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Younger severe asthma patients with interleukin 4 (CC variant) and dupilumab treatment are more likely to achieve clinical remission

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Abstract

Background and objectives Asthma is a complex condition characterized by variable respiratory symptoms and chronic inflammation. In recent years, the use of biologics in severe asthma patients led to significant improvements in symptom control and disease outcomes. This has prompted healthcare providers to explore the possibility of achieving clinical remission (CR). This study aimed to evaluate the prevalence of clinical remission in severe asthma patients treated with biologics. Additionally, to identify factors associated with achieving clinical remission.

Methods The study recruited 116 patients from a national severe asthma registry in Kuwait, focusing on patients who had been treated with biologic therapy for at least 12 months. CR was defined as the absence of exacerbations and oral corticosteroids (OCS) use, an Asthma Control Test (ACT) score of ≥ 20, Asthma Control Questionnaire (ACQ-6) score of ≤ 0.75 and forced expiratory volume in one second (FEV1) ≥ 80% predicted. Data were collected on demographics, clinical, and functional parameters; including biomarkers such as blood eosinophils count (BEC), total immunoglobulin E (IgE), and fractional exhaled nitric oxide (FeNO), as well as the polymorphism patterns of the interleukin-4 (*IL-4*) and tumor necrosis factor-alpha (*TNF-α*) genes.

Results Patients with severe asthma were predominantly female (68.9%) with an average age of 54.09 years. Most had adult-onset asthma (67.3%), comorbid allergic rhinitis (AR) (81.03%), and experienced frequent exacerbations, with a median of four corticosteroids-requiring flare-ups per year. The allergic eosinophilic phenotype was common (74.14%), and a significant portion carried the CC genotype of the *IL-4* gene (51.72%) or the GG genotype of the *TNFα* gene (57.76%). Biologic therapy significantly improved asthma control, reduced exacerbations and OCS use while improved lung function ($p = 0.001$ for all). About 18.1% of patients achieved CR after at least 12 months of biologic therapy, with dupilumab being the most effective, especially in biologic-naive patients. A multiple logistic regression

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analysis found that increasing age was negatively associated with CR (OR 0.95, $p=0.02$), while the CC genotype of the *IL-4* gene (OR 4.57, $p=0.008$) and the use of dupilumab (OR 3.63, $p=0.001$) were strong positive predictors of CR.

Conclusion This study suggested that CR can be achieved in patients with severe asthma. However, biologic therapy, particularly dupilumab, offers a promising avenue for achieving CR in comparison to other biologics, especially in younger patients with specific genetic profiles (CC genotype of the *IL-4* gene).

Keywords Severe asthma, Clinical remission, Biologic, IL4 gene polymorphism

Introduction

Severe asthma is a subset of difficult-to-treat asthma, affecting approximately 3–10% of adult asthma patients [1]. This form of asthma is characterized by persistently poor control despite optimal treatment with high-dose inhaled corticosteroids and a long-acting beta-agonist or requiring oral corticosteroids (OCS) to maintain control [2]. Although severe asthma patients represent a small proportion of the overall asthma population, they bear a disproportionate healthcare burden, significantly impacting their quality of life and leading to substantial healthcare costs [3].

Severe asthma can present with various inflammatory phenotypes [2]. Type 2 inflammation, characterized by eosinophilia and elevated type 2 cytokines, is a common phenotype often associated with allergies [4]. Neutrophilic inflammation, involving increased neutrophils in the airways, is less common but may contribute to severe asthma, especially in patients with coexisting infections or exposure to irritants [5]. Mixed inflammation, involving both eosinophils and neutrophils, represents a more severe phenotype and is often associated with a higher disease burden [6]. Additionally, a paucigranulocytic phenotype, which lacks significant inflammatory cells, is observed in some patients with severe asthma, suggesting alternative mechanisms of airway obstruction [7].

Beyond inflammatory phenotypes, severe asthma may also involve structural changes in the airways, known as airway remodeling. This includes collagen deposition, smooth muscle proliferation, and excessive mucus production, all of which contribute to airway obstruction and impaired lung function. Persistent airway hyperresponsiveness, along with these structural changes, further exacerbates respiratory difficulties [8–9].

In recent years, considerable progress has been made in understanding and treating severe asthma. Key advancements include the development of a standardized definition, evidence-based guidelines, the identification of phenotypic patterns and biomarkers, and the introduction of innovative targeted therapies [10]. Since 2003, several targeted therapies for severe asthma have emerged, focusing on personalized treatment approaches based on clinical features and biomarkers [11, 12]. Identifying patients who would benefit most from these treatments, especially since they are costly, remains a challenge. For patients unresponsive to standard multidisciplinary management, assessments of biomarkers like blood eosinophils count (BEC), fractional exhaled nitric oxide (FeNO) and total immunoglobulin E (IgE) levels guide therapy selection [13].

Omalizumab, an IgE-targeting monoclonal antibody introduced in 2003, has been effective for allergic asthma, reducing exacerbations and hospitalizations significantly [14]. Anti-interleukin-5 therapies like mepolizumab and benralizumab are effective for severe eosinophilic asthma, reducing exacerbations and allowing glucocorticoid tapering, with efficacy linked to BEC [15].

Anti-interleukin-13 agents, however, have shown inconsistent results in improving outcomes in type 2 inflammation, though they reduce FeNO and may increase eosinophil counts [16]. Dupilumab, targeting both interleukin-4 and interleukin-13, has shown promise by reducing exacerbations and improving lung function, without dependency on baseline BEC [16, 17].

