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Authors' response



We read the correspondence by Andersen et al¹ with great interest. They made a number of important comments on our study of skin pain in atopic dermatitis (AD)² that we would like to address. Severe pain and itch were found to exist concomitantly in a significant proportion of patients with AD. To clarify this point, we re-evaluated the data and found that most patients had some itch in the past 24 hours (98.4%). Interestingly, there were numerically lower rates of skin pain in those with vs without itch in the past 24 hours (46.2% vs 75.0%). This fits with the observation that pain generally inhibits itch as observed in healthy subjects. In contrast, 97.4% of patients who reported any skin pain also reported itch in the past 24 hours. There also was a modest correlation between itch and skin pain published in our study (Spearman $\rho = 0.43$).² Together, there appears to be a substantial proportion of patients with AD who experience itch and pain simultaneously. These results could certainly fit with the speculated mechanism of a maladaptive central inhibitory processing of itch leading to a blunting of normal pain-induced itch suppression.

Unfortunately, we did not explicitly ascertain whether the patients actually experienced itch and pain simultaneously or sequentially as itch bouts resulting in scratching and pain. However, we found that 16.8% of patients believed their skin pain was part of their itch and not at all related to scratching. Of course, patients might not recognize the connection of their scratching and skin pain. We further examined the group of patients with pain reportedly from itch and unrelated to scratching and found some

fascinating associations. Patients who reported their skin pain was related to itch alone had significantly lower Patient-Oriented Eczema Measure ($P = .01$ by Mann-Whitney U test) and self-reported global AD severity ($P = .006$), but no differences of Dermatology Life Quality Index, 5-Dimensions Itch Scale, Eczema Area and Severity Index, or Scoring Atopic Dermatitis. These results should be interpreted cautiously because of limited statistical power. Nevertheless, they suggest that even patients with mild AD can experience skin pain. In addition, they suggest that some patients experience itch and pain simultaneously.

We agree that skin pain is an important symptom with potential therapeutic implications. We hope further studies from our group and other research groups will shed light on the best treatment approaches for skin pain in AD.

Jonathan I. Silverberg, MD, PhD, MPH*[†]
Kevin R. Patel, BS[‡]
Vivek Singam, BS[‡]

*Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Feinberg School of Medicine at Northwestern University, Chicago, Illinois

[†]Northwestern Medicine Multidisciplinary Eczema Center, Chicago, Illinois

[‡]Department of Dermatology, Feinberg School of Medicine at Northwestern University, Chicago, Illinois
JonathanSilverberg@gmail.com

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Baseline asthma burden, comorbidities, and biomarkers in omalizumab-treated patients in PROSPERO



We read with interest comments from Oppenheimer and Greenberger¹ highlighting the baseline findings of the PROSPERO

trial that describe a real-world population with moderate to severe asthma accompanied by multiple comorbidities, a substantial disease burden, and a heterogeneous biomarker profile who began a treatment regimen with omalizumab.² We agree with their conclusions that patients with severe asthma represent a challenging population and that multiple factors must be considered when evaluating patients as candidates for biologic therapies. Highlighting imperfections in some of the supporting data cited in the editorial is important.

Oppenheimer and Greenberger¹ refer to a pharmacoeconomic analysis conducted by Oba and Salzman³ to describe the economic impact of omalizumab. Notably, as reflected by their discussion, this model included only direct costs and did not account for important indirect costs associated with poorly controlled asthma that also impact its global economic burden, including presenteeism and

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absenteeism. Beyond true indirect costs are additional costs that should be considered, including corticosteroid-associated adverse events that extend well beyond the low acquisition costs associated with oral corticosteroids,^{4,5} and comorbid conditions that increase asthma morbidity and mortality.⁶ Importantly, treatment with omalizumab has been shown to improve allergic rhinitis, one of the most common comorbid conditions, and withdrawal of omalizumab has been associated with increased exacerbations in patients with allergic asthma.⁷ Moreover, successfully stepping down omalizumab in a group of patients on long-term therapy has been described, decreasing long-term treatment costs while maintaining asthma control.⁸ Unfortunately, high-quality pharmacoeconomic data evaluating biologic treatment costs in patients with uncontrolled asthma that include all relevant components are limited, and application of analyses that use limited inputs must be approached cautiously.

Oppenheimer and Greenberger¹ review evidence that patients with type 2 phenotype asthma are more likely to respond favorably to omalizumab.⁹ Although this assertion is in part designed to be addressed by the full results of PROSPERO, the interpretation that type 2 asthma responds “better” to omalizumab may not be accurate. The data indicate that both high- and low-biomarker asthma respond to a similar favorable degree, and the important difference is in the placebo group. Thus, the difference in apparent response to omalizumab between high- and low-biomarker asthma reflects a higher risk for adverse outcomes if asthma is not effectively treated. This finding does not appear to be unique to omalizumab; data from other biologic therapies also have displayed this influence of the placebo group on results that imply better responses in type 2 high-phenotype asthma.¹⁰ Therefore, among the biologics as a group, biomarkers that define a type 2 high phenotype likely define patients who will not do as well clinically, without a biologic therapy.

With the availability of biologics for the treatment of uncontrolled allergic asthma, clinicians need additional data that help them ascertain the economic impact of treatment based on models that account for indirect as well as direct treatment costs.

Allan T. Luskin, MD*
Bradley E. Chipps, MD†

Thomas B. Casale, MD‡
Noelle M. Griffin, PhD§

*HealthyAirways, LLC
Madison, Wisconsin

†Capital Allergy & Respiratory Disease Center
Sacramento, California

‡Morsani College of Medicine
University of South Florida
Tampa, Florida

§Genentech, Inc.
South San Francisco, California
griffin.noelle@gene.com

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Authors' response

In our editorial, “Baseline asthma burden, comorbidities, and biomarkers in omalizumab-treated patients in PROSPERO,”¹ regarding the observational study,² we stated that “the clinician must consider the great cost associated with these agents,” referring to omalizumab. A supporting reference³ did not include indirect costs (absenteeism from school or work, psychologic harms, and economic hardships of uncontrolled asthma), although we did mention them. Luskin et al⁴ point out that there are indirect benefits from omalizumab that would improve its value (benefits vs costs; ie, cost-effectiveness ratio). Recent studies from Japan⁵ and Canada⁶ described

limited effectiveness of omalizumab from the cost-benefit perspective, but neither study included an analysis of indirect costs. The approximate average acquisition costs in US dollars from a wholesaler of subcutaneously administered biologics for persistent asthma are more than \$1,000 for 150 mg of omalizumab, more than \$2,800 for 100 mg of mepolizumab, and more than \$4,700 for 30 mg of benralizumab. Biologic therapies for persistent asthma have helped many patients reach levels of control not achievable with pharmacotherapy, avoidance measures, and allergen immunotherapy and, in particular, have decreased the number of exacerbations and hospitalizations. Perhaps data and consensus will emerge such that biologic therapies should be used for phenotype-, endotype-, or genotype-derived good-responder patients with persistent asthma at steps 3 or 4 (instead of solely step 5) of the Global Initiative for Asthma guidelines.⁷ Nevertheless, as we argued, “In light of the expense of biologic agents, we need as much useful information as possible to identify the best responders and to know when it is time to discontinue a specific therapy and consider others.”¹

Paul A. Greenberger, MD*
John J. Oppenheimer, MD†

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