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SHORT REPORT

Evaluating Safety and Effectiveness of Switching Biologics in Managing Severe Asthma Patients

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Background: The Saudi Initiative for Asthma (SINA) defines severe asthma as asthma that is uncontrolled at SINA step 4 despite optimized management. Choosing the biologic agent that is most appropriate for each patient can be difficult for clinicians. Thus, switching to another biologic agent due to no or suboptimal response is a common practice among asthma specialists. Therefore, this study aims to evaluate the safety and efficacy of switching biologics in patients with severe asthma at a tertiary care center.

Methods: This was an observational retrospective cohort single-center study conducted at King Abdulaziz Medical City-Central Region, Riyadh, Saudi Arabia. All adult patients ≥18 years of age with a confirmed diagnosis of severe asthma and who were switched from one biologic agent (omalizumab, mepolizumab and dupilumab) to another were included.

Results: Thirty-three patients were included in the final analysis. In the majority of patients (81%), switching occurred due to lack of clinical efficacy. Most patients were maintained on the first and second biologic for 6 months or more. Most switching occurred from omalizumab to mepolizumab and dupilumab was the most frequently used last-line biologic (54%). Compared to the first biologic, the mean number of exacerbations decreased after switching to a different biologic (6.6 vs 3.9, p = 0.1). On the other hand, sinus symptoms improved after patients were switched to a different biologic (18.5% vs 37.5%, p = 0.1).

Conclusion: Switching from one biologic agent to another is effective and safe in patients who are not optimally controlled on the initial treatment. National and international guidelines should define and include criteria for switching biologics.

Keywords: asthma, biologics, switching, effectiveness, safety

Background

The Saudi Initiative for Asthma (SINA) defines severe asthma as asthma that is uncontrolled at SINA step 4 despite optimized management. Patients with severe asthma represent a minority of 5–10% of adult asthma, however, morbidity and mortality as well as the health costs associated with this condition are rather high.[1] In the last ten years, severe asthma has been classified according to the level of type 2 inflammation, either type 2 high or type 2 low.[2,3] Type 2 inflammation occurs in almost 70% of severe asthma cases and is characterized by the over-expression of cytokines, such as IL-4, IL-5 and IL-13 and/or elevated immunoglobulin E (IgE).[2,3.]

Currently, there are six biologic agents that target specific components in type 2 asthma and have been approved for use in patients with severe asthma, which are omalizumab (anti-IgE), mepolizumab (anti-IL5), reslizumab (anti-IL5), benralizumab (anti-IL5Rα), dupilumab (anti-IL4Rα) and tezepelumab (antiTSLP).[3,4] Choosing the biologic agent that is most appropriate for each patient can be difficult for clinicians especially with the presence of other comorbidities.[5,6] Therefore, switching to another biologic agent due to no or suboptimal response is a common practice among asthma specialists.[4] There are circumstances other than treatment failure that may necessitate switching to a different biologic agent, such as development of adverse events, patient's choice, agent availability, as well as certain safety

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considerations.[5] Although asthma control improves after switching in some patients, data from the real-world has shown that following switch, patients can have a partial response or even worsen.[6]

In Saudi Arabia, omalizumab was the first biologic agent to be registered in the Saudi Food and Drug Authority (SFDA) in 2006, which was followed by the registration of mepolizumab (2017), dupilumab (2018) and benralizumab (2022). Of note, one study found that use of these medications in Saudi patients was associated with less doses of systemic corticosteroids, severe asthma symptoms and exacerbations.[7]

Despite the numerous studies that assessed response to different biologics, criteria for evaluating response to biologic agents and when to consider a patient to be either a responder or non-responder have not been firmly established.[6,8] Consequently, patients are required to switch the biologic agent in pursuit of the ideal drug.[9] However, there is no consensus on the appropriate measures that need to be considered before switching the biologic agent, in terms of timing, effectiveness and safety.[10,11] Therefore, this study aims to evaluate the safety and efficacy of switching biologics in patients with severe asthma at a tertiary care center.

Materials and Methods

This was an observational retrospective cohort single-center study conducted at King Abdulaziz Medical City-Central Region, Riyadh, Saudi Arabia after granting an IRB approval (IRB/0134/24 on 23/1/2024). All adult patients ≥18 years of age with a confirmed diagnosis of severe asthma and who were switched from one biologic agent (omalizumab, mepolizumab and dupilumab) to another were included. Data was obtained for 117 patients who were following up in severe asthma clinic and receiving a biologic agent. Collected data included patients' demographics, baseline clinical and laboratory data. Additionally, number of exacerbations, hospitalizations and ICU admissions, oral corticosteroid use, and sinus symptoms pre-biologic, post-biologic and post-switch were assessed.

Summary statistics were used to report demographic and clinical characteristics. The categorical variables were presented as number with percentage and the continuous were presented as mean (standard deviations, SD) and median (Interquartile range, IQR) as appropriate . The comparisons of the pre-biologic, post-first biologic and post-second biologic categorical variables were analysed by using McNemar test, and the continuous variables between these stages were done by paired *t*-test and Wilcoxon signed ranks test as appropriate. Differences were considered significant at $p < 0.05$. All the statistical analyses will be performed using SAS 9.4 and R software.

