



Clinical use of biologics for asthma treatment by allergy specialists

A questionnaire survey

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ABSTRACT

Background: Asthma is a heterogeneous disease with emerging phenotypes and endotypes. At present, 5 distinct biologics are Food and Drug Administration–approved as an add-on therapy for difficult-to-control type 2–high asthma. Because allergy specialists manage a spectrum of diseases for which biologics may be appropriate, it is important to understand their prescribing patterns.

Objective: To elucidate the allergist's use of biologics in the treatment of asthma, including barriers, preferences, indications for prescribing, measures to determine effectiveness, and cost-effectiveness.

Methods: A survey was performed among allergists using a semistructured 10-item self-administered web-based questionnaire and the responses were analyzed using one-way frequencies and multiple logistic regression.

Results: The response rate was approximately 9%. Omalizumab was the most prescribed biologic for asthma (98%), and “uncontrolled asthma despite adherence to controller medication” was the most common reason. The common selection criteria among the biologics included elevated peripheral eosinophil count, asthma with nasal polyps, and asthma type (type 1; type 2; nonallergic). A decreased exacerbation frequency was the best standard to determine the efficacy among biologics. Benralizumab was considered the most cost-effective.

Conclusion: This study represents one of the largest surveys among allergy specialists regarding the real-world use of asthma biologics. It seems that there has been reasonably good dissemination and application of current guidelines among allergists based on prescribing patterns. However, their responses reflect the need for the continued modification of asthma guidelines that incorporate novel biologics and other pathway-specific agents into step therapy. As clinical phenotypes and predictive biomarkers develop, allergy specialists will be better prepared to practice precision medicine that optimizes the use of asthma biologics.

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Introduction

Asthma is recognized as a heterogeneous disease with emerging phenotypes and endotypes.¹ It has been broadly categorized into 2

subtypes. One is referred to as type 2–high, characterized by increased eosinophils in peripheral blood and lung tissue associated with increased proinflammatory interleukin (IL)-4, IL-5, and IL-13 cytokines released from a variety of effector cells. The other subtype, type 2–low, is characterized by either neutrophilic or paucigranulocytic airway inflammation with T_H1-type cytokines and greater resistance to glucocorticoids.^{1,2} There are 5 distinct biologics currently approved by the Food and Drug Administration as an add-on therapy for difficult-to-control type 2 (T2) asthma.³ These agents are now recommended as step 5 add-on treatments for patients with severe asthma not responsive to a combination of inhaled corticosteroids/long-acting β -agonists (ICS, LABA), long-acting muscarinic receptor blockers (LAMA) and or leukotriene-modifying

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agents. With the emergence of new asthma phenotypes and endotypes, the management of asthma will require a more tailored precision medicine approach requiring the expertise of allergy and pulmonary specialists to help advise patients on which agent is most appropriate for their condition using shared decision making.^{4,5} Because allergy specialists manage a spectrum of diseases, such as asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), atopic dermatitis, and urticaria—for which biologics are now approved—it is important to understand their prescribing patterns. Therefore, the objective of this study was to elucidate the use of biologics by allergists in the treatment of asthma, including the barriers, preferences, indications for prescribing, measures to determine effectiveness, and cost-effectiveness by conducting a survey using a web-based physician questionnaire.

Methods

A semistructured 10-item self-administered web-based questionnaire was designed and hosted on REDCap, Vanderbilt University, Nashville, Tennessee, to elicit information from allergy specialists regarding their use and experiences with biologics in the management of asthma (eSupplement). The survey was conducted between September 2019 and December 2019. Participation in this study was unpaid and voluntary. Specific information was obtained about the physician's opinion regarding patient selection criteria, the most appropriate biologic for their patient's specific clinical profile, and the cost-effectiveness of biologics in asthma. The survey questionnaire was intended to be applied very similarly to in-person interviews or paper-based methods used in clinical research. However, web-based survey methods maintain data or information equivalence and avoid bias resulting from sociocultural differences among survey participants. Data equivalence refers to the extent to which the elements of a research design have the same meaning and can be applied equally in diverse cultural settings.⁶ The inability to establish data equivalence in cross-cultural studies may bias experimental conclusions and statistical inferences. When collecting data from groups or individuals working in apparently different settings with the aim to pool or compare such data, the data collection instruments must have similar measurement qualities across such settings. As such, the research methods and the data collection instrument should be equivalent in different stages of survey research to minimize the sources of heterogeneity among subgroups. In this web-based survey, we aimed to maximize the equivalence at the design phase.

The questionnaire excluded sensitive personal information and was, therefore, exempted from continuing oversight by the institutional review board at each participating site. The survey questionnaire was distributed only once in September 2019 by the American College of Allergy, Asthma, and Immunology (ACAAI) to registered clinicians who are members of the ACAAI (n = 3505), of which 300 responded (8.6%) till December 2019.

