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Thalidomide for the Treatment of Cough in Idiopathic Pulmonary Fibrosis

A Randomized Trial

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Background: Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal disorder of unknown cause with no effective treatment. Cough affects up to 80% of patients with IPF, is frequently disabling, and lacks effective therapy.

Objective: To determine the efficacy of thalidomide in suppressing cough in patients with IPF.

Design: 24-week, double-blind, 2-treatment, 2-period crossover trial. (ClinicalTrials.gov registration number: NCT00600028)

Setting: 1 university center.

Participants: 98 participants were screened, 24 were randomly assigned, 23 received treatment (78.3% men; mean age, 67.6 years; mean FVC, 70.4% predicted), and 20 completed both treatment periods.

Measurements: The primary end point was cough-specific quality of life measured by the Cough Quality of Life Questionnaire (CQLQ). Secondary end points were visual analogue scale of cough and the St. George's Respiratory Questionnaire (SGRQ). For all measures, lower scores equaled improved cough or respiratory quality of life.

Results: CQLQ scores significantly improved with thalidomide (mean difference vs. placebo, −11.4 [95% CI, −15.7 to −7.0]; $P < 0.001$). Thalidomide also significantly improved scores on the visual analogue scale of cough (mean difference vs. placebo, −31.2 [CI, −45.2 to −17.2]; $P < 0.001$). In participants receiving thalidomide, scores from the total SGRQ, SGRQ symptom domain, and SGRQ impact domain improved compared with those of participants receiving placebo. Adverse events were reported in 74% of patients receiving thalidomide and 22% receiving placebo; constipation, dizziness, and malaise were more frequent with thalidomide.

Limitation: This was a single-center study of short duration and small sample size focused on symptom-specific quality of life.

Conclusion: Thalidomide improved cough and respiratory quality of life in patients with IPF. A larger trial is warranted to assess these promising results.

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Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal fibrotic lung disorder of unknown cause with no proven pharmacologic therapy (1). It is the most common idiopathic interstitial pneumonia, accounting for greater than 60% of cases, but it is also the least treatable and has the worst prognosis (1–3). Most patients with IPF die within 3 to 5 years of diagnosis (1, 2).

One of the most prominent features of IPF is a persistent, nonproductive, often disabling cough that has no effective treatment (4, 5). Recent studies suggest that this cough affects up to 80% of patients with IPF and may be an independent predictor of disease progression and death (6). The cause of cough in IPF is unknown.

Studies have demonstrated a functional upregulation of sensory fibers within the respiratory tracts of patients with IPF (4). The reason for this is unclear, but it may be due to induction of nerve growth factors (4). Although the pathogenesis of IPF itself is unknown, compelling evidence implicates dysregulation of the immune system (7, 8).

See also:

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Summary for Patients. I-38

This immune dysregulation may also play a role in IPF-related cough. However, immunomodulatory treatments for IPF have had little to no effectiveness on IPF progression or cough (1, 9, 10). Cough-specific treatments, such as narcotics and airway topical anesthetic agents, also have had little effect on IPF-related cough (4, 5, 11). No drugs are currently approved in the United States for treatment of IPF or the associated cough.

Thalidomide is a drug with an infamous history. Its use as an antiemetic during the first trimester of pregnancy caused serious birth defects (12). In recent years, thalidomide has been "rediscovered" as an effective treatment of cancer, including multiple myeloma, myelodysplastic syndromes, renal cell cancer, and prostate cancer (13–15). Thalidomide is a potent immunomodulatory, antiinflammatory, and antiangiogenic drug (13–15). Its immunomodulatory properties suggest that it may be a potential therapy for IPF.

During a previous open-label clinical trial evaluating thalidomide as an IPF treatment, patients receiving this agent reported a marked reduction in cough, although no conclusions could be made about the effect of the drug on the course of IPF itself because of poor recruitment (16). That trial unfortunately was not designed or powered to evaluate the effect of thalidomide on cough. In this article, we present the results of a double-blind, 2-treatment,

2-period crossover trial assessing the effect of thalidomide on cough in patients with IPF.

METHODS

Design Overview

This study was a double-blind, 2-treatment, 2-period crossover trial with two 12-week treatment periods separated by a 2-week drug-free washout period performed at Johns Hopkins University School of Medicine, Baltimore, Maryland. All participants provided written informed consent, and the trial was approved by the Johns Hopkins Investigational Review Board and registered at ClinicalTrials.gov (NCT00600028).

Consecutive eligible patients, as determined by the investigators, were informed of the study, and interested patients were recruited directly by the investigators from their clinics and through self-referral from the ClinicalTrials.gov Web site between February 2008 and March 2011. During this time, 98 persons contacted our study coordinator with queries about the trial, 22 from the Johns Hopkins Interstitial Lung Disease Clinic and 76 in response to the ClinicalTrials.gov Web site.

Of these participants, 25 were interested and traveled to our center for further evaluation (8 from the clinics and 17 from the Web site). The remaining participants did not enroll because of lack of interest or because they did not have IPF (8), were too sick to travel (6), had too far to travel (4), or died before the coordinator contacted them (2). Of the 25 participants enrolled, 1 person was ineligible because of an FVC greater than 90% predicted.

