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ORIGINAL RESEARCH

The Impact of Biological Therapies and the Significance of Their Adherence on Asthma Outcomes in a Single Tertiary Asthma Center

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Purpose and Methods: Biological therapies have revolutionized the approach to treating asthma. This retrospective study evaluates the biologics impact on asthma outcomes, clinical remission, adherence prevalence, and the influence of adherence on outcomes. Baseline characteristics and post-therapy changes were analysed, and adherence was measured using percentage of days covered with therapy (PDC%).

Results: A total of 67 patients initiated on biologics were included. Clinical improvements and statistically significant outcomes were observed across all biologics, including reduced asthma attacks, a lower dose of daily steroids, and improved symptom control and FEV1. Clinical remission was achieved in 24% of those who started on biologics. Patients demonstrated high adherence to biologics in the first year (average PDC% of 86%), though a modest decline to 84.5% was noted in the following year. Logistic regression revealed that adherence trends were not significantly associated with worsening asthma outcomes in the study cohort.

Conclusion: These findings underscore the importance of sustained patient support and education in maintaining high adherence to biological therapies, which can lead to improved asthma outcomes and, in some cases, clinical remission. The study highlights the potential of personalized treatment strategies and adherence-focused programs to optimize asthma management, particularly in severe asthma patients. Future research should explore long-term adherence patterns and the impact of patient-specific factors on treatment success.

Keywords: severe asthma, biological therapy, adherence, asthma outcome, King Fahad Medical City, Saudi Arabia

Introduction

Asthma affects an estimated two million individuals in Saudi Arabia, with the majority experiencing uncontrolled symptoms.[1] Severe asthma, a particularly concerning subset, impacts approximately 5–10% of asthmatics. It is defined as uncontrolled symptoms requiring high-dose inhaled corticosteroids (ICS) plus a second controller (either alone or in combination with systemic corticosteroids [SCS]) to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.[2] Severe asthma is associated with significant healthcare costs, accounting for up to 50% of asthma-related expenditures.[3] Beyond the financial burden, severe asthma significantly increases the risk of life-threatening exacerbations and negatively impacts patients' quality of life, productivity, and daily activities.[4] Therefore, it is crucial to identify and effectively manage severe asthma in order to improve patients' outcomes and quality of life.

The exact prevalence of severe eosinophilic asthma in Saudi Arabia remains unknown. However, one study by Aljahdali et al found that 45% of severe asthma cases were eosinophilic, with approximately half also having allergic asthma.[5] The introduction of biological therapies has revolutionized the management of severe asthma, offering new hope for better outcomes. However, the relationship between adherence to biological therapy and asthma outcomes remains underexplored. While Maddux et al observed no statistically significant initial reduction in exacerbation rates with biologics,[6] other studies have identified factors influencing adherence, such as age, socioeconomic status, insurance, and frequency of physician visits.[7] The CHRONICLE study is an ongoing real-world clinical trial that demonstrated

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home-administered biologics were associated with lower adherence and more delays in dose administration compared to facility-based administration.[8] This single-centre study aims to bridge the knowledge gap regarding the impact of adherence on asthma outcomes, particularly clinical remission, within the understudied Middle Eastern population. By examining these factors, this study seeks to provide valuable insights into the use of biologics for asthma treatment and contribute to the development of effective strategies to improve clinical outcomes.

