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Clinical Symptoms and Microbiological Outcomes in Tuberculosis Treatment Trials

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Summary

During a recent Food and Drug Administration workshop on clinical trials to evaluate new TB drugs, questions were raised regarding the use of bacteriologic endpoints such as treatment failure and relapse as measures of improvement in health status and long term outcome after treatment. FDA scientists asked how patients' clinical signs and symptoms changed during therapy, noting that while such information is usually collected during clinical trials, it is not often reported. We analyzed data from an internationalphase 3 TB treatment trial that included systematic assessments of symptoms. The percentage of subjects with self-reported symptoms at baseline ranged from 30% for dyspnea to 81% for cough, with 51% reporting fever. During therapy, fever, sweats, and dyspnea decreased most rapidly, with near resolution by the end of therapy. Chest pain and cough resolved more slowly; 13% of subjects reported cough at six months.Symptom resolution during treatment did not differ between those who relapsed and those who did not.Among those with microbiological relapse, symptoms returned with significant increases in the proportion with fever, cough, and chest pain. At the time of relapse, cough was the most frequent symptom, occurring in 75% of subjects who relapsed but only 12% of those who did not. Our data support the continued use of bacteriologic endpoints based on sputum culture assurrogate measures of the relief of symptoms, improvement in health status and favorable long term treatment outcome in TB drug trials.

Keywords

tuberculosis; symptoms; surrogate endpoints

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INTRODUCTION

Tuberculosis (TB) is a global health emergency and new drugs and treatment regimens are urgently needed by patients and TB control programs. TB is transmitted mainly by inhalation of cough-generated aerosols. The main goals of treatment from the public health standpoint are to rapidly eliminate the pathogen from respiratory secretions thereby eradicating the infection, curing the patient, and preventing transmission to other uninfected persons in the community.

From a regulatory perspective, the most important outcomes of the treatment of disease are survival, disability and the capacity for functioning in daily life.[1]These endpoints focus on symptom resolution and patient-reported outcomes. During a recent Food and Drug Administration public workshop on the design of clinical trials for new tuberculosis drugs, FDA scientists and others raised important questions regarding the use of surrogate endpoints in TB treatment trials. Specifically they asked the research community for data that captures the relationship between clinical symptoms and trial endpoints.[2] Current phase 3 trials of TB treatment rely heavily on microbiological endpoints. The most common are treatment failure, defined as persistent sputum culture positivity, and relapse, defined as sputum culture positivity after completion of successful anti-TB treatment.[3] While these provide objective measures for assessing treatment efficacy in a reproducible and efficient manner, they are surrogate endpoints. The ultimate goal of TB treatmentfor patientsis to cure the patient of disease: to restore health and prevent death. With supervised treatment of drug-susceptible TB, death is infrequent, limiting its utility as an endpoint in clinical trials. In regard to restoring health, studies have demonstrated improved quality of life measures after successful TB treatment[4, 5], but no contemporary studies have evaluated resolution of symptoms.

Recent TB treatment trials have included assessments of symptoms, weight, and chest radiographs that would allow for correlation with the primary study outcomes. To better characterize the relationship between microbiologically-defined outcomes and clinical symptoms we analyzed data from an international, multicenter phase 3 trial that included systematicserial assessments of symptoms before, during, and after TB treatment.

METHODS

Study Population

Our study sample included 394 patients who participated in a multicenter clinical trial of shortening treatment of drug-susceptible TB conducted in Uganda, Brazil, and the Philippines (ClinicalTrials.gov Identifier NCT00130247) and reported previously.[6]Patients enrolled were ambulatory HIV-uninfected adults aged 18-60 years with smear positive or negative, culture-confirmed, non-cavitary pulmonary TB, and negative sputum cultures at 2 months. Subjects were treated with 2 months of daily isoniazid (H), rifampin (R), ethambutol, and pyrazinamide followed by HR for 2 months. Patients whose sputum cultures were negative at 2 months were randomly assigned to stop treatment after 4 months or complete a full six months of HR. Therapy was directly observed at least 5 days a week. Subjects were evaluated monthly during treatment, then every 3 months for the first year post-treatment and every 6 months for the second year post-treatment for a total of 30 months. Subjects gave informed consent prior to participation. The protocol was approved by institutional review boards at each site.

