MUL-1867, A DRUG CANDIDATE FOR INHALATION THERAPY OF PULMONARY EXACERBATIONS CAUSED BY *BURKHOLDERIA CEPACIA* COMPLEX IN CYSTIC FIBROSIS AND COPD PATIENTS

Tetz V, Tetz G

Abstract

Burkholderia cepacia complex is a group represented by 18 genetically distinct but phenotypically similar gram-negative bacterial species causing lung infection with poor prognosis. Most patients with cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) are infected with *B.cepacia* complex that, once established, is impossible to eradicate and is associated with major morbidity[1]. The objective of this study was to assess the *in vivo* efficacy of Mul-1867 in patients with CF and COPD during pulmonary exacerbation. Mul-1867 is a first-in class (hydrazine derivative) novel, nanosized (1.5-2.0-nm), broad-spectrum inhaled antimicrobial.

Methods

Study design

Open-labeled study was conducted in patients with COPD and CF during pulmonary exacerbation.

Total **10 patients** were enrolled. The patients were evaluated at **day 0** and **day 14**. Each participant was its own control. Subjects were not allowed to use antibiotics within the 28 days before enrolment. Maintenance therapy with antibiotics, including oral, intravenous or aerosolized dosage forms, were not permitted during the study. Presence of *B.cepacia* as a primary cause of CF and COPD exacerbation was proved by microbiological analysis. The MICs were determined using the broth macrodilution method.

Baseline characteristics of enrolled subjects

Characteristics	Men (n = 7)	Women (n = 3)	Total (n = 10)
Age, yr	24,4	27,7	25,4
FEV1 (% pred.) baseline	57,5	59	57,9
Pulmonary total symptom severity score	10,2	11,5	10,6

Treatment regimen and monitoring

Mul-1867 0.25% solution was nebulized **3 times dail**y for 14 days (10 mg Mul-1867 dissolved in 4 ml of sterile NaCl 0,9%) with an Omron Compressor Nebulizer System NE-C25. The microbiological response was assessed at day 14 based as the **log10 value of CFU** per gram of sputum after plating on selective *B.cepacia* agar medium (Oxoid, UK).

End points

The primary efficacy end point

I. clinical outcome assessment at day 14 (categorized as "cured," "failed," or "indeterminate")

The secondary efficacy end point

I. Symptom severity score on a scale of 0 – 4 (cough, shortness of breath, sputum production [frequency and severity], fatigue)

II. Microbiological response

III. The change in FEV1 expressed as a percentage of initial FEV1.

Results

In vitro antibiotic susceptibilities of *B.cepacia* isolates from patients

Antimicrobial agent	Range (mg/L)	Conclusion
Mul-1867	0.03 – 0.5	Mul-1867 inhibited the growth of all clinical isolates strains of *B.cepacia*, with MIC values ranging from **0.03 to 0.5** mg/L.
Piperacillin	2-256	
Minocycline	0.5 - 64	

The primary efficacy end point

I. Clinical assessments of test of cure in study population at 14 day

Clinical Assessment	N of patients	Conclusion
Cured	10	Mul-1867 achieved its primary endpoint
Failed	0	
Indeterminate	0	

The secondary efficacy end point

I. Clinical outcome assessments

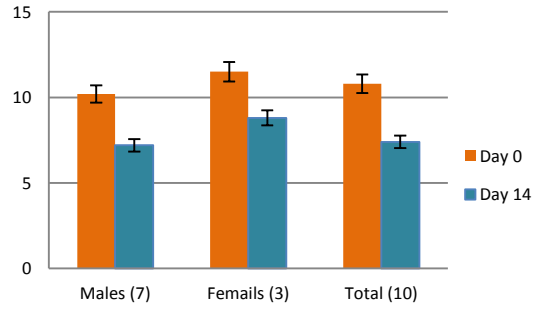

Fig.1 Effect of therapy on mean pulmonary total symptom severity scores in men, women, and the total patient population. Mean baseline (Day 0) and end-of-study (Day 14) scores are shown

Mul-1867 significantly reduced symptom severity score at day 14

II. Microbiological response

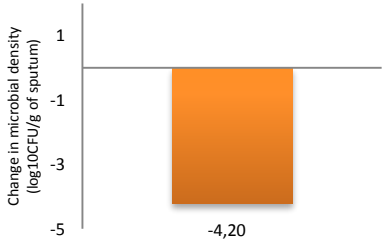

Fig.2 Mean Change in the Density of B.cepacia in samples of expectorated sputum.

III. The change in FEV1

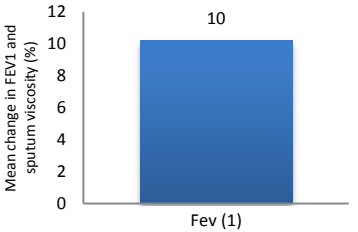

Fig.3 Mean Change in the FEV1
The mean change from day 0 in FEV1 (expressed as the percentage of the value predicted).

Conclusion

Our study demonstrated that a nanoglobular antimicrobial Mul-1867 possesses great *in vivo* activity against *B.cepacia* infection in CF and COPD patients. Mul-1867 is an original small molecular entity and is not relative to existing antibiotics.

Short-term, administration of inhaled MUl-1867 improves pulmonary function, decreases the density of *B.cepacia* in sputum, and reduces the need for oral and intravenous antibiotics and hospitalization.

As was shown in preliminary experiments, it is effective against various antibiotic resistant strains of major respiratory pathogens in cystic fibrosis patients. This data corresponds to that received in this study as Mul-1867 was effective against piperacillin-resistant and minocycline - resistant *B.cepacia* infection.

Further studies are required for the development of Mul-1867 as an inhaled antimicrobial.

References

1. Delhaes, Laurence, et al. "The airway microbiota in cystic fibrosis: a complex fungal and bacterial community—implications for therapeutic management." *PloS one* 7.4 (2012): e36313.
2. Zeng, Pengyun, et al. "Concentration dependent aggregation properties of chlorhexidine salts." International journal of pharmaceutics 367.1 (2009): 73-78.

georgetets@gmail.com
vtetzv@yahoo.com