Setting and Participants

Eligibility criteria were age older than 50 years with a clinical history consistent with IPF (symptom duration ≥3 months and ≤5 years) and chronic cough, defined as cough of more than 8 weeks' duration, that adversely affected quality of life and was not due to other identifiable causes. All participants had high-resolution chest computed tomography scans consistent with IPF or surgical lung biopsy results demonstrating usual interstitial pneumonitis, FVC between 40% and 90% predicted, total lung capacity between 40% and 80% predicted, and DL_{CO} between 30% and 90% predicted at screening.

All participants adhered to the U.S. Food and Drug Administration–mandated System for Thalidomide Education and Prescribing Safety program to minimize the chance of fetal exposure to the drug. The main exclusion criteria were pregnancy, female sex with childbearing potential, toxic or environmental exposure to respiratory irritants, collagen vascular disease, airflow obstruction, active narcotic antitussive use, peripheral vascular disease or neuropathy, inability to give informed consent, allergy or intolerance to thalidomide, or a life expectancy less than 6 months in the opinion of the investigators.

Context

Patients with idiopathic pulmonary fibrosis frequently have debilitating cough for which there is no known therapy.

Contribution

In this randomized, controlled trial, cough-specific quality of life and cough severity improved in patients receiving thalidomide compared with placebo.

Caution

The trial was conducted at a single center and included a small number of patients.

Implication

Thalidomide may be an effective therapy for cough in patients with idiopathic pulmonary fibrosis. Additional studies are needed.

—The Editors

Randomization and Interventions

All participants were randomly assigned to receive either thalidomide ($n = 12$) or placebo ($n = 12$). Both the study investigators and the participants were blinded to treatment assignment. The Johns Hopkins Investigational Drug Service prepared the randomization schedule by using a manual algorithm (17). A random seed number was generated by using the RAND function in Microsoft Excel (Microsoft, Seattle, Washington). The pharmacist dispensing the study drug was the only person who had access to the treatment assignment.

Patients received each treatment for 12 weeks in a crossover design with a 2-week washout period between the 2 treatments. All patients began receiving 50 mg of the study drug by mouth at bedtime, and the dose was increased to 100 mg if no improvement in cough occurred after 2 weeks (21 of the 22 patients receiving thalidomide and all 23 patients receiving placebo).

To avoid the constipation associated with thalidomide, all participants received sodium docusate, 100 mg by mouth daily, during the trial. To mitigate possible undiagnosed coexisting vitamin B deficiency, all participants also received a daily vitamin B complex supplement. Any prescription therapy specifically prescribed for cough was discontinued 2 weeks before the study, and no new prescription therapy specifically prescribed for cough was started during the trial. No patients began benzonatate therapy during the trial or reported changes in their angiotensin-converting enzyme (ACE) inhibitor, angiotensin-receptor blocker (ARB), gastroesophageal reflux disease (GERD), or sinus therapies.

Outcomes and Follow-up

The primary end point was cough-specific quality of life as measured by the Cough Quality of Life Questionnaire (CQLQ) (18). The CQLQ consists of 28 questions

about cough and its effects using Likert-like 4-point scales, with lower scores indicating less effect of cough on health-related quality of life (18). Primary analysis was a comparison of CQLQ scores after treatment with placebo and after treatment with thalidomide.

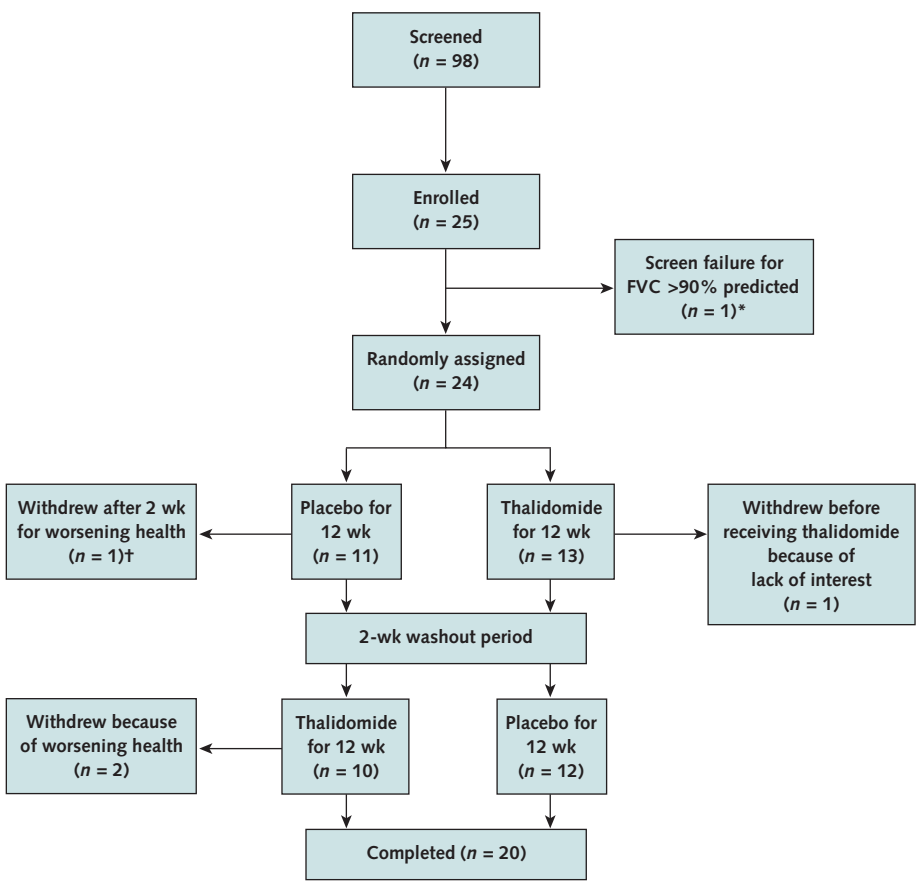
Secondary end points were cough as measured by a 10-cm visual analogue scale and respiratory quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) (19). The SGRQ is a disease-specific measure of the effect of respiratory disease on overall health, daily life, and perceived well-being through 50 items (76 responses) that produces 3 domain scores and 1 overall score measuring symptom (frequency and severity), activity (activities that cause or are limited by breathlessness), and impacts (social functioning and psychological disturbances resulting from airways disease). The SGRQ is widely used in clinical trials of IPF and has been demonstrated to be a valid tool for differentiating changes in IPF (20–23).

