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CASE SERIES

Secondary Non-Response to Biologic Treatment in Patients with Severe Asthma

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Abstract: Biologic therapies have revolutionized the management of severe asthma (SA), offering significant symptom control and reduced exacerbations for many patients. However, up to 25% of individuals do not show satisfactory responses to these treatments and are categorized as non-responders. Definitions of response and primary non-response to biologics in SA are well-established. In secondary nonresponse, patients show initial response to biological treatment in the first 6–12 months but later lose asthma control, and in SA this phenomenon remains undefined and unstudied in literature. We present 4 cases of severe asthma treated with different biologic agents. All patients demonstrated significant clinical improvement during the first 12 months of therapy but followed by a gradual loss of asthma control, indicative of secondary nonresponse. We discuss the clinical features, potential mechanisms, and implications of secondary nonresponse to biologics in severe asthma, highlighting an unmet need for further research to define this phenomenon and guide future therapeutic strategies.

Keywords: severe asthma, biological treatment of severe asthma, non-response to biologics in severe asthma, secondary nonresponse to biologics in severe asthma, type 2 severe asthma

Introduction

Biological drugs have demonstrated positive impact on the lives of many patients with SA by reducing the frequency of exacerbations and dose of OCS and by improving lung function. In treatment of SA, two terms are considered the response to treatment and disease remission.[1]

Response to treatment occurs in the majority of patients with SA, but the degree of response varies. Various systems were proposed for assessment of response based on parameters and thresholds. The parameters used include symptom load [measured by the Asthma Control Test (ACT) or Asthma Control Questionnaire (ACQ)], exacerbation, use of OCS, lung function (measured by FEV1 and FeNO), eosinophil count (EOS), subjective assessment of the patients, and physicians' global assessment. All proposals are based on combinations of these parameters, but they are composed differently and use different thresholds. There are no universally accepted criteria to define response to biologics in SA, however there is wide agreement on including four main parameters in the definition of response: severe exacerbations, oral corticosteroid (OCS) use, symptoms, and FEV1. Minimal clinically important difference (MCID) is often used for assessing the threshold in response; this is defined as the smallest relevant within-person change between treatments. Response can be estimated 6 months after starting treatment.[2] The Biologic Asthma Response Score (BARS) is a simple objective tool to evaluate response to biologic therapy using the three main criteria asthma control, exacerbations, and OCS use.[3] In responders there are ≥50% reduction in severe exacerbations over the past 12 months AND ≥50% reduction in OCS dose AND improvement in ACT by ≥3 points.[3]

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Non-response (NR) of SA to biological treatment varies and is estimated to be up 25%.[4] Non-Response to biologics is defined as <50% reduction in maintenance OCS dose AND <50% reduction in severe exacerbations AND <3-point increase in ACT questionnaire MCID), and <100-mL and <10% increase in FEV1.[2]

Disease remission in asthma is a new term introduced by an expert consensus and includes clinical remission (where there are no significant symptoms 12 months or more, with optimization or stabilization of lung function, patient/provider's agreement on remission, and no use of systemic corticosteroids) and complete remission (clinical remission in addition to objective resolution of inflammation).[2]

Secondary NR is defined as loss of response to treatment after initial response for 6–12 months.[5,6] Secondary NR to biologics in SA remains undefined and unreported in literature, however it is well defined in other inflammatory diseases, such as rheumatoid arthritis (RA), psoriasis, and inflammatory bowel disease.[5,6]

We suggest applying the three-level classification of NR in rheumatoid arthritis to SA. Primary NR refers to no significant response within 6 months, early secondary NR to loss of effectiveness within 12 months of response, and late secondary NR to loss after ≥12 months of sustained response.[5]

Using this framework, we present four cases of SA that initially responded to biologics but later required treatment modifications due to late secondary NR.

Case Series

We present 4 patients with SA who were treated with different biological agents. All patients demonstrated significant clinical improvement during the first 12 months of therapy but later followed by a gradual loss of asthma control. All cases were treated at severe asthma clinic in Hamad General Hospital, Doha, Qatar through the whole period of study. Ethical approval from the local IRB (MRC-04-24-882) was obtained and written informed consents for publication of their details were obtained from the study participants. In all cases the diagnosis of asthma was confirmed with reversibility. No one was smoker or had COPD. Adherence to asthma medications and technique of inhalation were verified and triggering factors and comorbid conditions were addressed. Inhaled asthma medications were optimized, and baseline laboratory and radiological investigations were carried out to exclude other differential diagnosis, that included complete blood count, renal and liver function tests, ANA, ANCA, anti-protein 3 antibodies, eosinophil count, total IgE, specific IgE or skin prick testing for inhaled allergens, CT scan of the chest and CT of paranasal sinuses if indicated, and stool examination was done for patients with hypereosinophilia to exclude secondary causes. All biologics were FDA approved for SA and CRS at the time of initiation and were administered in a supervised setting at the severe asthma clinic, ensuring perfect adherence. Patients were assessed at regular intervals (6, 9, 12, 15, 18, and 24 months) and then annually if clinically stable using asthma control test (ACT), Mini-AQLQ, rate of exacerbation, pre and post Bronchodilator spirometry, eosinophil count, and FeNO when available. Patients who have CRS/CRSwNP were initially assessed by ENT surgeons. Nasal symptoms were evaluated at baseline and at regular interval during follow up using SNOT-22 scores and sense of smell scores 0–3 (Where 0 complete absence of smell and 3 normal).

