Effectiveness of Biologics in Severe Eosinophilic Asthma

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Abstract

Background: Severe asthma represents a minority of all asthma cases but contributes disproportionately to morbidity , healthcare utilization and costs to society. Biological therapies target key inflammatory cytokines, receptors or immune cells that are driving eosinophilic activation and airway damage in the T2 inflammation cascade. This study aims to evaluate the evidence on effectiveness of biologics in Saudi Arabia. Study Objectives: The main objective of the research is to investigate the clinical effectiveness of biologic therapies, including dupilumab, benralizumab, and omalizumab, for the treatment of severe eosinophilic asthma in patients from Saudi Arabia, as well as the impact of the comorbidities of chronic rhinosinusitis and nasal polyps on treatment outcomes. Materials and Methods: This is a narrative review using an exploratory research design where the data is gathered from various sources based on pre defined inclusion and exclusion criteria. The preferred Reporting Items for Systematic Review and Meta-Analysis PRISMA is used to segregate and screen the collected studies. Results: The KSA population showed a robust efficacy in biologics: Asthma control improved in 91.8% to 92.8% of patients. OCS use was practically eliminated, improving from 77.3% (75/97) to 10.3% (10/97) (86.7% reduction). CS use was one of at least three measures of asthma control. The number of patients with one or more asthma exacerbations decreased from 84.5% pre-treatment to 14.4% post-treatment. Conclusion: Local real-world evidence demonstrates a high level of effectiveness for these targeted agents; with more than 90% of patients who previously had poor control of asthma moved to either 'controlled' or 'partly controlled' status. The total clinical benefit is impressive, including an 83% reduction in the annualized rates of severe exacerbations and significant rates of oral corticosteroid treatment cessation, with a clear impact on long-term morbidity.

Keywords: Severe Eosinophilic Asthma, Biologic Therapy, Dupilumab, Benralizumab, Clinical Outcomes.

1. INTRODUCTION

Severe asthma is a significant public health concern, globally and specifically within the Kingdom of Saudi Arabia (KSA). [1] Although severe asthma only represents a minority of all asthma cases, it accounts for a disproportionate burden of morbidity and healthcare utilization and costs to society. Individuals categorized with severe asthma often experience impaired quality of life affected by recurrent exacerbations requiring systemic glucocorticoids and emergency department visits and hospitalization. [3], [5] Current guidelines for patients with persistent asthma recommend treatment predominantly with inhaled corticosteroids (ICS) and a long-acting β2 agonist (LABA). Severe asthma is clinically defined as persistent , uncontrolled asthma despite optimizing management ,and is frequently classified within the Global Initiative for Asthma (GINA) or Saudi Initiative for Asthma (SINA) Step 4 or Step 5. [2] When asthma control cannot be achieved or sustained with high-dose inhaled maintenance therapy, further advanced targeted therapies are indicated, particularly monoclonal antibody (mAb) biologics, targeting the specific inflammatory pathways associated with the disease. [6]

Diagnostic and Phenotypic Criteria

The diagnosis of Severe Eosinophilic Asthma SEA includes both major and minor diagnostic criteria. Major criteria involve either a diagnosis of severe asthma plus evidence of eosinophilic disease, assessed as high load, on the basis of sustained blood or sputum eosinophilia on two or more occasions. **[5], [7]** Other major markers of severity may also include frequent exacerbations (2 or more per year) and the need for constant or intermittent oral corticosteroids (OCS) to achieve adequate asthma control. Associated minor criteria also commonly occur with this phenotype, including late onset of disease and co-morbid upper airway disease (e.g. chronic rhinosinusitis with nasal polyps). Other biomarkers such as fractional exhaled nitric oxide (FeNO), periostin and fixed airflow obstruction may also help identify individuals with a T2-high phenotype. **[8], [2]**

