Azithromycin for the Treatment of Chronic Cough in Idiopathic Pulmonary Fibrosis: A Randomized Controlled Cross-over Trial

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Abstract

Rationale: Patients with idiopathic pulmonary fibrosis (IPF) frequently suffer from difficult to treat chronic cough, which substantially affects their quality of life. Azithromycin has been demonstrated to relieve chronic cough in some populations, however this has not been investigated in IPF.

Objectives: To determine the safety and efficacy of azithromycin for the treatment of chronic cough in patients with IPF.

Methods: In a double-blind randomized controlled cross-over trial, patients with IPF underwent two 12-week intervention periods (azithromycin 500mg or placebo 3 times per week). The primary outcome was change in cough-related quality of life measured by the Leicester cough questionnaire (LCQ). Secondary outcomes included cough severity measured using Visual Analog Scale (VAS), health-related quality of life assessed by the St. George's Respiratory Questionnaire (SGRQ), and objective cough frequency using audiovisual readings from 24h respiratory polygraphy.

Results: 25 patients were randomized (23 men, 2 women), 20 patients completed the study. Mean (standard deviation, SD) age was 67 (8) years, mean (SD) forced vital capacity (FVC) was 65 (16) %-predicted, and diffusion capacity (DLCO) 43 (16) %-predicted. Mean (SD) baseline LCQ was 11.7 (3.7) and 11.3 (3.3) for the azithromycin and the placebo period, respectively, and the corresponding mean (SD) cough VAS 5.6 (2.3) and 5.8 (2.1). There was no significant change in LCQ and VAS with azithromycin or placebo. Similarly, there was no significant difference in change in polygraphy measured cough frequency between the azithromycin and placebo

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periods. Gastrointestinal adverse effects were more frequent with azithromycin than with placebo (diarrhea 43% vs 5%, p=0.03).

Conclusions: This randomized controlled trial does not support the use of low dose azithromycin for chronic cough in patients with IPF.

Clinical trial registered with ClinicalTrials.gov (NCT02173145).

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Idiopathic pulmonary fibrosis (IPF) is a progressive interstitial lung disease with poor prognosis, high burden of symptoms, and typically poor quality of life.(1-3) Dyspnea and cough are the most frequent and most debilitating symptoms in these patients. Chronic cough contributes to the reduced quality of life in IPF patients,(4) and is associated with disease progression.(5) Antifibrotic drugs reduce disease progression and potentially prolong survival, but have no clearly established effect on quality of life or symptoms.(6, 7)

Azithromycin is an immunomodulatory and anti-inflammatory antibiotic with anti-fibrotic properties in *in vitro* and in animal models for lung fibrosis.(8, 9) Low-dose azithromycin improves cough-related quality of life in chronic obstructive pulmonary disease (COPD) and in patients with idiopathic cough.(10, 11) In patients with IPF, prophylactic treatment with azithromycin might decrease the frequency of hospitalizations and the need for antibiotics.(12) Based on these findings, some centers pragmatically administer empiric azithromycin treatment to patients with IPF suffering from debilitating cough. However, the potential benefit or harm of long-term treatment with azithromycin in patients with IPF has not been demonstrated in controlled prospective clinical trials.

The overall objective of this randomized-controlled study was to determine the safety, tolerability and efficacy of low-dose, long-term azithromycin for the treatment of chronic cough in IPF.

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Methods

Study Design, Participants, and Procedures

This multi-center, investigator-initiated, double-blinded, randomized controlled cross-over trial included patients with IPF recruited from four major pulmonary centers in Switzerland (University Hospital of Bern Inselspital, University Hospital of Zurich, University Hospital of Basel, and Cantonal Hospital of St. Gallen). The hospital pharmacy Inselspital, Bern prepared the study medication and controlled randomization. Patients underwent a 12-week treatment period with azithromycin 500mg 3 times per week and a 12-week treatment period with placebo 3 times per week in random order. In between, there was a 4-week wash-out period to minimize carry-over effects (**Figure E1**). Key inclusion criteria were age over 18 years and a diagnosis of IPF according to current diagnostic guidelines.(1) Patients were invited to participate in the study if they suffered from stable chronic cough that affected their daily life, despite optimal treatment of potential co-factors of chronic cough. Antifibrotic treatment was permitted if pirfenidone had been initiated at least three months and nintedanib at least one month before study inclusion. Similarly, concomitant treatment with long-term oxygen therapy and proton-pump inhibitors were allowed. Key exclusion criteria were any change in medication or respiratory infection within four weeks before inclusion. Furthermore, we excluded patients with one or more of the following criteria: a known allergy or intolerance to macrolide antibiotics, a known cardiac arrhythmia, severe renal failure, a history of hepatitis, current alcohol or drug abuse, serum bilirubin levels of > 50 µmol/L, elevated aspartate transaminase or alanine transaminase by more than three times the upper limit of normal, or a QTc

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prolongation on 12-lead electrocardiogram. Ethical approval was obtained before start of the study (KEK 002/14), and all patients provided written informed consent before inclusion. The study was registered on ClinicalTrial.gov (NCT02173145).

The primary outcome of the study was the difference in change in cough-related quality of life (measured by Leicester cough questionnaire, LCQ) between the azithromycin and the placebo period. Secondary outcomes included difference in changes in health-related quality of life assessed by the St. George's Respiratory Questionnaire (SGRQ), in subjective cough severity (VAS), in objective cough frequency derived from audiovisual readings of 24h respiratory polygraphy, and tolerability of the study medication.

