

Authors' response



We express our appreciation to the authors of the correspondence in response to our article. Fractional exhaled nitric oxide (FeNO) is a noninvasive biomarker reflecting allergic airway inflammation in asthma. Some reports have suggested relations between FeNO and bronchial hyperresponsiveness and airway obstruction. In our study, we concluded that increased mean FeNO levels could indicate annual declines of forced expiratory volume in 1 second in patients with asthma. This suggests that increased FeNO levels might provide useful information on airway impairment and inflammation in asthma. We could not find an association between FeNO and asthma exacerbation.¹ However, our previous studies have shown that fluctuations and changes in FeNO levels might be indicative of asthma control and predictive of exacerbation.^{2,3} In support of these findings, a recent study reported that FeNO and forced expiratory volume in 1 second changing in opposite directions boosted the ability of FeNO to reflect asthma control.⁴

The correspondence authors have advocated a crucial point regarding the role of FeNO in obstructive airway diseases. Their recent work showed the usefulness of FeNO as a risk identifier of perioperative and postoperative pulmonary complications in patients who smoke and have chronic obstructive pulmonary disease (COPD).⁵ For application to the clinical setting, further research into the mechanism of NO production in patients with COPD might be required. However, the clinical relevance of FeNO in COPD has been gradually established in recent studies,⁶ several of which have shown that increased FeNO in COPD also could be a variable signal for increased spirometric response to inhaled corticosteroids.⁷ In COPD, FeNO might be not only an inflammatory marker but also a marker of therapeutic effect.

Asthma and COPD overlap has gained attention and raised primordial questions about the definition and discrimination of each disease. A recent study described a classification of chronic obstructive airway diseases based on the presence of a T-helper cell type 2 signature.⁸ This T-helper cell type 2 classification

appropriately differentiated 2 groups of patients with different clinical expressions that can be considered treatable traits to guide therapy, irrespective of taxonomic diagnoses. In this regard, FeNO might be an adjunct for simply identifying the presence of high inflammation associated with T-helper cell type 2.

Regarding future studies, concomitant use of FeNO and other biomarkers such as periostin and blood eosinophil counts would provide new insights into the classification of obstructive airway diseases. These biomarkers that integrate with airway inflammation and functional change could help the adaptation of precision medicine to clinical practice.

Suguru Sato, MD, PhD
Junpei Saito, MD, PhD
Department of Pulmonary Medicine
School of Medicine
Fukushima Medical University
Fukushima, Japan
suguru@fmu.ac.jp

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Treatment with omalizumab or cyclosporine for resistant chronic spontaneous urticaria?



Koski and Kennedy¹ review omalizumab and cyclosporine for the treatment of antihistamine-resistant chronic spontaneous (idiopathic) urticaria. Although appropriately indicating cetirizine to be used in up to 4 times the maximum recommended dose, they indicate adding a leukotriene receptor antagonist, diphenhydramine, or hydroxyzine as a second step. However, a systematic review concluded that leukotriene receptor antagonists were not effective as monotherapy or in combination with antihistamines.² Diphenhydramine is a less potent and shorter-acting antihistamine than hydroxyzine,³ and hydroxyzine is a prodrug for cetirizine, so its addition would just add more cetirizine.⁴

Of greater interest is the potential for omalizumab or cyclosporine to induce a sustained remission. Chronic spontaneous urticaria can continue for years, although eventual spontaneous resolution occurs.

A questionnaire of 372 adults with a 68% response rate reported complete spontaneous remission after the diagnosis for 29% and 44% at 5 and 10 years, respectively.⁵ A study of 92 children with chronic spontaneous urticaria, aged 4 to 15 years, identified remissions of 18.5%, 54.0%, and 67.7% at 1, 3, and 5 years, respectively.⁶

A placebo-controlled clinical trial of omalizumab for chronic urticaria unresponsive to antihistamines provided complete resolution of symptoms for 44%; others had varying degrees of improved symptoms.⁷ Hives generally returned on discontinuation of omalizumab therapy. Patients with chronic spontaneous urticaria needed continuous omalizumab treatment for longer than 6 months without evidence that the natural course of chronic urticaria was altered.⁸ Treatment would therefore need to be continued until the natural history of spontaneous remission occurred.

