Treatment of Refractory *Mycobacterium abscessus* Lung Infection with Inhaled Intermittent Nitric Oxide

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Background

- *Mycobacterium abscessus,* is an increasingly more common pathogen in cystic fibrosis patients associated with decreased lung function, worsened quality of life, and increased mortality.[1,2]
- Antibiotic therapy for *M. abscessus* is frequently ineffective at eradicating the mycobacteria and poorly tolerated.
- Nitric oxide (NO), a small lipophilic free radical, plays a key role in host defense mechanisms against infections. NO displays broad-spectrum antibacterial activity in preclinical models, including NTM such as *M. smegmatis*.[3,4]
- Previous studies have suggested that inhaled nitric oxide is bactericidal to common CF pathogens including *M. abscessus* and is tolerated well at in-vitro derived bactericidal concentrations.[5,6]
- A novel NO-generating device for inhalational delivery of intermittent, high-concentration NO was used under an IRB approved compassionate treatment protocol for a CF patient with refractory *M. abscessus* lung disease.

Methods

Patient: A 25 year old patient with CF and an 8 year history of chronic *M. abscessus* infection unresponsive to multiple antibiotics and with deteriorating lung function, functional status and quality of life was treated with intermittent, inhaled nitric oxide added to background antibiotics. No changes to baseline regimen were made during treatment and follow-up.

Treatment Protocol: Under an IRB and FDA approved compassionate use experimental treatment protocol, NO therapy was delivered during a 21-day inpatient regimen. After baseline data assessment, NO at 160 parts per million (ppm) was inhaled in 1) five 30-minute treatments every 3.5 hours during daytime for days 1-14 and 2) three 30-minute treatments administered every 3.5 hours for days 15-21. Vital signs, continuous pulse oximetry assessment of oxyhemoglobin and methemoglobin saturations (Radical-7 monitor, Masimo, Irvine, CA), and continuous ambient and facemask concentrations of NO, nitrogen dioxide and FiO2 (AeroNOx, Biomedical International, Austin, TX) were assessed with each treatment. Weekly assessment of lung function, 6 minute walk distance/oxygenation, serum inflammatory markers, and mycobacterial stain and culture quantitation were assessed during the treatment period and every 4 weeks post treatment for 16 weeks. Quality of life assessment via the Cystic Fibrosis Questionnaire - Revised (CFQ-R, Alexandra Quittner, Univ of Miami) was done at baseline, Day 21, and at each monthly follow-up.

Delivery system: NO was delivered via a novel, portable generator with a bi-valve facemask (AIT Therapeutics, Garden City, NY). Prototype devices were used to supply NO at 160 ppm, 15 liters per minute (lpm) total flow and an FiO2 of 0.21 through a coaxial reservoir tubing system. The mask had separate inlet and outlet ports. Delivered gas concentrations were monitored at the inhalation port of the mask.