Assessments at baseline included pulmonary function tests and 6-minute walk test according to established protocols,(13-15) electrocardiograms, and blood analysis, including hematology, inflammatory markers, renal and hepatic function.

Assessment of Cough and Quality of Life

At baseline patients provided a qualitative assessment of their cough as a mild, moderate, or severe issue for daily living. Cough severity and impact of cough on quality of life were assessed by cough VAS (range 0-10, higher numbers indicate worse cough) and the LCQ.(16-19) The LCQ is a validated questionnaire that has been used previously in clinical trials including patients with IPF.(20) The LCQ captures the impact of cough on physical, psychological, and social aspects of quality of life. A higher LCQ score (range 3-21) indicates a better cough-related quality of life. Health-related quality of life was assessed by the SGRQ.(21) The 50 items of the SGRQ cover the domains symptoms, activity, and impact, with a total score ranging from 0-100.

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A higher score indicates worse quality of life. The SGRQ has been validated and is commonly used in patients with IPF.(22, 23)

Objective cough frequency was quantified by continuous audiovisual recordings of 24h respiratory polygraphies using NOX T3 with Noxturnal software (Nox Medical, Höfðatorg, Reykjavík, Iceland), a portable monitor frequently used for home sleep apnea diagnosis. Patients were instructed to follow their normal daily routine during the recording period and to keep an activity log.(24) The NOX T3 device has a built-in microphone placed on the chest over clothing. Sampling and storage frequency are 1 MHz and 8 kHz, respectively, at a bandwidth of 3.6 kHz. Validation against calibrated industrial sound level meters has shown accuracy with <3dBc error.(25) Sound data were downloaded to a computer and audio signals were converted to European data format. Data was stored and coughs subsequently identified and analysed manually. Some of the initial polygraphy data including the detailed methodology for the analysis have been published previously.(26) In short, the Cough Index and Cough Attack Index were calculated as the average number of single cough events or cough attack events per hour of recording. Single cough events were defined as cough sounds with less than 4 second duration. Cough attacks were defined as coughing events ≥4 seconds.

Subjective cough, quality of life, and objective cough frequency were assessed at baseline, before and after the azithromycin and placebo study periods.

Statistical Analysis

Participant characteristics are reported as frequency (percentage), mean (standard deviation, SD) or median (interquartile range, IQR) depending on the distribution of the data.

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Cough assessments before and after treatment periods, and mean differences were compared using paired t-tests or Wilcoxon signed rank tests, as appropriate. Spearman's correlation was used to determine the association between continuous variables. Frequencies were compared using Fisher's exact test. A two-sided $p < 0.05$ was used to indicate statistical significance for all comparisons. Data were analysed using R version 3.6.0. (R Foundation for Statistical Computing, Vienna, Austria).

Sample size calculation for the primary outcome and the null hypothesis that azithromycin does not improve total LCQ in a clinically important manner (1.3) was performed. Based on a minimally clinically important difference in total LCQ of 1.3, a standard deviation of 2, a significance level (α) of 0.05, and a power of 0.90, a required sample size of 25 patients was calculated. Inclusion of an additional 2 patients (total 27 patients) as a safety margin for early drop-out was intended, however due to challenging recruitment the study was closed after inclusion of 25 patients.

Results

Patient Characteristics

We included 23 men and 2 women with IPF. Patients had a mean (SD) age of 67 (8) years, with a restrictive pulmonary physiology and mean (SD) forced vital capacity (FVC) of 65 (16) %-predicted, and diffusing capacity of the lung for carbon monoxide (DLCO) of 43 (16) %-predicted. Most patients had been diagnosed by multidisciplinary team discussion, with a definite usual interstitial pneumonia (UIP) pattern in 72% and a surgical lung biopsy available in

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48%. Eighty percent of patients were treated with antifibrotic medication at baseline, and 36% required long-term oxygen therapy. Cardiac disease was the most common comorbidity (44%). 16% and 32% of patients had stable gastroesophageal reflux and chronic rhinitis, respectively (**Table 1**). At baseline all but one patient (who was excluded after randomization) had relevant chronic cough, 17 patients (68%) reported productive cough. Overall, 3 (12%), 16 (64%), and 5 (20%) patients indicated their cough was a mild, moderate, or a severe problem, respectively.

Twelve patients were initially randomized to the intervention period and 13 to the placebo period. One patient died due to disease progression before starting the study medication, and two patients dropped out between randomization and start of the study medication. One patient discontinued azithromycin during the first period due to personal reasons unrelated to the study, and one patient died because of progressive IPF during the placebo period. The remaining patients completed the study (**Figure 1**).

Baseline characteristics of patients who entered the study and patients who completed all study visits were similar (**Table 1**).

Effect of Azithromycin on Subjective Cough and Quality of Life

Mean (SD) baseline LCQ scores before the azithromycin and placebo study periods were 11.7 (3.7) and 11.5 (3.1), respectively. There was no significant change in total LCQ, physical, psychological, or social LCQ subscores during the azithromycin or during the placebo period, without significant differences between change during the azithromycin and placebo periods. Mean (SD) VAS cough severity before azithromycin and placebo were 5.6 (2.3) and 5.8 (2.1), respectively, without a significant change during treatment with azithromycin or placebo.