Case 1

A 30-year-old woman with SA and AR since childhood was maintained on Fluticasone/Salmeterol Diskus 500/50 mcg twice daily, montelukast, and budesonide nasal spray. Asthma symptoms were uncontrolled despite maximum inhaled therapy, with 5 exacerbations in the past 12 months that required multiple courses of OCS. Other comorbidities: diabetes mellitus (DM) with BMI of 30. The initial workup showed a total IgE of 330 Kunit/L, positive SPT for house dust mites, and an eosinophil count of 350/μL. Baseline ACT 10/25, and Mini-AQLQ 3.6/7, with FEV1 of 1.38 L (45% predicted). Subcutaneous omalizumab 450 mg every 4 weeks was initiated according to the body weight and the level of total IgE in May 2014. Assessment after 12 months revealed significant improvement in asthma symptoms with absence of exacerbations. ACT 24/25, Mini-AQLQ: 6.8/7 and FEV1: 2.18 L (78% predicted), and EOS was 200/μL. Assessment at 24 months showed a recurrence of symptoms with 4 exacerbations in the last 6 months, and ACT 9/25, Mini-AQLQ 3.1/7, FEV1: 1.7 L (50% predicted), and EOS 260/μL. She was switched to mepolizumab, which yielded a good response after 6 months of the new biological treatment (see Table 1).

Table 1 Characteristics of Patients with Severe Asthma and Secondary Nonresponse

Parameter		Case 1	Case 2	Case 3	Case 4
Age (years)		30	56	68	60
Age at Onset (years)		Childhood	32	30	46
Sex		Female	Female	Female	Female
BMI		30	36	34	27
Comorbidities		AR	CRS	CRSwNP	CRS
Type of biologic		Omalizumab	Mepolizumab	Benralizumab	Benralizumab
Secondary Nonresponse (months)		18	15	18	13
Switched to		Mepolizumab	Dupilumab	Dupilumab	Mepolizumab
Exacerbations	**Baseline**	5	4	5	3
	12 m	0	0	0	0
	15 m	0	0	0	2
	18 m	0	3	0	N/A
	24 m	4	N/A	3	N/A
	6 m after switch	0	0	0	0
ACT	**Baseline**	10	6	13	12
	12 m	24	21	20	20
	15 m	23	23	23	11
	18 m	24	12	23	N/A
	24 m	9	N/A	14	N/A
	6 m after switch	20	22	24	21
Mini-AQLQ	**Baseline**	3.6	2.2	3.3	3
	12 m	6.8	5.2	5.4	5.2
	15 m	6.9	6	5.7	2.1
	18 m	6.8	3.7	5.8	N/A
	24 m	3.1	N/A	2.9	N/A
	6 m after switch	6	5	6.5	5
FEV1 (L)	**Baseline**	1.38	1.55	1.45	2.1
	12 m	2.18	1.92	1.65	2.55
	15 m	NA	1.9	1.68	2.25
	18 m	2.09	1.6	N/A	N/A
	24 m	1.7	N/A	1.25	N/A
	6 m after switch	2.1	1.85	1.6	2.3
Eosinophil Count (cell/μL)	**Baseline**	350	320	1400	1200
	12 m	200	50	0	0
	15 m	NA	50	0	950
	18 m	280	40	0	N/A
	24 m	260	N/A	0	N/A
	6 m after switch	50	130	500	100

Abbreviations: AR, Allergic Rhinitis; CRS, Chronic Rhinosinusitis; CRSwNP, Chronic Rhinosinusitis with Nasal Polyposis; m, months; ACT, Asthma Control Test; Mini-AQLQ, Asthma Quality of Life Questionnaire; FEV1, Forced Expiratory Volume in the first second; N/A, non applicable; NA, not available.