Statistical Analysis

Survey responses were retrieved and analyzed for the 300 participants who completed the cross-sectional survey. After the assessment of the data quality using standard procedures, the percentage of respondents for each value of the individual questions in the questionnaire was determined by one-way frequency tables.

Multiple logistic regression analysis determined the significant factors associated with the cost-effectiveness of biologics. Although the outcomes were subjective measures, they were recorded and analyzed as a dichotomous response (ie, whether a biologic is considered cost-effective, by the clinicians, for the treatment for asthma). The analysis was adjusted for the different methods used for determining a biologic's effectiveness (eg, increased forced

expiratory volume in 1 second [FEV1], decreased exacerbation), selection criteria for biologics (eg, asthma phenotype, age of asthma onset), practice settings, and clinical experience of the clinician. All statistical analyses were performed using SAS, version 9.4 (Cary, North Carolina).

The Chi-square Test of Homogeneity

The sample data were compared by clinical training (ie, pediatric vs internal medicine [IM] or medicine-pediatric) among the participants. The χ^2 test was performed to determine significant differences in the type of clinical training with their age range, sex, clinical experience, board certification, preferences for prescribing specific biologics for treating asthma, and their opinion on the cost-effectiveness of biologics.

Results

Demographics

Among the 300 respondents, 161 (56%) were men, 133 (48%) had been in practice for more than 20 years, 159 (57%) practiced in private single-specialty setting, and 120 (45%) were trained in internal medicine vs 129 (49%) in pediatrics (Table 1). The distribution of respondents by their age range is also listed in Table 1. Respondents in the age group greater than 55 years (n = 125) represent approximately 45% of the total respondents, whereas those aged between 31 and 55 years (n = 157) represent approximately 57% of the total number of respondents (missing = 22). Thus, there was fair representation by age groups. The average age of the US allergy/immunology physician workforce was 52 years in 2009 (n = 4446).⁷ Among them, 29% were women, 95% had completed an allergy/immunology training program, and 91% were board-certified. Thus, in comparison with the allergy/immunology physician workforce (2009), this study had a greater proportion of respondents who were women (ie, 41% of all respondents vs 29% of the total workforce) and a lower percentage were board-certified (ie, 83% of respondents vs 94% of the total workforce). Geographic and racial data distribution were not collected.

Univariate Analysis

Frequently Prescribed Biologics

A total of 287 (98%) reported prescribing biologics for asthma (Table 2). Omalizumab was the most prescribed biologic (262; 89%) followed by benralizumab (238; 80%), and reslizumab was the least prescribed (32, 11%).

Reasons for Prescription

The most frequent reasons for prescribing a biologic were uncontrolled asthma despite adherence to controller medication as instructed (280; 95%) and recurrent exacerbations requiring treatment with glucocorticoids (271; 92%) (Table 3).

Selection of Biologics

The common criteria for selection of biologics to treat patients with asthma were as follows: (1) elevated peripheral blood eosinophil counts (271; 92%); (2) asthma with CRSwNP (247; 83%); (3) type of asthma (ie, type 1 [T1]/T2/nonallergic) (244; 82%); and (4) exacerbation frequency (226; 76%) (Table 4). In addition, insurance coverage of the biologic, as a nonclinical factor, influenced the choice of a biologic in most respondents (246; 83%). Among them, the consideration for insurance coverage was greater among women respondents than men (90% vs 80%, $P = .02$) and the among younger age group (<30 years old); although this age group included only 6 respondents, all considered insurance coverage of the biologic while prescribing biologics. It was not influenced

Table 1

Demographics of the Physicians Participating in the Survey with Descriptive Features Classified by Age Groups

Odds ratio	Age group (y)						Row total	P value
	≤30	31–35	36–40	41–45	46–55	>55		
Sex, n (%)								
Female	5 (83%)	26 (79%)	16 (57%)	16 (42%)	19 (39%)	35 (28%)	117	<.0001
Male	1 (17%)	7 (21%)	12 (43%)	22 (58%)	29 (59%)	90 (72%)	161	
Years of clinical experience, n (%)								
≤5	4 (67%)	30 (91%)	12 (43%)	3 (8%)	1 (2%)	1 (1%)	51	<.0001
6–10	2 (33%)	3 (9%)	12 (43%)	20 (53%)	1 (2%)	0 (0%)	38	
11–15	0 (0%)	0 (0%)	1 (4%)	14 (37%)	18 (37%)	0 (0%)	33	
16–20	0 (0%)	0 (0%)	2 (7%)	1 (3%)	17 (35%)	2 (2%)	22	
>20	0 (0%)	0 (0%)	1 (4%)	0 (0%)	10 (20%)	122 (98%)	133	
Type of practice, n (%)								
Academic	3 (50%)	12 (36%)	6 (21%)	9 (24%)	9 (18%)	19 (15%)	58	.03
Other	0 (0%)	2 (6%)	2 (7%)	2 (5%)	3 (6%)	1 (1%)	10	
Private multispecialty	2 (33%)	7 (21%)	7 (25%)	4 (11%)	4 (8%)	27 (22%)	51	.04
Private single-specialty	1 (17%)	12 (36%)	13 (46%)	22 (59%)	33 (67%)	78 (62%)	159	
Training, ^a n (%)								
Internal Medicine	1 (20%)	14 (47%)	13 (50%)	14 (39%)	21 (48%)	57 (46%)	120	
Medicine–Pediatrics	0 (0%)	4 (13%)	2 (8%)	4 (11%)	5 (11%)	0 (0%)	15	
Pediatrics	4 (80%)	12 (40%)	11 (42%)	18 (50%)	18 (41%)	66 (54%)	129	