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(**Table 2, Figure 2**). Similarly, there were no significant changes in total SGRQ, and SGRQ subscores during the study periods with azithromycin and placebo. (**Table 2**)

The order of the treatment periods (azithromycin or placebo first) had no impact on change in LCQ, VAS, and SGRQ. Furthermore, we could not identify differences in baseline characteristics between patients with and without cough improvement by more than the previously reported minimal clinical important differences (**Table E1**).(17-19, 23)

Effect of Azithromycin on Objective Cough Measurements

Objective cough frequency measured with respiratory polygraphy demonstrated a total median (IQR) Cough Index of 4.5/h (3.4-5.9) before the azithromycin period, and 5.7/h (2.7-9.7) before the placebo period. Across all measurements, median (IQR) baseline Cough Index during wakefulness was higher than Cough Index during sleep (7.5/h [5.4-13.7] versus 0.9/h [0.5-2.0]). On average, total cough frequency and cough frequency during sleep decreased during the placebo period, without a significant difference in mean changes during the azithromycin and placebo periods. Cough Index during wakefulness showed no relevant change during azithromycin and placebo study periods (**Table 3**).

Total median (IQR) Cough Attack Indices before azithromycin and placebo were 0.7/h (0.5-0.9) and 1.2/h (0.5-1.8), respectively. Overall, baseline Cough Attacks were more frequent during wakefulness than during sleep (median [IQR] Cough Attack Index 1.0/h [0.8-1.5] versus 0.2/h [0.1-0.6]).

Total and wake Cough Attack Index did not change significantly during the azithromycin and placebo study periods. However, Cough Attack Index during sleep decreased in the placebo

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period, with a significant mean between period difference in favor of placebo. This difference in nightly cough attacks needs to be interpreted in context of the higher baseline Cough Attack Index in the placebo period compared to the azithromycin period (**Table 3**).

Safety and Tolerability

No serious adverse events related to azithromycin were observed. Two patients died during the study due to IPF progression, one patient died before start of the study medication, and one patient during the placebo period. Gastrointestinal adverse events were more frequently reported after the azithromycin period, particularly diarrhea (43% vs 5%, p=0.03), abdominal pain (19% vs none, p=0.11), and nausea (19% vs 5%, p=0.35). Four patients (19%) had a respiratory infection during the azithromycin period and three patients (14%) during the placebo period (**Table 4**).

Correlation between Subjective and Objective Cough Measurements

Cough related quality of life assessed by the LCQ showed a moderate negative correlation with VAS cough severity (r=-0.42), and a strong negative correlation with health-related quality of life measured by SGRQ (r=-0.70). Cough VAS correlated moderately with SGRQ (r=0.42).
The Cough Index assessed by the respiratory polygraphy showed a weak to moderate correlation with the Cough Attack Index (r=0.40). Overall, frequency of cough attacks showed a stronger correlation with measures of subjective cough and quality of life than overall cough frequency. The Cough Attack Index correlated strongest with SGRQ (r=0.57), with a significant negative correlation with LCQ (r=-0.44) but no relevant correlation with subjective assessment

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of cough severity (cough VAS). Overall Cough Index was not associated with subjective cough and quality of life (**Figure 3**).

Discussion

This is the first prospective randomized placebo-controlled study investigating azithromycin as treatment for cough in patients with IPF. The safety and efficacy of a 12-week low-dose treatment with azithromycin or placebo was assessed in a cross-over study design including 25 patients with IPF. Overall, azithromycin led to more frequent adverse events, without any evidence for improvement in cough-related or overall health-related quality of life, subjective cough severity or objective cough measured by 24-hour respiratory polygraphy.

More than half of the patients with IPF report cough, which is often severe and impacts on patients' well-being.(4, 27) Furthermore, IPF-associated cough might be a sign of disease progression and is associated with worse prognosis.(5) The participants of this study suffered from advanced IPF, with 40% requiring long-term oxygen therapy. The average FVC (65% predicted) was lower compared to the average FVC in large clinical trial cohorts (FVC 73% predicted),(6, 7, 28) and in studies investigating the effect of thalidomide and omeprazole on cough in IPF (FVC 70% and 75% predicted, respectively).(20, 29) Correspondingly, average health-related quality of life at baseline was poorer in our cohort compared to the INPULSIS cohort (SGRQ score 40),(22) but comparable to the SGRQ in the thalidomide study.(29) Similarly, cough-related quality of life in our patients was poorer compared to the participants of the omeprazole study (11.7 versus 15.3).(20) Subsequently our study findings are

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generalizable to IPF patients with severe functional impairment, poor quality of life and severe cough.

