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RESEARCH ARTICLE

Understanding Differential Response to Biologic Therapies in Severe Asthma: Retrospective study

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ABSTRACT

Severe asthma, characterized by airway inflammation and debilitating symptoms, poses a significant challenge to millions of people worldwide. Traditional treatments for treating severe cases are limited, leading to the emergence of biologic therapies as promising alternatives. This retrospective cohort study from a tertiary hospital in Dubai aimed to explore the differential response to biologics in severe asthma patients and identify predictors of treatment outcomes.

The baseline characteristics of 129 severe asthma patients receiving biologic therapy were analyzed, revealing a greater incidence of allergic diseases among responders. Multivariate Cox regression analysis revealed that early-onset asthma, urticaria, and rhinosinusitis (p =0.027, 0.037, and <0.001, respectively) were predictors of a positive treatment response. Compared with non-responders, responders demonstrated improved asthma control, reduced exacerbations, and decreased oral corticosteroid usage.

Despite the limitations inherent in retrospective studies, our findings underscore the significant clinical benefits of biologic therapy in severe asthma patients. Tailored treatment strategies based on patient characteristics and biologic class could optimize outcomes in this population, emphasizing the importance of personalized medicine in managing severe asthma. Further research into predictive biomarkers and larger cohort studies are warranted to validate these findings and enhance treatment efficacy in severe asthma management.

1. Introduction

Severe asthma is a chronic and heterogeneous disease that affects millions of people worldwide [1]. It is characterized by inflammation of the airways, which can lead to difficulty breathing, wheezing, coughing, and chest tightness. In severe cases, these symptoms can be so severe that they can interfere with daily activities and quality of life. Traditional treatments for asthma, such as inhaled corticosteroids and bronchodilators, can be effective at managing symptoms in many people [1]. However, for people with severe asthma, these treatments may not be enough. In recent years, a new class of drugs called biologics has emerged as a promising treatment option for severe asthma [2]. Biological therapies have emerged as the standard of care for eligible patients with severe asthma characterized by type 2-high inflammation. Monoclonal antibodies targeting specific pathways, such as anti-IgE agents, anti-interleukin (IL) 4/13 (anti-IL4/13), and anti-interleukin 5 receptors (anti-IL5/5R), have demonstrated efficacy in reducing asthma exacerbations, alleviating symptoms, improving lung function, and enhancing overall quality of life [3-6]. Furthermore, these biologics have shown promise in decreasing the long-term oral corticosteroid (LTOCS) burden [3].

The complex nature of the biological response in severe asthma presents a significant challenge for outcome assessment. The annualized exacerbation rate, forced expiratory volume in one second (FEV1), asthma control questionnaire (ACQ) score, quality-of-life instrument score, and oral corticosteroid (OCS) dependence adequately capture the full spectrum of treatment benefit [7]. The inherent heterogeneity of the severe asthma population further necessitates a multidimensional approach, as individual patients may exhibit differential responses across these various domains [8]. Furthermore, clinical trials paint a promising picture of biologics for severe asthma, but the real-world landscape presents significant translational obstacles. The stringent inclusion criterion excludes a substantial portion of the severe asthma population, casting doubt on the generalizability of the trial findings [9].

Elucidating the differential response to biologics in severe asthma patients is a critical unmet need. Unraveling why some patients experience good response outcomes while others exhibit limited or no benefit is paramount for optimizing treatment strategies and personalized medicine. To address this knowledge gap, investigating the biological and clinical disparities between biologic responders and non-responders is crucial.

This study investigated data obtained from a single tertiary hospital in Dubai, emphasizing the significance of a more localized and focused approach. The rationale behind this choice lies in the unique patient demographics, treatment protocols, and contextual factors inherent to the hospital in Dubai. Exploring various asthma outcome domains, such as annualized exacerbations, lung function, asthma control, and the dosage of oral corticosteroids (OCSs), has become particularly relevant in this setting. The focus on a single tertiary hospital in Dubai enhances the applicability of the findings to the local population, contributing to the development of tailored and region-specific strategies for managing severe asthma.