Statistical Analysis

Calculations of sample size were based on the primary end point, the CQLQ. When the study was designed, there were no data on the minimum clinically important difference (MCID) for the CQLQ or published data on the variance in patients with IPF. Therefore, we based power calculations on our ability to recruit 20 participants, which would provide 80% power to detect a difference of 4.67 units with a 2-sided α error level of 5% in a 2-treatment crossover study. This was based on the assumption that the within-patient SD of the response variable would be 5.0.

The Shapiro–Wilks test was used to test for normality of distribution. The visual analogue scale of cough was not normally distributed. The McNemar chi-square test was used to compare categorical variables. The association between thalidomide and the primary and secondary outcomes was analyzed by using linear mixed-effects models.

Figure 1. **Study flow diagram.**



We collected data for all planned study visits from 20 participants and incomplete data on 3 participants who received placebo first but withdrew before completion of the thalidomide group. Analysis included all available data.

* One participant signed consent but was found to be ineligible because of an FVC >90% predicted.

† One participant withdrew because of hospitalization and inability to attend visits due to worsening health.

Table 1. **Baseline Characteristics of Randomly Assigned Participants**

Variable	Description
Total participants, *n*	23
Women, *n (%)*	5 (21.7)
Mean age (SD), *y*	67.6 (7.8)
Race, %	
White	91.2
Black	4.4
Hispanic	4.4
Mean time from diagnosis (range), *mo*	20.5 (3–59)
VATS lung biopsy, *n (%)*	5 (21.7)
HRCT, *n (%)*	23 (100)
Previous IPF treatment, *n (%)*	15 (65)
N-acetylcysteine	12 (52)
Oxygen	5 (22)
Prednisone	3 (13)
Previous cough treatment, *n (%)*	8 (35)
Benzonatate	5 (22)
Narcotic	5 (22)
GERD, *n (%)*	12 (52)
Therapy for GERD reported at entry into study	
Proton-pump inhibitor	10 (43)
High-dose proton-pump inhibitor	2 (9)
Chronic sinusitis, *n (%)*	8 (34)
Therapy for chronic sinusitis reported at entry into study	
Antihistamine	5 (22)
Nasal steroids	5 (22)
Decongestant	4 (17)
Leukotriene receptor antagonist	1 (4)
ACE inhibitor/ARB use, *n (%)*	7 (30)
Mean FVC (SD), *% predicted*	70.4 (13.7)
Mean FEV_1–FVC ratio (SD)	0.85 (0.54)
Mean TLC (SD), *% predicted*	63.6 (11.4)
Mean DLco (SD), *% predicted*	57.4 (14.4)

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; GERD = gastroesophageal reflux disease; HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; TLC = total lung capacity; VATS = video-assisted thoracoscopic surgery.

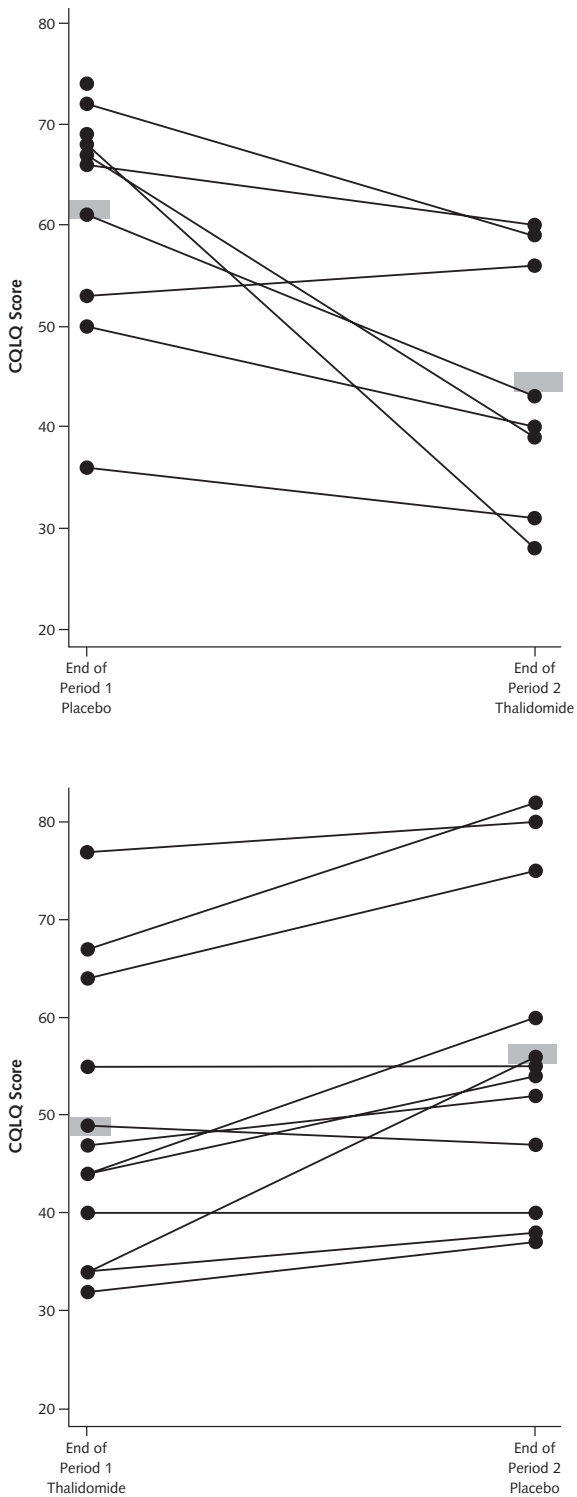
For each outcome measure, we used only the value at week 12 of thalidomide or placebo therapy (24).

