Co-trimoxazole to reduce mortality, transplant, or unplanned hospitalisation in people with moderate to very severe idiopathic pulmonary fibrosis: the EME-TIPAC RCT

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Scientific summary

The EME-TIPAC RCT

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Scientific summary

Background

Idiopathic pulmonary fibrosis is a chronic, progressive, usually fatal, fibrotic lung disease with a 5-year survival rate of 20–40%. It is characterised by breathlessness, cough and bibasilar fine late inspiratory crepitations and is typically diagnosed at a multidisciplinary team meeting following clinical, radiological and histopathological review.

At the time of planning the research, only oxygen and lung transplantation were recommended by guidelines (Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, *et al.* An official American Thoracic Society/European Respiratory Society/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;**183**:788–824). Immunosuppressive therapy, the mainstay treatment for more than a decade, had recently been proven to be harmful and is no longer advised. International guidelines (Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An official American Thoracic Society/European Respiratory Society/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;**198**:e44–68) now conditionally include antifibrotic [pirfenidone (Esbriet, Roche Holding AG) and nintedanib (Ofev®, Boehringer Ingelheim, Brackness, UK)] and antiacid therapies. Pirfenidone and nintedanib are known to reduce the rate of decline in lung function, but they are not curative. Antiacid therapies have not, to our knowledge, been evaluated in randomised controlled trials.

In a previous randomised clinical trial, we evaluated the effect of 960 mg of co-trimoxazole (SEPTRIN®; Essential Generics Ltd, Egham, UK; Chemidex Generics Ltd, Egham, UK) twice daily for 12 months in 181 patients with idiopathic interstitial pneumonia, 166 of whom had idiopathic pulmonary fibrosis. There was no effect on forced vital capacity (the primary end point) or other lung function measurements; however, we found that co-trimoxazole improved quality of life (in terms of the St George's Respiratory Questionnaire score). The percentage of patients requiring an increase in oxygen therapy alongside the results of a health economic cost–utility analysis indicated that co-trimoxazole may be cost-effective. In a per-protocol analysis, the active treatment (co-trimoxazole-treated) group experienced a fivefold reduction in mortality compared with the placebo group.

The potential mechanisms of action of co-trimoxazole are uncertain. Although the role of infection in the pathogenesis of idiopathic pulmonary fibrosis has not been fully evaluated, infection is common in patients with idiopathic pulmonary fibrosis – even in those not receiving immunosuppression. People with idiopathic pulmonary fibrosis are known to have pathogenic bacteria in their airways, as determined by both culture and non-culture techniques. In fact, two independent groups of researchers have shown that bacteria, and the lung microbiota profile enriched with *Streptococcus* and *Staphylococcus* spp., predict poor outcome in idiopathic pulmonary fibrosis. In addition, innate immune responses may be abnormal in idiopathic pulmonary fibrosis, potentially increasing susceptibility to infection. These results suggest that co-trimoxazole's broad spectrum of activity may be beneficial in idiopathic pulmonary fibrosis. Alternatively, co-trimoxazole may be immunomodulatory in idiopathic pulmonary fibrosis in terms of reducing neutrophil activation and neutrophil-derived oxidative stress.

The previous study was designed to evaluate differences in forced vital capacity; thus, all other end points were exploratory, but are nonetheless intriguing because no other study in idiopathic pulmonary fibrosis had shown this magnitude of effect on survival. Furthermore, because prescribing practices have changed, with the cessation of corticosteroid treatment and the commencement of antifibrotic therapies, an adequately powered clinically relevant trial of co-trimoxazole given in addition to standard care was required. This also provided an opportunity to explore the potential mechanism of action of co-trimoxazole.

Objectives

The primary objective of the study was to determine the clinical efficacy of co-trimoxazole in patients with moderate to severe idiopathic pulmonary fibrosis (defined as forced vital capacity of $\leq 75\%$ predicted), compared with placebo, when given in addition to standard care. The primary clinical outcome was unplanned hospitalisation-free survival, defined as the time to death (all causes), first non-elective (all causes) hospital admission or lung transplant.

Secondary objectives were to evaluate the effects of co-trimoxazole in terms of:

- time to respiratory-related death, lung transplant or first respiratory-related hospital admission
- time to respiratory-related and all-cause hospital admission
- time to respiratory-related and all-cause death
- quality-adjusted life-years
- health-related quality of life
- cough-related quality of life
- breathlessness and Cough Symptom Scores
- lung function
- oxygen saturation.

Mechanistic objectives were to compare blood biomarkers between the active treatment group and placebo group in terms of markers of (1) infection/inflammation, (2) monocyte activity, (3) neutrophil activity, (4) alveolar epithelial injury, (5) fibroproliferation, (6) pulmonary hypertension and (7) bronchial epithelium.