SINA (Saudi Initiative for Asthma) Perspective

The Saudi Initiative for Asthma (SINA) provides Guidance on local clinical practice, and their definition of severe asthma is considered uncontrolled at SINA step 4 despite optimal management. **[11], [9]** The SINA panel supports the personalized treatment plans, The use of OCS indicates a lack of control, but importantly, patients are at risk of developing severe long-term potentially systemic adverse effects, including osteoporosis, diabetes, and increased cardiovascular risk. Therefore, the ability of a biologic agent to provide an OCS-sparing effect is not only a clinical advantage but also a primary measure of therapeutic success. This outcome directly supports pharmacoeconomic analyses which are critical to justifying the high financial investment required for biologics in national health programs such as those in KSA. **[13]** The SINA guidelines also emphasize a thorough pre treatment assessment prior to the initiation of any high-cost biological therapy. **[13]**

The SINA guidelines indicate some degree of thorough treatment initiation assessment prior to the initiation of any high-cost biological therapy. This includes an objective assessment of asthma control using the Asthma Control Test (ACT), a physiological assessment using spirometry and FeNO assessment, and a complete review of current medication, adherence, and inhaler technique. This structured approach prior to treatment is designed to safeguard appropriate, off-label usage of biologics for patients with true refractory disease driven by inflammation, and not by modifiable factors, and in this way, will allow for clinically and cost effective use of biologics. **[14], [8]**

Biologics and Mechanisms of Action

Biological therapies are specifically targeting inflammatory cytokines, receptors or immune cells that are driving eosinophilic activation and airway damage in the T2 inflammation cascade. **[9]** There are six biologic agents approved worldwide, and five currently licensed and in use in the KSA: Omalizumab, Mepolizumab, Reslizumab, Benralizumab, Dupilumab. **[15]**

Omalizumab (Anti-IgE): Omalizumab is a monoclonal antibody that targets immunoglobulin E (IgE) and prevents IgE from binding to the high-affinity receptor (FcεRI) on mast cells and basophils, thereby inhibiting the allergic inflammatory cascade. Omalizumab was the first biologic in KSA and registered with the Saudi Food and Drug Authority (SFDA) in 2006. **[12]**

Mepolizumab and Reslizumab (Anti-IL-5 Ligand): Mepolizumab is another monoclonal antibody that binds directly to the circulating cytokine ligand, interleukin-5 (IL-5), neutralizing it and preventing binding to the IL-5 receptor on eosinophils. IL-5 is critical for eosinophil maturation, activation, survival, and recruitment, therefore, neutralization of IL-5 is an important mechanism to reduce eosinophil dependent inflammation. Mepolizumab was registered in KSA in 2017. **[17]**

Table 1: Mechanism of Action and Targeted Endotypes of Biologics in Severe Asthma Relevant to KSA

Biologic Agent	Therapeutic Target	Mechanism of Action	Primary Effect/Pathway	SFDA Registration in KSA
Omalizumab	Immunoglobulin E (IgE)	Anti-IgE; prevents IgE from binding to FcεRI.	Allergic Inflammation	2006
Mepolizumab	Interleukin-5 (IL-5)	Anti-IL-5; binds to IL-5 ligand, preventing receptor binding.	Eosinophil Maturation/Survival	2017
Benralizumab	Interleukin-5 Receptor α (IL-5Rα)	Anti-IL-5Rα; causes apoptosis of eosinophils via ADCC.	Rapid Eosinophil Depletion	2022
Dupilumab	Interleukin-4 Receptor α (IL-4Rα)	Anti-IL-4Rα; blocks signaling of both IL-4 and IL-13.	Broad T2 Cytokine Blockade	2018

Source: Based on the matter given above

Benralizumab (Anti-IL-5Rα): Benralizumab takes a different approach in that it binds the alpha subunit of the IL-5 receptor (IL-5Rα) on the surface of eosinophils and basophils. Benralizumab is afucosylated, to promote binding of benralizumab to FcγRIIIa on natural killer (NK) cells, resulting in antibody-dependent cell-mediated cytotoxicity (ADCC), leading to apoptotic (programmed cell death) and phagocytic clearance of eosinophils and basophils by macrophages. ADCC results in rapid and sustained depletion of eosinophils and basophils. Benralizumab was the most recently registered product in KSA, in 2022. **[18], [5]**

