mean (SD) [N]	0.8 (0.1)	0.8 (0.1) [171]
DLCO, mean (SD) [N]	3.6 (1.8) [123]	3.7 (1.5) [127]
Percent predicted		
FVC, mean (SD)	56.2 (8.9)	55.2 (10.0)
FEV1, mean (SD) [N]	61.5 (9.3)	60.0 (10.6) [171]
DLCO, mean (SD) [N]	43.3 (20.2) [123]	44.5 (18.0) [127]
Outcome measures		
MRC score, median (IQR) [N]	3.0 (2.0, 3.0) [167]	2.00 (2.00, 3.00) [171]
EQ-5D-5L utility: mean (SD) [N]	0.67 (0.20) [168]	0.69 (0.22) [171]
Cough score, mean (SD) [N]	39.5 (27.5) [167]	40.89 (26.6) [168]
Leicester Cough Questionnaire[e]		
total, mean (SD) [N]	16.1 (3.6) [161]	15.8 (3.7) [164]
physical, mean (SD) [N]	5.2 (1.1) [161]	5.1 (1.0) [165]]
psychological, mean (SD) [N]	5.4 (1.4) [167]	5.3 (1.5) [166]
social, mean (SD) [N]	5.4 (1.4) [167]	5.4 (1.4) [168]
King's Brief Interstitial Lung Disease questionnaire [f]		

total, mean (SD) [N]	53.7 (9.7) [168]	53.6 (10.6) [171]
breathlessness, mean (SD) [N]	37.7 (15.3) [168]	38.9 (14.3) [171]
chest, mean (SD) [N]	62.9 (20.8) [168]	62.6 (20.7) [171]
psychological, mean (SD) [N]	55.2 (14.9) [168]	54.9 (17.1) [171]

SD = standard deviation, COPD = chronic obstructive pulmonary disease, PPI = proton pump inhibitor, FVC = forced vital capacity, FEV1 = forced expiry volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide, MRC = medical research council, IQR = inter-quartile range, EQ-5D-%L = Euroqol 5-dimension 5-level questionnaire, LCQ = Leicester Cough Questionnaire, N = number. [a] These data exclude the individual excluded post randomisation. [b] Comorbidities were as detailed in the medical records. [c] Medications represent maintenance treatments [d] The lung function test values were obtained at screening. [e] The Leicester Cough Questionnaire score ranges from 3 (lowest quality of life) to 21 (highest quality of life) and the domain scores range from 1 (lowest quality of life) to 7 (highest quality of life), [f] The King's Brief Interstitial Lung Disease questionnaire total and domain scores ranges between 0 (worse health status) and 100 (best heath status).

Table 2 Between-group differences for secondary outcomes at 12 months analysed for all patients according to the group that they were randomised.

Outcome	Co-trimoxazole		Placebo		Adjusted for site and baseline anti-fibrotic therapy		Adjusted for site, baseline anti-fibrotic therapy and baseline value	
	N	Mean (SD)	N	Mean (SD)	Mean difference (95% CI)	p-value	Mean difference (95% CI)	p-value
Kings Brief Interstitial Lung Disease questionnaire[a]								
Total	71	50.3 (12.3)	85	50.7 (11.20)	0.4 (-3.3, 4.1)	0.83	0.1 (-2.8, 3.0)	
Breathless-ness	72	34.4 (17.4)	86	35.0 (14.55)	0.9 (-4.1, 5.9)	0.73	-0.5 (-4.4, 3.3)	0.79
chest	72	59.9 (20.3)	86	56.8 (22.82)	-3.4 (-10.2, 3.4)	0.33	-2.0 (-7.8, 3.8)	0.5
psychological	71	49.7 (17.9)	85	51.9 (16.9)	2.0 (-3.5, 7.5)	0.48	1.5 (-3.0, 5.9)	0.53
Leicester Cough Questionnaire, mean (SD) [b]								
total	69	15.4 (4.09)	71	14.6 (4.0)	-0.8 (-2.1, 0.6)	0.27	-0.6 (-1.6, 0.4)	0.22
physical	69	4.9 (1.2)	72	4.7 (1.2)	-0.2 (-0.6, 0.2)	0.36	-0.1 (-0.4, 0.2)	0.43
psychological	69	5.2 (1.4)	75	4.9 (1.5)	-0.3	0.25	-0.3	0.17

