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Non-tuberculous mycobacteria infection treated with intermittently inhaled high-dose nitric oxide

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SUMMARY

Mycobacterium abscessus is an emerging multidrug-resistant non-tuberculous mycobacterium (NTM) with high prevalence in patients with cystic fibrosis. However, studies on antimicrobial susceptibilities and effective treatments against *M. abscessus* are still limited. Nitric oxide (NO) is important in innate immune response to various infections, including mycobacterial infections. In this case study, we describe a compassionate treatment of inhaled NO (iNO) at 150–250 ppm for 4 weeks. The dosing strategy proposed for this treatment was selected to minimise the potential of adverse events, while maximising the antibacterial effectiveness of NO, and was found to be safe, well tolerated and resulted in positive clinical findings including improvement in patient well-being, CT scan values, quality of life and bacterial load. Taken together, these observations may indicate that iNO could play a crucial role and potentially serve as a reliable option in the treatment of patients with chronic refractory NTM lung infection.

BACKGROUND

Non-tuberculous mycobacterium (NTM), especially *Mycobacterium abscessus* (*M. abscessus*), causes chronic lung infection that is difficult to treat. NTMs are opportunistic pathogens placing several populations at increased risk, including those with underlying lung disease or suppressed immune systems. The current recommended treatment regimen for *M. abscessus* includes a multiphase multiantibiotic protocol, with no reliable treatment to date.[1]

Nitric oxide (NO) is part of the innate defence mechanism of the immune system[2 3] that is elevated following the activity of inducible NO synthase during numerous microbial infections and inflammatory conditions.[4]

NO production and metabolism contribute to the pathophysiology of several pulmonary conditions.[5] It has been hypothesised that NO's antimicrobial and cellular messenger regulatory properties, when delivered via inhalation, may be effective in the treatment of uncontrolled pulmonary disease via reduction of bacterial burden and inflammation and improving clinical symptoms.

Multiple studies and compassionate treatments with Intermittent inhaled NO (iNO) demonstrated that the treatment is safe, tolerable and effective.[6–11]

CASE PRESENTATION

Here, we describe a compassionate treatment of iNO at high dose in a 27-year-old Asian patient with cystic fibrosis (CF). His diagnosis was based on two sweat tests results with 80 and 81 mmol/L of chloride and molecular genetic investigation summarised him as heterozygotic for cystic fibrosis transmembrane conductance regulator (CFTR): c.1657C>T (p.Arg 553) and CFTR:c.1390A>C, that with his background clinical course was consistent with CF, He was diagnosed with *M. abscessus* in 2012. The patient was treated prior to and during treatment with different antibiotic regimens that are currently standard of care for CF and NTM, including 150 mg/day clofazimine, 250 mg/day azithromycin, 300 mg/day mycobutin, 150 mg/day acetylcysteine and ventolin (6% Sodium Chloride (NaCl)). Additional concomitant medications were given for haemoptysis and high blood pressure. The patient underwent left upper lobe lobectomy in 2017. Chest CT from January 2018 showed bronchiectasis and fibrosis with development of multifocal consolidation and patchy ground glass opacities involving the left lung (figure 1A). The patient reported recurrent minor haemoptysis events since 2011.

INVESTIGATIONS

After signing the informed consent, the patient was admitted to Soroka University Medical Center (Beer-Sheva, Israel) in November 2018 for a local Institutional Review Board (IRB) and Israeli Ministry of Health approved compassionate treatment of intermittent iNO. Baseline assessments were performed and included: routine complete blood count, chemistry, liver function tests, methaemoglobin (MetHb) level, sputum sample analysis, spirometry test, 6 min walk testing (6MWT) and Quality of Life-Cystic Fibrosis Questionnaire-Revised.

TREATMENT

The patient was hospitalised for the first 14 days, followed by 15 days as an ambulatory patient, resulting in a 29-day treatment course. During treatment, in addition to standard care (ongoing medication, as aligned in table 1), the patient was treated with intermittent iNO (mixed with O_2/air), administered for 40 min, four times a day for the first 2 weeks, twice a day in the following two ambulatory weeks, and a single inhalation in the last day of treatment (day 29). The NO concentration was gradually elevated starting from 150 ppm until reaching a level of 250 ppm, given on days 4–29 of the course.