NOTE: The number and percentages (column percentage) indicate the number of respondents and their percentages within the respective age group. The row total for the features (ie, sex, years of clinical experience) do not add up to 300 because of missing values for those features.

^aIncludes all respondents irrespective of board certification.

significantly by the type of practice (academic vs private), or training (IM vs pediatrics) (data not indicated).

Measures to Determine the Effectiveness of Biologics in Asthma

The common measures used in clinical practice were decreased exacerbation (279; 94%), glucocorticoid-sparing effect (254; 85.8%), and decreased use of rescue albuterol (243; 82%) (Table 5). Surprisingly, biomarkers such as peripheral blood eosinophilia, fractional exhaled nitric oxide (FeNO), or asthma quality of life questionnaire were less frequently used as determinants of effectiveness, despite the fact that the first biomarker was the chief criterion for the selection of biologics.

Perceptions on Cost-Effectiveness

Opinions regarding cost revealed that 28 (10%) respondents considered biologics to be very cost-effective, and 33 (11.5%) considered them as not cost-effective (Table 6). Approximately half of the respondents considered cost-effectiveness to be either partial (82; 28.7%), or variable among patients (83; 29%). Several others (60; 21%) found it difficult to estimate the cost-effectiveness in clinical practice.

Multiple Logistic Regression

Use-Case for Biologics

Use-case for biologics refers to the specific clinical condition or therapeutic purpose in which a specific biologic could potentially be prescribed or preferred. Omalizumab was the biologic of choice for the atopic asthma phenotype (Table 7). The odds of selecting this therapy for atopic asthma was 3.7 times greater than other biologics ($P = .005$). Benralizumab, mepolizumab, and dupilumab were the

Table 2

Total Number of Respondents Who Prescribe Biologics for Treating Asthma

Biologics prescribed	n (%) (out of 294)
Omalizumab (2003)	262 (88.5%)
Benralizumab (2017)	238 (80.4%)
Dupilumab (2017)	224 (75.7%)
Mepolizumab (2015)	214 (72.3%)
Reslizumab (2016)	32 (10.8%)

Abbreviation: FDA, Food and Drug Administration.

NOTE: There are 287 of 294 respondents (97.6%, missing = 6). The year of FDA approval for treating asthma is indicated in parenthesis.

most preferred biologics for asthma with CRSwNP, the respective odds ratios (OR) were 3.6 ($P = .006$), 4.1 ($P = .0004$), and 5.8 ($P < .0001$), respectively. Benralizumab was preferred because of its less frequent dosage schedule, whereas mepolizumab was preferred when adherence to maintenance treatment (ICS/LABA or LAMA inhaler) was indicated. Dupilumab was highly preferred for T2 asthma (OR, 4.0; $P = .001$) and in patients with elevated FeNO (OR, 2.7, $P = .01$). Reslizumab was preferred for aspirin-exacerbated disease (OR, 3.2, $P = .01$) and in adult patients (OR, 4.0, $P = .0008$) (Table 7).

Cost-Effectiveness of Biologics in Asthma

Among all biologics, benralizumab was considered most cost-effective when an increase in FEV1 was used as an effectiveness measure (Table 8). The adjusted OR for such cost-effectiveness was 2.3 ($P = .01$).

Most medicine-pediatric physicians were in the mid–age range compared with pediatrics/IM-trained physicians, but there were no significant differences in sex distribution ($P = .17$), by type of training among the respondents, or with respondents with less than 5 years of clinical experience.

Comparison by Clinical Training

The medicine-pediatrics–trained respondents were in the age range of 33 to 55 years, and nearly half of the adult- and pediatrics-trained respondents were above 55 years old (Table 9). In terms of sex distribution, approximately a third (33.3%) of the adult-trained

Table 3

Reasons for Prescribing Biologics in Asthma

Reason	Number of respondents out of 296, % (n) (missing = 4)
Uncontrolled asthma despite adherence to controller medication as instructed	94.6% (280)
Uncontrolled asthma despite avoidance of triggers for asthma (eg, occupational exposures, tobacco smoke)	53.7% (159)
When treatment of associated medical conditions could make asthma worse (eg, ASA or other drug desensitization, allergen immunotherapy, food allergy)	36.8% (109)
Recurrent exacerbations requiring treatment with glucocorticoids	91.6% (271)

Abbreviation: ASA, acetylsalicylic acid.

