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Impact of biological therapies on laboratory outcomes and FEV_1 in patients with severe eosinophilic asthma with chronic rhinosinusitis: a real-life study from Saudi Arabia

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ABSTRACT

Background: Few studies have addressed the effects of biological therapies on laboratory outcomes and changes in FEV_1 in patients with severe asthma (SA) and chronic rhinosinusitis (CRS). We aimed to study the effect of three biological therapies on laboratory outcomes and FEV_1 in Saudi Arabian patients with SA and CRS.

Methods: From March to September 2022, a retrospective observational cohort study was undertaken at the severe asthma clinics of the Armed Forces Hospital—Southern Region (AFHSR) and King Khalid University Hospital, Abha, Saudi Arabia, to delineate the effects of 3 biological therapies (benralizumab, dupilumab, and omalizumab) in adults with SA and concomitant CRS in terms of FEV_1 and laboratory parameters (serum IgE and eosinophilic counts).

Results: Eighty patients were enrolled, with a mean age of 46.68. There were 45 (56%) females and 35 (44%) males. There were significant improvements in FEV_1 and laboratory parameters (serum IgE and eosinophilic counts) after 6 & 12 months of biological therapies compared to pre-biological therapies ($p<0.001$, each). The response was different among different biological therapies. The improvements in FEV_1, serum IgE, and eosinophilic counts were manifest with benralizumab and dupilumab but not with omalizumab.

Conclusions: 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. One-year follow up of patients with SA and CRS showed the effectiveness of benralizumab and dupilumab, but not omalizumab, regarding FEV_1, serum IgE, and eosinophilic counts. Further prospective multicenter studies are warranted.

Key words: Severe asthma, chronic rhinosinusitis, FEV_1, IgE, eosinophils, outcomes, retrospective

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Ethics approval and consent to participate: The Armed Forces Hospital Southern Region (AFHSR) Institutional Review Board (IRB) approved the study, with Approval number AFHSRMREC/2022/PULMONOLOGY-INTERNAL MEDICINE/681. Since the study was a retrospective analysis, the IRB waived the need for written informed consent.

Availability of data and material: For the current study, the data are available from the corresponding author upon reasonable request from the requester(s).

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Introduction

The definition of severe asthma (SA) is "asthma that requires therapy with high-dose inhaled corticosteroids (ICS) plus a second controller (e.g., long-acting beta-2 agonist (LABA), long-acting muscarinic antagonist (LAMA), leukotriene modifier and/o oral corticosteroids (OCS) to prevent it from becoming "uncontrolled" or that remains uncontrolled despite such therapy" [1,2]. SA affects 3-10% of asthma patients and is associated with increased mortality, hospitalization, decreased quality of life, and higher healthcare costs [1].

Chronic rhinosinusitis (CRS) affects patients worldwide, with a prevalence rate of 6.95–13% [3], and the burden of medical expenses caused by it is exceptionally high. Depending on the presence or absence of nasal polyps (NPs), CRS can be classified as CRS with NPs (CRSwNP) or CRS without NPs (CRSsNP) [4].

Chronic Rhinosinusitis with nasal polyposis (CRSwNP) coexists in over 30% of persons with severe asthma, with or without aspirin-exacerbated respiratory disease (AERD) [5]. CRSwNP has a high rate of recurrence after sinonasal surgery, can be refractory to topical nasal therapies, and can be effectively treated by biologics, with dupilumab, omalizumab, and mepolizumab having a regulatory indication separate from asthma [6].

Many worldwide studies have addressed the impact of biological therapies in patients with SA combined with CRS [7-9]. However, few studies have focused on the effects of those therapies in terms of laboratory outcomes and changes in FEV_1 [10]. Recently, an interesting systematic review of the literature was conducted to address the role of biological therapies in lung function and quality of life in patients with SA and CRSwNP [11]. It concluded that using biological therapies is associated with significant improvements in lung function and quality of life in patients with SA and CRSwNP.