Surrogate Endpoints

In the clinical trial, treatment failure was defined as a continued positive sputum culture after 4 months of TB treatment. There were no treatment failures. The primary surrogate

endpoint of the original trial was bacteriological or clinical relapse at 30 months. Relapse was defined as recurrent disease with a positive sputum culture after completing treatment.Relapse with the initial *M. tuberculosis* isolate was confirmed by IS6110 DNA fingerprinting of the patient's initial *M. tuberculosis* isolate and isolates obtained at the time of recurrence. The primary study was terminated early due to an increased incidence of relapse in the 4-month arm.[6]

Assessment and Analysis of Symptoms

At each follow-up visit data was collected including vital signs, weight, physical examination, sputum culture, and self-reported symptoms. These symptoms were reported as present or absent and included fever, sweats, cough, chest pain, sputum production, hemoptysis, and dyspnea on exertion among others. Disease severity was compared with symptoms by analysis of baseline symptom proportions by pre-treatment sputum AFB smear grade[7] and extent of disease on chest radiograph[8] using the Cochran-Armitage test for trend. Proportions of subjects with fever, cough, chest pain, sweats, and dyspnea were calculated at baseline, 2 months, 4 months, and 6 months. McNemar'sTest for Matched Pairs was used to compare the change in symptoms between baseline and six months. Change in body mass index (BMI) from baseline to six months was compared using a paired t-test.

To compare symptoms between patients who relapsed and those who did not, we used data from the patient's visit at the time of relapse and the cured patient's follow-up visit that was closest to the average time of relapse [352 days (SD 142) from the start of treatment]. A two-sided Fisher's exact test was used to compare symptom proportions between those who relapsed and those who did not relapse.

Time to resolution of symptoms was estimated using Kaplan-Meier curves. A combination of symptoms including fever, cough, sweats, chest pain, and dyspnea was used to assess time to complete resolution of all symptoms among those subjects with at least one symptom at baseline. Time to resolution of fever and cough also were calculated for subjects who reported each symptom at baseline.Patients without resolution of symptoms were censored at their 6 month follow-up visit.

RESULTS

This study included all 394 subjects enrolled in the original trial. The mean age was 31 years, 61% were male, and the mean BMI was 20.5 kg/m^2. Eighteen subjects developed recurrent TB during follow-up. Based on IS6110 DNA fingerprint patterns, 16 of 18 (4.1% of all subjects enrolled) relapsed with their initial isolate. Two patients had recurrence due to exogenous infection and were excluded from therelapse analysis.

At baseline 55% of subjects had moderate to far-advanced disease on chest radiograph.[8]Thirty-four percent had a negative AFB smear, 25%had grade 1-2+, and 41% had grade 3-4+. Increasing extent of disease on chest radiograph and increasing AFB smear grade showed a significant positive trend with the prevalence of fever, cough, and sweats at baseline (Cochran-Armitage, $p< 0.005$). Chest pain also showed a positive trend with increasing AFB smear grade (Cochran-Armitage, $p < 0.05$).

The prevalence of symptoms declined rapidly during treatment. The proportion of subjects with symptoms including fever, cough, chest pain, sweats or dyspnea decreased sharply by month 2 of therapy, and continued to decline through its completion (Table 1). Matched comparison by subject between baseline and 6 months reflected a significant decline in all five symptoms (McNemar's test, $p<0.001$) and showed that few subjects with symptoms absent at baseline reported symptoms at 6 months (Table 2). Notably, cough persisted after

therapy in 13% of subjects who reported this symptom at baseline. BMI significantly increased between baseline and 6 months from 20.5 to 21.5 kg/m^2 (paired t-test, $p < 0.001$).