As a safety measure, during NO administration, NO (ppm), NO_2 (ppm) and O_2 (%) were continuously monitored from a sampling port, using a dedicated monitor (AeroNox International Biomedical,

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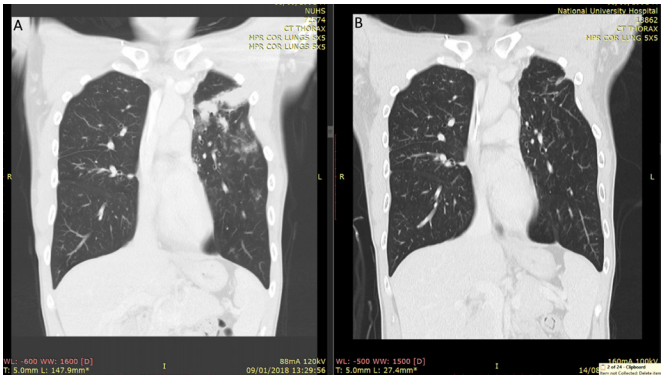

Figure 1 High-resolution chest CT scan (A) 10 months before compassionate treatment; (B) 269 days after no treatment.

USA), and the patient's MetHb and O_2 saturation in the blood as well as heart rate were monitored utilising a commercial pulse co-oximeter (Masimo Corporation Model RAD 87). Respiratory rate and blood pressure were recorded at both pre-treatment and end of each inhalation. Adverse events (AEs) and serious AEs were continuously documented.

Assessment of *M. abscessus* bacterial load in the patient's sputum, physical capacity (6MWT), lung function (first second of forced expiration (FEV1) and forced vital capacity (FVC))) and Quality of Life (QOL) questionnaire[12] were performed at baseline (day 0–1), mid-treatment (day 15–16) and end of treatment (day 28–29) and at follow-up (FU) at various time points according to patient's and clinic availability (table 2). Sputum sample analysis was made by semiquantitation evaluation obtained from solid cultures, time to positive *M. abscessus* liquid culture and *M. abscessus* counts in the acid-fast bacilli smear.

OUTCOME AND FU

The patient completed the full treatment regimen with no significant AEs. As expected, transient effect on MetHb levels was noted during each treatment, however, levels remained within the predefined safety limit of 10%. MetHb level recorded at discharge was similar to baseline (2% vs 1.3%). Inspired NO_2 did not exceed 5 ppm during treatment. Mean NO_2 levels remained constant throughout treatments (3.0–3.3 ppm). All safety parameters remained well within the protocol's acceptance criteria; therefore, no inhalation treatment was prematurely discontinued.

An improvement in QOL was noted during the treatment period in several parameters including physical, vitality, body image, respiratory, emotion, treatment burden, health perceptions and role. The overall improvement was maintained during the FU period (day 93). Minor improvement was shown in 6MWT distance (from 510 m in baseline to 549 m at day 29) as demonstrated in table 2. A positive effect on bacterial growth was noted mid-treatment, with two samples testing negative (one liquid, one solid). However, eradication was not achieved.

Following NO treatment, minor recurrent haemoptysis improved, documenting no bleeding until August 2019. Embolisation was needed in October 2019.

Chest CT performed on FU day 44 noted interval development of multifocal consolidation and patchy ground glass opacities in the left lower lobe, describing improvement in patchy consolidation. Additional chest CT (day 269) showed that previously noted patchy consolidation and reticulonodular tree in bud opacities in both lungs have improved (figure 1B). The large confluent consolidation present in the lingula previously had resolved. The largest nodule in the left lower lobe reduced from 17 to 9 mm. Previous extensive evidence of infectious changes has largely resolved with residual changes in the right upper lobe and left lower lobe. No interval confluent consolidation was noted.

DISCUSSION

NTM infection poses a clinical challenge due to the lack of a reliable treatment protocol. The ability of NO to eradicate multiple drug-resistant bacteria and synergistically act with antimicrobial compounds, and to disperse biofilm-embedded bacteria is highly relevant for the treatment of various infectious pathologies, especially in chronic lung diseases.

