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Effectiveness of a novel cellular therapy to treat multidrug-resistant tuberculosis

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ABSTRACT

Introduction: We urgently need novel treatments for multidrug-resistant tuberculosis (MDR-TB). Autologous mesenchymal stromal cell (MSC) infusion is one such possibility due to its potential to repair damaged lung tissue and boost immune responses. We aimed to assess the effectiveness of MSC to improve outcomes among MDR-TB patients.

Methods: We analyzed outcomes for 108 Belarussian MDR-TB patients receiving chemotherapy. Thirty-six patients ("cases") also had MSCs extracted, cultured and re-infused (average time from chemotherapy start to infusion was 49 days); another 36 patients were "study controls". We identified another control group: 36 patients from the Belarussian surveillance database ("surveillance controls") 1:1 matched to cases.

Results: Of the cases, 81% had successful outcomes versus 42% of surveillance controls and 39% of study controls. Successful outcome odds were 6.5 (95% Confidence Interval: 1.2–36.2, $p = 0.032$) times greater for cases than surveillance controls (age-adjusted). Radiological improvement was more likely in cases than study controls. Culture analysis prior to infusion demonstrated a poorer initial prognosis in cases, yet despite this they had better outcomes than the control groups.

Conclusion: MSC treatment could vastly improve outcomes for MDR-TB patients. Our findings could revolutionize therapy options and have strong implications for future directions of MDR-TB therapy research.

1. Introduction

Despite recent reductions in tuberculosis (TB) incidence and mortality [1], slow progress is threatened by emerging drug resistant strains, responsible for 480,000 multidrug-resistant TB (MDR-TB; TB strains resistant to isoniazid and rifampin) cases in 2013 [1]. Current MDR-TB drugs are more toxic and have to be taken for longer than those for drug susceptible TB [2]; successful outcome rates are poorer [3] and only around half of treated MDR-TB cases globally are cured or complete treatment successfully [1,4]. Currently, the development of anti-tuberculosis drugs lags behind that of *Mycobacterium tuberculosis* drug resistance. We urgently need novel treatment options to improve outcomes for MDR-TB cases [5].

Belarus, in Eastern Europe, has the highest reported percentage of TB cases with MDR-TB in the world (45.5% of all TB cases in Belarus have MDR-TB) [6] and less than 50% of these patients are treated successfully (as per the World Health Organization [WHO] definition, treated successfully includes those cured and completed treatment with no evidence of failure of treatment) [4]. In 2009,

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a pilot study began in Belarus to assess the safety and effectiveness of autologous mesenchymal stromal cell (MSC) infusion as adjunct treatment in MDR-TB patients [7]. Although host-directed therapies have been hailed as a breakthrough for cancer [8], new concepts and clinically relevant trials are needed to achieve similar life-changing progress in infectious diseases.

The study motivation came from evidence that MSCs can facilitate organ homoeostasis and repair damaged lung tissue [9]. Additionally, it is possible that immunotherapeutic methods could reduce high inflammatory immune response in TB [10] with MSCs being one such potential method [11]. In the pilot study, the MSC treatment was found to be safe [7]. Here, we use these Phase I trial data to obtain a preliminary assessment of the MSC treatment effectiveness and give an indication of the potential value of Phase II/III trials.

2. Methods

We conducted an observational study using (1) outcome data from a non-randomised controlled trial in Belarus, and (2) data collected from the Belarussian surveillance database.

2.1. Patient recruitment to the trial

An ongoing open-label phase I non-randomized controlled trial of MSC infusion as adjunct treatment in MDR-TB patients has been conducted since September 2009 at the Republican Research and Practical Centre for Pulmonology and TB (RRPCPTB), Minsk, Belarus [7]. This includes those with extensively drug resistant TB (XDR-TB; MDR-TB plus resistance to an injectable drug and a fluoroquinolone), those with "pre-XDR-TB" (MDR-TB plus resistance to either an injectable or a fluoroquinolone) and MDR-TB patients without additional resistance. Seventy-two patients have been recruited: 36 that agreed to receive the MSC therapy ("cases") and 36 that did not agree to the treatment but consented to the monitoring necessary for the study ("study controls"). The main inclusion criteria were pulmonary TB confirmed by culture; MDR-, pre-XDR- or XDR-TB confirmed by drug susceptibility testing; age between 18 and 65 years; and absence of lesion compatible with a malignant process or ongoing tuberculosis in organs other than lungs and pleura [7]. Individuals with the following co-morbidities were also excluded: HIV, hepatitis B and/or C, autoimmune diseases, multi-organ failure, sepsis (any bacterial sepsis), abscess formation other than TB etiology, cancer and other malignancies, anti-DNA antibodies, allergies and any other disease that researchers believed was clinically significant and could affect the study results or cause an additional risk to the patient. Participants were not compensated for taking part in the study or for their travel expenses. Full details of this study are available elsewhere [7] and in the Appendix.