Ninety-one percent(357) of subjects had at least one symptom at baseline (including fever, cough, chest pain, sweats, or dyspnea). The median time to complete resolution of all symptoms was 117 days (Figure: a). Twenty-one percent (75) had at least 1 symptom during the entire 6 months. There was no significant difference in time to resolution of symptoms when stratified by being underweight (BMI < 18.5 kg/m^2) at baseline or by relapse status. Separate analysis of time to resolution of cough and fever revealed that cough cleared more slowly (median time to resolution 79 vs 64 days, Figure: b,c).

Symptoms among the 16 subjects that relapsed were compared with symptoms in subjects that did not relapse. At 6 months 2 subjects (13%) of the 16 that relapsed still had at least one symptom compared with 11.8% among subjects that did not relapse. At the time of relapse, subjects that relapsed were significantly more likely to have fever (31% vs 5.1%, Fisher's exact, p<0.002), cough (75% vs 12%, Fisher's exact, p<0.001), and chest pain (25% vs 7.6%, Fisher's exact, p=0.036) when compared with subjects who did not relapse. The prevalence of sweats or dyspnea was less than 2% at the time of relapse and did not differ between the two groups.

Discussion

In a detailed analysis of data from an international, multicenter phase 3 trial, we found that subjects who successfully completed TB treatment had a rapid decrease in symptoms during therapy. After the first 2 months of treatment the proportion of subjects with symptoms declined by 94% for fever, 59% for cough, 77% for chest pain, 94% for sweats, and 81% for dyspnea. Fever, sweats, and dyspnea decreased most rapidly, with near resolution by the completion of therapy. Chest pain and cough resolved more slowly, and 13% of subjects reported cough even at the end of therapy. While cough was the most frequent symptom prior to beginning therapy, it was also the most common symptom after therapy, which may reflect its limited specificity. In an earlier study, Boon and colleagues reported that only 7% of randomly screened South Africans who reported cough for 2 or more weeks had active TB.[9] In addition, TB can cause lung damage such as bronchiectasis, leading to persistence of cough even after completion of successful treatment.[10] The percentage of subjects with self-reported symptoms in our study ranged from 30% for dyspnea to 81% for cough. Nearly 20% of subjects did not report a cough and only about 50% reported fever. When a combination of symptoms was analyzed, 91% of subjects had at least one symptom at baseline and the median time to resolution of all symptoms during treatment was 117 days.

Relapse of TB as defined by positive sputum culture after successful treatment was also associated with a significant increase in symptoms. Among those who relapsed, only 2 (13%) had any symptoms at 6 months. Symptoms then returned at the time of relapse with significant increases in the proportion with fever, cough, and chest pain. Cough was the most frequent symptom, occurring in 75% of subjects that relapsed but only 12% of subjects that did not relapse.

Our study has several limitations. The primary study excluded patients with either cavitary pulmonary TB or positive sputum cultures at 2 months. Patients included likely had less severe pulmonary TB than the general population, which is reflected in the lack of subjects with treatment failure and the 4% relapse rate. These selection criteria could have led to an underestimation of the prevalence of symptoms existing in the general population. Still, the patients included in this study represent a significant proportion of patients with pulmonary TB as roughly one-half of patients with TB have non-cavitary disease worldwide and

previous studies showeda similar prevalence of symptoms, including a large study conducted in Hong Kong that found the first symptom of TB was cough in 81% of participants.[11]Strengths of our study include the use of standardized forms for serial collection of data about symptoms during treatment,supervised anti-TB treatment, standardized serial bacteriologic assessment of patients using sensitive liquid as well as solid culture media, and inclusion of patients from South America, subSaharan Africa and Asia.

The surrogate markers for successful treatment of TB and relapse as defined by sputum culture status were closely associated with self-reported symptoms in subjects treated forpulmonary TB. Our study found that microbiologically defined success and failure mirrored the resolution and reappearance of symptoms. In Fleming and DeMets's commentary on surrogate endpoints they argue that the ideal surrogate is "in the only causal pathway of the disease process, and the intervention's entire effect on the true clinical outcome is mediated through its effect on the surrogate."[12] In many ways, the microbiological endpoints of sputum culture conversion used in TB trials meet these criteria. Replication of *M. tuberculosis*in the lungs is the only causal process of active pulmonary disease, and treatment and cure of TB is mediated through the clearance of *M. tuberculosis* infection demonstrated by culture conversion to negative.While larger studies would be required for validation, our data support the continued use of bacteriologic endpoints based on sputum culture as surrogate markers of long term cure and relief of symptoms in trials of new TB drugs and regimens.

