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JOURNAL CLUB

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ARTICLE

Pilot study to test inhaled nitric oxide in cystic fibrosis patients with refractory Mycobacterium abscessus lung infection. Bentur L, Gur M, Ashkenazi M, Livnat-Levanon G, Mizrahi M, Tal A, Ghaffari A, Geffen Y, Aviram M, Efrati O. *Journal of Cystic Fibrosis*. 2020 Mar;19(2):225-231.

CLINICAL QUESTION

Is intermittent high-dose inhaled nitric oxide (iNO) a safe and tolerable treatment as an adjuvant therapy for refractory *Mycobacterium abscessus* in people with cystic fibrosis (CF)? Is the treatment efficacious?

SUMMARY

Nontuberculous mycobacterial (NTM) lung infections have increased in prevalence among people with CF over the last decade. People with CF and *M. abscessus* pulmonary disease have challenging infections, notable for significant antibiotic resistance, requiring prolonged multi-drug treatment regimens that are complicated by adverse events and high treatment failure rates. CF airways have a relative deficiency of nitric oxide (NO) and elevation of airway NO in these patients is associated with lung function improvement. In pre-clinical models, NO has activity against a broad range of multi-drug resistant pathogens. Short-term administration of intermittent high-dose inhaled NO (iNO) was reported to be safe in both healthy adults and people with CF. A case report of compassionate use of intermittent high-dose iNO for 2 people with CF and *M. abscessus* pulmonary disease reported improvement in lung function, improvement in 6-minute walk distance (6MWD), and reduction in *M. abscessus* sputum burden. However, there have been no randomized controlled trials of iNO as a potential treatment for *M. abscessus* lung infection.

This article describes a prospective, open-label, multi-center pilot study to test the safety and efficacy of intermittent high-dose iNO as an adjuvant treatment of refractory *M. abscessus* lung infection in 9 people with CF admitted to 3 medical centers in Israel. Inclusion criteria were >6 and <65 years of age with at least 6 months of *M. abscessus* lung infection, FEV1 >30% predicted, and able to perform a 6MWD test. Exclusion criteria included pregnancy, pulmonary hypertension, hypertension, >30 ml hemoptysis in the last 30 days, lung transplantation, continuous oxygen supplementation, and tuberculosis.

The primary outcome was safety and tolerability of 160 ppm iNO with a blood methemoglobin (MetHb) safety threshold of <7% and NO_2 safety threshold of <5 ppm. Vital signs, mean and peripheral oxygen saturation, physical examination, and hematological and coagulation markers were assessed. Efficacy measurements included FEV1, FVC, and 6MWD (screening, day 1, week 1, week 2, week 3, week 7, and week 11), as well as sputum culture, rpoB gene sequence, and time to positivity in liquid culture (day 1, week 1, week 2, week 3, week 7, and week 11).

All patients received 160 pm iNO combined with O_2/air blend for 30 minutes in addition to routine care for CF-NTM pulmonary disease (not defined). iNO was administered for a total of 21 days beginning with 5 times daily during a 14-day hospitalization and 3 times daily for 7 days in the ambulatory setting.

With respect to safety, all 9 enrolled patients completed iNO treatment. There were no iNO-related serious adverse events (SAE). Twenty-five adverse events (AE) were reported with 3 patients having 5 probable treatment-related AEs that were minor, transient and self-recovered, and included 1 episode of elevated MetHb (7.1%). NO_2 levels did not exceed the 5 ppm threshold.

With respect to efficacy, mean FEV1 and FVC as well as 6MWD increased at the completion of treatment (week 3), but were not sustained at follow-up. All 9 patients were *M. abscessus* culture-positive at screening and 3/9 experienced a negative culture during the study, with 1 patient culture negative at 7- and 11-week follow-up visits. Culture conversion, defined as 3 consecutive negative cultures, was not achieved. Time to positivity in liquid culture increased (suggesting a reduction in mycobacterial burden) relative to baseline during treatment and at follow-up.

GROUP OPINION

M. abscessus treatment in people with CF requires prolonged administration of multiple antibiotics, complicated by significant toxicity and high rates of treatment failure. Novel approaches to treatment are needed to improve tolerability and efficacy. Low-dose iNO (<80 ppm) is FDA-approved for treatment of persistent pulmonary hypertension in neonates. In this pilot study, intermittent high-dose iNO demonstrated overall safety and tolerability in CF patients undergoing standard treatment for *M. abscessus* with no treatment-related SAEs and 5 possible/probable treatment related AEs (dizziness, dry mouth, hemoptysis, and MetHb elevation). All AEs were minor, transient, and all patients were able to complete the study. Efficacy of treatment was not demonstrated in FEV1, FVC, 6MWD, or *M. abscessus* culture conversion. Median time to culture positivity of *M. abscessus* increased relative to baseline at all observed time periods, suggesting decreased mycobacterial burden. This study was limited by the small number of patients and was not powered to demonstrate statistical significance. Larger populations will need to be studied to better determine the risk and frequency of SAEs and AEs. A Phase I/II clinical trial will be required to investigate safety and efficacy of treatment.

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