The introduction of targeted biologic therapies has opened new possibilities for achieving remission in severe asthma. While a complete cure for asthma remains an elusive goal, the concept of remission offers a more realistic and achievable target. Remission can be defined as a prolonged absence of symptoms and signs of asthma, with or without normalization of underlying airway pathology [18, 19]. This trend first emerged in fields like rheumatology and gastroenterology [18] and was recently extended to asthma by expert panels in 2020 [20, 21]. These panels suggest that asthma can be classified as being in "clinical remission" (CR) if specific criteria are met for at least one year. These criteria include no requirement for systemic steroids, stable or improved lung function, minimal symptoms as assessed by tools like the Asthma control Test (ACT), and a mutual agreement between the patient and physician on the state of remission [22, 23]. By shifting our focus from disease control to disease remission, we can aim to improve the quality of life and long-term outcomes for patients with asthma. This study aimed to evaluate the prevalence of CR in severe asthma patients treated with biologic therapy. Additionally, it tried to identify factors associated with achieving CR.

Patients and methods

Study design and target populations

A follow up study included participants from an ongoing national severe asthma registry. The inclusion criteria were adult patients more than 18 years old with severe asthma and treated with a single biologic therapy for at least one year without switching. Patients who switched to another biologic before completing one year of continuous use were also included. The diagnosis of severe asthma based on ATS/ERS criteria [23]. Severe asthma is characterized by persistent symptoms, frequent exacerbations, regular use or interpreted use of oral corticosteroids, and substantial limitations in lung function [24, 25].

Sample size calculation

The sample size was calculated using Minitab 17.1.0.0 for Windows (Minitab Inc., 2013, Pennsylvania, USA). Based on a previous study [26] indicating a 9.6% prevalence of asthma in Kuwait population and less than 10% of asthmatic patients suffered from severe asthma [27–29], we determined the necessary sample size for our study. To ensure sufficient statistical power (80%) while controlling for a type I error rate of 0.05 (5% chance of a false positive) and a type II error rate of 0.2 (20% chance of missing a true effect), and confidence level of 90% a minimum total sample size of 93 participants was calculated.

Ethics approval and consent to participate

The study was approved by the Kuwait Ministry of Health Ethical Committee (approval number 2256/2023), adhering to local guidelines and the Helsinki Declaration. All participants provided written informed consent, confirming their understanding of the study's purpose and procedures. Their voluntary participation was based on this informed consent. This ensured ethical conduct and alignment with global research standards.

Data collection and study end point

- Demographic features as age, sex, smoking habits, and comorbidity were extracted from the medical records.
- Genetic Data: Genotypic patterns for *IL4* and *TNF-α* genes were retrieved from previous studies [30, 31], where about 10 mL of venous blood had been collected from each participant. The blood was separated into two tubes: one for serum/plasma separation and another containing EDTA for DNA extraction. After centrifugation, serum, plasma, and the buffy coat (containing leukocytes) were isolated. Genomic DNA was extracted using QIAamp Blood Kits, and its quantity and purity were measured using a Nanodrop 8000 spectrophotometer, with a target A260/A280 ratio of 1.8–2.0. The genotyping of the *IL4* (rs2243250) and *TNF-α* (-308 A/G) gene polymorphisms was performed using PCR-RFLP: For IL4 -C590T, PCR followed by BsmF1 restriction enzyme digestion was used. The C→T transition in the T-allele eliminated the BsmF1 restriction site. Gel electrophoresis showed product sizes of 192 and 60 bp for the CC genotype, 252 bp for the TT genotype, and 252, 192, and 60 bp for the heterozygous CT genotype. For TNF-α (-308 A/G), PCR was performed, followed by restriction enzyme digestion with NcoI. The PCR products (107 bp for the A-allele, and 87 bp and 20 bp for the G-allele) were analyzed by electrophoresis on a 3% agarose gel and visualized under UV light.
- Clinical and functional data:
  1. The Asthma Control Test (ACT), with scores ranging from 5 (poor control) to 25 (complete control) [32].
  2. The Asthma Control Questionnaire (ACQ), which assesses both symptoms and functional limitations related to asthma over the previous week. The ACQ-6 version consists of six questions that evaluate asthma symptoms and the use of rescue bronchodilators. A score of ≤ 0.75 indicates well-controlled asthma, while a score of ≥ 1.5 reflects poorly controlled asthma. Scores falling between these values indicate partially controlled asthma [33, 34].
  3. The number of exacerbations per year and the number of oral corticosteroids (OCS) courses per year.
  4. Spirometry data, which included post-bronchodilator FEV1% predicted, FVC% predicted, and FEV1/FVC% predicted.
  5. Biomarkers such as blood eosinophil count (BEC), total IgE, and fractional exhaled nitric oxide (FeNO).

These parameters were used at two specific time points:

1. Baseline (Pre-Treatment): Immediately before the initiation of biologic therapy.
2. Follow-Up (Post-Treatment): At the end of the one-year follow-up period.

Data at the end of the one-year follow-up period were compared with baseline data to evaluate the impact of biological therapy on patient's clinical and functional parameters plus measuring the rate of clinical remission, the criteria of clinical remission were:

Table 1 General characteristics of patients with severe asthma before starting biologic therapy

Factors	Total (*n* = 116)	
Age (mean, SD)	54.09	11.63
Sex (*n*, %)		
Female	80	68.97
Male	36	31.03
BMI (mean, SD)	31.257	5.298
Smoking (*n*, %)		
Ex-smoker	11	9.48
Non-smoker	97	83.62
Smoker	8	6.9
Disease onset (*n*, %)		
Adult-onset	87	75
Childhood-onset	29	25
Comorbidity (*n*, %)		
AR (*n*, %)	94	81.03
NP (*n*, %)	60	51.72
Eczema (*n*, %)	8	6.9
DM (*n*, %)	20	17.24
HTN (*n*, %)	16	13.79
Hypothyroid (*n*, %)	11	9.48
Clinical evaluation		
Exacerbation number (median, IQR)	4	(3–6)
OCS course number (median, IQR)	4	(3–6)
ACT (median, IQR)	12	(8–17)
ACQ-6 (median, IQR)	1.8	(0.8-3)
FeNO (median, IQR)	23.5	(15-38.5)
Investigations		
Total IgE (median, IQR)	268	(131.3-652.5)
BEC (median, IQR)	480	(260–790)
FEV1% predicted (median, IQR)	55.1	(44.8–67.9)
FVC % predicted (median, IQR)	60.8	(53.9–73.3)
FEV1: FVC % predicted (median, IQR)	77.2	(68.3–83.1)
Phenotypes (*n*, %)		
Allergic	30	25.86
Allergic eosinophilic	86	74.14
***IL-4*gene polymorphism (*n*, %)**		
CC	60	51.72
CT	47	40.52
TT	9	7.76
CC + CT (dominant)	107	92.24
CT + TT (Recessive)	56	48.28
***TNF-α*gene polymorphism (*n*, %)**		
GG	67	57.76
GA	43	37.07
AA	6	5.17
GG + GA (dominant)	110	94.83
GA + AA (recessive)	49	42.24

