

have consistently suggested that they are of limited value but hoped that future development of more potent CCBs would demonstrate efficacy.^{4–6}

In this month's *Annals*, Chiu et al⁷ examine the efficacy of CCBs on lung function in asthma by performing a meta-analysis of the data, specifically assessing their potential effects on exercise-induced asthma, BHR, and resting lung function. For exercise-induced asthma, CCB use resulted in a statistically significant decrease in mean maximal percentage of decrease in postexercise forced expiratory volume in 1 second, lessening the decrease by approximately one third ($P < .001$). For resting lung function, postdose forced expiratory volume in 1 second significantly improved ($P = .01$), but only by 0.08 L, with no significant change in forced vital capacity or peak flows. This modest bronchodilation was further confirmed with studies of BHR with direct-acting bronchoconstrictors (histamine and methacholine) that failed to demonstrate significant improvement with the addition of CCBs.

There are several limitations to this analysis as noted by Chiu et al. There were several different classes of CCBs analyzed, including dihydropyridines (nifedipine, felodipine, and darodipine), phenylalkylamines (gallopamil and verapamil), and benzothiazepines (diltiazem). Although all these CCBs block the L-type calcium channel, which is responsible for airway smooth muscle contraction,⁸ consideration of the specific CCB could be of importance. This is exemplified in the case of resting lung function, in which nifedipine and darodipine demonstrated significant improvement in baseline forced expiratory volume in 1 second ($P < .01$ for each), whereas diltiazem and felodipine demonstrated no such efficacy ($P = .24$ and $P = .5$, respectively). In addition, the studies included only patients with mild asthma, and heterogeneity, unknown selection bias, small samples, and lack of control of baseline medicines were problematic.

Overall, this meta-analysis confirms prior reviews on the topic, that there is minimal bronchodilator effect and no antagonism against direct-acting bronchoconstrictive agents that measure BHR. Hoping for more potent CCBs is unlikely to be fruitful because they could produce greater systemic adverse effects. Of interest is the modest protection in exercise-induced asthma that could

indicate a significant mast cell stabilizing effect. Although not as great as that produced by β_2 -agonists or leukotriene receptor antagonists,⁹ further research might be warranted on this topic. Future studies should include larger numbers of subjects and consider stratification of the CCB used. In the meantime, CCBs are certainly reasonable agents to consider in patients with cardiac disease and asthma, but alas do not result in the treatment of 2 illnesses with 1 pill.

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



The Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) study was designed to better understand the types of patients who are begun on omalizumab in the real-world setting, including asthma burden, comorbidities, and biomarker profiles, and to evaluate what clinical parameters might be associated with better outcomes with the use of this biologic agent. In this month's issue of the *Annals*, Griffin et al¹ report on the first of these 2 outcomes.

Disclosures: Dr Oppenheimer is a consultant for GSK, Teva, DBV, Kaleo, and Church & Dwight; is on the adjudication committees of Quintiles, PRA, and ICON; is associate editor of the *Annals of Allergy, Asthma and Immunology* and *Allergy Watch*; is chief editor of *Medscape* (pulmonary); and a reviewer for *UptoDate*. Dr Greenberger has received consulting fees from Allergy Therapeutics; is on the Food and Drug Administration Pulmonary and Allergy Drugs Advisory Committee; receives royalties from *UptoDate* and Wolters, Kluwer, Lippincott, Williams and Wilkins; is a reviewer for *UptoDate*; and receives research support from the Immune Tolerance Network (including Amgen) of the National Institute of Allergy and Infectious Diseases.

To make this trial as real world as possible, minimal inclusion and exclusion criteria were required for enrollment, thus allowing the physician to use solely clinical judgment when identifying appropriate candidates for omalizumab treatment in subjects at least 12 years old with persistent allergic asthma. To better understand the characteristics of patients begun on omalizumab, extensive baseline assessment was undertaken, including spirometry, fractional exhaled nitric oxide, complete blood cell count and differential, periostin levels, Asthma Control Test, Asthma Quality of Life Questionnaire for 12 Years and Older, Work Productivity and Activity Impairment: Asthma, Mini Rhinoconjunctivitis Quality of Life Questionnaire, and evaluation of total and specific immunoglobulin E levels to perennial and seasonal allergens.