2. Methods

2.1 STUDY POPULATION

This was an observational retrospective cohort study. All severe asthmatic patients met the study eligibility criteria, with the aim of describing a real-world severe asthma population treated with biological agents; all patients had asthma confirmed by standard lung function criteria described previously and had uncontrolled asthma according to the Global Initiative for Asthma (GINA) 5 treatment. This study included adults aged ≥18 years who were prescribed biologic medication after they were unresponsive to traditional inhalers for asthma management (these visits were considered baseline visits) and had a follow-up visit ≥24 weeks after biologic initiation. Patients within the eligible cohort were excluded if they stopped using the biologic before 24 weeks after initiation or had incomplete follow-up data (<24 weeks). Patients who had incomplete data (i.e., no follow-up data related to that particular domain) or no capacity to respond in a particular outcome domain, such as those who had no exacerbations at baseline, had well-controlled asthma, or were not using OCSs, were excluded from the analysis.

Table 1. Main domains definitions of response to biological agents in patients with severe asthma

Outcome domain	Definition of responders	Definition of non-responders	Excluded from analysis if:
Asthma exacerbations	≥50% reduction in annualized exacerbation rate or elimination of exacerbation	Exacerbation ≥ 50%	No exacerbations at baseline
FEV_1	≥100 mL improvement in post bronchodilator FEV_1	No improvement in post bronchodilator FEV_1	Not applicable
Asthma control	Improved asthma control by category (controlled, partial, uncontrolled)	No improvement in asthma control	Well-controlled asthma at baseline
OCS burden	Any reduction in OCS usage or cessation	No reduction of OCS usage	Not on OCS at baseline
Blood eosinophil count	NA	NA	

FEV1, forced expiratory volume in 1 second, OCS, oral corticosteroid.

Patients were subdivided by biologics class to compare response and nonresponse attainment among patients receiving anti-immunoglobulin E (anti-IgE), anti-IL5/5R, or anti-IL4/13. Biological prescription criteria are usually based on physician's preference (10).

2.2 ETHICAL APPROVAL

The study protocol was reviewed and approved by the Dubai Scientific Research Ethical Committee (DSREC) Dubai Health Authority; the ethical approval number of the study is DSREC-07/2021_17.

2.3 STATISTICAL ANALYSIS

Baseline characteristics and subgroup analyses as well as analyses by biologic class are presented on cross tables with Fisher's exact test. The chi-square test and Cox logistic regression were applied for association analysis and comparison of categorical variables or one-way ANOVA with the post hoc Tukey test (for more than two groups) for continuous variables. P values <0.05 were considered to indicate statistical significance. The statistical package SPSS (version 24) was used for statistical analyses.

3- Results

3.1 BASELINE CHARACTERISTICS WITH UNIVARIATE ANALYSIS

A dataset of a cohort of 129 asthma patients from the UAE population was collected from Rashid Hospital, Dubai, and the UAE and retrospectively analyzed. The dataset contains anonymized patient profiles. Several patient-related parameters, such as age, sex, nationality, body mass index (BMI), asthma biological agents that the patient is currently taking, and diseases that the patients currently have, such as diabetes, hypertension, cancer, and thyroid problems, and allergic diseases, such as allergic rhinitis and eczema. Moreover, the dataset contains quantitative metrics describing the percentage of improvement that the patients experienced after taking certain prescribed asthma biological agents. The percentage of improvement can be estimated using different metrics (ACT, number of exacerbations, OCS usage, eosinophil counts and FEV1). In addition, the overall status of improvement, a binary variable describing the improvement status of the patient as a 'responder' or 'non-responder' after taking the prescribed medication, was also reported. This variable was determined by the doctor after a holistic evaluation of the patient.