The numerical data presented as mean and standard deviation, or median and inter quartile range, and categorical data as number and percentage. N: number, SD: standard deviation, IQR: interquartile range, BMI: body mass index, AR: allergic rhinitis, NP: nasal polyp, DM: diabetes mellitus, HTN: hypertension, OCS: oral corticosteroid, ACT: asthma control test, ACQ-6: Asthma control quality of life, BEC: Blood eosinophil count, FeNO: Fractional exhaled nitric oxide, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity

1. No asthma exacerbations requiring emergency visits or hospital admissions in the past year.
2. No OCS use in the past year.
3. ACT score ≥ 20.
4. ACQ-6 ≤ 0.75.
5. Predicted Forced Expiratory Volume in one second (FEV1%) ≥ 80%.

Statistical analysis

The data were collected in an Excel spreadsheet and statistically analyzed using Minitab 17.1.0.0 for Windows (Minitab Inc., 2013, Pennsylvania, USA). The normality of the data was assessed using the Shapiro-Wilk test. A paired t-test or Mann-Whitney test was employed to evaluate the changes in mean or median factors before and after treatment with biologics. One-way ANOVA or the Kruskal-Wallis test was utilized for comparing means or medians, while the Chi-square test was used to compare frequencies. Logistic regression analysis with a backward elimination technique was applied to identify independent predictors of successful remission. All tests were two-sided, with a significance level set at less than or equal 0.05.

Results

General characteristics of patients with severe asthma

Table 1 provided an overview of the characteristics of patients with severe asthma who were candidates for biologic therapy. Many patients were female (68.9%) with an average age of 54.09 years, and a significant proportion had adult-onset asthma (67.3%). Most patients (81.03%) had comorbid allergic rhinitis (AR), and more than half (51.72%) had nasal polyps. The median number of exacerbations requiring OCS courses was 4 per year, indicating frequent flare-ups. Asthma control was generally poor, with an ACT score of 12 and an ACQ score of 1.8. Lung function was also compromised, with low median values for both FEV1 and FVC. The elevated BEC (median: 741) suggests a type 2 inflammatory phenotype. The allergic eosinophilic phenotype was the most common (74.14%) in this cohort. Genotypic evaluation showed that about half of the patients (51.72%) carried the CC genotype of the *IL-4* gene, while 57.76% had the GG genotype of the *TNFα* gene.

Figure 1 illustrated the frequency of different biologic therapies used in treating patients with severe asthma, categorized as either "naive" (used as the first biologic without prior or subsequent switching) or "switch" (used after another biologic or later switched to a different one). The data indicate that omalizumab has the highest number of patients, with 42 naive and 24 switched. Dupilumab follows, with 29 naive patients compared to 17 switched. Mepolizumab and benralizumab are less commonly used, with mepolizumab showing 10 naive and 3