Dupilumab (Anti-IL-4Rα): Dupilumab functions by blocking the IL-4 receptor α subunit (IL-4Rα), which is a shared component of IL-4 and IL-13 receptors. This blockade of the receptor will inhibit the signaling of these two dominant T2 cytokines, providing a broader blockade of inflammation, mucus hypersecretion, and airway remodeling. Dupilumab was registered in KSA in 2018. **[13], [7]**

Asthma is a chronic disease that has emerged as a significant public health issue in Saudi Arabia, with prevalence estimates as high as 6-8% in the general population. The burden of SEA is further exacerbated by inequities in healthcare access, limited awareness of accessibility to the new treatment options, and disparities in clinical management. Biologic therapy is offered at some tertiary care centers, but the utilization of biologics are constrained due to cost and lack of insurance coverage and national evidence based guidelines reinstating the use of biologics. This review aims to summarize the existing evidence for the effectiveness of biologic therapies for SEA in the context of healthcare in Saudi Arabia. The paper will evaluate local data and place the information from worldwide studies into context to offer clinical practice recommendations to enhance patient care. Furthermore, this review will address personalized medicine, purpose of

multidisciplinary work and healthcare policy objectives aligned with Vision 2030 to enhance asthma care and reduce the disease burden.

Research Objective

This study aims to evaluate the clinical effectiveness of biologic therapies (dupilumab, benralizumab, omalizumab) in patients with severe eosinophilic asthma in Saudi Arabia, and to assess the impact of the comorbid chronic rhinosinusitis and nasal polyps on treatment outcomes.

Research Methodology

Research Question

Based on the demand of topic and description given above, following are the respective research questions:

Q1.How do biologics (e.g., dupilumab, benralizumab, omalizumab) influence asthma control, exacerbation rates, and lung function in patients with Severe Eosinophilic Asthma (SEA) in a Saudi tertiary care setting?
Q2. hat are the current patterns of biologic therapy use and availability in Saudi Arabia?

Research Design

This study followed a structured narrative review design to evaluate the effectiveness and utilization of biologic agents in patients with Severe Eosinophilic Asthma (SEA) in Saudi Arabia. This approach was selected to summarize real-world evidence rather than interventional or experimental findings.

Search Strategy

A detailed research was conducted on the kind and type of studies, mostly the electronic database was touched that included the following:
- Priority was given to studies that were most relevant and of adequate scientific quality.
- The selected articles were documented and grouped according to their main focus.
- Only studies published between 2010 and 2024 in English or Arabic were included.

Types of Studies Included

Interventional studies were not included in this research, since the focus was on real-world effectiveness rather than procedural effects. Studies conducted outside Saudi Arabia or the Middle East were generally excluded, except for selected international works used to provide global comparison.

Prticipants

Adults in Saudi Arabia diagnosed with severe eosinophilic asthma (SEA) based on clinical criteria like persistent eosinophilic inflammation despite high-dose inhaled corticosteroids or additional controller medications; Regular history of exacerbations and/or dependence on oral corticosteroids with blood eosinophil counts of ≥150 cells/μL or ≥300 cells/μL depending on biologics Then biologic therapy of Benralizumab (anti-IL-5 receptor), Dupilumab (anti-IL-4/IL-13), or Omalizumab (anti-IgE) Comorbidities could also include chronic rhinosinusitis, nasal polyp, allergic rhinitis (AR), or other atopic diseases.

Keywords

In order to enhance the sensitivity of search, following keywords were used seperated by Boolean operators (AND, OR) :

("Severe eosinophilic asthma" OR "SEA") AND ("biologic therapy" OR "biologics" OR "monoclonal antibodies") AND ("dupilumab" OR "benralizumab" OR "omalizumab") AND ("effectiveness" OR "clinical outcomes" OR "treatment response") AND ("Saudi Arabia" OR "Middle East").