Table 4
Selection Criteria for Biologics

Criteria	Number of respondents out of 296, % (n) (missing = 4)
Eosinophilia (peripheral blood)	91.6% (271)
Chronic rhinosinusitis with nasal polyps	83.45% (247)
Insurance coverage of the biologic	83.1% (246)
Type of asthma (T1/T2/nonallergic) ^a	82.4% (244)
Exacerbation frequency	76.4% (226)
Route of administration (intravenous vs subcutaneous)	71.9% (213)
Atopy	69.6% (206)
FDA approval status of the biologic	66.2% (196)
Decreased FEV1	63.5% (188)
Adherence to treatment	60.8% (180)
Efficacy of biologic in clinical trials	57.8% (171)
Comorbidities	52.7% (156)
Less frequent dosage	51% (151)
Aspirin-exacerbated disease	47.97% (142)
Elevated NO	40.9% (121)
Less adverse effects	40.5% (120)
Age of asthma onset	20.9% (62)
Race	3% (9)

Abbreviations: FDA, Food and Drug Administration; FEV1, forced expiratory volume in 1 second; NO, nitric oxide; T1, type 1; T2, type 2.

^aThis choice in the questionnaire intended to ask whether the type of asthma (ie, whether allergic asthma or nonallergic asthma, without any specification) influenced the physician's prescriptions for biologics for treating asthma. However, there were no distinct choices for allergic or nonallergic asthma.

respondents were women compared with 46.5% of pediatric- and 53.3% of medicine-pediatrics-trained respondents. Nearly half of both the adult- and pediatrics-trained but only 6.7% of medicine-pediatrics-trained respondents reported being in clinical practice for more than 20 years ($P = .06$). However, training background did not influence the type of practice (ie, academic or private) ($P = .51$). Omalizumab was equally preferred for treating asthma regardless of their training ($P = .50$), whereas mepolizumab ($P = .05$), dupilumab ($P = .005$), and benralizumab ($P = .03$) were more frequently preferred by adult-trained than pediatrics-trained respondents. Opinions on the cost-effectiveness of biologics for treating asthma did not differ significantly between these respondents ($P = .80$). Approximately 92% of the adult-trained, 40% of medicine-pediatrics-trained, and 85% of pediatrics-trained respondents reported themselves to be board-certified ($P < .0001$).

Discussion

The results of this survey conducted among 300 allergists offer a glimpse into the real-world management practices using biologics in the United States. In view of the 5 biologic therapies now available and the pipeline for severe asthma, there has been recent interest in identifying the optimal patient selection strategies for these treatments. The choice between biologics becomes difficult, given the lack of head-to-head data to expedite these decisions.

Table 5
Measures to Determine Effectiveness in Decreasing Order of Frequency

Measure	Number of respondents out of 296, % (n) (missing = 4)
Decreased exacerbation	94.26% (279)
Glucocorticoid-sparing effect	85.81% (254)
Decreased use of rescue albuterol	82.09% (243)
Asthma control test	58.78% (174)
Increased FEV1	55.1% (163)
Biomarkers (Eos % in peripheral blood, FeNO)	25% (74)
Asthma Quality of Life Questionnaire	15.88% (47)
Other	4.73% (14)

Abbreviations: Eos %, relative eosinophil count; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second.

Table 6
Perceptions on Cost-Effectiveness (A Subjective Measure) of Biologics in Asthma

Cost-effectiveness	Number of respondents out of 286, % (n) (missing = 14)
Varies among patients	29.02% (83)
Partially cost-effective	28.67% (82)
Difficult to estimate in clinical practice	20.98% (60)
Not cost-effective	11.54% (33)
Very cost-effective	9.79% (28)

Although indirect treatment comparisons have been performed, the results are often incongruent.⁸ Several recent treatment paradigms have aimed at standardizing this approach, but the question of how biologics are chosen in clinical practice remains unanswered. This survey indicates that most of those surveyed (97.6%) are prescribing biologics, and to a large extent, real-life practices correspond to evidence-based recommendations. However, there were some interesting thought processes in their prescribing patterns that warrant further discussion.

First, respondents considered biologic therapy to be very cost-effective if the FEV1 increased, as compared with all other efficacy measures. Although the measurement of lung function is a quantifiable, objective, standardized outcome, it was not the primary outcome for the omalizumab studies or any of the anti-IL-5 studies, none of which exhibited increases in prebronchodilator percent FEV1 of more than 160 mL.^{9–11} This specific end point improvement may be considered modest when compared with dupilumab, which was exhibited to increase this value by up to 300 mL in clinical trials.¹² However, many patients with severe asthma who have fixed airway obstruction with marginal improvements in FEV1 still report significant benefits from these biologic therapies, manifested as significant changes in other clinically relevant end points such as reduced asthma exacerbations.

