Prospective open-label phase IIa trial of Adjuvant Nitric Oxide Cystic Fibrosis Therapy

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Introduction

Chronic microbial lung infections, particularly with *P. aeruginosa*, are the leading cause of morbidity and mortality in CF patients. Nitric oxide (NO) is a major signaling molecule in innate defense against infection but levels are surprisingly low in CF. Following a successful phase I safety study in healthy adults, we aimed to assess the safety and tolerability of inhaled NO, at an antimicrobial dose of 160ppm, as adjuvant therapy for CF lung disease..

Subjects and methods

We conducted a Phase 2a open label safety study in 2 centers: Soroka Medical Center and Schneider Children's Medical Center of Israel.

Patients received intermittent (30 minutes, three times a day) inhalations of 160 ppm NO formulation, five days a week, over a two week period.

Safety parameters:

•Inhaled NO, Nitrogen dioxide (NO_2) and FiO_2 concentrations as well as Methemoglobin (%MetHb), oxygen saturation (SaO_2) and vital signs were continuously monitored.

Preliminary efficacy measures:

•Measurements of forced exhaled volume of 1st second (FEV1)

Preliminary observational measures:

•Determination of reduction in bacterial and fungal sputum load

•Systemic Inflammation assessed by C- reactive protein (CRP) levels

Results (1)

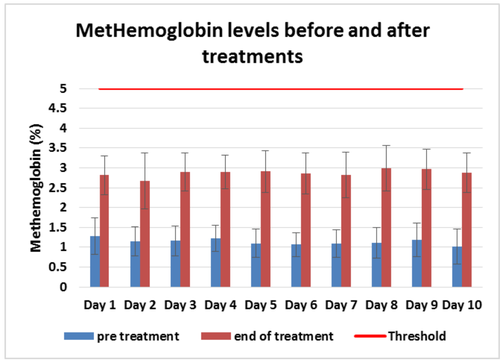
- 9 CF patients (7 female, aged 13-46y) were enrolled.
- Baseline FEV1 was 38-77%,
- All patients tolerated the treatment and completed the study
- There were no serious adverse events.
- No clinically significant changes in vital signs were observed

1) It should be noted that results are preliminary and have not been audited.

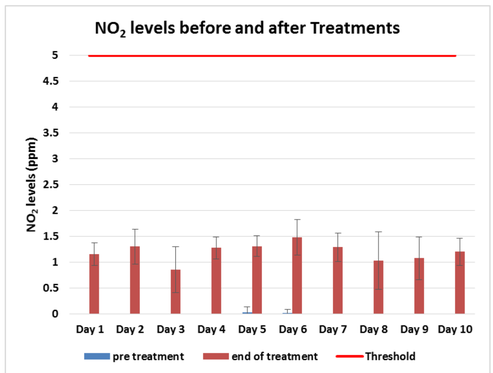
Results

Safety Parameters:

Average %MetHb levels post treatments were 2.9 ± 0.5% (mean ± SD), well beneath the study threshold of 5%.



Average NO_2 levels were 1.2 ± 0.3 ppm (mean ± SD) post treatments and remained ≤3 ppm, well beneath the study threshold of 5ppm.

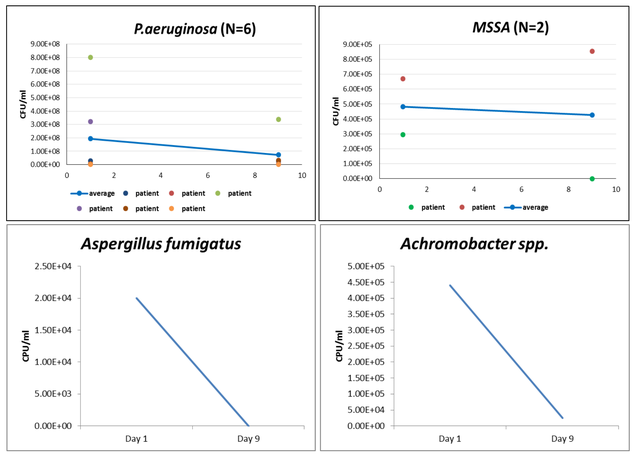


Mean oxygen saturation levels post treatment remained ≥ 94% and did not decrease significantly in any of the patients.

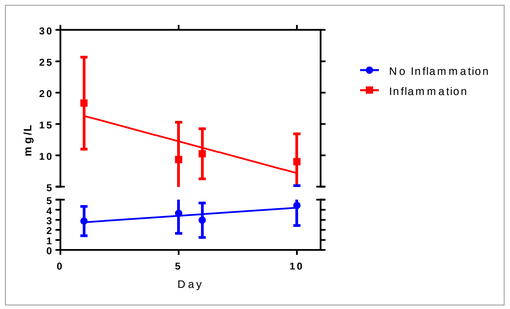
Bacteriology:

Colony forming units for bacteriology were tested on days 1, 4, 6 and 9. The study results demonstrated a reduction in the total microbiological infection levels of above 60% and elimination of fungal infection in one patient during the study.

Results



Reduction of the inflammatory marker C reactive protein (CRP) was observed and found to be directly attributed to NO treatment in patients with active systemic inflammation (3 out of 9 patients).



As a downstream effect, FEVI tests results were greatly varied between patients. Results show that for all subjects FEVI levels returned to baseline by the second follow-up visit indicating the safety of the treatment.

Conclusions

We believe that the results of this Phase IIa clinical trial suggest that 160 ppm NO treatment is **safe & tolerable** in CF patients. The treatment resulted in differential yet significant reduction of microbiological load.

A reduction in systemic inflammation was shown in patients with initially increased CRP levels.

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