Table 2. Baseline characteristics of severe asthma cohorts who on or off biologics

	Responder N = 71	**Non-responders** N = 58	**P value**
Demographics			
Female, % (number)	65 (46)	67(39)	0.770
Age (years), mean ± SD (number)	47 ± 15	51 ± 15	0.583
BMI (mg/m²), mean ± SD	30 ± 6	30.2 ± 6	0.612
Asthma status			
Asthma onset			
Childhood asthma %(number)	62(44)	23(40)	**0**.021
Adult Asthma %(number)	38(27)	35(60)	
PB-FEV_1 (L), mean ± SD	2.2 ± 0.6	2.1 ± 0.47	0.818

	Responder N = 71	Non-responders N = 58	P value
Asthma control test (ACT), mean ± SD	11.5 ± 3	11.6 ± 3	0.078
Annualized exacerbations, mean ± SD	6 ± 4	7± 4	0.506
Annualized OCS usage mean ± SD	5 ± 3	5 ± 3	0.367
Medications			
Omalizumab (Anti-IgE), % (number)	34 (24)	78(45)	
Dupilumab (Anti-IL4/13), % (number)	29 (21)	16(9)	
Mepolizumab (Anti-IL5), % (number)	20(14)	5(3)	
Benralizumab (Anti-IL5R), % (number)	17 (12)	2(1)	
Biomarkers			
Blood eosinophil count (cells/μL), mean ± SD (number)	365 ± 298	300 ± 280	0.519
Blood eosinophil count (cells/μL), mean ± SD (number) post	248 ± 226	237 ± 213	0.079
IgE (IU/mL), mean ± SD (number)	654±1045	820±1232	0.512

SD, standard deviation; BMI, body mass index; PB-FEV1, prebronchodilator forced expiratory volume in 1 second; OCS, oral corticosteroids; IgE, immunoglobulin E; IL5, interleukin 5; IL5R, interleukin 5 receptor; IL4/13, interleukin 4/13; IU, International Units.

Our analysis revealed a significant association (*P*<001) between responder status to biological agents and a greater incidence of allergic diseases among responders. Compared to non-responders, responders had significantly greater rates of allergic rhinitis (63%), urticaria (15%), rhinosinusitis (39%), and nasal polyposis (25%), which suggests a potential role for allergic sensitization in enhancing the efficacy of biologics. Notably, no significant differences were observed in the prevalence of other comorbidities, including GERD, OSA, HTN, T2DM, cancer, or thyroid problems, between the responder and non-responder groups.

Table 3. Common allergic diseases and comorbidities among patients in the severe asthma cohort who were on or stopped biologics.

	Responder N = 71	Non-responders N = 58	P value
Allergic Rhinitis, % (number)	63 (45)	43(25)	<0.001
Urticaria , % (number)	15 (11)	9(5)	<0.001
Rhinosinusitis , % (number)	39 (28)	24(14)	<0.001
Nasal polyposis , % (number)	25 (18)	17(10)	<0.001
Eczema , % (number)	8 (6)	3 (2)	0.084
Comorbidities			
GERD , % (number)	60 (43)	55(32)	0.537
OSA , % (number)	27 (19)	24(14)	0.441
HTN , % (number)	23 (16)	19(11)	
T2DM , % (number)	15 (11)	24(14)	0.199
Cancer , % (number)	6 (4)	10(6)	0.425
Thyroid problems , % (number)	18 (13)	25(15)	0.229

SD, standard deviation; GERD, gastroesophageal reflux disease; OSA, obstructive sleep apnea; T2DM, type 2 diabetes mellitus; HTN, hypertension.

3.2 MULTIVARIATE ANALYSIS USING Cox MODEL

Table 4 shows the multivariate analysis results generated using the Cox model. In this model, we used the variables "biological responders" and "non-responders" (dichotomous variables) as dependent variables and all the variables that were significant according to univariate analysis (asthma onset, allergic rhinitis, urticaria, rhinosinusitis and nasal polyposis).

Table 4: multivariate analysis using Cox-Model of the significant variables identified from the univariate analysis of the biological responders compared to non-responders.