The model contained covariates for treatment (thalidomide vs. placebo), period, and treatment sequence as fixed effects and participant nested within sequence as a random effect. Additional analyses were performed to test the sensitivity of our findings to missing data. We repeated the primary analysis by replacing missing CQLQ scores with scores from day 0 and with the highest CQLQ score. We also used a model that included a covariate for the CQLQ at day 0. Results are presented as means (SDs) unless otherwise specified. A *P* value less than 0.05 was considered significant for all analyses. Statistical analyses were performed by using Stata MP, version 12.1 (Stata Corp, College Station, Texas).

Role of the Funding Source

This was an investigator-initiated trial. Celgene Corporation provided the study drug and funding but had no role in study design, conduct, analysis, or manuscript preparation.

Figure 2. **Cough-specific quality-of-life scores after thalidomide and placebo treatments.**



Cough-specific quality-of-life scores for each participant after 12 wk of treatment with thalidomide or placebo. Shaded areas represent the mean CQLQ scores. CQLQ = Cough Quality of Life Questionnaire. **Top.** Participants who received thalidomide in the first period. **Bottom.** Participants who received placebo in the first period.

Table 2. **CQLQ, VAS, and SGRQ Scores After Placebo and Thalidomide Treatments***

Measure	Mean Score at Baseline (SD)	Mean Score After 12 wk of Placebo (SD)	Mean Score After 12 wk of Thalidomide (SD)	Mean Difference (95% CI)†	*P* Value†
CQLQ	60.5 (12.0)	58.7 (14.0)	47.2 (13.4)	−11.4 (−15.7 to −7.0)	<0.001
Cough VAS	64.8 (21.4)	61.9 (26.5)	32.2 (26.1)	−31.2 (−45.2 to −17.2)	<0.001
SGRQ total	57.4 (18.8)	56.9 (17.1)	43.9 (16.0)	−11.7 (−18.6 to −4.8)	0.001
SGRQ symptom domain	67.7 (19.7)	62.0 (18.3)	50.3 (20.9)	−12.1 (−22.2 to −2.0)	0.018
SGRQ impact domain	48.1 (20.7)	49.0 (19.4)	34.3 (16.1)	−13.1 (−19.7 to −6.6)	<0.001
SGRQ activity domain	64.3 (22.7)	65.8 (18.7)	60.9 (14.2)	−3.3 (−9.8 to 3.2)	0.31

CQLQ = Cough Quality of Life Questionnaire; SGRQ = St. George's Respiratory Questionnaire; VAS = visual analogue scale.
* All but the SGRQ activity score was statistically significantly better after thalidomide than after placebo.
† Difference = thalidomide minus placebo. These data are from linear mixed-effects models that accounted for treatment period, sequence, and participant nested within sequence (full results in **Appendix Tables 1** to **10**, available at www.annals.org).

RESULTS

Between February 2008 and March 2011, 98 patients inquired about the study. Of the 25 patients who signed informed consent, 24 were eligible for the trial and were randomly assigned. Of these, 23 were treated and 20 completed both treatment periods (**Figure 1**).

Table 1 shows the demographic characteristics of participants. There were 18 men and 5 women with a mean age of 67.6 years. Idiopathic pulmonary fibrosis was diagnosed a mean 20.5 months before enrollment by high-resolution chest computed tomography in all patients and was further confirmed with a video-assisted thoracoscopic lung biopsy in 21.7%. The mean pulmonary function tests revealed no obstruction, moderate restriction, and a moderate gas transfer defect.

At the beginning of the trial, 65% of participants reported receiving previous IPF-specific treatments and 35% had received previous prescription cough medicines; all of the prescription cough medications were discontinued at least 2 weeks before the trial, and no therapy with new prescription cough medications was started during the trial. The most commonly reported treatments by participants specifically for IPF were *N*-acetylcysteine (52%) and oxygen (22%) and benzonatate or narcotics (22%) for their IPF-associated cough (**Table 1**).

