

Preparing for the Next Big Thing in Asthma Management

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The discovery of corticosteroids in 1936,¹ their subsequent application for asthma treatment first reported in 1950,² the development and testing of inhaled corticosteroid products allowing for safer chronic use in the 1970s,³ and the diffusion of guidelines in the 1990s recommending inhaled corticosteroids as controller medications⁴ have substantially improved the outlook for the millions of individuals around the world suffering from asthma. What's the next big thing for asthma? Currently, there are several candidate asthma drugs and potential biomarkers that may allow prediction of treatment response undergoing various testing phases.⁵ The introduction of omalizumab to the United States in 2003 as treatment for individuals with moderate to severe persistent allergic asthma has taught us many important lessons about the use of a biologically targeted asthma treatment.⁶ One of these important lessons is that we need to be able to identify the individuals who are most likely to benefit from these medicines, because not all patients with asthma will respond to these targeted treatments and because the costs of new drugs are likely to be too high to allow for anything but application to a narrowly targeted group of patients with asthma. Preparing for the next big thing in asthma management requires research focused on populations of patients with asthma who stand to benefit most from new treatments.

In this issue of *Journal of Allergy and Clinical Immunology: In Practice*, Zeiger et al⁷ share the results of an observational study involving nearly 10,000 patients cared for within a health care maintenance organization in California from 2010 to 2011. The authors capitalize on health care data collection within this organization that includes electronic administrative pharmacy data, allowing them to determine asthma risk level and to estimate adherence to asthma medications. Four comparator groups were created using the baseline year (2010): high-risk/high-adherent, high-risk/low-adherent, low-risk/high-adherent, and low-risk/low-adherent. Using these baseline designations, the outcomes in the subsequent year were compared. Not surprisingly, the risks for asthma exacerbations in the follow-up year (2011) were higher in those with baseline high-risk and those in the high-risk/low-adherent group had the poorest outcomes. The main limitations of the findings are inherent to retrospective studies. The investigators were limited to

previously collected data and in particular the lack of pulmonary function testing data and the inability to more accurately define medication adherence. In addition, the report included adult patients only and may not apply similarly to children with asthma.

One of the main findings of this report is the high disease burden for patients in the high-risk/high-adherent group. This group, which comprised 11% of the cohort, has poor outcomes despite receiving asthma controller medications at an adherence level of at least 75%. What are the possible explanations for these findings?

The first and most obvious explanation is that currently available medical therapy is not effective for this group of patients. These findings are similar to those reported in The Epidemiology and Natural History of Asthma: Outcomes and Treatment regimens study, which also found a high disease burden in patients currently being treated at step levels 4 to 6.⁸ Similarly, in a prospective study involving asthma medication step up until control was achieved—the Gaining Optimal Asthma Control study—most but clearly not all individuals achieved asthma control.⁹ Indeed, many investigators are addressing this gap by pursuing novel drug trials targeting individuals not responding adequately to existing therapies; an example of this activity is a recent trial with mepolizumab.¹⁰

A second explanation for these findings is that there are factors besides medications that contribute significantly to outcomes. The authors pursued this explanation by exploring relationships between other variables besides risk and adherence that influence subsequent-year outcomes, and identified care with an allergist as significantly associated with a lower frequency of 2 or more asthma exacerbations and excessive short acting β -agonist dispensing. They also identified several comorbid conditions, including obesity, rhinitis, chronic sinusitis, and pneumonia, as associated with increased asthma exacerbations, highlighting the authors' conclusions that attention to comorbid conditions in the management of asthma is warranted.

A third explanation for the findings that 11% of the current study population is high-risk despite high adherence is that adherence is inadequately captured with pharmacy-dispensing data; some patients may not be actually taking the inhalers with proper technique after they are dispensed.¹¹ Thus, some individuals counted within that 11% may actually not be highly adherent. However, some of the individuals in the high-risk/low-adherent cohort may be intentionally nonadherent because adequate trials of existing medications were ineffective. Some of these patients may be excellent candidates for trials of novel asthma medications. It is likely that all 3 explanations—current treatments are not completely effective in all patients, non-medication factors are important, and true adherence may be overestimated—are partly correct. This leaves many promising pathways to target as we aim for improved care for individuals with asthma in the future.

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Conflicts of interest: M. A. Rank declares that he has no relevant conflicts of interest. Received for publication June 25, 2015; accepted for publication June 26, 2015.

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J Allergy Clin Immunol Pract 2015;3:991-2.
2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2015.06.022>

There are a couple of additional key messages for clinicians that can be taken away from this analysis. First, population-based outcome tracking is likely a useful approach to identify individuals who may be targeted for interventions, such as higher step level treatment, more specialist care, attention to comorbidities, and use of existing and future biologicals. Whether categorizing patients into a high-risk/high-adherent category and targeting them with such interventions will specifically lead to improved population-level asthma outcomes remains to be studied. Second, 26% of this study cohort was in the high-risk/low-adherent category, suggesting an even larger group of individuals who may benefit from programs that promote adherence to asthma controller medications. Third, the authors have confirmed a previous finding that meeting the Healthcare Effectiveness Data and Information Set quality measure for asthma medication prescribing is insufficient to change asthma outcomes.¹² This information may be very helpful when choosing asthma quality measures.

In summary, Zeiger et al used a rich data set to identify, characterize, and describe outcomes of high-risk and highly adherent adult patients with asthma. We should keep these patients in mind as we think about whom to target when the next big thing for asthma comes along.

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