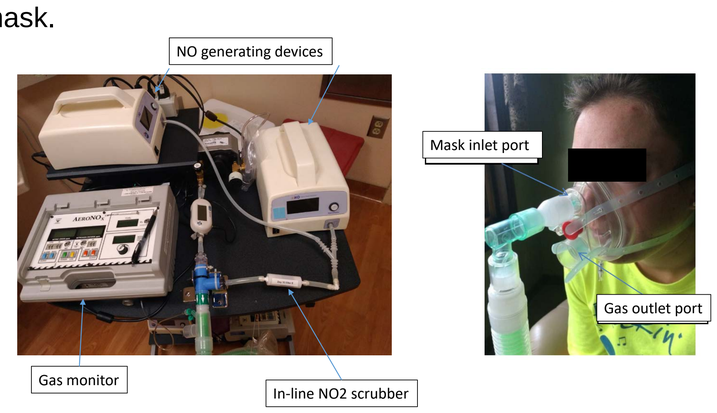

Fig. 1. Inhaled NO Delivery System

Results

Phase	Time	FEV1 (%)	FVC (%)	6MWT (m)	CRP (mg/dL)	ESR (mm/hr)	AFB Stain	AFB Culture
Pre-Trial	Baseline	39	50	410	50.7	29	Many	Heavy
Trial	Day 7	37	53	399	31.9	25	Many	Heavy
	Day 14	40	59	379	13.8	18	Many	Heavy
	Day 21	42	58	426	37	22	Many	Heavy
Post-Trial	Day 51	41	59	503	20.3	17	Many	Heavy
	Day 81	42	60	459	35.4	34	Many	Heavy
	Day 111	41	56	471	17.4	26	Many	Heavy
	Day 141	38	58	362	17.7	28	Many	Heavy

Fig. 2. Efficacy measures. Relative to baseline, pulmonary function tests and lab tests showed an improvement in FVC and 6-Minute Walk Test (6MWT) distance as well as decreased levels of inflammatory markers (CRP and ESR). There were no significant changes in *M. abscessus* stain or culture results.

