Treatment of chronic obstructive pulmonary disease in patients with different fractional exhaled nitric oxide levels

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Abstract

Some patients with chronic obstructive pulmonary disease (COPD) have eosinophilic inflammation which may be evaluated via the measurement of fractional exhaled nitric oxide (FeNO) like asthma. The aim of this prospective study was to assess whether FeNO levels can be used to identify patients with COPD with eosinophilic inflammation who may respond to inhaled corticosteroid (ICS) therapy.

This study included patients (N = 112) with COPD (age > 18 years) who were divided into 4 groups depending upon whether they had high (≥25 parts per billion [ppb]) or low (<25 ppb) pretreatment (baseline) FeNO and if they were treated with either ICS plus long-acting β-agonist (ICS + LABA) or a long-acting muscarinic antagonist (LAMA). The 4 groups were: high FeNO/ICS + LABA, high FeNO/LAMA, low FeNO/ICS + LABA, and low FeNO/LAMA. Outcomes assessed included FeNO, COPD assessment test (CAT), and pulmonary function.

The high FeNO/ICS + LABA group had the greatest reduction from baseline in FeNO levels (−25.80 ppb ± 27.14) compared with the high FeNO/LAMA, low FeNO/ICS + LABA, and low FeNO/LAMA groups (range, −4.45 to 1.31 ppb; P < .001). The high FeNO/ICS + LABA group also showed the greatest volume improvement in CAT (−7.20), which was statistically larger than the low FeNO/ICS + LABA and low FeNO/LAMA groups (−1.72 and −2.03, respectively). No difference in pulmonary function following treatment was observed across the 4 groups.

This study found that patients with high FeNO showed the greatest reduction in FeNO and improvement in CAT with ICS + LABA therapy, supporting the use of FeNO to identify patients who would benefit from ICS use.

Abbreviations: CAT = COPD assessment test, COPD = chronic obstructive pulmonary disease, FeNO = fractional exhaled nitric oxide, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = Global Initiative for Chronic Obstructive Lung Disease, ICS = inhaled corticosteroid, IL = interleukin, LABA = long-acting β-agonist, LAMA = long-acting muscarinic antagonist, MMEF = maximum mid-expiratory flow, ppb = parts per billion.

Keywords: chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, fractional exhaled nitric oxide, inhaled corticosteroid, inflammation, inhaled corticosteroids

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow obstruction that is poorly reversible and has an enhanced chronic inflammatory response.\textsuperscript{[1]} COPD is one of the most prevalent noninfectious diseases worldwide and is anticipated to become the 3rd leading cause of death across the world by 2020.\textsuperscript{[1]} The cost and health burden of COPD is high as it contributes to other comorbidities such as fractures, respiratory infections, osteoporosis, lung cancer, and cardiovascular disease.\textsuperscript{[1]}

Airway inflammation in COPD is thought to be mainly characterized by CD8+ lymphocytes, neutrophils, and macrophages. However, some patients with COPD may have features of asthma, a condition called asthma COPD overlap syndrome, and subsequently have Th2-mediated airway eosinophilia-based inflammation; about 20% to 40% of patients with COPD have eosinophilic inflammation.\textsuperscript{[1]} Th2-mediated airway inflammation can be evaluated through the measurement of fractional exhaled nitric oxide (FeNO).\textsuperscript{[1]} Epithelial cells of the bronchial wall produce nitric oxide gas in response to interleukin (IL) 13 and IL4 through the STAT-6 pathway.\textsuperscript{[2]} Several studies have found that FeNO levels are a strong predictor of the presence of eosinophilic inflammation in patients with COPD.\textsuperscript{[3,4]} One study found that aggressive treatment of patients with COPD to minimize sputum eosinophilia may decrease the incidence of severe exacerbations and hospitalizations.\textsuperscript{[3]} Measurement of FeNO using hand-held analyzers is a quick and easy method for measuring FeNO in clinical practice.
The COPD is a heterogeneous disease and patients can have differing phenotypes. The different phenotypes can affect treatment response to therapy.\[6,7\] Prior studies have found that patients with sputum eosinophilia during an exacerbation may be more responsive to corticosteroid treatment than those without eosinophilia.\[7\] In addition, other investigators have shown that FeNO levels may also be predictive of corticosteroid and bronchodilator treatment response.\[8-9\]

