

ORIGINAL ARTICLE

Monitoring treatment response in sputum smear positive pulmonary tuberculosis patients: comparison of weight gain, sputum conversion and chest radiograph

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Abstract

Background: Monitoring treatment response to anti-tuberculous therapy remains unsatisfactory in resource-limited countries where sophisticated and expensive tests are not readily available. Sputum culture for mycobacterium is desirable, but not obtainable in many developing countries. Sputum acid-fast bacilli (AFB) smear alone can be misinterpreted in the presence of unviable bacilli or non-tuberculous mycobacteria. Hence the search for a cheaper but reliable monitoring tool, or a combination of several tools, continues. Interesting reports from studies in third world nations have considered weight gain/loss as one such monitoring tool. Since pulmonary tuberculosis is endemic in this country, we take the opportunity to evaluate weight gain and chest radiograph, compared to sputum AFB smear in monitoring patient's response. **Methods:** This was a retrospective study of confirmed positive sputum AFB smear patients from January 1999 to December 2004 who attended the Chest Clinic at Hospital Tengku Ampuan Afzan, Kuantan, Malaysia. Data on weight, chest radiograph and sputum AFB smear from initiation of therapy to end of treatment and follow-up were collected and analyzed. **Results:** 201 patients were included. At week-4 of anti-tuberculous treatment, only 14.7% had positive sputum smear. At completion of therapy 93.1% had improved chest radiographs. 90% had weight gain, 5% had weight loss and the remaining had no change in weight. Amongst patients with weight loss, there were no significant differences in the underlying illnesses ($p=0.376$), sputum smear at 4 weeks ($p=0.697$) and chest X-ray changes ($p=0.731$). Three patients who initially showed sputum smear conversion had reappearance of positive smear results towards the end of treatment. One of them was diagnosed as treatment failure while the other two remained well after discontinuation of therapy. **Conclusion:** Weight gain is very common among smear-positive tuberculosis patients after treatment even though weight gain does not correlate well with underlying disease, sputum conversion and chest X-ray changes. Reappearance of smear-positive sputum must be interpreted with caution and not to be regarded as treatment failure without other evidence.

Keywords: Pulmonary tuberculosis, weight gain, positive sputum smear.

INTRODUCTION

Pulmonary tuberculosis (PTB) continues to be a significant public health problem in developing countries especially with the emergence of HIV infection and increased immigration from countries with high prevalence. The treatment regime has been well established but monitoring of the treatment response is still unsatisfactory. Sputum direct smear for acid-fast bacilli (AFB) is commonly used. The definition of treatment failure i.e. persistence of positive direct smear for 5 months is widely accepted despite knowing that

smear microscopy does not distinguish between dead and live AFB.^{1,2} Sputum culture is superior to direct smear AFB since it is more specific but it is time consuming and expensive.

Weight loss is a common symptom in pulmonary tuberculosis and one of the signs of response to treatment is weight gain. However, Kennedy *et al*³ found that weight gain during therapy is not a reliable indicator of overall treatment response. On the other hand, radiographic resolution as a marker of treatment response is thought to be inadequate as well because it lags significantly

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behind clinical improvement. Assessment of symptomatic response can be difficult due to concurrent illness. Weight gain, symptomatic response and radiographic resolution when used in combination would have been more sensitive than sputum direct smear alone in monitoring treatment response.

The objectives of this study are to determine the sensitivities of weight gain, chest radiograph either alone or in combination in assessing the treatment response of patients with sputum smear positive pulmonary tuberculosis as compared to sputum AFB direct smear. The outcome of patients with persistent positive sputum direct smear despite adequate treatment is also determined.

MATERIALS AND METHODS

This is a retrospective study which was carried out in the Chest Clinic of Hospital Tengku Ampuan Afzan (HTAA) Kuantan, Malaysia from February 2004 to February 2006. Patients who were diagnosed with pulmonary tuberculosis clinically and had positive sputum direct smear for AFB treated in the Chest Clinic, HTAA from January 1999 to December 2004 were included in the study. The hospital is an 800-bedded tertiary referral centre for medical and surgical disciplines. On average, the Chest Clinic reviews 30 patients with tuberculosis in a week. The local guideline on tuberculosis (TB) management⁴ during the time of the study recommended that the standard intensive phase treatment regime for patients with TB is to include a daily combination of four first-line anti-tuberculous drugs [e.g. streptomycin (S), ethambutol (E), isoniazid (H), pyrazinamide (Z), rifampicin R] for 2 months (or 8 weeks), to be followed by a maintenance phase treatment regime consisting of R and H taken twice weekly (R2H2) for 4 months (or 16 weeks). The authors are aware that in the new guideline on TB management published in 2012,⁵ R and H are recommended to be taken daily (4HR), instead of twice weekly, during the maintenance phase which may influence adherence and hence, treatment outcomes. For the contextual purposes of this study, the previous guideline⁴ was referred to for definitions of chest radiographic appearances, treatment regimes and outcomes.

