International Journal of Infectious Diseases 23 (2014) 20–24

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Weight variation over time and its relevance among multidrug-resistant tuberculosis patients

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ARTICLE INFO

Article history:
Received 7 October 2013
Received in revised form 28 December 2013
Accepted 3 January 2014

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculosis
Multidrug-resistant tuberculosis
Weight
Treatment outcome

SUMMARY

Objectives: We aimed to assess the variation in patient body weight over time according to the treatment outcome among multidrug-resistant tuberculosis (MDR-TB) cases.
Methods: This was a retrospective cohort study. The data of patients commencing MDR-TB therapy were analyzed. Data were collected from different public TB treatment facilities located in peri-urban areas to the south of Lima, Peru. The outcome was patient body weight (kilograms) from treatment commencement, measured monthly. A random effects model was fitted using robust standard errors to calculate 95% confidence intervals.
Results: Of a total of 1242 TB cases, 243 (19.6%) were MDR-TB. Only 201 cases were included in the analysis; 127 (63.2%) were males and the mean patient age was 33.6 (standard deviation 16.2) years. Weight changes over time among the patients who were cured differed from changes in those who died during therapy ($p < 0.001$). Weight curve divergence was important at the end of the third, fourth, and fifth treatment months: on average, the weight difference was 2.18 kg ($p < 0.001$), 3.27 kg ($p = 0.007$), and 3.58 kg ($p = 0.03$), respectively, when cured patients were compared to those who died.
Conclusions: Our results show that weight variation during treatment can be a useful surrogate for the treatment outcome, specifically death during therapy. MDR-TB patients with weight loss should be followed more closely, as they are at greater risk of death.

1. Introduction

According to the World Health Organization (WHO), multidrug-resistant tuberculosis (MDR-TB) is present in 3.7% of new TB cases and 20% of previously treated TB cases, with an estimated total of 630 000 cases worldwide.[1,2]

The treatment of MDR-TB cases is complex because it requires the use of second-line TB drugs,[3] which are associated with a greater probability of adverse effects,[4,5] longer treatment duration, as well as increasing costs.[6,7] Mortality is also increased among MDR-TB patients. Two recent systematic reviews reported that around 11% of patients on MDR-TB treatment died at the end of follow-up, whereas only 62% had a successful outcome.[8,9]

Body weight variation has been identified as a potential predictor of TB treatment outcome, especially in drug-sensitive TB.[10–13] A previous study reported that patients under DOTS (directly observed treatment, short course) had gained 3.2 kg on average at the end of treatment.[11] A further two studies found a cutoff of 5% weight gain to predict the TB treatment outcome.[12,13] A study reporting a longitudinal analysis established that differences in weight could be found from the first month of therapy.[14] In several countries with standardized schemes of treatment, patients are weighed routinely during follow-up to assess the treatment response. Thus, body weight might be a helpful test to predict the TB treatment outcome; however, to our knowledge, no information regarding this potential association is available for MDR-TB cases.

The objective of this study was to evaluate variation in patient body weight over time according to the treatment outcome among MDR-TB cases. We hypothesized that the weight variation that

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http://dx.doi.org/10.1016/j.ijid.2014.01.001

occurs during follow-up among those who die during treatment differs from the variation that occurs among those who are cured at the end of treatment.

2. Methods

2.1. Study design, setting, and participants

A retrospective cohort study was carried out using the data of patients commencing therapy for MDR-TB from January 2000 to December 2012. Data were collected from different public TB treatment facilities located in peri-urban areas to the south of Lima (DISA II – Lima Sur). The medical records were obtained from the National Health Strategy for Prevention and Control of Tuberculosis (ESN-PCT) and were reviewed for sociodemographic data, TB treatment history, treatment scheme, weight measures, and outcomes.

Patients included in the analysis were at least 18 years old and had been diagnosed with pulmonary MDR-TB, confirmed by a positive culture and appropriate drug susceptibility testing.[15] Those abandoning therapy or failing during follow-up were excluded from the statistical analysis. We decided to exclude data for treatment failure patients because of the small number of cases ($n = 7$) and hence a lack of appropriate power to detect differences. See Figure 1 for detailed information regarding participation.