Case 2

A 56-year-old woman with SA and CRS diagnosed at the age of 32-year was maintained on Fluticasone Furoate/Vilanterol Ellipta 200/25 mcg once daily, montelukast, and mometasone nasal spray. Asthma remained uncontrolled, with 4 exacerbations

in the last 12 months required OCS courses. Total IgE 210 Kunit/L with negative SPT for inhaled allergens, FeNO 42 PPB, and EOS 320/μL. ACT 6/25, Mini-AQLQ 2.2/7, and FEV1 was 1.55 L (70% predicted). Mepolizumab 100 mg SC every 4 weeks was added in March 2022. After 12 months, the assessment showed absence of exacerbation and improvement of ACT to 21/25, Mini-AQLQ 5.2/7, FEV1 1.92 L (89% predicted), and EOS 50/μL. At 18 months of mepolizumab the assessment showed a recurrence of symptoms with 3 exacerbations in 3 months. ACT 12/25, Mini-AQLQ: 3.7/7. FEV1 1.6 L (73% predicted), and EOS was 40/μL. She was switched to dupilumab with a good subsequent response (see Table 1).

Case 3

A 68-year-old woman with SA and CRSwNP started at the age of 30 year was maintained on Budesonide/Formoterol turbohaler 320/9 mcg 2 inhalations twice daily, Tiotropium Respimat, montelukast, levocetirizine, and budesonide nasal spray. She experienced 5 severe exacerbations in the past 12 months. She has dyslipidemia with BMI of 34. Total IgE 420 Kunit/L with negative SPT for inhaled allergens, and EOS of 1400/μL. Work up to exclude secondary causes of hypereosinophilia did not reveal any cause such as parasitic infestation. ACT 13/25, Mini-AQLQ 3.3/7, SNOT-22 scores 78, sense of smell 0, FEV1 1.45 L (74% predicted), and FeNO 39 PPB. Benralizumab 30 mg SC every 4 weeks for the first 3 doses, then every 8 weeks, was added in July 2019. At 12 month she showed marked improvement with no exacerbations, ACT 20/25, Mini-AQLQ 5.4/7, SNOT-22 scores 10, sense of smell was 3/3, FEV1 of 1.65 L (85% predicted), FeNO 18 PPB, and EOS 0/μL. By 24 months of Benralizumab, symptoms recurred, with 3 exacerbations in 6 months, ACT 14/25, Mini-AQLQ 2.9/7, FEV1 of 1.25 L (64% predicted), FeNO 46 PPB, and EOS of 0/μL. Nasal symptoms deteriorated, and sense of smell was lost. She was switched to dupilumab with a favorable response at 6 months of treatment (see Table 1).

Case 4

A 60-year-old woman with SA and CRS since the age of 46 was maintained on Budesonide/Formoterol turbohaler 320/9 mcg 2 inhalations twice daily, montelukast, desloratadine, and mometasone nasal spray. Other comorbidities: diabetes mellitus with BMI 27. She experienced 3 severe exacerbations in the past 12 months. Total IgE 110 Kunit/L with negative SPT for inhaled allergens, and an EOS 1200/μL. ACT was 12/25, Mini-AQLQ 3/7, FEV1 2.1 L (84% predicted). Benralizumab 30 mg SC every four weeks for the first three doses, then every eight weeks, was added in April 2022. At 12 month, she had no exacerbations, ACT improved to 20/25, Mini-AQLQ 5.2/7, FEV1 2.55 L (95% predicted), and EOS was 0/μL. By 15 months, she had recurrence of symptoms with 2 exacerbations in 2 months, ACT dropped to 11/25, Mini-AQLQ 2.1/7, FEV1 2.25 L (87% predicted), and eosinophil count rose to 950/μL. She was switched to mepolizumab, with a subsequent good response (see Table 1).

Discussion

In primary NR, the drug is ineffective, with no clinical response within the initial treatment period, while in secondary NR, the effectiveness of the drug is lost after a period of initial response, so, physicians should expect that loss of response may occur at any time even if patients show good response for the first 12 month or more. The underlying mechanisms for primary and secondary NR may differ. While primary NR may be due to a mechanistic failure, secondary NR may be driven by immunogenicity. Thus, developing clear definitions of primary and secondary NR is essential to accelerate research that aims to predict the optimal therapy for a given patient which may improve clinical practice guidelines.[5] For example, if a patient showed a primary NR to anti-IL5, the best practice would likely be to switch to a biologic with different mechanism of action such as anti-IL4R. However, if the patient was able to achieve initial response prior to secondary nonresponse, it would be reasonable to proceed with another anti-IL5 or anti-IL5R. We believe that defining the type of non-response is key to improving patient care.

Potential causes of primary NR to biologics in SA when patients show no response to treatment from the start include incorrect identification of the specific T2 pathways, comorbidities, insufficient dose, infections, change in the initial inflammatory endotype, adverse drug events, and autoimmune phenomena.[2]

We think that causes of secondary NR to biologics in SA may include the development of anti-drug antibodies (ADAs), autoimmune phenomena, change in the initial inflammatory endotype, incorrect T2 pathway identification, nonadherence to medications and other factors, however, causes of secondary NR in SA were not studied before.

