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Impact of biological therapies on clinical outcomes in patients with severe eosinophilic asthma with chronic rhinosinusitis: an observational study from Saudi Arabia

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Abstract

Background We aimed to study the impact of biological therapies in Saudi Arabia on patients with severe asthma (SA) combined with chronic rhinosinusitis (CRS) in terms of clinical outcomes.

Methods This is a retrospective observational cohort research that was undertaken at the severe asthma clinics of the Armed Forces Hospital of the Southern Region (AFHSR) and King Khalid University Hospital, Abha, from March to September 2022 to delineate the effects of 3 biological therapies (dupilumab, benralizumab, and omalizumab) in adults with SA and concomitant CRS. Clinical outcomes assessed included asthma exacerbation frequency, hospitalization rates, use of oral corticosteroids (OCs), and the asthma control test (ACT) scores before and 1 year after biological therapies.

Results Eighty patients were enrolled, with a mean age of 46.68. There were 45 (56%) females and 35 (44%) males. There was a notifiable decrease in the frequency of exacerbations and hospitalization and in the number of patients who received OCs after 6 and 12 months of biological therapies compared to pre-biological therapies, respectively ($p < 0.001$ each), while there was a significant increase in the ACT scores at 6 and 12 months post-biological therapies, compared to pre-biological therapies, respectively ($p < 0.001$). These significant differences were maintained with all the 3 biologics used.

Conclusions Results from the first study from two large Saudi Arabian tertiary centers for patients with SA and CRS agree with and support those of worldwide real-life ones. One-year follow-up showed the effectiveness of the 3 drugs in terms of reduced frequency of asthma hospitalizations and exacerbations, the use of OCs, and improved ACT scores. Further prospective multicenter studies are warranted.

Keywords Outcomes, Clinical, Severe asthma, Rhinosinusitis, Saudi Arabia, ACT, Exacerbations, Steroids

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Introduction

Severe asthma (SA) is known as "asthma, which requires therapy with high-dose inhaled corticosteroids (ICS) plus a second controller to prevent it from becoming uncontrolled. This second controller could be a long-acting beta-2 agonist (LABA), long-acting muscarinic antagonist (LAMA), leukotriene modifier, and/or oral corticosteroids (OCs) [1, 2]. It affects 3–10% of asthma patients and is associated with increased healthcare costs, hospitalization, and decreased quality of life [1].

Recently, asthma has been best categorized as a heterogeneous syndrome rather than a single disease. Attempts to categorize this heterogeneity using clinical characteristics/phenotypes are less effective at targeting therapies than subtypes based on inflammatory mechanisms/endotypes. Our understanding of the molecular mechanisms underlying airway inflammation has resulted in the employment of monoclonal antibody therapies (biological therapies) to target these pathways [3].

It was observed that biologics that target T2 inflammatory pathways are highly effective in reducing the risk of exacerbations and achieving asthma control in patients with T2 inflammation whose asthma is uncontrolled with conventional therapies [1, 3]. Biologics act on critical points of the T2 inflammatory cascade, such as immunoglobulin E (IgE), interleukin 5 (IL-5) or its receptor, and interleukin four receptor alpha subunit (IL4rα) [4].

The combination of severe asthma with chronic rhinosinusitis (CRS), particularly CRS with nasal polyposis (CRSwNP), represents a unique phenotype with T2 inflammation as shared core pathophysiological mechanisms [5].

Thus, an enhanced response to biologics is expected in patients with SA and CRSwNP, which is evident and reflected in several aspects (e.g., the reduction of asthma exacerbations, improvement in asthma control, and pulmonary function) [5–7].

Many worldwide studies have addressed the impact of biological therapies in patients with SA combined with CRS [3, 6, 8, 9]. However, no studies addressed that issue in Saudi Arabian patients. Only one real-life study discussed the impact of biological therapies for SA in Saudi Arabian patients [10]. However, that study did not enroll patients with combined SA and CRS. Therefore, the current research aims to study the impact of 3 biological therapies on clinical outcomes in Saudi Arabian patients with SA and CRS admitted into two large tertiary centers.