Data on clinical presentation, weights during follow up, change of symptoms after treatment, microbiology results, response to treatment and outcome during follow up were obtained from the case records. Patients' chest radiographs at

8 weeks and at completion of anti-tuberculous drugs were reviewed by a radiologist who was blinded to the history and outcome of the patients, and recorded as "improving", "static" or "worsening". Weight gain was defined as gaining at least 1 kg after treatment. Weight loss was defined as losing at least 1 kg after treatment.

Statistical analysis

The data was analyzed using Statistical Package for the Social Sciences (SPSS) version 14 software package. Categorical variables were tested using Chi-square test. Statistical significance was taken at p value of 0.05.

RESULTS

From January 1999 to December 2004, a total of 201 case records of patients who had sputum smear positive pulmonary tuberculosis were reviewed. There were 171 Malays (85%), 20 Chinese (10%), 6 Indians (3%), 2 other Malaysians (1%) and 2 foreigners (1%). The median age was 37 years [interquartile range (IQR): 24 years] and 65% were males. 12% of the patients had previous tuberculosis. Most of the patients presented with cough (98%; 8.8% had haemoptysis), loss of weight (85%), fever (80%), loss of appetite (80%) and night sweat (67%). History of contact with pulmonary tuberculosis patients were found in only 32%. Only 7 patients had extra-pulmonary involvement (six tuberculous lymphadenitis and one laryngeal tuberculosis). Among those patients, 71 patients had underlying illnesses (49 with diabetes mellitus, 20 with HIV positive and 4 with chronic lung diseases). Chest X-ray was minimal, moderately advanced and far advanced in 24.2%, 61.4% and 14.4% respectively. White blood count was low in 2.6% and high in 35.0% of patients. 78.6% of patients completed treatment but 13.4% of the patients defaulted treatment. Only one patient (0.5%) died and the rest were transferred to other hospitals.

Among 156 patients who completed treatment, 26.2% had minimal disease based on chest X-ray. 60.8% had moderately advanced and the rest had far advanced disease. 64.1% had improvement in chest X-ray at 8 weeks of intensive therapy and static in 29.0% of patients. Only 6.9% of patients were reported by the radiologist to have worsened chest radiograph in which 55.5% of them remained sputum smear positive at 4 weeks (as compared to 9.5% in patients with improved chest X-ray and 21.1% in patients with static chest X-ray, $p=0.025$) but only 11.1% remained

sputum smear positive at 8 weeks and 12 weeks. None of them were smear positive after 12 weeks. There were no significant differences in chest X-ray changes of patients with underlying illnesses ($p=0.327$). At completion of anti-tuberculous drug, 93.1% of patients had improved chest radiographs and for the rest of the patients the chest radiographs remained unchanged.

After 4 weeks of anti-tuberculous drug, only 14.7% of the patients had sputum AFB smear positive further reduced to 7.7%, 3.2% and 1.3% at 8, 12 and 16 weeks respectively. There were two patients who had sputum smear negative at 8 to 16 weeks but sputum smear turned positive again at the 20th week. One of them was started on EHRZ daily for 3 months followed by R2H2 for 2 months. He had recurrence of symptoms, slight weight loss and worsened chest X-ray. He had sputum culture for mycobacterium performed, which was positive indicating treatment failure. Another patient was treated with EHRZ daily for 3 months followed by R2H2 for two months. Her sputum direct smear turned positive but she had no worsening symptoms or deterioration in chest X-ray appearance; her weight increased from 35 kg to 40 kg after treatment; she was continued with maintenance therapy for another two months and anti-tuberculous drug was stopped thereafter. Subsequent sputum direct smear was negative but there was no MTB culture performed. She remained well at 16 months of follow up.

A patient who had sputum AFB smear negative from 8 to 20 weeks but sputum smear turned

positive at the 24th week. At that time, he had no new symptoms; his weight rose from 57 kg to 69 kg and chest X-ray was improving. He was diagnosed to have treatment failure by the attending doctor, who changed the maintenance therapy (R2H2) to SEHRZ daily. After one month, he was reviewed by the consultant chest physician who thought that the patient might have unviable AFB in the expectorated sputum. The treatment was changed to R2H2 for another 2 months and discontinued. *Mycobacterium tuberculosis* (MTB) culture result at 24 weeks which was available later turned out to be negative. He remained well 9 months after stopping the anti-tuberculous drugs. No patient had smear positive after 24 weeks of treatment.