To the best of our knowledge, no studies addressed the impact of biological therapies on laboratory outcomes and FEV_1 in Saudi Arabian patients with SA and CRS. Therefore, the current research aims to study the effect of three biological therapies on laboratory outcomes and FEV_1 in Saudi Arabian patients with SA and CRS admitted to two large tertiary centers.

Materials and methods

Study design and population

The current research is a retrospective observational cohort study undertaken at the severe asthma clinics of the Armed Forces Hospital—Southern Region (AFHSR) and King Khalid University Hospital, Abha, Saudi Arabia, from March to September 2022. This study 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 laboratory outcomes and FEV_1. Outcomes assessed included routine clinic evaluations, exacerbation frequency, hospitalization rates, oral corticosteroid (OC) use, Asthma Control Test (ACT) scores, FEV_1, serum IgE, and eosinophilic counts from the year before 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 Global Initiative for Asthma; GINA 2023 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), 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

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 (CRS) 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]. FEV_1: Pulmonary function was measured using spirometry equipment according to ATS recommendations [13]. For FEV_1, the largest values from three acceptable efforts were recorded. Serum IgE and eosinophilic count were assessed one year before, six months after, and twelve months after biological therapies.

Biological therapy indication: biological therapy followed the ERS/ATS 2020 recommendations [14], 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.

Outcome measures and data collection

Data encompassing demographics, clinical evaluations, laboratory results, FEV_1, and treatment histories were systematically extracted from electronic health records for analysis.

Ethical considerations

The Armed Forces Hospital Southern Region (AFHSR) Institutional Review Board (IRB) approved the study, with Approval number AFHSRMREC/2022/PULMONOLOGY-INTERNAL MEDICINE/681. Since the study was a retrospective analysis, the IRB waived the need for written informed consent.

Statistical analyses

Descriptive data were expressed as mean±SD for normally distributed variables and median (IQR) for non-normally distributed ones, while 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 variables. In contrast, the Chi-square test was utilized for categorical variables. Treatment response before biological therapy, six 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, Wilcoxon signed rank test or McNemar test. $P < 0.05$ is statistically significant, and IBM SPSS for Windows version 29 was used for the statistical analysis.

Results

Baseline (pre-biologics) demographics, laboratory, and FEV_1 characteristics

Eighty patients were enrolled in the current study, with a mean age of 46.68 ± 12.81 years, and they were 45 (56%) females and 35 (44%) males. The mean body mass index (BMI) was 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. Baseline demographics, laboratory, and FEV_1 characteristics 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%)
	Min - Max	1 - 5
Asthma duration (years)	Mean ± SD	9.25 ± 4.76
	Min - Max	1 - 25
Exacerbations/year (before the biologics)	Mean ± SD	2.35 ± 0.92
	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%)
Pre FEV_1%	Mean ± SD	54.82 ± 8.83
	Min - Max	33 - 78
Pre IgE	Mean ± SD	353.81 ± 249.81
	Min - Max	21 - 1150
Pre Eosinophils	Mean ± SD	666.23 ± 352.27
	Min - Max	100 - 1600

BMI, Body mass index; GERD, gastroesophageal reflux disease; ACO, Asthma-COPD overlap; OSA, obstructive sleep apnea; OCS, oral corticosteroid; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist.

The mean baseline FEV_1 values were 54.82 ± 8.83 ml. The mean serum IgE and eosinophilic counts were 353.81 ± 249.81 IU/ml and 666.23 ± 352.27 μL–1, respectively. Table 1 shows these results.

Asthma medications and biological therapies

Before biological therapies, all the study subjects received the standard therapies for severe asthma: high-dose ICs, LABA, and LAMA. Remarkably, all patients received OCs.

Regarding biological therapies, omalizumab, benralizumab, and dupilumab were used in 8 (10.0%), 22 (27.5%), and 50 (62.5%) patients, respectively (Table 2).