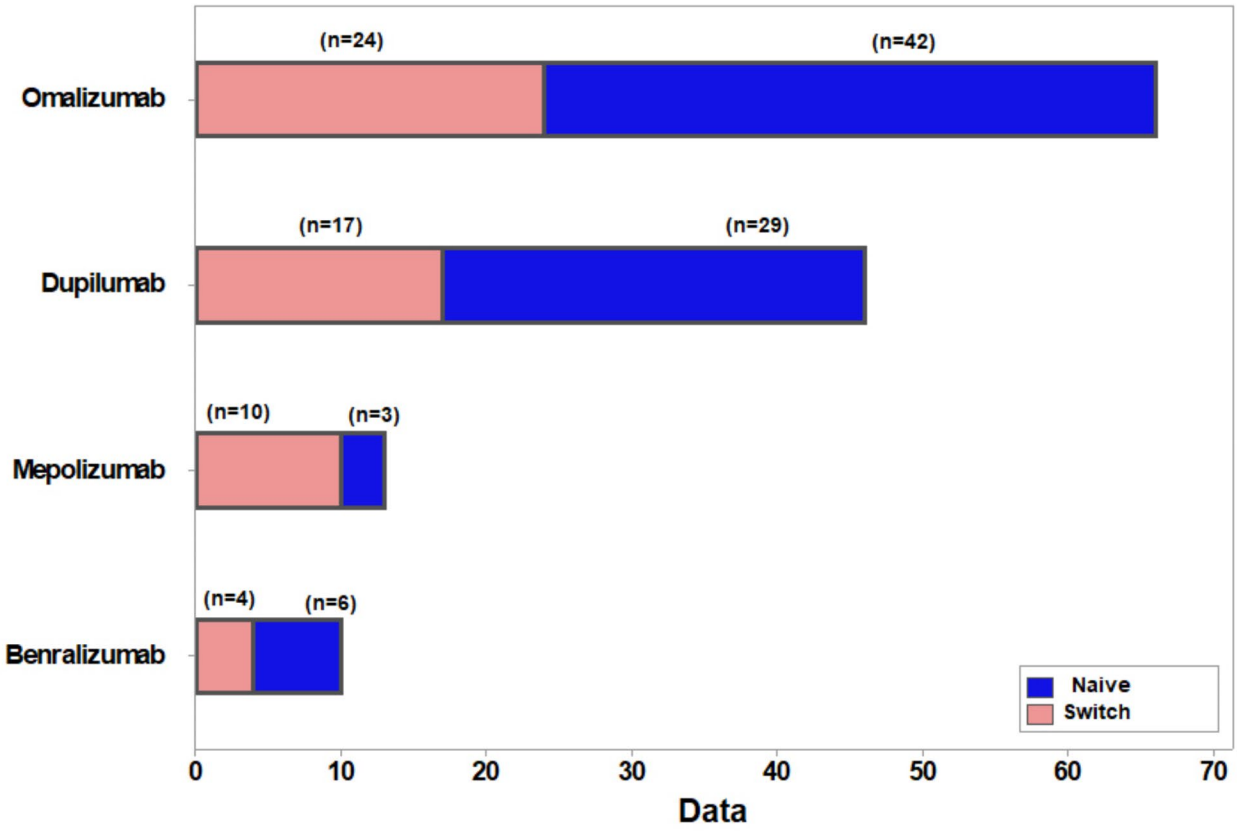

Fig. 1 Biologic types used in patients with severe asthma

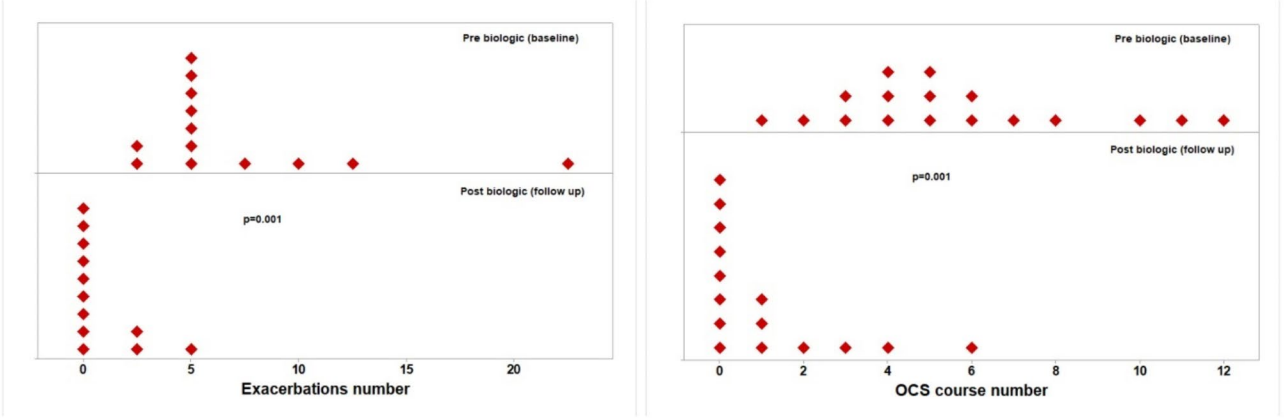

Fig. 2 Changes in asthma exacerbation number and OCS course number after biologic

switched, and benralizumab exhibiting a near-equal distribution of 4 naive and 6 switched patients.

Impact of biologic therapy on asthma control parameters

Supplementary Table 1 illustrated the impact of biologic therapy on various parameters used to evaluate asthma control. The Mann-Whitney test was applied for paired analysis of non-normally distributed data, and the results revealed significant improvements across multiple parameters following treatment.

Figure 2 showed that biologic therapy was associated with a significant reduction in the number of exacerbations ($p = 0.001$) and the need for OCS courses ($p = 0.001$).

Moreover, Fig. 3 illustrated lung function measures, including FEV1% predicted and FVC % predicted, and showed marked improvements, as evidenced by