Methods

Study design and population

This research is a retrospective observational cohort study that was undertaken at the severe asthma clinics of the Armed Forces Hospital of the Southern Region (AFHSR) and King Khalid University Hospital, Abha, Saudi Arabia, from March to September 2022. The research team aimed to delineate the effects of biological therapy in adults with severe eosinophilic asthma and concomitant CRS who were maintained on medium to high ICS, LABA, and LAMA, with some receiving montelukast, in terms of clinical outcomes. Clinical outcomes assessed included routine clinic evaluations, exacerbation frequency, hospitalization rates, oral corticosteroid (OC) use, and Asthma Control Test (ACT) scores from the year prior to the year after initiating biological therapy.

Inclusion and exclusion criteria

Participants were adults (≥ 18 years) diagnosed with SA as per the diagnostic criteria of the 2023 Global Initiative for Asthma (GINA) guidelines [1] and concomitant rhinosinusitis, meeting criteria from Orlandi et al. [2]. Exclusion criteria were chest X-ray abnormalities suggestive of interstitial lung disease (ILD) and type 2 low asthma. Patients with allergic bronchopulmonary aspergillosis; ABPA; patients with eosinophilic granulomatosis with polyangiitis; EGPA or having positive anti-nuclear cytoplasmic antibodies (ANCA), patients with hemoglobin < 10 g/dl, those with significant cardiac or autoimmune conditions, fixed or irreversible airway obstruction, paradoxical vocal fold motion, and those with documented history or high resolution computed tomography (HRCT) findings of bronchiectasis or ILD.

Assessments

Asthma exacerbations

We defined exacerbations as episodes with worsened respiratory symptoms and decreased lung function requiring treatment alteration, in alignment with the statements of the American Thoracic Society/European Respiratory Society (ATS/ERS) [11].

Clinical assessment

Routine clinic evaluations included biannual serum eosinophils, IgE measurements, and pulmonary function tests (PFTs). ACT scores were recorded semiannually and retrieved from the patient's medical records.

Chronic rhinosinusitis was assessed per the criteria from Orlandi et al. [2].

ACT

ACT scores, ranging from 5 to 25, assessed asthma control levels, with higher scores indicating better management [12].

Oral corticosteroids (OCs) use

OCs use was referred to any corticosteroid prescription filled during the study's maintenance or exacerbation

management time frame, averaged from pharmacy dispensation records to quantify systemic exposure.

Hospitalizations were collected over 1 year before and 1 year after the initiation of biological therapy. The following data were retrieved for each hospitalization: site of hospitalization (ward vs intensive care unit), hospitalization duration, and invasive or noninvasive mechanical ventilation.

Biological therapy indication

Biological therapy followed the ERS/ATS 2020 recommendations [13], with the anti-IL-5 benralizumab initiated at eosinophil counts ⩾ 150 μL^{-1} and omalizumab considered at counts ⩾ 260 μL^{-1}. Dupilumab served as an adjunct for those inadequately controlled on conventional regimens.

A monthly follow-up was conducted to assess asthma control, adherence, use of OCs, and treatment compliance. To ensure patient safety and detect early allergic reactions, each asthma biologic was administered and followed by at least 30 min of observation.

Outcome measures and data collection

Data encompassing demographics, clinical evaluations, and treatment histories were systematically extracted from electronic health records for analysis.

Ethical considerations

The AFHSR ethical committee approved the study. (AFHSRMREC/2022/PULMONOLOGY-INTERNAL MEDICINE/681).