Griffin et al found, not surprisingly, that most adolescents were male, whereas most adults were female in this study's makeup. Prior to the use of short acting beta agonist, baseline forced expiration volume in 1 second was 87.9% in the adolescent group and 74.2% in the adult group, with a bronchodilator response of 7.9% and

8%, respectively, and with 48.1% of the population classified by physicians as having moderate and 47.8% as having severe persistent asthma.

Although most patients were on combination therapy, the group still had a mean of 3.3 exacerbations in the past year, with 22% who required hospitalization within the 12 months before study onset. Approximately 10% of patients had been previously intubated for exacerbations of asthma. Asthma control as measured by the Asthma Control Test demonstrated that most cases were “not well controlled,” with multiple comorbidities, including allergic rhinitis, gastroesophageal reflux disease, sinusitis, and depression reported by 22% of patients. Most patients had poly-sensitization, with 80% of adolescents and 74% of adults demonstrating sensitization to at least 3 allergens.

There are several points demonstrated by this study that deserve special attention. Although physicians categorized 48.1% as having moderate and 47.8% as having severe asthma, control measures would indicate that most of this population should have been categorized as having severe asthma. Griffin et al¹ suggest several potential explanations for this discordance, including lack of physician understanding of guideline stratification or difficulty in applying this stratification in the real world, especially when patients are already receiving therapy. Furthermore, this study demonstrated that significant heterogeneity was seen in the biomarker profile of those enrolled in the study. As an example, the mean fractional exhaled nitric oxide was 34.3 ppb (SD 33.7). Similarly, the mean level for immunoglobulin E was 580.7 IU/mL (SD 2654.8) and the mean absolute eosinophil count was 297 cells/ μ L (SD 256). All these issues are of potential concern when one considers that disease severity and phenotypic discriminators are guides for appropriate use of biologic agents. Furthermore, many patients likely would not have met the inclusion criteria for a randomized controlled trial that required a particular biomarker be elevated.

When considering the use of biologic agents such as omalizumab, the clinician must consider the great cost associated with the use of these agents.² As an example, a study by Oba and Salzman³ argued that in light of the cost, this agent should be considered only in patients with severe and uncontrolled asthma with high health care use. In their analysis, they suggested that only patients who are hospitalized more than 5 times or more than 20 days per year be candidates for omalizumab from a pharmacoeconomic perspective. However, one might argue that in those patients with uncontrolled asthma, there are significant indirect costs such as missed school or work, or in those able to go to work, there is decreased productivity owing to encumbrance from uncontrolled asthma. Certainly patients with asthma with less severe disease would likely benefit from the use of biologic agents; however, the health care system would be further stressed with the use of biologic agents in this population. Thus, even when taking indirect costs into account, this medicine would be best used in patients with persistent asthma, as suggested by the Global Initiative for Asthma guidelines, in which biologics are placed in step 5 or the most severe group of patients.⁴ Furthermore, when considering the patient population who will

have greatest efficacy through the use of omalizumab, studies demonstrate that those with a type 2 high phenotype will most likely benefit from its addition. This is clearly demonstrated in the EXTRA study, in which Hannania et al⁵ found that in a group of patients with severe asthma who had demonstrated sensitivity to a perennial allergen, greater efficacy to omalizumab was seen in those with further indication of a type 2 high phenotype. Specifically, they found that after 48 weeks of therapy, decreases in protocol-defined exacerbations were greater in the subgroup with a type 2 high vs low inflammatory profile: fractional exhaled nitric oxide, 53% (95% confidence interval [CI] 37–70; $P = .001$) vs 16% (95% CI 232–46; $P = .45$); eosinophils, 32% (95% CI 11–48; $P = .005$) vs 9% (95% CI 224–34; $P = .54$); and periostin, 30% (95% CI 22–51; $P = .07$) vs 3% (95% CI 243–32; $P = .94$).

When considering all these factors, the near real-world PROSPERO study highlights the need to be more selective when considering appropriate patients to be begun on biologic agents. Moreover, the current classification system for asthma causes confusion in its use, because if even 1 criterion is in the severe range, the patient is considered to have severe, not moderate, asthma. Further, when considering the addition of a biologic agent in patients with uncontrolled or severe asthma, we need to better understand which inflammatory profile(s) or phenotype(s) would indicate greater likelihood of efficacy. We also must take into account the fact that this patient population is very complex, often with concomitant comorbidities that can contribute to asthma symptoms. 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. In the end, there is no substitute for careful monitoring of our clinical decisions and reassessing intervention based on the level of control.

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