Cough in IPF is likely caused by multiple concurrent factors including architectural distortion of the lung parenchyma, increased sensitivity of the cough reflex, airway inflammation, and changes in mucus production and clearance.(30-33) Gastroesophageal reflux is a prevalent and difficult to treat cause of cough in the general population,(34) with a frequently discussed role in IPF pathogenesis and progression.(35, 36) These complex mechanisms might explain why treatment of cough in IPF is challenging. Few controlled clinical trials have addressed cough in IPF, and no effective and safe treatment options emerged so far. Low dose opiates have been suggested for the management of cough in ILD in a palliative care setting, without any trials demonstrating a benefit in this population.(37) Low dose thalidomide improved cough-specific quality of life in patients with IPF but its use is limited by severe potential side effects.(29) A pilot study with omeprazole found a statistically non-significant trend towards a reduction in objective cough frequency in the omeprazole group, however without an effect on cough-related quality of life. Compared to the placebo group, twice as many patients in the omeprazole group had respiratory infections.(20) Other potential cough treatments in IPF include inhaled sodium cromoglicate,(38) and pirfenidone which improved subjective and objective cough after 12 weeks treatment in an observational study.(39)

Azithromycin is commonly used for its immunomodulatory properties in patients with bronchiectasis and COPD, in whom azithromycin can lead to a reduction in exacerbation frequency, and improvement in productive cough severity and LCQ.(11, 40, 41) The beneficial effects of azithromycin can be explained by various mechanisms, including inhibition of

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pathogens, influence on the microbiome, immunomodulatory effects, and promotilic properties of the drug.(42-47) Overall, there are multiple reasons to hypothesize that long-term treatment with low-dose azithromycin reduces chronic cough in IPF. Nonetheless, in this prospective randomized placebo-controlled trial we could not confirm that azithromycin has any effect on cough in patients with IPF. Despite the lack of overall effect, we cannot exclude a benefit in specific IPF subpopulations. For example, our few responders to azithromycin had the most severe cough at baseline (supplemental **Table E1**). Furthermore, cough assessments might not be sensitive enough to short-term changes across different cough severities.

Azithromycin is an antibiotic with broad-spectrum activity, and there is a risk of producing resistant pathogens by its long-term administration.(48, 49) Furthermore, antibiotic drugs affect the natural microbiome, which might be involved in the pathogenesis and progression of chronic lung diseases and specifically IPF.(50, 51) This emphasizes that a potential detrimental effect of a treatment with azithromycin in IPF cannot be excluded, and the drug should not be used pending solid evidence demonstrating its efficacy.

The characteristics and impact of cough in IPF is still not sufficiently described, and it is unclear how to assess cough in this population.(24, 52) Our study adds to the current knowledge on cough assessment in IPF. For example, we confirm that polygraphy measured cough in IPF is more prevalent during wakefulness than during sleep.(26, 27) The frequency of cough attacks (≥4 seconds) showed a weak to moderate correlation with single cough events. We found that frequent single cough events were not perceived as severe and did not seem to affect cough- and overall health-related quality of life. In contrast, frequency of cough attacks significantly correlated with poorer quality of life. Similarly, a previous study had demonstrated

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the strongest association between LCQ and cough recorded as “prolonged series of explosive phases”.(24)

Our study has limitations. Of the 25 patients included in the study only 20 completed the study, this led to the study being potentially underpowered to confidently reject the null hypothesis that there is no benefit of azithromycin on total cough-related quality of life (LCQ). Assuming a MCID of 1.3 and the observed SD of differences (2) for LCQ, a sample size of 20 provides a power of 0.78. Consequently, there is a 22% chance that we wrongly conclude that azithromycin does not improve cough measured by LCQ. We did not objectively assess reflux as a possible trigger of cough (e.g. by esophageal-gastric pH measurements), furthermore some patients reported ongoing chronic rhinitis. Best possible treatment of these potential co-factors was initiated at least one month before the study, without any later change in treatment.

Previous studies have validated the objective quantification of cough by audiovisual recording and manual counting of cough events by trained technicians,(19) however audiovisual tracks from NOX T3 respiratory polygraphy have not been used specifically for this purpose. We showed significant correlations between cough attack frequency and (cough-related) quality of life, which supports the construct validity of audiovisual cough assessment by NOX T3 respiratory polygraph. Lastly, we cannot exclude that 12 weeks treatment duration might be too short, or the dosage of 500mg three times per week not optimal.(10, 12, 53)

Overall, our prospective randomized placebo-controlled cross-over study does not support the use of azithromycin for the treatment of chronic cough in patients with IPF. We did not find any effect of azithromycin on the primary outcome cough-related quality of life in our study. Objectively measured cough attacks impact significantly on perceived cough severity and

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quality of life in patients with IPF, emphasizing the importance of future studies focusing on the management of cough in IPF.

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Figure Legends:

Figure 1. CONSORT diagram of the study. Abbreviations: AZT, azithromycin; CONSORT = Consolidated Standards of Reporting Trials

Figure 2. Individual cough-related quality of life before and after placebo and azithromycin study periods. p-values were derived from paired t-tests. Abbreviation: VAS, Visual Analogue Scale

Figure 3. Pairwise correlation between measures of subjective and objective cough. Cough Index/h and Cough Attack Index/h assessed by polygraph. Abbreviations: LCQ, Leicester Cough Questionnaire score; p, p-value; r, correlation coefficient; SGRQ, St. George's Respiratory Questionnaire score; VAS, Visual Analogue Scale

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Table 1. Baseline characteristics