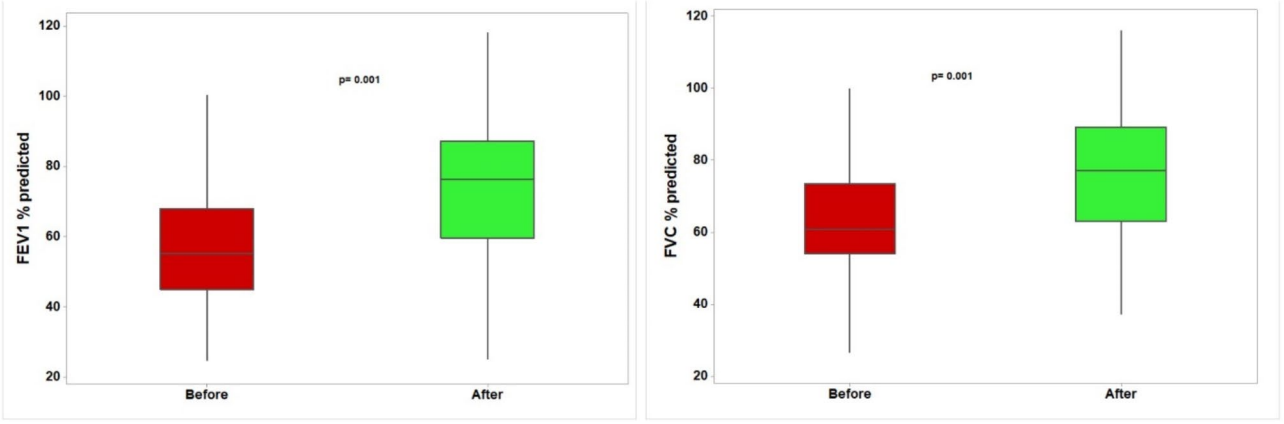

Fig. 3 Changes in FEV1 and FVC % predicted after biologic

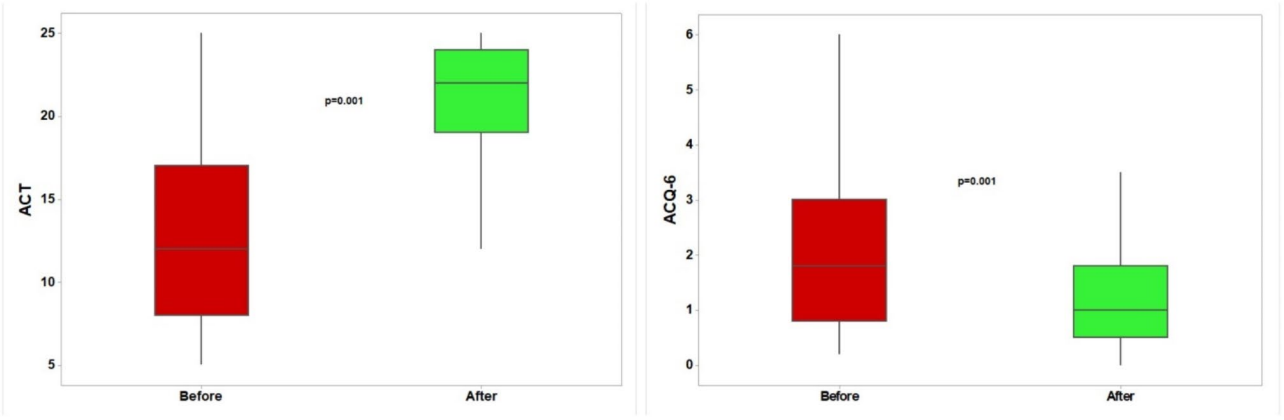

Fig. 4 Changes in ACT and ACQ-6 after biologic

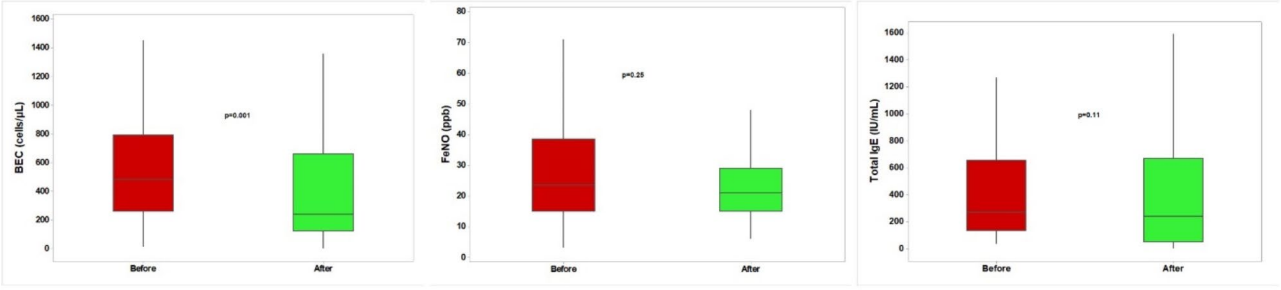

Fig. 5 Changes in BEC, FeNO and total IgE after biologic

significant differences in their median and interquartile range (IQR) values after treatment ($p = 0.001$ for both).

Furthermore, the ACT score significantly increased ($p = 0.001$), while the ACQ-6 score significantly decreased ($p = 0.001$), reflecting better asthma control and an improved quality of life for patients (Fig. 4).

Regarding inflammatory markers, BEC showed a significant reduction ($p = 0.02$), whereas total IgE and FeNO levels exhibited less notable changes (Fig. 5).

Table 2 compared the effect of most frequently used naïve biologics (omalizumab and dupilumab) on patients with severe asthma. The Kruskal Wallis test was applied for comparing the non-normally distributed data, the finding showed that dupilumab seemed to be the most effective for overall asthma control, as indicated by lower median and IQR of ACQ-6 scores ($p = 0.01$), while dupilumab showed significant elevation of the median and IQR of BEC than omalizumab ($p = 0.001$), the lung function improvements were comparable across treatments.

Table 2 Comparison between the effect of different Naïve biologic used in treatment of patients with severe asthma

Factors	Omalizumab ($n=42$)		Dupilumab ($n=29$)		p
	Median	IQR	Median	IQR	
ACT	22	(20–25)	23	(21–25)	0.11
ACQ-6	0.8	(0.33–1.7)	0.6	(0.1-1)	**0.01**†††
FeNO	19	(14–27)	20	(16.5–26)	0.22
IgE	458.5	(235.5-953.5)	447	(223–866)	0.11
BEC	200	(145–360)	440	(195–930)	**0.001**†††
FEV1% predicted	76.3	(60.45–87.5)	81	(73–90)	0.33
FVC % predicted	77	(63.5–88.5)	78.5	(75.25–90.5)	0.52
FEV1:FVC % predicted	77.8	(76.6–79.3)	79.2	(76.9–80)	0.16

The numerical data presented as median and inter quartile range, N: number, IQR: interquartile range, ACT: asthma control test, ACQ-6: Asthma control quality of life, BEC: Blood eosinophil count, FeNO: Fractional exhaled nitric oxide, FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity. †††: The test of significant: Kruskal Wallis test, $p \leq 0.05$ considered significant