Methods

This was a Phase II, double-blind, placebo-controlled, parallel-group, randomised multicentre study of oral co-trimoxazole when added to standard care, with outcomes assessed during a median treatment period of 27 months (range 12–42 months). The aim was to recruit 330 patients with moderate to severe idiopathic pulmonary fibrosis (defined as forced vital capacity of $\leq 75\%$ predicted). Patients continued on treatment from randomisation until withdrawal, death, first non-elective admission of any cause or the end of the study follow-up period, with a minimum duration of 12 months.

Study setting

The study was conducted in UK secondary care centres that either met the specifications required for specialist interstitial lung disease centre status or worked in association with specialist centres.

Patient inclusion criteria

- Male or female, aged ≥ 40 years.
- A diagnosis of idiopathic pulmonary fibrosis based on multidisciplinary consensus, following a review of appropriate clinical history, and radiological or histological features of usual interstitial pneumonia, according to the latest international guidelines.
- Patients could receive oral prednisolone up to a dose of 10 mg per day, antioxidant therapy, pirfenidone, nintedanib or other licensed medications for idiopathic pulmonary fibrosis. Patients were receiving a stable treatment regimen for at least 4 weeks to ensure that baseline values were representative.
- A Medical Research Council Dyspnoea Scale score of > 1, to exclude asymptomatic patients.
- Able to provide informed consent.

Patient exclusion criteria

- A forced vital capacity of > 75% predicted.
- A recognised significant co-existing respiratory disease.
- Patients with obstructive airways disease, defined as a forced expiratory volume in 1 second/forced vital capacity of < 60%.
- Patients with a self-reported respiratory tract infection within 4 weeks of screening.
- Significant medical, surgical or psychiatric disease that, in the opinion of the patient's attending physicians, would affect the patient's safety or influence the study outcome.
- Patients receiving immunosuppressant medication (except low-dose prednisolone).
- Female patients of child-bearing potential.
- Known allergy or intolerance to trimethoprim or sulfonamides or their combination, for safety reasons.
- Untreated folate or B_{12} deficiency.
- Known glucose-6-phosphate dehydrogenase (G6PD) deficiency or a deficiency measured in the screenings of male patients of African, Asian or Mediterranean descent.
- Receipt of an investigational drug or biological agent within the 4 weeks prior to study entry or five times the drug's half-life, whichever is longer.
- Receipt of short-course antibiotic therapy for respiratory and other infections within 4 weeks of screening.
- Patients receiving long-term (defined as > 1 month) prophylactic antibiotics.
- Serum potassium level of > 5.0 mmol/l.

Interventions

Patients were randomised on a 1 : 1 basis to receive one of the following, for between 12 and 42 months (median 27 months):

- oral (non-proprietary) 960 mg of co-trimoxazole twice daily, taken as two tablets of 480 mg twice daily
- oral placebo tablets [manufactured by the pharmacy at Guy's and St Thomas's Hospital (London, UK) to be identical to the 480-mg tablets of co-trimoxazole]; two tablets taken twice daily.

All patients received 5 mg of folic acid orally once daily and treatments were given in addition to standard care as defined by National Institute for Health and Care Excellence (NICE) guidelines [National Institute for Health and Care Excellence. *Idiopathic Pulmonary Fibrosis in Adults: Diagnosis and Management*. 2013. URL: www.nice.org.uk/CG163 (accessed 31 March 2020)].

Patients from both the active treatment and the placebo group had the option of reducing the dose to two tablets (i.e. 960 mg or two placebo tablets) plus 5 mg of folic acid three times weekly if they experienced adverse events or hyperkalaemia or at patient/physician choice.

Measurements

Details of patients admitted to hospital or dying were captured by examining serious adverse event reports, hospital patient databases and tracing patients who missed appointments by contacting their primary care physician as required.

The following questionnaires were undertaken at baseline, after 3 and 6 months, and then 6-monthly throughout the study:

- the King's Brief Interstitial Lung Disease questionnaire
- the Medical Research Council Dyspnoea Scale
- EuroQol-5 Dimensions, five-level version
- the Leicester Cough Questionnaire
- Cough Symptom Score.

Lung function was measured at recruitment and at 6 and 12 months. Spirometry and gas transfer were measured in accordance with American Thoracic Society/European Respiratory Society standards. The percentage predicted values for spirometry were obtained from Crapo *et al.* (Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet American Thoracic Society recommendations. *Am Rev Respir Dis* 1981;**123**:659–64) and percentage predicted values for diffusing capacity for carbon monoxide were obtained from the European Coal and Steel Community.