	Patients after randomization (n=25)	Patients completing the study (n=20)
DEMOGRAPHICS AND DIAGNSTOC CHARACTERISTICS		
Sex, men	23 (92%)	17 (80%)
Age, years	67 (8)	64 (7)
Previous smokers	17 (68%)	15 (75%)
Current smoker	1 (4%)	0 (0%)
Smoked pack years	24.5 (15.1)	24.1 (15.5)
DIAGNOSIS		
Definite UIP pattern on HRCT	18 (72%)	13 (65%)
Surgical lung biopsy available	12 (48%)	12 (60%)
MDTD performed	19 (76%)	13 (65%)
TREATMENT		
Pirfenidone	9 (36%)	8 (40%)
Nintedanib	11 (44%)	9 (45%)
Proton pump inhibitor	13 (52%)	11 (55%)
ACE-Inhibitor	1 (4%)	1 (4%)
Oxygen therapy	9 (36%)	8 (40%)
Oxygen flow rate liters/min	2 (0.8)	3 (0.8)
PULMONARY FUNCTION TESTS		
TLC, liters	4.10 (1.0)	4.12 (1.0)
TLC, % predicted	60.1 (12.4)	61.1 (12.6)
FVC, liters	2.6 (0.8)	2.65 (0.84)
FVC, % predicted	65 (16)	66 (17)
FEV1/FVC, %	86 (7)	86 (8)
DLCO, % predicted	43 (16)	44 (16)
6-MWD, meters	451 (95)	473 (84)
COMORBIDITIES		
Chronic rhinitis	8 (32%)	6 (30%)
Sinusitis	2 (8%)	2 (10%)
Gastroesophageal reflux disease	4 (16%)	4 (20%)
Cardiac disease	11 (44%)	9 (45%)
Pulmonary hypertension	3 (12%)	1 (5%)
Diabetes	4 (16%)	4 (20%)

Data is presented as frequency and percentage or mean and standard deviation (SD).
Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; ACE, angiotensin converting enzyme; FEV1, forced vital capacity in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography of the lung; MDTD, multidisciplinary team discussion; TLC, total lung capacity; UIP, usual interstitial pneumonia; 6-MWD, 6-minute walk distance

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Table 2. Subjective assessments before and after treatment with azithromycin or placebo.

	Azithromycin (n=20)			Placebo (n=20)			Between period difference in change[2]	
	Before	*After*	*p*	*Before*	*After*	*p*	*Mean difference (95% CI)*	*p*
	Leicester Cough Questionnaire, Score							
Total	11.7 (3.7)	11.3 (3.7)	0.29	11.5 (3.1)	11.7 (3.3)	0.65	0.68 (-0.64 to 1.99)	0.29
Physical	4.3 (1.1)	4.0 (1.0)	0.10	4.3 (0.9)	4.2 (0.9)	0.93	0.28 (-0.23 to 0.73)	0.28
Psychological	3.6 (1.4)	3.5 (1.5)	0.31	3.5 (1.1)	3.6 (1.4)	0.86	0.20 (-0.24 to 0.64)	0.35
Social	3.8 (1.5)	3.8 (1.5)	0.85	3.7 (1.4)	3.9 (1.3)	0.32	0.23 (-0.37 to 0.82)	0.44
	Cough Visual Analogue Scale, /10							
VAS	5.6 (2.3)	5.8 (2.1)	0.75	5.8 (2.1)	6.3 (2.1)	0.39	0.25 (-1.12 to 1.63)	0.70
	St. George's Respiratory Questionnaire Score							
Total	57.2 (18.6)	59.1 (16.6)	0.32	57.0 (13.8)	60.4 (18.6)	0.18	1.92 (-6.1 to 9.9)	0.62
Activity	69.7 (17.1)	73.1 (18.1)	0.08	70.0 (15.0)	73.8 (17.2)	0.14	0.86 (-6.74 to 8.47)	0.81
Impact	47.6 (21.8)	49.5 (19.5)	0.41	47.4 (14.9)	50.9 (22.5)	0.25	1.88 (-7.30 to 11.1)	0.67
Symptoms	65.3 (22.2)	64.1 (17.8)	0.78	63.7 (17.9)	65.9 (19.3)	0.55	4.59 (-10.9 to 20.0)	0.54

[2]positive/negative numbers reflect larger/smaller increase in the placebo period than in the azithromycin period.

Before-after scores reported as mean (standard deviation). P-values derived from paired t-tests.

Abbreviations: CI, confidence interval; VAS, Visual Analogue Scale

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Table 3. Objective cough measurement before and after treatment with azithromycin or placebo.

	Azithromycin (n=15)			**Placebo (n=12)**			**Between period difference in change**[2]	
	Before	*After*	*p*	*Before*	*After*	*p*	*Mean difference (95% CI)*	*p*
	Cough Index, /h							
Total	4.5 (3.4-5.9)	3.7 (2.8-4.3)	0.73	5.7 (2.7-9.7)	4.1 (2.4-7.4)	0.04	-3.9 (-10.2 to 2.3)	0.19
Wake	6.2 (4.4-8.2)	6.0 (4.7-9.5)	0.62	7.4 (3.5-13.7)	6.1 (2.6-11)	0.20	-7.0 (-16.4 to 2.4	0.13
Sleep	0.6 (0.1-1.1)	0.8 (0.2-1.3)	0.58	1.0 (0.5-2.1)	0.5 (0.2-0.7)	0.04	-2.9 (-7.5 to 1.6)	0.17
	Cough Attack Index, /h							
Total	0.7 (0.5-0.9)	0.8 (0.2-1.3)	0.48	1.2 (0.5-1.8)	0.7 (0.1-1.0)	0.12	-0.35 (-1.1 to 0.4)	0.29
Wake	0.9 (0.7-1.3)	1.1 (0.2-1.0)	0.81	1.5 (0.6-2.5)	0.8 (0.2-1.2)	0.15	-0.8 (-1.9 to 0.4)	0.16
Sleep	0.1 (0-0.4)	0.2 (0-0.5)	0.92	0.4 (0.2-0.6)	0.1 (0-0.35)	0.04	-0.4 (-0.6 to -0.1)	0.02

[2]positive/negative numbers reflect larger/smaller increase in the placebo period than in the azithromycin period.

