

detecting alterations in systemic vasodilatory response in patients with abnormalities of the pulmonary vasomotor biology. ■

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Fractional Exhaled Nitric Oxide Monitoring Does Not Improve Asthma Management in Children with Concordant and Discordant Asthma Phenotypes

To the Editor:

Fractional exhaled nitric oxide (F_{ENO}) is a biomarker of eosinophilic airway inflammation, but studies on adjusting asthma therapy on repeated measurements of F_{ENO} have shown only minor benefits (1). However, patients with specific asthma phenotypes might benefit from F_{ENO} monitoring. In particular, in patients with “discordant phenotypes” (high inflammation, low symptoms or high symptoms, low inflammation), an inflammation-driven strategy might be beneficial (2). The aim of our study was (1) to assess the presence and stability of concordant and discordant asthma phenotypes in children and (2) to assess whether children with a discordant phenotype were more likely to benefit from adjusting treatment to F_{ENO} than children with a concordant phenotype.

We performed a preplanned subgroup analysis of the Better Asthma Treatment: Monitoring with ACT and Nitric Oxide (BATMAN) study, a prospective randomized controlled trial on monitoring strategies in children with asthma (3). At baseline, children with atopic asthma aged 4 to 18 years who used inhaled corticosteroids for at least 3 months completed the (childhood) asthma control test (C-ACT or ACT) (4), and their F_{ENO} was measured. Subsequently, a 4-week diary was filled in, and treatment was not changed. After these 4 weeks, ACT and F_{ENO} were repeated, and children were randomly allocated either to a group in which treatment was adapted every 4 months to F_{ENO} and ACT or to a standard care group with ACT measurement every 4 months. After 1 year, the 4-week diary, ACT, and F_{ENO} were repeated. Primary endpoint was the proportion of symptom-free days (SFD), defined as days without daytime or nighttime symptoms.

On the basis of their ACT and F_{ENO} , patients were classified as having a concordant or discordant phenotype. Concordant

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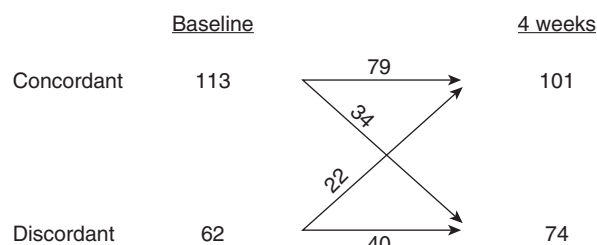


Figure 1. Number of children with a concordant or discordant phenotype at baseline and after 4 weeks.

was defined as well-controlled asthma and normal F_{ENO} , or uncontrolled asthma and elevated F_{ENO} . Discordant was defined as uncontrolled with normal F_{ENO} or well controlled with high F_{ENO} . Cutoffs were an ACT score of 20 and 25 ppb for F_{ENO} . Significance of differences was compared by analysis of covariance. Data were analyzed with SPSS 21.0 (SPSS for Windows 21.0). Limit of significance, $P = 0.05$ (two-sided).

Ninety-two children were allocated to the F_{ENO} group, and 89 to the standard care group. Six patients dropped out. At the start, 113 children (65%) had a concordant and 62 (35%) a discordant phenotype. After 4 weeks, the phenotype had remained stable in 119 children (68%); the remainder had switched from concordant to discordant or the reverse (Figure 1).

Forty (34%) of 119 children had a stable discordant phenotype. Their change in SFD did not differ between the F_{ENO} and the standard care group after 1 year ($P = 0.9$). Seventy-nine children (66%) had a stable concordant phenotype. Again, the changes in SFD did not differ between the groups after 1 year. Similarly, the change in SFD did not differ between the F_{ENO} group and the standard care group in children with an unstable phenotype.

Overall, children with stable phenotypes showed no change in SFD during the study, whereas children with unstable phenotypes showed a significant and substantial improvement in SFD during the 1-year follow-up, with or without F_{ENO} monitoring (Table 1).

We demonstrated that F_{ENO} monitoring did not improve SFD in children with asthma (3) and hypothesized that F_{ENO} monitoring might be specifically useful for patients with a discordant phenotype, but the present analysis showed that this was not the case.

Our results seem to disagree with findings by Haldar and colleagues, who found that management aimed at reducing sputum eosinophils reduced exacerbations in the inflammation-predominant discordant cluster and reduced inhaled corticosteroids in the symptom-predominant discordant cluster (2). Although patient numbers were similar, different populations (refractory asthma vs. mild to moderate asthma), different ages (adults vs. children), the use of sputum eosinophils versus F_{ENO} , and different endpoints (exacerbations vs. SFD) may all account for these discrepancies. It could be argued that our cut-off value of 25 ppb for F_{ENO} to define the phenotype may have been too low. However, this seems unlikely, as results were similar when we repeated our analysis with a higher cut-off of 50 ppb (data not shown). Similarly, our cut-off for ACT may have been too low (5), but here also, results were similar with cut-offs ACT ≥ 23 and C-ACT ≥ 22 . As the agreement among F_{ENO} , sputum eosinophils, eosinophils in bronchoalveolar lavage, or endobronchial biopsies is moderate to weak, the use of more direct markers of inflammation might have led to different results (6).