Statistical analyses

The descriptive statistics were expressed as mean ± standard deviation for the normally distributed variables and the median (IQR) for the non-normally distributed ones. At the same time, frequencies and percentages were used with categorical variables. The three biological treatment groups were compared using one-way ANOVA or the Kruskal–Wallis test for numerical ones. The chi-square test was utilized for the categorical variables. Treatment response before biological therapy, 6 months, and 12 months after biologic therapy was compared using repeated measures ANOVA for numerical variables, or Cochrane *Q* test for categorical variables, while the comparison between pre-treatment and 12 months after was done using paired-samples *t*-test, Mcnemar test, or Wilcoxon signed-rank test. p-value < 0.05 is statistically significant, and SPSS for Windows version 29 was used for the statistical analysis.

Results

Demographic and clinical characteristics before biological therapies

Eighty patients were enrolled in the current study, with an encountered mean age of 46.68 ± 12.81 years and 45 (56%) females and 35 (44%) males. The study cohorts had a mean body mass index (BMI) of 31.14 ± 4.68 kg/m^2, with obesity found in 49 (61%) patients. Chronic rhinosinusitis (CRS) was a comorbid disease in all patients. The following most common comorbidities were nasal polyps (34/80,42%) and gastro-oesophageal reflux disease, GERD (28/80, 35%), respectively. Table 1 shows these results.

Asthma medications and biological therapies

Before biological therapies, all the study subjects received the standard treatments for severe asthma: high-dose ICS, LABA, and LAMA. Remarkably, all patients received OCs. With regards to biological therapies, omalizumab, benralizumab, and dupilumab were used in 8 (10.0%), 22 (27.5%), and 50 (62.5%), patients, respectively (see Table 1).

Characteristically, we did not encounter significant differences in the demographic features, associated comorbidities, or asthma exacerbations per year between patients who received omalizumab, benralizumab, or dupilumab, respectively. Only for pre-treatment serum IgE, there was a significant difference between patients who used benralizumab, dupilumab, and omalizumab ($p = 0.024$), respectively. The pre-treatment mean serum IgE level was the highest in patients who used dupilumab (405.43 ± 291.09 IU/ml), while it was 290.88 ± 122.61 IU/ml and 259.36 ± 121.76 IU/ml for omalizumab and benralizumab, respectively (Table 2).

Treatment response (before and after biological therapies)

The following parameters were compared before and 6 and 12 months after using biological therapies: frequency of asthma exacerbations and hospitalizations, the OCs use, and the ACT (Table 3 and Figs. 1 and 2).

There was a significantly decreased frequency of both exacerbations and hospitalizations after 6 and 12 months of biological therapies compared to pre-biological therapies ($p < 0.001$). The mean ACT scores increased significantly to 19.12 ± 2.83 and 19.25 ± 2.54 at 6 and 12 months post-biological therapies, respectively, compared to 13.40 ± 2.32 pre-biological therapies ($p < 0.001$). The number of patients who received oral corticosteroids decreased significantly from 80 (100%) pre-biological therapies to 9 (11.3%) and 3(3.8%) at 6 and 12 months

Table 1 The demographic features and comorbidities of the enrolled patients ($N=80$)

		***N* (%)**
Age	Mean ± SD	46.68 ± 12.81
	Min–max	18–83
Sex	Male	35 (43.75%)
	Female	45 (56.25%)
BMI	Mean ± SD	31.14 ± 4.68
	Min–max	18.57–46.2
Obesity	No	31 (38.75%)
	Yes	49 (61.25%)
Smoking	Active smoker	4 (5%)
	Non/former smoker	76 (95%)
Exacerbations/year (before the biologics)	Mean ± SD	2.35 ± 0.92
	Min–max	1–5
Asthma duration (years)	Mean ± SD	9.25 ± 4.76
	Min–max	1–25
	Min–max	1–5
Comorbidities		
GERD		28 (35.44%)
Anxiety		27 (33.75%)
ACO		4 (5%)
Chronic rhinosinusitis		80 (100%)
OSA		10 (12.5%)
Nasal polyps		34 (42.5%)
Asthma medications before the biologics		*N* (%)
High ICS		80 (100%)
LABA		80 (100%)
LAMA		80 (100%)
OCs		80 (100%)
Biological type used	Benralizumab	22 (27.5%)
	Dupilumab	50 (62.5%)
	Omalizumab	8 (10%)