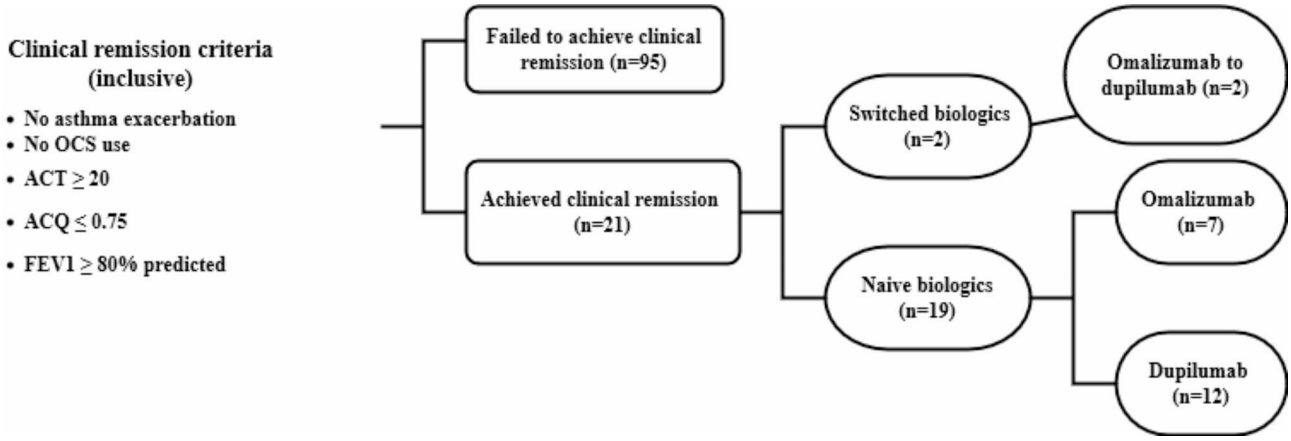

Fig. 6 Prevalence of CR of severe asthma patients on biologics

Clinical remission on treatment biologic therapy

In the flowchart (Fig. 6), the prevalence of CR in the severe asthma cohort was 18.1% (21 out of 116 patients). Most of these patients were treated with dupilumab as a naïve biologic (12 out of 21) or had switched from omalizumab (2 out of 21). The remaining 7 patients were on omalizumab as a naïve biologic.

Table 3 compared patients who failed and succeeded in achieving CR in severe asthma. Age, sex, BMI, smoking status, and disease onset did not show statistically significant differences between the two groups. While inflammatory markers such as FeNO, IgE, and BEC did not differ significantly, genetic factors played a notable role. The Chi square test demonstrated that patients with the CC genotype of the *IL4* gene were significantly more likely to achieve remission than those with the CT or TT genotypes ($p=0.04$). Similarly, the GG genotype of the *TNFα* gene was associated with higher remission rates ($p=0.05$), while the AG genotype was more common in those who failed remission ($p=0.04$). The use of dupilumab was a strong predictor of successful remission, with 66.67% of users achieving remission compared to 33.68% of those who failed ($p=0.005$), whereas omalizumab did not show a significant difference between the groups ($p=0.15$).

Table 4 summarized the predictors of CR in severe asthma as determined through multiple logistic regression analysis. The analysis identified several significant predictors of remission. Increasing age was significantly associated with a lower likelihood of remission, with each additional year reducing the odds by 5% (OR 0.95, $p=0.02$). Sex, BMI, and the *TNFα* gene polymorphism did not show significant effects on remission. Notably, patients with the CC genotype of the *IL4* gene were 4.57 times more likely to achieve remission compared to those with the (CT + TT) genotypes (OR 4.57, $p=0.008$). The use of dupilumab (compared to another biologic) was also a strong positive predictor, increasing the odds of remission by 3.63 times (OR 3.63, $p=0.001$).

Discussion

Targeting disease remission has emerged as a key goal in asthma management, particularly in the era of biologics [17]. Remission signifies not just a reduction but an elimination of disease manifestations. It can be temporary or sustained, with definitions varying across diseases [35]. In asthma, remission is characterized by optimal

Table 3 Factors associated with CR of severe asthma

Factors	Failed to achieve clinical remission ($n=95$)		Achieved clinical remission ($n=21$)		p
Age (mean, SD)	55	11.2	50.1	13	0.12
Sex (*n*, %)					
Female	66	69.47	14	66.67	0.81
Male	29	30.53	7	33.33	
BMI (mean, SD)	31.27	5.29	31.21	5.46	0.96
Smoking (*n*, %)					
Ex-smoker	8	8.42	3	14.29	0.15
Non-smoker	79	83.16	18	85.71	
Smoker	8	8.42	0	0	
Disease onset (*n*, %)					
Adult-onset	73	76.84	14	66.67	0.33
Childhood-onset	22	23.16	7	33.33	
Comorbidity (*n*, %)	77	81.05	17	80.95	0.99
AR (*n*, %)	46	48.42	14	66.67	0.13
NP (*n*, %)	5	5.26	3	14.29	0.14
Eczema (*n*, %)	19	20	1	4.76	0.09
DM (*n*, %)	15	15.79	1	4.76	0.18
HTN (*n*, %)	8	8.42	3	14.29	0.41
Investigations					
FeNO (median, IQR)	22	(14–31)	21	(17–26)	0.95
Total IgE (median, IQR)	261	(69–691)	98	(24–563)	0.18
BEC (median, IQR)	235	(113–610)	410	(130–755)	0.27
Phenotypes (*n*, %)					
Allergic	25	26.32	5	23.81	0.81
Allergic eosinophilic	70	73.68	16	76.19	
***IL-4*gene polymorphism (*n*, %)**					
CC	45	47.37	15	71.43	**0.04***
CT	42	44.21	5	23.81	0.07
TT	8	8.42	1	4.76	0.57
CC + CT (dominant)	87	91.58	20	95.24	0.57
CT + TT (Recessive)	50	52.63	6	28.57	**0.04***
***TNF-α*gene polymorphism (*n*, %)**					
GG	51	53.68	16	76.19	**0.05***
GA	39	41.05	4	19.05	**0.04***
AA	5	5.26	1	4.76	0.92
GG + GA (dominant)	90	94.74	20	95.24	0.92
GA + AA (recessive)	44	46.32	5	23.81	**0.05***
Biologic Treatment (*n*, %)					
Dupilumab	32	33.68	14	66.67	**0.005***
Omalizumab	57	60	9	42.86	0.15

The numerical data presented as mean and standard deviation or median and inter quartile range and categorical data as number and percentage, N: number, SD: standard deviation, IQR: interquartile range, BMI: body mass index, AR: allergic rhinitis, NP: nasal polyp, DM: diabetes mellitus, HTN: hypertension, BEC: Blood eosinophil count, FeNO: Fractional exhaled nitric oxide, IL: interleukin, *: The test of significant: Chi square test, $p \leq 0.05$ considered significant

disease control, including the absence of symptoms and exacerbations, as well as normalized lung function. While current treatments, especially biologics and azithromycin, can achieve certain aspects of remission, ongoing research aims to fully understand and target remission as a long-term therapeutic goal [17].