In addition, the respondents felt that benralizumab had significantly higher odds of being considered more cost-effective in treating asthma than other biologics (Table 8); this is despite the lack of head-to-head comparison trials among agents and that the current recommendations for individual biologic use among various asthma phenotypes are generally of low-quality evidence.¹³ Furthermore, indirect estimates of interdrug efficacy reveal incongruous results and do not support overt benefit for any one agent.¹⁴ It should also be noted that all IL-5 biologics and dupilumab were found to be effective in both atopic and nonatopic eosinophilic phenotypes.^{13,15} Interestingly, fewer pediatric-trained respondents noted a preference for benralizumab. Whereas 2 of the 3 anti-IL-5 agents are approved for pediatric use, childhood asthma is phenotypically distinct from adult asthma, which could account for this discordance with the internal medicine-trained respondents. Ideally, direct comparisons among anti-IgE, anti-IL-4/IL-13, and anti-eosinophil agents are necessary to facilitate optimal treatment selection in this population and in all severe asthma phenotypes, although it is unlikely to happen in the near future.¹⁶

A comorbid CRSwNP was also a relevant influence in selecting a specific treatment choice. However, there was a discordance between the preferential prescription of biologics for CRSwNP as a distinct disease compared with its treatment as a component of aspirin-exacerbated respiratory disease (AERD). Although the survey indicates an overall inclination toward the use of dupilumab, benralizumab, and mepolizumab for all patients with CRSwNP, respondents were 3 times as likely to prescribe reslizumab for a diagnosis of AERD. Whereas the underlying mechanisms of AERD have yet to be fully delineated, recent studies have evaluated the efficacy of biologics in this condition. Omalizumab seemed to decrease urinary leukotriene E4 levels in 1 small trial.¹⁷ Dupilumab (approved for CRSwNP) and both mepolizumab and benralizumab

Table 7
Criteria For Selecting One Biologic Over Another

Biologic	Odds ratio ^a (95% CL), <i>P</i> value	Comments (references)
Omalizumab		
Atopy	3.65 (1.47, 9.06), <i>P</i> = .005	
Benralizumab		
CRSwNP	3.64 (1.46, 9.07), <i>P</i> = .006	Less preferred by respondents who are pediatric-trained only vs med, med-ped, and board-certified.
Less frequent dosage	2.91 (1.30, 6.50), <i>P</i> = .009	
Mepolizumab		
CRSwNP	4.09 (1.88, 8.89), <i>P</i> = .0004	The efficacy of mepolizumab is not affected by the presence of NP, making it a viable treatment option for patients with concurrent SEA and NP. DOI: https://doi.org/10.1016/j.jaci.2016.12.082
Adherence to treatment	2.6 (1.46, 4.72), <i>P</i> = .001	Clinical improvement may, however, lead some patients to modify treatments themselves. The study assessed whether adherence (number of doses issued on prescription/expected number of doses to be used) changed between the 12 mo before and after initiation of mepolizumab. One year of mepolizumab treatment did not appear to significantly affect how patients used their maintenance ICS/LABA or LAMA inhalers; however, SABA inhaler use declined significantly, a very reassuring finding given the significant reduction in OCS use. DOI: https://doi.org/10.1136/thorax-2018-212555.87
Dupilumab		
Type of asthma (T1/T2/nonallergic)	4.03 (1.76, 9.25), <i>P</i> = .001	
Elevated eNO	2.70 (1.26, 5.78), <i>P</i> = .01	
CRSwNP	5.8 (2.69, 12.58), <i>P</i> < .0001	
Reslizumab		
Age of asthma onset	4.03 (1.76, 9.2), <i>P</i> = .0008	References related to age of patients but not age of onset. Indicated for treatment of patients with severe asthma aged 18 y and older and with an eosinophilic phenotype (vs dupilumab, which is indicated for treatment in patients with moderate-to-severe asthma aged 12 y and older).
Aspirin-exacerbated disease	3.22 (1.29, 8.01), <i>P</i> = .01	

Abbreviations: CL, confidence level; CRSwNP, chronic rhinosinusitis with nasal polyps; eNO, Exhaled Nitric Oxide; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; LAMA, long-acting muscarinic antagonist; med, internal medicine; med-ped, medicine-pediatric; NP, nasal polyp; OCS, oral corticosteroid; SABA, short-acting β -agonist; SEA, severe eosinophilic asthma; T1, type 1; T2, type 2.

^aOdds of the biologic being selected for treating asthma given the existing condition.