GERD Gastroesophageal reflux disease, *BMI* Body mass index, *ACO* Overlap of asthma-COPD, *OSA* Obstructive sleep apnea, *OCs* Oral corticosteroids, *ICS* Inhaled corticosteroids, *LAMA* Long-acting muscarinic antagonist, *LABA* Long-acting beta-2 agonist

Table 2 Baseline general characteristics according to biological therapies

		Benralizumab ($n=22$)	**Dupilumab ($n=50$)**	**Omalizumab ($n=8$)**	***p*-value**
Age (years)	Mean ± SD	45.64 ± 8.52	46.56 ± 13.93	50.25 ± 16.08	0.685^{+}
BMI	Mean ± SD	32.75 ± 3.46	30.52 ± 4.27	30.52 ± 8.49	0.099^{+}
Gender	Male	9 (40.9%)	23 (46%)	3 (37.5%)	0.838^{+++}
	Female	13 (59.1%)	27 (54%)	5 (62.5%)	
Comorbidities	Yes	15 (68.2%)	34 (68%)	8 (100%)	0.166^{+}
Exacerbations/year (pre)	Mean ± SD	2.51 ± 0.82	2.32 ± 0.94	2.13 ± 1.13	0.572^{+}
Asthma duration (years)	Mean ± SD	8.05 ± 1.96	9.26 ± 5.28	12.5 ± 5.73	0.079^{+}

BMI Body mass index

$^{+}$ One-way ANOVA test was used

$^{++}$ Kruskal–Wallis test was used

$^{+++}$ Chi-square test was used

* *p*-value is statistically significant at 0.05 level using the Welch test. Games-Howell method was used for post-hoc pairwise comparison

Table 3 Treatment response before, 6 and 12 months after the biological therapy

	Before the biological therapy	6 months after the biological therapy	12 months after the biological therapy	*p*-value
ACT	13.40 ± 2.32[a]	19.12 ± 2.83[b]	19.25 ± 2.54[b]	< 0.001
	Median (IQR)	Median (IQR)	Median (IQR)	
Frequency of exacerbation	2 (1)		0 (0)	< 0.001
Frequency of hospitalization	1 (0)		0 (0)	
OCs use, *N*(%)	80(100%)[a]	9(11.3%)[b]	3(3.8%)[b]	< 0.001

ACT Asthma control test, *OC2* Oral corticosteroids. Different superscript letters indicate statistically significant differences upon comparison using post-hoc analysis