Methods

Study Design

A retrospective review was conducted on all patients who initiated biological therapies for severe asthma at the Severe Asthma Clinic in King Fahad Medical City, a tertiary hospital, between 2020 and 2023. The study included individuals who were at least 14 years old with a diagnosis of asthma on biological therapies for at least 6 months. The asthma diagnosis was confirmed by either a spirometry with reversibility test or a direct bronchial provocation test. The participants had demonstrated proper inhaler technique, and compliance and received a formal assessment for optimized asthma management skills, as per their medical records. The study was conducted after the diagnosis of severe asthma is confirmed, as defined by the Global Initiative for Asthma (GINA) guideline 2023,[9] which suggested medication as described in Steps 4–5. Treatment with medium/high-dose ICS/long-acting beta-agonist [LABA] plus a second controller was used to prevent asthma from becoming uncontrolled, or asthma that remained uncontrolled despite treatment. Our patients were optimized on inhaler treatments, which included medium to high doses of inhaled corticosteroids/long-acting beta-agonists (ICS/LABA) ± long-acting muscarinic antagonists (LAMA) and these therapies were maintained alongside biological treatments. Patients receiving biological therapy for diagnoses other than asthma, such as hyper eosinophilic syndrome, and eosinophilic granulomatosis with polyangiitis were also excluded.

Patient data were extracted from the electronic medical records system of the specialized Severe Asthma Clinic. The study evaluated the biological therapies Omalizumab, Benralizumab, Mepolizumab, and Dupilumab. Baseline characteristics, including age, sex, medical history, and comorbidities such as obesity, chronic rhinosinusitis, and smoking status, were analysed. Changes in key asthma parameters were recorded before and after biologic initiation, including Asthma Control Test (ACT) score, exacerbation rates, short courses of steroids, hospitalization rates, eosinophil counts, spirometry, and total serum immunoglobulin (IgE) concentration. Additionally, comorbidities like obesity, chronic rhinosinusitis, and smoking were recorded to evaluate their influence on the treatment outcomes. Baseline data were collected before biological therapy initiation, and patients received therapy either in-clinic or through a structured home-based administration program. Follow-up assessments were conducted at three, six, and twelve months after commencing treatment.

Adherence was evaluated using the Percentage of Days Covered (PDC) metric during the first 52 weeks of therapy. Adherence was measured by calculating the proportion of days covered (PDC), which involves dividing the number of days covered by the total days in the assessment period for each biologic. This assessment traced back through medical records for the first 52 weeks, using a cut-off of ≥75% for compliance. For instance, for a biologic administered every 4 weeks, a patient is considered covered on the day of administration and for the subsequent 4 weeks. We also calculated the average number of days patients waited to receive their expected doses at 13, 26, and 52 weeks. In this scenario, perfect adherence would mean receiving 4 doses in 13 weeks (including the initial dose on day 0), 7 doses in 26 weeks, and 14 doses in 52 weeks. We then calculated the differences between the observed average days to receive the expected doses and the ideal intervals (91, 182, and 364 days) to highlight the average delays in completing the expected dosing schedule, referencing published studies that adapted this method.[6,8] Compliance was defined as a PDC cut-off of ≥75%. The mean number of days before patients received their expected doses for 13, 26, and 52 weeks was also calculated. PDC metrics were determined according to methods established in prior studies.[6,8] The effect of adherence was examined on different asthma outcomes including clinical remission which is defined in our study as absence of asthma exacerbation, no daily Oral Corticosteroids and ACT above 19 for a one-year period on biological therapy.

Statistical Methods

Data were analysed using STATA software (version 14). Differences in patient characteristics and outcomes before and after biological therapy were assessed, with statistical significance defined as $p < 0.05$. In the matched analysis, we have included exacerbations per year, Emergency room (ER) visits, hospitalizations, and long-term oral steroid use (LTOCS) including daily dose reductions, the proportion of patients discontinuing OCS, and the percentage achieving <5 mg/day prednisolone equivalent doses. Potential confounding variables were adjusted during the analysis to ensure accuracy. A logistic regression model was applied to evaluate relationships between biological therapy adherence and asthma outcomes. The primary outcome was the exacerbation rate, while secondary outcomes included reductions in oral corticosteroid doses, improved lung function, and attainment of clinical remission.