Variables	B	Sig	Exp(B)	95 % CI For Exp(B)	
				Lower	Upper
Asthma Onset	-0.604	0.027	0.547	0.321	0.932
Allergic Rhinitis	0.401	0.126	1.493	0.894	2.494
Urticaria	-0.639	0.037	0.528	0.289	0.963
Rhinosinusitis	-1.236	0.000	0.290	0.148	0.569
Nasal Polyposis	-0.213	0.444	0.808	0.468	1.395

A multivariate Cox proportional hazards regression analysis adjusted for asthma onset, allergic rhinitis, urticaria, rhinosinusitis and nasal polyposis revealed that individuals with early asthma onset had a lower risk of experiencing a negative response to biological agents than did those with adult-onset asthma ($p = 0.027$). Similarly, urticaria and rhinosinusitis were associated with significantly decreased risk (P=0.37 and <001, respectively). However, allergic rhinitis and nasal polyposis did not exhibit statistically significant associations with biological responder status in this analysis ($p = 0.126$ and 0.808, respectively).

3.3 PREDICTORS OF TREATMENT RESPONSE

Our analysis confirmed (Table 5) that biological responders had better asthma control with higher ACT scores ($p =<0.001$). Crucially, they experienced far fewer annual exacerbations and required significantly less oral corticosteroid treatment ($p=<0.001$). There was a slightly greater FEV1 in these patients, though the difference was not statistically significant ($p =0.72$). Interestingly, the blood eosinophil count did not significantly differ between the groups. Overall, these findings suggest that for eligible patients, biologics can significantly improve lung function and asthma control and reduce the need for corticosteroids, although eosinophil levels might not be a reliable predictor of response.

Table 5: Differences in the response scores between responders and non-responders in the main domain after the use of the biological agents

	Responder N = 71	Non-responders N = 58	P value
PB-FEV1 (L), mean ± SD	2.39 ± 0.6	2.1 ± 0.47	0.72
Asthma control test (ACT), mean ± SD	**22 ± 2**	17 ± 4	<0.001
Annualized exacerbations, mean ± SD	1 ±1	2.3 ± 2.4	<0.001
Annualized OCS usage, mean ± SD	0.6 ± 1	2.2 ± 2.4	<0.001
Blood eosinophil count (cells/µL), mean ± SD	248 ± 226	237 ± 213	0.079

3.4 SUB-ANALYSES BY BIOLOGIC AGENTS

Sub-analyses of baseline characteristics by subsequent biologic class revealed differences in asthma onset age and annualized OCS usage, as patients who were treated with anti-IL5 agents (mepolizumab and benralizumab) were more likely to use oral corticosteroids but not biomarkers between subgroups (Table 6).

Table 6. Baseline characteristics according to biologic Agents initiated

	Omalizumab n = 69	Dupilumab n = 30	Mepolizumab n = 17	Benralizumab n = 13	P value
Demographics					
Female, % (number)	68 % (47)	53% (16)	59%(10)	92%(12)	.080
Age (years), mean ± SD	49 ± 15.4	50 ± 15	50 ± 15	46 ± 13	0.87
BMI (mg/m^2), mean ± SD	30 ± 6	30 ± 5	28 ± 4	33 ± 8	0.16
Asthma status					
Asthma onset age (years), mean ± SD	27 ± 14	29 ± 11	25 ± 16	14 ±7†	0.008
PB-FEV1 (L), mean ± SD	2.1 ± 0.6	2.4 ± 0.5	2.2 ± 0.5	2.1 ± 0.6	0.1
Asthma control test (ACT), mean ± SD	11 ± 3	12 ± 3	13 ± 2	12 ± 2	0.14
Annualized exacerbations, mean ± SD	6 ± 4	6 ± 3	6 ± 3	8 ± 4	0.40
Annualized OCS usage, mean ± SD	4 ± 3	4 ± 2	6 ± 3	7 ± 4†	0.005
Biomarkers					
IgE (IU/mL), mean ± SD	945 ± 1286	410 ± 770	529 ± 954	372 ± 479	0.70
Blood eosinophil count (cells/μL), mean ± SD	323 ± 314	397 ± 363	250 ± 168	378 ± 230	0.43

†Denote columns with significant difference on post hoc testing ($p<0.05$).