Study Selection Process

Researcher had prepared a format for recording the relevant information, main heading include, design of study and location, demographics of the patients and number, specific measures of outcome, like effectiveness of biologics, related procedures, long term and short term effects, etc.

At this level, the studies were allotted certain codes for the sake of differentiation. At a later stage some of the studies were found to be duplicate and removed.

Data Management

The information cited in this review was derived from available peer-reviewed literature, clinical trials, and institutional reports regarding the use of biologics for severe eosinophilic asthma in Saudi Arabia. A standardized data extraction form was created to extract relevant key variables, such as study design, sample size, type of biologic agent, clinical outcomes (i.e., ACT score, FEV_1, exacerbation rates), and patient descriptors. Data were extracted to Microsoft Excel, and data were independently verified by two reviewers for accuracy, and consensus was reached when necessary. Reference managing and formatting followed NLM style by utilizing EndNote software.

Ethical Considerations

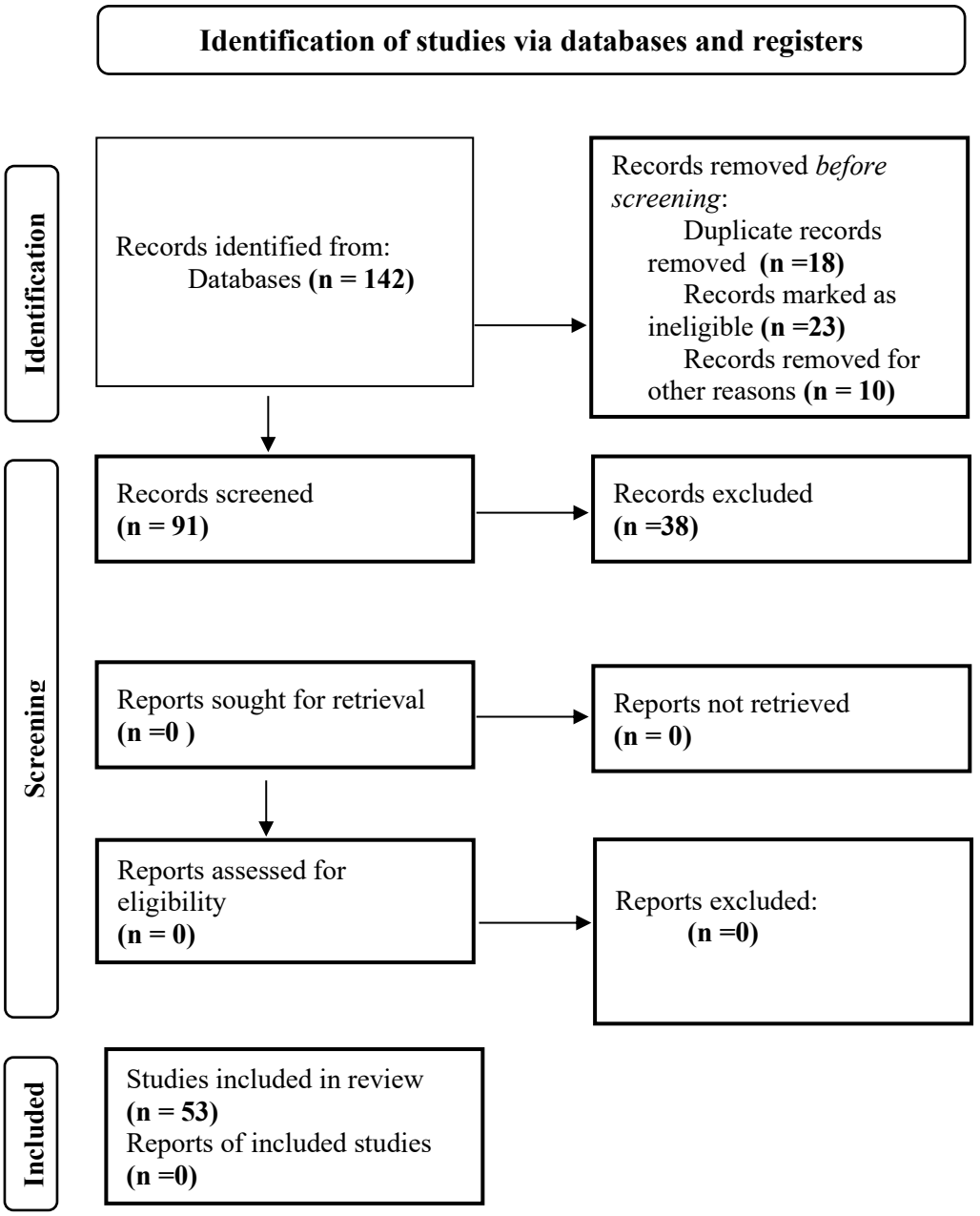
This study used previously published data only; no new patient information was collected. Therefore, ethical approval was not required. The review was conducted in accordance with research integrity and academic standards.