Despite these medications, all participants believed that their cough adversely affected their lives. Although 52% of participants reported having GERD (all received proton-pump inhibitor treatment before and during the trial) and 34% had chronic sinusitis, none identified these conditions as causing their cough. In addition, 30% received ACE inhibitors or ARBs before and during the trial. No new ACE inhibitor or ARB therapies were started during the trial.

Primary Outcome

The primary end point, suppression of cough as measured by the CQLQ, was significantly lower during treatment with thalidomide than with placebo. **Figure 2** shows the CQLQ values after 12 weeks of thalidomide therapy and after 12 weeks of placebo. To determine whether there were differences in response based on order of treatment, separate graphs are shown for participants assigned to thalidomide first and those assigned to placebo first. In the mixed-effect linear regression model, the CQLQ score was 11.4 points lower with thalidomide than with placebo (95% CI, −15.7 to −7.0) (**Table 2**). **Appendix Tables 1** to 7 (available at www.annals.org) show the complete results of the mixed-effects models. Thalidomide use resulted in a statistically significant improvement in CQLQ scores in each of the sensitivity analyses conducted to explore the effect of missing data. The results are included in **Appendix Tables 8** to **9** (available at www.annals.org).

Secondary Outcomes

Cough severity as measured by a visual analogue scale also improved significantly with thalidomide treatment compared with placebo (−31.2 points [CI, −45.2 to 17.2]; $P < 0.001$) (**Figure 3**, *top*, and **Table 2**). Respiratory health–related quality of life as measured by the SGRQ improved with thalidomide treatment. The total SGRQ score and symptoms and impact domains all improved significantly with thalidomide but not with placebo (**Figure 3**, *bottom*, and **Table 2**). The activity domain of the SGRQ did not change significantly with thalidomide.

Adverse Events

Significantly more participants receiving thalidomide than placebo reported adverse events (77% vs. 22%; $P = 0.001$) (**Table 3**). The most common event reported in the placebo group was dyspnea (9%), followed by constipation, sleepiness, and viral upper respiratory infection (all 4%). In the thalidomide group, the most common adverse events that the investigators attributed to thalidomide were constipation (36%), dizziness (27%), malaise (14%), anorexia (5%), and asymptomatic bradycardia (5%).

One serious adverse event occurred 2 weeks after starting the trial in the placebo group. The participant was hospitalized for influenza and was withdrawn from the trial because of progressive illness and inability to continue to attend study visits. Overall, 3 participants required a decrease in the dose of the study drug while receiving thalidomide, 2 for constipation and 1 for bradycardia. Three

participants discontinued the study drug: 1 participant assigned to placebo in the first half of the trial withdrew while receiving placebo because of progressive illness and inability to travel for study visits, and 2 participants assigned to receive thalidomide in the second half of the trial withdrew from the study while receiving thalidomide because of progression of their IPF and inability to return for study visits.

DISCUSSION

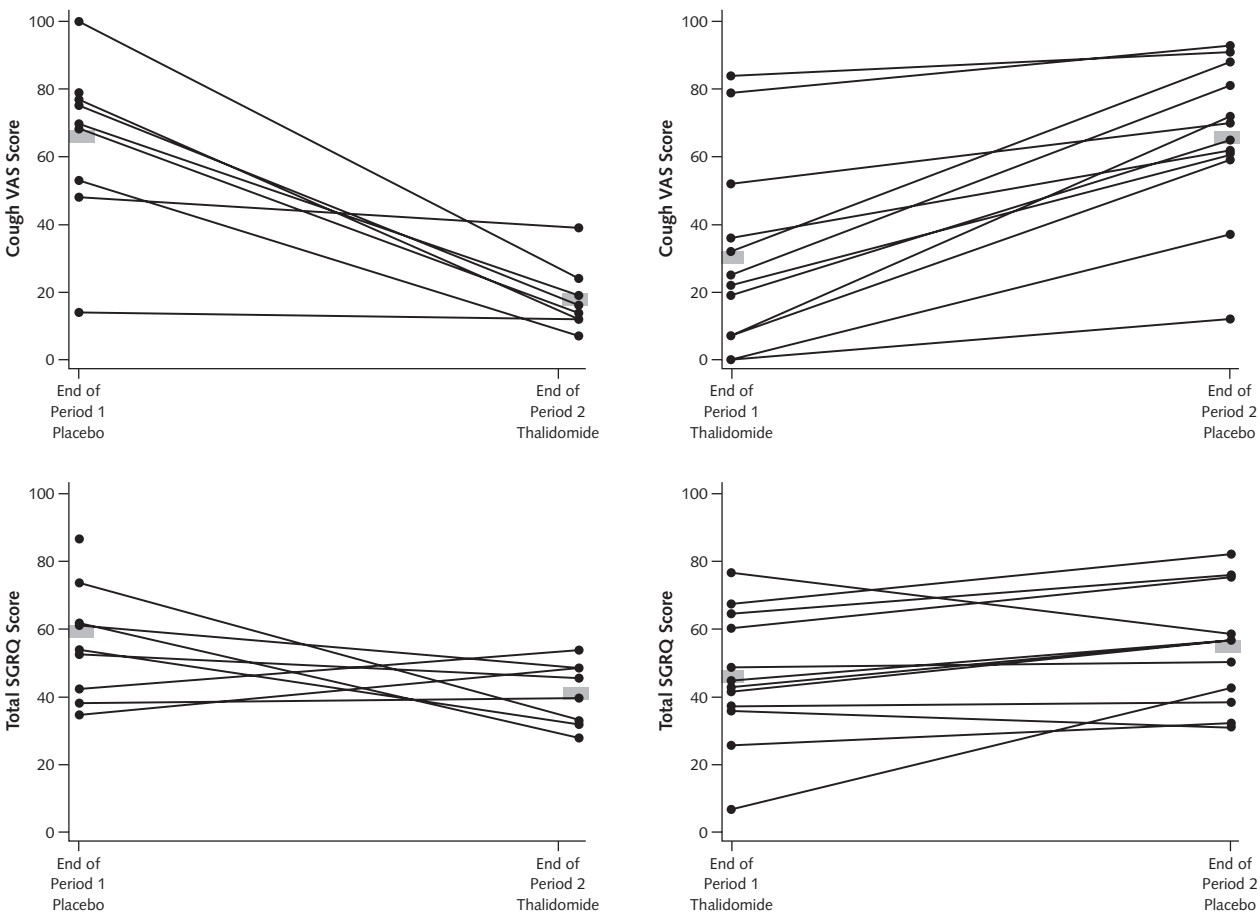
In this study, we demonstrate that low-dose thalidomide not only significantly improves cough in patients with IPF, as evidenced by the improvement in the CQLQ and visual analogue scale scores, but also improves overall respiratory quality of life. The magnitude of these changes seems to be clinically significant and notable to patients. Thus, to our knowledge, this trial represents the first randomized, placebo-controlled trial to demonstrate an effective pharmacologic treatment of cough in IPF.