In this study, CR was defined as sustained treatment with a single biologic therapy for over a year without switching, no exacerbations requiring oral corticosteroids during this period, high levels of asthma control (ACT ≥ 20 and ACQ ≤ 0.75), and preserved lung function (FEV1% predicted ≥ 80%). Approximately 18.1% of our cohort met these criteria and achieved clinical remission. Remission definitions varied widely across studies, with most defining clinical remission as a 12-month period without symptoms or asthma medication; however, only a few included objective assessments [17]. For adult-onset asthma, remission rates range from 2 to 17%, while rates in mixed-age populations (childhood- and adult-onset asthma) range from 6 to 52%, likely influenced by

Table 4 Predictors of CR of severe asthma

Factors	CE	OR	95% CI	*p*
Age	-0.05	0.95	(0.9072, 0.9935)	**0.02**
Sex (M) to (F)	-0.54	0.58	(0.1611, 2.1025)	0.39
BMI	0.03	1.04	(0.9321, 1.1570)	0.43
IL4 gene: (CC) to (CT + TT)	1.52	4.57	(1.3494, 15.5086)	**0.008**
TNFa gene: GG to (GA + AA)	0.66	1.93	(0.1585, 23.5413)	0.23
Dupixent: Yes, to another biologic	1.29	3.63	(1.2533, 10.5394)	**0.001**

CE: Coefficient, OR: odd ratio, CI: confidence interval, M: male, F: female, BMI: body mass index, IL: interleukin. The test of fitness: Hosmer-Lemeshow test: $X^2 = 4.1$, $p = 0.88$. The test of significant: Multiple logistic regression with backward elimination technique, $p \leq 0.05$ considered significant, the sign before CE represents the direction of relationship

the higher remission rate in childhood asthma [17, 21, 36]. A supportive study from the UK Severe Asthma Registry reported that 18.3% of severe asthma patients achieved clinical remission on biologic therapy [37]. However, their definition of remission differed from ours, as it required an ACQ-5 score < 1.5, no OCS use, and near-normal lung function. Despite this difference, the characteristics of patients who achieved remission in the study [37] were consistent with our findings in several points. In our cohort, patients who achieved CR were more likely to be younger female, non-smokers, with a lower BMI. They tended to have fewer comorbidities. Remission was also associated with higher levels of T2 biomarkers, such as BEC.

Our study introduced a novel factor that may influence remission rates: the genetic profile of patients. Specifically, we evaluated the association of *IL-4* and *TNF-α* gene polymorphisms with achieving CR. Results showed that patients with the CC genotype were more likely to reach CR than those with CT or TT genotypes, the likelihood of achieving CR increased 5 times more. This finding highlights the critical role of IL4, a cytokine integral to type 2 inflammation, in asthma pathophysiology. IL4 mediates IgE class switching and Th2 differentiation, processes that are central to the development and persistence of allergic inflammation in asthma [38]. The CC genotype may influence the IL4 gene's expression or signaling pathway, potentially reducing its pro-inflammatory effects and enhancing responsiveness to therapies, such as dupilumab, which specifically targets the IL4/IL13 axis [39]. Moreover, a recent study found significant link between the CC genotype of the *IL-4* gene and mild asthma activity [30], which could facilitate a better response to biologic therapy and lead to a higher remission rate. In contrast, the T allele was associated with greater disease severity [30] and significantly linked to increased IL-4 cytokine production [40]. Additionally, it correlated with increased resistance to combined antiviral therapy [41], potentially reducing the likelihood of achieving CR, even with a stringent treatment protocol.

Similarly, our analysis revealed that the GG genotype of the *TNF-α* gene was significantly associated with achieving CR, whereas the GA genotype was linked to failure in achieving remission. This finding aligns with previous research, which demonstrated that the *TNF-α* GG genotype is associated with milder asthma activity [31]. This connection may partly explain its role in enhancing the likelihood of CR in patients receiving biologic therapies. Moreover, genetic variants of the *TNF-α* gene can influence cytokine production and modify the inflammatory environment within the lungs [42]. Such alterations may contribute to differences in individual responses to biologic therapies like dupilumab, which targets type 2 inflammatory pathways. Additionally, carriers of the A allele exhibited higher levels of LDL cholesterol, insulin, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) [43], suggesting a potential link to insulin resistance. Furthermore, a significant association was observed between this polymorphism and asthma patients with metabolic syndrome [43], highlighting the complex factors that make CR more challenging to achieve in this group of patients. The TNF-α gene, located on chromosome 6p21, plays a crucial role in the pathogenesis of asthma [44]. Of particular interest is the rs1800629 polymorphism within this gene, as the A allele is associated with increased transcription and secretion of TNF-α [45]. This pro-inflammatory cytokine significantly influences asthma pathogenesis by inducing inflammation and regulating immune responses [46]. Elevated levels of TNF-α in the airways and serum have been linked to increased airway hyperresponsiveness [47]. Furthermore, TNF-α affects various aspects of asthma, including neutrophil release, epithelial cell permeability, and macrophage activation [45–47]. Although some studies have indicated that this gene polymorphism does not confer susceptibility to asthma in certain populations [44], a significant correlation has been reported between the A allele and increased TNF-α serum levels [45]. This suggests that while the *TNF-α* rs1800629 polymorphism may not directly influence asthma susceptibility, it could contribute to disease pathogenesis by modulating TNF-α expression and potentially exacerbating inflammation.