Limitations

The review is limited by the small number of local studies and possible publication bias toward English sources. Variations in study design and reported outcomes may also affect result comparability

Results

A total of 142 research studies were identified, all of them were based on the effectiveness, role and importance of biologics in severe eosinophilic asthma.



Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71 https://creativecommons.org/licenses/by/4.0/

Out of these identified studies, 18 were removed because of duplication of records, references and location and 23 studies were marked as ineligible, as not including the concept of biologics or related terms in severe eosinophilic asthma and 10 for some other unavoidable conditions. Further 91 records were saved for screening, then in the screening process 38 records were further removed on the basis of exclusion criteria stated above. Total studies finalized for review were 53. No reports were included in the study.

The availability of biologic therapies in the Kingdom of Saudi Arabia (KSA) has changed over the past years, following the approval from the Saudi Food and Drug Authority: Omalizumab (2006), Mepolizumab (2017), Dupilumab (2018), and Benralizumab (2022). Given the nature of this response, the sequence of availability has led to the downstream utilization, whereby Omalizumab and Mepolizumab are used in higher rates compared to later cohorts in KSA. **[3], [17], [12]** Access to biologic therapy is under strict regulations from the health systems in KSA, and patients must meet certain phenotyping exclusion criteria to qualify for reimbursement and generally require a referral from a specialist doctor for therapy eligibility which indicates the regulated and high-value nature of biologic therapy in the national health systems. **[18], [19]** The SINA guidelines have

clear recommendations separated into phenotypes for the use of these therapies; that is, the anti IgE therapy (Omalizumab) is recommended for allergic phenotypes only if the IgE levels are in therapeutic range and allergy testing is positive, and anti-IL5 therapy is only recommended for uncontrolled eosinophilic asthma patients after having 2 or more corticosteroid exacerbations in the past year. Moreover, some real world evidence from KSA has been published affirming the established efficacy of biologics in severe asthma from the global data. A multicenter retrospective observational study conducted recently evaluated outcomes in patients with severe asthma and included a total of 97 patients. **[20]**

Before receiving biologic therapy, every member of this cohort had uncontrolled asthma, and 77.3% (75/97) were on OCS. **[21]** Their mean blood eosinophils were markedly elevated at 750.5±498.5 cells/μl, and their mean FEV1 was markedly reduced at 59.0±12.9%. **[22], [23]** The breakdown by agent represents their historical availability; Mepolizumab was utilized the most frequently (54.6%), Omalizumab (22.7%), Dupilumab (12.4%), and Benralizumab (10.3%). **[21]** The KSA population showed a robust efficacy in biologics: Asthma control improved in 91.8% to 92.8% of patients. OCS use was practically eliminated, improving from 77.3% (75/97) to 10.3% (10/97) (86.7% reduction). **[21]** CS use was one of at least three measures of asthma control. The number of patients with one or more asthma exacerbations decreased from 84.5% pre-treatment to 14.4% post-treatment. **[23]** The average number of exacerbations per year decreased from 2.9 to 1.6, or 83% improvement in the severity of the events. Mean blood eosinophils significantly improved to 188.0±122.4 cells/μl. Mean FEV1 significantly improved from 59.0±12.9% to 76.0±10.2%. **[24], [22]**