(under clinical investigation for CRSwNP) also seem to have a prominent effect on asthma control and sinus symptoms in this subgroup.^{18–20} Notably, although reslizumab may also have an effect on CRSwNP, it has not been directly investigated as an adjunct therapy for patients with AERD, and therefore, its underlying effect for this condition remains unclear.²¹

An elevated FeNO was significantly associated with the selection of dupilumab by respondents. This is consistent with data indicating that FeNO is a robust predictor of response to dupilumab and that its progressive decline correlates with treatment response.¹² Dupilumab-treated subjects with a FeNO measurement of less than 25 ppb did not indicate reductions in asthma exacerbation rates or increase in FEV1 similar to placebo treatment. In contrast, there is still no consensus regarding the use of FeNO on its use as a biomarker for prescribing anti-IL-5 therapies.²² Because FeNO levels reflect IL-13–induced nitric oxide synthase expression in the airway epithelium, and FeNO and eosinophilia are driven by IL-13 and IL-5, respectively, correlation with a therapeutic response is complicated because of the involvement of multiple biological pathways. Furthermore, given that FeNO production is regulated by IL-4, IL-5, and IL-13 cytokines that influence a number of effector cells involved in airway inflammation, it is not surprising that as an inflammatory marker, it reflects T2 inflammation and not specifically eosinophilic

inflammation. Of note, the predictive value of FeNO for asthma exacerbation risk in conjunction with other T2 biomarkers such as blood eosinophils and periostin was also relevant for omalizumab treatment, further supporting its role as a T2 inflammatory biomarker.²³

Another interesting finding from this survey was that respondents selected the asthma population most frequently considered for biologic use as those with inadequately controlled asthma despite adherence to guideline-recommended therapy (94%) and selected recurrent exacerbations requiring treatment with glucocorticoids as the second most frequent reason for prescribing a biologic (91%). This is consistent with 76% of respondents also selecting exacerbation frequency as a selection criterion. These responses are in line with the biologic prescribing guidelines that advocate the use of a biologic in the exacerbation-prone patient with asthma to provide the greatest treatment benefit because each of these aforementioned questions pertains to the exacerbation-prone patient. Also reassuring was that a decrease in acute asthma exacerbations and cumulative glucocorticoid use was the most frequently used measure to determine a biologic's effectiveness.

Not surprisingly, only a small proportion of respondents (<10%) considered biologic therapy to be highly cost-effective. With the exponential increase in asthma diagnosis over recent decades, direct and indirect costs related to severe asthma have increased in parallel. In 1 observational study of patients with poorly-controlled asthma that did not address the costs of using biologics, annual direct asthma-related costs were \$1056 more per patient compared with patients with controlled asthma.²⁴ However, a recent report from the Institute for Clinical and Economic Review estimated that manufacturers would still have to substantially reduce pharmacy costs by 60% to align drug clinical therapeutic benefits with their current prices.²⁵ Therefore, several factors must be taken into consideration

Table 8
Cost-Effectiveness of Biologics Prescribed for Treating Asthma

Effects	Odds ratio (95% CL), <i>P</i> value
Benralizumab (yes vs no)	2.29 (1.27, 4.15), <i>P</i> = .01
Increased FEV1 (yes vs no)	1.80 (1.15, 2.80), <i>P</i> = .009

Abbreviation: CL, confidence level; FEV1, forced expiratory volume in 1 second.

Table 9

Comparison of the Demographic Features, Type of Clinical Practice, Preferred Biologics for Treating Asthma, Perceptions on the Cost-Effectiveness of Biologics, and the Frequency of Board Certification Among Respondents Grouped by Their Clinical Training

Training	Age (y)		Sex		Clinical experience (y)			Practice		Biologics preferred for treating asthma					Cost-effective		Board-certified
	≤30	33–55	>55	Female	≤5	≤11–15	>20	Acad.	Private	Omalizumab age ≥6 ^a	Reslizumab age ≥18 ^a	Mepolizumab age ≥6 ^a	Dupilumab age ≥12 ^a	Benralizumab age ≥12 ^a	No	Very/Part.	
Internal Medicine	1 (0.8%)	62 (51.7%)	57 (47.5%)	40 (33.3%)	22 (18.3%)	12 (10%)	58 (48.3%)	24 (20%)	96 (80%)	110 (91.7%)	17 (14.2%)	97 (80.8%)	103 (85.8%)	105 (87.5%)	13 (11%)	46 (39%)	110 (91.7%)
Med-Ped	0 (0%)	15 (100%)	0 (0%)	8 (53.3%)	5 (33.3%)	5 (33.3%)	1 (6.7%)	6 (42.9%)	8 (57.1%)	14 (93.3%)	2 (13.3%)	12 (80%)	9 (60%)	10 (66.7%)	3 (20%)	6 (40%)	6 (40%)
Pediatrics	4 (3.1%)	59 (45.7%)	66 (51.2%)	60 (46.5%)	23 (17.8%)	14 (10.9%)	70 (54.3%)	28 (21.7%)	101 (78.3%)	113 (87.6%)	9 (7%)	87 (67.4%)	91 (70.5%)	99 (76.7%)	15 (12.1%)	45 (36.3%)	110 (85.3%)
P value ^b	.04			.06		.06		.51		.51	.17	.05	.005	.03	.81		<.0001

Abbreviations: Acad, academic center; Med-Ped, medicine-pediatric.