Monotherapy with inhaled corticosteroids (ICSs) is not recommended in the treatment of COPD, instead it is recommended to be co-administered with a long-acting β-agonist (LABA).\[1\] ICS treatment can be costly and can increase the risk of certain complications such as cataracts, glaucoma, pneumonia, and osteoporosis. Hence, it would be of benefit if ICS therapy could be targeted to patients with COPD with Th2-mediated inflammation who would have a greater likelihood of responding to ICS combination treatment.\[3\]

The purpose of the study was to evaluate if FeNO can be used to identify patients with COPD with eosinophilic inflammation who are more likely to respond to ICS+LABA therapy.

2. Methods

This prospective study was performed in accordance with the Declaration of Helsinki and complied with International Conference on Harmonization Good Clinical Practice and applicable regulatory requirements. The study was approved by Taipei Buddhist Tzu-Chi General Hospital’s Institutional Review Board. All subjects gave their written informed consent. The COPD is a heterogeneous disease and patients can have differing phenotypes. The different phenotypes can affect treatment response to therapy.\[6,7\] Prior studies have found that patients with sputum eosinophilia during an exacerbation may be more responsive to corticosteroid treatment than those without eosinophilia.\[7\] In addition, other investigators have shown that FeNO levels may also be predictive of corticosteroid and bronchodilator treatment response.\[8-9\]

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groups. Using the findings presented in Table 4, the cut-off for CAT improvement from baseline to 5 was established, and it could be determined whether baseline values influenced changes in CAT. In the high FeNO group receiving ICS+LABA, no differences were observed in baseline FeNO values between subjects with changes in CAT of <5 from baseline (n = 9) (43.22 ± 21.95) and those with a changes in CAT of >5 from baseline (n = 11) (61.73 ± 34.57) (P = .182). The patients in the high FeNO/ICS+LABA group had the greatest improvement in pulmonary function from baseline compared with the other 3 groups, although this did not reach statistical significance (P ≥ .072).

4. Discussion

The aim of this study was to assess whether baseline (pretreatment) FeNO can be used to identify patients who will respond to ICS+LABA therapy. The high FeNO/ICS+LABA group had the highest levels of FeNO at baseline, and was the only group to show a significant reduction (about –25.8%) from baseline in FeNO levels following therapy. This reduction was greater than the high FeNO/LAMA, low FeNO/ICS+LABA, and low FeNO/LAMA groups (~4.45%, +1.31%, +0.5% change, respectively; P < .001). However, the levels of FeNO in the FeNO/ICS/LABA group were still significantly higher than that in the 2 low FeNO groups. The high FeNO/ICS+LABA group showed the greatest improvement in CAT, which was statistically larger compared with the 2 groups with low baseline FeNO. No difference in pulmonary function was observed across the 4 groups. These findings indicate that FeNO can be used as a biomarker to identify patients with COPD who will respond to ICS+LABA treatment. Our findings are consistent with other studies that found that FeNO levels may predict treatment response to ICS and bronchodilatory therapy. Antus et al (2010) found that in patients with COPD (N = 58), who were hospitalized due to an exacerbation and treated with ICS and bronchodilators, a significant correlation between FeNO at admission and increase

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### Table 1

Summary of pretreatment FeNO, CAT, and pulmonary function test.