This study found that treatment with dupilumab in severe asthma significantly increased the likelihood of achieving CR, with a fourfold higher chance compared to other biologics. Dupilumab, an anti-IL-4 receptor α monoclonal antibody that blocks IL-4 and IL-13, represents a promising option for personalized treatment in severe asthma [48].

Recent clustering studies including the Leicester Study, SARP, ADEPT, and UBIOPRED have identified distinct asthma phenotypes based on lung function, atopy, symptoms, age of onset, and inflammatory patterns [49–52].

These studies identified two primary asthma phenotypes, T2-high and T2-low, each defined by different inflammatory pathways. Type 2 (T2) asthma is characterized by eosinophilic inflammation and Th2-mediated immune responses, although elevated eosinophil levels do not always indicate atopy. T2-high asthma includes both allergic and non-allergic subtypes, with allergic asthma generally presenting early and showing elevated IgE against specific antigens [53]. Our studied cohort was predominantly composed of allergic eosinophilic phenotypes, where IL-4, IL-5, and IL-13 play key roles, making them essential targets in managing T2-high allergic asthma. This phenotype is associated with high levels of airway eosinophils, which produce cytokines like IL-5, a mediator of eosinophil recruitment, maturation, and activation in the airways [53].

A post hoc analysis of the phase 3 QUEST and open-label TRAVERSE studies evaluated CR in patients with moderate-to-severe T2 inflammatory asthma treated with dupilumab [54]. In QUEST, 35.0% of patients achieved CR after one year of dupilumab treatment, compared to 20.4% in the placebo group. This rate increased slightly to 36.1% after an additional year in TRAVERSE, with 70.2% of patients maintaining remission from Year 1 to Year 2. In this study [54], CR was defined by meeting four criteria: no exacerbations, no OCS use, an ACQ score below 1.5, and FEV1 improvement. However, the remission rate observed was higher than in our study, likely due to the use of a randomized control trial design with strict criteria rather than real-world data. Additionally, the QUEST and TRAVERSE studies focused solely on patients receiving dupilumab, whereas our study included patients on various biologics, including those who switched therapies.

A comparable study examined asthma remission rates in severe asthmatics treated for at least 12 months with one of four biologics: omalizumab, mepolizumab, benralizumab, and dupilumab [55]. Remission was defined by symptom disappearance, no exacerbations, cessation of OCS, and FEV1% ≥ 80%. In this study [55], benralizumab showed the highest remission rate at 35.8%, while the rates for the other three biologics were similar: 21.8% for omalizumab, 23.6% for mepolizumab, and 23.5% for dupilumab. In contrast, our results indicated that only patients on dupilumab and omalizumab achieved CR, with no remission observed in those treated with benralizumab or mepolizumab. While both studies used similar criteria for defining remission, the difference in outcomes could be attributed to several factors, the most significant being sample size. The comparable study included a larger number of patients: 302 on omalizumab, 55 on mepolizumab, 95 on benralizumab, and 34 on dupilumab [55], allowing for a broader range of treatment responses compared to our study. Additionally, variations in baseline disease severity likely influenced remission rates across different biologics. Real-world variability, including factors like adherence, comorbidities, and environmental influences, may also contribute to differing results compared to clinical trials.

In another study [56], which reported an even higher remission rate, dupilumab achieved CR in 38.9% of patients with severe Type-2 asthma after 12 months. Remission was more likely among patients with lower BMI and higher baseline blood eosinophils. High BMI is often linked to poorer asthma control and reduced response to biologics [57, 58], while patients with elevated baseline eosinophil levels showed better outcomes [59], likely because dupilumab's mechanism targets the eosinophil-driven inflammation prevalent in severe asthma. Additionally, dupilumab's ability to reduce airway inflammation may help address structural changes over time, enhancing both CR rates and functional stability [59].

Strength and limitation

The study offers a comprehensive evaluation of biologics in severe asthma, leveraging real-world patient data to enhance clinical applicability. A notable strength is its exploration of genetic factors, specifically *IL-4* and *TNF-α* gene polymorphisms, as potential predictors of remission, providing valuable insights for personalized asthma management. Moreover, the longitudinal design of the study allows for a more nuanced understanding of the causal relationship between genetic variations and treatment outcomes. However, this study is not without limitations. The relatively small sample size, particularly for certain biologics such as benralizumab and mepolizumab, limited the ability to perform more detailed statistical analyses. This constraint may reduce the generalizability of our findings, as remission outcomes could vary in a larger, more diverse patient population. Additionally, the lack of stratification of the study cohort based on factors such as age, sex, and comorbidities were a limitation. These variables, alongside inherent genetic heterogeneity, may have introduced confounding factors that could influence treatment outcomes and remission rates. Future prospective studies with larger, stratified cohorts are necessary to validate these findings and further explore the role of genetic and demographic factors in predicting responses to biologic therapies.

Conclusion

This study highlights the transformative potential of biologic therapies, specifically dupilumab, in achieving CR for severe asthma patients. By integrating genetic markers, such as *IL-4* and *TNF-α* gene polymorphisms, as predictors of remission, this research paves the way for more tailored asthma management strategies. The results

not only confirm the efficacy of biologics in improving asthma control but also emphasize the importance of personalized medicine in optimizing outcomes for severe asthma patients. However, future studies with larger cohorts are essential to validate these findings and further refine remission criteria, ultimately offering patients improved quality of life and long-term disease stability.

Supplementary Information

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Supplementary Material 1

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M.A. and A.A. wrote the main manuscript text and W.T. prepared the flow chart. All authors reviewed the manuscript.

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Data availability
The datasets used during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All participants had provided written informed consent, indicating their complete understanding of the nature and objectives of the research. Participation was voluntary, and they willingly agreed to participate after being fully informed. The study approved from Kuwait Ministry of Health ethical committee office with approval number: 2256/2023, which was aligned with local guideline as well the Helsinki Declaration protocol. This protocol ensured that the research was conducted ethically and adhered to globally recognized standards.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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