Discussion

The arrival of biologic therapies is changing how we manage patients with severe eosinophilic asthma (SEA) through mechanisms that target the immunopathological mechanisms implicated in SEA. **[14], [9]** In Saudi Arabia a country where asthma remains highly prevalent and SEA is disproportionately associated with increased morbidity, biologic choices such as dupilumab, benralizumab, and omalizumab have shown great clinical efficacy. **[18]** In this review we summarize the findings, specifically focusing on the more recent observations studies, of patients receiving treatment with biologic therapies at tertiary care centers across the Kingdom. We summarize both the clinical benefit and experiences of using these products in day-to-day clinical work. **[25]** The results from Saudi data show that after treatment initiated with biologics the patients reported an absolute improvement in their asthma control as measured by ACT scores. **[26]** After initiation of biologics, patients were seen less often in health care settings, (exacerbation and hospitalizations) with many patients achieving sustained symptom control at 6-12 months. **[27]** On a hospital level, patients with severe eosinophilic asthma demonstrated absolute improvement in lung function (FEV_1) after treatment with dupilumab, and patients across all biologics demonstrated consistent reductions in blood eosinophils and serum IgE levels. **[23]** Collectively these findings are consistent with trial data from almsgate and indicate the potential of biologics to modify type 2 inflammation to restore airway homeostasis. **[8], [13]**

The Saudi studies illustrate the real effect of biologics on decreasing oral steroid dependency, which is an important goal given the side effects associated with long-term systemic steroids. **[25]** Patients with comorbid chronic rhinosinusitis, with and without nasal polyps, had good responses with biologic therapy and there were no statistically significant differences between the polyp and non-polyp subgroups, indicating that biologics may have clinical utility across all SEA phenotypes of asthma, regardless of involvement of the upper airway. With those successes come challenges that must be considered. **[26]** Biologics are only offered through limited tertiary care facilities and thus have geographic access limitations to biologics. Cost of biologics, and lack of coverage, subtract from the benefit of biologic therapy, especially regarding chronicity. **[13], [27]** Additionally, there are no national guidelines regarding appropriate use of biologics for asthma which leads to variation in prescribing patterns and patient selection. To implement use of

biologics into asthma care in Saudi Arabia, there needs to investment in clinician education, expansion of clinics that administer biologics outside of urban centers, and align with the goals stated in Vision 2030 regarding healthcare transformation. **[24]**

To confirm the findings of the present study, explore long-term safety, and consider local cost-effectiveness, multicenter prospective studies are warranted. Furthermore, identifying a national SEA registry may also allow the data to inform policy decisions and treatment pathways. The biologics represented a paradigm shift in the management of SEA in Saudi Arabia. Given their demonstrated efficacy when combined with effective implementation strategies, they have the potential to reduce the disease burden and improve patient quality of life.**[9], [10]**

Conclusion

Biologic therapy has revolutionized the management of Severe Eosinophilic Asthma for patients in tertiary care in the Kingdom of Saudi Arabia. Local real-world evidence demonstrates a high level of effectiveness for these targeted agents; with more than 90% of patients who previously had poor control of asthma moved to either 'controlled' or 'partly controlled' status. The total clinical benefit is impressive, including an 83% reduction in the annualized rates of severe exacerbations and significant rates of oral corticosteroid treatment cessation, with a clear impact on long-term morbidity. Patterns of use follow the order of regulatory authorization, with the anti IL5 pathway (Mepolizumab and Benralizumab) and dual IL4/IL13 pathway (Dupilumab) for patients unable to control their asthma with conventional treatment and high doses. Some data from Saudi Arabia supports the eosinophil-depleting efficacy of Benralizumab and evidence shows Dupilumab demonstrates a broad blockade of T2 compared to other medications with a particular strength in complex T2-high phenotypes.

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