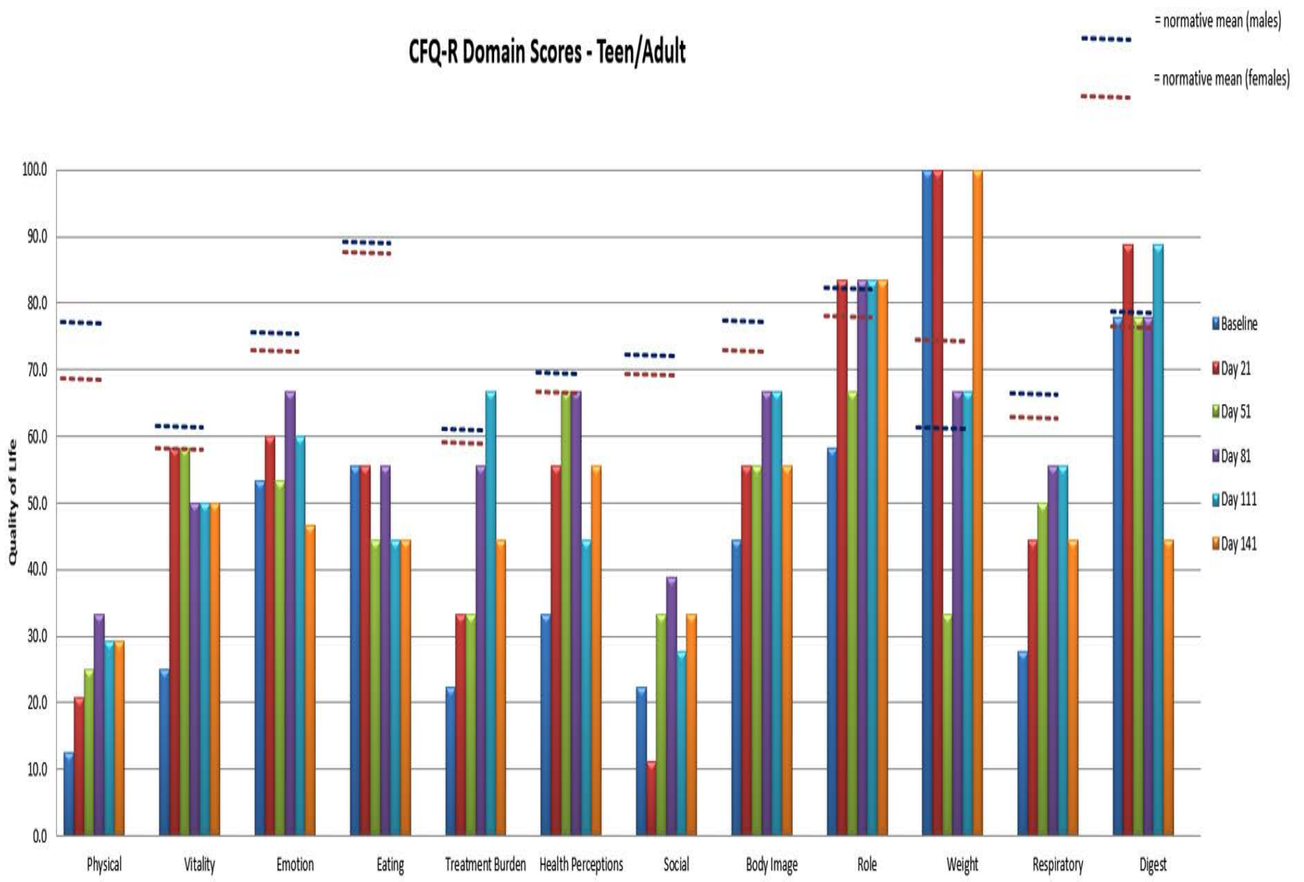

Fig. 3. Health related quality of life. Cystic Fibrosis Questionnaire - Revised (CFQ-R) scores demonstrated, relative to baseline, large improvements in physical, vitality, health perceptions and respiratory domains during and after completion of NO treatment. Following therapy, she was able to complete her degree and obtain a job.

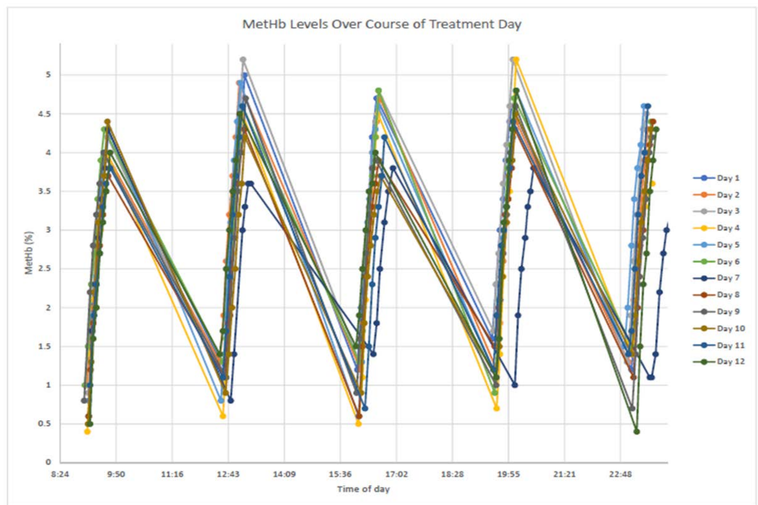

Fig. 4. Methemoglobin levels, 30 minutes x 5 times/day Days 1-12. Reproducible and expected increases (range 0.3–5.2 ppm) in methemoglobin that did not exceed safety parameters. NO treatments were not held or delayed due to elevated methemoglobin levels. Similarly, inhaled (1.1-1.8 ppm) and ambient NO2 levels did not exceed 2ppm and no treatments were held or delayed due to elevated NO2 levels.

Conclusions

- Intermittent, high concentration inhalation of NO via a portable generator system was well tolerated with no significant adverse effects related to the treatments.
- Improvements were seen in quality of life and functional status. However, no microbiologic effect was seen.
- Inhaled NO is a novel approach to severe NTM infection that may offer improvement in various parameters to patients with severe chronic infections.
- Further investigation is required to determine the most effective concentration and treatment schedule to reduce mycobacterial burden and potentially achieve eradication.
- “At-home” self-administration may be possible

References

1. Qvist T, et al. J Cystic Fibrosis 2016; 15(3): 380-385
2. Mehta M, et al. Respir Med 2011; 105: 1718-1725
3. Ghaffari A., et al. Nitric Oxide 2005; 12(3):129–140
4. Miller C, et al. Antimicrob Agents Chemother 2007; 51(9):3364-3366
5. Deppisch c, et al. Infection 2016; 44(4):513-20
6. Yaacoby-Bianu K, et al. Pediatr Infect Dis J. 2018;37(4):336-338

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