Thalidomide has potent immunomodulatory, anti-inflammatory, and antiangiogenic properties that have been exploited in recent years as a novel therapy for various types of cancer (13–15). It may also affect nerve function, as idiosyncratic peripheral neuropathies often limit its use (25). Given data about a possible upregulation of sensory cough fibers in IPF, the effectiveness of thalidomide as an antitussive may be caused by its effects on airway nerves (4). Of note, no participants experienced peripheral neuropathy during this short trial despite significant cough relief.

An alternative mechanism of action might relate to the anti-inflammatory properties of thalidomide. Thalidomide may have beneficial immunomodulatory effects by directly affecting inflammation leading to fibrosis. In this regard, the potential use of thalidomide as a treatment of IPF awaits the initiation of large-scale prospective clinical trials.

Cough in IPF is very common and often disabling. Patients with IPF often have additional comorbid illnesses,

Figure 3. **Cough VAS and respiratory-specific quality-of-life scores after thalidomide and placebo treatments.**



Cough VAS and SGRQ scores for each participant after 12 wk of thalidomide or placebo treatments. Shaded areas represent mean values. SGRQ = St. George's Respiratory Questionnaire; VAS = visual analogue scale. **Left.** Participants who received thalidomide in the first period. **Right.** Participants who received placebo in the first period.

Table 3. **Adverse Events Reported by Participants***

Variable	Placebo (*n* = 23)	Thalidomide (*n* = 22)
Participants with ≥1 adverse event	5 (22)	17 (77)
Participants with a serious adverse event	1 (4)	0 (0)
Adverse events requiring dose reduction		
Constipation	0	2
Bradycardia	0	1
Adverse events requiring drug discontinuation		
Progressive illness or inability to travel for visits	1	2
GI adverse events		
Constipation	1 (4)	8 (36)
Change in taste	0 (0)	2 (9)
Dry mouth	0 (0)	2 (9)
General adverse events		
Dizziness	0 (0)	6 (27)
Malaise	0 (0)	3 (14)
Edema	0 (0)	2 (9)
Rash	0 (0)	2 (9)
Respiratory adverse event: worsening dyspnea	2 (9)	2 (9)
Infectious adverse event: viral URI	1 (4)	5 (23)
Cardiac adverse event: bradycardia	0 (0)	1 (5)

GI = gastrointestinal; URI = upper respiratory tract infection.
* Values are reported as numbers (percentages).

and their cough may be due to concomitant disease or medication use. Recent studies have found no correlation with cough in IPF and the presence or treatment of GERD or sinus disease (6, 11, 26). In our study, all participants had self-reported cough that adversely affected quality of life, and 70% reported GERD, 22% sinus disease, and 30% use of ACE inhibitors or ARBs for hypertension.

Of the patients with GERD and sinus disease, 75% received treatment for GERD and 100% received treatment for sinus disease before and during the trial. Because they self-reported cough that adversely affected quality of life despite current therapies, their cough was probably due to IPF. Therapy with ACE inhibitors or ARBs is a well-known cause of cough. While participating in the trial, no participants discontinued or started ACE inhibitor or ARB therapy. Therefore, we do not believe that the improvement in cough in this study was due to treatment of other comorbid conditions.

No approved therapy for IPF in the United States and no reports of pharmacologic agents that reverse fibrosis or improve lung function exist, according to a MEDLINE search up to and including March 2012. There is also a paucity of pharmacologic trials of IPF showing significant improvement in health-related quality of life (27–29).

Two recent studies evaluating the effect of interferon-α or pirfenidone on the progression of IPF but not specifically IPF-related cough report subgroup analysis suggesting that these drugs may improve cough in some patients with IPF (30, 31). An open-label, noncontrolled trial of low-dose oral interferon-α in 20 patients with IPF demonstrated improvement in chronic cough in 5 participants (31). In addition, subgroup reanalysis of participants in a pirfenidone trial noted a decreased reporting of cough in participants receiving high-dose active drug but not in an analysis of the full set of participants (30). However, neither trial was designed to evaluate the effect of the drug on IPF-associated cough.