2.2. Outcomes and variables of interest

The main outcome of the study was patient body weight, recorded in kilograms (kg), from treatment commencement, and measured monthly. The ESN-PCT staff usually assess patients at the end of every month of treatment and the data available were used for this analysis. The main exposure was overall mortality, defined as those patients who died during the first 6 months of MDR-TB treatment. We specifically used data from the first months of therapy because deaths could be directly attributable to TB.[16]

Other variables of interest included in the analysis were: age (categorized in tertiles), sex (male or female), education level (primary school, incomplete secondary school, or complete secondary school or higher), number of previous TB episodes (none, one, or two or more), baseline body mass index (BMI; categorized as underweight (<18.5 kg/m^2), normal (≥ 18.5 and <25 kg/m^2), or overweight/obese (≥ 25 kg/m^2) based on the World Health Organization definition[17]), HIV infection status (positive or negative), sputum result at baseline (positive or negative), treatment scheme (individualized or standardized), and enrollment year (before 2005, from 2005 to 2009, or from 2010 onwards).

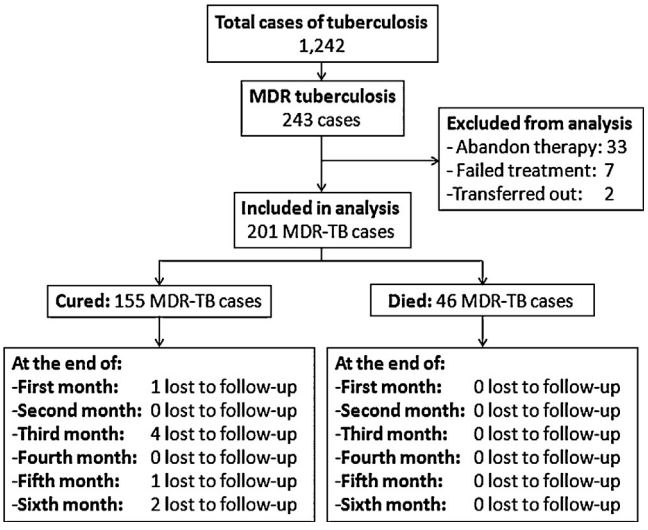

Figure 1. Flowchart of enrollment and inclusion of patients in the study.

2.3. Procedures

All MDR-TB patients were treated by the ESN-PCT using individualized or standardized treatment schemes. The ESN-PCT uses monthly food packages as an incentive for adherence, and these are given to all patients. Before receiving treatment, MDR-TB cases are assessed by an expert committee based on clinical records, previous TB treatment history, sputum cultures, TB drug susceptibility testing, HIV infection status, and pulmonary X-rays. The usual management of MDR-TB cases includes programmatic monitoring with monthly sputum cultures and weight measures. Weight data are usually recorded using clinic scales with established programmatic training for their use.[15] The accuracy of the scales used was not systematically confirmed, but repeat measurements made for each patient were done using the same scales, and weights were generally recorded to the nearest 0.1 kg.

2.4. Data management and statistical analysis

Data were entered into a database using Microsoft Excel by double data entry and were then transferred to Stata 11.0 for Windows (StataCorp, College Station, TX, USA) for the statistical analysis. Initially, a brief description of the demographic and clinical characteristics according to the outcome was tabulated and compared using the Chi-square test or Fisher's exact test, as appropriate. Next, the weight average was calculated for each outcome group according to our exposure of interest and the month of follow-up. Although total follow-up data were available, information for the first 6 months was used in the analysis because of the small number of deaths reported after that time. Finally, a longitudinal analysis was carried out to assess weight variation over time. A random effects regression model was fitted to assess average body weight changes of the patients according to outcome results.[18] Random effects models are needed when the observations (i.e. patient weights in this analysis) are not obtained by simple random sampling, but come from a cluster or multilevel sampling design (i.e., a patient being followed-up during treatment). Thus, this type of design induces additional sources of variation that need to be taken into account by the model. The crude model was specified as follows: $Y_{ij} = \beta_0 + \beta_1.\text{Outcome} + \beta_2.T_{ij} + \beta_3.T_{ij}.\text{Outcome}$, where Y_{ij} is the mean weight (kg) of patient '*i*' at time '*j*', β_0 is the intercept, i.e. weight in kilograms among those cured at baseline, β_1 is the difference in weight at baseline in patients who died compared to those who were cured, β_2 quantifies the change in weight between baseline and one selected month for patients who were cured, and the sum of β_2 and β_3 (interaction term) represents the change in weight between baseline and one selected month for participants who died.[18] In this model, the time variable was included as a categorical variable, because weight over time did not show linearity in patients who died during follow-up.

Additionally, the model was controlled for potential confounders including age, sex, education level, number of previous TB episodes, baseline BMI, HIV infection status, treatment scheme, and enrollment year. The Wald test was used to report *p*-values, especially for the interaction term, whilst robust standard errors, in the case of misspecification of the variance correlation structure, were used to calculate 95% confidence intervals for coefficients in the model.

2.5. Ethics

Institutional review board approval for this project was granted by the Universidad Peruana de Ciencias Aplicadas (UPC), Lima,