					(-0.8, 0.2)		(-0.6, 0.1)	
social	69	5.3 (1.5)	75	5.0 (1.5)	-0.3 (-0.8, 0.2)	0.28	-0.2 (-0.6, 0.1)	0.2
MRC score [v], Median (IQR)	72	3.0 (2.0, 4.0)	86	3.0 (2.0, 4.0)		0.94		0.29
Cough score:[d] (mm)	72	44.7 (27.0)	84	49.7 (26.7)	5.1 (-3.4, 13.6)	0.24	2.2 (-5.4,9.9)	0.57
EQ-5D-5L utility[e]	103	0.41 (0.36)	118	0.45 (0.35)	0.04 (-0.05,0.13)	0.37	0.03 (-0.06,0.11)	0.55
Lung function tests								
Absolute								
FVC (L)	63	2.26 (0.53)	77	2.23 (0.51)	-0.02 (-0.19, 0.15	0.81	-0.01 (-0.09, 0.07)	0.8
FEV1 (L)	63	1.86 (0.43)	77	1.86 (0.42)	0 (-0.14, 0.14)	1	-0.02 (-0.08, 0.05)	0.62
DLCO (mmol/min/Ka)	50	3.49 (1.75)	60	3.71(1.50)	0.19 (-0.39, 0.77	0.51	0.3 (-0.26, 0.85)	0.3
Percent predicted								
FVC (%)	63	54.0 (8.9)	77	53.6 (9.1)	-0.5 (-3.56,	0.72	-0.6 (-2.6, 1.5)	0.59

					2.47)			
FEV1 (%)	63	57.8 (9.7)	77	58.2 (10.4)	0.2 (-3.2, 3.6	0.93	-0.7 (-2.8, 1.5)	0.55
DLCO (%)	50	40.2 (17.7)	60	43.2 (16.3)	2.5 (-3.7, 8.7)	0.43	3.9 (-2.4, 10.3)	0.22

[a] The Leicester Cough Questionnaire score ranges from 3 (lowest quality of life) to 21 (highest quality of life) and the domain scores range from 1 (lowest quality of life) to 7 (highest quality of life), [b] The King's Brief Interstitial Lung Disease questionnaire total and domain scores ranges between 0 (worse health status) and 100 (best heath status),[c] The MRC dyspnea score is a 5 point scare ranging from 1 (Not troubled by breathlessness except on strenuous exercise) to 5 (Too breathless to leave the house or breathlessness on dressing or undressing), [d] Cough score was a visual analogue score between 0 mm (I have not been bothered by my cough at all) to 100 mm (My cough has been the worst it can be). [e]EuroQol 5-Dimension 5-Level utility ranges between 0 (death) and 1 (perfect health). There data was incomplete for some patients as they did not complete the questionnaires or attend for lung function assessments

n = number, SD = standard deviation, CI = confidence interval, MRC = medical research council, IQR = inter-quartile range, FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide. L: Liters, mmol/min/KPa: millimoles per minute per kilopascal, %: percent

Table 3 Adverse events

	Co-trimoxazole: number of events	Placebo: number of events	Co-trimoxazole number of people with an event	Placebo: number of people with an event
			N = 169	N = 172
Blood and lymphatic system disorders	3	3	3 (2%)	3 (2%)
Cardiac disorders	6	4	6 (4%)	3 (2%)
Ear and labyrinth disorders	3	0	2 (1%)	0
Eye disorders	5	6	5 (3%)	5 (3%)
Gastrointestinal disorders	216	224	92 (54%)	81 (47%)
- Nausea	89	67	53 (31%)	42 (24%)
- Diarrhoea	52	84	36 (21%)	53 (31%)
- Vomiting	28	20	20 (12%)	16 (9%)
General disorders and administration site conditions	36	20	25 (15%)	17 (10%)
- Chest pain	8	6	7 (4%)	5 (3%)
- Fatigue	15	11	15 (9%)	10 (6%)
- Edema peripheral	5	0	4 (2%)	0
Immune system disorders	1	1	1 (1%)	1(1%)
Infections and infestations	110	127	57 (33%)	70 (41%)
Injury, poisoning and procedural	7	10	5 (3%)	10 (6%)0

complications				
Investigations	44	22	34 (20%)	16 (9%)
- Weight decrease	24	16	21 (12%)	14 (8%)
Metabolism and nutrition disorders	57	27	38 (22%)	19 (11%)
- Hyperkalemia	24	14	18 (11%)	11 (6%)
- Decreased appetite	26	9	18 (11%)	6 (3%)
Musculoskeletal and connective tissue disorders	21	20	18 (11%)	14 (8%)
Neoplasm/s benign, malignant and unspecified (incl cysts and polyps)	3	1	2 (1%)	1 (1%)
Nervous system disorders	41	32	29 (17%)	24 (14%)
- Headache	22	14	16 (9%)	11 (6%)
Psychiatric disorders	5	2	4 (2%)	2 (1%)
Renal and urinary disorders	14	7	12 (7%)	7 (4%)
Reproductive system and breast disorders	0	2	0	2 (2%)
Respiratory, thoracic and mediastinal disorders	77	95	46 (27%)	61 (35%)
Skin and subcutaneous tissue disorders	46	30	29 (17%)	23 (13%)
- Rash	31	20	23 (14%)	15 (9%)
Surgical and medical	1	2	1 (1%)	2 (1%)

procedures				
Vascular disorders	0	5	0	3 (2%)
Total AEs	696	640		
Number with at least one AE			146 (86%)	142 (83%)
Number with at least two AEs			119 (70%)	121 (23%)

Adverse events were captured at each study visit