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Short Communication

Pilot trial of tobramycin inhalation powder in cystic fibrosis patients with chronic *Burkholderia cepacia* complex infection

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Abstract

There is no effective chronic suppressive therapy *Burkholderia cepacia* complex infection in cystic fibrosis (CF) patients. This was a pilot, open-label clinical trial of tobramycin inhalation powder (TIP) delivered via Podhaler twice daily for 28 days in adults and children with CF and chronic *B. cepacia* complex infection in Toronto, Canada. A total of 10 subjects (4 pediatric, 6 adult patients) were treated. There was a mean drop of 1.4 log (CFU/ml) in sputum bacterial density ($p = 0.01$) and sputum IL-8 levels decreased significantly after 28 days of TIP ($p = 0.04$). The mean relative change in FEV_1 (L) from Day 0 to Day 28 of TIP administration was a 4.6% increase but this was not statistically significant. The majority of patients (70%) had no or mild adverse events.

Keywords: *Burkholderia cepacia*; Cystic fibrosis; Inhaled tobramycin

1. Introduction

Pulmonary infection with *Burkholderia cepacia* complex is known to accelerate lung function decline and contribute to earlier mortality in patients with cystic fibrosis (CF) [1–4]. However, there are no effective suppressive antibiotic regimens for those chronically infected with *B. cepacia* complex [5].

In an in vitro study of 180 *B. cepacia* complex CF isolates, we demonstrated that both the minimum inhibitory concentration (MIC_{50}) based on planktonic growth and the minimum tobramycin concentration at which biofilm formation was inhibited in 50% of the isolates tested (BIC_{50}), were100 μg/ml [6]. Newer inhalation devices can administer high intrapulmonary drug concentrations that may be able to overcome such MICs and BICs [7]. As a proof of concept of our in vitro findings, we conducted a pilot, open-label clinical trial of TIP delivered via Podhaler twice daily for 28 days in adults and children with CF and chronic *B. cepacia* complex infection. The primary outcome was reduction in sputum *B. cepacia* complex density with secondary outcomes of changes in lung function, sputum inflammatory markers and adverse events.

2. Materials and methods

2.1. Study design

This was an open-label study of tobramycin inhalation powder 112 mg delivered via Podhaler twice daily for 28 days. CF patients

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followed at the Hospital for Sick Children and St Michael's Hospital, Toronto, Canada, with chronic *B. cepacia* complex infection, were eligible for enrollment into the study (Supplemental methods). Patients were enrolled from clinic when clinically stable and no other treatments were added or changed from Day 0 to Day 28. Study outcomes, assessed at Day 0 and Day 28 of TIP treatment, consisted of spirometry [8], sputum *B. cepacia* complex density measured in colony forming units/ml (CFU/ml) [9], sputum Interleukin-8 (IL-8) (Enzo Life Science) and neutrophil elastase measurements (Enzo Life Science) and adverse events (patients were called at day 14 to ask about adverse events and were asked about adverse events at the day 28 clinic visit). Questionnaires assessing respiratory symptoms were not collected. In addition, a sputum sample was obtained just prior to (pre) and 30 min after (post) the last TIP dosing on Day 28 to measure sputum tobramycin concentrations using the VITROS Tobra assay (Ortho-Clinical Diagnostics, Rochester, New York). *B. cepacia* complex isolates were speciated by amplification and sequencing the *recA* gene. The MIC and BIC for tobramycin were determined for each *B. cepacia* complex isolate [6].

This trial was approved by the Research Ethics Board (REB) at the Hospital for Sick Children (REB#1000038054) and St Michael's Hospital (REB#15-104) (ClinicalTrials.gov identifier NCT02212587).

2.2. Statistical analysis

All analyses were done based on the intention to treat protocol (>1 dose of TIP). Sputum bacterial density counts were log transformed before analysis. Paired t-test was used to compare continuous outcomes measured at Day 0 and Day 28. Correlation was assessed using Spearman correlation coefficients. Statistical analysis was done on GraphPad Prism 5.04.