Characteristically, we noticed no significant differences in demographics, comorbidities, or asthma exacerbations per year among patients who received omalizumab, benralizumab, or dupilumab, respectively. Only for pre-treatment serum IgE, there was a significant difference among patients who used benralizumab, dupilumab, and omalizumab (p=0.024), respectively. The pre-treatment mean serum IgE level was the highest in patients who received dupilumab (405.43 ± 291.09 IU/ml), while it was the lowest in those who received benralizumab (259.36 ± 121.76 IU/ml), and it was 290.88 ± 122.61 IU/ml in those who received omalizumab, respectively. (Table 2)

Treatment response (before and after biological therapies)

There were significant improvements in FEV_1 and laboratory parameters (serum IgE and eosinophilic counts) after 6 &12 months of biological therapies compared to pre-biological therapies (p<0.001, each). There was a significant increase of pre-biologics FEV_1 from 54.82 ± 8.83 ml to 65.47 ± 9.49 ml and 68.44 ± 8.04 ml after 6 &12 months of biological therapies, respectively (p<0.001). There was a significant decrease of pre-biologics serum IgE from 353.81±249.81 IU/ml to 161.91±144.69 IU/ml and 115.10±93.21 IU/ml, after 6 &12 months of biological therapies, respectively (p<0.001). Also, there was a significant decrease of pre-biologics serum eosinophilic counts from 666.23 ± 352.27 μL–1 to 339.08 ± 321.48 μL–1 and 242.25 ± 212.01 μL–1 after 6 &12 months of biological therapies, respectively (p<0.001) (Table 3).

Treatment response before and after individual biological therapies

There was a significant increase in the FEV_1 6 and 12 months after, compared to the year before benralizumab and dupilumab (p<0.001). There were statistically significant decreases in serum IgE and eosinophilic counts 6 and 12 months after, compared to

Table 2. General characteristics, FEV_1, and lab findings according to the used biologic drugs.

		Benralizumab (N=22)	Dupilumab (N=50)	Omalizumab (N=8)	P
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[+]
Sex	Male	9 (40.9%)	23 (46%)	3 (37.5%)	0.838[+++]
	Female	13 (59.1%)	27 (54%)	5 (62.5%)	
Exacerbations/year (pre)	Mean ± SD	2.51 ± 0.82	2.32 ± 0.94	2.13 ± 1.13	0.572[+]
BA duration years	Mean ± SD	8.05 ± 1.96	9.26 ± 5.28	12.5 ± 5.73	0.079[+]
Pre Eosinophils	Median (IQR)	666.23 (274.75)	563.5 (639.25)	415 (315)	0.149[++]
Pre IgE	Mean ± SD	259.36 ± 121.76	405.43 ± 291.09	290.88 ± 122.61	0.024[+]
Pre FEV_1%	Median (IQR)	54.82 (10)	55 (12)	52 (21.25)	0.641[++]

[+] One-way ANOVA test, [++] Kruskal Wallis test, [+++] Chi-square test, Games-Howell method was used for *post-hoc* pairwise comparison.

Table 3. Treatment response before, compared to 6 and 12 months after biological therapies.

	Before the biological therapy	6 months after the biological therapy	12 months after the biological therapy	P
ACT (Mean ± SD)	13.40±2.32	19.12±2.83	19.25±2.54	<0.001
Frequency of exacerbation Median (IQR)	2 (1)		0 (0)	<0.001
Frequency of hospitalization Median (IQR)	1 (0)		0 (0)	<0.001
OCs use, N(%)	80(100%)	9(11.3%)	3(3.8%)	<0.001
FEV_1%	54.82 ± 8.83	65.47 ± 9.49	68.44 ± 8.04	<0.001
IgE	353.81±249.81	161.91±144.69	115.10±93.21	<0.001
Eosinophils	666.23 ± 352.27	339.08 ± 321.48	242.25 ± 212.01	<0.001

the year before benralizumab and dupilumab (p<0.001, each).

On the other hand, there were no statistical differences in FEV_1 6 and 12 months after compared to the year before omalizumab (p=0.286). There was a borderline statistically insignificant decrease in serum IgE (p=0.053) and a non-significant decrease in the eosinophilic count (p=0.131), 6 and 12 months after compared to the year before omalizumab, respectively (Table 4 details these results).