Because there is no cure for IPF, more focus is being placed on improving health-related quality. Our study used the CQLQ and the SGRQ to evaluate cough-specific and respiratory quality of life in patients with IPF (18). When we selected these measures at the start of the trial in 2007, no IPF-specific tools for health-related quality of life or cough existed; however, the IPF-specific SGRQ and the Leicester Cough Questionnaire measuring respiratory-specific quality of life and cough in IPF have subsequently been developed (32, 33).

The CQLQ is a sensitive tool to measure the effect of interventions on cough-specific quality of life, with lower scores indicating less effect of cough on quality of life (18). Although the CQLQ is a sensitive tool to measure the effect of interventions on cough-specific quality of life, the MCID for the CQLQ in IPF is unknown. The MCID for the Leicester Cough Questionnaire, which has been shown to be similar to the CQLQ in cough measurement, is 1.3 (34, 35). Thus, the decrease in the CQLQ score of more than 10 points during thalidomide treatment suggests that this change is probably clinically meaningful.

The SGRQ is similarly often used in IPF studies and has been shown to be both sensitive and specific for noting changes in quality of life, with an estimated MCID for IPF of 5 to 8 units. Thus, our findings of changes of more than 10 units on all but one of the SGRQ scores would suggest that these are clinically significant (22, 36). Future studies may benefit from the use of the validated IPF-specific SGRQ and the Leicester Cough Questionnaire.

We found a higher incidence of adverse events in participants receiving thalidomide, although these were generally mild. Of interest, dyspnea and constipation were also the main adverse events in participants receiving placebo, and the only serious adverse event requiring discontinuation of the drug occurred in the placebo group. The most frequent adverse event in the treatment group was constipation, a known adverse effect of thalidomide. This condition was easily treatable but did require dose reduction in 2 participants.

The only other adverse event that required dose reduction in the thalidomide group was bradycardia. Thalidomide is known to cause bradycardia, and this condition was incidentally found and was not associated with hypotension or other symptoms (37). Although thromboembolism and peripheral neuropathy are well-recognized adverse effects of thalidomide, none of the participants experienced new neuropathy or thromboembolism during the trial. Long-term use of this medication would necessitate close monitoring for these potential adverse events.

After finishing both treatment periods and completing their participation in the trial, all of the participants were offered thalidomide and all participants accepted it,

despite any adverse events that they might have experienced. Of note, several new analogues of thalidomide with fewer adverse effects are now available. Whether these analogues will be as effective in treating IPF-related cough is uncertain.

Although we found large treatment effects with thalidomide, this study has several potential limitations. First, the study size was small, 17 participants referred themselves after learning of the study online, and the study was conducted at a single site; thus, participants may not be representative of patients elsewhere. Twenty-two participants completed 12 weeks of the placebo regimen, and 20 participants completed 12 weeks of thalidomide treatment. Greater loss to follow-up in the thalidomide group could lead to bias. In an attempt to address this concern, we performed several sensitivity analyses, including replacing the missing items with the highest CQLQ scores obtained. Thalidomide treatment resulted in significant decreases in CQLQ score in every analysis. In addition, our study was of relatively short duration, only 3 months in each group of the study, which may not allow for full appreciation of drug-associated adverse events or assessment of the durability of cough suppression beyond 3 months. Longer-term assessments of the durability and safety of thalidomide in IPF are needed.

The mean FVC was relatively high (70.4% predicted [SD, 13.7]) but similar to that in other trials (38, 39). This may reflect relatively mild disease and thus may limit our results to patients with mild to moderate IPF and cough. Analysis of our dropout group (**Table 4**) revealed similar FVCs but significantly lower DLCO and a higher CQLQ score at baseline in those who dropped out. Thus, sicker patients may have withdrawn early because of progressive illness.

Both the investigators and the participants were blinded to the identity of the study drug in each group through the entire 3 years of the study; however, thalidomide has many characteristic effects, notably constipation and sedation. This may have alerted the patients to the identity of the drug and influenced their responses. We did not formally assess whether the patients knew whether they were receiving the active drug.

Table 4. **Comparison of Participants Who Withdrew From the Study Versus Those Who Completed the Study**

Variable	Participants Who Withdrew From the Study	Participants Who Completed the Study	*P* Value
Mean age, *y*	68.25	63.00	0.28
Mean time from diagnosis, *mo*	16.50	23.85	0.49
Mean FVC, *% predicted*	61.1	71.8	0.21
Mean TLC, *% predicted*	58.9	64.3	0.46
Mean DLCO, *% predicted*	40.10	60.04	0.022
Mean CQLQ score, week 0	75.33	58.25	0.018
Men, %	75	100	0.33

CQLQ = Cough Quality of Life Questionnaire; TLC = total lung capacity.

We did not use a general health-related quality-of-life measure in this study, and some of the adverse effects of thalidomide may have had a negative effect on overall quality of life. However, as noted, all participants, despite any adverse effects, requested thalidomide at the end of the study.

To our knowledge, this study represents the first clinical trial to demonstrate an effective treatment of cough in IPF with subsequent improvement in cough and respiratory-specific quality of life. We believe that our results warrant the initiation of a large-scale, multiinstitutional prospective trial evaluating the efficacy and safety of thalidomide in the suppression of IPF-associated cough with subsequent improvement in respiratory-related quality of life.