2.2. Selection of alternative controls from surveillance data

Since the study was non-randomized, there was potential for differences between cases and study controls that could have influenced the apparent MSC treatment effectiveness. Therefore, for a parallel analysis we selected matched controls ("surveillance controls") from the Belarussian TB surveillance database. Briefly, this database contains all reported TB cases in Belarus since 2009 and their demographic and clinical data. We 1:1 matched cases to controls (who met the original study inclusion criteria [7]) from the surveillance database on: (1) drug resistance profile (MDR-TB, pre-XDR-TB or XDR-TB), (2) previous TB treatment history (<one month of treatment ("new") or ≥one month of treatment ("previously treated")) and (3) baseline smear microscopy status (positive/negative). Previously treated patients in the trial were further stratified into "previously treated" (previous treatment(s) with first line drugs and/or less than two treatments with second line drugs) and "chronic" (≥2 previous second line regimens) but surveillance controls were not stratified in this way, due to lack of information regarding the number of times they had previously received treatment. Matching criteria were selected after reviewing the baseline differences between cases and study controls. We randomly selected surveillance controls although patients from Minsk city were prioritised due to logistical difficulties elsewhere in obtaining matching and potential confounder data.

2.3. Treatment and monitoring

All patients received an individualized optimal background regimen throughout their treatment period in accordance with WHO guidelines [12] (Appendix Table S1-3). In addition, bone marrow aspirates of 40–80 mL were obtained from the iliac crest of the cases, MSCs were isolated, cultured, prepared for infusion and reinfused on average 49 days after chemotherapy initiation, as described previously [7]. The entire MSC cell dose was given as a slow (5 min) bolus injection via a peripheral intravenous line.

For cases and study controls, chest X-rays were taken at chemotherapy initiation and approximately eight months later to assess changes. X-rays were assessed by experienced radiologists, who were blind to treatment, and scored as per Ralph et al. [13] (briefly, the score equals the percentage of lung involvement, plus 40 if cavities are present). Adverse event information among cases and study controls was collected during the first six months after MSC infusion and six months corresponding period (starting one month after chemotherapy initiation) for the study controls.

Microbiological data were collected from patient medical records or from reporting systems for National TB control program. The RRPCPTB received External Quality Assurance from the Swedish Institute for Infectious Disease Control throughout the study period. TB was confirmed with direct microscopy after Ziehl–Neelsen staining and culture and drug susceptibility testing were done using the BACTEC MGIT 960 system (Becton Dickinson, Sparks, MD, USA).

2.4. Baseline characteristics

We compared the baseline characteristics of cases with each control group using a *t*-test (for continuous variables) or Fisher's exact test (for categorical variables). Since the patient's choice to receive the MSC treatment may have been associated with hard to quantify factors such as motivation to be cured or general knowledge about and desire for optimal health, we examined potential proxies for these factors (smoking, employment, education and marital status).

2.5. Analysis of outcomes

All outcome definitions were consistent with the 2008 WHO guidelines [12] for MDR-TB patients (2008 guidelines used because the original trial began in 2009).

Successful outcomes included "cured" and "treatment completed" and all other outcomes were "unsuccessful" (e.g. death, treatment failure, treatment default/lost to follow-up). "Cured" is defined as treatment completed as recommended by the national policy without evidence of failure and five or more consecutive cultures taken at least 30 days apart negative in the final 12 months of treatment. "Treatment completed" is defined as treatment completed as recommended by the national policy without evidence of failure but with fewer than five cultures performed in the final 12 months of treatment. Both of these categories consist