ADAs can develop at any stage during biological therapy, potentially neutralizing the drug or reducing serum drug concentrations to sub-therapeutic levels, resulting in a loss of clinical response. An overall ADAs incidence was 2.91% across biologics in SA, with the highest being with benralizumab (8.35%) and the lowest with omalizumab (0.00%). ADAs incidences for dupilumab, mepolizumab, and tezepelumab were 7.61%, 3.63%, and 1.12%, respectively.[7]

Autoimmune responses may also contribute to secondary NR. Adults with SA show elevated autoantibodies linked to asthma severity, including higher levels of a-enolase-specific IgG and anti-EPx/ECP IgG/IgE compared to mild asthma or healthy controls.[8] EPX-specific IgGs were detected in the sputum of 37% of eosinophilic asthmatics, indicating localized autoimmune activity in SA.[9]

Inflammatory endotypes of asthma are dynamic, fluctuating with external factors such as infections, smoking, or treatment effects. This variability was observed in up to 50% of patients and necessitates a re-evaluation of phenotypes and biomarkers periodically.[10,11]

T2 complexity can contribute to misidentifying T2 pathways and inappropriate biological selection, with current biomarkers inadequately defining endotypes. A study on mice done by Scott G. et al showed that eosinophils are not the sole contributor to asthma pathophysiology or lung function decline and emphasized the need to block additional mediators IL-4/IL-13 not only IL5, to modify lung inflammation and impact lung function.[12]

This report presents four cases of SA, highlighting the heterogeneity of secondary NR to biological therapies where patients showed initial response in the first 12 months then the response was lost. In our cases, late secondary NR occurred at 15, 18, and 24 months, marked by loss of asthma control despite initial improvement. The first case demonstrated an overlap inflammatory phenotype (allergic and eosinophilic), responded initially to omalizumab (the only available biologic treatment for SA at that time) for 1 year but at 18 month she lost the response suggesting that shifts in the inflammatory pathway may drive secondary NR between Th2 cells and ILC2 cells.[13] Th2 inhibition might over-activate the ILC2 pathway, which is targeted by mepolizumab but not by omalizumab, warranting further research. Development of ADAs to omalizumab are extremely rare, so it is unlikely to be the cause for secondary NR in this patient.[7] Autoimmunity could be the cause for secondary NR but could not be confirmed.

The second case demonstrated eosinophilic phenotype and showed initial response to mepolizumab in the first 12 months then lost the response and maintained low EOS despite secondary NR arguing against ADAs, though autoimmune responses remain a potential factor that could not be confirmed. The third case was eosinophilic in phenotype and showed good response to Benralizumab in the first 12 months then lost the response despite maintaining low EOS indicating that ADAs is unlikely to be the cause for secondary NR, though autoimmune responses remain a potential factor that could not be confirmed. The fourth case showed eosinophilic phenotype and responded well to benralizumab initially but after 12 months she lost the response and EOS rose after that suggesting ADAs development, aligning with trials reporting ADAs to benralizumab in 13–15% of cases without adverse outcomes.[14] However, real-world data link ADAs to treatment failure in 10%, necessitating a treatment switch in 62% of patients.[15]

Conclusion

The definition of secondary non-response in severe asthma remains unexplored in literature, creating a significant knowledge gap. Its proposed mechanisms, such as immune signaling alterations or drug variability, are poorly understood and highlight the need for further research to improve diagnosis and treatment strategies. Patients with severe asthma on biologics should undergo continuous reevaluation even if they showed initial improvement for a year or more to detect this phenomenon.

Abbreviations

ACT, Asthma Control Test; AR, Allergic Rhinitis; Anti-IgE, Anti Immunoglobuline E; Anti-IL5, Anti Interleukin 5; Anti-IL5R, Anti Interleukin 5 Receptor; Anti-IL4R, Anti Interleukin 4 Receptor; ADAs, Anti-Drug Antibodies; ANA, Anti-Nuclear Antibodies; ANCA, Anti-Neutrophilic Cytoplasmic Autoantibodies; CRS, Chronic rhinosinusitis; CRSWNP, Chronic RhinoSinusitis with Nasal Polyposis; COPD, Chronic Obstructive Pulmonary Disease; DM, Diabetes Mellitus; EOS, Eosinophil count; FeNO, Fractional exhaled Nitric Oxide; FEV1, Forced expiratory volume in 1 sec; IgE, Immunoglobulin E; IgG, Immunoglobulin G; Mini-AQLQ, Mini Asthma Quality of Life Questionnaire;

NR, Non-Response; OCS, Oral Corticosteroid; RA, Rheumatoid Arthritis; SA, Severe Asthma; SPT, Skin Prick Testing; SNOT-22, Sino-Nasal Outcome Test 22; SC, Subcutaneous.

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Disclosure

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