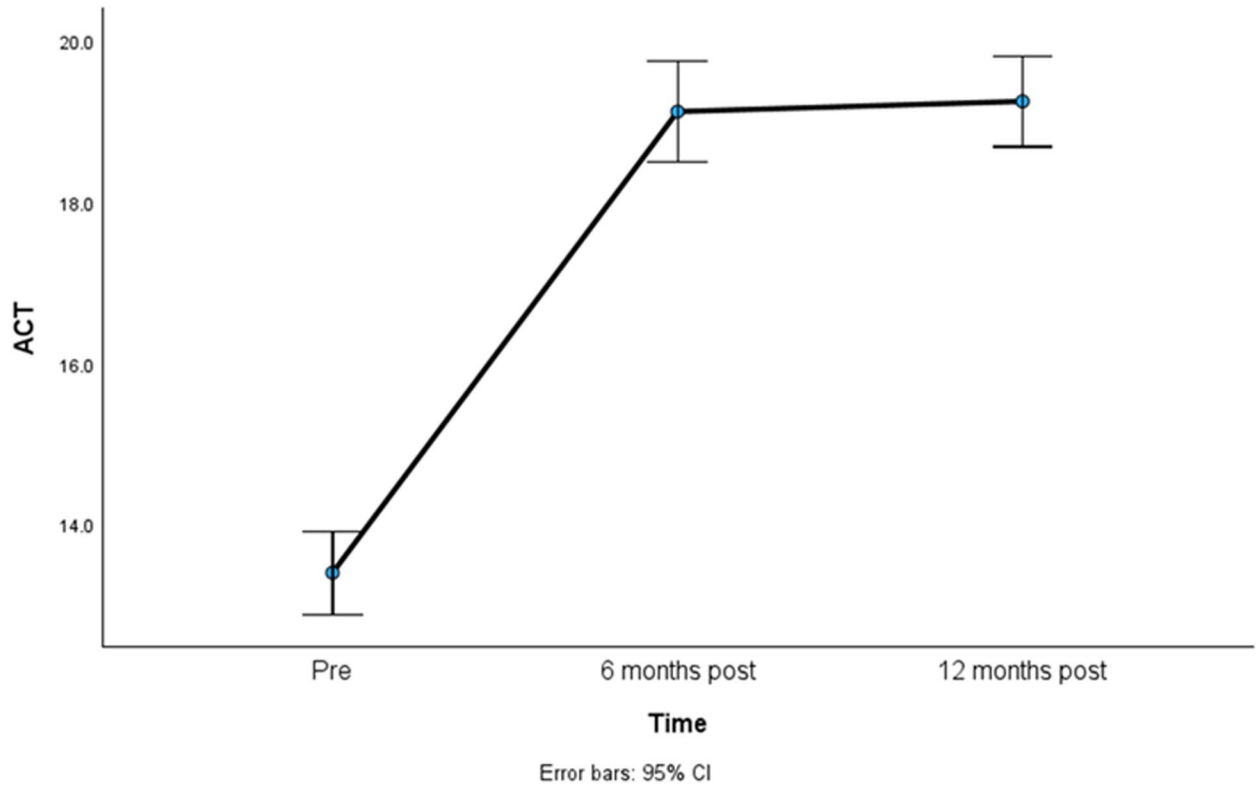

Fig. 1 Effect of biological therapies on asthma control test (ACT) scores of patients with severe asthma and chronic rhinosinusitis after 6 and 12 months

post-biological therapies, respectively ($p < 0.001$) (Table 3 and Figs. 1 and 2 show these details).

Treatment response before and after individual biological therapies

Also, the differences between before and after biological therapies were studied regarding the frequency of asthma hospitalizations and exacerbations, the OCs use, and the ACT among individual drugs (Table 4).

Regarding benralizumab, the frequency of exacerbation and hospitalization significantly decreased 1 year after, compared to the year before benralizumab ($p < 0.001$). For the ACT scores, there was a significant increase at 6 months and 12 months after, in comparison to the level before benralizumab ($p < 0.001$). For the use of OCs, there was a significant decrease at 6m and 12 m after, compared to the level before benralizumab ($p < 0.001$).

Regarding dupilumab, the frequency of exacerbation and hospitalization significantly decreased 1 year after, compared to the year before dupilumab ($p < 0.001$). For the ACT, the scores increased significantly at 6 months and 12 months after, compared to the level before dupilumab ($p < 0.001$). For the use of OCs, there was a