We showed for the first time that discordant phenotypes are common, but often unstable, in children. This could be explained by the fact that airway inflammation in a highly selected population of children is variable and does not necessarily

Table 1. Baseline Values and Changes from Baseline

	Fractional Exhaled Nitric Oxide			Standard Care		
	Stable Discordant (n = 19)	Stable Concordant (n = 42)	Unstable Phenotype (n = 26)	Stable Discordant (n = 21)	Stable Concordant (n = 37)	Unstable Phenotype (n = 30)
Baseline (t = 4 wk)						
Age, yr	9.7 (3.7)	10.5 (2.8)	10.6 (3.1)	11.1 (3.7)	9.9 (2.7)	9.9 (3.2)
Sex, male, n (%)	13 (68)	29 (69)	16 (62)	16 (76)	26 (70)	18 (60)
Inhaled corticosteroids, μ g	400 (400–800)	400 (400–800)	400 (400–800)	400 (400–800)	400 (400–800)	400 (400–500)
Fractional exhaled nitric oxide, ppb [†]	26.2 (16.0–45.1)	14.8 (10.2–22.3)	14.7 (9.8–28.2)	35.2 (19.6–55.5)	15.7 (10.0–23.7)	21.7 (8.5–33.2)
FEV ₁ , %pred	97.3 (10.4)	98.3 (11.3)	89.6 (13.8)	93.8 (15.9)	91.9 (14.6)	95.7 (11.9)
(C-)ACT	20.1 (5.4)	22.0 (4.1)	19.5 (3.0)	21.1 (3.4)	21.6 (3.4)	20.4 (3.1)
SFD, %	53 (33)	62 (32)	39 (35)	57 (34)	62 (33)	42 (35)
Changes from baseline						
SFD, %	6 (–5 to 18)	2 (–9 to 14)	20* (4 to 36)	8 (–8 to 23)	–1 (–12 to 10)	18* (5 to 30)
SFD (per 28 d)	1.7 (–1.4 to 5)	0.6 (–2.5 to 3.9)	5.6 (1.1 to 10)	2.2 (–2.2 to 6.4)	–0.3 (–3.4 to 2.8)	5 (1.4 to 8.4)
(C-)ACT	1.9* (0.4 to 3.4)	1.0 (–0.3 to 2.2)	2.6* (0.9 to 4.3)	0.2 (–2.0 to 2.4)	–0.2 (–1.4 to 1.0)	1.2 (–0.2 to 2.6)
ICS, μ g	116 (–10 to 242)	–212 (–299 to –125)	–108 (–243 to 28)	10 (–134 to 154)	–137 (–225 to –49)	0 (–114 to 114)

Definition of abbreviations: %pred = % predicted; ACT = asthma control test; C-ACT = childhood asthma control test; ICS = inhaled corticosteroids; SFD = symptom-free days.

Data shown are mean (SD), median (interquartile range), or mean difference (95% confidence interval of the difference) unless otherwise indicated.

*Significant at $P < 0.05$.

[†]Geometric mean.

correlate with symptom changes (7, 8). Indeed, several studies have indicated that correlations between inflammation and symptoms are weak or absent in patients with asthma (9, 10), suggesting these reflect different aspects of asthma. We speculate that common exposures, specifically viral airway infections, may transiently alter the relationship between inflammation and symptoms in children with asthma.

We conclude that discordant phenotypes were common and often unstable in children with asthma. FeNO-guided treatment was not more effective in children with discordant phenotypes. ■

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Toward Primary Prevention of Asthma: Role of Corticosteroids for the First Rhinovirus Wheeze

To the Editor:

We thank Dr. Feldman and colleagues for the interesting review on the association between early-life respiratory syncytial virus and rhinovirus (RV)-induced lower respiratory tract infections and subsequent asthma (1). In line with the review, we have shown in our Vinku study that RV is the most common pathogen causing the first wheezing episode necessitating hospitalization in the first 3 years of life (2–4). Also, RV-induced first wheezing episode in these children was an important risk factor for the initiation of regular asthma control therapy in a 7-year follow-up (hazard ratio [HR], 3.5; 95% confidence interval [CI], 1.5–8.3) (3). Other clinical factors included sensitization (HR, 3.5; 95% CI, 1.6–8.3), eczema (HR, 2.3; 95% CI, 1.1–4.9), and age younger than 1 year (HR, 2.5; 95% CI, 1.3–4.7) (3).

Feldman and colleagues emphasize finding early intervention strategies to prevent asthma in children who are susceptible to early-life RV infections. We have found that treatment with oral corticosteroids (OCS) may decrease the risk for recurrent wheezing and asthma in the hospitalized first-time wheezing children affected by RV (2, 3, 5). The Vinku study showed in a *post hoc* analysis of a randomized controlled trial that OCS reduced the risk for recurrent wheezing in 12-month (HR, 0.2; 95% CI, 0.05–0.7, adjusted to young age, eczema, sensitization, and maternal asthma) (2) and 7-year (HR, 0.3; 95% CI, 0.1–0.9, adjusted respectively) follow-ups (3). The Vinku2 study, using a prospective randomized controlled trial

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