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Ethical Approval

The protocol for the original trial was approved by institutional review boards at each site. Subjects gave informed consent prior to participation.

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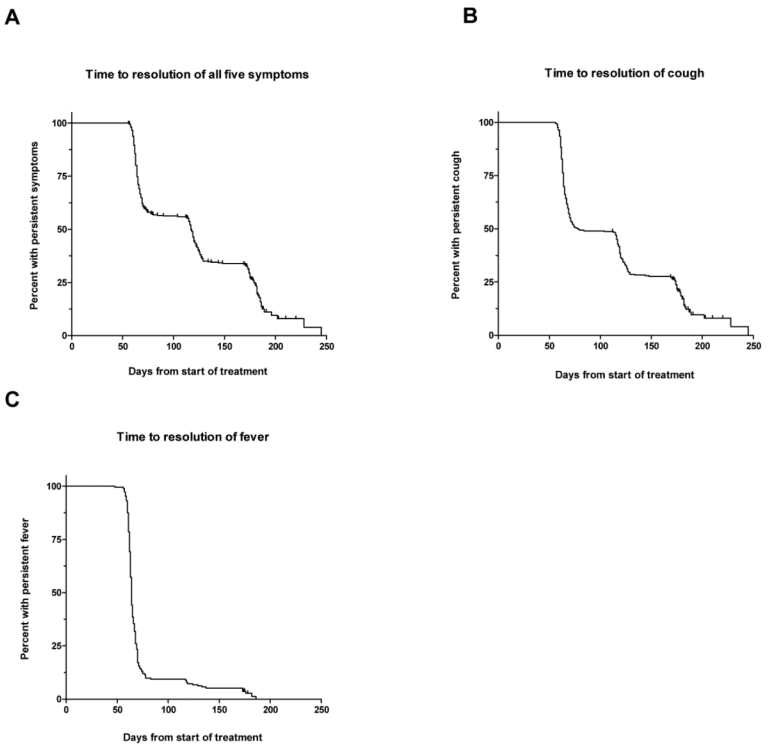

Figure.

Kaplan Meier curve showing the cumulative percentage of subjects with persistent symptoms during TB treatment; A. Time to resolution of a combination of symptoms including fever, cough, chest pain, sweats and dyspnea among 357 subjects with at least one symptom at baseline; B. Time to resolution of cough among 308 subjects with cough at baseline; C. Time to resolution of fever among 192 subjects with fever at baseline.

Table 1

Proportion of patients with symptoms at baseline and eachfollow-up visit during treatment.

	Time from start of therapy			
	Baseline % (n)	**Month 2 % (n)**	**Month 4 % (n)**	**Month 6 % (n)**
Fever	51 (199)	3.1 (12)	2 (8)	1.1 (4)
Cough	81 (317)	33 (131)	18 (72)	13 (50)
Chest Pain	57 (224)	13 (52)	8.4 (33)	6.8 (26)
Sweats	45 (176)	2.5 (10)	1 (4)	0.8 (3)
Dyspnea	30 (119)	5.8 (23)	3.6 (14)	2.6 (10)

Table 2

Comparison of the presence or absence of symptoms between baseline and 6 months by subject, using McNemar's Test.

Symptom	Present at baseline, absent at 6 months % (n)	Present at baseline, present at 6 months % (n)	Absent at baseline, absent at 6 months % (n)	Absent at baseline, present at 6 months % (n)	p value
Fever	51% (193)	1.1% (4)	48% (184)	0% (0)	p<0.001
Cough	69% (262)	13% (48)	18% (70)	0.5% (2)	p<0.001
Chest Pain	51% (193)	6.5% (25)	43% (163)	0.3% (1)	p<0.001
Sweats	44% (169)	0.5% (2)	56% (209)	0.3% (1)	p<0.001
Dyspnea	28% (105)	2.4% (9)	70% (267)	0.3% (1)	p<0.001