

month of HCQ treatment, and as we clearly emphasized, a trial of 3 to 12 months is necessary to assess the effectiveness of HCQ in antihistamine-refractory CSU patients. As we stated, the delay in onset of action for CSU is consistent with what has been observed with HCQ in treating autoimmune disorders.³

Our study was unique because it described treatment outcomes in a large, well-defined CSU patient population that had failed standard therapy before starting HCQ (n = 111) or omalizumab (n = 134). We acknowledge in the discussion that the retrospective nature of the study is a limitation, and a prospective placebo-controlled trial should be conducted in the future. This would be possible in an ideal world in which extramural funding is readily available for conducting well-powered controlled clinical trials to justify repurposing old drugs such as HCQ for a new CSU indication. For this reason, it is unlikely that large double-blind placebo controlled studies of HCQ or other anti-inflammatory drugs (eg, methotrexate or sulfasalazine) will ever be conducted. Cyclosporin is one exception for which placebo-controlled studies have shown efficacy for CSU.⁴ However, more than 60% of patients experience adverse effects to cyclosporin, and close laboratory monitoring for renal toxicity is required, which limits its use.^{5,6}

There is clearly an unmet need for alternative therapeutic agents to address refractory CSU patients who are unresponsive to omalizumab and for patients who are unable to afford long-term treatment with biologic agents. We are hopeful that future treatment parameters or guideline committees will consider HCQ in future CSU treatment algorithms, even in the absence of DBPC studies. The authors applaud *The Journal of Allergy and Clinical Immunology: In Practice* for publishing these retrospective real-world data showing the clinical effectiveness and safety of HCQ in CSU. Ultimately, clinicians and patients are the final arbiters in selecting safe and effective management options, including some not yet incorporated in practice guidelines.

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Clinically accessible biomarkers to assess the modifiable risk of asthma/wheezing attacks in toddlers



To the Editor:

We read with interest the work by Fitzpatrick et al¹ on the prognostic and theragnostic value of blood eosinophils in pediatric asthma. In their *post hoc* analysis of three randomized controlled trials, the authors combined patients of all treatment arms to deliver a biomarker-stratified analysis of asthma attack occurrence according to the baseline blood eosinophil count. The analysis, conducted in 1,074 toddlers (12- to 71-month-olds) with recurrent wheezing, showed a higher risk for wheezing episodes requiring rescue systemic corticosteroids or hospitalization with increasing blood eosinophil counts. Sensitization to one or multiple allergens was associated with 54% to 92% increased odds of exacerbations requiring rescue systemic corticosteroids, compared with none. The prognostic value of blood eosinophils was enhanced when associated with atopic sensitization, particularly food sensitization. Finally, using the single trial with FeNO measurements (CARE-MIST), the authors report that reductions in FeNO were greater with maintenance than with intermittent inhaled corticosteroids, but did not report the prognostic and theragnostic value of FeNO.

It struck us that the observations of Fitzpatrick et al¹ regarding the modifiable risk for wheezing episodes conferred by raised blood eosinophil counts in these pediatric trials are concordant with those observed in school-age children, adolescents, and adults with asthma of any severity (aged 6 to less than 12 years² and aged 12 years and older^{3,4}). Considering the established association between FeNO and the number of sensitizations,⁵ it is likely that the study population's toddlers with a greater number of sensitizations also would have had a raised FeNO. We note the absence of a predictive/responder analysis using combinations of blood eosinophils and FeNO in the report, but we understand that this would have been underpowered. Nevertheless, it would have been interesting to show the attack rates of the two treatment arms in CARE-MIST stratified by blood eosinophils and FeNO quadrants, similar to the *post hoc* analysis of the VOYAGE trial in 6- to less than 12-year-olds with moderate to severe asthma. In VOYAGE, placebo-treated children with higher baseline blood eosinophils and FeNO ($\geq 0.15 \times 10^9/L$ and ≥ 20 parts per billion (ppb), respectively) had a sixfold increase in adjusted annualized asthma attack rates compared with those with low-low biomarker values ($< 0.15 \times 10^9/L$ and 20 ppb): 0.82 versus 0.13 attacks/y. Moreover, children with high-high baseline biomarkers showed the greatest relative and absolute treatment effects of type 2 targeting anti-inflammatory therapy compared with placebo, and those with low-low values showed no effect: $\downarrow 65\%$ (-0.53 attacks/y) versus $+35\%$ ($+0.04$ attacks/y).² FeNO may have additive value to the blood eosinophil count with regard to the prediction of asthma attacks with placebo and the likelihood of treatment response with type 2 targeting anti-inflammatory therapy. Were these results also seen in the trial population of toddlers in Fitzpatrick et al¹ who had blood eosinophils and FeNO measured?

Differences between children and adults with regard to the modifiable risk posed by type 2 inflammation seem to be minimal.

Indeed, the results of the VOYAGE biomarker-stratified analysis are similar to those observed in adults, with the exception of a greater prognostic and theragnostic value of FeNO in children with low blood eosinophils.² We suggested that blood eosinophils and FeNO identify an abnormal inflammatory process in the systemic and airway compartments, respectively.⁶ Therefore, children with asthma may have more epithelial/atopic-driven type 2 inflammation and would benefit more from anti-inflammatory therapies directed toward that process.⁷

There is a growing case for an asthma attack risk scale based on the additive prognostic and theragnostic value of clinically accessible biomarkers across asthma severities.^{3,4} The results of the research by Fitzpatrick et al¹ and VOYAGE² suggest a potential utility for stratifying risk plus treatment opportunities by blood eosinophils and other clinically accessible biomarkers, including atopic sensitization when FeNO is not feasible.

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Reply to "Clinically accessible biomarkers to assess the modifiable risk of asthma/wheezing attacks in toddlers"



To the Editor:

Couillard and colleagues¹ raise important and interesting questions about the utility of FeNO measurements in detecting the risk for future asthma and/or wheezing exacerbations in preschool children. Our recent analysis² demonstrated that elevated blood eosinophil cut points in preschool children, particularly when combined with sensitization variables, were associated with higher exacerbation rates and improved responses to initiation of daily inhaled corticosteroid (ICS) treatment in exploratory analyses. Given the limited number of children with FeNO measurements in our study, we did not perform a predictive/responder analysis with combinations of blood eosinophils and FeNO. We present here the results of an exploratory analysis to address the authors' queries.

Baseline offline FeNO measurements were available from 178 children from the Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers study (NCT00675584), including 85 children assigned to intermittent ICS treatment and 93 children assigned to daily ICS treatment. FeNO concentrations were divided into tertiles according to the following cut points: 7.01 parts per billion (ppb) or less (defined as low FeNO), 7.02 to 12.86 ppb, and 12.87 ppb or greater (defined as high FeNO). We then examined exacerbation occurrence and exacerbation rates after treatment initiation in children with higher FeNO and higher blood eosinophils (using two selected blood eosinophil cut point thresholds: 150 cells/ μ L and greater and 300 cells/ μ L and greater), comparing them with those of children with lower FeNO and lower blood eosinophils (Figure 1). When combined with higher blood eosinophils, higher baseline FeNO concentrations were associated with a reduction in exacerbation occurrence with daily ICS treatment