Table (7) shows the postoperative responses to the use of biological agents in the main domains for the outcomes of the patients who were receiving treatment. Generally, the fourth biologic has similar effects, as indicated by significant improvements in FEV1 and ACT and a reduction in the eosinophil count (P= <0.001, 0.12, and 0.04, respectively). Most of the differences were observed for benralizumab, for which there was a significant change in FEV1 and improvement in ACT; these changes were also significant for mepolizumab and, ultimately, for the largest decrease in the eosinophil count.

Table 7: The difference in change for each biological agent in the main domains of the outcome.

	Omalizumab n = 69	Dupilumab n = 30	Mepolizumab n = 17	Benralizumab n = 13	P value
Main Domains for outcomes post					
PB-FEV1 (L), mean ± SD (post)	2.2 ± 0.6	2.5 ± 0.5	2.3 ± 0.6	2.3 ± 0.4 †	<0.001
Asthma control test (ACT), mean ± SD (post)	19 ± 5	19 ± 4	22 ± 2 †	22 ± 2 †	0.012
Annualized exacerbations, mean ± SD (post)	1 ± 1	2 ± 3	1 ± 1	2 ± 2	0.10
Annualized OCS usage, mean ± SD (post)	1 ± 1	2 ± 3	1 ± 1	1 ± 2	0.10
Blood eosinophil count (cells/μL), mean ± SD (post)	261 ± 227	310 ± 280	147 ± 128	150 ± 160 †	0.04

†Denotes columns with significant differences according to post hoc test ($p<0.05$).

Discussion:

Our study has revealed valuable insights into the differential response to biologics in severe asthma patients. Notably, patients exhibiting a "responder" profile had a greater incidence of allergic diseases than did non-responders. This finding aligns with the existing understanding of asthma phenotypes, where the allergic-T2 phenotype, defined by polysensitization and a classic T2 inflammatory response, is often associated with favorable outcomes with biologics [10].

The aforementioned association may be rooted in the underlying immunological differences between phenotypes. While the allergic-T2 phenotype exhibits a robust Th2 response and increased IgE

production, the nonallergic eosinophilic phenotype, which is typically present in adults and characterized by chronic rhinosinusitis and nasal polyps, often lacks allergen sensitization and displays a less pronounced Th2 response. This finding suggested that targeting the Th2 pathway with biologics might be more effective in patients already primed for a T2 response due to allergic sensitization[10].

Furthermore, our analysis demonstrated that biologics significantly improved key asthma outcomes across all responder groups, as indicated by reduced exacerbation, enhanced lung function, improved asthma control, and decreased dependence on oral corticosteroids. While our findings align with existing clinical trial data, they extend the applicability to a real-world population not restricted by stringent inclusion criteria[3,4,6,11-14]. This strengthens the case for considering biologics as a viable treatment option for a broader range of severe asthma patients.

Treating severe asthma effectively requires tackling the problem of non-responders to biologics, as current biomarker tests fail to identify such patients. Given the complex nature of the disease and the multitude of factors affecting its course, a personalized approach targeting each patient's unique, treatable traits beyond just inflammation is crucial [15]. Additionally, the emergence of non-responders solicits the question of whether earlier or more frequent biologic switches could be beneficial, but further research on switching outcomes is needed before definitive recommendations can be made [16,17].

Our analysis, , demonstrated the significant benefits of biological agents for eligible patients with severe asthma who respond well to treatment (responders). Compared to non-responders, responders exhibited a marked improvement in asthma control ($p < 0.001$), reflected by higher ACT scores. Crucially, they experienced a notable reduction in the frequency of exacerbations and significantly reduced their reliance on oral corticosteroids, showcasing a substantial improvement in their quality of life. While an increase in FEV1 was observed in responders, it did not reach statistical significance. Interestingly, a trend toward a lower eosinophil count emerged in responders, and these findings align with those of previous studies, highlighting that a reduced number of eosinophils does not translate to improved symptoms—leading to questions about whether eosinophilic inflammation has as important a role in asthma as initially thought[18-20].