Before-after scores reported as median (interquartile range). P-values derived from Wilcoxon Signed Rank Tests and paired t-tests.

Abbreviations: AZT, azithromycin; CI, confidence interval; h, hour

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Table 4. Adverse events in the azithromycin and placebo periods.

Adverse events Numbers (%)	**Azithromycin (n=21)**	**Placebo (n=21)**	**p-value**
Diarrhea	9 (43%)	1 (5%)	0.03
Nausea	4 (19%)	1 (5%)	0.35
Vomiting	3 (14%)	1 (5%)	0.61
Abdominal	4 (19%)	-	0.11
Chest pain†	-	2 (10%)	0.49
Fall†	1 (5%)	1 (5%)	>0.99
IPF worsening†	3 (14%)	3 (14%)	>0.99
Dyspnea worsening†	3 (14%)	4 (19%)	>0.99
Increasing cough†	2 (10%)	2 (10%)	>0.99
Skin erythema†	1 (5%)	1 (5%)	>0.99
Conjunctivitis†	-	1 (5%)	>0.99
Respiratory infection†	4 (19%)	3 (14%)	>0.99
Fever†	-	1 (5%)	>0.99
Headaches†	-	1 (5%)	>0.99
Cardiac failure†	1 (5%)	1 (5%)	>0.99
Pulmonary embolism†	1 (5%)	-	>0.99
Inguinal hernia†	1 (5%)	-	>0.99
Hospitalization, respiratory related†	-	1 (5%)	>0.99
Death, respiratory related†	-	1 (5%)	>0.99

†unlikely related to the study
p-values derived from Fisher's exact tests

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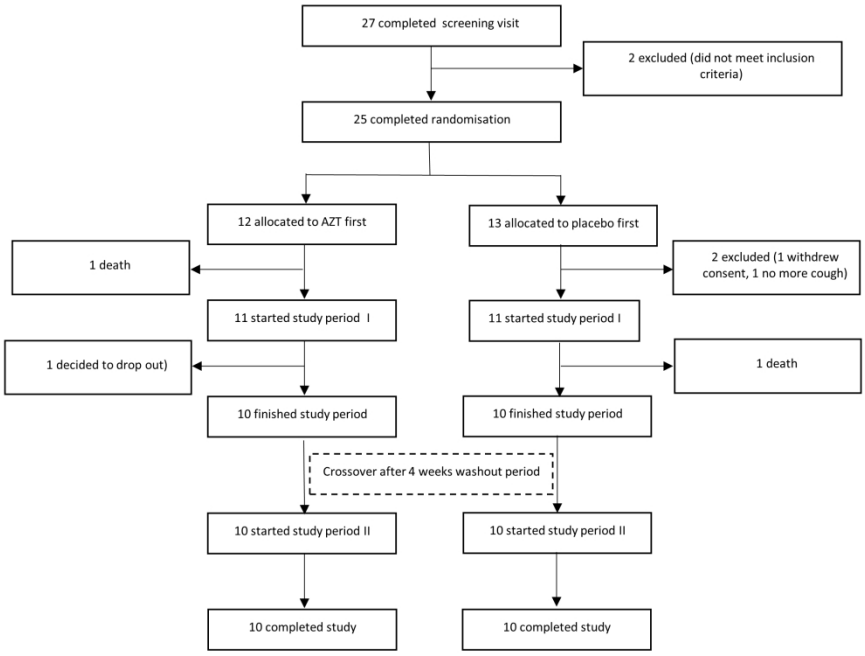

Figure 1. CONSORT diagram of the study.
Abbreviations: AZT, azithromycin; CONSORT = Consolidated Standards of Reporting Trials