Previous studies testing iNO delivery (in a concentration of 160 ppm) were performed on healthy volunteers,[6] patients with CF[7 8] and NTM patients.[9–11] These studies and additional compassionate treatments revealed that this treatment regimen is safe and tolerable and may benefit physical and respiratory performance, and in some cases relieve bacterial burden. Yaacoby-Bianu *et al*[10] reported no AEs, during treatment and a showed significant reduction in quantitative PCR results for *M. abscessus* load in sputum estimated by colony-forming unit for 2 CF patients. Additionally, Bentur *et al*[9] studied the effect of iNO on nine patients with CF who were infected with NTM Abscessus and found that mean FEV1 and 6WMD were increased relative to baseline following NO treatment. *M. abscessus* culture

Table 1 Concomitant medications

Generic name	Indication	Daily dose	Units	Frequency	Route	Start date	Status
Clofazimine	NTM	150	mg	X1/day	PO	2017	Ongoing
Atenolol	Primarily used to treat high blood pressure and heart-associated chest pain	50	mg	X1/day	PO	2017	Ongoing
Hexakapron	Haemoptysis	100	mg	X1/day in the evening	PO	2017	Ongoing
Hexakapron	Hsemoptysis	500	mg	X1/day in the morning	PO	2017	Ongoing
Azithromycin	CF, NTM	250	mg	X1/day	PO	2017	Ongoing
Mycobutin	NTM	150	mg	X2/day	PO	2017	Ongoing
Acetylcysteine	CF	600	mg	X1/day	PO	2017	Ongoing
Ventolin	Beta-agonist	1	g	X2/day	INH	2016	Ongoing
6% Sodium Chloride (NaCl)	Expectorant	2	ml	X2/day	INH	2016	Ongoing

CF, cystic fibrosis; INH, Inhaled; NTM, non-tuberculous mycobacterium; PO, per OS - refer to oral administration.

Table 2 Summary of patient parameters at baseline, treatment period and follow-up (FU)

Treatment/ FU	Day	6MWT distance (metres)	FVCex (litres)	FEV1 (litres)	FEV1/FVC	Mean time to positive (hour)-liquid	Mean CFU/ mL-solid
Pretreatment	−134	ND	4.04	3.17	78	ND	ND
Baseline	0–1	510	3.84	3.03	79	92.5	9
iNO	15–16	504	3.78	2.91	77	132.5	2
	28–29	549	3.58	2.86	80	101	4
FU*	35	ND	4.01	3.22	80	ND	ND
	69	ND	ND	ND	ND	95	4
	146	ND	ND	ND	ND	126.5	6.5
	172	480	4.34	3.38	78	ND	ND

*FU visits were performed at patient's local CF-clinic.
CF, cystic fibrosis; CFU, colony-forming unit; iNO, inhaled Nitric oxide; 6MWT, 6 min walk testing; ND, not done.

conversion was not achieved, but three of nine patients with CF experienced at least one negative culture during the study. Also, mean time to positivity in *M. abscessus* culture, and qPCR analysis showed reductions in sputum bacterial load.

The intermittent dosing strategy proposed for this treatment was selected to minimise the potential of AEs, while maximising the antibacterial effectiveness of NO as well as the added treatment benefits on biofilm, inflammation and mucociliary clearance.

The treatment regimen used in this compassionate use was found safe, well tolerated and resulted in positive clinical findings that included improvement in patient well-being. Most notably, CT chest scans showed major improvement although this could not be attributed only to NO treatment. Together, these observations, along with the findings of previous reports described here, may indicate that iNO could play a crucial role and serve as a reliable option in the treatment of patients with chronic refractory NTM lung infection.

Learning points

- Non-tuberculous mycobacterium (NTM)-abscessus lung disease is a threat to patients with cystic fibrosi (CF) swith increasing rate of antibiotics resistance.
- Inhaled nitric oxide (NO) emerges as a potential safe and effective treatment in such patients as well in other lower respiratory tract infections.
- The present case shows the safety and efficacy of intermittent high dose inhaled NO, encouraging its inclusion in the current arsenal for NTM abscessus in patients with CF.

Correction notice This article has been corrected since it was published online. The article title has been corrected to "Non-tuberculous mycobacteria infection treated with intermittently inhaled high-dose nitric oxide".

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