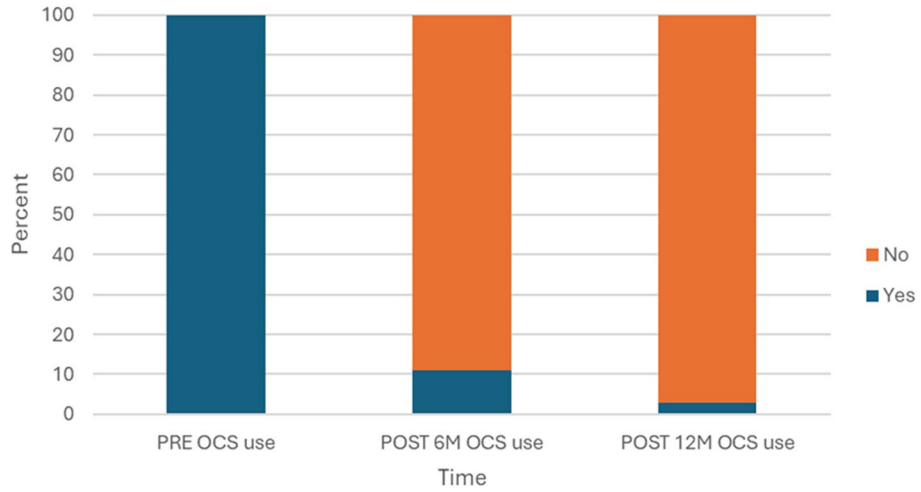

Fig. 2 Effect of biological therapies on oral corticosteroids use of patients with severe asthma and chronic rhinosinusitis after 6 and 12 months

Table 4 Treatment response before, 6 and 12 months after biological therapy in different treatments

	Before the biologic therapy	6 months after the biologic therapy	12 months after the biologic therapy	*p*-value
Benralizumab				
ACT (Mean ± **SD)**	13.89 ± 2.17 [a]	18.91 ± 2.29 [b]	19.01 ± 1.72 [b]	< 0.001
Frequency of exacerbation Median (IQR)	2.0 (1.0)		0.0 (1.0)	< 0.001
Frequency of hospitalization Median (IQR)	1.0 (1.0)		0.0 (0.0)	< 0.001
OCS use, *N* (%)	22 (100%) [a]	0 (0%) [b]	0 (0%) [b]	< 0.001
Dupilumab				
ACT	13.63 ± 2.62 [a]	18.13 ± 1.55 [b]	19 ± 1.85 [b]	< 0.001
Frequency of exacerbation	2.0 (1.0)		0.0 (0.0)	< 0.001
Frequency of hospitalization	1.0 (1.0)		0.0 (0.0)	< 0.001
OCS use	50 (100%) [a]	6 (12%) [b]	2 (4%) [b]	< 0.001
Omalizumab				
ACT	13.63 ± 2.62 [a]	18.13 ± 1.55 [b]	19 ± 1.85 [b]	< 0.001
Frequency of exacerbation	2.0 (2.0)		0.0 (0.00)	0.011
Frequency of hospitalization	1.0 (0.75)		0.0 (0.0)	0.058
OCs use	8 (100%) [a]	3 (37.5%) [ab]	1 (12.5%) [b]	0.004

ACT Asthma control test, *OC2* Oral corticosteroids. Different superscript letters indicate statistically significant differences upon comparison using post-hoc analysis

significant decrease at 6 months and 12 months after, compared to the level before dupilumab ($p < 0.001$).

About omalizumab, the frequency of exacerbations showed a significant decrease 1 year after compared to the year before omalizumab ($p = 0.011$). For the frequency of hospitalization, there was a decrease 1 year after compared to the year before omalizumab, which was not statistically significant ($p = 0.058$).

The ACT scores showed a statistically significant increase at 6 months and 12 months after, compared to the level before omalizumab ($p < 0.001$). The percentage of OCs used significantly decreased at 6 months and 12 months compared to the level before omalizumab ($p = 0.004$) (Table 4 shows details of these results).

Patient safety profile

The patients tolerated the therapies with benralizumab, dupilumab, and omalizumab well. No major adverse events were reported during the treatment.