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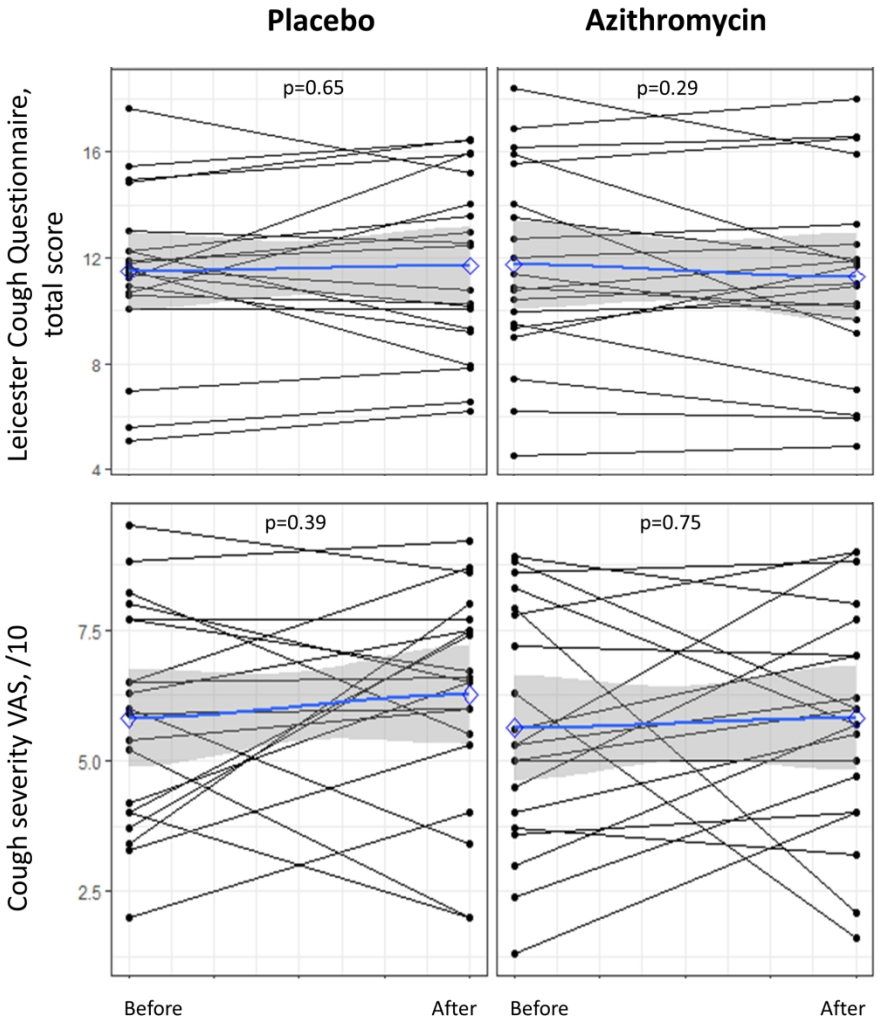

Figure 2. Individual cough-related quality of life before and after placebo and azithromycin study periods.
p-values were derived from paired t-tests.
Abbreviation: VAS, Visual Analogue Scale

190x219mm (300 x 300 DPI)

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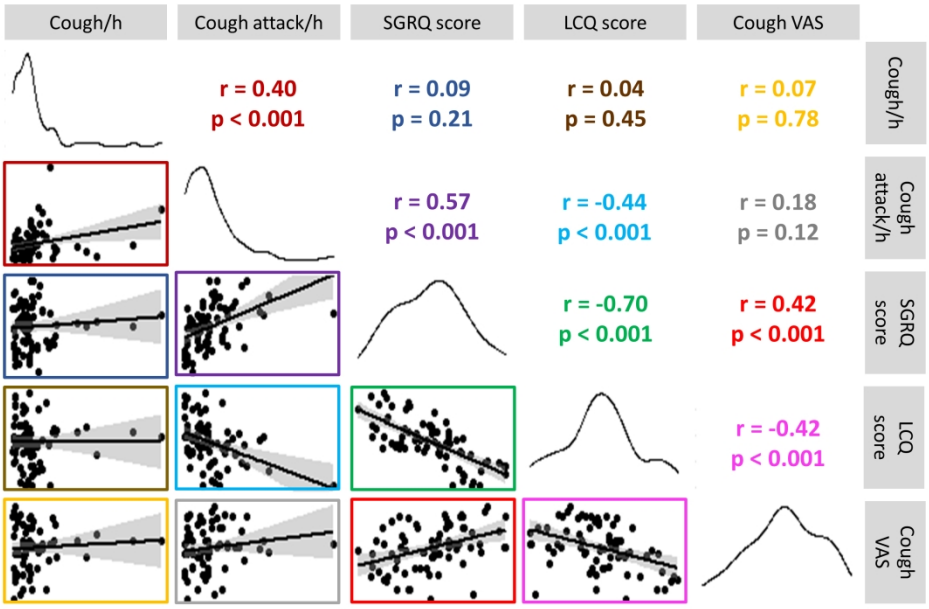

Figure 3. Pairwise correlation between measures of subjective and objective cough.
Cough Index/h and Cough Attack Index/h assessed by polygraph
Abbreviations: LCQ, Leicester Cough Questionnaire score; p, p-value; r, correlation coefficient; SGRQ, St. George's Respiratory Questionnaire score; VAS, Visual Analogue Scale

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ONLINE SUPPLEMENT

Azithromycin for the treatment of chronic cough in idiopathic pulmonary fibrosis: a randomized controlled cross-over trial.

Sabina A. Guler, Christian Clarenbach, Martin Brutsche, Katrin Hostettler, Anne-Kathrin Brill, Anke Schertel, Thomas K. Geiser, Manuela Funke-Chambour

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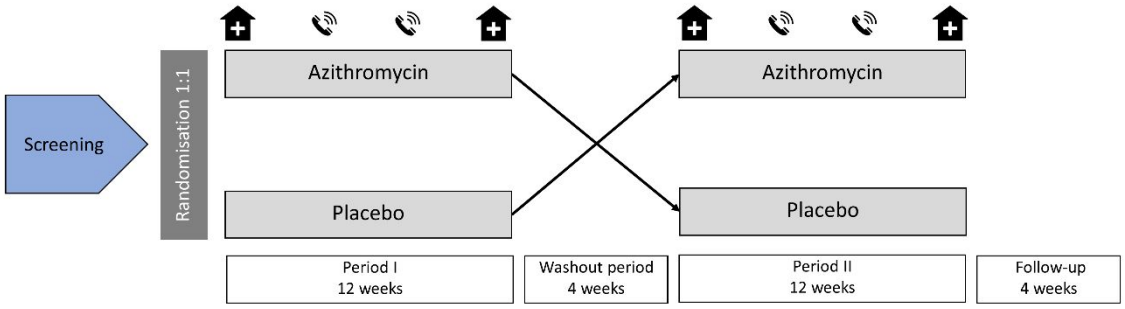
Figure E1. Study design.