Results

We identified 67 patients who met our inclusion criteria. Table 1 shows the baseline profile of these patients. The average age of the cohort was 49.2 years (SD 13.7) ranging from 20 to 71 years. The majority of patients were female, constituting 83.6% of the group with an average BMI of 32.1 indicating a tendency toward obesity. Chronic Rhinosinusitis with Nasal Polyps (CRSNP) was present in 24% of the patients. Smoking was uncommon, with 97% categorized as non-smokers. The Asthma Control Test (ACT) yielded an average score of 14.53, suggesting poor level of asthma control with 77.6% of patients classified as having uncontrolled asthma (ACT<20). On average, patients experienced 6.49 emergency department visits (SD 9.13) per year and required 4.14 short-course of corticosteroid (SCS) annually. Hospitalizations were infrequent, with an average of 0.89 admissions per patient per year, and only 12% of patients were on Maintenance Oral Corticosteroids (mOCS), with an average dose of 16.75 mg. The average eosinophil count was 309.4 cells per microlitre (SD 460), and total IgE levels averaged 438.7 IU/mL (SD 589.5). Pulmonary function tests revealed an average pre bronchodilator (BD) Forced Expiratory Volume in one second (FEV1) of 1.77 liters (SD 0.68) and an average pre–BD FEV1% predicted of 68.1% (SD 19.76).

Table 1 Baseline Characteristics and Outcomes After 12 Months of Biologic Therapy

Characteristic	Baseline (N=67)	12 Months Post Therapy	P-Value
Age, average (SD), years	49.2 (13.7)	N/A	N/A
Female subjects, No. (%)	56 (83.58%)	N/A	N/A
BMI, average (SD), kg/m²	32.1 (6.4)	N/A	N/A
Chronic rhinosinusitis with nasal polyps (CRSNP), No. (%)	16 (24%)	N/A	N/A
Non-Smoker, No. (%)	65 (97%)	N/A	N/A
Asthma Control Test (ACT), average (SD)	14.53 (5.2)	17.8 (5.3)	<0.0001
Uncontrolled patients, No. (%)	52 (77.6%)	39 (58%)	0.004
Exacerbations requiring Emergency Department visits/year, average (SD)	6.49 (9.13)	0.97 (1.57)	<0.0001
Exacerbations requiring short courses of steroids/year, average (SD)	4.16 (6.1)	0.77 (1.25)	<0.0001
Exacerbations requiring hospitalization/year, average (SD)	0.89 (1.72)	0.1 (0.35)	<0.0001
Patients on daily oral corticosteroids (mOCS), No. (%)	8 (12%)	4 (5.9%)	<0.0001
Dose of daily oral corticosteroids (mOCS), average (SD), mg	16.75 (12.13)	10.6 (7.18)	
Blood eosinophil count (cells × 10^9 /L), average (SD)	309.4 (460.3)	417.2 (629)	0.39
FEV1, average (SD), liters	1.55 (0.16)	1.93 (0.21)	0.0119

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Table 1 highlights significant clinical improvements observed at 6 and 12 months following the initiation of biological therapy. ACT scores improved significantly from a baseline of 14.53 to 18.1 at 6 months and 17.8 at 12 months ($p<0.0001$). The percentage of patients with uncontrolled asthma decreased from 77.6% to 58% at 12 months ($p=0.004$). The average number of ED visits per year reduced from 6.49 to 0.97 ($p<0.0001$). Similarly, SCS use decreased from 4.16 to 0.77 courses annually ($p<0.0001$), and hospitalizations declined from 0.89 to 0.1 per year ($p<0.0001$). Additionally, The proportion of patients requiring daily mOCS dropped from 12% to 5.9%, and the average daily dose decreased from 16.75 mg to 10.6 mg. Pre-BD FEV1 improved significantly from 1.55 to 1.93 litres post-therapy ($p=0.0119$). While eosinophil counts increased from 309.4 to 417.2 cells per microliter, the change was not statistically significant ($p=0.39$). This increase was particularly observed in the Dupilumab and Benralizumab cohorts. For Dupilumab, this is likely attributed to its known side effect of transient eosinophilia, while for Benralizumab, the higher proportion of patients who had previously switched from Mepolizumab, which had already reduced eosinophil levels in earlier treatment, may explain the lack of further decline. Total IgE levels showed a nonsignificant decline from 438.7 to 209 IU/mL ($p=0.0795$). However, paired analysis revealed a significant reduction in IgE levels from 361.7 to 230 IU/mL ($p=0.0204$). Table 2 presented data on the effectiveness of different biological therapies in our sample. Biological therapy achieved clinical remission in 16 patients out of 67 (24%), which is comparable to real-world data.