Results

A total of one hundred and seventeen patients were screened for eligibility, and 33 patients were included in the final analysis. As shown in Table 1, the majority of patients were female (69.7%), overweight (39.4%), had allergic rhinitis (97%) and sinusitis with polyposis (75.8%), were on salbutamol (97%), high-dose budesonide-formoterol (81.8%) and montelukast (81.8%) prior to biologic initiation. In almost half of the patients, diagnosis of severe asthma was based on clinical diagnosis, and clinical diagnosis along with pulmonary function test in the other half. All patients had an ACT score of less than 19 and eosinophil count of more than 150 at baseline (Refer to Table 2).

Pre-Biologic vs Post-First Biologic

In 82% of patients, biologics were initiated due to uncontrolled asthma despite maximal treatment, followed by high IgE and eosinophil count in 57% of participants (IgE level ≥30 IU/mL and eosinophil count ≥150 cells/μL). Patients were initially treated with either Omalizumab, Mepolizumab or Dupilumab. As presented in Table 3, in terms of asthma exacerbations and hospital admissions, there was no statistically significant difference between the two stages ($p = 0.1$ and $p = 0.5$ respectively). However, sinus symptoms improved (14.3% vs 18.5%, $P = 0.6$), and frequency of oral corticosteroid use (26.7% vs 21.2%, $p = 1$) for asthma maintenance decreased after patients were started on the first biologic.

Post-First Biologic vs Post-Second Biologic

In the majority of patients (81%), switching occurred due to lack of clinical efficacy. However, half of the patients were also switched due to other reasons, of which persistent nasal symptoms was the most frequent one (refer to Table 4). Prior

Table 1 Baseline Characteristics

Variable (N = 33)	Frequency (%)
Age (mean ± SD)	50.15 ± 12.85
Gender	
Male	10 (30.3)
Female	23 (69.7)
Diagnosis	
Clinical diagnosis	17 (51.5)
Pulmonary function test and Clinical diagnosis	16 (48.5)
Smoking	
Current smoker	3 (9.1)
Never-smoked	7 (21.2)
Ex-smoker	2 (6.1)
Unknown	21 (63.6)
BMI	
<25	11 (33.3)
25-30	13 (39.4)
30-35	6 (18.2)
>35	3 (9.1)
Co-morbidities	
Allergic rhinitis	32 (97)
Sinusitis with polyposis	25 (75.8)
Sinusitis without polyposis	7 (21.2)
History of atopy	11 (33.3)
Hyperparathyroidism	1 (3)
GERD	24 (72.7)
OSA	1 (3)
DM	7 (21.2)
Osteoporosis	7 (21.2)
ACT score	
Uncontrolled (<19)	33 (100%)
Inhalers	
Fluticasone	1 (3)
Fluticasone propionate/Salmeterol	5 (15.2)
Budesonide/Formoterol	27 (81.8)
SABA	32 (97)
LAMA	21 (63.6)
Montelukast	27 (81.8)

Table 2 Laboratory and Respiratory Characteristics

Baseline	Median (IQR)
Eosinophils	670 (540, 800)
IgE (KU/L)	320 (177, 522)
FeNo	29.50 (14.75, 57.50)
FEV1 (%/L)	57 (45.67, 81.5)
FVC (%/L)	74.50 (65.50, 89.75)
FEV1/FVC (%)	71.12 (62.37, 78.89)

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Table 3 Response to Treatment (Pre-Biologic vs Post-First Biologic)

Variable	Pre-Biologic	Post-First Biologic	p-value
Number of exacerbations Median (IQR)	3 (2, 4)	7 (1, 9)	0.17
Number of hospitalizations Mean (SD)	2 (1.7)	3 (2)	0.580
Number of ICU admissions Mean (SD)	1 (1)	1 (0)	-
Sinus Symptoms Improved n (%)	2 (14.3)	5 (18.5)	0.625
Corticosteroid Use n (%)	4 (26.7)	7 (21.2)	1

Table 4 Reasons for Switching Biologics

Reason	n (%)
Lack of clinical efficacy	27 (81.8)
Treatment duration for particular agent[a]	2 (6)
Changing physician	2 (6)
Other[b]	17 (51)

Notes: [a]i.e. patients who were on omalizumab for a prolonged period (eg 5 years) and initially showed improvement but later experienced loss of efficacy. [b]sinus symptoms (n = 15), pregnancy (n = 1), and chronic rhinosinusitis with nasal polyps (CRSwNP) (n = 1).

to switching, patients were assessed for appropriate inhaler technique (75.8%), and compliance (100%). Switching occurred from omalizumab to mepolizumab, or mepolizumab to dupilumab, or omalizumab to dupilumab in 39%, 30% and 24% of participants, respectively. Of note, dupilumab was the most frequently used last-line biologic (54%). One exception was a patient who was switched from dupilumab to omalizumab during her pregnancy. Almost 70% of patients remained on the same inhaled therapy after switching, while in 30%, inhaler therapy was modified. The majority of patients were maintained on the first and second biologic for 6 months or more.