Discussion

To the best of our current knowledge, this is the first real-world study that addresses the impacts of biological therapies on clinical outcomes in patients with severe asthma combined with CRS in Saudi Arabia, followed at two large tertiary centers. The current study was a real-world study that followed patients with severe asthma who received biological therapies for 12 months. This was a good follow-up duration, giving us robust data about the response to biological therapies regarding clinical improvements. Interestingly, previous studies had shorter follow-up durations [14]. Biological therapies were necessary for our cohorts. All the study subjects received standard asthma medications, yet their asthma was uncontrolled. Thus, they were candidates for biological therapies.

On the other hand, the current study's results reflect the role and magnitude of T2 inflammation in our cohorts with SA. Gender-related effects could affect the prevalence of SA in our cohorts. Females represented 56% of the study cohorts, which was in alignment with GINA reports [1]. Women are likely to be more affected by asthma than men due to the effects of hormones on respiratory cells [15]. Sixty-one percent of our cohorts were obese. Many factors contribute to less or no control of asthma in obese individuals, including lack of fitness, poor lung capacity, sleep apnea, dysfunction of the small airways, and GERD [16].

The current study cohorts had high percentages of associated comorbidities. Chronic rhinosinusitis was evident in all patients. Nasal polyps, GERD, and anxiety were prevalent in 42.5%, 35.4%, and 33.7% of our cohorts, respectively. An interesting point is that proper detection, diagnosis, and management of comorbidities could reduce asthma morbidity and improve quality of life.

Our recent understanding of asthma pathobiology, heterogeneity, and the molecular mechanisms underlying airway inflammation has greatly improved and led scientists to deal with asthma as subtypes based on inflammatory mechanisms or endotypes [3]. One of these mechanisms is the paradigm of 2 endotypes, type 2 low and type 2 high, which has strongly emerged in recent years [17]. In this type 2 (T2) immune response, T helper two cells (Th2) are the main players. These cells produce interleukins 4(IL4), 5 (IL5), and 13 (IL13), which are classically linked to eosinophilic airway inflammation and atopic disease [18]. The true prevalence of the T2 paradigm in severe asthma is difficult to ascertain, but studies estimated it to be in the range of 50 to 95% of those with SA [3, 17, 18].

Consequently, it was observed that biologics that target T2 inflammatory pathways are highly effective in reducing the risk of exacerbations and achieving asthma control in those patients with T2 inflammation whose asthma is uncontrolled with conventional therapies [1]. These biologics target critical points of the T2 inflammatory cascade, including interleukin 5 (IL-5) (reslizumab, mepolizumab) or its receptor (benralizumab), and immunoglobulin E (IgE) (omalizumab).

The current study noted that the enrolled patients' baseline clinical characteristics did not differ significantly among the three biological therapies used. However, there was a significant decrease in the frequency of hospitalization and exacerbations, in the number of patients who received oral corticosteroids, and in the mean ACT scores after 6 and 12 months of biological therapies compared to pre-biological therapies, respectively.

Asthma exacerbations still represent a significant burden in patients with severe asthma. Despite dedicated care, high-intensity ICS, and chronic use of OCs, as many as 53.5% and 12.3% of such patients experience an exacerbation and asthma hospitalization annually, respectively [19]. Moreover, chronic use of oral corticosteroids has been related to unwanted adverse effects, including steroid-induced diabetes, infections, bone and ocular abnormalities, and psychiatric disorders [20]. These sequelae are closely related to poor QOL, notifiable morbidity, and increased utilization of healthcare resources [21]. Our results agree with those published previously and demonstrate that biologics targeting T2 inflammatory cascades are highly effective in reducing the risk of exacerbations/hospitalizations and achieving asthma control in T2 inflammation patients with uncontrolled asthma with conventional medications [1, 8–10, 14].

The more SA subtypes often present with more comorbidities. The most important is chronic rhinosinusitis with nasal polyposis (CRSwNP), which coexists in one-third of individuals with SA [22]. CRSwNP is usually refractory to topical nasal therapies and has a high rate of post-surgical recurrence, but fortunately, it can be effectively managed by biologics. Dupilumab, mepolizumab, and omalizumab have a regulatory indication for CRSwNP, separate from asthma [23, 24].