NOTE: The row totals for some comparisons may not add up to 100% either because of missing values or because only subcategories of the comparison parameters are indicated (eg, for cost-effectiveness).

^aAge is the recommended age (in years) for the treatment of severe asthma.

^bThe P value is the probability value for χ^2 test of association between the type of training and other variables, such as age range, sex, clinical experience, type of practice, preferred biologics for treating asthma, cost-effectiveness of biologics, and board certification.

when deciding to step-up asthma therapy with a biologic. This must begin with a rigorous assessment of patient adherence to environmental control measures, currently prescribed asthma therapies and optimal management of underlying comorbidities (eg, chronic rhinitis with or without sinusitis, gastroesophageal reflux, vocal cord dysfunction).²⁶ Furthermore, after initiating a biologic, it is essential to monitor the patient closely for efficacy every 3 to 6 months to determine whether it should be continued (or discontinued) based on improvement in patient-reported outcomes and objective measures. One alternative strategy to improve cost-effectiveness that has been proposed for prescribing these agents would be to confine biologic administration to preseasonal use. However, this would likely only be relevant for patients with asthma with seasonal allergen exacerbations, as indicated for omalizumab, which was found to decrease exacerbations in the fall season.²⁷ Given the nontrivial costs of biologics and their unknown long-term effects, improved clinical management of patients with asthma is paramount before initiating this therapy.

The criteria for treatment with biologics for severe asthma include poor disease control despite a full medication plan according to the Global Initiative for Asthma steps 4 to 5. However, adherence to inhaled therapy needs to be verified before and during treatment with such biologics.²⁸ It helps in the evaluation of adjustment for the different treatment options for achieving precise asthma control.²⁹ Previous studies have investigated the adherence rate to ICS/LABA in patients affected by severe asthma before and during treatment with omalizumab or mepolizumab. These studies have determined that adherence rates for ICS, LABA combination therapy did not differ significantly before and after prescribing either of these biologics.^{30,31} In this study, we measured the odds of selecting a biologic over others, using multiple logistic regression analysis by having specific clinical or therapeutic factors as determinants. Accordingly, it is determined that mepolizumab is preferred by responders, with an odds ratio of 2.6, when adherence to treatment is a prime concern (ie, a determinant in the regression equation) (Table 7).

There are several limitations to this study that require mentioning. First, the respondents represented less than 10% of the sample size queried, which could lead to sampling bias. The study lacks geographic and racial data that could have helped determine how representative the sample was for the total ACAAI membership and whether it affected prescribing patterns. With such a very small response rate (~10%), this study was unable to truly determine how representative the study sample with respect to many demographic factors. Second, those responding may have been more likely to prescribe a biologic, and thus, their responses to this survey may not be generalizable to those who chose not to participate. An additional analysis was performed based on the clinical training of the respondents to compensate for these limitations (Table 9). The third limitation is the possibility of additional bias owing to the underrepresentation of adult-trained and academic allergists in the survey sample. Among those who completed the survey, 49.1% (134) were primarily pediatric-trained, and 45% (123) were internal medicine-trained. The remaining respondents received dual training in medicine and pediatrics. Fourth, more than 75% (219) of respondents worked in single or multispecialty private practices, whereas only 20% (59) worked in an academic center. These factors may have a pertinent influence on the specific biologic selected based on their patient populations and insurance coverage. For example, the low frequency of reslizumab prescription may reflect either pediatric training or limited availability of infusion facilities in private practice, and the decreased use of benralizumab by pediatric-trained respondents may reflect its age indications. Finally, the questionnaire did not specifically collect geographic, racial, ethnic, or cultural differences of respondents that could affect prescribing patterns. However, these limitations should be put into proper context when considering that, to the best of our knowledge, this is the largest

survey to date that provides information about prescribing patterns of practicing allergy specialists.

Overall, this survey provides significant insights into those variables that affect the decision-making process by clinicians in starting a biologic therapy for asthma. Recent publications have highlighted inappropriate patient selection and misuse of biologic therapies in real-world practice settings^{31,32}; however, the results of this survey illustrate that asthma specialists are reporting themselves to be adhering to consensus recommendations. The results of this survey reemphasize the need for direct head-to-head trials using more homogeneous, and thus, comparable populations that would more readily permit the determination of baseline clinical predictors of biologic therapy response. The heterogeneity among established T2 severe asthma is reflected by the lack of uniform or complete response to biologics regardless of how carefully the patient is phenotyped.¹⁶ Thus, it seems prudent that future studies should assess patient factors in conjunction with biomarkers beyond peripheral eosinophils or FeNO and linked to treatment response. Perhaps a composite index score of many T2 biomarkers (thymus and activation–related chemokine, periostin, peripheral eosinophils, or FeNO) may be the best prognosticator for responses to biologic therapies targeting T2 inflammation.^{23,33}

In summary, the results of this large survey study highlight the benefits of ongoing modifications of asthma treatment guidelines, which have now begun to incorporate biologic therapy to provide a clearer direction for allergy/clinical immunology and pulmonary specialists in selecting the optimal therapy for their patients.

