National Jewish Health
Breathing Science is Life.

JOURNAL CLUB

Article Summary by: Mohammad Dalabih, MBBS, MHA & Patricia George, MD

ARTICLE

A Randomized, Double-Blind, Placebo-Controlled Study of Pulsed, Inhaled Nitric Oxide in Subjects at Risk of Pulmonary Hypertension Associated With Pulmonary Fibrosis.
https://pubmed.ncbi.nlm.nih.gov/32092321/

CLINICAL QUESTION

In patients with fibrosing ILD (fILD) on supplemental oxygen with echocardiographic evidence of pulmonary hypertension, does iNO result in improved activity level, measured by actigraphy, compared to placebo? Is the level of physical activity an optimal end-point for an upcoming phase 3 study on iNO in fILD?

SUMMARY

Pulmonary hypertension can complicate fILD and is associated with lower physical activity and worse prognosis. Treatment options for PH-ILD are limited.

This study is a double-blind, placebo-controlled phase 2b/3 study, in which the investigators studied the effects of iNO at 30 mcg/kg/hr for 8 weeks on patient's level of activity measured by actigraphy. Safety and efficacy data were collected.

Subjects:
All patients had CT-confirmed fILD, and were on continuous supplemental oxygen (mean 3.6 L/min, SD 1.4 L/min. Patients were stratified according to echocardiographic findings into low, intermediate, or high risk for PH according to the 2015 ESC/ERS PH guidelines.

Methods:
23 patients were randomized to iNO30 and 18 patients to placebo. The groups were comparable except for a higher percentage of patients with IPF in the treatment arm. After 8 weeks, patients were transitioned to an open-label extension period (OLE) with possible dose escalation to iNO45 then iNO75. iNO was administered using an investigational device as pulsed therapy, and the level of activity measured using a wearable actigraphy device. 6-minute walk distance (6MWD) was also measured at 0 and 8 weeks. Notably, patients were enrolled by assumed PH based on echocardiography and it remains unclear how many patients had RHC prior to enrollment.

Results:
At 8 weeks, the iNO30 group remained stable in overall level activity while a decline was observed in the placebo group (p 0.06). 23% of patients of the iNO30 arm had a >15% improvement in moderate/vigorous physical activity (MVPA) and 39% had a >15% decline in MVPA, compared to 0% and 71% respectively in the placebo arm. The largest difference in activity between the iNO30 treatment and placebo arms was in MVPA, with a 34% placebo

Article Summary by: Mohammad Dalabih, MBBS, MHA & Patricia George, MD

adjusted difference in favor of the active treatment arm (p = 0.02). Change in 6MWD and impact on oxygenation (SpO2 nadir during 6MWT, relative oxygen desaturation and distance saturation product) were not statistically significant between the experimental and control groups.
The therapy was well-tolerated with similar side effect profiles in the experimental and control groups.

GROUP OPINION

This is a 2b study that aimed at identifying the optimal end point for a phase 3 study of iNO in fILD. This study showed an overall improvement in MVPA in patients in the iNO group and a decline in the placebo group. Notably, a RHC was not required for enrollment and the patients were enrolled and stratified according to echocardiographic changes suggestive of PH. Further, the cohort size was small and may not be representative of the broader population. Despite the limitations, the short duration of the blinded period, and the requirement of continuous supplemental oxygen for the delivery of iNO, the results are encouraging and point toward the role of another inhaled agent as a potential therapeutic intervention in the challenging group of PH-ILD patients. A larger and more rigorous trial could help to determine where iNO belongs in the group 3 PH treatment cascade. A phase 3 study is currently ongoing to confirm these results in a larger cohort of patients.

On behalf of the PH Physicians: Mohammad Dalabih, MBBS, MHA; Andrew Freeman, MD; Marjorie P. George, MD; Darlene Kim, MD; Tim Lahn, MD, ATSF; Vera Pillitteri, DNP, FNP-BC; Suraj Sunder, MD

PH Journal Club dates and times njhealth.org/PHJournalClub