Discussion

To the best of our knowledge, this is the first real-world study that addresses the impacts of biological therapies on FEV_1 and laboratory outcomes in patients with severe asthma combined with CRS in Saudi Arabia, followed at two large tertiary centers. The current study followed patients with severe asthma who received biological therapies for 12 months. Interestingly, previous studies had shorter follow up durations [10].

Current advances in our understanding of asthma heterogeneity and the molecular mechanisms underlying airway inflammation have led us to treat asthma as subtypes based on inflammatory mechanisms or endotypes [15]. The paradigm of 2 endotypes, type 2 high and type 2 low, has emerged in recent years [15,16]. Type 2 (T2) immune responses, attributed to subsets of CD4 + T cells known as T helper two cells (Th2) that produce interleukins 4, 5, and 13 (IL4, IL5, IL13), have classically been associated with

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

	Before the biologic therapy	6 months after the biologic therapy	12 months after the biologic therapy	P
Benralizumab				
ACT	13.89±2.17	18.91±2.29	19.01±1.72	<0.001
OCs use	22 (100%)	0 (0%)	0 (0%)	<0.001
FEV_1%	56.86±6.34	67.34±9.56	71.76±6.93	<0.001
IgE	259.36±121.76	214.1±132.4	135.68±81.39	<0.001
Eosinophils	746.78±350.15	152.65±124.19	94.83±86.87	<0.001
Dupilumab				
ACT	13.63±2.62	18.13±1.55	19±1.85	<0.001
OCs use	50 (100%)	6 (12%)	2 (4%)	<0.001
FEV_1%	53.58±9.05	65.11±8.82	67.05±7.07	<0.001
IgE	405.43±291.09	131.93±149.33	96.11±94.88	<0.001
Eosinophils	657.79±363.24		295.77±198.90	<0.001
Omalizumab				
ACT	13.63±2.62	18.13±1.55	19±1.85	<0.001
OCs use	8 (100%)	3 (37.5%)	1 (12.5%)	0.004
FEV_1%	57.00±12.49	62.63±13.30	68.00±13.66	0.286
IgE	290.88±122.61	205.76±101.96	177.25±82.69	0.053
Eosinophils	497.50±235.78	-	313.13±336.46	0.131

eosinophilic airway inflammation and atopic disease [16]. This study showed significant improvements in FEV_1 and laboratory parameters after 6 & 12 months of biological therapies compared to those before use. Recently, a systematic search was conducted to address the effectiveness of biologics in terms of lung function as well as quality of life in patients with severe asthma and CRSwNP [11].

Results revealed that significant FEV_1 improvements were consistently observed after 24 weeks of treatment, as shown in real-world studies that enrolled variable proportions of patients with severe asthma/CRSwNP [11].

Our results agree with and support the effectiveness of biological therapies in addressing the underlying inflammatory processes driving severe uncontrolled asthma and CRSwNP. Improving lung function is crucial as it is associated with reduced symptoms, enhanced exercise capacity, and improved quality of life for asthma patients [7-10]. Our study showed a significant decrease in pre-biologics serum IgE and eosinophilic counts after 6 and 12 months of biological therapies, respectively.

These results are in concordance with previous ones [7,8,10,17]. In their study, Khan and colleagues [10] observed that, after six months, biological treatment for 30 patients significantly reduced eosinophils (540 cells/μL to 290 cells/μL) and IgE levels (410 IU/mL to 280 IU/mL). Notably, the reduction in eosinophil levels post-biologic therapy is consistent with the mechanism of action of these agents, which specifically target eosinophilic inflammation [5, 6, 9].

The combination of severe asthma with chronic rhinosinusitis (CRS), particularly CRS with nasal polyposis (CRSwNP), presents a unique phenotype, and the relationship between asthma and CRSwNP is not just a simple association. Core pathophysiological mechanisms are shared, with T2 inflammation being the cornerstone of these disorders. This T2 inflammation strongly impacts the symptoms and burdens of both diseases. Thus, patients who have severe asthma will often experience severe CRSwNP symptoms, too,

and vice versa [4,18]. Consequently, one may expect a better response to biological treatment in patients with SA and CRSwNP. This is evident in reducing asthma exacerbations, using maintenance steroids, and improving lung function, control, and quality of life [18,19].