Peripheral blood was taken at baseline, at 3, 6 and 12 months, and at the end of the study. The peripheral blood was stored throughout the study. Blood was analysed for levels of C-reactive protein; chemokine ligand 18; myeloperoxidase; tumour necrosis factor-related apoptosis-inducing ligand and its decoy receptor, osteoprotegerin; surfactant protein D; matrix metalloproteinase 7; heat shock protein 47, pro-brain natriuretic protein; carbohydrate antigen 19-9; and cancer antigen 125. Sputum was obtained, when possible, and sent for local microbiological culture and sensitivity testing; for all patients, a nasal swab was sent for viral culture if clinically indicated.

The following safety measurements were undertaken at baseline, 6 weeks, 3, 6, 9 and 12 months, and then 6-monthly for the duration of the study plus at the end of the study/hospitalisation:

- full blood count and differential white cell count
- urea and electrolytes
- liver function.

Sample size

The primary outcome measure was unplanned hospitalisation-free survival, which is a composite end point of the time to death (all causes) or first non-elective (all-cause) hospital admission. The study duration was estimated to be 30 months of recruitment and an additional 12 months of follow-up after the last patient was recruited (a total of 42 months after the first patient was enrolled), which approximated a median patient study duration of 27 months.

The trial was designed to have 80% power (two-sided significance level of 5%) to show a change in hospitalisation-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 of 0.56) over the study period, assuming that 264 patients were randomised in a 1 : 1 ratio. This calculation assumed that the time to event follows an exponential distribution and that accrual was linear over the recruitment period. This was based on a sensitivity analysis of patients from the Treating Idiopathic Pulmonary Fibrosis with the Addition of Co-trimoxazole (TIPAC) trial with reduced lung function (forced vital capacity of < 70% predicted) using an intention-to-treat analysis.

Statistical analysis

A statistical analysis plan was produced and agreed prior to analysis. Analysis was conducted on an intention-to-treat basis, with sensitivity analyses in the form of a per-protocol analysis and those remaining on high-dose therapy. The primary outcome was analysed using a Cox proportional hazards model.

Results

The study recruitment period was April 2015–April 2018. In total, 342 patients (active treatment group, $n = 170$; placebo group, $n = 172$) were randomised from 39 sites. One patient was randomised in error to the active treatment group. A total of 185 patients received high-dose co-trimoxazole for the duration of the study. No patients were excluded from the analysis.

Overall, baseline characteristics of patients allocated to co-trimoxazole or placebo were balanced, although there were proportionally more female patients and more people with diabetes in the active

treatment group than in the placebo group. The mean age was 71.3 years (standard deviation 7.47 years), with a mean forced vital capacity of 2.25 l (standard deviation 0.56 l); 137 (40%) patients were taking pirfenidone and 116 (34%) were taking nintedanib. A total of 295 (86.5%) patients were male.

Intention-to-treat analysis

Primary outcome

The average compliance in the active treatment group was 81.4%, compared with 85.5% in the placebo group. A total of 164 events occurred for the primary outcome, 80 in the placebo group and 84 in the active treatment group. The rate of events was 0.45 (84/185.6) per person-year in the active treatment group and 0.38 per person-year (80/209.1) in the placebo group. There was no statistically significant difference between the two groups. The estimated unadjusted hazard ratio was 1.2 (95% confidence interval 0.9 to 1.6) and after adjusting for the factors used in the minimisation algorithm this was virtually unchanged, at 1.2 (95% confidence interval 0.9 to 1.6).

Secondary outcomes

There was no statistically significant difference between the two groups for components of the primary outcome (either all cause or respiratory related), with unadjusted hazard ratios (active vs. placebo) for deaths (all cause: hazard ratio 1.5, 95% confidence interval 0.8 to 2.8, $p = 0.167$; respiratory related: hazard ratio 1.4, 95% confidence interval 0.7 to 2.6; $p = 0.343$) and for hospitalisation (all cause: hazard ratio 1.1, 95% confidence interval 0.7 to 1.5, $p = 0.754$; respiratory related: hazard ratio 1.0, 95% confidence interval 0.7 to 1.6, $p = 0.731$; $p = 0.857$) all including unity. There was no statistically significant difference in the King's Brief Interstitial Lung Disease questionnaire score (hazard ratio 0.4, 95% confidence interval −3.31 to 4.11; $p = 0.834$), Leicester Cough Questionnaire score (hazard ratio −0.75, 95% confidence interval −2.08 to 0.58; $p = 0.267$) or Cough Symptom Score (hazard ratio 5.08, 95% confidence interval −3.45 to 13.6; $p = 0.243$). Likewise, there was no statistically significant difference in the forced vital capacity (hazard ratio −0.02 l, 95% confidence interval −0.19 to −0.15 l; $p = 0.81$) or other lung function measures. There was no statistically significant difference for any of the prespecified biomarkers.