The percentage of patients who responded well and did not discontinue the second biologic was 63%, while treatment was discontinued in the remaining patients due to no clinical improvement. As shown in Table 5, compared to the first biologic, the median number of exacerbations decreased after switching to a different biologic (4 vs 2, p = 0.1), and this was clinically significant as per documentation. Furthermore, the median number of admissions did not change (2 vs 2, p = 1). Additionally, the mean number of ICU admissions did not differ between the two stages (1 vs 1). On the other hand, sinus symptoms improved after patients were switched to a different biologic irrespective of the agent used (18.5%

Table 5 Response to Treatment (Post-First Biologic vs Post-Second Biologic)

Variable	Post-First Biologic	Post-Second Biologic	p-value
Number of exacerbations Median (IQR)	4 (2, 8)	2 (1, 5)	0.11
Number of hospitalizations Median (IQR)	2 (1, 4.5)	2 (1, 5.25)	1.00
Number of ICU admissions Mean (SD)	1 (0)	1	-
Sinus Symptoms Improved n (%)	5 (18.5)	9 (37.5)	0.109
Corticosteroid Use n (%)	7 (21.2)	7 (21.2)	1

vs 37.5%, p = 0.1), while oral corticosteroid use did not change between the two stages (21.2% vs 21.2%, p = 1). In particular, in patients with sinusitis with polyposis, sinus symptoms seemed to improve after switching to dupilumab.

In terms of safety outcomes, none of the patients had to switch to a different biologic due to an adverse event and none developed an adverse event after switching.

Discussion

This study investigated the safety and effectiveness of switching biologics in patients with severe asthma regardless of the agent used. Baseline ACT score and biomarkers for the study participants were similar to what was reported by published research.[12] Most patients were initially started on omalizumab then switched to another biologic agent, as it was the first biologic agent to be registered in Saudi Arabia. Dupilumab was the most frequently used last-line biologic as it was approved after omalizumab and mepolizumab. The most frequent reason for biologic switch in this study was lack of clinical efficacy as well as sinus symptoms in half of the patients, which is in line with what was reported by other data.[13,14]

In 63% of patients, there was a good response to the second biologic agent, while treatment was discontinued in the remaining patients due to no improvement. Clinical improvement in terms of decreased number of exacerbations and reduced frequency of ER visits is the main goal of bronchial asthma experts when switching biologic agents. Our study results, which revealed a clinically but not statistically significant decrease in the median number of asthma exacerbations between the post-first and post-second biologic stages (4 vs 2, respectively, p = 0.1), were in line with this objective as well as most of the published data which found a reduction in the number of exacerbations when patients were switched to a different biologic agent.[13,15,16]

The use of maintenance oral corticosteroids did not differ between the two stages (21.2% post-first biologic and 21.2% post-second biologic, p = 1), and these findings contradict published data[17] which showed a reduction in the number of oral corticosteroids–dependent patients (from 15 to 12) in those who were switched to dupilumab specifically. On the other hand, sinus symptoms improved after patients were switched to a different biologic irrespective of the agent used (18.5% post-first biologic and 37.5% post-second biologic, p = 0.1), which is in line with results from a study that found 87% improvement in sinus symptoms in 23 patients with eosinophilic chronic sinusitis.[12] Particularly, sinus symptoms in patients with sinusitis with polyposis seemed to improve after switching to dupilumab.

Regarding safety outcomes, none of the patients switched to a different biologic due to an adverse event and none developed an adverse event after switching. This is in disagreement with published data which reported that treatment was discontinued in 8% of patients due to an adverse event.[13]

The study has several limitations. First, it is a single-center, retrospective study . Second, the small sample size, which can be explained by the strict criteria of prescribing and switching biologics at the institution, which might have resulted in failure to detect a statistically significant difference in terms of post-first biologic and post-second biologic stages. Thus, this might limit the generalizability of the findings. Third, at pre-biologic, post-first biologic and post-second biologic stages, data were missing for the main efficacy outcomes due to poor documentation which was partly due to some patients visiting other healthcare facilities, therefore not all the medical progress notes were documented in their charts at the study institution.

Conclusion

Switching from one biologic agent to another is effective and safe in patients who are not optimally controlled on the initial treatment. Future studies with a larger sample size to evaluate more clinical outcomes as well as the corresponding risk factors for switching biologics are needed. National and international guidelines should define and include criteria for switching biologics.

Ethical Statement

The protocol was approved by the IRB Committee of King Abdullah International Medical Research Center-Ministry of National Guard Health Affairs, under reference number IRB/0134/24. The requirement for informed consent was waived

by the ethics committee due to the absence of patient interventions or collection of biological samples. This study complies with the Declaration of Helsinki.

Disclosure

The authors report no conflicts of interest in this work.

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