Adherence, assessed using the Percentage of Days Covered (PDC), was relatively high across all biologics during the first year, exceeding 75% as shown in Table 3. The mean PDC% was 86.6 (SD 11.7), with 88% of patients classified as compliant. Benralizumab had the highest adherence rate (PDC 87.5%; 91.4% compliant) followed by Dupilumab which showed slightly lower adherence (PDC 86.07%; 84.2% compliant). Mepolizumab demonstrated the lowest adherence rates (PDC 81.4%; 75% compliant) which could be related to the small sample size. The association between adherence and asthma outcomes was evaluated through regression analyses (Figures 1–4). Higher PDC in the first year was associated with fewer ED visits (coefficient = −0.17, $p=0.056$), nearing statistical significance (Figure 1). For Benralizumab, a stronger trend was noted (coefficient = −0.21, $p=0.132$), while Dupilumab and Omalizumab showed weaker association. No significant relationship was observed between PDC and SCS use (coefficient = −0.047, $p=0.472$; Figure 2). There was a potential but nonsignificant association between higher adherence and fewer hospitalizations (coefficient = −0.019, $p=0.303$; Figure 3). A nonsignificant positive trend suggested better adherence might improve ACT scores (coefficient = 0.014, $p=0.373$; Figure 4).

Discussion

One year after initiating biological therapy, significant improvements were observed across various asthma outcomes. ACT scores demonstrated both clinical and statistically significant enhancements at 6 and 12 months, with a notable reduction in the percentage of patients with uncontrolled asthma. Additionally, ER visits, short-course corticosteroid (SCS) use, and hospitalizations significantly decreased, while FEV1 values improved. These findings align with the systematic review and guidelines issued by the European Academy of Allergy and Clinical Immunology (EAACI),[10] which emphasize the efficacy of biological therapies in managing severe asthma. Clinical remission, defined as sustained asthma control over 12 months, was achieved in 23.9% of cases in this cohort. This aligns with real-world data from the International Severe Asthma Registry (ISAR), which reported clinical remission rates of 18.7% (strict definition) and 26.3% (alternative definition).[11] Similarly, a UK-based study reported clinical remission in 18.3% of patients receiving biological therapy.[12]

Despite these promising results, few studies have specifically evaluated the relationship between adherence to biological therapy and asthma outcomes. In our cohort, adherence rates were high, with 88% of patients deemed compliant during the first year of therapy. Among the biologics studied, Benralizumab showed a trend toward significance, with higher adherence associated with fewer ED visits. This can be attributed to its 8-week dosing schedule, which reduces the frequency of hospital visits required for administration. However, the effect of adherence on other outcomes (eg, SCS use, hospitalizations, and ACT scores) was minimal and not statistically significant. Nevertheless, the demonstrated efficacy of biologics in reducing these outcomes highlights the potential benefits of maintaining or improving adherence over the long term. The CHRONICLE study, which evaluated real-world adherence to biologic therapies in severe asthma patients, highlighted significant variability across biologics. The median proportion of days covered (PDC) was 87%, with notable challenges observed for biologics like Dupilumab, which had the lowest PDC rates and highest dosing delays. This may be attributed to the shorter dosing intervals and at-home administration of