Significant improvements in clinical outcomes of our cohorts (in terms of reduced frequency of exacerbations and hospitalizations, increased ACT scores, and decreasing OCs were observed with the use of each of the three biological therapies (omalizumab, bineralizumab, and dupilumab) for 1 year in comparison to baseline characteristics.

This agrees with those meta-analyses and real-wide studies that reported such improvements with individual biologics [10, 25–29].

A recently published systematic review of the safety and effectiveness of biological therapy found that each biologic added to asthma treatment significantly reduced

exacerbation rates compared to standard therapy (omalizumab 56%, benralizumab 53%, dupilumab 44%, and mepolizumab 49%) [4]. Randomized trials of the management of SA with adjunctive biologic therapy in adults with frequent exacerbations showed that omalizumab reduced the use of OCs by 40–50%, and reduced exacerbations by 50–65%. Reslizumab, mepolizumab, and benralizumab reduced severe exacerbations by 55% and the use of OCs by 50% [1, 30]. It is to be noted that dupilumab is currently the only asthma biologic that has a dedicated indication for OCs-dependent asthma without the need for a biomarker. Notably, this has its practical advantages as blood eosinophilia can be masked in chronic use of OCs [25]. As a double-edged weapon, anti-IgE and anti-IL5/IL5R reduced the need for nasal surgery and the frequency of OC use in patients with CRS and SA, respectively [1, 30]. It was observed that omalizumab, benralizumab, dupilumab, and mepolizumab could improve asthma control [4, 26].

A meta-analysis of real-world studies [27] showed that the use of omalizumab over 12 months reduced the proportion of patients receiving hospitalizations, severe exacerbations, and oral steroids by 85%, 59%, and 41%, respectively [27]. Also, real-world data on the effectiveness of biologics in SA revealed that the use of omalizumab [27, 28], benralizumab [29], and dupilumab [31] significantly results in better asthma control.

The results obtained in the current study have significant implications for daily clinical practice. Patients with severe asthma and CRS can benefit from a multidisciplinary team discussion of the best therapeutic options, including biologics. Considering the highly significant benefits of biologics in such patients will help them improve their asthma control and, importantly, their quality of life.

Our study has several points of strength. It is the first Saudi Arabian real-world study on biologics' effectiveness in clinical outcomes in patients with severe asthma and chronic rhinosinusitis. Our 1-year follow-up period was also more extended than that of most similar studies. The number of enrolled patients gives the results considerable robustness. However, our study has several limitations. As it is a retrospective study, it is inherently affected by the limitations of retrospective studies. Further prospective multicenter studies are needed.

Conclusion

Results from the first study from two large Saudi Arabian tertiary centers for patients with severe asthma and chronic rhinosinusitis agree with and support those of worldwide real-life ones. Twelve-month follow-ups of patients with SA and CRS showed the effectiveness of omalizumab, benralizumab, and dupilumab regarding the reduced frequency of asthma exacerbations and hospitalizations, use of oral corticosteroids, and improved ACT scores. Further prospective multicenter studies are warranted.

Authors' contributions

EA, AA, SK, MA, HA, SM, and ME PS framework the study's design, facilitated data collection, and organized the interpretation of data. EA, SM, OA, SA, KA, and AM analyzed data. EA, FA, and MQ contributed to data quality control and drafted the manuscript. All authors have made their relative contributions to the revisions of the manuscript. All the authors prepared and approved the final version of the manuscript and agreed to contribute to all aspects of the work.

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Declarations

Ethics approval and consent to participate

The AFHSR ethical committee approved the study. (AFHSRMREC/2022/PULMONOLOGY-INTERNAL MEDICINE/681).

Consent for publication

Not applicable (written informed consent for the publication was not obtained from all participants, as the research is a retrospective analysis).

Competing interests

The authors declare that they have no competing interests.

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