In contrast, a controlled clinical trial of cyclosporine use in adults in 2000 suggested that sustained remission occurred for some patients after cessation of use of the medication.⁹ A subsequent report described sustained remissions in a pediatric population after

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treatment of antihistamine-resistant chronic urticaria with cyclosporine.¹⁰ That study used a microemulsion formulation with improved absorption characteristics compared with the product used in the older study of adults. In addition, safety and efficacy were improved by use of therapeutic drug monitoring to guide cyclosporine dose. The addition of cyclosporine to the 16 patients in that study resulted in initial resolution of urticaria after a median of 7 days. A slow taper and discontinuation of cyclosporine treatment followed the cessation of hives. Eleven of the 16 continued free of hives with no relapse or medication requirements for up to several years of follow-up. Five responded initially with absence of hives but subsequently relapsed after a median of 6 months. All 5 responded promptly to resumption of cyclosporine therapy. Thus, cyclosporine promptly controlled the antihistamine-resistant urticaria and was associated with prolonged periods free of hives after discontinuation of cyclosporine therapy. Toxic effects of the cyclosporine were not apparent in these patients.

Cyclosporine therefore appears to induce sustained remission of antihistamine-resistant chronic spontaneous urticaria, permitting patients to be free of hives even on early discontinuation of use of the medication, a feature not associated with omalizumab. Further investigation of cyclosporine as a treatment that induces sustained remission of antihistamine-resistant chronic urticaria is therefore indicated, using the most appropriate formulation of cyclosporine with therapeutic drug monitoring to guide the dosage.

Miles Weinberger, MD
Department of Pediatrics
University of Iowa
Iowa City, Iowa

Department of Pediatrics
University of California
Rady Children's Hospital
San Diego, California
miles-weinberger@uiowa.edu

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Authors' response

We thank the author for placing a spotlight on our review¹ and for pointing out additional areas of discussion regarding the treatment of resistant chronic spontaneous urticaria. The intent of our review was to briefly summarize the efficacy, safety, and drug characteristics of omalizumab and cyclosporine, the medications currently recommended to treat resistant chronic spontaneous urticaria.

The author mentions the need to consider a prior systematic review from 2008 focusing on the use of leukotriene receptor antagonists that was not included in our analysis.² Because our article focused on the 2014 practice parameter update³ and the use of omalizumab and cyclosporine, we did not include reviews of other medications. Also, we focused on randomized controlled trials of omalizumab and cyclosporine that assessed medication efficacy and safety. Thus, survey-type or disease progression studies not looking at omalizumab or cyclosporine were excluded from our review.

The author also highlights the study by Maurer et al⁴ that was included in our review and evaluated sustained remission. It is important to note that we focused our analysis on the primary efficacy end point related to symptom scores but realize that sustained remission is an important long-term outcome. The author also points out 2 other studies (Grattan et al⁵ and Neverman et al⁶) published in 2000 and 2014, respectively, that evaluated cyclosporine treatment. Our National Library of Medicine–PubMed search conducted in early 2017 did not produce these studies. We agree with the

author that these studies provide additional information that support cyclosporine's use in chronic spontaneous urticaria. We also agree that further investigation into cyclosporine's ability to induce sustained remission of antihistamine-resistant chronic urticaria is needed, including investigation into formulation dependency and systemic exposures required for efficacy.

Renee Koski, PharmD, CACP, FMPA*
Katelin K. Kennedy, PharmD†

*Ferris State University College of Pharmacy
Marquette, Michigan
†Walgreens
Marquette, Michigan
renee.koski@mghs.org

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