| Variables | Total | High FeNO | Low FeNO | P-value |
|-----------|-------|-----------|----------|---------|
| Demography |       | ICS + LABA | LAMA | ICS + LABA | LAMA |       |
| Gender, n (%) |       |           |        |          |        |        |
| Male       | 96 (85.7) | 17 (85.0) | 18 (90.0) | 30 (83.3) | 31 (86.1) | .923 |
| Female     | 16 (14.3) | 3 (15.0)  | 2 (10.0)  | 6 (16.7)  | 5 (13.9)  |       |
| Age, median (range) | 71.98 ± 12.29 | 67.33 ± 12.62 | 74.62 ± 11.02 | 74.03 ± 10.19 | 71.04 ± 14.18 | .72 |
| BMI, median (range) | 23.50 ± 3.74 | 22.17 ± 4.30 | 23.96 ± 3.31 | 23.80 ± 4.09 | 23.58 ± 3.31 | .36 |
| Smoking, n (%) |       |           |        |          |        |        |
| Never      | 31 (27.7) | 4 (20.0)  | 4 (20.0)  | 7 (19.4)  | 16 (44.4) | .059 |
| Ex-smoker  | 81 (71.2) | 16 (80.0) | 18 (90.0) | 30 (83.3) | 31 (86.1) |       |
| GOLD, n (%) |       |           |        |          |        |        |
| A          | 24 (21.4) | 3 (15.0)  | 4 (20.0)  | 6 (16.7)  | 11 (30.6) | .001 |
| B          | 59 (52.7) | 11 (55.0) | 13 (65.0) | 16 (44.4) | 19 (52.8) |       |
| C          | 6 (5.4)   | 0         | 1 (5.0)   | 4 (11.1)  | 1 (2.8)   |       |
| D          | 23 (20.5) | 6 (30.0)  | 2 (10.0)  | 10 (27.8) | 5 (13.9)  |       |
| Bronchodilator test, n (%) |       |           |        |          |        |        |
| Positive   | 30 (26.8) | 6 (30.0)  | 3 (15.0)  | 11 (30.6) | 10 (27.8) | .615 |
| Negative   | 82 (73.2) | 14 (70.0) | 17 (85.0) | 25 (69.4) | 26 (72.2) |       |

FeNO = fractional exhaled nitric oxide, GOLD = Global Initiative for Chronic Obstructive Lung Disease, ICS = inhaled corticosteroid, LABA = long-acting β-agonist, LAMA = long-acting muscarinic antagonist.

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### Table 2

Summary of pretreatment FeNO, CAT, and pulmonary function test.

| Variables | Pretest | High FeNO | Low FeNO | P-value |
|-----------|---------|-----------|----------|---------|
| FeNO, ppb | 53.40 (40.09–66.71) | 36.80 (31.43–42.17) | 14.25 (12.54–15.96) | 14.36 (12.65–16.07) | <.001 |
| CAT       | 20.85 (16.69–25.01) | 15.05 (12.40–17.70) | 16.11 (13.17–19.05) | 14.19 (11.98–16.40) | .062 |
| Pulmonary function test | | | | | |
| FVC, L    | 2.27 (1.94–2.60) | 2.31 (2.02–2.63) | 1.93 (1.75–2.11) | 2.32 (2.10–2.54) | .024 |
| FVC % predicted | 77.95 (69.74–86.16) | 81.35 (76.47–86.23) | 72.42 (68.15–78.69) | 78.50 (73.95–83.00) | .204 |
| FEV, L    | 1.31 (1.09–1.53) | 1.42 (1.16–1.66) | 1.16 (1.02–1.30) | 1.48 (1.32–1.64) | .019 |
| FEV, % predicted | 57.30 (48.85–65.75) | 64.50 (57.97–71.03) | 54.86 (50.06–59.66) | 64.08 (59.87–68.29) | .029 |
| FEV, FVC  | 58.15 (52.61–63.79) | 61.30 (56.68–66.02) | 61.50 (56.36–66.64) | 64.14 (61.18–67.10) | .305 |
| MMEF, L/s | 0.71 (0.53–0.89) | 0.85 (0.67–1.03) | 0.76 (0.56–0.96) | 0.91 (0.75–1.07) | .394 |
| MMEF % predicted | 30.50 (23.03–37.97) | 39.60 (32.45–46.75) | 33.72 (27.47–39.97) | 37.94 (33.06–42.82) | .267 |

CAT = COPD assessment test, FeNO = fractional exhaled nitric oxide, FVC = forced expiratory volume in 1 second, FVD = forced vital capacity, ICS = inhaled corticosteroid, LABA = long-acting β-agonist, LAMA = long-acting muscarinic antagonist, MMEF = maximum mid-expiratory flow, ppb = parts per billion.

* All values are mean (95% confidence interval).

† Paired t-test indicated findings were significantly different than the high FeNO and ICS + LABA group.