Per-protocol analysis

The percentage of patients who met the 80% threshold was roughly equal in both groups: 120 (71.9%) in the active treatment group and 125 (72.1%) in the placebo group. A total of 123 events occurred for the primary outcome, 64 in the placebo group and 59 in the active treatment group. The rate of events was 0.44 (59/132.6) per person-year in the active treatment group and 0.48 per person-year (64/132) in the placebo group. There was no statistically significant difference between the two groups. The estimated unadjusted hazard ratio was 0.9 (95% confidence interval 0.7 to 1.3) and adjusting for the factors used in the minimisation algorithm left the hazard ratio virtually unchanged, at 0.9 (95% confidence interval 0.7 to 1.3).

Secondary outcomes

There was no statistically significant difference between the two groups for components of the primary outcome (either as all cause or respiratory related), with unadjusted hazard ratios (active vs. placebo) for deaths (all cause: hazard ratio 1.5, 95% confidence interval 0.8 to 2.8, $p = 0.167$; respiratory related: hazard ratio 1.4, 95% confidence interval 0.7 to 2.6, $p = 0.343$) and for hospitalisation (all cause: hazard ratio 1.1, 95% confidence interval 0.7 to 1.5, $p = 0.754$; respiratory related: hazard ratio 1.0, 95% confidence interval 0.7 to 1.6, $p = 0.731$; $p = 0.857$) all including unity. There was no statistically significant difference in the King's Brief Interstitial Lung Disease questionnaire score (hazard ratio −0.66, 95% confidence interval −5.01 to 3.68; $p = 0.765$), Leicester Cough Questionnaire score (hazard ratio −1.53, 95% confidence interval −3.11 to 0.04; $p = 0.057$) or Cough Symptom Score (hazard ratio 6.33, 95% confidence interval −5.31 to 17.98; $p = 0.287$). However, in the adjusted analysis there was a significant difference in the total score (hazard ratio −1.24, 95% confidence interval −2.37 to −0.11; $p = 0.032$), the social domain score of the Leicester Cough Questionnaire (hazard ratio −0.44, 95% confidence interval −0.85 to −0.03; $p = 0.037$)

and the chest domain score of the King's Brief Interstitial Lung Disease questionnaire (hazard ratio −6.85, 95% confidence interval −13.29 to −0.41; $p = 0.037$). There were missing data for some of the secondary end points. The repeated measures analysis showed a significant overall difference in Cough Symptom Score favouring active treatment. There was no statistically significant difference in forced vital capacity (hazard ratio 0.05 l, 95% confidence interval −0.16 to −0.25 l; $p = 0.65$) or other lung function measures. There was no statistically significant difference for any of the prespecified biomarkers.

Safety

More people in the active treatment group ($n = 26$) than in the placebo group ($n = 8$) reduced from the high-dose to low-dose treatment. However, there was no significant difference in the number of adverse events between the two groups or in the number of people with an adverse event. There were more reports of nausea in the active treatment group than in the placebo group ($p = 0.044$), but diarrhoea was more frequently reported in the placebo group ($p = 0.013$). There were more incidents of hyperkalaemia ($p = 0.084$), rash ($p = 0.094$) and headache ($p = 0.148$) with the co-trimoxazole treatment than with the placebo treatment. There were no significant differences in the number of people with adverse reactions for any symptom/event.

Conclusion

This study found no significant or clinically meaningful difference between co-trimoxazole and placebo in total, all-cause or respiratory-related hospitalisation or death. In the prespecified adjusted per-protocol analysis, there was an improvement in several measures of cough with co-trimoxazole therapy, despite incomplete data, but there was no change in other patient-reported outcomes, measures of lung function or blood biomarkers.

Implications for health care

Our results do not suggest that routine prescription of prophylactic co-trimoxazole for individuals with advanced idiopathic pulmonary fibrosis reduces a composite score of mortality or hospitalisations.

Implications for research

A study to evaluate the effect of co-trimoxazole on cough in individuals with idiopathic pulmonary fibrosis should be considered. Although this study rules out a role for co-trimoxazole in unselected individuals with moderate to severe idiopathic pulmonary fibrosis (i.e. those not chosen for any characteristic other than their severity), the possibility that specific subgroups (e.g. 'frequent exacerbators' or those with a high bacterial burden) may benefit from treatment with co-trimoxazole cannot be excluded, nor can the possibility that alternative antibiotics may be more effective than co-trimoxazole. Additional studies in subgroups or with different antibiotic regimens are warranted.

Trial registration

This trial is registered as ISRCTN17464641.

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