Supplementary Data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.jana.2020.06.041>.

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Biologics in Allergic Disease

Questionnaire Survey Developed by the ACAAI Asthma Committee to Determine the Prescription of Biologics for Respiratory and Dermatological Allergic Disorders Among Physicians

Biologics for Asthma

Do you treat asthma with biologics?

- ☐ Yes
☐ No

(Select all that apply)

- ☐ Omalizumab (XOLAIR®)
☐ Reslizumab (CINQAIR®)
☐ Mepolizumab (NUCALA®)
☐ Dupilumab (DUPIXENT®)
☐ Benralizumab (FASENRA®)

(Select all that apply)

- ☐ Uncontrolled asthma despite adherence to controller medication as instructed
☐ Uncontrolled asthma despite avoidance of triggers for asthma (e.g., occupational exposures, tobacco smoke)
☐ When treatment of associated medical conditions could make asthma worse (e.g., ASA or other drug desensitization, allergen immunotherapy, food allergy)
☐ Recurrent exacerbations requiring treatment with glucocorticoids
☐ Other reasons

Please specify the other reasons for considering treatment of asthma with biologics?

- ☐ Type of asthma (T1/T2/Non-allergic)
☐ Age of asthma onset
☐ Exacerbation frequency
☐ Race
☐ Elevated eNO
☐ Eosinophilia (peripheral blood)
☐ Decreased FEV1
☐ Nasal Polyps
☐ Aspirin Exacerbated Disease
☐ Atopy
☐ Comorbidities
☐ Adherence to treatment
☐ Efficacy of biologic in clinical trials
☐ Less frequent dosage
☐ Route of administration (iv vs. sc)
☐ Less adverse effects
☐ FDA approval status of the biologic
☐ Insurance coverage of the biologic

☐ ≤6 months ☐ 7-12 months ☐ >12 months ☐ Indefinitely

How do you determine the effectiveness of biologics and adjust dosage while treating asthma?
(Select all that apply)

- ☐ Increased FEV1
 - ☐ Decreased Exacerbation
 - ☐ Biomarkers (Eos% in peripheral blood, FeNO)
 - ☐ Glucocorticoid sparing effect
 - ☐ Decreased use of rescue albuterol
 - ☐ Asthma Control Test
 - ☐ Asthma Quality of Life Questionnaire
 - ☐ Other
-

Guidelines

(Select all that apply)

- ☐ NAEPP EPR-3 (2007) by the NHLBI
 - ☐ Global Strategy for Asthma Management and Prevention (2019 update) by GINA
 - ☐ Other
-

Cost-Effectiveness

- ☐ Very cost-effective
 - ☐ Partially cost-effective
 - ☐ Not cost-effective
 - ☐ Varies between patients
 - ☐ Difficult to estimate in clinical practice
-

If you have not prescribed biologics yet, do you wish to?

- ☐ Yes
 - ☐ No
-

Any specific reason/s for not treating asthma with biologics even if you wish to do so?
(Select all that apply)

- ☐ less information on safety of biologics
 - ☐ cost of biologics
 - ☐ increased out-of-pocket expenses
 - ☐ less information on effectiveness of biologics
 - ☐ have not have found an appropriate patient yet
-

Any reason or concern for not treating asthma with biologics at all?

- ☐ hypersensitivity reactions
 - ☐ other major side effects
 - ☐ immune suppression
 - ☐ injection site reactions
 - ☐ not cost-effective
 - ☐ other reasons (specify)
-

Please specify other reasons?

Demographic Information of the Participants

Please select your age-range (years)
((optional))

- ☐ ≤30 31-
☐ 35
☐ 36-40
☐ 41-45
☐ 46-55
☐ >55
☐ Decline to answer

Gender
((optional))

- ☐ Female
☐ Male
☐ Other
☐ Decline to answer

Years in Practice
((optional))

- ☐ ≤5
☐ 6-10
☐ 11-15
☐ 16-20
☐ >20
☐ Decline to answer

Type of Practice
((select all that apply))

- ☐ Academic
☐ Private single specialty practice
☐ Private multi-specialty practice
☐ Other

Training & Certifications
((select all that apply))

- ☐ Pediatric trained
☐ Internal medicine trained Med-
☐ Peds trained
☐ Board certified
☐ Board Re-certified