In the current study, the results of treatment response before and after individual biological therapies were interesting.

Laboratory outcomes and FEV_1 were significantly improved after 6 and 12 months of benralizumab and dupilumb. However, for omalizumab, there were no statistical differences in FEV_1 after its use. There was a borderline statistically insignificant decrease in serum IgE and a non-significant decrease in the eosinophilic count after its use compared to the year before omalizumab, respectively. The clinician should consider these differences in response among biological therapies when choosing a particular biologic for a patient category. Previous reports had demonstrated differences in responses among patients with severe asthma and those with SA and CRS for different biological therapies [11, 17, 20].

Recent reports have shown that dupilumab may be more effective than omalizumab and mepolizumab in decreasing asthma-related exacerbations and improving lung function [20, 21]. The greater effectiveness of dupilumab may be related to its mechanism of action. Dupilumab is a broad-spectrum type 2" biologic. It blocks IL-4 and IL-13 signaling, decreasing the B-cell class switch to IgE.33 In addition, it prevents differentiation of naive TH cells to TH2 cells, thus decreasing canonical TH2 cytokines such as IL-5– and IL-5–induced eosinophil recruitment, the mechanism deployed by the anti–IL–5, mepolizumab [6, 9, 21]. By blocking IL-13, dupilumab may also affect airway hyperreactivity, goblet cell hyperplasia, and smooth muscle dysfunction associated with asthma, and it may account for dupilumab's remarkable effect in improving prebronchodilator FEV_1 value [6, 9, 21].

In a real-world study from Italy [22], 137 patients with late-onset asthma were treated with benralizumab for 24 weeks. Among them, 79 (57.7%) presented with CRwNP. Again, a real-life study from Italy [23] included 123 severe asthma patients, of whom 17 (13.8%) had comorbid CRSwNP. After using omalizumab, there was no significant difference in ACQ, FEV_1, or annual exacerbation rate between those with CRSwNP and those without NP. However, the proportion of patients who improved all three outcomes was numerically more significant in the CRSwNP group (35.7% vs. 23.0%) [23].

On the other hand, in another real-life study [24] with 24 patients with severe allergic asthma and CRSwNP, a 6-month treatment with omalizumab resulted in significant improvements in asthma outcomes (symptoms, rescue medication, ACT, lung function, exacerbations) and sinonasal symptoms but not on nasal polyp endoscopic score [24].

Overall, the results of the current study have important implications for daily clinical practice. Applying a multidisciplinary approach to managing patients with SA and CRS is still a challenge and an unmet need. Given the lack of recommendations for joint management in current clinical practice guidelines [1,4], an evidence-based approach could help decision-making processes.

Given the importance of including lung function and QOL among the primary outcomes of studies in patients with asthma and CRSwNP, future research could analyze the potential correlation between these outcomes.

Our study has many strengths. It is the first Saudi Arabian real-world study on biologics' effectiveness in FEV_1, laboratory, and nasal outcomes in patients with severe asthma and chronic Rhinosinusitis. Our one-year follow up period was also more extended than most similar studies. The number of enrolled patients gives the results considerable robustness. However, our study has several limitations. This is a retrospective study, which is affected by the limitations of retrospective studies. Also, fractional exhaled nitric oxide (FeNO) was not available to assess the enrolled subjects. Further Saudi studies are needed to provide an in-depth understanding of the baseline characteristics of patients with multimorbid conditions and allow a more comprehensive evaluation of the effect of biologics in patients with both SA and CRS.

Conclusions

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. One-year follow up of patients with SA and CRS showed the effectiveness of benralizumab and dupilumab regarding FEV_1, serum IgE, and eosinophilic counts. For omalizumab, there were neither improvements in FEV_1 nor eosinophilic counts and a borderline decrease in serum IgE, respectively. Further prospective multicenter studies are warranted.

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