Table 2 Effectiveness of Biologic Therapies on Asthma Outcomes

Biologic	n	Baseline ACT Mean ± SD	6-Month ACT Mean ± SD	P-Value	12-month ACT Mean ± SD	P-Value	Baseline ED Visits Mean ± SD	12-month ED Visits Mean ± SD	P-Value	Baseline SCS Mean ± SD	12-month SCS Mean ± SD	P-Value	Baseline Admission Mean ± SD	12-Month Admission Mean ± SD	P-Value
Benralizumab	35	16.6 ± 0.89	18.3 ± 0.92	0.045	17.9 ± 0.83	0.227	2.43 ± 0.89	0.48 ± 0.19	0.0378	1.62 ± 0.31	0.7 ± 0.20	0.0093	0.5 ± 0.22	0.08 ± 0.04	0.05
Dupilumab	19	12.6 ± 0.97	17.8 ± 1.18	0.0014	17 ± 1.49	0.023	7.1 ± 1.67	1.6 ±0.45	0.0027	6.68 ± 1.79	0.9 ± 0.37	0.0063	1.26 ± 0.53	0.15 ± 0.11	0.06
Mepolizumab	4	10 ± 2.41	15 ± 3.31	0.23	15.5 ± 3.23	0.17	17.8 ± 8.85	1 ± 0.41	0.15	6.5 ± 1.25	4 ± 0.75	0.0139	1.75 ± 1.03	0.25 ± 0.25	0.2967
Omalizumab	9	12.6 ± 1.3	19.1 ± 1.74	0.016	20 ± 1.09	0.006	16 ± 3.19	1.4 ± 0.64	0.0026	7.6 ± 3.17	0.6 ± 0.29	0.068	1.11 ± 0.45	0.00 ± 0	0.04
All	67	14.5 ± 5.2	18.1 ± 5.35	<0.0001	17.8 ± 5.3	0.0003	6.5 ± 9.13	0.97 ± 1.57	<0.0001	4.2 ± 6.1	0.8 ± 1.25	<0.0001	0.89 ± 1.72	0.1 ± 0.35	0.0005

Abbreviations: ACT, Asthma Control Test; SD, Standard Deviation; ED, Emergency Department; SCS, Short Course of Steroids.

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Table 3 Adherence to Biological Therapy at year 1

Biologic	n	PDC% (Mean ± SD)	Compliant, n (%)
Benralizumab	35	87.5 ± 13.3	32 (91.4%)
Dupilumab	19	86.07 ± 9.71	16 (84.2%)
Mepolizumab	4	81.4 ± 16.0	3 (75.0%)
Omalizumab	9	86.3 ± 6.5	8 (88.9%)
All	67	86.6 ± 11.7	59 (88.0%)

Abbreviation: PDC%, percentage of days covered with therapy.

Dupilumab following the loading dose in the hospital, which often results in adherence challenges. Conversely, biologics administered in healthcare facilities showed better adherence. The study also found that treatment by subspecialists and commercial insurance coverage played a role in maintaining higher compliance rates.[8] Similarly, ISAR data demonstrated that high adherence to biologics leads to improved asthma control and fewer exacerbations, emphasizing the importance of patient-specific factors, including the need for careful monitoring when switching between therapies.[13]

This study underscores the need for tailored interventions and programs designed to prioritize adherence to biological therapy in severe asthma management. Implementing educational tools, personalized care plans, and integrated support systems can help patients understand the importance of consistent medication use. Such initiatives can not only sustain high adherence rates but also improve outcomes, as demonstrated in our study. For healthcare providers and researchers, this paper establishes a framework for addressing adherence barriers in biologic therapies. It highlights the importance of