‡ Paired t-test indicated findings were significantly different than the low FeNO and ICS + LABA group.
in FEV₁ following treatment (r=0.441; P < .001); patients with higher FeNO levels at admission responded better to treatment. They found that the best cut point for FeNO as a predictor for significant increase in FEV₁ was 26.8 ppb. Kunisaki et al (2008) observed that among smokers with severe COPD (mean FEV₁, 1.07 L, 36% predicted) patients who responded to ICS treatment (fluticasone propionate 500 µg twice daily) had higher FeNO levels at baseline compared to nonresponders (46.5 ppb vs 25 ppb, P = .028). Akamatsu et al (2011) investigated 14 patients with COPD treated with tiotropium plus fluticasone propionate plus salmeterol found that baseline FeNO > 35 ppb and the presence of atopy were predictive of improvement in FEV₁ with ICS+LABA therapy. Zietkowska et al (2005) evaluated the usefulness of FeNO in anticipating ICS response in patients (N = 47) with stable COPD. They found FeNO levels were elevated in current and ex-smokers and that in both these groups ICS therapy resulted in a significant reduction in FeNO without significant changes in FEV₁ after 2 months of treatment. Similar to Zietkowska et al, we found ICS+LABA treatment resulted in significant reduction in FeNO with little change in pulmonary function. The difference in findings between our study and that of Zietkowska et al compared with the other studies may reflect differences in patient populations and treatment regimens used.

Endogenous nitric oxide is a signaling molecule that is made by airway epithelium and inflammatory cells. Nitric oxide plays an important role in regulating airway and vascular function. Nitric oxide is produced by 3 isoforms of nitric oxide synthase and the activity of at least 1 isoform may be inhibited by corticosteroids in COPD. The levels of FeNO in COPD appear to be influenced by several factors such as smoking status and severity of disease. Increased levels of FeNO have been observed in patients during an exacerbation of COPD. Also lower levels of FeNO were observed in ex-smokers and mild/moderate COPD. Smoking may confound measurement of eosinophilic inflammation using FeNO as it may induce nitric oxide independent of inflammation. However, 1 study found a significant correlation between the levels of FeNO and sputum eosinophils regardless of smoking status in patients with COPD. Increases in exercise tolerance due to pulmonary rehabilitation may also increase FeNO.

Current guidelines for the management of COPD recommend limiting ICS use to patients with more severe disease and/or at risk...
for an exacerbation.\textsuperscript{11} ICS use is associated with several negative effects such as cataracts, glaucoma, pneumonia, and osteoporosis. Currently, there is inappropriate overuse of ICS in real-life practice, raising questions regarding the clinical benefit and long-term risk of ICS use, and the waste of health care resources.\textsuperscript{7} Many patients being prescribed ICS do not meet the recommended criteria for ICS use.\textsuperscript{18} It is estimated that ICS are used by >70\% of patients with COPD and is given as initial therapy in >50\% of newly diagnosed cases, usually in combination with a LABA.\textsuperscript{20} A recent large randomized controlled study (N = 2485) designed to evaluate the effect of withdrawal ICS from background LABA therapy on treatment of COPD found that not all patients benefit from the inclusion of ICS in their treatment regimen.\textsuperscript{6} They found only certain COPD phenotypes benefited from ICS therapy, particularly those with severe-to-very-severe COPD.\textsuperscript{6} These findings highlight the need to identify biomarkers that can distinguish which patients with COPD may benefit the most from ICS use so as to help guide the management of the disease. Our findings indicate that high pretreatment FeNO levels may be a biomarker for patients who will respond to ICS + LABA therapy.

The present study has several limitations that must be considered. The study population was small and was performed in a single institution in Taiwan. Hence, it is not clear if the results would be translatable to other types of healthcare systems or geographic regions. Larger international studies are required to further assess the role of FeNO levels for indicating ICS treatment response in patients with COPD.

In conclusion, this study found that patients with COPD with high pretreatment FeNO respond better to ICS + LABA therapy, as evaluated by reduction in FeNO and improved CAT, than patients with high baseline FeNO not treated with an ICS or patients with low baseline FeNO treated with either ICS + LABA or LAMA. The results are consistent with FeNO being a biomarker that can be used to help identify patients with COPD in which ICS therapy may be beneficial.

Author contributions
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Mei-Chen Yang: Data acquisition; Critical manuscript revision
Sin-Yi Chen: Data analysis or interpretation; Manuscript drafting; Critical manuscript revision
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