Individuals with early-onset asthma, compared to those with adult-onset asthma, demonstrated a significantly lower risk of experiencing a negative response to biological agents ($p = 0.027$). To our knowledge, there are no previous studies reporting the effectiveness of biological agents for early-onset asthma compared to adult-onset asthma, but these findings align with studies suggesting that, compared with childhood-onset asthma, adult-onset asthma has a worse prognosis and poorer response to standard asthma treatment [21-23]. Similarly, patients with urticaria and rhinosinusitis exhibited substantially decreased risks of nonresponse ($p = 0.037$ and < 0.001, respectively), suggesting that these comorbidities potentially serve as predictive indicators for positive treatment outcomes. This aligns with the findings of other studies exploring the effectiveness of the use of biological agents for the treatment of different allergic diseases, such as urticaria and rhinosinusitis [24].

Contrary to our expectations, allergic rhinitis and nasal polyposis did not exhibit significant associations with biological responder status in our analysis. While these conditions are commonly comorbid with asthma and may contribute to disease severity, their specific influence on treatment responses remains unclear and warrants further exploration.

The findings from our analysis, presented in Table 5, underscore the substantial clinical benefits associated with biological therapy in individuals with severe asthma. Responders to biological agents demonstrated significantly improved asthma control, as evidenced by higher Asthma Control Test (ACT) scores than did non-responders, along with a notable reduction in annual exacerbations and decreased reliance on oral corticosteroids for asthma management. OCSs represent one of the most crucial metrics in severe asthma management, given the significant burden of toxicity associated with their prolonged use [25]. A trend toward improved lung function was observed in responders, although the difference was not statistically significant. Interestingly, the blood eosinophil count did not significantly differ between responders and non-responders, challenging the conventional notion that elevated eosinophil levels predict treatment response. These findings highlight the complexity of

treatment response prediction in severe asthma [15]. However, the lack of a significant association between blood eosinophil count and treatment response warrants caution because relying solely on eosinophil levels is a predictor of therapeutic efficacy.

Sub-analyses of baseline characteristics according to initial biologic class revealed differences in asthma onset age and annualized oral corticosteroid (OCS) usage among patients receiving different biologic agents. Specifically, individuals receiving anti-IL5 biologics (mepolizumab and benralizumab) had a significantly earlier asthma onset age and greater annualized OCS usage than did those receive other biologic agents. However, no significant differences were observed in biomarker levels between the subgroups. These findings emphasize the importance of considering baseline characteristics when selecting biologic therapies for severe asthma and suggest the need for further investigation into treatment response variability among different biologic classes.

Overall, the four biological agents demonstrated comparable efficacy, with significant improvements observed in forced expiratory volume in one second (FEV1), asthma control test (ACT) scores, and reductions in eosinophil count ($p < 0.001$, 0.012, 0.04, respectively). Notably, benralizumab exhibited the most pronounced changes, with significant improvements in FEV1 and ACT scores, which were also observed, albeit to a lesser extent, with mepolizumab. Moreover, benralizumab induced the largest reduction in eosinophil count [26]. These findings suggest that while all biological agents are effective at improving asthma-related outcomes, benralizumab may offer additional benefits in terms of improving lung function, controlling asthma, and suppressing eosinophils.

However, several limitations need to be considered. Our study is retrospective and observational, limiting causal inferences. Additionally, the sample size within each biologic class was relatively small, necessitating further research with larger cohorts to confirm these findings.

Conclusion:

In summary, our study highlights the differential response to biologic therapies in patients with severe asthma, with a "responder" profile showing improved outcomes, particularly among those with allergic diseases. Biological therapies significantly improved asthma control, reduced exacerbations, and decreased oral corticosteroid usage across all responder groups. Challenges remain in identifying non-responders and optimizing treatment strategies, emphasizing the need for personalized approaches and further research into predictive biomarkers. Sub-analyses revealed differences in treatment response among patients receiving different biologic agents, with benralizumab showing the most pronounced improvements. Despite these limitations, our findings underscore the significant clinical benefits of biologic therapy for severe asthma, emphasizing the importance of targeted treatment approaches in this population.

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