From Johns Hopkins University School of Medicine and Mercy Medical Center, Baltimore, Maryland.

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Appendix Table 1. Mixed-Effects Model for CQLQ*

Covariate	Mean Difference (95% CI)	*P* Value
Study drug (thalidomide minus placebo)	−11.37 (−15.7 to −7.0)	<0.001
Period (period 1 minus period 2)	−3.95 (−8.3 to 0.4)	0.076
Treatment order (placebo first minus thalidomide first)	−1.31 (−11.6 to 9.0)	0.80

CQLQ = Cough Quality of Life Questionnaire.
* Model also contained a term for participant nested within treatment order.

Appendix Table 2. Mixed-Effects Linear Regression Model for Cough VAS*

Covariate	Mean Difference (95% CI)	*P* Value
Study drug (thalidomide minus placebo)	−31.22 (−45.2 to −17.2)	<0.001
Period (period 1 minus period 2)	−10.72 (−24.7 to 3.3)	0.133
Treatment order (placebo first minus thalidomide first)	2.95 (−13.7 to 19.6)	0.73

VAS = visual analogue scale.
* Model also contained a term for participant nested within treatment order.

Appendix Table 3. Mixed-Effects Linear Regression Model for Total SGRQ Score*

Covariate	Mean Difference (95% CI)	*P* Value
Study drug (thalidomide minus placebo)	−11.71 (−18.6 to −4.8)	0.001
Period (period 1 minus period 2)	−3.01 (−10.0 to 3.9)	0.39
Treatment order (placebo first minus thalidomide first)	−1.4 (−13.1 to 10.3)	0.80

SGRQ = St. George's Respiratory Questionnaire.
* Model also contained a term for participant nested within treatment order.

Appendix Table 4. Mixed-Effects Linear Regression Model for SGRQ Symptom Domain*

Covariate	Mean Difference (95% CI)	*P* Value
Study drug (thalidomide minus placebo)	−12.13 (−22.2 to −2.0)	0.018
Period (period 1 minus period 2)	−5.87 (−15.9 to 4.2)	0.25
Treatment order (placebo first minus thalidomide first)	2.40 (−10.1 to 14.9)	0.71

SGRQ = St. George's Respiratory Questionnaire.
* Model also contained a term for participant nested within treatment order.

Appendix Table 5. Mixed-Effects Linear Regression Model for SGRQ Activity Domain*

Covariate	Mean Difference (95% CI)	*P* Value
Study drug (thalidomide minus placebo)	−3.30 (−9.8 to 3.2)	0.322
Period (period 1 minus period 2)	0.17 (−6.4 to 6.7)	0.959
Treatment order (placebo first minus thalidomide first)	2.52 (−10.1 to 15.1)	0.695

SGRQ = St. George's Respiratory Questionnaire.
* Model also contained a term for participant nested within treatment order.

Appendix Table 6. Mixed-Effects Linear Regression Model for SGRQ Impact Domain*

Covariate	Mean Difference (95% CI)	*P* Value
Study drug (thalidomide minus placebo)	−13.14 (−19.7 to −6.6)	<0.001
Period (period 1 minus period 2)	−4.67 (−11.2 to 1.9)	0.162
Treatment order (placebo first minus thalidomide first)	−3.94 (−17.5 to 9.6)	0.57

SGRQ = St. George's Respiratory Questionnaire.
* Model also contained a term for participant nested within treatment order.

Appendix Table 7. **Results of Sensitivity Analyses on the Primary Outcome Obtained From a Model Including a Covariate for CQLQ at Week 0**

Covariate	Mean Difference (95% CI)	*P* Value
Study drug (thalidomide minus placebo)	−10.7 (−14.98 to −6.44)	<0.001
Period (period 1 minus period 2)	−3.3 (−7.6 to 0.97)	0.130
Treatment order (placebo first minus thalidomide first)	3.02 (−2.3 to 8.4)	0.27
CQLQ at week 0	0.96 (0.72 to 1.19)	<0.001

CQLQ = Cough Quality of Life Questionnaire.

Appendix Table 8. **Results of Sensitivity Analyses on the Primary Outcome Obtained From Replacing Missing CQLQ Values With Baseline CQLQ Values**

Covariate	Mean Difference (95% CI)	*P* Value
Study drug (thalidomide minus placebo)	−8.5 (−13.02 to −4.03)	<0.001
Period (period 1 minus period 2)	−1.1 (−5.6 to 3.4)	0.63
Treatment order (placebo first minus thalidomide first)	−5.07 (−15.9 to 5.8)	0.36

CQLQ = Cough Quality of Life Questionnaire.

Appendix Table 9. **Results of Sensitivity Analyses on the Primary Outcome Obtained From Replacing Missing CQLQ Values With the Highest CQLQ Value From Period 2**

Covariate	Mean Difference (95% CI)	*P* Value
Study drug (thalidomide minus placebo)	−8.1 (−12.8 to −3.4)	0.001
Period (period 1 minus period 2)	−0.66 (−5.4 to 4.0)	0.79
Treatment order (placebo first minus thalidomide first)	−6.44 (−17.9 to 5.1)	0.27

CQLQ = Cough Quality of Life Questionnaire.