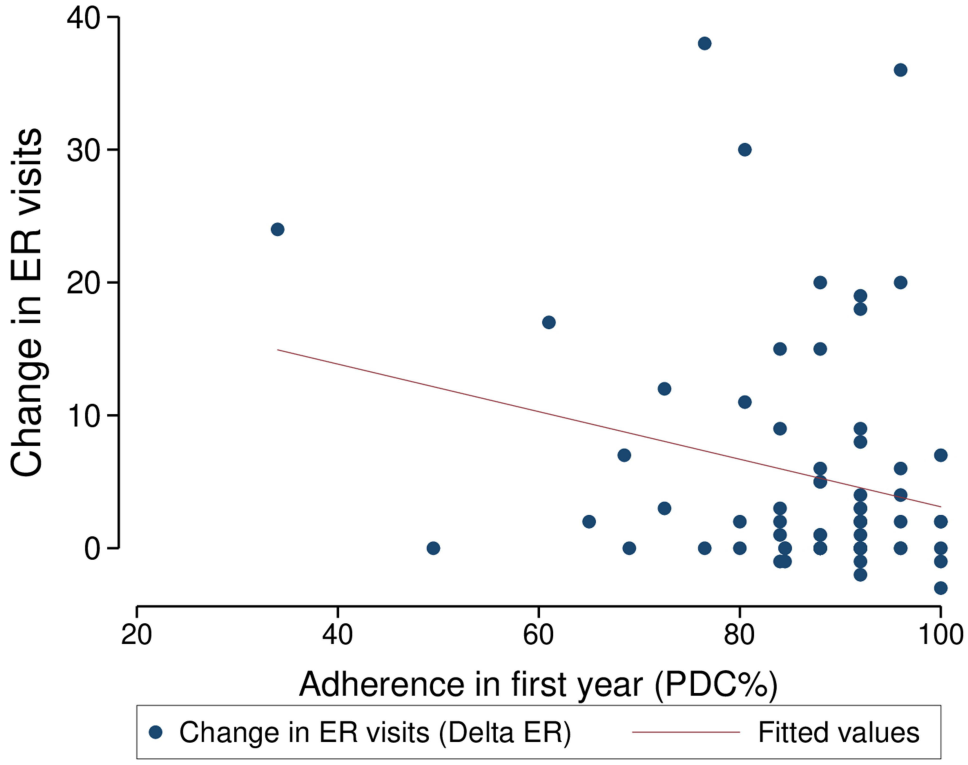

Figure 1 The effect of biologics compliance using percentage of days covered with therapy (PDC%) on emergency room (ER) visits due to asthma exacerbations.