3. Results

3.1. Patient characteristics

A total of 10 subjects were enrolled in the study (4 pediatric, 6 adult patients) (Table 1). Subjects had a wide range of ages, lung function and nutritional status. The majority of patients (70%) were infected with *Burkholderia cenocepacia*; the median duration of infection was 8.5 years (range 1.4–17.3 years).

3.2. Changes in sputum markers and lung function

Fig. 1 illustrates the change in sputum bacterial density and inflammatory markers during the study. *B. cepacia* complex density decreased a mean 1.4 log (CFU/ml $\log_{10}$) from Day 0 to Day 28 of TIP treatment ($p = 0.01$) (Fig. 1A). Of note, in one pediatric subject, the sputum bacterial density decreased from 1.4×10^3 CFU/ml to 0 after 28 days of TIP. In addition, sputum IL-8 levels decreased significantly from Day 0 to Day 28 ($p = 0.04$) and there was a trend towards decreased sputum neutrophil elastase levels with TIP treatment ($p = 0.08$) (Fig. 1B, C).

The change in forced expiratory volume in 1 s (FEV_1) % predicted from Day 0 to Day 28 is illustrated in Supplemental Fig. 1A. The mean relative increase in FEV_1 (L) from Day 0 to Day 28 of TIP administration was 4.6% (median 2.4%) (Supplemental Fig. 1B). This change was not statistically significant and there was considerable variability in lung function response, ranging from −6.6% to 28.1% relative change improvement in FEV_1. The median pre-TIP sputum tobramycin concentration was 194 μg/ml (range 11–2100 μg/ml) with a median post-TIP sputum tobramycin concentration of 1025 μg/ml (range 306–4700 μg/ml).

Table 1
Baseline (day 0) patient characteristics.

	Total subjects N = 10
Male, n (%)	8 (80)
Age, years, median (range)	19 (6–38)
Pancreatic insufficient, n (%)	9 (90)
CFRD, n (%)	2 (20)
Liver disease, n (%)	0 (0)
FEV_1% predicted, median (range)	81 (28–119)
FEV_1% predicted change/yr, mean (SD)[c]	−1.35 (8.1)
BMI centile, median (range)	34.0 (2.4–96.6)
Burkholderia cepacia complex, n (%)	10 (100)
Burkholderia cenocepacia IIIA	4 (40)
Burkholderia cenocepacia IIIB	3 (30)
Burkholderia multivorans	3 (30)
Sputum density $\log_{10}$ CFU/ml, median (range)	7.9 (3.1–8.8)
Positive culture at baseline, n[a] (%)	
Staphylococcus aureus	2 (20)
Aspergillus species	1 (10)
Stenotrophomonas maltophilia	1[b] (10)
Pseudomonas aeruginosa	1[b] (10)

CFRD: cystic fibrosis related diabetes.
FEV_1% predicted: forced expiratory volume in 1 s % predicted.
SD: standard deviation.
BMI: body mass index.
CFU: colony forming unit.
[a] Culture results available for 7 of 10 patients.
[b] Same patient had co-infection with *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa* on day 0 sputum culture and did not complete 28 days of the study drug.
[c] FEV_1% predicted change per year calculated over 5 years prior to day 0.

3.3. Safety outcomes

Four of the ten (40%) subjects had no adverse events. One subject had throat pain and difficulty swallowing on day 3 related to TIP administration and discontinued the study drug. Another subject was admitted for intravenous antibiotic therapy at day 28 of TIP for pre-existing low lung function; another was prescribed oral antibiotics on day 28 for increased cough and sputum production. The remaining 3 subjects had mild adverse events (not related to study drug or leading to drug discontinuation). There were no significant changes in the susceptibility (MIC or BIC) of *B. cepacia* complex to tobramycin noted during the 1 month trial (Supplemental Table 1).

4. Discussion

This pilot study of inhaled tobramycin powder demonstrated a decrease in sputum bacterial density and pulmonary inflammatory markers but did not result in a statistically