90% of the patients had weight gain after treatment but in 10% of patients, they either experienced weight loss (5%) or their weights remained unchanged (5%). Among those patients with weight loss, three were diabetics; one had HIV infection and two were without underlying illnesses. Among patients with weight loss, there were no significant differences in the underlying illnesses, sputum smear at 4 weeks or chest X-ray changes (Table 1).

DISCUSSION

During the course of treating tuberculosis, a clinician relies on the subjective evidence i.e. the patient's symptoms and objective evidence i.e. the laboratory results and radiographic

TABLE 1: Weight change in patients with underlying illness, sputum smear for AFB at 4 weeks and chest X-ray appearance at 8 weeks.

	Weight loss No. of patients (%)	No change in weight No. of patients (%)	Weight gain No. of patients (%)	p
Underlying illness				
No	3(3%)	5(5.1%)	91(91.9%)	0.376
Yes	4(8.2%)	2(4.1%)	43(87.8%)	
AFB direct smear at 4 weeks				
Positive	2(8.7%)	0(0%)	21(91.3%)	0.697
Negative	5(4.0%)	7(5.6%)	113(90.4%)	
Chest X-ray at 8 weeks				
Improving	4(5.0%)	5(6.2%)	71(88.8%)	0.731
Static	1(2.7%)	1(2.7%)	35(94.6%)	
Worsening	0(0%)	0(0%)	9(100%)	

Weight gain was defined as gaining at least 1 kg after treatment. Weight loss was defined as losing at least 1 kg after treatment. Patients' chest radiographs at 8 weeks and at completion of anti-tuberculous drugs were reviewed by a radiologist who was blinded to the history and outcome of the patients.

appearance to monitor the patient's response.

One of the objective evidence clinicians rely upon is sputum smear and/or culture conversion. Fortun *et al*⁶ reported that sputum smear conversion during therapy occurred later than sputum culture conversion. In this study of 184 patients, the mean times from the initiation of appropriate therapy to sputum culture and smear conversion were 4.8 ± 3.7 and 5.5 ± 4.6 weeks, respectively. Almost 40% and 53% obtained smear and culture conversion respectively at 4 weeks. All patients, with the exception of patients with drug-resistant infection, received isoniazid, rifampicin and pyrazinamide, with or without ethambutol. Factors contributing to the delay in sputum smear conversion to negative were previous administration of anti-tuberculous drugs (therapy or prophylaxis), a high baseline sputum AFB stain, a duration of symptoms longer than 3 months and infection with a resistant strain (isoniazid resistance or multiresistance). A study conducted by Al-Moamary *et al*⁷ demonstrated that 48% of the patients had smear positive for AFB at 4 weeks, 7% at 20 weeks, and 3% at 36 weeks. Of the patients with persistent positive smear at 20 weeks, 77% had negative sputum culture results and 23% had positive sputum culture results. They also found that beyond 12 weeks of therapy approximately two-thirds of the patients with positive smear results had negative culture results. Factors contributing to treatment failures included more localized disease on chest radiographs, minimal radiographic improvement at follow-up, a higher prevalence of drug resistance and less compliance with medications. Only nine of their 23 patients with persistent positive sputum smear but negative sputum culture results received directly observed treatment short-term (DOTS). Our results showed that the majority of the patients (85.3%) had sputum smear conversion to negative at 4 weeks of treatment with daily EHRZ or SHRZ. Positive sputum smear continued to decline to 7.7% at 8 weeks, 3.2% at 12 weeks and 1.3% at 16 weeks. Our smear conversion rate at 4 weeks was much higher than that of the two studies aforementioned probably because we encountered fewer resistant infections in our community and more than 90% of our patients received DOTS, which improved compliance.