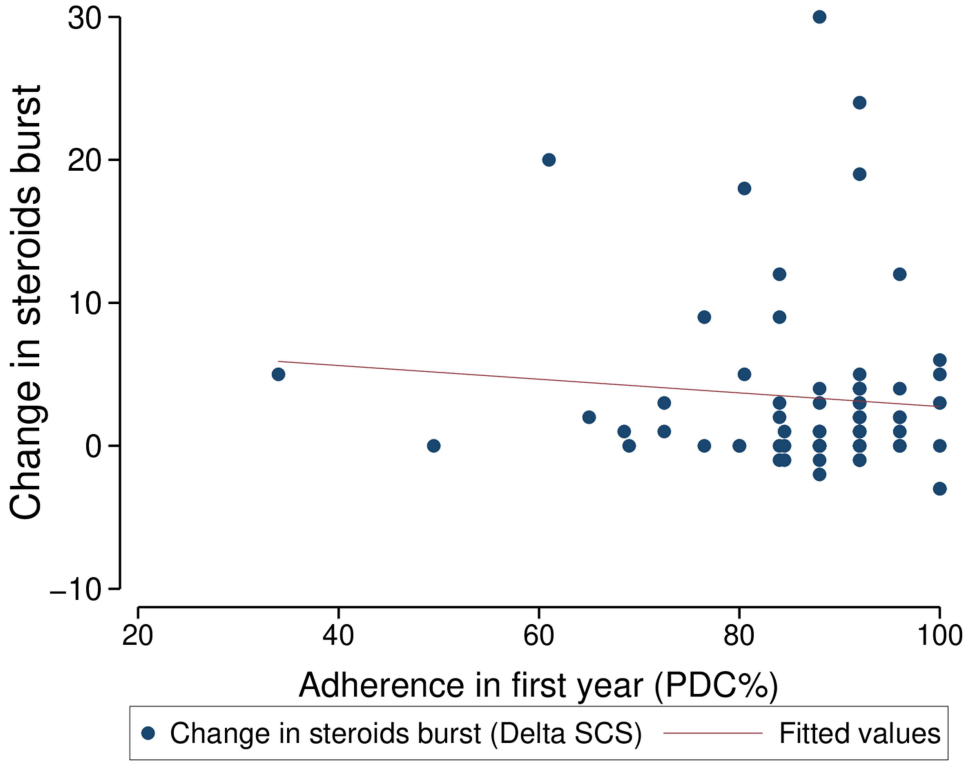

Figure 2 The effect of biologics compliance using percentage of days covered with therapy (PDC%) on steroids bursts for asthma exacerbations.
Abbreviation: SCS, short course of steroids.

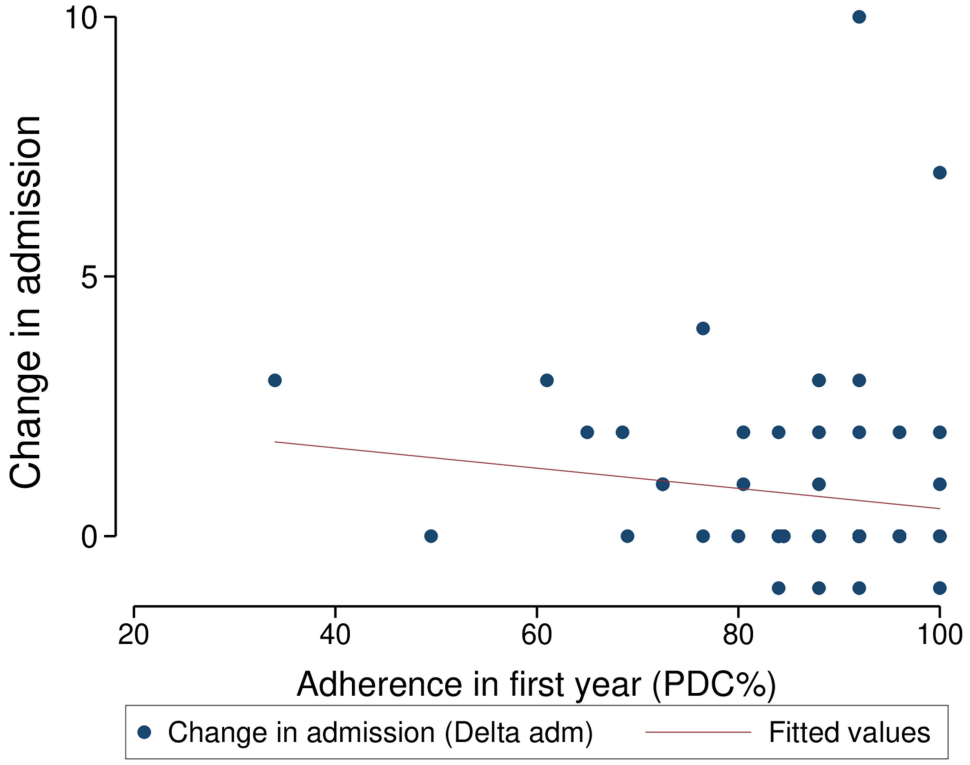

Figure 3 The effect of biologics compliance using percentage of days covered with therapy (PDC%) on admissions (adm) due to asthma exacerbations.