After screening and study inclusion participants were randomised to receive either azithromycin or placebo for the first 12-week study period. After a 4-week washout period, participants crossed to either placebo or azithromycin for the second 12-week study period. Outcome assessments before and after study periods I and II were performed in the outpatient clinics and included subjective and objective cough assessments, blood draws, and assessment of drug tolerability. Two phone calls during each study period (after 4 and 8 weeks) were scheduled to assess for adherence and drug tolerability.

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Table E1. Baseline characteristics by response to azithromycin or placebo.

	Azithromycin		Placebo	
	Leicester Cough Questionnaire, Score			
Baseline characteristics	*Responders (n=2)*	*Non-responders (n=18)*	*Responders (n=4)*	*Non-responders (n=16)*
Age, years	67 (8)	65 (8)	69 (9)	65 (7)
Sex, men	1 (50%)	17 (94%)	4 (100%)	14 (88%)
FVC, %-predicted	50 (17)	67 (17)	50 (9)	69 (17)
DLCO, %-predicted	36 (3)	43 (18)	51 (21)	44 (14)
Proton pump inhibitor	2 (100%)	9 (50%)	3 (75%)	8 (50%)
Oxygen therapy	1 (50%)	7 (39%)	2 (50%)	6 (38%)
Pirfenidone	1 (50%)	7 (39%)	2 (50%)	6 (38%)
Nintedanib	1 (50%)	8 (44%)	2 (50%)	7 (44%)
LCQ baseline	9.2 (0.3)	12.0 (3.8)	12.3 (1.8)	11.3 (3.4)
Cough VAS baseline	8.1 (1.2)	5.4 (2.2)	4.2 (1.3)	6.2 (2.1)
SGRQ baseline	69.8 (7.9)	55.8 (19.0)	54.8 (11.8)	57.5 (14.6)
Phase I azithromycin	1 (50%)	9 (50%)	1 (25%)	9 (56%)
	Cough Visual Analogue Scale, /10			
	Responders (n=4)	*Non-responders (n=16)*	*Responders (n=4)*	*Non-responders (n=16)*
Age, years	66 (5)	66 (8)	64 (7)	66 (8)
Sex, men	4 (100%)	14 (88%)	4 (100%)	14 (88%)
FVC, %-predicted	68 (16)	64 (18)	62 (21)	66 (17)
DLCO, %-predicted	33 (9)	44 (18)	44 (19)	45 (15)
Proton pump inhibitor	2 (50%)	9 (56%)	2 (50%)	9 (56%)
Oxygen therapy	3 (75%)	5 (31%)	2 (50%)	6 (38%)
Pirfenidone	1 (25%)	7 (44%)	1 (25%)	8 (50%)
Nintedanib	3 (75%)	6 (38%)	3 (75%)	5 (31%)
LCQ baseline	8.3 (2.9)	12.6 (3.4)	11.1 (4.1)	11.6 (2.9)
Cough VAS baseline	7.8 (1.1)	5.1 (2.2)	6.8 (1.8)	5.6 (2.2)
SGRQ baseline	74.2 (17.1)	52.9 (16.7)	72.1 (10.0)	53.2 (14.2)
Phase I azithromycin	1 (25%)	9 (56%)	2 (50%)	8 (50%)
	St. George's Respiratory Questionnaire Score			
	Responders (n=4)	*Non-responders (n=16)*	*Responders (n=3)*	*Non-responders (n=17)*
Age, years	62 (2)	66 (8)	58 (4)	66 (7)
Sex, men	3 (75%)	15 (94%)	3 (100%)	14 (82%)
FVC, %-predicted	71 (29)	63 (14)	60 (10)	67 (18)
DLCO, %-predicted	36 (12)	44 (18)	42 (6)	45 (16)
Proton pump inhibitor	3 (75%)	8 (50%)	3 (100%)	8 (47%)
Oxygen therapy	1 (25%)	7 (44%)	1 (33%)	6 (35%)
Pirfenidone	1 (25%)	7 (44%)	2 (67%)	6 (35%)
Nintedanib	2 (50%)	7 (44%)	1 (33%)	7 (41%)
LCQ baseline	11.6 (2.7)	11.8 (4.0)	12.5 (2.7)	11.4 (3.3)
Cough VAS	6.8 (3.7)	5.3 (1.9)	6.5 (1.3)	5.8 (2.2)
SGRQ baseline	62.4 (12.0)	55.9 (20.0)	61.0 (8.3)	55.8 (15.0)
Phase I azithromycin	2 (50%)	8 (50%)	2 (67%)	8 (47%)

Mean (standard deviation) or number (precent of total).

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Responders are defined according to change of more than the respective minimal important differences. LCQ responders are those with an increase in LCQ score ≥1.3;(1, 2) cough VAS responders are those with a cough VAS decrease of ≥1.7;(1, 3) and SGRQ responders are those with a decrease in SGRQ score ≥5.(4)

Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; LCQ, Leicester Cough Questionnaire score; SGRQ, St. George's Respiratory Questionnaire total score; VAS, visual analogue scale /10

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