Three of our patients who initially showed smear conversion had positive smear results towards the end of treatment i.e. two patients at 20th week and one patient at 24th week. One of them was diagnosed as treatment failure while

the other two remained well after completion of anti-tuberculous therapy. Rafael *et al*⁸ also observed a similar occurrence in a study of 453 patients out of which 2.2% (10 patients) had positive AFB sputum smears at the end of treatment. In most cases (8 of 10 patients), the AFB in sputum smears corresponded to unviable bacilli and less frequently to colonization by non-tuberculous mycobacteria. They found no treatment failure in any of the cases. Due to these misleading positive AFB smears, it is essential to obtain culture sample for confirmation when such cases are encountered. Lee *et al*⁹ also concluded that although most sputum with a positive AFB smear but negative culture could be classified as a laboratory failure, clinicians should consider the possibility of false positive AFB smear. More than five decades ago, Weir *et al*,¹ using optic microscopy, observed bacilli with mycobacterial morphologic features that failed to grow on cultures. Later, Warring *et al*² showed that they were either dead bacilli or bacilli unable to reproduce originating from necrotic tuberculous lesions. These unviable bacilli do not require change or prolongation in therapy.

Non-tuberculous mycobacteria isolated from sputum cultures may or may not be clinically significant. Koh *et al*¹⁰ from South Korea studied 1548 non-tuberculous mycobacteria isolates recovered from 794 patients and reported that only 25% had clinically significant non-tuberculous mycobacteria lung infections. The common organisms were *Mycobacterium avium* complex (48%) and *Mycobacterium abscessus* (33%). There are more than 100 species of non-tuberculous mycobacteria. The organisms that commonly cause disease in humans are *Mycobacterium avium* complex, *Mycobacterium fortuitum* complex, *Mycobacterium kansasii* and *Mycobacterium abscessus*. In diseased lungs, they can be found as colonizers or clinically significant pathogens. In a separate study, Koh *et al*¹¹ identified 34% of 105 patients with bilateral bronchiectasis and bronchiolitis had non-tuberculous pulmonary infection. Fowler *et al*¹² similarly showed that 10% of 98 patients with bronchiectasis had non-tuberculous mycobacteria positive in sputum but only 3% fulfilled the American Thoracic Society diagnostic criteria for infection. Therefore reappearance of positive AFB sputum smears of patients at the end of therapy for pulmonary tuberculosis, who are otherwise asymptomatic, should be reviewed with caution before considering a change in

treatment regimens as the positive smears could be non-tuberculous mycobacteria which may not be the pathogens that cause the disease.

In resource-limited countries, other monitoring tools for treatment response besides sputum smear are being sought. Weight gain has been studied for its role as one of the cheaper monitoring tools. A study in Tanzania³ looked at nutritional status of 200 smear-positive pulmonary tuberculosis patients. They concluded that weight gain during therapy was an unreliable factor of overall treatment response but the patients from that area of Tanzania frequently had evidence of malnutrition before and after completion of treatment. In contrast, Krapp *et al*¹³ assessed 650 patients in two health centres in Peru and observed that a body weight gain of $\leq 5\%$ was associated with unsuccessful outcome (treatment failures and relapses) at the end of treatment but not after one month or completion of initial phase of treatment. Median body weight gain was higher in cured patients ($p=0.007$). We too found that 90% of our patients had weight again after completion of treatment but no significant difference was observed in sputum AFB smear conversion at 4 weeks. In a stratified analysis by Khan and coworkers,¹⁴ the 2-year relapse rates were 4.2%, 11.9%, and 20.3% among those not underweight, those underweight but gaining $> 5\%$ weight at 2 months, and those underweight and not gaining weight respectively. Lack of early weight gain was found to be an independent predictor of relapse in underweight patients with tuberculosis. It would seem to suggest that weight gain has prognostic significance in patients with tuberculosis and should be considered as a surrogate marker to monitor response to TB treatment especially in developing countries where extensive laboratory tests are not feasible.

The main limitation of this study was the absence of sputum culture results which is regarded as the gold standard in the diagnosis of tuberculosis. Sputum culture for the fastidious mycobacteria is time consuming and laborious. In addition, the results are often delayed due to logistics reasons and not uncommonly complicated by laboratory failure. Due to the above reasons, we did not routinely send sputum for culture at diagnosis but only when resistant infections or treatment failures are suspected. However the current guideline⁵ recommends that sputum culture for *Mycobacterium tuberculosis* be routinely performed for all patients at diagnosis. This study was retrospective in design

and data on other nutritional aspects (e.g. diet and supplements) which could influence weight gain were not available for analysis. A prospective study with the potential for multivariate analysis will provide more evidence to consider weight gain as a monitoring tool for treatment response.

In conclusion, weight gain is very common among smear-positive tuberculosis patients after treatment even though weight gain does not correlate well with underlying disease, sputum conversion and chest X-ray changes. Reappearance of smear-positive sputum during treatment must be interpreted with caution and should not be assumed as treatment failure without other compelling evidence.

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