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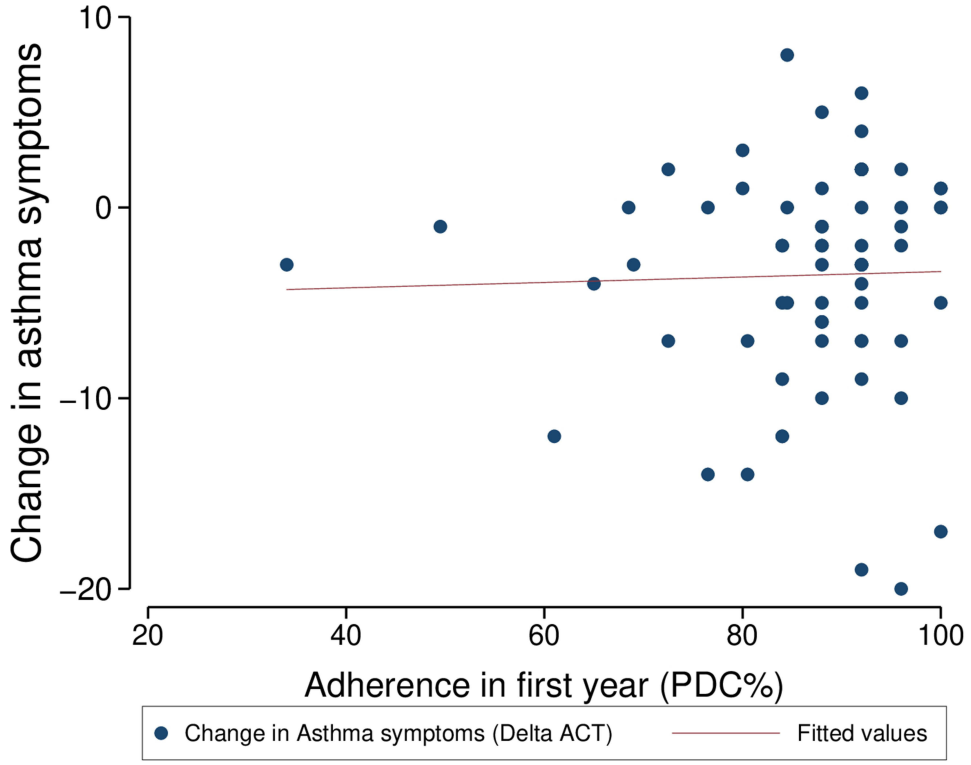

Figure 4 The effect of biologics compliance using percentage of days covered with therapy (PDC%) on asthma symptoms using Asthma Control Test (ACT).

incorporating patient education and robust support systems into asthma care. Future research should explore strategies to enhance adherence, particularly for at-home therapies with shorter dosing intervals.

Limitations in our study include the relatively smaller sample size, as it is a single-centre study which limits the generalizability of findings. Additionally, A considerable proportion of Benralizumab-treated patients had switched from Mepolizumab, which may have influenced certain outcomes, such as eosinophil counts. This limits the interpretation of findings specific to these biologics. Future multicentre studies involving larger and more diverse populations are warranted to address these limitations and validate the observed trends.

Conclusion

Our study underscores the vital role of adherence to biological therapies in optimizing asthma management and achieving better patient outcomes. The findings highlight the potential of personalized treatment strategies tailored to individual patient needs to maximize the benefits of these therapies. Moving forward, future research should include larger and more diverse populations, as well as evaluate additional factors such as quality of life, cost-effectiveness, and the long-term sustainability of treatment approaches. Enhancing adherence strategies must remain a priority to further improve asthma control, reduce healthcare utilization, and ultimately deliver more effective and sustainable care.

Data Sharing Statement

The raw data supporting the conclusions of this article were made available by the first author upon approval from the local ethics committee, without undue restrictions.

Ethics Approval

As this study is a retrospective analysis of existing data, the need for informed consent was reviewed and waived by the Institutional Review Board (IRB) at King Fahad Medical City, Riyadh, Saudi Arabia under the provision that the study

involved no direct patient contact, utilized anonymized data, and posed minimal risk to patient privacy. This determination was formally approved by the IRB under IRB log number 23-095. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki, ensuring the protection of the rights, safety, and well-being of all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Riyad Al-Lehebi reports having given lectures at meetings supported by AZ and participated in advisory board fees from AZ, given lectures at meetings supported by GSK and participated in advisory board fees from GSk, and given lectures at meetings supported by Sanofi and participated in advisory board fees from Sanofi outside the submitted work. The authors report no other conflicts of interest for this work.

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